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On the oxido-degradation of emetine

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Abstract

The reaction series occurring during the degradation process of a complex molecule is seldom disclosed. The interest is enhanced if the molecule under consideration has biological activity, as is the case of emetine. In this communication we provide the reactions that take place during the oxidation of this five ringed molecule. The electron flow, step by step, is given from the alkaloid to the different oxidation products obtained with several oxidizers. Since chloric acid is a strong oxidant, we describe the degradation process with this reagent. The route is correct inasmuch as the same products were obtained, including the intermediates.

Keywords: Carbon acid; Chloric acid; Chloryl cation; Free radicals; Hyper conjugation; Reactive intermediates

1. Introduction

Emetine is a five-ringed alkaloid featuring a tetrahydroisoquinoline unit, and a quinolizidine bicycle fused with a substituted benzene ring, forming a second tetrahydroisoquinoline.

Emetine is used as antinematodal agent, amebicide, cathartic, emetic and expectorant.

Several degradation products have been obtained oxidizing emetine with different reagents. In this communication we provide the electron flow, step by step, from the alkaloid to the different products obtained experimentally. In the discussion we employed chloric acid, a powerful oxidant that covers all the oxidation stages. That the reaction route presented is correct can be deduced since we arrived to the described products, including the intermediates obtained with weaker reagents. This paper is a follow up of our studies on reaction mechanisms [1-5].

2. Antecedents

Emetine was first isolated by Pelletier and Magendie in 1817 from roots of *Psychotria emetica*, ipecacuanha brown species [6]. They isolated the vomitive substance after various separations and named it emetine. It was obtained as brownish-red transparent flakes. They are odourless and have bitter taste, a little sour. They carried out tests with different solvents and reagents, as well as physiological experiences with varying doses.

The emetine properties were pointed out in England, emphasizing that emetine, a first principle, can be advantageously substituted for ipecacuanha, as an emetic, it being divested of the offensive odour and taste of that substance, and which Caventou found by experiment to be foreign to the emetic qualities of the medicine [7].

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The complete isolation of emetine from two cognate alkaloids has been described [8]. Emetine hydrochloride is a white powder.

The biological activities of emetine have been reviewed, [9], as well as potential applications of emetine as anti-cancer agent [10]. A recent study on emetine isolated from *Hedera helix*, ivy, includes IR, UV, NMR, MS and preparation of derivative, [11].

The chemical structure of emetine is in Figure 1.

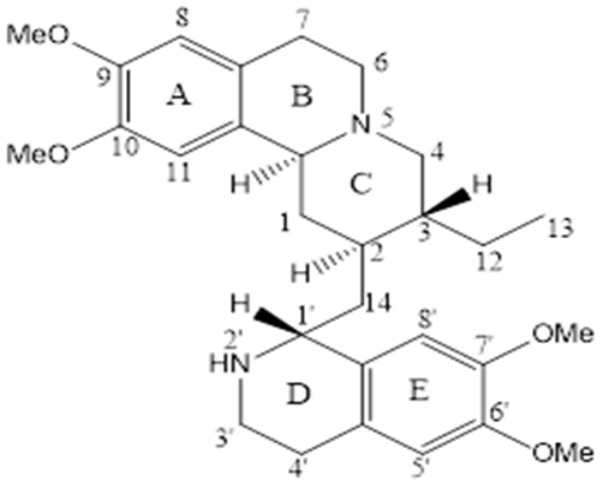

Figure 1 Graphic formula of emetine

Several oxido-degradations have been carried out [12]. The strong degradation product, 4, 5-dimethoxyphthalic acid (m-hemipinic acid), is obtained by oxidation with potassium permanganate in acetone, Figure 2, **a**. The use of alkaline potassium permanganate yields a mild oxidation product, 6, 7-dimethoxy-1-oxo-1, 2, 3, 4-tetrahydroisoquinoline, **b**.

Further oxidation with chromic acid affords 4, 5-dimethoxyphthalonimide, **c**.

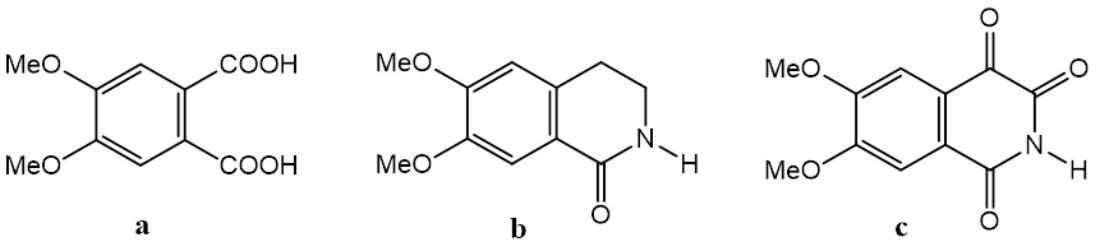

Figure 2 Oxido-degradation products derived from emetine

In this study we used chloric acid as reagent since it is a powerful oxidant. In our mechanistic route we arrived to the intermediate oxidation products that were described. The electron flow is given step by step, not in bold strokes as is usual in other degradations.

Chloric acid is a strong and unstable oxidizer, which in absence of a chemical reducer undergoes oxido-reduction reactions. The preparation of chlorine dioxide is based on the reaction of potassium chlorate with sulphuric acid. After formation of potassium sulphate and chloric acid, the last dismutates into chlorous acid and perchloric acid.

Finally chlorine dioxide results from reaction of chloric acid with chlorous acid [13, 14].

3. Discussion

Chloric acid is formed by reaction of potassium chlorate with sulphuric acid. Acid catalyzed dehydration provides the reactive species, the chloryl cation (ClO_2^+), which has the tendency to take an electron to form chlorine dioxide, which is an odd electron molecule.

In emetine there are two nitrogen atoms; the one in the quinolizidine is not prone to react due to steric hindrance. Thus, reaction takes place at the unshared electron pair of the isoquinoline nitrogen, N-2'. Figure 3, **a**.

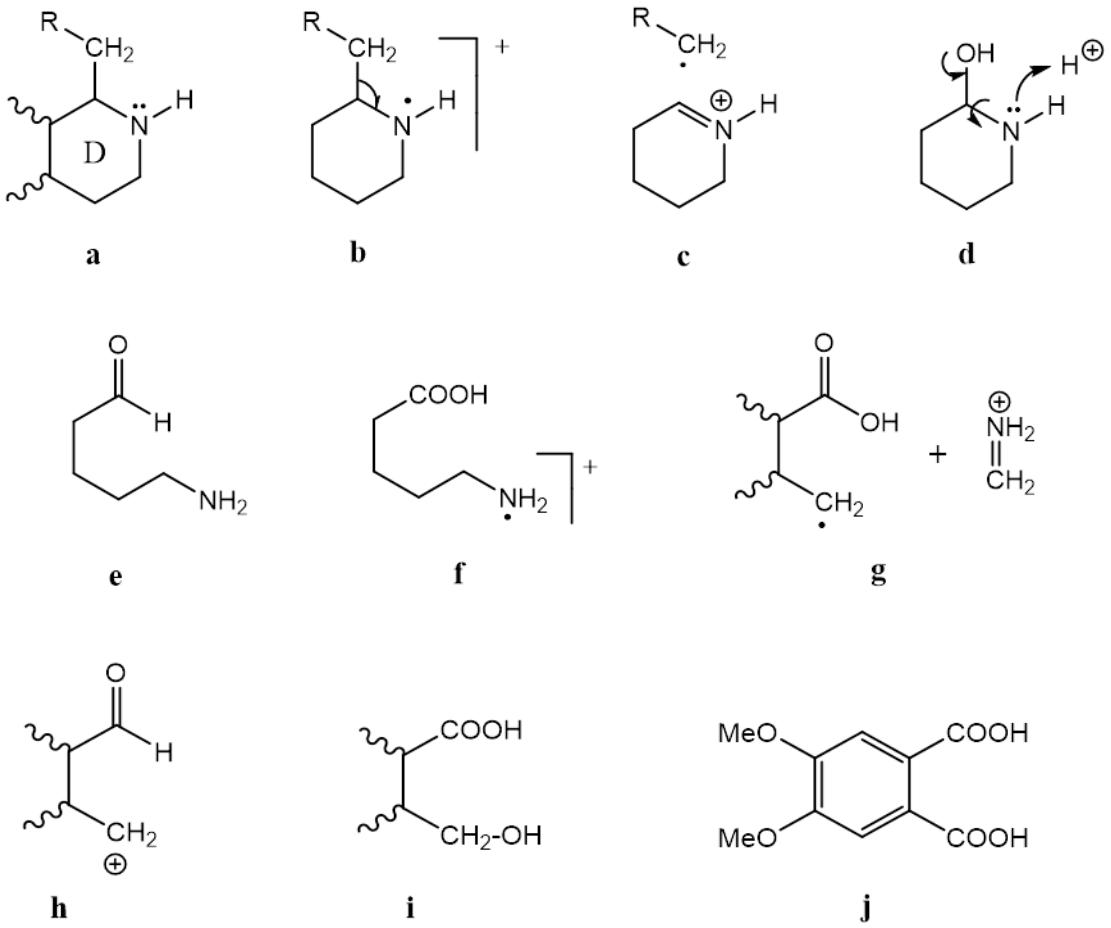

Figure 3 Oxido-degradation of emetine to m-hemipinic acid

The resulting radical cation promotes molecular fission and an iminium ion is formed, **b**, **c**. Hydration of the last cation gives rise to a carbinolamine, **d**; ring opening yields an aldehyde, **e**, which is oxidized to carboxylic acid, and an aliphatic amine that reacts with chloryl giving a formiminium ion, **f, g**. This way a benzyl radical also results. Electron removal forms a benzyl cation which is neutralized by water, **h, i**. This benzyl alcohol is oxidized to aldehyde and to carboxylic acid. The obtained product is 4, 5-dimethoxy-phthalic acid (m-hemipinic acid), **j**.

The phthalonimide derivative is obtained by an alternate route, Figure 4.

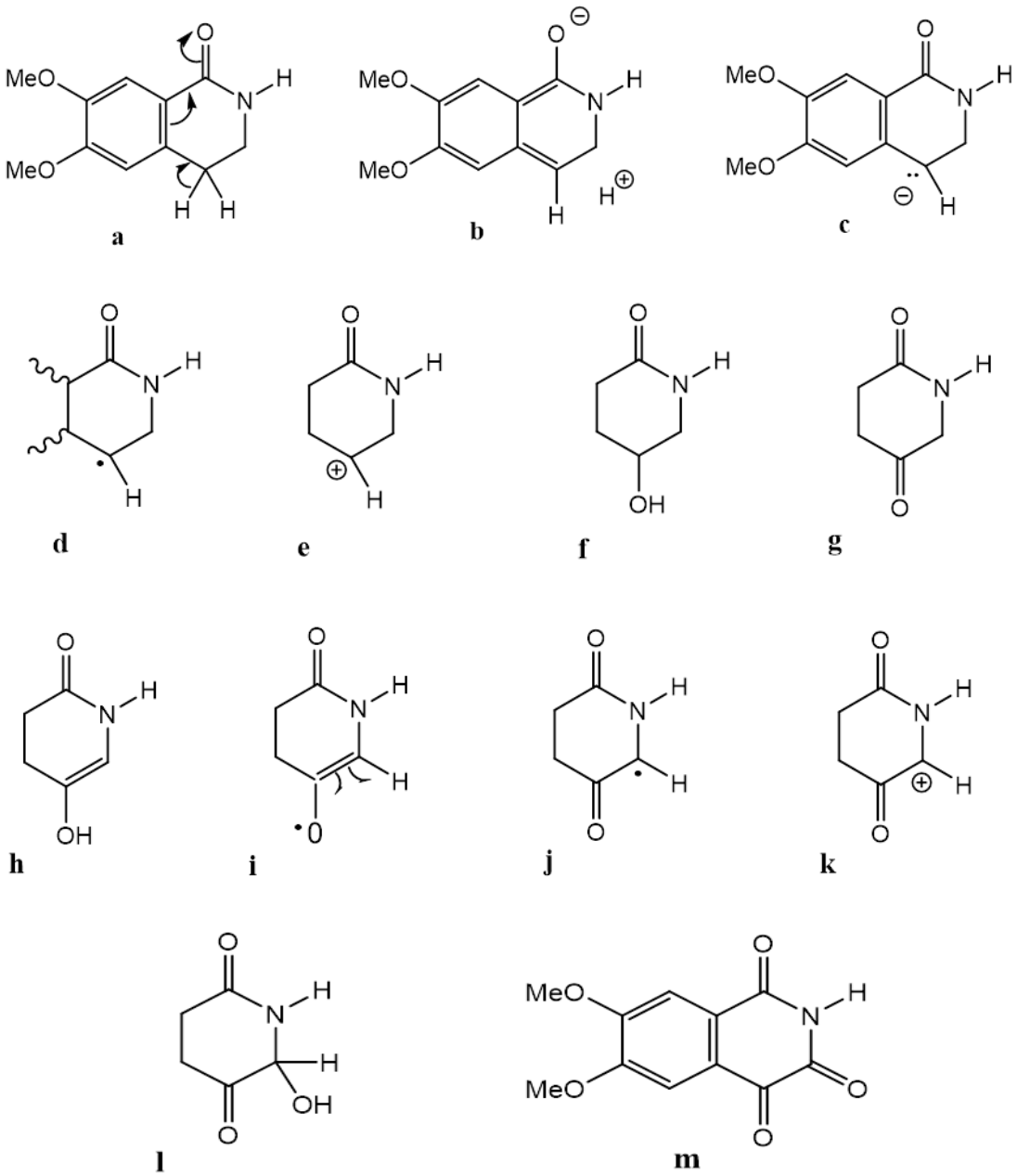

Figure 4 Oxido-degradation steps from emetine to 4, 5-dimethoxyphthalonimide

The previous carbinolamine can be oxidized at oxygen, prior to ring opening, yielding a lactam, Figure 4, **a**. This intermediate, 6, 7-dimethoxy-1-oxo-1, 2, 3, 4-tetrahydro-isoquinoline, has been isolated.

Reaction of C-4' as carbon acid in this lactam can be explained by hyperconjugation since this methylene group is in γ-position to the α, β- unsaturated group, compare [15, 16]. Participation of such vinylene bridge in this electromeric change also occurs in other reactions, via an o-semiquinoid structure, **b**, [17]. Electron transfer from the benzyl group to the aromatic ring is discarded due to the electron donor effect of the two methoxy groups. The carbanion from the above mentioned carbon acid, **c**, reacts with chloryl cation giving a benzyl radical, **d**. Further reaction yields a benzyl cation, **e**, which is neutralized by water to the corresponding benzyl alcohol, **f**. Oxidation to carbonyl gives **g**, enolization and reaction with chloryl cation forms a keto group and a free radical at C-3', **h, i, j**. Electron removal affords a carbocation, **k**, which neutralized by water and oxidized, **l, m**, gives 4,5-dimethoxy-phthalonimide. This compound can be obtained by oxidation of emetine with chromic acid.

This way we arrived to all the described emetine oxido-degradation products.

4. Conclusion

The oxido degradation process of emetine was cleared up. The formation of the different products obtained experimentally can be explained using chloric acid as reagent. This powerful oxidant gives reason for the abstention of the described compounds via two alternate routes. The reactions that take place are: electron removal by chloryl cation, iminium ion formation, hydration, oxidation, fragmentation, alcohol formation an oxidation to carboxylic acid. Most of them are repeated.

This way the oxido degradation of emetine has been unraveled.

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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