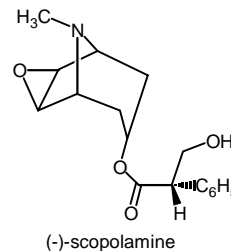


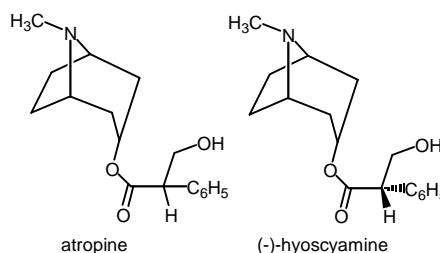
## The Tropane Alkaloids

The tropane alkaloids, which have the 8-azabicyclo[3.2.1]octane nucleus, are commonly found in plants of three families, the Solanaceae, Erythroxylaceae, and Convolvulaceae families. The alkaloids isolated from plants of these families, while having several legitimate medicinal uses, are probably best known for their toxic properties. This can be a major problem since the plants produce very attractive berries which are tempting to small children. As few as three berries of henbane (*Hyoscyamus niger*) or deadly nightshade (*Atropa belladonna*) can cause death in infants. Many of the plants in the Solanaceae family contain tropane alkaloids, which are responsible for the toxic effects of the plants. Cleopatra is reputed to have tested the effects of henbane and deadly nightshade on her slaves to investigate the possibility of using these extracts to commit suicide (she found the toxic effects too painful). The wives of the Roman emperors, Augustus and Claudius, used deadly nightshade to murder large numbers of Romans. The mandrake (*Mandragora officinarum*) was reputed to possess aphrodisiac properties and was prized for these properties. However, the roots also contain large quantities of the tropane alkaloid hyoscine (scopolamine), making the plant highly toxic.



*Datura stramonium*, a plant common to Virginia, and other *Datura* species are widely distributed throughout the world. These plants have a long history of being used as both sedatives and as poisons. Extracts of *Datura metel*, sometimes called Hindu Datura, were used as knockout drops to lure virgins into prostitution and then by the prostitutes to sedate their clients. The Roman army led by Mark Antony in Asia Minor was severely crippled by deaths caused by eating a *Datura* species. Indians in Colombia used another *Datura* species for infanticide. Infants died after nursing when an extract of *Datura* was smeared on the nipples of the mother. *Datura stramonium* is also known as jimsonweed and, after nearly taking the lives of some of the Jamestown settlers, was widely used for medicinal purposes, primarily as a sedative. In the 1960's and 1970's, there were a number of cases of poisoning due to jimsonweed when people ingested the plant to try to induce a high similar to cocaine.

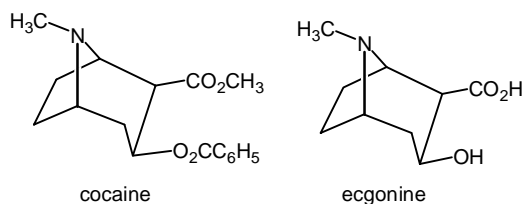
The Solanaceae alkaloids derived from these plants, while very toxic, are often important medicinal agents. Atropine, the racemic form of (-)-hyoscyamine, was first isolated from *Atropa belladonna* in 1833. (-)-Hyoscyamine was also isolated in 1833 from *Hyoscyamus niger*. This tropane alkaloid is a muscarinic receptor antagonist. Muscarinic receptors are involved in constriction of the pupil, vasodilation, moderating the heartbeat, and stimulating secretions. The most familiar use of atropine, as the sulfate salt, is as a mydriatic to dilate the pupil of the eye during an ophthalmological examination. In fact, the



juice of the berries of *A. belladonna* was used during the Renaissance by ladies of the Italian courts to exaggerate the size of their eyes by dilating the pupils. (The rough translation of belladonna from Italian is beautiful lady.) Atropine has also found use as a CNS stimulant and is useful in treating poisoning cases, particularly anticholinesterase poisoning induced by organophosphorous insecticides and nerve gas and poisoning induced by the toxic principles of the mushroom *Amanita muscaria*. Scopolamine, (-)-hyoscyamine, which was first isolated in 1881 from *Hyoscyamus muticus* and *Scopolia atropides* is a CNS depressant at high doses, and has been used in combination with morphine to induce "twilight sleep" before and during labor, and in smaller doses, to prevent motion sickness.

In recent years, a tropane alkaloid isolated from several Erythroxylaceae species has become more notorious. This, of course, is cocaine, which was first isolated from coca, the dried leaves of *Erythroxylum coca* (Bolivian coca) or *Erythroxylum truxillense* (Peruvian coca), in 1862 by Wohler. The anesthetic properties of cocaine have been known since the 1880's.

The hydrochloride of cocaine is used as a topical anesthetic in ophthalmology as 1% solution (maximum). Cocaine is toxic in large enough doses when taken internally, particularly when taken by injection, but is also a potent CNS stimulant which has led to its abuse. It is addictive but withdrawal effects are reputed to be mild. (These effects have also been known since the late 19th



century. Remember that Sherlock Holmes, Sir Arthur Conan Doyle's legendary detective, was a habitual user of cocaine.)

Coca has been of economic importance in Western cultures since the 1500's. But coca was also important to the Indian cultures of South America, particularly the Incas in Peru, for at least 1000 years before the Spanish arrived in the New World. Chewing coca leaves provided a stimulatory effect for herdsmen and other workers in the Inca culture, but it was not in common usage by every Indian. Once the Spanish arrived, coca leaves became an important commodity, and for a while was used in place of money in South America. Coca chewing increased among both natives and Europeans, but many churchmen and missionaries were opposed to its use, particularly among the natives (who needed to be converted to Catholicism). Since the alkaloid content of the coca leaves degraded upon long storage, it wasn't until the 1800's that coca made larger inroads into Europe. In the late 1800's, a number of beverages based on coca began to appear, including several coca wines, for use as mild stimulants. In 1886, John Styth Pemberton reformulated his coca wine into a nonalcoholic beverage, which he named Coca-Cola, to get around a developing temperance movement. The original formulation of Coca-Cola used coca leaf from South America which contains very low amounts of cocaine. One estimate is that the original formulation contained, at most, 1.5 mg of cocaine per ounce of Coca-Cola, not enough to provide any stimulation or cause addiction. (The stimulatory effect of Coca-Cola more likely comes from the caffeine content.) By 1906, all cocaine had been eliminated from the formula of Coca-Cola, and in 1911, in a strange turn of events, the makers were sued by the government for false advertising because the beverage did not contain cocaine!

Ecgonine is the parent alkaloid of cocaine, and can be easily produced from cocaine and other esters isolated from the plant by acid hydrolysis. Cocaine can then be prepared from ecgonine by treatment with methanol followed by benzoic acid. This is the basic procedure used in the clandestine drug labs.