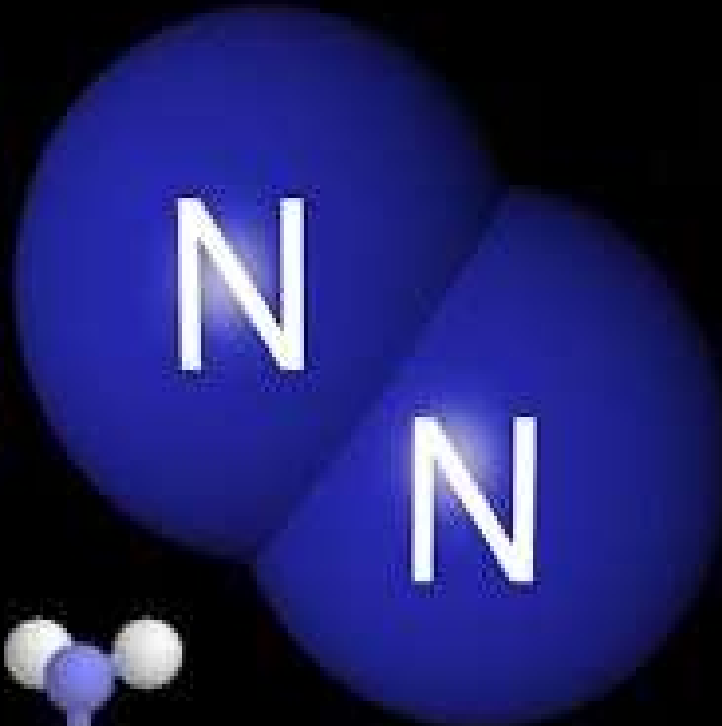
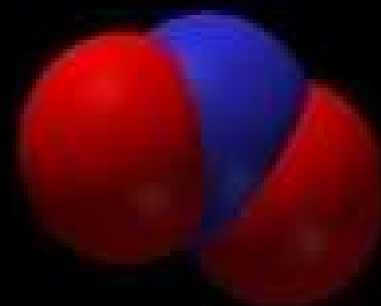
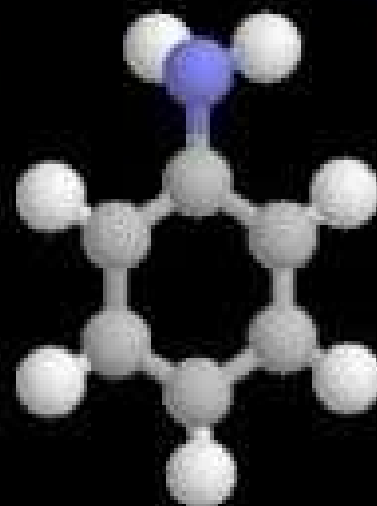
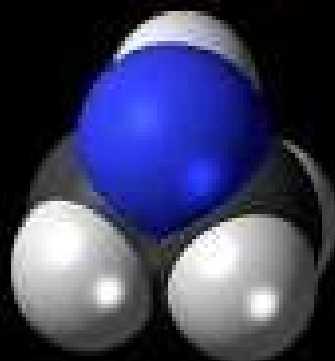


NITROGEN DERIVATIVES

(AMINES)

Part Two:
Reactions



Dr. Munther Abdujaleel M.A.
Assist. Prof. Org. Chem.

Reactions of Amines

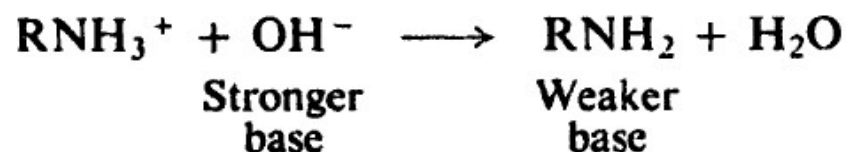
The three classes of amines contain nitrogen that bears an unshared pair of electrons. The tendency of nitrogen to share this pair of electrons underlies the entire chemical behavior of amines: their **basicity**, their **action as nucleophiles**, and the unusually **high reactivity of aromatic rings** bearing amino or substituted amino groups.

Therefore, there are several types of reactions of amines:

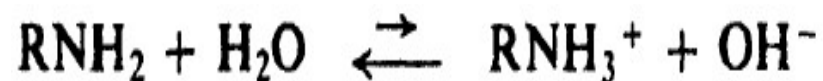
1. Basicity, salt formation.
2. Alkylation.
3. Conversion into amides.
4. Ring substitution in aromatic amines.
5. Hofmann elimination from quaternary ammonium salts.
6. Reaction with nitrous acid.

1- Basicity of amines. Basicity constant

Amines are converted into their salts by aqueous mineral acids and are liberated from their salts by aqueous hydroxides.



Basicity of amines showed by measuring the extent to which they **accept hydrogen ion from water**. The equilibrium constant for this reaction represents by K_b (basicity constant).



$$K_b = \frac{[\text{RNH}_3^+][\text{OH}^-]}{[\text{RNH}_2]}$$

Aliphatic $\sim 10^{-3}$ - 10^{-4} > ammonia 10^{-5} > aromatic amine 10^{-9}

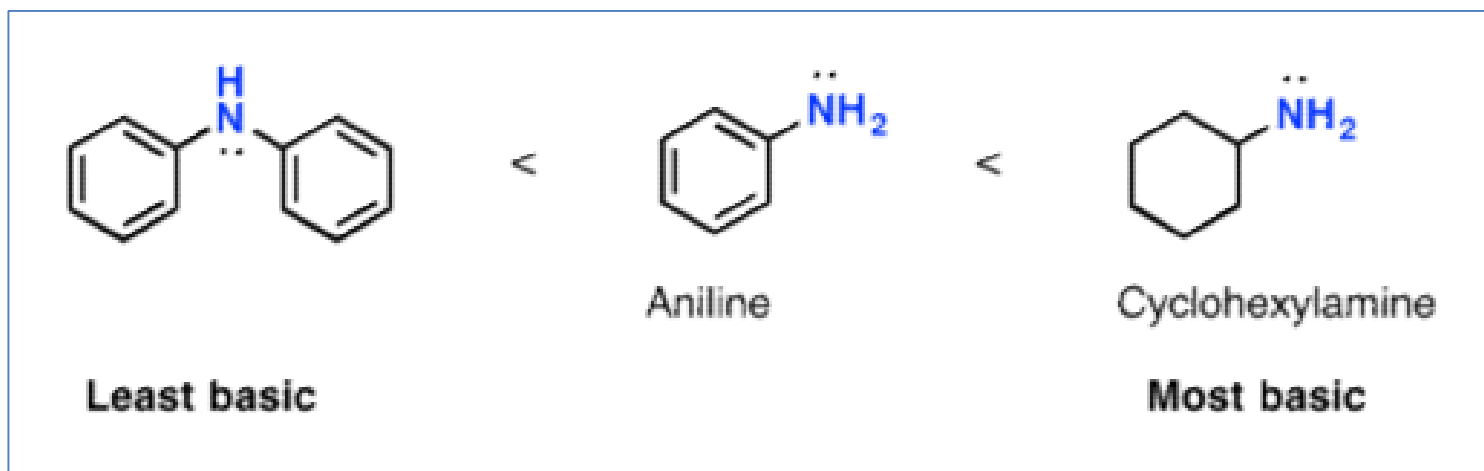
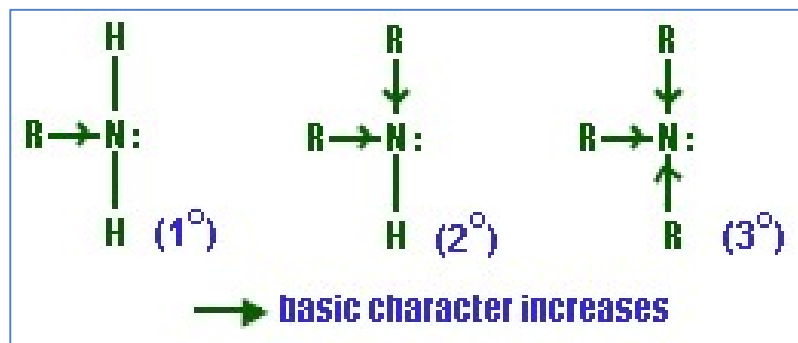
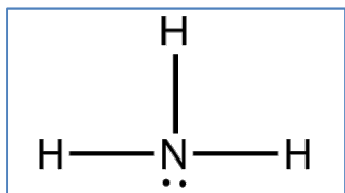
pKb 3-4 < 5 < 9

Structure and basicity

More basic : **** e: more available (N:) ****

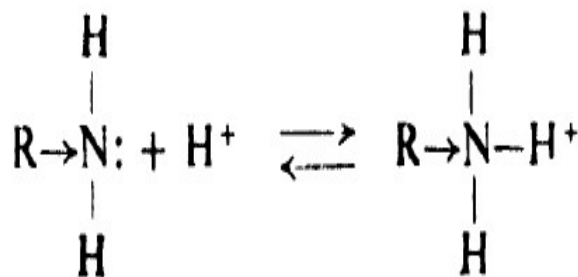
**** salt more stable (N⁺) ****

The stabilities of amines with the stabilities of their ions; the more stable the ion relative to the amine from which it is formed, the more basic the amine.



An aliphatic amine is more basic than ammonia because:

1. The electron-releasing alkyl groups tend to disperse the positive charge of the **substituted ammonium ion**.
2. Alkyl group pushes electrons toward nitrogen, and thus makes the **fourth pair more available** for sharing with an acid.

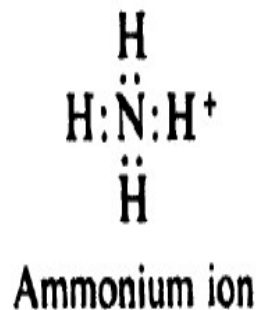
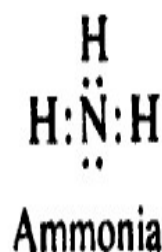


*R releases electrons:
makes unshared pair
more available*

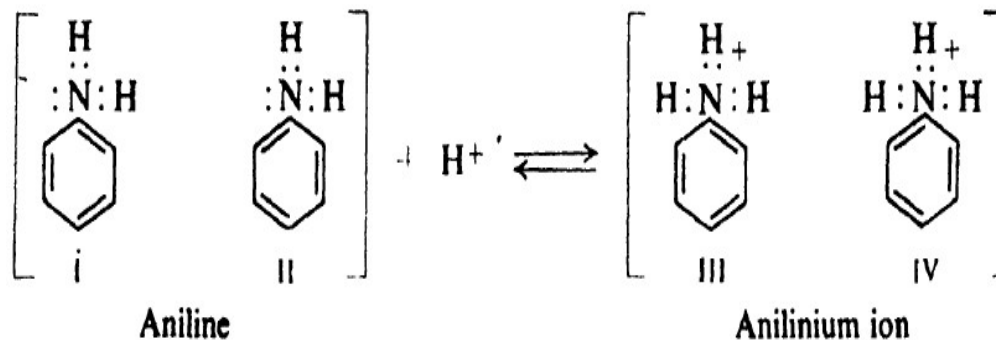
*R releases electrons
stabilizes ion,
increases basicity*

Aromatic amines are weaker bases than ammonia because:

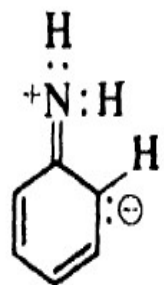
Ammonia and the ammonium ion are each represented satisfactorily by a single structure:



Aniline and anilinium ion contain the benzene ring and therefore are hybrids of the **Kekule structures I and II, and III and IV**. This resonance presumably stabilizes both amine and ion to the same extent.



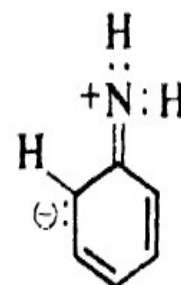
Thus **aniline** is a hybrid not only of **structures I and II** but also of **structures V, VI, and VII**. We cannot draw comparable structures for the anilinium ion.



V



VI



VII

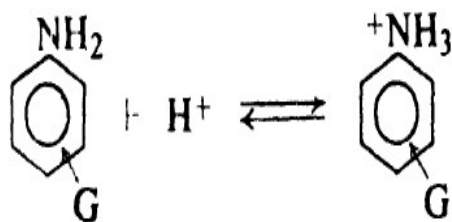
Contribution from the three structures V, VI, and VII **stabilizes the amine** in a way that is not possible for the ammonium ion; resonance thus lowers the energy content of aniline more than it lowers the energy content of the anilinium ion.

Effect of substituents on basicity of aromatic amines

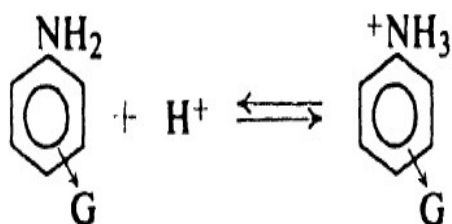
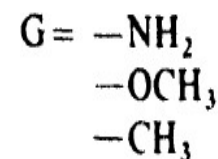
Electron-releasing substituent like $-\text{CH}_3$ increases the basicity of aniline, and an electron-withdrawing substituent like $-\text{X}$ or $-\text{NO}_2$ decreases the basicity.

Electron release tends to disperse the positive charge of the anilinium ion, and thus stabilizes the ion relative to the amine. Electron-releasing group pushes electrons toward nitrogen and makes the fourth pair more available for sharing with an acid

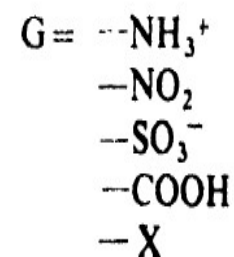
Basicity of Aromatic Amines



*G releases electrons:
stabilizes cation,
increases basicity*

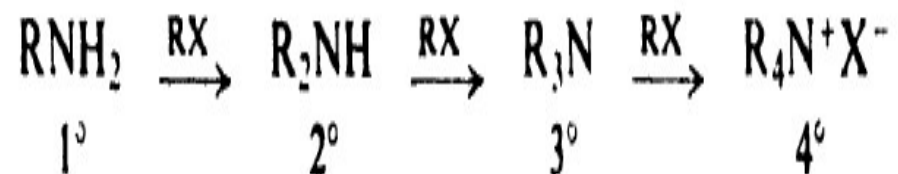


*G withdraws electrons
destabilizes cation,
decreases basicity*

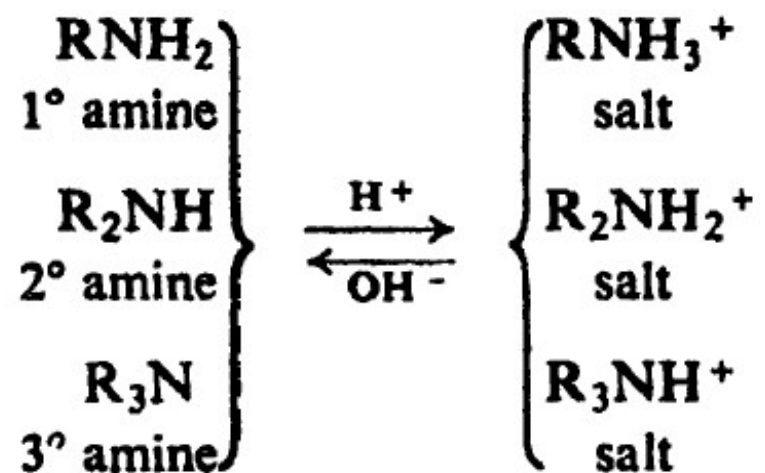


2- Quaternary ammonium salts. Exhaustive methylation. Hofmann elimination

An amine can react with an alkyl halide; the product is an amine of the next higher class.

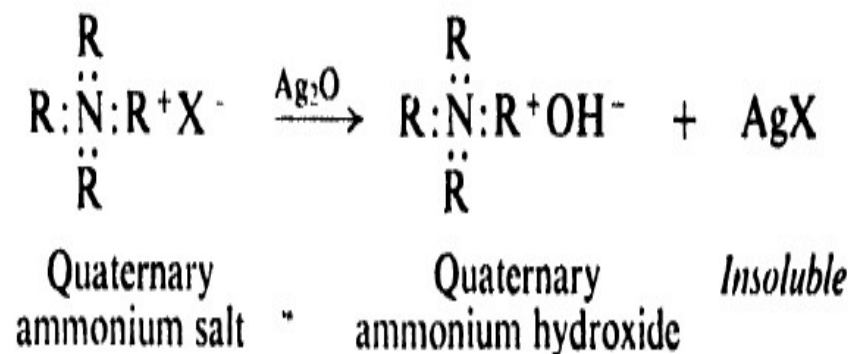


When the salt of a primary, secondary, or tertiary amine is treated with hydroxide ion, nitrogen gives up a hydrogen ion and the free amine is liberated

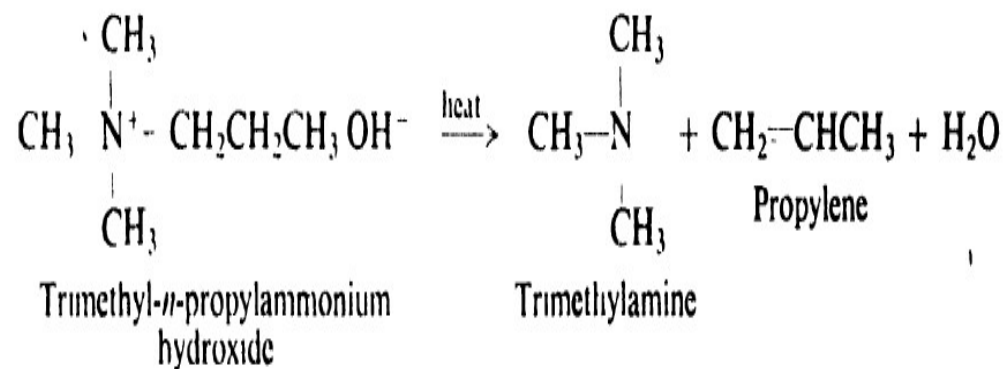


The quaternary ammonium ion, having no proton to give up, is not affected by hydroxide ion.

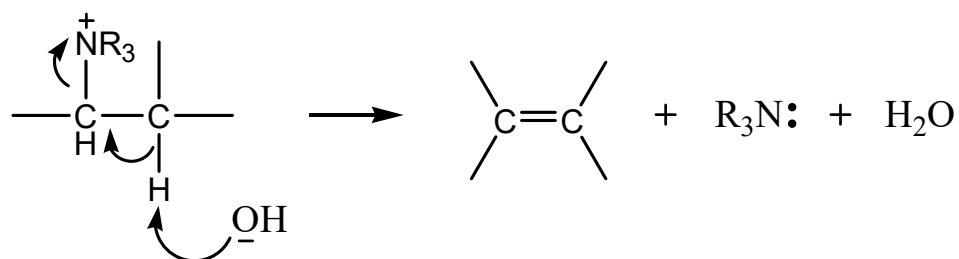
When a solution of a quaternary ammonium halide is treated with silver oxide, silver halide precipitates and a compound of a quaternary ammonium hydroxide. It has the structure $R_4N^+OH^-$



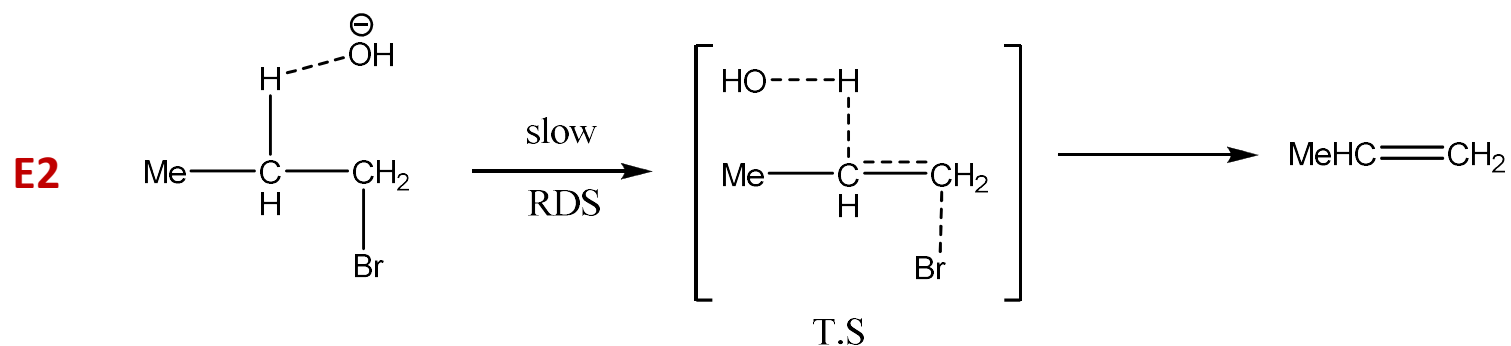
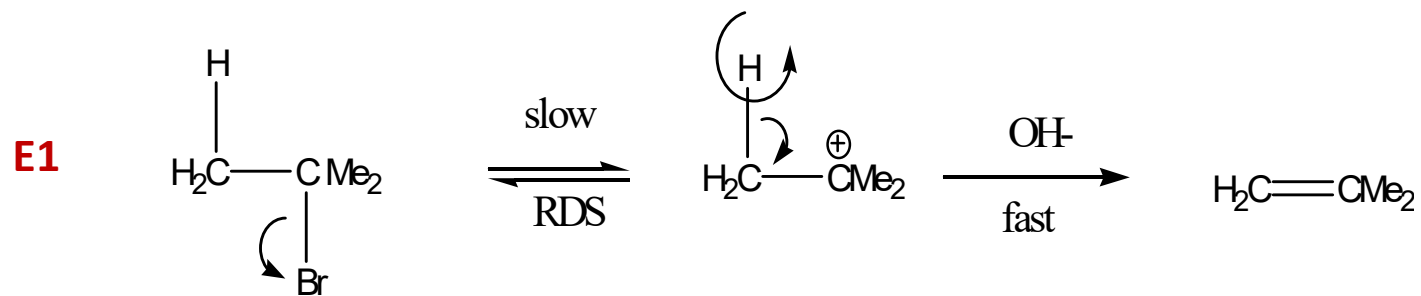
When a quaternary ammonium hydroxide is heated strongly (to 125 or higher), it decomposes to yield water, a tertiary amine, and an alkene



This reaction, called the **Hofmann elimination, E2**

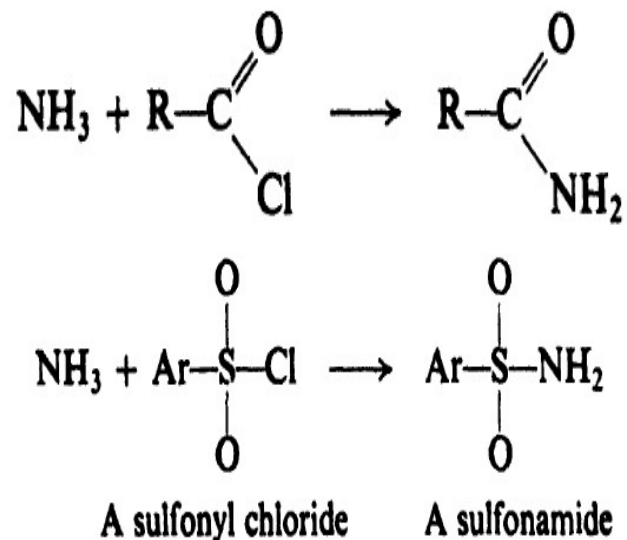


In general, there are two types major of **elimination reactions, E1 and E2**.
As shown in the following reactions:

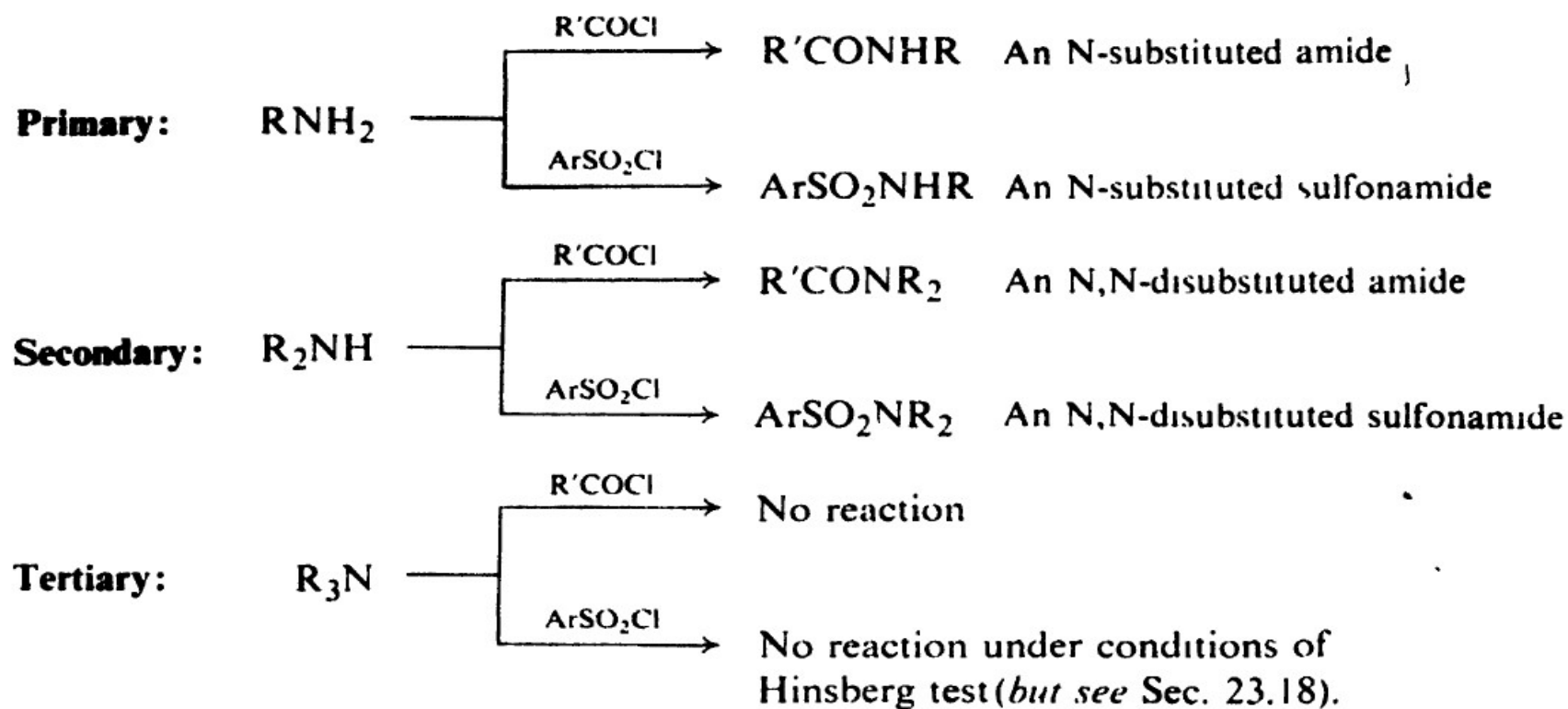


3- Conversion of amines into substituted amides

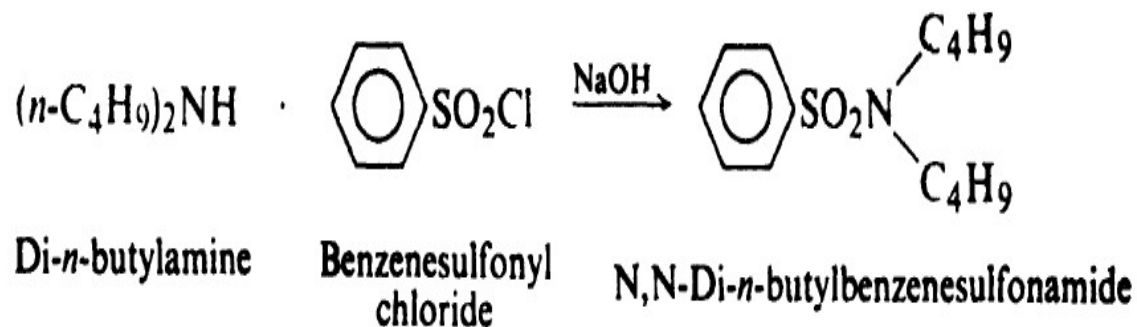
Ammonia reacts with **acid chlorides of carboxylic acids** or **acid chlorides of sulfonic acids** to yield amides



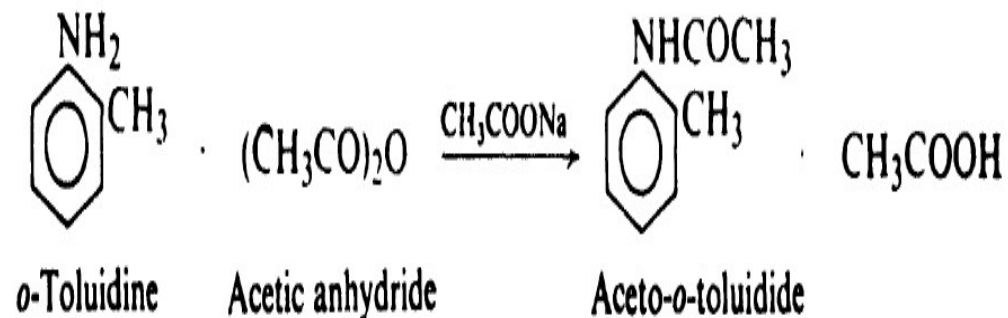
Primary and secondary amines can react with acid chlorides to form **substituted amides**. Whereas, tertiary amines, although basic, fail to yield amides, presumably because they cannot lose a proton



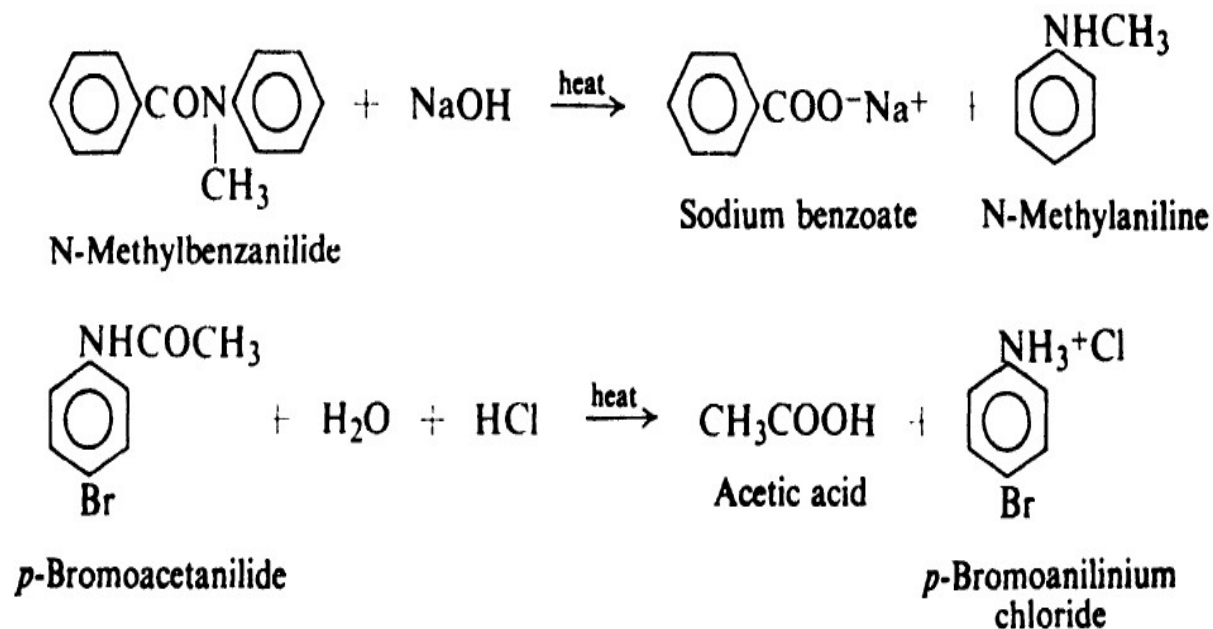
Substituted amides of aromatic carboxylic acids or of sulfonic acids are prepared by the **Schotten-Baumann technique**, in the presence of a base



Acetylation is generally carried out using acetic anhydride rather than acetyl chloride. For example:

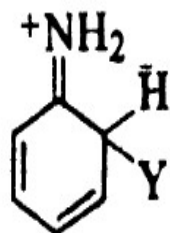


Like simple amides, substituted amides undergo **hydrolysis**; the products are the acid and the amine, although one or the other is obtained as its salt, depending upon the **acidity** or **alkalinity** of the medium.

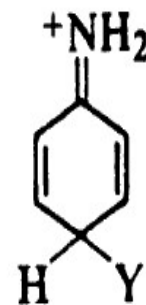


4- Ring substitution in aromatic amines

$-\text{NH}_2$, $-\text{NHR}$, and $-\text{NR}_2$ groups act as powerful activators and ortho, para directors in electrophilic aromatic substitution. Because of stabilization of the intermediate carbocation by structures like I and II.



I



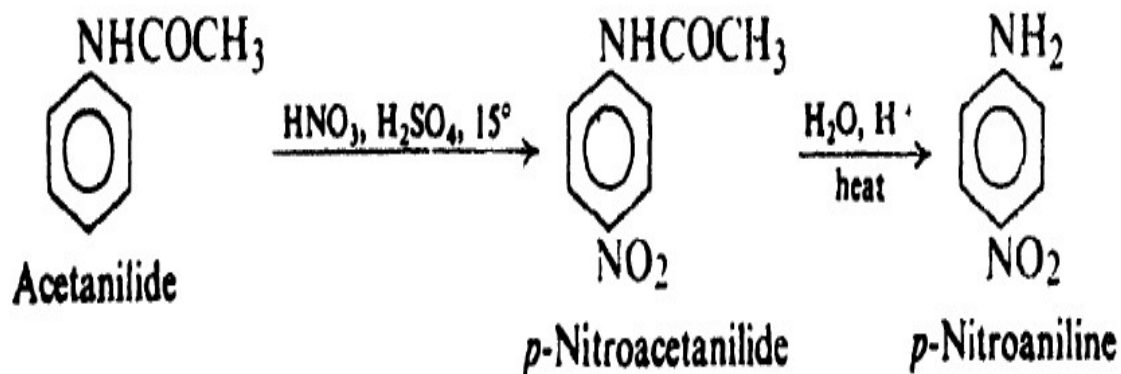
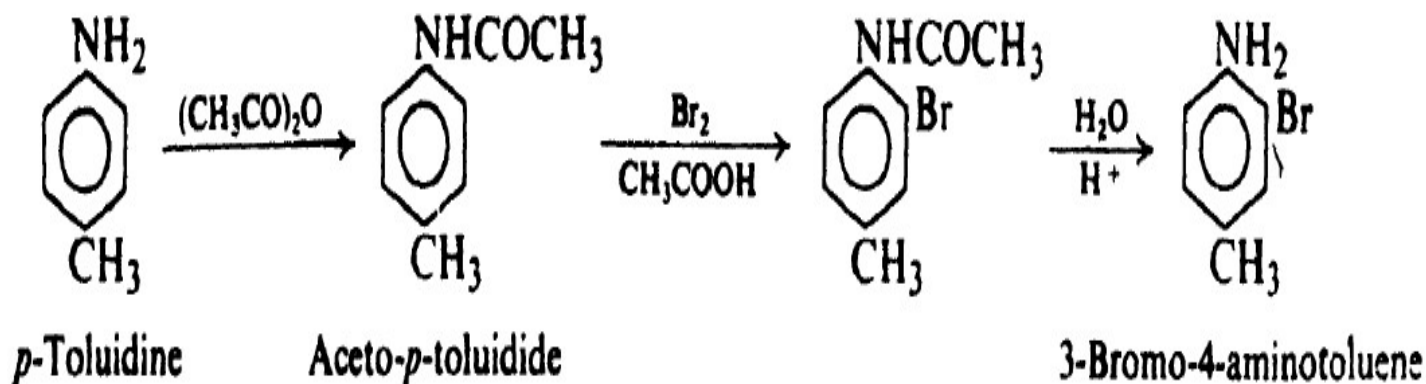
II

The acetamido group, $-\text{NHCOCH}_3$, is also activating and ortho, para-directing, but less powerfully so than a free amino group

the $-\text{NR}_3^+$ group is a powerful deactivator and meta director

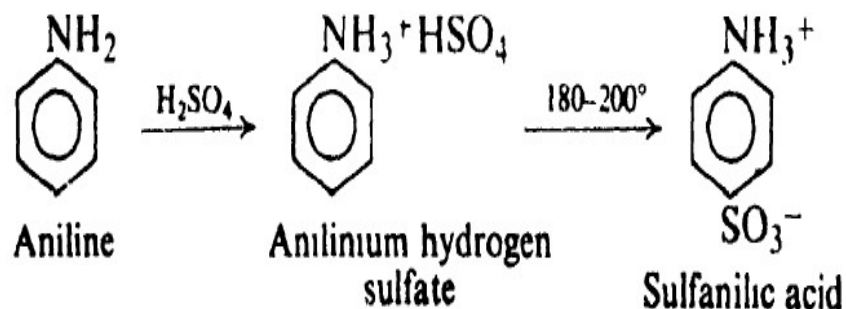
In the **strongly acidic nitration medium**, the aniline is converted into the **anilinium ion**; substitution is thus controlled not by the $-NH_2$ group but by the $-NH_3^+$ group which, because of its positive charge, directs much of the substitution to the **meta** position.

Therefore, we **protect the amino group**: we **acetylate the amine**, then carry out the substitution, and finally hydrolyze the amide to the desired substituted amine. For example:

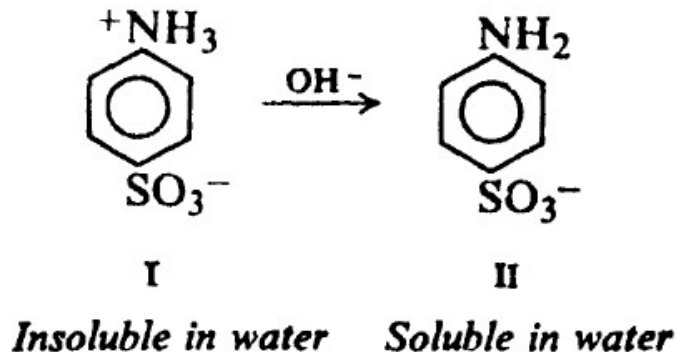


Sulfonation of aromatic amines. Dipolar ions

Aniline is usually sulfonated by "baking" the salt, **anilinium hydrogen sulfate**, at 180-200; the chief product is the p-isomer, **p-aminobenzenesulfonic acid**, known as **sulfanilic acid**.

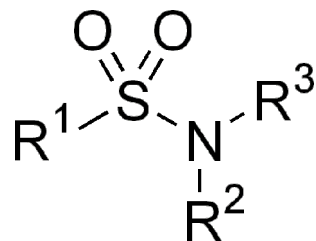


Sulfanilic acid actually has the structure I which contains the $-\text{NH}_3^+$ and $-\text{SO}_3^-$ groups. Sulfanilic acid is a **salt**, but of a rather special kind, called a **dipolar ion** (sometimes called a **zwitterions**).

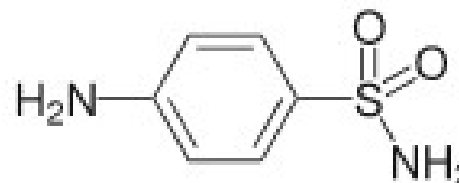


Sulfanilamide. The sulfa drugs

Sulfonamides $R_1-SO_2-N-(R_2)(R_3)$ are prepared by the reaction of a sulfonyl chloride ($R-SO_2-Cl$) with ammonia or an amine.

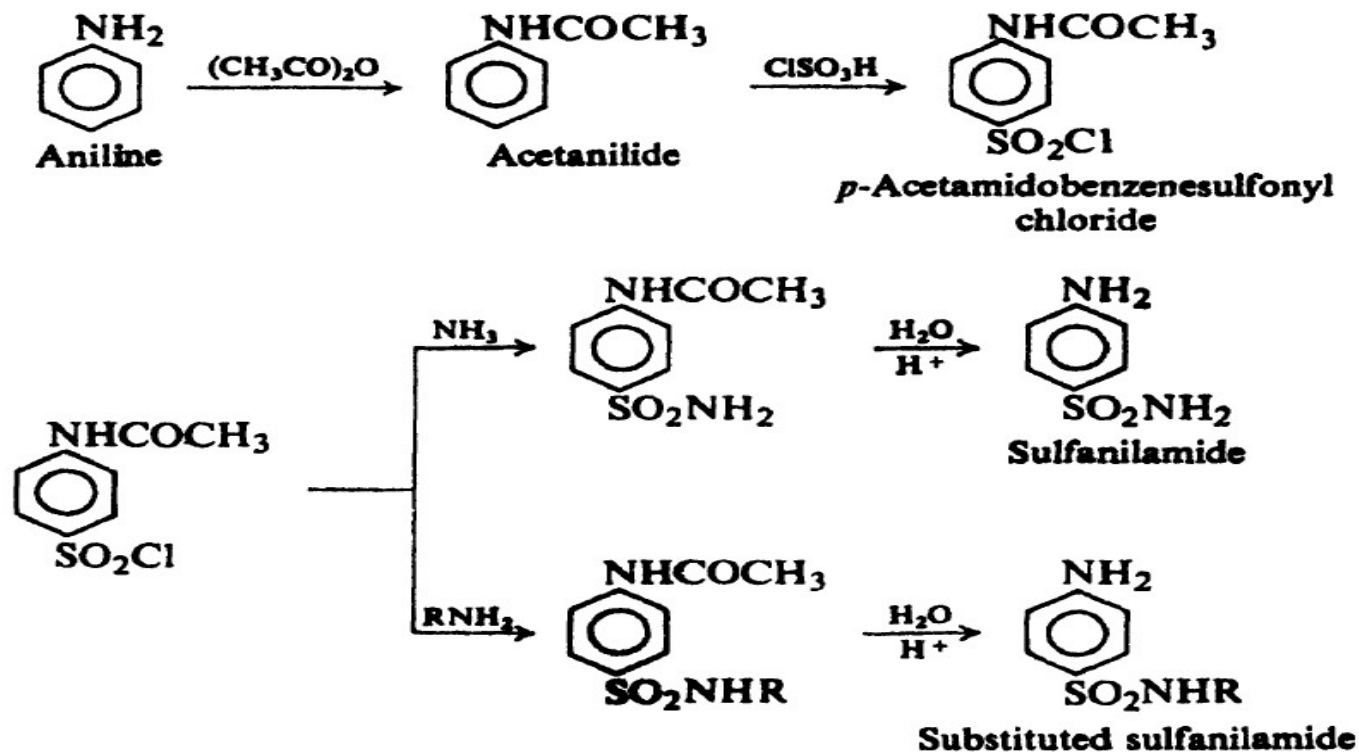


Sulfonamides

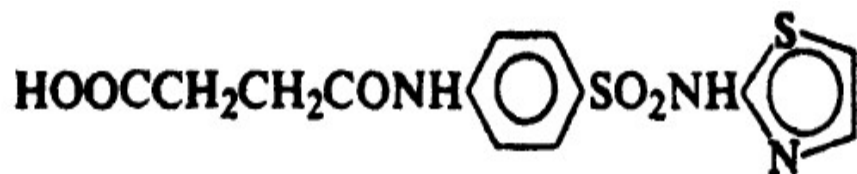


Sulfanilamide

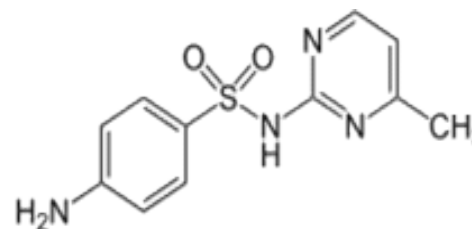
Sulfanilamide and related compounds are generally prepared in the following way:



Just how good a drug the sulfanilamide is depends upon the nature of the group R attached to amido nitrogen. More effective compounds where the group R contains a heterocyclic ring. Such as:



Succinoylsulfathiazole

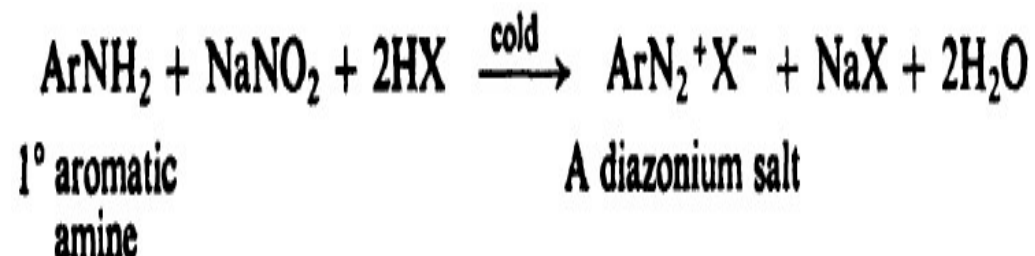


Q/ Give five examples (name with structure) for sulfa drugs containing heterocyclic ring.

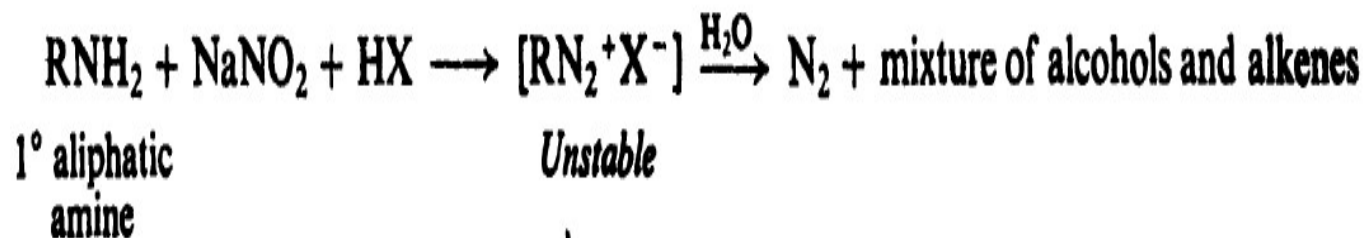
5- Reactions of amines with nitrous acid

Each class of amine yields a different kind of product if its reaction with nitrous acid, HONO . This unstable reagent is generated in the presence of the amine by the action of **mineral acid** on **sodium nitrite**.

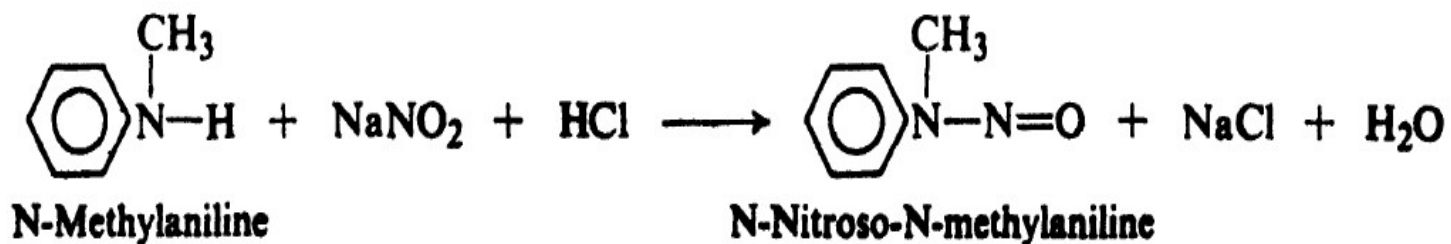
- ❖ **Primary aromatic amines** react with nitrous acid to yield **diazonium salts**.



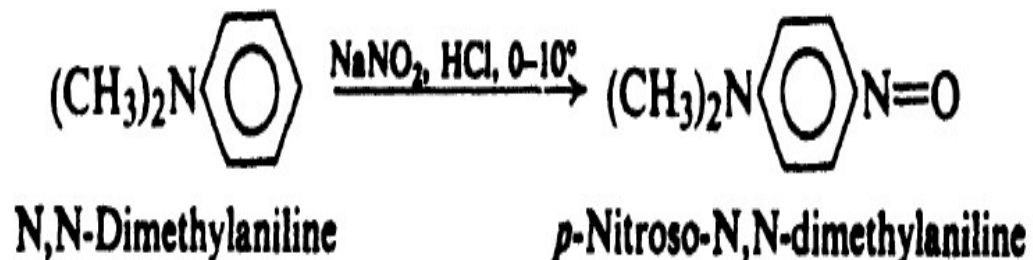
- ❖ **Primary aliphatic amines** also react with nitrous acid to yield diazonium salts; but since aliphatic diazonium salts are quite unstable and break down to yield a complicated mixture of organic products.



- ❖ **Secondary amines**, both aliphatic and aromatic, react with nitrous acid to yield **N-nitrosoamines**.

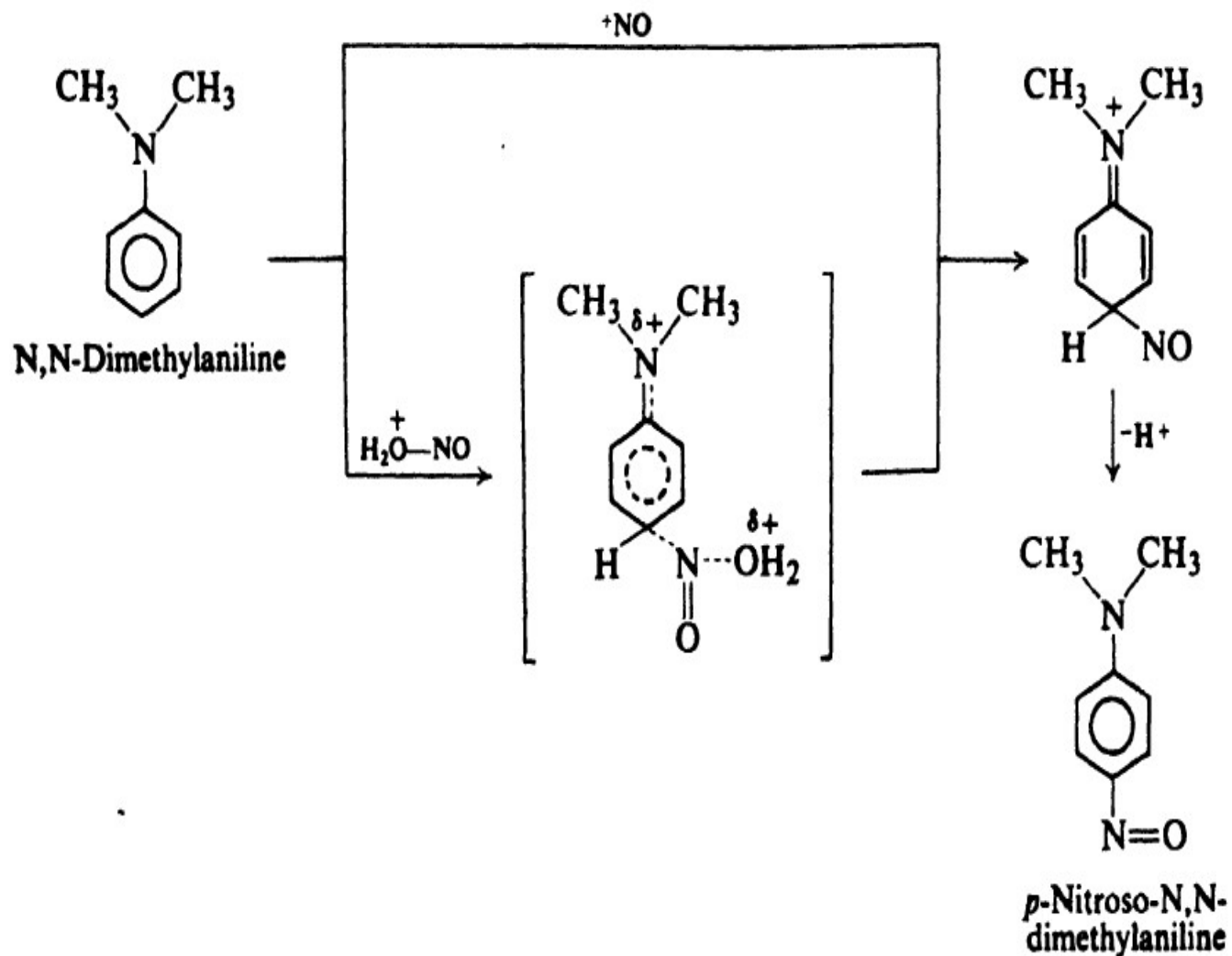


- ❖ **Tertiary aromatic amines** undergo ring substitution, to yield compounds in which a nitroso group, -N=O, is joined to carbon; thus N,N-dimethylaniline yields chiefly *p*-nitroso-N,N-dimethylaniline.



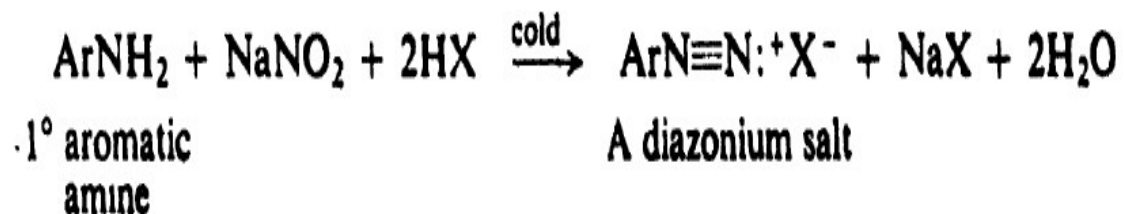
Ring nitrosation is an **electrophilic aromatic substitution** reaction, in which the attacking reagent is either the nitrosonium ion, ^+NO , or some species (like $\text{H}_2\text{O}^+-\text{NO}$ or NOCl) that can easily transfer ^+NO to the ring.

The nitrosonium ion is very weakly electrophilic; nitrosation ordinarily occurs only in rings bearing the powerfully activating dialkylamino ($-\text{NR}_2$) or hydroxy ($-\text{OH}$) group.



Diazonium salts. Preparation and reactions

When a **primary aromatic amine**, dissolved or suspended in **cold aqueous mineral acid**, is treated with **sodium nitrite**, there is formed a **diazonium salt (diazotization)**.

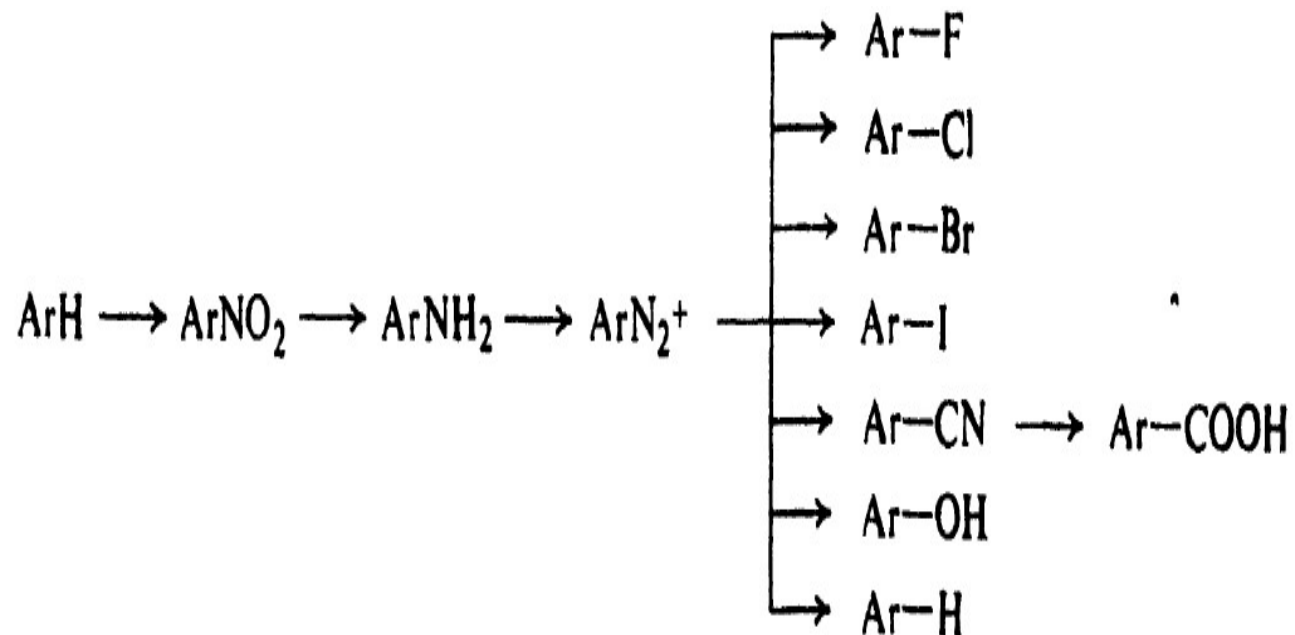


The large number of reactions undergone by diazonium salts may be divided into two classes:

replacement, in which nitrogen is lost as N_2 , and some other atom or group becomes attached to the ring in its place; and

coupling, in which the nitrogen is retained in the product.

Replacement of the diazonium group is the best general way of introducing F, Cl, Br, I, CN, OH, and H into an aromatic ring.



The **coupling** of diazonium salts with aromatic phenols and amines yields **azo** compounds **-N=N-**, which are of tremendous importance to the dye industry.

Replacement by halogen, Sandmeyer reaction

- Replacement of the diazonium group by **-Cl** or **-Br** is carried out by mixing the solution of freshly prepared diazonium salt with **cuprous chloride or cuprous bromide** to yield **aryl chloride or aryl bromide**.



- Replacement of the diazonium group by **-I** using potassium iodide.



Replacement of the diazonium group by **-F** is carried out by Addition of fluoboric acid, HBF_4

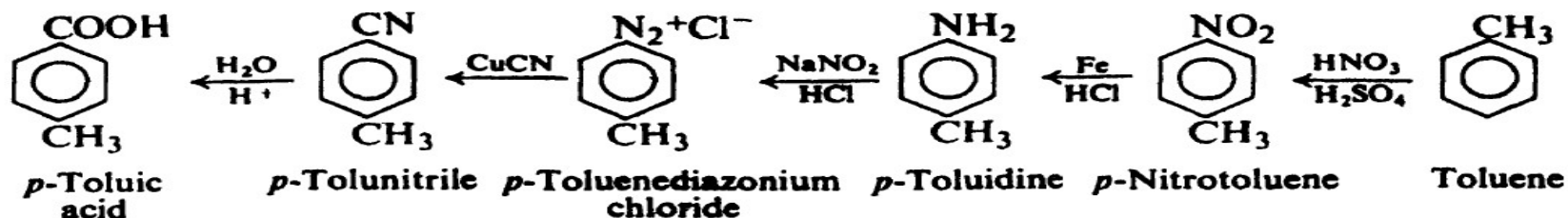


Replacement by -CN. Synthesis of carboxylic acids

Replacement of the diazonium group by -CN is carried out by reaction the diazonium salt with cuprous cyanide.



Hydrolysis of nitriles yields **carboxylic acids**.



Replacement by -OH. Synthesis of phenols

Diazonium salts react with water to yield phenols. This reaction takes place slowly in the ice-cold solutions of diazonium salts.



Replacement by -H

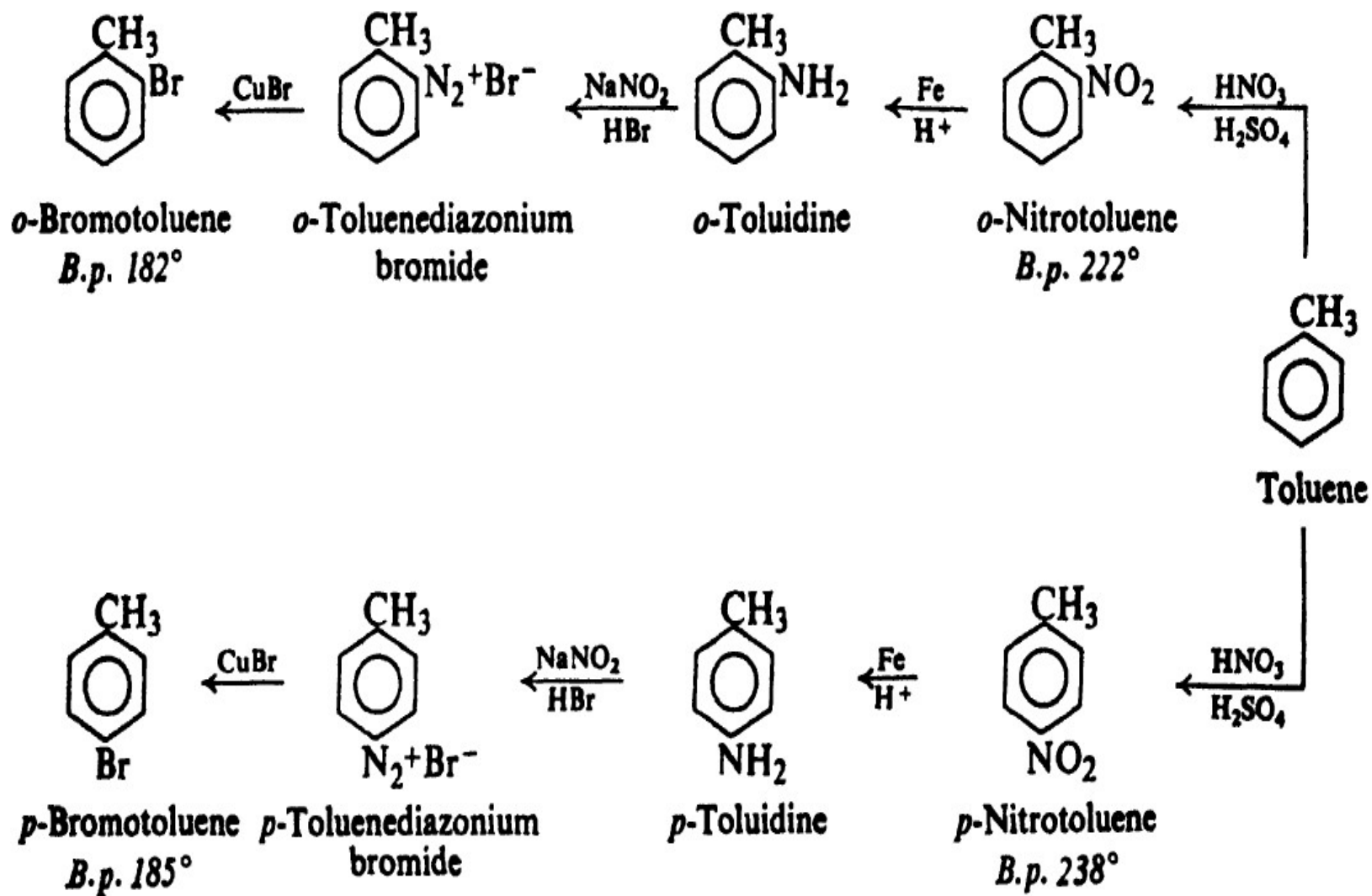
Replacement of the diazonium group by -H can be brought about by a number of reducing agents; perhaps the most useful of these is hypophosphorous acid H_3PO_2 .



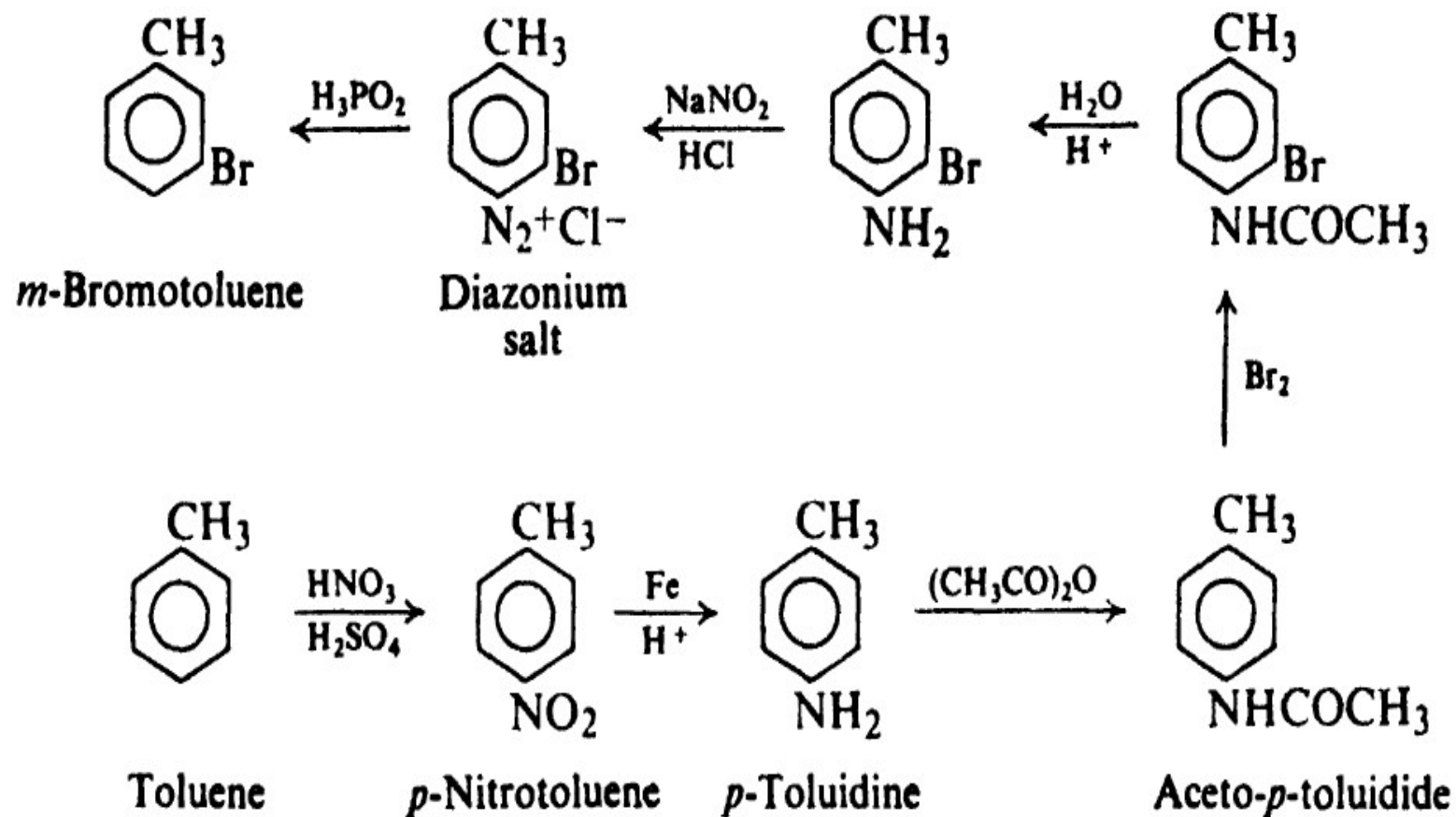
Syntheses using diazonium salts

Examples of how diazonium salts can be used in organic synthesis?

The *o*- and *p*-bromotoluenes are prepared from the corresponding *o*- and *p*-nitrotoluenes:

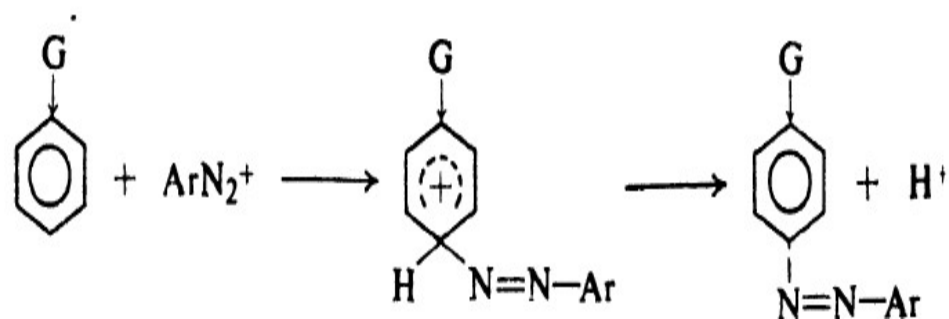


m-Bromotoluene is prepared from toluene:

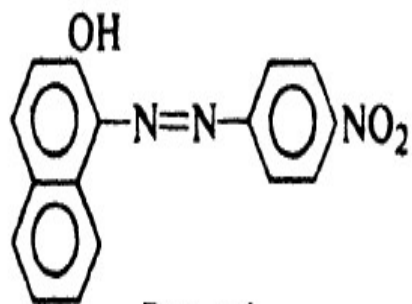


Coupling of diazonium salts. Synthesis of azo compounds

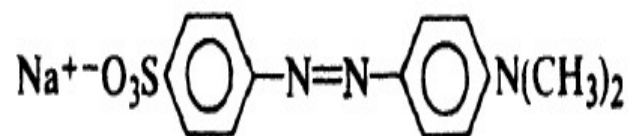
Diazonium salts react with certain aromatic compounds to yield products of the general formula $\text{Ar-N=N-Ar}'$, called **azo** compounds. The aromatic ring ($\text{Ar}'\text{H}$) undergoing attack by the diazonium ion must, in general, contain a **powerfully electron-releasing group, generally $-\text{OH}$, $-\text{NR}_2$, $-\text{NHR}$, or $-\text{NH}_2$** . Substitution usually occurs **para** to the activating group.



Some of the **acid-base indicators** with which the student is already familiar are azo compounds



Para red
A red dye

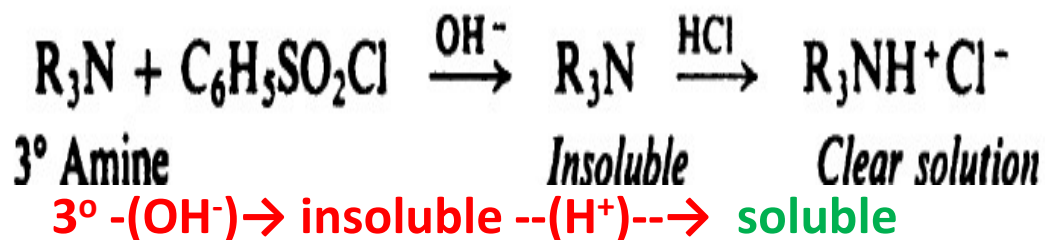
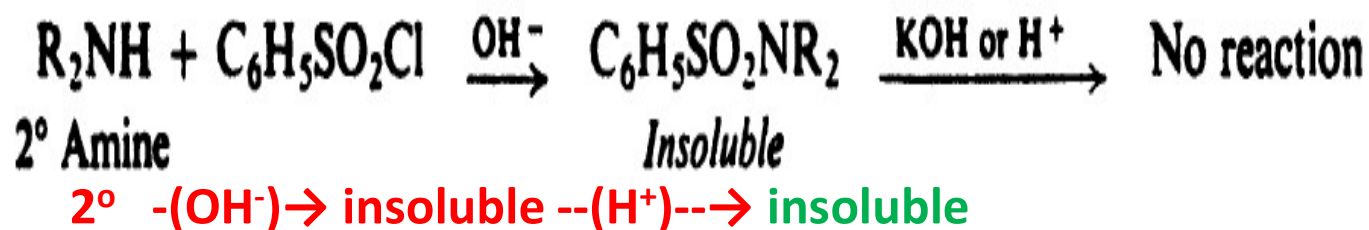
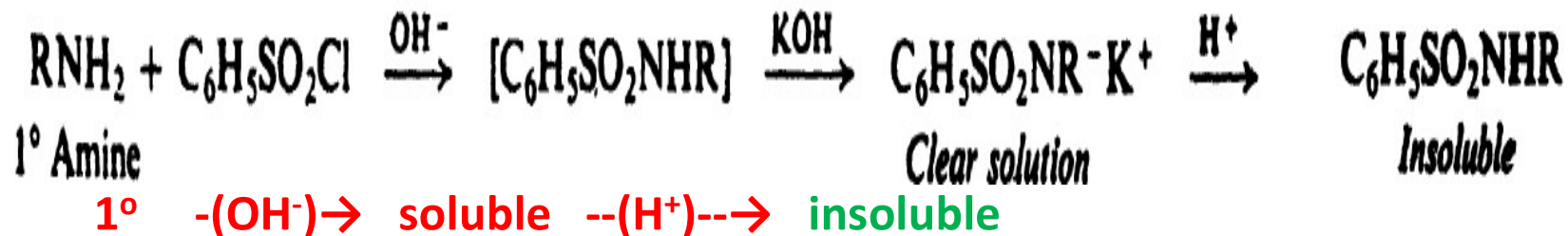


Methyl orange
An acid-base indicator:
red in acid, yellow in base

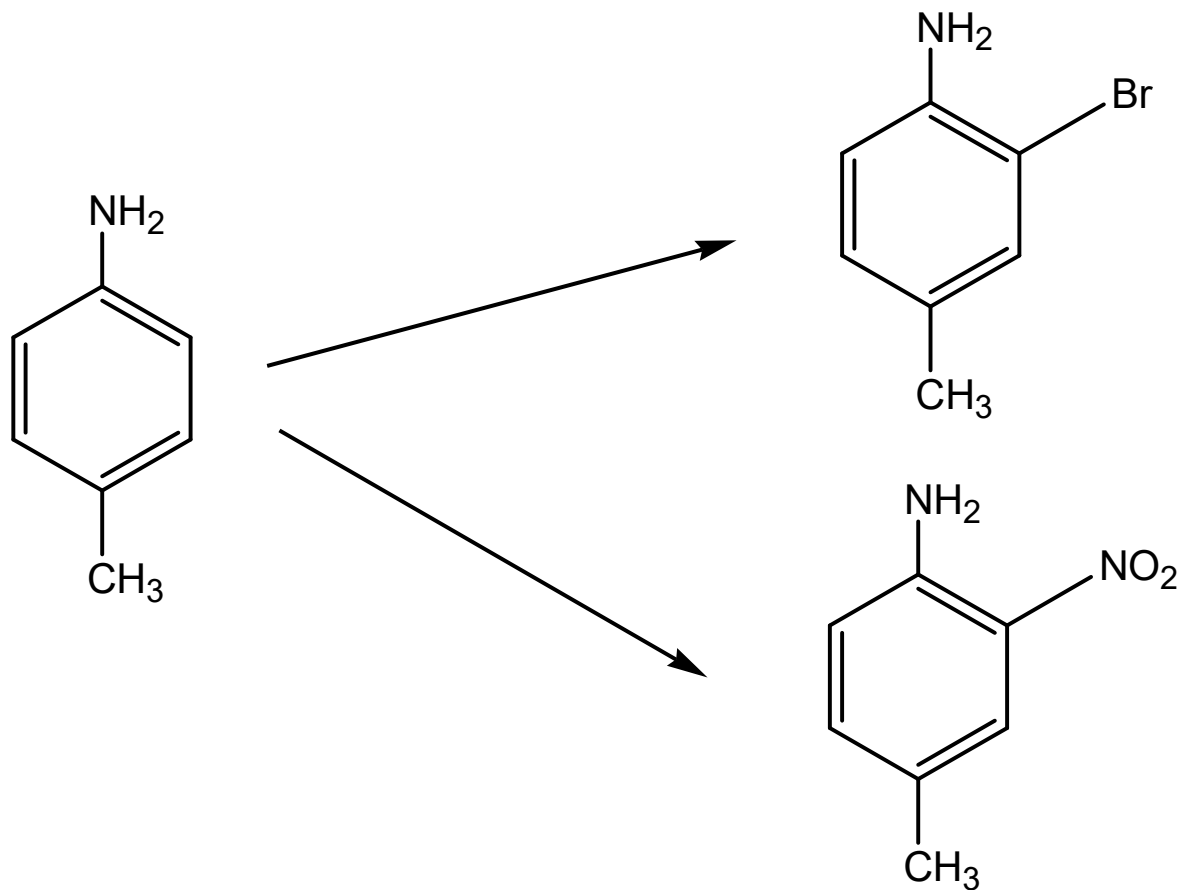
Analysis of amines. Hinsberg test

The amine is shaken with **benzenesulfonyl chloride** in the presence of **aqueous potassium hydroxide**. **Primary** and **secondary amines** form substituted sulfonamides; **tertiary amines** do not.

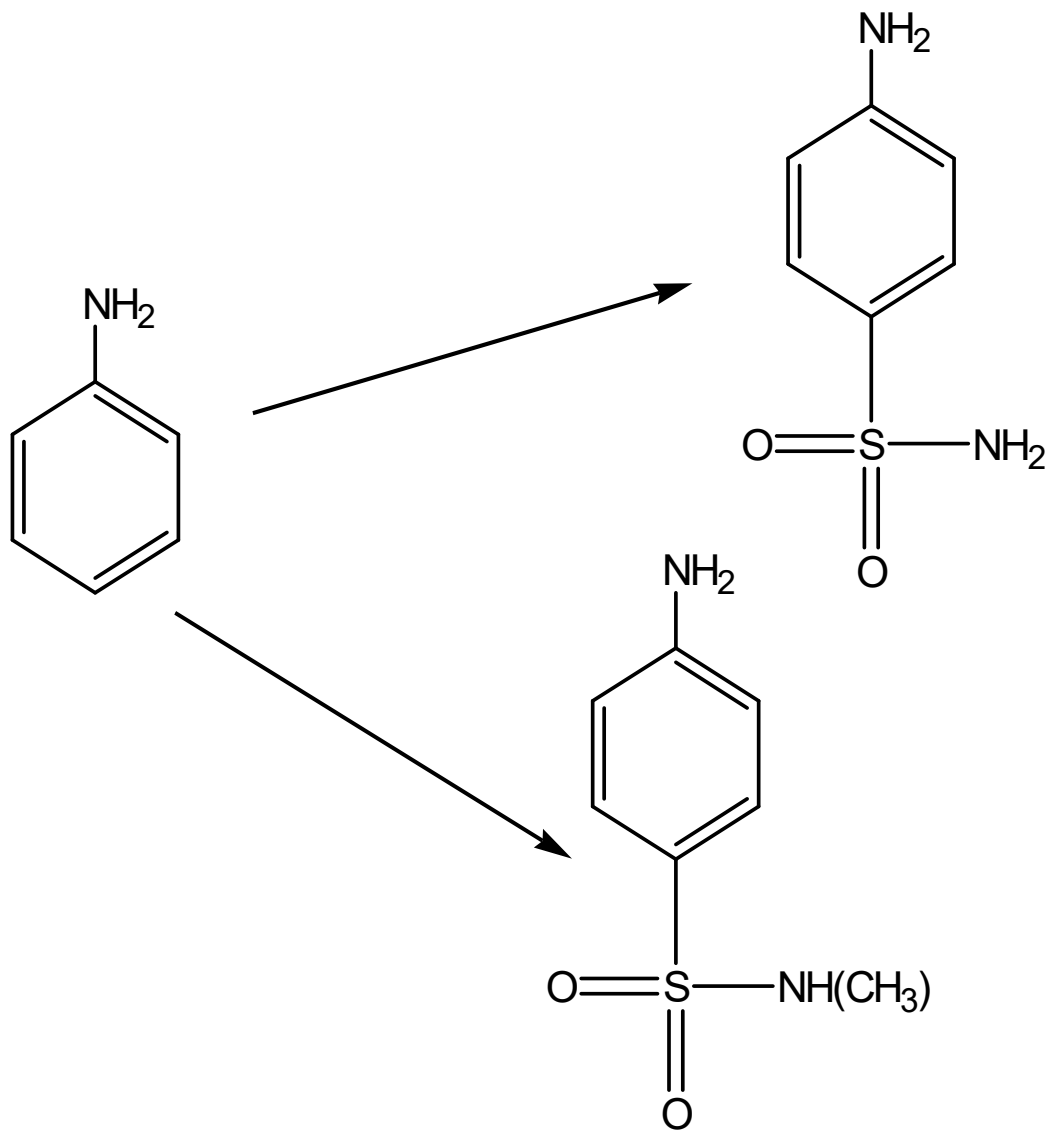
- A primary amine yields a clear solution, from which, upon acidification, an **insoluble** material separates.
- A secondary amine yields an insoluble compound, which is unaffected by acid.
- A tertiary amine yields an insoluble compound (the unreacted amine itself) which dissolves upon acidification of the mixture.



Starting with p-methylaniline and use any material or reagent to prepare the following compounds:



Starting with aniline and use any material or reagent to prepare the following compounds:



Starting with aniline and use any material or reagent to prepare the following compounds:

