# A Facile Synthesis of 7-Hydroxy-9-deazaxanthines

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Pyrrolo[3,2-*d*]pyrimidine, as a 9-deaza analogue of purines, can be expected to have interesting biological properties. Although 9-deazaxanthines have previously been prepared by various methods[1], their 7-hydroxy derivatives have not hitherto been known. The present paper describes a convenient method of synthesising 7-hydroxy-9-deazaxanthines **(3)** involving alkylation of the methyl group at C-6 of 1,3,6-trimethyl-5-nitrouracil followed by base-catalysed cyclisation.

The sodium salt **(1)** of 1,3,6-trimethyl-5-nitrouracil was used as a starting material; it was easily prepared by refluxing 1,3,6-trimethyl-5-nitrouracil in ethanolic sodium ethoxide according to Ref.[2]. The reaction of **1** with methyl iodide and benzyl bromide in dry dimethylformamide at 80 °C afforded the 6-ethyl- and 6-phenethyl-5-nitrouracils **(2a)** and **(2b)** in 78 and 93% yields, respectively. When compound **1** was treated with aralkyl chlorides such as benzyl chloride, aralkylation

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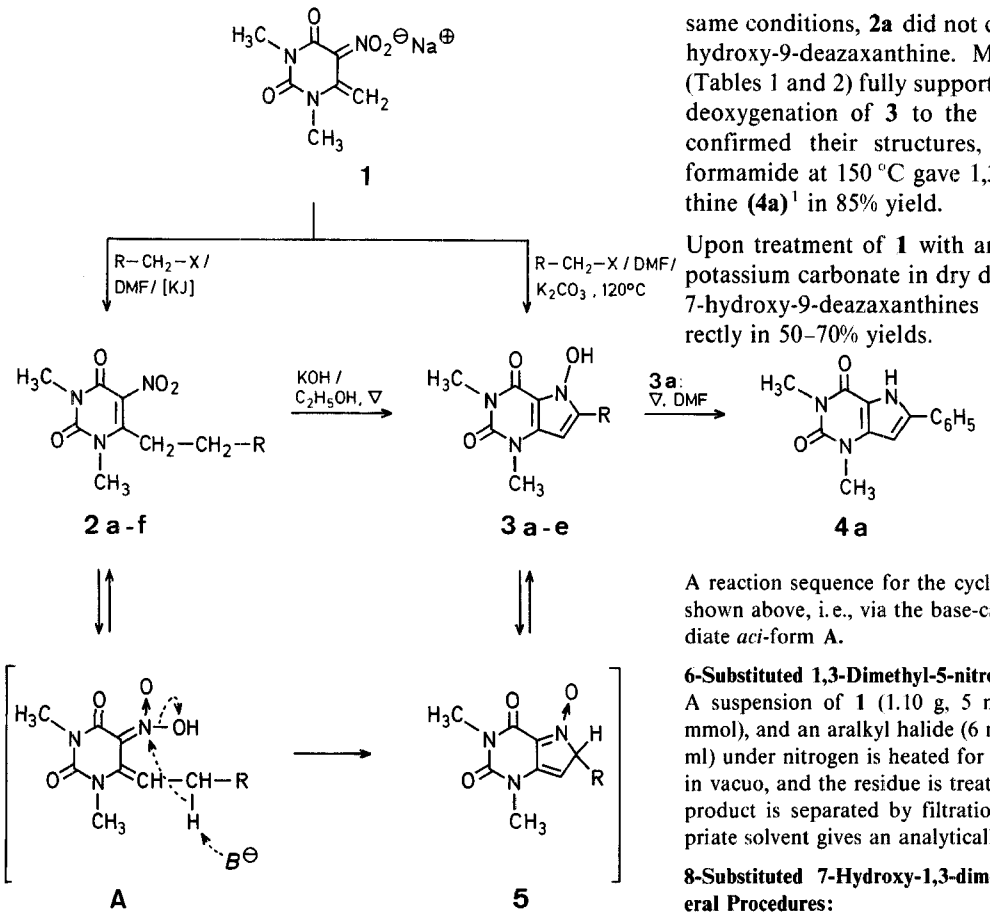


did not occur. The addition of potassium iodide as a catalyst, however, overcame this difficulty and gave the corresponding aralkylated derivatives **2b–f** in high yields. Further treatment of **2b–f** with potassium hydroxide in refluxing ethanol led to the formation of 7-hydroxy-9-deazaxanthines **3a–e**. Under the same conditions, **2a** did not convert into the corresponding 7-hydroxy-9-deazaxanthine. Microanalyses and spectral data (Tables 1 and 2) fully support the structures of **3a–e**. A simple deoxygenation of **3** to the corresponding 9-deazaxanthines confirmed their structures, e.g., heating **3a** in dimethylformamide at 150 °C gave 1,3-dimethyl-8-phenyl-9-deazaxanthine **(4a)**[1] in 85% yield.

Upon treatment of **1** with aralkyl halides in the presence of potassium carbonate in dry dimethylformamide at 120 °C, the 7-hydroxy-9-deazaxanthines **3a–e** were easily prepared directly in 50–70% yields.

A reaction sequence for the cyclisation of **2** to **3** can be outlined as shown above, i.e., via the base-catalysed dehydration[3] of an intermediate *aci*-form **A**.

**6-Substituted 1,3-Dimethyl-5-nitrouracils 2a–f; General Procedure:**
A suspension of **1** (1.10 g, 5 mmol), potassium iodide (0.3 g, 1.8 mmol), and an aralkyl halide (6 mmol) in dry dimethylformamide (10 ml) under nitrogen is heated for 2 h at 80 °C. The solvent is removed in vacuo, and the residue is treated with water (10 ml). The insoluble product is separated by filtration. Recrystallisation from an appropriate solvent gives an analytically pure sample (Table 1).

**8-Substituted 7-Hydroxy-1,3-dimethyl-9-deazaxanthines (3a–e); General Procedures:**

Method A (from **2**): To a solution of potassium hydroxide (0.12 g, 2.2 mmol) in ethanol (30 ml) is added **2a–e** (2 mmol) and the mixture is refluxed for 1–2 h. The solvent is removed in vacuo. The residue is dissolved in water (10 ml) and neutralised with acetic acid. The precipitate is filtered and washed with water. Recrystallisation from ethanol gives an analytically pure sample (Table 2).

**Table 1.** Preparation of 6-Substituted 5-Nitrouracils **2a–f**

| Product No. | R | Aralkyl halide X in $RCH_2X$ | Yield [%] | m.p. [°C] (solvent) | Molecular formula[a] | |
|---|---|---|---|---|---|---|
| **2a** | H | J | 78 | 119–120° (ligroin) | $C_8H_{11}N_3O_4$ | (213.2) |
| **2b** | $C_6H_5$ | Br | 93 | 165° (ethanol) | $C_{14}H_{15}N_3O_4$ | (289.3) |
| **2b** | $C_6H_5$ | Cl[b] | 90 | | | |
| **2c** | 4-$H_3C$—$C_6H_4$ | Cl[b] | 91 | 152° (ethanol) | $C_{15}H_{17}N_3O_4$ | (303.3) |
| **2d** | 4-$H_3CO$—$C_6H_4$ | Cl[b] | 87 | 157° (ethanol) | $C_{15}H_{17}N_3O_5$ | (319.3) |
| **2e** | 4-Cl—$C_6H_4$ | Cl[b] | 86 | 185° (ethanol) | $C_{14}H_{14}ClN_3O_4$ | (323.7) |
| **2f** | 1-naphthyl | Cl[b] | 89 | 235° (ethyl acetate) | $C_{18}H_{17}N_3O_4$ | (339.3) |

[a] All products gave satisfactory microanalyses (C ±0.24, H ±0.11, N ±0.27).
[b] Potassium iodide is added to the reaction mixture as catalyst for the preparation of **2**.

**Table 2.** Preparation of 8-Substituted 7-Hydroxy-9-deazaxanthines **3a–e**

| Product No. | R | Yield [%] | | m.p.[a] [°C] | Molecular formula[b] | | $^1$H-N.M.R. (DMSO-$d_6$) $\delta$ [ppm] | |
|---|---|---|---|---|---|---|---|---|
| | | Method A | Method B | | | | H—C-9 | HO—N-7 |
| **3a** | $C_6H_5$ | 93 | 73 | 220–225° (dec.) | $C_{14}H_{13}N_3O_3$ | (271.3) | 6.25 | —[c] |
| **3b** | 4-$H_3C$—$C_6H_4$ | 92 | 59 | 210–215° (dec.) | $C_{15}H_{15}N_3O_3$ | (285.3) | 6.28 | 11.8 |
| **3c** | 4-$H_3CO$—$C_6H_4$ | 87 | 65 | 214–216° (dec.) | $C_{15}H_{15}N_3O_4$ | (301.3) | 6.25 | 11.8 |
| **3d** | 4-Cl—$C_6H_4$ | 80 | 55 | 230–235° (dec.) | $C_{14}H_{12}ClN_3O_3$ | (305.7) | 6.40 | —[c] |
| **3e** | 1-naphthyl | 93 | 59 | 230–235° (dec.) | $C_{18}H_{15}N_3O_3$ | (321.3) | 6.23 | 11.6 |

[a] All products are recrystallised from ethanol.
[b] All products gave satisfactory microanalyses (C ±0.23, H ±0.14, N ±0.20).
[c] Could not be detected.

Method B (from **1**): A suspension of **1** (1.10 g, 5 mmol), aralkyl chloride (6 mmol), potassium iodide (0.3 g, 1.8 mmol), and anhydrous potassium carbonate (0.76 g, 5.5 mmol) in dry dimethylformamide (10 ml) unter nitrogen is heated at 120 °C for 2–3 h. The solvent is removed in vacuo, and the residue is treated as described above to give **3a–e.**

**1,3-Dimethyl-8-phenyl-9-deazaxanthine (4a):**
A solution of **3a** (0.27 g, 1 mmol) in dimethylformamide (5 ml) is heated under reflux for 2 h. The solvent is removed in vacuo and the residue is recrystallised from ethanol; yield: 0.22 g (85%); m.p. >300 °C (Ref.[1], m.p. >300 °C).

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