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On the reaction mechanism of strychnine oxidation

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Abstract
In the colour reactions for strychnine identification several oxidizing reagents are employed. These tests give the same succession of colours, violet-blue, purple, and then red. On standing it changes to orange. This result points out a same course of reaction and that the colours come from the tested substance, not from the employed reagents, as has been proposed recently for some tests. We looked for Organic Chemistry information about strychnine oxidation. Apart from the structure of the complex oxidation product, there is no sequence or reaction mechanism advanced. So, we provided the electron, flow, step by step, from strychnine to the oxidation product described. We employed chromic acid and reached the same final product obtained when potassium permanganate was used. This result confirmed that a unique reaction course takes place during these oxidations.

Keywords: chromium (IV), halochromism, oxidation of olefins, reaction mechanisms, reactive intermediates, strychnine colour tests

1. Introduction

Strychnine is a complex alkaloid; it has seven fused rings, with five, six, or seven members. Its structure determination required continued efforts, as well as its synthesis. A striking property of strychnine is it reaction, in concentrated sulphuric acid, with a series of oxidants: it gives the same sequence of colours independently of the reagent employed. This peculiar chemical deportment prompted us to revise the particular colour tests used.

Since there is no reaction mechanism with any of the reagents, we chose chromic acid, derived from the dichromate anion and sulphuric acid, and provided the electron flow, step by step, from the alkaloid to the oxidation compound obtained using potassium permanganate, and whose structure was cleared decades after the analytical work. This result proved a single oxidation course.

This communication is a follow up of our studies on reaction mechanisms [1, 2, 3, 4, 5].

2. Antecedents

There is a beautiful succession of colours produced when some oxidizers are brought in contact with strychnine, in the presence of sulphuric acid. The substances usually employed are the peroxides of lead and manganese, dichromate of potassium, ferricyanide of potassium (red prussiate), and permanganate of potassium.

When a small fragment of strychnine is placed upon a white porcelain plate, and a drop of strong sulphuric acid is added, and then a small portion of any of the oxidizing substances is stirred with it, a beautiful violet-blue colour will be given, which very soon changes to a mulberry-purple, and ultimately to a light red tint. This play of colours is quite peculiar to strychnine, [6].

Of these cognate tests, Otto used potassium dichromate, [7, 8]. The test for strychnine using manganese dioxide is known as Allen's test [9, 10]. However, Allen in a note in the *Analyst* states: my method of procedure has no claim to novelty. There is considerable choice in the oxidizing agent employed, [11]. He only preferred the use of manganese dioxide, despite the black colour of the reagent that may obscure the violet colour. This test had been mentioned sixteen years before, [6].

The use of potassium permanganate and sulphuric acid is the Wenzell test, [12].

Other test for strychnine is due to Mandelin. He used as reagent a solution of sodium vanadate in sulphuric acid, [13].

The colour changes in the chromic acid test and with the vanadium reagent have been considered recently as due to changes in the oxidation states of chromium and vanadium, [14]. This is a misconception since the colour changes are the same when reagents with other elements are used, such as lead, manganese and iron. These have very different oxidation states, and ions of different colours are produced.

Other example that gives the colours proper of strychnine is the Sonnenschein test, [15]. He used the oxide Ce_3O_4. This has been named ceroceric oxide, [16]. That is ($2CeO.CeO_2$), similar to Pb_3O_4.

The observed colours in the tests for strychnine are due to halochromism, proper of a substance in strong acidic medium, [17]. The colour changes come from different cations formed as the oxidation reaction proceeds.

The sulphuric acid-dichromate test is described in *Modern Methods of Plant Analysis* [18]; the colors differ slightly from those above mentioned**:** deep blue-violet, which changes through purple and crimson to cherry-red. The statement that on long standing the colour changes to orange or yellow, is interesting.

In a book on *Drug Identification* [19], strychnine is recognized by means of the potassium dichromate test.

The same play of colours obtained in the oxidation tests for strychnine that were studied, pointed to the same oxidation course in the organic compound. Thus, we looked for Organic Chemistry information on strychnine oxidation and see if a reaction mechanism had been advanced or not. This point will be treated in the next section.

3. Discussion

The strychnine molecule has the following groups: a lactam, a cyclic ether, a double bond, and a tertiary amine, Figure 1.

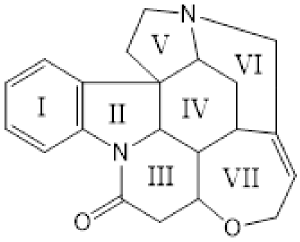

Fig 1: The strychnine structure.

In oxidation conditions, the double bond is expected to be the favourable reaction site, that is, the beginning of reaction.

The oxidation product isolated from potassium permanganate oxidation exhibits a carbonyl group vicinal to the tertiary nitrogen, that is, a new lactam group. There are also a ketone and a carboxylic acid. An uptake of four oxygen atoms and loss of two hydrogen atoms has occurred, [20].

We tried a reaction mechanism using chromic acid, derived from potassium dichromate and sulphuric acid, because the Otto test ($K_2Cr_2O_7/H_2SO_4$) and the Wenzell test ($KMnO_4/H_2SO_4$) gave the same results. So, if the same oxidation product were obtained this would confirm the expectations derived from the results observed in all the cognate spot tests for strychnine identification.

The reactive species from chromic acid is the $HO\text{-}Cr{+}O_2$ cation, [21]. Thus, an electrophilic attack at the double bond gave a transient carbonium ion that was neutralized by proton elimination from the allylic position, Figure 2, formulas a, b.

This gave rise to a reactive intermediate due to the electron acceptance properties of chromium and the electron donor effect of the resulting enamine. The organo-metallic compound is broken, chromium (VI) is reduced to chromium (IV), chromous acid, and two double bonds are formed in the organic molecule, c.

Neutralization of the iminium ion by water yields a carbinolamine which on oxidation forms a new lactam, d. Other allylic oxidations have been reported, [22]. In the case of indene oxidation [23], the absence of a nitrogen atom in the allylic position prevents allylic oxidation.

Addition of a chromic acid molecule to the α,β-unsaturated system affords a mixed chromate ester, which is broken down to a chromium(IV) intermediate, with concomitant epoxide formation, e, f. This kind of intermediates has been postulated in some double bond oxidations with chromic acid, [24].

Ring opening of the oxirane gives an alcohol and a carbocation which promotes addition of a chromic acid molecule, g. A push-pull mechanism generates rupture of the chromic ester and formation of ketone in the alpha position to the lactam, as well as a vicinal aldehyde, h, i. This group is oxidized to carboxylic acid, j, [25].

This sequence of reactions led to the same product obtained with $KMnO_4$. This result confirmed the conclusion that can be draw from the cognate spot tests: a single oxidation course takes place since the visual results are similar. Some slight variations can be expected due to the different colour of each reagent used.

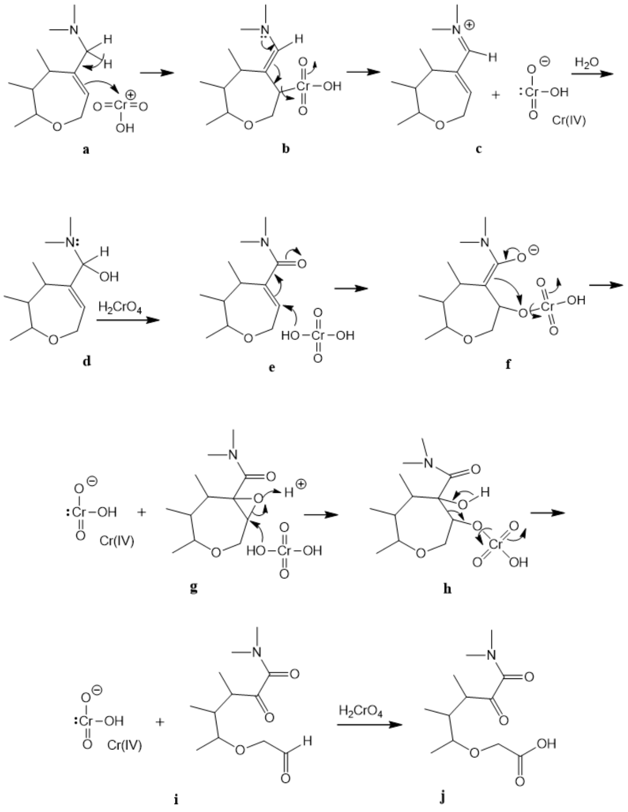

Fig 2: Reaction mechanism of strychnine oxidation.

4. Conclusions

The process of strychnine oxidation by means of chromic acid has been explained. The electron flow, step by step, has been provided. This sequence comprises the following reactions: electrophilic attack at double bond, proton elimination, several oxido-reductions, addition to an α, β-conjugated system, epoxide formation, ring opening, ketone and aldehyde formation and oxidation to carboxylic acid.

This oxidation process consumed five chromic acid molecules**:** the final oxidation product gained four oxygen atoms and lost two hydrogens, and this compound coincides with the product obtained by potassium permanganate oxidation.

Since the various spot tests used for strychnine identification employ an oxidant and sulphuric acid, and the same sequence of colours is obtained, we consider that the same oxidation product is obtained.

5. Acknowledgements

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