American Journal of Chemistry 2022, 12(4): 73-75
DOI: 10.5923/j.chemistry.20221204.02

The Mechanism of the Morphine-Apomorphine Rearrangement

Francisco Sánchez-Viesca*, Reina Gómez

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

Abstract Apomorphine is obtained from morphine by cationic rearrangement of morphine and is used in the diagnosis and treatment of Parkinson's disease and also in erectile dysfunction. A reaction mechanism for apomorphine formation was suggested 60 years ago. In this communication a direct and well supported mechanism is given. Acid catalyzed dehydration of the allylic alcohol in the morphine molecule causes double bond migration and formation of an allylic carbonium ion at C-8. This ion is the driving force for a 1,3-migration by C-C breaking of the ethanamine chain of the piperidine ring, eliminating the three dimensional overhanging bridge, forming an almost flat new D-ring. A more stable carbonium ion is formed at C-13 which is neutralized by deprotonation giving a double bond conjugated with the benzene ring. Protonation of the dihydrofuran ring forms an oxonium ion and fission at the side of the cyclohexadiene ring. Neutralization of the carbonium ion by double bond migration and deprotonation affords the second benzene ring in apomorphine. The old mechanism is discarded since it includes a step forbidden by thermodynamics.

Keywords Apomorphine, Electron dynamics, Morphine, Reactive intermediates, Stereochemistry, Thermodynamics

1. Introduction

Apomorphine is synthetic derivative of morphine (από, from) and it is sold as expensive brand medicine, Figure 1.

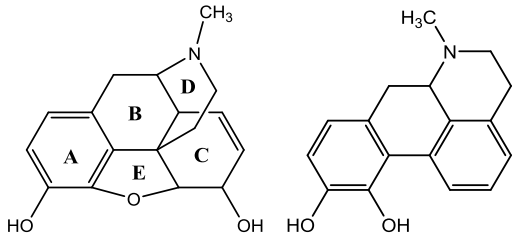

Figure 1. Morphine and apomorphine molecules

Apomorphine is used in the diagnosis and treatment of Parkinson's disease as a dopamine agonist, as well as, in erectile dysfunction (urological), [1].

Shortly after the introduction of levodopa in the therapeutics of Parkinson's disease, it became clear that its chronic use was associated with some adverse effects. Considering that dopamine agonists act directly on the nigrostriatal system and that their half lives are longer, it was hypothesized that using them could prevent these adverse effects [2-4].

In this communication a direct and sustained mechanism for the morphine-apomorphine rearrangement is provided, in lieu of the old one published 60 years ago.

This paper is a follow up of our studies on reaction mechanism [5-9].

2. Antecedents

Arpe dissolved morphine in an excess of sulphuric acid and the acidic liquid was slid off until decomposition begins. The white body separated by water addition contains no morphine. This is the first obtention of apomorphine, [10].

Apomorphine has been prepared by heating morphine with 10 times the weight of 35% HCl for two to three hours at 140° to 150°. The base is precipitated with sodium bicarbonate, extracted with ether, and crystallized as the hydrochloride on addition of concentrated HCl to the ether. [11].

A sensitive test for apomorphine was described by Grimbert and Leclère**:** a solution of apomorphine salt is boiled a few seconds with 5 drops of saturated $HgCl_2$ solution and 5 drops of 10% sodium acetate solution, and extracted with amyl alcohol, the latter is coloured blue; sensitive to 1 part in 500,000. If much apomorphine is present, a blue precipitate is formed, which is soluble in amyl alcohol, [11].

Apomorphine is prepared by heating morphine (1.00 g) in phosphoric acid (5.01 g) in the presence of phosphorus pentoxide (0.48 g) as water scavenger, heating at 90-100℃ under an inert atmosphere. The resulting solution was stirred at that temperature for 2 hours to provide crude apomorphine

* Corresponding author:
franviesca2@gmail.com (Francisco Sánchez-Viesca)
Received: Aug. 26, 2022; Accepted: Sep. 16, 2022; Published: Sep. 24, 2022
Published online at http://journal.sapub.org/chemistry

in 63% yield. Pure apomorphine hydrochloride was obtained after hydrolysis of the phosphate, pH adjusting to liberate the base, extraction and conversion into the hydrochloride, [12].

A Hungarian method uses methansulphonic acid for the microwave assisted rearrangement of morphine to apomorphine, heating at 90℃ during five minutes. Yield, 73%, [13].

A reaction mechanism for this transformation was advanced by Bentley in 1965, Figure 2, [14]. Bryant repeated it in 1987 [15], and appeared in the 2014 edition of Bentley's book [16].

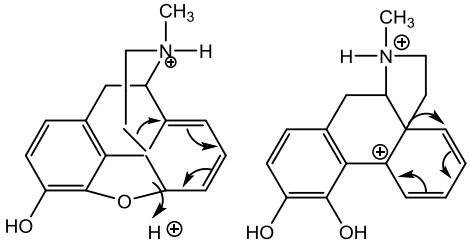

Figure 2. Bentley's sketch for apomorphine formation. Two key intermediates are missing

3. Discussion

In the present Theoretical Organic Chemistry study we provide a direct and sustained mechanism. It is based on the chemical deportment of the functional groups present in morphine, is in accordance with the reaction medium, and is supported by the dynamics of electrons in organic reactions, the stereochemistry and by thermodynamics. The old mechanism is discarded as indicated for wards.

The morphine-apomorphine rearrangement starts by the acid promoted dehydration of the allylic alcohol at C-6, Figure 3. Double bond shift generates an allylic carbonium ion at C-8. This carbocation is the driving force for a 1,3-migration via ring opening of the bridged piperidine ring. This structural reorganization shift removes the three dimension ethanamine chain forming now an almost planar new D-ring, that is, the expected fused ring. There has been steric improvement.

The tertiary, benzylic carbonium ion resulting from the 1,3-migration is thermodynamical favourable since a more stable carbonium ion is formed. This carbocation is neutralized by deprotonation and gives rise to a double bond conjugated with the benzene ring.

In the alkaloid cytisine there is a transformation that also occurs via 1,3-migration, [17]. The new rearrangement makes easier the following reaction steps since in the Bentley's proposal there is contraction to a five member ring followed by ring enlargement to six member ring again. This forth and back process involves two C-C fissions instead of one. Reactions tend to go straight. This was confirmed since Bentley's mechanism involves a thermodynamical forbidden step, that is, the formation of a less stable carbonium ion from a more stable one. So, the carbonium ion at C-8 cannot be formed by this route, Figure 4. Thus the whole mechanism is discarded.

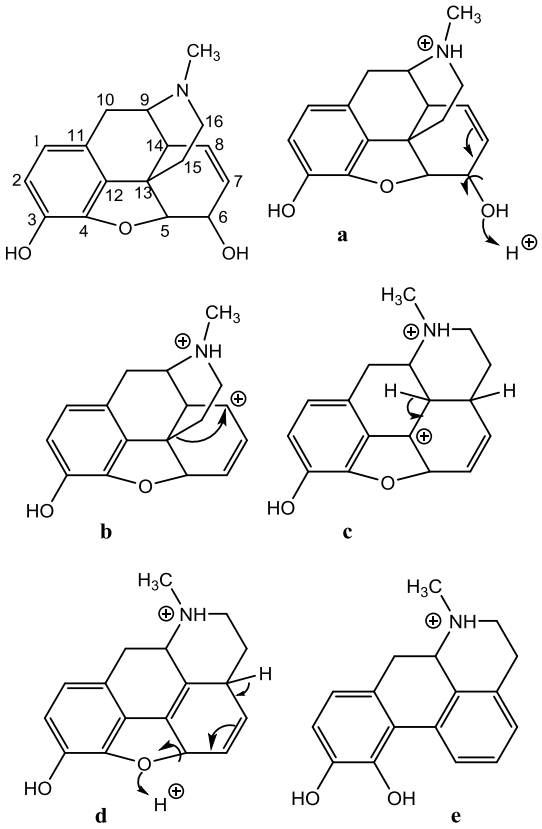

Figure 3. The supported mechanism of the morphine-apomorphine rearrangement

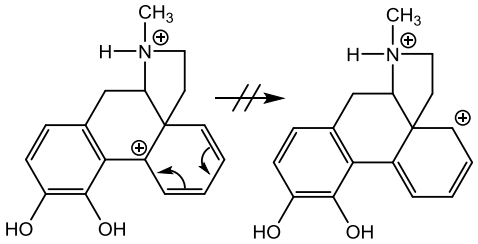

Figure 4. This step is forbidden by thermodynamics

Bentley did not take into account the carbonium ion at C-8 (missing in his sequence) already formed from the beginning, and least its influence for a rapid and convenient 1,3-migration. Moreover, the use of an old representation of the piperidine ring in morphine was not really suitable for the rearrangement.

The second part of the morphine-apomorphine rearrangement is reaction at the 1,2-dihydrofuran ring, Figure 3. Protonation of the oxygen forms a transient tri-coordinated oxonium cation that provokes ring opening at the alicyclic side. An allylic carbonium ion is generated which is neutralized by aromatization. Now rings C and D form a tetrahydro-isoquinoline system.

Thus, a direct and detailed mechanism for apomorphine formation has been advanced. It is in accordance with the dynamics of electrons in organic reactions, with stereochemistry and thermodynamics. The electron flow is

given in each step.

4. Conclusions

A new reaction mechanism for the morphine apomorphine rearrangement is provided. After dehydration of the allylic alcohol in morphine a carbonium ion at C-8 is formed which was overlooked in the old mechanism. This reactive intermediate is very important since C-8 is the position for ring closure of the new ring D, and the carbonium ion is the driving force for a 1,3-migration that eliminates the bulky bridge of the piperidine ring in favour of an almost planar new D-ring. The carbonium ion formed after migration is more stable than the previous one, that is, tertiary, benzylic instead of secondary, allylic. Moreover, it is more distant from the positive charge at nitrogen. The rest of the rearrangement is described in the "Discussion".

In the old mechanism there is a detour involving contraction to a five-member ring followed by expansion again through a step that is forbidden by thermodynamics. Besides, by this way there would be to C-C cleavages instead of one. Thus that route is discarded.

ACKNOWLEDGEMENTS

Tanks are given to Martha Berros for support.

REFERENCES

[1] Apomorphine hydrochloride. PubChem CID 9410. National Library of Medicine. National Center for Biotechnology Information.

[2] I. Estrada, C. Cámara, G. Delgado, and Ch. Cerda. "Contexto histórico de los agonistas dopaminérgicos", Rev. Mex. Neuroci. 19(3), 74-84, 2018.

[3] J. A. Subramany, "Apomorphine in dopaminergic therapy", Mol. Pharm., 3, 380-385, 2006.

[4] F. Carbone, A. Djamshidian, K. Seppi, and W. Poewe, "Apomorphine for Parkinson's disease. Efficacy and safety of current and new formulations", CNS Drugs, 33, 905-918, 2019.

[5] F. Sánchez-Viesca, and R. Gómez, "The mechanism of the oxido-degradation of cinchona alkaloids", Am. J. Chem., 12(1), 18-21, 2022.

[6] F. Sánchez-Viesca, and R. Gómez, "The chemistry of Heller's test for urine indican detection". Magna Scientia Adv. Res.& Rev., 05(01), 025-029, 2022.

[7] F. Sánchez-Viesca, and R. Gómez, "The chemistry of the Wellcome test for morphine", OAR J. Chem. & Pharm., 01(02), 1-4, 2021.

[8] F. Sánchez-Viesca, and R. Gómez, "On the mechanism of the Serullas test for morphine", World J. Org. Chem. 8(1), 7-10, 2020.

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

[10] A. E. Arpe, "Ueber eine merkwürdige Veränderung des Morphins durch Schwefelsäure", Liebigs Ann. der Chem., 55(1), 96-101, 1845.

[11] L. F. Small, and R. E. Lutz, "Chemistry of the Opium Alkaloids", U.S. Treasury Department, Public Health Services, Public Health Reports, Suppl. 103, pp. 261-267, Washington, U.S. Government Printing Office, 1932.

[12] N. Gurusamy, Process for making apomorphine and apocodeine. Patent WO2007126659A1 Publication: 2007-11-08.

[13] Cs. Csutorás. "Acid catalyzed rearrangement of morphinans using microwave heating", Acta Acad. Paed. Agriensis, Sectio Pericemonologica, 34, 105-109. 2007.

[14] K. W. Bentley, The Morphine Alkaloids, in the Isoquinoline Alkaloids, Oxford, Pergamon Press, 1965.

[15] R. J. Bryant, "Medicinal alkaloids from the opium poppy", http://www.brychem.co.uk/docs/opiates.pdf
Accessed, August 24, 2022.

[16] K. W. Bentley, The Isoquinoline Alkaloids, Amsterdam, Elsevier Science, 2014.

[17] F. Sánchez-Viesca, and R. Gómez, "The chemistry of van de Moer test for cytisine", Earthline J. Chem. Sci. 6(1), 15-22, 2021.