International Journal of Chemical and Pharmaceutical Research Updates

Journal homepage: https://orionjournals.com/ijcpru/

(Research Article)

On the mechanism of Siebold's test for morphine

Francisco Sánchez-Viesca * and Reina Gómez Gómez

Department of Organic Chemistry, Faculty of Chemistry, National Autonomous University of Mexico, Mexico City (CDMX), Mexico.

International Journal of Chemical and Pharmaceutical Research Updates, 2024, 02(01), 010–013

Publication history: Received on 13 January 2024; revised on 23 February 2024; accepted on 26 February 2024

Article DOI: https://doi.org/10.53430/ijcpru.2024.2.1.0021

Abstract

In this communication the reaction course of Siebold's test for morphine is provided. The test is based on the interaction of the alkaloid in sulphuric acid with potassium perchlorate. Perchloric acid is the intermediate that gives rise the reactive species, ClO_3**+.** A mixed perchlorate is formed by interaction with the phenolic group at C-3 in morphine. Protonation of this ester induces nucleophilic reaction at C-2 (Umpolung). A new perchlorate results with concomitant ketone formation at C-3 and elimination of chloric acid (first redox reaction). Enolization restores ring aromatization, and protonation of the perchlorate at C-2 produces a concerted push-pull mechanism, via three electron-shifts, that gives rise separation of chloric acid and formation of an ortho-quinone (second redox reaction).

Keywords: o-Benzoquinone component; Organic-inorganic ester; Perchloric acid; Potassium perchlorate; Reactive intermediates; Redox reactions

1 Introduction

Morphine, previously known as Morphia, exists in opium as bi-meconate. Mohr isolated morphine making a strong infusion with water, added lime in the state of milk, boiled the mixture and filtered through linen. While still hot, ammonium chloride in fine powder is added, and morphine is deposited as the liquid cools. Good opium yields 10-13% of morphine. Smirna opium contains the most morphine. However, opium is to be preferred as a stimulant and sudorific, and for suppressing excessive mucous discharges.

The morphine of commerce is a white crystalline powder, but when crystallised from 30 parts of boiling alcohol, it forms brilliant prismatic crystals of adamantine lustre. It exhibits alkaline reaction on test paper, and imparts a perceptible bitter taste to water. Solubility: 1/1160 parts of water, [1].

Siebold proposed a test for morphine in which the alkaloid is warmed in a few drops of sulphuric acid and a very small quantity of pure potassium perchlorate is added. A deep brown colour is observed; 0.1 mg of morphine can be distinctly recognised in this way. No other alkaloid is acted upon. Figure 1.

* Corresponding author: Francisco Sánchez-Viesca

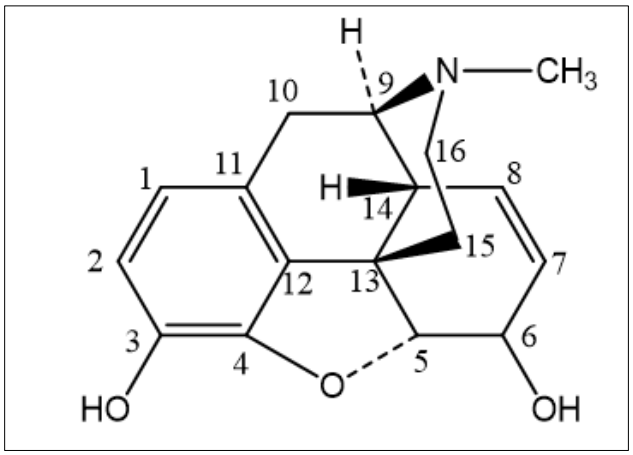

Figure 1 Morphine structure

In this paper the reaction mechanism of this test is provided for first time. This communication is a follow up of our studies on reaction mechanism (2-6).

2 Antecedents

The test for morphine discovered by Professor Louis Siebold was published in England [7] and reproduced in the United States [8], and in Cooley's Cyclopaedia, [1]. The test was also registered in books on chemical tests, [9-11].

The reagent, potassium perchlorate, can be prepared by melting potassium chlorate (50g), maintaining the temperature at ~ 400°C. After 15 min the melt is cooled thoroughly and covered with 50 ml of cold water. The melt disintegrates, the mixture is kept cool in running water and then filtered. The residue is recrystallised from 200 ml of boiling water and the mixture cooled ~ 0°C overnight. The potassium perchlorate is washed in the filter with 40 ml of ice water and dried in air. It must be free of potassium chloride, [12, 13]. The reaction is:

$$KClO_3 \text{ (donor)} + 3KClO_3 \text{ (receiver)} = 3KClO_4 + KCl$$

Potassium perchlorate can be prepared by treating an aqueous solution of sodium perchlorate with potassium chloride (precipitation reaction). It can also be produced by bubbling chlorine through a solution pf potassium chlorate and potassium hydroxide, [14], via nascent oxygen from potassium hypochlorite.

Potassium perchlorate can be used to treat hyperthyroidism. It is a common oxidizer used in fireworks and in the manufacture of ammonium perchlorate. This compound is the oxidant, together with the reducing agent aluminium in rockets for spacecraft, [15].

Perchloric acid is a reactive intermediate in Siebold's test. Potassium perchlorate gives with concentrated sulphuric acid white fumes of perchloric acid. This acid is obtained distilling in vacuo at 160° potassium perchlorate and concentrated sulphuric acid, [16, 17]. The boiling point at atmospheric pressure is unknown because over 100° it decomposes into ClO_2, water and oxygen. With a water molecule a crystalline solid is formed, hydronium perchlorate, which melts at 50°C.

The atomic group ClO_4 is tetrahedral, [18]. Pure perchloric acid is a colourless liquid that can explode unpredictable. Contact with organic materials such as wood or paper causes an immediate fire.

3 Discussion

Potassium perchlorate in contact with sulphuric acid forms perchloric acid. Acidolysis of this acid produces water and the reactive species, ClO_3**+**. This on reaction with the phenolic group in morphine yields a mixed perchlorate. Protonation of this ester induces a reaction at the ortho-position by electron attraction. Reaction with perchloric acid gives a new perchlorate and a ketone, with concomitant separation of chloric acid (first redox reaction). Enolization of the ketone is favoured by aromatization of the ring. Protonation of the organic perchlorate, plus the electrodotic property [19] of the phenolic group, produces formation of an ortho-benzoquinone, and elimination of chloric acid, via

a push-pull mechanism (second redox reaction). This way the oxidation of morphine by means of perchloric acid (Siebold test) has been cleared, Figure 2.

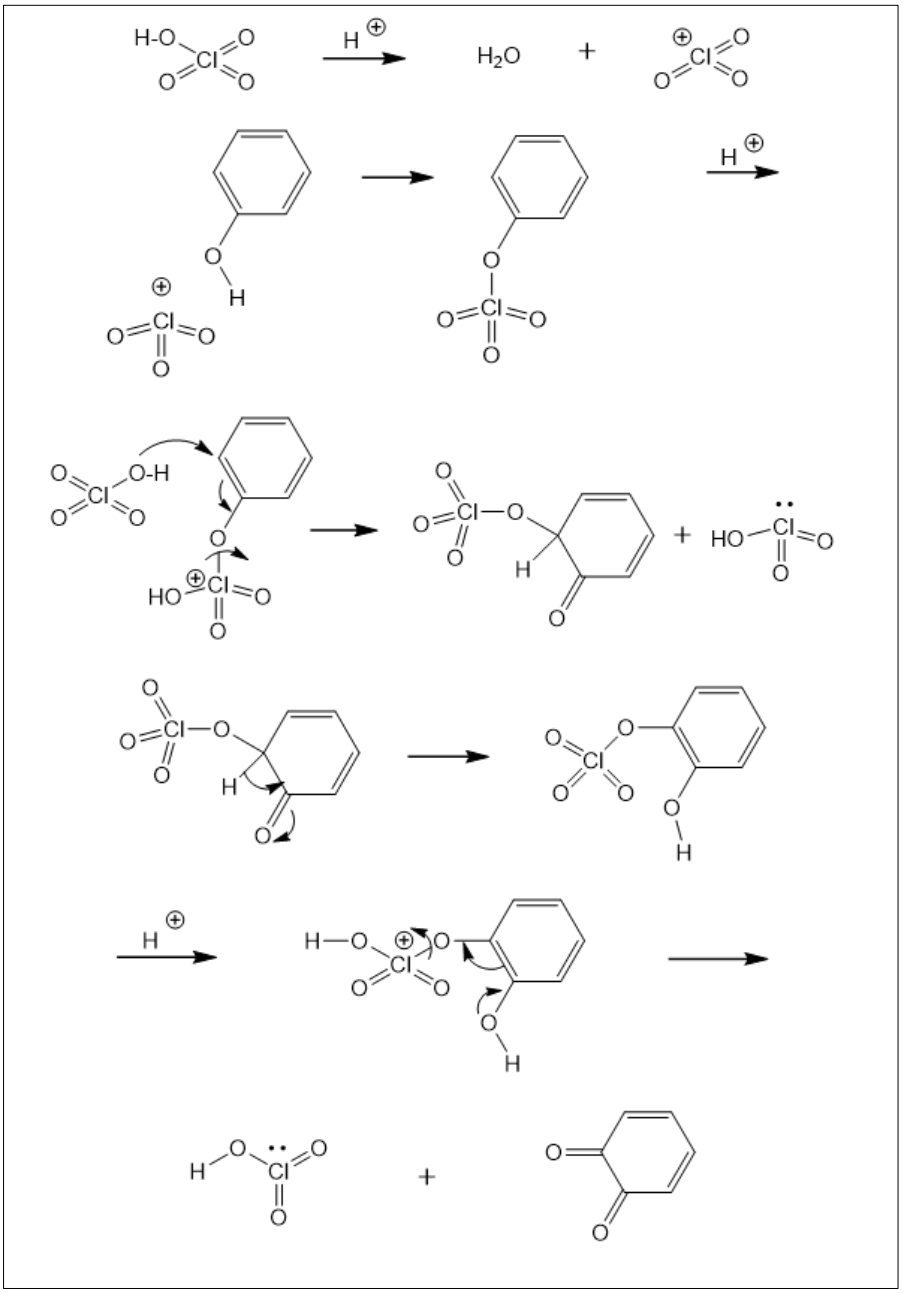

Figure 2 Interaction of morphine with potassium perchlorate in sulphuric acid

In the Seibold test the substance for analysis is heated gently (warmed) in sulphuric acid before the reagent is added, whereas in the Huseman's test for morphine [20] the substance for assay is heated during half an hour, boiled, or heated al 150° during brief time; thus, the strong heating transforms morphine into apomorphine, not mentioned in the test. This makes the difference between the two tests, not the employed reagents, potassium perchlorate or chlorine water, respectively. This structural change is confirmed since in the Siebold test a deep brown colour is observed, whereas in the Husemann test a beautiful blue- to violet-red colour appears, which soon changes to blood red, [21].

4 Conclusion

The Siebold test for morphine is based on the interaction of the alkaloid with potassium perchlorate in sulphuric acid. Perchloric acid formed in situ is the intermediate that gives the reactive species by dehydration. Reaction with the

phenolic group in morphine affords a mixed ester whose protonation originates a nucleophilic reaction at the free ortho-position, ketone formation, and elimination of chloric acid. Enolization gives an ortho-quinone and chloric acid via protonation of an ester at C-2.

Compliance with ethical standards

Acknowledgments

Thanks are given to Luz Clarita for support.

Disclosure of conflict of interest

There is no conflict of interest to declare.

References

[1] Cooley A, Tuson R. Cooley's Cyclopaedia of Practical Receipts, 6th ed., v. II, Morphia, Hard Press Publishing, Madrid, Spain, 2015. https://gutenberg.org/files/41957/41957.txt

[2] Sánchez-Viesca F, Gómez R. Organometallic intermediates in Böttger test for glucose in urine. Magna Scientia Adv. Res. and Rev. 2023, 09(02), 051-054.

[3] Sánchez-Viesca F, Gómez R- The chemistry of Hager's test for brucine. Earthline J. of Chemical Sc. 2024, 11(1), 31-37.

[4] Sánchez-Viesca F, Gómez R. The Chemistry of Anderson's test for codeine. Int. J. Scholarly Res. Chem. and Pharm. 2023, 03(01), 001-004.

[5] Sánchez-Viesca F, Gómez R. On Dulcin detection by electron transfer. World J. Chem and Pharm. 2023, 03(01), 001-004.

[6] Sánchez-Viesca F, Gómez R. On the chemistry of Beckurt's test for physostigmine: A novel hydride transfer. Magna Scientia Adv. Res. and Rev. 2023, 08(02), 022-025.

[7] Siebold L. A new test for Morphia. Pharm. Journal and Transactions (London), October 18, 1873, ser. 3, v. 4, 309. (Biodiversity Heritage Library)

[8] Siebold L. A new test for Morphia. Amer. Journ. Pharm. (Philadelphia), 1873, 45, 544-545.

[9] Merck E. Merck's Reagienten Verzeichnis. Springer, Darmstadt, 1903, 135.

[10] Cohn AI. Tests and Reagents. J. Wiley & Sons, New York, 1903, 283.

[11] Wilder HM. List of Tests, Reagents, Arranged in alphabetical order according to the names of the originators. P. W. Bedford, New York, 1885, 67, no.731.

[12] Schlessinger G. Inorganic Laboratory Preparations. Chemical Publishing Co., New York, 1962, 49.

[13] Giral F, Rojahn CA. Chemical and Pharmaceutical Products, vol 1. Atlante, México, 1956, 41.

[14] Potassium perchlorate. https://en.wickipedia.org/wicki/Potassium_perchlorate#Production

[15] Rayner-Canham G, Overton T. Descriptive Inorganic Chemistry, 6th ed. W. H. Freeman and Co. New York, 2014, 494.

[16] Partington JJR. Treatise on Inorganic Chemistry. Porrúa, México, 1952, 254, 263.

[17] Bruni G. Inorganic Chemistry. UTEHA, México, 1964, 272.

[18] Bargalló M. Treatise on Inorganic Chemistry, Perchloric acid, Porrúa, México, 1962, 798.

[19] Luder WF, Zuffanti S. The electronic theory of acids and bases. 2nd ed. Dover, New York, 1961, 73.

[20] Sánchez-Viesca F, Gómez R. The chemistry of Husemann's test for morphine. International J. of Chemical and Pharmaceutical Research Updates, 2023, 01(01), 025-028.

[21] Husemann A. Detection of morphine. Journal of the Chemical Society (London), 1876, vol. 30, part I, 777.