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On the Mechanism of the Serullas Test for Morphine

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Abstract The reaction of iodic acid with morphine (Serullas colour test) has not been studied. It is a very sensitive reaction published in France that had a great resonance in Europe and in the United States. However, there is no reaction mechanism advanced. We provide the electron flow, step by step, of this oxidation of morphine. An aromatic hydroxylation and then ortho-quinone formation are described. This spot test opens a route to o-quinones from phenols, and this is important. A brief Serullas' profile and references of the test are included.

Keywords: *aromatic hydroxylation, colour test, iodic acid, o-quinones, reactive intermediates*

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1. Introduction

Serullas colour test for morphine is based in the reaction of iodic acid with minute quantities of the alkaloid. A brown-red colour was observed, which was identified as iodine by its colour and odour, and by reaction with starch gel giving a Prussian-blue colour.

In this communication we give the reaction mechanism as well as the references related to this test. This is a follow up of our studies on reaction mechanisms [1,2,3,4,5].

2. Antecedents

The test under study is due to the French chemist Georges Simon Serullas, who prior to his work on morphine prepared for the first time hydroiodide of carbon, a better name than iodoform. He added potassium to a solution of iodine in alcohol and water. After water addition yellow flocks separates, [6].

So, he performed the first haloform reaction, [7]. Two remarks: the previous oxidation of ethanol to acetaldehyde implies a hydride transfer from the alkoxide to a potential iodonium ion. This is frequently overlooked. The other remark is that iodoform has been used until now as antiseptic in dermatological medical dressings, [8]. It prevents the festering of wounds.

Bromoethane was first synthesized by Serullas from alcohol, phosphorus and bromine, the last added in small portions, [9]. Due to its volatility he named it hydrobromic ether, a synonym that is still registered, [10]. This method shows the role of phosphorous as halogen carrier and is considered a general method for the preparation of alkyl bromides, [11]. Other cognate preparation was ethyl iodide, hydroiodic ether, [12]. An improved and detailed description of the method is available, [13].

Then, Serullas published his test for morphine and its salts, [14]. He found that when iodic acid was brought in contact with the alkaloid, even in very minute quantities, iodine was disengaged. A brown-red colour is observed, or a Prussian-blue colour was communicated to starch glue. This effect is peculiar to morphine. Other 'vegetable alkalies' as strychnine, veratrine, brucine, etc., have no action on iodic acid

The communication of Serullas was not only cited but reproduced in other Journals, like The Lancet, in London, [15], in which we found: with quinine, iodic acid forms a salt which crystallizes in silky needles, like the sulphate of that base. With cinchonine, iodic acid forms a salt in very fine prismatic crystals. Brucine also forms a salt with iodic acid; the solution at first is of a deep-red colour, but soon loses that tint, becomes transparent and yields colourless crystals of the neutral salt. This show the striking difference between the comportment of morphine and the other 'vegetable alkalies' to iodic acid, morphine decomposing the acid, while the others unite with it and forms definite series of neutral and acidulous salts.

Serullas test for morphine was also reproduced in other British journal [16], and in the Dublin Journal of Medical and Chemical Science [17], and in Philadelphia, USA, [18].

Serullas published his test 37 years before Froehde presented other test for morphine [19], being the latter less specific. Serullas' test caused much interest when it appeared, as we have seen.

3. Discussion

Iodic acid, HIO3, can be prepared by nitric acid oxidation of iodine. It is a white water-soluble solid and is one of the most stable oxo-acids of the halogens. It is strongly oxidizing in acidic solution.

Morphine was isolated from opium by Sertuerner in 1805 as a crystallisable substance, [20]. The structure

elucidation was achieved by Gulland and Robinson in 1925, [21], Figure 1.

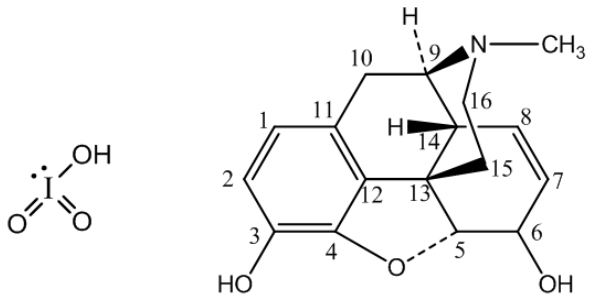

Figure 1. The reactants: iodic acid and morphine

Due to the oxidizing properties of iodic acid, there must be a redox reaction with morphine. This is in accord with the electrodoting properties [22] of the phenol group in morphine. We will use an abbreviated form instead of the complete morphine structure.

The electronegativities in the iodoso group (-I=O) are I=2.4; O=3.5, [23], that is, similar to C=O, (2.5 and 3.5). Thus, protonation of a double bonded oxygen in iodic acid favours electron acceptance at the other polarisable oxygen atom. Thus, a redox reaction occurs through an electron push-pull mechanism, a synchronous process with a back donation electron shift. A ketone and a mixed iodous ester are formed. There is no reaction at p-position since it is not free in morphine. Aromatization by enol formation followed by protolysis would yield iodous acid and a pyrocatechol derivative, Figure 2.

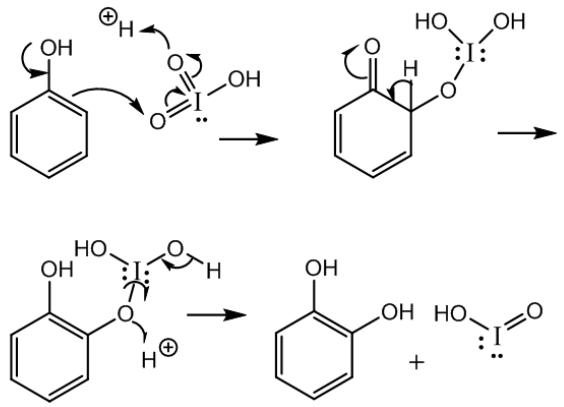

Figure 2. Ortho-hydroxylation and iodous acid formation

Nevertheless, the iodous ester is apt as starting point for the second oxido-reduction step. Protonation of one hydroxy group attached to the iodine atom in the iodite molecule favours the reduction to hypoiodous acid with concomitant formation of an ortho-quinone, Figure 3.

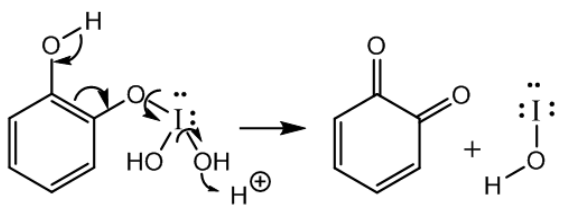

Figure 3. Redox reaction to o-quinone and hypoiodous acid

Once more, a push-pull mechanism is operating. Then, reaction of the pyrocatechol analogue with protonated hypoiodous acid, halogen containing complex equivalent to iodonium ion [24], gives an organic hypoiodite. This reactive intermediate loses an iodide ion, forming the respective quinone (synchronous mechanism and third redox reaction). Finally, the liberated iodide reacts with protonated hypoiodous acid to form the iodine observed in the colour test, Figure 4.

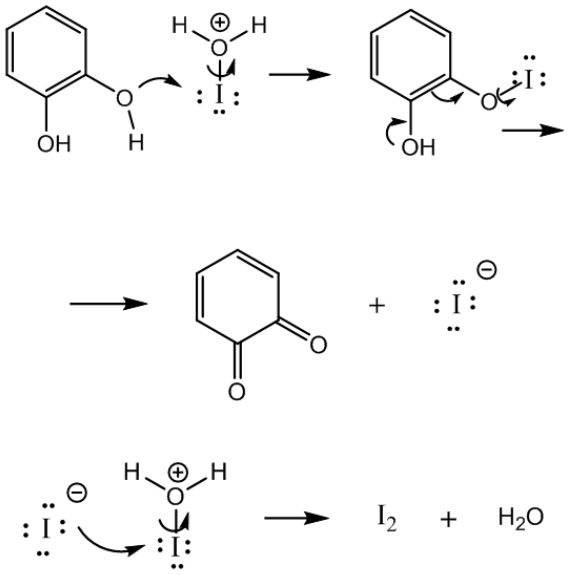

Figure 4. o-Diphenol forms labile mixed hypoiodite. Elimination of HI gives o-quinone and iodine

The key intermediate and the final reaction product are in Figure 5.

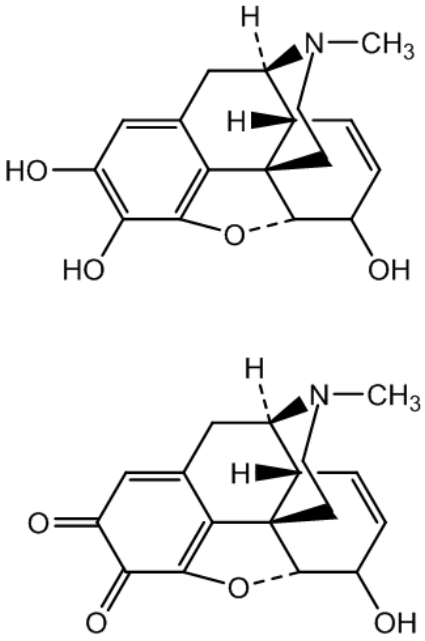

Figure 5. First and second oxidation products of morphine

A last comment, why the other alkaloids tested by Serullas gave negative results? None of the other alkaloids tested contained a phenol group. This reveals that this

functional group is indispensable for the reaction, in accordance with the mechanism advanced in this communication. The negative reaction to iodic acid of the other functional groups present in these alkaloids (principally alcohols, or ester, amide, or ether) shows the specificity of the reagent towards phenols.

Thus, this test could be used for phenol identification, but the common ferric chloride test makes it unnecessary.

However, Serullas' colour test opens a route to o-quinones from phenols.

Then, what about the importance of this test for morphine? In order to avoid the interference of phenols, the iodic acid test must be carried only with an alkaloid to be identified as a phenol, and which is suspected to be morphine, a controlled drug.

Other phenolic alkaloid is hordenine, a phenyl-ethylamine derivative [25], but this product is not restricted. It is a purchasable chemical with antibacterial and antibiotic properties found in several plants in the family Cactacea. The major occurrence of hordenine, N,N-dimethyl-2(4-hydroxyphenyl)ethylamine, in humans is beer brewed from barley. Hordenine in urine interferes with tests for morphine, heroin and other opiod drugs, [26]. This is totally in accord with this study.

Other compounds are out of consideration since only have certain academic interest and are not common.

The tests for identification of morphine are based either in direct detection of the phenol group or in oxidation reactions as in the Serullas, Froehde or other procedures. The use of sulphuric acid and a saturated solution of potassium iodate is a variant of Serullas' test found in the classic book of 'Drug Identification', [27]. Due to dilution with the acid and water, the observed color is amber, paler than the original brown-red of iodine.

Actually, the 'Recommended methods for testing opiates', from the United Nations, retain the well known color reactions, [28].

The reaction mechanism here advanced transfers the simple laboratory work to the understanding of theoretical chemistry.

4. Conclusions

The Serullas test for morphine deserves this study for several reasons. It is a very sensitive test, rapid and easy to perform. In order to eliminate the interference of phenols, the test for morphine must be carried only with an alkaloid to be identified. Serullas test is preferable to other tests that actually are officially in use.

Spot tests must not remain only in the laboratory work. It is the labour of the theorist clear up the reaction series that sometimes occurs in a simple spot test. This is the case with the Serullas Test here studied.

We found that the reagent undergoes three reduction steps. The reaction mechanism involves electron push-pull effects, organic-inorganic esters formation, and acid catalysis, either as initial protonation or as final protolysis. Aromatic hydroxylation and o-quinone formation are described.

This test opens a route to o-quinones from phenols.

Some Serullas' achievements were mentioned as well as the international reception of his test, in order to show the relevance of his work.

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References

[1] Sánchez-Viesca, F. and Gómez, R., "On the mechanism of the Treumann test for theobromine", Internat. J. of Chemical Sci., 3(6), 46-49, 2019.

[2] Sánchez-Viesca, F. and Gómez, R., "The mechanism of nitric acid degradation of C-glycoside aloin to aloe-emodin", Am. J. Chem., 10(1), 1-5, 2020.

[3] Sánchez-Viesca, F. and Gómez, R., "Formation mechanism of the colored compounds derived from eserine (physostigmine)", World J. Org. Chem., 8(1), 1-4, 2020.

[4] Sánchez-Viesca, F. and Gómez, R., "On the mechanism of the Neumann-Wender glucose test", Am. J. Chem., 9(4), 123-126, 2019.

[5] Sánchez-Viesca, F. and Gómez, R., "The chemistry of the Folin test for uric acid", Am. J. Chem., 9(3), 91-94, 2019.

[6] Serullas, G., "Nouveau compose d'iode, d'hydrogéne et de carbone ou hydroiodure de carbone", Annales de Chimie et de Physique, 20, 165-166, 1822.

[7] Bouchardat, A., "On the influence of temperature on the production of iodoform", The Chemist, London, 4, 399, 1843.

[8] Iodoform-Drug Bank, drugbank.ca/drugs/DB13813, Retrieved, March 30, 2020.

[9] Serullas, G., "Ether hydro-bromique", Annales de Chimie et de Physique, 34, 99-100, 1827.

[10] Bromoethane, PubChem CID: 6332; 2.4.2, Synonyms. U.S. National Library of Medicine.

[11] Cumming, W. M., Hopper, I. V. and Wheeler, T. Sh., Systematic Organic Chemistry, Modern Methods of Preparation, 4th. ed., Constable, London, UK, 1950, 343.

[12] Serullas, G., "Sur l'ether hydriodique", Annales de Chimie et de Physique, 42, 119-120, 1829

[13] Gattermann, L. and Wieland, H., Laboratory Methods of Organic Chemistry, 24th. ed., Macmillan, London, UK, 1957, 95-96.

[14] Serullas, G., "De l'action mutuelle de l'acide iodique et de la morphine, ou de l'acetate de cette base", Annales de Chimie et de Physique, 43, 211-216, 1830.

[15] Vegetable alkalies, The Lancet, London, 2, 4-5, 1830-31.

[16] Serullas, G., "On the precipitation of the vegeto-alkalies by iodic acid" The Journal of the Royal Institution of Great Britain, 1, 615, 1831.

[17] Serullas test, The Dublin Journal of Medical and Chemical Science, 13, 214, 1834.

[18] Beck, Th. R. and Beck, J. B., Elements of Medical Jurisprudence, 5th. ed., Desilver & Thomas, Philadelphia, USA, 1835; vol. 2, 537.

[19] Froehde, A., "Sur le recherché de la morphine", Bull. Soc. Chim. Paris, 8(1), 166, 1867.

[20] Krisnamurti, Ch. and Rao, S. S. C., "The isolation of morphine by Sertürner", Indian J. Anaesth., 60(11), 861-862, 2016.

[21] Szántay, Cs., Blaskó, G., Bárczai-Beke, M., Dornyei, G., and Péchy, P., "Studies in the synthesis of morphine. VI", Planta Medica, J. Medicinal Plant Research, 48, 207-224, 1983.

[22] Luder, W. F. and Zuffanti, S., The Electronic Theory of Acids and Bases, 2nd. ed., Dover, New York, USA, 1961, 71-72.

[23] Brown, D. A., Comparative Inorganic Chemistry, McGraw-Hill, London, UK, 1967, 71.

[24] Sykes, P., Mechanism in Organic Chemistry, Longmans, London, UK, 1967, 107.

[25] Smith, T. A., "Phenylethylamine and related compounds in plants", Phytochemistry 16, 9-18, 1977.

[26] Hordenine PubChem CID: 68313, U.S. National Library of Medicine. On line, access with the title. Last login, March 28, 2020.

[27] Johnson, C. A. and Thornton-Jones, A. D., Drug Identification, Pharmaceutical Press, London, UK, 1966, 48.

[28] Recommended methods for testing opium, morphine and heroin, Manual for use by National Drug Testing Laboratories, United Nations, New York, USA, 1998. p 25..