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# PHARMACEUTICAL ORGANIC CHEMISTRY – III

## UNIT 4

TOPIC :

- **Synthesis, reactions and medicinal uses of following compounds/derivatives**

Pyrazole, Imidazole, Oxazole and Thiazole.

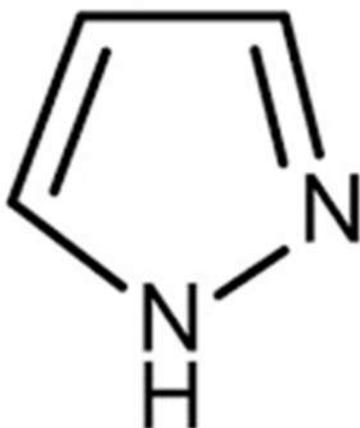
Pyridine, Quinoline, Isoquinoline, Acridine and Indole. Basicity of pyridine

Synthesis and medicinal uses of Pyrimidine, Purine, azepines and their derivatives

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## Pyrazole

- Pyrazole is a five-membered aromatic heterocyclic compound containing three carbon atoms and two adjacent nitrogen atoms at positions 1 and 2.
- Molecular formula:  $C_3H_4N_2$
- Structure: It has a planar cyclic structure with delocalized  $\pi$ -electrons, making it aromatic.
- It is a weak base due to the presence of nitrogen atoms.
- Pyrazole can form hydrogen bonds, making it soluble in polar solvents like water and alcohol.



## Synthesis of Pyrazole

Pyrazole can be synthesized by different methods:

1. **From Acetylene (Autylene method):**
  - Acetylene reacts with diazomethane derivatives leading to the formation of pyrazole.
2. **From Pyrazole Carboxylic Acid:**
  - Decarboxylation of pyrazole carboxylic acid yields pyrazole.
3. **From Acrolein and Hydrazine (Acraldehyde method):**
  - Condensation of acrolein with hydrazine forms dihydropyrazole, which on oxidation gives pyrazole.

## Chemical Reactions of Pyrazole

### 1. Alkylation:

- Pyrazole undergoes alkylation at the nitrogen atom when treated with alkyl halides.

### 2. Electrophilic Substitution Reactions:

- Electrophilic substitution mainly occurs at the C-4 position of the ring.
- Examples: Nitration, sulfonation, halogenation.

### 3. Reduction:

- Catalytic hydrogenation of pyrazole gives pyrazoline and then pyrazolidine (saturated product).

## Medicinal Uses of Pyrazole and its Derivatives

### 1. Anti-inflammatory & Analgesic:

- Used in treatment of pain and arthritis.
- Example: Phenylbutazone.

### 2. Antipyretic:

- Reduces fever.

### 3. Antigout:

- Lowers uric acid levels in gout patients.
- Example: Allopurinol (pyrazolopyrimidine derivative).

### 4. Antimicrobial Activity:

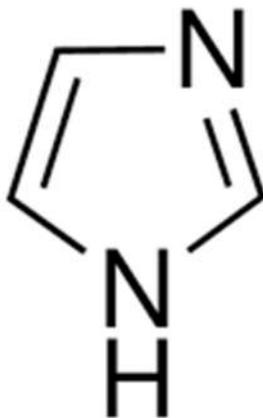
- Some derivatives show antibacterial and antifungal actions.
- Example: Sulphaphenazole (sulfonamide derivative).

### 5. CNS Activity:

- Certain derivatives act as sedatives, hypnotics, and antidepressants.

## Imidazole

- Imidazole is a five-membered heteroaromatic compound containing three carbon atoms and two non-adjacent nitrogen atoms (at positions 1 and 3).
- Molecular formula:  $C_3H_4N_2$
- Structure:
  - It has a planar cyclic structure with 6  $\pi$ -electrons (aromatic by Hückel's rule).
  - One nitrogen atom (N-1) behaves like pyrrole-type nitrogen (non-basic, lone pair involved in aromaticity).
  - The other nitrogen atom (N-3) behaves like pyridine-type nitrogen (basic, lone pair not in aromatic system).
- Due to this, imidazole is amphoteric (can act as acid and base).
- It is soluble in polar solvents (like water, alcohol) due to hydrogen bonding.



### Synthesis of Imidazole

1. **Debus Synthesis (Classical method):**
  - Condensation of glyoxal, ammonia, and formaldehyde gives imidazole.
2. **Radiszewski Synthesis:**
  - Condensation of 1,2-dicarbonyl compounds, aldehyde, and ammonia forms imidazole derivatives.
3. **From  $\alpha$ -amino ketones:**
  - Cyclization of  $\alpha$ -amino ketones with formamide yields imidazole.

## Chemical Reactions of Imidazole

### 1. Electrophilic Substitution:

- Occurs mainly at C-4 and C-5 positions due to high electron density.
- Examples: nitration, halogenation, sulfonation.

### 2. Nucleophilic Substitution:

- Can occur at C-2 position.

### 3. Alkylation & Acylation:

- Nitrogen atom (N-3) undergoes alkylation/acylation.

### 4. Reduction:

- Catalytic hydrogenation produces imidazoline (partially reduced) or imidazolidine (fully reduced).

## Medicinal Uses of Imidazole and its Derivatives

### 1. Antifungal Agents:

- Imidazole derivatives inhibit fungal ergosterol synthesis.
- Examples: Clotrimazole, Ketoconazole, Miconazole.

### 2. Antihistaminic Agents:

- Example: **Cimetidine, Ranitidine** ( $H_2$ -receptor blockers, used in peptic ulcer).

### 3. Antiprotozoal Activity:

- Example: Metronidazole (active against amoeba, Giardia, Trichomonas).

### 4. Enzyme Cofactor:

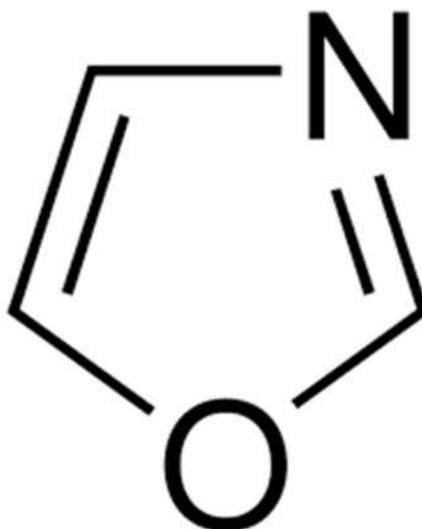
- **Histidine (an amino acid containing imidazole group)** acts as an important catalytic site in many enzymes.

### 5. Anti-inflammatory & Analgesic:

- Some imidazole derivatives show anti-inflammatory properties.

## Oxazole

- Oxazole is a five-membered aromatic heterocyclic compound containing three carbon atoms, one oxygen atom, and one nitrogen atom.
- The oxygen atom is at position-1 and nitrogen at position-3 in the ring.
- Molecular formula:  $C_3H_3NO$
- Structure:
  - Planar and aromatic (follows Hückel's rule,  $6 \pi$ -electrons).
  - The presence of both oxygen and nitrogen makes the ring electron-deficient compared to pyrrole or imidazole.
  - It is less basic because the electron-withdrawing oxygen decreases electron density on nitrogen.
- Oxazole is a colorless liquid with characteristic odor, soluble in polar solvents.



### Synthesis of Oxazole

1. **Robinson-Gabriel Synthesis:**
  - Cyclodehydration of  $\alpha$ -acylaminoketones gives oxazole.
2. **From  $\alpha$ -haloketones and amides:**
  - Reaction between  $\alpha$ -haloketones and amides followed by cyclization yields oxazole derivatives.
3. **From Cyanohydrins:**
  - Cyanohydrins condensed with aldehydes and ammonia can give oxazoles.

## Chemical Reactions of Oxazole

### 1. Electrophilic Substitution:

- Oxazole is electron-deficient, hence less reactive towards electrophiles.
- When it reacts, substitution occurs mainly at C-5 position.

### 2. Nucleophilic Substitution:

- Can occur at **C-2 position**, especially under strong conditions.

### 3. Reduction:

- Catalytic hydrogenation of oxazole yields oxazoline (partially reduced) and oxazolidine (fully reduced).

### 4. Ring-Opening Reactions:

- Under acidic or basic hydrolysis, oxazole ring can open to give amino acid derivatives.

## Medicinal Uses of Oxazole and its Derivatives

### 1. Anti-inflammatory & Analgesic:

- Some oxazole derivatives show anti-arthritic and analgesic properties.

### 2. Antibacterial & Antifungal Agents:

- Oxazole derivatives are used as broad-spectrum antimicrobials.

### 3. Anticancer Agents:

- Oxazole nucleus is present in some antitumor drugs.

### 4. CNS Activity:

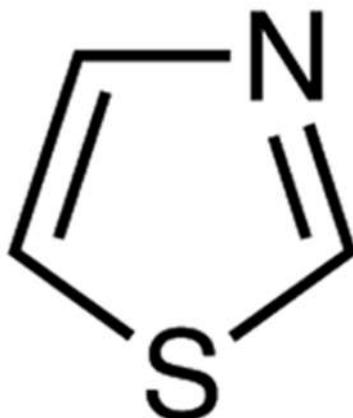
- Some oxazole derivatives act as anticonvulsants and sedatives.

### 5. Examples of Drugs Containing Oxazole Ring:

- **Oxaprozin** – NSAID (anti-inflammatory).
- **Oxacillin** –  $\beta$ -lactam antibiotic.
- **Benzoxazole derivatives** – used in antimicrobial therapy.

## Thiazole

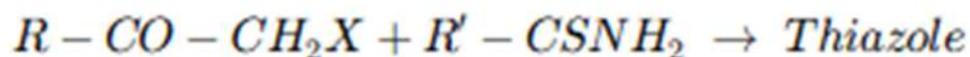
- Thiazole is a five-membered aromatic heterocyclic compound containing three carbon atoms, one nitrogen atom, and one sulfur atom.
- Molecular formula:  $C_3H_3NS$
- Structure:
  - Nitrogen at position-1 and sulfur at position-3.
  - Planar structure with 6  $\pi$ -electrons  $\rightarrow$  aromatic (Hückel's rule).
  - Like imidazole, thiazole has one pyridine-like nitrogen (basic) and one sulfur atom, which influences reactivity.
  - More aromatic and stable compared to oxazole (due to sulfur's larger orbital overlap).



### Synthesis of Thiazole

1. **Hantzsch Thiazole Synthesis (most important):**
  - Condensation of  $\alpha$ -haloketone with thioamide gives thiazole.

Example:



1. **Cook-Heilbron Synthesis:**
  - From  $\alpha$ -aminonitriles with dithioacids  $\rightarrow$  thiazole derivatives.
2. **Gabriel Synthesis:**
  - From  $\alpha$ -haloketones and thiourea.

## Chemical Reactions of Thiazole

### 1. Electrophilic Substitution:

- Occurs mainly at C-5 position (most electron-rich).
- Examples: Nitration, sulfonation, halogenation.

### 2. Nucleophilic Substitution:

- Takes place at C-2 position, where electron deficiency is higher.

### 3. Reduction:

- Hydrogenation produces thiazoline (partially reduced) or thiazolidine (fully reduced).

### 4. Metalation:

- At C-2 position with strong bases → useful in synthesis of substituted thiazoles.

## Medicinal Uses of Thiazole and its Derivatives

### 1. Vitamin Component:

- Present in Thiamine (Vitamin B<sub>1</sub>), essential for carbohydrate metabolism.

### 2. Antibacterial Agents:

- Example: Sulfathiazole (sulfonamide antibiotic).

### 3. Antifungal Agents:

- Example: Abafungin (thiazole-based antifungal).

### 4. Anti-inflammatory & Analgesic:

- Some thiazole derivatives show NSAID activity.

### 5. Anticancer Activity:

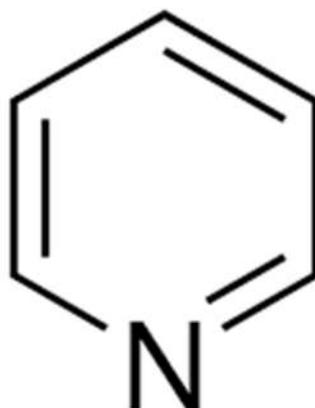
- Thiazole nucleus is used in anticancer drug design.

### 6. Examples of Drugs Containing Thiazole Ring:

- **Riluzole** – used in amyotrophic lateral sclerosis (ALS).
- **Meloxicam** – NSAID (pain & arthritis).
- **Sulfathiazole** – antimicrobial.
- **Thiamine (Vitamin B<sub>1</sub>)** – coenzyme in metabolism.

## Pyridine

- Pyridine is a six-membered heteroaromatic compound containing five carbon atoms and one nitrogen atom.
- Molecular formula:  $C_5H_5N$
- Structure:
  - Analog of benzene, where one CH group is replaced by nitrogen.
  - The lone pair of nitrogen is in an  $sp^2$  orbital (not part of aromatic sextet)  $\rightarrow$  hence pyridine is aromatic with 6  $\pi$ -electrons.
  - Nitrogen atom makes pyridine a weak base ( $pK_b \approx 8.8$ ).
- Physical properties: Colorless liquid, unpleasant fish-like odor, miscible with water and polar solvents.



### Synthesis of Pyridine

1. **From Acetylene + Hydrogen Cyanide (HCN):**
  - Trimerization of acetylene with HCN gives pyridine derivatives.
2. **Chichibabin Synthesis (important):**
  - Condensation of aldehydes, ketones, and ammonia  $\rightarrow$  pyridine derivatives.

Example: Acetaldehyde + Formaldehyde + Ammonia  $\rightarrow$  Pyridine.

3. **Hantzsch Synthesis:**
  - Condensation of  $\beta$ -ketoesters, aldehyde, and ammonia  $\rightarrow$  dihydropyridine (then oxidation  $\rightarrow$  pyridine).

## Chemical Reactions of Pyridine

### 1. Electrophilic Substitution:

- Pyridine is less reactive than benzene (electron-deficient ring).
- Substitution occurs mainly at C-3 position.
- Examples:
  - Nitration → 3-nitropyridine.
  - Sulfonation → 3-pyridinesulfonic acid.

### 2. Nucleophilic Substitution:

- Due to electron deficiency, pyridine undergoes nucleophilic substitution at C-2 and C-4 positions.
- Example: Chichibabin amination (introduces -NH<sub>2</sub> at C-2).

### 3. Addition Reactions:

- Hydrogenation → piperidine (saturated cyclic amine).

### 4. Oxidation:

- Pyridine ring is resistant, but side chains (if present) can be oxidized.

## Medicinal Uses of Pyridine and Its Derivatives

### 1. Vitamin Component:

- **Nicotinamide, Nicotinic acid (Niacin, Vitamin B<sub>3</sub>)** – essential coenzymes in metabolism (NAD, NADP).

### 2. CNS Stimulants:

- Example: **Nicotine** (from tobacco, pyridine derivative).

### 3. Antitubercular Agents:

- **Isoniazid (INH)** – first-line anti-TB drug.

### 4. Antihypertensive Agents:

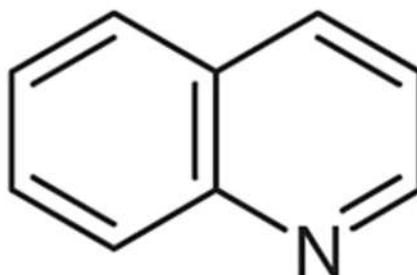
- Example: **Nifedipine** (calcium channel blocker, dihydropyridine derivative).

### 5. Other Drugs:

- **Pyridoxine (Vitamin B<sub>6</sub>)** – coenzyme in amino acid metabolism.
- **Piroxicam** – NSAID.
- **Nicotinamide** – used in pellagra treatment.

## Quinoline

- Quinoline is a bicyclic heteroaromatic compound consisting of a benzene ring fused with a pyridine ring.
- Molecular formula:  $C_9H_7N$
- Structure:
  - Aromatic (10  $\pi$ -electrons; satisfies Hückel's rule).
  - Nitrogen atom is in the pyridine ring, hence shows basic properties.
  - Colorless oily liquid with a strong odor, slightly soluble in water but soluble in organic solvents.



### Synthesis of Quinoline

1. **Skraup Synthesis (important):**
  - Aniline + Glycerol (with oxidizing agent like nitrobenzene and catalyst  $H_2SO_4$ )  $\rightarrow$  Quinoline.
2. **Doebner–Miller Synthesis:**
  - Aniline +  $\alpha,\beta$ -unsaturated carbonyl compound (e.g., crotonaldehyde)  $\rightarrow$  Quinoline derivative.
3. **Combes Synthesis:**
  - Aniline +  $\beta$ -diketone  $\rightarrow$  Quinoline derivative.
4. **Friedländer Synthesis:**
  - o-Aminobenzaldehyde + ketone/aldehyde  $\rightarrow$  Quinoline derivative.

## Chemical Reactions of Quinoline

### 1. Electrophilic Substitution:

- Occurs in the benzene ring (C-5 and C-8 positions), since pyridine ring is electron-deficient.
- Examples: nitration, sulfonation, halogenation.

### 2. Nucleophilic Substitution:

- Takes place in the pyridine ring (C-2 and C-4 positions).

### 3. Reduction:

- Partial hydrogenation → 1,2,3,4-tetrahydroquinoline.
- Complete hydrogenation → Decahydroquinoline.

### 4. Oxidation:

- Side-chain oxidation produces quinolinic acid.

## Medicinal Uses of Quinoline and Its Derivatives

### 1. Antimalarial Agents:

- **Quinine** – natural alkaloid from cinchona bark, used in malaria.
- **Chloroquine, Hydroxychloroquine, Mefloquine** – synthetic derivatives, widely used antimalarials.

### 2. Antibacterial Agents:

- **Ciprofloxacin, Norfloxacin, Levofloxacin** – fluoroquinolone antibiotics.

### 3. Anthelmintic:

- **Oxamniquine** – used in schistosomiasis.

### 4. Anticancer Activity:

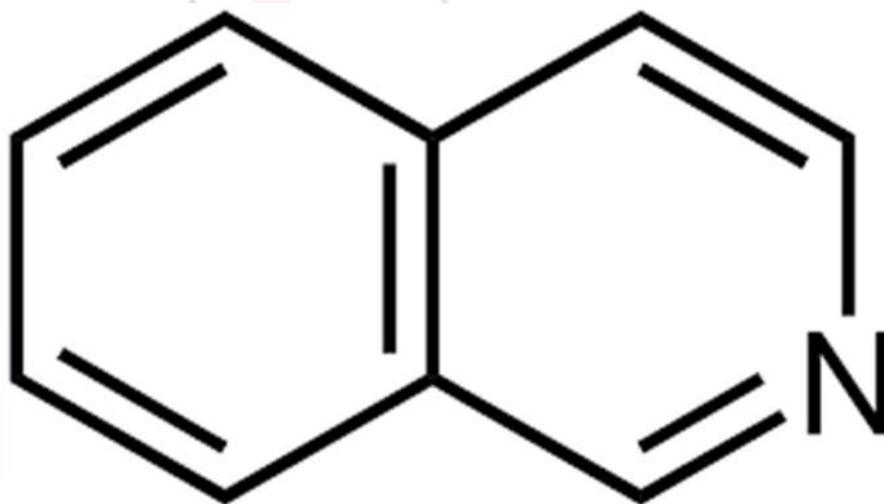
- Some quinoline derivatives used in anticancer drug development.

### 5. Other Uses:

- Used in dyes, antiseptics, and chemical synthesis.

## Isoquinoline

- Isoquinoline is a bicyclic heteroaromatic compound consisting of a benzene ring fused with a pyridine ring, but the nitrogen atom is at the 2-position (unlike quinoline where N is at position-1).
- Molecular formula:  $C_9H_7N$
- Structure:
  - Aromatic, planar, and stable (10  $\pi$ -electrons; satisfies Hückel's rule).
  - Isoquinoline is isomeric with quinoline but differs in position of nitrogen atom.
  - It is a colorless liquid, slightly soluble in water, miscible with organic solvents, and has a pungent odor.



### Synthesis of Isoquinoline

1. **Bischler–Napieralski Synthesis (important):**
  - $\beta$ -phenylethylamine derivatives are cyclized using  $POCl_3$  or  $P_2O_5$  → dihydroisoquinoline → oxidation → Isoquinoline.
2. **Pomeranz–Fritsch Synthesis:**
  - Benzaldehyde + aminoacetaldehyde diethyl acetal → Isoquinoline after acid cyclization.
3. **From Phenylacetaldehyde:**
  - Cyclization of phenylacetaldehyde derivatives with ammonia → Isoquinoline derivatives.

## Chemical Reactions of Isoquinoline

### 1. Electrophilic Substitution:

- Takes place mainly in the **benzene ring at C-5 and C-8 positions**.
- Examples: nitration, halogenation, sulfonation.

### 2. Nucleophilic Substitution:

- Occurs in the **pyridine ring at C-1 and C-3 positions** (due to electron deficiency).

### 3. Reduction:

- Partial hydrogenation → tetrahydroisoquinoline.
- Complete hydrogenation → decahydroisoquinoline.

### 4. Oxidation:

- Side chains undergo oxidation to give isoquinoline carboxylic acids.

## Medicinal Uses of Isoquinoline and Its Derivatives

### 1. Alkaloids:

- Isoquinoline is the parent nucleus of many **plant alkaloids** (e.g., **Papaverine, Morphine, Codeine, Berberine**).

### 2. Antispasmodic:

- **Papaverine** – smooth muscle relaxant, used in vasodilation.

### 3. Analgesic & Narcotic:

- **Morphine, Codeine** – isoquinoline-derived opium alkaloids.

### 4. Antimicrobial:

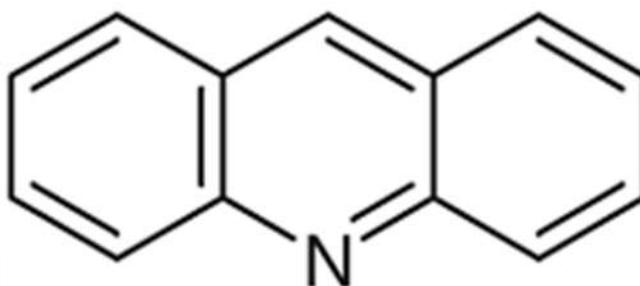
- **Berberine** – antibacterial and antiprotozoal isoquinoline alkaloid.

### 5. Antihypertensive & CNS Agents:

- Some isoquinoline derivatives act as antihypertensives and sedatives.

## Acridine

- Acridine is a tricyclic heteroaromatic compound consisting of two benzene rings fused on either side of a pyridine ring.
- Molecular formula:  $C_{13}H_9N$
- Structure:
  - Planar, aromatic, and stable (14  $\pi$ -electrons; satisfies Hückel's rule).
  - Nitrogen atom is in the central pyridine ring.
  - It is a weak base ( $pK_b \approx 9.5$ ) due to the lone pair on nitrogen (similar to pyridine).
- Physical properties: Yellow crystalline solid with a characteristic irritating odor, slightly soluble in water, soluble in alcohol, benzene, and ether.



### Synthesis of Acridine

1. **From Diphenylamine (Berntsen Acridine Synthesis – important):**
  - Diphenylamine + carboxylic acid (or its derivative) in presence of  $ZnCl_2 \rightarrow$  acridine.
2. **From Benzyl Chloride and Aniline:**
  - Benzyl chloride reacts with aniline  $\rightarrow$  intermediate  $\rightarrow$  cyclization to acridine.
3. **Oxidation of Acenaphthene:**
  - Oxidation leads to acridine derivatives.

## Chemical Reactions of Acridine

### 1. Electrophilic Substitution:

- Takes place in the benzene ring (positions 2 and 4 are most reactive).
- Examples: nitration, sulfonation, halogenation.

### 2. Nucleophilic Substitution:

- Can occur in the central pyridine ring (at C-9 position).

### 3. Oxidation:

- Acridine can be oxidized to acridone.

### 4. Reduction:

- Catalytic hydrogenation produces dihydroacridine and tetrahydroacridine derivatives.

## Medicinal Uses of Acridine and Its Derivatives

### 1. Antiseptic and Antibacterial Agents:

- Acridine derivatives show antibacterial action against Gram-positive organisms.
- Example: **Acriflavine** – antiseptic and topical antimicrobial.

### 2. Antiprotozoal Agents:

- Quinacrine (acridine derivative) – used as antimalarial and in giardiasis.

### 3. Antitumor Agents:

- Acridine derivatives act as DNA intercalating agents, useful in cancer research.

### 4. Antiseptic Dyes:

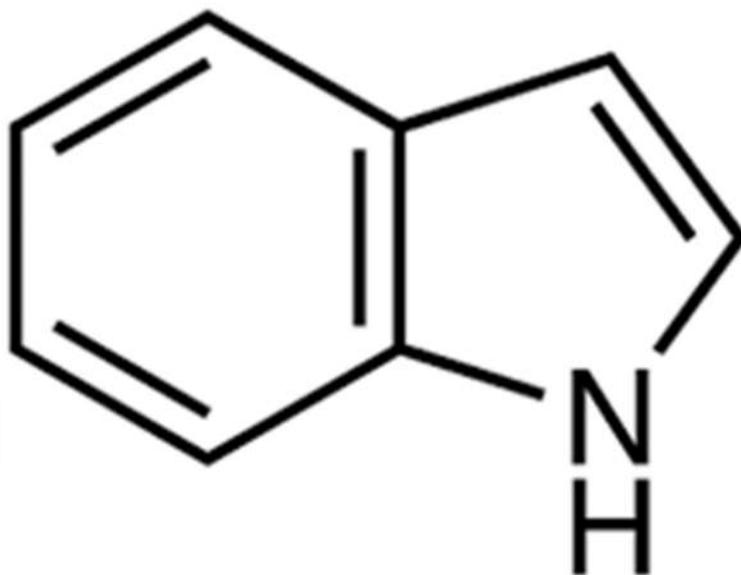
- Acridine orange and related dyes are used as fluorescent stains in microbiology.

### 5. Other Uses:

- Used as analytical reagents, dyes, and fluorescent markers.

## Indole

- Indole is a bicyclic heteroaromatic compound consisting of a benzene ring fused to a pyrrole ring.
- Molecular formula:  $C_8H_7N$
- Structure:
  - Aromatic with 10  $\pi$ -electrons (satisfies Hückel's rule).
  - Nitrogen atom is part of the pyrrole ring, hence weakly basic (lone pair involved in aromaticity).
  - Colorless crystalline solid, slightly soluble in water, soluble in organic solvents, has a fecal odor in concentrated form but floral odor in dilute form.



### Synthesis of Indole

1. **Fischer Indole Synthesis (important):**
  - Reaction of phenylhydrazine with aldehyde or ketone  $\rightarrow$  hydrazone  $\rightarrow$  rearrangement and cyclization  $\rightarrow$  Indole.
2. **Bischler-Möhlau Indole Synthesis:**
  - Condensation of aniline with  $\alpha$ -haloketone derivatives  $\rightarrow$  Indole.
3. **From o-nitrocinnamic acid:**
  - Cyclization and reduction give Indole.

## Chemical Reactions of Indole

### 1. Electrophilic Substitution:

- Indole is highly reactive towards electrophiles (like pyrrole).
- Most reactive position: C-3 of pyrrole ring.
- Examples:
  - Nitration → 3-nitroindole.
  - Halogenation → 3-haloindole.

### 2. Nucleophilic Substitution:

- Less common, but can occur in the benzene ring.

### 3. Oxidation:

- Indole is sensitive to oxidation → forms isatin and other derivatives.

### 4. Reduction:

- Partial reduction → indoline.
- Complete reduction → indoline → octahydroindole.

## Medicinal Uses of Indole and Its Derivatives

### 1. Alkaloids:

- Indole is the nucleus of many natural alkaloids such as strychnine, reserpine, and ergometrine.

### 2. Neurotransmitters:

- **Serotonin (5-hydroxytryptamine)** – an indole derivative, important neurotransmitter.
- **Melatonin** – indole hormone regulating sleep.

### 3. Anticancer Agents:

- Indole derivatives like indole-3-carbinol show anticancer activity.

### 4. Anti-inflammatory & Analgesics:

- Example: Indomethacin – NSAID (anti-inflammatory).

### 5. Antimicrobial Agents:

- Some indole derivatives act as antibacterial and antifungal drugs.

### 6. Other Drugs:

- **Reserpine** – antihypertensive, tranquilizer.

## Basicity of Pyridine

- Pyridine is a six-membered heteroaromatic compound with five carbon atoms and one nitrogen atom.
- The nitrogen atom in pyridine is  $sp^2$  hybridized and has a lone pair of electrons.
- This lone pair is not involved in aromaticity (unlike pyrrole), hence it is available for protonation.
- Thus, pyridine behaves as a weak base.

### Basicity of Pyridine

- The basic character of pyridine refers to its ability to accept a proton ( $H^+$ ) at the nitrogen atom.
- When protonated, pyridine forms a pyridinium salt:



- Pyridinium salts are usually water-soluble crystalline solids.

### Comparison of Basicity

#### 1. Pyridine vs Aliphatic Amines

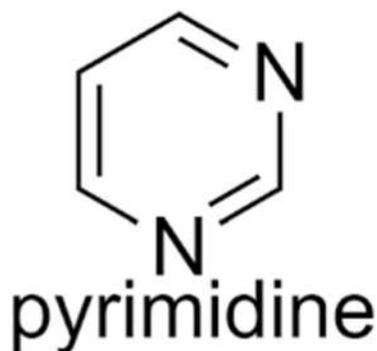
- Pyridine is less basic than aliphatic amines.
- Reason: In pyridine, nitrogen is  $sp^2$  hybridized  $\rightarrow$  higher electronegativity  $\rightarrow$  lone pair held tightly  $\rightarrow$  less available for protonation.
- In aliphatic amines, nitrogen is  $sp^3$  hybridized  $\rightarrow$  lone pair is more available  $\rightarrow$  stronger base.

#### 2. Pyridine vs Pyrrole

- Pyridine is **more basic** than pyrrole.
- In pyridine, nitrogen lone pair is not part of aromatic  $\pi$ -system  $\rightarrow$  free for protonation.
- In pyrrole, nitrogen lone pair is involved in aromaticity  $\rightarrow$  not available for protonation  $\rightarrow$  very weak base.

## Pyrimidine

- Pyrimidine is a six-membered heteroaromatic compound containing two nitrogen atoms at positions 1 and 3.
- Molecular formula:  $C_4H_4N_2$
- Structure: Similar to pyridine but has two nitrogens.
- Weakly basic (due to  $sp^2$  hybridized nitrogen atoms holding lone pairs tightly).
- Parent nucleus of many biological molecules like uracil, thymine, cytosine (nucleic acid bases).



## Synthesis of Pyrimidine

1. **Biginelli Reaction** (important):
  - Condensation of urea (or thiourea),  $\beta$ -ketoester, and aldehyde  $\rightarrow$  Dihydropyrimidinone  $\rightarrow$  Oxidation  $\rightarrow$  Pyrimidine derivatives.
2. **From Barbituric Acid Derivatives:**
  - Condensation and cyclization reactions lead to pyrimidine ring formation.
3. **From Malic Acid Derivatives:**
  - Malic acid + urea derivatives  $\rightarrow$  Pyrimidine skeleton.
4. **Laboratory Method:**
  - Condensation of 1,3-dicarbonyl compounds with amidines or urea  $\rightarrow$  Pyrimidines.

## Medicinal Uses of Pyrimidine and Its Derivatives

### 1. Nucleic Acid Bases:

- Uracil, Thymine, Cytosine → Essential components of DNA and RNA.

### 2. Anticancer Agents:

- 5-Fluorouracil (5-FU): Antimetabolite used in treatment of breast, colon, and skin cancers.
- Cytarabine (Ara-C): Pyrimidine nucleoside analog, used in leukemia.

### 3. Antiviral Agents:

- Zidovudine (AZT): Pyrimidine analog, used in HIV/AIDS.
- Idoxuridine & Trifluridine: Used in herpes virus infections (ocular antiviral).

### 4. Barbiturates (CNS Depressants):

- Barbituric acid derivatives (e.g., Phenobarbital) – used as sedatives, hypnotics, anticonvulsants.

### 5. Antibacterial Agents (Sulfonamides):

- Sulfadiazine and other sulfa drugs are structurally related to pyrimidines.

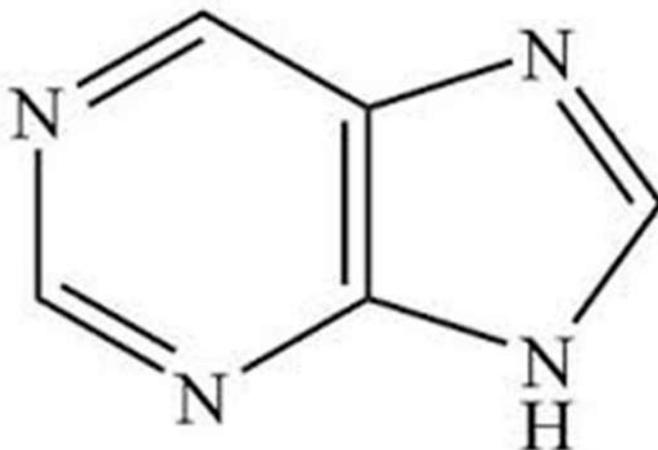
### 6. Other Biological Importance:

- Allopurinol (pyrimidine-related drug) – used in gout (xanthine oxidase inhibitor).

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## Purine

- Purine is a bicyclic heteroaromatic compound made of a pyrimidine ring fused with an imidazole ring.
- Molecular formula:  $C_5H_4N_4$
- It is aromatic (10  $\pi$ -electrons, Hückel's rule satisfied).
- Occurs widely in nature as nucleic acid bases (adenine, guanine), coenzymes, and alkaloids.



## Synthesis of Purine

1. **Traube's Synthesis:**
  - From imidazole derivatives and pyrimidine compounds → condensation → Purine.
2. **Fischer Synthesis (Modified):**
  - Stepwise cyclization of pyrimidine derivatives with formamide groups → purine nucleus.
3. **From Uric Acid (Laboratory Degradation):**
  - Uric acid → reduction/derivatization → purine skeleton identified.

## Chemical Reactions of Purine

### 1. Electrophilic Substitution:

- Less reactive than pyrimidine or imidazole.
- Substitution usually occurs at C-8 position.

### 2. Oxidation:

- Purine can be oxidized to uric acid (important biologically).

### 3. Reduction:

- Leads to dihydropurine or tetrahydropurine derivatives.

## Medicinal Uses of Purine and Its Derivatives

### 1. Nucleic Acid Bases (Genetic Material):

- **Adenine and Guanine** – essential purine bases in DNA & RNA.

### 2. Energy Molecules:

- **ATP, GTP** – purine nucleotides, act as cellular energy currency.

### 3. Coenzymes:

- **NAD, NADP, FAD, Coenzyme A** – all contain purine nucleotides.

### 4. CNS Stimulants (Alkaloids):

- **Caffeine, Theobromine, Theophylline** – purine alkaloids used as mild stimulants, bronchodilators, diuretics.

### 5. Anticancer Agents:

- **6-Mercaptopurine** – used in leukemia treatment (antimetabolite).
- **Azathioprine** – immunosuppressant, used in organ transplantation.

### 6. Antigout Agent:

- **Allopurinol** – xanthine oxidase inhibitor, reduces uric acid synthesis.

### 7. Antiviral Agents:

- **Acyclovir, Ganciclovir** – guanine analogs used in herpes and CMV infections.

## Azepines

- Azepines are a class of seven-membered heterocyclic compounds that contain one nitrogen atom in the ring.
- General formula:  $C_6H_7N$
- They are less common than five- and six-membered heterocycles but are important in medicinal chemistry.
- They exist in aromatic and non-aromatic forms.
- Related systems include benzazepines (azepine fused with a benzene ring).

### Types of Azepines

1. **Azepine (Parent structure):**
  - Seven-membered ring with one nitrogen atom.
2. **Benzazepines:**
  - Azepine ring fused with benzene (e.g., dibenzazepines).
3. **Derivatives of Azepines:**
  - Clozapine, Imipramine, Carbamazepine – widely used drugs.

### Synthesis of Azepines

1. **Cyclization Reactions:**
  - From 1,6-diaminohexane derivatives by ring closure.
2. **From Benzazepine Precursors:**
  - Oxidative or reductive cyclization gives benzazepines.
3. **From Dibenzazepine Systems:**
  - Used in synthesis of psychotropic drugs (like clozapine, carbamazepine).

## Medicinal Uses of Azepine Derivatives

1. **Antipsychotics (Benzazepines):**
  - **Clozapine, Olanzapine** – atypical antipsychotics used in schizophrenia.
2. **Antidepressants (Tricyclic Compounds):**
  - **Imipramine, Desipramine** – tricyclic antidepressants (TCAs), act by blocking reuptake of norepinephrine and serotonin.
3. **Anticonvulsants:**
  - **Carbamazepine** – used in epilepsy, trigeminal neuralgia, and bipolar disorder.
4. **Antihypertensives:**
  - Some benzazepine derivatives act as calcium channel blockers (e.g., diltiazem).
5. **Research Importance:**
  - Simple azepine compounds are used in studying heteroaromaticity and ring strain in larger heterocycles.

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