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On the mechanism of the Folin test for uric acid

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Abstract

The mechanism of the interaction of uric acid with sodium tungstate in phosphoric acid (Folin test) is described. This insight involves the following steps: addition of tungstic acid to the carbon-carbon double bond in uric acid. Protolysis of the organometallic ester gives rise to dihydroxyoxotungsten and an epoxide, via a concerted mechanism. Acid catalyzed ring opening of the oxirane produces a vicinal diol via reaction of the intermediate carbocation with water. Isomerization of the resulting carbinolamide groups is enhanced by the resonance of the ureido group. Breaking of the second carbinolamide gives urea and alloxan, 5-ketobarbituric acid hydrate. Uric acid oxidation in strong acidic medium like phosphoric acid produces alloxan, whereas oxidation in alkaline, neutral, or slightly acidic medium, gives allantoin.

Keywords: Addendum to alkene; Alloxan; Epoxidation; Reactive intermediates; Ring opening; Ureido chain

1 Introduction

Uric acid is a normal waste product that the body produces when it breaks down purines, these come from the cells when they die. Purines are also found in many foods and beverages. Most uric acid dissolves in the blood, and the kidneys filter the uric acid out of the body in the urine. It must be monitored in people with cancer chemotherapy because when treatment kills cancer cells quickly they release large amounts of purines into the blood. This can lead to serious problems from high uric acid levels, [1]. So, this biomarker is an analyte.

In this communication we give the mechanism of the oxido degradation of uric acid that takes place during its interaction with phosphotungstic reagent (Folin test). This paper is a follow up of our studies on reaction mechanism, [2-6].

2 Antecedents

Some highlights are given**:**

In 1776 the Swedish chemist Carl Wilhelm Scheele discovered uric acid in human urine and kidney stones. Uric acid is found in the feces of birds, reptiles, and some mammals.

In 1848 A. B. Garrod in Edinburgh provided a semi-quantitative method for the measurement of uric acid in serum or urine. It was the first clinical test, [7]. It involves evaporation of the sample to dryness on the water bath, elimination of soluble compounds in alcohol, concentration to syrup and repeated extractions with water, concentration and crystallization.

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His results on gout were**:** blood with little or no increase of urea, but rich in uric acid**;** urine with little or no decrease of urea, but very deficient in uric acid. Thus, this appears that the kidneys had almost entirely lost their power of excreting uric acid, but not the other solids in the urine.

The uric acid synthesis by Cavalieri et al. [8], is the best one due to the high yield in each step. It is as follows**,** Figure 1.

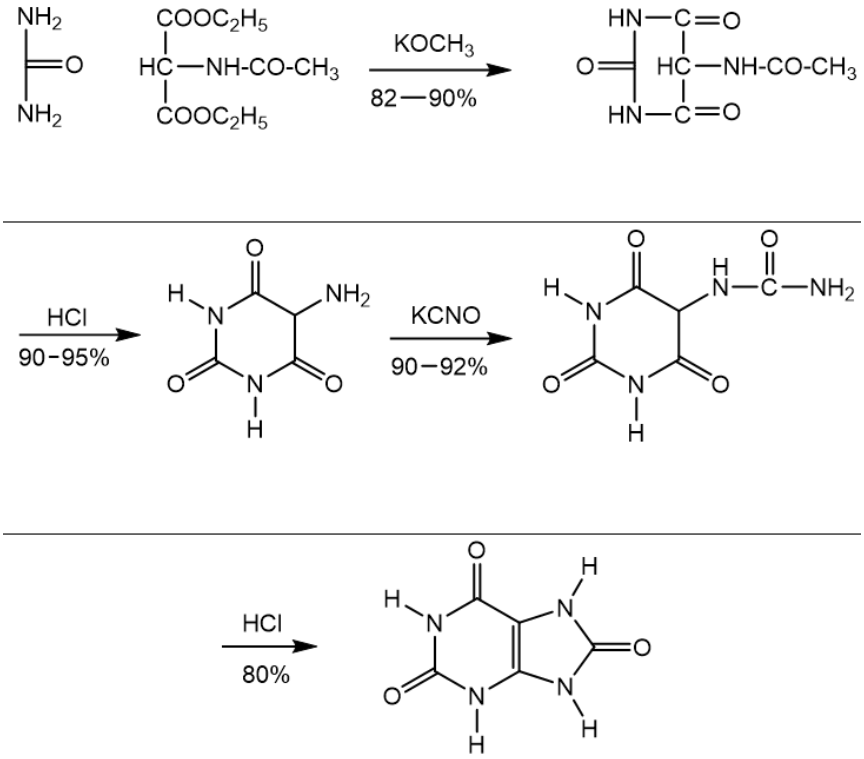

Figure 1 Optimal synthesis of uric acid

Recent studies are devoted to decrease uric acid level. There are interesting researches employing natural products such as cherry juice on serum uric acid levels [9], cherry consumption and decreased risk of recurrent gout attacks [10], and Montmorency tart cherry concentrate in order to lower uric acid [11]. Besides, there are veggie capsules of Swanson and Solaray brands for Uric Acid Cleanse.

3 Discussion

Uric acid oxido degradation by phosphotungstic reagent occurs as follows: protonation of the carbon-carbon double bond yields the more stable carbonium ion at C-4, which is neutralized by a tungstate anion, Figure 2, a .

Protolysis of the organometallic ester breaks down the tungstic acid addendum by a concerted mechanism. Dihydroxyoxotungsten and an epoxide are formed, b. In this redox step tungsten has been reduced to tungsten (IV) and the organic compound has gained an oxygen atom. Epoxides are formed in chromic acid oxidation of alkenes [12], but no mechanism was advanced for this reaction. On the other hand, we must remember that tungsten is a transition element in the d-block, group VI (the chromium group) and it is expected similar chemical deportment.

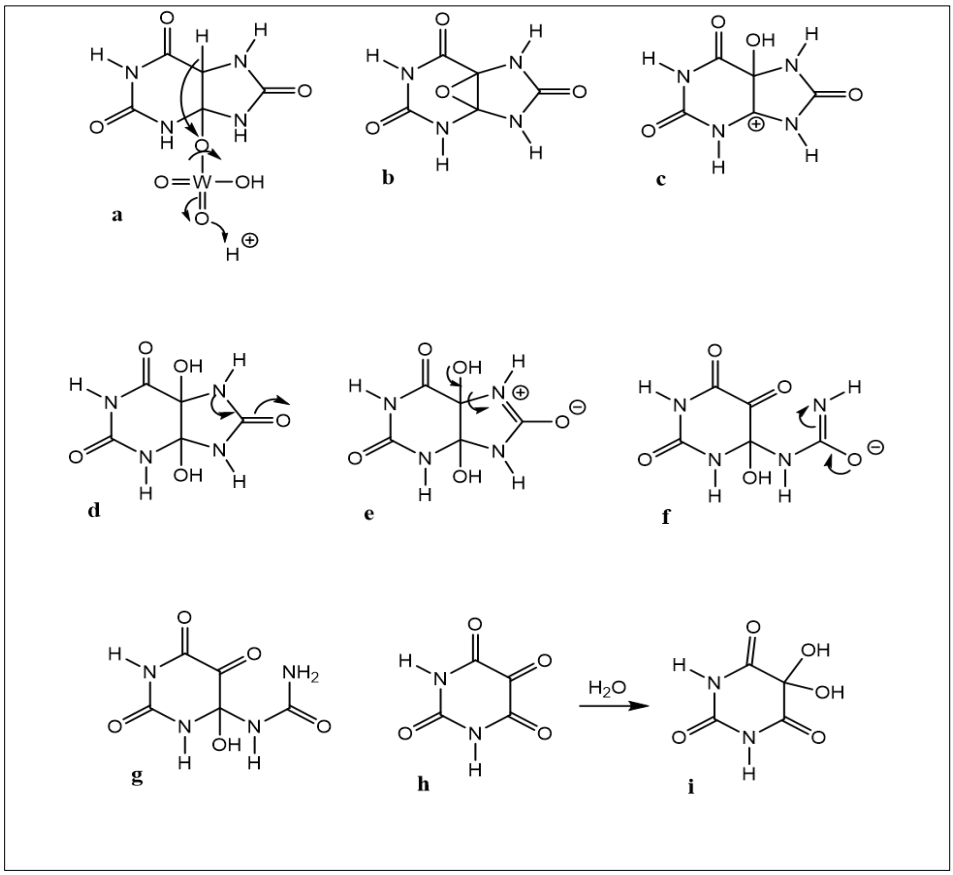

Figure 2 Mechanism of the oxido degradation of uric acid by phosphotungstic reagent

Acid catalyzed opening of the oxirane gives a vicinal diol after neutralization by water of the intermediate carbocation, c, d. Two carbinolamide groups result whose isomerization to carbonyl and opening of the five member ring is assisted by the dipolar resonance structure e, intermediate to imidol**;** in this manner urea and alloxan are obtained, g, h. The latter, 2,4,5,6-tetra-oxo-hexahydropyrimidine, is readily hydrated, i.

This reaction route is in accordance with the remark that uric acid oxidation in strong acidic medium, like phosphoric acid, produces alloxan, whereas oxidation in alkaline, neutral, or slightly acidic medium, gives allantoin [13].

Acidified tungstates when reduced give blue pigments and colourations [14]. The blue colour observed in this test develops after alkalinization with sodium carbonate, [15].

The anion of the formed $O=W(OH)_2$ splits off a hydroxyl group giving WO_2 (tungsten suboxide). The blue colours are W_2O_5 [16], and W_3O_8 [17]. Their formation is explained as follows. The first compound comes from the condensation of WO_2 and WO_3 and one electron transfer from the suboxide. The second product results from dehydration of two molecules of amphoteric tungstic acid giving a salt, WO_2^{++} $WO_4^{=}$ (W_2O_6), which on reaction with: WO_2 gives W_3O_8 via one electron transfer to the previous oxycation.

Thus, the colour comes exclusively from the resulting inorganic compounds and not from any organic component.

4 Conclusion

The oxido degradation of uric acid that occurs in the Folin test has been explained. Protonation of the alkene in uric acid is followed by addition of tungsten anion at C-4. Protolysis of the organometallic ester breaks down the addendum by a concerted mechanism. In this synchronous step tungsten (VI) acid is reduced to tungsten (IV) subacid with concomitant oxygenation of the double bond.

Ring opening of the oxirane gives rise to two carbinolamide groups. Isomerization to carbonyl and ureido chain is assisted by an intermediate dipolar structure. A second cleavage yields the final products: alloxan and urea.

The composition and formation of the resulting blue inorganic products is discussed.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest among the authors or any other person.

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