BP305T · B.PHARM THEORY

BP305T Heterocyclic Compounds and Stereochemistry

Unit V — Other Heterocycles & Medicinal Uses

FINAL NOTES · UNIT V

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit V (7 hours).

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Chapter 4 — Synthesis of Pyrazole, Imidazole, Pyridine, and Quinoline; Electrophilic Substitution of Pyrazole and Imidazole

Learning Objectives

After studying this chapter, the student will be able to:

1. Write the Knorr pyrazole synthesis with mechanism.
2. Write the Debus–Radziszewski imidazole synthesis with mechanism.
3. Write the Hantzsch pyridine synthesis with mechanism.
4. Write the Skraup quinoline synthesis with mechanism.
5. Explain electrophilic substitution of pyrazole and imidazole, including position selectivity.

Definitions

- **Knorr pyrazole synthesis:** Formation of a pyrazole by condensing a β-ketoester (or 1,3-dicarbonyl compound) with hydrazine.
- **Debus–Radziszewski reaction:** Formation of an imidazole from a 1,2-diketone, an aldehyde, and ammonia.
- **Hantzsch pyridine synthesis:** A three-component condensation of two molecules of β-ketoester, one aldehyde, and ammonia to give a 1,4-dihydropyridine, which is then oxidised to a substituted pyridine.
- **Skraup quinoline synthesis:** Formation of quinoline by heating aniline with glycerol in concentrated sulphuric acid in the presence of an oxidising agent (classically nitrobenzene).
- **Annular tautomerism:** The rapid shifting of a hydrogen between two nitrogens in rings like imidazole and pyrazole, making positions 4 and 5 equivalent.

Simple explanation: The same "zip-up" plot as Chapter 3, but now with two nitrogens (pyrazole, imidazole) or a six-membered ring (pyridine, quinoline). Hydrazine ($H_2N–NH_2$) donates both nitrogens for pyrazole; a diketone + aldehyde + ammonia donate the two nitrogens for imidazole; two keto-esters + aldehyde + ammonia build the pyridine ring; and aniline + glycerol (which becomes acrolein) build quinoline.

Terminology

- **Hydrazine:** $H_2N–NH_2$, a molecule with two linked nitrogens; the nitrogen source in Knorr synthesis.
- **1,4-Dihydropyridine (DHP):** The partially saturated intermediate in the Hantzsch synthesis; also the core of calcium-channel-blocker drugs (nifedipine family).
- **Acrolein:** CH_2=CH–CHO (propenal), formed by dehydrating glycerol; the hidden reagent in the Skraup synthesis.
- **Oxidant:** A chemical that removes hydrogen/electrons (nitrobenzene in Skraup; nitric acid in Hantzsch work-up).
- **Knoevenagel condensation:** Base-catalysed condensation of an aldehyde with an active-methylene compound (used in the Hantzsch mechanism).
- **Michael addition:** Conjugate (1,4-) addition of a nucleophile to an α,β-unsaturated carbonyl compound (used in both Hantzsch and Skraup mechanisms).

4A. Knorr Pyrazole Synthesis — Mechanism (Numbered Steps)

Reaction: ethyl acetoacetate (CH_3–CO–CH_2–COOEt) + hydrazine (H_2N–NH_2) → 3-methylpyrazol-5-one → (tautomerises to the aromatic pyrazole form; with simple 1,3-diketones, directly a pyrazole) + EtOH + H_2O.

Step 1: The more nucleophilic nitrogen of hydrazine attacks the ketone carbonyl of the β-ketoester → hydrazone (C=N–NH_2) + H_2O. **Step 2:** The second nitrogen (the –NH_2 end) attacks the ester carbonyl intramolecularly (ring closure) → a 5-membered cyclic intermediate. **Step 3:** Ethoxide leaves (as ethanol) → a cyclic dihydropyrazole. **Step 4:** Tautomerisation/dehydration → the aromatic pyrazole ring. Aromaticity drives the reaction.

Regiochemistry note: With unsymmetrical 1,3-diketones and substituted hydrazines, two regioisomeric pyrazoles can form; the more nucleophilic (less hindered) nitrogen attacks the more reactive carbonyl first — a favourite exam question.

Key takeaway: β-ketoester + hydrazine → pyrazole + EtOH + H_2O. Hydrazine supplies both nitrogens.

4B. Debus–Radziszewski Imidazole Synthesis — Mechanism (Numbered Steps)

Reaction: glyoxal (OHC–CHO) + formaldehyde (HCHO) + 2 NH_3 → imidazole + 3 H_2O. (Classic example: glyoxal + formaldehyde + ammonia → imidazole itself.)

Step 1: Ammonia adds to the aldehyde (formaldehyde) → an imine (CH_2=NH) + H_2O. **Step 2:** A second molecule of ammonia adds to one carbonyl of the 1,2-diketone (glyoxal) → a hemiaminal/imine intermediate. **Step 3:** The imine nitrogen from Step 1 attacks the second carbonyl carbon of the diketone → ring closure to a 5-membered ring containing two nitrogens. **Step 4:** Dehydration (loss of water molecules) → the aromatic imidazole ring.

Variants: Using benzil (Ph–CO–CO–Ph) + benzaldehyde + NH_3 gives 2,4,5-triphenylimidazole (lophine) — a classic example. Substituted diketones/aldehydes give substituted imidazoles.

Key takeaway: 1,2-diketone + aldehyde + ammonia → imidazole + water. The two nitrogens come from the two ammonia molecules.

4C. Hantzsch Pyridine Synthesis — Mechanism (Numbered Steps)

Reaction: 2 CH_3–CO–CH_2–COOEt (ethyl acetoacetate) + CH_3CHO (acetaldehyde) + NH_3 → 1,4-dihydropyridine derivative → [O] (oxidation, e.g., HNO_3) → substituted pyridine (a 2,4,6-trisubstituted pyridine-3,5-diester).

Step 1 (Knoevenagel): Acetaldehyde condenses with one molecule of ethyl acetoacetate (base-catalysed) → an α,β-unsaturated keto-ester (CH_3–CH=C($COCH_3$)–COOEt) + H_2O. **Step 2 (Enamine formation):** Ammonia condenses with the second molecule of ethyl acetoacetate → an enamine (CH_3–C(NH_2)=CH–COOEt) + H_2O. **Step 3 (Michael addition):** The enamine carbon adds to the β-carbon of the unsaturated keto-ester from Step 1 (conjugate addition) → an open-chain 1,5-dicarbonyl-like intermediate bearing nitrogen. **Step 4 (Cyclisation):** The nitrogen attacks the remaining ketone carbonyl intramolecularly → ring closure + loss of water → the 1,4-dihydropyridine (DHP) ring. **Step 5 (Oxidation):** The DHP is oxidised (classically with nitric acid) → the fully aromatic substituted pyridine.

Pharmacy link: The 1,4-dihydropyridine intermediate is the exact core of **nifedipine-type calcium-channel blockers** (amlodipine etc.) — drugs you will study in pharmacology. This is why the Hantzsch synthesis is pharmaceutically famous.

Key takeaway: 2 keto-esters + 1 aldehyde + NH_3 → dihydropyridine → (oxidise) → pyridine. Count: 2 + 1 + 1 components.

4D. Skraup Quinoline Synthesis — Mechanism (Numbered Steps)

Reaction: aniline (Ph–NH_2) + glycerol + conc. H_2SO_4 + oxidant (nitrobenzene), heat → quinoline.

Step 1 (Dehydration): Glycerol is dehydrated by hot concentrated H_2SO_4 (two molecules of water lost) → acrolein (CH_2=CH–CHO). **Step 2 (Michael addition):** Aniline adds to the β-carbon of acrolein (conjugate addition) → 3-(phenylamino)propanal (Ph–NH–CH_2–CH_2–CHO). **Step 3 (Cyclisation):** The aldehyde carbonyl is protonated by the strong acid; the aromatic ring attacks it intramolecularly (electrophilic aromatic substitution, ring closure) → a tetrahydroquinoline intermediate + H_2O. **Step 4 (Oxidation):** Nitrobenzene (the oxidant) removes hydrogen → the fully aromatic quinoline ring. (Nitrobenzene is itself reduced to aniline, which can re-enter the reaction.)

Conditions: The reaction is strongly exothermic and vigorous — temperature control is essential (a classic exam point: "the Skraup synthesis is violent").

Regiochemistry note: A meta-substituted aniline gives a mixture of 5- and 7-substituted quinolines; the 7-isomer usually predominates (less steric crowding during ring closure).

Key takeaway: Aniline + glycerol (→ acrolein) + acid + oxidant → quinoline. The new pyridine ring is built onto the aniline benzene ring.

Comparison Table — The Four Syntheses

Feature	Knorr (pyrazole)	Debus–Radziszewski (imidazole)	Hantzsch (pyridine)	Skraup (quinoline)
Starting materials	β-ketoester + hydrazine	1,2-diketone + aldehyde + NH_3	2 β-ketoester + aldehyde + NH_3	Aniline + glycerol
Nitrogen source	Hydrazine (both N)	Two NH_3 molecules	Ammonia	Aniline
Conditions	Heat	Heat, mild	Base, then oxidation	Conc. H_2SO_4, heat, oxidant
By-products	EtOH + H_2O	3 H_2O	3 H_2O (then oxidation)	3 H_2O (from glycerol)
Product type	5-membered, 2N (adjacent)	5-membered, 2N (1,3)	6-membered, 1N	Fused 6+6, 1N

4E. Electrophilic Aromatic Substitution of Pyrazole and Imidazole

Pyrazole EAS: Pyrazole is π-excessive (like pyrrole) but less reactive than pyrrole because the second nitrogen (pyridine-like) withdraws electrons. Electrophilic attack occurs at **C-4** (the carbon between the two β-positions, para to the pyrrole-like NH).

- Bromination (Br_2) → 4-bromopyrazole.
- Nitration (fuming HNO_3/H_2SO_4) → 4-nitropyrazole.
- Sulphonation (oleum) → pyrazole-4-sulphonic acid.

Why C-4? Attack at C-4 gives a σ-complex in which the positive charge can be delocalised without placing it on the already electron-poor pyridine-like nitrogen; attack at C-3/C-5 is disfavoured because those carbons sit next to the nitrogens. (Simple version: C-4 is the most electron-rich carbon, furthest from the withdrawing nitrogen.)

Imidazole EAS: Imidazole is even less reactive toward electrophiles (the two nitrogens deactivate the ring); vigorous conditions are needed, and reaction often occurs on the protonated or substituted ring.

- Nitration (conc. HNO_3/H_2SO_4, heat) → 4(5)-nitroimidazole (positions 4 and 5 are identical because of annular tautomerism — the H jumps between the two nitrogens).
- Sulphonation (oleum) → imidazole-4-sulphonic acid.
- Bromination (Br_2 water) → 2,4,5-tribromoimidazole (polybromination is hard to stop — exam trap).

Why the 4(5)-position? Same logic as pyrazole: C-4/C-5 are the carbons most distant from the pyridine-like nitrogen's withdrawing effect, and tautomerism makes C-4 ≡ C-5.

Textual diagram: Draw pyrazole with E^+ approaching C-4; show the σ-complex with the + charge delocalised over N-1, C-3, C-5 (resonance forms) and note "positive charge avoids the pyridine-like N-2". Same for imidazole at C-4/C-5.

Infographic Concept Box — Chapter 4

Title: "Four Rings, Four Recipes" **Layout:** Four recipe cards in a 2×2 grid. Card 1 (Pyrazole): "β-ketoester + hydrazine → –EtOH $–H_2O$". Card 2 (Imidazole): "diketone + aldehyde + NH_3 → $–3H_2O$". Card 3 (Pyridine): "2 keto-esters + aldehyde + NH_3 → DHP → [O] → pyridine". Card 4 (Quinoline): "aniline + glycerol →(acrolein)→ $+H_2SO_4$ +[O] → quinoline ⚠ violent!". Bottom banner: "EAS: pyrazole → C-4; imidazole → C-4(5). Tautomerism makes 4 ≡ 5."

Flowchart — Choosing the Synthesis

1. Target has N–N adjacent (pyrazole)? → Knorr: β-ketoester + hydrazine.
2. Target has N–C–N pattern (imidazole)? → Debus–Radziszewski: diketone + aldehyde + NH_3.
3. Target is a substituted pyridine? → Hantzsch: 2 keto-esters + aldehyde + NH_3, then oxidise.
4. Target is quinoline (benzene fused to pyridine)? → Skraup: aniline + glycerol + conc. H_2SO_4 + nitrobenzene.

Examples

1. Ethyl acetoacetate + hydrazine → 3-methylpyrazol-5-one (tautomer of hydroxypyrazole) — the core of the antipyretic drug edaravone's ring system family.
2. Glyoxal + formaldehyde + NH_3 → imidazole.
3. Benzil + benzaldehyde + NH_3 → 2,4,5-triphenylimidazole (lophine).
4. 2 ethyl acetoacetate + acetaldehyde + NH_3 → diethyl 1,4-dihydro-2,4,6-trimethylpyridine-3,5-dicarboxylate → oxidation → the pyridine diester.
5. Aniline + glycerol/conc. H_2SO_4/nitrobenzene → quinoline.

Analogies

- The Hantzsch synthesis is like **assembling a jigsaw puzzle from three bags of pieces**: two identical keto-ester pieces, one aldehyde piece, and one ammonia piece — and the picture only appears after the final oxidation step "laminates" it.
- The Skraup synthesis is like **cooking with a pressure cooker**: glycerol secretly turns into acrolein (the real cook), and if you don't control the heat, it boils over — hence "violent reaction".

Pharmacy Relevance

- The Hantzsch DHP core is the scaffold of calcium-channel blockers (nifedipine, amlodipine) — among the most prescribed antihypertensives in the world.
- The Skraup quinoline core is the scaffold of antimalarials (chloroquine) and fluoroquinolone antibiotics (ciprofloxacin).
- Imidazole/pyrazole cores appear in antifungals, antiulcer, and anti-inflammatory drugs.

India Context

India is one of the world's largest producers of **ciprofloxacin** (quinoline core) and **metronidazole** (imidazole core); both syntheses taught here are the conceptual ancestors of the industrial routes. Quinoline-based antimalarials remain relevant where chloroquine-sensitive malaria persists.

Key Points

1. Knorr: β-ketoester + hydrazine → pyrazole (N–N adjacent).
2. Debus–Radziszewski: 1,2-diketone + aldehyde + NH_3 → imidazole (1,3-N pattern).
3. Hantzsch: 2 β-ketoesters + aldehyde + NH_3 → 1,4-DHP → oxidation → pyridine.
4. Skraup: aniline + glycerol →(conc. H_2SO_4, via acrolein)→ + oxidant → quinoline; vigorous reaction.
5. Pyrazole EAS at C-4; imidazole EAS at C-4(5); annular tautomerism makes C-4 ≡ C-5 in imidazole.
6. Imidazole bromination gives the tribromo product (hard to stop at mono).

Common Confusions

- **Confusion:** "Knorr synthesis makes imidazole." **Clarification:** Knorr makes **pyrazole** (N–N adjacent, from hydrazine); Debus–Radziszewski makes **imidazole** (N–C–N, from diketone + aldehyde + ammonia).
- **Confusion:** "The Hantzsch product is directly pyridine." **Clarification:** The direct product is a **1,4-dihydropyridine**; oxidation is a separate, essential step.
- **Confusion:** "Glycerol reacts directly with aniline in the Skraup synthesis." **Clarification:** Glycerol first dehydrates to **acrolein**, which is the true electrophile.

Common Mistakes

1. Forgetting the oxidation step in the Hantzsch synthesis.
2. Writing the Skraup product as a substituted aniline instead of quinoline.
3. Assigning pyrazole EAS to C-3 instead of C-4.

Mnemonics

- Syntheses: "**K**norr = **K**etoester + hydra**z**ine → pyra**z**ole" (Z links them); "**D**ebus = **D**iketone + al**d**ehyde → imi**d**azole" (D links them); "**H**antzsch = **H**alf-dozen components → pyridine" (2+1+1); "**S**kraup = **S**ulphuric acid + aniline → quinoline".
- EAS positions: "**4** is the **door**" — electrophiles enter pyrazole/imidazole at C-4.

Exam Summary

Pyrazole is prepared by the Knorr synthesis (β-ketoester + hydrazine), imidazole by the Debus–Radziszewski reaction (1,2-diketone + aldehyde + ammonia), pyridine by the Hantzsch synthesis (two β-ketoesters + aldehyde + ammonia → 1,4-DHP → oxidation), and quinoline by the Skraup synthesis (aniline + glycerol/conc. H_2SO_4 via acrolein + oxidant; vigorous). Electrophilic substitution of pyrazole occurs at C-4 and of imidazole at C-4(5) (tautomerism equates the two), because these are the most electron-rich carbons.

One-Minute Revision

- Knorr → pyrazole (hydrazine gives both N).
- Debus–Radziszewski → imidazole (diketone + aldehyde + NH_3).
- Hantzsch → pyridine (2 keto-esters + aldehyde + NH_3 → DHP → [O]).
- Skraup → quinoline (aniline + glycerol → acrolein → cyclise → [O]); violent!
- EAS: pyrazole C-4; imidazole C-4(5).

Exam Questions

Long answer:

1. Describe the Knorr, Debus–Radziszewski, Hantzsch, and Skraup syntheses with mechanisms. (15 marks)
2. Discuss electrophilic substitution reactions of pyrazole and imidazole, explaining the orientation with resonance structures. (10 marks)

Short notes:

1. Write the mechanism of the Skraup quinoline synthesis. Why is the reaction described as violent?
2. What is the role of oxidation in the Hantzsch pyridine synthesis?
3. Explain annular tautomerism in imidazole with structures.
4. Why does bromination of imidazole give the tribromo product?

MCQs:

1. Knorr pyrazole synthesis uses: (a) diketone + aldehyde + NH_3 (b) β-ketoester + hydrazine (c) aniline + glycerol (d) 2 keto-esters + aldehyde + NH_3 → **(b)**
2. Debus–Radziszewski reactants are: (a) 1,2-diketone + aldehyde + ammonia (b) 1,4-diketone + amine (c) haloketone + ketoester (d) aniline + glycerol → **(a)**
3. The intermediate in Hantzsch synthesis is: (a) quinoline (b) 1,4-dihydropyridine (c) acrolein (d) hydrazone → **(b)**
4. In the Skraup synthesis, glycerol is first converted to: (a) acetaldehyde (b) acrolein (c) acetone (d) formaldehyde → **(b)**
5. Electrophilic substitution of pyrazole occurs at: (a) C-3 (b) C-4 (c) N-1 (d) C-5 → **(b)**
6. The oxidant classically used in Skraup synthesis: (a) HNO_3 (b) nitrobenzene (c) $KMnO_4$ (d) H_2O_2 → **(b)**

Viva:

1. Which nitrogen atoms of hydrazine end up where in the Knorr product?
2. Why does a meta-substituted aniline give mainly the 7-substituted quinoline in the Skraup synthesis?
3. What is the pharmaceutical importance of the 1,4-dihydropyridine ring?

Application-based:

1. A student condenses an unsymmetrical 1,3-diketone (CH_3COCH_2COPh) with methylhydrazine (CH_3NHNH_2). How many pyrazole regioisomers are possible, and which nitrogen attacks first? (Two regioisomers; the more nucleophilic, less hindered $–NH_2$ nitrogen attacks the more electrophilic carbonyl (the methyl ketone) first, so the major product has the methyl-bearing nitrogen adjacent to the phenyl-bearing carbon — discuss both possibilities.)

References

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Chapter 5 — Nomenclature of Fused Heterocycles, Chemical Structures, and Basicity of Imidazole, Pyridine, and Quinoline

Learning Objectives

After studying this chapter, the student will be able to:

1. Name fused heterocyclic systems using fusion prefixes (benzo-, furo-, pyrrolo-, imidazo-).
2. Draw and identify the chemical structures of indole, pyrimidine, benzimidazole, purine, azepine, pyrazole, oxazole, phenothiazine, benzotriazole, and quinoxaline.
3. Compare the basicity of imidazole, pyridine, and quinoline using conjugate-acid pKa values and orbital reasoning.
4. Distinguish pyrrole-like and pyridine-like nitrogens and predict basicity from structure.

Definitions

- **Fused (annelated) heterocycle:** Two or more rings sharing a common bond, at least one ring containing a heteroatom (e.g., quinoline = benzene fused to pyridine).
- **Fusion prefix:** The name of the smaller/fused-on ring used as a prefix: benzo- (benzene), furo- (furan), thieno- (thiophene), pyrrolo- (pyrrole), imidazo- (imidazole), pyrido-/pyridino- (pyridine).
- **Base component:** The larger or principal ring whose name forms the end of the fused name (e.g., "-quinoline", "-imidazole").
- **Fusion descriptor:** A letter (a, b, c…) indicating which side of the base ring is shared, e.g., benzo**[b]**furan.
- **Basicity:** The tendency of a molecule to accept a proton (H^+); measured by the pKa of its conjugate acid — higher pKa = stronger base.
- **Pyrrole-like nitrogen:** N whose lone pair is part of the aromatic sextet (not available for protonation; very weakly basic).
- **Pyridine-like nitrogen:** N whose lone pair is in an sp^2 orbital in the ring plane, free to accept a proton (basic).

Simple explanation: Fused naming is like describing a house extension: you name the original house (base component, e.g., pyridine) and say which wall the extension was built on (benzo[b] = benzene on side "b"). Basicity is about whether nitrogen's lone pair is "free" (pyridine-like, in the plane) or "busy" (pyrrole-like, holding the aromatic ring together) — free lone pairs grab protons; busy ones don't.

Terminology

- **Peripheral numbering:** The fixed numbering of a fused system (e.g., quinoline N is always position 1).
- **Conjugate acid:** The species formed when a base accepts H^+ (pyridine → pyridinium ion).
- **pKa (of conjugate acid):** –log Ka; higher value = weaker conjugate acid = stronger base.
- **Amidine:** A –N–C(=NH)–N– grouping; imidazole's conjugate acid is amidine-like and resonance-stabilised.
- **Azepine:** A 7-membered unsaturated ring with one nitrogen (1H-azepine).

5A. Nomenclature of Fused Heterocyclic Compounds

Rules (simplified for this course):

1. Choose the **base component**: the heterocycle (or larger ring) that gives the suffix.
2. Name the fused-on ring as a **prefix**: benzo-, furo-, thieno-, pyrrolo-, imidazo-, pyrazino-.
3. Indicate the shared side with a **letter**: sides of the base are lettered a, b, c… starting from the 1–2 bond.
4. Number the whole fused system to give heteroatoms the lowest locants (many common systems have fixed traditional numbering — learn quinoline, isoquinoline, indole, purine by heart).

Examples:

- **Quinoline** = benzo**[b]**pyridine (benzene fused to the b side of pyridine). Traditional numbering: N = 1.
- **Isoquinoline** = benzo**[c]**pyridine (N = 2 in traditional numbering).
- **Indole** = benzo**[b]**pyrrole (benzene fused to pyrrole).
- **Benzimidazole** = benzo**[d]**imidazole.
- **Benzofuran** (coumarone) = benzo**[b]**furan.
- **Benzothiophene** = benzo**[b]**thiophene.
- **Purine** = imidazo**[4,5-d]**pyrimidine (imidazole fused to pyrimidine).
- **Quinazoline** = benzo**[d]**[1,3]diazine (benzene fused to pyrimidine).
- **Quinoxaline** = benzo**[b]**pyrazine (benzene fused to 1,4-diazine).
- **Phenothiazine** = dibenzo-1,4-thiazine (two benzenes fused to a central S,N ring).

Textual diagram: Draw pyridine with sides labelled a (N1–C2), b (C2–C3), c (C3–C4); show benzene fused at side b → quinoline; at side c → isoquinoline.

5B. Chemical Structures (Textual Diagrams)

Learn to draw each; the description tells you how:

1. **Indole:** Benzene fused to pyrrole (benzo[b]pyrrole). Draw a benzene hexagon sharing one side with a pentagon containing N–H. (The core of indomethacin, reserpine.)
2. **Pyrimidine:** Six-membered ring with N at positions 1 and 3 (1,3-diazine). Draw a hexagon, put N at top-right (1) and bottom-right (3). (Core of fluorouracil, sulphadiazine; also of DNA bases cytosine, thymine, uracil.)
3. **Benzimidazole:** Benzene fused to imidazole (benzo[d]imidazole). (Core of albendazole, mebendazole.)
4. **Purine:** Pyrimidine fused to imidazole (imidazo[4,5-d]pyrimidine); nitrogens at 1, 3, 7, 9. Draw a hexagon (pyrimidine) sharing a side with a pentagon (imidazole). (Core of mercaptopurine, thioguanine; also adenine and guanine of DNA.)
5. **Azepine:** Seven-membered unsaturated ring with one N (1H-azepine). Draw a 7-sided ring with one N–H corner and three double bonds. (The diazepine cousin appears in diazepam; dibenzazepine in loxapine-type structures.)
6. **Pyrazole:** Five-membered ring, N–N adjacent (1,2-diazole). (Core of sildenafil, celecoxib.)
7. **Oxazole:** Five-membered ring, O at 1, N at 3 (1,3-oxazole).
8. **Phenothiazine:** Two benzene rings fused to a central six-membered ring containing S and N opposite each other (dibenzo-1,4-thiazine). Draw two hexagons left and right sharing sides with a central hexagon containing S (top) and N–H (bottom). (Core of classic antipsychotics like chlorpromazine.)
9. **Benzotriazole:** Benzene fused to 1,2,3-triazole (three adjacent nitrogens in the five-membered ring).
10. **Quinoxaline:** Benzene fused to pyrazine (1,4-diazine) — nitrogens opposite each other in the six-membered ring.

Memory table — structures:

Heterocycle	Ring system	Heteroatoms	Found in (drug examples)
Indole	6+5 fused	1 N (pyrrole-like)	Indomethacin, reserpine
Pyrimidine	6-membered	2 N (1,3)	Fluorouracil, sulphadiazine
Benzimidazole	6+5 fused	2 N	Albendazole, mebendazole
Purine	6+5 fused	4 N	Mercaptopurine, thioguanine
Azepine	7-membered	1 N	Diazepam (diazepine), loxapine
Pyrazole	5-membered	2 N (adjacent)	Sildenafil, celecoxib
Oxazole	5-membered	O + N	Oxaprozin-type NSAIDs
Phenothiazine	6+6+6 fused	S + N	Chlorpromazine-type antipsychotics
Benzotriazole	6+5 fused	3 N	Corrosion inhibitors, antifungals
Quinoxaline	6+6 fused	2 N (1,4)	Antibiotics (e.g., echinomycin family)

5C. Basicity of Imidazole, Pyridine, and Quinoline

Data (conjugate-acid pKa, approximate, aqueous):

Base	Conjugate acid	pKa (approx.)	Basicity rank
Imidazole	Imidazolium	~7.0	1 (strongest)
Pyridine	Pyridinium	~5.2	2
Quinoline	Quinolinium	~4.9	3
(Pyrrole — for contrast)	Pyrrolium	~–4	Extremely weak

Order of basicity: imidazole > pyridine > quinoline >> pyrrole.

Reasoning (numbered logic):

1. **Pyridine:** The nitrogen lone pair is in an sp^2 orbital in the plane of the ring, NOT part of the aromatic sextet → free to accept H^+. The ring nitrogens' electronegativity slightly reduces availability, but it is a reasonable base (pKa ~5.2).
2. **Quinoline:** Same pyridine-like nitrogen, but the fused benzene ring withdraws electron density by resonance and the larger system stabilises the neutral form slightly more → marginally weaker base than pyridine (pKa ~4.9).
3. **Imidazole:** Has BOTH a pyrrole-like N–H (lone pair in the sextet) and a pyridine-like N (free lone pair). Protonation occurs at the pyridine-like nitrogen, and the resulting imidazolium ion is stabilised by **two equivalent resonance forms** (positive charge shared equally by both nitrogens — amidine-type resonance). This extra stabilisation makes imidazole the strongest base of the three (pKa ~7.0).
4. **Pyrrole (contrast):** Its only lone pair is the aromatic sextet; protonation destroys aromaticity → conjugate acid pKa ~–4 → essentially non-basic.

Textual diagram: Draw imidazolium ion with the + charge shown delocalised between N-1 and N-3 (two resonance arrows, "equivalent structures — extra stable"). Below, draw pyridinium (charge localised on one N) captioned "one form only — less stable".

Simple explanation: Imidazole wins because its protonated form can "share the burden" of the positive charge between two identical nitrogens — like two friends splitting a bill. Pyridine and quinoline carry it alone.

Infographic Concept Box — Chapter 5

Title: "Fuse It, Name It, Base It" **Layout:** Left panel: fusion naming — pyridine hexagon with sides a/b/c labelled, benzene snapping onto side b → "benzo[b]pyridine = quinoline". Middle panel: 10 structure icons in a grid, each labelled with name + heteroatom count. Right panel: basicity ladder — imidazole (7.0) on top, pyridine (5.2) middle, quinoline (4.9) lower, pyrrole (–4) at the bottom in red, with the caption "free lone pair = base; busy lone pair = not a base".

Flowchart — Predicting Basicity of a Nitrogen Heterocycle

1. Look at the nitrogen's lone pair: is it part of the aromatic sextet (pyrrole-like)? → Yes: very weak base (stop).
2. Is it pyridine-like (lone pair in ring plane)? → Yes: moderate base.
3. After protonation, can the + charge be shared by two equivalent nitrogens (amidine resonance)? → Yes (imidazole): strong base.
4. Is the ring fused to benzene (quinoline vs pyridine)? → Fused = slightly weaker.

Examples

1. Histidine (amino acid) uses its imidazole side chain (pKa ~6) as a proton shuttle in enzyme active sites — basicity in action.
2. Nicotine contains a pyridine ring (basic nitrogen — forms salts) and a pyrrolidine ring.
3. Quinine (antimalarial) contains a quinoline ring.
4. Caffeine contains a purine (xanthine) core — a fused imidazo-pyrimidine.

Analogies

- Fusion nomenclature is like **naming a duplex house**: "benzo[b]pyridine" = "the benzene flat built on wall b of the pyridine house".
- Imidazolium resonance is like **two pillars sharing a roof's weight** — the structure is stronger than one pillar alone, which is why imidazole is the strongest base here.

Pharmacy Relevance

Basicity controls whether a drug forms salts (better solubility, e.g., ciprofloxacin hydrochloride), how it is absorbed in the stomach vs intestine, and how it binds targets. The imidazole ring's near-neutral pKa (~7) is why histidine is nature's favourite acid–base catalyst.

India Context

Indian manufacturers produce huge volumes of **quinoline-based ciprofloxacin** and **imidazole-based metronidazole**; understanding their basicity helps in salt selection during formulation (a core industrial-pharmacy skill tested in GPAT).

Key Points

1. Fused name = fusion prefix (benzo-, imidazo-...) + base component + fusion letter (a, b, c...).
2. Quinoline = benzo[b]pyridine; isoquinoline = benzo[c]pyridine; indole = benzo[b]pyrrole; purine = imidazo[4,5-d]pyrimidine.
3. Ten structures to draw: indole, pyrimidine, benzimidazole, purine, azepine, pyrazole, oxazole, phenothiazine, benzotriazole, quinoxaline.
4. Basicity: imidazole (~7.0) > pyridine (~5.2) > quinoline (~4.9) >> pyrrole (~–4).
5. Reason: pyridine-like lone pairs are free; imidazolium has two equivalent resonance forms; pyrrole's lone pair is busy in the aromatic sextet.

Common Confusions

- **Confusion:** "Quinoline is more basic than pyridine because it is bigger." **Clarification:** Slightly less basic (pKa 4.9 vs 5.2) — the fused benzene withdraws electron density.
- **Confusion:** "Imidazole has two nitrogens so it is twice as basic." **Clarification:** Only the pyridine-like nitrogen is protonated; the strength comes from resonance stabilisation of the conjugate acid, not from "two nitrogens".
- **Confusion:** "Purine is just another name for pyrimidine." **Clarification:** Purine = pyrimidine FUSED to imidazole (a bigger, 4-nitrogen system).

Common Mistakes

1. Writing fusion letters as numbers (benzo[2]pyridine — wrong; letters a, b, c are used).
2. Drawing purine with wrong nitrogen positions (learn N-1, 3, 7, 9).
3. Ranking quinoline above pyridine in basicity.

Mnemonics

- Fusion: "**B**ig **F**amilies **P**refer **I**nvitations" — Benzo-, Furo-, Pyrrolo-, Imidazo-.
- Basicity: "**I P**refer **Q**uiet" — Imidazole > Pyridine > Quinoline.
- pKa ladder: "**7 – 5 – 5**" (imidazole ~7, pyridine ~5.2, quinoline ~4.9).

Exam Summary

Fused heterocycles are named with a fusion prefix (benzo-, furo-, imidazo-...), the base component, and a fusion letter (a, b, c) for the shared side. Students must draw indole, pyrimidine, benzimidazole, purine, azepine, pyrazole, oxazole, phenothiazine, benzotriazole, and quinoxaline. Basicity follows imidazole > pyridine > quinoline >> pyrrole because pyridine-like lone pairs are free for protonation, the imidazolium ion enjoys two equivalent resonance forms, and pyrrole's lone pair is committed to the aromatic sextet.

One-Minute Revision

- Fused name = prefix + base + letter (benzo[b]pyridine = quinoline).
- 10 structures: indole, pyrimidine, benzimidazole, purine, azepine, pyrazole, oxazole, phenothiazine, benzotriazole, quinoxaline.
- Basicity: I > P > Q (pKa ~7.0 > 5.2 > 4.9); pyrrole ~–4.
- Imidazole wins: amidine-type resonance in its conjugate acid.

Exam Questions

Long answer:

1. Explain the nomenclature of fused heterocyclic compounds with five examples. (10 marks)
2. Compare the basicity of imidazole, pyridine, and quinoline with orbital diagrams and conjugate-acid pKa values. (10 marks)

Short notes:

1. Draw the structures of purine, phenothiazine, and quinoxaline.
2. What is the difference between pyrrole-like and pyridine-like nitrogen? Give one consequence for basicity.
3. Write the systematic fused name of indole and isoquinoline.

MCQs:

1. Quinoline is systematically: (a) benzo[b]pyridine (b) benzo[c]pyridine (c) benzo[d]pyridine (d) dibenzopyridine → **(a)**
2. Purine is: (a) imidazo[4,5-d]pyrimidine (b) benzo[d]imidazole (c) pyrrolo[2,3-d]pyrimidine (d) 1,3-diazine → **(a)**
3. Strongest base among: (a) pyrrole (b) pyridine (c) quinoline (d) imidazole → **(d)**
4. The conjugate-acid pKa of pyridine is approximately: (a) –4 (b) 4.9 (c) 5.2 (d) 7.0 → **(c)**
5. Phenothiazine contains: (a) two nitrogens (b) S and N (c) two oxygens (d) three nitrogens → **(b)**

Viva:

1. Why is imidazole more basic than pyridine?
2. What does the letter in benzo[b]furan signify?
3. Name the heterocycle in caffeine. (Purine/xanthine.)

Application-based:

1. A formulation scientist must choose between a pyridine-containing and an imidazole-containing analogue for a drug that needs good solubility as a hydrochloride salt at stomach pH (~2). Which scaffold is the safer choice for reliable salt formation, and why? (The imidazole analogue — its conjugate-acid pKa ~7 means it is essentially fully protonated at pH 2, giving dependable salt formation; the pyridine analogue (pKa ~5.2) is also protonated at pH 2 but the imidazole's higher basicity gives a wider margin. Discuss both.)

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Chapter 6 — Medicinal Uses of Drugs Containing Pyrazole, Imidazole, Pyridine, Quinoline, Indole, Benzimidazole, Pyrimidine, Purine, and Azepine Heterocycles

Learning Objectives

After studying this chapter, the student will be able to:

1. Name two drugs for each listed heterocycle class and state their medicinal uses.
2. Relate each drug's heterocyclic ring to its pharmacological class in simple words.
3. Recall the India-relevant importance of at least five of these drugs.

Definitions

- **Heterocyclic drug:** A medicine whose structure contains at least one heterocyclic ring; the ring usually forms key interactions (hydrogen bonds) with the biological target.
- **Pharmacophore:** The part of a drug molecule responsible for its biological action — often the heterocyclic ring.
- **Antimetabolite:** A drug that mimics a natural building block (like a purine or pyrimidine base) and sabotages the cell's machinery — used in cancer and infection.

Simple explanation: This chapter is a "drug parade": for each heterocycle you have studied, meet two famous medicines that carry it. You don't need deep pharmacology — just know the drug's class, what disease it treats, and which ring it contains. In the exam, "give the medicinal uses of two drugs containing X heterocycle" is one of the most repeated questions in this subject.

The Drug Parade — Class by Class

1. Pyrazole drugs

Drug	Class	Use (simple words)
Sildenafil	PDE5 inhibitor	Erectile dysfunction; also pulmonary hypertension — relaxes blood vessels by raising cGMP
Celecoxib	COX-2 selective NSAID	Arthritis and pain relief with lower stomach-ulcer risk than older painkillers

2. Imidazole drugs

Drug	Class	Use (simple words)
Metronidazole	Nitroimidazole antiprotozoal/antibacterial	Amoebiasis, giardiasis, anaerobic bacterial infections — the nitro group is activated inside the germ to damage its DNA
Pilocarpine	Muscarinic (cholinergic) agonist	Glaucoma — constricts the pupil and drains eye fluid, lowering eye pressure; also treats dry mouth

3. Pyridine drugs

Drug	Class	Use (simple words)
Isoniazid	Anti-tubercular	First-line treatment of tuberculosis — blocks mycolic-acid synthesis in the TB bacterium's cell wall
Chlorpheniramine	First-generation antihistamine (H1 blocker)	Allergy, cold, sneezing, itching — blocks histamine; causes drowsiness

4. Quinoline drugs

Drug	Class	Use (simple words)
Chloroquine	Antimalarial (4-aminoquinoline)	Malaria treatment and prevention — concentrates in the parasite and stops it detoxifying haem
Ciprofloxacin	Fluoroquinolone antibiotic	Urinary, respiratory, and gut bacterial infections — blocks bacterial DNA gyrase/topoisomerase

5. Indole drugs

Drug	Class	Use (simple words)
Indomethacin	NSAID (non-selective COX inhibitor)	Arthritis, gout, inflammation and pain relief
Reserpine	Antihypertensive (from *Rauwolfia serpentina*)	High blood pressure — depletes noradrenaline/serotonin stores in nerve endings; one of India's classic plant-derived drugs

6. Benzimidazole drugs

Drug	Class	Use (simple words)
Albendazole	Broad-spectrum anthelmintic	Worm infections (roundworm, hookworm, tapeworm) — binds worm β-tubulin, starving the worm; used in India's National Deworming Day
Mebendazole	Anthelmintic	Pinworm, roundworm, whipworm infections in children — same tubulin-blocking action

7. Pyrimidine drugs

Drug	Class	Use (simple words)
Fluorouracil (5-FU)	Antimetabolite anticancer	Cancers (colorectal, breast, skin) — mimics uracil and blocks thymidylate synthase, stopping DNA synthesis
Sulphadiazine	Sulphonamide antibacterial	Bacterial infections; combined with pyrimethamine for toxoplasmosis — blocks bacterial folic-acid synthesis

8. Purine drugs

Drug	Class	Use (simple words)
Mercaptopurine	Purine antimetabolite	Acute lymphoblastic leukaemia (childhood blood cancer) — fake purine that disrupts DNA/RNA synthesis
Thioguanine	Purine antimetabolite	Acute myeloid leukaemia — similar fake-purine action

9. Azepine drugs

Drug	Class	Use (simple words)
Diazepam	Benzodiazepine (fused 1,4-diazepine) anxiolytic/anticonvulsant	Anxiety, seizures, muscle spasm, pre-surgery sedation — boosts GABA calming signals in the brain
Loxapine	Dibenzazepine-type (dibenzoxazepine) antipsychotic	Schizophrenia — blocks dopamine (and serotonin) receptors; the seven-membered oxazepine ring is an azepine relative

Master table — all 18 drugs at a glance:

Heterocycle	Drug 1	Drug 2
Pyrazole	Sildenafil (PDE5 inhibitor)	Celecoxib (COX-2 NSAID)
Imidazole	Metronidazole (antiprotozoal)	Pilocarpine (glaucoma)
Pyridine	Isoniazid (anti-TB)	Chlorpheniramine (antihistamine)
Quinoline	Chloroquine (antimalarial)	Ciprofloxacin (antibiotic)
Indole	Indomethacin (NSAID)	Reserpine (antihypertensive)
Benzimidazole	Albendazole (anthelmintic)	Mebendazole (anthelmintic)
Pyrimidine	Fluorouracil (anticancer)	Sulphadiazine (antibacterial)
Purine	Mercaptopurine (antileukaemic)	Thioguanine (antileukaemic)
Azepine	Diazepam (anxiolytic/anticonvulsant)	Loxapine (antipsychotic)

Infographic Concept Box — Chapter 6

Title: "The Heterocycle Drug Parade" **Layout:** Nine floats in a parade, one per heterocycle, each carrying two drug banners with a one-word use: Pyrazole float — sildenafil/circulation, celecoxib/pain; Imidazole — metronidazole/germs, pilocarpine/eyes; Pyridine — isoniazid/TB, chlorpheniramine/allergy; Quinoline — chloroquine/malaria, ciprofloxacin/infection; Indole — indomethacin/inflammation, reserpine/BP; Benzimidazole — albendazole & mebendazole/worms; Pyrimidine — fluorouracil/cancer, sulphadiazine/germs; Purine — mercaptopurine & thioguanine/leukaemia; Azepine — diazepam/calm, loxapine/mind. Bottom strip: "Spot the ring → name the class → state the use".

Flowchart — Answering "Medicinal Uses" Exam Questions

1. Read the heterocycle named in the question.
2. Recall its two syllabus drugs from the master table.
3. For each drug: write class → disease treated → one-line action in simple words.
4. Add an India line if you know one (TB, malaria, deworming, essential medicines).

Examples (how to write a 5-mark answer)

- **Q:** Give the medicinal uses of two drugs containing a pyridine heterocycle. **A:** (1) Isoniazid — first-line anti-tubercular; kills *Mycobacterium tuberculosis* by blocking mycolic-acid cell-wall synthesis; cornerstone of India's TB programme. (2) Chlorpheniramine — H1 antihistamine for allergy/cold symptoms; first-generation, hence sedative.

Analogies

> - Learning these drugs is like learning **cricket players by their team jerseys**: the heterocycle is the jersey colour — once you spot it, you know which team (drug class) the player belongs to.

Pharmacy Relevance

This chapter is the bridge between organic chemistry and pharmacology. In every pharmacology class next semester, you will meet these drugs again — recognising their heterocyclic cores will make their mechanisms easier to remember.

India Context

- **Isoniazid** is the backbone of India's National TB Elimination Programme (Ni-kshay).
- **Albendazole** is distributed free to crores of schoolchildren every National Deworming Day.
- **Chloroquine** and **ciprofloxacin** are on India's National List of Essential Medicines.
- **Reserpine** comes from *Rauwolfia serpentina* (sarpagandha), an Indian medicinal plant — a matter of national scientific pride.
- India manufactures **metronidazole**, **ciprofloxacin**, and **albendazole** at globally significant scale.

Key Points

1. Pyrazole: sildenafil (PDE5), celecoxib (COX-2).
2. Imidazole: metronidazole (antiprotozoal), pilocarpine (glaucoma).
3. Pyridine: isoniazid (anti-TB), chlorpheniramine (antihistamine).
4. Quinoline: chloroquine (antimalarial), ciprofloxacin (antibiotic).
5. Indole: indomethacin (NSAID), reserpine (antihypertensive).
6. Benzimidazole: albendazole, mebendazole (anthelmintics).
7. Pyrimidine: fluorouracil (anticancer antimetabolite), sulphadiazine (antibacterial).
8. Purine: mercaptopurine, thioguanine (antileukaemic antimetabolites).
9. Azepine: diazepam (anxiolytic/anticonvulsant), loxapine (antipsychotic).

Common Confusions

- **Confusion:** "Sildenafil and celecoxib are both painkillers because both have pyrazole." **Clarification:** Same ring, different targets — sildenafil inhibits PDE5 (vessels), celecoxib inhibits COX-2 (inflammation). The ring is a scaffold, not the whole story.
- **Confusion:** "Metronidazole is an antibiotic for all bacteria." **Clarification:** It works against anaerobic bacteria and protozoa (its nitro group needs low-oxygen activation).
- **Confusion:** "Loxapine is a benzodiazepine like diazepam." **Clarification:** No — diazepam is a benzodiazepine (anxiolytic); loxapine is a dibenzoxazepine antipsychotic. Different classes, different uses.

Common Mistakes

1. Writing only one drug when the question asks for two.
2. Mixing up sulphadiazine (pyrimidine) with sulphadiazine-like sulpha drugs' class — remember it IS the pyrimidine example.
3. Forgetting to mention the heterocycle explicitly in the answer.

Mnemonics

- Learn pairs with rhymes/links: "**S**ildenafil–**C**elecoxib **p**arty in the **p**yrazole"; "**M**etronidazole for **m**icrobes, **p**ilocarpine for **p**upils"; "**I**soniazid fights TB **i**n **I**ndia"; "**C**hloroquine–**C**iprofloxacin, **q**uinoline **q**uells germs"; "**I**ndomethacin–**R**eserpine, **i**ndole **i**n both"; "**A**lbendazole–**M**ebendazole **a**nnihilate worms"; "**F**luorouracil **f**ights cancer, **s**ulphadiazine **s**tops germs"; "**M**ercaptopurine–**T**hioguanine **m**imic purines"; "**D**iazepam **d**e-stresses, **l**oxapine **l**ifts psychosis.

Exam Summary

Each heterocycle class maps to two syllabus drugs: pyrazole — sildenafil, celecoxib; imidazole — metronidazole, pilocarpine; pyridine — isoniazid, chlorpheniramine; quinoline — chloroquine, ciprofloxacin; indole — indomethacin, reserpine; benzimidazole — albendazole, mebendazole; pyrimidine — fluorouracil, sulphadiazine; purine — mercaptopurine, thioguanine; azepine — diazepam, loxapine. Answers should give drug class, disease treated, and a one-line mechanism, with India-context notes where relevant.

One-Minute Revision

- Pyrazole: sildenafil, celecoxib. Imidazole: metronidazole, pilocarpine. Pyridine: isoniazid, chlorpheniramine.
- Quinoline: chloroquine, ciprofloxacin. Indole: indomethacin, reserpine. Benzimidazole: albendazole, mebendazole.
- Pyrimidine: fluorouracil, sulphadiazine. Purine: mercaptopurine, thioguanine. Azepine: diazepam, loxapine.
- Formula for answers: ring → drug → class → disease → one-line action.

Exam Questions

Long answer:

1. Discuss the medicinal uses of two drugs each containing pyrazole, imidazole, pyridine, and quinoline heterocycles. (15 marks)
2. Write the medicinal uses of two drugs each containing indole, benzimidazole, pyrimidine, purine, and azepine heterocycles. (15 marks)

Short notes:

1. Give the medicinal uses of sildenafil and celecoxib. Which heterocycle do they share?
2. Why is metronidazole effective against anaerobic organisms?
3. Name two anthelmintic drugs containing the benzimidazole ring and state their uses.
4. Give the medicinal uses of diazepam and loxapine.

MCQs:

1. Which pair shares the pyrazole ring? (a) sildenafil–celecoxib (b) diazepam–loxapine (c) isoniazid–chlorpheniramine (d) albendazole–mebendazole → **(a)**
2. Metronidazole is used for: (a) hypertension (b) amoebiasis (c) epilepsy (d) glaucoma → **(b)**
3. Isoniazid is a: (a) first-line anti-tubercular (b) antimalarial (c) diuretic (d) antiplatelet → **(a)**
4. Chloroquine acts against: (a) worms (b) malarial parasite (c) viruses (d) fungi → **(b)**
5. Albendazole acts by: (a) blocking β-tubulin in worms (b) inhibiting COX-2 (c) blocking PDE5 (d) inhibiting DNA gyrase → **(a)**
6. Fluorouracil is a: (a) pyrimidine antimetabolite (b) purine antimetabolite (c) alkylating agent (d) antibiotic → **(a)**
7. Pilocarpine is used in: (a) TB (b) glaucoma (c) malaria (d) leukaemia → **(b)**
8. Reserpine is obtained from: (a) *Rauwolfia serpentina* (b) *Cinchona* (c) *Opium* (d) *Digitalis* → **(a)**

Viva:

1. Name two purine-containing anticancer drugs and their uses.
2. Which heterocycle is common to albendazole and mebendazole?
3. Give one India-specific importance of isoniazid. (Backbone of the National TB Elimination Programme.)

Application-based:

1. A patient with a history of stomach ulcers needs long-term arthritis pain relief. Between indomethacin and celecoxib, which is the more rational choice and why? (Celecoxib — COX-2 selective, lower GI ulcer risk; indomethacin is non-selective and harsher on the stomach. Both contain heterocycles — indole vs pyrazole — but selectivity differs.)

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