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REACTION OF 5-NITROSO-6-AMINOURACILS WITH GLYOXYLIC ACID – A SIMPLE SYNTHETIC PATHWAY TO URIC ACID DERIVATIVES

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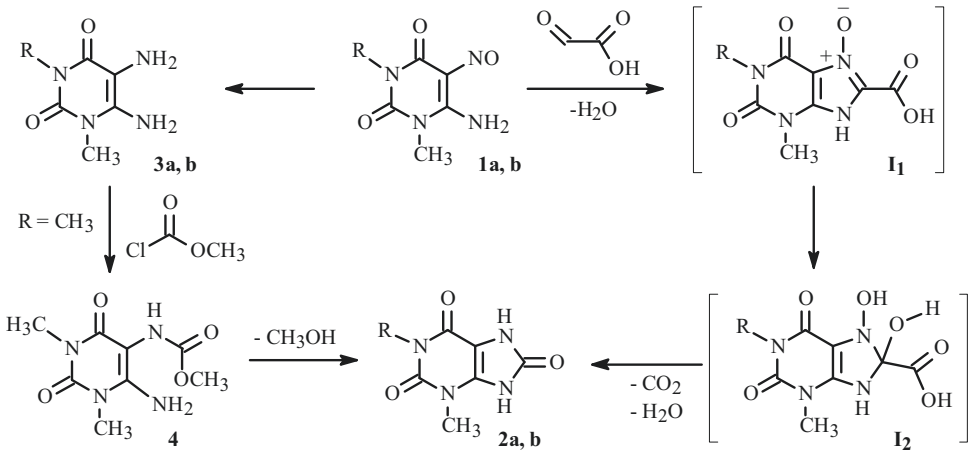
Purines are commonly synthesized by the method proposed by Traube that is based on cyclization of 4,5-aminopyrimidines with urea, formamide, or formic acid [1]. The reaction of 4,5-aminopyrimidines with C_2 cyclizing agents (glyoxal, glyoxylic acid derivatives, etc.) synthesized pteridine derivatives [1, 2]. Heating 5-nitroso-6-aminouracils with aldehydes formed 7-hydroxyxanthine derivatives [3]. Uric acid is the final product from oxidation (metabolism) of purines in living organisms. Its level characterizes the metabolic condition. Serious diseases can manifest if its *in vivo* content increases. Therefore, monitoring of the secretion level of uric-acid and its derivatives is especially significant [4]. Practically the whole set of natural purine bases or the nucleic acids incorporated into the structure or resulting from purine metabolism can be synthesized from uric acid [1].

The reactions of uracil amine derivatives with C_2 cyclizing agents were investigated in order to develop simple and convenient synthetic pathways to purine and pteridine derivatives. An unusual transformation of 5-nitroso-6-aminouracils **1a** and **1b** during the reaction with glyoxylic acid was discovered during the work. Thus, brief heating of **1a** and **1b** and glyoxylic acid in formic acid formed smoothly and in high yield uric-acid derivatives **2a** and **2b** (Scheme 1).



Scheme 1

The masses of **2a** and **2b** that were determined by mass spectrometry agreed with those calculated. PMR spectra of **2a** and **2b** exhibited resonances for the corresponding methyl protons. Furthermore, the structures of **2a** and **2b** were confirmed by convergent syntheses. Thus, heating known 5,6-diamino-1,3-dimethylpyrimidine-2,4-(1*H*,3*H*)-dione (**3b**) and methyl chloroformate produced methyl (6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate (**4**), the structure of which was confirmed using PMR spectroscopy and mass spectrometry.

Heating **4** to the melting point (225–230°C) formed dimethyluric acid that was identical to **2b**.

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The uric-acid derivatives were presumably formed as a result of initial cyclization of nitrosoaminouracils **1a** and **1b** with glyoxylic acid to form intermediate $\mathbf{I}_1$, which transformed during the reaction into intermediate $\mathbf{I}_2$. Subsequent hydroxylation and simultaneous decarboxylation of intermediate $\mathbf{I}_2$ gave uric-acid derivatives **2a** and **2b**.

The observed transformation of the nitrosoaminouracils represented a simple pathway to uric-acid derivatives under mild conditions and in one step. The uric-acid derivatives were formed in high yields and could be easily isolated and identified. Obviously, the observed transformation would be useful for studying purine metabolism in biological systems.

PMR spectra were recorded on a Bruker Avance-400 spectrometer. Mass spectra were obtained on a Shimadzu GCMS-QP2010 Ultra at ionization potential 75 eV and 200°C.

Starting nitrosoaminouracils **1a** and **1b** and diaminouracils **3a** and **3b** were synthesized by the literature methods [2, 5].

Reaction of Nitrosopyrimidines 1a and 1b with Glyoxylic Acid. The appropriate 6-amino-5-nitrosopyrimidine-2,4-dione **1** (1.5 mmol) and glyoxylic acid (6.0 mmol) in formic acid (5.0 mL) were heated at 50°C for 15–20 min. The resulting precipitate of the corresponding uric-acid derivative **2** was filtered off and recrystallized from H_2O.

3-Methyl-1*H*-purino-2,6,8(3*H*,7*H*,9*H*)-trione (2a). Yield 67%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.24 (3H, s, CH_3), 10.69 (1H, s, NH), 10.96 (1H, s, NH), 11.78 (1H, s, NH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel},%): 182 ([M^+], 67), 139 (67), 111 (16), 83 (34), 68 (100). $C_6H_6N_4O_3$.

1,3-Dimethyl-1*H*-purino-2,6,8(3*H*,7*H*,9*H*)-trione (2b). Yield 70%, mp > 300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.11 (3H, s, CH_3), 3.21 (3H, s, CH_3), 10.65 (1H, s, NH), 11.79 (1H, br.s, NH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel},%): 196 ([M^+], 95), 139 (43), 111 (15), 83 (36), 68 (100). $C_7H_8N_4O_3$. The PMR spectrum of **2b** agreed with that in the literature [6].

Methyl (6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)carbamate (4). Compound **3b** (60.0 mg, 0.35 mmol) and methyl chloroformate (0.5 mL, 5.3 mmol) in MeCN (2.0 mL) were heated at 80°C for 4 h. The resulting precipitate of **4** was filtered off. Yield 85%, mp 214–215°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 3.09 (3H, s, CH_3), 3.15 (3H, s, CH_3), 3.61 (3H, s, CH_3), 6.56 (2H, s, NH_2), 7.48 (1H, s, NH). Mass spectrum (EI, 70 eV), *m/z* (I_{rel},%): 228 ([M^+], 24), 196 (100), 168 (15), 142 (13), 83 (70). $C_8H_{12}N_4O_4$.

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