BP305T · B.PHARM SEMESTER III · THEORY

BP305T HETEROCYCLIC COMPOUNDS AND STEREOCHEMISTRY

Unit IV — Five-Membered Heterocycles

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Hantzsch–Widman nomenclature · Aromaticity and reactivity · Synthesis, reactions and medicinal uses

Unit IV · 10 hours

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Chapter 1 — Hantzsch–Widman Nomenclature and Classification of Heterocyclic Compounds

Learning Objectives

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

1. Define a heterocyclic compound and give examples.
2. Name heterocyclic compounds using the Hantzsch–Widman system.
3. Apply the priority order of heteroatoms (O > S > N) and the rules for numbering.
4. Classify heterocycles by ring size, number of heteroatoms, and saturation.
5. Recognise common retained (trivial) names such as furan, pyrrole, thiophene, and pyridine.

Definitions

- **Heterocyclic compound:** A cyclic (ring-shaped) organic compound in which at least one atom of the ring is a **heteroatom** — an atom other than carbon. The most common heteroatoms are nitrogen (N), oxygen (O), and sulphur (S).
- **Carbocyclic compound:** A ring compound made only of carbon atoms (for example, benzene, cyclohexane). Heterocycles are the opposite of this.
- **Hantzsch–Widman system:** The official IUPAC system for naming heterocyclic rings. It builds a name from three parts: a **prefix** (which tells the heteroatom), a **stem** (which tells the ring size), and a **suffix/ending** (which tells whether the ring is saturated or unsaturated).

> **Simple explanation:** Think of the Hantzsch–Widman name as a small sentence. The prefix says *who is in the ring* (oxygen, sulphur, nitrogen), the stem says *how big the ring is* (3, 4, 5, 6, 7 atoms), and the ending says *whether the ring has double bonds or not*. Example: **ox** (oxygen) + **a** + **zole** → oxazole: a five-membered unsaturated ring with O and N.

Terminology

- **Heteroatom:** Any ring atom that is not carbon (usually N, O, S).
- **Prefix:** The part of the name that identifies the heteroatom: oxa- (O), thia- (S), aza- (N), phospha- (P).
- **Locant:** The number that shows the position of a heteroatom in the ring (for example, the "1" and "3" in 1,3-oxazole).
- **Retained name:** An old common name that IUPAC still allows, such as furan, pyrrole, thiophene, pyridine.
- **Elision:** Dropping the final "a" of a prefix when the next part starts with a vowel (aza + ole → **azole**, not "azaole").
- **Annulation/fusion:** Two rings sharing a common bond (covered in detail in Chapter 5).

The Hantzsch–Widman System — Explanation

Step 1 — Choose the heteroatom prefix (priority order). When a ring has more than one type of heteroatom, they are listed in a fixed priority order. For this course, remember:

O > S > N (oxygen first, then sulphur, then nitrogen)

> Mnemonic: "**O**ld **S**aints **N**ever" — O, S, N. The full IUPAC order continues with phosphorus and others, but O > S > N covers this syllabus.

Step 2 — Choose the stem and ending from the ring size.

Ring size	Unsaturated (with double bonds) ending	Saturated ending	Example
3-membered	-irene	-irane / -iridine	aziridine (saturated, N)
4-membered	-ete	-etane / -etidine	oxetane (saturated, O)
5-membered	-ole	-olane / -olidine	oxole = furan (unsaturated)
6-membered	-ine	-ane	azine = pyridine (unsaturated)
7-membered	-epine	-epane	azepine (unsaturated, N)

Step 3 — Number the ring.

- Heteroatoms get the **lowest possible numbers**.
- With different heteroatoms, numbering follows the priority order (O gets position 1 before S, S before N).
- The direction of numbering is chosen so that the next heteroatom gets the lowest possible locant.

Worked Naming Examples

1. **Oxazole:** 5-membered unsaturated ring with O and N. Priority O first → positions 1 (O) and 3 (N) → **1,3-oxazole**. (Oxa + zole; "a" elided before the vowel.)
2. **Thiazole:** S and N in a 5-membered unsaturated ring → **1,3-thiazole**.
3. **Imidazole:** two nitrogens, 5-membered unsaturated → **1,3-diazole** (systematic); the retained name is imidazole.
4. **Pyrazole:** two adjacent nitrogens → **1,2-diazole**.
5. **Pyrrole:** one nitrogen, 5-membered unsaturated → **1H-azole** (retained name pyrrole; "1H" shows the hydrogen is on nitrogen at position 1).
6. **Furan:** systematic name **oxole** (retained name furan).
7. **Thiophene:** systematic name **thiole** (retained name thiophene).
8. **Pyridine:** systematic name **azine** (retained name pyridine).
9. **Piperidine:** saturated 6-membered N ring → **azinane** (retained name piperidine).
10. **Morpholine:** 6-membered ring with O and N at opposite corners → **1-oxa-4-azacyclohexane** (retained name morpholine).

Classification of Heterocyclic Compounds

A. By ring size:

- 3-membered: aziridine, oxirane (ethylene oxide), thiirane
- 4-membered: azetidine, oxetane, thietane
- 5-membered: pyrrole, furan, thiophene, oxazole, thiazole, imidazole, pyrazole
- 6-membered: pyridine, pyran, pyrimidine, piperidine, morpholine
- 7-membered: azepine, oxepine, thiepine

B. By number of heteroatoms: mono-hetero (pyrrole), di-hetero (imidazole, pyrimidine), tri-hetero (1,2,3-triazole), tetra-hetero (tetrazole).

C. By saturation: saturated (pyrrolidine, piperidine), partially unsaturated (pyrroline, dihydropyridine), fully unsaturated/aromatic (pyrrole, pyridine).

D. By aromatic character: aromatic (pyrrole, furan, thiophene, pyridine), non-aromatic (pyrrolidine, tetrahydrofuran), anti-aromatic (rare in pharmacy).

E. Fused vs non-fused: single ring (pyrrole) vs fused systems (indole = benzene fused to pyrrole; quinoline = benzene fused to pyridine) — Chapter 5.

Flowchart — How to Name a Heterocycle (Hantzsch–Widman)

1. Count the ring atoms → fixes the stem/ending from the table.
2. Identify heteroatoms → pick prefixes in priority order O > S > N.
3. Check double bonds → choose unsaturated or saturated ending.
4. Number the ring → heteroatoms get lowest locants; priority atom gets position 1.
5. Join the parts (elide "a" before a vowel) → write locants first.
6. Check whether a retained name exists (furan, pyrrole, thiophene, pyridine) — it may be used instead.

Infographic Concept Box — Chapter 1

Title: "Name That Ring in 3 Steps" **Layout:** Three connected panels. Panel 1: WHO — heteroatom badges O (oxa), S (thia), N (aza) in priority order. Panel 2: HOW BIG — ring-size ladder 3→7 with endings (-irene, -ete, -ole, -ine, -epine). Panel 3: WHERE — a numbered pentagon showing O at position 1, N at position 3, captioned "1,3-oxazole". Bottom strip: "O > S > N — Old Saints Never".

Tables

Table 1.1 — Heteroatom prefixes and priority

Heteroatom	Prefix	Priority
Oxygen (O)	oxa-	1st
Sulphur (S)	thia-	2nd
Nitrogen (N)	aza-	3rd
Phosphorus (P)	phospha-	4th

Table 1.2 — Retained names you must memorise

Systematic (Hantzsch–Widman)	Retained name	Ring
oxole	furan	5-membered, O
thiole	thiophene	5-membered, S
1H-azole	pyrrole	5-membered, N
azine	pyridine	6-membered, N
1,3-diazole	imidazole	5-membered, 2N
1,2-diazole	pyrazole	5-membered, 2N
1-oxa-4-azacyclohexane	morpholine	6-membered, O + N

Examples

- Pyridine in vitamin B3 (niacin) — a 6-membered N heterocycle.
- The thiazole ring in vitamin B1 (thiamine) and in penicillin antibiotics.
- The imidazole ring in the amino acid histidine.
- The pyrrole ring repeated four times in haem (haemoglobin) and chlorophyll.

Analogies

- A heterocycle is like a **committee**: mostly carbon members, but one or more "outsiders" (heteroatoms) sit on it — and the outsiders usually run the show (they decide the chemistry).
- Hantzsch–Widman naming is like an **address**: heteroatom = street name, ring size = house number block, saturation ending = city.

Pharmacy Relevance

Almost every modern drug contains at least one heterocyclic ring — the heteroatoms form hydrogen bonds with the drug's target in the body, which is why heterocycles are the backbone of medicinal chemistry. Naming them correctly is the first step to reading any drug structure.

India Context

Indian pharmacopoeia monographs and B.Pharm question papers routinely ask students to "name the heterocyclic ring present" in drugs like isoniazid (pyridine) or metronidazole (imidazole). The Hantzsch–Widman system is the language examiners expect.

Key Points

1. Heterocycle = ring with at least one non-carbon atom (N, O, S commonest).
2. Hantzsch–Widman name = heteroatom prefix + ring-size stem + saturation ending.
3. Priority order: O > S > N.
4. Heteroatoms get the lowest locants; the priority atom gets position 1.
5. Five-membered unsaturated ending is "-ole"; six-membered is "-ine".
6. Many rings keep old names: furan, pyrrole, thiophene, pyridine.

Common Confusions

- **Confusion:** "Oxazole and isoxazole are the same." **Clarification:** No — oxazole is 1,3-oxazole; isoxazole is 1,2-oxazole. The locants matter.
- **Confusion:** "The 'a' in aza/oxa/thia is always kept." **Clarification:** It is dropped before a vowel: aza + ole = azole, oxa + ole = oxole.
- **Confusion:** "Hantzsch–Widman is only for 5- and 6-membered rings." **Clarification:** It covers 3- to 10-membered rings; 5- and 6-membered are simply the commonest in pharmacy.

Common Mistakes

1. Numbering so that a carbon gets position 1 — heteroatoms always come first.
2. Writing "azaole" or "oxaole" — remember elision before vowels.
3. Giving O position 2 when N is present — O outranks N and takes position 1.

Mnemonics

- Prefix priority: "**O**ld **S**aints **N**ever" (O, S, N).
- Ring-size endings: "**I**rene **E**ats **O**range **I**ce-cream **E**very **O**ctober **N**ight" — irene, ete, ole, ine, epine… (3

Exam Summary

The Hantzsch–Widman system names heterocycles from heteroatom (oxa/thia/aza, priority O>S>N), ring size (3: -irene, 4: -ete, 5: -ole, 6: -ine, 7: -epine for unsaturated rings), and saturation. Heteroatoms take the lowest locants. Retained names (furan, pyrrole, thiophene, pyridine, imidazole, pyrazole, morpholine) are still officially allowed. Heterocycles are classified by ring size, number of heteroatoms, saturation, aromaticity, and fusion.

One-Minute Revision

- Heterocycle = ring with N/O/S.
- Name = prefix (O>S>N) + size stem + saturated/unsaturated ending.
- 5-unsaturated = -ole; 6-unsaturated = -ine; 7-unsaturated = -epine.
- Heteroatoms get lowest numbers; O gets position 1 over S and N.
- Elide "a" before vowels: azole, oxole.
- Retained: furan, pyrrole, thiophene, pyridine.

Exam Questions

Long answer:

1. Explain the Hantzsch–Widman system of nomenclature for heterocyclic compounds with suitable examples. (10 marks)
2. Classify heterocyclic compounds giving two examples of each class. (10 marks)

Short notes:

1. Write the priority order of heteroatoms with the corresponding prefixes.
2. Give the Hantzsch–Widman names of oxazole, thiazole, and piperidine.
3. What are retained names? Give four examples with structures.

MCQs:

1. In the Hantzsch–Widman system, the prefix for sulphur is: (a) oxa- (b) thia- (c) aza- (d) phospha- → **(b)**
2. The systematic name of pyrrole is: (a) azole (b) 1H-azole (c) azine (d) diazole → **(b)**
3. Which heteroatom gets position 1 in 1,3-thiazole? (a) N (b) S (c) C (d) either → **(b)** (S outranks N)
4. The unsaturated 7-membered N-heterocycle ending is: (a) -ine (b) -ole (c) -epine (d) -ete → **(c)**
5. Morpholine is systematically: (a) 1,4-oxazine (b) 1-oxa-4-azacyclohexane (c) 1,4-dioxane (d) piperazine → **(b)**

Viva:

1. Why is the "a" dropped in "azole"? (Elision before a vowel.)
2. Name one drug containing a pyridine ring. (Isoniazid / niacin.)
3. What is a locant?

Application-based:

1. A student names a 5-membered unsaturated ring with O at position 1 and N at position 2 as "1,3-oxazole". Correct the error and explain. (It is 1,2-oxazole, i.e., isoxazole — numbering must give the second heteroatom the lowest possible locant.)

Chapter 2 — Relative Aromaticity and Reactivity of Pyrrole, Furan, and Thiophene

Learning Objectives

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

1. Explain why pyrrole, furan, and thiophene are aromatic using Hückel's rule.
2. Show the orbital picture of each ring (where the 6 π electrons come from).
3. Arrange benzene, thiophene, pyrrole, and furan in order of aromaticity.
4. Arrange pyrrole, furan, thiophene, and benzene in order of reactivity toward electrophilic substitution.
5. Predict the preferred position of electrophilic attack (C-2 vs C-3) using resonance structures of the intermediate.

Definitions

- **Aromaticity:** A special stability shown by flat, cyclic, fully conjugated systems containing (4n + 2) π electrons (Hückel's rule). Aromatic compounds undergo substitution rather than addition, because substitution preserves the stable π system.
- **Hückel's rule:** A ring is aromatic if it is cyclic, planar, fully conjugated, and has (4n + 2) π electrons, where n = 0, 1, 2, … (2, 6, 10, … electrons).
- **π-Excessive heterocycle:** A heterocycle in which the heteroatom donates electrons into the π system, making the ring carbons electron-rich (pyrrole, furan, thiophene). These rings are attacked by electrophiles very easily.
- **π-Deficient heterocycle:** A heterocycle (like pyridine) in which the heteroatom withdraws electrons, making the ring electron-poor. (Contrast point for Chapter 5.)
- **Resonance (delocalisation) energy:** The extra stability of the real molecule compared with an imaginary molecule with localised double bonds. Larger value = more aromatic.
- **Wheland intermediate (σ-complex):** The positively charged intermediate formed when an electrophile adds to an aromatic ring during electrophilic substitution.

> **Simple explanation:** Benzene is the "gold standard" of aromatic stability. Pyrrole, furan, and thiophene each borrow the same trick — 6 π electrons in a flat ring — by letting the heteroatom's lone pair join the π cloud. But the heteroatom is greedier than carbon about holding its electrons, so the rings are *less* aromatic than benzene — and, paradoxically, *more* reactive toward electrophiles, because their carbons are electron-rich.

Terminology

- **Pyrrole-like nitrogen:** A nitrogen whose lone pair is part of the aromatic sextet (as in pyrrole, indole).
- **Pyridine-like nitrogen:** A nitrogen whose lone pair sits in an sp^2 orbital outside the π system and is available for bonding/protonation (as in pyridine).
- **α-position:** Carbon next to the heteroatom (C-2/C-5 in five-membered rings).
- **β-position:** Carbon one step away from the heteroatom (C-3/C-4).
- **Delocalisation:** Spreading of π electrons over the whole ring.

Explanation — The Orbital Picture

Pyrrole (C_4H_5N): Each carbon contributes one p electron (4 total). Nitrogen is sp^2 hybridised; its lone pair sits in the unhybridised p orbital and contributes 2 electrons. Total = 6 π electrons → aromatic (n = 1 in 4n + 2).

Furan (C_4H_4O): Same story — 4 electrons from carbons + 2 from one lone pair of oxygen (oxygen has two lone pairs; one is in the p orbital and joins the sextet, the other stays in an sp^2 orbital in the plane of the ring). Total = 6 π electrons → aromatic.

Thiophene (C_4H_4S): 4 electrons from carbons + 2 from a lone pair on sulphur in a p orbital. Total = 6 π electrons → aromatic. (Older books mention sulphur d-orbitals; the modern picture is the same lone-pair donation as furan.)

Textual diagram — the aromatic sextet: Imagine a pentagon. At each corner sits an atom. Draw a circle inside the pentagon (the delocalised π cloud). For pyrrole, label one corner "N–H" and note "lone pair joins the circle"; for furan, "O" with "one lone pair joins the circle"; for thiophene, "S" with "one lone pair joins the circle".

Relative Aromaticity

Measured by resonance (delocalisation) energies, approximately:

Compound	Resonance energy (approx.)	Aromaticity rank
Benzene	~36 kcal/mol	1 (most aromatic)
Thiophene	~29 kcal/mol	2
Pyrrole	~21 kcal/mol	3
Furan	~16 kcal/mol	4 (least aromatic)

Order of aromaticity: benzene > thiophene > pyrrole > furan.

Why? The heteroatom's electronegativity fights delocalisation: oxygen holds its lone pair tightest (least willing to share → furan least aromatic), sulphur's larger orbitals overlap well with carbon p orbitals (thiophene most aromatic of the three). Nitrogen is in between.

Key takeaway: More aromatic = more stable = *less* reactive. So the reactivity order is the exact reverse.

Relative Reactivity Toward Electrophilic Substitution

Order of reactivity: pyrrole > furan > thiophene > benzene.

- Pyrrole is enormously reactive — roughly 10^{17}–10^{21} times faster than benzene (values vary with the reaction; the point is "many orders of magnitude").
- Furan is roughly 10^{11} times faster than benzene.
- Thiophene is roughly 10^{5} times faster than benzene.

> **Simple explanation:** The heteroatom pumps electrons into the ring, making the carbons electron-hungry-targets for electrophiles (electron-seekers). The less the lone pair is tied up in aromatic stability, the more it activates the ring — so the least aromatic (furan, pyrrole) are the most reactive.

Practical consequence: Pyrrole and furan are so reactive that strong acids destroy them (pyrrole polymerises in strong acid; furan ring-opens). Their electrophilic substitutions must use mild conditions — a favourite exam trap.

Position of Attack — Why C-2 (α) Wins

When an electrophile E^+ attacks C-2 of pyrrole, the Wheland intermediate's positive charge can be spread over **three** resonance forms (charge on C-3/C-5 and on nitrogen). Attack at C-3 gives an intermediate with only **two** resonance forms. More resonance forms = more stable intermediate = faster reaction.

Textual diagram: Draw pyrrole; arrow from E^+ to C-2; show the σ-complex with + charge delocalised to C-3, C-5, and N (three structures). Below, draw attack at C-3 with only two resonance structures. Caption: "C-2 attack: 3 resonance forms (more stable) vs C-3 attack: 2 resonance forms."

The same logic holds for furan and thiophene: electrophiles go to the α-position (C-2; if C-2 is blocked, then C-5, the other α-position).

Flowchart — Predicting Reactivity and Orientation

1. Is the ring π-excessive (pyrrole/furan/thiophene)? → Yes: very reactive toward electrophiles.
2. Rank: pyrrole > furan > thiophene > benzene.
3. Electrophile attacks α-carbon (C-2) first — intermediate has most resonance forms.
4. If C-2 blocked → attack C-5 (other α); then C-3 (β).
5. Use mild conditions for pyrrole/furan (they polymerise or open in strong acid).

Infographic Concept Box — Chapter 2

Title: "The Aromaticity Seesaw" **Layout:** A seesaw diagram. Left side (high): "Aromaticity — benzene > thiophene > pyrrole > furan". Right side (high): "Reactivity — pyrrole > furan > thiophene > benzene". Centre pivot labelled "heteroatom lone pair". Bottom: three pentagon icons with "6 π e^-" badges and the note "O holds tightest → furan least aromatic, most jumpy".

Tables

Table 2.1 — Five-membered heterocycles at a glance

Property	Pyrrole	Furan	Thiophene
Formula	C_4H_5N	C_4H_4O	C_4H_4S
Heteroatom	N–H	O	S
π electrons	6 (lone pair on N)	6 (one lone pair on O)	6 (lone pair on S)
Resonance energy (approx.)	~21 kcal/mol	~16 kcal/mol	~29 kcal/mol
Reactivity vs benzene	Highest	High	Moderate
Behaviour with strong acid	Polymerises	Ring opens	Stable (can be sulphonated)
Preferred EAS position	C-2 (α)	C-2 (α)	C-2 (α)

Examples

- Pyrrole units linked together make **porphyrins** — the core of haemoglobin (carries oxygen in blood) and chlorophyll (captures sunlight).
- Furan derivatives appear in the drug **furosemide** and in **nitrofurazone**.
- Thiophene appears in **clopidogrel** (antiplatelet) and **cephaloridine** (antibiotic).

Analogies

- The heteroatom lone pair is like a **generous neighbour** who shares food (electrons) with the whole street (ring) — the street becomes lively (reactive), but the neighbour's own house becomes less secure (less aromatic).
- C-2 vs C-3 attack is like choosing the **wider bridge**: the C-2 intermediate spreads the positive charge over three resonance "lanes" instead of two.

Pharmacy Relevance

The π-excessive nature of pyrrole/furan/thiophene explains why drugs containing them are electron-rich and often metabolised by oxidation in the liver. It also explains formulation caution: furan-containing drugs can be acid-sensitive.

India Context

Pyrrole chemistry underpins the manufacture of **porphyrin-related diagnostics**, and thiophene chemistry is used in Indian bulk-drug units making clopidogrel — one of India's major cardiovascular exports.

Key Points

1. Pyrrole, furan, thiophene each have 6 π electrons (4 from carbons + 2 from the heteroatom lone pair) → aromatic by Hückel's rule.
2. Aromaticity: benzene > thiophene > pyrrole > furan.
3. Reactivity toward electrophiles is the reverse: pyrrole > furan > thiophene > benzene.
4. Electrophilic attack prefers C-2 (α) — the intermediate has three resonance forms.
5. Pyrrole polymerises in strong acid; furan ring-opens — use mild conditions.

Common Confusions

- **Confusion:** "More aromatic means more reactive." **Clarification:** The opposite — aromaticity is stability; the more stable ring reacts more slowly. Reactivity order is the reverse of aromaticity order.
- **Confusion:** "The nitrogen lone pair in pyrrole is basic like in amines." **Clarification:** No — it is part of the aromatic sextet. Protonating it would destroy aromaticity, so pyrrole is an extremely weak base.
- **Confusion:** "Oxygen in furan uses both lone pairs for aromaticity." **Clarification:** Only one lone pair joins the π system; the other stays in the ring plane.

Common Mistakes

1. Writing the reactivity order same as the aromaticity order.
2. Forgetting that furan needs mild, non-acidic conditions for EAS.
3. Drawing the electrophile attacking nitrogen — EAS happens on carbon (C-2).

Mnemonics

- Aromaticity: "**B**ig **T**igers **P**rowl **F**orests" — Benzene > Thiophene > Pyrrole > Furan.
- Reactivity: just reverse it — "**P**rowling **F**orests, **T**igers **B**ite" — Pyrrole > Furan > Thiophene > Benzene.

Exam Summary

Pyrrole, furan, and thiophene are 6π-electron aromatic heterocycles (Hückel's rule, n = 1), with the heteroatom lone pair completing the sextet. Aromaticity decreases benzene > thiophene > pyrrole > furan, while electrophilic substitution reactivity increases in the reverse order. Attack occurs preferentially at C-2 because the σ-complex has three resonance contributors. Pyrrole polymerises in strong acid and furan undergoes ring opening, so mild conditions are essential.

One-Minute Revision

- 6 π electrons each: 4 (carbons) + 2 (heteroatom lone pair).
- Aromaticity: B > T > P > F. Reactivity: P > F > T > B (reverse!).

Exam Questions

Long answer:

1. Explain the aromatic character of pyrrole, furan, and thiophene with orbital diagrams. Arrange them in order of aromaticity and reactivity, giving reasons. (10 marks)
2. Why does electrophilic substitution in pyrrole occur preferentially at C-2? Explain with resonance structures of the intermediate. (10 marks)

Short notes:

1. What are π-excessive heterocycles? Give two examples.
2. Why is pyrrole a very weak base although it contains nitrogen?
3. Compare the behaviour of pyrrole, furan, and thiophene towards strong acids.

MCQs:

1. The order of aromaticity is: (a) furan > pyrrole > thiophene (b) thiophene > pyrrole > furan (c) pyrrole > furan > thiophene (d) benzene < thiophene → **(b)**
2. Most reactive toward electrophilic substitution: (a) benzene (b) thiophene (c) furan (d) pyrrole → **(d)**
3. How many π electrons make pyrrole aromatic? (a) 4 (b) 5 (c) 6 (d) 8 → **(c)**
4. Electrophilic attack on furan occurs mainly at: (a) C-3 (b) C-2 (c) oxygen (d) C-4 → **(b)**
5. Which is π-deficient? (a) pyrrole (b) furan (c) thiophene (d) pyridine → **(d)**

Viva:

1. What is Hückel's rule? Apply it to thiophene.
2. Why does pyrrole undergo polymerisation in strong acid?
3. Define the Wheland intermediate.

Application-based:

1. Two bottles contain pyrrole and pyridine. Using only dilute HCl, how would you distinguish them? (Pyridine dissolves forming a soluble salt — its lone pair is available; pyrrole does not form a stable salt and may darken/polymerise — its lone pair is tied up in aromaticity.)

References

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Chapter 3 — Synthesis, Electrophilic Substitution Mechanisms, and Medicinal Uses of Pyrrole, Furan, and Thiophene

Learning Objectives

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

1. Write the Paal–Knorr synthesis of pyrrole with mechanism.
2. Write the Feist–Bénary synthesis of furan with mechanism.
3. Write the Hinsberg synthesis of thiophene with mechanism.
4. Write stepwise mechanisms for electrophilic substitution (nitration, sulphonation, halogenation, Friedel–Crafts acylation) of pyrrole, furan, and thiophene.
5. Name the medicinal uses of ethosuximide, procyclidine, furosemide, nitrofurazone, cephaloridine, and clopidogrel.

Definitions

- **Paal–Knorr synthesis:** Formation of a pyrrole by heating a 1,4-dicarbonyl compound (e.g., hexane-2,5-dione) with ammonia or a primary amine.
- **Feist–Bénary synthesis:** Formation of a substituted furan from an α-haloketone and a β-ketoester in the presence of base.
- **Hinsberg synthesis (thiophene):** Formation of a thiophene derivative by base-catalysed condensation of a 1,2-dicarbonyl compound (e.g., glyoxal) with diethyl thiodiglycolate (diethyl 2,2'-thiodiacetate).
- **Electrophilic substitution:** Replacement of a ring hydrogen by an electrophile (E^+) via a positively charged σ-complex, restoring aromaticity at the end.

> **Simple explanation:** Each synthesis follows the same plot: take an open-chain molecule that already has the right atoms in the right order, then "zip it up" into a ring and throw out small molecules (water, alcohol) to become aromatic. Paal–Knorr zips a 1,4-diketone with an amine into pyrrole; Feist–Bénary zips a haloketone with a keto-ester into furan; Hinsberg zips a 1,2-diketone with a sulphur-containing diester into thiophene.

Terminology

- **1,4-Dicarbonyl compound:** A molecule with two C=O groups separated by two carbons (O=C–C–C–C=O), e.g., hexane-2,5-dione (acetonylacetone).
- **α-Haloketone:** A ketone with a halogen on the carbon next to the C=O (e.g., phenacyl bromide, Ph–CO–CH_2Br).
- **β-Ketoester:** An ester with a ketone two carbons away (e.g., ethyl acetoacetate, CH_3–CO–CH_2–COOEt).
- **Enolate:** A negatively charged species formed by removing a proton next to a carbonyl group; a strong nucleophile.
- **σ-Complex (Wheland intermediate):** The cationic intermediate in electrophilic substitution.

3A. Paal–Knorr Pyrrole Synthesis — Mechanism (Numbered Steps)

Reaction: hexane-2,5-dione (CH_3–CO–CH_2–CH_2–CO–CH_3) + R–NH_2 (amine or ammonia), heat → N-substituted pyrrole + 2 H_2O.

Step 1: The amine nitrogen attacks one carbonyl carbon of the diketone → a hemiaminal (C–OH with N attached). **Step 2:** Loss of water (dehydration) from the hemiaminal → an imine (C=N). **Step 3:** The imine nitrogen attacks the second carbonyl carbon intramolecularly (ring closure) → a cyclic hemiaminal (5-membered ring). **Step 4:** Dehydration of the cyclic hemiaminal → a dihydropyrrole. **Step 5:** Tautomerisation/dehydration (loss of the second water) → the fully aromatic pyrrole ring. Aromaticity is the driving force.

Conditions: Heating, often with a trace of acid catalyst. With ammonia → pyrrole itself (N–H); with a primary amine R–NH_2 → N-alkyl/N-aryl pyrrole.

Key takeaway: 1,4-diketone + amine → pyrrole + 2 H_2O. Count atoms: the two carbonyl carbons and the two middle carbons become the ring carbons; the amine nitrogen becomes the ring nitrogen.

3B. Feist–Bénary Furan Synthesis — Mechanism (Numbered Steps)

Reaction: α-haloketone (e.g., phenacyl bromide, Ph–CO–CH_2Br) + β-ketoester (e.g., ethyl acetoacetate) + base (pyridine) → substituted furan.

Step 1: Base removes the acidic proton between the two carbonyls of the β-ketoester → enolate ion. **Step 2:** The enolate carbon attacks the CH_2Br carbon of the α-haloketone (SN2), displacing bromide → a 1,4-dicarbonyl compound. **Step 3:** Intramolecular attack: the enol form of one carbonyl attacks the other carbonyl → ring closure to a cyclic hemiacetal-like intermediate (5-membered). **Step 4:** Dehydration (loss of water) → the aromatic furan ring.

Conditions: Mild base (pyridine is the classic choice), gentle heating.

Key takeaway: Haloketone + keto-ester + base → furan. The oxygen of the furan comes from one of the carbonyl oxygens.

3C. Hinsberg Thiophene Synthesis — Mechanism (Numbered Steps)

Reaction: glyoxal (OHC–CHO, a 1,2-diketone) + diethyl thiodiglycolate (EtOOC–CH_2–S–CH_2–COOEt) + sodium ethoxide (base) → diethyl 3-hydroxythiophene-2,5-dicarboxylate.

Step 1: Base abstracts a proton from the CH_2 next to sulphur → enolate (carbanion stabilised by the ester). **Step 2:** The enolate attacks one aldehyde carbon of glyoxal → new C–C bond (aldol-type addition). **Step 3:** A second enolate (on the other CH_2–S arm) attacks the second aldehyde carbon → ring closure to a 5-membered sulphur ring. **Step 4:** Elimination of water (dehydration) → aromatisation to the thiophene ring (isolated as the 3-hydroxy diester, which exists mainly in the aromatic hydroxy form).

Note: The 3-hydroxy group can later be removed (convert –OH to –Cl, then reduce) to give the parent thiophene-2,5-diester if needed.

Key takeaway: 1,2-diketone + S-containing diester + base → thiophene. The sulphur atom in the product comes from the thiodiglycolate reagent.

Comparison Table — The Three Syntheses

Feature	Paal–Knorr (pyrrole)	Feist–Bénary (furan)	Hinsberg (thiophene)
Starting materials	1,4-diketone + amine/NH_3	α-haloketone + β-ketoester	1,2-diketone + diethyl thiodiglycolate
Key reagent/condition	Heat (± acid)	Base (pyridine)	Base (NaOEt)
Heteroatom source	The amine nitrogen	A carbonyl oxygen	The sulphide sulphur
By-products	2 H_2O	HBr + H_2O (as salts)	2 H_2O
Product	N-substituted pyrrole	Substituted furan	3-hydroxythiophene-2,5-diester

3D. Mechanisms of Electrophilic Substitution

General mechanism (all three rings), numbered steps: Step 1: The π electrons of the ring (richest at C-2) attack the electrophile E^+ → a σ-complex (Wheland intermediate) with the positive charge delocalised over C-3, C-5, and the heteroatom (three resonance forms). **Step 2:** A base removes the proton from the carbon bearing E → the double bonds reform → aromaticity is restored. Product: 2-substituted heterocycle.

Textual diagram: Pyrrole + E^+ → [σ-complex, + charge shared by three resonance structures] → ($-H^+$) → 2-E-pyrrole. Show the three resonance forms of the intermediate with the + on C-3, C-5, and N.

Pyrrole — typical reactions (mild conditions!):

- Nitration: HNO_3 in acetic anhydride, low temperature → 2-nitropyrrole.
- Sulphonation: pyridine–SO_3 complex → pyrrole-2-sulphonic acid (conc. H_2SO_4 would polymerise pyrrole — exam trap).
- Halogenation: Br_2 in acetic acid → bromopyrroles (excess gives polybromo products).
- Friedel–Crafts acylation: $(CH_3CO)_2O$ with $SnCl_4$ → 2-acetylpyrrole ($AlCl_3$ with RCOCl is too harsh — causes polymerisation).
- Gattermann formylation: HCN/HCl (or DMF/$POCl_3$) → pyrrole-2-carbaldehyde.

Furan — typical reactions (mild, non-acidic conditions!):

- Nitration: HNO_3/acetic anhydride → 2-nitrofuran.
- Sulphonation: SO_3–pyridine complex → furan-2-sulphonic acid.
- Friedel–Crafts acylation: $(CH_3CO)_2O/BF_3$ → 2-acetylfuran.
- Diels–Alder: furan acts as a diene with maleic anhydride → oxabicyclic adduct (shows its lower aromaticity — benzene does not do this).

Thiophene — typical reactions (tolerates stronger conditions):

- Nitration: fuming HNO_3/acetic anhydride → 2-nitrothiophene.
- Sulphonation: conc. H_2SO_4 → thiophene-2-sulphonic acid (thiophene survives strong acid).
- Bromination: Br_2/acetic acid → 2-bromothiophene → 2,5-dibromothiophene.
- Friedel–Crafts acylation: RCOCl/$AlCl_3$ → 2-acylthiophene (thiophene tolerates $AlCl_3$).
- Desulphurisation: Raney nickel → the sulphur is removed as NiS, giving the corresponding alkane (used in structure proof).

3E. Medicinal Uses of Drugs Containing Pyrrole, Furan, and Thiophene

Drug	Heterocycle present	Class	Medicinal use (simple words)
Ethosuximide	Pyrrole ring (as reduced pyrrolidine/succinimide)	Anti-absence-seizure (antiepileptic)	Treats absence seizures ("petit mal" — brief staring spells) in epilepsy; blocks T-type calcium channels in the thalamus
Procyclidine	Pyrrole ring (pyrrolidine)	Anticholinergic, antiparkinsonian	Treats Parkinson's disease symptoms (tremor, rigidity); blocks muscarinic receptors
Furosemide	Furan ring	Loop diuretic	Removes excess water ("water tablet") in heart failure, swelling (oedema), and high blood pressure; blocks the Na^+–K^+–$2Cl^-$ transporter in the kidney's loop of Henle
Nitrofurazone	Furan ring (nitrofuran)	Topical antibacterial	Applied on burns, wounds, and skin infections to kill bacteria; the nitro group generates bacteria-damaging species
Cephaloridine	Thiophene ring	Cephalosporin antibiotic (1st generation)	Treats bacterial infections by blocking cell-wall synthesis; contains a thienyl side chain
Clopidogrel	Thiophene ring (fused thienopyridine)	Antiplatelet	Prevents blood clots after heart attack/stroke; blocks the platelet ADP (P2Y12) receptor

Simple explanation of each drug's link to the chapter:

- **Ethosuximide** = a pyrrole that has been "calmed down" (reduced to pyrrolidine-2,5-dione, a succinimide). The ring you studied as aromatic pyrrole appears here in saturated form, calming abnormal brain electrical activity.
- **Procyclidine** carries a pyrrolidine ring attached to a bulky alcohol — the nitrogen-containing ring helps it block acetylcholine receptors, reducing Parkinsonian tremor.
- **Furosemide** hides a furan ring in its structure (the furfuryl group) — the same furan whose reactivity you studied; in the body it rides to the kidney and forces out salt and water.
- **Nitrofurazone** = 5-nitrofurfural semicarbazone — a furan with a nitro group; bacteria reduce the nitro group into toxic fragments that destroy bacterial DNA.
- **Cephaloridine** = a cephalosporin with a thiophene (2-thienyl) side chain — the stable thiophene ring survives in the body while the β-lactam part kills bacteria.
- **Clopidogrel** = a thienopyridine (thiophene fused to pyridine); the liver converts it to the active form, which permanently blocks platelet clumping.

Infographic Concept Box — Chapter 3

Title: "Three Rings, Three Recipes" **Layout:** Three vertical recipe cards. Card 1 (Pyrrole): ingredients "1,4-diketone + amine", method "heat, $-2H_2O$" → pyrrole icon. Card 2 (Furan): "α-haloketone + β-ketoester", "base, $-H_2O$" → furan icon. Card 3 (Thiophene): "1,2-diketone + S-diester", "base, $-H_2O$" → thiophene icon. Bottom banner: "E^+ always goes to C-2 (α) — 3 resonance forms beat 2". Side strip: six drug badges (ethosuximide, procyclidine, furosemide, nitrofurazone, cephaloridine, clopidogrel) matched to their ring.

Flowchart — Electrophilic Substitution of Five-Membered Heterocycles

1. Identify the ring: pyrrole / furan / thiophene (all π-excessive).
2. Choose mild conditions (pyrrole, furan) or normal conditions (thiophene).
3. E^+ attacks C-2 → σ-complex with 3 resonance forms.

Examples (reactions to memorise)

1. Pyrrole + $(CH_3CO)_2O/SnCl_4$ → 2-acetylpyrrole.
2. Furan + maleic anhydride → Diels–Alder adduct (oxabicyclo compound).
3. Thiophene + Br_2/AcOH → 2-bromothiophene.
4. Pyrrole + HNO_3/Ac_2O (cold) → 2-nitropyrrole.
5. Thiophene + conc. H_2SO_4 → thiophene-2-sulphonic acid.

Analogies

- The Paal–Knorr synthesis is like **closing a bracelet**: the 1,4-diketone is the open chain, the amine is the clasp, and heating snaps it shut into a ring.
- The σ-complex is like a **hot potato** (positive charge) passed between three players (resonance forms) — the more players, the cooler each one stays, so C-2 attack (3 players) wins.

Pharmacy Relevance

These three syntheses are textbook models for how heterocyclic drug scaffolds are built in industry. The drug examples show that the same rings appear in epilepsy, Parkinson's, heart-failure, infection, and clot-prevention medicines — heterocycles are truly everywhere in the pharmacy.

India Context

- **Clopidogrel** is manufactured in large volumes by Indian generic companies and is a mainstay after cardiac stenting in Indian hospitals.
- **Furosemide** (Lasix) is on India's essential medicines list and is among the most prescribed diuretics in Indian practice.
- **Nitrofurazone** ointment is still found in Indian first-aid and burn-care kits.

Key Points

1. Paal–Knorr: 1,4-diketone + amine → pyrrole + $2H_2O$ (heat).
2. Feist–Bénary: α-haloketone + β-ketoester + base → furan.
3. Hinsberg: 1,2-diketone + diethyl thiodiglycolate + base → thiophene derivative.
4. EAS mechanism: E^+ attacks C-2 → σ-complex (3 resonance forms) → $-H^+$ → 2-substituted product.
5. Pyrrole/furan need mild conditions (acid destroys them); thiophene tolerates strong acid and $AlCl_3$.
6. Drugs: ethosuximide (absence seizures), procyclidine (Parkinson's), furosemide (diuretic), nitrofurazone (topical antibacterial), cephaloridine (antibiotic), clopidogrel (antiplatelet).

Common Confusions

- **Confusion:** "Feist–Bénary makes pyrrole." **Clarification:** Feist–Bénary makes **furan**; Paal–Knorr makes **pyrrole**. (Both are "named chemist" syntheses — learn them as a pair.)
- **Confusion:** "Hinsberg synthesis is for pyrrole." **Clarification:** The Hinsberg *thiophene* synthesis makes thiophene (there is also a Hinsberg test for amines — a different reaction).
- **Confusion:** "Friedel–Crafts acylation of pyrrole uses $AlCl_3$." **Clarification:** $AlCl_3$ polymerises pyrrole; use milder $(CH_3CO)_2O/SnCl_4$. Thiophene, however, tolerates $AlCl_3$.

Common Mistakes

1. Writing the electrophile attacking the heteroatom instead of C-2.
2. Forgetting the 2 molecules of water lost in Paal–Knorr.
3. Using conc. H_2SO_4 for pyrrole sulphonation (use pyridine–SO_3 instead).

Mnemonics

- Syntheses: "**P**aal makes **P**yrrole; **F**eist makes **F**uran; **H**insberg makes **T**hiophene" (H→T is the odd one — remember "Hinsberg's **T**").
- Drugs: "**E**very **P**atient **F**eels **N**ew **C**ourage **C**oming" — Ethosuximide, Procyclidine, Furosemide, Nitrofurazone, Cephaloridine, Clopidogrel.

Exam Summary

Pyrrole is made by the Paal–Knorr synthesis (1,4-diketone + amine, heat, –2H_2O), furan by the Feist–Bénary reaction (α-haloketone + β-ketoester, base), and thiophene by the Hinsberg synthesis (1,2-diketone + diethyl thiodiglycolate, base). All three undergo electrophilic substitution preferentially at C-2 via a σ-complex with three resonance forms; pyrrole and furan require mild conditions. Medicinal examples: ethosuximide and procyclidine (pyrrole), furosemide and nitrofurazone (furan), cephaloridine and clopidogrel (thiophene).

One-Minute Revision

- Paal–Knorr → pyrrole (1,4-diketone + amine).
- Feist–Bénary → furan (haloketone + ketoester + base).
- Hinsberg → thiophene (1,2-diketone + S-diester + base).
- EAS: E^+ → C-2 → σ-complex (3 forms) → –H^+.
- Mild conditions for pyrrole/furan; thiophene is tougher.
- Drugs: ethosuximide, procyclidine | furosemide, nitrofurazone | cephaloridine, clopidogrel.

Exam Questions

Long answer:

1. Describe the Paal–Knorr, Feist–Bénary, and Hinsberg syntheses with mechanisms. (10 marks)
2. Discuss the mechanism of electrophilic substitution in pyrrole, furan, and thiophene with two examples each. (10 marks)

Short notes:

1. Write the mechanism of the Paal–Knorr pyrrole synthesis.
2. Why are mild conditions necessary for electrophilic substitution of pyrrole and furan?
3. Give the medicinal uses of any two drugs containing a thiophene ring.
4. Write the synthesis of furan by the Feist–Bénary reaction.

MCQs:

1. Paal–Knorr synthesis uses: (a) 1,2-diketone + amine (b) 1,4-diketone + amine (c) haloketone + ketoester (d) diketone + hydrazine → **(b)**
2. Feist–Bénary reaction gives: (a) pyrrole (b) furan (c) thiophene (d) pyridine → **(b)**
3. Hinsberg thiophene synthesis uses diethyl thiodiglycolate and: (a) an amine (b) a 1,2-diketone (c) a haloketone (d) hydrazine → **(b)**
4. Nitration of pyrrole is carried out with: (a) conc. HNO_3/H_2SO_4 (b) HNO_3 in acetic anhydride at low temperature (c) KNO_3/heat (d) N_2O_5 → **(b)**
5. Furosemide is a: (a) antibiotic (b) loop diuretic (c) antiplatelet (d) antiepileptic → **(b)**
6. Clopidogrel contains which heterocycle? (a) pyrrole (b) furan (c) thiophene (d) pyridine only → **(c)** (thienopyridine — thiophene fused to pyridine)

Viva:

1. What is the driving force of the Paal–Knorr synthesis? (Formation of the aromatic pyrrole ring.)
2. Why does furan undergo Diels–Alder reaction but benzene does not? (Furan is less aromatic; it can act as a diene.)
3. Name the heterocycle in nitrofurazone and its use.

Application-based:

1. A student tries Friedel–Crafts acylation of pyrrole using $CH_3COCl/AlCl_3$ and gets a black tar instead of 2-acetylpyrrole. Explain what went wrong and suggest correct conditions. ($AlCl_3$ is a strong Lewis acid that polymerises pyrrole; use $(CH_3CO)_2O$ with $SnCl_4$ under mild conditions.)

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