Oxidative Transformation of 5-Aminouracil into Imidazolone by Thallium(III) Nitrate Trihydrate in Methanol

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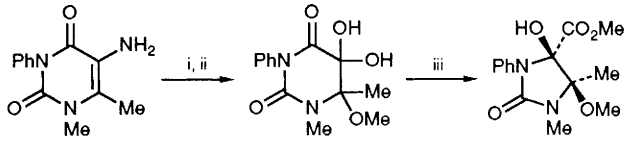
Oxidation of 5-amino-1,6-dimethyl-3-phenyluracil **1** by means of thallium(III) nitrate trihydrate in methanol gives 5,5-dihydroxy-1,6-dimethyl-3-phenyl-1,2,3,4,5,6-hexahydropyrimidine-2,4-dione **2**, which is easily transformed into 1,5-dimethyl-4-hydroxy-5-methoxy-4-methoxycarbonyl-3-phenylimidazolin-2-one **3** by treatment with methanol.

Various studies on the synthesis and reactions of pyrimidines which have potential biological activities have been reported.[1] 5-Aminouracil derivatives are important precursors of xanthines or purines, and it will be of interest to examine their reactivities. In the course of medicinal and chemical studies of pyrimidines in our laboratory,[2] we previously encountered the novel ring transformation of 5-aminopyrimidin-4(3*H*)-one into 2-alkoxy-1*H*-imidazole with oxidative metal salts in alkyl alcohols.[3] Since 5-aminouracils have a similar pyrimidinone skeleton, we were interested to examine their oxidative transformations. In this paper we describe the oxidative transformation of 5-aminouracil into imidazolone by thallium(III) nitrate trihydrate in methanol.

5-Aminouracil **1**[4] was allowed to react with thallium(III) nitrate trihydrate for 1.5 h at room temperature in methanol. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and the dichloromethane was removed. The residue was purified by silica gel column chromatography to give **2** (m.p. 107–108 °C) in 93% yield (Scheme 1). The electron-impact mass spectrum (EI-MS) of **2** showed the molecular ion peak at *m/z* 280. Elemental analysis gave results consistent with the formula $C_{13}H_{16}N_2O_5$. Its ^1H NMR spectrum gave signals due to a phenyl, two hydroxy, a methoxy, an *N*-methyl and a *C*-methyl groups. The ^{13}C NMR spectrum involving a DEPT (distortionless enhancements by polarization transfer) experiment indicated the presence of two carbonyl carbons, three quaternary carbons, five tertiary carbons (phenyl ring) and three primary carbons. Furthermore, the IR spectrum showed absorptions ascribable to hydroxy groups at 3350 and 3250 cm^{-1} and carbonyl groups at 1720, 1675, 1665 cm^{-1}. However, these physical data did not provide an unambiguous structure for compound **2**. So its structure was determined by X-ray crystallographic analysis,† which established **2** to be 5,5-dihydroxy-1,6-dimethyl-3-phenyl-1,2,3,4,5,6-hexahydropyrimidine-2,4-dione, as depicted in Scheme 1. Fig. 1 shows a perspective view of **2**. When **2** was stirred for 10 min at room temperature in methanol, an interesting ring contraction to give **3** (m.p. 125–126 °C) in quantitative yield was observed. The EI-MS of **3** showed the molecular ion peak at *m/z* 294. From the elemental analysis, its formula was determined to be $C_{14}H_{18}N_2O_5$. The ^1H NMR spectrum of **3** showed signals due to one hydroxy and two methoxy groups. The ^{13}C NMR spectrum involving a DEPT experiment indicated the presence of two methoxy groups, two methyl groups, a phenyl group, two carbonyl groups. Since an unambiguous structure was not obtained from these data, an X-ray crystallographic analysis was carried out.‡ Fig. 2 shows the perspective view of **3**. The structure of **3** was established to be 1,5-dimethyl-4-hydroxy-5-methoxy-4-methoxycarbonyl-3-phenylimidazolin-2-one. Since prolonged reaction of **1** with thallium(III) nitrate in methanol did not give **3**, it seems to be necessary to isolate **2** which would be formed by the reaction with water during the work-up.

A possible mechanism for the formation of **2** and **3** from **1** is shown in Scheme 2. Initially the 5-amino group of **1** would be oxidized by thallium(III) nitrate accompanied by nucleophilic



1 **2** **3**

Scheme 1 *Reagents*: i, $Tl(NO_3)_3 \cdot 3H_2O$ in MeOH; ii, H_2O (work-up); iii, MeOH

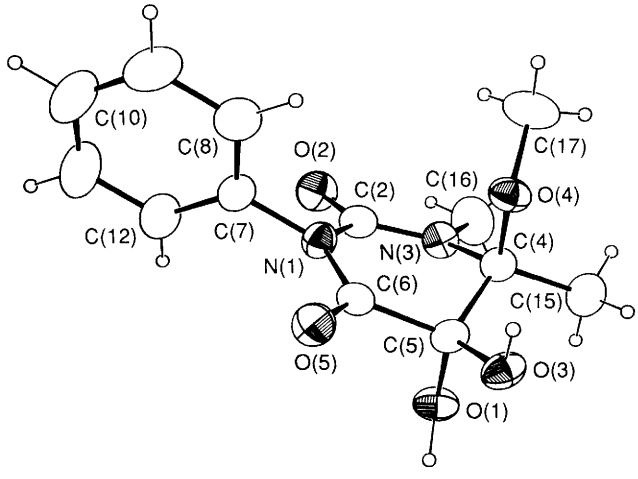


Fig. 1 Perspective view of **2** with thermal ellipsoids at 50% probability for non-hydrogen atom. Hydrogens in calculated positions are shown as arbitary circles. Octant shaded ellipsoids are heteroatoms.

† *Crystal data* for **2**: $C_{13}H_{16}N_2O_5$, M = 280.3, monoclinic, a = 10.771(1), b = 10.710(2), c = 12.237(1) Å, α = 90.0, β = 110.805(4), γ = 90.0°, U = 1319.6(22) Å^3, Z = 4, space group $P2_1/n$, D_c = 1.411 g cm^{-3}, μ(Mo-Kα) = 0.9 cm^{-1}. Data were collected on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-Kα radiation. Intensity data were reduced with the suite of programs of SDP. The structure was solved by direct methods (MULTAN82). The hydrogen positions were idealized and included in subsequent cycles of full-matrix least-squares refinement as fixed contributors. The final cycle of refinement of 182 variable parameters converged at R = 0.042.

‡ *Crystal data* for **3**: $C_{14}H_{18}N_2O_5$, M = 294.3, triclinic, a = 7.874(1), b = 9.956(1), c = 10.292(1) Å, α = 96.72(1), β = 103.43(1), γ = 110.60(1)°, U = 716.9(40) Å^3, Z = 2, space group $P\bar{1}$, D_c = 1.363 g cm^{-3}, μ(Mo-Kα) = 0.9 cm^{-1}. Data were collected on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-Kα radiation. Intensity data were reduced with the suite of programs of SDP. The structure was solved by direct methods (MULTAN82). The hydrogen positions were idealized and included in subsequent cycles of full-matrix least-squares refinement as fixed contributors. The final cycle of refinement of 191 variable parameters converged at R = 0.037.

Atomic coordinates, bond lengths and angles, and thermal parameters for both compounds **2** and **3** have been deposited at the Cambridge Crystallogrpahic Data Centre. See Notice to Authors, Issue No. 1.

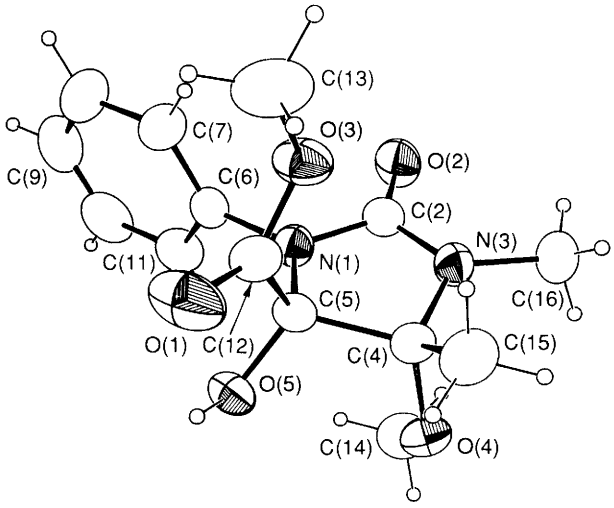


Fig. 2 ORTEP plot for **3** showing similar information as in Fig. 1

attack of methanol on C(6) to give the intermediate **ii** *via* **i**. Water from the work-up or the water of crystallization of thallium(III) nitrate trihydrate may participate[5] in the hydrolysis of the imino group and following deamination. The transformation of **2** into **3** would be explained by the nucleophilic attack of methanol on C(5) of **2** followed by dehydration and rearrangement of the C(5)–C(6) bond to the C(4) carbonyl carbon **iii**.

It is noteworthy that the structurally uncommon *gem*-diol **2** was isolated in a stable and good yield from the oxidation of 5-aminouracil **1** by thallium(III) nitrate, and that **2** was easily contracted to imidazolone **3**.

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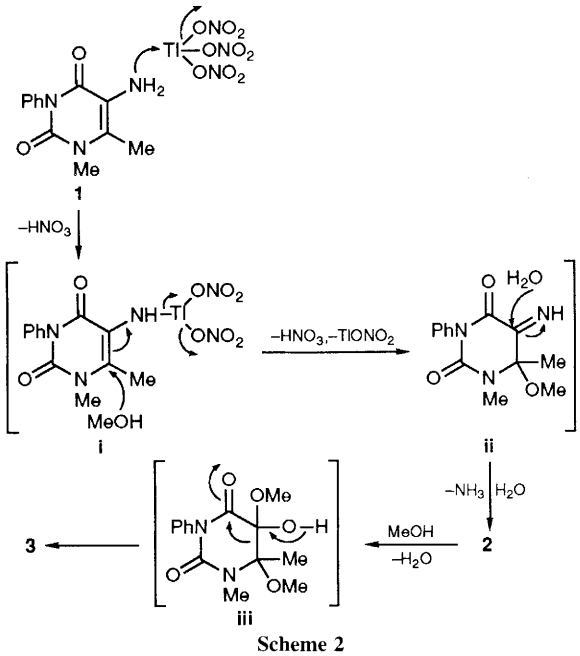

Scheme 2

References

1 D. J. Brown, *The Pyrimidines*, Interscience, New York, 1962; D. J. Brown, *The Pyrimidines, Supplement I*, Wiley-Interscience, New York, 1970.
2 T. Ueda, I. Matsuura, N. Murakami, S. Nagai, J. Sakakibara and M. Goto, *Tetrahedron Lett.*, 1988, **29**, 4607; I. Matsuura, T. Ueda, N. Murakami, S. Nagai and J. Sakakibara, *J. Chem. Soc., Perkin Trans. I*, 1991, 2821.
3 I. Matsuura, T. Ueda, N. Murakami, S. Nagai and J. Sakakibara, *J. Chem. Soc., Chem. Commun.*, 1991, 1688.
4 S. Senda, K. Hirota and K. Banno, *J. Med. Chem.*, 1972, **15**, 471.
5 E. Fujita, Y. Nagao and K. Kaneko, *Chem. Pharm. Bull.*, 1976, **24**, 1115; 1978, **26**, 3743.