

Pharmaceutical Organic Chemistry II

Theory Sessional Examination ST2 Solutions

This model solution covers every question in the supplied paper, including all optional questions.

How to present the answers

- For a synthesis, identify the starting material, write each intermediate, and put the reagent and condition with the arrow.
- For oil constants, write the definition, unit, principle, equation, and significance. Define all symbols in calculation formulas.
- For medicinal derivatives, give a recognizable structure or complete condensed substituent, drug class, and one principal use.

Section A

Q1a. Define fatty acids and give one example.

Fatty acids are aliphatic monocarboxylic acids, usually with an unbranched hydrocarbon chain. They occur free or esterified with glycerol in fats and oils, and may be saturated or unsaturated.

General form $R-C(=O)-OH$; **Example- Palmitic acid** $CH_3-(CH_2)_{14}-COOH$; $[C_{16}H_{32}O_2]$

Palmitic acid is a saturated fatty acid because its carbon chain contains no carbon-carbon double bond.

Q1b. What is saponification? Write its general reaction.

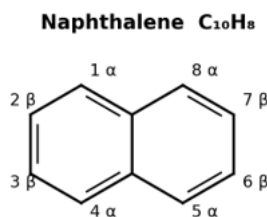
Saponification is alkaline hydrolysis of fats or oils with sodium hydroxide or potassium hydroxide, producing glycerol and salts of fatty acids called soaps.



Condition: heat with aqueous or alcoholic alkali. The equation represents a triacylglycerol with three identical acyl groups; natural fats commonly contain different fatty acid residues.

Q1c. Analyse the fused-ring arrangement of naphthalene, draw its structure, and write its molecular formula.

Naphthalene contains two fused six-membered aromatic rings sharing two adjacent carbon atoms and one carbon-carbon bond. It is a planar, conjugated system with 10 π electrons. Its molecular formula is $C_{10}H_8$; the fused carbon atoms carry no hydrogen.



Q1d. State the meaning of acid value and mention its significance in evaluating the quality of oils.

Acid value is the number of milligrams of potassium hydroxide required to neutralize the free fatty acids present in 1 g of oil or fat.

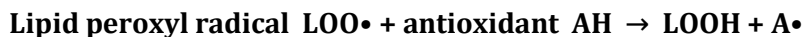
$$\text{Acid value} = 56.1 \times (V - V_{\beta}) \times N / W \text{ mg KOH g}^{-1}$$

V and V_{β} are sample and blank titration volumes in mL; N is alkali normality; W is sample mass in grams.

- A higher acid value generally indicates increased free fatty acids from hydrolysis, poor storage, or deterioration. It helps assess freshness and suitability of an oil for formulation.

Q1e. Using your knowledge of rancidity, explain one suitable method for preventing rancidity in pharmaceutical or food products.

One suitable method is addition of an appropriate antioxidant, such as tocopherol, to the oil-containing product. Oxidative rancidity begins when oxygen attacks unsaturated lipid chains, forming hydroperoxides that subsequently break down into unpleasant-smelling products.



The antioxidant donates hydrogen and forms a relatively stable radical, slowing propagation of lipid oxidation. Its identity and concentration must suit the particular food or pharmaceutical formulation. This method mainly controls oxidative rancidity; protection from moisture is also needed to limit hydrolytic rancidity.

Section B**Q2a. Applying your knowledge of naphthalene, explain its synthesis and chemical reactions, and relate its important derivatives to their medicinal uses with suitable examples.****Structure and reactivity**

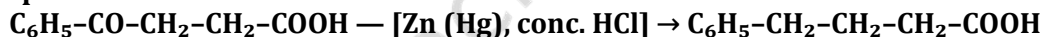
- Naphthalene is a fused aromatic hydrocarbon, C_{10}H_8 , with 10 delocalized π electrons.
- Positions 1, 4, 5, and 8 are α positions; positions 2, 3, 6, and 7 are β positions.
- Electrophilic substitution commonly occurs at an α position because the corresponding intermediate has more favorable resonance contributors retaining an aromatic ring.

Haworth synthesis

The Haworth sequence constructs a second six-membered ring on benzene, followed by reduction and dehydrogenation. C_6H_5 denotes the complete phenyl ring in the condensed structures below.

Step 1 Friedel Crafts acylation

Product: 4-oxo-4-phenylbutanoic acid, also called β -benzoylpropionic acid. The cyclic anhydride provides the four-carbon side chain.

Step 2 Clemmensen reduction

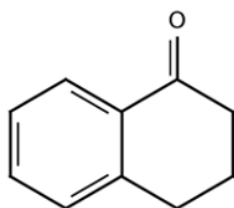
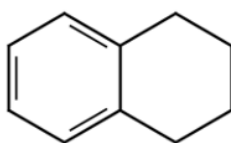
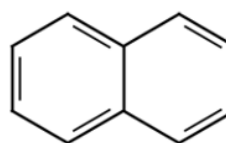
Product: 4-phenylbutanoic acid. The ketone carbonyl is reduced to a methylene group.

Step 3 Intramolecular cyclization

Intramolecular acylation occurs at the ortho position and closes a six-membered ring.

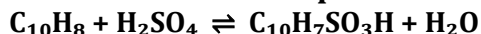
Steps 4 and 5 Reduction and aromatization

Reduction removes the ketone oxygen; subsequent dehydrogenation creates the second aromatic ring. The net dehydrogenation is $\text{C}_{10}\text{H}_{12} \rightarrow \text{C}_{10}\text{H}_8 + 2 \text{H}_2$.

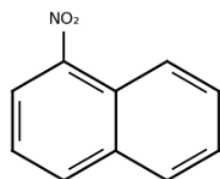
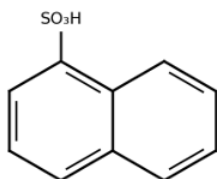
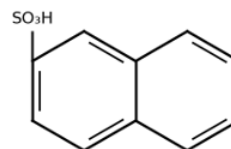
**1 Tetralone****Tetralin****Naphthalene**

Chemical reactions of naphthalene**1. Nitration**

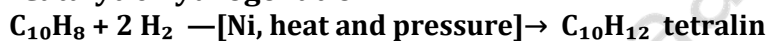
- Electrophile: nitronium ion, NO_2^+ . The major product is the α -substituted compound, $\text{C}_{10}\text{H}_7\text{NO}_2$.

2. Sulfonation and temperature dependence

- At about 80 °C, naphthalene-1-sulfonic acid is the major product under kinetic control.
- At about 160 °C, naphthalene-2-sulfonic acid predominates under thermodynamic control. Sulfonation is reversible; temperature and equilibration affect the product ratio.

**1 Nitronaphthalene****Naphthalene 1 sulfonic acid****Naphthalene 2 sulfonic acid****3. Halogenation**

Electrophilic substitution gives predominantly the 1-substituted product. Excess reagent can lead to further substitution.

4. Catalytic hydrogenation

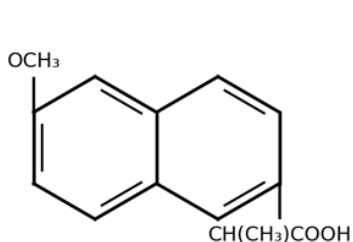
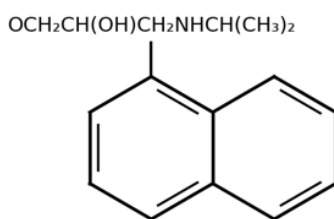
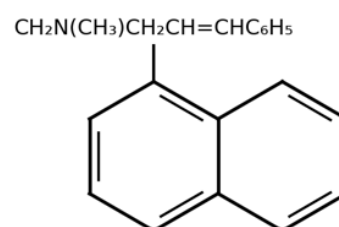
Partial reduction gives tetralin; complete saturation gives decalin, which can exist as cis and trans isomers.

5. Oxidation

Product: phthalic anhydride, $\text{C}_8\text{H}_4\text{O}_3$. Hydrolysis gives phthalic acid, ortho- $\text{C}_6\text{H}_4(\text{COOH})_2$. One ring is oxidatively degraded while the other benzene ring remains.

Medicinal derivatives of naphthalene

The naphthalene nucleus occurs in several drug molecules. Their biological activity depends on their substituents and overall structure; the parent hydrocarbon is not a substitute for these medicines.

**Naproxen S configuration****Propranolol****Naftifine E alkene**

Derivative	Structural description	Class and principal use
Naproxen	(S)-2-(6-methoxynaphthalen-2-yl)propanoic acid; $-\text{CH}(\text{CH}_3)\text{COOH}$ and $-\text{OCH}_3$ substituents	Nonsteroidal anti-inflammatory drug; relief of pain and inflammation, including arthritis.
Propranolol	1-(Naphthalen-1-yloxy)-3-(propan-2-ylamino)propan-2-ol	Nonselective β -adrenoceptor blocker; hypertension and selected cardiovascular indications.
Naftifine	N-Methyl-N-(naphthalen-1-ylmethyl)-3-phenylprop-2-en-1-amine; E alkene	Allylamine antifungal; topical treatment of dermatophyte skin infections.

Structure notation: unlabeled vertices represent carbon, with hydrogens completing valence.

C_6H_5 represents a phenyl ring. Condensed side chains show their full connectivity.

Naproxen has the S configuration at the side-chain carbon.

Naftifine has an E-configured double bond.

Link between nucleus and medicinal use

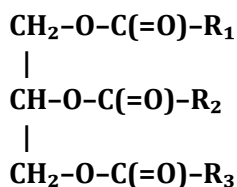
- The fused aromatic nucleus provides a hydrophobic surface that can contribute to interaction with biological targets.
- The acidic side chain in naproxen, amino alcohol side chain in propranolol, and allylamine side chain in naftifine produce different pharmacological profiles.

Section B

Q2b. Analyze the important chemical reactions of fats and oils including hydrolysis, saponification, hydrogenation, and oxidation. Explain each with a suitable chemical equation.

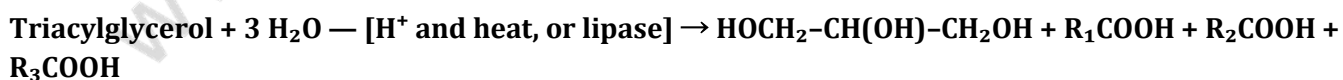
Chemical nature of fats and oils

Fats and oils consist mainly of triacylglycerols, the triesters of glycerol and fatty acids. Their reactions occur either at the ester linkages or at unsaturated sites in the fatty acid chains. Fats are generally solid and oils liquid at ordinary room temperature, depending on fatty acid composition.



R_1 , R_2 , and R_3 are hydrocarbon residues; they may be the same or different.

1. Hydrolysis:



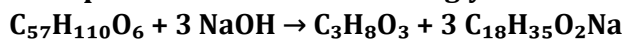
- Water cleaves the ester linkages, releasing glycerol and free fatty acids. Partial hydrolysis may first yield diacylglycerols and monoacylglycerols.
- Acid hydrolysis is reversible; enzyme-catalysed hydrolysis can occur under milder conditions.
- Release of short-chain fatty acids can cause hydrolytic rancidity. Increasing free fatty acids generally raises the acid value.

2. Saponification:

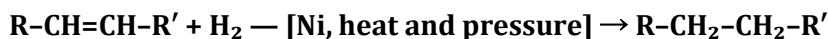


- Alkali cleaves the ester bonds and gives fatty acid salts rather than free acids. Carboxylate formation makes the process effectively irreversible under ordinary reaction conditions.
- NaOH produces sodium soaps; KOH produces potassium soaps. This reaction is used in soap manufacture and measurement of saponification value.

Example Tristearin + 3 NaOH → glycerol + 3 sodium stearate



3. Hydrogenation:



- Hydrogen adds across carbon-carbon double bonds in the acyl chains; glycerol ester linkages remain intact.
- Saturation generally increases melting point and converts a liquid oil into a more solid fat. Hydrogenation lowers iodine value.
- Partial hydrogenation may also cause cis-trans isomerization and produce trans fatty acids; complete hydrogenation removes double bonds.

4. Oxidation and oxidative rancidity:

Unsaturated acyl chains undergo autoxidation, commonly initiated at allylic sites. L denotes a lipid chain; L• is a lipid radical. Heat, light, oxygen, and traces of metals can accelerate the process.

Initiation- $\text{LH} \rightarrow \text{L}\cdot + \text{H}\cdot$

Propagation- $\text{L}\cdot + \text{O}_2 \rightarrow \text{LOO}\cdot$, $\text{LOO}\cdot + \text{LH} \rightarrow \text{LOOH} + \text{L}\cdot$

Termination $\text{L}\cdot + \text{L}\cdot \rightarrow \text{L-L}$

The initiation line is a simplified representation; in practice initiators abstract hydrogen from LH. LOOH is a lipid hydroperoxide, the primary oxidation product.

Lipid hydroperoxides — [heat or metal ions] → secondary oxidation products including aldehydes, ketones, and acids

- Secondary products cause unpleasant odour and taste. Oxidation reduces product stability and can damage nutritionally important lipids.
- Peroxide value measures primary peroxide products; a low value in an extensively oxidized oil may reflect peroxide breakdown. Acid value alone cannot establish oxidative stability.

Reaction	Site affected	Main result
Hydrolysis	Ester linkage	Glycerol and free fatty acids
Saponification	Ester linkage in alkali	Glycerol and fatty acid salts
Hydrogenation	C=C double bonds	More saturated acyl chains
Oxidation	Primarily unsaturated acyl chains	Hydroperoxides and secondary breakdown products

Section C

Q3a. Explain the ester value and Reichert–Meissl value and state their significance in evaluating fats and oils.

Ester value:

Ester value is the number of milligrams of KOH required to saponify the esterified fatty acids present in 1 g of fat or oil, excluding the alkali used to neutralize free fatty acids.

$$\text{Ester value} = \text{Saponification value} - \text{Acid value}; \text{EV} = \text{SV} - \text{AV mg KOH g}^{-1}$$

Principle: saponification value includes alkali consumption by ester groups and free fatty acids; subtracting the acid value isolates alkali consumption by ester groups.



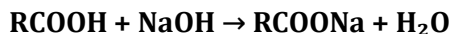
- It indicates the amount of saponifiable ester groups per unit mass and helps characterize or compare oils and fats.
- For a comparable composition, hydrolysis decreases ester content while increasing free fatty acids. Unsaponifiable matter lowers ester value per gram of sample.

$$\text{Illustrative calculation } \text{SV} = 190 \text{ \& AV} = 4; \text{EV} = 190 - 4 = 186 \text{ mg KOH g}^{-1}$$

Reichert Meissl value:

Reichert–Meissl value is the number of millilitres of 0.1 N aqueous alkali required to neutralize the water-soluble volatile fatty acids distilled from 5 g of fat or oil under prescribed conditions.

Principle: saponify the sample, acidify to liberate fatty acids, distil the volatile acids, filter to separate the water-insoluble fraction, and titrate the water-soluble distillate with standard alkali.



It chiefly reflects short-chain water-soluble volatile fatty acids such as butyric and caproic acids. The insoluble volatile fraction is assessed separately by the Polenske value.

$$\text{RM} = (\text{V} - \text{V}_\beta) \times (\text{N} / 0.1) \times (\text{Vd} / \text{Va})$$

V and V_β : sample and blank titres in mL; N: alkali normality; Vd: total prescribed distillate volume; Va: aliquot volume (a smaller portion). This form assumes the prescribed 5 g sample and quantitative method conditions. With 110 mL distillate, a 100 mL aliquot, and 0.1 N alkali, $\text{RM} = 1.1(\text{V} - \text{V}_\beta)$.

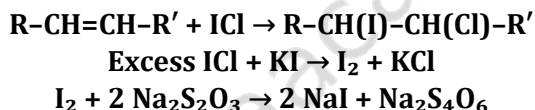
- Butterfat has appreciable short-chain volatile acids; RM value supports its identification and detection of adulteration with fats having lower values.
- Interpretation requires method-specific reference ranges and other tests; RM value alone does not prove purity.

Section C

Q3b. Compare iodine value and acid value with respect to their definition, principle, formula, chemical reaction, and significance in the evaluation of fats and oils.

Aspect	Iodine value	Acid value
Definition and unit	Grams of iodine equivalent absorbed by 100 g of fat or oil; g I ₂ per 100 g	Milligrams of KOH required to neutralize free fatty acids in 1 g; mg KOH g ⁻¹
Principle	Addition of halogen across C=C bonds; excess Wijs reagent is measured iodometrically	Neutralization of free fatty acids by standard alkali in a suitable solvent
Formula	$IV = 12.69 \times (B - S) \times N / W$	$AV = 56.1 \times (V - V_{\beta}) \times N / W$
Main significance	Estimates degree of unsaturation; supports identification and assessment of hydrogenation	Assesses free fatty acid content and hydrolytic deterioration
Interpretation	Higher value generally means greater unsaturation; not a direct rancidity measurement	Higher value generally means more free fatty acids; not a complete oxidation test

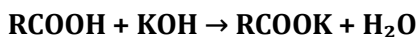
Iodine value reaction and calculation:



Wijs reagent is iodine monochloride in acetic acid. The addition product shown is schematic; its orientation is not the analytical endpoint. After reaction, KI liberates iodine from excess reagent, which is titrated with sodium thiosulfate.

B and S: blank and sample thiosulfate titres in mL; N: thiosulfate normality; W: sample mass in grams. The blank titre is greater because the sample consumes reagent. The constant 12.69 expresses iodine equivalent in grams per 100 g.

Acid value reaction and calculation:



V and V_β: sample and blank alkali titres in mL; N: alkali normality; W: sample mass in grams. The factor 56.1 is the equivalent mass of KOH expressed for mL-based calculation. A suitable neutralized solvent and appropriate endpoint are used.

Key distinction

Iodine value describes unsaturation in fatty acid chains, whereas acid value describes unesterified fatty acids. A fresh unsaturated oil may have a high iodine value and a low acid value. Neither test alone establishes the complete quality or safety of an oil.

Section C

Q3c. Classify polynuclear hydrocarbons and explain their importance and applications with suitable examples.

Polynuclear aromatic hydrocarbons contain two or more aromatic rings. In the conventional pharmaceutical organic chemistry classification, they are divided into isolated or non-fused ring compounds and fused or condensed ring compounds.

Class	Ring arrangement	Examples and formula
Isolated or non-fused rings	Rings do not share carbon atoms. They are directly linked or separated by a carbon group.	Biphenyl, $C_{12}H_{10}$; diphenylmethane, $C_{13}H_{12}$
Fused or condensed rings	Adjacent rings share two carbon atoms and one bond.	Naphthalene, $C_{10}H_8$; anthracene, $C_{14}H_{10}$; phenanthrene, $C_{14}H_{10}$

Biphenyl $C_6H_5-C_6H_5$

Diphenylmethane $C_6H_5-CH_2-C_6H_5$

- Naphthalene has two fused rings.
- Anthracene has three linearly fused rings.
- Phenanthrene has three angularly fused rings. Anthracene and phenanthrene are structural isomers.

Importance and applications

- **Medicinal chemistry:** the naphthalene nucleus is present in naproxen and propranolol. Their substituted structures provide distinct therapeutic actions.
- **Drug scaffolds (backbone of a medicine molecule):** hydrogenated phenanthrene forms part of the fused framework associated with steroids; morphine also has a phenanthrene-derived framework. These compounds are derivatives, not simple hydrocarbon drugs.
- **Chemical manufacture:** naphthalene is a feedstock for phthalic anhydride and naphthol derivatives. Anthracene is used to prepare anthraquinone intermediates for dyes.
- **Environmental relevance:** some fused polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, are carcinogenic pollutants formed during incomplete combustion. This property should not be generalized to every polynuclear compound.