



## On the interaction of morphine with Lugol's iodine in alkaline medium

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### Abstract

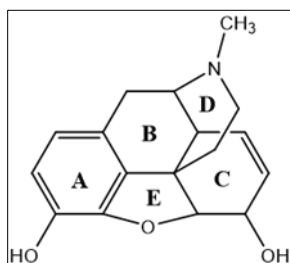
The purpose of this communication is to clear up what is happening in the test tube during the interaction of an alkaline solution of morphine with Lugol's iodine (Kippenberger test for morphine). The formation mode and reactivity of potassium triiodide, the salt present in Lugol's solution, are commented. Reaction of iodine molecule (formed in a reversible manner) with sodium hydroxide gives rise to hypo-iodous acid. This reacts with the morphine phenolate formed in situ yielding an organic hypoiodite. This labile intermediate loses iodide ion, producing a ketone and Umpolung at the ortho-position which enhances reaction with hypoiodous acid (nucleophilic reaction). A new hypoiodite and a dienone are formed (first oxidation step). Enolization recovers aromatization and the phenoxide ion produces a synchronic mechanism involving three electron-shifts. This way an ortho-benzoquinone is obtained (second redox reaction). The observed colour in the test is due to halochromism.

**Keywords:** Concerted mechanism; Hypoiodous acid; Organic hypoiodites; Potassium triiodide; Redox reaction; Umpolung

### 1. Introduction

Morphine, previously known as Morphia, is a colourless crystalline opioid alkaloid. The word 'alkaloid' was first coined by the German chemist Carl F. W. Meissner in 1819, derived from the Arabic name *al-qali*, which is associated to the plant from which soda was first sequestered, [1].

In this communication we present the chemistry involved in the Kippenberger's test for morphine, Figure 1.



**Figure 1** Morphine structure

Testing for the use or misuse of opioids may be performed for a variety of purposes. Drug screening is used as a way to monitor the use of prescription opioids. Drug testing may be used in emergency settings to identify acute intoxication. An employer may require drug testing for job applicants. There is also athletic testing, and forensic testing, [2].

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Natural opioids are derived from the seeds of the opium poppy. Semi-synthetic opioids include oxycodone, hydrocodone, hydromorphone, and oxymorphone. Synthetic opioids act on the same receptors in the brain as natural opioids. They may not look chemically similar to natural opioids, like fentanyl.

A positive drug screening often detects only natural opioids. Urine detection window after morphine or codeine use, up to 3 days.

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

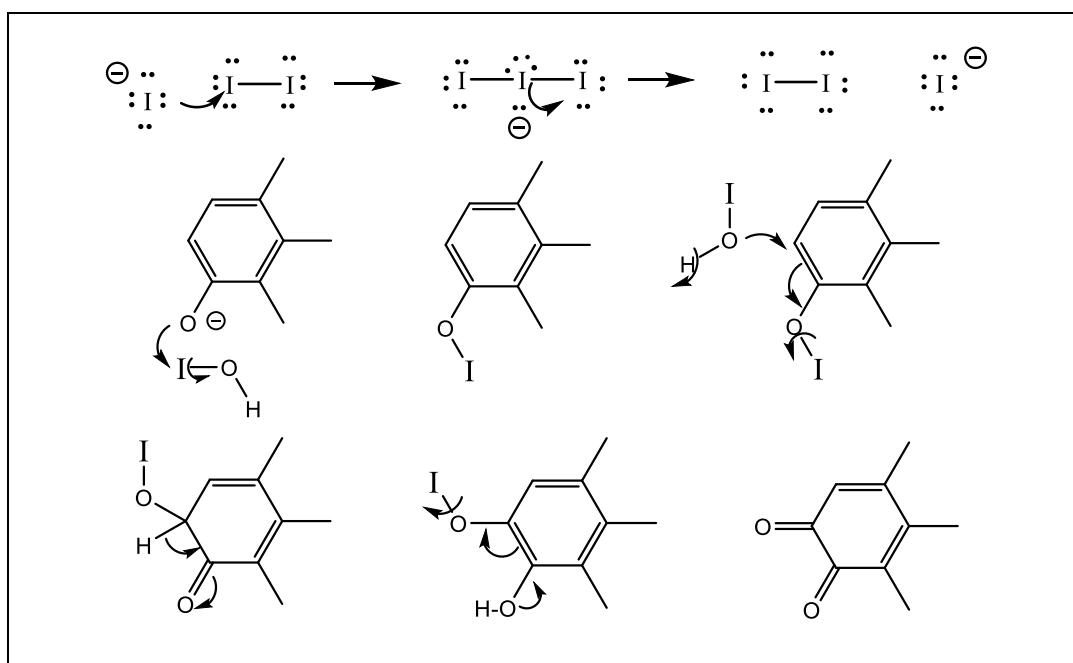
## 2. Antecedents

The test under study is due to Professor Karl Kippenberger (1868-1937). He studied chemistry at Hesse, and pharmacy in Erlangen, [8]. The test is as follows: a green colour is observed when to a strong alkaline morphine solution, iodine-potassium iodide solution is added, [9-11]. Lugol's iodine is made up of two parts of potassium iodide to one part elemental iodine in water. The standard concentration contains 100 mg/ml potassium iodide and 50 mg/ml iodine, [12, 13]. This solution was first prepared by the French physician Jean Guillaume Auguste Lugol in 1829. Iodophors are solutions that contain iodine complexed with a solubilizing agent. The resulting molecule is potassium triiodide. The  $I_3^-$  ion is linear, with a single bond between each iodine atom, there are 3 lone pairs around each of the iodines, with the central atom having a formal charge of 1<sup>-</sup> (Lewis electron dot structure), [14]. Molecular weight: 419.8 dalton (g/mol). Pesticide type: fungicide.

## 3. Discussion

The formation of the triiodide anion, present in the employed reagent, takes place via attack of iodide ion to the iodine molecule, having each iodine atom 3 pairs of lone electrons and single bonds connecting the atoms. The central iodine atom has a formal negative charge and the resulting salt, potassium triiodide, is water soluble. However, elimination of iodide ion from the  $I_3^-$  ion can afford free iodine (equilibrium reaction).

The iodine molecule reacts with a hydroxide ion from the alkaline medium forming hypoiodous acid and sodium iodide. The morphine phenoxy ion formed in situ reacts with the iodine atom in hypoiodous acid (equivalent to iodonium ion), and liberation of a hydroxy group, compare [15, 16], Figure 2. The labile organic hypoiodite loses iodide ion, a ketone is formed, producing Umpolung at the ortho-position. This favours addition of hypoiodous acid, and a new hypoiodite is formed.



**Figure 2** Oxidation of the morphine molecule with hypoiodous acid

Enolization recovers aromatization. Finally, the electrodotic property [17] of the phenoxy group gives rise to a concerted mechanism: an ortho-benzoquinone is formed with elimination of iodide ion. As it can be seen in this sequence of reactions there have been two oxidation steps.

The colour reaction observed in the test is due to halochromism, [18].

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#### 4. Conclusion

The aqueous-iodine-containing solution employed in the test under study reacts with the alkaline medium forming hypoiodous acid and sodium iodide. The oxyacid is a source of reactive iodine (iodonium ion). Then occurs a halogen transfer between hypoiodous acid to the phenoxy group in the morphine molecule. The organic hypoiodite thus formed is labile and can lose iodide ion, giving a ketone and Umpolung at the ortho-position. A new hypoiodite is formed. Enolization and subsequent reaction of the phenoxy ion originates a synchronous mechanism affording an o-quinone.

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#### Compliance with ethical standards

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##### *Disclosure of conflict of interest*

There is no conflict of interest to declare.

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