# THE SYNTHESIS OF XANTHINE-8-ACETIC ACID AND SOME OF ITS DERIVATIVES

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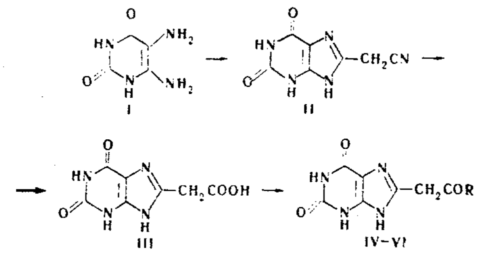
Condensation of 5, 6-diaminouracil with ethyl cyanoacetate yields xanthine-8-acetonitrile which is hydrolyzed by alkalis to xanthine-8-acetic acid. Also synthesized were its ethyl ester, acid chloride, and bis(2'-hydroxyethyl)amide.

The synthesis of some N-methylated derivatives of xanthine-8-carboxylic acid has been described in the literature. Acylation of ring N-methylated 5, 6-diaminouracils with aliphatic dicarboxylic acids followed by cyclization of the intermediate 5-acylaminopyrimidines [1–3], and condensation of N-methylated 8-halo- and 8-formylxanthines with malonic acid derivatives [4, 5], both give the corresponding purines. The acylation of nonmethylated 5, 6-diaminouracil (I) has not been achieved. There is only reference to an unsuccessful attempt to acylate I with glycolic acid, the failure of which was attributed to the low solubility of I in the acylating agent [6].

We have investigated the reaction of I with ethyl cyanoacetate. The latter was used, rather than the free acid, because higher reaction temperatures could be reached without decomposition of the starting materials. It has been shown that the reaction of I with an excess of ethyl cyanoacetate begins at 160° C and proceeds most rapidly at 190–200° C.



IV R = Cl; V R = $OC_2H_5$; VI R = $N(CH_2CH_2OH)_2$

Examination of the reaction product showed that the closure of the imidazole ring proceeded simultaneously with acylation at the 5-amino group to give xanthine-8-acetonitrile (II), in almost quantitative yield. The formation of II is indicated by the liberation of ethanol and water during the reaction, and also by the negative reaction for the possible presence of 6-amino-5-cyanoacetamidouracil in the reaction product (evaporation of II with fuming nitric acid leaves a yellow residue).

Treatment of II with aqueous alkali in the presence of ethanol affords xanthine-8-acetic acid (III). The structure of III was confirmed by decarboxylation to the known 8-methylxanthine in boiling aqueous solution, or on heating in vacuo to 140–150° C.

Treatment of III with an excess of boiling thionyl chloride gives the acid chloride IV in high yield. This compound is rather unstable, undergoing hydrolysis rapidly in air and decomposing on attempted recrystallization from organic solvents.

Xanthine-8-ethylacetate (V) was prepared by passing dry hydrogen chloride through a suspension of III in absolute ethanol.

Reaction of IV with an excess of diethanolamine yields the bis(2-hydroxyethyl) amide (VI), identical with the product from the reaction of V with aqueous diethanolamine.

## EXPERIMENTAL

**Xanthine-8-acetonitrile (II).** Dry finely-ground I (5 g; 0.035 mole) was placed in a thermostated flask, and freshly-distilled ethyl cyanoacetate (40 ml) was added. The mixture was heated with vigorous stirring at 195–200° C for 10 hr. The fraction boiling up to 110° C was collected in a special receiver. After cooling, the mixture was treated with twice its volume of ether, and the yellow solid was filtered off, washed with ether, and dried in air. Yield of II 6.5 g (97.5%), bright yellow crystals (from water), mp 250° C (decomp.). Found, %: C 44.03; H 2.71; N 36.57. Calculated for $C_7H_5N_5O_2$, %: C 43.91; H 2.62; N 36.64.

**Xanthine-8-acetic acid (III).** Compound II (6.5 g; 0.034 mole) was dissolved in 2 N aqueous NaOH (43.6 ml), and ethanol (1 ml) added. The dark red solution formed was heated at 100–105° C for 2 hr. After treatment with decolorizing charcoal the hot filtrate was neutralized with 20% hydrochloric acid to pH 6 and cooled by adding ice. The precipitate was filtered off, washed with a small quantity of ice water and then with acetone, and dried in a vacuum desiccator over $H_2SO_4$. Yield 4.71 g (60.8%). A sample was purified for analysis by reprecipitation from NaOH (2 N) with 20% HCl. Cooling gave III; bright yellow crystals, mp 260° C (decomp.). Found, %: C 36.64; H 3.43; N 24.37. Calculated for $C_7H_6N_4O_4 \cdot H_2O$, %: C 36.76; H 3.51; N 24.66. Heating in vacuo at 130° C caused simultaneous loss of water of crystallization and decarboxylation. Decarboxylation to 8-methylxanthine was complete after 2 hr in boiling water.

**Xanthine-8-acetyl chloride (IV).** A mixture of III (2 g; 0.009 mole) and thionyl chloride (15 ml) was boiled with stirring for 5 hr. The mixture was cooled, and the solid was isolated, washed with anhydrous ether, and dried in a vacuum desiccator over $H_2SO_4$. Yield 2.05 g (96%), yellow crystals mp 270° C (decomp.). Hydrolysis of **IV** took place rapidly in the presence of atmospheric moisture. Found, %: Cl 15.68; N 24.59. Calculated for $C_7H_5ClN_4O_3$, %: Cl 15.51; N 54.51.

**Xanthine-8-ethylacetate (V).** A suspension of III (2 g; 0.01 mole) in absolute ethanol (100 ml) was saturated with dry hydrogen chloride with stirring. After 48 hr at room temperature, the ethanol was distilled in vacuo, and the residue was treated with ether and air-dried to give 1.5 g (71%) of colorless crystals mp 235° C (decomp.) (from ethanol). Found, %: C 45.61; H 4.11; N 23.54. Calculated for $C_9H_{10}N_4O_4$, %: C 45.48; H 4.21; N 23.49.

**Bis(2'-hydroxyethyl)amide of xanthine-8-acetic acid (VI).** a) Freshly-prepared **IV** (2 g; 0.009 mole) and diethanolamine (15 g) were stirred at 60° C for 3 hr. The reaction mixture was mixed with absolute ethanol (100 ml), and cooled in ice, and the precipitate was filtered off, washed with ethanol and ether, and dried in a vacuum desiccator over $H_2SO_4$. Yield of **VI** 2 g (80.1%), colorless crystals mp 240° (decomp., from aqueous acetone). Found, %: C 44.62; H 5.09; N 23.38. Calculated for $C_{11}H_{15}N_5O_5$, %: C 44.51; H 5.04; N 23.56.

b) A mixture of **V** (2 g; 0.008 mole) and diethanolamine (2.5 g) in water (15 ml) was boiled with stirring for 3 hr. The water was removed completely in vacuo, the residue was washed several times with acetone, ethanol (25 ml) was added, and the crystals were filtered off and dried in a vacuum desiccator over $H_2SO_4$. Yield 1.35 g (54%). Recrystallization from aqueous acetone gave colorless crystals mp 240° C (decomp.). Found, %: C 44.38; H 5.14; N 23.60. Calculated for $C_{11}H_{15}N_5O_5$, %: C 44.51; H 5.04; N 23.56.

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