14.1: Prelude to Electrophilic Reactions

Introduction

Linnda Caporael probably should have paid a little more attention to the graduation requirements in her college catalog. Going through the graduation checklist during her senior year, she discovered to her dismay that she still needed to fulfill a social science requirement, so she promptly enrolled in an American History course. It was a decision that would in time lead to her authoring a paper in a prestigious scientific journal, being featured in a front page story in the New York Times, and changing our understanding of one of the most intriguing - and disturbing – episodes in American history.

Professor Caporael (Linnda went on to become a professor of Behavioral Psychology at Rensselaer Polytechnic Institute) recounted her story in an episode of the PBS documentary series Secrets of the Dead. Early in the semester, she learned that as part of her history course she would be required to complete a research paper on a topic of her own choosing. She had recently seen a performance of The Crucible, Arthur Miller's classic play about the Salem witch trials, and decided to do her research on Anne Putnam, one of the young Salem girls who accused several village women of bewitching them. The symptoms of 'bewitchment' that afflicted the girls were truly frightening: thrashing and convulsions, visions of snakes and ferocious beasts, a sudden inability to speak, and a feeling that ants were crawling under their skin.

> *These children were bitten and pinched by invisible agents: their arms, necks and backs turned this way and that way, and returned back again, so as it was, impossible for them to do of themselves, and beyond the power of any epileptick fits, or natural disease to effect. Sometimes they were taken dumb, their mouth flopped, their throats choaked, their limbs wracked and tormented. . .*

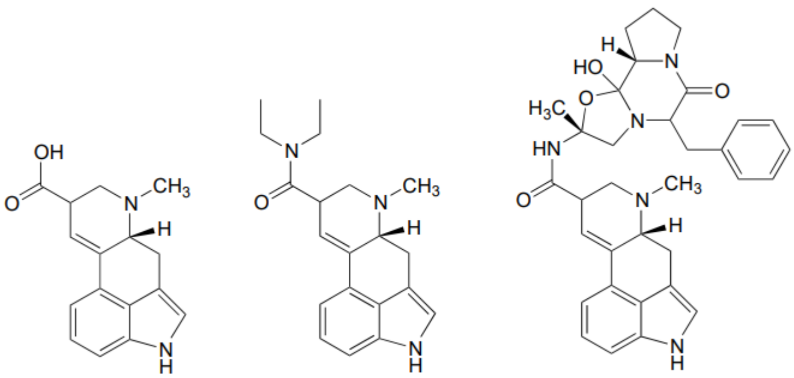
(From “A Modest Enquiry Into the Nature of Witchcraft” (1702) by Reverend John Hale. http://historyofmassachusetts.org/betty-parris-first-afflicted-girl-of-the-salem-witch-trials/)

As Linnda continued to read accounts of the 'fits' afflicting the Salem girls, she was suddenly struck by the similarities to another, more recent episode that she had read about. In the summer of 1951, in the French village of Pont Saint Esprit, a number of local people were simultaneously seized by hallucinations, convulsions, and other symptoms very much like those described during the Salem witch trials hundreds of years earlier. Leon Armunier, a former postman in Pont Saint Esprit, described his experience to the BBC:

> *It was terrible. I had the sensation of shrinking and shrinking, and the fire and the serpents coiling around my arms . . .Some of my friends tried to get out of the window. They were thrashing wildly. . . screaming, and the sound of the metal beds and the jumping up and down... the noise was terrible. I'd prefer to die rather than go through that again.*

There have been several explanations offered for what caused the Pont Saint Esprit outbreak (including that the CIA was experimenting with mass LSD poisoning as a form of chemical warfare), but the most widely accepted theory is that the hallucinations were caused by eating bread made from contaminated grain.

Claviceps purpurea, a fungus known to grow in rye and other grains, produces a class of hallucinogenic compounds called 'ergot alkaloids' which are derived from lysergic acid (the hallucinogenic drug LSD is a synthetic derivative of lysergic acid). Claviceps thrives in damp grain, and special care must be taken to avoid contamination when storing grain grown during warm, rainy summers.



(+)-lysergic acid (+)-lysergic acid diethylamide (LSD) ergotamine (an ergot alkaloid)

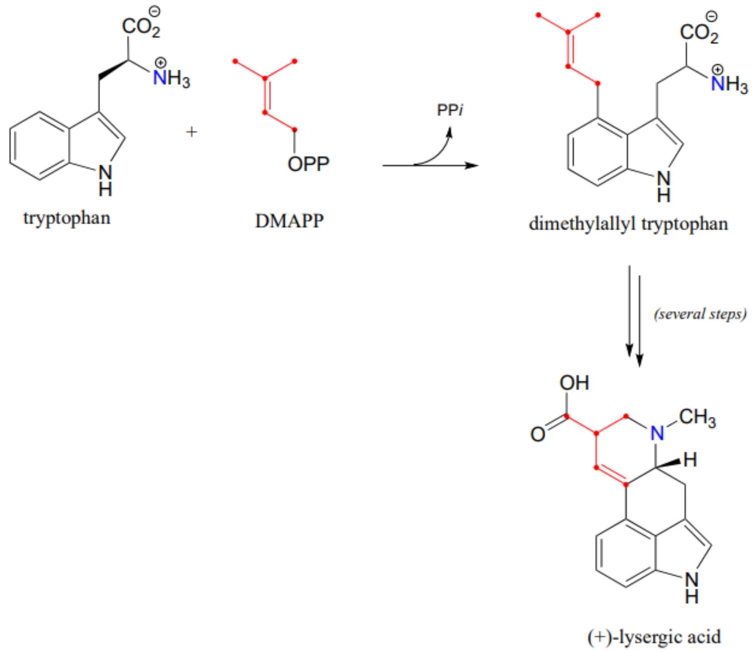
Digging deeper into the records of the Salem witchcraft episode, Linnda Caporael learned that the summer of 1691 was unusually damp. The first cases of 'bewitchment' in Salem village occurred in the winter of 1691-1692, when the villagers would have been consuming grain stored from the previous summer. Rye, the kind of grain most vulnerable to Claviceps contamination, was the staple crop in Salem at the time. Furthermore, nearly all of the affected girls lived on farms on the swampy western edge of the town, where Claviceps contamination would have been most likely to occur.

This was all circumstantial evidence, to be sure, but it was enough to convince Linnda that ergot poisoning was much more plausible as a root cause of the behavior of the afflicted girls than simply mass hysteria, which had long been the accepted theory. She summarized her findings in a paper that was later published in the journal Science, with the colorful title "Ergotism: The Satan Loosed in Salem?" (Science 1976, 192, 21). Her theory is still not universally accepted, but scientists and historians are for the most part in agreement that ergot poisoning was the cause of other outbreaks of convulsions and hallucinations, often called 'Saint Anthony's Fire', that have occurred throughout European history. It is possible that ergot poisoning may have played a role in literature as well: professor Caporael, in an interview with PBS, recounts how she was recently contacted by an historian with in intriguing idea. Is it possible that Caliban, the wild, half-human character in Shakespeare's The Tempest who is tormented by hallucinations inflicted upon him by the wizard Prospero, could be a literary manifestation of ergot poisoning episodes that occurred in England during Shakespeare's time?

> *For every trifle are they set upon me;*
> *Sometime like apes that mow and chatter at me*
> *And after bite me, then like hedgehogs which*
> *Lie tumbling in my barefoot way and mount*
> *Their pricks at my footfall; sometime am I*
> *All wound with adders who with cloven tongues*
> *Do hiss me into madness.*

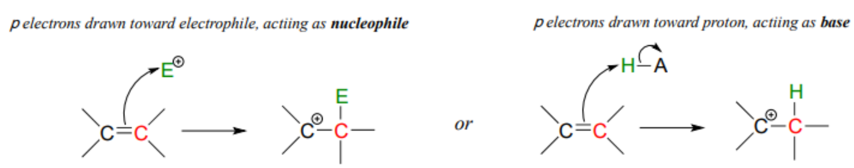
(William Shakespeare's The Tempest, Act II scene ii)

In this chapter, we will learn about a class of organic reaction that is central to the biosynthesis of ergot alkaloids in Claviceps. The key first step in the biosynthetic pathway is a reaction unlike any we have yet seen:



As you can see, the first step is condensation between the amino acid tryptophan and dimethylallyl diphosphate (DMAPP), the building block molecule for isoprenoids (section 1.3A). What you should also notice in the reaction figure above is that a new carbon-carbon bond is formed, and yet the chemistry involved is clearly very different from the carbon-carbon bonding forming aldol additions and Claisen condensations we learned about in the previous two chapters: there is no carbonyl to be found anywhere near the site of reaction, and one of the bond-forming carbons is part of an aromatic ring.

We will see later in this chapter that this reaction mechanism is classified as an 'electrophilic aromatic substitution', and is one of a broader family of organic reaction mechanisms that includes electrophilic additions, substitutions, and isomerizations. 'Electrophilic' is the key term here: in organic chemistry, an 'electrophilic' reaction mechanism is one in which the p-bonded electrons in a carbon-carbon double (or sometimes triple) bond are drawn towards an electron-poor species, often an acidic proton or carbocation. In essence, the p bond is acting as a nucleophile or base.



Notice above that, once the p bond breaks and a new σ bond forms, the second carbon that was part of the original p bond becomes a carbocation. Carbocation intermediates play a critical role in this chapter, because a carbocation is a highly reactive species and will quickly attract a pair of electrons. The stability of the carbocation intermediate (recall that we learned about carbocation stability in section 8.5), and the manner in which it accepts a pair of electrons, plays a key role in determining the outcome of the reaction.