World Journal of Organic Chemistry, 2020, Vol. 8, No. 1, 1-4
Available online at http://pubs.sciepub.com/wjoc/8/1/1
Published by Science and Education Publishing
DOI:10.12691/wjoc-8-1-1

Formation Mechanism of the Colored Compounds Derived from Eserine (Physostigmine)

Francisco Sánchez-Viesca*, Reina Gómez

Organic Chemistry Department, Faculty of Chemistry, National Autonomous University of Mexico, Mexico City (CDMX), Mexico
*Corresponding author: franviesca@yahoo.com

Received November 15, 2019; Revised December 21, 2019; Accepted January 07, 2020

Abstract Physostigmine (eserine) is an indole alkaloid isolated from a plant of Western Africa. It is interesting due its striking properties: a potent venom and a drug for open-angle glaucoma treatment. It gives two color reactions, a dark red due to rubreserine, a three ring o-quinone, and a seven ring phenoxazone with a splendid blue color. Though the structures of these compounds have been determined, there is no reaction mechanism related to their formation. We provide the reaction pathway and the electron flow for each reaction. Especially interesting is the case of eserine blue, to know how the molecule is integrated through many reaction intermediates and electron shifts.

Keywords: *Calabar bean, eserine blue, indole alkaloid, physostigmine, reaction intermediates, reaction mechanisms*

Cite This Article: Francisco Sánchez-Viesca, and Reina Gómez, "Formation Mechanism of the Colored Compounds Derived from Eserine (Physostigmine)." *World Journal of Organic Chemistry*, vol. 8, no. 1 (2020): 1-4. doi: 10.12691/wjoc-8-1-1.

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' from 'eseré', the local name of the black Calabar bean. The alkaloid has been known by both names.

Eserine is a three ring indole alkaloid, having an additional pirrolidine ring. It is a very reactive compound that gives red color with sodium hydroxide. In preparative scale, dark red crystals of rubreserine are obtained.

Eserine reacts with ammonium hydroxide, giving an intense blue color after heating. The product (eserine blue) is a seven ring compound, and has an oxazone.

Though the structures of the colored products have been determined, there are no advanced mechanisms for the formation mode of these compounds. We provide them in this communication as a follow-up of our studies on reaction mechanisms [1-5].

2. Antecedents

A brief account is given, from the early references to the structure determination of the colored compounds derived from the red and the blue eserine-tests. This will suffice to understand and sustain the reaction mechanisms advanced in the next section.

Jobst and Hesse, in Stuttgart, isolated from a handful of Calabar beans a crude alkaloid in the form of a brownish-yellow amorphous mass and named it physostigmine. However, an aqueous solution of this mixture produced strong and persistent contraction of the eye pupil, [6,7].

This myotic or myositic effect had been reported in Edinburg journals some years earlier, [8,9].

A year later was announced in France the obtention, from the same plant, of the alkaloid in crystalline form. Veé and Leven obtained it as thin rhomboid plates that on heating melt and evolve abundant white fumes. They named the alkaloid 'eserine', after the local name 'eseré' in West Africa. The isolation method is described and they also made physiological tests that are in accord with the previous ones, [10,11].

Petit and Polonovsky [12] obtained big crystals of eserine by slow evaporation of a benzene solution, prisms melting at 105-106°.

They remarked that alkaline solutions of the alkaloid are oxidized rapidly on air contact, giving a dark red coloration.

Other unstable crystal form melts at 86-87°, [13].

The eserine structure, Figure 1, was established simultaneously in France [14,15] and in Edinburg [16,17].

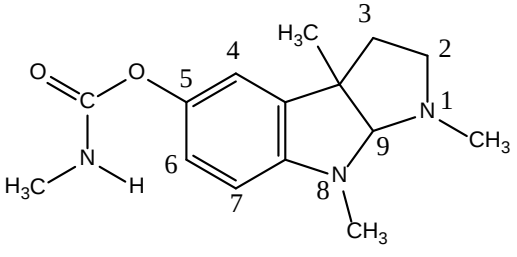

Figure 1. Eserine molecule

The compound is the methyl carbamate of a phenol in a system of three fused rings. This indole alkaloid has an additional pirrolidine ring. The numeration and substituents are indicated.

The crystal and molecular structure of eserine was determined by Pauling and Petcher in an X-ray diffraction study [18].

The structure of the red product above mentioned, rubreserine, Figure 2, was proposed by Ellis on well grounds, [19]. A sample of crystalline rubreserine which, when dried over solid potassium hydroxide, melted at 144-145°.

The o-quinone structure was confirmed by reaction with o-phenylenediamine which afforded the phenazine [20].

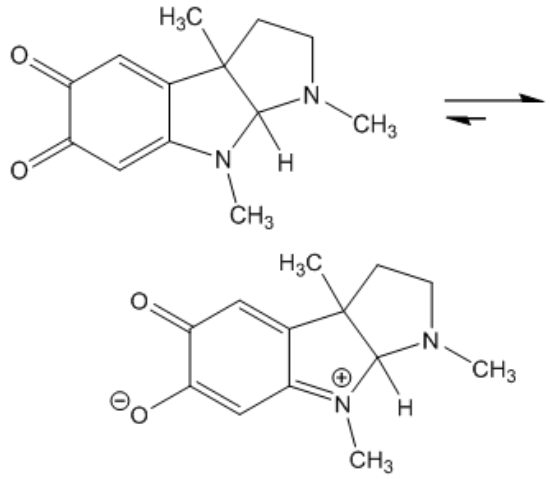

Figure 2. Rubreserine, canonical and dipolar structures

Now let us turn our attention to the eserine blue-test.

Petit found [21] that when eserine salts are treated with excess of ammonium hydroxide, and the liquid heated on the water bath, it turns in succession pale red, yellowish red, yellow, green, and finally blue. If the liquid be evaporated to dryness, a blue residue is left, eserine blue. This is soluble in alcohol and crystallizes in long prisms, capable of dyeing silk without a mordant, and staining the skin, etc.

Eserine blue, Figure 3, was prepared from rubreserine in ethanol with introduction of NH_3 gas, and its structure determined [20,22].

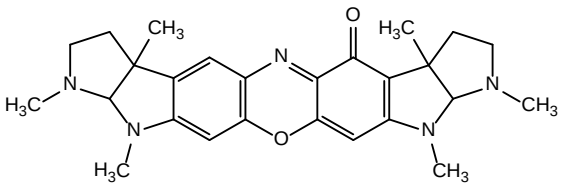

Figure 3. Seven ring structure of eserine blue showing an oxazone group

3. Discussion

The first reaction of eserine with sodium hydroxide solution is hydrolysis of the methyl carbamate. The degradation product, by loss of the unstable N-methyl-carbamic acid, is eseroline or physostigmol, Figure 4.

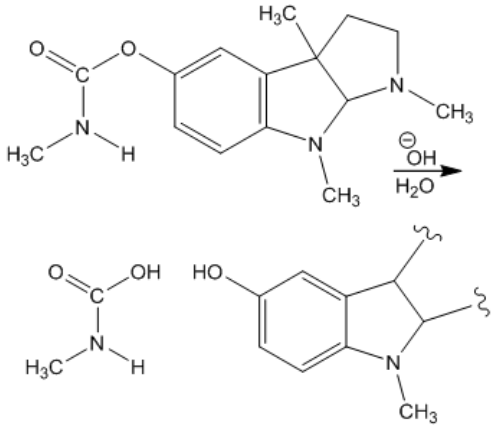

Figure 4. N-Methylcarbamic acid and eseroline

The phenolic reactive-intermediate is prone to base catalyzed air oxidation. Since the p-position is not free, the phenolate forms a carbanion in an ortho-position.

But there are two non-equivalent o-positions. However, a carbanion vicinal to the pirroline ring is not favored due to the inductive effect from the ring. In p-dimethylamino-phenol both o-positions are equivalent, but in 5-hydroxy-indoline the inductive effect of the ethylene group hinders carbanion formation at C-4. Eserine is an analogous case.

Steric hindrance must also be taken into account.

Thus, the preferred carbanion reacts with aerial oxygen giving a peroxianion that is neutralized by reaction with water, Figure 5.

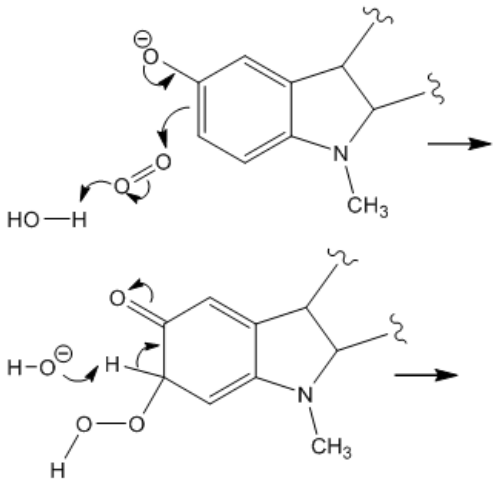

Figure 5. Reactive intermediate ketone

The obtained ketone, a carbon acid, is ionized and forms again a phenolate. Finally, this intermediate originates an o-quinone by elimination of a hydroxyl ion from the hydroperoxide via a concerted mechanism. This way the dark red compound rubreserine results, Figure 6.

Now let's see eserine blue formation. As said before, it can be prepared from rubreserine, [20].

Nucleophilic addition of ammonia to a carbonyl of the o-quinone leads to the carbinolamine and then to the imine by a water loss. The imine reacts with other rubreserine molecule, giving a key intermediate, a dipolar ion.

Immediate neutralization implies a slow four member reaction. Proton exchange in an alkaline medium is faster than neutralization of the alkoxide. Thus, a more rapid internal reaction occurs, Figure 7.

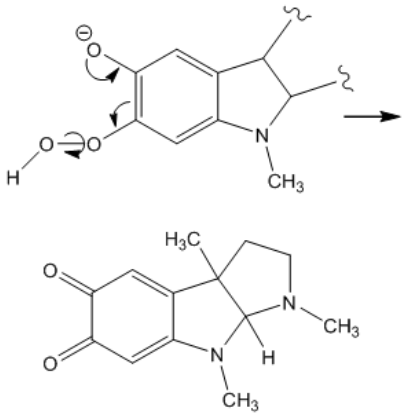

Figure 6. Last step in rubreserine formation

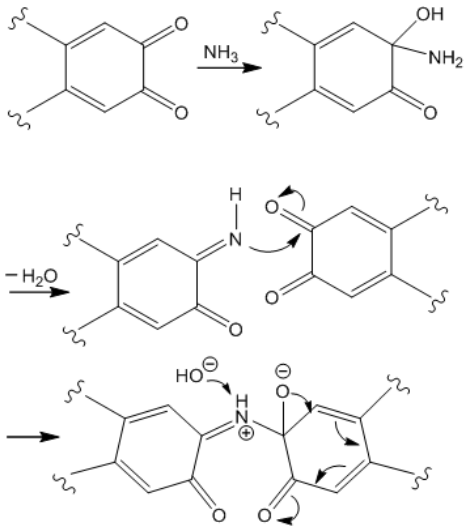

Figure 7. First concerted reaction mechanism

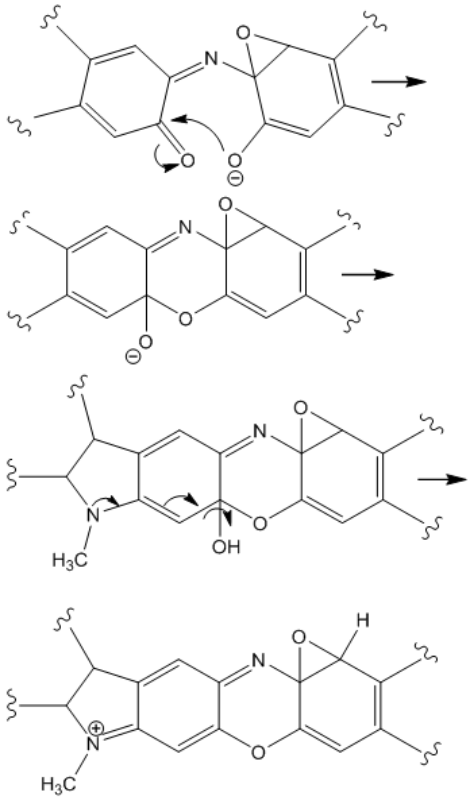

Figure 8. Indamine structure

The alkoxide reacts with the δ^+ carbon of a double-conjugated ketone. This push-pull concerted mechanism gives an epoxide and originates the intermediate that forms a new ring and a hemiketal.

Then the vicinal enamine favors elimination of the allylic hydroxyl group and a quinone-di-imine structure results. Figure 8.

In the other ring, there is an acidic hydrogen since its elimination by ionization causes epoxide opening and aromatization of the nucleous.

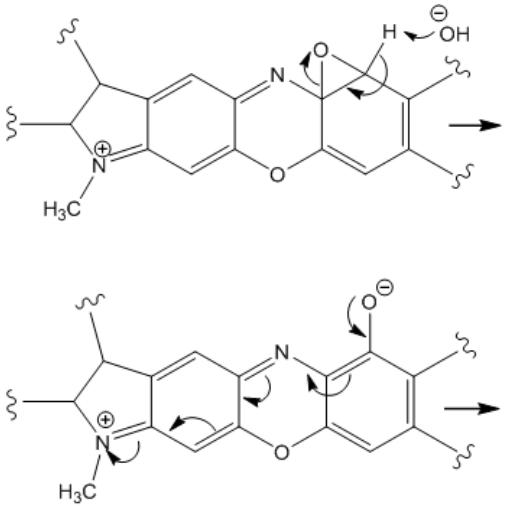

Figure 9. Dipolar intermediate with cross conjugation, and concerted mechanism

The last step of this long route is another push-pull concerted mechanism in a dipole intermediate. That is, an electron flow from an enolate to an ammonium ion, through four conjugated double bonds. The target molecule, eserine blue, a seven ring compound with an oxazone, has been formed, Figure 10.

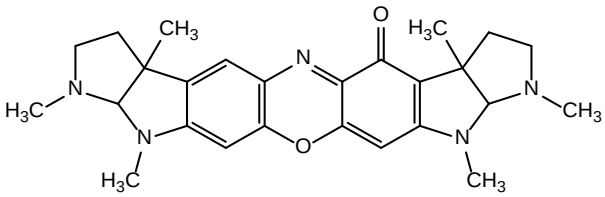

Figure 10. Final product, the eserine blue molecule

4. Conclusions

This study was undertaken in order to clear-up the formation mode of the red and the blue compounds formed in the tests for eserine. This three ring indole alkaloid is found in the Calabar bean (*semen physostigmatis*). It is venomous but can be used for glaucoma treatment due to its miotic properties.

So we browsed and commented the references on the theme, from the early communications to the structure determination of the red and the blue compound formed in the eserine color tests.

We have provided the missing reaction mechanisms regarding the formation of these color products. Especially interesting is the intricate formation route for eserine blue.

References

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

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

[3] Sánchez-Viesca, F., Berros, M. and Gómez, R., "A complete and sustained Clemmensen reduction mechanism", Am. J. Chem., 8(1), 8-12, 2018.

[4] Sánchez-Viesca, F. and Gómez, R., "Reactivities involved in the Seliwanoff reaction", Modern Chemistry, 6(1), 1-5, 2018.

[5] Sánchez-Viesca, F., Berros, M. and Gómez, R., "On the mechanism of the Baeyer-Drewsen synthesis of indigo", Am. J. Chem., 6(1), 18-22, 2016.

[6] Jobst, J and Hesse, O, "Preparation of physostigmin", Am. J. Pharm., 36, 334-336, 1864.

[7] Jobst, J. and Hesse, O., "New alkaloid from the Calabar bean", Am. J. Pharm., 36, 365-366, 1864.

[8] Lloyd, J. U., *Physostigma Venenosum (Calabar)*, The Western Druggist, Chicago, USA, 1897, 1-8.

[9] Proudfoot, A., "The early toxicology of physostigmine", Toxicol. Rev., 25(2), 99-138, 2006; references 50-53.

[10] Veé, A. and Leven, M., "De l'alcaloïde de la fève de Calabar et expériences physiologiques avec ce même alcaloïde", Journ. de Pharm. et de Chim.., [4], 1, 70-72, 1865. (Gallica, BnF).

[11] Vee, A. and Leven, M., "On eserine, the alkaloid of the Calabar bean", Chemical News (London), 11, 78, 1865.

[12] Petit, A. and Polonovsky, M., "Étude sur l'ésérine", Bull. Soc. Chim. France, [3], 9, 1008-1015, 1893.

[13] Paech, K. and Tracey, M. V., Eds., *Modern Methods of Plant Analysis*, Springer, Berlin, Germany, 1955, vol. 4, 391-392.

[14] Polonovski, M. and Polonovski, M., "Constitution de l'ésérine et des dérivés oxéséreniques", Bull. Soc. Chim. France, 37, 744-759, 1925.

[15] Karrer, P., *Organic Chemistry*, 3rd. ed., Elsevier, Amsterdam, The Netherlands, 1947, 877-878.

[16] Stedman, E. and Barger, G., "Physostigmine (eserine). Part III", J. Chem. Soc (London), 127, 247-258, 1925.

[17] Morton, H. A., *The Chemistry of Heterocyclic Compounds*, McGraw-Hill, New York, USA, 1946, 116-117.

[18] Pauling, P., and Petcher, T. J., "Crystal and molecular structure of eserine (physostigmine)", J. Chem. Soc., Perkin Trans., (RSC), 2(10), 1342-1345, 1973.

[19] Ellis, S., "Chemical studies on physostigmine breakdown products and related epinephrine derivatives", J. Pharmacol. & Exp. Ther., 79(4), 364-372, 1943.

[20] Autcrhoff, H. and Hamacher, H., "Color reactions of eserine", Arch. Pharm., 300(10), 849-856, 1967; Chem. Abstr., 68, 6207y, 1968.

[21] Petit A., "Sur une nouvelle matière colorante bleue dérivé de l'ésérine", Compt. Rend. Acad. Sci., 62, 569-570, 1871.

[22] Manske, R. H. F. and Holmes, H. L., Eds., *The Alkaloids: Chemistry and Physiology*, Academic Press, New York, USA, 1971, vol. 13, p 221.