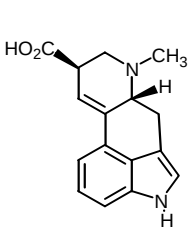
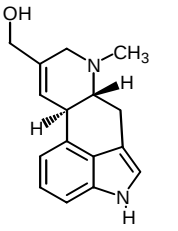
The Ergot Alkaloids

One of the pharmacologically most important groups of indole alkaloids is the ergoline, or ergot, alkaloids. These alkaloids are isolated from the dried sclerotium of the fungus *Claviceps purpurea* (Hypocreaceae) (ergot). This fungus is a parasite on rye and wheat and other grains. Ingestion of contaminated grain, most often after the grain has been made into bread, causes ergotism, also known as the "Devil's curse" or "St. Anthony's fire," and has been a problem for centuries. It has been noted in writings from China as early as 1100 B.C. and in Assyria in 600 B.C., and Julius Caesar's legions suffered an epidemic of ergotism during one of the campaigns in Gaul. In 994 A.D., an epidemic in France killed between 20,000 and 50,000 people, and in 1926, at least 11,000 cases of ergotism occurred in Russia. Ergotism can cause convulsions, nausea, and diarrhea in mild forms, and there is some thought that an outbreak of ergotism may have been the cause of the "bewitchings" which led to the Salem witch trials in the United States in 1691. Ergotism may also have caused some of the extreme destruction associated with the French Revolution. In the Middle Ages, ergotism was described as causing victims to dies "miserably, their limbs eaten up by the holy fire that blacked like charcoal." People turned to the church for help, assuming that the disease was retribution for their sins. In particular, they prayed to St. Anthony for deliverance, giving rise to the name for the disease. Ergotism takes two forms, gangrenous ergotism, in which tingling effects were felt in fingers and toes followed in many cases by dry gangrene of the limbs and finally loss of the limbs, and convulsive ergotism, in which the tingling was followed by hallucinations and delerium and epileptic-type seizures. In both cases, death was slow and painful. Ergotism has now been recognized as a result of infection by a mycotoxin, and the ergotism plagues have been eliminated. However, the alkaloids derived from ergot have assumed new importance for their pharmacological properties, and ergot is produced commercially for the preparation of these alkaloids.

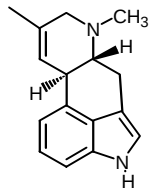
There are three main groups of ergot alkaloids, the clavine type, the water-soluble lysergic acid type, and the water-insoluble lysergic acid type or peptide ergot alkaloids. The clavine type of alkaloids, such as agroclavine and elymoclavine, are generally regarded as precursors to the other groups of ergot alkaloids in the biogenetic pathway. These alkaloids are among several of the ergot alkaloids also isolated from higher plants, particularly the seeds of *Ipomoea violacea* and *Rivea corymbosa* ('ololiuqui," the Mexican morning glory), both members of the Convolvulaceae family. These alkaloids are not used pharmacologically, but agroclavine is a powerful uterine stimulant, and many of the ergot alkaloids are prolactin release inhibitors.



lysergic acid

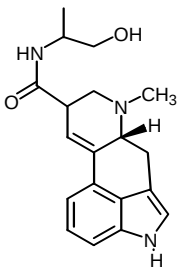


elymoclavine

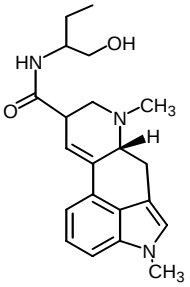


agroclavine

The water-soluble lysergic acid derivatives are most often amide derivatives. Among the most important of these are ergonovine and methysergide. Ergonovine has potent uterine contraction activity and is used in treating postpartum hemorrhages. It has low vasoconstrictor action. Methysergide is used as a cranial vasodilator in the treatment of migraine headaches.

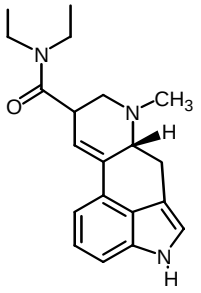


ergonovine



methysergide

Perhaps the most infamous of the semi-synthetic derivatives of the ergot alkaloids is lysergic acid diethyl amide (LSD). It was first synthesized by Albert Hofmann of Sandoz AG in 1938, but its hallucinogenic properties were not known until 1943. While working with a sample of LSD in his laboratory, Hoffmann accidentally ingested some. He described how "On a Friday afternoon, April 16, 1943, while working in the laboratory, I was seized by a peculiar sensation of vertigo and restlessness. Objects, as well as the shape of my associates in the laboratories, appeared to undergo optical changes. I was unable to concentrate on my work. In a dreamlike state, I left for home, where an irresistable urge to lie down and sleep overcame me. Light was so intense as to be unpleasant. I drew the curtains and immediately fell into a peculiar state of 'drunkenness', characterized by an exaggerated imagination. With my eyes closed, fantastic pictures of extraordinary plasticity and intensive color seemed to surge towards me. After two hours, this state gradually subsided

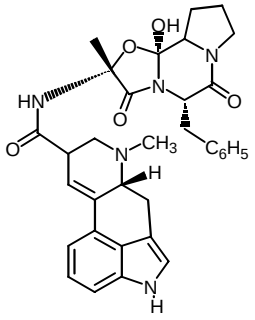


lysergic acid diethylamide

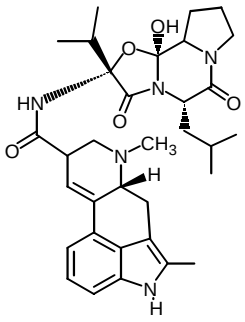
and I was able to eat dinner with a good appetite." The following Monday, to confirm that he had indeed ingested some of the LSD, Hoffmann prepared a solution containing 250 µg of LSD and deliberately ingested it. After 40 minutes, he found he had " difficulty in concentration, visual disturbances, marked desire to laugh" and left for home. On the ride home "I had great difficulty in speaking coherently, my field of vision swayed before me....I had the impression of being unable to move from the spot." The symptoms continued for six hours after Hoffmann reached his home and he described how "all objects appeared in unpleasant, constantly changing colors, the predominant shades being sickly green and blue...A remarkable feature was the manner in which all acoustic perceptions were transformed into optical effects." Hoffmann had taken approximately five times the "normal" dose of LSD and had experienced the first "bad trip."

For a while following the discovery of the pharmacological effects of LSD, it was used in psychiatry, particularly in the treatment of alcoholic schizophrenia. In recent years, evidence has come out that it was used in the 1950s on military "volunteers" to study its effect, presumably as a chemical warfare weapon. In the early 1960s, proponents of its use as a way to achieve a state of nirvana, such as Dr. Timothy Leary, began using it heavily and distributing it throughout the high school and college age population, often adsorbed into a sugar cube. This attitude that LSD was a "good drug" was fostered by popular songs, like the Jefferson Airplane's "White Rabbit" and the Beatles' "Lucy In The Sky With Diamonds", which supposedly described the effects of "good" LSD trips. Unfortunately, many LSD trips turned out to be bad trips, and many heavy users of LSD experienced bad flashback trips at a later time. (One sidelight to the hallucinogenic effects of LSD is the result of finding ergot alkaloids in Mexican morning glory seeds. Some seekers of nirvana through hallucinogens began ingesting large quantities of morning glory seeds. Rather than hallucinogenic activity, these foolish people experienced primarily toxic reactions thus obtaining nirvana in an unintended way.) After a relatively brief time, the popularity of LSD as a hallucinogen diminished, and it became somewhat of a historical relic. However, it has started to make a comeback in the drug underground in recent years. This time, the target seems to be grade school age children, and the pushing of LSD to these children may be viewed by some as a means of hooking them on hard drugs like cocaine and heroin as they grow older.

The water-insoluble lysergic acid derivatives are primarily peptide ergot alkaloids like ergotamine. This compound was first isolated in 1918, but its structure was not determined until 1951. Ergotamine, as its tartrate salt, is a analgesic specifically used for treatment of severe migraine headaches. It is often used in conjunction with caffeine, which constricts cerebral blood vessels, and a dose of 2 mg taken orally often results in quick relief. 2-Bromo-α-ergocryptine, a semisynthetic derivative, has reduced toxicity and is now commercially available to be used in the reduction of lactation in women. It has also been used in treatment of sexual disorders, and has been shown to enhance sexual libidos in both men and women.



ergotamine



2-bromo-α-ergokryptine