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Mendeleev Commun., 2008, **18**, 223–224
Mendeleev Communications

Oxidation of 5-hydroxy-6-methyluracil to 5,5,6-trihydroxy-6-methylpyrimidine-2,4-dione with molecular oxygen

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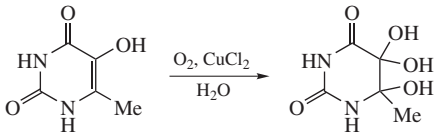
DOI: 10.1016/j.mencom.2008.07.020

The oxidation of 5-hydroxy-6-methyluracil with molecular oxygen in aqueous solutions in the presence of copper(II) chloride gave 5,5,6-trihydroxy-6-methylpyrimidine-2,4-dione in a quantitative yield.

Pyrimidine bases are DNA and RNA units. Uracils, which are generally used as their precursors, have four donor centres. In the presence of metal ions, these centres form donor–acceptor bonds with both N atoms of the pyrimidine ring and O atoms of carbonyl groups.[1] This accelerates considerably the highly selective oxidation of organic compounds under mild conditions. Copper complexes that simulate the action of monooxygenase enzymes catalysing the hydroxylation of aliphatic and aromatic compounds are widely used in practice.[2] The formation conditions, physicochemical properties and reactivity of copper complexes with molecular oxygen have been reported.[3–6] Oxygen fixation and activation can result in (η^1-hydroperoxo) and (η^2-peroxo) complexes.



1 **2**

Scheme 1

We studied the oxidative hydroxylation of 5-hydroxy-6-methyluracil **1**, which is an immunomodulatory drug,[7] with molecular oxygen in the presence of copper(II) chloride in aqueous solution (Scheme 1). The reaction, which was monitored by UV spectroscopy and HPLC,[†] resulted in a decrease in the intensity of the absorption band of compound **1** at 278 nm. On reaching a minimum absorbance at this wavelength, the solvent was slowly evaporated (1 h) under ambient pressure at 45 °C. As a result, the reaction product precipitated from the solution as clear rhombic crystals (yield, 85%). ^{13}C NMR spectroscopy and GC-MS[†] combined with X-ray diffraction analysis revealed that this product was 5,5,6-trihydroxy-6-methylpyrimidine-2,4-dione **2** (Figure 1).[‡] Compound **2** is a rare case of gem diols, which are usually unstable and eliminate a water molecule to give a ketone. Presumably, the structure of this compound is stabilised by intra- and intermolecular hydrogen bonds.

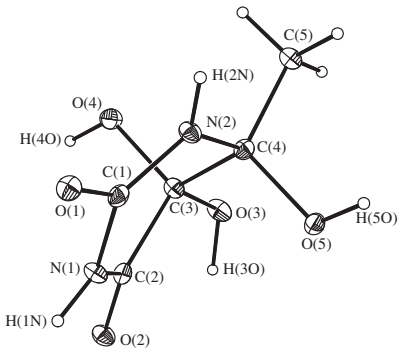


Figure 1 Molecular structure of compound **2**. Bond lengths (Å): O(1)–C(1) 1.235(2), O(2)–C(2) 1.218(2), O(3)–C(3) 1.392(2), O(4)–C(3) 1.406(2), O(5)–C(4) 1.423(2).

[†] The UV spectra were recorded on a Specord M40 spectrophotometer. The ^{13}C NMR spectrum was recorded on a Bruker AM-300 pulse spectrometer (75 MHz) in D_2O. The chromatographic study of the oxidation of compound **1** was carried out on a Shimadzu LC-20 AD chromatograph using a 250×4.6 cm column packed with a Luna C18 phase, 5 μm (Phenomenex, USA). A water–acetonitrile mixture (95:5) (flow rate of 1 ml min^{-1}) was used as the mobile phase. Detection was carried out at 215 nm.

5-Hydroxy-6-methyluracil **1** was obtained using the reported technique.[12] The compound was recrystallised from an aqueous solution; the purity of compound **1** was 97%.[13] Copper(II) chloride of reagent grade was used. Solutions were prepared using twice distilled water.

Oxidation of compound **1**. Copper(II) chloride (1.8 mmol) was added to a solution of compound **1** (3.6 mmol) in water (50 ml). The reaction mixture was stirred for 1 h with a magnetic stirrer under ambient pressure at 45 °C. Slow evaporation of the solvent gave clear rhombic crystals of compound **2**. ^{13}C NMR (D_2O) δ: 156.01 [C(2)], 173.97 [C(4)], 84.83 [C(5)], 92.19 [C(6)], 20.98 (Me). MS, *m*/*z* (%): 158 (44) [M – H_2O]$^+$, 157 (1.32) [M – H_3O]$^+$, 141 (10.8), 140 (74.36), 115 (100) [158 – NCOH]$^+$, 89 (0.53) [158 – CONCMe]$^+$, 42 (12.1) [CNO]$^+$.

[‡] *Crystallographic data for compound* **2**: colourless rhombic crystals ($C_5H_8N_2O_5{\cdot}H_2O$, M = 194.15), triclinic, space group $P\bar{1}$, at 120(2) K: a = 6.7916(6), b = 11.1930(11) and c = 11.4330(11) Å, α = 110.041(2)°, β = 97.817(2)° and γ = 106.531(2)°, V = 755.97(12) Å^3, Z = 4, d_{calc} = = 1.706 g cm^{-3}, R_1 = 3.93 [for 2397 independent reflections with $I > 2\sigma(I)$], wR_2 = 0.1059 and GOF = 1.009 (for 2865 independent reflections).

The intensities of 4442 reflections [R(int) = 0.0172] were measured with a Bruker SMART 1000 CCD area detector diffractometer [λ(MoKα) irradiation, graphite monochromator, ω-scanning, $\theta < 26.0°$] at 120(2) K. The structure was solved by direct methods and refined in anisotropic approximation for all non-hydrogen atoms. The hydrogen atoms of NH and OH groups and water molecules were localised by differential syntheses. The hydrogen atoms of methyl groups were calculated based on the molecule geometry. All hydrogen atoms were included in the refinement in isotropic approximation based on the 'riding' model.

CCDC 671168 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2008.

The formation of uracil and thimine glycols by the oxidation of such compounds with potassium permanganate,[8] hydrogen peroxide,[9] osmium tetroxide[10] and various sources of hydroxyl radicals[11] has been observed.

The results allowed us to believe that the complexation of Cu^{II} with compound **1** occurs at the first stage, as suggested by UV spectroscopic data. The oxidative conversion of compound **1** into **2** occurs under mild conditions and involves atmospheric oxygen. It presumably occurs due to the fixation and activation of molecular oxygen with a copper-uracil complex to give the $[Cu(\mathbf{1})_2(O_2)]^{2+}$ complex.

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Received: 24th December 2007; Com. 07/3066