

Heterocyclic Compounds

Heterocyclic Compounds

Those cyclic compounds in which **one or more** of the **ring carbons are replaced by another atoms** (referred as heteroatoms).

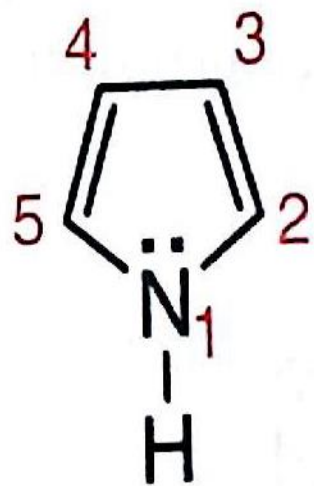
The most common heteroatoms are **Nitrogen, Oxygen and Sulphur**.

But,

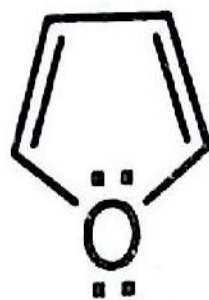
Other atoms such as **Boron, Phosphorous, or Silicon** can also be members of heterocyclic rings.

A variety of heterocyclic compounds of different ring sizes are known, the most important ones are made of **five and six-membered rings**.

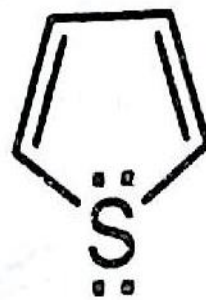
Five-membered Rings



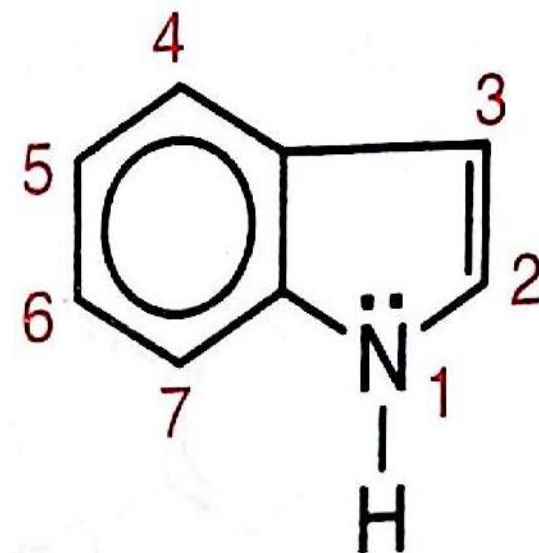
Pyrrole



Furan

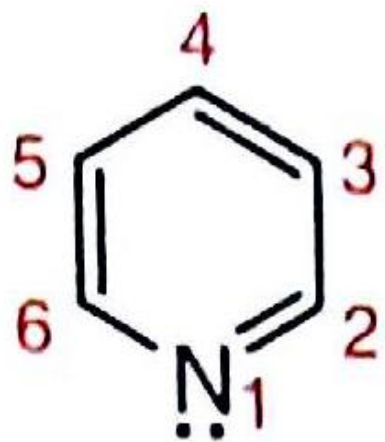


Thiophene

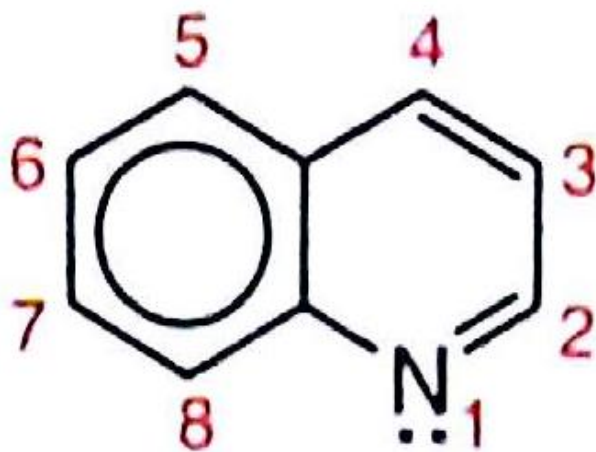


Indole

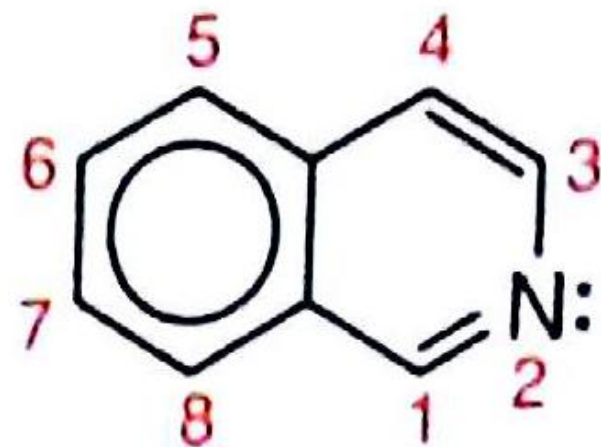
Six-membered Rings



Pyridine

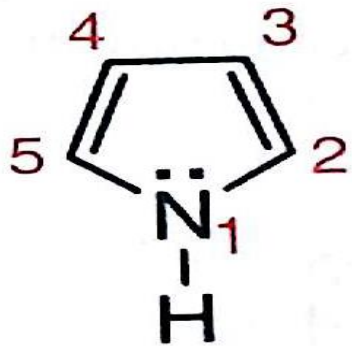


Quinoline

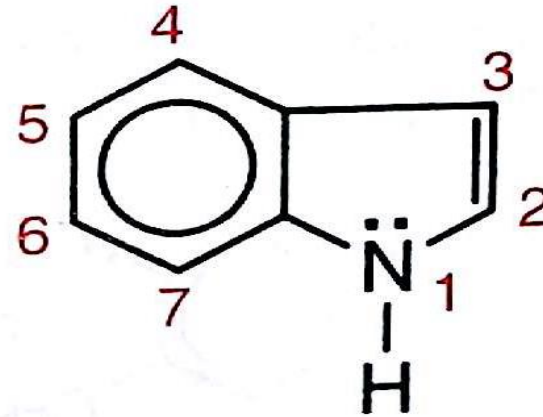


Isoquinoline

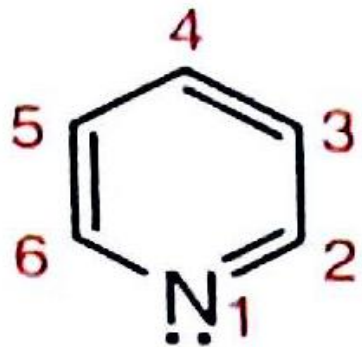
Notice that the rings containing nitrogen usually end with *-ole* if **five-membered** and with *-ine* if **six-membered**. The hetero atom is always numbered as 1 (**isoquinoline is an exception**)



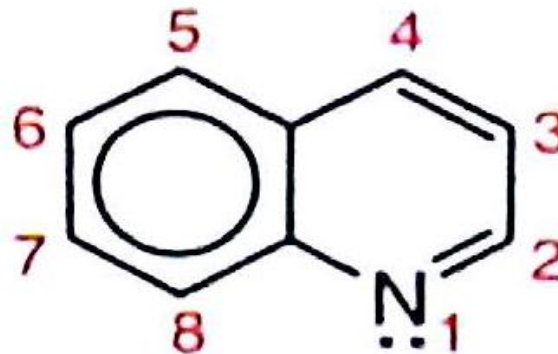
Pyrrole



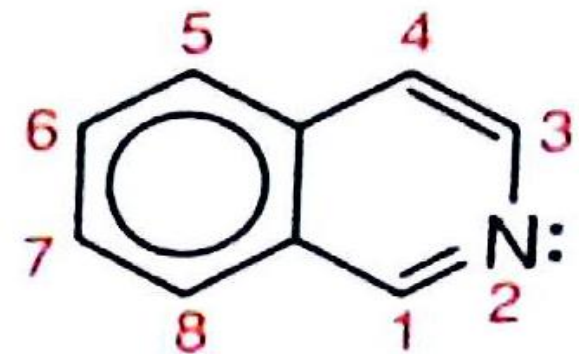
Indole



Pyridine

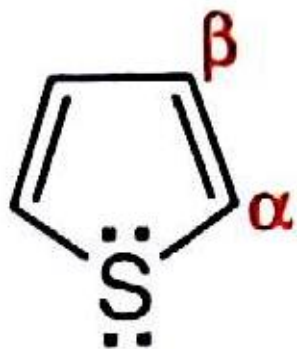


Quinoline

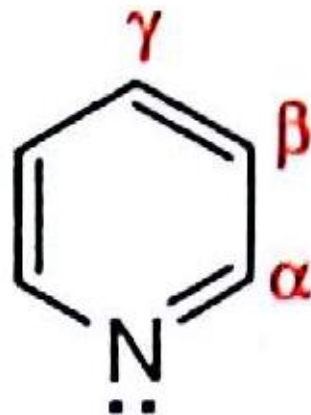


Isoquinoline

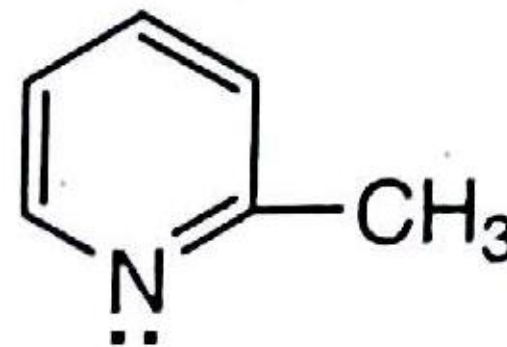
The carbon atoms next to the hetero atom are sometimes referred to as the **α -carbon** atoms and those further away as **β - and Υ -carbon** atoms



Thiophene



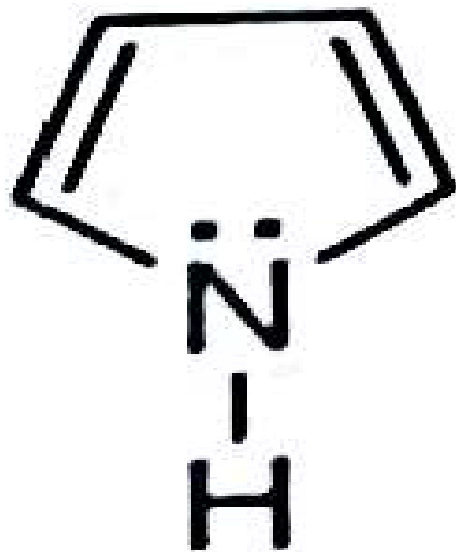
Pyridine



α -Methylpyridine
(2-Methylpyridine)

Pyrrole

It is an important five-membered heterocyclic compound because many naturally occurring substances contain the pyrrole ring e.g., **chlorophyll**, **hemoglobin** and **some of the alkaloids**.



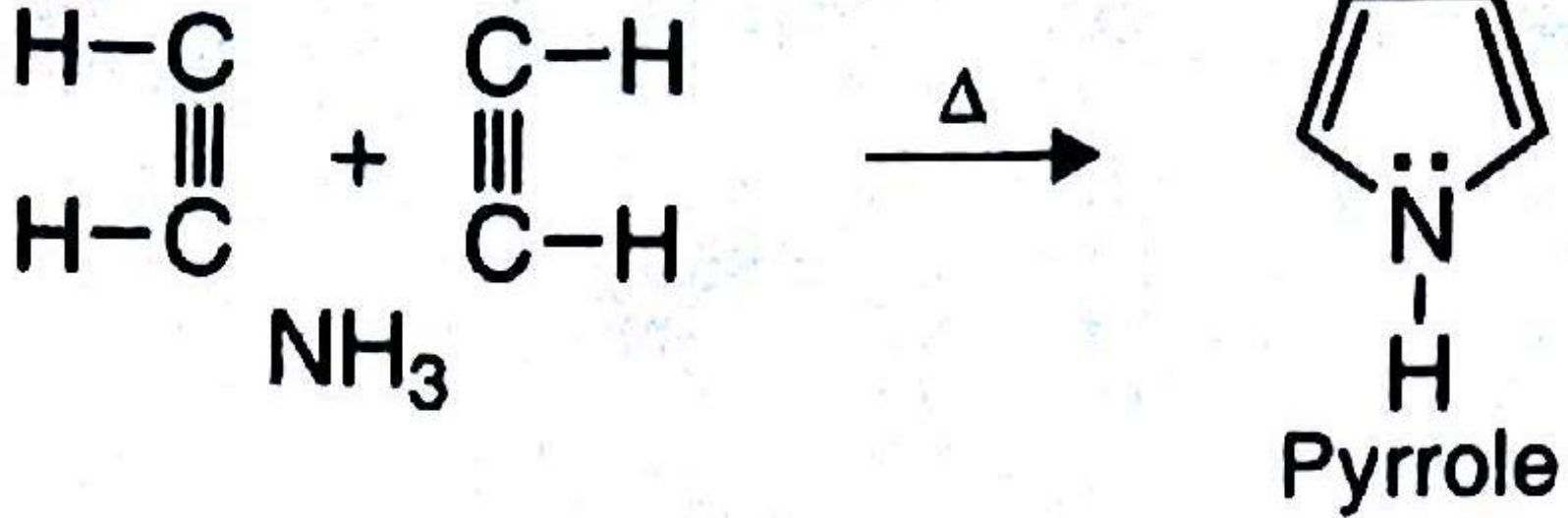
Occurrence

Pyrrole occurs in **coal-tar and in bone oil** (Dippel's oil). The latter is obtained by the dry distillation, or pyrolysis, of animal by-products such as horns, hooves, and bones.

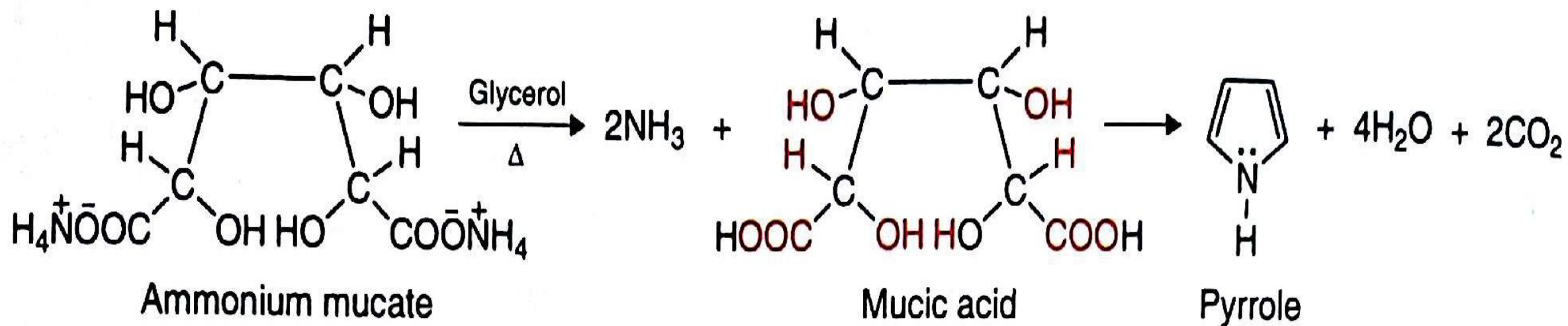
It may be isolated from bone oil by first washing it with **dilute sulphuric acid to remove the basic substances, and then with dilute alkali to remove the acidic substances.** It is next subjected to **fractional distillation.** The fraction passing over between **100°C to 150°C** contains pyrrole, which may be removed by **boiling with potassium hydroxide.** The potassium salt is formed which on steam distillation gives pyrrole. This is finally purified by **distillation.**

Preparation Methods

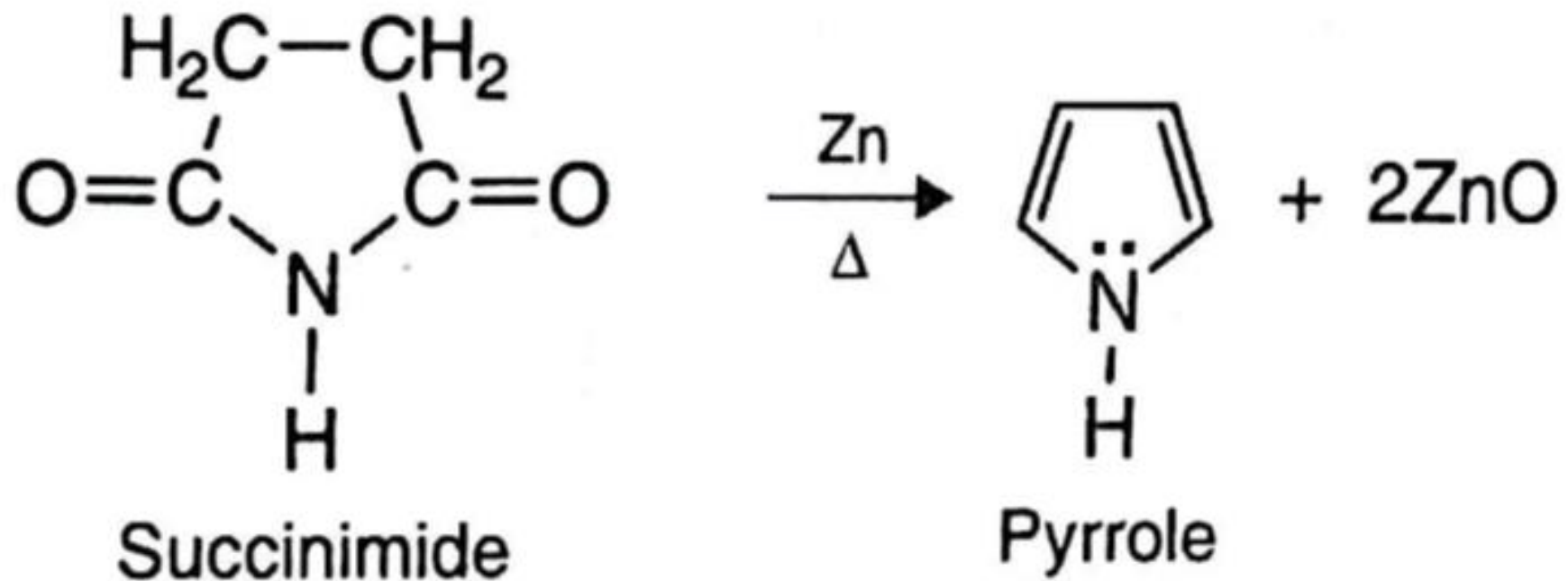
1. By passing a mixture of **acetylene and ammonia** through a red-hot tube



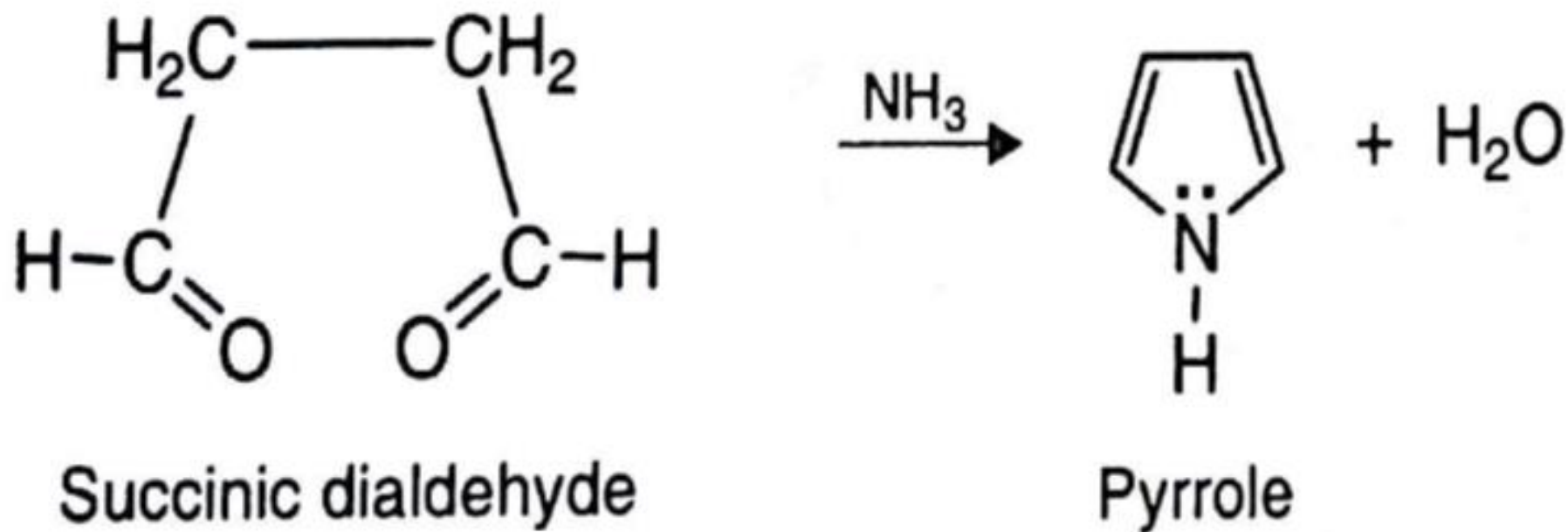
2. By heating **ammonium mucate** with glycerol at 200 degrees. At this temperature, ammonium mucate is dissociated into mucic acid and ammonia. The acid then undergoes dehydration, decarboxylation and ring-closure by reaction with ammonia.



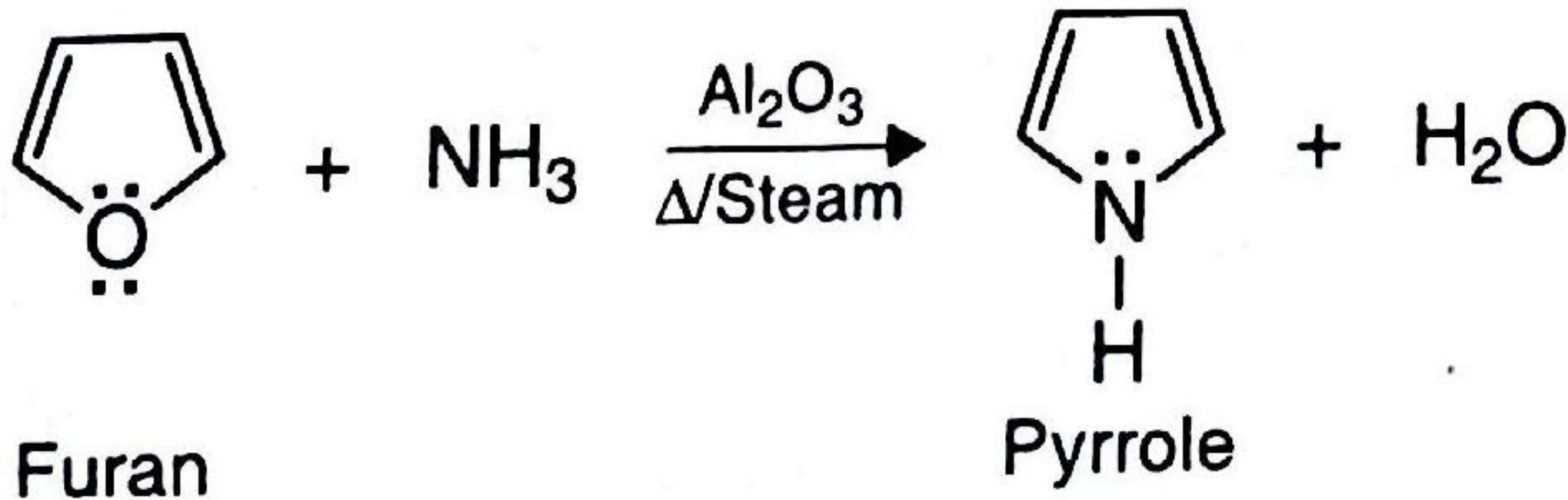
3. By heating **Succinimide** with zinc dust.



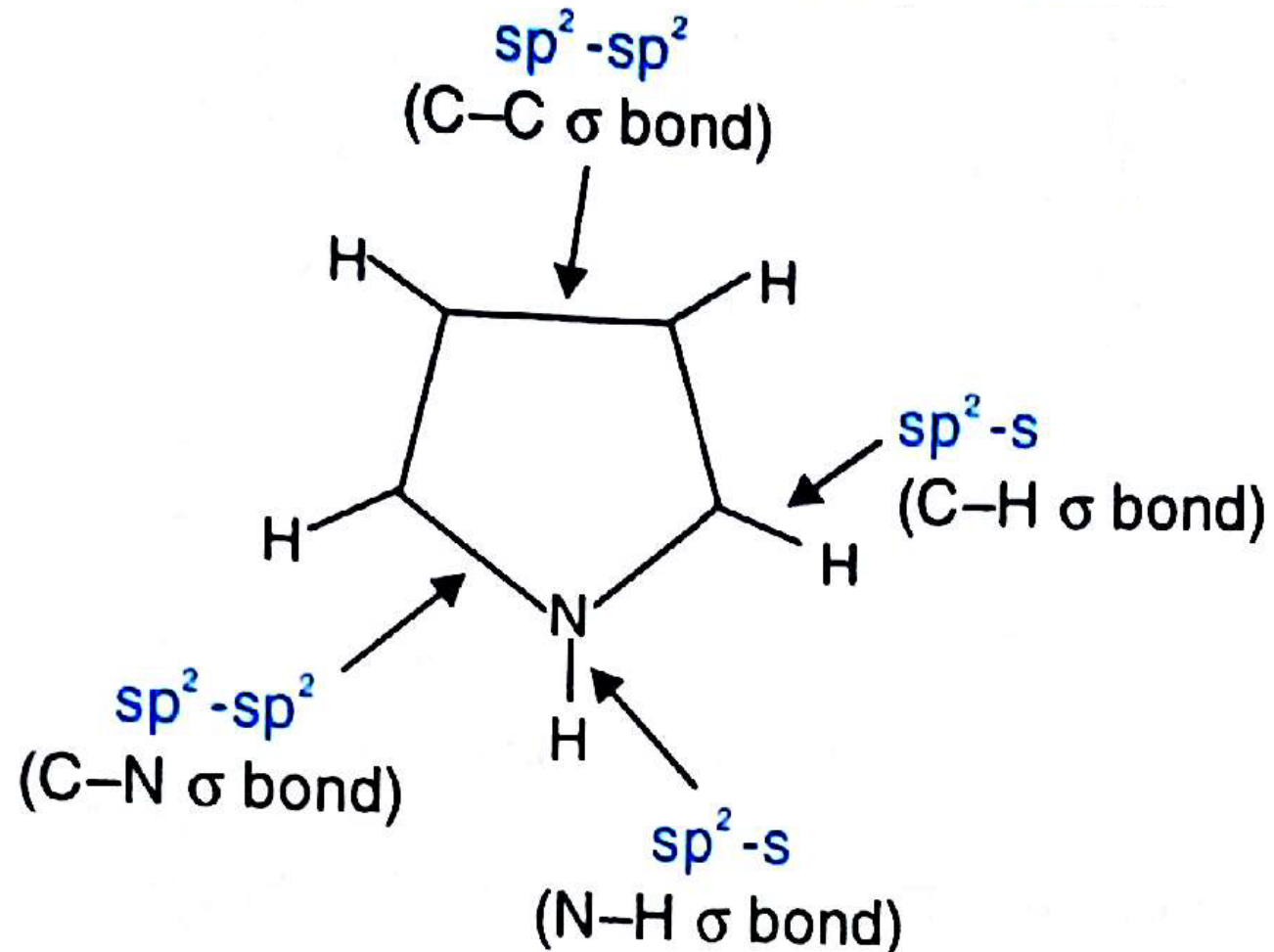
4. By warming succinic dialdehyde with ammonia



5. **Commercial Method:** By passing a mixture of furan, ammonia, and steam over aluminium oxide catalyst at 480-490°C.



Structure of Pyrrole



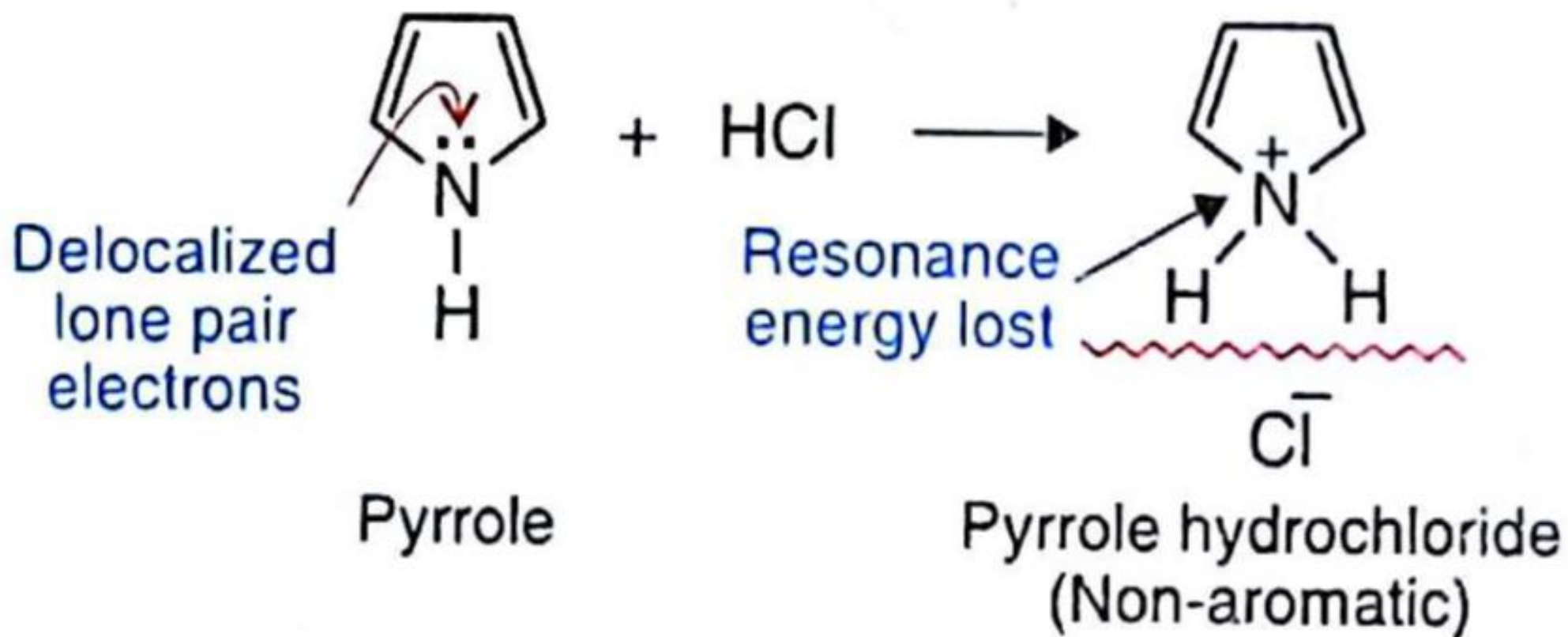
Physical Properties of Pyrrole

- Pyrrole is colorless liquid,
- Boiling point 131°C , which rapidly turns brown on exposure to air.
- Its odour is like that of chloroform.
- Pyrrole is sparingly soluble in water but dissolves in ethanol and ether.

Chemical Properties of Pyrrole

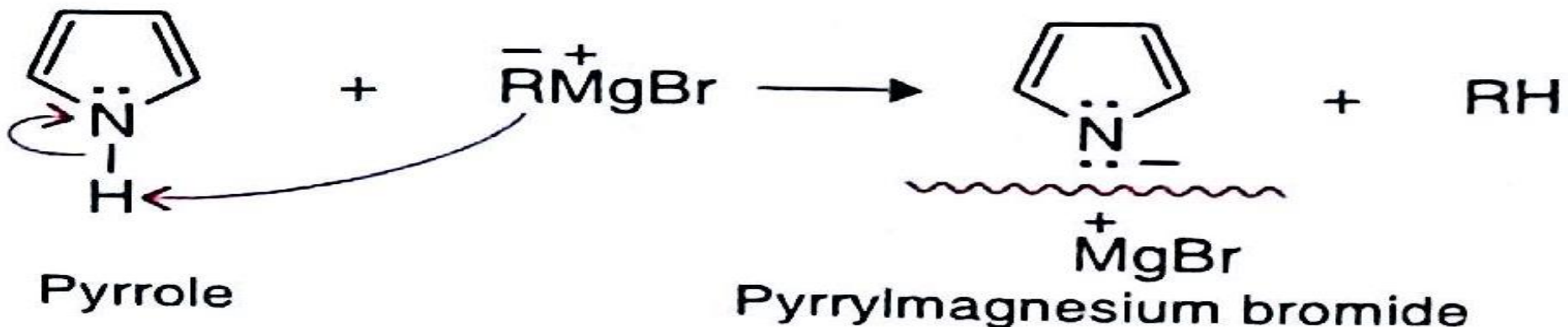
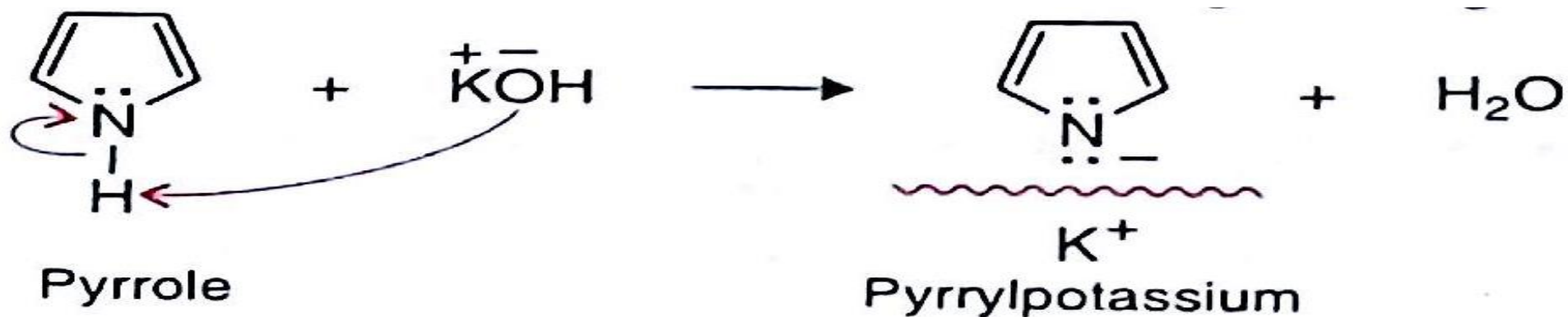
1. Basic Character:

Pyrrole reacts with dilute hydrochloric acid to give a crystalline hydrochloride.



2. Acidic Character

Pyrrole is not only a weak base but also a very weak acid. This is shown by its reactions with potassium hydroxide and Grignard reagents.

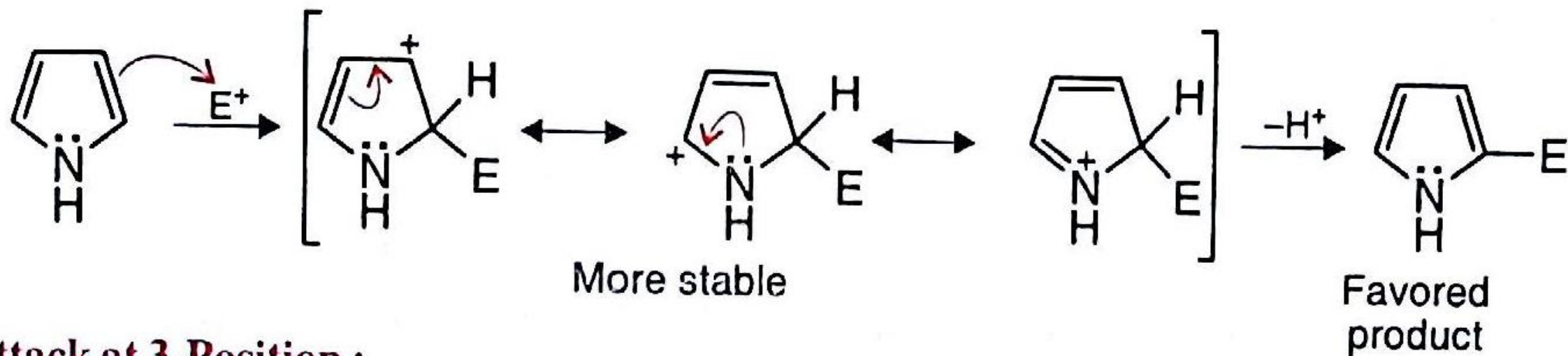


3. Electrophilic Substitution Reactions

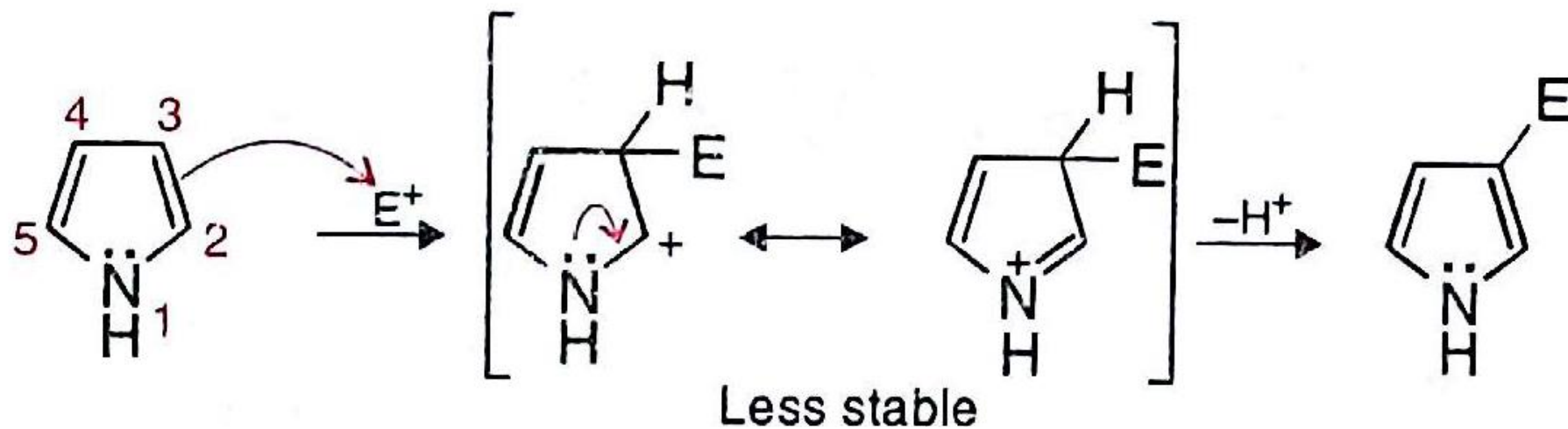
Pyrrrole undergoes electrophilic substitution reactions at C-2 because three resonance forms can be written for the intermediate obtained from attack at C-2, whereas only two such forms are possible for substitution at C-3.

Consequently the C-2 intermediate is more stable and the product with a substituent at C-2 predominates. **Substitution at C-3 occurs only when both the 2-positions (that is, α and α') are blocked.**

Attack at 2-Position :

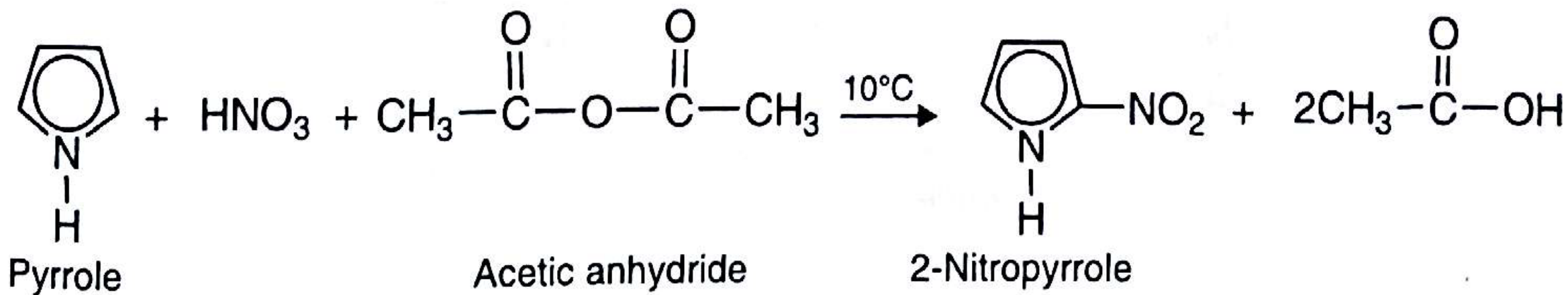


Attack at 3-Position :

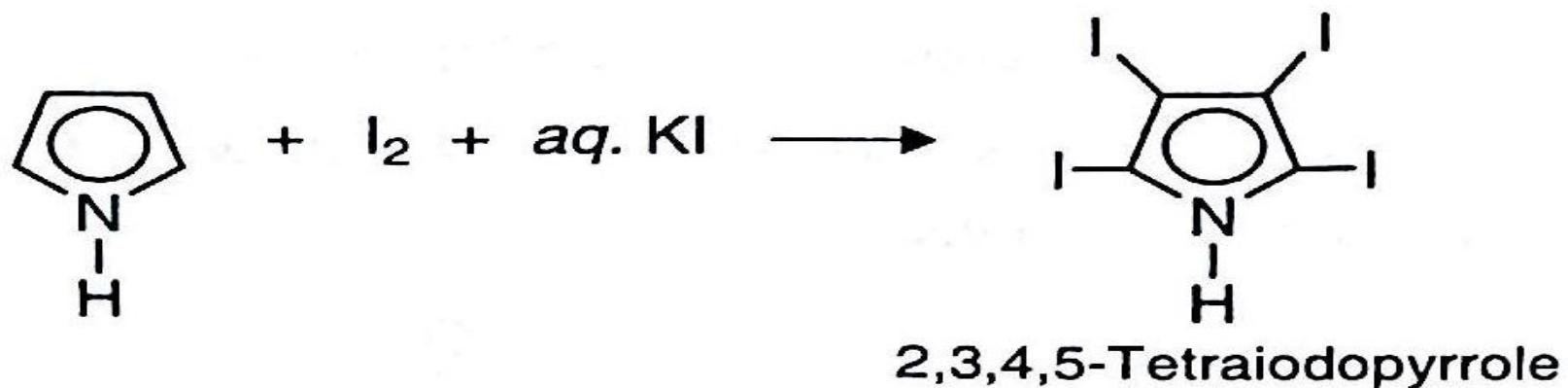
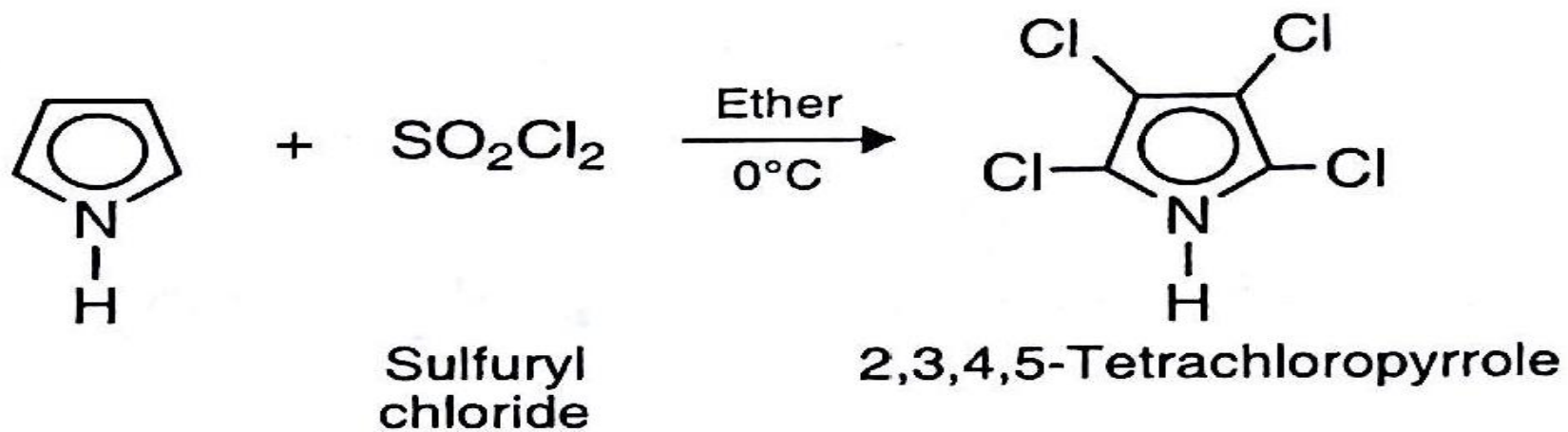


a. Nitration

Pyrrole can be nitrated by a *cold* solution of nitric acid in acetic anhydride to give 2-nitropyrrole.

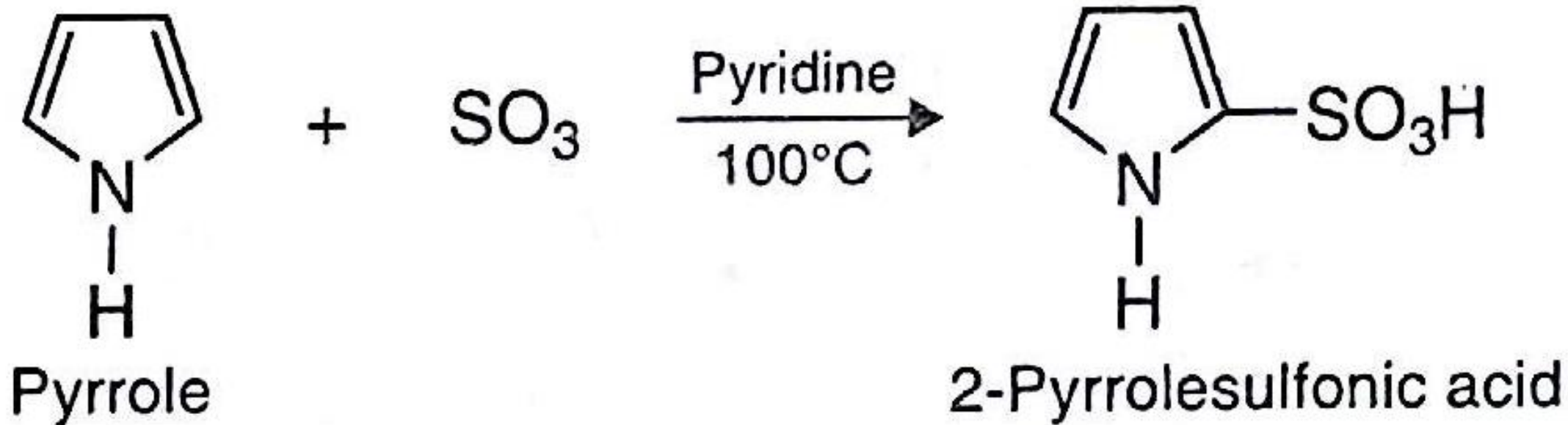


b. Halogenation



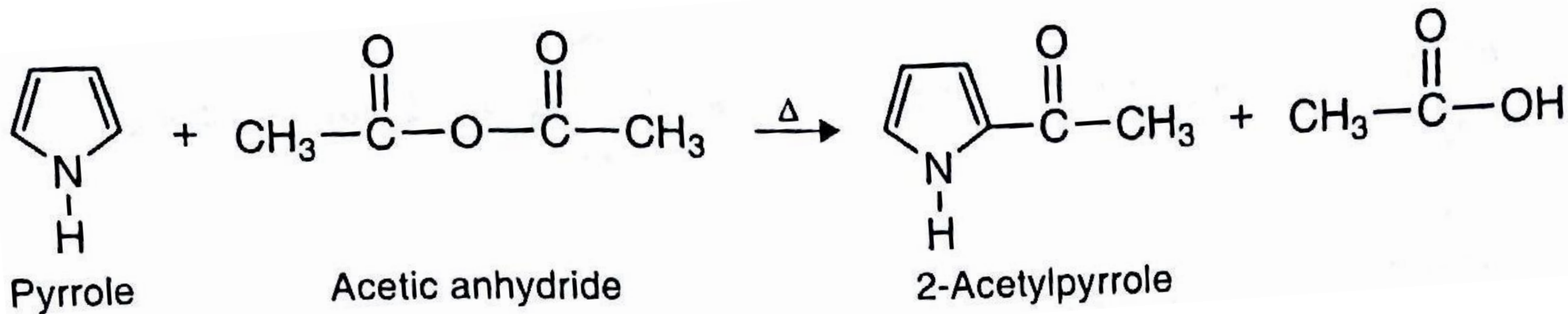
c. Sulphonation

Pyrrole may be sulphonated with sulphur trioxide in pyridine at about 100°C to yield 2-pyrrolesulfonic acid.



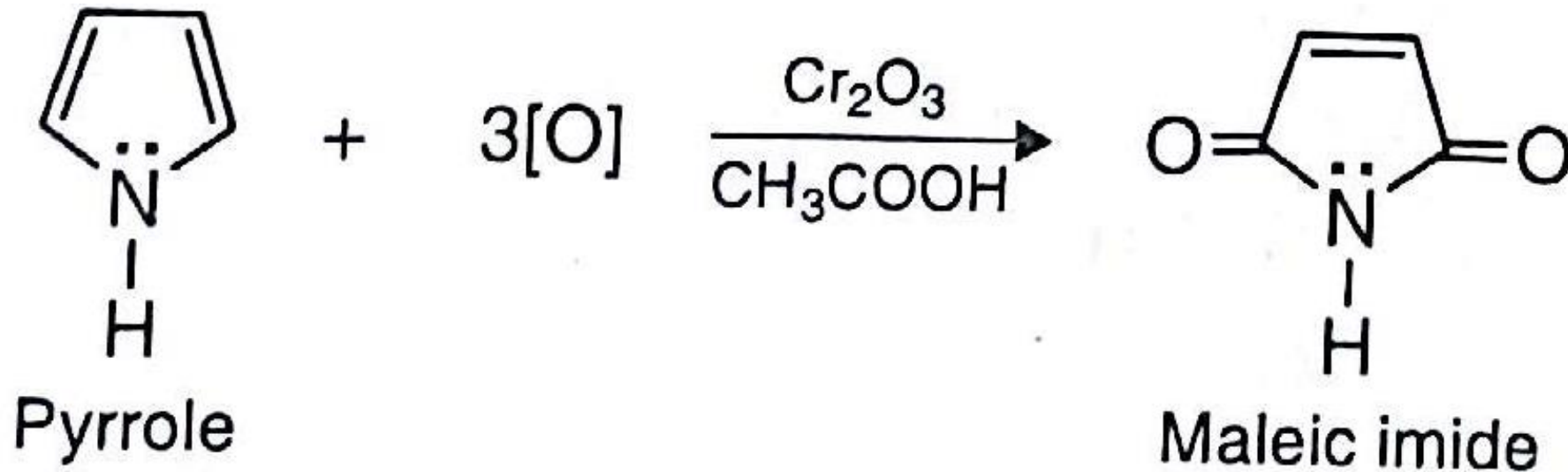
d. Friedel-Craft Acylation

Pyrrole may be acetylated with acetic anhydride at 250°C to give 2-acetylpyrrole. Notice that no catalyst is required in this reaction.



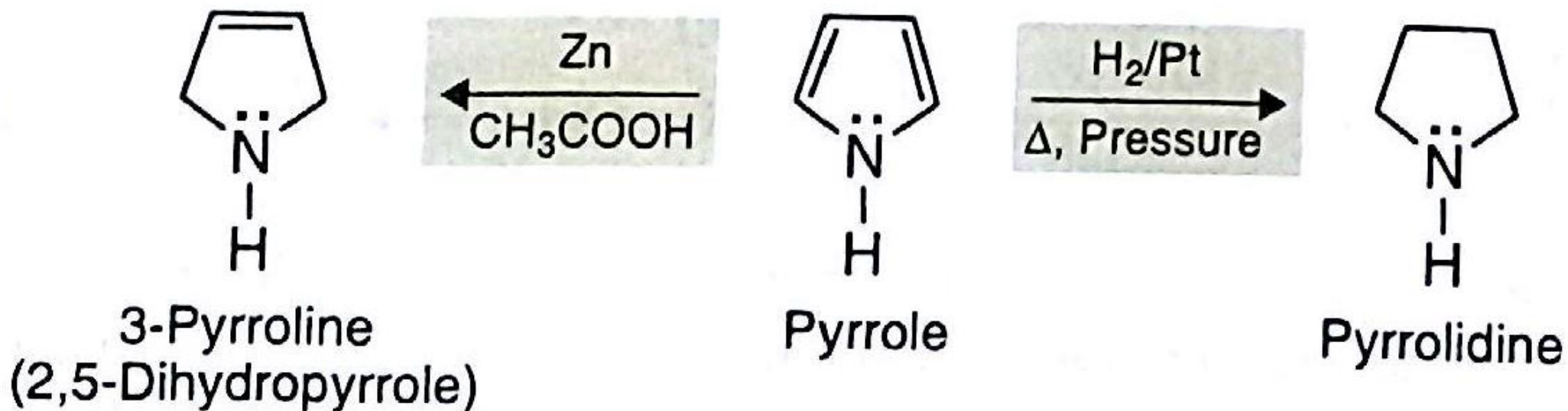
4. Oxidation

Pyrrole is oxidized by chromium trioxide in acetic acid to give the imide of maleic acid.



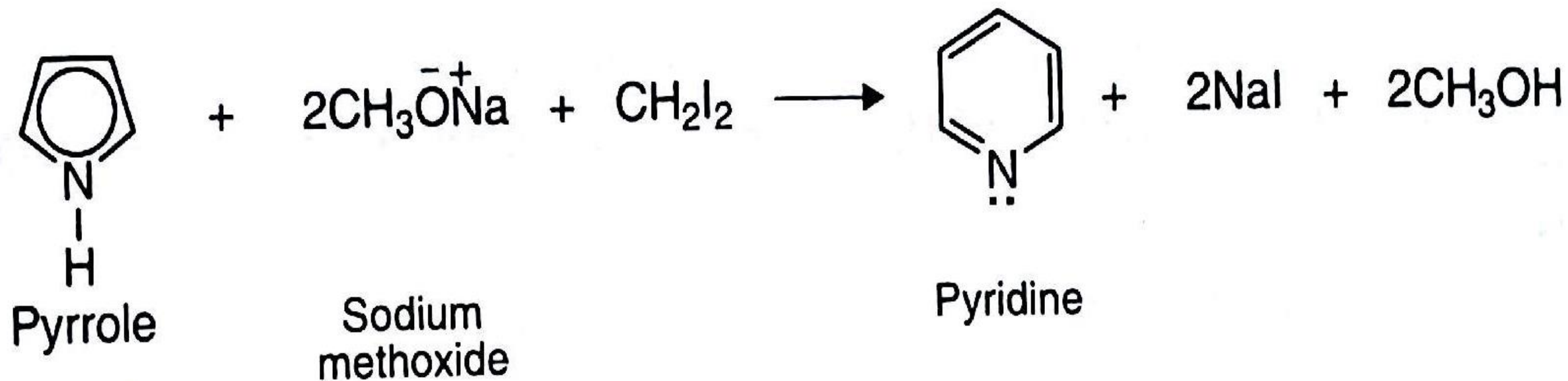
5. Reduction

Mild reduction of pyrrole with zinc and acetic acid yields 3-pyrroline (2,5-dihydropyrrole). Catalytic reduction completely hydrogenates the ring system and produces pyrrolidine.



6. Ring Expansion Reaction

When treated with sodium methoxide and Methylene iodide, pyrrole undergoes ring expansion forming pyridine.



7. Ring Opening Reaction

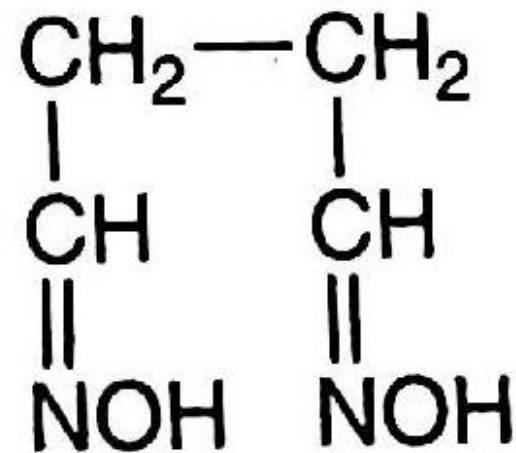
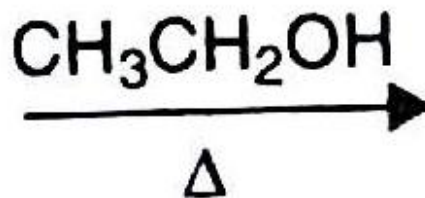
When treated with hot ethanolic hydroxylamine, pyrrole undergoes ring opening forming the dioxime of succindialdehyde



Pyrrole



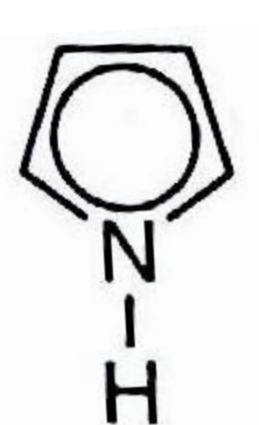
Hydroxylamine



Succindialdoxime

7. Kolbe-Schmitt Carboxylation

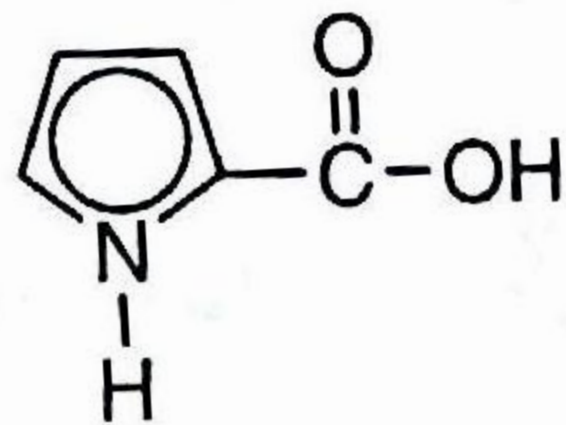
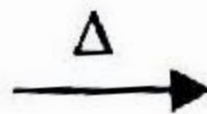
Pyrrole reacts with aqueous potassium carbonate at 100°C to give pyrrole-2-carboxylic acid.



Pyrrole

+

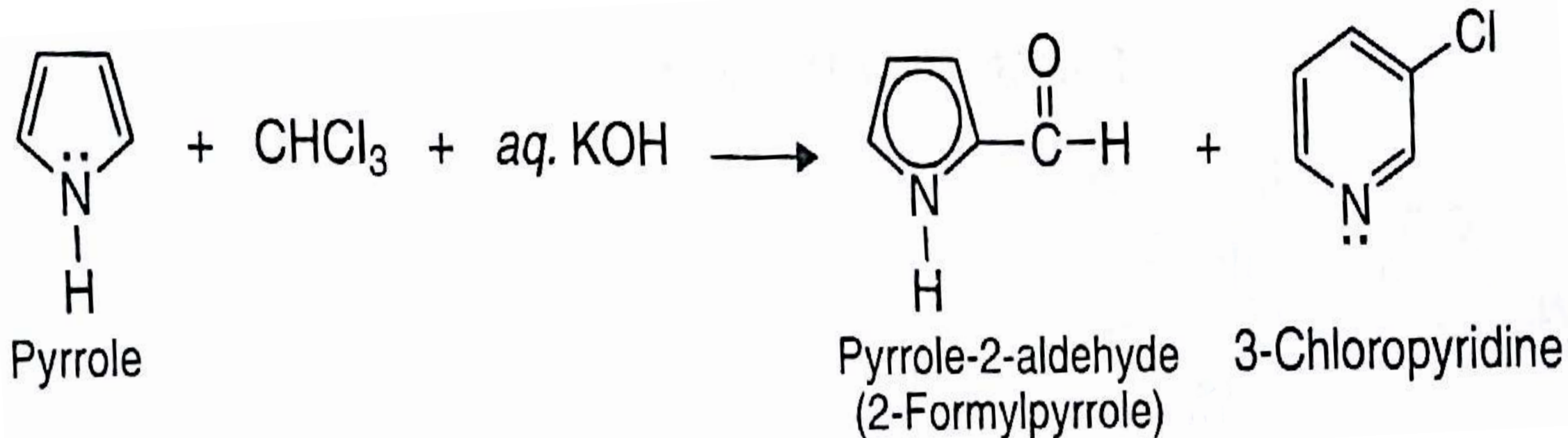
aq. K_2CO_3



Pyrrole-2-carboxylic acid

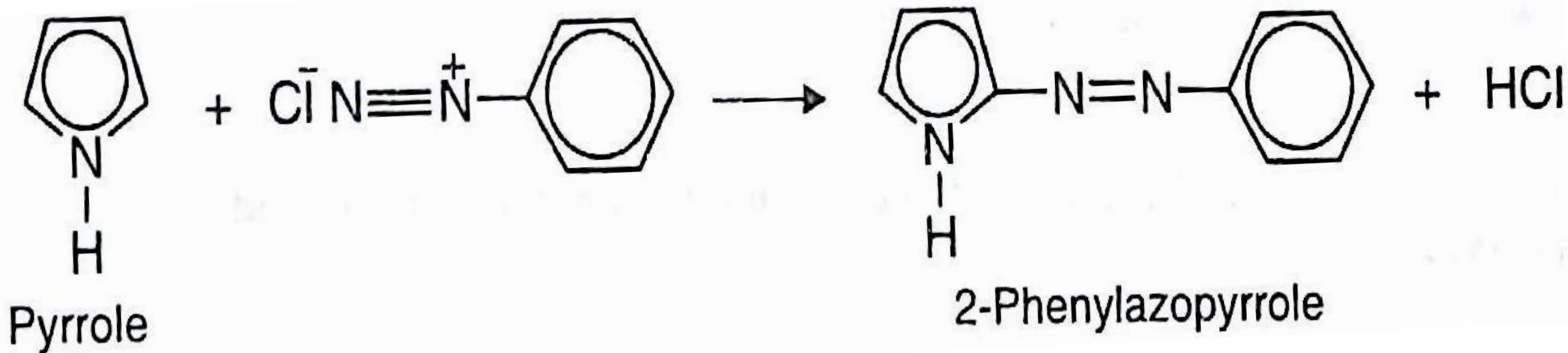
8. Reimer-Tiemann Formylation

Pyrrole reacts with chloroform in the presence of alkali to yield pyrrole-2-aldehyde (2-formylpyrrole) and 3-chloropyridine.



9. Diazo Coupling

Pyrrole couples with benzenediazonium chloride in a weakly acidic solution to give 2-phenylazopyrrole.



Medicinal Importance

