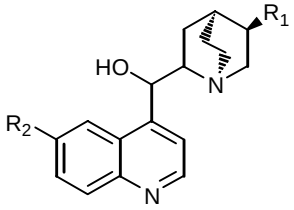
The Quinine Alkaloids

The *Cinchona* alkaloids are another very important subgroup of the polycyclic β-carboline alkaloids. Prior to about 300 years ago, malaria was the scourge of the Western world. Malaria was probably the most common disease in Rome and London at the time. Even today, millions of people die each year from malaria, and hundreds of millions of people suffer from the disease. The disease is caused by a protozoa of the genus *Plasmodium* spread as spores contained in the *Anopheles* mosquito which spreads them into the bloodstream of human victims. The major cure for this dread disease is quinine, the principal alkaloid of the *Cinchona* tree which is indigenous to the tropical Andes mountains. There are many tales of how the antimalarial properties of *Cinchona* bark was first discovered, but the first written report of its efficacy was by Father Calancha in the *Chronicle of St. Augustine* in 1633. It was at least twelve more years before a Father Tafur brought some of the bark back to Rome. The cures which were accomplished by drinking a "beverage" made from the powdered bark were nothing short of amazing. However, the fact that it was coming from the Catholic church made the cure suspect to Protestants, and Oliver Cromwell died in 1658 from malaria, even though the cure was available. The actual *Cinchona* or fever tree was not discovered until 1737. Before that time, the Jesuits who discovered the cure had to make due with trading with the Indians for the bark. Supposedly, the Indians hid the tree from the Europeans as a means of driving them from South America. Supplies of the tree were rapidly depleted in South America, and Java, under the Dutch, became the main supplier of *Cinchona* alkaloids until World War II when synthetic antimalarial agents became widely available. In recent years, strains of malaria which are resistant to the synthetic antimalarials have begun to make their appearance, and the value of quinine as an antimalarial agent is once again on the rise.



R_1	R_2	(+)-isomer	(-)-isomer
$-CH=CH_2$	-H	cinchonine	cinchonidine
$-CH=CH_2$	$-OCH_3$	quinidine	quinine
$-CH_2CH_3$	-H	dihydrocinchonine	dihydrocinchonidine
$-CH_2CH_3$	$-OCH_3$	dihydroquinidine	dihydroquinine

Quinine was first isolated in 1820 by Joseph Pelletier and Joseph Caventou, but the structure determination took over 100 years. By 1884, 25 additional alkaloids related to quinine had been isolated, and an additional 6 were added between 1884 and 1941. Approximately 13 out of the 31 still have unknown structures. There are eight major alkaloids which occur as four pairs of enantiomers, as shown above. The (+)-isomers have the 2R,3S configuration, and the (-)-isomers have the 2S,3R configuration. Quinine has typically been the most used of the alkaloids for pharmacological purposes, simply because it was the first isolated. Quinine, in addition to its antimalarial properties, is a bacteriocide, local anesthetic, cardiosvascular stimulant, and analgesic. Quinidine, in addition to its antimalarial properties, has been used to prevent certain types of cardiac arrythmias.