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Theoretical study on apomorphine formation

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Abstract

The morphine-apomorphine rearrangement starts by the acid promoted dehydration of the allylic alcohol at C-6, and double bond shift generates an allylic carbonium ion at C-8. This carbocation is the driving force for a 1,3-migration via opening of the bridged piperidine ring. Thus, the definitive D ring is formed. The tertiary, benzylic carbonium ion resulting from the migration is thermodynamically correct since a more stable carbonium ion is formed. Deprotonation gives a double bond conjugated with the benzene ring. Finally, protonation of the oxygen in the 1,2-dihydrofuran ring provokes ring opening at the alicyclic side. An allylic carbonium ion is generated whose neutralization forms the aromatic ring C.

However, there are in Internet other two sequences for apomorphine formation. The Kate tutorials start by breaking a cyclic ether, instead of dehydration of a much more reactive allylic alcohol. So, the route is wrong from the beginning and must be discarded. Besides, the following intermediates carry a very unstable primary carbonium ion. The other proposed sequence is due to Elsinghorst and start by dehydration of the allylic alcohol, but it misses the allylic carbonium ion at C-8, which is the driving force for a 1,3-migration that creates the new ring D. Then is opening of the dihydrofuran ring, a secondary carbonium ion is formed, and a thermodynamically forbidden step is proposed: formation of a primary carbonium ion. Thus, this route cannot be accepted-

Keywords: Allylic alcohol; Dihydrofuran; Driving force; Primary carbonium ion; Thermodynamically forbidden

1. Introduction

Apomorphine is an interesting drug in use for Parkinson's disease, [1-3]. It is prepared from morphine by acid promoted rearrangement, [4-6].

In addition to the medical studies, laboratory methods, and patents concerning the preparation of apomorphine, there is the chemical study in depth of the above-mentioned transformation, how the hydrion promotes structural change, step by step.

The mechanism of the morphine-apomorphine rearrangement was published in 2022, [7]. However, there are two other routes on apomorphine formation that must be critically commented, pointing out the correctness or not of each proposal.

In this paper we provide these studies, they are follow-up of other communications on reaction mechanism, [8-12].

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2. Antecedents

The other two routes on apomorphine formation are Kate Tutorials [13], Figure 1, and Elsinghors, [14], Figure 2. The critical comments about them are in the next section.

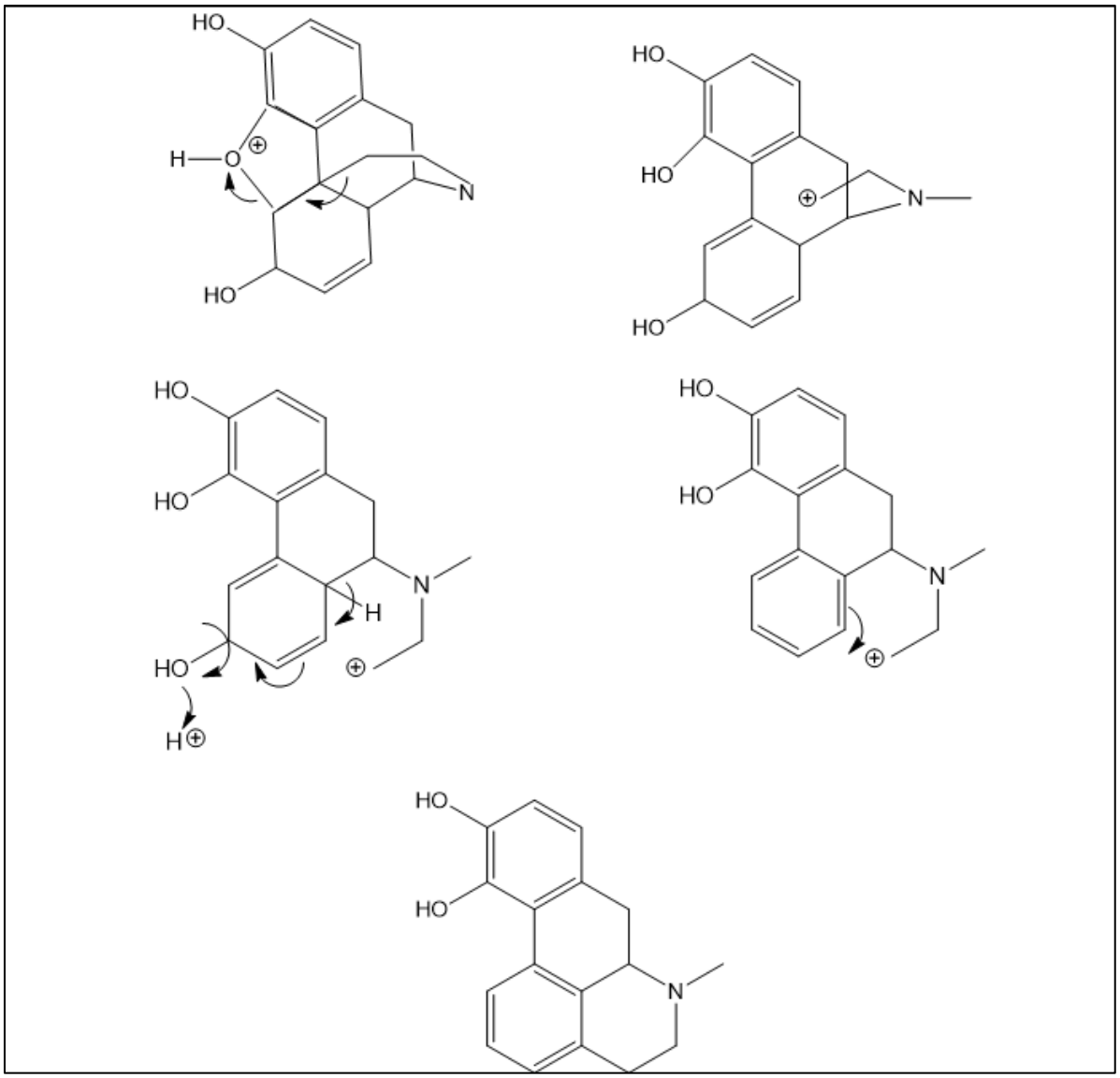

Figure 1 Kate Tutorials proposition for apomorphine formation

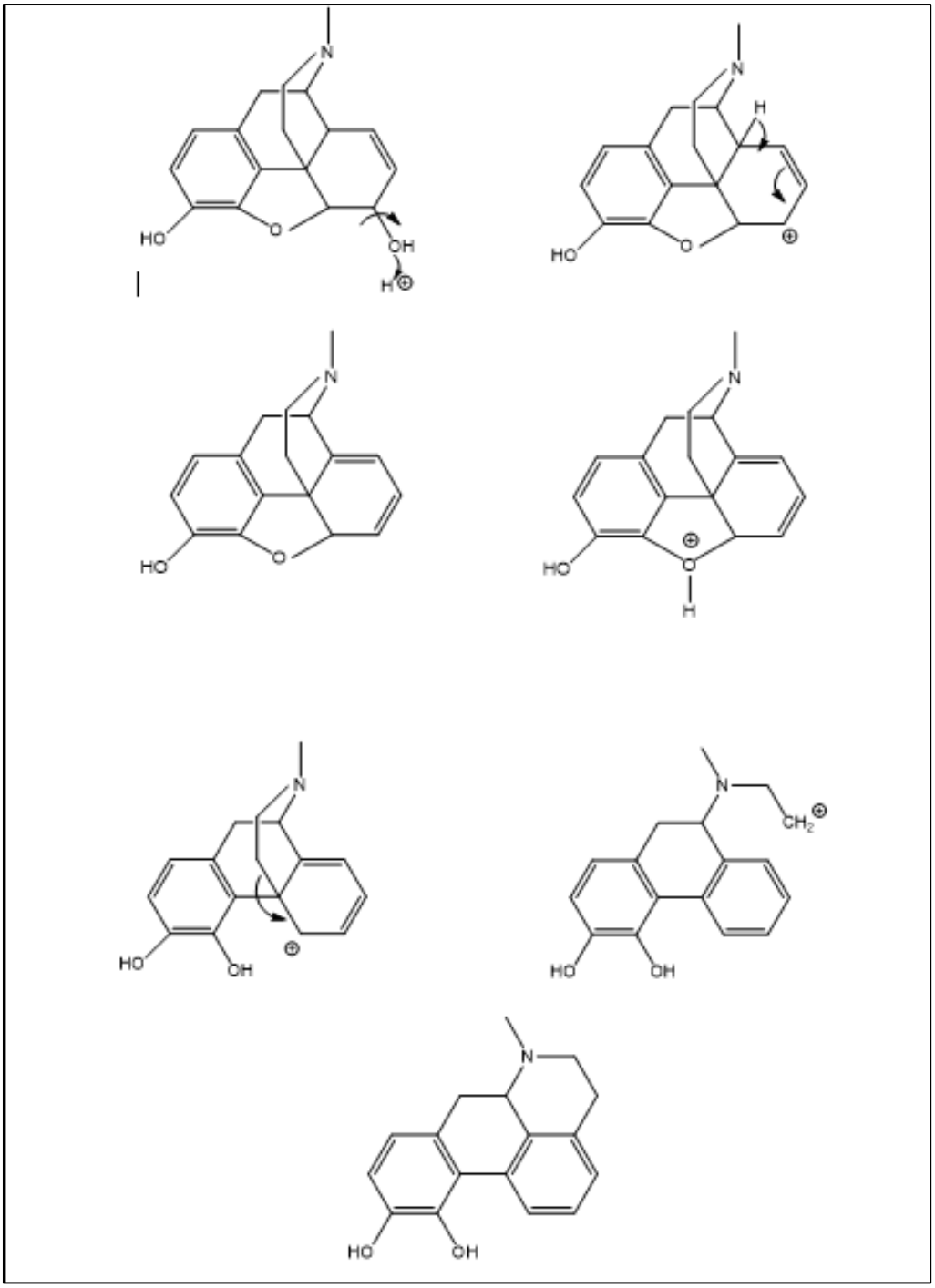

Figure 2 Elsinghorst proposal for apomorphine formation

3. Discussion

The Kate Tutorials on apomorphine formation begins with protonation of the oxygen in the five-member ring. This is totally incorrect because an alcohol is more reactive than the ether in the ring. Besides, the alcohol at C-6 is allylic which is more reactive than a simple alcohol due to stabilization of the carbocation by resonance.

The opening of the piperidine ring is proposed. giving a primary carbonium ion, the most unstable of this kind of ions. Thus, this tutorial must be discarded.

The Elsinghorst route begins with the dehydration of the allylic alcohol and shift of the double bond. However, the carbonium ion at C-8 is not indicated, but this ion is very important because has the stability of being allylic, and besides,

is the driving force in order to form ring D, attracting the electrons of a primary carbanion formed in the opening of the piperidine bridge, that is, a 1,3 migration occurs.

On the contrary, in the Elsinghorst route, ring D is formed in the last steps and involves a thermodynamically forbidden step, that is, formation of a less stable carbonium ion (primary), from a more stable one (secondary). Thus, the entire proposal must be discarded.

These two routes are in Internet but not in a scientific chemical journal.

For the correct and complete reaction mechanism see reference [7].

4. Conclusion

There are in Internet two proposals for apomorphine formation: Kate tutorials, and the other is due to Elsinghorst. Both have been compared to a correct and complete sequence published in 2022 in an American journal of chemistry. The errors found in these proposals have been noted and the routes therefore discarded. This is important because both sequences are being used for tutorial purposes.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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