# A Brief History of Organic Compounds Related to Aspirin*

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

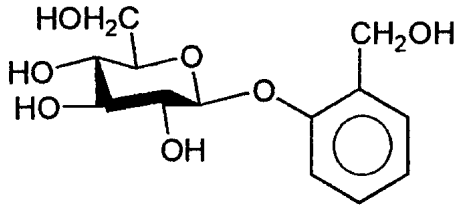
The underlying chemistry of the action of this natural material was unraveled in the 19th century. An examination of the developments surrounding organic compounds related to aspirin provides an interesting perspective on the state of development of this aspect of chemistry.

## 1763

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

## 1827

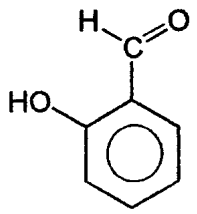
The active ingredient in willow bark, **salicin**, was isolated.




Salicin

## 1831

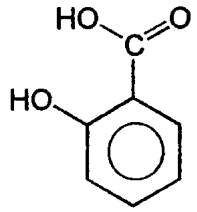
A Swiss pharmacist, Johann Pagenstecher, distilled meadowsweet flowers and obtained and characterized a substance called **salicylaldehyde**. One variety of meadowsweet has the scientific name *Spiraea salicifolia*.




Salicylaldehye

## 1835

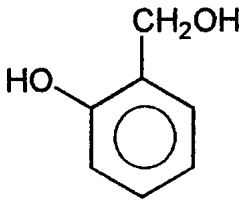
The German chemist, Karl Löwig, isolated **salicylic acid** (which he named Spirsäure) from a mixture of products obtained from the alkaline hydrolysis of **salicylaldehyde**.




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.



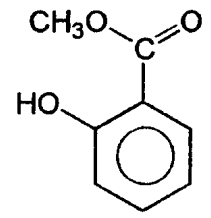

Salicyl alcohol

---

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

## 1843

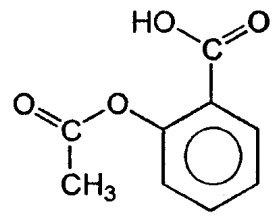
A related compound, **methyl salicylate**, was found by the French chemist, Auguste Cahours, and the American chemist, William Proctor, to be a major constituent of oil of wintergreen, which was extracted from the leaves of the wintergreen plant. Methyl salicylate continues to be used as a flavorant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



Methyl Salicylate

## 1853

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



Acetylsalicylic acid
(Aspirin)

## 1859

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

## 1859–1893

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.

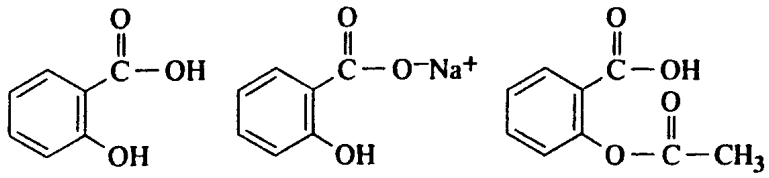
The synthetic material called **aspirin** (a for acetyl, and the ***spir*** root, undoubtedly borrowed from the Latin name for meadowsweet) was shown to have all of the desirable properties of salicylic acid, but lacked the strong acidity of the acid and the unpleasant taste of the its sodium salt.

## Essay: Aspirin

Aspirin is one of the most popular cure-alls of modern life. Even though its curious history began over 200 years ago, we still have much to learn about this enigmatic remedy. No one yet knows exactly how or why it works, yet more than 15 billion aspirin tablets are consumed each year in the United States.

The history of aspirin began on June 2, 1763, when Edward Stone, a clergyman, read a paper to the Royal Society of London entitled "An Account of the Success of the Bark of the Willow in the Cure of Agues." By *ague,* Stone was referring to what we now call malaria, but his use of the word *cure* was optimistic; what his extract of willow bark actually did was to reduce the feverish symptoms of the disease. Almost a century later, a Scottish physician was to find that extracts of willow bark would also alleviate the symptoms of acute rheumatism. This extract was ultimately found to be a powerful **analgesic** (pain reliever), **antipyretic** (fever reducer), and **anti-inflammatory** (reduces swelling) drug.

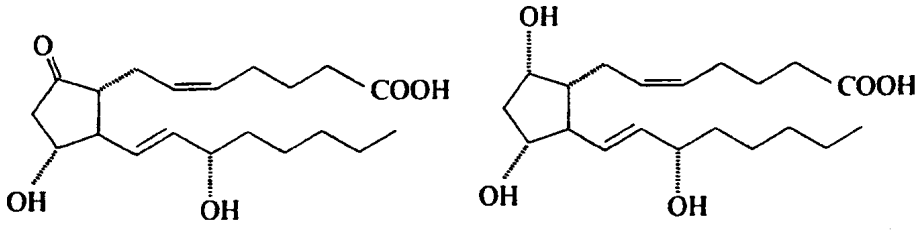
Soon thereafter, organic chemists working with willow bark extract and flowers of the meadowsweet plant (which gave a similar compound) isolated and identified the active ingredient as salicylic acid (from *salix,* the Latin name for the willow tree). The substance could then be chemically produced in large quantities for medical use. It soon became apparent that using salicylic acid as a remedy was severely limited by its acidic properties. The substance irritated the mucous membranes lining the mouth, gullet, and stomach. The first attempts at circumventing this problem by using the less acidic sodium salt (sodium salicylate) were only partially successful. This substance was less irritating but had such an objectionable sweetish taste that most people could not be induced to take it. The breakthrough came at the turn of the century (1893) when Felix Hofmann, a chemist for the German firm of Bayer, devised a practical route for synthesizing acetylsalicylic acid, which was found to have all the same medicinal properties without the highly objectionable taste or the high degree of mucosal-membrane irritation. Bayer called its new product "aspirin," a name derived from *a-* for acetyl, and the root *-spir,* from the Latin name for the meadowsweet plant, *spirea.*




Salicylic acid | Sodium salicylate | Acetylsalicylic acid (aspirin)

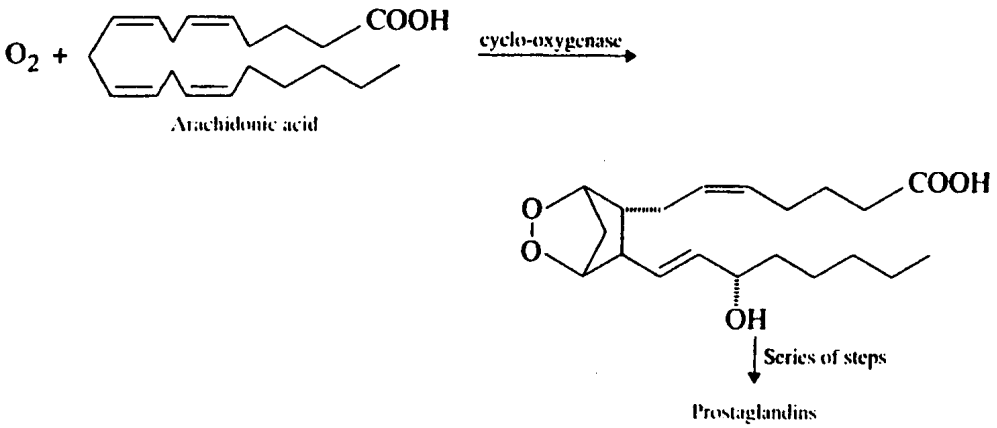
The history of aspirin is typical of many of the medicinal substances in current use. Many began as crude plant extracts or folk remedies whose active ingredients were isolated and structure were determined by chemists, who then improved on the original.

In the last few years, the mode of action of aspirin has just begun to be explained. A whole new class of compounds, called **prostaglandins**, has been found to be involved in the body's immune responses. Their synthesis is provoked by interference with the body's normal functioning by foreign substances or unaccustomed stimuli.




Prostaglandin $E_2$ | Prostaglandin $F_{2\alpha}$

These substances are involved in a wide variety of physiological processes and are thought to be responsible for evoking pain, fever, and local inflammation. Aspirin has recently been shown to prevent bodily synthesis of proslaglandins and thus to alleviate the symptomatic portion (fever, pain, inflammation, menstrual cramps) of the body's immune responses (that is, the ones that let you know something is wrong). One report suggests that aspirin may inactivate one of the enzymes responsible for the synthesis of prostaglandins. The natural precursor for prostaglandin synthesis is **arachidonic acid**. This substance is converted to a peroxide intermediate by an enzyme called **cyclo-oxygenase**, or prostaglandin synthase. This intermediate is converted further to pro-

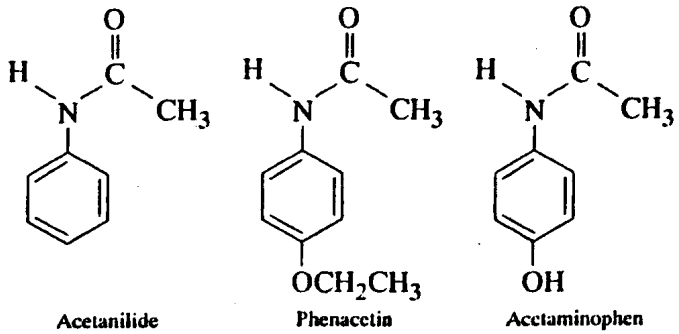



staglandin. The apparent role of aspirin is to attach an acetyl group to the active site of cyclo-oxygenase, thus rendering it unable to convert arachidonic acid to the peroxide intermediate. In this way, prostaglandin synthesis is blocked.

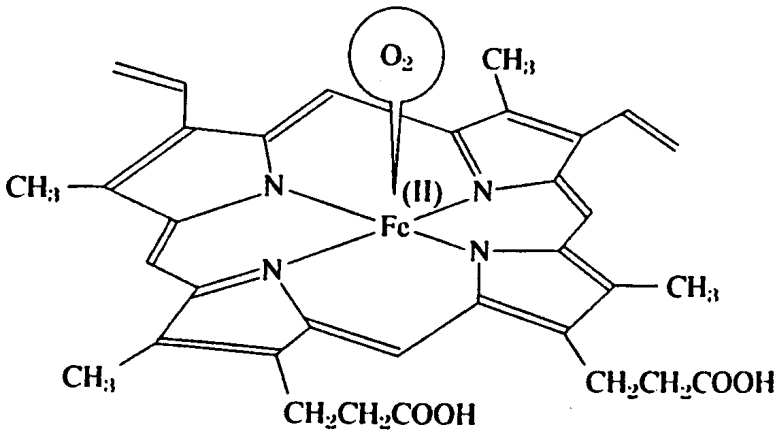
Aspirin tablets (5-grain size) are usually compounded of about 0.32 g of acetylsalicylic acid pressed together with a small amount of starch, which binds the ingredients. Buffered aspirin usually contains a basic buffering agent to reduce the acidic irritation of mucous membranes in the stomach, because the acetylated product is not totally free of this irritating effect. Bufferin contains 0.325 g of aspirin together with calcium carbonate, magnesium oxide, and magnesium carbonate as buffering agents. Combination pain relievers usually contain aspirin, acetaminophen, and caffeine. Extra-Strength Excedrin, for instance, contains 0.250 g aspirin, 0.250 g acetaminophen, and 0.065 g caffeine.

## Essay: Analgesics

Acylated aromatic amines (those having an acyl group, $R-\overset{\overset{O}{\|}}{C}-$ , substituted on nitrogen) are important in over-the-counter headache remedies. Over-the-counter drugs are those you may buy without a prescription. Acetanilide, phenacetin, and acetaminophen are mild analgesics (relieve pain) and antipyretics (reduce fever) and are important, along with aspirin, in many nonprescription drugs.



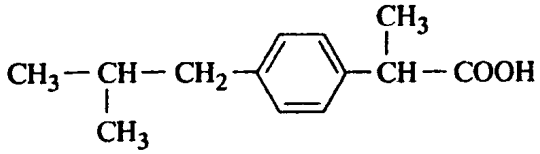
On continued or excessive use, acetanilide can cause a serious blood disorder called **methemoglobinemia**. In this disorder, the central iron atom in hemoglobin is converted from Fe(II) to Fe(III) to give methemoglobin. Methemoglobin will not function as an oxygen carrier in the bloodstream. The result is a type of anemia (deficiency of hemoglobin or lack of red blood cells).




**Heme portion of blood-oxygen carrier, hemoglobin.**

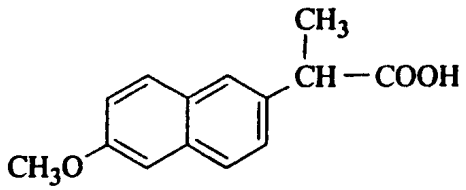
Phenacetin and acetaminophen cause the same disorder, but to a much lesser degree. Because they are also more effective as antipyretic and analgesic drugs than acetanilide, they are preferred remedies. Acetaminophen is marketed under a variety of trade names, including Tylenol, Datril, and Panadol, and is often successfully used by people who are allergic to aspirin.

More recently, a new drug has appeared in over-the-counter preparations. This drug is **ibuprofen**, which was first marketed as a prescription drug in the United States under the name Motrin. Ibuprofen was first developed in England in 1964. United States marketing rights were obtained in 1974. Ibuprofen is now sold without prescription under brand names, which include Advil, Motrin, and Nuprin. Ibuprofen is principally an anti-inflammatory drug, but it is also effective as an analgesic and an antipyretic. It is particularly effective in treating the symptoms of rheumatoid arthritis and menstrual cramps. Ibuprofen appears to control the production of prostaglandins, which parallels the mode of action of aspirin. An important advantage of ibuprofen is that it is a very powerful pain reliever. One 200 mg tablet is as effective as two tablets (650 mg) of aspirin. Furthermore, ibuprofen has a more advantageous dose-response curve, which means that taking two tablets of this drug is approximately twice as effective as one tablet for certain types of pain. Aspirin and acetaminophen reach their maximum effective dose at two tablets. Little additional relief is gained at doses above that level. Ibuprofen, however, continues to increase its effectiveness up to the 400 mg level (the equivalent of four tablets of aspirin or acetaminophen). Ibuprofen is a relatively safe drug, but its use should be avoided in cases of aspirin allergy, kidney problems, ulcers, asthma, hypertension, or heart disease.

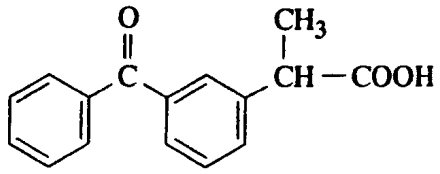



Ibuprofen

The Food and Drug Administration has also approved two other drugs with similar structures to ibuprofen for over-the-counter use as pain relievers. These new drugs are known by their generic names, **naproxen** and **ketoprofen**. Naproxen is often administered in the form of its sodium salt. Naproxen and ketoprofen can be used to alleviate the pain of headaches, toothaches, muscle aches, backaches, arthritis, and menstrual cramps, and they can also be used to reduce fever. They appear to have a longer duration of action than the older analgesics.



Naproxen



Ketoprofen

**Analgesics and Caffeine in Some Common Preparations**

| | *Aspirin* | *Acetaminophen* | *Caffeine* | *Salicylamide* | *Ibuprofen* | *Ketoprofen* | *Naproxen* |
|---|---|---|---|---|---|---|---|
| Aspirin* | 0.325 g | — | — | — | — | — | — |
| Anacin | 0.400 g | — | 0.032 g | — | — | — | — |
| Bufferin | 0.325 g | — | — | — | — | — | — |
| Cope | 0.421 g | — | 0.032 g | — | — | — | — |
| Excedrin (Extra-Strength) | 0.250 g | 0.250 g | 0.065 g | — | — | — | — |
| Tylenol | — | 0.325 g | — | — | — | — | — |
| B.C. Tablets | 0.325 g | — | 0.016 g | 0.095 g | — | — | — |
| Advil | — | — | — | — | 0.200 g | — | — |
| Aleve | — | — | — | — | — | — | 0.220 g |
| Orudis | — | — | — | — | — | 0.0125 g | — |

Note: Nonanalgesic ingredients (e.g., buffers) are not listed.
*5-grain tablet (1 grain = 0.0648 g).

**Reference:** The two Essays and Brief History are excerpted from K. F. Cerny and M. H. Schwartz, "Laboratory Manual for Organic Chemistry," Revised Printing, Kendall / Hunt Publishing Co., Dubuque, Iowa, 2001, pp.65-72, 84-87.