Learning Organic Chemistry Through Natural Products

3. From Molecular and Electronic Structures to Reactivity

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N R Krishnaswamy was initiated into the world of natural products by T R Seshadri at University of Delhi and has carried on the glorious traditions of his mentor. He has taught at Bangalore University, Calicut University and Sri Sathya Sai Institute of Higher Learning. Generations of students would vouch for the fact that he has the uncanny ability to present the chemistry of natural products logically and with feeling.

In this part of the series, dynamic organic chemistry and organic reaction mechanisms are illustrated using the comparatively simple alkaloid papaverine.

As mentioned in the introduction to this series, (*Resonance*, Vol.1, No.1, 1996) the structure of a compound is like a milestone on a highway. What is more interesting, as pointed out by one of the giants in organic chemistry, Robert Robinson, is the surrounding countryside. In other words, it is not enough to know what a molecule looks like in a particular 'frozen' posture or profile. We need to find out what the molecule can do or be made to do. The most interesting chemical aspect of a molecule is its reactivity pattern.

A structure is similar to a single photographic exposure of a subject. It is sufficient for identification but does not directly convey the complete character and the potential of the subject for action and reaction. It is true that an experienced and expert character reader may be able to get a great deal of significant

The most interesting chemical aspect of a molecule is its reactivity pattern.

Robert Robinson was one of the all-time greats among organic chemists. This outstanding British chemist was a student of W H Perkin, Jr., who himself was trained by the great German chemist Adolf von Baeyer. Robinson once drew up a 'family tree' in which he traced his organic chemical training to Baeyer and from himself drew it down to some of his outstanding students which included two Indians: T R Seshadri and K Venkataraman. Among the other students of Robinson are Alexander Todd and Arthur Birch, names commonly encountered in organic chemistry text books.

information out of a single picture, but this is subjective. On the other hand, an album of photographs of a single subject taken at different times under different circumstances designed to bring out different moods can give a more comprehensive idea of the subject's character. In terms of molecular structure, what this means is a collection of structural formulae representing different possible conformations. It is also important to include details concerning the electronic structure of the molecule. One of the most efficient ways to accomplish this is by means of canonical (resonance) structures. The latter can be used to identify the electron rich and deficient regions of a molecule. Therefore, the information about electronic structure can be used to derive the nature of reactivity under different conditions.

Dynamic organic chemistry and organic reaction mechanisms can be profusely and effectively illustrated with examples from natural products. In this article, using the comparatively simple alkaloid papaverine as an example, the principles governing a few common organic reactions are highlighted, bringing out at the same time some of the subtle nuances which make them interesting and 'colourful'!

Papaverine (1) is one of the several nitrogenous basic constituents of opium[1] which is the dried latex of the unripe fruits of the plant *Papaver somniferum*. This compound is a (tetramethoxy)-1-benzylisoquinoline derivative. The compound is a mono tertiary base. Therefore, it readily forms a mono hydrochloride with HCl and reacts with a mole of methyl iodide to form a quaternary ammonium compound. For the mono hydrochloride (2), one can write an extreme canonical form (2A) which is a benzylic carbocation. Therefore, it can be attacked by any nucleophile, for example, an electron pair which can be supplied by a metal. Thus, the reduction of papaverine by tin and hydrochloric acid gives a dihydro derivative (3) in which the 1, 2-double bond of the pyridine part of the isoquinoline unit has undergone selective reduction. It is important to understand the principle involved in this selective reduction (as illustrated with structure 2A) and to

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[1] Opium contains a large number of alkaloids derived from the amino acid phenylalanine. The most important among these compounds is the narcotic analgesic morphine named after the Greek god of sleep, Morpheus. Robinson also called it a chemical Proteus, after another Greek god who could change his form, as the compound is susceptible to rearrangement.

compare this reaction with catalytic hydrogenation which, in this case, would not have been selective.

[2] The amino group of an enamine, like that of an amide, is either weakly basic or non-basic due to interaction between the orbital containing the lone pair and the π^* orbital of the neighbouring double bond. This makes the non-bonding electron pair less available for interaction with an extraneous acid. An extreme case is pyrrole in which this type of conjugation results in the generation of aromatic character which signifies molecular stability of a high order.

The resulting dihydro compound, being an enamine[2], then undergoes protonation, not on the nitrogen atom, but at position 4 as shown in *Scheme 1*. This is a consequence of the conjugation between the lone pair of electrons on the nitrogen atom and the double bond, and is similar to what one finds in a compound like pyrrole. The result is the formation of an iminium ion (4) for which one can write a carbocationic canonical form (4A). The latter then undergoes an intramolecular cyclization to yield a tetracyclic compound, known as pavine (5). As can be seen from the structural formulae, for this reaction to occur, the intermedi-
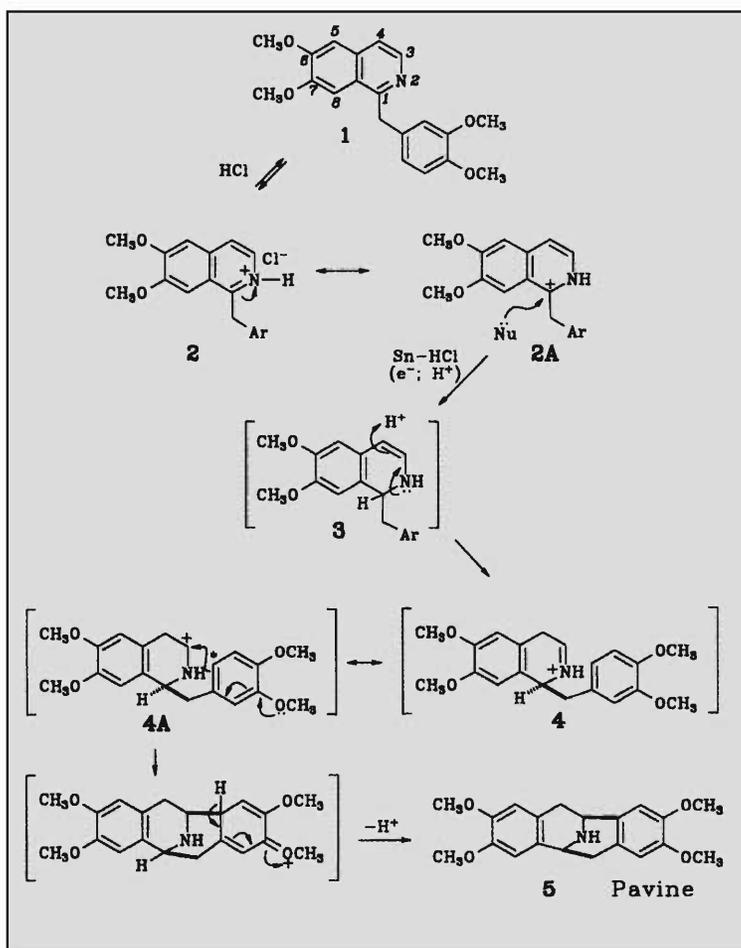
**Scheme 1 Transformation of Papaverine to Pavine.**

ate carbocation should be in the appropriate conformation, in which the side dimethoxyphenyl group can 'see' the reactive centre from a strategic angle and supply the electron pair needed for the formation of the new bond. The non-planar conformation of the partially reduced pyridine ring ensures proximity of the reactive centres which thus come within bonding distance.

The above example of a one pot reaction brings to light more than one fundamental principle which governs the course of organic reactions. The reaction can be classified as an intramolecular Friedel-Crafts alkylation[3] which is an aromatic electrophilic substitution reaction. The benzene ring which undergoes the 'alkylation' is activated by one of the two methoxyl groups which exerts a $+M$ effect. The nitrogen containing ring loses its planarity when it undergoes reduction and this has the effect of raising the benzyl group at position 1 (i.e., the benzyl group can now occupy a pseudo-axial position). The carbon marked with an asterisk in structure 4A can now come close to carbon 3 of the original isoquinoline unit. As in archery, so also in organic reactions, the trajectory of the attacking group is crucial. With the help of framework models, students should understand and appreciate this 'steric' aspect of organic reactions. Two-dimensional projectional formulae are inadequate for this purpose.

While the nitrogen atom is the chief basic centre in papaverine, the oxygen atoms of the four methoxyl groups, with their lone electron pairs, can also serve as Lewis bases. Thus, they can also be protonated with a strong acid. When heated with hydriodic acid, compound 1 undergoes demethylation to yield 6 as the final product (*see Scheme 2*). The methyl iodide generated in this reaction can be estimated after conversion into silver iodide. The Zeisel estimation of methoxyl groups is based on this principle and reaction.

Although the transformation in Scheme 2 is shown as a single reaction, it occurs in a step-wise manner. Interestingly, demethylation of the four methoxyl units does not follow a random

[3] The Friedel-Crafts alkylation reaction is one of the aromatic electrophilic reactions which find wide application in preparative organic chemistry (and industrial chemistry). The reaction is usually catalysed by a Lewis acid and the alkylating agent can be an alcohol, an aldehyde or an alkyl halide. In each case the reagent reacts with the Lewis acid to generate a carbocation which is the effective electrophile.
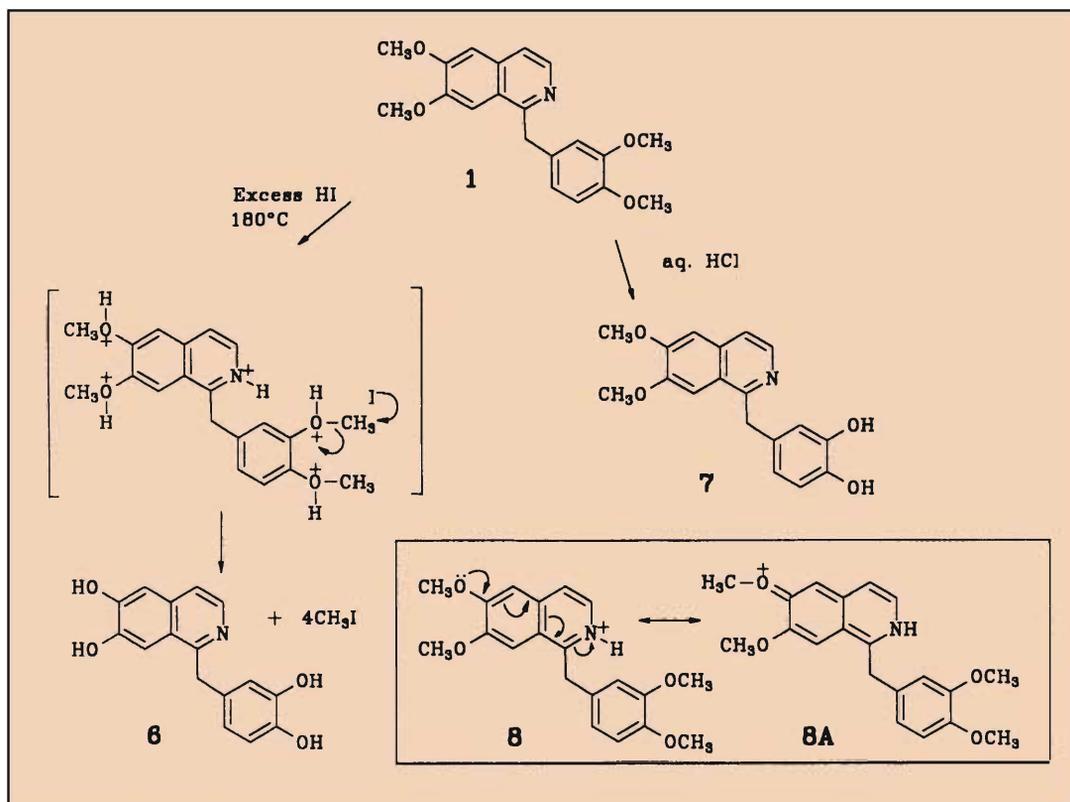
Scheme 2   Demethylation of Papaverine.

sequence. This is because the four groups are not equally basic. In other words, they do not undergo protonation with equal ease. The differences between them are revealed with the help of a weaker acid and under less vigorous conditions. The result is selective demethylation since demethylation is preceded by protonation. For instance, by heating with *aq*. HCl, papaverine can be demethylated to a dihydroxy compound (7) which still retains the two methoxyl groups on the isoquinoline unit. Under slightly more vigorous conditions, the methoxyl group at position 7 also undergoes demethylation. The oxygen atom of the methoxyl group which survives at position 6 is, therefore, the least basic of the four.

The above reactivity pattern can be understood in terms of the electronic structure of the molecule. The +M effect of the methoxyl group comes into play to different extents. The group at position 6 is in direct conjugation, through the intervening π

electrons, with the protonated nitrogen of the pyridine ring (see **8** and **8A** in *Scheme 2*). In contrast, the methoxyl group at position 7 is not in conjugation with the protonated nitrogen, but the electron withdrawing effect of the isoquinolinium unit certainly lowers its basicity compared to the two methoxyl groups on the dimethoxybenzyl unit. These two methoxyl groups are 'insulated' from the protonated nitrogen, and are therefore free to react with an extraneous proton (i.e., they are more basic than the other two methoxyls).

Another example which reveals the subtle differences between differently located methoxyl groups is compound **9**, the trimethyl ether of wedelolactone[4] **10**. Like papaverine, this compound also has four methoxyl groups. But unlike papaverine, it is non-nitrogenous and is not an alkaloid. However, its behavior towards acidic demethylating agents is similar. In this case also selective demethylation under controlled conditions gives a product which retains two of the methoxyl groups to produce **11**. Under more vigorous conditions a third one is lost and the product is wedelolactone as shown in *Scheme 3*.

In this case, the different methoxyl groups are differentiated by the presence of the carbonyl group of the lactone, which, like the

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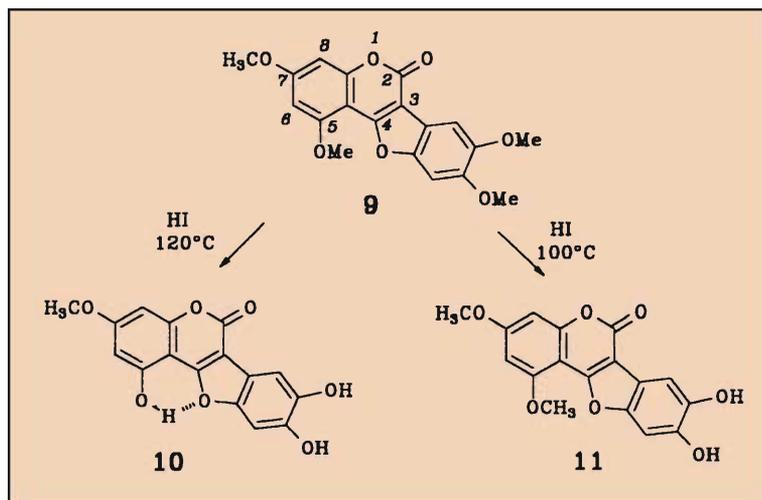
Scheme 3 Demethylation of wedelolactone.

What matters is not the label but the fundamental forces responsible for the building and demolition of molecules!

protonated nitrogen of papaverine is electron-attracting. The methoxyls at positions 5 and 7 are in direct conjugation with this carbonyl group and, therefore, are not sufficiently basic to undergo protonation at the rate necessary for demethylation under mild conditions. On the other hand, the other two methoxyls are not in direct conjugation with the lactone carbonyl. Hence, protonation and demethylation occur readily at these positions. Between the methoxyl groups at positions 5 and 7, protonation at the former is favored. This is because of the possibility of a strong hydrogen bond with the neighbouring oxide bridge. The same stabilising interaction is present in the phenol formed in the reaction (10). Intramolecular hydrogen-bonding can significantly influence ground-state properties as well as reactivities of organic compounds.

Taken together as a complementary pair, papaverine and tri-O-methylwedelolactone bring out the subtle relationships between the structural parameters and the mechanism of acid-catalysed dealkylations of phenolic ethers. When studied this way one can clearly perceive the few controlling principles which govern the behavior of organic molecules, whether synthetic or natural, and irrespective of whether a compound is an alkaloid or a flavonoid or a terpenoid. What matters is not the label but the fundamental forces responsible for the building and demolition of molecules! It is like looking into a kaleidoscope which, with each shake, gives a different pattern with the same number of glass pieces.

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Albert Einstein ... who refused to believe that "God plays dice with the world" writing to Niels Bohr in 1924 said: "I cannot bear the thought that an electron exposed to a ray should by its own free decision choose the moment and the direction in which it wants to jump away. If so, I'd rather be a cobbler or even an employee in a gambling house than a physicist".