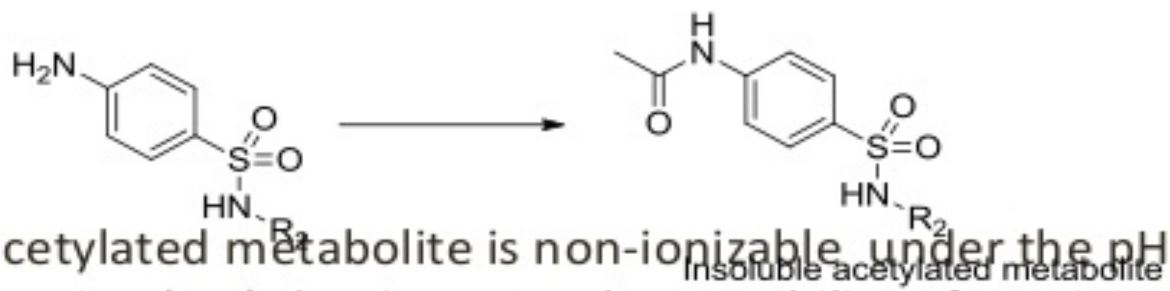
Sulphonamides -II

The problem of crystalluria

- Sulfonamides are mostly excreted in urine as acetylated metabolite.
- They are relatively water insoluble mainly due to the formation of the acetylated metabolites.

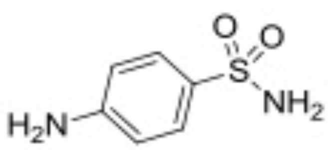


- The acetylated metabolite is non-ionizable under the pH conditions of the urine (≈ 7) that increase the possibility of precipitation and the formation of crystals in the urine (crystalluria)

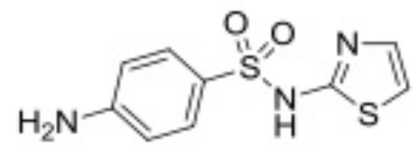
The problem of crystalluria

- How to minimize the possibility of crystalluria formation with sulfonamides:
  - Increase the urine flow.
  - Increase the pH of the urine to increase the ionization of sulfonamides and the formation of water soluble salts (this can be done by taking sodium bicarbonate or potassium citrate.
  - Lowering the pKa of the sulfonamide group which will help to increase the ionization under the acidic conditions. This can be done by adding electron withdrawing group on the sulfonamide side chain

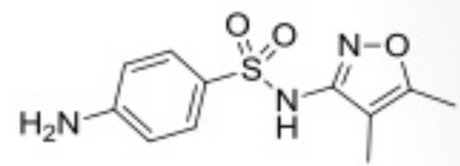
Sulfonamides with reduced crystalluria formation



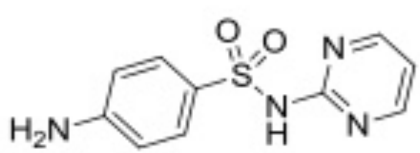
Sulfanilamide pKa = 10.4



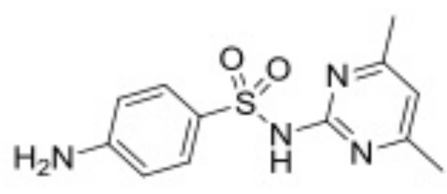
Sulfathiazole pKa = 8.5



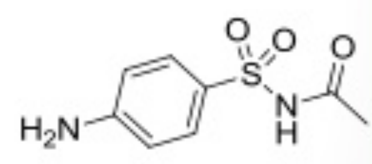
Sulfisoxazole pKa = 5.0



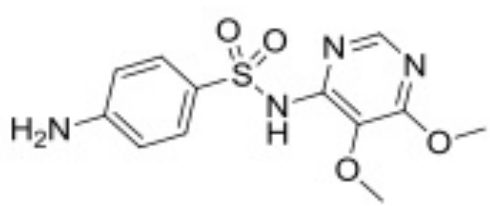
Sulfadiazine pKa = 6.5



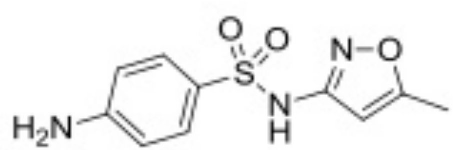
Sulfamethazine pKa = 7.4



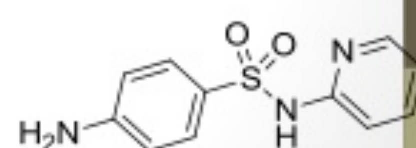
Sulfacetamide pKa = 5.4



Sulfadoxine pKa = 8.1



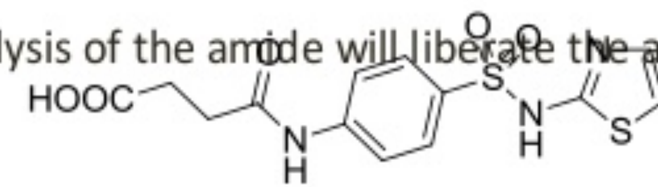
Sulfamethoxazole pKa = 6.1



Sulfapyridine pKa = 8.4

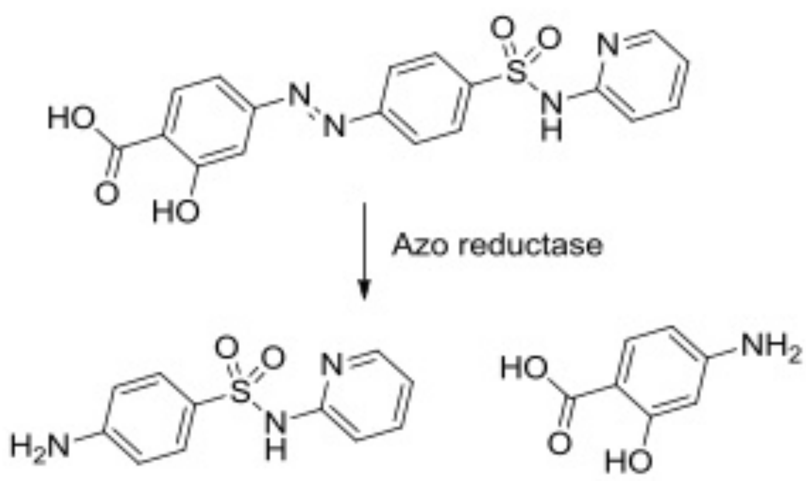
Sulfonamide prodrugs

- Succinyl sulfathiazole:
  - Mainly used for intestinal infections.
  - It has a carboxylic acid at the amine side chain… ionized in intestine… will not be absorbed…. So it has only local effect.
  - The gradual hydrolysis of the amide will liberate the active form; sulfathiazole.



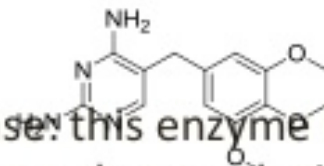
Sulfonamide prodrugs

- Sulfasalazine:
  - Used in local intestinal infections.
  - Gives sulfapyridine and 5-aminosalicylic acid upon the breakdown of the azo bond.
  - Used mainly in ulcerative colitis.



5-amino salicylic acid

Other folate reductase inhibitors



- Trimethoprim:
  - Inhibits dihydrofolate reductase: this enzyme has human homologue but they do not have that much similarity in structure…. Therefore trimethoprim is 1000 more active on the bacterial copy of this enzyme..
  - Normally used in combination with sulfamethoxazole (cotrimoxazole):
    - Lower dose from both drugs means less side effects.
    - More effective than the monotherapy since they are targeting two different enzymes in the same metabolic pathway… this is what is called sequential blocking.

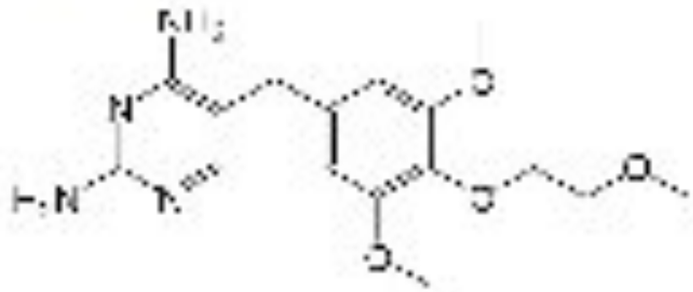
Protein binding of sulfonamides

- Vary in plasma protein binding: Sulfaisoxazole… 76%, Sulfamethoxazole… 60%, sulfadiazine…. 38%.

- The fraction that is protein bound is not available for enzyme inhibition, therefore this fraction is inactive.
- The protein binding is a reversible process, so there will be a gradual release of sulfonamide which will become available.

- Factors affecting protein binding of sulfonamides:
  - Lipophilicity of the structure.
  - Substitution on the free amine will increase protein binding (such as the acetylayed metabolite is more protein bound than the parent sulfonamide).

Tetroxoprim

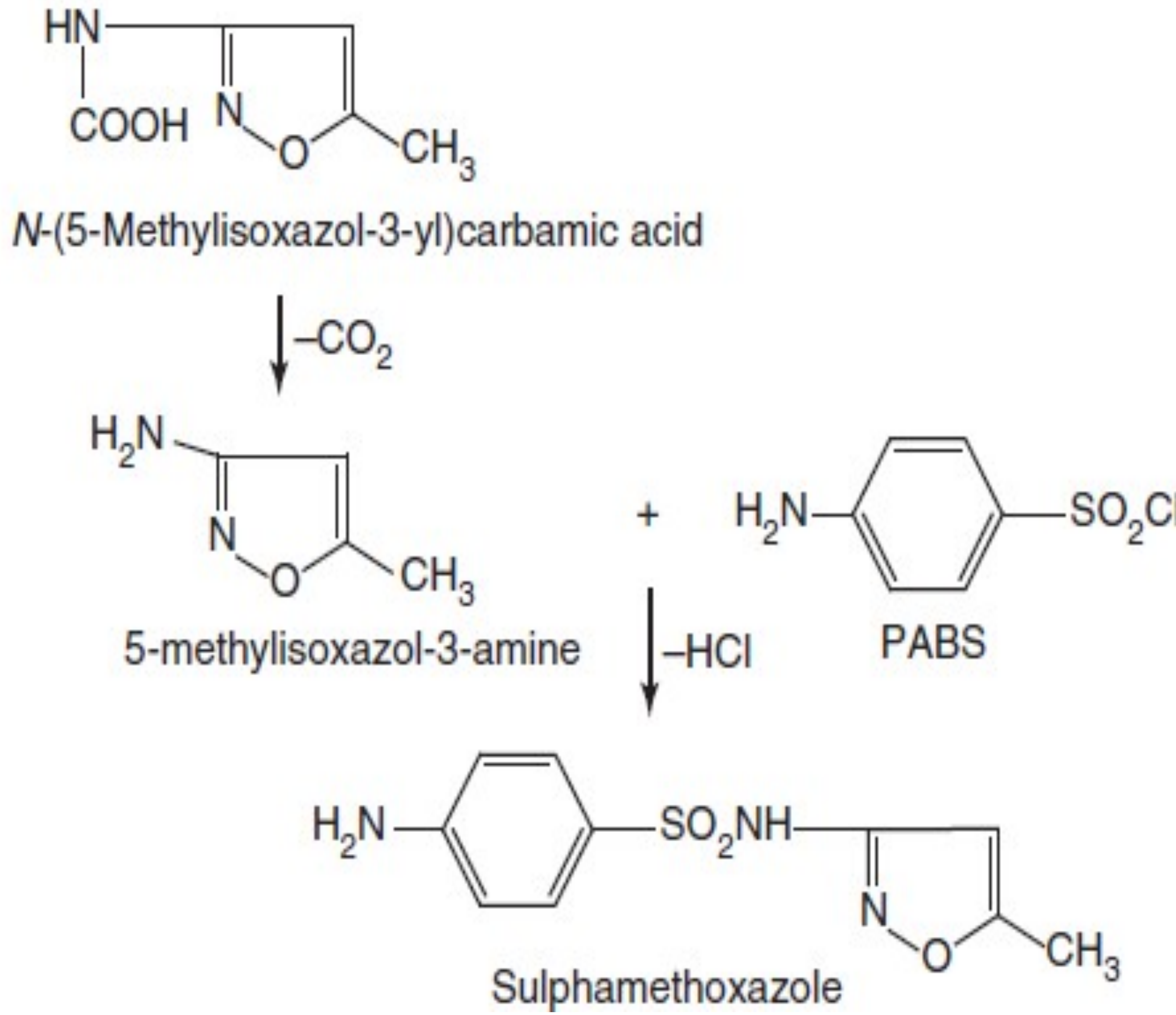


Uses of Sulfadiazine+Tetroxoprim:

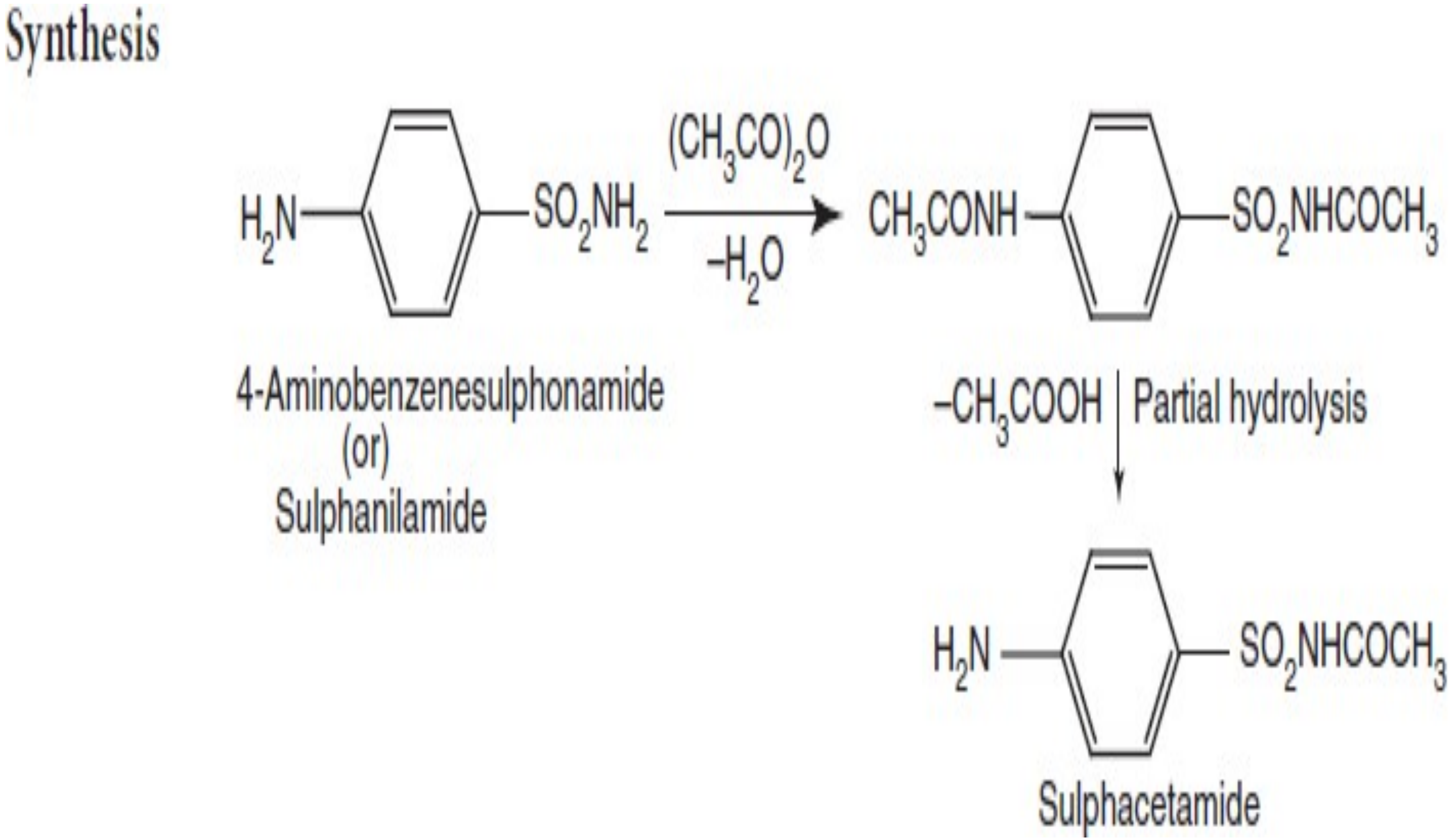
Sulfadiazine And Tetroxoprim is used in the treatment of:

AIDS-Related Opportunistic Infections
Chlamydiaceae Infections
Enterobacteriaceae Infections
Malaria
Nocardia Infections
Toxoplasmosis
Urinary Tract Infections
Sulfadiazine And Tetroxoprim is used in the prevention of:
Rheumatic Fever

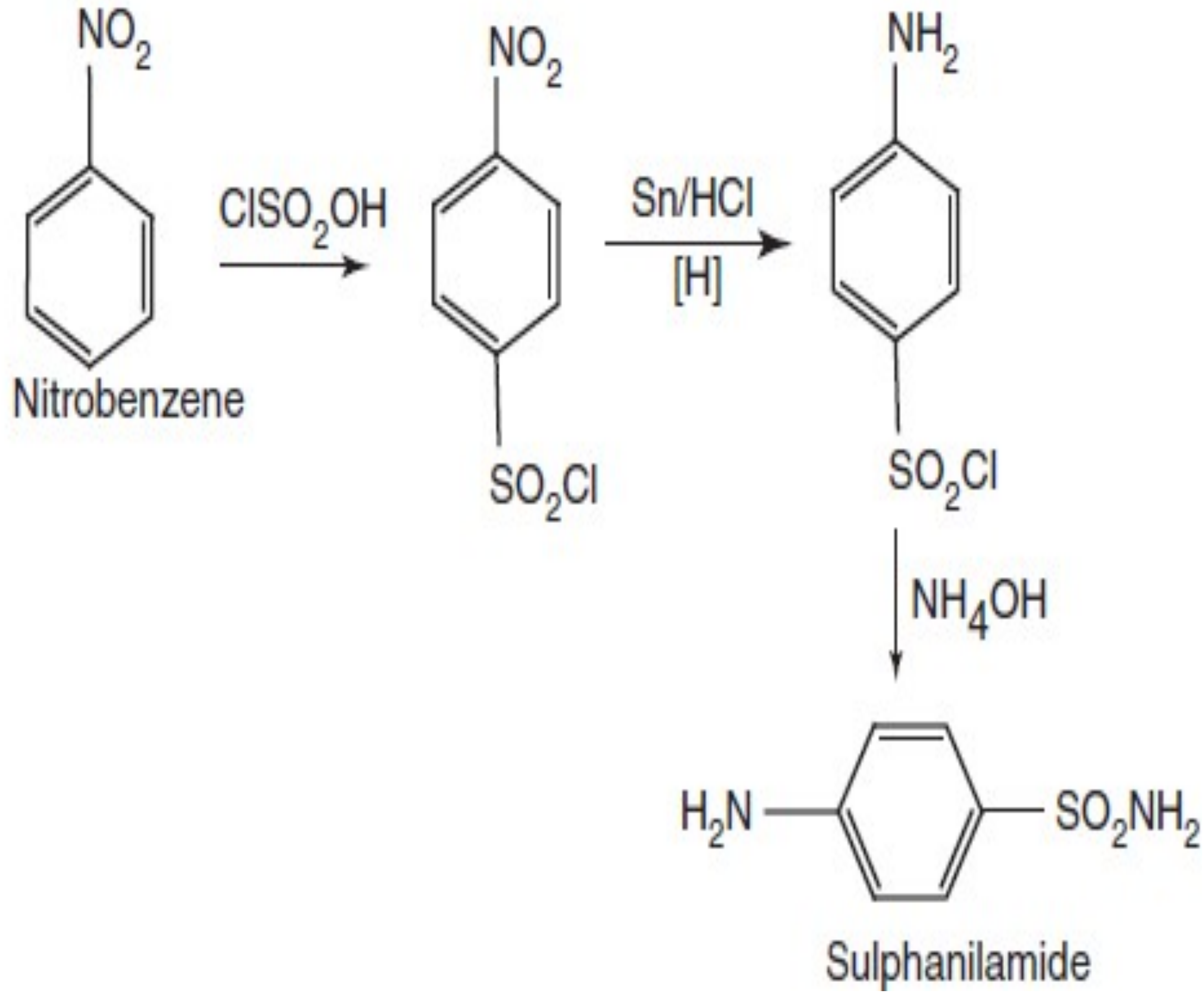
Synthesis


HN
COOH
N
O
CH3
N-(5-Methylisoxazol-3-yl)carbamic acid
–CO2
H2N
N
O
CH3
5-methylisoxazol-3-amine
+
H2N
SO2Cl
PABS
–HCl
H2N
SO2NH
N
O
CH3
Sulphamethoxazole

Synthesis of Sulphacetamide



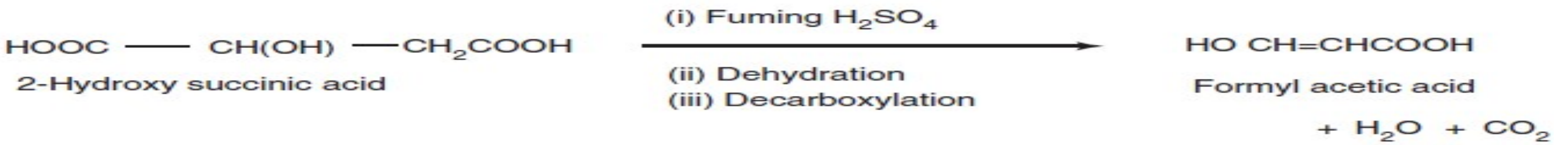
Route-II. From: Nitrobenzene



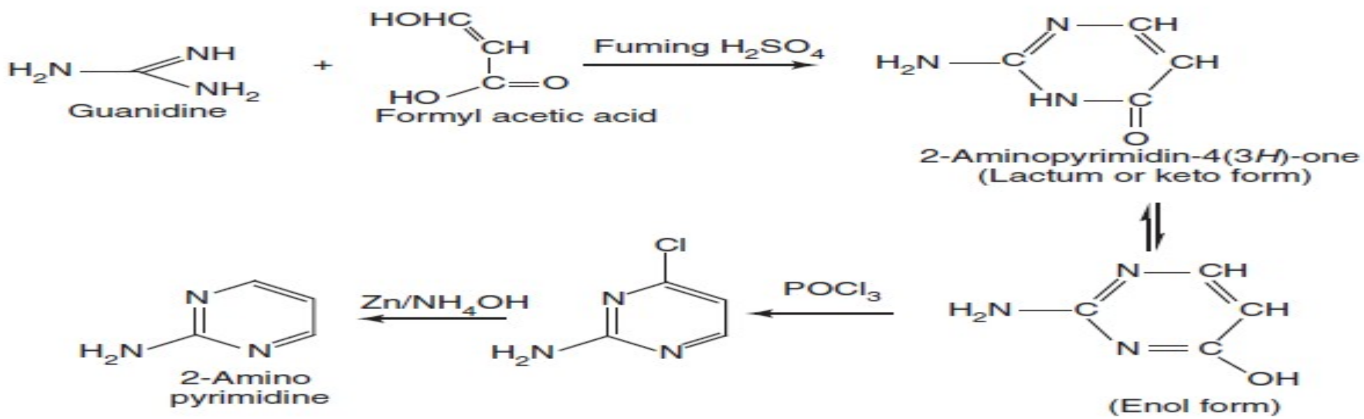
Synthesis of Sulphadiazine

Synthesis

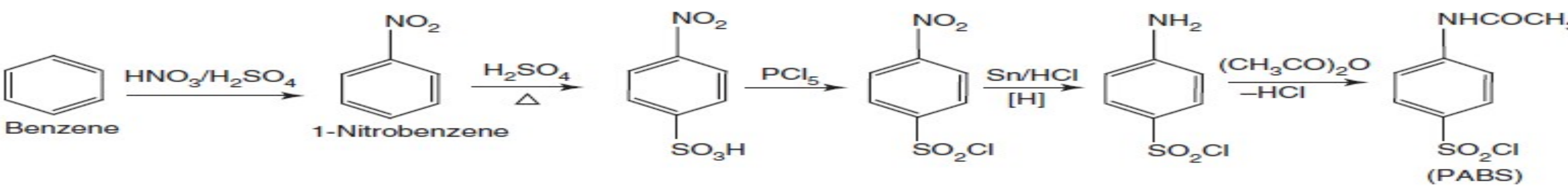
Step-I. Preparation of formyl acetic acid



Step II. Synthesis of 2-Aminopyrimidine



Step III. Synthesis of *p*-acetamido benzene sulphonyl chloride (PABS)



Step IV. Condensation of *p*-acetamido benzene sulphonyl chloride with 2-aminopyrimidine