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The chemistry of the vulpius test for morphine

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Abstract

The interaction of sodium phosphate, sulphuric acid, and morphine, produces a series of reactions (Vulpius test) that is given for the first time. Protonation and water loosening of ortho-phosphoric acid formed in situ yields the reactive intermediate required to react with the phenol in morphine and produce the phosphate. Protonation of this ester and water detachment gives a cationic intermediate which originates a δ^+ at the oxygen linked to carbon (Inductive effect). This causes polarity inversion at the ortho position and reaction with phosphoric acid via a concerted mechanism, thus a new phosphate, a dienone, and meta-phosphorous acid result. Aromaticity is recovered by enolization. A final protonation of the phosphate and water elimination affords meta-phosphorous acid and an ortho-quinone via a synchronous sequence. The latter compound gives the red colour of the test.

Keywords: Concerted mechanism, inductive effect, meta-phosphorous acid, ortho-quinone, phosphate ester, polarity inversion

Introduction

The opium poppy, *Papaverum somniferum*, has been used since antiquity. In 1805 the German pharmacist Friedrich Sertuerner isolated from opium the sleeping agent, in crystalline form, and named it morphine. This psychoactive alkaloid is classified as a depressant.

Morphine is used in medicine as narcotic analgesic in the form of its hydrochloride, sulphate, acetate, and tartrate salts, being of use in the treatment of pain in cancer and in other severe conditions, ^[1,2].

The morphine molecule compresses five rings: phenolic ring, cyclohexane, piperidine, cyclohexenol and dihydrofuran.

Morphine is readily oxidized and this property is responsible of the several colour reactions for its identification ^[3].

In this communication we provide the reaction series that takes place during the interaction of morphine with sodium phosphate and sulphuric acid (Vulpius test).

This paper is a follow up of our studies on reaction mechanism, ^[4-8].

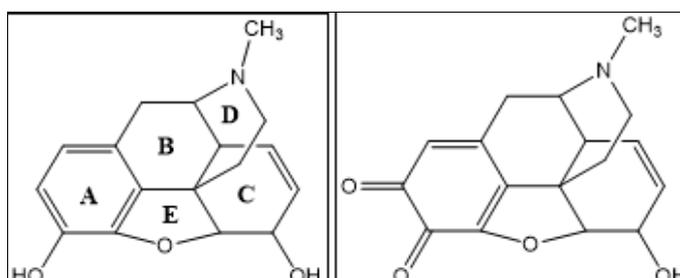


Fig 1: Structures of morphine and its oxidation product

Antecedents

The test under study is due to G. Vulpius and was published in journals of Pharmacy ^[9], Chemistry ^[10] and Analysis ^[11]. This colour test was also recorded in lists of analytical reagents ^[12] and in books ^[13].

The test is as follows: Sodium phosphate (40 mg) in concentrated sulphuric acid (6 drops), and morphine (1/4 mg), give on warming violet colour, turning to red with water, from which chloroform extracts a blue colour.

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Other test for morphine is the Serullas test ^[14, 15], it employs iodic acid which is reduced to iodine giving brown-red colour, and confirmed with starch gel (Prussian blue colour).

The Froehde test for morphine ^[16, 17], uses sodium molybdate which is reduced to molybdene blue.

Another test is due to Welcome ^[18, 19], he employs chlorinated lime, calcium chloro-hypochlorite. Though the reagent is not expensive, it has the pungent odour of chlorine.

The sodium phosphate in the Vulpius procedure is suitable as field test.

Discussion

Ortho-phosphoric acid is formed in situ from the potassium salt and sulphuric acid (metathesis).

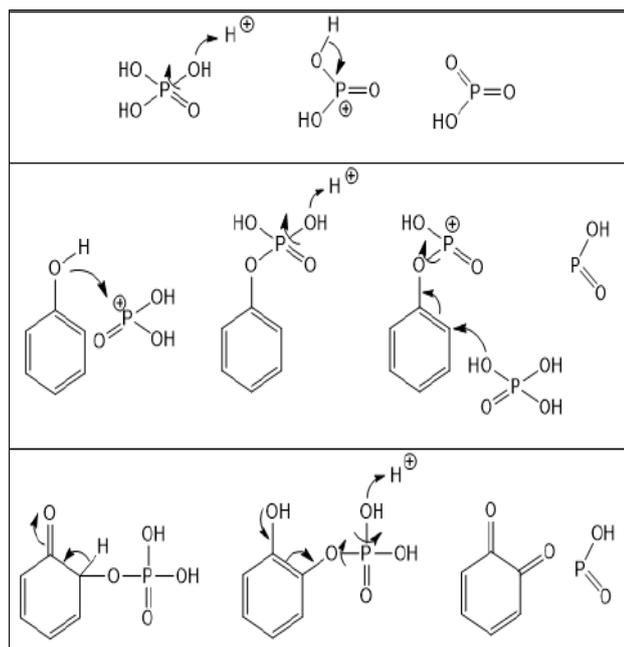


Fig 2: Abbreviated structures of the reaction route from morphine to its ortho-quinone

Protonation of the phosphoric acid and water detachment affords the reactive intermediate that interacts with the phenol group in morphine giving the phosphate. Meta-phosphoric acid is the dehydration product of the ortho-acid and comes by deprotonation of the reactive intermediate. The meta-acid can form too the reactive intermediate.

Protonation of the phosphate ester and water loosening gives rise to a cation and a δ^+ charge at the oxygen linked to carbon (inductive effect), activating the near double bond for nucleophilic attack from phosphoric acid. There has been Umpolung (polarity inversion) and synchronous formation of phosphate ester, a conjugated dienone and release of meta-phosphorous acid. The ketone is aromatized by enolization to the phenol.

Protonation of the new phosphate and water elimination causes a concerted mechanism giving meta-phosphorous acid and ortho-quinone.

Conclusion

The formation of a red ortho-quinone in the Vulpius test is explained by the series of reactions outlined in Figure 2. The reactive intermediate comes from phosphoric acid formed in situ. A cationic intermediate from morphine phosphate

produces polarity inversion at the ortho-position. Nucleophilic addition of phosphoric acid yields a new phosphate and a dienone, with simultaneous release of meta-phosphorous acid (first redox reaction). The phenol is recovered by aromatization. Protonation and water detachment from the phosphate affords an ortho-quinone and meta-phosphorous acid (second redox reaction), via a concerted mechanism. The electron flow is given in each step.

This mechanism via activation of the phosphate ester and Umpolung at ortho position prompted a short route to the reaction product and it is a novelty since no electron back donation is invoked in order to explain the redox reactions that occur during a process.

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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