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PHARMACEUTICAL ORGANIC CHEMISTRY – III

UNIT 4

TOPIC :

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

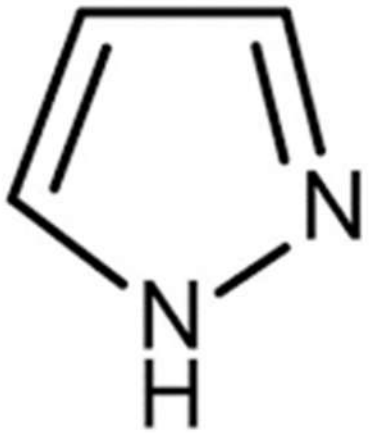
  Pyrazole, Imidazole, Oxazole and Thiazole.

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

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

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 π-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

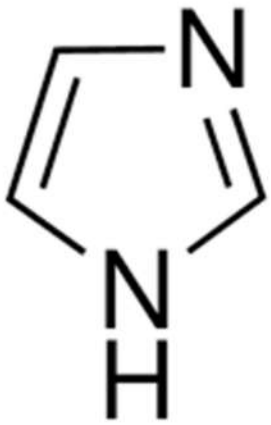
1. **Alkylation:**
   - Pyrazole undergoes alkylation at the nitrogen atom when treated with alkyl halides.
2. **Electrophilic Substitution Reactions:**
   - Electrophilic substitution mainly occurs at the C-4 position of the ring.
   - Examples: Nitration, sulfonation, halogenation.
3. **Reduction:**
   - 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 π-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 α-amino ketones:**

- Cyclization of α-amino ketones with formamide yields imidazole.

Chemical Reactions of Imidazole

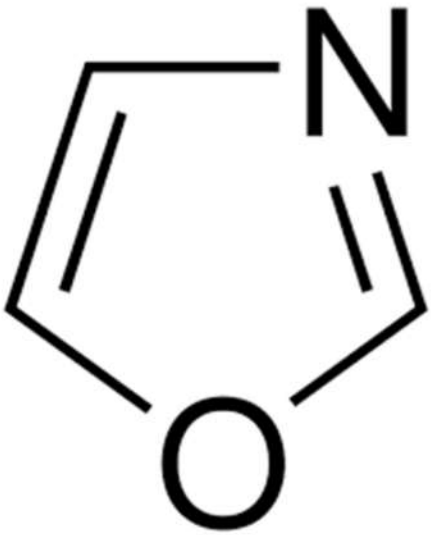
1. **Electrophilic Substitution:**
   - Occurs mainly at C-4 and C-5 positions due to high electron density.
   - Examples: nitration, halogenation, sulfonation.
2. **Nucleophilic Substitution:**
   - Can occur at C-2 position.
3. **Alkylation & Acylation:**
   - Nitrogen atom (N-3) undergoes alkylation/acylation.
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 π-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 α-acylaminoketones gives oxazole.
2. **From α-haloketones and amides:**
   - Reaction between α-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

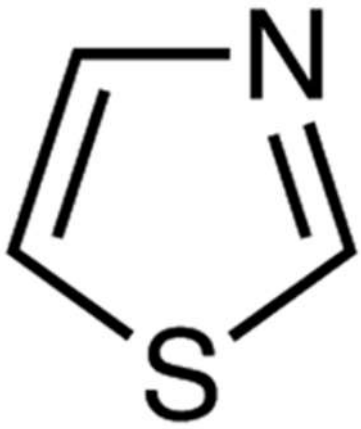
1. **Electrophilic Substitution:**
   - Oxazole is electron-deficient, hence less reactive towards electrophiles.
   - When it reacts, substitution occurs mainly at C-5 position.
2. **Nucleophilic Substitution:**
   - Can occur at **C-2 position**, especially under strong conditions.
3. **Reduction:**
   - 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** – β-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 π-electrons → 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 α-haloketone with thioamide gives thiazole.

   Example:

$$R-CO-CH_2X + R'-CSNH_2 \rightarrow Thiazole$$

1. **Cook-Heilbron Synthesis:**
   - From α-aminonitriles with dithioacids → thiazole derivatives.
2. **Gabriel Synthesis:**
   - From α-haloketones and thiourea.

Chemical Reactions of Thiazole

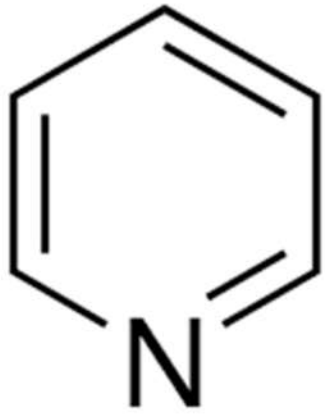
1. **Electrophilic Substitution:**
   - Occurs mainly at C-5 position (most electron-rich).
   - Examples: Nitration, sulfonation, halogenation.
2. **Nucleophilic Substitution:**
   - Takes place at C-2 position, where electron deficiency is higher.
3. **Reduction:**
   - Hydrogenation produces thiazoline (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_1), 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_1)** – 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) → hence pyridine is aromatic with 6 π-electrons.
  - Nitrogen atom makes pyridine a weak base (pKb ≈ 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 → pyridine derivatives.

   Example: Acetaldehyde + Formaldehyde + Ammonia → Pyridine.

3. **Hantzsch Synthesis:**

- Condensation of β-ketoesters, aldehyde, and ammonia → dihydropyridine (then oxidation → pyridine).

Chemical Reactions of Pyridine

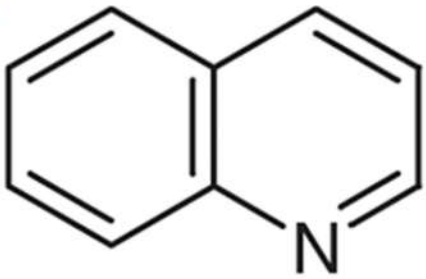
1. **Electrophilic Substitution:**
   - Pyridine is less reactive than benzene (electron-deficient ring).
   - Substitution occurs mainly at C-3 position.
   - Examples:
     - Nitration → 3-nitropyridine.
     - Sulfonation → 3-pyridinesulfonic acid.
2. **Nucleophilic Substitution:**
   - Due to electron deficiency, pyridine undergoes nucleophilic substitution at C-2 and C-4 positions.
   - Example: Chichibabin amination (introduces -NH_2 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_3)** – 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_6)** – coenzyme in amino acid metabolism.

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 π-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) → Quinoline.
2. **Doebner–Miller Synthesis:**
   - Aniline + α,β-unsaturated carbonyl compound (e.g., crotonaldehyde) → Quinoline derivative.
3. **Combes Synthesis:**
   - Aniline + β-diketone → Quinoline derivative.
4. **Friedländer Synthesis:**
   - o-Aminobenzaldehyde + ketone/aldehyde → Quinoline derivative.

Chemical Reactions of Quinoline

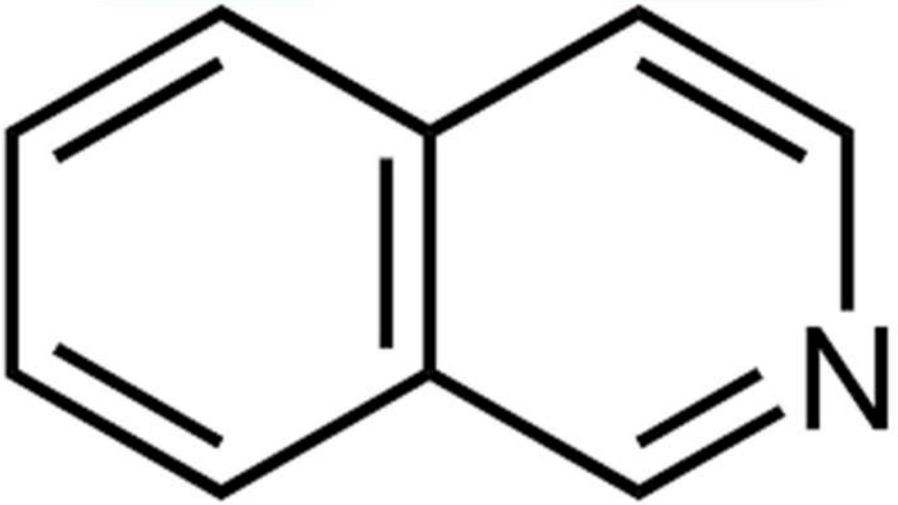
1. **Electrophilic Substitution:**
   - Occurs in the benzene ring (C-5 and C-8 positions), since pyridine ring is electron-deficient.
   - Examples: nitration, sulfonation, halogenation.
2. **Nucleophilic Substitution:**
   - Takes place in the pyridine ring (C-2 and C-4 positions).
3. **Reduction:**
   - 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 π-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):**
   - β-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

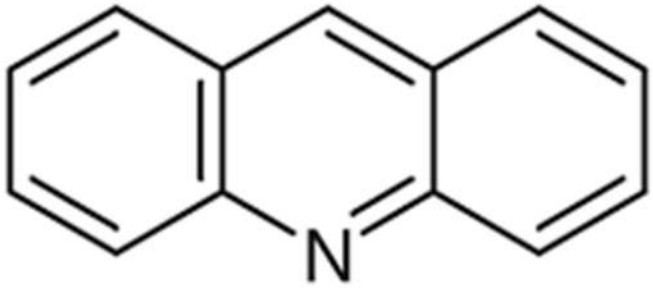
1. **Electrophilic Substitution:**
   - Takes place mainly in the **benzene ring at C-5 and C-8 positions**.
   - Examples: nitration, halogenation, sulfonation.
2. **Nucleophilic Substitution:**
   - Occurs in the **pyridine ring at C-1 and C-3 positions** (due to electron deficiency).
3. **Reduction:**
   - 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 π-electrons; satisfies Hückel's rule).
  - Nitrogen atom is in the central pyridine ring.
  - It is a weak base (pKb ≈ 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 (Bernthsen Acridine Synthesis – important):**
   - Diphenylamine + carboxylic acid (or its derivative) in presence of $ZnCl_2$ → acridine.
2. **From Benzyl Chloride and Aniline:**
   - Benzyl chloride reacts with aniline → intermediate → cyclization to acridine.
3. **Oxidation of Acenaphthene:**
   - Oxidation leads to acridine derivatives.

Chemical Reactions of Acridine

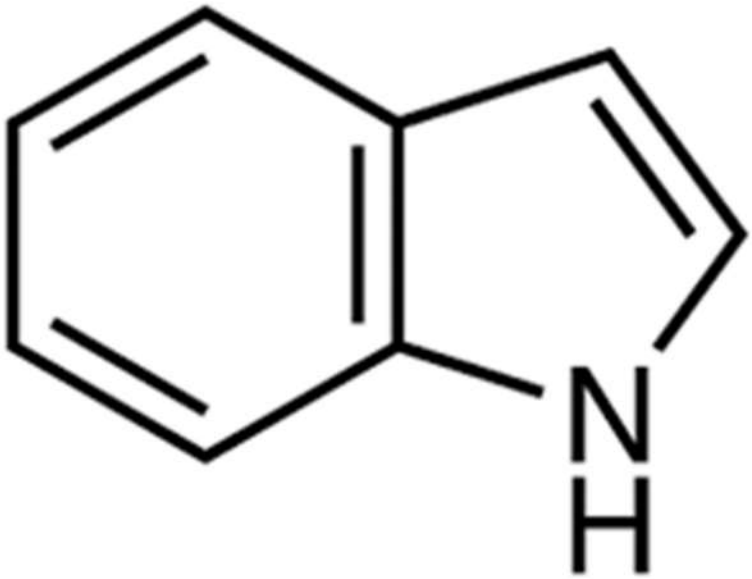
1. **Electrophilic Substitution:**
   - Takes place in the benzene ring (positions 2 and 4 are most reactive).
   - Examples: nitration, sulfonation, halogenation.
2. **Nucleophilic Substitution:**
   - Can occur in the central pyridine ring (at C-9 position).
3. **Oxidation:**
   - Acridine can be oxidized 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 π-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 → hydrazone → rearrangement and cyclization → Indole.
2. **Bischler–Möhlau Indole Synthesis:**
   - Condensation of aniline with α-haloketone derivatives → 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:

$$C_5H_5N + H^+ \rightarrow C_5H_5NH^+$$

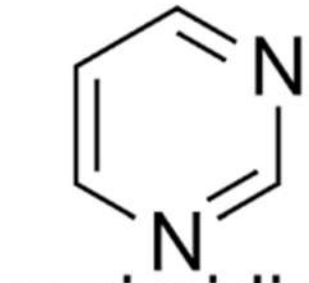
- Pyridinium salts are usually water-soluble crystalline solids.

Comparison of Basicity

1. **Pyridine vs Aliphatic Amines**
   - Pyridine is less basic than aliphatic amines.
   - Reason: In pyridine, nitrogen is sp^2 hybridized → higher electronegativity → lone pair held tightly → less available for protonation.
   - In aliphatic amines, nitrogen is sp^3 hybridized → lone pair is more available → stronger base.
2. **Pyridine vs Pyrrole**
   - Pyridine is **more basic** than pyrrole.
   - In pyridine, nitrogen lone pair is not part of aromatic π-system → free for protonation.
   - In pyrrole, nitrogen lone pair is involved in aromaticity → not available for protonation → 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).



pyrimidine

Synthesis of Pyrimidine

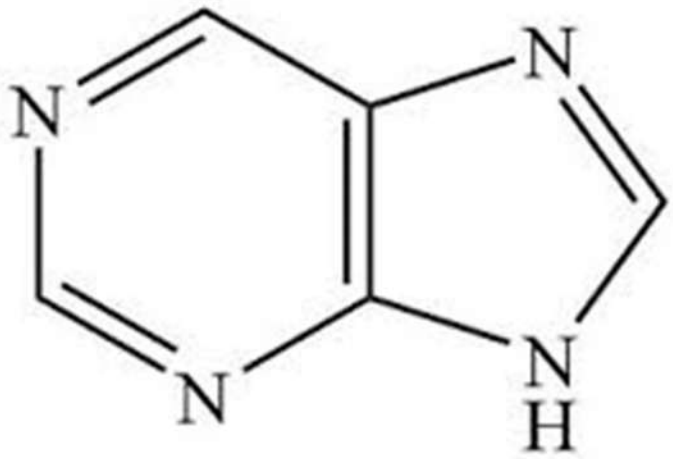
1. **Biginelli Reaction** (important):
    - Condensation of urea (or thiourea), β-ketoester, and aldehyde → Dihydropyrimidinone → Oxidation → Pyrimidine derivatives.
2. **From Barbituric Acid Derivatives:**
    - Condensation and cyclization reactions lead to pyrimidine ring formation.
3. **From Malic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

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 π-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.