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Insight into the mechanism of the Froehde test for morphine

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Abstract

The Froehde reaction for morphine employs a solution of sodium molybdate in concentrated sulphuric acid. This test has been extended to other alkaloids giving different colours. In this communication we present an insight into the reaction with morphine. It has the particularity that it does not invoke the concept of electron back donation since this known point of view reverses the normal polarization of a functional group. This route is based on a novel theoretical finding: the activation of a mixed ester (organic-inorganic) by means of protonation and water loosening. This causes Umpolung (polarity inversion) at ortho position, favouring a nucleophilic attack instead of the electrophilic one due to the original phenol group in morphine. The final part of the route to morphine ortho-quinone goes smooth via a six member concerted mechanism.

Keywords: Activated ester; Bimolybdene pentoxide; Electron back donation; Molybdene blue; Molybdene dioxide; Reactive intermediates

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 mechanism of the morphine-apomorphine rearrangement has been totally changed [1] instead of the old one suggested 60 years ago by Bentley [2].

In the present communication we present a new route for the chemistry of the Froehde test for morphine which has been extended to other synthetic opioids [3].

2. Study Method and Process

This is a Theoretical Organic Chemistry Study. It is based on the chemical deportment of reagents and substrate. All is in accordance with the reaction medium, the nature of the oxidizer and catalyst employed. The several steps leading to morphine ortho-quinone and the blue reduced inorganic compounds are fully commented and the electron flow is given in each reaction.

3. Antecedents

This paper opens a new route without the necessity to invoke electron back donation in order to explain some oxido-reduction steps. The concept of back donation can be found in chemistry journals and in well-known texts on organic

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oxidations [4], and in modern heterocyclic chemistry books [5]. 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 of a functional group.

The direct route presented in this communication explains very well the Froehde test for morphine [6], Figure 1, instead of a previous one [7].

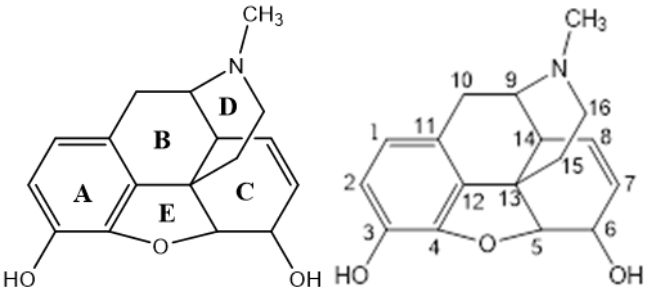

Figure 1 Structure of the morphine molecule

This paper is a follow up of our studies on reaction mechanism [8-12].

4. Discussion

The reactive species is protonated molybdic acid at the hydroxyl group. Reaction with the phenolic group at C-3 in morphine yields morphine molybdate and water, Figure 2, a, b.

Protonation of the remaining hydroxy group in this ester and water loosening creates a reactive intermediate with a δ+ at the oxygen linked to the aromatic ring, c. This causes Umpolung (polarity inversion) at ortho-position, favouringnucleophilic attack at C-2.

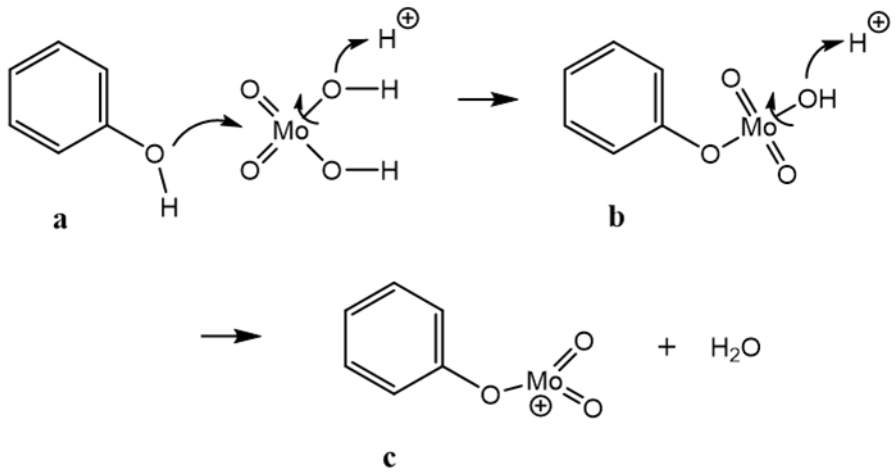

Figure 2 Abbreviated structure of morphine ring A, showing the key cationic intermediate in this mechanism

Addition of a molybdic acid molecule brings about a concerted mechanism yielding a new molybdic ester and a cyclohexadienone, with concomitant elimination of molybdene dioxide (first redox reaction), Figure 3, d, e. Enolization of the dienone recovers aromaticity, f, g. This intermediate is the mono-ester of a pyrocatechol derivative and these last steps are equivalent to aromatic hydroxylation. Dehydration of this ester affords molybdene dioxide and morphine ortho-quinone via a concerted mechanism (second oxido-reduction step), h, i.

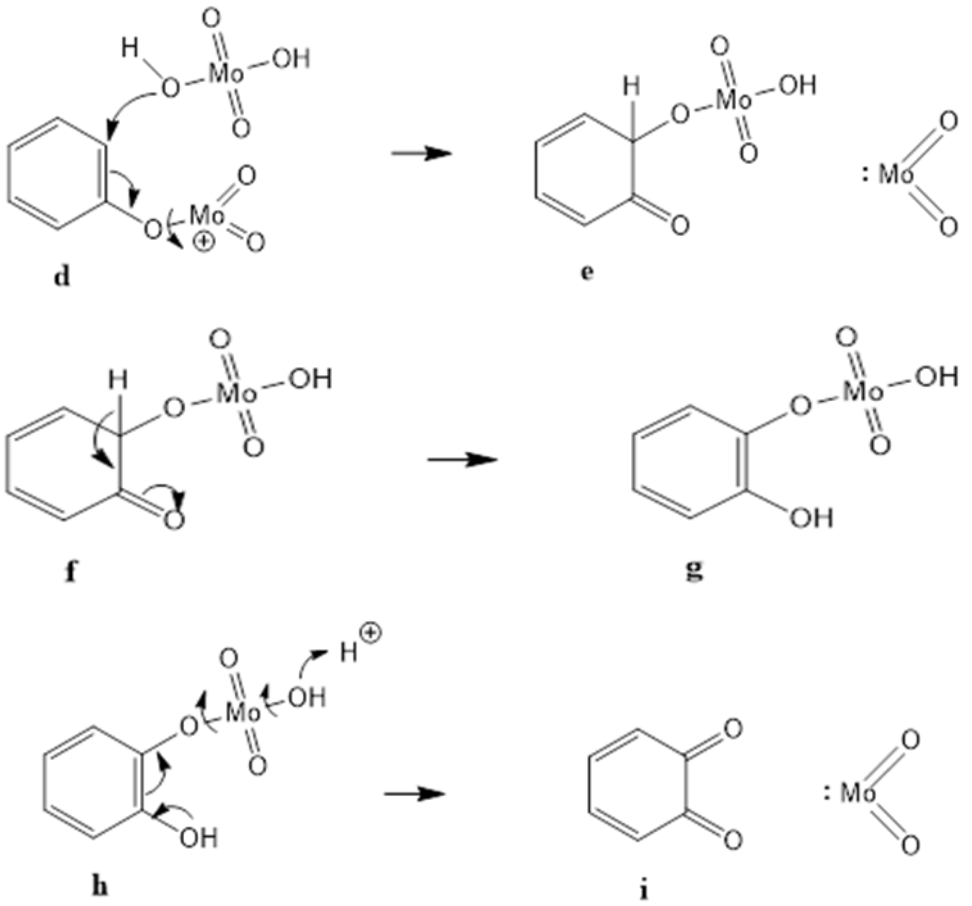

Figure 3 Last steps to morphine ortho-quinone and molybdene dioxide via a pyrocathecol derivative

This route to morphine ortho-quinone is a real mechanistic improvement since it is free from electron back donation. Besides it is short and direct.

The violet colour observed in the test is due to molybdene dioxide [13] and to two products derived from it: dimolybdene pentoxide (dark violet), and molybdene blue (Mo_3O_8), [14].

Regarding the reactivity of other semisynthetic opioids, hydromorphone, with a keto group at C-6, behaves in a similar manner as morphine, giving a blue colour that turns purple. Heroin, 3,6-diacetyl morphine, gives a purple colour, that is, the acetyl groups can be removed in the test conditions, releasing the free phenol group.

The opioids with a methoxy group at C-3 cannot form easily a phenol group and give very different colours in this test**:** codeine (methyl morphine), green**;** hydrocodone (dihydrocodeinone), yellow**;** and oxycodone (14-hydroxyhydrocodone), strong yellow. So there have not been production of the blue-violet compounds resulting from reduction of molybdic acid and the observed colours are due to halochromism [15, 16].

5. Conclusion

In this paper a new mechanism for the Froehde test for morphine is presented. It is based on activation of the mixed ester (morphine molybdate) by means of protonation and water loosening. This cationic intermediate produces polarity inversion at ortho-position (C-2) due to the δ+ at the oxygen linked to the aromatic ring (inductive effect). This Umpolung is favourable for nucleophilic reaction. Addition of molybdic acid yields a new molybdic ester and a cyclohexadienone with concomitant molybdene dioxide elimination. Aromatization followed by dehydration of the ester affords morphine ortho-quinone and molybdic dioxide via a concerted mechanism.

The blue colour observed in the test is due to several reduced inorganic products.

This route to morphine ortho-quinone is a novel mechanistic improvement since it does not involve electron back donation. Besides, this sequence is short and direct.

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.

References

[1] Sánchez-Viesca F, Gómez R. The mechanism of the morphine-apomorphine rearrangement. Am. J. Chem. 2022; 12(4): 73-75.

[2] Bentley KW. The morphine alkaloids, in the Isoquinoline Alkaloids. Oxford: Pergamon Press. 1965.

[3] Merck E. Merck's Reagienten-Verzeichnis. Darmstadt: Springer. 1903; 46.

[4] Waters WA. Mechanisms of Oxidation of Organic Compounds. London: Methuen. 1964; 63, 93-95.

[5] Newkome GR, Paudler WW. Contemporary Heterocyclic Chemistry. New York: J. Wiley & Sons. 1982; 253.

[6] Frohde A. Sur la recherché de la morphine. Bull. Soc. Chim. Paris. 1867; 8(1): 166.

[7] Sánchez-Viesca F, Gómez R. On the mechanism of the Froehde Reaction. World J. Org. Chem. 2019; 7(1): 1-4.

[8] Sánchez-Viesca F, Gómez R. The mechanism of the oxido-degradation of the Cinchona Alkaloids. Am. J. Chem. 2022; 12(1): 18-21.

[9] Sánchez-Viesca F, Gómez R. The chemistry of Heller's Test for urine indican detection. Magna Scientia Adv. Res. & Rev. 2022; 05(01): 025-029.

[10] Sánchez-Viesca F, Gómez R. On the mechanism of the Caro Synthesis of methylene blue. Eathline J. Chem. Sci. 2021; 6(2): 209-214.

[11] Sánchez-Viesca F, Gómez R. The mechanism of the Davy Test for strychnine. Int. Res. J. Pure & Appl. Chem. 2021; 22(10): 36-39.

[12] Sánchez-Viesca F, Gómez R. The chemistry of Crismer's Test for glucose in urine. OAR J. Chem. & Pharm. 2021; 01(02): 005-008.

[13] The molybdenum (IV) oxide, datasheets.scbt.com/sc-235882.pdf. Accessed: October 29, 2022.

[14] Weigh M, Poirier P. Methods and reactions of organic analysis. Paris: Mason. 1954, vol. 3, 9.

[15] Miall S, Mackenzie Miall L. Diccionario de Quimica, 2a. ed., Mexico: Atlante. 1953; 515.

[16] Weigh M, Poirier P. Methods and reactions of organic analysis. Paris: Mason. 1954, vol. 3, 227