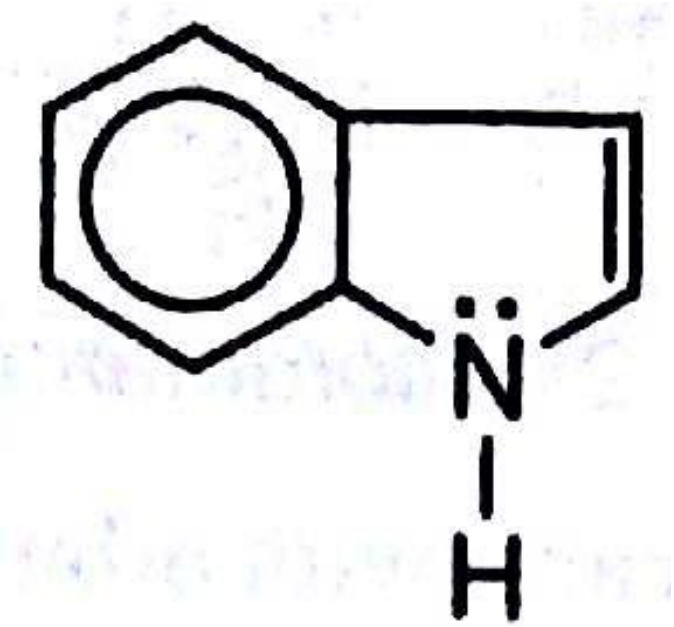
Preparation and Properties of INDOLE

Indole

Indole consists of a benzene ring fused to the **Alpha and Beta positions of a pyrrole ring.**

Indole occurs in coal-tar and in the oils of jasmine and orange blossoms.

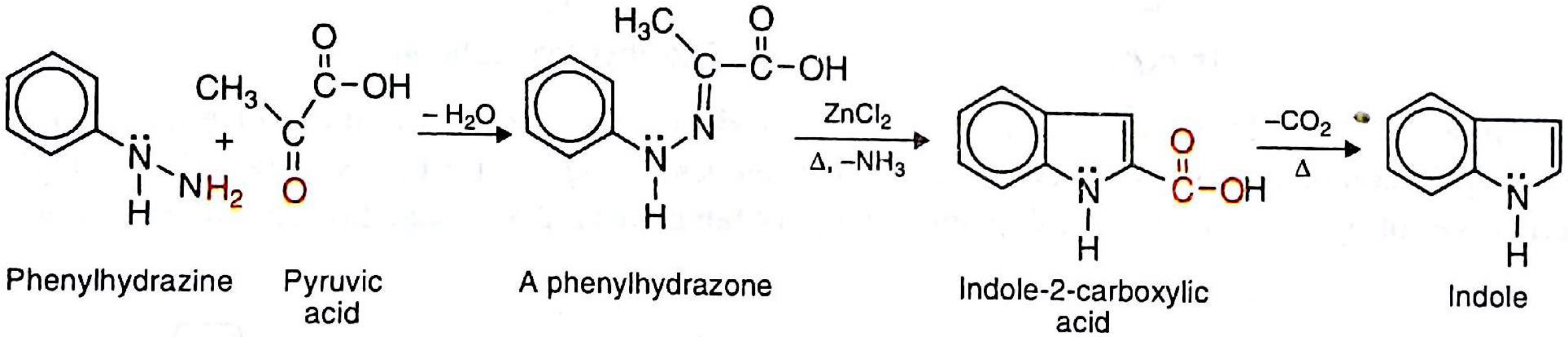
It is also found as a part of the total structure of a number of alkaloids and amino acids e.g., **serotonin, reserpine, and tryptophan**.



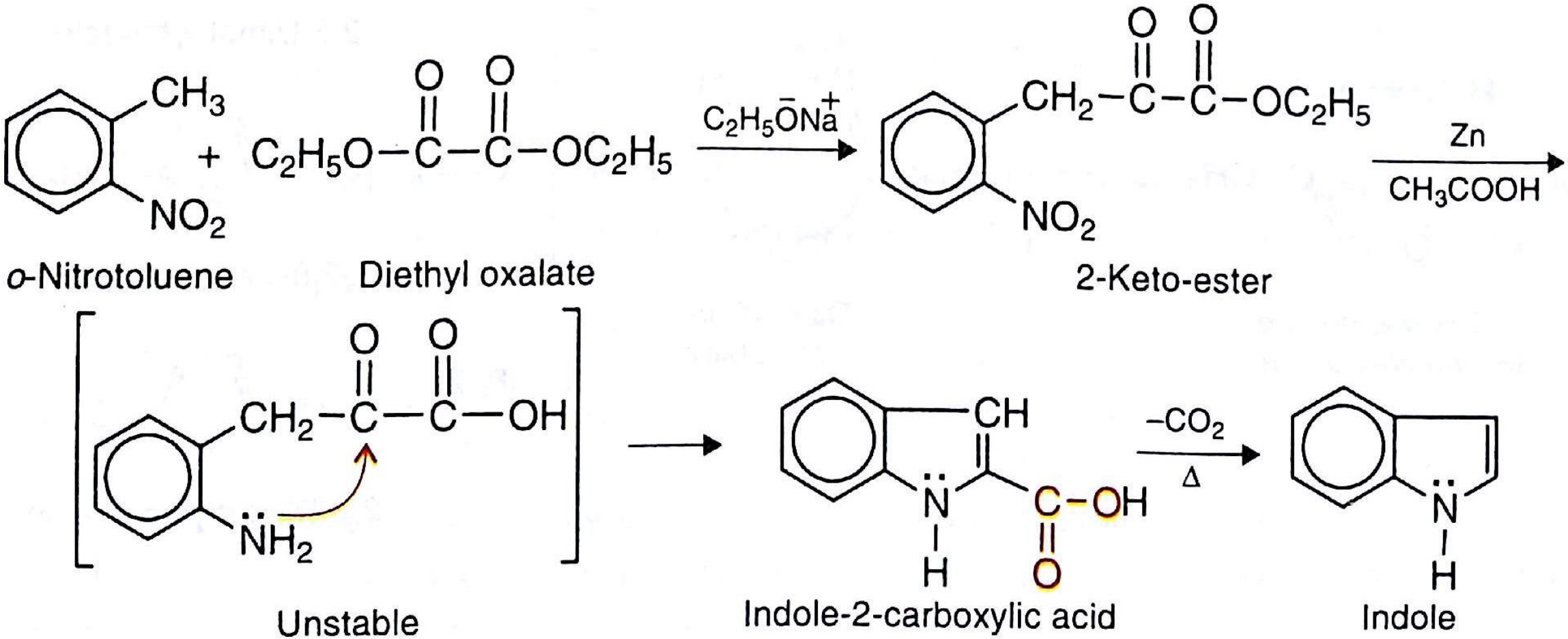
Preparation Methods

Indole may be obtained;

1. <u>By Fischer-indole synthesis:</u> In this method pyruvic acid is first treated with phenylhydrazine to form the corresponding phenylhydrazone. The hydrazone is heated with anhydrous zinc chloride to give indole-2-carboxylic acid which on decarboxylation yields indole.



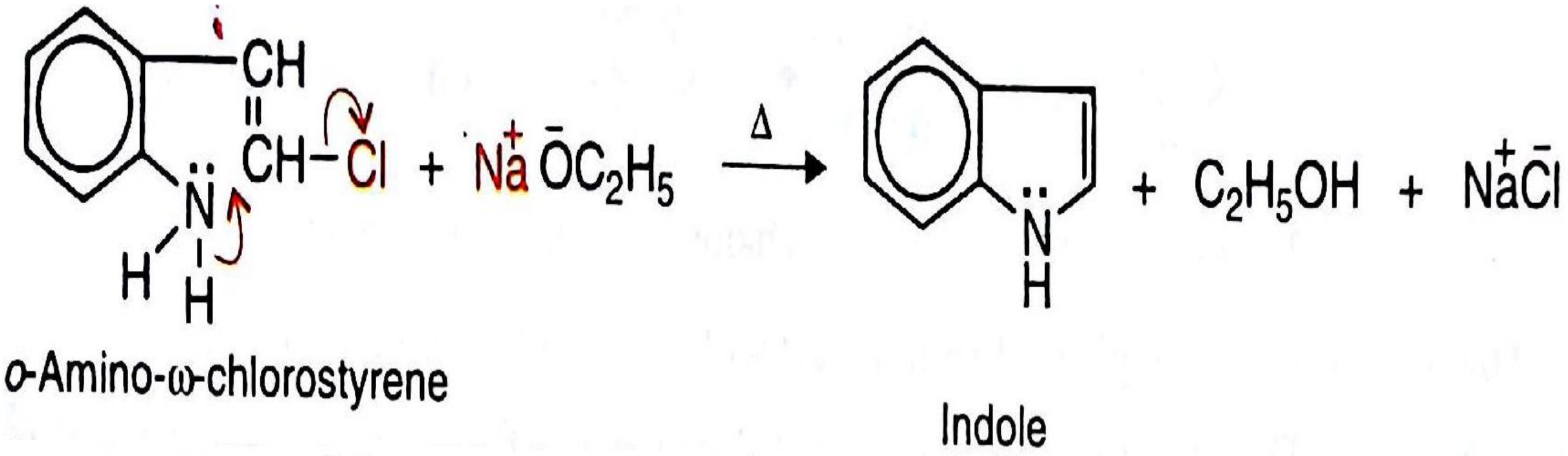
2. By the Reissert Synthesis. In this method o-nitrotoluene is condensed with diethyl oxalate in the presence of a base to form a 2-keto-ester. This is then reduced with zinc and glacial acetic acid to give indole-2-carboxylic acid which on decarboxylation gives indole.



3. From o-Toluidine: This involves treatment of o-toluidine with formic acid to form N-formyl-o-toluidine. This undergoes dehydration on heating with potassium t-butoxide to yield indole.

o-Toluidine Formic acid *N*-Formyl-*o*-toluidine Indole

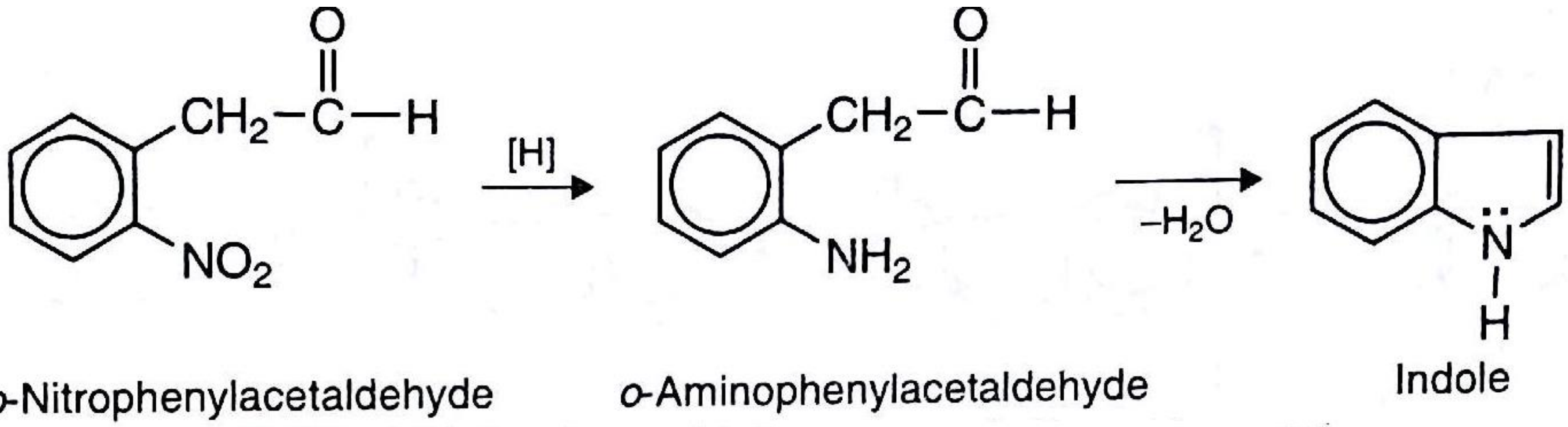
4. By the Lip Synthesis. In this method o-amino-w-chlorostyrene is heated with sodium ethoxide at l60-170°C,



o-Amino-ω-chlorostyrene

Indole

5. From o-Nitrophenylacetaldehyde: This involves reduction of o-nitrophenylacetaldehyde with iron powder and sodium bisulphite to give o-aminophenylacetaldehyde which cyclises spontaneously to yield indole.



o-Nitrophenylacetaldehyde *o*-Aminophenylacetaldehyde Indole

Physical Properties of Indole

- Indole is a colorless, volatile solid,
- Melting point **52C**
- It is sparingly soluble in cold water, but dissolves in hot water and most organic solvents.
- Indole has a powerful odour which is pleasant and flowery in low concentrations. It is, in fact, used commercially as a perfume base. In contrast, indole and its 3-methyl derivative (Skatole) are responsible for the strong offensive odour of faeces.

Chemical Properties of Indole

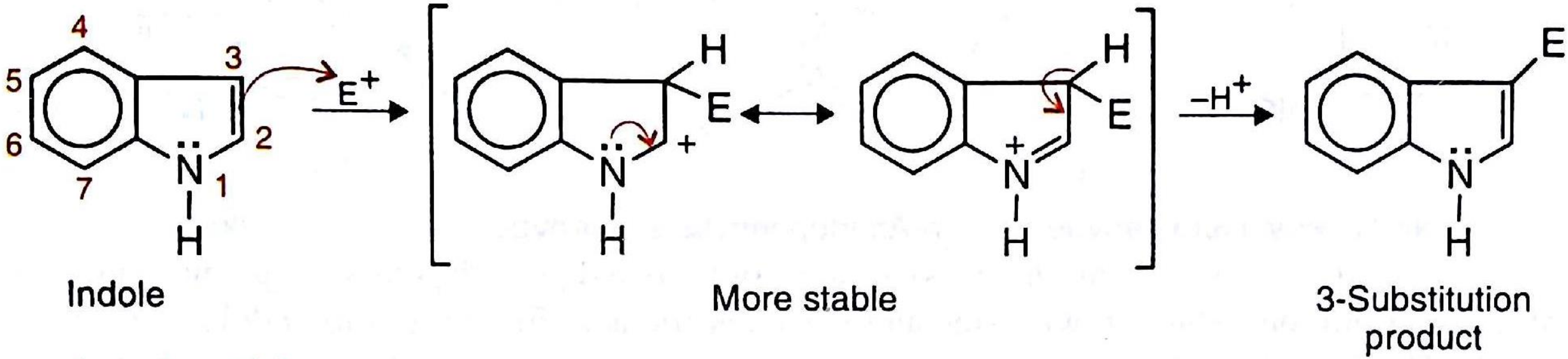
1. **Basic and Acidic Character:**

   Like pyrrole, indole is a weak base and also *a* weak acid. It is polymerized by strong acids and reacts with potassium hydroxide and Grignard reagents.

2. Electrophilic Substitutions:

Unlike pyrrole, indole undergoes electrophilic substitution at C-3. This is because two resonance forms can be written for intermediate cation obtained from attack at C-3 (without disturbing the benzene ring), whereas only one such form is possible for substitution at C-2.

Attack at C-3 :

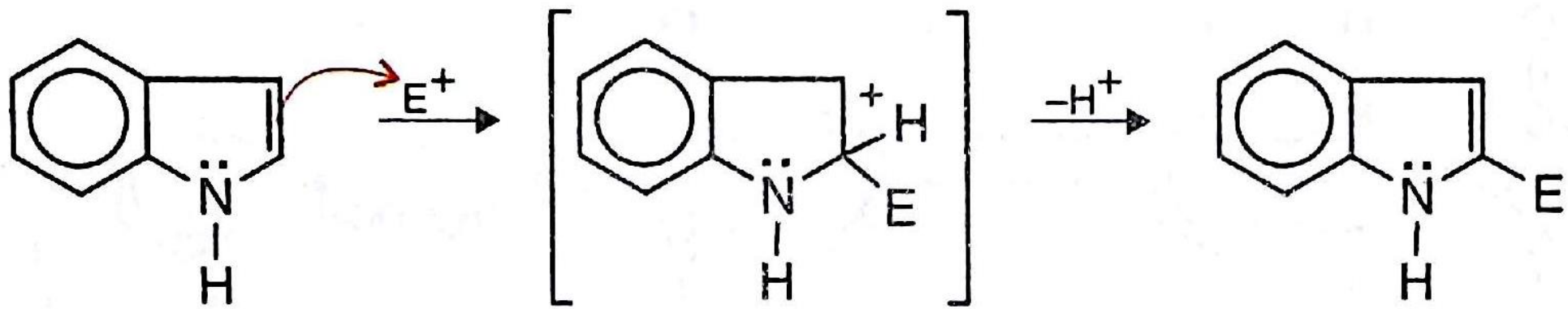


Indole

More stable

3-Substitution product

Attack at C-2 :



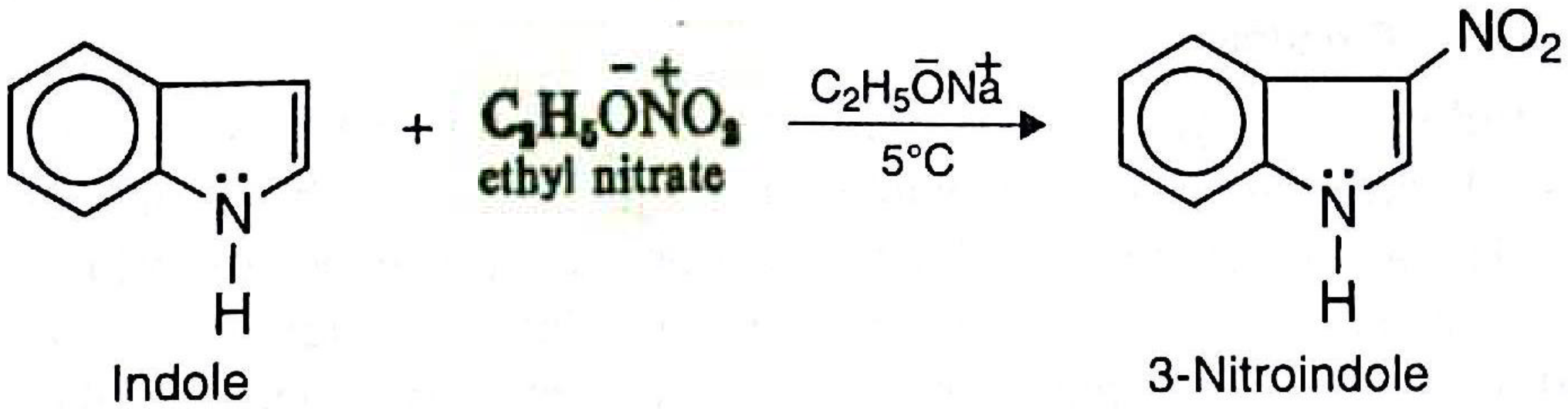
Indole

Less stable

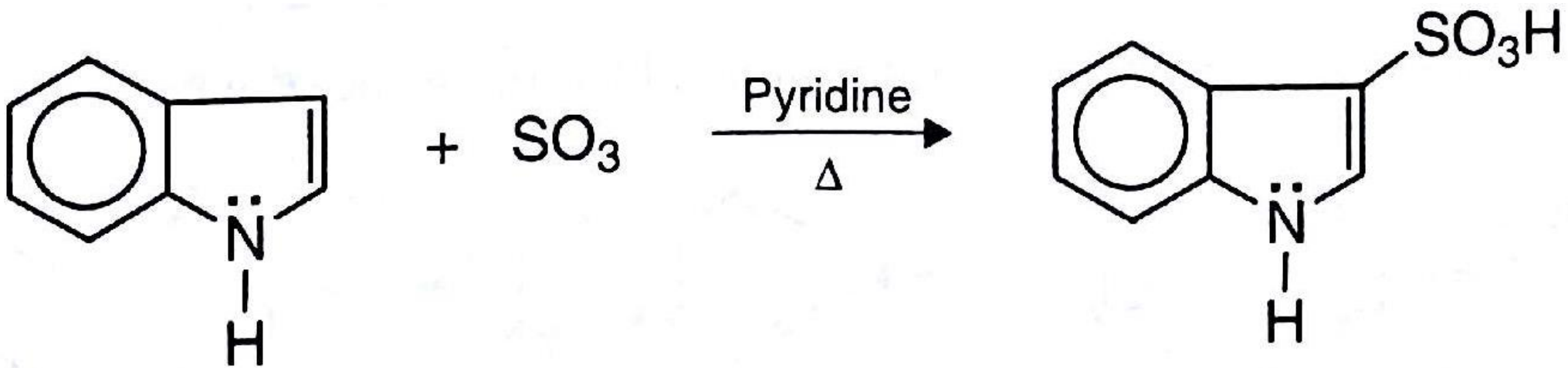
2-Substitution product

a. Nitration

Indole may be nitrated at low temperature with ethyl nitrate in the presence of sodium ethoxide to yield 3-nitroindole.



(b) Sulphonation: Indole undergoes sulphonation with sulphur trioxide in pyridine at 110°C to give indole-3-sulphonic acid.

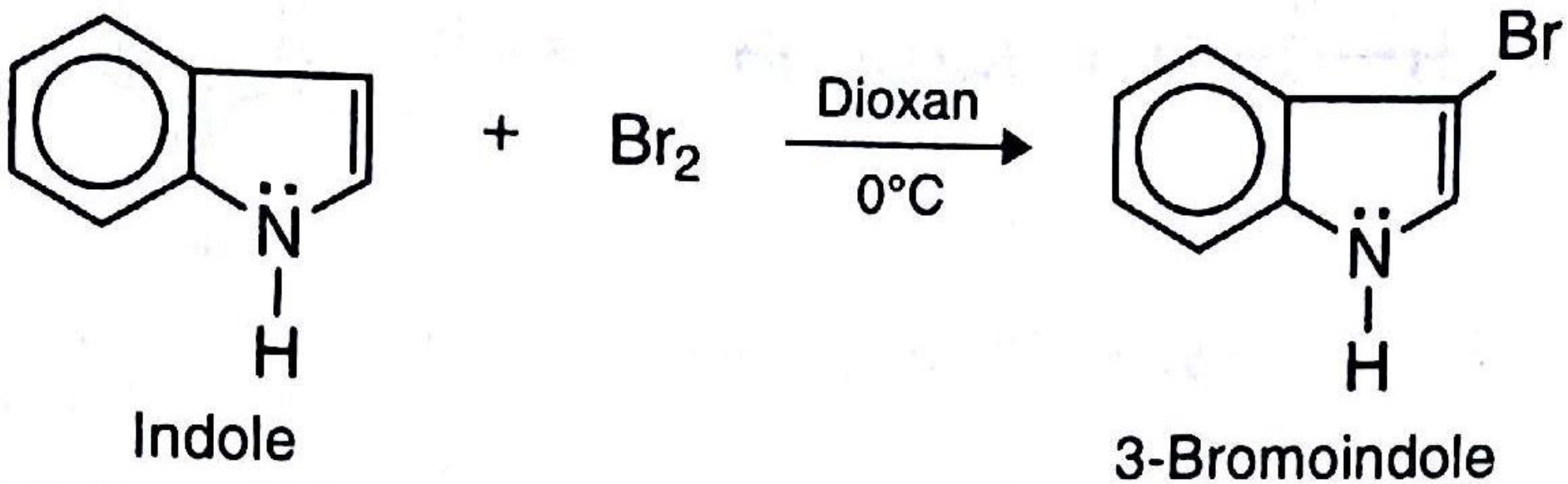


Indole

Indole-3-sulfonic acid

C. Bromination

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

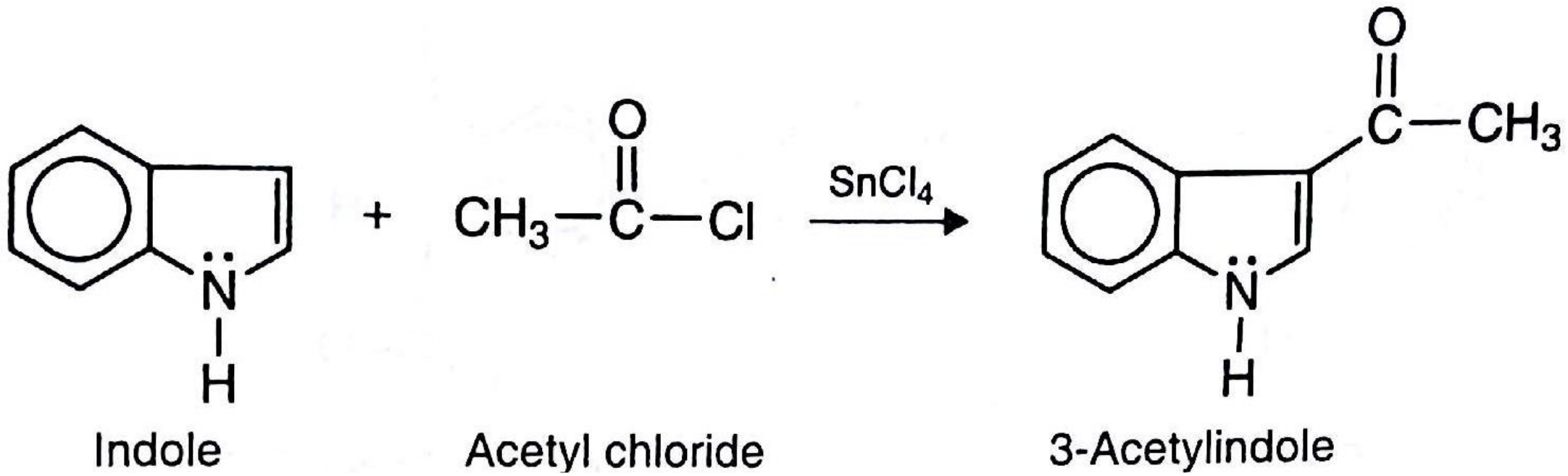


Indole

3-Bromoindole

d. Friedel-Craft Acylation

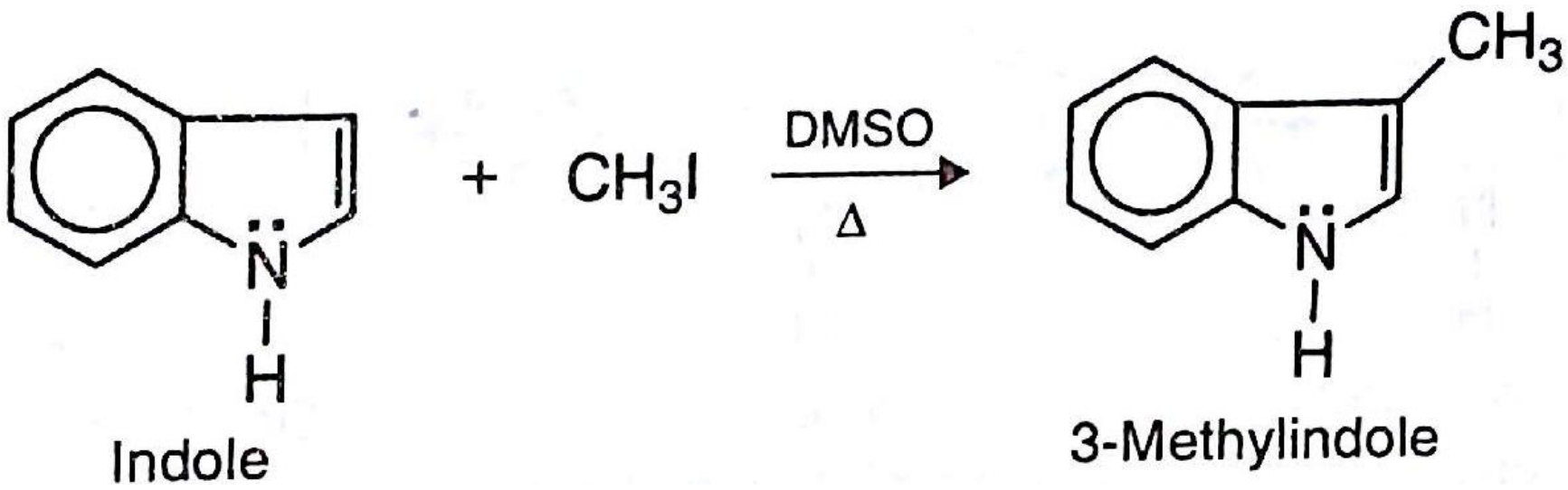
- Indole may be acetylated with acetyl chloride in the presence of $SnCl_4$ (Tin tetrachloride) to yield 3-acetylindole.



Indole + Acetyl chloride → 3-Acetylindole

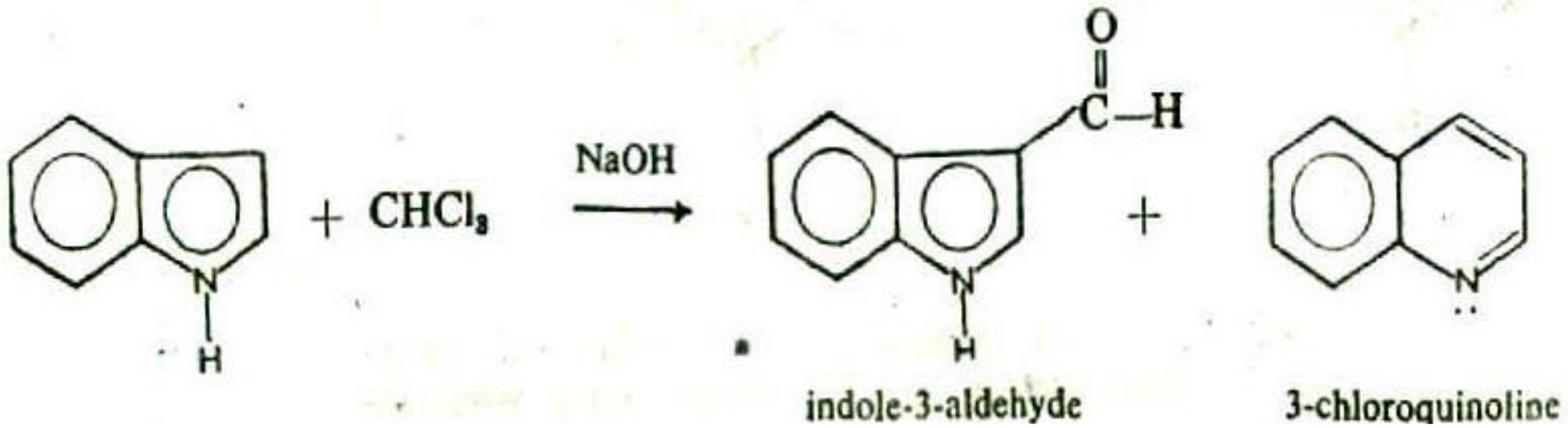
e. Alkylation

- Indole reacts with methyl iodide in dimethyl sulphoxide *(DMSO)* at about 80°C to give 3-methylindole *(skatole).*



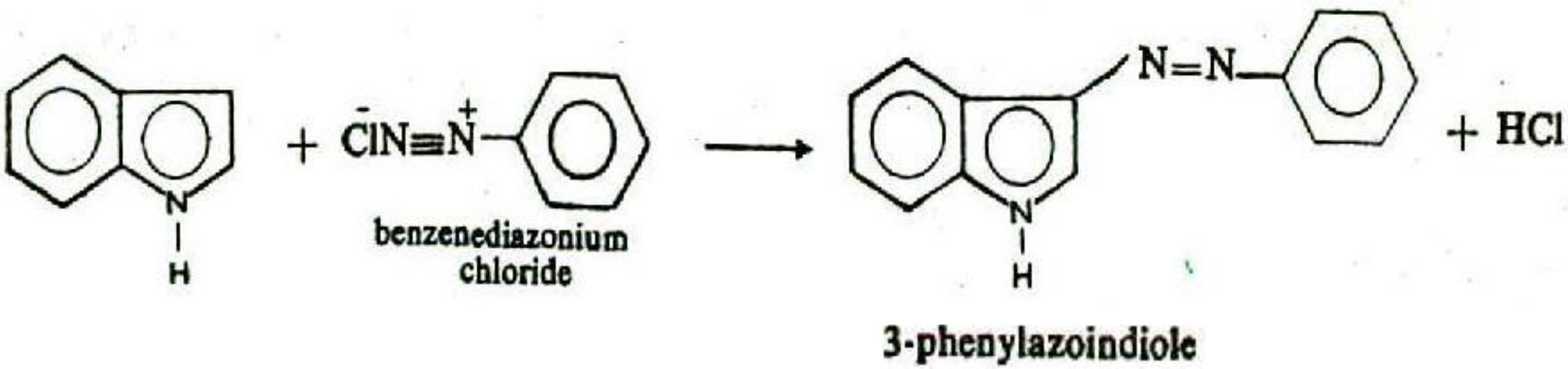
Reimer-Tiemann Formylation

- Indole reacts with chloroform in the presence of alkali to yield indole-3-aldehyde (3-formylindole) and 3-chloroquinoline.



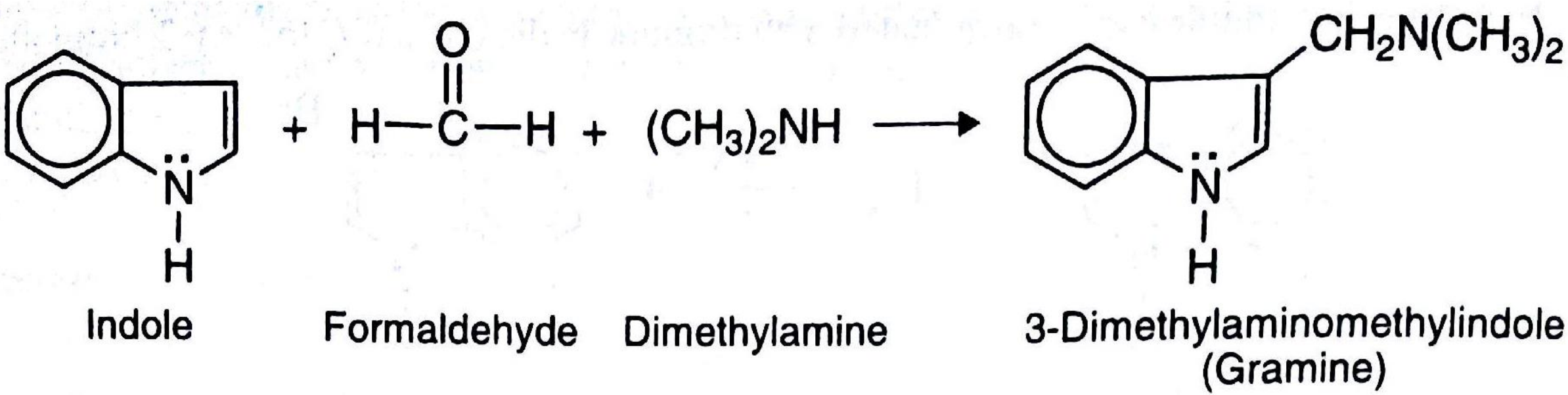
Diazo Coupling

Indole couples with benzenediazonium chloride in a weakly acidic solution to yield 3-phenylazoindole.



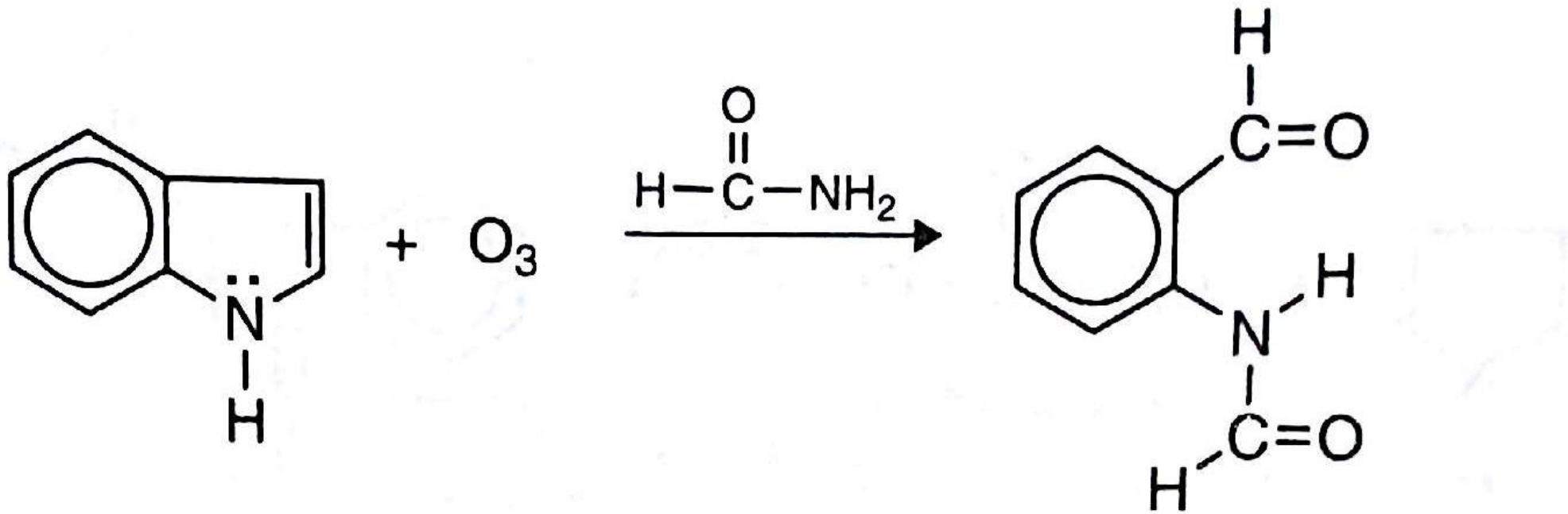
Mannich Reaction:

Indole undergoes Mannich reaction with formaldehyde and dimethylamine to give 3-dimethylaminomethylindole (**Gramine**).



(3) Oxidation

Indole may be oxidized by ozone in formamide to give 2-formamido-benzaldehyde.

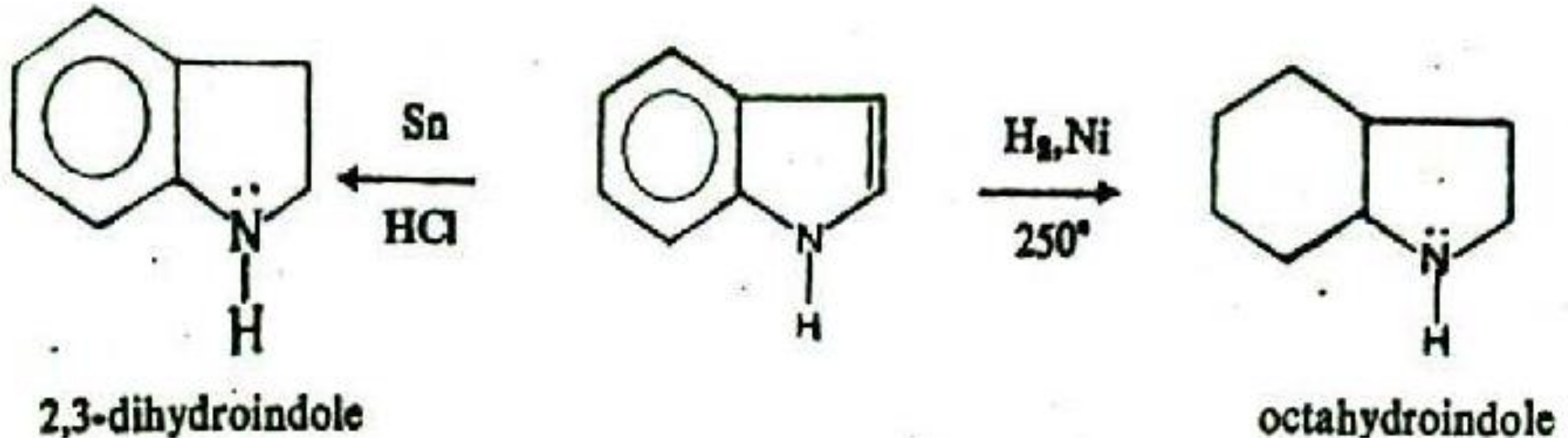


Indole

2-Formamidobenzaldehyde

(4) Reduction

Mild reduction of indole with zinc (or tin) and hydrochloric acid yields 2,3-dihydroindole *(Indoline).* Catalytic reduction hydrogenates both rings and produces ocatahydroindole.



Medicinal Importance of indole

List of drugs containing indole

Drug	*Application*	*Drug*	*Application*	*Drug*	*Application*
Vincristine	Anticancer	**Vincamine**	Vasodilator	**Roxindole**	Schizophrenia
Vinblastine	Anticancer	**Reserpine**	Antihypertensive	**Delavirdine**	Anti-HIV
Vinorelbine	Anticancer	**Peridopril**	Antihypertensive	**Atevirdine**	Anti-HIV
Vindesine	Anticancer	**Pindolol**	Antihypertensive	**Arbidol**	Antiviral
Mitraphylline	Anticancer	**Binedaline**	Antidepressant	**Zafirlukast**	Anti-Asthmatic
Cediranib	Anticancer	**Amedalin**	Antidepressant	**Bucindolol**	β-Blockers
Panobinostat	Anti-leukamic	**Oxypertine**	Antipsychotic	**Pericine**	Opioid agonist
Apaziquone	Anticancer	**Siramesine**	Antidepressant	**Mitragynine**	Opioid agonist
Tropisetron	Antiemetic	**Indalpine**	Antidepressant	**Pravadoline**	Analgesic
Doleasetron	Antiemetic	**Yohimbine**	Sexual Disorder	**Bufotenidine**	Toxin
Oglufanide	Immunomodulatory	**Indomethacin**	Anti-inflammatory	**Proamanullin**	Toxin