NATURAL PRODUCTS

Dr. Nisha V K
Asst. Professor
Payyanur College

INTRODUCTION

- Natural products are organic compounds that are found in plant, animals and microbes.

- Natural products are small molecules produced by living organisms including plants, animals and microorganisms

- They are also known as secondary metabolites being non essential for life; but they play key roles in defence and cell to cell communication.

- By **natural products**, it means that the molecules of nature. Of course, all life is made of molecules, and we will not be discussing in great detail the major biological molecules, such as **proteins** and **nucleic acids**.

Alkaloids

- Alkaloids are a class of basic, naturally occurring organic compounds that contain at least one nitrogen atom.
- The term alkaloid was coined by Meissner, a German pharmacist, in 1819
- Alkaloids were known in ancient times because they are easy to extract from plants and some of them have powerful and deadly effects.
- A study of the structures and properties of alkaloids has shown that most of them possess the following common characteristics:

1. Plant origin
2. Basic nature
3. Complex stuctures with nitrogen heterocycles
4. Significant physiological activity

Properties

- Majority of alkaloids are colourless crystalline solids. Except for a few like coniine, nicotine etc.

- They are optically acive, majority being laevorotatory.

- They are basic in nature and thereby react with acids to form salts.

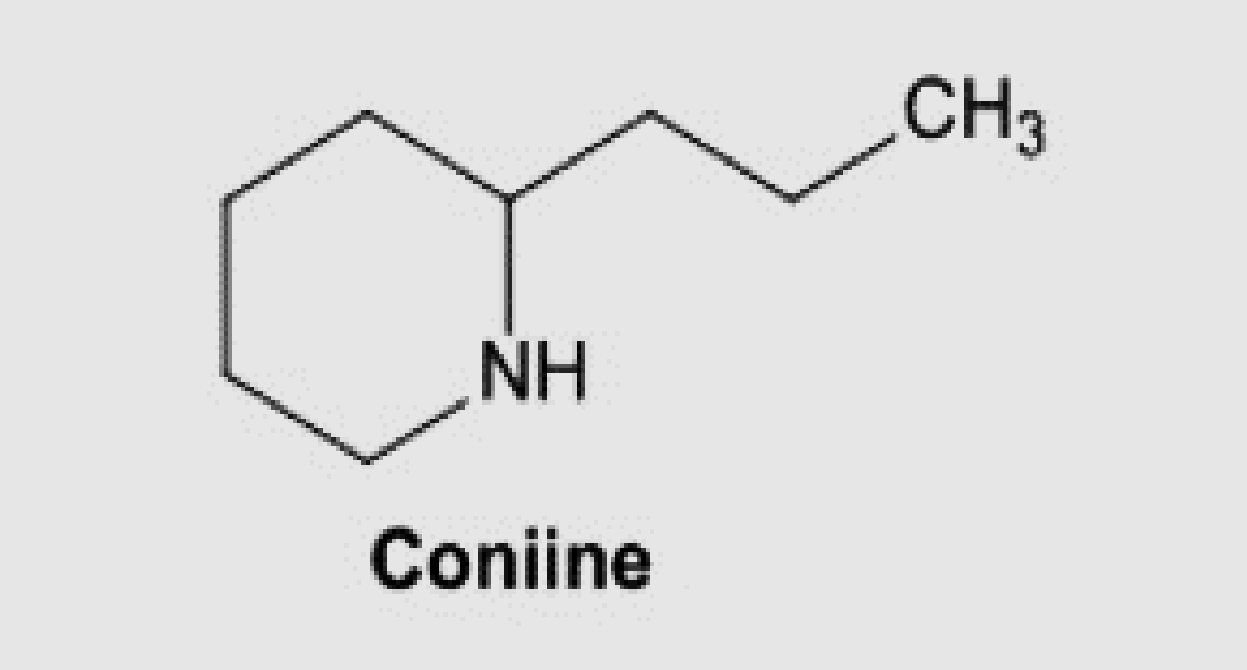
- Solutions of alkaloids in dilute mineral acids react with certain reagents to form compounds with characteristics colours and melting points. These reagents are thus used for the identification of alkaloids and hence are known as alkaloidal reagents.

CONIINE

Type of Piperidine alkaloid

$C_8H_{17}N$

STRUCTURE



Coniine

- Coniine is a poisonous alkaloid found in poisonous hemlock and the yellow pitcher plant.

- It is a neurotoxin which disrupts the peripheral nervous system. It is toxic to humans and all classes of livestock.

- It was first synthesized by Albert Ladenburg in 1886. It was the first of the alkaloids to be synthesized.

Properties

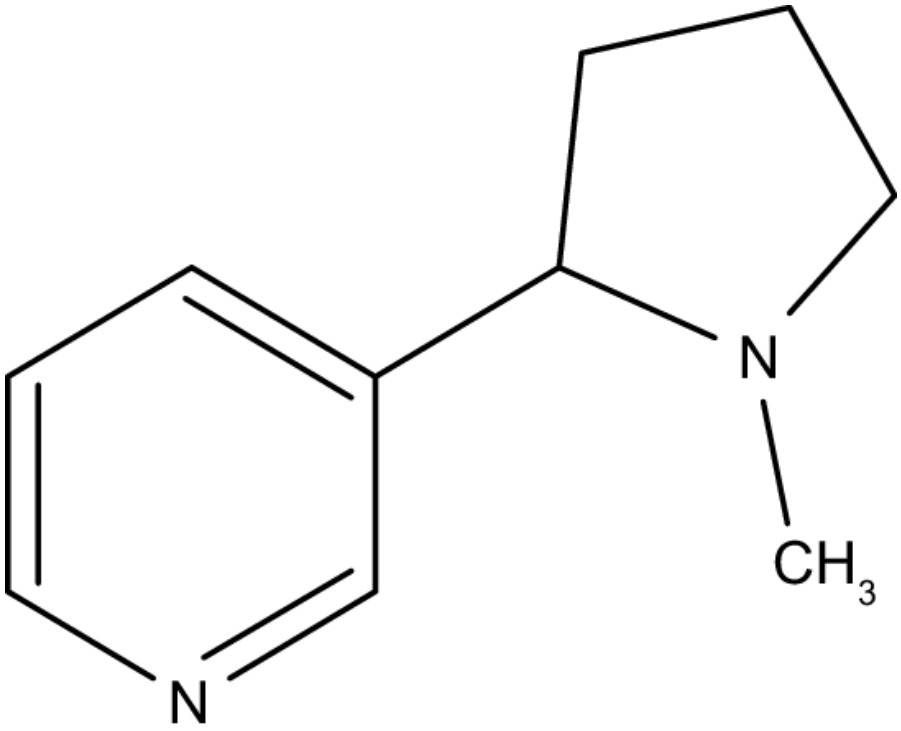
- Optically active
- Strong base
- Coniine is slightly soluble in cold water, less so in hot water.
- Coniine is a colorless alkaline liquid, with a penetrating odour and a burning taste
- Coniine solidifies into a soft crystalline mass at −2 °C. It slowly oxidizes in the air.
- Coniine and its salts are deadly poisonous. When taken in excess the death is caused because of the paralysis of motor nerve endings and respiratory failure.

NICOTINE

$C_{10}H_{14}N_2$

Tobacco plant

STRUCTURE



NICOTINE

- Nicotine is Chief alkaloid of Tobacco Plant.
- IUPAC name 3-(1-methyl-2-pyrrolidinyl) pyridine.
- It is a bicyclic compound with a pyridine and a pyrrolidine cycle.
- The alkaloid was named after the Frenchman NICOT who introduced tobacco in France in 1560.

Properties

- It is the most important tobacco alkaloid occuring in Nicotinana tobacum and other nicotiana species.
- Nicotine is one of the few liquid alkaloids.
- In its pure state it is a colourless, liquid with an oily consistency.
- when exposed to light or air, it acquires a brown colour and gives off a strong odour of tobacco.
- It is very poisonous (dose 30-50 mg) and paralyses nervous system & respiratory failure.

Medicinal importance-Nicotine

- Nicotine is used to help to treat addiction to or dependence on smoking cigarettes. Quting smoking abruptly can cause one to experience many severe effects and cravings called withdrawal symptoms. Products that deliver low doses of nocotine are sometimes used to ease quitting and manage withdrawal symptoms. This form of treatment is called nicotine replacement therapy (NRT). NRT products contains less nicotine that cigarettes and do not contain many harmful chemicals typically found in cigarettes

- Nicotine increases the brain metabolism. It also acts on its pleasure centers, which is why nicotine is being used in people with a tendency for depression.

Medicinal importance-Nicotine

➢Nicotine has a lot of therapeutic uses. There's evidence that it is useful in treating Parkinson's disease, Alzheimer's - their level of concentration, their ability to focus. It is being used for that purpose.

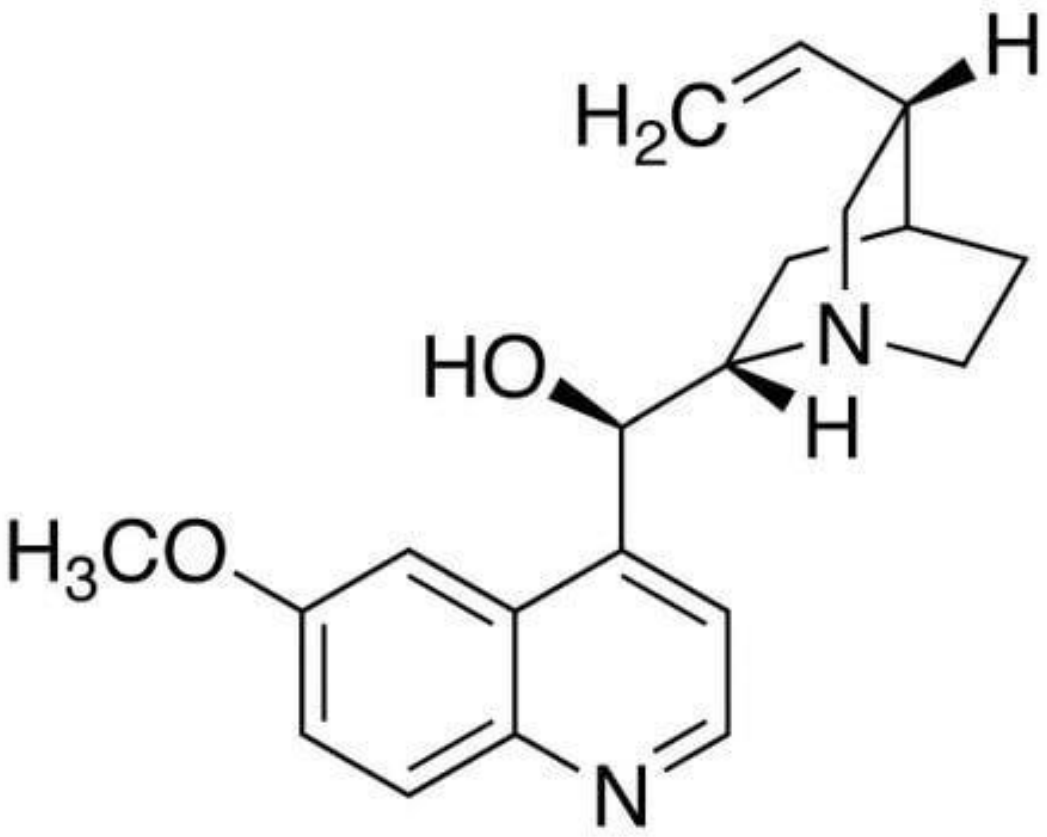
➢Nicotine acts as a weight suppressant. Recent study shows how nicotine affects metabolism by triggering the body to burn certain kinds of fat cells through a process called thermogenesis.

QUININE

$C_{20}H_{24}O_2N_2$

- Quinine is a cinchona alkaloid . It is occur in the bark of cinchona tree. It has a role as an antimalarial, a muscle relaxant and a non-narcotic analgesic.
- It was used commonly and as a flavoring agent, and is still useful for the treatment of babesiosis.
- White solid having bitter taste.
- Insoluble in water.
- Naturally occuring product is laevorotatory.

STRUCTURE



Quinine was first isolated from the bark of a cinchona tree

Medicinal importance- Quinine

- Quinine is a medication used to treat malaria, this medication is used alone or with other medication to treat malaria caused by mosquito bites in countries where malaria is common. It is used to kill the malaria parasites living inside red blood cells.
- Quinine is used to treat lupus and arthritis. Quinine was frequently prescribed as an off-label treatment for leg cramps at night(off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group).
- Common side effects include headache, trouble seeing sweating etc. More severe side effects include deafness, low blood platelets and irregular heartbeat.

Uses

- **Quinine** is used mainly as **anti-malarial** in a dose of 2g of quinine sulfate or other salt for 14 days.
- **Quinidine** is used as a **cardiac depressant** (**anti-arrhythmic**), particularly to inhibit auricular fibrillation in a dose of 0.6-1.6 g of quinidine sulfate daily.
- **Cinchonine** and **cinchonidine** are used as **anti-inflammatory**.
- **Quinine** is used as a flavor in carbonated beverages.

Medicinal importance- Morphine

- Morphine works by blocking pain signals from travelling along the nerves to the brain. Morphine is used to treat moderate to severe pain.
- Pain relief in terminal cancer patients. This is part of the palliative care or end-of-life care given to cancer patients with advanced disease.
- Pain relief in pulmonary edema or water collected in the lungs, as seen in acute left ventricular failure or severe acute heart failure.
- Relief of severe joint pain caused by disabling diseases such as rheumatoid arthritis and osteoarthritis.
- General anaesthesia to sedate a patient

Medicinal importance- Cocaine

- Cocaine is a stimulant that speeds up the workings of the brain.
- Cocaine is used medically as an anesthetic, vasoconstrictor and as a diagnostic tool.
- Acute exposure to cocaine has many effects on humans, including euphoria, increases in heart rate and blood pressure, and increases in cortisol secretion from the adrenal gland.
- Cocaine overdose may cause seizures, abnormally high body temperature and a marked elevation of blood pressure, which can be life-threatening, abnormal heart rhythms, and death.

Medicinal importance- Reserpine

- Reserpine is used to treat severe agitation in patients with mental disorders.

- Reserpine is recommended as an alternative drug for treating hypertension.

- It works by slowing the activity of the nervous system, causing the heartbeat to slow and the blood vessels to relax.

Steroids

- A steroid is a biologically active organic compound with four rings arranged in a specific molecular configuration.

- Steroids have two principal biological functions: as important components of cell membranes that alter membrane fluidity; and as signaling molecules. Hundreds of steroids are found in plants, animals and fungi

Steroids

- The steroid core structure is typically composed of seventeen carbon atoms, It has bonded in four "fused" rings: three six-member cyclohexane rings (rings A, B and C) and one five-member cyclopentane ring (the D ring).

- Steroids are a man-made version of chemicals, known as hormones, that are made naturally in the human body. Steroids are designed to act like these hormones to reduce inflammation.

Cholesterol

- Cholesterol is biosynthesized by all animal cells and is an essential structural component of animal cell membranes.
- When chemically isolated, it is a yellowish crystalline solid.
- Cholesterol is a waxy type of fat, or lipid, which moves throughout your body in your blood.
- Every cell in the body needs cholesterol, which helps the cell membranes form the layers.
- These layers protect the contents of the cell by acting as the gatekeeper to what things can enter or leave the cell. Cholesterol is also needed to make certain hormones and to produce vitamin D.

Type of cholesterol

- Cholesterol moves throughout the body carried by lipoproteins in the blood. These lipoproteins include:

- Low-density lipoprotein (LDL) is one of the two main lipoproteins. LDL is often called “the bad cholesterol.”
- High-density lipoprotein (HDL) is the other main lipoprotein. HDL is often called “the good cholesterol.”
- Very-low-density lipoproteins (VLDL) are particles in the blood that carry triglycerides.

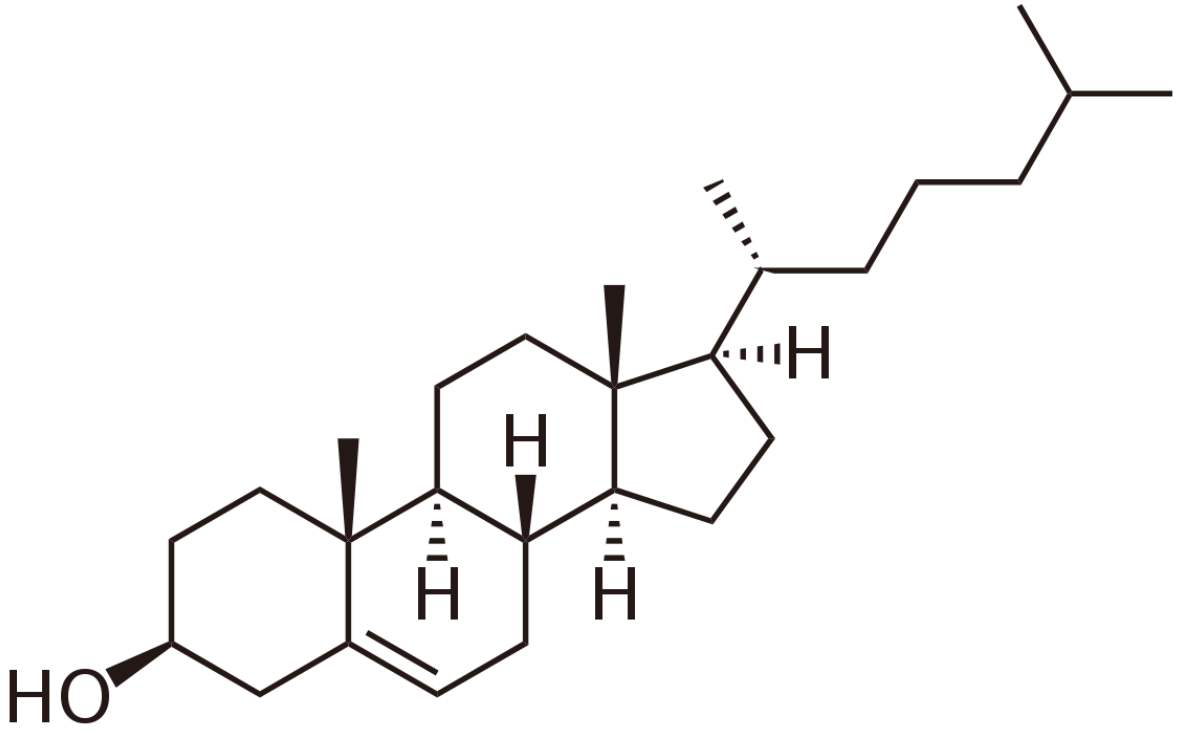
Low-density lipoprotein (LDL)

- Low-density lipoprotein is called the **bad cholesterol** LDL can build up on the walls of your arteries. The fatty deposits form plaque that lines your arteries and may cause blockages. This build-up is called **atherosclerosis.** High levels of LDL cholesterol raise your risk for heart disease and stroke.

High-density lipoprotein (HDL)

- HDL is called the **good cholesterol**. It's good because it carries away other kinds of cholesterol, (including LDL), from the arteries. HDL drops off other types of cholesterol at the liver to be removed from the body. Higher levels of HDL reduce the risk for heart disease.

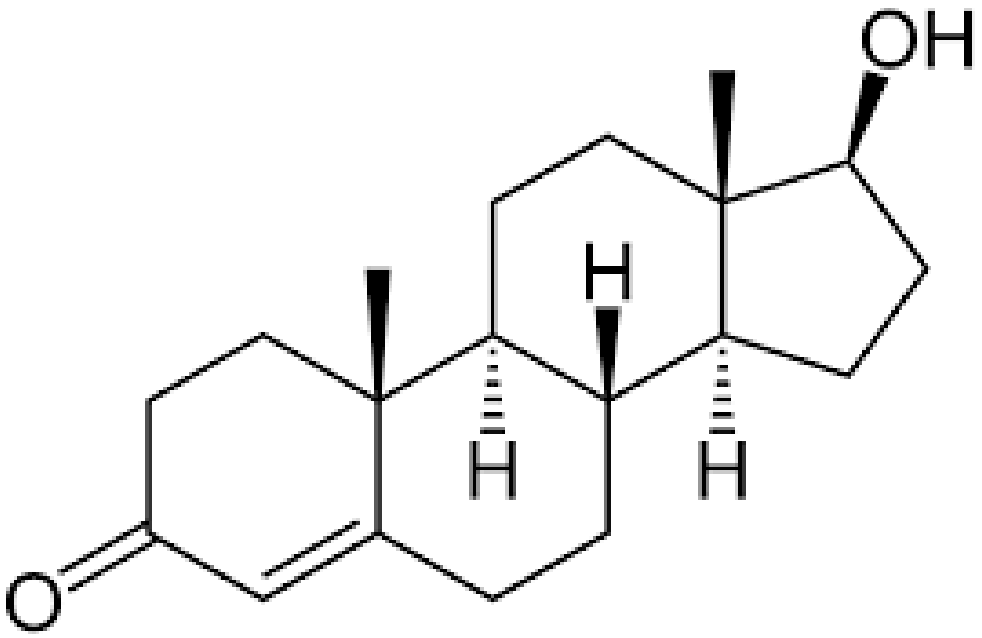
Structure of Cholesterol



- Cholesterol is a 27 carbon compound with a unique structure with a hydrocarbon tail, a central sterol nucleus made of four hydrocarbon rings, and a hydroxyl group. The center sterol nucleus or ring is a feature of all steroid hormones.

- Cholesterol is a structural component of cell membranes and serves as a building block for synthesizing various steroid hormones, vitamin D, and bile acids. Besides their structural role providing stability and fluidity, cholesterol also plays a crucial role in regulating cell function.

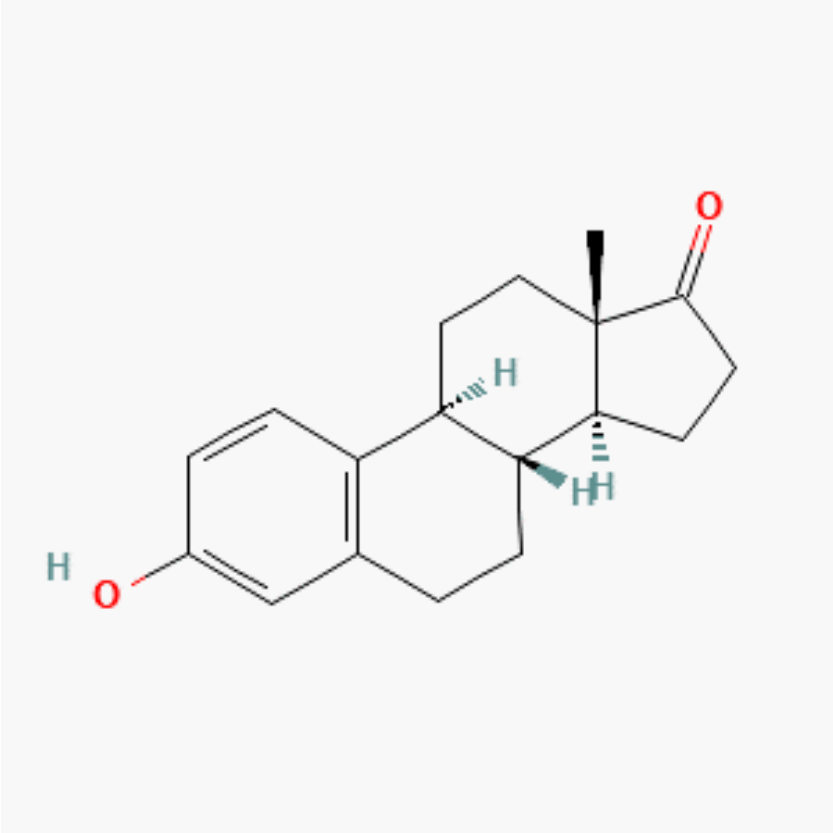
Structure of Testosterone



- **Testosterone** is the primary sex hormone and anabolic steroid in males. In humans, testosterone plays a key role in the development of male reproductive tissues such as testes and prostate, as well as promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair.

- Testosterone in both sexes is involved in health and well-being, including moods, behaviour, and in the prevention of osteoporosis. Insufficient levels of testosterone in men may lead to abnormalities including frailty and bone loss.

Structure of Oestrone



- **Oestrone** , also spelled **estrone**, is a steroid, a weak estrogen, and a minor female sex hormone. It is one of three major endogenous estrogens, the others being estradiol and estriol.

- Estrone, as well as the other estrogens, are synthesized from cholesterol and secreted mainly from the gonads, though they can also be formed from adrenal androgens in adipose tissue. Relative to estradiol, both estrone and estriol have far weaker activity as estrogens. Estrone can be converted into estradiol, and serves mainly as a precursor or metabolic intermediate of estradiol. It is both a precursor and metabolite of estradiol.

Vitamin

- A vitamin is an organic molecule.
- It is an essential micronutrient which an organism needs in small quantities for the proper functioning of its metabolism.
- Essential nutrients cannot be synthesized in the organism therefore must be obtained through the diet.
- **Vitamins are grouped into two categories:**

1. Fat-soluble vitamins are stored in the body's liver, fatty tissue, and muscles. The four fat-soluble vitamins are vitamins A, D, E, and K. These vitamins are absorbed more easily by the body in the presence of dietary fat.

2. Water-soluble vitamins are not stored in the body

Water-soluble vitamins

- Water-soluble vitamins are those that are dissolved in water and readily absorbed into tissues for immediate use. Because they are not stored in the body, they need to be replenished regularly in our diet.
- The water-soluble vitamins include the B-complex group and vitamin C.

Fat-soluble vitamins

- Fat-soluble vitamins are dissolved in fats. They are absorbed by fat globules that travel through the small intestines and distributed through the body in the bloodstream.
- Unlike water-soluble vitamins, excess fat-soluble vitamins are stored in the liver and fatty (adipose) tissues for future use.
  Eg:Vitamin A, Vitamin D ,Vitamin E , and Vitamin K

B-complex group

Vitamin B1 (thiamine)

Vitamin B2 (riboflavin)

Vitamin B3 (niacin)

Vitamin B5 (pantothenic acid)

Vitamin B6 (pyridoxine)

Vitamin B7 (biotin)

Vitamin B9 (folate or folic acid

Vitamin B12 (cobalamin)

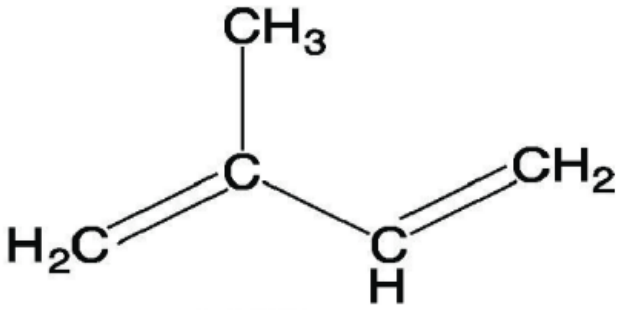
Terpenes

- The term ‘terpene’ was given to the compounds isolated from terpentine, a volatile liquid isolated from pine trees.
- The term ‘terpene’ was originally employed to describe a mixture of isomeric hydrocarbons of the molecular formula C10H16 occurring in the essential oils obtained from sap and tissue of plants, and trees. But there is a tendency to use more general term ‘terpenoids’ which include hydrocarbons and their oxygenated derivatives.
- Definition: “Terpenoids are the hydrocarbons of plant origin of the general formula (C5H8)n as well as their oxygenated, hydrogenated and dehydrogenated derivatives.
- The terpenoids, also known as isoprenoids, are a large and diverse class of naturally occurring organic chemicals derived from the 5-carbon compound isoprene, and the isoprene polymers called terpenes.

Isoprene rule

- Thermal decomposition of terpenoids give isoprene as one of the product. Otto Wallach pointed out that terpenoids can be built up of isoprene unit.

- Isoprene rule states that *the terpenoid molecules are constructed from two or more isoprene unit*. *Special isoprene rule states that the terpenoid molecule is constructed of two or more isoprene units joined in a 'head to tail' fashion.*



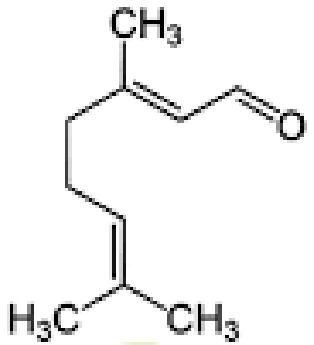
Classification of terpenoids

- The terpenoids are classified on the basis of the number of isoprene units they contain. Since the simplest combination of these would contain at least two isoprene units, the suffix ‘mono’ is used for such a combination and the terpenoids are classified accordingly as follows

S. No.	Number of carbon atoms	Value of *n*	Class
1.	10	2	Monoterpenoids ($C_{10}H_{16}$)
2.	15	3	Sesquiterpenoinds ($C_{15}H_{24}$)
3.	20	4	Diterpenoids ($C_{20}H_{32}$)
4.	25	5	Sesterpenoids ($C_{25}H_{40}$)
5.	30	6	Triterpenoids ($C_{30}H_{48}$)
6.	40	8	Tetraterpenoids ($C_{40}H_{64}$)
7.	>40	>8	Polyterpenoids $(C_5H_8)n$

Citral($C_{10}H_{16}O$)

Citral is an acyclic monoterpene aldehyde, it is made of two isoprene units.



Citral

Source,Isolation

It is a major terpene of lemon grass oil.It is also present in oils of citronella.

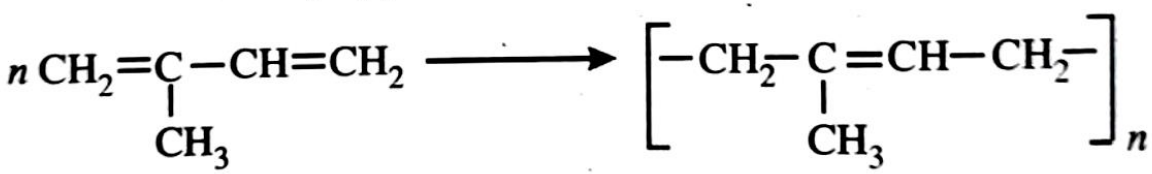
Isolation:It is obtained from lemon grass oil by fractional distillation in vacuo and purified via crystalline sodium bisulphite adduct.

Natural rubber

- Natural rubber occurs as latex (a colloidal dispersion of rubber particles in water) that oozes from the barks of rubber trees when they are cut.
- Latex is diluted (so that it contains 15-20% rubber), filtered and treated with formic acid or acetic acid when rubber gets coagulated as a soft white mass. This is separated, rolled into sheets using soft rollers and smoked at a temperature of 40-50°C.
- Crude rubber is a soft, sticky and elastic solid. It is insoluble in water, alcohol and acetone but soluble in ether, CCl4, and gasoline.

Structure of Natural Rubber

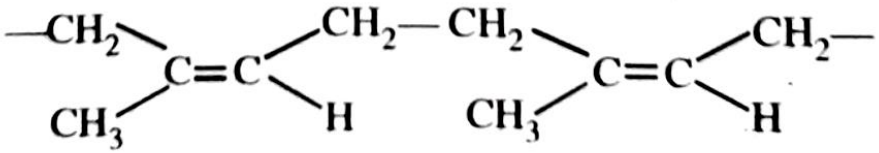
Natural rubber is a polymer of *isoprene* [*i.e.*, 2-methylbuta-1,3-diene] and thus has the molecular formula $(C_5H_8)_n$.



Isoprene

Poyisoprene
(Natural rubber)

The structure results from the 1,4-addition of the isoprene units in a head-to-tail fashion. Natural rubber is, in fact, *cis*-polyisoprene.



Natural rubber (*cis*-Polyisoprene)

Lipids

- Lipids are organic compounds that contain hydrogen, carbon, and oxygen atoms, which forms the framework for the structure and function of living cells.
- These organic compounds are nonpolar molecules, which are soluble only in nonpolar solvents and insoluble in water.
- The word lipid" originates from the Greek word "lipos" which means "fat".
- The simplest of lipids are esters of long chain fatty acids and alcohols, and include fats, oils and waxes.

Classification of lipids

(a)Simple lipids: Simple lipids are esters of fatty acids with various alcohols. For eg., fats and waxes.

(b)Complex lipids: Complex lipids are esters of fatty acids with groups other than alcohol and fatty acids. For eg., phospholipids and sphingolipids.

Classification of lipids

The simplest and advantageous classification of lipids is as **hydrolysable lipids and non-hydrolysable lipids**

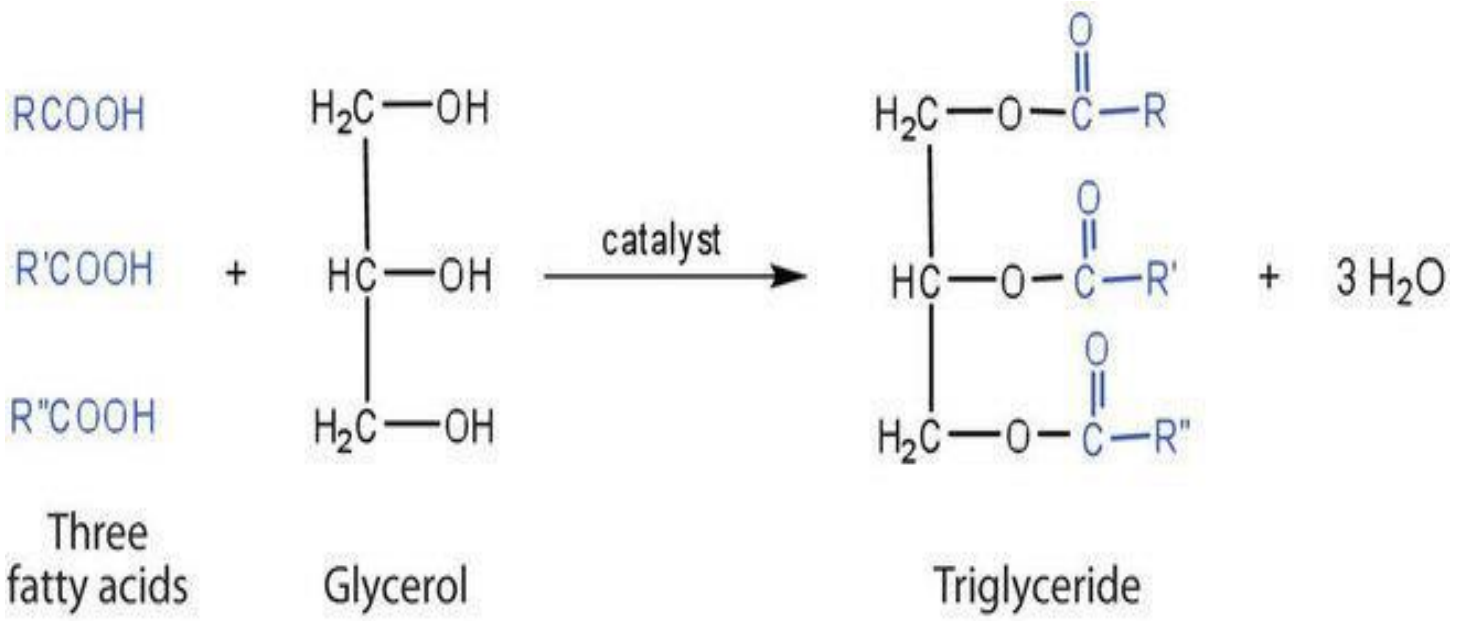
(i) **Hydrolysable lipids** are those that can be cleaved into smaller molecules by acidic or alkaline hydrolysis. Fats, oils, waxes etc are examples for hydrolysable lipids.

(ii) **Non-hydrolysable lipids** are those that cannot be cleaved into smaller units by acidic or alkaline hydrolysis. Steroids, terpenes, carotenoids etc are examples for non-hydrolysable lipids.

Oils and Fats

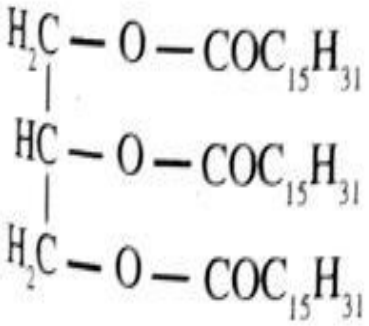
- Fats and oils are mixtures of triglycerides.
- Physically, triglycerides of saturated fatty acids are solids at ordinary temperature and are called fats.
- Triglycerides of unsaturated fatty acids are liquids at ordinary temperature and are termed oils.
- However, there is no clear line of demarcation between fats and oils. We can only say that oils generally contain a greater proportion of unsaturated glycerides than fats.
- Fats are solid triglycerides whereas oils are liquids at room temperature.
- Triglycerides are triesters of glycerol with unbranched long chain fatty acids. These fatty acids may be saturated ones like palmitic acid ($C_{15}H_{31}COOH$), stearic acid ($C_{17}H_{35}COOH$), etc or unsaturated ones like oleic acid ($C_{17}H_{33}COOH$), linoleic acid ($C_{17}H_{31}COOH$), etc.

Oils and Fats

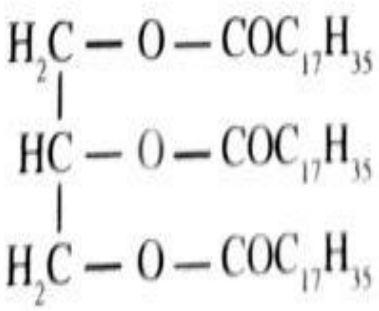


If the three fatty acid component chains R, R' and R'' are the same in triglycerides, it is called a simple triglycerides. On the other hand, a triglyceride that has two or all of the fatty acid component chains R, R', R'' different is called a mixed triglycerides.

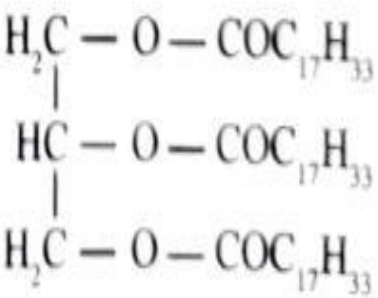
Examples



Tripalmitin

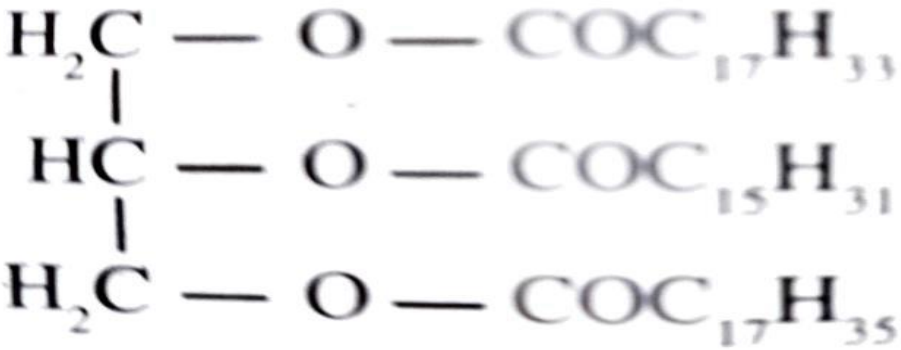


Tristearin



Triolein

Simple triglycerides



α -Oleo- β -palmito- α′ -stearin

Mixed triglycerides

Trivial name	*Systematic name**	*Carbon skeleton*	*Structure†*	*Common source*
Butyric	*n*-Butanoic	4 : 0	$CH_3(CH_2)_2COOH$	Butter
Caproic	*n*-Hexanoic	6 : 0	$CH_3(CH_2)_4COOH$	Coconut and palm oils
Caprylic	*n*-Octanoic	8 : 0	$CH_3(CH_2)_6COOH$	Coconut and palm oils
Capric	*n*-Decanoic	10 : 0	$CH_3(CH_2)_8COOH$	Coconut and palm oils
Lauric (*laurus*^{L} = laurel plant)	n-Dodecanoic	12 : 0	$CH_3(CH_2)_{10}COOH$	Laurel oil, Spermaceti
Myristic (*Myristica*^{L} = nutmeg genus)	*n*-Tetradecanoic	14 : 0	$CH_3(CH_2)_{12}COOH$	Butter and wool fats
Palmitic (*palma*^{G} = palm tree)	*n*-Hexadecanoic	16 : 0	$CH_3(CH_2)_{14}COOH$	Animal and plant fats
Stearic (stear = hard fat)	*n*-Octadecanoic	18 : 0	$CH_3(CH_2)_{16}COOH$	Animal and plant fats
Arachidic (*Arachis*^{L} = legume genus)	*n*-Eicosanoic	20 : 0	$CH_3(CH_2)_{18}COOH$	Groundnut oil
Behenic	*n*-Docosanoic	22 : 0	$CH_3(CH_2)_{20}COOH$	Groundnut oil
Lignoceric (*lignum*^{L} = wood; *cera*^{L} = wax)	*n*-Tetracosanoic	24 : 0	$CH_3(CH_2)_{22}COOH$	Groundnut and Rapeseed oils
Cerotic	*n*-Hexacosanoic	26 : 0	$CH_3(CH_2)_{24}COOH$	Wool fat
Montanic	*n*-Octacosanoic	28 : 0	$CH_3(CH_2)_{26}COOH$	—

* The prefix *n*- indicates the "normal" unbranched structure. For instance, "octadecanoic" simply indicates 18 carbon atoms, which could be arranged in a variety of branched forms. Thus, *n*-octadecanoic specifies the linear, unbranched form.

† All fatty acids are shown in their unionized form. At pH 7, all free fatty acids have an ionized carboxylate. Note that the numbering of carbon atoms begins at the carboxyl group carbon.

Analysis of fats and oils

- Fats and oils are obtained from natural sources and different samples may vary in purity and composition.

- Further, prolonged contact with air and moisture causes many non-drying oils and fats to undergo complex chemical changes. These include their hydrolysis by enzymes from microorganisms, oxidation of unsaturated fatty acids formed by hydrolysis, oxidation and decarboxylation of saturated fatty acids etc.

- The product formed from chemical changes due to atmospheric exposure are often foul smelling and foul-tasting aldehydes and ketones. This in turn causes the samples of fats and oils to develop unpleasant odours and flavours, commonly described by the term rancidity; the term rancidification summarizes the overall changes.

Acid value or Acid number

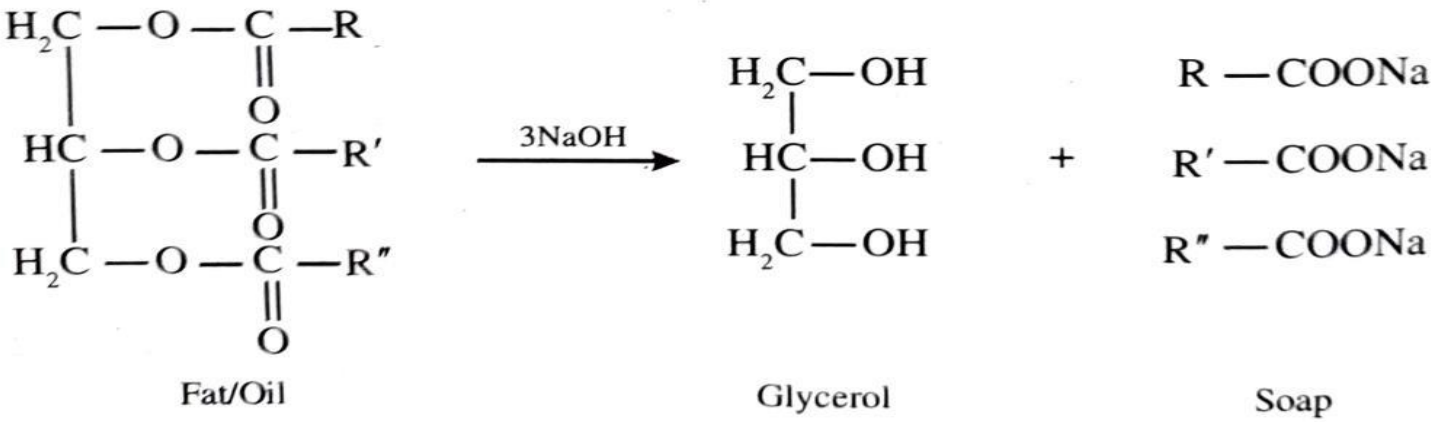
- The acid value of a particular sample of fat/oil is a parameter that gives us an idea about the amount of free acids present in it, and thus an idea about the rancidity that it has suffered under the conditions in which it is stored.
- The acid value or acid number of a sample of fat or oil is defined as the number of milligrams of potassium hydroxide (KOH) required to neutralize the free carboxylic acids present in I g of the fat or oil.

- The acid value of a fat/oil is determined by dissolving a known quantity of it in ethanol and then titrating it against standardised potassium hydroxide solution using phenolphthalein as indicator.

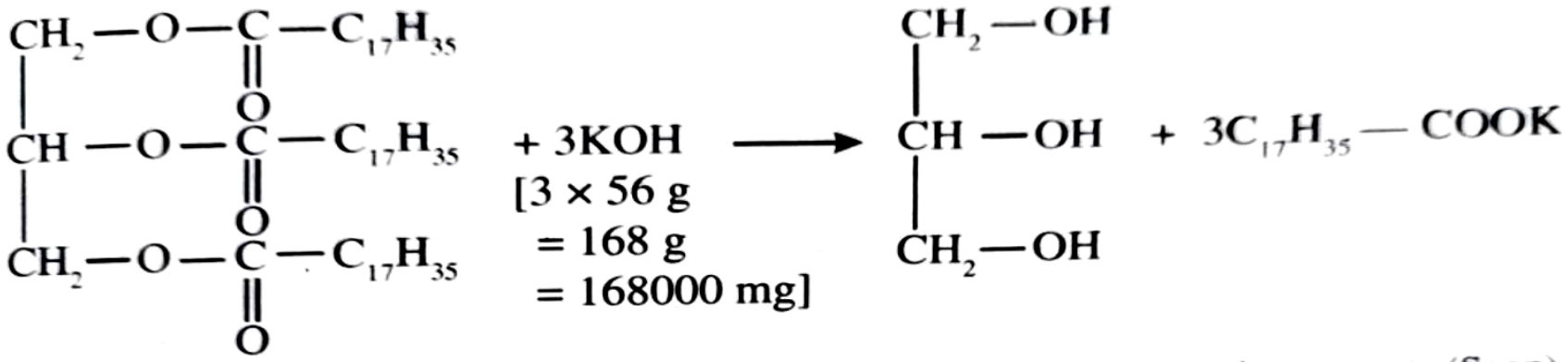
- Higher the acid value of a sample of fat/oil, the higher is the amount of free acids in it, and the higher is its rancidity due to improper storage. A properly stored sample of fat/oil would be less rancid and would have a lower acid value.

Saponification value or Saponification number

- Alkaline hydrolysis (by boiling with aq. NaOH or KOH) of fats and oils yields glycerol as well as soap which is a mixture of the alkali metal salts (sodium or potassium salts) of fatty acids. The reaction is called saponification. [The name originates from the Latin word saponis which means "soap"]



- The saponification value or saponification number of a fat or an oil is defined as the number of milligrams of KOH required to saponify (or hydrolyze) I gram of the fat or oil."



Tristearin (Glyceryl tristearate) (890 g)

Glycerol

Potassium stearate (Soap)

From the equation it is evident that:

890 g of tristearin (molar mass = 890 g mol^{-1}) requires 168000 mg of KOH for complete saponification.

Hence, 1 g of tristearin requires $\frac{168000}{890}$ mg of KOH for complete saponification.

$$= 188.76 \text{ mg}$$

i.e., The saponification value of tristearin = 188.76.

Obviously, if M g mol^{-1} is the molar mass of a fat or oil,

its saponification value $= \frac{168000}{M}$.

Saponification value or Saponification number

- It is obvious that the higher the saponification value of a fat or an oil the lower the average molar mass of the fat or oil.

- In other words, a high saponification value indicates that the percentage of the shorter chain fatty acid portions in the triglyceride is higher.

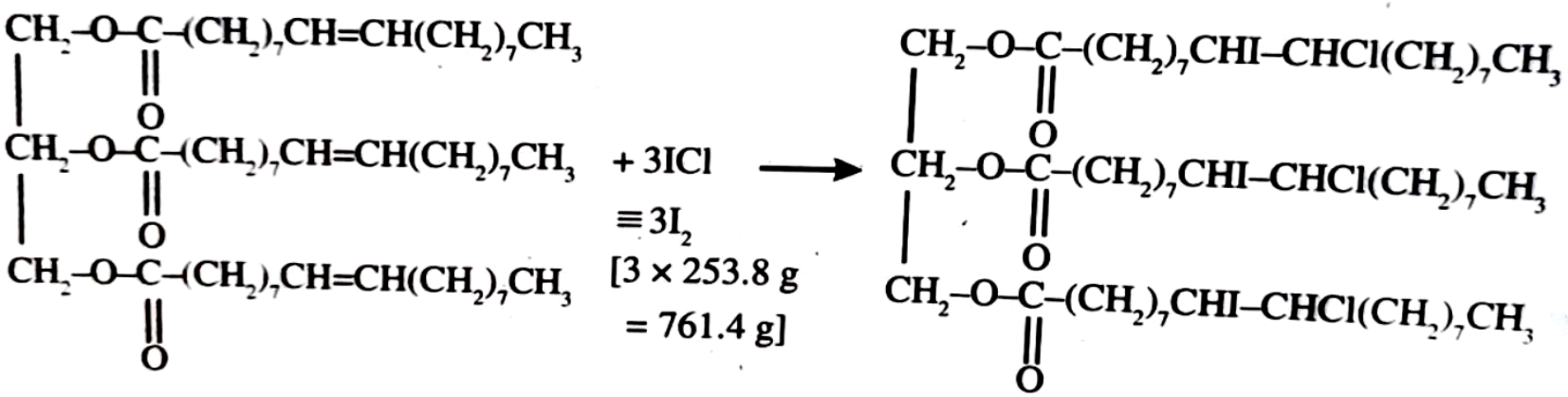
Iodine value or Iodine number

- The iodine value or iodine number of a fat or oil is defined as the number of grams of iodine (as calculated from the number of equivalents of ICl) that will add to 100 gram of the fat or oil."

- Determination of the iodine value of a fat or an oil (a mixture of triglycerides) provides an idea about the extent of unsaturation in the fat or oil.

- It is obvious that the higher the iodine value of a fat or an oil, the greater is the extent of unsaturation (i.e, the number of double bonds) in it. For a fat having no double bonds in its components, i.e , for a completely saturated sample, the iodine value would be zero.

In order to understand the significance of iodine value, let us consider that of a single glyceride, *e.g.*, *triolein* or *glyceryl trioleate*, which contains three carbon-carbon double bonds. The addition of ICl to it may be represented as follows. [Only one product isomer is shown here.]



Triolein
(Glyceryl trioleate)
(884 g)

(Addition product)

From the equation it is evident that:

884 g of triolein (molar mass = 884 g mol^{-1}) adds 3 moles of ICl, equivalent to 3 moles of I_2 or 761.4 g of I_2.

Hence, 100 g of triolein adds $\frac{761.4}{884} \times 100$ g of I_2.

$= 86.13$ g

i.e., The iodine value of triolein $= 86.13$.