

(RESEARCH ARTICLE)



On the chemistry of Beckurt's test for physostigmine: A novel hydride transfer

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Abstract

Beckurt treated physostigmine hydrochloride with dilute potassium permanganate solution and observed separation of manganese dioxide. Since at first sight there is no reaction site for this oxidation, it was interesting to clear up the reaction route of this test. Acid hydrolysis of this O-phenylcarbamate yielded the phenolic derivative of the three-ring indole alkaloid hydrochloride. Now are present at para-position an electrodotic group and a positive charged nitrogen atom. However, this nitrogen has an octet of electrons; thus, for reaction to occur a hydride ion must be displaced. This can happen in the presence of a hydride acceptor, that is, by reduction of permanganate ion. This chemical department has been postulated recently in a completely different reaction sequence. So, our proposal is a novel one. The mechanism of the following inorganic steps to the final product has not been advanced, and it is provided in this communication.

Keywords: Hydride transfer; Indole alkaloid; Primary carbamate; Redox reactions; Reduced permanganic ion

1. Introduction

Physostigmine is an alkaloid isolated from *Physostigma Venenosum*, a plant growing in the Calabar region of Nigeria. It has also the name Eserine. Its aqueous extracts produce strong and persistent contraction of the eye pupil. This myotic effect was reported in Edinburgh journals [1, 2].

Physostigmine is an indole alkaloid with an additional pyrrolidine ring. It shows an O-phenylcarbamate and four methyl groups, Figure 1

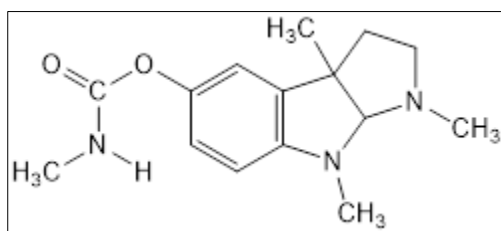


Figure 1 Physostigmine structure

Beckurt oxidized physostigmine hydrochloride with potassium permanganate, yielding manganese dioxide. Since at first sight there is no functional group prone to react with the reagent, it was of interest to study the chemistry of this tube test. In this paper is disclosed the reaction route from the substrate to the final inorganic product, each step is fully commented and the electron flow is also given.

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This communication is a follow up of our studies on reaction mechanism, [3-7].

2. Study Method and Process

This is a Theoretical Study involving both Organic and Inorganic Chemistry. It is based in the chemical department of reagent and substrate. All is in accordance with the reaction medium, the nature of the oxidizer employed and catalyst present. The several steps leading to the final inorganic product are entirely commented and the reaction mechanism is given too.

3. Antecedents

The test under study is due to Heinrich Beckurt (1885-1929), Professor of Pharmaceutical Chemistry at Braunschweig, Germany. His test for alkaloids was published in *Pharmacognosy, Pharmacy and Toxicology Advances* [8], and was registered in a book of chemical tests, [9].

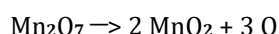
The reagent of Beckurt's test is a 0.1 N solution of potassium permanganate, which is added to the hydrochloride of the assayed alkaloid. The result can be colour development, or separation of brown manganese dioxide, which is the case with physostigmine hydrochloride.

Some notes about the substrate. Physostigmine was first obtained in crystalline form by Veé and Leben, in France [10, 11]. Its structure was determined simultaneously in France [12], and in Edinburgh [13].

Remarks on the reagent. Manganese has an electron configuration of $[Ar]4s^23d^5$ —in ascending order of orbital energies— resulting in one unpaired electron in each 3d orbital, [14].

However, MnO_4^- has d^3s hybridization [15]. thus, permanganate ions are tetrahedral.

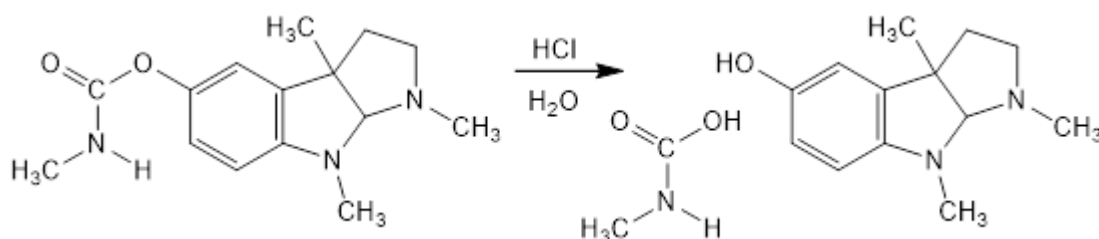
In neutral solution, as in Beckurt's test for alkaloids, potassium permanganate is reduced to manganese dioxide plus three active oxygen atoms [16], according to the following equations: $2 HMnO_4 \rightarrow H_2O + Mn_2O_7$



Now let's see the final product in this test. The electronic configuration of MnO_2 is $[Ar]4^03d^3$, that is, it has 3 unpaired electrons, each in a d orbital and thus it is paramagnetic, [17].

4. Discussion

At first glance, there is no an adequate site for oxidation in physostigmine hydrochloride. However, hydrolysis of this primary carbamate can happen by means of catalytic amount of HCl from the hydrochloride. Being the carbamate an ester and an amide of meta-carbonic acid, hydrolysis occurs first at the carbonic ester. For the mechanism of acid hydrolysis of esters see ref. [18]. The reaction products are unstable carbamic acid that yields methylamine and carbon dioxide, and the phenolic derivative of physostigmine hydrochloride, Figure 2. This product has an electron donor group, the phenol, and a positive charged nitrogen atom at para-position. This particularity invokes reaction, but that nitrogen atom, although positive, has a complete octet of electrons. Nonetheless, reaction can proceed if there is hydride elimination, or better, a hydride transfer to a reducible ion like permanganate. This sequence is a novel reaction. There is a communication of hydride transfer to MnO_4^- , but in a very different reaction process, [19, 20].



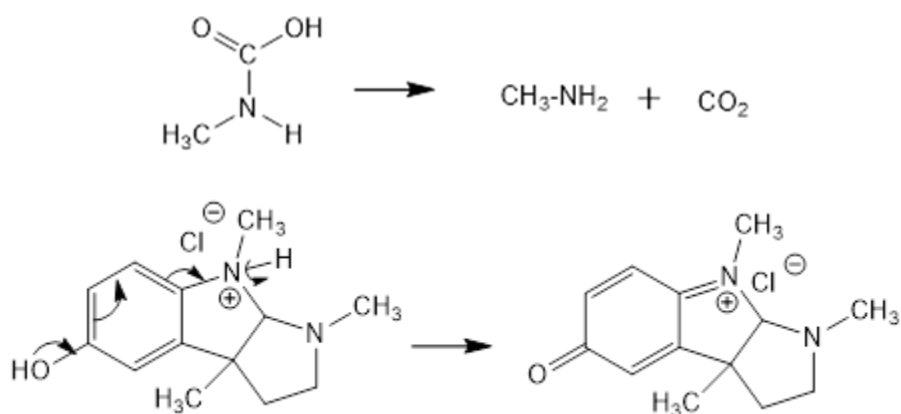


Figure 2 Organic part of Beckurt's test for physostigmine

The inorganic mechanism, not previously advanced, goes as follows: the hydride ion adds to a Mn=O double bond, followed by proton transfer to the oxygen atom, Figure 3. The unstable negative charged Mn atom is neutralized by hydroxyl elimination and formation of a Mn (V) anion.

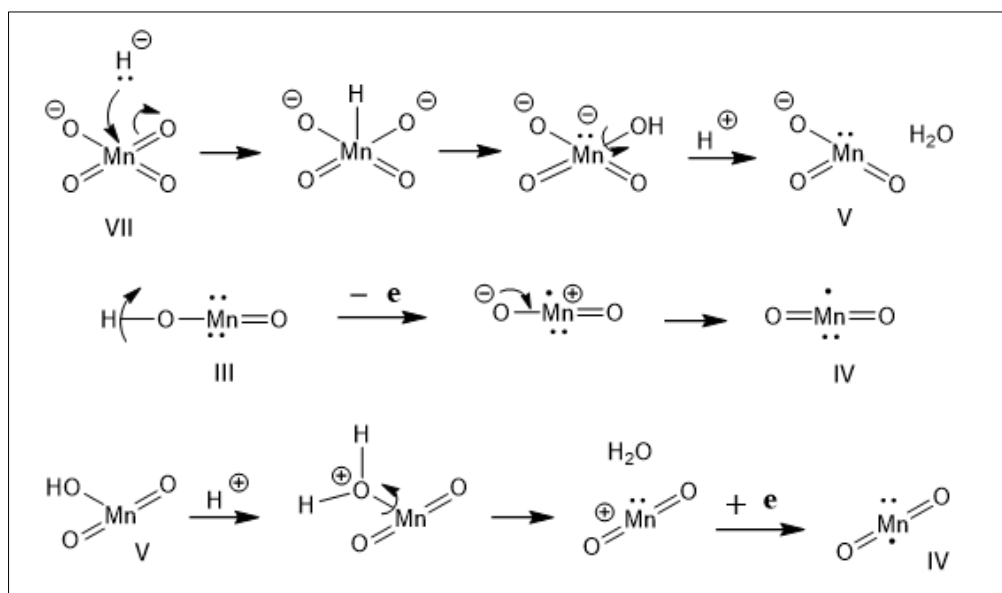


Figure 3 Inorganic part of Beckurt's test

In a similar manner, manganese (V) can be reduced to Mn (III). These two ions in its neutral forms, as HO-MnO₂ and HO-Mn=O, disproportionate to Mn (IV), affording 2 MnO₂ and water. The mechanism is as follows: the HMnO₂ intermediate protonates the HO-MnO₂ molecule; yielding water and ⁺MnO₂, which is neutralized by electron transfer from [•]O-Mn=O (first MnO₂ molecule is formed). Internal neutralization of the resulting dipolar free radical in the remaining intermediate gives a second MnO₂ molecule.

As it can be seen, the MnO₂ molecules show three electrons in accordance with MnO₂ electron configuration: [Ar]4⁰3d³.

5. Conclusion

The oxidation of physostigmine hydrochloride by means of potassium permanganate doesn't takes place directly. However, the phenolic derivative obtained after acid hydrolysis of this N-methyl-O-phenyl carbamate, is an idoneous intermediate for a push-pull mechanism since the electron donor phenoxy group is in para-position to a positive charged nitrogen atom. Nonetheless, this quaternary nitrogen atom has a complete octet of electrons. Thus, for reaction to happen there must be a hydride elimination. This can take place via reduction of permanganate by hydride ion. This

novel reaction explains the formation of manganese dioxide, although this occurs after several inorganic steps including combination and disproportionation via electron transfer.

Therefore, the chemistry of the Beckurt's test has been explained.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict of interest to declare.

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