American Journal of Chemistry 2022, 12(1): 18-21
DOI: 10.5923/j.chemistry.20221201.03

The Mechanism of the Oxido-degradation of the Cinchona Alkaloids

Francisco Sánchez-Viesca*, Reina Gómez

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

Abstract The cinchona alkaloids, so important for malaria treatment, have been studied from different points of view such as chemical structure, biological properties and synthesis. However the reaction mechanisms involved in several oxidative degradations have not been advanced. In this communication we provide the electron flow that takes place in the reaction series with different oxidizers and substrates. The chemical deportment of both reagent and substrate has been taken into account: the dual function of chromic acid, that is, as nucleophile (chromate anion) and as electrophile (protonated chromium trioxide), as well as the successive reduction of Mn(VII) to Mn(V) and Mn(III), yielding finally Mn(IV) in manganese dioxide; also the reactivity of α-diketones to form a hydrate, a key intermediate for C─C fission to give a couple of carboxylic acids. The oxido-degradation by means of acidic potassium permanganate of the vinyl and carboxymethyl groups, present in quinuclidine and piperidine rings, has been traced to the end.

Keywords Cinchonine, Cinchoninic acid, Cinchotenine, Meroquinene, Piperidine, Quinuclidine

1. Introduction

Malaria is caused by three species of protozoa, *Plasmodium vivax*, tertian parasite, *Plasmodium malaria*, quartan parasite, and *Plasmodium falciparum*, malignant tertian malaria, frequently results in fatalities unless a suitable drug is administered properly.

The natural cinchona alkaloids have antimalaria activity, quinine and cinchonine are found in *Cinchona officinalis*. Cinchonine is more efficient than quinine, it lacks a methoxy group present in quinine. One of the best sources of cinchonine is *Cinchona micrantha* bark.

Although the structures of these compounds and the degradation products are known, the mechanism of the oxidations carried out has not been advanced. In this communication we provide the electron flow in the reaction series that occurs during different oxido-degradation processes.

This paper is a follow up of our studies on reaction mechanism [1-5].

2. Antecedents

The nomenclature of the cinchona alkaloids is based in the ruban structure, Figure 1, from *Rubiaceae* [6], since Cinchona is a genus in that family.

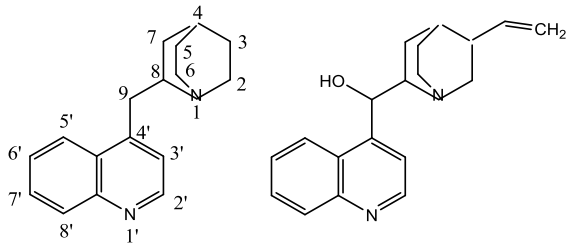

Figure 1. Ruban and cinchonine structures

Cinchonine is 3-vinyl-9-rubanol, and quinine has an additional 6'-methoxyl. The alkaloidal molecule is composed of two portions, the quinoline ring and the quinuclidine nucleous, generally called the second half of the molecule. The two portions are connected by an alcoholic grouping. The presence of this secondary alcohol is essential.

The formula of cupreine is the same as for quinine except for the replacement of a methoxy by a hydroxy group. Hydrocuprein (ethyl for vinyl) has considerable value as an antimalarial [7].

There is a study on the response of *Plasmodium falciparum* to the main cinchona alkaloids [8], and an interesting communication on the therapeutics of the cinchona alkaloids [9].

By moderate oxidation of cinchonine with chromic acid a ketone, cinchoninone is produced [10], 3 vinyl-9-rubanone. Further oxidation with chromic and sulphuric acids [11] gives cinchoninic acid (quinoline-4-carboxylic acid) and meroquinene which is also an acid (3-vinyl-piperidin-4-yl-acetic acid), Figure 2.

* Corresponding author:
franviesca@yahoo.com (Francisco Sánchez-Viesca)
Received: Mar. 1, 2022; Accepted: Mar. 16, 2022; Published: Mar. 24, 2022
Published online at http://journal.sapub.org/chemistry

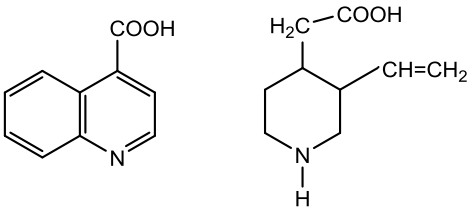

Figure 2. Cinchoninic acid and meroquinene

When meroquinene is oxidized with an ice-cold mixture of sulphuric acid and potassium permanganate it gives formic acid plus cincholoiponic acid [12], the latter being a dicarboxylic acid (3-carboxypiperidin-4-yl-acetic acid).

The formation of formic acid shows the existence of a vinyl group in meroquinene. This was confirmed by the formation of formaldehyde on ozonolysis of meroquinene [13].

Cincholoiponic acid on further oxidation with $KMnO_4$ yields loiponic acid, another dicarboxylic acid [14], piperidin-3,4-dicarboxylic acid, Figure 3.

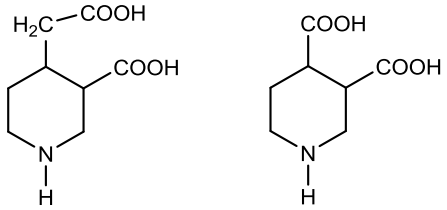

Figure 3. Cincholoiponic acid and loiponic acid

Cinchotenine is produced when cinchonine is treated at ordinary temperatures with dilute permanganate [15]. This oxidation product contains a hydroxyl and a carboxyl group [16], (3-carboxy-9-rubanol).

When cinchonine is warmed with acetic acid and phosphoric acid it is converted into an isomeric compound cinchotoxine containing a ketone with concomitant ring opening of the quinuclidine nucleous, remaining a substituted piperidine ring. That is 3-(3-vinylpiperidin-4-yl)-1-(quinolin-4-yl)propan-1-one, Figure 4. This hydramine fission takes place in compounds carrying a hydroxyl group and an amino group in vicinal carbon atoms [17].

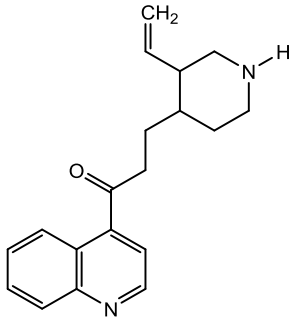

Figure 4. Cinchotoxine (Cinchonicine)

3. Discussion

The oxidative degradation of cinchonine to cinchoninic acid and meroquinene goes through the first oxidation product, cinchoninone. The enolic form of this ketone reacts with protonated chromic trioxide, this electrophile coming from acid catalysed dehydration of chromic acid.

Acid hydrolysis of the organometallic intermediate yields the reduced H_2CrO_3 with Cr(IV) and a reactive carbinol-amine which forms a diketone and a secondary amine via ring fission, Figure 5.

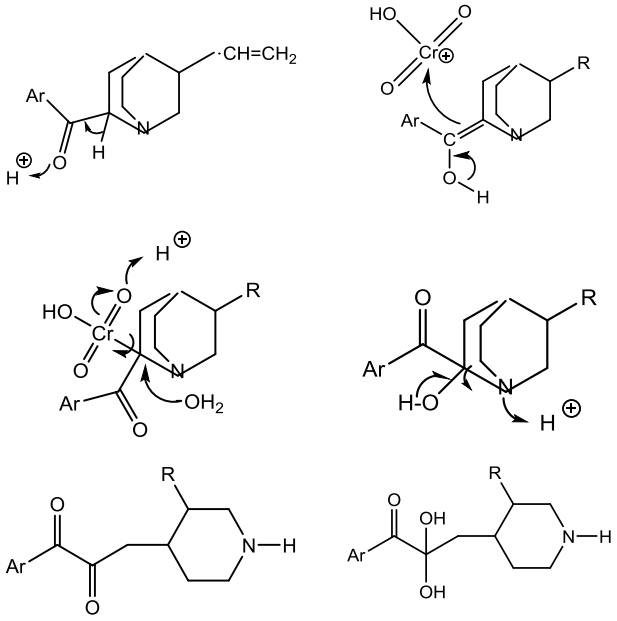

Figure 5. From cinchoninone to the hydrated diketone after quinuclidine ring opening

After hydration of the aliphatic keto group to a geminal diol, a chromate anion adds to the protonated aromatic ketone (nucleophilic addition). Protonation of the chromic ester gives rise to a concerted mechanism, resulting H_2CrO_3 and two carboxylic acids are formed: cinchoninic acid and meroquinene, Figure 6.

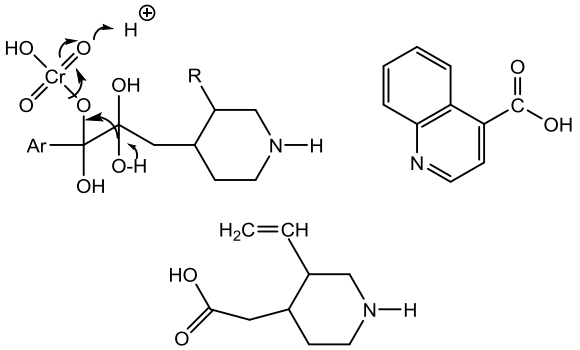

Figure 6. Formation of H_2CrO_3, cichoninic acid and meroquinene

Ice cold oxidation of meroquinene with potassium permanganate and sulphuric acid gives formic acid and 3-carboxypiperidin-4-yl-acetic acid. Permanganic acid forms a cyclic ester with the vinyl group. The double bond disappears and manganese(VII) is reduced to manganese(V).

In absence of alkaline medium for hydrolysis to the diol, there is an oxidative cleavage via a concerted mechanism

with reduction to manganese(III), C─C fission and formation of two aldehydes (oxygen transfer) whose oxidation affords formic acid and cincholoiponic acid, Figure 7. Cf. other cleavages [18].

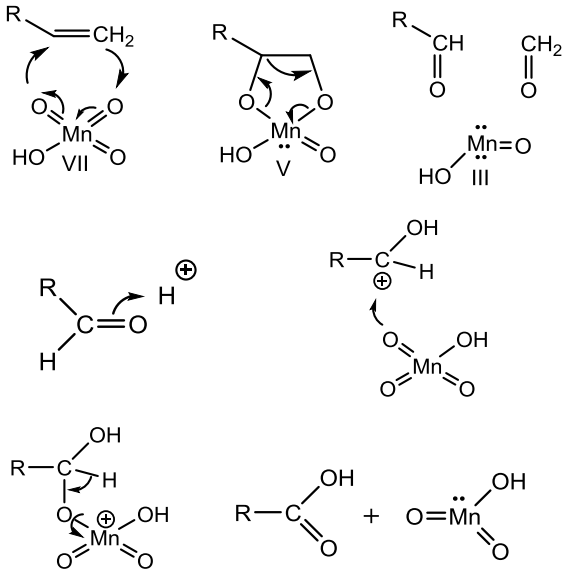

Figure 7. Oxidation of the vinyl group in meroquinene to cincholoiponic acid

Reaction between the intermediates $HMnO_2$ and $HMnO_3$, with Mn(III) and and Mn(V), respectively, gives rise to two molecules of manganese dioxide with Mn(IV), as shown in Figure 8.

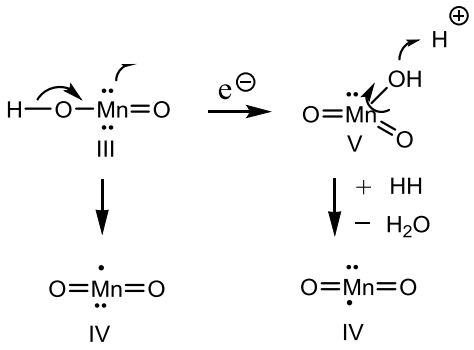

Figure 8. Formation of manganese dioxide from Mn(III) and Mn(V) intermediates

This equalization reaction, inverse to disproportionation [19] explains the formation of MnO_2, as was observed [20], and shows d3 configuration as indicated for MnO_2, [21].

Another permanganate oxidation transforms the $–CH_2$-COOH group into carboxyl via protonated acid. There is reaction of an oxonium ion with permanganic acid, followed by $HMnO_3$ elimination, and formation of carbonic acid and a primary carbonium ion. The latter reacts with water and the alcohol is oxidized to the aldehyde and to carboxyl, Figure 9.

When cinchonine is oxidized with potassium permanganate cinchotenine is obtained, as mentioned in 'Antecedents'.

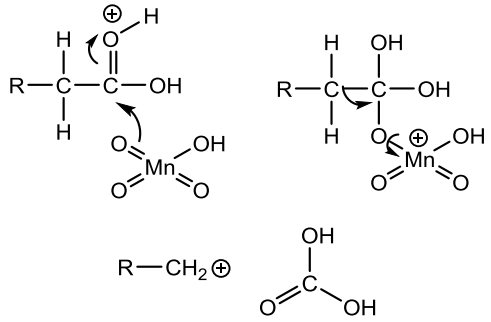

Figure 9. First steps of the degradation of cincholoiponic acid to loiponic acid via elimination of carbonic acid

4. Conclusions

The oxido-degradation of cinchonine by means of chromic acid goes through cinchoninone. An organometallic intermediate is formed via enolization and acid hydrolysis yields an unstable carbinolamine. A vicinal diketone is formed with concomitant ring fission of the quinuclidine moiety The aliphatic ketone is hydrated and the aromatic ketone adds a molecule of chromic acid. Protonation of the chromic ester gives raise a concerted mechanism affording cinchoninic acid and meroquinene.

$KMnO_4/H_2SO_4$ oxidation of meroquinene in two experimental steps forms cincholoiponic and loiponic acids. The first acid is produced by interaction with a vinyl group: a cyclic Mn(V) intermediate is cleaved by reduction to Mn(III) and C─C fission. Two aldehydes are produced whose further oxidation gives cincholoiponic acid and formic acid.

Loiponic acid results by shortening of the carboxymethyl group to carboxyl. Formation of an oxonium ion permits reaction with permanganic acid. There is elimination of $HMnO_3$ and carbonic acid, a primary carbocation remains whose reaction with water and two further oxidations affords a carboxyl.

This way the oxido degradations of cinchonine, representative cinchona alkaloid, have been studied.

ACKNOWLEDGEMENTS

Thanks are given to Martha Berros for support.

REFERENCES

[1] F. Sánchez-Viesca, and R. Gómez, "On the chemistry of Sonnenschein test for strychnine", Am. J. Chem., 11(3), 49-51, 2021.

[2] F. Sánchez-Viesca, and R. Gómez, "On the formation mechanism of indigo blue and indigo red from vegetable source", Modern Chemistry, 9(4), 88-91, 2021.

[3] F. Sánchez-Viesca, and R. Gómez, "The chemistry of van de

Moer test for cytisine", Earthline J. Chem. Sci., 6(1), 15-22, 2021.

[4] F. Sánchez-Viesca, and R. Gómez, "The Crismer's test for glucose in urine", OAR J. Chem. & Pharm., 01(02), 005-008, 2021.

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

[6] Ch. O. Wilson, and O. Gisvold, Textbook of Organic Medicinal and Pharmaceutical Chemistry, 4th. ed., Philadelphia, J. B. Lippincot, 1962; 275-280.

[7] A. A. Morton, The Chemistry of Heterocyclic Compounds, New York, McGraw-Hill, 1946; 291.

[8] A. Knauer, J. Sirichaisinthop, F. F. Reinthaler, and W. H. Wernsdorfer, "In vitro response of Plasmodium falciparum to the main alkaloids of Cinchona in northwestern Thailand", Wiener Klinische Wochenschrift, 115 Suppl. 3(3), 39-44, 2003.

[9] R. N. Chopra, "The therapeutics of the cinchona alkaloids", The Indian Medical Gazette, Nov. 1922, pp. 401-406.

[10] A. F. Holleman, and J. P. Wibaut, Organic Chemistry, New York, Elsevier, 1951; 608-610.

[11] W. Koenigs, "Sur les produits d'oxydation de la cinchonine", Bull. Soc. Chim. Paris, 33(1), 88-89, 1880.

[12] S. Chand, and R. L. Madan, Organic Chemistry, New Delhi, S. Chand & Co., 2008; 1045.

[13] M. R. Saluja, R. Kumar, and A. Agarwal, Advanced Natural Products, Meeruth, Krishna Prakashan Media, 2008; 110.

[14] Th. A. Henry, The Plant Alkaloids, London, J. & A. Churchill, 1913; 149-170.

[15] P. B. Saxena, Chemistry of Alkaloids, New Delhi, Discovery Publishing House, 2007; 46-49.

[16] A. W. Stewart, Recent Advances in Organic Chemistry, 3rd ed., London, Longmans, Green & Co., 1918; 137-142.

[17] A. Chatterjee, S. K. Srimany, B. Chaudhury, "The mechanism of hydramine fission", J. Chem. Soc, London, 1961, 4576-4579.

[18] W. A. Waters, Mechanisms of Oxidation of Organic Compounds, London, Methuen, 1964; 73.

[19] C. T. Rawcliffe, and D. M. Rawson, Principles of Inorganic and Theoretical Chemistry, London, Heinemann, 1960; 120. 121.

[20] Zd. H. Skraup, "Sur les produits d'oxydation de la quinine", Bull. Soc. Chim. Paris, 34, 180-181, 1880.

[21] J. A. Duffy, General Inorganic Chemistry, London, Longmans, 1966; 226.