STUDENT STUDY PROJECT

Title of the project: **SULFANILAMIDE-Preparation of ppt**			2018-2019 Guided by Dr .SB Ronald		
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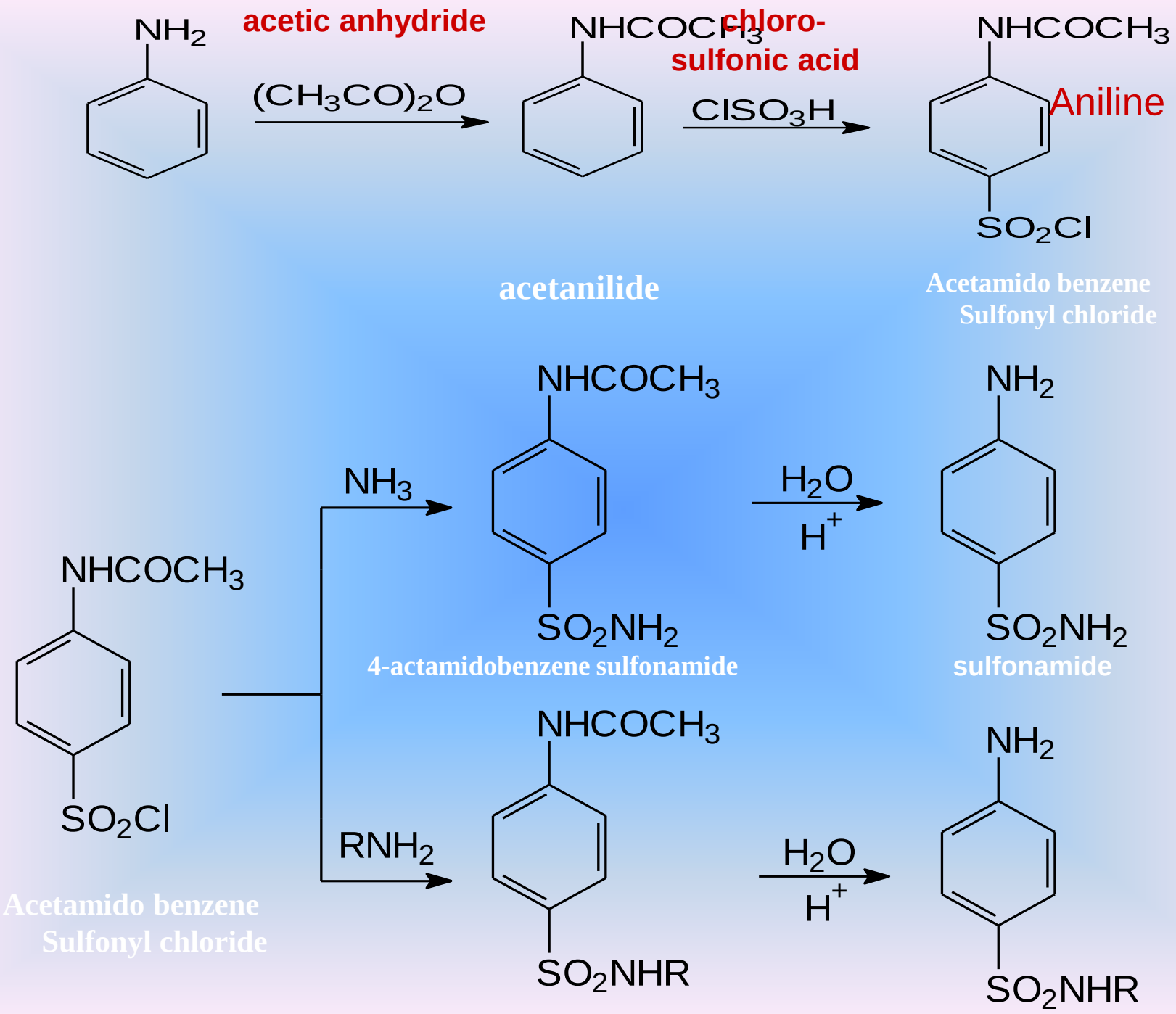
sulfanilamide

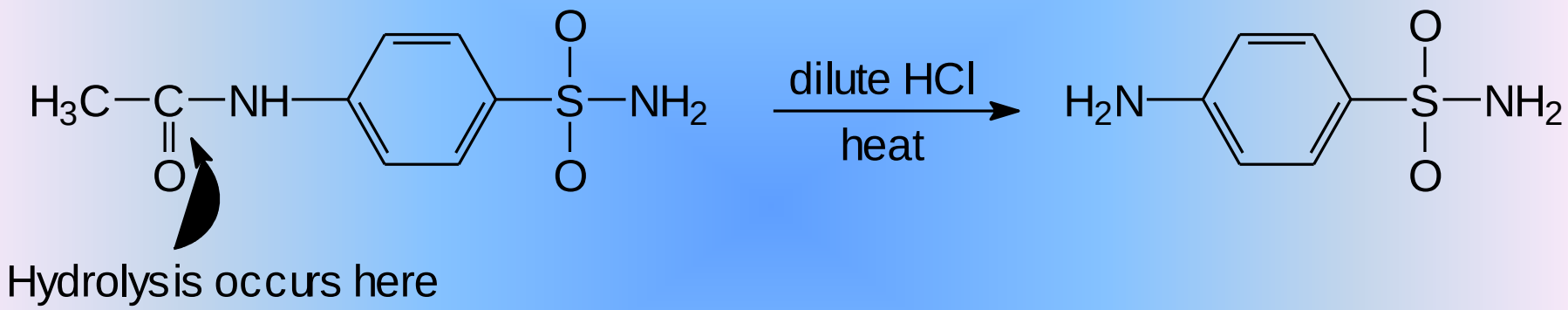
Sulfanilamide :

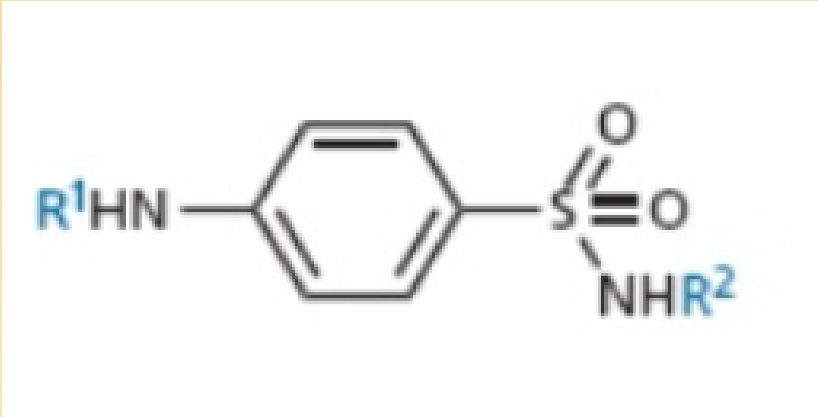
The amide of sulfanilic acid (sulfanilamide) and certain related substituted amides are of considerable medical importance as the sulfa drugs. Although they have been supplanted to a wide extent by the antibiotics (such as Penicillin ,Tetracyclin , Chloramphenicol and aureomycin) , the sulfa drugs still have their medical uses , and make up a considerable portion of the pharmaceutical industry .

Sulfonamides can be prepared by the reaction of a sulfonyl chloride with ammonia or an amine. The presence in a sulfonic acid molecule of an amino group ,however, poses a special problem: acid were converted to the acid chloride ,the sulfonyl group of one molecule could attack the amino group of another to form an amide linkage. This problem is solved by protecting the amino group through acetylation prior to the preparation of the sulfonyl chloride .Sulfanilamide and related compounds are generally prepared in the following way


NH2
acetic anhydride
(CH3CO)2O
NHCOCH3
chloro-
sulfonic acid
ClSO3H
NHCOCH3
Aniline
SO2Cl
acetanilide
Acetamido benzene
Sulfonyl chloride
NHCOCH3
NH3
SO2NH2
4-actamidobenzene sulfonamide
H2O
H+
NH2
SO2NH2
sulfonamide
NHCOCH3
SO2Cl
Acetamido benzene
Sulfonyl chloride
RNH2
NHCOCH3
SO2NHR
H2O
H+
NH2
SO2NHR

The selective removal of the acetyl group in the final step is consistent with the general observation that amides of carboxylic acids are more easily hydrolyzed than amides of sulfonic acids





1. *Para -amino group : This is essential for activity and* must be unsubstituted The only exception is when R1 = acyl (i.e. amides).
2. The aromatic ring and the sulphonamide functional group are both required and both must be directly attached to the aromatic ring;
3. The aromatic ring must be *para -substituted only.*
4. *T*he sulphonamide nitrogen must be primary or secondary.
5. **R2 is the only possible site that can be varied in sulphonamides.**

Importance of substitution at R2

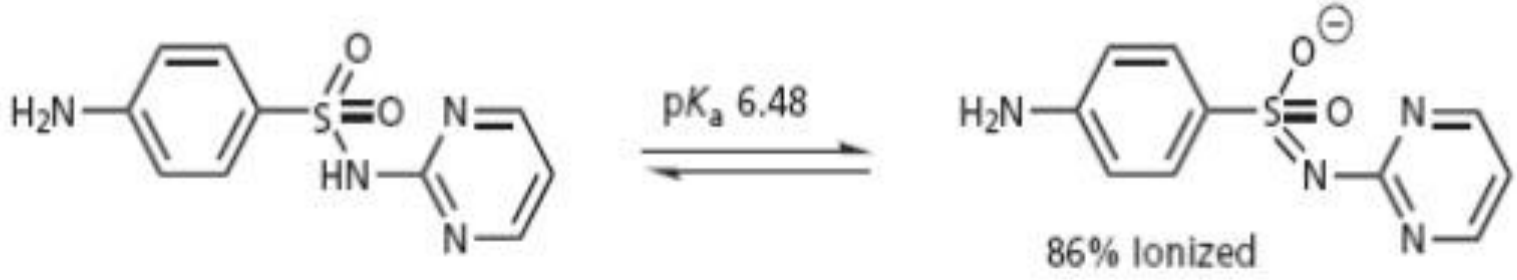
Sulphonamide analogues with reduced toxicity

The primary amino group of sulphonamides is acetylated in the body and the resulting amides have reduced solubility which can lead to toxic effects.

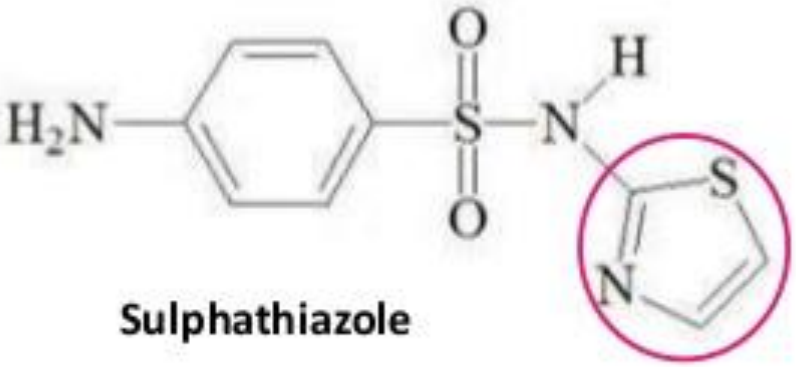
Ex : Sulphathiazole

Solution

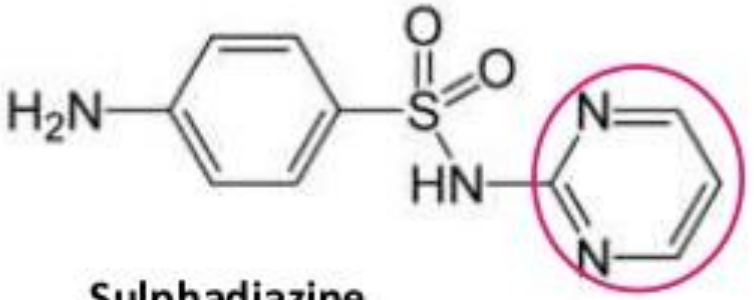
Substitute the thiazole ring in sulphathiazole with a pyrimidine ring to give **sulphadiazine**



Comparing solubility



Sulphathiazole



Sulphadiazine

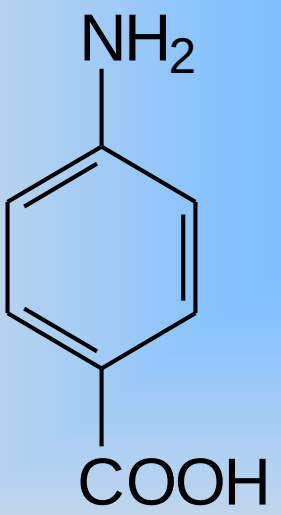
In this, NH proton is not very acidic (high p *K a*). *Therefore, sulphathiazole and its* metabolite are mostly un-ionized at blood pH.

Replacing the thiazole ring with a more electron-withdrawing pyrimidin ring increases the acidity of the NH proton by stabilizing the resulting anion.

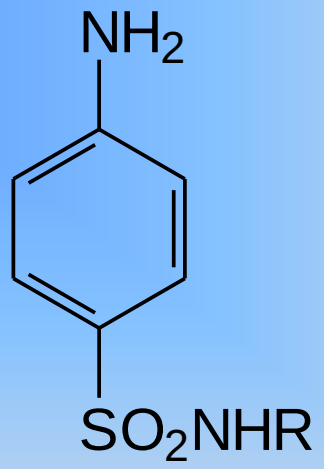
Hence, sulphadiazine and its metabolite are significantly ionized at blood pH. As a consequence, they are more soluble and less toxic.

Silver sulphadiazine cream is still used topically to prevent infection of burns

The antibacterial activity –and toxicity- of sulfanilamide can explained by a rather simple fact :enzyme in the bacteria (and in the patients) confuse it for *p*-aminobenzoic acid, which is an essential metabolite . In what is known as metabolite antagonism, the sulfanilamide competes with *p*-aminobenzoic acid for reactive Sites on the enzymes; deprived of the essential metabolite, the organism fails to reproduction, and dies .



P-Aino benzoic acid



Substituted sulfanilamide

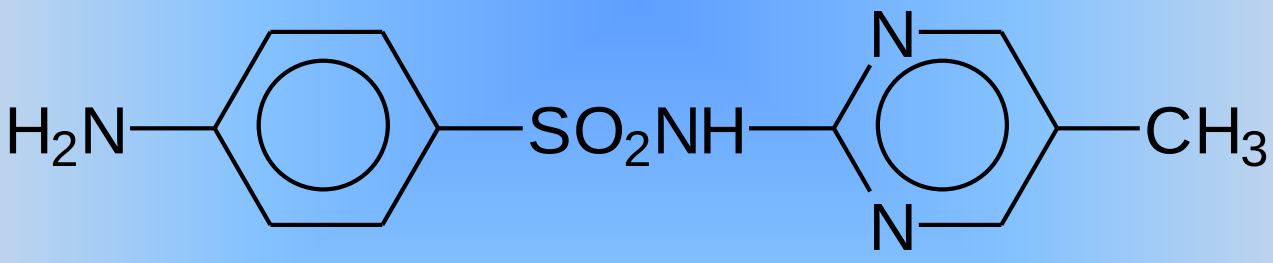
Sulfonamide drugs are structurally similar to PABA, and their antibacterial activity is due to their ability to interfere with the conversion of PABA to folate by the enzyme dihydropteroate synthetase. Thus, bacterial growth is limited through folate deficiency

Sulfonamides will affect the Human folic acid synthesis?

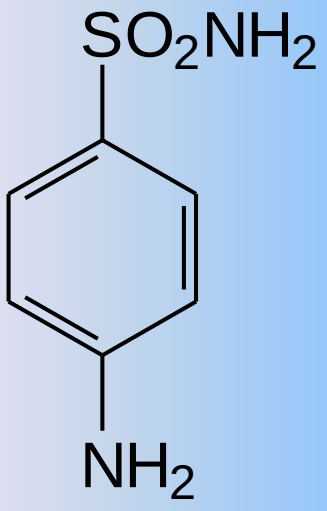
Human cells also require FA, but they utilize preformed FA supplied in diet and are unaffected by sulfonamides.

Only those microbes which synthesize their own FA and cannot take it from the medium are susceptible to sulfonamides.

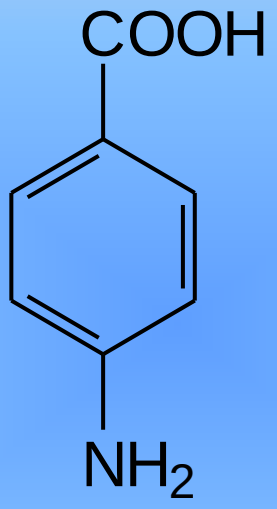
How good a drug the (sulfanilamide) is depends upon the nature of the R group attached to amido nitrogen. Of the hundreds of such compounds that have been synthesized, only a half dozen or so have had the proper combination of high antibacterial activity and low toxicity to human beings, that is necessary for an effective drug; in nearly all these effective compounds the R group contain a heterocyclic ring



Sulfamerazine

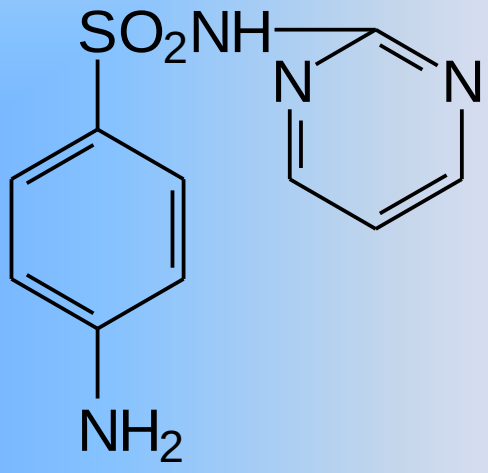


Sulfanilamide



p-Amino benzoic acid

(PABA)



Sulfadiazine