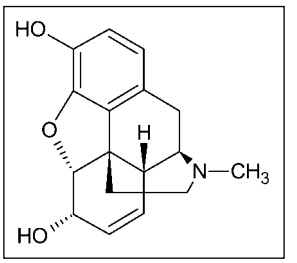
60. Morphine

CHEMICAL NAME = (5α,6α)-7,8-Didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol
CAS NUMBER = 57–27–2
MOLECULAR FORMULA = $C_{17}H_{19}NO_3$
MOLAR MASS = 285.3 g/mol
COMPOSITION = C(71.6%) H(6.7%)O N(4.9%) (16.8%)
MELTING POINT = 200°C
BOILING POINT = 254°C
DENSITY = 1.44 g/cm^3



Morphine is the principal alkaloid obtained from opium. Opium is the resinous latex that exudes from the seed pod of the opium poppy, *Papver somneferum*, when it is lacerated. Alkaloids account for approximately 25% of opium, and of this 25% about 60% is morphine. Remains of poppy seeds and pods have been found in Neolithic caves, indicating that the use of opium predates written history. The opium poppy is native to the eastern Mediterranean, but today it is chiefly cultivated from the Middle East through southern Asia and into China and Southeast Asia. The first civilization known to use opium was the Sumerians, who inhabited Mesopotamia in present-day western Iraq, around 3500 B.C.E. Sumerians traded opium with other civilizations, and this led to the cultivation of opium poppies and the production of opium in many geographic areas including Egypt, India, Persia (Iran), Southeast Asia, and China.

Opium has been used medicinally throughout history. Writings of ancient physicians in many cultures espoused the virtues of opium as a remedy for all types of ailments including pain relief, cough suppression, and diarrhea. Remedies prepared by alchemists and ancient physicians often contained opium. Galen (131–200) prescribed opium for headaches, deafness, melancholy, epilepsy, asthma, and colic. The famous European physician Paracelsus (1493–1541) produced an alcoholic potion containing opium called laudanum. Varieties of laudanum were used for several hundred years as medicinal drinks and were readily available in apothecaries.

Morphine was isolated from opium at the beginning of the 19th century, and several individuals are cited for its initial isolation. Jean François Derosne, a French pharmacist, isolated

an impure morphine salt in 1803. Another Frenchman, Armand Seguin (1767–1835), reported on the isolated salt of morphine in 1804, but he did not publish his findings until 1814. Most references credit the German pharmacist Friedrich Wilhelm Sertürner (1783–1841) as the discoverer of morphine. Sertürner worked on opium over a number of years and published his initial results in 1805. He continued his work on opium and administered the drug to himself and several others, producing severe narcotic effects. Sertürner published this research in 1817 and used the name morphium for his substance. The name morphium was derived from Morpheus, the Greek god of dreams. Upon reading Sertürner's work, the French chemist Joseph Louis Gay-Lussac (1778–1850) proposed that the name morphium be changed to morphine. This would be consistent with the proposal of that time that names for alkaloids carry an "ine" ending.

The process to obtain morphine from opium involves boiling a water-opium solution and adding calcium hydroxide ($Ca(OH_2)$). The calcium hydroxide combines with the morphine to form the water-soluble salt calcium morphenate. As the solution cools, other insoluble alkaloids precipitate out of solution, leaving morphine in solution. The solution is filtered and then reheated. Ammonium chloride (NH_4Cl) is added to increase the solution's pH level to 9–10, and the insoluble salt morphine hydrochloride is formed, which precipitates out upon cooling.

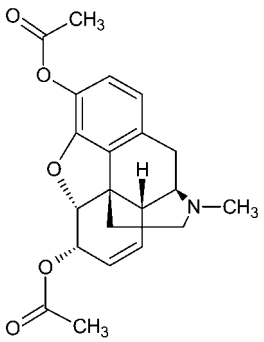
Once morphine had been determined to be the principal pain-killing ingredient in opium, it was substituted for opium in many treatments. Morphine's analgesic ability is due to its ability to bind and activate opioid receptors in the central nervous system (brain and spinal cord). There are different types of receptors found in the central nervous system, and the primary ones involving morphine are called μ-receptors (mu receptors). Morphine and related alkaloids have chemical structures that allow them to bind to opioid receptors. The structures follow what is known as the morphine rule. The morphine rule spells out how chemical units are bonded to form compounds so that the compounds attach to the opioid receptors. According to the morphine rule, pain-killing opioid compounds possess a phenyl ring attached to a quaternary carbon atom, which is attached to a tertiary amine group by two carbon atoms. The structure of the opioid receptor makes it possible to bind to different units of opioid analgesics. A flat part on the receptor binds to the phenyl ring, a cavity accepts the two carbon atoms, and an anionic region attracts the nitrogen in the tertiary amine group. When morphine or another opioid analgesic binds to the opioid receptors, it reduces the neurological transfer of pain signals to the brain. Morphine mimics natural pain relievers produced by the body called endorphins. When these natural pain-relieving compounds were discovered in the 1970s, the word *endorphin* was coined from the words endogenous and morphine.

Morphine was initially hailed as a miracle cure and was incorporated into many medications. It was erroneously thought that morphine use would eliminate the addictive effects of opium, and among its many uses in the 18th century was treating alcoholism. Morphine's addictive properties were quickly recognized and abuse of the drug ensued. Morphine addiction results from the drug's ability to produce an internal dreamlike euphoria, relaxation, and reduced anxiety. As addictive side effects were recognized, various governments attempted to combat opium and morphine abuse by curtailing its use. China lost two major confrontations with Britain over Britain's right to import illegal opium into China during the middle of the 19th century. The Opium Wars were fought as Britain sought to balance trade with China by using opium produced in India to supply addicted Chinese. Morphine was used extensively

during wars to alleviate the pain and suffering associated with battle wounds. Thousands of Civil War survivors became addicted as a result of morphine use. Thus the use of morphine was a two-edged sword: it was an effective analgesic, but it could lead to addiction.

In a search to retain morphine's analgesic property without causing addiction, modifications of morphine were explored. In 1874, C. R. Alder Wright (1844–1894), an English pharmacist working at St. Mary's Hospital Medical School in London, boiled morphine and acetic anhydride ($C_4H_6O_3$) and produced diacetylmorphine. Wright's experiments on animal subjects produced negative effects and convinced him to abandon diacetylmorphine as a morphine substitute. Twenty years after Wright's work, the German pharmaceutical company, Bayer, examined diacetylmorphine as a remedy for tuberculosis, pneumonia, and other respiratory ailments. The work at Bayer was done simultaneously as the company developed aspirin.

Diacetylmorphine was thought to be more potent than morphine and nonaddictive. It was also believed to be an effective substitute to wean addicts off morphine. Bayer marketed diacetylmorphine under the brand name Heroine, named because subjects used in clinical trials experienced a heroic feeling when it was taken. Initially, sale and use of heroine were quite liberal. It was used as a cough suppressant and to treat morphine addiction. The American Medical Association approved heroin use in 1906. As legal heroin use increased, so did reports that heroin was addictive and produced negative side effects. It was also discovered that heroin converts into morphine in the body. Therefore heroin is a prodrug, which is a substance that does not produce an effect when taken but converts into another drug within the body. Heroin's greater fat solubility allows it to move more readily across the blood-brain barrier, resulting in a greater supply of morphine to the brain and making it more potent than morphine.

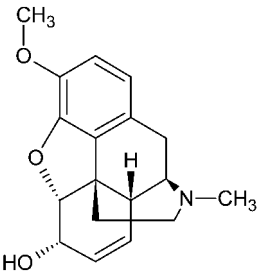


heroin

As knowledge of heroin's negative effects became known, regulations controlling the drug resulted in laws banning importation and use followed. The importation and use of heroin were banned in the United States in 1924. The regulation of heroin in most countries resulted in the illicit use and the rise of illegal syndicates to supply addicts. Today, the illicit production of opium for morphine used for heroin production is estimated to be 10 times that of licit production.

Morphine's licit use is as an analgesic and for the production of semisynthetic morphine analogs. Approximately 90% of the licit morphine produced is used to make codeine; codeine

is present in very small amounts in opium. Codeine is almost identical to morphine, with an $-OCH_3$ replacing one of the –OH groups in morphine. About 10% of codeine intake is metabolized to morphine in the liver. Thus, although codeine does not have analgesic properties, its ability to be converted into morphine enables its use as a pain reliever. Codeine is used extensively in over-the-counter cough suppressants. Although codeine is more toxic than morphine, it is preferred in medications because it is much less addictive than morphine.



codeine

The structure of morphine was first determined in 1925 by Sir Robert Robinson (1886–1975) and John Masson Gulland (1898–1947). A total synthesis of morphine was achieved in 1952 at the University of Rochester by Marshall D. Gates (1915–2003) and his co-worker Gilg Tschudi. Since its first synthesis, a number of other processes have been used to synthesize morphine in the laboratory, but none of these is economically viable. Therefore morphine continues to be obtained through biosynthesis from poppy plants.