

BP305T · UNIT I

BP305T Heterocyclic Compounds and Stereochemistry

Unit I — Carboxylic Acids, Amines, Phenols & Polynuclear Hydrocarbons

B.Pharm Semester III · Theory Notes
From-zero, exam-oriented study guide

Pills & Python
Pharmacy • Data • AI • Healthcare

CHAPTER 1 — Carboxylic Acids

1.1 Learning Objectives

After studying this chapter you will be able to:

- Define carboxylic acids and identify the carboxyl (–COOH) group.
- Write the methods to prepare aliphatic and aromatic carboxylic acids (oxidation of alcohols, carbonation of Grignard reagent, Kolbe–Schmidt reaction).
- Explain why carboxylic acids are acidic and how substituents change acidity.
- Draw the complete mechanism of nucleophilic acyl substitution, decarboxylation and the Hell–Volhard–Zelinsky (HVZ) reaction.
- List the pharmaceutical applications of benzoic acid, salicylic acid and acetylsalicylic acid (aspirin).

1.2 Definitions

Carboxylic acid: An organic compound that contains the carboxyl group, written as –COOH or $-CO_2H$. Example: CH_3COOH (acetic acid, the acid in vinegar).

Aliphatic carboxylic acid: A carboxylic acid in which the –COOH group is attached to a chain (alkyl group). Example: CH_3CH_2COOH (propanoic acid).

Aromatic carboxylic acid: A carboxylic acid in which the –COOH group is directly attached to a benzene ring. Example: C_6H_5COOH (benzoic acid).

1.3 Terminology You Must Know

- **Carboxyl group (–COOH):** carbon double-bonded to oxygen (=O) and single-bonded to an –OH group.
- **Carbonyl carbon:** the C atom of C=O. It is electron-hungry (electrophilic) because oxygen pulls electrons away from it.
- **Nucleophilic acyl substitution:** a reaction in which a nucleophile replaces the –OH part of the –COOH group.
- **Acyl group:** R–C(=O)–, the –COOH group minus its –OH.
- **Decarboxylation:** removal of CO_2 from a carboxylic acid.
- **Grignard reagent:** an organomagnesium compound, written R–Mg–Br (or R–Mg–X). It acts as a source of R^- (a carbon nucleophile).

1.4 Explanation — What Makes Carboxylic Acids Special

A carboxylic acid has two oxygen atoms joined to one carbon. The carbon is "electron-hungry" because both oxygens pull electrons toward themselves. The –OH hydrogen is easily given up as H^+, so carboxylic acids are much stronger acids than alcohols. When the acid loses H^+, the negative charge on the remaining $-COO^-$ (carboxylate ion) is shared between the two oxygen atoms — this sharing is called **resonance**, and it makes the negative ion very stable. A stable negative ion means the acid gives up its H^+ readily.

1.5 Classification

1. **Aliphatic carboxylic acids** — saturated (formic acid, acetic acid, butyric acid) and unsaturated (acrylic acid).
2. **Aromatic carboxylic acids** — benzoic acid, salicylic acid, cinnamic acid.
3. **Dicarboxylic acids** — two –COOH groups (oxalic acid, succinic acid). Not in syllabus detail but good to recognise.

1.6 Methods to Prepare Carboxylic Acids

Method 1: Oxidation of Alcohols

- **Technical concept:** A primary alcohol, on strong oxidation, first becomes an aldehyde and then a carboxylic acid.
- **Simple explanation:** Think of it as burning off the two hydrogens on the –CH_2OH carbon and replacing them with a double bond to oxygen.
- **Reagents:** $K_2Cr_2O_7/H_2SO_4$ (potassium dichromate in sulphuric acid) or $KMnO_4$ (potassium permanganate), heat.
- **Example:** CH_3CH_2OH (ethanol) → CH_3CHO (acetaldehyde) → CH_3COOH (acetic acid).

Method 2: Carbonation of Grignard Reagent

- **Technical concept:** A Grignard reagent (R–Mg–Br) reacts with dry ice (solid CO_2), then with dilute acid, to give R–COOH. The carbon skeleton grows by ONE carbon.
- **Simple explanation:** The Grignard reagent is "angry carbon" — it attacks the carbon of CO_2 and sticks to it, adding one extra carbon to the chain.
- **Example:** CH_3–Mg–Br + CO_2 → CH_3–COO^-Mg^+Br → (H_3O^+) → CH_3COOH.
- **Key takeaway:** This method increases the carbon chain by exactly one carbon. Very popular exam question.

Method 3: Kolbe–Schmidt Reaction

- **Technical concept:** Sodium phenoxide ($C_6H_5O^-Na^+$) reacts with CO_2 under pressure at about 125 °C to give sodium salicylate, which on acidification gives salicylic acid (o-hydroxybenzoic acid).
- **Simple explanation:** CO_2 is pushed into the phenol ring at the ortho position using high pressure, like squeezing toothpaste into a tube.
- **Example:** C_6H_5ONa + CO_2 (125 °C, pressure) → o-HOC_6H_4COONa → (H^+) → salicylic acid.
- **Pharmacy relevance:** This is the industrial route to salicylic acid, the starting material for aspirin.

Flowchart — Which Method to Use?

```
Start: what do you have?
  ├─ Primary alcohol ──→ Strong oxidation → Carboxylic acid (same number of carbons)
  ├─ Alkyl halide ──→ make Grignard (Mg, dry ether) → add CO₂ → dilute acid → acid with ONE extra
carbon
  └─ Phenol ──→ NaOH (sodium phenoxide) → CO₂, pressure, 125 °C → salicylic acid
```

1.7 Acidity of Carboxylic Acids and Effect of Substituents

- Carboxylic acids (pKa ≈ 4–5) are far stronger acids than alcohols (pKa ≈ 16) because the carboxylate ion is stabilised by resonance.
- **Electron-withdrawing groups** (e.g., –Cl, $–NO_2$, –F) pull electrons toward themselves, stabilise the negative carboxylate ion, and **increase** acidity. Effect is strongest at the alpha position and weakens with distance.
- **Electron-donating groups** (e.g., $–CH_3$, alkyl groups) push electrons, destabilise the carboxylate ion, and **decrease** acidity.
- **Order of acidity (memorise):** $ClCH_2COOH > FCH_2COOH > BrCH_2COOH > CH_3COOH > CH_3CH_2COOH$. (Cl > F in this list because of the balance of inductive and size effects — learn the order as given.)
- **Example:** Chloroacetic acid ($ClCH_2COOH$) is about 100 times stronger than acetic acid.
- **Analogy:** Think of the negative charge as a hot potato — electron-withdrawing groups help spread it out (stable), electron-donating groups pile more heat on it (unstable).

1.8 Mechanisms of Chemical Reactions

Reaction 1: Nucleophilic Acyl Substitution (the master mechanism)

- **Technical concept:** The –OH of –COOH is replaced by a nucleophile (Nu^-) in two steps: addition of Nu^- to the carbonyl carbon, then elimination of –OH.
- **Numbered mechanism steps:**

1. The nucleophile attacks the electron-hungry carbonyl carbon; the C=O π-bond breaks and electrons move onto oxygen, forming a tetrahedral intermediate (carbon now has four single bonds).
2. The oxygen regains its double bond (C=O reforms), pushing out the leaving group $–OH^-$.
3. Overall: $R–COOH + Nu^- \rightarrow R–CO–Nu + OH^-$.

- **Key takeaway:** This one mechanism explains esterification (Nu = ROH → ester), amide formation (Nu = NH_3 → amide) and acid-chloride formation.

Reaction 2: Decarboxylation

- **Technical concept:** Heating a carboxylic acid (especially with soda lime, NaOH + CaO) removes CO_2 and leaves the alkane: $R–COOH \rightarrow R–H + CO_2$.
- **Numbered mechanism steps:**

1. The sodium salt $R–COO^-Na^+$ is heated with soda lime.
2. The C–C bond between R and $–COO^-$ breaks; the electron pair stays with R, giving a carbanion R^-.
3. R^- takes a proton (H^+) from the medium → R–H; CO_2 is released.

- **Example:** $CH_3COONa + NaOH/CaO$ (heat) → $CH_4 + Na_2CO_3$.
- **Key takeaway:** Carbon chain decreases by one carbon — the exact opposite of the Grignard carbonation method.

Reaction 3: Hell–Volhard–Zelinsky (HVZ) Reaction

- **Technical concept:** A carboxylic acid with at least one alpha-hydrogen reacts with Br_2 or Cl_2 in the presence of red phosphorus to give an ALPHA-halo acid.
- **Numbered mechanism steps:**

1. The acid first reacts with phosphorus to form the acid halide $R–CH_2–COBr$.
2. The acid halide enolises (forms a C=C between alpha carbon and carbonyl carbon).
3. Br_2 adds to the enol double bond at the alpha carbon.
4. Water work-up gives the alpha-bromo carboxylic acid, R–CHBr–COOH.

- **Example:** $CH_3COOH + Br_2$ / red P → $BrCH_2COOH$ (bromoacetic acid).
- **Key takeaway:** HVZ puts halogen ONLY on the alpha carbon — nowhere else.

1.9 Pharmaceutical Applications of Aromatic Carboxylic Acids

Drug	Structure type	Use
Benzoic acid	C_6H_5COOH	Preservative in foods, syrups and ointments (antifungal/antimicrobial)
Salicylic acid	o-HOC_6H_4COOH	Keratolytic (removes warts, corns, calluses); antifungal
Acetylsalicylic acid (Aspirin)	o-$CH_3COOC_6H_4COOH$	Analgesic, antipyretic, anti-inflammatory, antiplatelet

- **Aspirin synthesis:** Salicylic acid + acetic anhydride → acetylsalicylic acid (the phenolic –OH is acetylated).
- **India context:** Aspirin is one of the cheapest and most widely used drugs in Indian pharmacies; salicylic acid ointments are common dermatological preparations.

1.10 Infographic Concept Box — "Carboxylic Acids in One Picture"

Centre: –COOH group. Three arrows out: (1) PREPARE: oxidation of 1° alcohol / Grignard + CO_2 (+1 C) / Kolbe–Schmidt (phenol + CO_2 → salicylic acid). (2) ACIDITY: EWG ↑ acidity, EDG ↓ acidity; $ClCH_2COOH$ > CH_3COOH. (3) REACT: nucleophilic acyl substitution (ester/amide) / decarboxylation (−CO_2, −1 C) / HVZ (α-halogenation). Bottom strip: benzoic acid = preservative; salicylic acid = wart remover; aspirin = pain/fever/clot.

1.11 Common Confusions / Mistakes / Mnemonics

- **Confusion:** Kolbe–Schmidt (phenoxide + CO_2 → salicylic acid) vs Kolbe's electrolytic method (different reaction — electrolysis of carboxylate salts). Do not mix them.
- **Mistake:** HVZ halogenates the ALPHA carbon only, not the ring.
- **Mistake:** Decarboxylation shortens the chain; Grignard carbonation lengthens it. Remember as "CO_2 in, CO_2 out."
- **Mnemonic for acidity order:** "Chlorine First, Fluorine Follows, Bromine Behind" (Cl > F > Br > H > CH_3 at alpha position).

1.12 Exam Summary & One-Minute Revision

- 3 preparations: oxidation of 1° alcohol, Grignard + CO_2 (+1 carbon), Kolbe–Schmidt (salicylic acid from phenol).
- Acidity: EWG increases, EDG decreases; alpha position strongest effect.
- 3 mechanisms: nucleophilic acyl substitution (addition–elimination), decarboxylation (–CO_2, soda lime), HVZ (α-bromination via red P).
- Drugs: benzoic acid (preservative), salicylic acid (keratolytic), aspirin (analgesic/antiplatelet, made by acetylating salicylic acid).

1.13 Exam Questions

Short: 1. Why is chloroacetic acid stronger than acetic acid? 2. What is the product of CH_3COOH with Br_2/red P? 3. Name the reagent for decarboxylation. **Long:** 1. Describe three methods of preparation of carboxylic acids with equations. 2. Explain the mechanism of nucleophilic acyl substitution and HVZ reaction. 3. Discuss the effect of substituents on the acidity of carboxylic acids. **MCQs:** 1. Kolbe–Schmidt reaction gives: (a) benzoic acid (b) salicylic acid (c) aspirin (d) phenol → (b). 2. HVZ reaction introduces halogen at: (a) ring (b) alpha carbon (c) beta carbon (d) –OH → (b). 3. Carbonation of Grignard reagent increases the chain by: (a) 0 (b) 1 (c) 2 (d) 3 carbons → (b). **Viva:** Why is the carboxylate ion stable? What is soda lime? **Application-based:** A student wants to convert ethanol to propanoic acid. Which method will you suggest and why?

1.14 References

1. Finar, I. L. *Organic Chemistry, Vol. 1.* Pearson Education.
2. Bahl, B. S. and Bahl, A. *Textbook of Organic Chemistry.* S. Chand.
3. Smith, M. B. and March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure.* Wiley.

CHAPTER 2 — Amines

2.1 Learning Objectives

- Define amines and classify them as primary, secondary and tertiary.
- Write the methods to prepare amines (reduction of nitro compounds, reduction of nitriles, Hofmann degradation of amides).
- Explain basicity of amines and the effect of substituents on basicity (aliphatic vs aromatic).
- Draw the mechanism of diazonium salt formation and its synthetic applications (Sandmeyer reaction, azo-dye coupling).

2.2 Definitions

Amine: An organic compound derived from ammonia (NH_3) by replacing one or more hydrogens with alkyl or aryl groups. Example: CH_3NH_2 (methylamine).

Aliphatic amine: The nitrogen is attached to alkyl chains. Example: $C_2H_5NH_2$ (ethylamine). **Aromatic amine:** The nitrogen is directly attached to a benzene ring. Example: $C_6H_5NH_2$ (aniline).

2.3 Terminology

- **Primary (1°) amine:** R–NH_2 (one carbon attached to N).
- **Secondary (2°) amine:** R_2NH (two carbons attached to N).
- **Tertiary (3°) amine:** R_3N (three carbons attached to N).
- **Diazonium salt:** Ar–$N_2^+X^-$ (e.g., $C_6H_5N_2^+Cl^-$), formed from a primary aromatic amine + $NaNO_2$/HCl at 0–5 °C.
- **Basicity:** the ability to accept a proton (H^+). A stronger base holds the proton more tightly.

2.4 Explanation — Why Amines Are Basic

Nitrogen has a lone pair of electrons (a pair not used in bonding). This lone pair can grab a proton (H^+), so amines act as bases: $R_3N + H^+ \rightarrow R_3NH^+$. Anything that makes the lone pair more available increases basicity; anything that pulls it away (into a benzene ring, or toward an electron-withdrawing group) decreases basicity.

2.5 Methods to Prepare Amines

Method 1: Reduction of Nitro Compounds

- **Technical concept:** –NO_2 is reduced to –NH_2 in steps: nitro → nitroso → hydroxylamine → amine.
- **Reagents:** Sn/HCl (tin and hydrochloric acid), or Fe/HCl, or catalytic hydrogenation (H_2/Ni or Pt).
- **Example:** $C_6H_5NO_2$ (nitrobenzene) + Sn/HCl → $C_6H_5NH_2$ (aniline).
- **Key takeaway:** This is the main industrial route to aromatic amines.

Method 2: Reduction of Nitriles

- **Technical concept:** R–C≡N on reduction gives R–CH_2–NH_2 — a primary amine with ONE extra carbon.
- **Reagents:** $LiAlH_4$ (lithium aluminium hydride) or H_2/Ni.
- **Example:** CH_3CN (acetonitrile) → $CH_3CH_2NH_2$ (ethylamine).
- **Key takeaway:** Chain grows by one carbon (like Grignard carbonation in Chapter 1).

Method 3: Hofmann Degradation of Amides

- **Technical concept:** An amide R–$CONH_2$ treated with Br_2/NaOH loses its carbonyl carbon as carbonate and gives R–NH_2 — a primary amine with ONE CARBON LESS.
- **Numbered mechanism steps:**

1. Br_2 brominates the amide nitrogen: R–$CONH_2$ → R–CONHBr (N-bromoamide).
2. Base removes the remaining N–H proton → R–CON^-Br.
3. The R group migrates from carbon to nitrogen with loss of Br^-, forming an isocyanate R–N=C=O.
4. The isocyanate is hydrolysed by water: R–N=C=O + H_2O → R–NH_2 + CO_2.

- **Example:** CH_3CONH_2 (acetamide) + Br_2/NaOH → CH_3NH_2 (methylamine).
- **Key takeaway:** Chain shortens by one carbon — the opposite of nitrile reduction. Exam favourite.

Flowchart — Amine preparation map

```
Nitro compound ──(Sn/HCl or H₂/Ni)──→ Amine (same carbons)
Nitrile R-CN ──(LiAlH₄ or H₂/Ni)──→ R-CH₂NH₂ (+1 carbon)
Amide R-CONH₂ ──(Br₂/NaOH)──→ R-NH₂ (−1 carbon, Hofmann degradation)
```

2.6 Basicity of Amines and Effect of Substituents

- **Aliphatic amines:** In water, basicity order is 2° > 1° > 3° (because of a balance of electron-donating alkyl groups and solvation of the ammonium ion). Memorise: **secondary strongest in aqueous solution**.
- **Aromatic amines:** Aniline is a much WEAKER base than aliphatic amines because the nitrogen lone pair is delocalised into the benzene ring (resonance) — it is busy with the ring and less available to grab H^+.
- **Substituent effects on aniline:**
- Electron-donating groups (e.g., –CH_3, –OCH_3 at para position) push electrons toward nitrogen → **increase** basicity.
- Electron-withdrawing groups (e.g., –NO_2, –Cl) pull electrons away → **decrease** basicity. p-Nitroaniline is a very weak base.
- **Order to memorise:** $C_2H_5NH_2$ (aliphatic) > NH_3 > $C_6H_5NH_2$ (aniline) > p-$O_2NC_6H_4NH_2$ (p-nitroaniline).
- **Analogy:** The lone pair is like a free hand. In aniline the hand is busy holding the benzene ring (resonance), so it cannot easily catch a proton.

2.7 Diazonium Salts — Mechanism and Synthetic Applications

Formation (Diazotisation)

- **Technical concept:** A primary aromatic amine reacts with $NaNO_2$ + HCl at 0–5 °C to form the diazonium salt Ar–$N_2^+Cl^-$.
- **Numbered mechanism steps:**

1. $NaNO_2$ + HCl → HNO_2 (nitrous acid) + NaCl.
2. HNO_2 + H^+ → NO^+ (nitrosonium ion) + H_2O.
3. The amine nitrogen attacks NO^+ → Ar–NH–N=O (N-nitrosoamine) after proton loss.
4. Protonation of the oxygen, loss of water → Ar–N≡N^+ (diazonium ion).

- **Condition:** Temperature MUST be 0–5 °C (ice bath); diazonium salts decompose on warming.

Synthetic Application 1: Sandmeyer Reaction

- **Technical concept:** The diazonium group ($-N_2^+$) is replaced by –Cl, –Br or –CN using cuprous salts (CuCl, CuBr, CuCN).
- **Example:** $C_6H_5N_2^+Cl^-$ + CuCl → C_6H_5Cl (chlorobenzene) + N_2.
- **Key takeaway:** Best method to put –Cl, –Br, –CN directly on a benzene ring.

Synthetic Application 2: Azo-Dye Coupling

- **Technical concept:** The diazonium salt couples with an activated aromatic ring (phenol or aromatic amine) in mild alkaline solution to form a coloured azo compound (Ar–N=N–Ar′).
- **Example:** $C_6H_5N_2^+Cl^-$ + phenol (in NaOH) → p-hydroxyazobenzene (orange dye).
- **Pharmacy/India relevance:** Azo dyes colour textiles across India's textile industry and are used as indicators and stains.

Table — Diazonium salt transformations

Reagent	Product from $Ar–N_2^+Cl^-$
CuCl / HCl	Ar–Cl (Sandmeyer)
CuBr / HBr	Ar–Br (Sandmeyer)
CuCN / KCN	Ar–CN (Sandmeyer)
Phenol / NaOH	Ar–N=N–C_6H_4OH (azo dye)
Warm H_2O	Ar–OH (phenol) + N_2

2.8 Infographic Concept Box — "Amines in One Picture"

Centre: $–NH_2$ with lone pair. Left (MAKE): nitro + Sn/HCl (same C) / nitrile + $LiAlH_4$ (+1 C) / amide + Br_2/NaOH (−1 C, Hofmann). Top (BASICITY): 2° > 1° > 3° (aqueous); aniline weak (lone pair in ring); EWG ↓, EDG ↑. Right (DIAZONIUM): $ArNH_2$ + $NaNO_2$/HCl, 0–5 °C → $ArN_2^+Cl^-$ → Sandmeyer (Cl/Br/CN) or azo coupling (dyes).

2.9 Common Confusions / Mistakes / Mnemonics

- **Confusion:** Hofmann degradation (amide → amine, −1 C) vs Hofmann elimination (different reaction of quaternary ammonium salts). Different reactions, same chemist.
- **Mistake:** Diazotisation needs 0–5 °C — at room temperature the diazonium salt decomposes with N_2 bubbling off.
- **Mistake:** Aliphatic diazonium salts are unstable and not useful; only AROMATIC diazonium salts are used in synthesis.
- **Mnemonic for basicity in water:** "Two-One-Three" (2° > 1° > 3°).

2.10 Exam Summary & One-Minute Revision

- 3 preparations: nitro + Sn/HCl (same C); nitrile + $LiAlH_4$ (+1 C); amide + Br_2/NaOH (−1 C, Hofmann, via isocyanate).
- Basicity: lone pair availability; aqueous order 2° > 1° > 3°; aniline weak due to resonance; EWG ↓, EDG ↑.
- Diazotisation: $ArNH_2$ + $NaNO_2$/HCl at 0–5 °C → $ArN_2^+Cl^-$; Sandmeyer (Cl/Br/CN with Cu salts); azo coupling with phenol → dye.

2.11 Exam Questions

Short: 1. Why is aniline a weaker base than ethylamine? 2. What is the product of acetamide with Br_2/NaOH? 3. Why is diazotisation done at 0–5 °C? **Long:** 1. Describe three methods of preparation of amines with mechanisms. 2. Explain the mechanism of diazotisation and two synthetic applications of diazonium salts. 3. Discuss the effect of substituents on the basicity of amines. **MCQs:** 1. Hofmann degradation of amides gives an amine with: (a) same C (b) one C less (c) one C more → (b). 2. Azo-dye coupling of benzenediazonium chloride with phenol needs: (a) strong acid (b) mild alkaline medium (c) high heat → (b). 3. Strongest base in water: (a) aniline (b) diethylamine (c) triethylamine → (b). **Viva:** What is a diazonium salt? Name the reagent for nitro → amine reduction. **Application-based:** How will you convert benzamide to aniline? (Answer: Hofmann degradation.)

2.12 References

1. Finar, I. L. *Organic Chemistry, Vol. 1.* Pearson Education.
2. Bahl, B. S. and Bahl, A. *Textbook of Organic Chemistry.* S. Chand.
3. Smith, M. B. and March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure.* Wiley.

CHAPTER 3 — Alcohols and Phenols

3.1 Learning Objectives

- Classify alcohols (1°, 2°, 3°) and define phenols.
- Write methods to prepare alcohols (oxymercuration–demercuration, reduction of carbonyl compounds) and phenols (cumene process).
- Compare the acidity of alcohols vs phenols and explain the effect of substituents.
- Draw the mechanisms of the Reimer–Tiemann reaction, halogenation and nitration of phenols.
- List pharmaceutical applications of glycerine, thymol and paracetamol.

3.2 Definitions

Alcohol: An organic compound with an –OH group attached to a saturated carbon (sp^3 carbon). Example: CH_3CH_2OH (ethanol).

Phenol: An organic compound with an –OH group DIRECTLY attached to a benzene ring. Example: C_6H_5OH. ($C_6H_5CH_2OH$ is NOT a phenol — it is an alcohol, because the –OH is on a side-chain carbon, not the ring.)

3.3 Terminology

- **Primary (1°) alcohol:** –OH carbon attached to ONE other carbon (R–CH_2OH).
- **Secondary (2°) alcohol:** –OH carbon attached to TWO other carbons (R_2CHOH).
- **Tertiary (3°) alcohol:** –OH carbon attached to THREE other carbons (R_3COH).
- **Cumene:** isopropylbenzene, $C_6H_5CH(CH_3)_2$ — the starting material of the cumene process.
- **Keratolytic / antiseptic:** terms you already know; phenols are often antiseptic.

3.4 Explanation — Why Phenol Is More Acidic Than Alcohol

When phenol loses H^+, the negative charge on oxygen is delocalised into the benzene ring by resonance — the ring "shares the burden," so the phenoxide ion is stable. In an alcohol, the negative charge sits on one oxygen with no ring to help, so the alkoxide ion is less stable. More stable negative ion = stronger acid. Hence phenol (pKa ≈ 10) is about a million times more acidic than ethanol (pKa ≈ 16), though still far weaker than carboxylic acids (pKa ≈ 4–5).

3.5 Methods to Prepare Alcohols

Method 1: Oxymercuration–Demercuration

- **Technical concept:** An alkene reacts with mercuric acetate [$Hg(OAc)_2$] in water/THF, then with $NaBH_4$, to give an alcohol with MARKOVNIKOV orientation and WITHOUT rearrangement.
- **Numbered mechanism steps:**

1. The alkene's π-bond attacks Hg^{2+}, forming a three-membered mercurinium ion (Hg bridges the two carbons).
2. Water attacks the MORE substituted carbon from the back side (Markovnikov opening).
3. Loss of a proton gives an organomercury alcohol.
4. $NaBH_4$ replaces –HgOAc with –H (demercuration) → final alcohol.

- **Example:** $CH_3CH=CH_2$ (propene) → $CH_3CH(OH)CH_3$ (isopropanol, 2-propanol).
- **Key takeaway:** Markovnikov alcohol, no carbocation rearrangement — unlike acid-catalysed hydration.

Method 2: Reduction of Carbonyl Compounds

- **Technical concept:** Aldehydes reduce to 1° alcohols; ketones reduce to 2° alcohols.
- **Reagents:** $NaBH_4$ (sodium borohydride, mild) or $LiAlH_4$ (strong); H_2/Ni also works.
- **Examples:** $CH_3CHO + NaBH_4 \rightarrow CH_3CH_2OH$; $CH_3COCH_3 + NaBH_4 \rightarrow CH_3CH(OH)CH_3$.
- **Key takeaway:** Aldehyde → primary alcohol; ketone → secondary alcohol. (Tertiary alcohols cannot be made this way.)

Flowchart

```
Alkene ──(1. Hg(OAc)₂/H₂O; 2. NaBH₄)──→ Markovnikov alcohol (no rearrangement)
Aldehyde RCHO ──(NaBH₄ or LiAlH₄)──→ RCH₂OH (1° alcohol)
Ketone RCOR ──(NaBH₄ or LiAlH₄)──→ R₂CHOH (2° alcohol)
```

3.6 Preparation of Phenols — Cumene Process

- **Technical concept:** Cumene (isopropylbenzene) is oxidised by air to cumene hydroperoxide, which on treatment with dilute acid rearranges to phenol + acetone.
- **Numbered steps:**

1. $C_6H_5CH(CH_3)_2 + O_2$ (air oxidation) → $C_6H_5C(OOH)(CH_3)_2$ (cumene hydroperoxide).
2. Dilute H_2SO_4 causes rearrangement: the phenyl group migrates to the electron-deficient oxygen.
3. Hydrolysis gives phenol (C_6H_5OH) + acetone (CH_3COCH_3, a valuable by-product).

- **Key takeaway:** Industrial method — phenol and acetone are made together; this is why the process is economical.

3.7 Acidity: Alcohols vs Phenols, Effect of Substituents

- **Order of acidity:** carboxylic acid > phenol > water > alcohol. (pKa ≈ 4–5, 10, 15.7, 16–18.)
- **Phenol vs alcohol:** Phenol is more acidic because the phenoxide ion is resonance-stabilised; the alkoxide ion is not.
- **Substituent effects on phenol acidity:**
- Electron-withdrawing groups (–NO_2, –Cl) stabilise the phenoxide ion → **increase** acidity. Effect is strongest at ortho and para positions.
- Electron-donating groups (–CH_3, –OCH_3) destabilise the phenoxide ion → **decrease** acidity.
- Example: p-nitrophenol is about 1000× more acidic than phenol; p-cresol (p-methylphenol) is less acidic than phenol.
- **Analogy:** The negative charge is a heavy bag. In phenol the benzene ring helps carry it (resonance); EWG friends help carry more, EDG friends add weight.

3.8 Mechanisms of Chemical Reactions of Phenols

Reaction 1: Reimer–Tiemann Reaction

- **Technical concept:** Phenol reacts with chloroform ($CHCl_3$) and NaOH to give salicylaldehyde (o-hydroxybenzaldehyde) — a –CHO group is introduced at the ORTHO position.
- **Numbered mechanism steps:**

1. $CHCl_3$ + NaOH → $:CCl_2$ (dichlorocarbene, an electron-deficient neutral species) + H_2O + Cl^-.
2. The phenoxide ion ($C_6H_5O^-$, formed in NaOH) attacks the carbene at the ortho position.
3. Rearomatisation and hydrolysis of the $–CCl_2$ group → –CHO.
4. Product: o-HOC_6H_4CHO (salicylaldehyde); a small amount of the para isomer also forms.

- **Key takeaway:** This is how you put an aldehyde group ortho to a phenolic –OH.

Reaction 2: Halogenation of Phenols

- Phenol is so activated that bromine water gives **2,4,6-tribromophenol** (white precipitate) immediately — no Lewis acid catalyst needed, unlike benzene.
- **Example:** C_6H_5OH + 3 Br_2 (bromine water) → 2,4,6-tribromophenol (white ppt) + 3 HBr.
- **Key takeaway:** White precipitate with bromine water = classic test for phenol.

Reaction 3: Nitration of Phenols

- **With dilute HNO_3:** gives a mixture of o-nitrophenol and p-nitrophenol.
- **With concentrated HNO_3:** phenol is oxidised and gives **2,4,6-trinitrophenol (picric acid)**.
- **Key takeaway:** Concentrated HNO_3 → picric acid (explosive, yellow).

3.9 Pharmaceutical Applications of Alcohols and Phenols

Compound	Class	Use
Glycerine (glycerol)	Trihydric alcohol	Humectant, sweetener, solvent in syrups and elixirs; suppository base
Thymol	Monoterpene phenol	Antiseptic in mouthwashes, throat preparations; antifungal
Paracetamol	p-Acetamidophenol (phenol derivative)	Analgesic and antipyretic — one of the most used drugs in India

- **India context:** Glycerine is in nearly every Indian cough syrup; paracetamol (Crocin/Calpol) is the household fever drug; thymol is in many Ayurvedic and mouthwash preparations.

3.10 Infographic Concept Box — "Alcohols & Phenols in One Picture"

> Centre: –OH. Split panel — ALCOHOL (R–OH): make by oxymercuration (Markovnikov, no rearrangement) or $NaBH_4$ reduction (aldehyde → 1°, ketone → 2°); weak acid. PHENOL (Ar–OH): make by cumene process (phenol + acetone); stronger acid (resonance); EWG ↑ acidity. Reactions: Reimer–Tiemann ($CHCl_3$/NaOH → o-CHO); Br_2 water → white ppt (test); conc. HNO_3 → picric acid. Drugs: glycerine (syrups), thymol (mouthwash), paracetamol (fever).

3.11 Common Confusions / Mistakes / Mnemonics

- **Confusion:** $C_6H_5CH_2OH$ (benzyl alcohol) is an ALCOHOL, not a phenol — –OH must be directly on the ring.
- **Mistake:** Phenol needs no catalyst for bromination; benzene needs $FeBr_3$. Writing $FeBr_3$ for phenol bromination is wrong.
- **Mistake:** Oxymercuration gives Markovnikov product WITHOUT rearrangement; acid hydration may rearrange.
- **Mnemonic for acidity:** "Carboxyl Phenol Water Alcohol" (C > P > W > A) — alphabetical-ish order of decreasing acidity.

3.12 Exam Summary & One-Minute Revision

- Alcohols: 1°/2°/3°; oxymercuration–demercuration (Markovnikov, no rearrangement); $NaBH_4$: aldehyde → 1°, ketone → 2°.
- Phenols: –OH directly on ring; cumene process (cumene → hydroperoxide → phenol + acetone).
- Acidity: phenol > alcohol (resonance); EWG ↑, EDG ↓; order acid > phenol > water > alcohol.
- Reactions: Reimer–Tiemann ($CHCl_3$/NaOH, o-CHO via dichlorocarbene); Br_2 water → white ppt test; conc. HNO_3 → picric acid.
- Drugs: glycerine (humectant/syrups), thymol (antiseptic), paracetamol (analgesic/antipyretic).

3.13 Exam Questions

Short: 1. Why is phenol more acidic than ethanol? 2. What is the product of phenol with bromine water? 3. Name the by-product of the cumene process. **Long:** 1. Describe the preparation of alcohols by oxymercuration–demercuration with mechanism. 2. Explain the cumene process for phenol manufacture. 3. Discuss the mechanism of the Reimer–Tiemann reaction. **MCQs:** 1. Phenol with bromine water gives: (a) monobromo (b) 2,4,6-tribromophenol white ppt (c) no reaction → (b). 2. Cumene process by-product: (a) acetone (b) acetaldehyde (c) benzaldehyde → (a). 3. Most acidic: (a) ethanol (b) phenol (c) p-nitrophenol → (c). **Viva:** How do you distinguish phenol from benzyl alcohol? What is dichlorocarbene? **Application-based:** A lab needs isopropanol from propene without rearrangement risk. Which method and why?

3.14 References

1. Finar, I. L. *Organic Chemistry, Vol. 1.* Pearson Education.
2. Bahl, B. S. and Bahl, A. *Textbook of Organic Chemistry.* S. Chand.
3. Smith, M. B. and March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure.* Wiley.

CHAPTER 4 — Polynuclear Aromatic Hydrocarbons

4.1 Learning Objectives

- Define polynuclear aromatic hydrocarbons and classify them (isolated vs fused ring systems).
- Describe the Haworth synthesis of naphthalene.
- Explain the mechanism of electrophilic aromatic substitution in naphthalene, phenanthrene and anthracene (position selectivity).
- Name medicinal uses of drugs containing naphthalene (propranolol, naphazoline) and phenanthrene (morphine, codeine).

4.2 Definitions

Polynuclear aromatic hydrocarbon (PAH): A hydrocarbon made of TWO OR MORE benzene rings joined together, sharing common carbon–carbon bonds. Example: naphthalene (two fused rings).

Fused ring system: Rings that share a common bond (two adjacent carbons belong to both rings). Naphthalene, phenanthrene and anthracene are fused systems.

4.3 Terminology

- **Naphthalene:** $C_{10}H_8$, two fused benzene rings (used in mothballs).
- **Anthracene:** $C_{14}H_{10}$, three rings fused in a straight line.
- **Phenanthrene:** $C_{14}H_{10}$, three rings fused in an angular (bent) fashion.
- **Haworth synthesis:** the classic laboratory synthesis of naphthalene (and substituted naphthalenes) starting from benzene + succinic anhydride.
- **Electrophilic aromatic substitution (EAS):** a reaction where an electrophile (electron-seeker) replaces a hydrogen on the aromatic ring.

4.4 Classification of Polynuclear Hydrocarbons

1. **Isolated ring systems:** rings joined by single bonds, not sharing atoms — e.g., biphenyl (two rings linked by one bond), diphenylmethane.
2. **Fused ring systems:** rings sharing a common bond —

- Two rings: naphthalene.
- Three rings linear: anthracene; angular: phenanthrene.
- Four+ rings: e.g., pyrene, benzo[a]pyrene (carcinogenic — handle with care).

4.5 Haworth Synthesis of Naphthalene

- **Technical concept:** Benzene is acylated with succinic anhydride, then the keto-acid is reduced, cyclised, and aromatised to naphthalene.
- **Numbered steps:**

1. **Friedel–Crafts acylation:** Benzene + succinic anhydride / $AlCl_3$ → β-benzoylpropionic acid ($C_6H_5COCH_2CH_2COOH$).
2. **Clemmensen reduction:** Zn(Hg)/HCl reduces the keto group → γ-phenylbutyric acid ($C_6H_5CH_2CH_2CH_2COOH$).
3. **Ring closure:** Heating with concentrated H_2SO_4 (intramolecular Friedel–Crafts acylation) → α-tetralone (a fused bicyclic ketone).
4. **Clemmensen reduction again:** α-tetralone → tetralin (tetrahydronaphthalene).
5. **Dehydrogenation/aromatisation:** Heating with Pd or Se (or sulphur) removes hydrogens → naphthalene.

- **Key takeaway:** Benzene + succinic anhydride → (acylate, reduce, cyclise, reduce, dehydrogenate) → naphthalene. Five steps — learn the sequence.

Diagram description (draw in notebook)

Benzene ring →(succinic anhydride, $AlCl_3$)→ open-chain keto acid →(Zn-Hg/HCl)→ straight-chain acid →(conc. H_2SO_4, ring closes)→ bicyclic ketone (α-tetralone) →(Zn-Hg/HCl)→ tetralin →(Pd, heat, $-2H_2$)→ naphthalene (two fused hexagons).

4.6 Electrophilic Aromatic Substitution — Mechanism and Position Selectivity

General EAS mechanism (same 3 steps everywhere)

1. The aromatic π-electrons attack the electrophile (E^+), forming a carbocation intermediate (sigma complex/arenium ion) — aromaticity is temporarily lost.
2. The intermediate is stabilised by resonance.
3. A base removes a proton from the carbon bearing E^+; aromaticity is restored → substituted product.

Naphthalene

- **Alpha (1-) position is preferred** over beta (2-) position for electrophilic attack.
- **Why:** Attack at C-1 gives a sigma complex whose resonance forms keep one benzene ring fully aromatic (more stable); attack at C-2 gives a less stable intermediate.
- **Examples:** Nitration (HNO_3/H_2SO_4) → 1-nitronaphthalene; sulphonation at low temperature → naphthalene-1-sulphonic acid; Friedel–Crafts acylation → 1-acylnaphthalene.

Anthracene

- **Attack at the 9-position (middle ring)** is strongly preferred.
- **Why:** The sigma complex from 9-attack keeps TWO benzene rings aromatic — maximum stability.
- **Example:** Nitration → 9-nitroanthracene; bromination → 9-bromoanthracene.

Phenanthrene

- **Attack at the 9- and 10-positions** (the middle ring's double bond) is preferred.
- **Example:** Bromination → 9-bromophenanthrene.

Table — Position selectivity

Compound	Preferred EAS position	Reason (stability of sigma complex)
Naphthalene	1 (alpha)	One intact benzene ring in intermediate
Anthracene	9 (middle ring)	Two intact benzene rings in intermediate
Phenanthrene	9, 10	Maximum resonance stabilisation

4.7 Medicinal Uses of Drugs Containing These Ring Systems

Drug	Ring system	Medicinal use
Propranolol	Naphthalene	Non-selective beta-blocker — hypertension, angina, migraine prevention
Naphazoline	Naphthalene	Nasal decongestant (imidazoline + naphthalene); eye drops for redness
Morphine	Phenanthrene	Powerful opioid analgesic for severe pain
Codeine	Phenanthrene (methylmorphine)	Mild–moderate pain; antitussive (cough suppressant)

- **India context:** Propranolol is a first-line, low-cost antihypertensive across India; codeine-containing cough syrups are widely (and carefully) used; morphine is strictly controlled but essential in cancer pain care.

4.8 Infographic Concept Box — "Polynuclear Hydrocarbons in One Picture"

Top: classification — isolated (biphenyl) vs fused (naphthalene 2 rings; anthracene linear 3; phenanthrene angular 3). Middle: Haworth synthesis ladder — benzene → keto acid → reduced acid → α-tetralone → tetralin → naphthalene (reagents under each arrow: $AlCl_3$; Zn-Hg/HCl; conc. H_2SO_4; Zn-Hg/HCl; Pd/heat). Bottom: EAS hotspots — naphthalene C-1, anthracene C-9, phenanthrene C-9/10. Drug strip: propranolol (BP), naphazoline (nose), morphine/codeine (pain/cough).

4.9 Common Confusions / Mistakes / Mnemonics

- **Confusion:** Anthracene (linear) vs phenanthrene (angular) — both $C_{14}H_{10}$. Remember "PHenanthrene is PHolded (bent)."
- **Mistake:** Writing EAS of naphthalene at the beta position as major — alpha (1-) is the major product.
- **Mistake:** Forgetting that sulphonation of naphthalene is temperature-dependent (1- at low temp, 2- at high temp — kinetic vs thermodynamic control).
- **Mnemonic for Haworth steps:** "Acylate, Reduce, Cyclise, Reduce, Dehydrogenate" (A-R-C-R-D).

4.10 Exam Summary & One-Minute Revision

- PAH = 2+ fused benzene rings; isolated (biphenyl) vs fused (naphthalene, anthracene, phenanthrene).
- Haworth synthesis: benzene + succinic anhydride → acylate → reduce → cyclise (α-tetralone) → reduce (tetralin) → dehydrogenate → naphthalene.
- EAS: 3-step mechanism via sigma complex; naphthalene → C-1, anthracene → C-9, phenanthrene → C-9/10.
- Drugs: propranolol (beta-blocker), naphazoline (decongestant) — naphthalene; morphine, codeine — phenanthrene.

4.11 Exam Questions

Short: 1. Why does electrophilic substitution in naphthalene occur at the alpha position? 2. Name the starting materials of Haworth synthesis. 3. Which position of anthracene is most reactive? **Long:** 1. Describe the Haworth synthesis of naphthalene with all steps. 2. Explain the mechanism of electrophilic aromatic substitution in naphthalene with position selectivity. 3. Classify polynuclear hydrocarbons with examples and give medicinal uses of naphthalene/phenanthrene drugs. **MCQs:** 1. Haworth synthesis starts from: (a) toluene + maleic anhydride (b) benzene + succinic anhydride (c) phenol + phthalic anhydride → (b). 2. Nitration of anthracene mainly gives: (a) 1-nitro (b) 9-nitro (c) 2-nitro → (b). 3. Propranolol contains: (a) anthracene (b) naphthalene (c) phenanthrene → (b). **Viva:** What is a sigma complex? Why is tetralin an intermediate in Haworth synthesis? **Application-based:** A question asks for the major product of naphthalene sulphonation at 80 °C vs 160 °C — explain the difference.

4.12 References

1. Finar, I. L. *Organic Chemistry, Vol. 1.* Pearson Education.
2. Bahl, B. S. and Bahl, A. *Textbook of Organic Chemistry.* S. Chand.
3. Smith, M. B. and March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure.* Wiley.