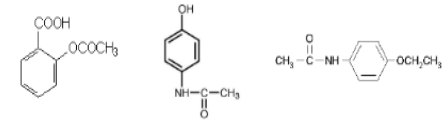
Chemistry of Antipyretics

Antipyretics:

- Chemical substances which are used to bring down body temperature with high fevers are called antipyretics. They don't have any effect on the human body when it is at normal temperature. This causes the body to lose heat and thus the temperature of body decreases.
- Aspirin, paracetamol, analgin, phenacetin acts as antipyretics.



2-Acetoxybenzoic acid
Aspirin

4-Acetamidophenol
Paracetamol

Phenacetin

- Aspirin is common antipyretic. But it has the side effect. on hydrolysis, it gives salicylic acid which causes bleeding in the stomach. It should not be taken on an empty stomach. Some persons are allergic to aspirin. The usual allergic reactions are rashes on the skin, lowering of blood pressure, profuse sweating, intense thirst, nausea, and vomiting.
- Calcium and sodium salts of aspirin are more soluble hence are less harmful.
- Aspirin has anti-blood clotting action. Hence it is used in the prevention of heart attacks.
- Other antipyretics used are novalgin, phenyl butazone, methacetin and butazolidine.

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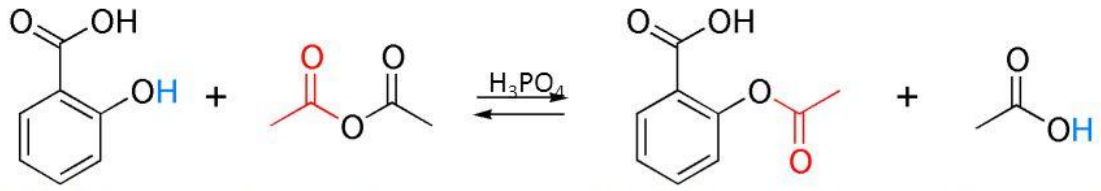
Everyday medicines : antipyretic
hemantmore.org.in/science/chemistry/everyday-medicines/2169/

- **Chemical Names:**
  - Aspirin: 2-Acetoxybenzoic acid
  - Paracetamol: 4-Acetamidophenol
  - Phenacetin: N-(4-Ethoxyphenyl)acetamide
  - Methacetin: 4-Methoxy acetanilide.

Preparation of Aspirin:

- When salicylic acid is treated with the mixture of acetic anhydride and glacial acetic acid in presence of concentrated sulphuric acid, acetylation of salicylic acid takes place and aspirin is obtained.

Aspirin: *synthesis*



Salicylic acid
$C_7H_6O_3$
MW = 138.12

Acetic anhydride
$C_4H_6O_3$
MW = 102.09

Acetyl salicylic acid
$C_9H_8O_4$
MW = 180.16

Acetic acid
$C_2H_4O_2$
MW = 60.05

- Place 1.5g of salicylic acid in a 125 mL Erlenmeyer flask
- In the fume hood, add 4 mL of acetic anhydride and 4 drops of 85% H_3PO_4
- Stir and place in a boiling water bath for 5 mins
- Remove the flask, and immediately stir in 3 mL of water stir for 2 mins then add another 30 mL
- Aspirin should start to precipitate
- Place flask in ice bath to complete precipitation

DISADVANTAGES OF ASPIRIN

- It causes bleeding in the lining of the stomach.
- It may also cause the formation of ulcers on the lining of the stomach.
- It is associated with bronchial asthma.
- Children under the age of twelve, who have been consuming Aspirin on a regular basis, have been associated with Reye's disease. Reye's disease is a fatal disease of the liver and the brain with symptoms of vomiting, lethargy, irritability, and confusion.
- Overdose of aspirin causes acidosis caused due to a lowering of the pH of the blood.

ADVANTAGES OF ASPIRIN

- It minimizes the coagulation of blood, and is thus given to individuals with the risk of a heart attack or stroke.
- It helps to relieve the symptoms of arthritis and rheumatism.
- It is non-addictive.

Paracetamol

- Paracetamol (acetaminophen) was first synthesized by Joseph von Mering in 1893.
- Paracetamol (acetaminophen) is widely used as an analgesic (pain reliever) and an antipyretic (for reducing fever).
- The systematic IUPAC name for paracetamol (acetaminophen) is *N*-(4-hydroxyphenyl)ethanamide or *N*-(4-hydroxyphenyl)acetamide.

  Paracetamol (acetominaphen) is also known as *N*-acetyl-*p*-aminophenol.
- Paracetamol (acetaminophen) is sold under the names Panadol®[1] in the UK, Australia and New Zealand and under the name Tylenol®[2] in the USA.
- Paracetamol (acetaminophen) is an aromatic compound containing an OH (hydroxyl) functional group and a HN-CO-R (amide) functional group.
- Paracetamol (acetaminophen) is a weak acid.
- Paracetamol (acetaminophen) is a white solid with a melting point of 170°C which is slightly soluble in water.
- Paracetamol (acetaminophen) can be prepared from phenol (hydroxybenzene) in a three step process involving:

  (i) nitration

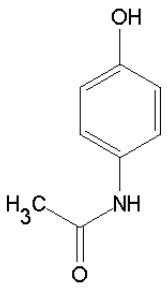
  (ii) reduction

  (iii) formation of the amide
- Paracetamol (acetaminophen) undergoes hydrolysis in acidic conditions to produce an amine and a carboxylic acid.

Structure of Paracetamol (acetaminophen)

Paracetamol (acetaminophen) contains three functional groups:

- hydroxyl group (OH)
- amide group (HN-CO-R)
- aromatic group (benzene ring)

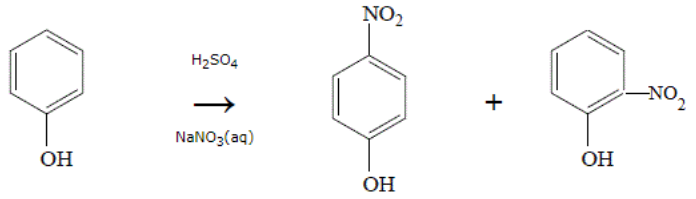


Synthesis of Paracetamol (acetaminophen)

Paracetamol (acetaminophen) can be synthesized from phenol in three steps:

Step 1:nitration of phenol

Phenol (hydroxybenzene) will react with sodium nitrate (an oxidizing agent) in the presence of sulfuric acid to produce a mixture of structural isomers of nitrophenol.



phenol (hydroxybenzene)

4-nitrophenol (*p*-nitrophenol) 25% yield

2-nitrophenol (*o*-nitrophenol) 36% yield

When concentrated sulfuric acid (H_2SO_4) is added to sodium nitrate ($NaNO_3$) the following reaction occurs:

$$H_2SO_4 + 2NaNO_3 \rightarrow Na_2SO_4 + 2HNO_3$$

Then, in excess sulfuric acid, reactive nitronium ion, NO_2^+, is produced:

$$HNO_3 + H_2SO_4 \rightarrow NO_2^+ + HSO_4^- + H_2O$$

The nitronium ion, NO_2^+, attacks the benzene ring of phenol to produce a mixture of various structural isomers of nitrophenol.

The OH (hydroxyl) functional group of phenol (hydroxybenzene) is said to activate the benzene ring at the 2- and 4- positions. This results in the formation of 2-nitrophenol and 4-nitrophenol.
The 3- and 5- positions of the benzene ring are not activated so 3-nitrophenol and 5-nitrophenol are NOT produced.

4-nitrophenol can be separated from the mixture containing 2-nitrophenol:

- by steam distillation: 2-nitrophenol forms fewer hydrogen bonds with water or other nitrophenol molecules than 4-nitrophenol so it is more volatile in steam than 4-nitrophenol
- or by column chromatography: 2-nitrophenol is less polar than 4-nitrophenol so it has less affinity for silica than 4-nitrophenol.

Step 2: reduction of a nitro group to an amine

In carbon chemistry (organic chemistry) a reduction reaction has occurred if[4]:

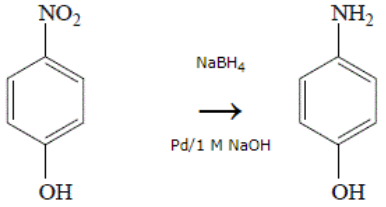
- a molecule loses oxygen

OR

- a molecule gains hydrogen

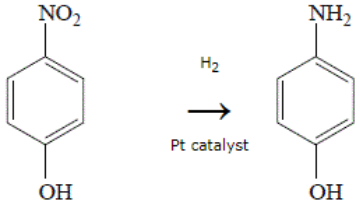
In the reaction shown below, oxygen is lost from the nitro group of 4-nitrophenol and hydrogen is added to form 4-aminophenol, so the reaction is a reduction reaction:

In the laboratory:



4-nitrophenol → **4-aminophenol 74% yield**

Industrial preparation:



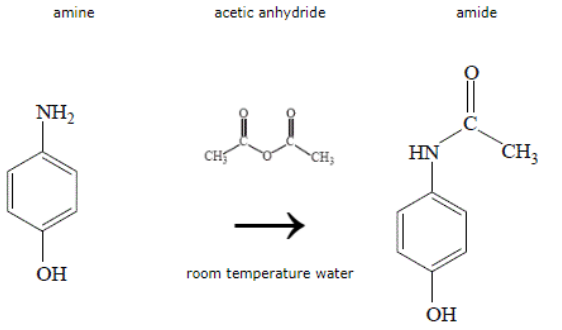
4-nitrophenol → **4-aminophenol**

A catalyst such as palladium in the laboratory reaction, or platinum in the industrial reaction, is required to provide a surface for the reaction to take place on.
The 4-nitrophenol molecules are held to the surface of the catalyst by weak forces of attraction, which then weakens the strong covalent bonds in the nitro group making it vulnerable to attack by hydrogen.

Step 3: formation of an amide

With the exception of tertiary amines, amines undergo reaction with anhydrides to produce amides.

4-aminophenol, an amine, suspended in water at room temperature readily reacts with ethanoic anhydride (acetic anhydride) to produce a precipitate of the amide paracetamol (acetaminophen) as shown below:



4-aminophenol → **paracetamol (acetaminophen)**

SIDE EFFECTS OF PARACETAMOL

If paracetamol is taken in recommended dose, it is safe medicine for adult but if dose exceed to limit it will cause some of side effects as following.

Liver Damage:

Overdose of paracetamol often causes liver damage (Moderate to Severe). In western world, Paracetamol toxicity is the foremost cause of liver failure. According to US FDA during 1990's 56000 emergency room visit, 26000 hospitalization and 458 death were reported in United States of America due to overdose of paracetamol.

SIDE EFFECTS OF PARACETAMOL Continue

Skin Reaction:

A new warning about paracetamol was issued by US FDA on 2nd August, 2013 that it may cause skin reaction very rare but overdose of paracetamol may convert it in to moderate to severe.

Except normal skin reaction it was reported that following two problems may be occurred due to overdose of paracetamol.

Steven-Johnson Syndrome

Toxic Epidermal Necrosis

SIDE EFFECTS OF PARACETAMOL Continue

Other some usual side effects are as follow:

Nausea
Vomiting
Stomach pain
Loss of appetite
dark urine
Yellowish skin

Some studies state that there is a relationship found between paracetamol and slight increase in kidney cancer.

PARACETAMOL USES

1. Fever

It is widely prescribed to relieve fever in person of all ages. Paracetamol is prescribed in children if temperature is greater than 38. 5 Celsius or 101.3 Fahrenheit.

2. Pain

It is also prescribed to relieve mild to moderate pain.

3. Osteoarthritis

Some studies state that paracetamol is also used to treat arthritis pain of knee, hand or hips.

4. Lower Back Pain

It is first line treatment of lower back pain.

PARACETAMOL USES Continue

5. Headache

Swiss, Austrian and German headache societies state that Paracetamol with caffeine is also used in Headache. In India paracetamol is also prescribed to relieve headache. Paracetamol is also used to relieve migraine in some countries.

6. Toothache

Some studies show that paracetamol is also used in pain of tooth.

7. Menstrual Period Pain

Paracetamol is often prescribe with Dicyclomine Hydrochloride or Mefenamic Acid to relieve pain during menstrual period.

8. Cold / Flu Pain

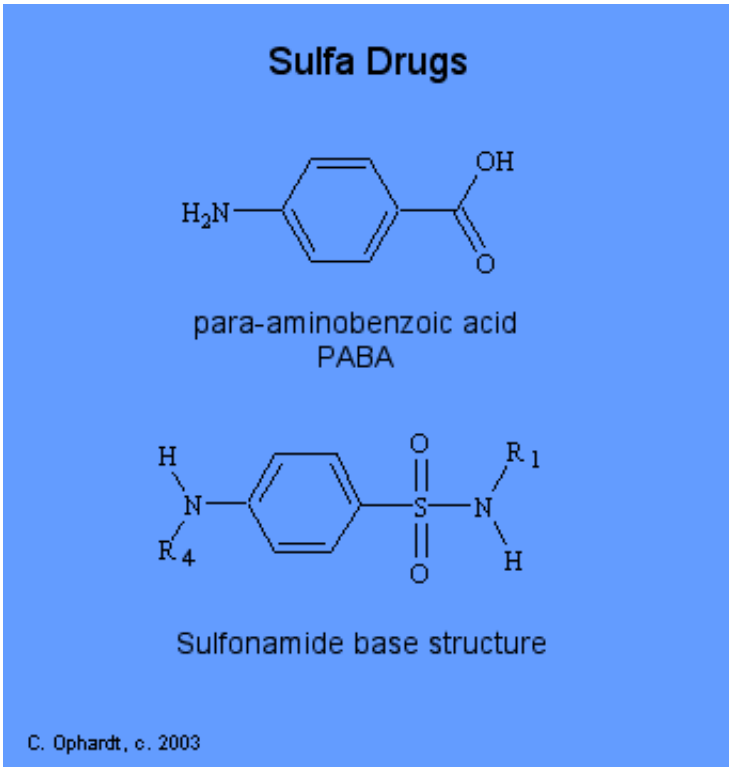
Paracetamol is also prescribed with Anti-Cold medicine to relieve Cold / Flu Pain.

Sulfa Drugs

Sulfonamides (sulfa drugs) are synthetic antimicrobial agents with a wide spectrum encompassing most gram-positive and many gram-negative organisms. These drugs were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections.

Introduction

Their use introduced and substantiated the concept of metabolic antagonism. Sulfonamides, as antimetabolites, compete with para-aminobenzoic acid (PABA) for incorporation into folic acid. The action of sulfonamides illustrates the principle of selective toxicity where some difference between mammal cells and bacterial cells is exploited. All cells require folic acid for growth. Folic acid (as a vitamin is in food) diffuses or is transported into human cells. However, folic acid cannot cross bacterial cell walls by diffusion or active transport. For this reason bacteria must synthesize folic acid from p-aminobenzoic acid. Sulfonamides or sulfa drugs have the following general structures as shown below.



Sulfanilamide which was the first compound used of this type has H's at R1 and R4. To date about 15,000 sulfonamide derivatives, analogues, and related compounds have been synthesized. This has lead to the discovery of many useful drugs which are

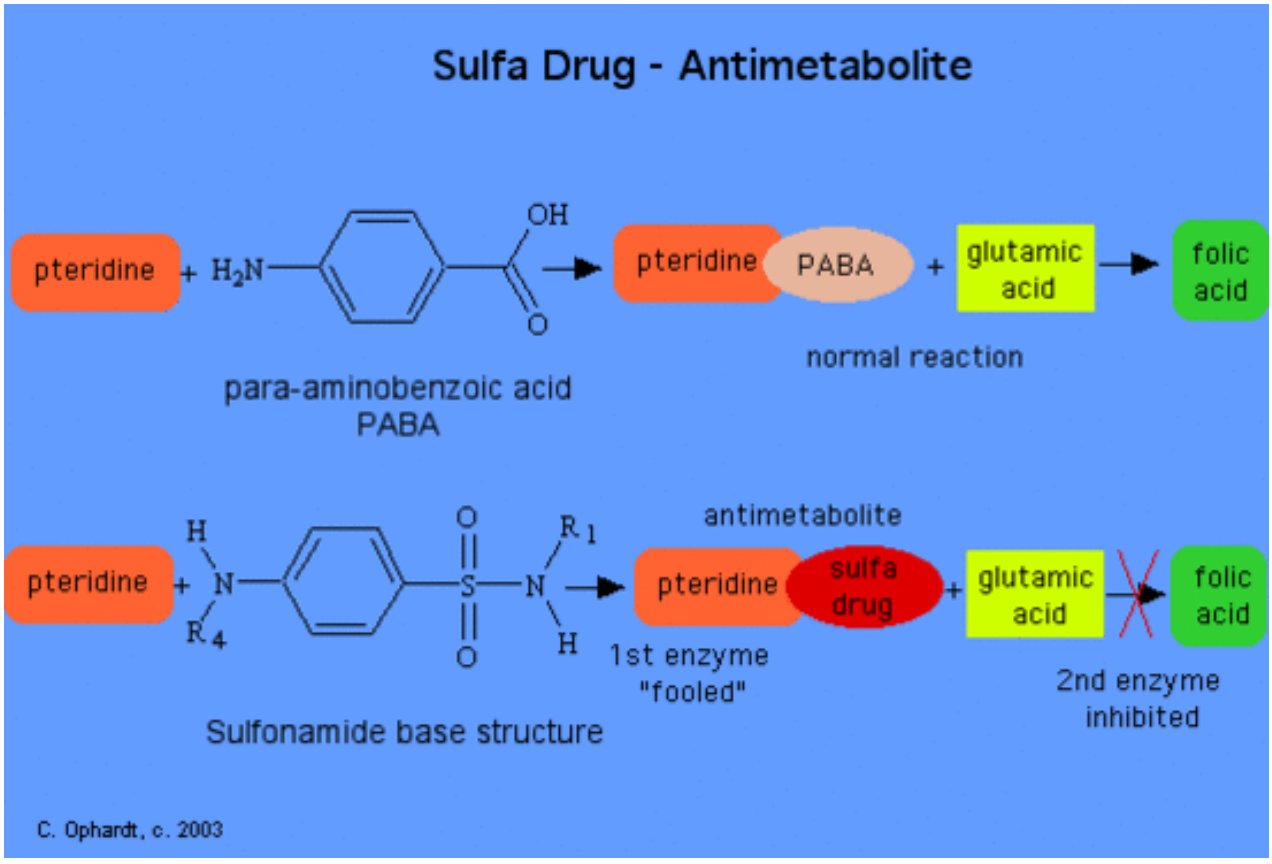
effective for diuretics, antimalerial and leprosy agents, and antithyroid agents. The basic structure of sulfonamide cannot be modified if it is to be an effective competitive "mimic" for p-aminobenzoic acid. Essential structural features are the benzene ring with two substituents para to each other; an amino group in the fourth position; and the singly substituted 1-sulfonamido group.

Mechanism for Action

Normally folic acid is synthesized in two steps in bacteria by the top reaction on the left. If A sulfa drug is used, the first enzyme is not to specific and can use the sulfonamide in the first reaction. This reaction produces the product containing pteridine and the sulfa drug. The next and final step is the reaction PABA + with glutamic acid to make folic acid. If the sulfa drug has been substituted for the PABA, then the final enzyme is inhibited and no folic acid is produced.

Recent studies indicate that substituents on the N(1) nitrogen may play the role of competing for a site on the enzyme surface reserved for the glutamate residue in p-aminobenzoic acid-glutamate through one of the following two ways:

1. Direct competition in the linking of PABA-glutamate with the pteridine derivative.
2. Indirect interference with the coupling of glutamate to dihydropteroic acid.



Examples of Sulfa-containing drugs :

- **sulfonamide antibiotics**, including sulfamethoxazole-trimethoprim (Bactrim, Septra) and erythromycin-sulfisoxazole (Eryzole, Pediazole)
- some diabetes **medications**, such as glyburide (Diabeta, Glynase PresTabs)

Sulfonamides (sulfa drugs) disadvantages:

- dizziness,
- headache,
- lethargy,
- diarrhea,
- anorexia,
- nausea,
- vomiting, and
- serious skin rashes.
- Sulfonamides also may cause sensitivity to the sun that leads to extensive sunburn after exposure to sunlight (photosensitivity). Patients receiving sulfonamides should avoid excessive exposure to sunlight and should wear sunscreen.
- Other rare side effects include liver damage, low white blood cell count (leucopenia), low platelet count (thrombocytopenia), and anemia. Formation of urinary crystals which may damage the kidney and may cause blood. Adequate hydration is needed to prevent the formation of urinary crystals.