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(RESEARCH ARTICLE)

# The chemistry of the Wellcome test for morphine

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## Abstract

The use of chlorinated lime for morphine identification has several advantages. The reaction is fast and simple, and the reagent is inexpensive. Besides, the developed red colour comes from the organic compound, not from a reduced inorganic reagent. The last case only indicates oxido-reduction reaction, but it is alien to the final structure of the organic compound under test. In the Wellcome assay the red colour is typical of an o-quinone, the inorganic compounds being colourless. Since the chemistry related to this test has not been described, we provide the route from the alkaloid to the final colourful compound, and also a new preparation of o-quinones from o-halo phenols.

**Keywords:** Calcium chlorohypoclorite; Concerted reaction mechanism; Gem-Dichloro ketone; O-Quinone; Sigma complex

## 1. Introduction

The opium poppy, *Papaver somniferum*, has been used since antiquity. The Sumerians referred to it as 'the joy plant'. This addictive plant is cultivated in several countries. Most of the opium poppies come from South-East Asia: Myanmar (Burma), Laos and Thailand.

In 1805 the German pharmacist Friedrich Sertuerner isolated from opium the sleeping agent, in crystalline form, and named it morphine. Psycoactive alkaloids are classified as Stimulants, like cocaine; Hallucinogens, mescaline; and Depressants, morphine.

Being morphine a restricted drug, a simple, fast, and inexpensive spot test, like the Wellcome assay, is most suitable for drug identification.

In this communication we unravel what is happening at atomic level in this test. This paper is a follow up of our studies on reaction mechanism, [1-5].

## 2. Antecedents

In the Wellcome test for morphine a red colour is produced when chlorinated lime is added to a solution of the alkaloid, [6].

Chlorinated lime is obtained by passing chlorine over slaked lime, $Ca(OH)_2$. The reaction product is calcium chlorohypochlorite, CaCl(OCl), [7]. This compound has also been named calcium oxychloride, $CaOCl_2$, but this term does not distinguish between the two anions present in the compound. In this preparation calcium hydroxide still remains.

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Other reagent involved in the 'Discussion section' is tert-butyl hypochlorite. The synthesis of this mixed ester has been described in detail, [8, 9].

Two other tests for morphine are the Serullas test and the Froehde reaction, [10, 11]. The first employs iodic acid and the second uses molybdic acid.

## 3. Discussion

The reactive group in morphine, Figure 1, is the phenol and reacts with the hypochlorite anion. A 4+2 sigma complex can be formed between reagent and substrate (electrostatic arrangement), Figure 2, a

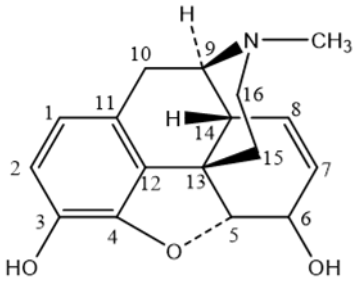


**Figure 1** Graphic structure of morphine

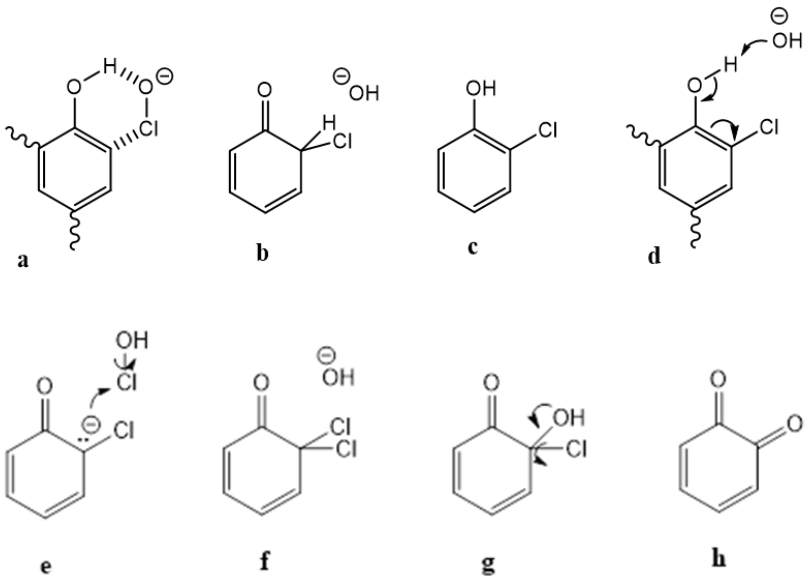


**Figure 2** Partial structures of the route from morphine to a red quinone derivative

Thus, a transient carbanion at ortho position reacts with an incipient chloronium ion and an alpha-chloro ketone is formed, b. Further enolization gives o-chloro phenol, c.

In the morphine molecule the p-position is blocked, thus reaction occurs at the available ortho locus. However, our proposed orientation-mechanism is confirmed since phenol, with free positions, reacts with tert-butyl hypochlorite in $CCl_4$ to yield o-chlorophenol, [12]. The bulky tert-butyl group can be secluded from the reaction site owing to convenient orientation prior to σ-complex formation, Figure 3. With this mixed ester the reaction time increases to hours and heating to boiling is necessary. This is due to the absence of the negative charge present in hypochlorite anion, which prompts reaction. A similar σ-complex explains the reactivity of acetanilide with acetyl nitrate, yielding o-nitro acetanilide, [13, 14].

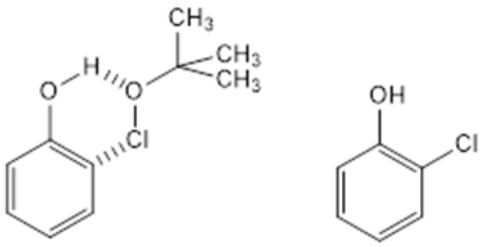


**Figure 3** Sigma complex between phenol and tert-butyl hypochlorite for ortho reaction

Having o-chlorophenol been formed, we looked for the possibility of obtaining catechol, since a catechol derivative is produced both in the Serullas test for morphine, as well as in the Froehde reaction. Indeed, catechol can be obtained from o-chlorophenol by reaction with sodium hydroxide, but in drastic conditions: at 190 °C, high pressure, and a copper catalyst ($CuSO_4$), [15]. Thus, o-hydroxylation was discarded because our spot test is rapid and carried out at room temperature.

Not being available in morphine a second reactive position for an electrophilic reaction, a repeated chlorination at the ipso carbon is invoked, Figure 2, d. The chlorine atom at C-2 precludes σ-complex formation. However, a formal carbanion at C-2 is stabilized by the electron attraction of the existing chlorine atom, e. There is no steric hindrance in the dichloro intermediate since now the carbon atom has $sp^3$ hybridization, f. Compare to $CCl_4$ molecule.

Reaction of the intermediate 6, 6-dichlorocyclohexa.2, 4-dien-1-one with sodium hydroxide (nucleophilic substitution) yields the geminal chloro alcohol (gem-halohydrin), g. Finally, basic catalyzed chloride elimination affords an ortho-quinone, h, (oxidative hydrolysis). Cf. [16]. This compound must be red colored as other o-quinones [17, 18, 19], and it is the colour observed in the Wellcome test. This result is important because the colour comes from the tested organic compound, not from reduced inorganic compounds as those obtained in other tests for morphine: brown-red iodine (Serullas), or molybdenum blue (Froehde).

The Wellcome test confirms completely that morphine oxidation with several reagents gives the ortho-quinone derivative. The route here proposed is in accordance with the fact that ortho-halogenated phenols are oxidatively equivalent to mono-protected catechols, and they have been reported to undergo reaction with Pb(IV) reagents to give o-quinones, [20].

Thus, in this communication we provide a new reagent that affords o-quinones from o-halo phenols.

## 4. Conclusion

The chemistry of the Wellcome test for morphine has been cleared up. We provided the route from the alkaloid to the red o-quinone that is responsible for the colour observed in the assay. The steps are ortho-halogenation via a 4+2 sigma complex (oxyphilic interaction), repeated chlorination at the ipso position, hydroxyl substitution, and base catalyzed chloride elimination with concomitant o-quinone formation (oxidative hydrolysis).

This test fully confirms the nature of the oxidized product in the morphine test.

## Compliance with ethical standards

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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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