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Review

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DARK Classics in Chemical Neuroscience: Opium, a historical perspective

Christopher C. Presley, and Craig W. Lindsley*

Vanderbilt Center for Neuroscience Drug Discovery, Nashville, Tennessee 37232, United States

Abstract

Opium is the latex from the opium poppy *Papaver somniferum* L. which man has utilized since ancient Mesopotamia all the way to modern times. Opium used to be surrounded in divine mystery or magic like abilities and was given to cure a wide verity of diseases until its analgesic, antitussive, and antidiarrheal properties were understood and the resulting alkaloids were isolated and their structure and properties unmasked. Opium went from being sold in any store front in the form of pills or tinctures with no prescription necessary for purchase, or smoked in an opium den down the street, to then bringing about consumer advocacy and the right to know what is in a medication. Legislation to limit the prescribing and selling of medications to doctors and pharmacists, as well as outlawing opium dens and smoking opium. This review will focus primarily on the uses of opium throughout history, the isolation of the principle alkaloids, and their structure elucidation.

Keywords: Papaver somniferum, opium, morphine, codeine, thebaine, noscapine, narceine, papaverine

Introduction

In this review the use of opium throughout history, the isolation of the principle alkaloids, their structure elucidations, and understanding how opium production relates to the current opioid crisis in the United States will be discussed. For an in-depth review focusing on morphine please see the DARK Classics in Chemical Neuroscience: Morphine.[1] Currently the United

States is in the midst of a national opioid crisis caused by the over prescribing of prescription opioids, such as hydrocodone, oxycodone and fentanyl, which created addicts who turned to illicitly produced fentanyl and heroin once the prescriptions run out.[2] The Drug Enforcement Administration (DEA) has begun upping their effort to reduce the supply of opioids and better inform communities about the dangers of opioid addiction.[3] However, this is not the first time the United States has faced an opioid crisis. In the nineteenth and the early years of the twentieth centuries there was an opiate crisis revolving around over-the-counter products that contained either opium, morphine, or heroin and the spread of opium dens where opium was smoked. Consumer advocacy and legislation brought about an end to the over the counter sale of opiate laced products, outlawed opium dens, and required a prescription for their use. Facing the current problems associated with heroin use in the United States it is important to reflect on the history of its source of origin, the opium poppy.

A History of the Opium Poppy and Opium

Three books were used as primary references for the historical uses of opium: *Opium: A History* by Martin Booth, *Opium for the Masses: Harvesting Nature's Best Pain Medication* by Jim Hogshire, and *The White Poppy: A History of Opium* by James Maurice Scott and other references were found to add more historical information and context when appropriate.[4-6]

Papaver somniferum L. (*P. somniferum*) also known as the "opium poppy" has been cultivated since ancient times for its poppy seeds and for the milky latex, opium. This dried latex, or opium, contains the pain reducing analgesic alkaloid morphine (**Figure 1**). *P. somniferum* is an angiosperm (flowering plant) from the family Papaveraceae. Poppies are also known for their beautiful white, red, or purple flowers and the seeds they produce are used in baking.[4, 5]

The opium produced by *P. somniferum* contains dozens of various alkaloids, however this review will discuss morphine, codeine, thebaine, noscapine, narceine, and papaverine, which are responsible for most of opium's narcotic and medicinal properties including analgesic, antitussive, and antidiarrheal effects (**Figure 2**). For a more in depth look at other minor constituents of *P. somniferum* please refer to Chapter 6 from the book entitled *Medicinal Plants*.[7]

P. somniferum, its straw, and poppy straw concentrate along with opium extracts, tincture, granulated, powdered, and raw opium are all listed as schedule two substances in the United States under the Controlled Substance Act of 1970. However, the seeds of *P. somniferum* are legal to purchase and consume.[4, 8]

The methods for cultivating *P. somniferum* for the illicit production of opium have remained the same for centuries. After about two weeks after the petals have dropped the pods are lanced/scored by hand to a depth of 1 to 1.5 mm with a specialized tool with three to five parallel blades attached to a handle (a nushtur). The milky-white opium will ooze out onto the pod where it will dry and oxidize into a dark brown sticky and viscous substance. The opium is then carefully scraped off of the pod with a blunt crescent shaped blade (a thallee) and allowed to air-dry in the sun until the consistency is similar to beeswax (**Figure 3**). This raw opium is then pressed into balls, cakes, or blocks. A single pod can be tapped up to a half dozen times and will secrete the opium latex for several days. Depending on the size of the pod and the efficiency of the farmer a single pod can yield around 80 mg of raw opium and a hectare of *P. somniferum* can produce between 8 and 15 kg of raw opium.[4, 5]

Before the raw opium can be sold off it has to be cooked. The cooking is done by dissolving the opium in boiling water, which will dissolve the opium and allow any plant material or other debris from the collection to be filtered off. The filtered opium, or liquid opium,

is left to simmer until enough water has been removed and all that is left is a thick, dark brown paste. This paste known as cooked or smoking opium is then molded into the desired shape, left to dry in the sun, and then shipped to the market or the laboratory.[5]

The legal production of opium poppies is done through licensing with the United Nations Office on Drugs and Crime. The process of collecting the alkaloids is conducted by harvesting, poppy straw from *P. somniferum*, which is the whole of the above ground plant. The plants are dried and the seeds removed, the poppy heads and stems are extracted, and then the principle alkaloids are isolated. The alkaloids are sold as is or are converted chemically into the desired products for pharmaceutical industry. One of the largest producers of legal opium is Tasmania Alkaloids located in Tasmania.[4]

In 2016 the global opium production increased by one third compared with the previous year, which was primarily the result of an improvement in opium poppy yields in Afghanistan. There were an estimated 304,800 hectares (ha) under opium poppies cultivation in 2016. The 2016 total opium production was 6,380 tons, which is still 20 per cent lower than in 2014. Of the 6,380 tons of opium produced in 2016 around 4,300 tons were processed into 448 tons of heroin and 2080 tons were consumed as opium. There were 587 tons of opium seized in global seizures in 2015, which was an increase of 11 per cent from 2014 (**Figure 4**). The leading producers for illicit opium poppy cultivation were Afghanistan and Myanmar who supply Europe, Asia and Africa, and Mexico who supplies the Americas. Opium compared to heroin is a bulky substance so it usually does not travel very far before the morphine is extract and converted into heroin.[9]

Most users of opium describe its effects and high in a similar manner, but opium eater Eric Detzer summarized the experience up in one word: comfortable.[5] Some user become energized very briefly before they become very relaxed. The user will become sleepy, their

problems will start to feel unimportant, they become more patient, and understanding. Some feel as if they have discovered some secret way of thinking. Gentle hallucinations may also occur and the user may experience a sensation of floating. Newer or first time users will feel nauseous, all users eventually become constipated, and they itch all over. Opium like with all opiates with continued use will eventually led to addiction and withdrawal if steady supply into the body is not maintained.[4, 5]

Ancient History (B.C.E)

The wild poppy, *Papaver setigerum* (*P. setigerum*), has oldest documented archaeological occurrence of poppy species with a single water-logged seed that was found at the bottom of a well along with some other radiocarbon-datable material (circa 6500 B.C.E.) at the submerged village of Atlit-Yam.[10] The most ancient recorded finding of the nefarious opium poppy, *Papaver somniferum* L. (*P. somniferum*), was discovered at the underwater La Marmotta site in Lake Bracciano, Italy where *P. somniferum* seeds dating back around 5600 B.C.E. were found preserved in lime at the bottom of the lake.[11, 12] To assume *P. somniferum* was being cultivated for opium production at this time is pure speculation and just as likely could have been cultivated for its seeds or for its oil.

The recorded history of the opium poppy, *P. somniferum*, dates back to around circa 3,400 B.C.E. where Sumerians cultivated poppies in lower Mesopotamia and used ideograms to write about the plant on stone tablets referring to it as "HUL GIL" or the "Joy Plant".[13, 14] Knowledge of the opium poppy spread to the Assyrians with references to poppy juice appearing in medical tablets found in Babylonian King Asurbanipal's royal library circa 1,700 B.C.E.[5] The knowledge of the opium poppy had spread to Egypt by 1500 B.C.E. with treatments for baby colic using opium were written about in the Ebers Papyrus, and one of the minor constituents of

opium, thebaine, got its name from the Thembic opium that was produced in the ancient city of Thebes.[15]

The first archaeological evidence of opium was believed to have been found in 1903 dating back to 1405 B.C.E. by Ernesto Schiaparelli from the tomb of the Egyptian architect Cha (Kha) within a clay vase that housed a medicated oil, which had its contents analyzed and the findings published in 1925.[16, 17] The oily contents of the vase were dissolved in ether, extracted with aqueous hydrochloric acid, the aqueous layer was dried, the resulting residue was re-dissolved in water, tested positive for alkaloids with Bouchardat's reagent (potassium triiodide), and displayed tranquillizing effects when injected into a frog and a mouse. These observations led the researcher to believe the medicated oil contained opium, however their findings were disputed in 1994 when the medicated oil was re-examined using then-layer chromatography (TLC) and gas chromatography mass spectroscopy (GCMS) to confirm there was no morphine in the medicated oil.[17]

In ancient Greece the goddess associated with harvests and the fertility of the earth Demeter and her daughter the goddess of the spring, Persephon, are often depicted with barley, wheat, or opium poppies, and Demeter is sometimes associated with or thought to be an evolution of the Minoan poppy goddess.[4, 5, 12] The personifications of sleep and death, Hypnos and Thanatos, are often associated with opium poppies.[12] The close proximity of opium poppies to figures involving yearly dormant cycles, deep sleeps, and eternal sleeps seem to indicate the ancient Greeks had an understanding of the effects of the opium poppy.

In Book 1V of Homer's The Odyssey, Helen poured a drug originating from Egypt called Nepenthe into the wine of those suffering from the emotional stresses from battle. This drug caused those who drank it to forget all sorrow and evil. It is possible that Homer is referring to

opium and not the fictional medicine Nepenthe. Not all ancient Greek writings of the opium poppy were fictional. Theophrastus wrote that the head of the opium poppy produces a milky sap in his botanical writing the *Historia Plantarum*.[18] Hippocrates, wrote of uses for the opium poppy as a soporific and as a means to help manage pain in his many medicinal collections.[19]

Current Era (C.E.)

During the early Roman Empire, around 40 to 50 C.E., Scribonius Largus wrote down treatments for various aliments in the *Compositiones*, several of which used opium.[20, 21] Scribonius also commented on acute opium intoxication stating that it caused "heaviness of the head" and "dullness of the mind". Another notable Greek physician of the Roman Empire during the first and second centuries C.E. was Galen, who not only helped popularize an opium containing concoctions called theriacs known as "Mithridate or Mithridatium" and "Galene", but also prescribed wool that had been soaked in an aqueous infusion of opium that was meant to be used as a suppository to treat intestinal pain and severe diarrhea.[5, 22]

In the ninth century C.E. Arab scholars and physicians had begun to publish texts on *afion* "af-yum" (opium) with the most famous being Avicenna.[5] Avicenna wrote the *Canon of Medicine* and has one chapter dedicated to opium were he discusses various effects of opium including: analgesic, hypnotic, cognitive, antitussive, respiratory depression, gastrointestinal, toxicology, and dosing.[23] After the death of Muhammed in 632 C.E. the Arab empire underwent a rapid expansion and along with it spreading their knowledge of the medicinal properties of opium, most likely via the silk road trading routes into India and arriving in China during the Tang dynasty.[5, 6]

The history of opium now takes a hiatus for the remainder of the dark-ages and a good chunk of the middle-ages in Europe and does not pick back up until the late thirteenth century,

with the Italian monk and physician named Theodoric. Theodoric designed a soporific sponge he called the "spongia somnifera" which had absorbed an aqueous infusion of opium, mandrake, henbane, mulberry, lettuce, and hemlock.[24] This sponge was sniffed during surgery as a form of anesthesia, however it has also been argued that soporifics sponge were already in use and were originally designed by Arabic physicians.[25]

The story of opium picks back up again in the sixteenth century with Philippus Aureolus Theophrastus Bombastus von Hohenheim, better known as Paracelsus.[5] Paracelsus is credited for reintroducing and popularizing opium to Europe. He often toted about the medicinal properties of opium to the point of making it almost seem magical even going as far as to call it the "stone of immortality".[4] Paracelsus also introduced pills of his own design that he coined Laudanum that he claimed to be superior to all other remedies.[5] Over the years several recipes for Paracelsus' laudanum have emerged and most contain opium and will be discussed later.

The next major event in the history of opium takes us to the mid seventeenth century where the British physician Thomas Sydenham, who some regard as the father of clinical medicine or as the British Hippocrates, introduced his personal take on laudanum as a tincture of opium.[4, 5, 26] When referring to laudanum most individuals are referring to this tincture of opium usually dissolved in wine or spirits, and not the pills of the same name developed by Paracelsus. Regarding opium, Sydenham wrote in Latin, which translates roughly to, "…of all the remedies which the almighty God has bestowed upon mankind, to lighten our miseries, there is none equal to opium, either in regard to the number of diseases it can control, or its efficiency in extirpating them…", this quote shows just how important Sydenham believed opium was to medicine.[4, 5] The nickname "Opiophilos" was given to Sydenham since opium was his favorite drug.[27, 28]

Around the turn of the eighteenth century a student of Sydenham's named Thomas Dover introduced an opium based powder known as Dover's powder.[29, 30] This powder was described as a diaphoretic to be used in the treatment of febrile illnesses and pain.[31] Dover earned himself the nickname "Dr. Quicksilver" for his eagerness to prescribe mercury to treat venereal diseases.[29]

The next major miles stones in the history of opium are the isolations and identifications of the principle alkaloidal components of opium at the start of the nineteenth century. The isolations and structure elucidations of the principle components of opium will be discussed later in this review.

Opium around the "Modern World"

Opium in Europe

The highest concentration of opium-eating in the United Kingdom was localized to the Fens during the nineteenth century. During this time the swamplands were being drained which required back-breaking manual labor which did not pay well. Opium was used as a medication for aches and pains, which was cheap with three pills of opium only costing a penny. The swamplands of this area also contained large amounts of standing water with high mosquito populations, which resulted in a large number of malaria outbreaks. Pharmacists and chemists in the Fens said the three scourges of the area were ague (malaria), poverty, and rheumatism. At the time quinine was available but was too expensive for the poor laborers of the Fens, so they used opium, the medicine they could afford, instead which does not combat malaria.[32, 33] Sales of opium (including pills, laudanum, and soothing syrups) in the Fens averaged around 90 kg per chemist or pharmacist per year during this time.[5] The smoking of opium in England is fictional and was popularized by novelists, which is supported by the *British Pharmacopoeia* requiring all imported opium be at least nine and a half percent morphine and was used by medical

professionals, also collectors cannot find paraphernalia related to smoking opium in England; however, opium smoking did take place in France.[34, 35] The sale of opium based products was limited to pharmacists by the Pharmacy Act of 1868 and finally the Pharmacy Act of 1908 made opium and opium products illegal in England.[36]

Opium in the United States

The United States had its own problems with opium primary with laudanum, soothing syrups, and smoking opium. Women were prescribed laudanum to treat menstrual problems, diseases of a "nervous character", and as an analgesic during pregnancy. The United States also had its problems with utilizing soothing syrups for medicating and quieting children such as Hooper's Anodyne. However the demand for opium based products great diminished after the passing of the Pure Food and Drugs Act, which allowed the customer to see exactly what they were taking.[5]

Opium smoking came to the United States during the gold rush and the construction of the railroad, during the mid-nineteenth century. The opium dens started in San Francisco's Chinatown and spread east from California to New York along the railroads and was banned nationwide in the Smoking Opium Exclusion Act of 1909.[5] Then in 1914 the importing, exporting, manufacturing, and distributing of opium was banned by the Harrison Narcotics Act.[37]

Opium in Asia

In 1729 the Chinese government banned the smoking of opium when the emperor Yinzhen was disturbed by the amount of madak (a mixture of opium and tobacco) that was being smoked, and thus the ritualistic methods for smoking opium were born. Chinese herbal tea was very popular in England and the Chinese demanded silver for the trade of their herbal tea. The

British utilized their East India Company, who had a monopoly on the opium trade in China, to use opium to ultimately obtain the herbal tea and recoup lost silver. In 1796 the East India Company sensed the growing tensions their importing of opium was causing and started using smugglers to get the opium into China, keeping their hands "clean". The Chinese government made the importation of opium illegal in 1799. Between 1814 and 1831 the Chinese government implemented stricter laws and punishments for the illegal importation, sale, and use of opium. During the years between 1836 and 1839 the Chinese government held discussions about legalizing and taxing opium but these debates did not work and using opium became a capital offense, also Lin Tseh-Sen was then tasked with ridding China of opium. Lin confiscated and destroyed over twenty thousand crates of opium, which started the First Opium War from 1839 to 1842. The British crushed Lin's army and the Chinese government signed the Treaty of Nanjing (Nanking) which handed over Hong Kong to the British Empire and gave the British better trading terms; however, opium remained illegal during this time in China. War broke out again in 1856 which the British were again victorious and the Treaty of Tientsin was signed, which ultimately led to the legalization of opium.[6, 38] In 1908 the British and Chinese signed the Ten Years Agreement, where the British agreed to decrease the amount of opium imported into China by one tenth a year over ten years effectively ending the import of opium from India into China.[39]

Opium Concoctions (Figure 5)

Mithridatium, Galene, and Theriac

Legends say that Mithridates from the first century B.C.E. was obsessed with the threat of being poisoned, so as a result he began to research what he believed were antidotes to various poisons and venoms.[40] Mithridates took the various remedies and antidotes he believed worked

and compounded them into a mixture that he consumed daily to gain an alleged immunity. Over the following years Mithridates recipe gained the name of Mithridatium or Mithridate, a few new ingredients including viper's flesh, and another name change to Galene when it fell into the hands of the Romans.[40] So, Mithridatium and Galene both became known as types of Theriac, however Galene is usually referred to as Theriac. Galen wrote about both concoctions listing 41 ingredients for Mithridatium and 55 ingredients for Galene. Besides having different ingredients Galene usually contained more opium than Mithridatium. However, some argue that the original recipes of Mithridatium did not contain opium and that it was not added until the mixture gained popularity in Rome.[41]

The recipes for Mithridatium and Galene have changed over the centuries but usually fluctuate between forty and sixty ingredients.[41] These theriacs were used to treat everything from falls to malaria, and were considered a cure-all. Theriacs were used as a treatment during the various plagues of Europe between the fourteenth and seventeenth centuries. In 1745 William Heberden attacked the efficacy of theriacs and the 1746 *London Pharmacopoeia* was the last British *Pharmacopoeia* to feature the recipes for Mithridatium and Galene, however Germany and France did not stop listing them until 1872 and 1884, respectively.[40]

Paracelsus pills of laudanum

Paracelsus laudanum pills were believed to contain opium, henbane, cinnamon, animal musk, oils, crushed pearls and some other totally legitimate ingredients like frog sperm and "unicorn horn".[4, 5, 42] These pills were said by Paracelsus to cure more believable conditions such as stomach ulcers to the ludicrous like death. Not everyone believes "his stone of immortality" or his laudanum pills contained opium since he prescribed opium wildly and most of his recipes

were disseminated by his followers the "Paracelsists" who claimed to know his secrets recipes to increase their own prestige.[43]

Laudanum tincture

The opium tincture developed by Thomas Sydenham also named laudanum was sold as a liquid composed primarily of opium and alcohol, and was used to treat dysentery, cholera, and prepare patients for surgery. Sydenham's laudanum had a simple recipe of 1 pound sherry wine, 2 ounces opium, 1 once saffron, 1 once cinnamon, and 1 once cloves.[24, 42] However, other pharmacists, physicians, and local chemists had their own recipes and names. The ease at which people were able to obtain laudanum and its similar products over the years may have relieved pain for some but produced way more addicts and caused the deaths of an unknown number of infants.

Black Drop

Another well-known tincture, Black Drop, also known as Lancaster or Quaker's Black Drop, was invented by Edward Runstall in the earlier half of the eighteenth century. This concoction was comprised of one-half pound of opium, 4 pints of verjuice (fermented crab-apple juice), one and a half ounce nutmeg, and one-half ounce saffron. The mixture was boiled and once cool enough two spoonfuls of yeast were added and the mixture was fermented for six to eight weeks before it was ready to be used. The resulting mixture had a potency of around three to four times that of regular laudanum.[5, 24, 42]

Paregoric Elixir

Paregoric Elixir or Elixir Paregoricum, and later known as Tinctura Opii Camphorata was deemed a soothing or consoling tincture "safe" for children and was good at allaying a cough.

This tincture was known as Tinctura Opii Benzoica in Germany and contained honey, licorice, opium, benzoic acid, camphor, aniseed oil, salt of tartar, and spirit of wine.[24, 42, 44]

Godfrey's Cordial and Dalby's Carminative

Infant soothing syrups like Godfrey's cordial and Dalby's carminative were often used between the eighteenth and twentieth centuries to treat infants suffering from colic, diarrhea, weaning, teething, and restlessness. An indolent nurses or wet nurse would often employ soothing syrup to avoid having to deal with crying children. During the industrial revolution new mothers from poorer families who could not afford a wet nurse would knock their babies out with soothing syrups and then go to work in the factories. Needless to say there were addiction problems and accidental deaths due to an overdose were common and by the end of the nineteenth and beginning of the twentieth centuries countries began to outlaw the use of opium tinctures.[5, 45, 46]

Dover's Powder

Thomas Dover's Powder was in use from its inception in early eighteenth century to around the end of World War Two, and combines the analgesic effects of opium with the expectorant effects of ipecacuanha.[31] The recipe for Dover's Powder consisted of adding four ounces of saltpeter (potassium nitrate) and vitriolated tartar (potassium sulfate) into a red-hot mortar and stirring them until they stop flaming, then grinding them together, adding one ounce of opium, grinding it into a powdered mixture, and then add one ounce of powdered ipecacuanha and liquorish.[30, 47] It was recommended by Dover to dissolve 40 to 70 grains (2.6 to 4.5 mg) of powder in a quart of white-wine posset, get into bed, and drink the quart of posset. Dover claimed that within two to three hours the user would be free of pain and may find walking difficult the next day.[5, 30]

Opium-Eating

Opium-eating refers to the act of ingestion opium, which includes opium tinctures, poppy tea, opium pills, and raw opium. The seeds of the poppy are interesting since they are viewed as safe in the eyes of the FDA and are not illegal in the eyes of the DEA, yet. This assumption comes from the few grams a person would ingest from eating a poppy bagel or in a slice of cake will not achieve any of the analgesic effects associated with eating opium, but it can make you fail a drug test.[48, 49]

Poppy Tea

Poppy tea, poppy head tea, poppy seed tea, poppy seed wash, or opium-poppy tea are as straightforward as they sound and have probably been consumed since antiquity. The teas are prepared by steeping unwashed poppy seeds or dried-ground parts of *P. somniferum* L. in boiling water, allow the suspension to cool, and then filter out the plant material to obtain the tea.[4]

It would be foolish to believe that home-brewed poppy tea produced in this manner is completely safe to consume, since deaths do and have occurred in recent years from opiate overdose from poppy teas prepared from seeds purchased on-line.[50] Researchers have examined twenty-two different on-line suppliers of poppy seeds for poppy tea production. From just performing aqueous extractions they found that four of the samples contained no morphine while three of the samples afforded between 108 – 237 mg of morphine from 85 g of poppy seeds, which would constitute a lethal dose. However, the companies' recipes suggested using between 454 – 908 g of seeds to brew the tea which would provide between 577 – 2532 mg of morphine in the extraction![50] Without proper analytical testing there is no way to just look at a poppy tea and assume it will be safe.

Pills of Opium

Before the days of acetaminophen, acetylsalicylic acid, and loperamide tablets to help alleviate aches, pains, and diarrhea there were pills of opium. These pills were made and sold, without prescriptions, by the local pharmacists and chemists who would take the opium and roll it into a pill shape, or cut the opium with soap before making the pills. It was also possible to just buy your very own block of opium and make your own pills at home.[5] One recipe listed to make one hundred opium pills requires 6.5 g of powdered opium, 2 g of hard soap, and enough water to make them malleable.[44] Members of society from a higher economic status could purchase their pills of opium with a coating of silver or gold leaf.[4]

Opium dens

Smoking opium is a ritualistic and time consuming hobby. The tools required for smoking opium are large, cumbersome, and require skill and knowledge on how to prepare the opium for smoking, which is why opium dens were utilized. Opium dens were kept dim and quiet since most smokers find this setting more pleasurable, also the dens were kept sealed to prevent drafts from interfering with the lamps, or beds surrounded on three sides would be used. Opium smokers are accompanied by a "Chef" who is skilled in the art of taking the chandu (generally a lower quality opium that has under gone extra preparation for smoking) and rolling it into a pea-sized pill, then baked over an open flame.[4] The pipes are usually around 0.5 m long and about 5 cm in diameter, which provided space between the smoker and the hot alcohol lamp. The pipes are traditionally made from either sugarcane, bamboo, or ivory and the bowls contained a tiny hole for inserting the opium pill, and can be made from earthenware or stone.[34] The dim light of an opium den was produced from the ornately decorated alcohol lamps whose flames were contained in a dimpled-glass dome. The smoker usually lays down on their side to make holding the pipe easier and to possibly help with the nausea. Once the pill was ready it

would be pierced with a needle like object called a "yen-hok", which was then inserted into the bowl of the opium pipe (**Figure 6**).[4] The smoker would then hold the pipe and place the bowl in the dimple of the glass lamp, and once the pill of opium began to vaporize the vapor would be inhaled.[34]

Opium dens were not always confined to back alleys basements or hidden back rooms. In Canton China during the eighteenth and nineteenth centuries it was possible to rent one the famous brightly colored "flower boats" for the evening and float around the river in your very own brothel and opium den combo.[51] In San Francisco's Chinatown opium dens were as common as bars during the gold rush and the construction of the railroads. They were decorated with Chinese tapestries and scrolls and all the accoutrements associated with smoking opium becoming very popular and drawing in visitors from all walks of life. The dens operated normally until local legislations forced them underground in 1875, 1878, and 1881.[37]

The author and opium smoker, Steven Martin (not to be confused with the actor), had amassed a massive collection of opium smoking paraphernalia, which he donated to the University of Idaho for scholars and researchers to keep and examine in 2012.[52] Martin's collection included pieces from Asia, France, and the USA. He published two to books, the first *The Art of Opium Antiques* in 2007, and the second *Opium Fiend: A 21st Century Slave to a 19th Century Addiction* in 2012 where he showcased just how intricate the craftsmanship on the various accoutrements for smoking opium can be.[34]

Chandu

Chandu was the name given to the pills of opium used for smoking in opium dens. When opium was graded the lower quality opium would sold off for the purpose of smoking.[4] The lower quality opium needed to be concentrated before it could be smoked. The chandu was

prepared by dissolving raw opium in water, boiling it, filtering the solution, and then evaporating the water unit a suitable consistency for forming pills was achieved.[5]

Dross and Madak

Dross was the name given to the opium residue left on the walls inside of the pipe. This residue could be skillfully scraped away and resold usually to poorer individuals. The dross would be smoked on its own, put into tea, or mixed with tobacco for smoking.[5] Another mixture used for smoking opium was known as Madak, which was a mixture of opium and tobacco.[53]

Chasing the Dragon

"Chasing the dragon" is a crude way of smoking drugs like opium, morphine, or heroin. The user heats opium in a piece of aluminum foil until the opium vaporizes. The user then has to chase the vapor trail with the tip of a cylindrical device which they are inhaling through.[4]

Constituents of opium

Morphine and Codeine

Isolation of Morphine

During the early 1800's the search for the principle narcotic component of opium was underway and the first breakthrough came in 1803 when the French chemist Jean-François Derosne published his work on a narcotic salt that he had isolated from a sample of opium.[54] Derosne obtained this salt by evaporating an aqueous solution of opium down to a syrup and allowed it to sit until a gritty substance solidified. The isolated substance could be easily recrystallized in alcohol or ether and displayed narcotic effects on animals, however this substance was not morphine and is believed to have actually been noscapine based on the descriptions given by Derosne.[5, 55, 56]

In the early 1800's a young man who was working as a pharmacist's assistant named Friedrich Wilhelm Adam Sertürner isolated two compounds from opium and published his findings in 1806.[57] The first compound isolated was meconic acid (**7**), Sertürner called it "poppy acid" (**Figure 7**), and the other was the first of its kind, an organic compound that behaved as a base. This alkaline organic compound formed salts with inorganic and organic acids, and was the principle sleep-inducing narcotic of opium, which he referred to as the "*principium somniferum*".

Sertürner isolated his "*principium somniferum*" by exhaustively extracting eight ounces of dry opium with water. The combined aqueous extracts were then saturated with ammonia and the crystals that formed were collected and washed with water. These crude crystals were then treated with dilute sulfuric acid and again precipitated with ammonia. The newly collected crystals were then recrystallized in alcohol multiple times until pure crystals were obtained.[58]

The crystals were colorless parallelopipeds that had a bitter taste and turned red litmus blue and turmeric brown. Sertürner also was able to react his crystals with acids to form neutral products which included: bicarbonate, sulfate, hydrochloride, nitrate, meconate, acetate, and tartrate salts. These were the observation that led Sertürner to believe he had isolated an organic base.

Unfortunately, Sertürner's grand discoveries went unnoticed until he republished his findings in 1817 and renamed his "*principium somniferum*" "morphium" after the Greek god of dreams Morpheus.[59] This time Sertürner's publication caught the eye of Joseph Louis Gay-Lussac, who helped shine a light on Sertürner's work, and changed the name "morphium" to morphine, a nomenclature naming convention that has presisted.[60, 61] In 1819 Whilhelm Meissner assigned the term "alkaloid" to these basic "alkali-like" organic compounds.[62]

The principle opium alkaloid, morphine, became very well known for its analgesic properties. Today morphine is classified as a schedule two drug by the Drug Enforcement Administration (DEA) and is only available by a prescription due to its high potential for abuse.[8] Morphine is also regulated since it is the precursor to heroin.

Isolation of Codeine

In 1832 a French chemist and pharmacist named Pierre-Jean Robiquet was commissioned by the Société de Pharmacie to examine a procedure proposed in 1831 by a Scottish physician and chemist, William Gregory, who claimed he had found a simplified method for isolating the pure hydrochloride salt of morphine "muriate of morphia" from opium and avoided the use of expensive alcohols.[63-65] William Gregory's procedure involved exhaustively extracting finely cut pieces of opium with 32˚ C water, and then concentrating the solution and adding a slight excess of ammonia. The precipitate was then collected, washed with cold water, and dried in an oven below 100˚ C. The dry powder was then mixed with cold water and dilute hydrochloric acid (muriatic acid) was added in portions until there was a permanent excess. The dark brown solution then contained both morphine and noscapine and was filtered to remove insoluble impurities. The solution was concentrated down to a syrup and cooled into a mass of brown crystals. The syrup was then subjected to "strong pressure" between folds of blotting paper (bibulous paper) which forced the noscapine which was still in solution into the blotting paper and left crude crystals of morphine HCl salt behind. The crystals were then recrystallized three times with boiling water.[65] Robiquet discovered that if he took the basic mother liquor that contained the ammonia after the removal of the morphine and noscapine crystals and dried it down, then mixed the residue with potassium hydroxide, washed with water, then dried the aqueous solution down he could obtain a powder. After recrystallizing this he found a crystalline

substance that he called codeine.[64] The isolated substance formed salts with acids just like morphine and had a similar narcotic effect. Robiquet later theorized that codeine has to be structurally similar to morphine since they both form salts with similar amounts of hydrochloric acid and have similar chemical formulas.[66]

Codeine possesses less potent but similar pharmacological actions to morphine and is used primarily for mild pain relief and as a cough suppressant.[56] Depending upon what codeine has been combined with will determine its drug classifications. If codeine is combined with aspirin or Tylenol then it is classified as a schedule three drug while cough medicines with codeine are classified as schedule four drugs by the DEA.[8]

Structure Elucidation

The structure elucidations of morphine and codeine are intertwined, since codeine is just the methyl ether of morphine. Two researchers, Grimaux and Hesse, both independently figured out that they could produce codeine from morphine with methyliodide under basic conditions, in 1881 and 1884, respectively.[67, 68] Grimaux was also able to draw comparisons between phenol and its methyl ether with morphine and codeine.

A very useful piece of structural information came from Beckett and Wright who were experimenting with organic acids and their anhydrides trying to see how many oxygens of morphine could be acylated between 1874 and 1875.[69-71] Once the correct chemical formula of morphine was known Wright in 1880 was able to figure out using benzoyl chloride that only two of the three oxygens could be acylated and the third must be involved in another type of bond.[72]

In 1881 Gerichten found after conducting zinc catalyzed pyrolysis of morphine that phenanthrene (**8**) could be isolated from the remaining hydrocarbons, confirming that morphine

contained a phenanthrene core.[73] Further evidence for the phenanthrene core was provided by Fischer and Gerichten in 1886 when they took morphine methyliodide and converted it into heroin methyliodide (**9**) with acetic anhydride, then performed a Hofmann elimination with silver acetate, then lastly the acetyl groups were removed with ammonia in alcohol to afford the dihydroxyphenanthrene or morphol (**10**).[74] The structure of **10** was not known at the time and was not determined until 1900 from a synthesis conducted by Pschorr.[75] Gerichten also discovered if codeine methyliodide underwent a Hofmann elimination with silver oxide, followed by a reduction methylmorphenol (**11**) could be obtained (**Figure 8**).[76-78] Thhese observations confirmed the presence of a morphenol-like ring system in morphine. Freund and Göbel were able to convert thebaine into thebaol (**12**) in 1895, and codeine was then converted into codeinone (**13**) by Knorr in 1906, which these two observations established the hydroxy at position 6 (**Figure 9**).[79, 80]

Then in 1911 Oldenberg found that morphine and codeine both had a double bond that was saturatable with hydrogen and palladium to form **14** and **15**.[81] A vast amount of work has been done on codeine with PCl_3, PCl_5, and $SOCl_2$ to convert the hydroxyl of codeine into α-chlorocodide (**16**), which can then be thermally isomerized to β-chlorocodide (**17**), a few examples from this breadth of work include Lees in 1907 and Pschorr in 1910.[82-84] Lees also conducted water catalyzed hydrolysis of **16** and **17** to form an isomeric mixture of codeines (**18** and **19**). The same year Knorr found that **18** and **19** could be oxidized to **13** and a pseudocodeinone (**20**) confirming the relationship between the hydroxyl at position 6 and the location of the double bond relative to the hydroxyl (**Figure 10**).[85, 86]

During the degradation experiments mentioned earlier with the methyliodides of morphine and codeine sometimes dimethylethanolamine was isolated, and from this compound

researchers were able to conclude that the N-methyl and the ethyl subunit must be attached to the phenanthrene core.[87, 88] The attachment of the N-terminus was made possible by Knorr first with the gentle transformation of codeine methyliodide with a controlled oxidation into hydroxycodeine (**21**) in 1903.[89] From there **21** was converted into the ketone **22**, which confirmed the attachment of the N-terminus.[90-92]

After thoroughly examining morphenol, codeinone, and thebaine it was decided that the ethylamino unit must be attached at either positions 5 or 13. The final differentiation between the two came in 1927 when Schöpf conducted a Beckmann rearrangement on the dihydrocodeinone oxime (**23**). If the reaction were to yield an aldehyde and a nitrile (**24**) then the attachment would be at position 13 but if a ketone and a nitrile (**25**) were formed then the attachment would be at position 5. After conducting the experiment **24** was obtained confirming the attachment of the ethyl-terminus at position 13 (**Figure 11**).[93] Lastly, the structural assignments were officially confirmed via total synthesis by Gates in 1952 and the crystal structure was obtained in 1955 by Mackay and Hodgkin to confirm the absolute configuration.[94-96]

Thebaine

Isolation

Pierre Joseph Pelletier was experimenting with the precipitate that was left after adding saturated calcium hydroxide (milk of lime) to an aqueous extract of opium to remove the morphine. The collected precipitate was washed with water, dried, and added to boiling alcohol. The alcohol solution was then evaporated and the remaining brown mass was mixed with ether. The ether was evaporated to afford brown crystals, which were dissolved in acid, precipitated with ammonia, and recrystallized in alcohol and ether.[97]

Thebaine is not used medicinally but it is used as a starting material for other narcotics.[56] Thebaine is classified as a schedule two drug by the DEA since it is a precursor to oxycodone.[8]

Structure Elucidation

The structure elucidation of thebaine was tied to morphine and codeine by showing how thebaine relates to those two once the structure of one was known then so was the other. To start Knorr demonstrated that acids convert thebaine into codeinone (**13**).[79] Later, in 1920 it was by shown by using the Zeisel determination that there were two methoxys in thebaine.[98] A year later in 1921 thebaine was determined to have two double bonds by examining the products of palladium catalyzed hydrogenation.[99] These experiments showed that thebaine differs from morphine by two methoxy groups and an extra double bond, so once the structure morphine was determined so was thebaine.

Noscapine (Narcotine, Nectodon, Nospen, Anarcotine, Opiane) Medicinal uses[100]

Isolation

The timeline and isolation of noscapine (original called narcotine) is a little muddy but credit is usually given to Pierre-Jean Robiquet in 1817. In his work Robiquet was repeating Sertürner's isolation of morphine and mecanoic acid from opium, and examining authentic samples of Derosne's salt prepared by Derosne himself for the presence of mecanoate of morphine salts. Robiquet was successful in repeating Sertürner's procedure for isolating morphine and mecanoic acid, however he was unable to find mecanoate of morphine salts in Derosne's salt. Robiquet did however find a new substance that was different from morphine and mecanoic acid in Derosne's salt. In order to isolate this substance from opium rather than extract the opium with water he exhaustively extracted it with ether. Evaporation of the ether yielded a

viscous oil impregnated with crystals. The crystals were isolated and treated with boiling alcohol to afford what was determined to be noscapine.[101, 102]

Noscapine does not possess any analgesic properties and is comparable to codeine as a antitussive agent.[56] Noscapine by its self is not technically a scheduled substance in the United States but is usually mixed with other controlled substances like codeine.[8]

Structure Elucidation

The structure elucidation of noscapine took around 100 hundred years and the efforts of dozen of researchers, but here only the highlights will be discussed. Wöhler found in 1844 that it was possible to decompose noscapine into cotamine (**26**) and opianic acid (**27**) with dilute sulfuric acid and manganese dioxide.[103] The correct chemical formula for noscapine was determined by Matthiessen in 1863, and during the same work found it was possible to convert opianic acid to meconin (**28**) with potassium hydroxide and some heat.[104] Beckett at the start of his long series of experiments on noscapine and its degradation products in 1875 found that it was possible to reduce noscapine into hydrocotamine (**29**) and **28** (**Figure 12**).[105] Freund was able to determine the positions of the methylenedioxy and methoxy in **26** and by comparison also **29**.[106, 107] Perkin took all of the available data and pieces and decided to couple **28** and **29** to give a racemic mixture of noscapine and upon chiral resolution gave a small amount of pure noscapine confirming the structure via synthesis.[108]

Narceine

Isolation

In 1832 Pelletier was working with an aqueous extraction of opium that he dried down and re-dissolved in water to crash-out the narcotine. An excess of ammonia was then added and the solution was boiled for ten minutes, and upon cooling the morphine precipitated out. The

precipitated morphine is removed and the volume of the solution is reduced by half and cooled again allowing even more morphine to precipitate. Aqueous barium sulfate (barite or baryte waters) is then added to precipitate the meconic acid as a low solubility barium salt, which the excess barium is then removed by adding ammonium carbonate. The excess ammonium carbonate is then removed by evaporation and the solution was allowed to evaporate down to a thick syrup. This thick syrup was allowed to cool for several days, which grew to a crystal-like lump, and this lump of crystals was separated by pressing it between cloths. The lump of crystals would only partially dissolve in boiling alcohol, the alcohol solution was concentrated, allowed to cool, and the crystals that formed were recrystallized in water. This new crystalline substance was named narceine (narcéine).[109, 110]

Pelletier describes narceine as an odorless, white and silky crystalline material that can be easily recrystallized in alcohol or water. His most interesting observation of narceine comes from the outdated taste test were Pelletier says narceine tastes slightly bitter like morphine and narcotine, but also produces a sensation that he compares to having his tongue electrocuted. Pelletier also confirmed that narceine can combine with acids to make neutral salts as well, making it another basic organic alkaloid.

Narceine is a non-addictive and unregulated compound in the United States. Narceine has been shown to possess potential anticancer properties by causing apoptosis in human colon and breast cancer cell lines.[111] Narceine is not listed as an approved drug by the Food and Drug Administration (FDA).

Structure Elucidation

The structure elucidation of narceine is tied to the structure elucidation of noscapeine, since they are very similar compounds. In 1888 Roser found that if noscapeine methychloride

(**30**) was subjected to a Hoffmann elimination with silver chloride and then heating with base that narceine was the resulting product (**Figure 13**).[112] A similar procedure was conducted by Hope and Robinson in 1914, and both Roser's procedure and Hope and Robinson's procedures were repeated in 1933 by Addinall.[113, 114]

Papaverine

Isolation

In 1848, a chemist named Georg Merck, related to the dynasty of Mercks, published a short note claiming to have isolated a new opium base he called "papaverin" (papaverine) from residues left over from his father's morphine factory.[115, 116] In this first note Merck did not describe how he had isolated papaverine but did demonstrate the characteristics of the crystalline substance. Merck said the papaverine was isolated in large white crystals, insoluble in cold alcohol and in cold ether, but can be dissolved in hot alcohol and hot ether. Merck also observed that papaverine barley turned red litmus paper blue indicating that is was a weak base. Two years later Merck published another paper were he detailed two extraction methods for obtaining papaverine. The residue he used from his father's lab was obtained by precipitating morphine from an aqueous opium extract with sodium carbonate (soda ash), the precipitated morphine was then washed with alcohol to obtain a brown tincture that was dried to afford the residue. For the first method the residue was treated with dilute hydrochloric acid and then mixed with acetic acid which forms a brown resinous mass that was then dissolved in boiling ether, and upon cooling crystals of papaverine grew. The second method takes the residue and re-dissolves it then concentrates it down to a thick syrup. The syrup was allowed to set for several days at room temperature until it solidified into a crystalline mass. The crystalline mass was recrystallized in alcohol and decolored with animal charcoal. The papaverine obtained this way was still

contaminated with noscapine (narcotine), so it was treated with hydrochloric acid and allowed to crystallize, the papaverine HCl salt was only slightly soluble in cold water while the noscapine HCl salt was highly soluble in cold water, so it can just be removed by washing with cold water to afford papaverine as the hydrochloride salt.[117]

Papaverine is used as a smooth muscle relaxant and a vasodilator.[56] Papaverine its self is not regulated but if it is mixed with codeine or hydrocodone then it is classified as a schedule three drug by the DEA.[8]

Structure Elucidation

Goldschmiedt conducted a large amount of the decomposition and structure elucidation papaverine from 1885 to 1888. It should also be stated that Goldschmiedt was only able to determine what type of compounds he had isolated and not which specific isomer. Some of his first experiments involved using potassium hydroxide to decompose papaverine and he found a dimethoxy homocatechol (**31**) and a dimethoxybenzoic acid (**32**).[118] Goldschmiedt also conclude that Merck was correct in assigning a chemical formula of $C_{20}H_{21}NO_4$ to papaverine.[119] Utilizing a 2% potassium permanganate solution papaverine was converted to papaveraldine (**33**), which was in turn reacted with potash (potassium hydroxide and potassium carbonate) to produce veratric acid (**34**) and a dimethoxy quinoline (**35**).[120, 121] Another product formed from the reaction of papaverine with a 2% potassium permanganate solution was a dimethoxy cinchoninic acid (**36**) that upon heating was converted into **35** from before (**Figure 14**).[122] Knowing that papaverine can be split into **31** and **35**, converted into **33**, and with its relationship to **36** Goldschmiedt then theorized that papaverine was just the combination of the **31** and the **35**.[123] Papaverine was also determined to be optically inactive which further supported Goldschmiedt's achiral structure.[124]

Then in 1909 papaverine was synthesized by Pictet, which confirmed Goldschmiedt had all the right pieces.[125] Crystal structures of papaverine were also obtained in 1974 and 2000 by Reynolds and Stephenson, respectively.[126, 127]

Opium in Current Society

According to the DEA today very little of the opium produced in Mexico during 2016 was consumed as opium and the majority of it was converted into heroin.[128] For the small percentage of opium users who remain it is highly recommended that if they have consumed opium since 2016 that they get tested for blood lead levels due to an increase of lead in opium.[129] The reason for the increased lead in opium is unknown but it is believed to be added to increase the weight for a higher price at market.

Currently in the United States there is an opioid epidemic with individuals suffering from oxycodone, heroin, and fentanyl addiction leading to overdose and death. In 2018 the battle to overcome this opioid epidemic has placed a spotlight on a legal method for obtaining opiates in the United States, poppy seeds and more specifically "poppy seed wash". Currently in the United States there are no official guidelines for the pretreatment of poppy seeds to remove trace amounts of opium or poppy straw concentrate from the outer shells before the seeds are sold, and these seeds are referred to as "unwashed poppy seeds". As mentioned earlier in the poppy tea section deaths have occurred in the United States from morphine overdose caused by drinking poppy seed wash.

The family of the deceased became very active in encouraging research to be conducted which as stated earlier found that poppy seeds from on-line suppliers can contain lethal doses of morphine.[50] Their family's story and the scientific evidence obtained were presented to the FDA

and their local legislators who supported their cause. Arkansas Senator, Tom Cotton, reached out to major on-line and physical retailers who sold unwashed poppy seeds and informed them what those seeds were being used for and the retailers pulled the items from their stores. Cotton then made a speech on April 25, 2018 on the Senate floor about unwashed poppy seeds and urging the Senate and the DEA to ban unwashed poppy seeds.[130] On July 12, 2018 the FDA classified poppy seed wash as a "new drug" in a warning letter to one of the unwashed poppy seed vendors.[131] This "new drug" classification means that the substance would have to undergo FDA approval before it can continue to be sold.

Unfortunately without actual legislation and guidelines on how poppy seed vendors must treat seeds before they can be sold all the unwashed poppy seed products pulled from stores can easily find their way back to major retailers. All these vendors need to do is remove the word "unwashed" and any medicinal terminology on their packaging and websites and then their products are back up on store shelves. As Senator Cotton stated in his speech, "This is not just a labeling problem. In fact, some of the most potent and deadly seeds … are not labeled as unwashed and are still available for purchase." Even in 2018 opium can still be purchased right down the street at the grocery store.

Conclusion

Opium has shaped how humans have viewed and managed pain for centuries. Opium helped revolutionize modern medicine from managing pain to saving lives from severe dehydration. Due to addiction and deaths of adults and children from opiate laced products consumer advocacy brought about the ability to know what chemicals were in products being sold and if they were hazardous. Our society now faces another opioid crisis and the moral and societal dilemmas that accompany combating addiction and how to treat those who are addicted

to opium, morphine, and its synthetic offspring. In the past legislation and educating the public on what opiates were and what they did helped alleviate the opiate crisis. Now the wheels of change have begun to turn again proposing new guidelines for the treatment of poppy seeds sold in the United States and new efforts from the DEA to reduce the supply of opioids and conducting community outreach programs to better inform the public on the dangers of opioid addiction. All the life it has given and all the life that has been lost, all from the latex of a plant.

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Figure 1. Left – The fresh milky opium latex oozes out from the fresh incisions with older scabbed-over incisions next to them. Right – The dry, oxidized opium ready to be scrapped off. Both images were reprinted with permission from the United Nation's Office on Drugs and Crime.

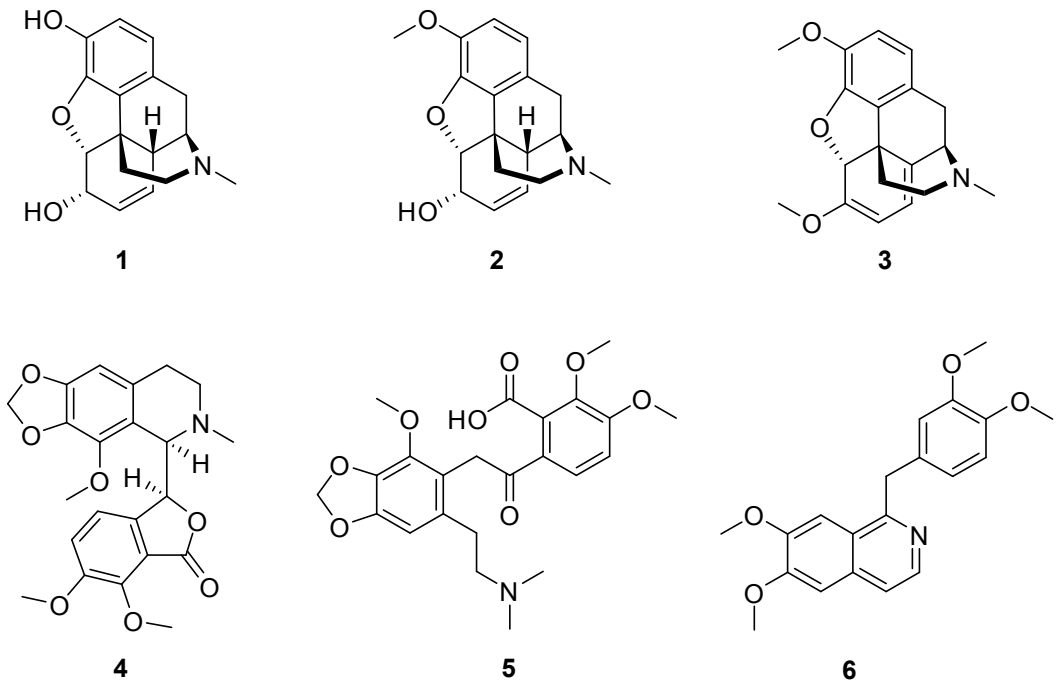


Figure 2. Structures of compounds isolated from *P. somniferum*, morphine (1), codeine (2), thebaine (3), noscapine (4), narceine, (5), and papaverine (6).

Figure 3. Left – Tools used for scoring the poppy pods and collecting the opium latex (image reprinted from the Drug Enforcement Administration Museum and is in the public domain). Right – The oxidized opium is being gently scrapped off the poppy capsule and is allowed to accumulate on the blade (image was reprinted with permission from the United Nation's Office on Drugs and Crime).

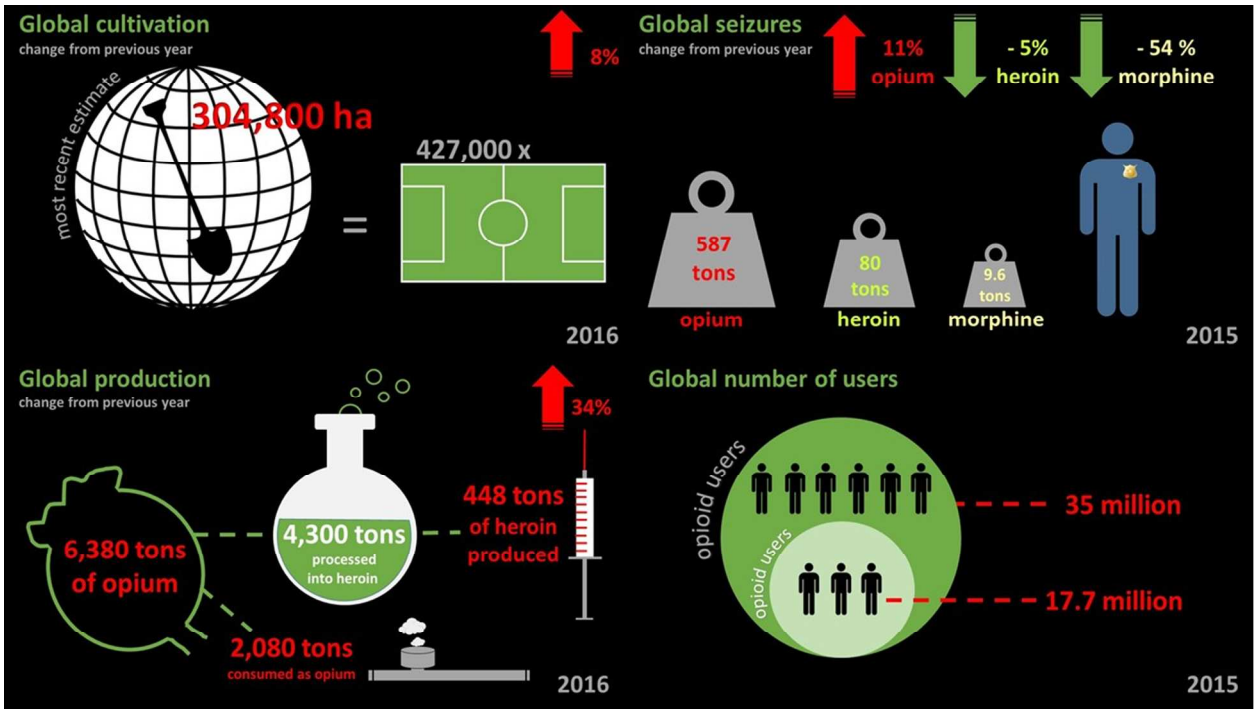
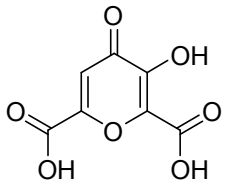


Figure 4. Global opium statistics reproduced from the United Nation's Office on Drugs and Crime World Drug Report 2017, Booklet 3.

Figure 5. Photos of various opium containing concoctions. Far Left – An earthenware vase used to store mithridatium (reprinted under Creative Commons Attribution 4.0 from the Welcome Collection). Left from Middle – An earthenware vase used to store theriac (reprinted under Creative Commons Attribution 4.0 from the Welcome Collection). Middle – A glass bottle of laudanum (a cropped image from the National Museum of American History and is in the public domain). Right from Middle – A glass bottle of the soothing syrup Godfrey's Cordial (image taken from the Nation Museum of American History, which was a Gift from Ben Posen, and is in the public domain). Far Right – A bottle of Dover's Powder from Merck (a cropped image from the National Museum of American History and the image is in the public domain).

Figure 6. Top Left – A tray with all the various accoutrements required to prepare the chandu pills and smoke them (Image courtesy of Steven Martin/Opium Museum). Bottom Left – Several opium users smoking opium and tobacco in China from 1932 (image used under Creative Commons 1.0 and is in the public domain). Right – An ornately decorated opium pipe (cropped image is from the National Museum of American History, which was provided by Mrs. Jean Mauze, and the image is in the public domain).



mecanoic Acid (**7**)

Figure 7. Structure of mecanoic acid.

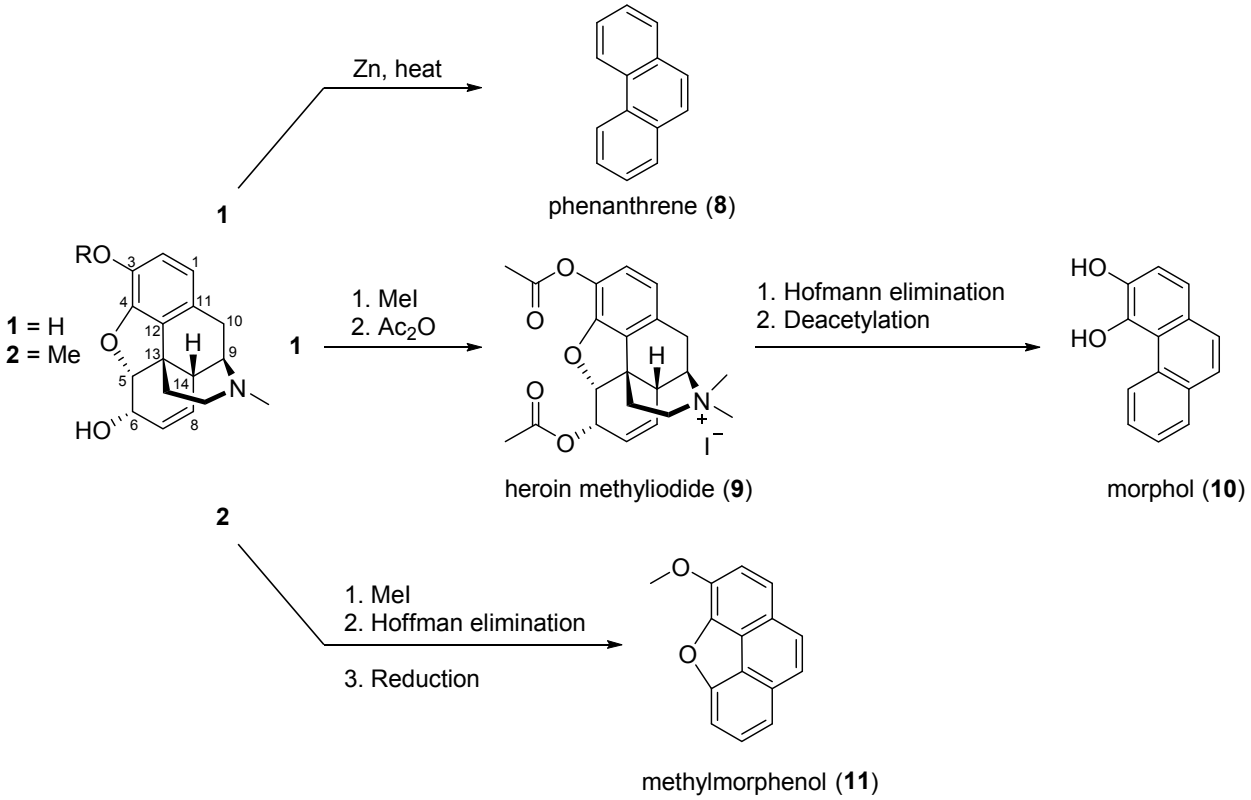


Figure 8. Determination that morphine, codeine, thebaine contain a phenanthrene and a methylmorphenol core.

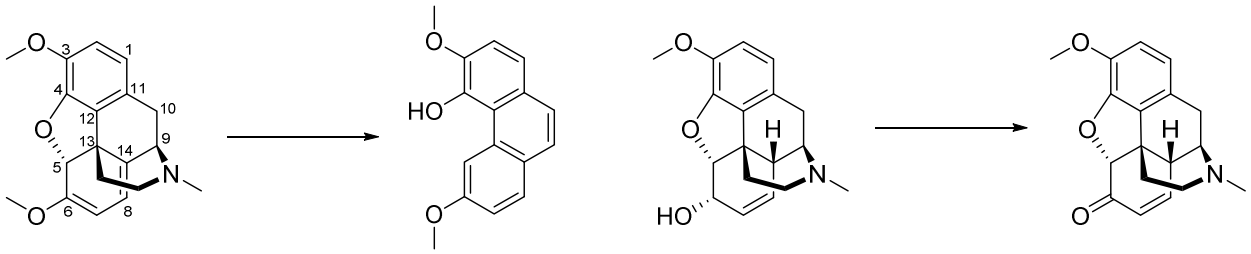


Figure 9. The isolations of thebaol and codeinone helped establish the hydroxyl at position 6.

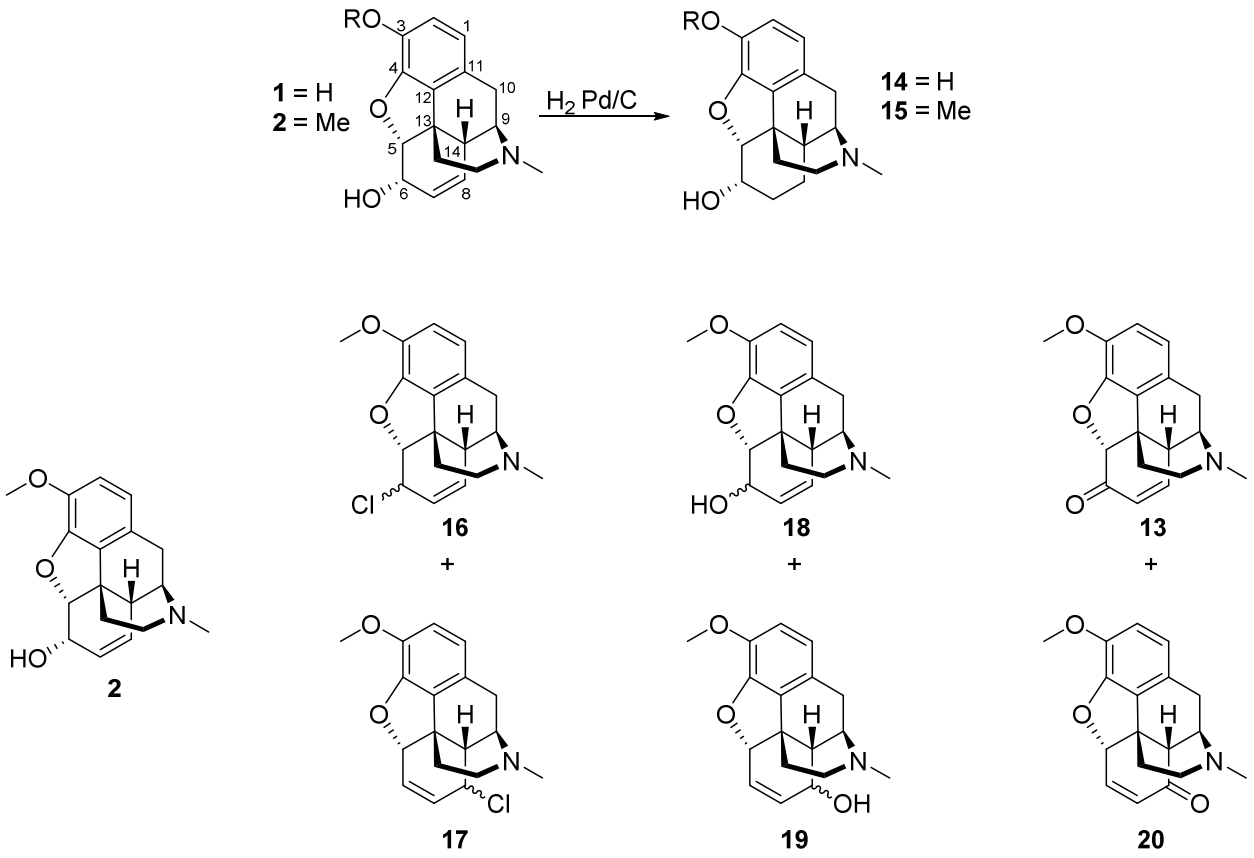


Figure 10. Determination of the relationship between the hydroxyl at position 6 and the double bond in morphine and codeine.

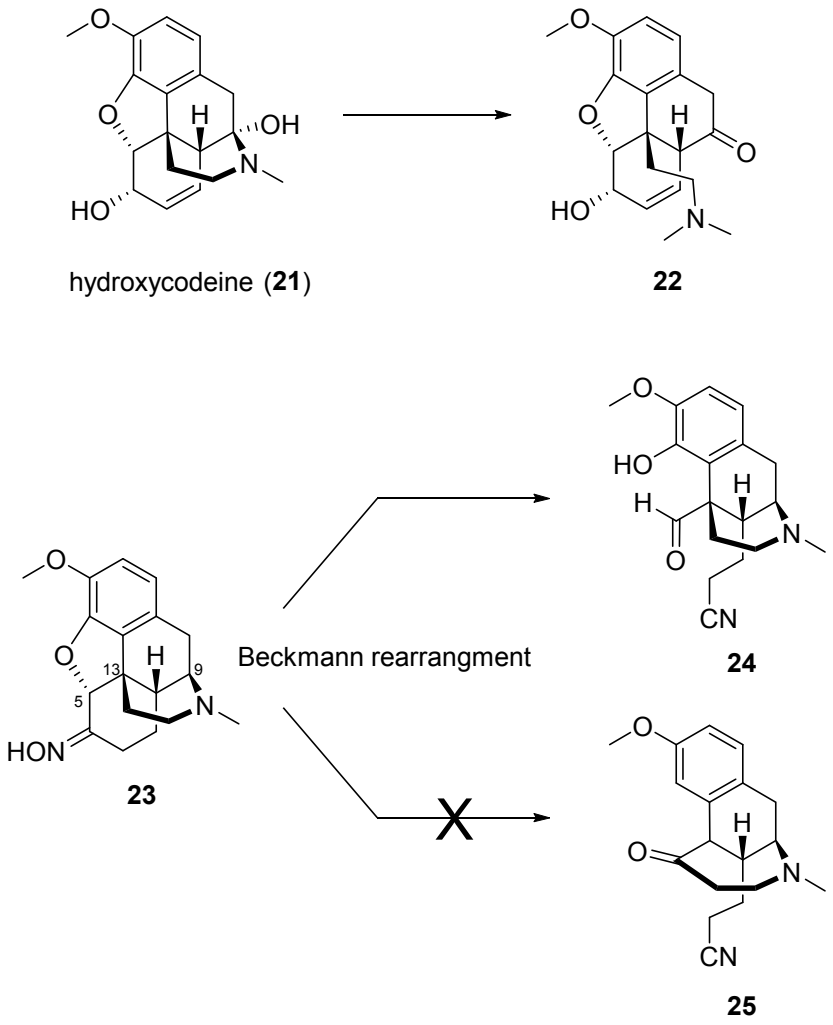


Figure 11. Confirmation for the attachments of the *N*- and ethyl terminuses.

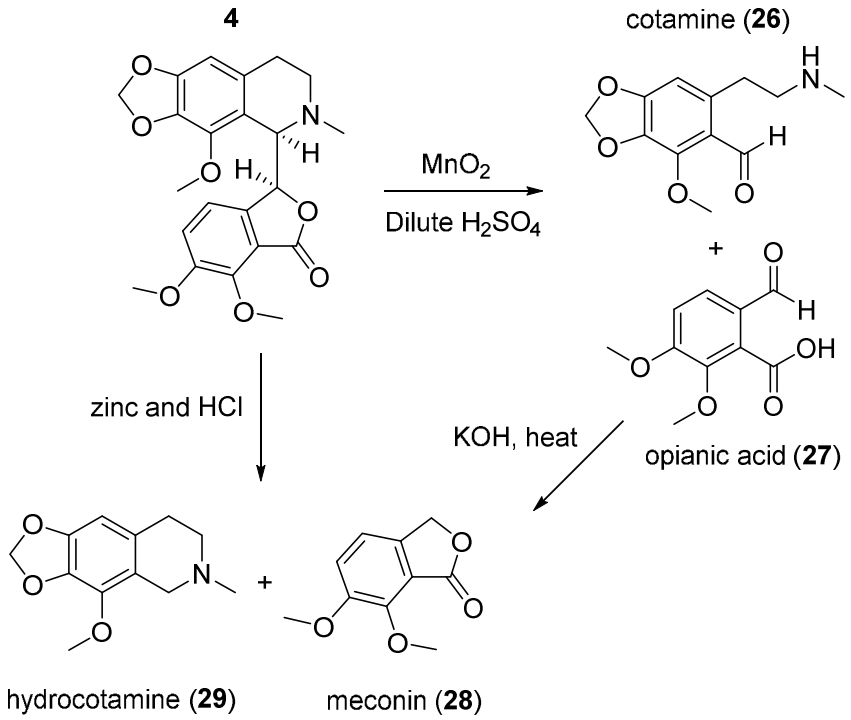


Figure 12. Degradation studies that led to the synthesis and structure determination of noscapine.

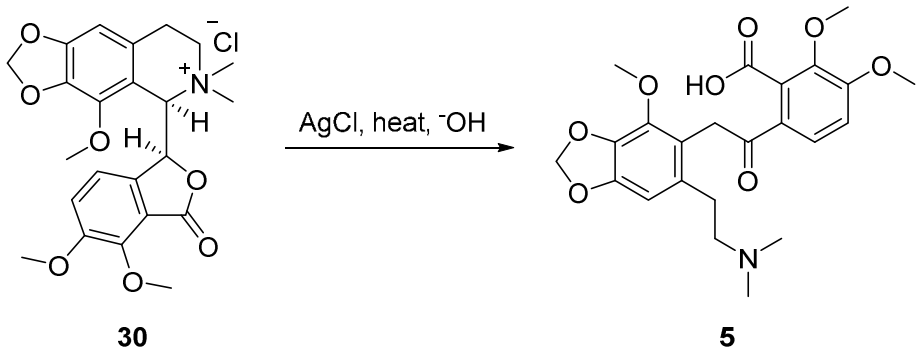


Figure 13. Structure determination of narceine via the synthesis of narceine by conversion of noscapine methylchloride into narceine.

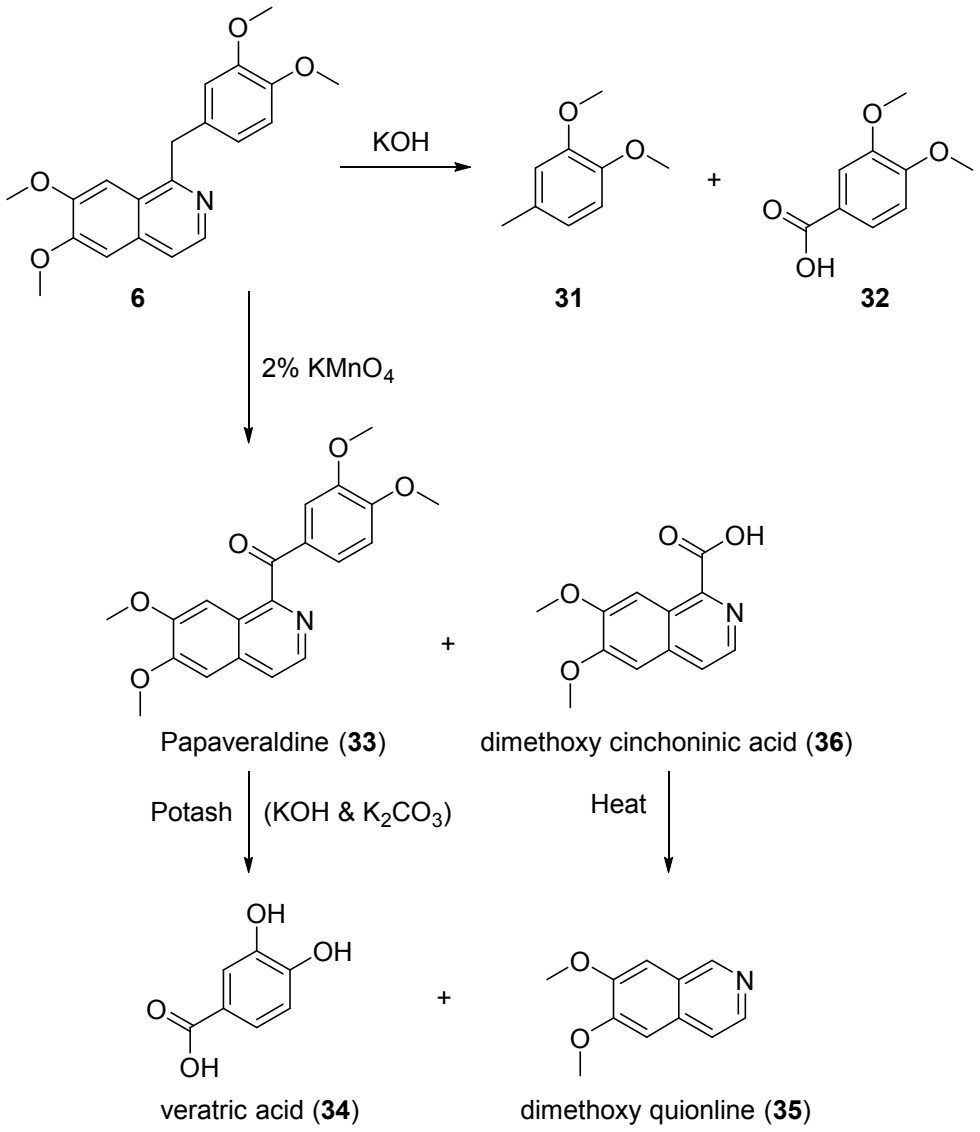
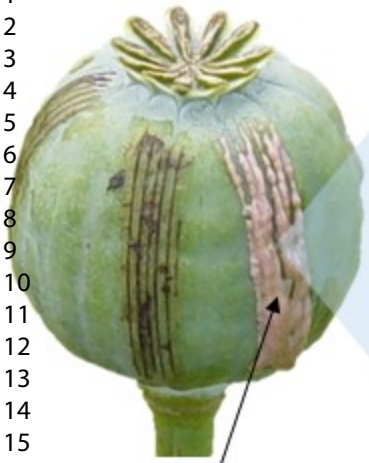
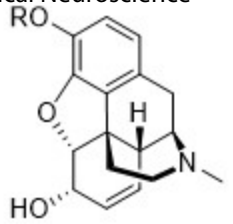


Figure 14. Degradation products of papaverine that led to the proposed structure of papaverine before it was synthesized to confirm the structure.

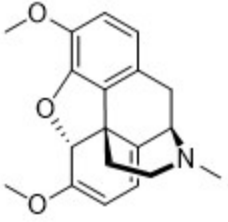
Papaver somniferum L.



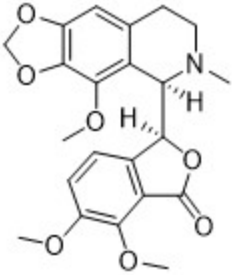
Opium Latex



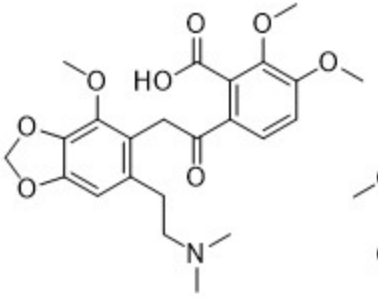
1 = OH Morphine
2 = Me Codeine



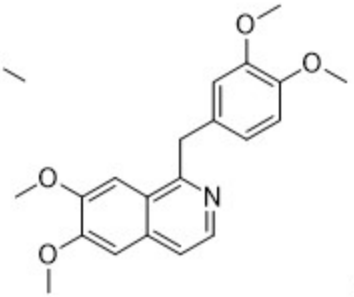
3 Thebaine



4 Noscapine



5 Narceine



6 Papaverine