

Pharmaceutical Chemistry

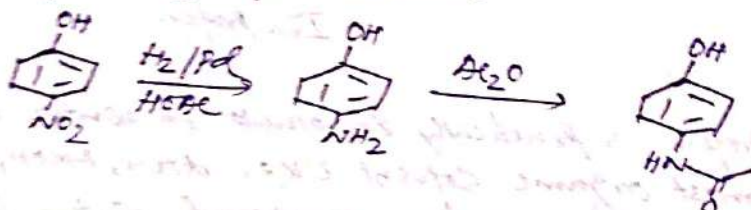
Paracetamol Synthesis:

Nitration of phenol is very fast and can be performed under the usual nitration conditions (conc. HNO_3 , conc. H_2SO_4) because concentrated HNO_3 oxidizes phenol. The solution is to use dilute nitric acid. The concentration of H_2O_2 will be small but does not matter with such a reactive benzene ring.



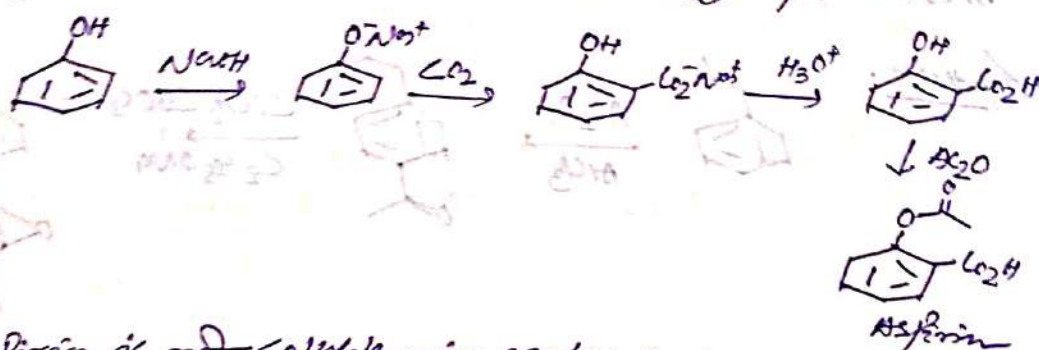
The product is a mixture of o- and p-nitrophenol from which the ortho compound can be separated by steam distillation.

The remaining para-nitrophenol is used in the manufacture of the painkiller paracetamol.

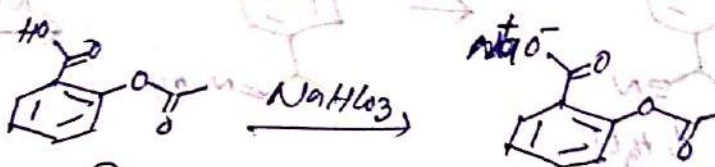


Aspirin

Kolbe-Schmitt process is used industrially to prepare salicylic acid, a precursor in making aspirin.



Aspirin is not soluble in water but its sodium salt is much more soluble. The sodium salt forms with the weak base, NaHCO_3 .



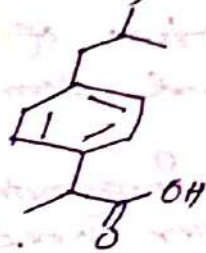
Aspirin not very soluble in water

The sodium salt is more soluble in water

The Sodium or Calcium Salt of 'Normal' Aspirin is called as 'Soluble aspirin'. But when the pH of a solution of Aspirin's Sodium Salt is lowered, the amount of the 'normal' acidic form present increases and the solubility decreases. In the acidic environment of the Stomach (around pH 1-2), soluble aspirin will be converted back to the normal acidic form and precipitate out of solution.

Ibuprofen

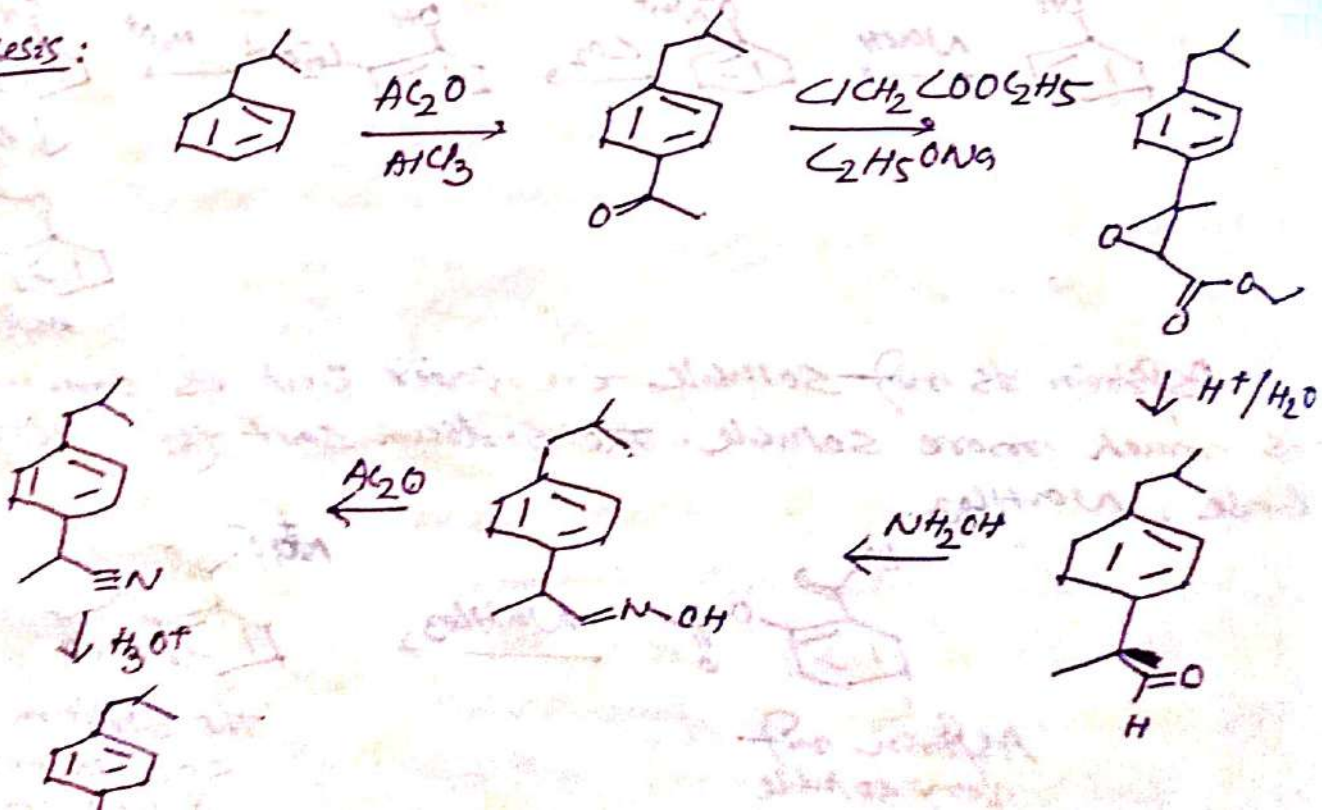
Ibuprofen is a medication in the nonsteroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever and inflammation.



Ibuprofen

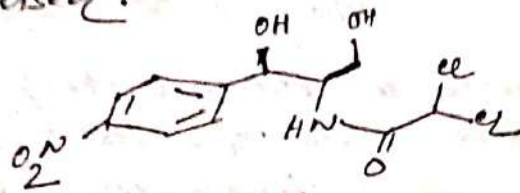
Ibuprofen is practically insoluble in water, but very soluble in most organic solvent like, EtOH, MeOH, CH_2COCH_3 etc. It is an optically active compound with both S and R isomers, of which the 'S' isomer is the more biologically active; this isomer has also been isolated and used medically.

Synthesis:

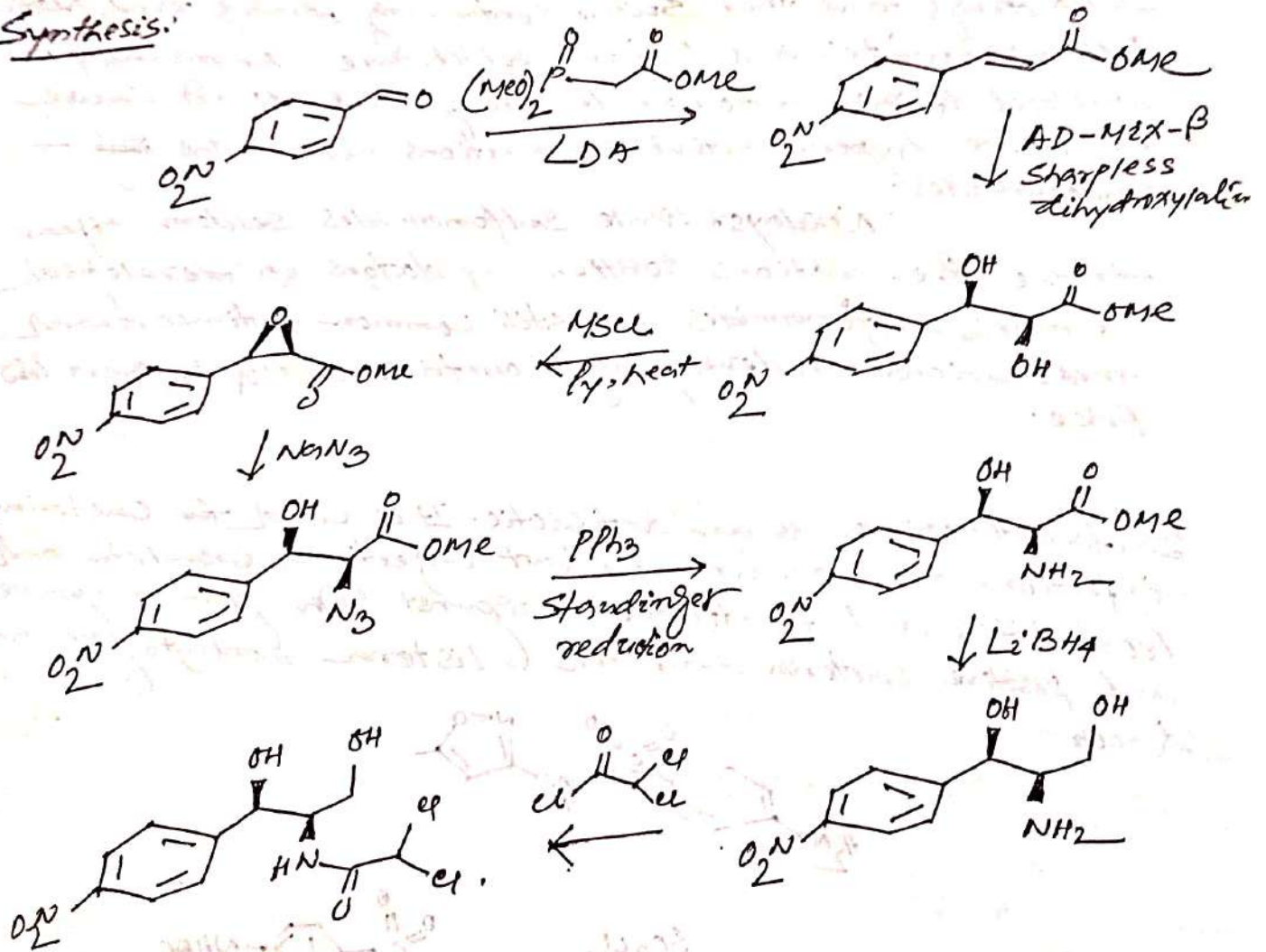


Chloramphenicol

Chloramphenicol is an antibiotic useful for the treatment of a number of bacterial infections. This includes as an eye ointment to treat conjunctivitis. By mouth or injection into a vein, it is used to treat meningitis, Plague, cholera and typhoid fever. Its use by mouth or by injection is only recommended when safer antibiotics cannot be used.



Synthesis:



Sulpha Drugs

Sulfonamide is a functional group (a part of a molecule) that is basis of several groups of drugs, which are called Sulfonamides, Sulfa drugs or Sulpha drugs. The original ~~antibiotics~~ antimicrobial agents that contain the Sulfonamide group.

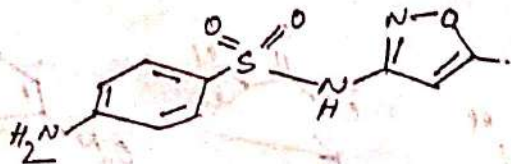
Advantages

Allergies to Sulfonamide are common.

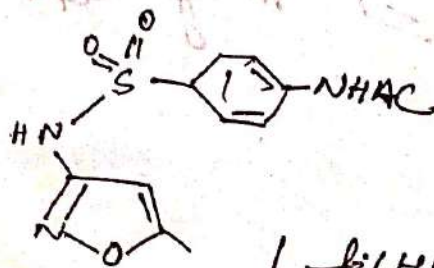
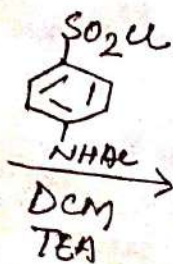
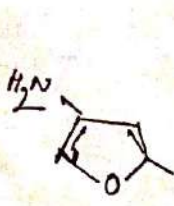
The overall incidence of adverse drug reactions to Sulfa antibiotics is approximately 3%, close to Penicilline, hence medications containing Sulfonamides are prescribed carefully. It is important to make a distinction between Sulfa drugs and other Sulfur-containing drugs and additives such as Sulfates and Sulfites, which are chemically unrelated to the Sulfonamide group, and do not cause the same hypersensitivity reactions seen in the ~~Sulfa~~ - Sulfonamides.

Nowadays, while Sulfonamides seldom appear in the prescriptions written by doctors in developed countries, Sulfonamides are still common antimicrobial medications in developing countries owing to their low price.

Sulfamethoxazole is an antibiotic. It is used for bacterial infections such as urinary tract infections, bronchitis and prostatitis and is effective against both gram negative and positive bacteria such as *Listeria monocytogenes* and *E. coli*.



Synthesis:



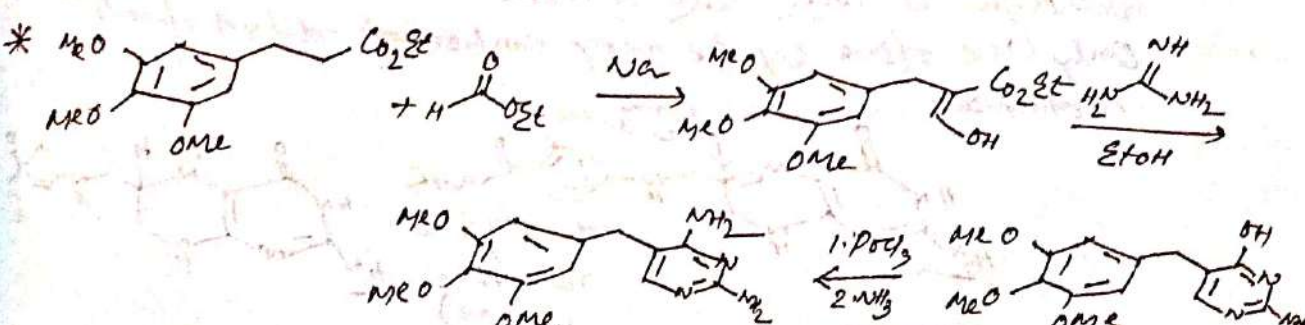
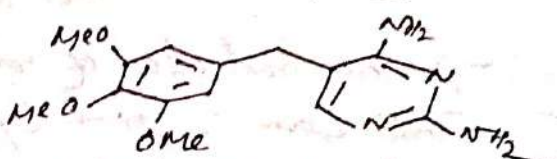
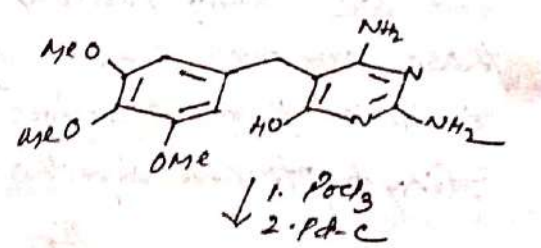
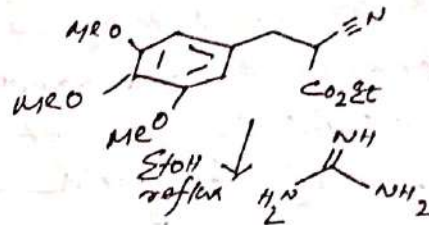
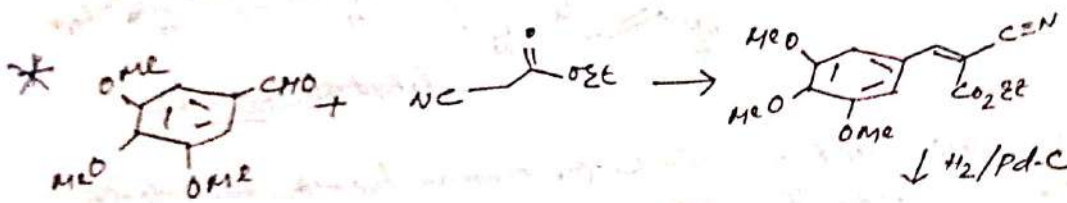
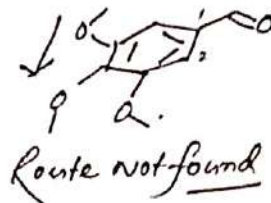
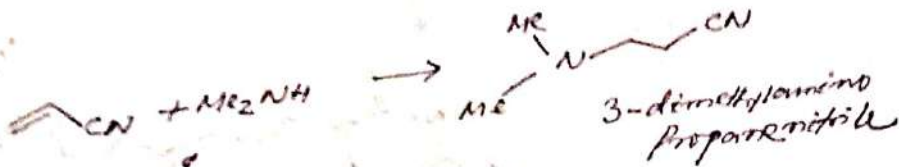
↓ dil HCl
followed by
bicarbonate
wash

Tremethoprim

Tremethoprim is an antipneumatic agent, primarily used for treatment of bladder infections. Also used in the treatment of ear infections and trachoma.

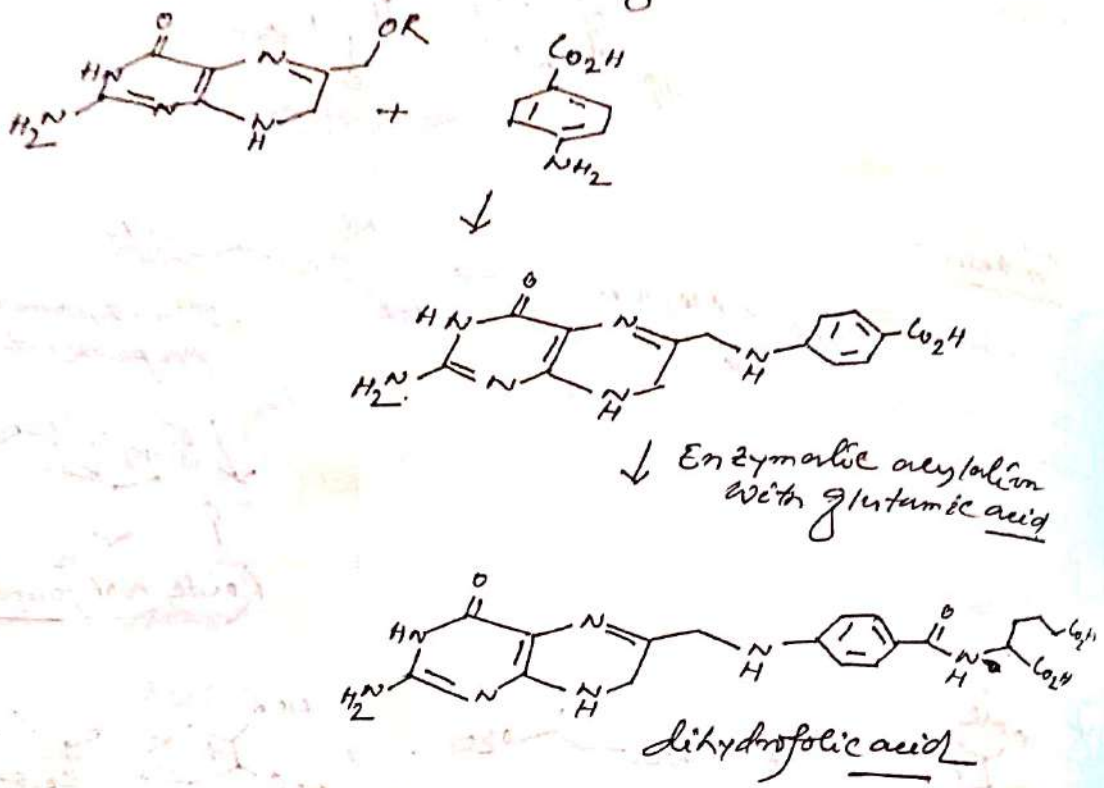


Synthesis:



Uses

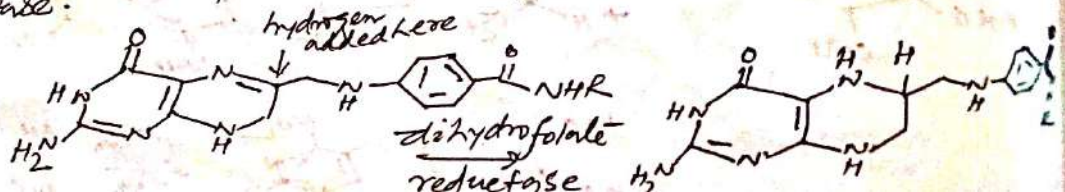
Folic acid is ~~much~~ involved in the metabolism of all living things. Folic acid is built up in nature from three pieces: a heterocyclic starting material, p-aminobenzoic acid, and the amino acid glutamic acid.



Although folic acid is vital for human health, we don't have the enzymes to make it; it's a vitamin, which means we must take it in our diet or we die.

Bacteria, on the other hand, do make folic acid. This is very useful because it means that if we inhibit the enzymes of folic acid synthesis we can kill bacteria but we ~~cannot~~ possibly harm ourselves as we don't have those enzymes. The sulfa drugs, such as sulfamethoxazole, imitate p-aminobenzoic acid and inhibit the enzyme dihydropteroyl synthase.

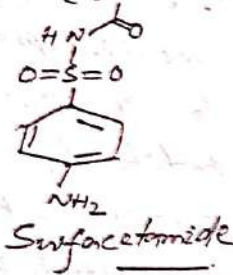
The next step in folic acid synthesis is the reduction of dihydrofolate to tetrahydrofolate. This can be done by both human and bacteria, and although it looks like a rather trivial reaction, it can only be done by the very important dihydrofolate reductase.



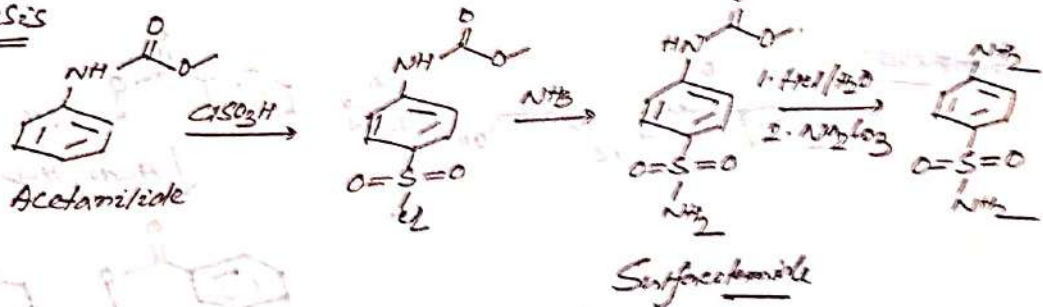
Although both bacteria and human have this enzyme, the bacterial version is different enough for us to inhibit it with specific drugs. An example is trimethoprim, a drug with pyrimidine core. These two types of drugs work together to attack the folic acid metabolism of bacteria, an action used together.

Sulfacetamide:

Sulfacetamide 10% topical solution, sold under the brand name Klaron or Ovoc, is approved for the treatment of acute and subacute ~~dermatitis~~ dermatitis. It exhibits anti-inflammatory properties when used to treat blepharitis or conjunctivitis (in eye-drop solution). It is believed to work by limiting the presence of folic acid which bacteria need to survive.



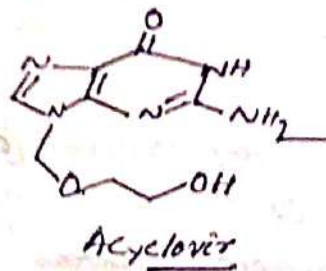
Synthesis



Mechanism of action: Sulfacetamide is a sulfonamide antibiotic. Sulfonamides are synthetic bacteriostatic antibiotics that are active against gram-positive and gram-negative bacteria. It blocks the synthesis of dihydrofolic acid - by inhibiting the enzyme dihydropteroate synthase. It is a competitive inhibitor of bacterial para-aminobenzoic acid (PABA). PABA is required for bacterial synthesis of folic acid and it is an essential component for bacterial growth. The multiplication of bacteria is therefore inhibited by the action of Sulfacetamide.

Acyclovir:

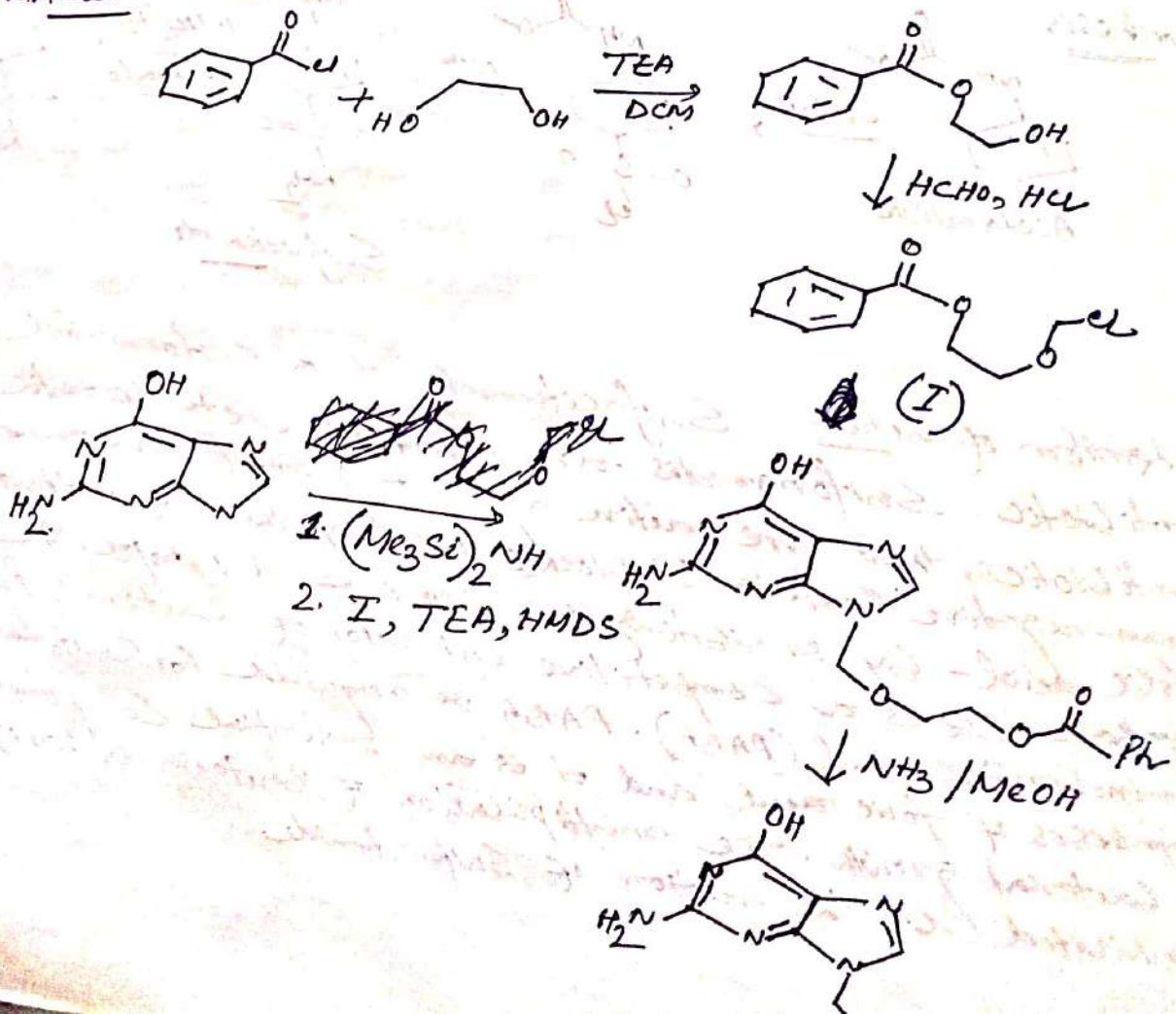
Acyclovir (ACV), also known as acyclovir, is an antiviral medication. It is primarily used for the treatment of herpes simplex virus infections, chicken pox and shingles.



Mechanism of action:

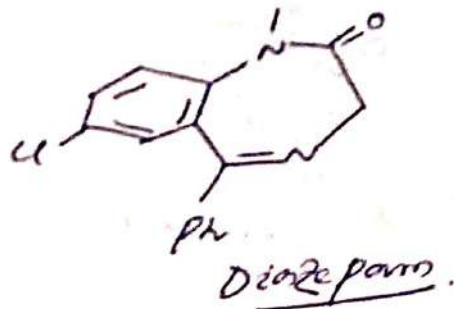
Acyclovir is converted by viral thymidine kinase to acyclovir monophosphate, which is then converted by host cell kinases to acyclovir triphosphate (ACV-TP). ACV-TP in turn, competitively inhibits and inactivates HSV-specified DNA polymerases preventing further viral DNA synthesis without affecting the normal cellular processes.

Synthesis:

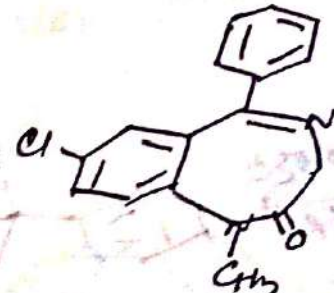
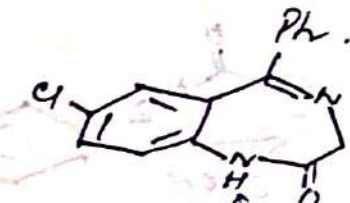
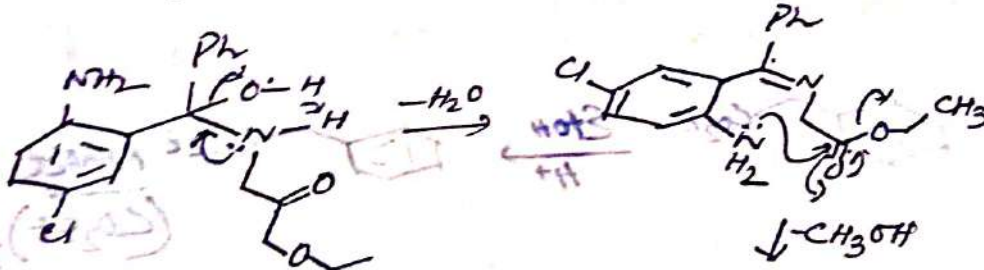
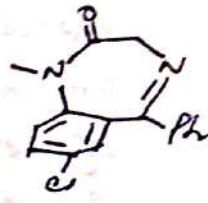
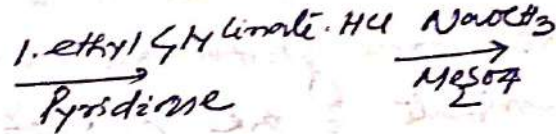
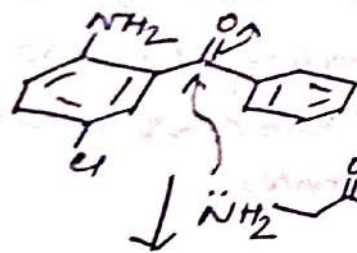


Diazepam

Diazepam, first marketed as Valium, is a member of the benzodiazepine family that typically produces a calming effect. It is commonly used to treat a range of conditions including anxiety, alcohol withdrawal syndrome, muscle spasms, seizures, trouble sleeping and restless legs syndrome.



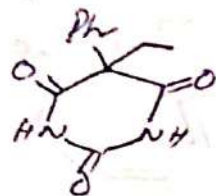
Synthesis:



K_2CO_3

Phenobarbital:

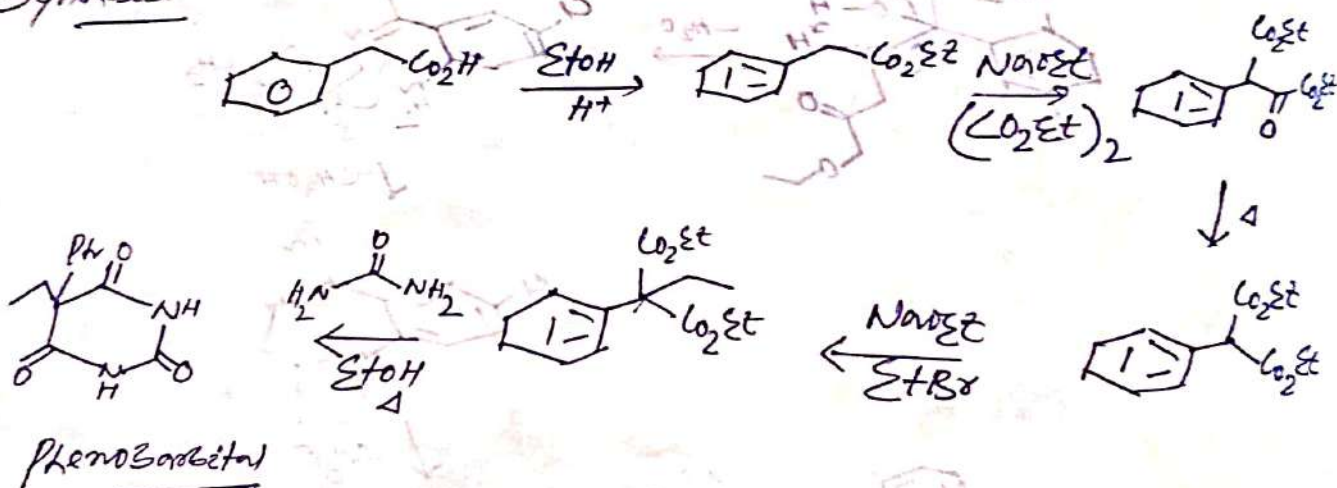
Phenobarbital, also known as phenobarbitone, is a medication recommended by WHO for the treatment of certain types of epilepsy in developing Country. In the developed world it is commonly used to treat seizures in young young children.



Phenobarbital

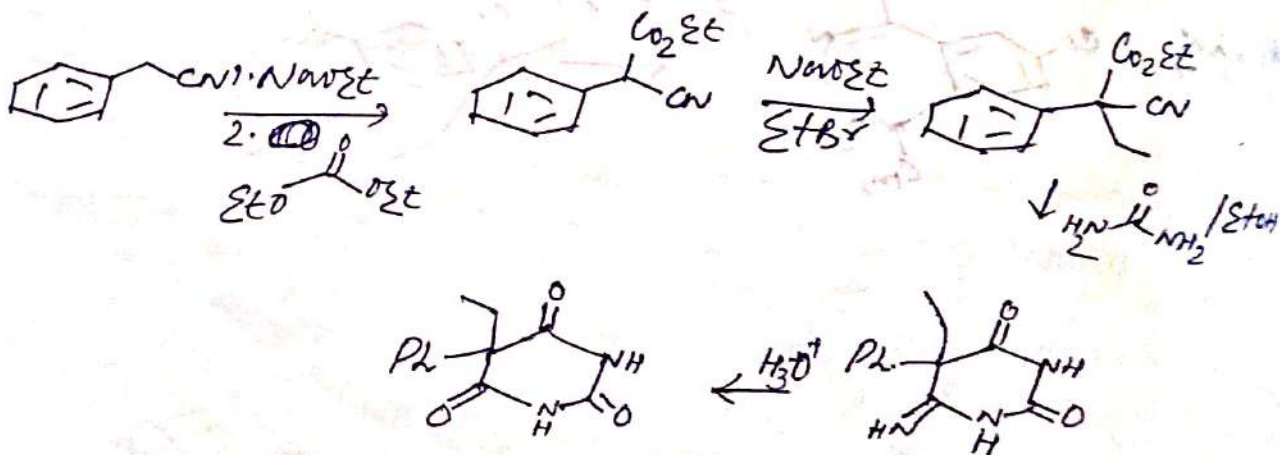
Mechanism of action: Through its action on GABA receptors, phenobarbital increases flux of chloride ions into the neuron which decreases excitability. Direct blockade of excitatory glutamate signaling is also believed to contribute to the hypnotic/anticonvulsant effect that is observed with the barbiturates.

Synthesis:



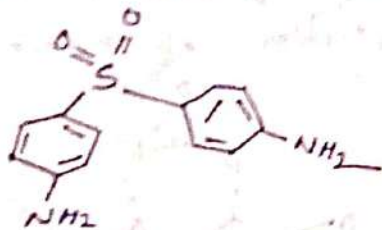
Phenobarbital

or



Dapsone:

Dapsone, also known as diamino diphenyl sulfone (DDS), is an antibiotic commonly used in combination with rifampicin and clofazimine for the treatment of leprosy. It is a second-line medication for the treatment and prevention of pneumocystis pneumonia and for the prevention of toxoplasmosis in those who have poor immune function.

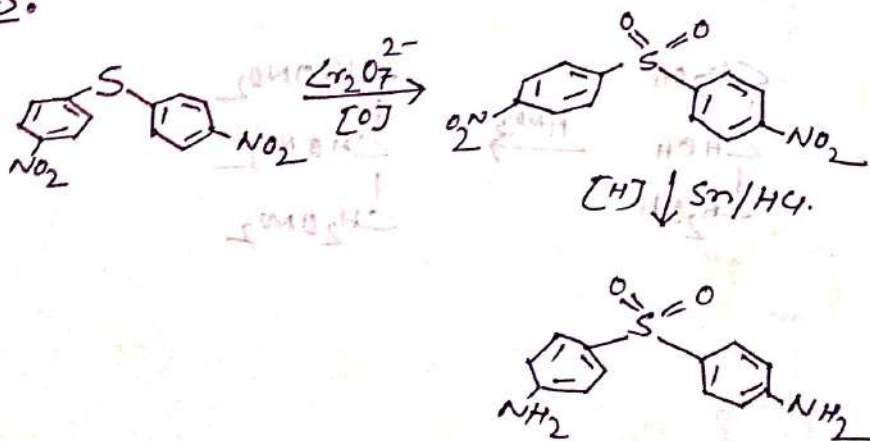


Mechanism of action:

As an antibacterial, dapsone inhibits bacterial synthesis of dihydrofolic acid, via competition with para-aminobenzoate for the active site of dihydropteroate synthase.

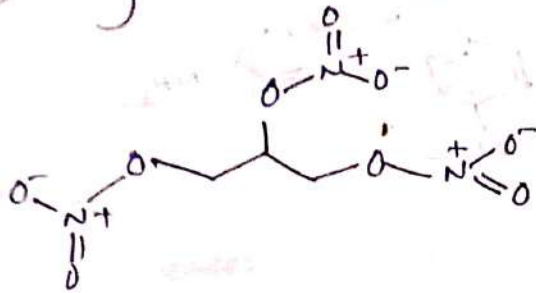
As an anti-inflammatory, dapsone inhibits the enzyme myeloperoxidase. As a part of the respiratory burst that neutrophils use to kill bacteria, myeloperoxidase converts H₂O₂ in HOCl. HOCl is the most potent oxidant generated by neutrophils, and cause significant tissue damage during inflammation. Dapsone arrests myeloperoxidase in an inactive intermediate form, reversibly inhibiting the enzyme. This prevents accumulation of HOCl and reduce tissue damage during inflammation.

Synthesis:



Glyceryl trinitrate

Nitroglycerin, also known as glyceryl trinitrate (GTN), is a medication used for heart failure, high blood pressure, and to treat and prevent chest pain from not enough blood flow to the heart (angina) or due to cocaine. This includes chest pain from a heart attack. It is taken by mouth, under the tongue, applied to skin, or by injection into a vein.

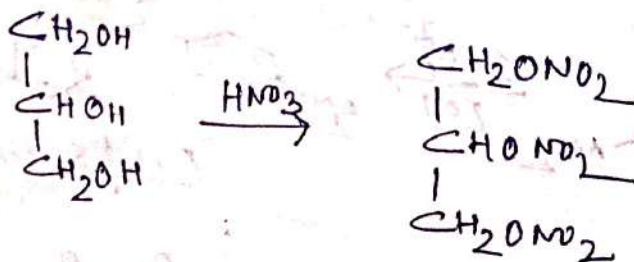


Mechanism of action:

GTN is a prodrug which must be denitrated, with the nitrite anion or a related species further reduced to produce the active metabolite nitric oxide (NO).

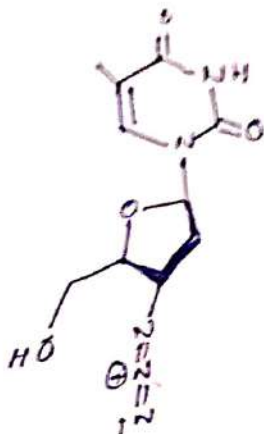
The 'NO' produced by this process is a potent activator of guanylyl cyclase (GC) by heme-dependent mechanism; this activation results in formation of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate (GTP). Thus production of NO from exogenous ~~sources~~ sources such as GTN increases the level of cGMP within the cell and stimulates dephosphorylation of myosin, which initiates ~~the~~ relaxation of smooth muscle cell in blood vessels.

Synthesis:



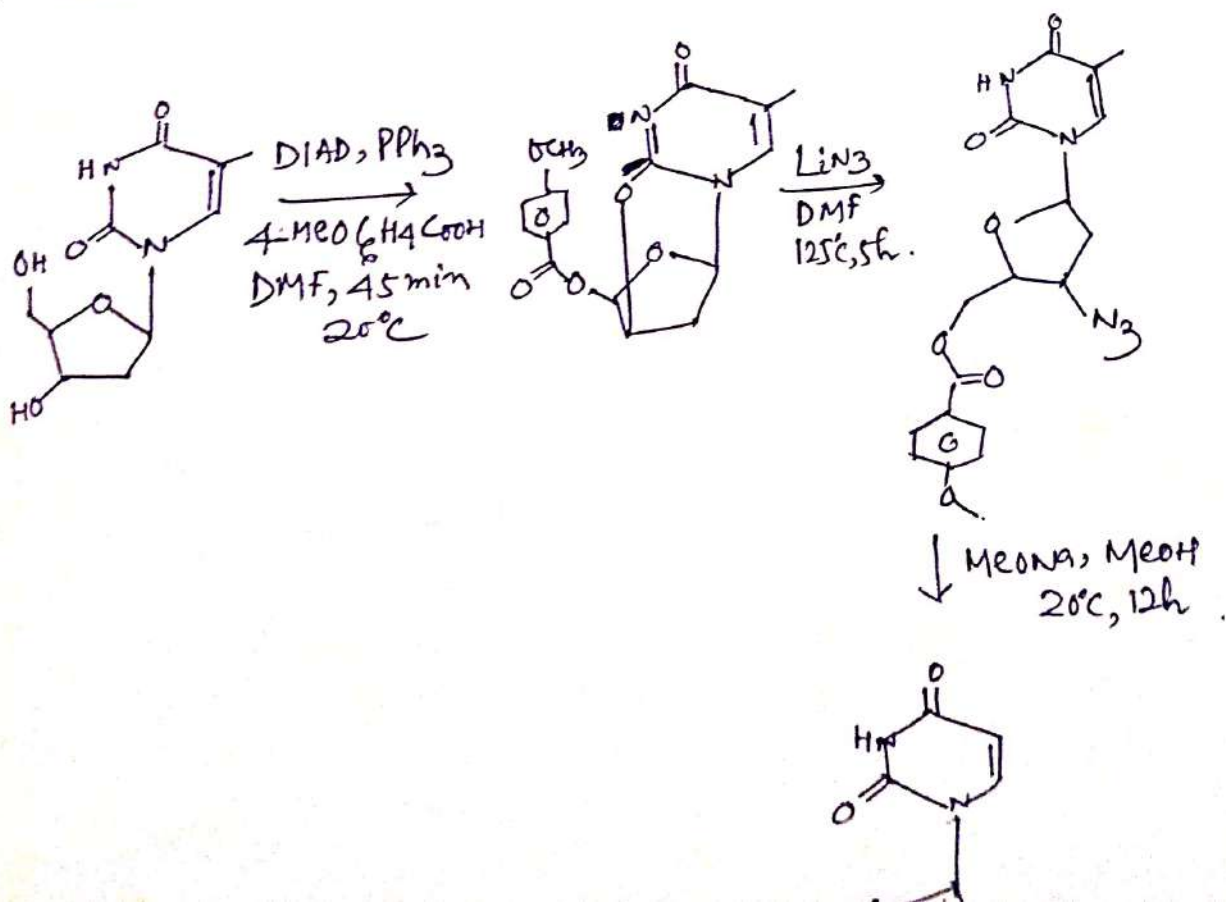
Zidovudine:

Zidovudine (ZDV), also known as *azidothymidine* (AZT), is an antiretroviral medication used to prevent and treat HIV/AIDS.



Mechanism of action: AZT is a thymidine analogue, AZT works by selectively inhibiting HIV's reverse transcriptase, the enzyme that the virus uses to make a DNA copy of its RNA. Reverse transcription is necessary for production of HIV's double-stranded DNA, which would be subsequently integrated into the genetic material of the infected cell.

Synthesis:



Antibiotics

What is antibiotic?

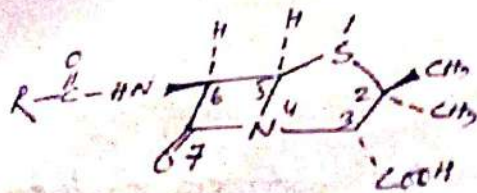
Antibiotics are chemical substances produced by various species of microorganisms which on low concentration destroy or inhibit the growth of other species of microorganisms. In the present usage the term antibiotic includes chemically related and derived substances often the term antibiotic is taken to extend to synthetic antibacterial agents such as sulphonamides and quinolones.

* Antibiotics are produced by various species of microorganisms such as bacteria, fungi and actinomycetes. The history of antibiotics is traced back to 500 to 600 BC when Chinese used a mouldy cord to treat cuts and lacerations.

Penicillins

In 1928, Scotland's Alexander Fleming while working at the Saint Mary's Hospital in London observed during his studies that a mould contaminant prevented the growth of staphylococcal bacteria in its vicinity. A broth culture of the mould definitely showed distinct antibacterial properties. The mould was identified as *penicillium notatum* and as such the antibacterial substance which it produced was termed as penicillin by Fleming.

The basic structure of the penicillins consists of a β -lactam ring, fused with a thiazolidine moiety. The positions are numbered as shown. There is side chain at position 6. The character of the R group is influenced by the components of the culture medium. The addition of phenylacetic acid, for example, led to the preferential formation of penicillin G. The 'natural' penicillins produced by *penicillium notatum* are listed here. Benzyl penicillin has the greatest antimicrobial activity and is the only 'natural' penicillin which is used clinically.



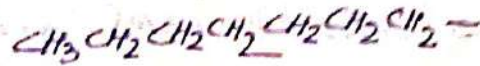
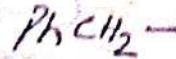
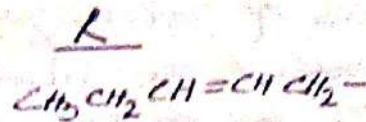
Penicillin

F (2-pentonyl)

G (Benzyl)

K (m-heptyl)

X (p-Hydroxybenzyl)



Penicillins are strong monobasic acids. The free acids are unstable. The alkali metal salts and salts with organic acids are relatively stable in the dry state.

In general following absorption, penicillins are widely distributed throughout the body. They are eliminated rapidly by glomerular filtration and renal tubular secretion. The half-lives in the body are short, the typical values are 30 to 60 minutes.

Benzylpenicillin can be considered to be the parent compound of the penicillin family. It is active against gram-positive bacteria, gram-negative cocci, actinomycetes and spirochetes. It is usually injected since it is unstable to the gastric acid.

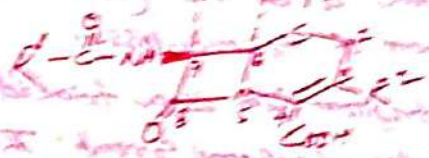
Penoxymethylpenicillin is acid stable and as such can be given by mouth. ~~It is also~~ It is generally used for relatively less severe infections. It is ~~not~~ generally used for relatively less severe infections. It is used mainly in the treatment of streptococcal infections and in rheumatic fever prophylaxis.

Cephalosporins

The discovery of cephalosporins may be traced to the year 1945 when a system cultured cephalosporium strains from sea water near a group of islands in the coast of Sardinia. It found that several different forms of the fungus produced the antibiotic activity against staphylococcal infections and spread from this source. Great interest and many studies by different workers showed that the cephalosporium produced several different antibiotics which were termed as cephalosporins.

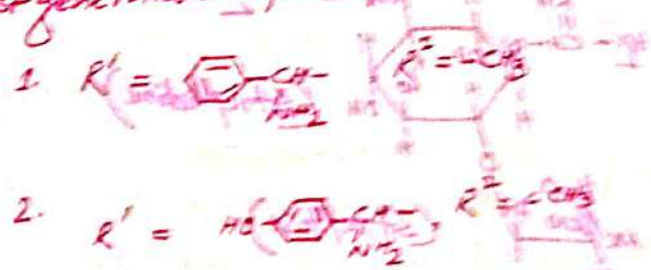
Four of the antibiotics were found, namely, cephalosporin C and one of them with structure like streptomycin. The other three were hydrophilic and were designated as cephalosporin A, B, and cephalosporin C.

Cephalosporins was found to be a β -lactam but had structural differences as compared with penicillins. The lactam moiety was fused to 6,6-dihydrothiazine ring instead of 5-membered thiazolidine ring. The thiazine ring is resistant to opening of acids and penicillins are sensitive to opening of acids and penicillins are sensitive to opening of acids and penicillins are sensitive to opening of acids.

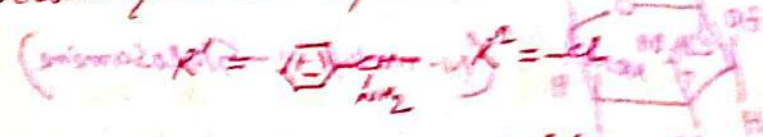


Cephalosporins General Structure

First generation cephalosporins:



Second generation cephalosporins:



Third generation cephalosporins:



The first generation Cephalosporins have good activity against gram-positive bacteria and they have relatively modest activity against gram negative bacteria:

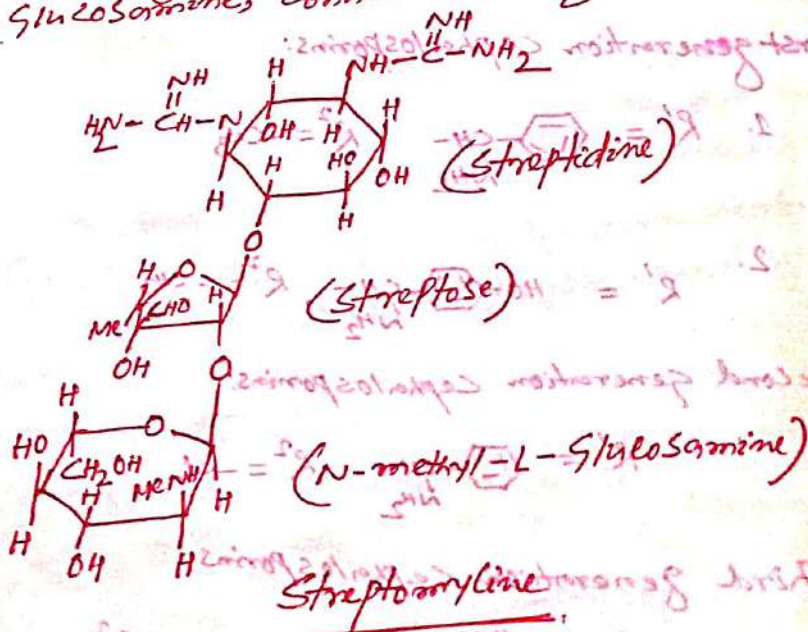
The second-generation Cephalosporins are slightly less active against gram-positive bacteria but are more stable to hydrolysis by beta-lactamases produced by gram-negative bacteria and have enhanced activity against many of the Enterobacteriaceae and Haemophilus influenzae.

The third-generation Cephalosporins are even more resistant to hydrolysis by beta-lactamases than the second-generation drugs. They have a wider spectrum of activity and are more active against gram-negative organisms.

Streptomycins:

Streptomycin was the first aminoglycoside antibiotic to become commercially available for chemotherapeutic use. It was isolated from strain of Streptomyces griseus. This proved to be the first clinically effective drug for the treatment of tuberculosis.

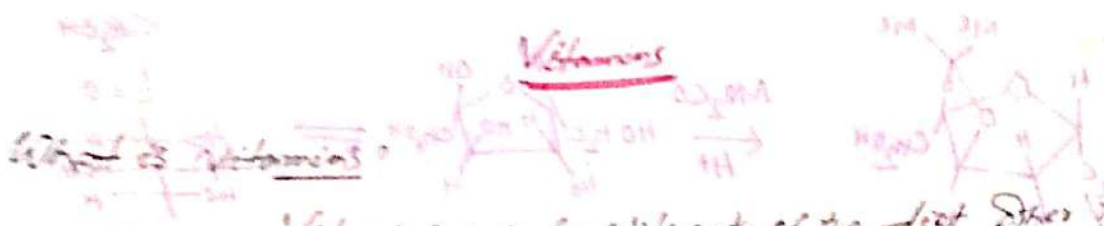
Streptomycin is a triacidic base and it possesses an aldehydic carbonyl group. The three structural units of the aminoglycoside are streptidine, streptose and N-methyl-L-glycosamine, connected through glycosidic linkage.



On hydrolysis under appropriate acidic conditions, streptomycin gives
 streptidine base streptidine.

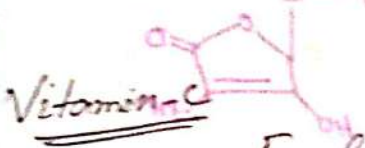


Streptomycin on aqueous hydrolysis is first converted to a Uron derivative
 and then into the diamine streptidine.



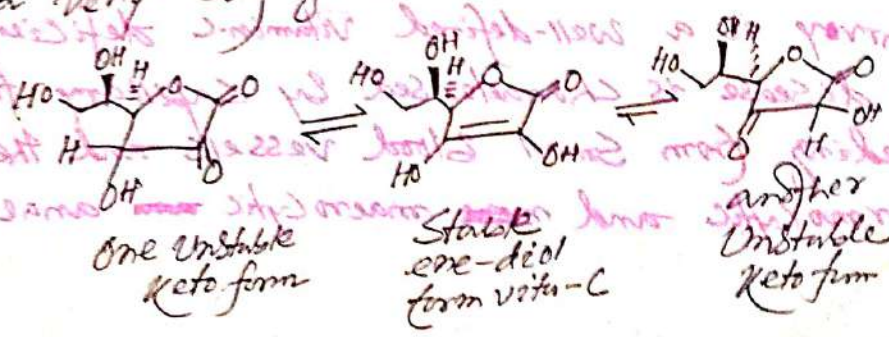
Vitamins are constituents of the diet other than
 carbohydrates, fats, proteins, and inorganic salts, and are
 necessary for the normal metabolic functioning of the body.

Vitamins are arbitrarily grouped according to
 the solubility in fats (lipid) and water. The water soluble
 vitamins are stored in the body only to a limited
 extent whereas the fat soluble vitamins are stored
 in significant quantity and body is able to conserve
 these factors. The fat-soluble vitamins are A and D
 and water soluble vitamins B, C and K.



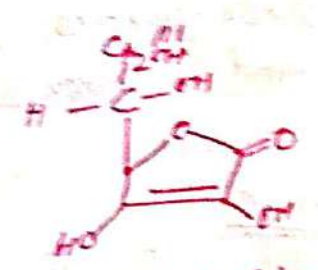
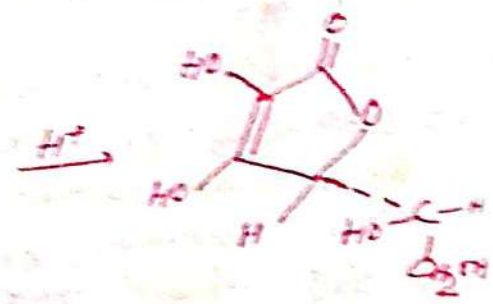
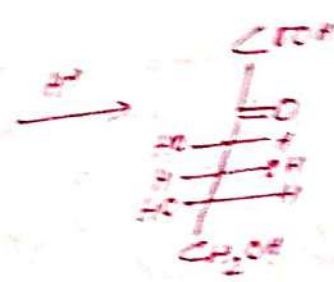
Found in fruits and vegetable and is used for
 preventing scurvy.

~~containing~~ Vitamin C has a five-membered ring
 containing two carbonyl groups but normally exists
 as a very conjugated che-diol.



well

Synthesis:



Ascorbic acid

The items rich in vit-C are citrus fruits, leafy vegetables, tomatoes, strawberries, potatoes, green and red peppers

Scurvy is a well-defined vitamin-C deficiency syndrome. The disease is characterised by capillary fragility, bleeding from small blood vessels and the gums, normochromic and ~~normochromic~~ macrocytic ~~normochromic~~ anaemia.

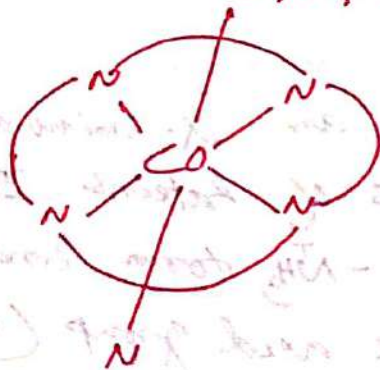
Vit-B₁₂

Use: Vitamin B₁₂, also called Cobalamin, is a water soluble vitamin that has key role in the normal functioning of the brain and nervous system via the synthesis of myelin, and the formation of red blood cells. It is involved in the metabolism of every cell of the human body, especially affecting DNA synthesis, fatty acid and amino acid metabolism.

Sources: No fungi, plants or animal are capable of producing Vitamin-B₁₂, only bacteria and archaeta have the enzymes needed for its synthesis. Some sources of B₁₂ include ~~the~~ animal products and dietary supplement.

Structure:

B₁₂ is the most chemically complex of all the vitamins. The structure of B₁₂ is based on a corrin ring, which is similar to the porphyrin ring found in hem, chlorophyll and cytochrome. The central metal ion is cobalt. Four of the six coordination sites are provided by the corrin ring, and a fifth by a dimethylbenzimidazole group. The sixth coordination site, the center of reactivity, is variable, being a cyano group (-CN), a hydroxy group (-OH), and a methyl group (-CH₃) or a 5-deoxyadenosyl group, respectively, to yield the four B₁₂ forms.



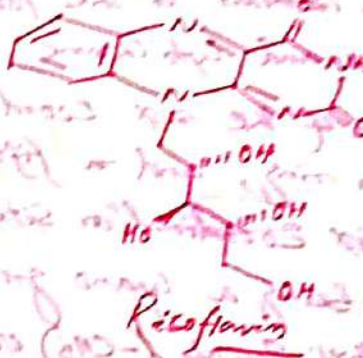
Vitamin B₁₂

Vitamin B₂ (Riboflavin)

Source: Riboflavin, also known as vitamin B₂, is a water-soluble vitamin found in food and used as a dietary supplement. Food sources include eggs, green vegetables, milk and other dairy products, meat, mushrooms and almonds.

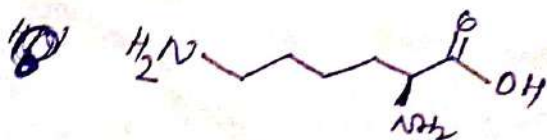
Deficiency: Ariboflavinosis, a syndrome due to riboflavin deficiency, may result if dietary intake of the vitamin is inadequate. The syndrome is characterized by cheilosis, angular stomatitis, glossitis, keratitis and seborrheic dermatitis.

Structure:



Lysine

Lysine is an α -amino acid that is used in the biosynthesis of proteins. It contains an α -amino group (potentially in the protonated $-NH_3^+$ form under biological conditions) and an α -carboxylic acid group (which is in the deprotonated $-COO^-$ form under biological conditions), and a side chain $(CH_2)_4NH_2$, classifying it as a basic, charged, aliphatic amino acid.



The human body cannot synthesize lysine, so it is essential for humans and must be obtained from the diet.

Lysine plays several roles in humans, most importantly proteinogenesis, but also in the crosslinking of collagen polypeptides, uptake of essential mineral nutrients and in the production of carnitine. It also is key in fatty acid metabolism.

Due to its important importance in several biological processes, a lack of lysine or lack of lysine can lead to several disease states including defective connective tissues, anemia, and systemic protein-energy deficiency.

In contrast, an overabundance of lysine can cause ~~various~~ severe neurological issues.

Biosynthesis:

