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On the mechanism of the treumann test for theobromine

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Abstract
The Treumann color test for theobromine consists of reaction of this alkaloid with chlorine water, followed by ammonia addition**:** a purple color is developed. This reaction can be related to the murexide test for uric acid, other purine derivative. However, different structure, uric acid is not a xanthine, and different reagent, hypochlorous instead of nitric acid, induced interest to the theorist since the reaction route and the mechanism necessarily will be different too. This study proved that they are so. We give the electron flow occurring in the multiple steps leading to a dimethyl analogue of purpuric acid whose ammonium salt is the purple compound.

Keywords: degradation, oxidation, reaction mechanisms, reactive intermediates, ring opening, xanthine

1. Introduction

Theobromine is a purine alkaloid derived from cocoa tree that crystallizes from water and poorly soluble in organic solvents. It is diuretic, bronchodilator, cardiotonic and vasodilator [1].

Theobromine is 3, 7-dimethylxanthine. As mild stimulants and bronchodilators, the xanthines are used in the treatment of asthma or influenza symptoms.

In the Treumann test for theobromine, a purple color develops on evaporating to dryness a mixture of the alkaloid and chlorine water, and then adding ammonia [2].

In the murexide test for uric acid the compound and dilute nitric acid are heated to dryness on the water bath, and ammonia is added when cold [3, 4, 5].

Though very close, the Treumann test is not a simple variant of the murexide test because uric acid is not a xanthine, its five member ring is an imidazolone, not an imidazole. This alters the degradation route. Besides, the use of very different oxidizing agents changes completely the oxidation mechanism.

In this communication we provide the reaction sequence until the final purple compound. The electron flow is given step by step.

This work is a follow up of our studies on reaction mechanisms [6, 7, 8, 9, 10].

2. Antecedents

The structures, of uric acid and theobromine are given bellow, Fig 1.

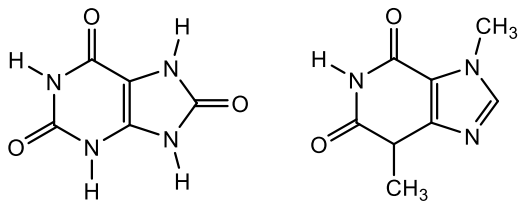


Fig 1: Uric acid and theobromine.

The five member ring in uric acid is an imidazolone, whereas in theobromine it is an imidazole. Besides, uric acid has not substituents, and this is important as we will see.

In the murexide reaction series, purpuric acid ammonium salt has the purple color observed in the test.

Purpuric acid can be formed by condensation of alloxan and uramil [11], Fig 2.

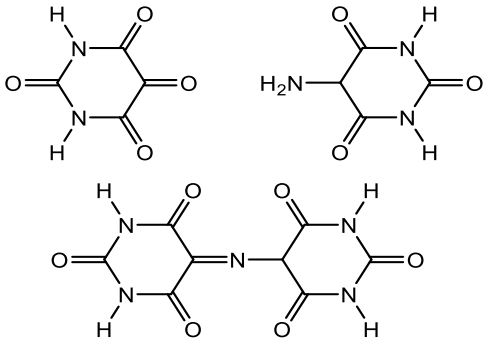


Fig 2: Purpuric acid formation.

A longer route to the final product implies ammonolysis of alloxantin, the hemiketal from dialuric acid and alloxan, yielding uramil and alloxan, Fig 3, followed by combination of these intermediates, as indicated in Fig 2 [12, 13].

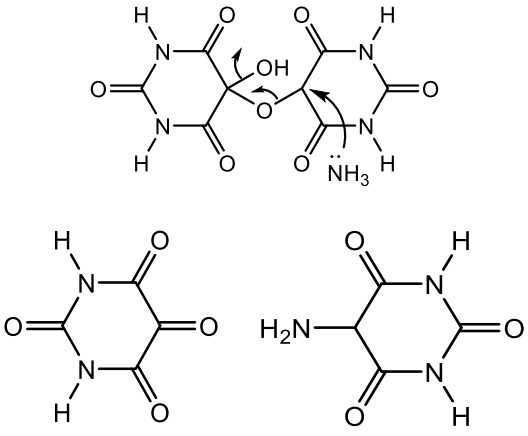


Fig 3: Indirect rout to purpuric acid

The structural and substitution differences between uric acid and theobromine will alter the degradation pathway, as well as the oxidation mechanism since a very different oxidant is used in the Treumann test, chlorine water instead of nitric acid.

The mechanism of ring opening, degradation, oxidation, and condensation steps occurring in the murexide test has been given in a recent communication [11].

3. Discussion

Alloxan, 5-oxobarbituric acid, Fig 2, is an unavoidable intermediate to purpuric acid, whose ammonium salt is a purple colored compound. Thus the route to alloxan or a derivative implies necessarily ring opening and degradation of the theobromine imidazole ring.

There are two double bonds capable of addition promoted by protonation**:** the C=C double bond and the imino group. The more reactive last one was considered the initial site of reaction. Thus hydration to a carbinolamine and ring scission by protolysis leads to a formamido derivative.

Then reactions in the ring and in the chain will take place. The hydration of the C=C double bond, now an enamine, originates a hemiaminal. Protolysis of this group yields ammonia and the third carbonyl group in the pyrimidine ring, Fig 4

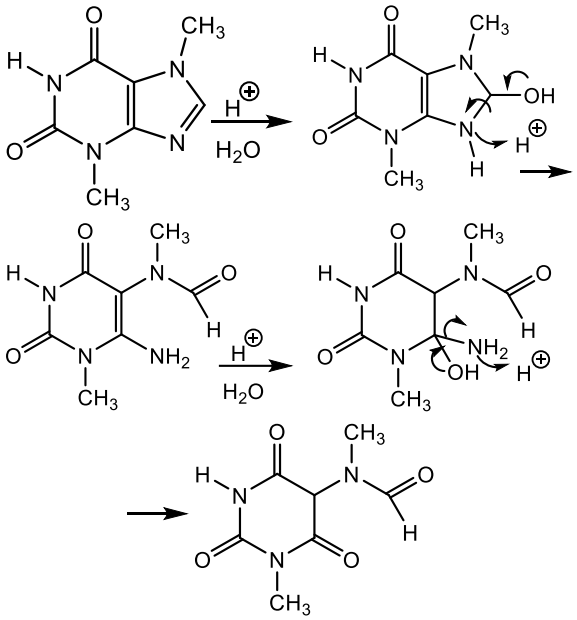


Fig 4: Route to 1-methyl-5-formylmethylaminobarbituric acid.

Subsequent acid hydrolysis of the amide via the dipolar form yields a tetrahedral intermediate which by protolysis affords formic acid and a methylamino group, cf. [14, 15].

This way a dimethyl uramil is obtained: 1-methyl-5-methylaminobarbituric acid, Fig 5.

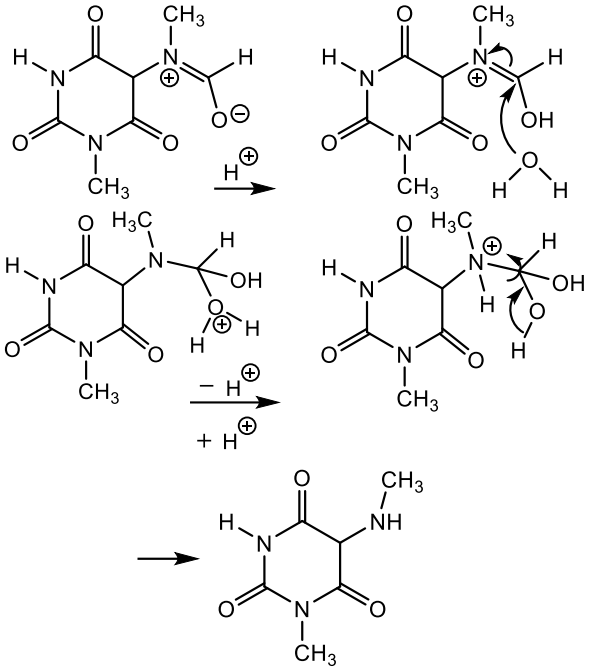


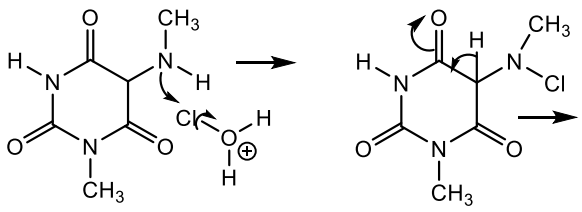
Fig 5: Degradation pathway to 1-methyl-5-methylaminobarbituric acid.

However, a primary amine is needed at C-5 for condensation with alloxan or similar, not a secondary one. Nevertheless, this compound can be oxidized to methylalloxan by means of hypochlorous acid formed in situ by hydrolysis of the chlorine. The resulting N-chloroamine has one active hydrogen which permits hydrogen chloride elimination to the imine. Hydrolysis of this group yields 1-methylalloxan, Fig 6.

The protonated hypochlorous acid as reactive species (halogen containing complex) is the alternative to the chlorine cation (chloronium ion), cf. [16, 17, 18]. The electronegativities of the involved atoms are: oxygen, 3.5; chlorine, 3.0 [19]. These values would favor the positive halogen against the oxonium ion. However, the chloronium ion has only six electrons in its valence shell (a Lewis acid) and besides it has a positive charge.

The oxidation in the Treumann Test for theobromine consists in reaction with a positive-halogen-releasing species, followed by its elimination as a negative chloride ion in the assisted dehydrohalogenation.

In our case, the elimination reaction is much easier than the reported in order to form N-butylpyrrolidine from N-chloro-N-dibutylamine [20], with no active hydrogen.



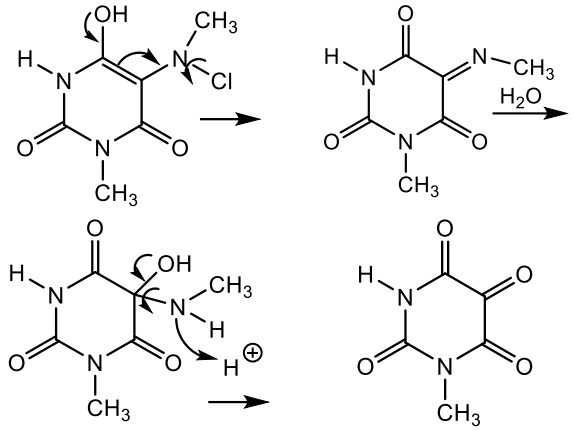


Fig 6: Hypochlorous oxidation to 1-methylalloxan.

The formation of a purpuric acid derivative must occur by the indirect route, via analogues of dialuric acid and alloxan to a substituted alloxantin. Assisted hydrolysis of 1-methyl-5-methylaminobarbituric acid by reaction with 1-methylalloxan yields 1-methyldialuric acid and 1-methylalloxan imine cf [21, 11], Fig 7.

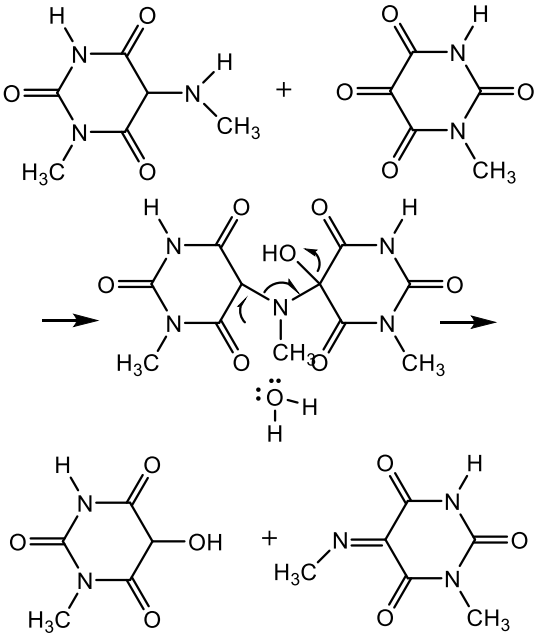
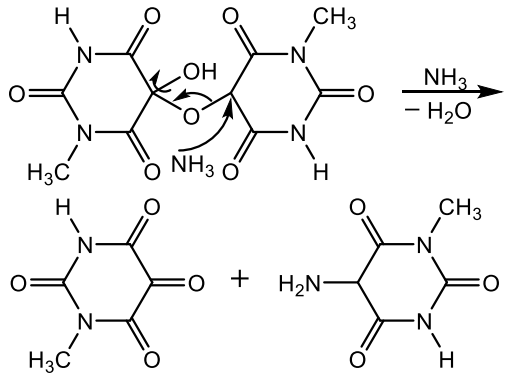


Fig 7: Obtention of 1-methyldialuric acid.

The methyldialuric acid obtained combines with a methylalloxan molecule, forming a dimethyl derivative of alloxantin. Ammonolysis of this hemiketal gives 1-methyluramil and 1-methylalloxan. Finally, condensation between them yields a dimethyl derivative of purpuric acid, whose ammonium salt is purple, Fig 8.



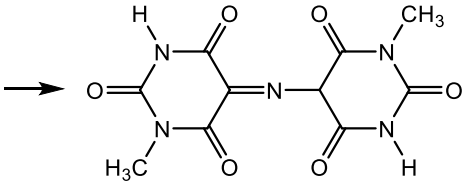


Fig 8: Last steps to dimethyl purpuric acid.

4. Conclusions

This study showed that in the Treumann test for theobromine the ring opening, chain degradation and oxidation occur in a different way that in the murexide test for uric acid. This is due both to difference in chemical structure, as well as change in the oxidizing agent (nitric acid, chlorine water). Uric acid and theobromine are purine derivatives, but the first has an imidazolone ring whereas the second, a xanthine, has an imidazole.

Especially interesting is the oxidation of a secondary amine by means of hypochlorous acid in the presence of hydrochloric acid, both originated in the chlorine water employed. The subsequent dehydrohalogenation is assisted by an enol intermediate. The oxidation process is fully discussed.

With theobromine the observed purple color is due to a dimethyl derivative of ammonium purpurate. This compound is formed via a longer route.

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