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The chemistry of Anderson's test for codeine

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Abstract

The Anderson test for codeine entails the interaction of codeine with concentrated nitric acid and heating to dryness. These drastic conditions give rise to a long series of reactions that is provided for the first time. The initial steps are salt formation, codeine nitrate, followed by nitration of the aromatic ring at the activated position, C-2. Then occurs a molecular rearrangement analogue to the transformation of morphine to apomorphine. This implies a series of reactions that include dehydration of the allylic alcohol, double bond migration, 1,3-chain migration, cyclohexadiene formation, ring opening of the dihydro-furane ring followed by formation of a dihydro-phenanthrene structure. The last stage involves methylamine evolution after two C—N fissions and alkalinization of the reaction medium in order to obtain the free amine.

Keywords: Allylic dehydration; Codeine nitrate; 1,3-migration; Molecular rearrangement; 2-Nitrocodeine; Phenanthrene derivatives

1 Introduction

Codeine is a morphinane alkaloid found in the opium poppy, *Papaver somniferum* var. album; it has analgesic, antitussive and antidiarrheal properties.

Codeine is found in concentrations of 1-3% in opium prepared by the latex method from unripe pods. The name codeine is derived from the Greek *kodeia*, poppy head.

Raw opium was used in diverse preparations known as laudanum.

Codeine crystallised from water or hydrous ether is obtained in crystals of considerable size that contain two equivalents of water of crystallization. Codeine is an extremely powerful base, rapidly restoring the blue of reddened litmus.

For cough control codeine is used as oral liquid containing codeine 10 mg and guaifenesin 100 mg/5 ml. It is a combination of a cough suppressant and an expectorant, an ether of guaiacol and glycerol [1, 2], Figure 1.

Codeine linctus (a syrup with the active ingredient: codeine phosphate) used to stop a dry cough, is being used recreationally for its opioid effects rather than for the intended use as cough suppressant, [3].

In this communication the chemistry of Anderson's test, not hitherto been described, is provided step by step with the electron flow.

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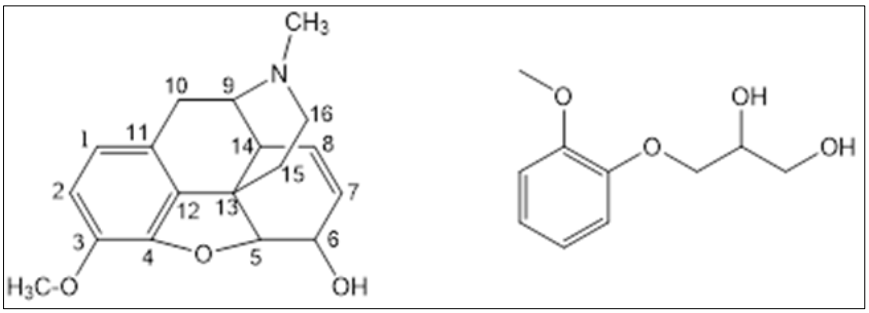

Figure 1 Codeine and guaifenesin structures

This paper is a follow up of our studies on reaction mechanism, [4-8].

2 Study Method and Process

This is an Organic Chemistry Theoretical Study. It is based in the chemical deportment of reagent and substrate. All is in accordance with the reaction medium and the catalyst present. The several steps leading to the final product have been entirely commented and the reaction mechanism is given too.

2.1 Antecedents

Codeine was first isolated from opium by French chemist Pierre Robiquet in 1832, [9, 10]. He used the mother liquor after the extraction of morphine following the procedure of William Gregory in Edinburgh. That liquor left after evaporation a crystalline mass that ground with a diluted solution of KOH and washed with water could be reduced to a powder. After dissolution in boiling water and cooling he obtained a crystalline substance in the form of white, silky clusters. He named it codeine. The nitrate crystallises with great facility.

The chemical structures of morphine and codeine were proposed by J. M. Gulland and R. Robinson in 1925, [11, 12].

The test under study is due to the Scottish chemist Thomas Anderson (1819-1874). In 1852 he was appointed Regius Professor of Chemistry at the University of Glasgow. In 1853 proposed the correct composition of codeine, [13] and the action of nitric acid on this alkaloid. Using nitric of specific gravity 1.06 he obtained nitrocodeine following a careful procedure. It crystallised from alcohol as slender silky needles. From a mixture of alcohol and ether it is obtained as yellowish crystals, four sided prisms under the microscope.

His test for codeine employs concentrated nitric acid heated at the water bath to dryness, and then warming with soda lye; methylamine is evolved, [14].

Codeine is also identified by nitric acid without heating, a light orange colour is produced, fading to greenish-yellow within 1 min.; distinction from morphine which changes from orange to red and finally yellow, [15, 16].

3 Discussion

The interaction of nitric acid with codeine can have several stages, depending on the strength of the acid and the reaction conditions.

Being codeine a strong base, the first reaction is salt formation, codeine nitrate is obtained.

The next step produces nitrocodeine by electrophilic attack at the benzene ring. This reaction must occur at C-2, ortho to the methoxy group, since the para-position is not free.

More strong acid and heating is convenient for a molecular rearrangement similar to the morphine-apomorphine transformation. [17-19].

Acid catalysed dehydration of the allylic alcohol at C-6, followed by double bond migration gives carbocation at C-8. This ion is the driving force for a 1,3-migration that eliminates the superposed chain. This way a tertiary carbonium ion is

derived from a secondary one, and is neutralised by deprotonation. A double bond conjugated with the benzene ring results. Figure 2.

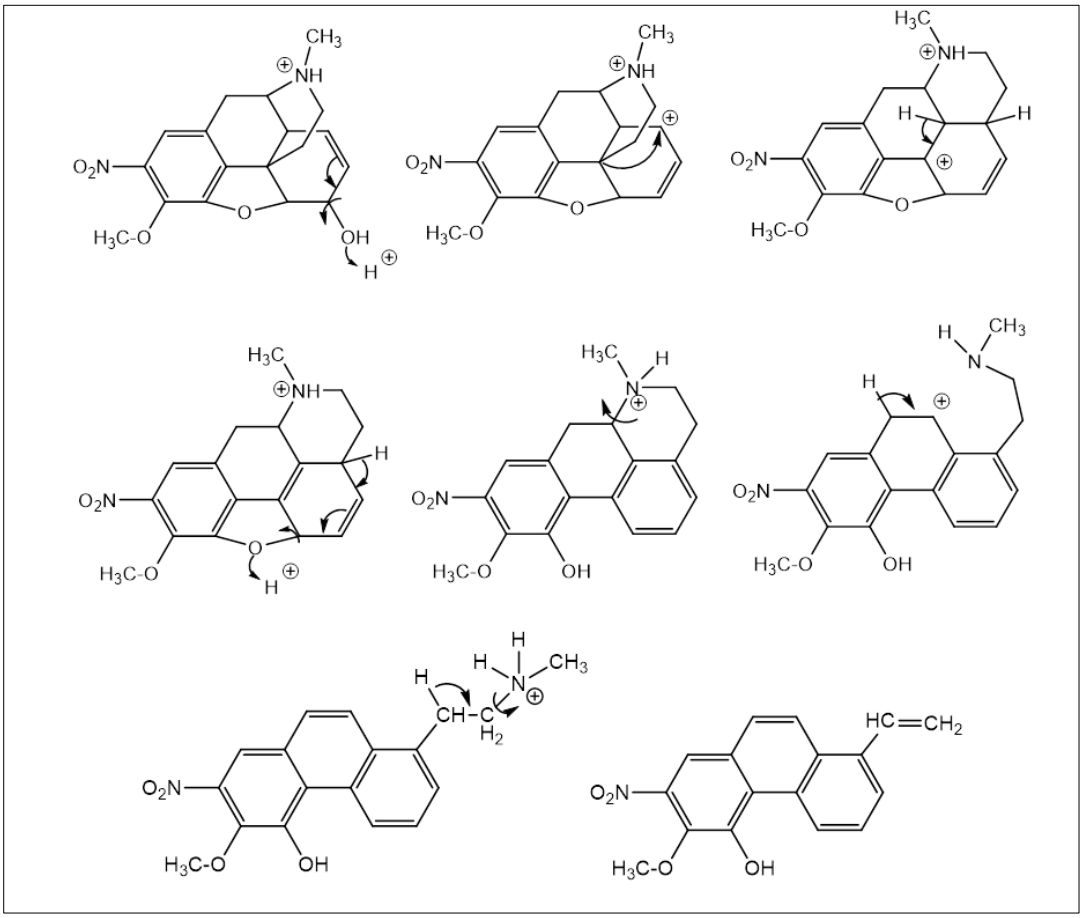

Figure 2 Codeine, salt formation and nitration, followed by molecular rearrangement and elimination of methylamine

The second part of this rearrangement is protonation of the oxygen atom in the dihydrofuran ring. The sp^3 link is broken, and a phenolic group is obtained. The remaining carbocation induces deprotonation giving rise to a new benzene ring, that is, a dihydro phenanthrene with a piperidine ring protonated at the N-methyl group.

The last stage in this sequence of reactions is elimination of methyl amine (Anderson test).

The first C—N fission must occur at the dihydro phenanthrene since neutralisation of the carbonium ion creates a phenanthrene derivative.

Protonation of the methylamino group in the resulting chain produces methyl amine elimination. A concerted mechanism gives an ethylene group conjugated with aromatic ring.

This way the complex series of reactions that takes place during the Anderson test for codeine has been cleared up.

4 Conclusion

The chemistry of the interaction of codeine with concentrated nitric acid under heating conditions and evolution of methylamine (Anderson test for codeine) has been cleared up. There are four principal stages: salt formation (codeine nitrate), aromatic nitration to 2-nitrocodeine nitrate, molecular rearrangement analogue to the conversion of morphine to apomorphine, and finally separation of methyl amine via double C—N breaking. Evolution of methylamine occurs after alkalinization with sodium hydroxide, liberating the amine from the nitrate.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

There is no conflict to declare.

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