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# A New Approach to the Chemistry of the Serullas Test for Morphine

Francisco Sánchez-Viesca[1,*] and Reina Gómez[2]

[1] Organic Chemistry Department, Faculty of Chemistry, National Autonomous University of Mexico, Mexico City (CDMX), Mexico; e-mail: franviesca@yahoo.com

[2] Organic Chemistry Department, Faculty of Chemistry, National Autonomous University of Mexico, Mexico City (CDMX), Mexico; e-mail: reinagomezg@yahoo.com.mx

[*] Corresponding author

## Abstract

The tests for morphine are very important since this alkaloid is used in medicine for pain release but also it is a restricted drug due to abuse. The interaction of morphine with iodic acid has been used for its identification. In this communication the several redox reactions taking place during this test are explained in a new way. Activation of the organic-inorganic ester (mixed iodate) by protonation and water loosening creates a cationic intermediate with inverted polarity at the ortho-position. This innovation is important because there is no need to invoke electron back donation since this concept reverses the normal polarization of a functional group. Our novelty worked very well and explained the three successive redox steps taking place during the test, that is, until the oxidation to an ortho-quinone and iodine formation which is detected by reaction with starch gel giving Prussian blue colour.

## 1. Introduction

The opium poppy has been used since antiquity to modern opium dens. In 1805 the German pharmacist Friedrich Sertuerner isolated from opium the sleeping agent, in crystalline form, and named it morphine. Two centuries have elapsed and morphine chemistry is still under study. The course of the morphine-apomorphine rearrangement has just been updated [1].

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In the present communication we present a new approach to the reactions taking place in the complex interaction between iodic acid and morphine, **Figure 1**.

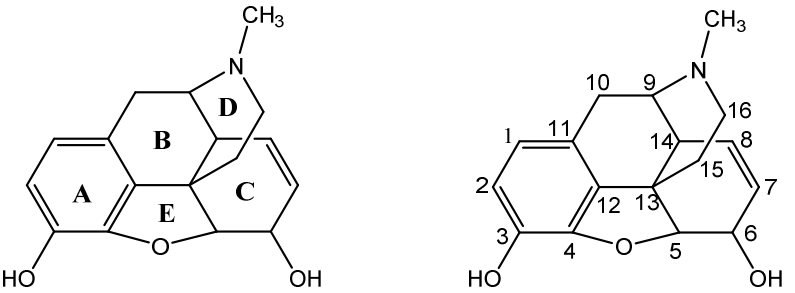



**Figure 1.** The morphine structure.

This paper is a follow up of our studies on reaction mechanism [2-6].

## 2. Antecedents

The present communication has opened a new point of view that removes the necessity to invoke electron back donation in order to understand some oxido-reduction steps. The concept of back donation can be found in reputed journals and in well known texts on organic oxidations [7], and in modern heterocyclic chemistry books [8]. However, this concept reverses the normal polarization of a functional group and it must be changed in favour of other mechanism not involving reverse polarization.

The route presented in this communication explains very well the Serullas test for morphine [9], instead of a previous route [10].

Other test for morphine is due to Froehde. He employed sodium molybdate which is reduced to molybdene-blue [11, 12]. Wellcome used chlorinated lime, calcium chlorohypochlorite. Though the reagent is not expensive, it has the pungent odour of chlorine, [13, 14].

## 3. Discussion

The reactive species in the interaction of iodic acid and morphine is protonated iodic acid at the hydroxyl group since protonation at the iodine-oxygen double bond causes resonance, **Figure 2**, a, b, c. Reaction with the phenolic group in morphine produces the iodate, d, e. This organic-inorganic ester is activated by protonation. The positive charged ester creates a δ+ at the oxygen linked to carbon (inductive effect), favouring nucleo-

philic attack at the ortho position due to polarity inversion. Addition of an iodic acid molecule, f, forms a new iodate and a dienone, g. Enolization of the latter recovers aromaticity, h. Protonation of the iodate causes a six member concerted mechanism yielding iodous acid and an ortho-quinone (first redox reaction), i.

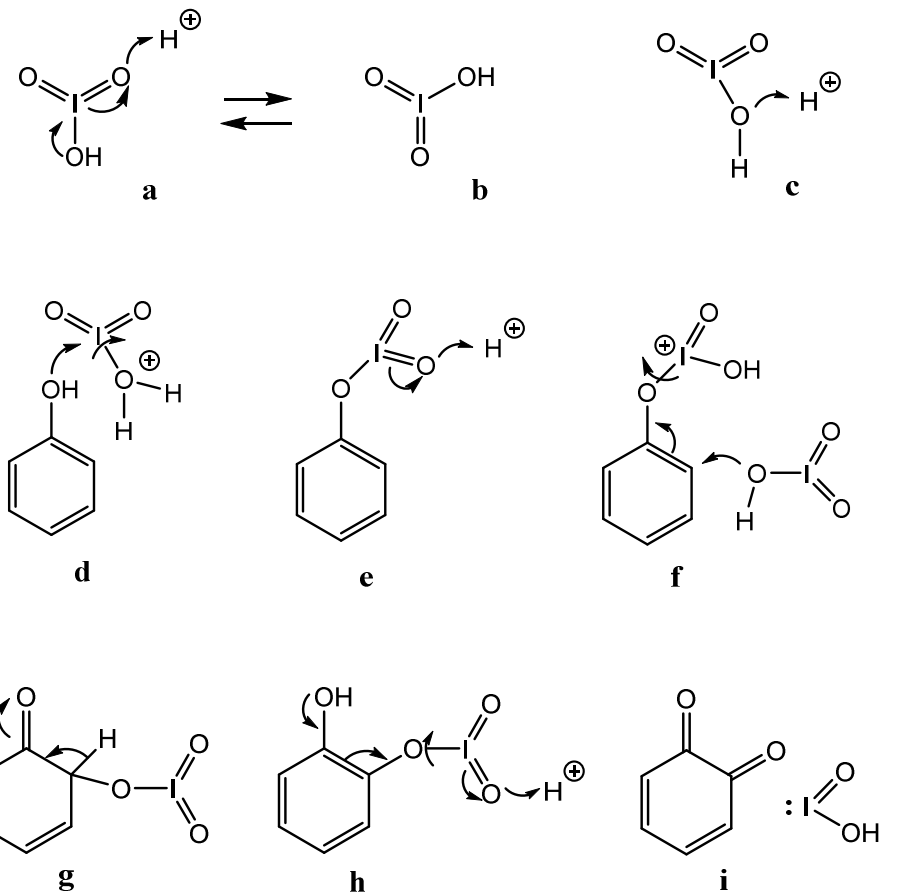



**Figure 2.** Abbreviated structures from morphine to its ortho-quinone and iodous acid.

The following reactions, **Figure 3**, are between morphine and iodous acid, whose concentration is increasing. This produces a similar reaction pattern as before: esterification to a iodite, j, k, formation of a new iodite, l. m, and elimination of hypoiodous acid with concomitant oxidation to quinone, n, o.

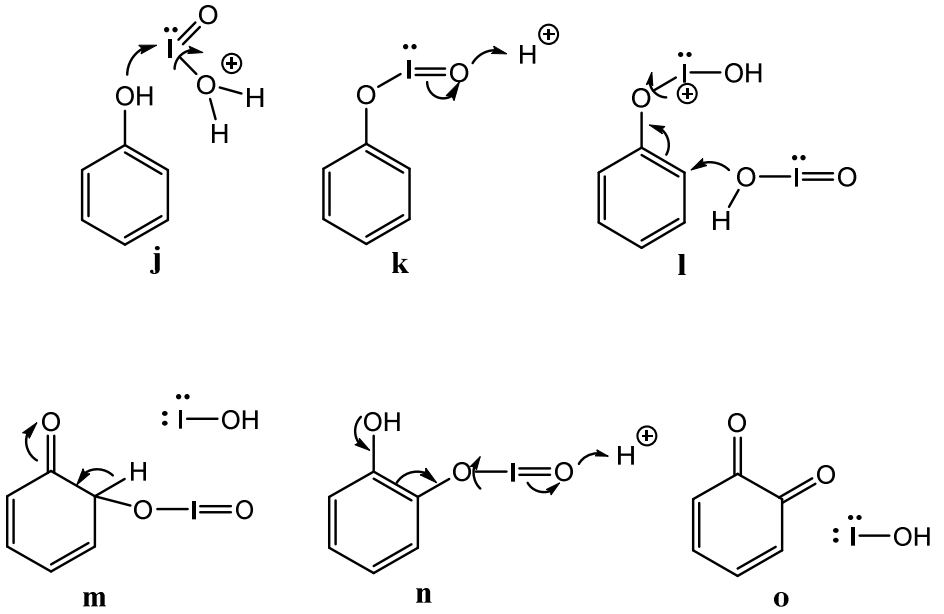
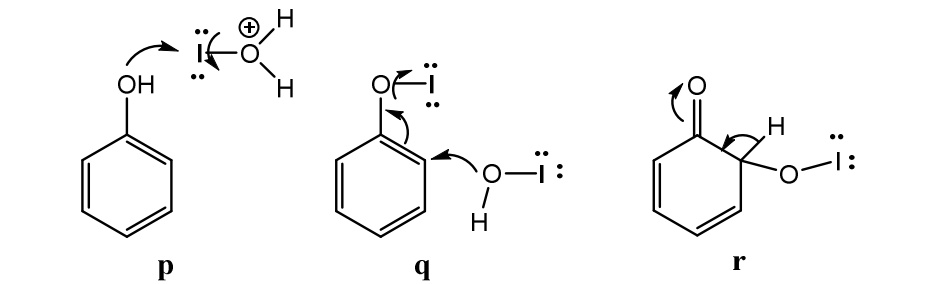



**Figure 3.** Second redox reaction producing hypoiodous acid.

The third oxido-reduction step, **Figure 4**, is interesting since the hypoiodite formed via protonated hypoiodous acid, p, q, creates a δ+ charge at oxygen capable to produce reaction at ortho-position, q, without a formal positive charge as in the two preceding cases, due to the lability of hypoiodites. Ortho-quinone and hydrogen iodide result, r, s, t, the latter forms iodine by reaction with hypoiodous acid, u.



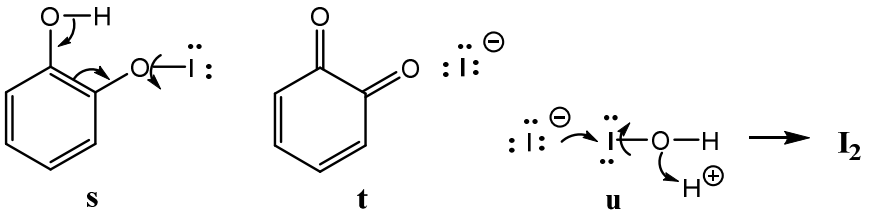



**Figure 4.** Formation of iodine by reaction of hydriodic acid with hypoiodous acid.

## 4. Conclusion

This Theoretical Organic Chemistry study explains in a novel way the reaction series that takes place during the reaction of morphine with iodic acid. There are successive redox reactions. The first reaction product is morphine iodate. Protonation of this ester produces a cationic intermediate with polarity inversion at ortho-position (Umpolung). Nucleophilic addition of iodic acid forms a new iodate and a cyclohexadienone with release of iodous acid. Aromatization and protonation of this iodate favours a concerted mechanism yielding iodous acid and morphine ortho-quinone.

A similar reaction pattern occurs between morphine and iodous acid yielding morphine ortho-quinone and hypoiodous acid. Reaction of morphine with hypoiodous acid affords the hypoiodite. This labile neutral intermediate favours a nucleophilic reaction at ortho-position due to the strong inductive effect of the iodine atom. In analogous way as before the ortho-quinone and hydrogen iodide result.

Finally, iodine, the detected product, is formed by reaction of hydriodic acid with hypoiodous acid.

## 5. Conflicts of Interest

There are no conflicts to declare.

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