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On the chemical oxidation of berberine

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Abstract

Berberine is an antiseptic isolated from several plants. Klunge proposed a test for identification of this four ring isoquinoline alkaloid. He used a solution of berberine, chlorine water and hydrochloric acid or sulphuric acid, obtaining a red colour. In this communication the reaction route to the oxidation product is described. There is a ionic mechanism that ends in a red ortho-benzoquinone. The key intermediate displays an organic hypochlorite and a hemiacetal with a hydroxymethyl group. The reactive species in this oxidation process is hypochlorous acidium ion. Finally, interaction with a hydrion degrades the molecule, giving a red o-benzoquinone, the colour observed in the test, plus formaldehyde. The quinone has been obtained by electrochemical oxidation of berberine, a much more complicated method than a simple and rapid chemical test. A second oxidation product was obtained electrochemically, involving oxidation of the methylene in the five member ring to carbonyl. We provide a synthesis of this compound.

1. Introduction

Berberine is a bitter crystalline yellow alkaloid, $C_{20}H_{19}NO_5$, obtained from the roots of various plants, as barberry, golden seal, and Oregon grape, and used in medicine for its antimicrobial properties, [1].

Oregon grape, Mahonia nervosa, has yellow flowers. It contains an isoquinoline alkaloid called berberine that acts as a strong antibacterial, antifungal, antiviral compound, [2]. Its formula is:

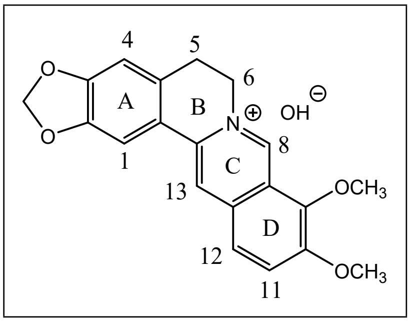

Figure 1. Berberine structure

It contains four fused rings with a quaternary nitrogen in the middle of the structure, a methylenedioxy ring at C-2 and C-3, and methoxy groups at C-9 and C-10.

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Klunge obtained a red colour by treating berberine with chlorine water. In this communication we provide the chemistry involved in this test.

This paper is a follow up of our studies on reaction mechanism, [3-7]

2. Antecedents

The test under study is due to Professor Klunge [8, 9]. The assay is as follows: A red colour is formed on adding chlorine water to an aqueous solution of berberine acidified with hydrochloric acid or with sulphuric acid.

Some remarks about the structure of berberine: besides the ionic structure [10], described above, there are other two closely related structures such as addition of the hydroxyl anion to the iminium group, yielding an OH at C-8, [11], that is, a carbinolamine.

The third structure derives from the previous neutral molecule: a ring rupture of the hemiaminal affords an aldehyde and an amine, [12]. These groups are in equilibrium with the preceding ring. Figure 2.

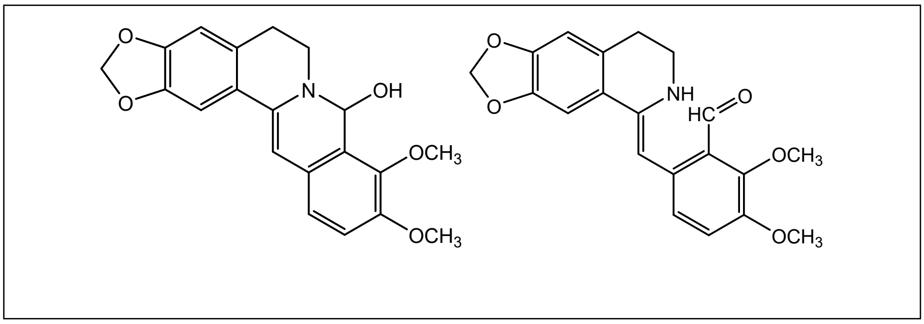

Figure 2. Derived structures of berberine

3. Discussion

The reaction of chlorine with water yields hypochlorous acid and hydrochloric acid. Protonated hypochlorous acid is a complex equivalent to chlorine cation (chloronium ion) and it is a reactive species, [13-15].

Thus, the first step in Klunge's test is chlorination of one oxygen at the methylenedioxy group. This is due since there are evidences that the above mentioned group reacts first than the methoxyls, [16, 17]. The oxonium ion is neutralised by ring opening assisted by reaction of a water molecule at the methylene group, yielding an organic hypochlorite. This labile group reacts with a hydrion, producing a concerted mechanism. An ortho-quinone is formed, as well as formaldehyde, via four electron shifts. Since o-quinones are red [18-20], we have explained the formation of red colour observed in this test, Figure 3.

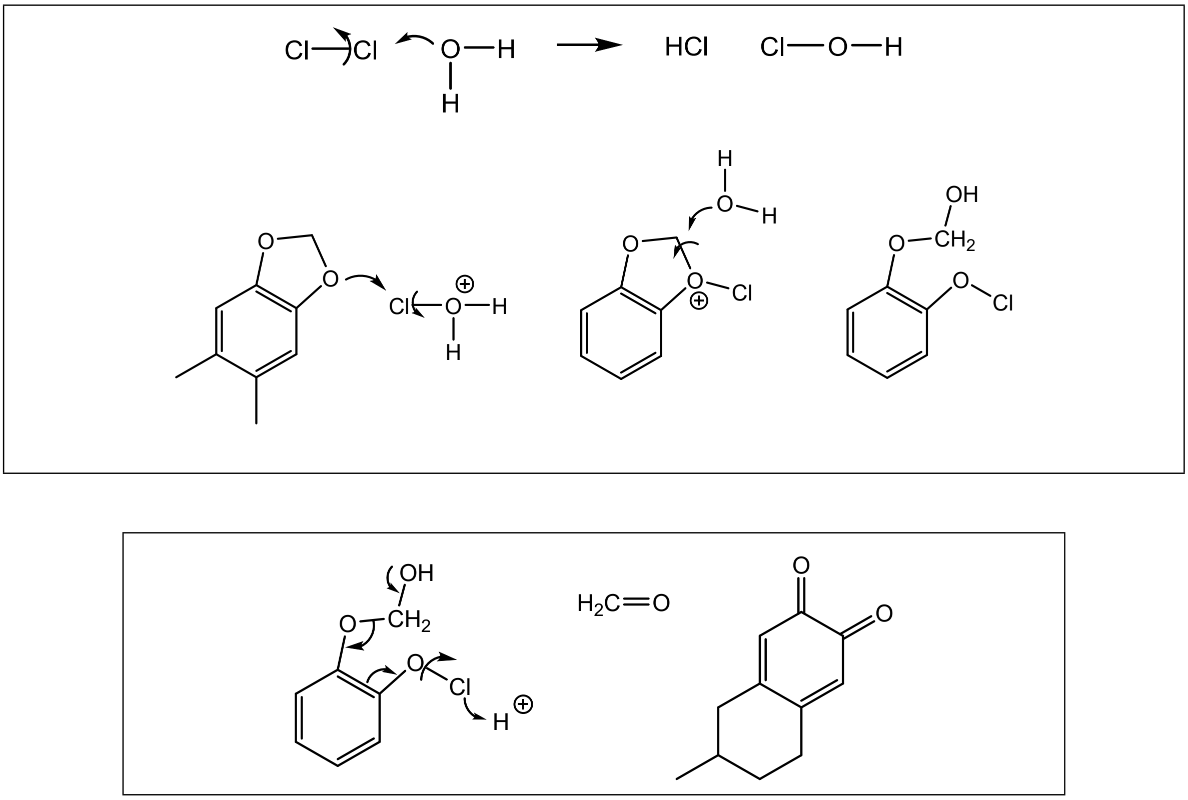

Figure 3. Reaction route from berberine to its o-quinone

The electrochemical oxidation of berberine [21], affords the same quinoidal compound and a second product involving oxidation of the methylene group in the five member ring. We provide a synthesis of this substance. The first step is free radical chlorination to monochloride, and then to gem-dichloride. This selective reaction (there are other two methylene groups) is due to stabilization of the free radical formed at the initio of the chlorination process by the presence of reactive electrons in the vicinal oxygen atom, forming a transient double bond.

Interaction of the geminal dichloride with water forms an unstable gem-chlorohydrin that gives a carbonyl group and hydrogen chloride. A cyclic organic carbonate is formed at C-2 and C-3, not named previously. Figure 4.

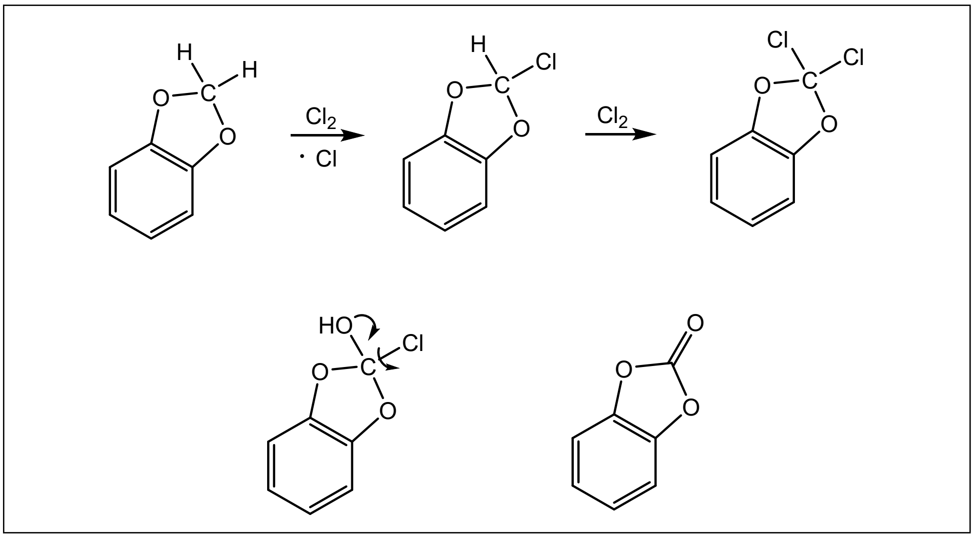

Figure 4. Synthesis of berberine 2,3-*cyclo*-carbonate

4. Conclusion

The reaction route of Klunge's test for berberine has been provided. It is an oxidation process that goes via chlorination of one oxygen in the five member ring by an equivalent of chloronium ion. Assisted ring opening by water gives a hemiacetal and organic hypochlorite. Interaction with a hydrion produces a red o-quinone and formaldehyde.

Besides the quinone, other oxidation product was obtained previously by electrolysis. It is a five membercyclic carbonate, not named before. Its synthesis is given.

5. Conflicts of Interest

There are no conflicts to declare.

6. Acknowledgement

Many thanks are given to Luz Clarita for support.

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