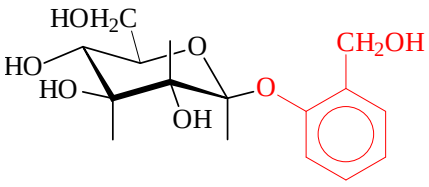
A BRIEF HISTORY OF ORGANIC COMPOUNDS RELATED TO ASPIRIN[1]

The antipyretic (fever reducing) property of the bark of the Willow tree (*Salix alba*) was known to the ancient Greeks.

The underlying chemistry of the action of this natural material was unraveled in the 19th century. An examination of the developments surrounding organic compounds related to to aspirin provides an interesting perspective on the state of development of this aspect of chemistry.

1763

Edward Stone noticed that chewing the bark of the willow tree helped to relieve the symptoms of malaria – chills and fever



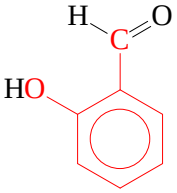
Salicin

1827

The active ingredient in willow bark, **salicin**, was isolated.

1831

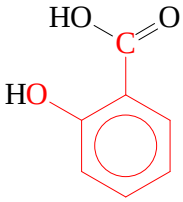
A Swiss pharmacist, Johann Pagenstecher, distilled meadowsweet flowers and obtained and characterized a substance called **salicylaldehyde**. One variety of meadowsweet has the scientific name *Spiraea salicifolia*.



Salicylaldehyde

1835

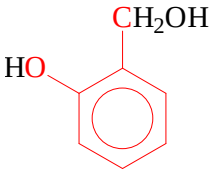
The German chemist, Karl Löwig, isolated **salicylic acid** (which he named Spirsäure) from a mixture of products obtained from the alkaline hydrolysis of **salicylaldehyde**.



Salicylic acid

1838

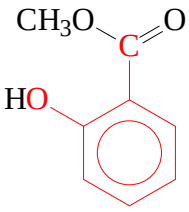
Raffaele Pivia, an Italian Chemist, hydrolyzes **salicin** to produce glucose and **salicyl alcohol**. He further oxidizes salicyl alcohol to salicylic acid, establishing a connection between that substance and the active ingredient in willow bark



Salicyl alcohol

1843

A related compound, **methyl salicylate**, was found by the French chemist, Auguste Cahours, and the American chemist, William Proctor, to be a major constituent of oil of wintergreen, which was extracted from the leaves of the wintergreen plant. Methyl salicylate continues to be used as a flavorant and a medicinal to this day. It is used in many medicines to relieve aching muscles.

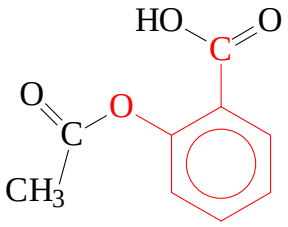


Methyl Salicylate

[1] This history draws heavily from the excellent book "Organic Molecules in Action" by Goodman and Morehouse (Gordon and Breach, 1973)

1853

Charles Gerhardt of Strasbourg replaced the OH of salicylic acid with an acetyl group using acetic anyhdride, the first synthesis of **acetyl salicylic acid**, which was later to become called aspirin.



Acetylsalicylic acid
(Aspirin)

1859

Hermann Kolbe developed a convenient and inexpensive synthesis of salicylic acid.

1859 – 1993

During this period, salicylic acid which is moderately strong acid ($pK_a = 3$) was widely used as a medicine. The acid burned the mouth. Efforts to moderate the effects of its acidity resulted in the administration of the sodium salt of salicylic acid, sodium salicylate. The salt, however has an unpleasant taste.

1893

In an effort to find a less unpleasant way to administer salicylic acid, Felix Hoffman, a chemist working for the Bayer pharmaceutical company in Germany, reinvestigated the acetylation reaction first conducted by Gerhardt in 1853. Hoffman's father was rheumatic, which added a personal motivation for finding such a substitute.

The synthetic material,.called **aspirin** (*a* for acetyl, and the *spir* root, undoubtedly borrowed from the Latin name for meadowsweet) was shown to have all of the desirable properties of salicylic acid, but lacked the strong acidity of the acid and the unpleasant taste of the its sodium salt.