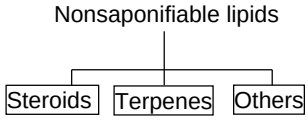
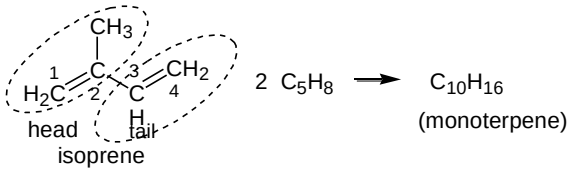
**№ 46. NONSAPONIFIABLE LIPIDS. TERPENES AND CAROTENOIDS – CHARACTERISTICS, TYPES, STRUCTURE, REPRESENTATIVES**

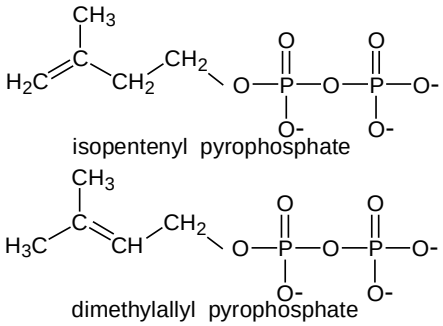



**Nonsaponifialbe lipids** (nonhydrolyzable) are those that are not broken apart by alkaline hydrolysis. They are large group that include steroids (cholesterol and sex hormones), terpenes, fat-soluble vitamins (such as vitamins A, D, E and K), prostaglandins etc.

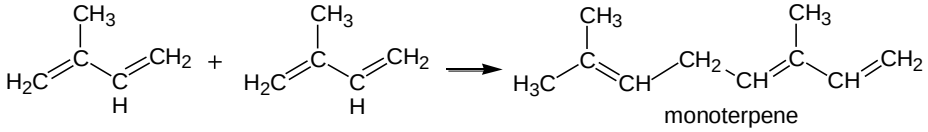
**Terpenes** are a large and varied class of hydrocarbons, produced primarily by a wide variety of plants and contained in essential oils. Terpenes are also called isoprenoids (terpenoids) which have also other functional groups (OH, CO etc). Well-known terpenoids include citral, menthol, and camphor. Along with proteins, carbohydrates, NA and other lipids, isoprenoids are widespread class of compounds in living organisms. Terpenes are abundant in essential oils of many plants and flowers. They are responsible for the odor of pine trees and contribute to the scent of eucalyptus, the flavors of cinnamon, clover and ginger. They determine the color of yellow flowers, carrots, and tomatoes. It has been found that the oil of turpentine and the entire group of piney-smelling compounds have ratio C:H of 5:8. The same ratio was found later in many other essential oils, hence their name – terpenes

Terpenes are biogenetically constructed from isoprene ($C_5H_8$, 2-methyl-1,3-butadiene) units. The terpenoids in Nature general formula is $(C_5H_x)_n$ (often x=8), however they are not produced directly from isoprene. The basic biochemically relevant isoprene subunits are isopentenyl pyrophosphate and dimethyl allyl pyrophosphate, which are isomers.




By definition the isoprene molecule has a "head" (the branched end) and a "tail" (the unbranched end). In terpenes the isoprene units are joined together **head-to-tail fashion** (but occasionally tail-to-tail). Such connectivity constitutes the **biogenetical "isoprene rule"**. Shown below is an illustration of the isoprene rule which is applicable to the constitution of carotenoids and steroids.



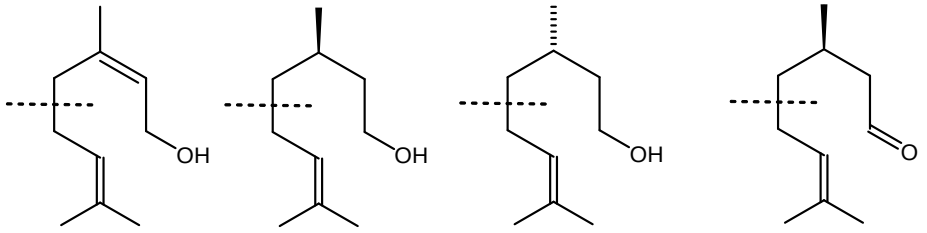

The biological precursors for similar reactions are the pyrophosphates above. As such derivatives, the estimated production rate of isoprene in the human body is 0.15 mmol/kg/h, equivalent to approximately 17 mg/day for a 70 kg person. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate are arranged in an alternating pattern (head-to-tail according to the isoprene rule) to make isoprene chains, also called polyprenyl chains, of varying lengths. Two of the main polyprenyl chains are farnesyl, which is the 15-carbon chain, and geranyl, which is the 20-carbon chain.

Terpenes can be classified according to the number of isoprene units they contain: two isoprene units generate a monoterpene with 10 carbon atoms. Examples of monoterpenes are: geraniol, limonene, and terpineol. Sesquiterpenes $(C_5H_8)_3$ have 15 carbon atoms (the *sesqui-* prefix means one and a half). Examples of sesquiterpenes are: farnesenes, farnesol. Diterpenes $(C_5H_8)_4$ contain four isoprene units and are common, with representatives phytol and vitamin A. Terpenes with 25 carbon atoms (sesterpenes) are rare, however triterpenes $(C_5H_8)_6$ are widely distributed. There are also tetraterpenes $(C_5H_8)_8$. Another classification account for the nature of the hydrocarbon chain – aliphatic (open chain) and cyclic (mostly monocyclic and bicyclic, but known are tricyclic). Many terpenes contain functional groups, especially carbonyl and hydroxyl groups.

**Physical properties and use**: Terpenes are insoluble in water. The lower members are volatile (without leaving oily residue) and with pleasant odor. They are main ingredient of essential oils and therefore are used widely in perfumery, cosmetics, for flavoring food and drinks, scenting incense and cleaning products.

Plant terpenoids are used extensively for their aromatic qualities. They play a role in traditional herbal remedies and are under investigation for antibacterial, antineoplastic, and other pharmaceutical functions.

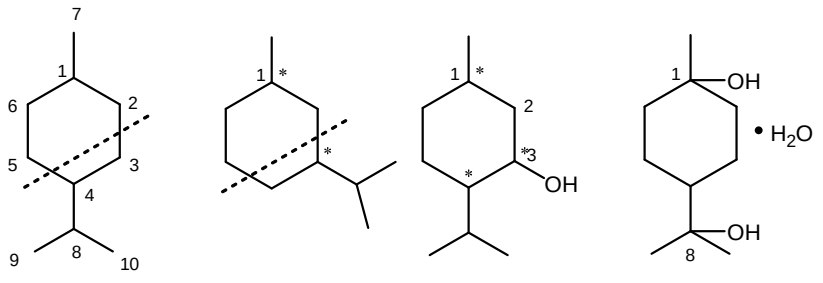
**Representatives**: **Monoterpenes** are a class of terpenes that consist of two isoprene units and have the molecular formula $C_{10}H_{16}$. Monoterpenes may be linear (acyclic) or they may contain rings. Biochemical modifications such as oxidation or rearrangement produce the related **monoterpenoids**. Examples of aliphatic (open chain) monoterpenes are geraniol, citronellol and citronellal which are mayor components of rose oil (in all structures below, the dashed line shows the disintegration to isoprene units). Geraniol is the primary part of rose oil, palmarosa oil, and citronella oil. It also occurs in small quantities in geranium, lemon, and many other essential oils. It appears as a clear to pale-yellow oil which is insoluble in water, but soluble in most common organic solvents. It has a rose-like odor and is commonly used in perfumes. (+)-Citronellol (as well as (-)-citronellol and (+)-citronellal, has single chiral carbon atom and therefore is optically active), which is found in citronella oil, is the more common isomer. (−)-Citronellol is found in the oils of rose (18-55%) and *Pelargonium* geraniums.




geraniol | (+)-citronellol in citronella oils | (-)-citronellol in rose and geranium oil | (+)-citronellal

rose oil is 10% geraniol and 45% citronellol - monoterpenoids

**Monocyclic monoterpenes.** One simple pattern of assembling two isoprene units into ring is that giving *p*-menthane or *m*-menthane skeleton. **Menthol** is a hydroxyl derivative of *p*-menthane, obtained from peppermint or other mint oils or made synthetically. It is a crystalline substance, clear or white in color, which is solid at r.t. and melts slightly above, sublimes. Menthol has three chiral centers (the asterisks), $2^3$=8 stereoisomers but the natural form is almost exclusively (−)-(1*R*,2*S*,5*R*)-menthol. The other stereoisomers differ in their odor and physical properties. Menthol has local anesthetic (in dentistry) and counterirritant qualities, and it is widely used to relieve minor throat irritation. Menthol's ability to chemically trigger the cold-sensitive receptors in the skin is responsible for the well known cooling sensation that it provokes when inhaled, eaten, or applied to the skin. In this sense it is similar to capsaicin, the chemical responsible for the spiciness of hot peppers (which stimulates heat sensors, also without causing an actual change in temperature). Menthol is used as an additive to toothpaste, soap bars, to aromatize foods and beverages, and some remedies.

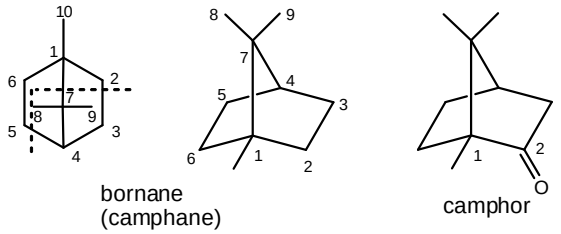



*p*-menthane | *m*-menthane | menthol | 1,8-mentahnediol monohydrate

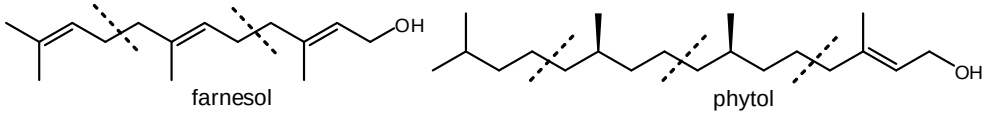
Terpenehydrate's name comes from the crystallization as a monohydrate. It is *p*-menthane-1,8-diol. It is used in coughing out (anticoughing) preparations. The *p*-menthane-3,8-diol isomer is known and used in mosquitoes and black flies repellents.

**Bicyclic monoterpenes. Camphor** is a waxy solid with a strong, aromatic odor. It is a terpenoid with the chemical formula $C_{10}H_{16}O$. It is found in wood of the camphor laurel (*Cinnamomum camphora*), a large evergreen tree found in Asia (particularly in Borneo and Taiwan). It also occurs in some other related trees in the laurel family. Camphor is almost insoluble in water, sublimes at room temperature because of high vapor pressure at r.t. Camphor is a ketone derived from bornane skeleton. It has two stereogenic centers and exhibits optical rotation. It is used in medicine. Camphor is readily absorbed through the skin and produces a feeling of cooling similar to that of menthol and acts as slight local anesthetic and antimicrobial substance.

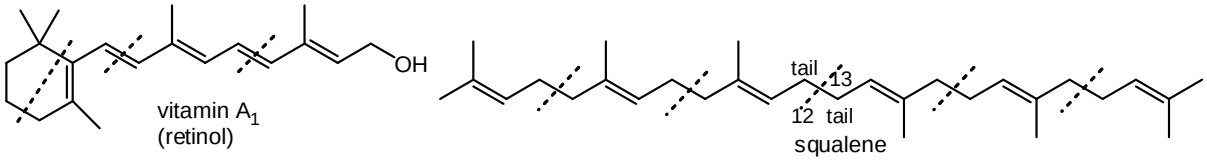
There are anti-itch gel and cooling gels with camphor as the active ingredient. Camphor is an active ingredient (along with menthol) in vapor-steam products, and it is effective as a cough suppressant. It may also be administered orally in small quantities for minor heart symptoms and fatigue.




**Sesquiterpenes** are $C_{15}$ compounds that are composed of three isoprene units. **Farnesol** which occurs in the essential oils of rose, acacia, and cyclamen, may be regarded as the parent acyclic alcohol. It has the characteristic odor of lily of the valley and is used in perfumery. **Diterpenes** are $C_{20}$ compounds consisting of four isoprene units. The alcohol **phytol** is a key acyclic diterpene alcohol that is a precursor for vitamins E and $K_1$. Phytol is an extremely common terpenoid, found in all plants, esterified to chlorophyll to confer lipid solubility. Phytol is found in petroleum sediments.



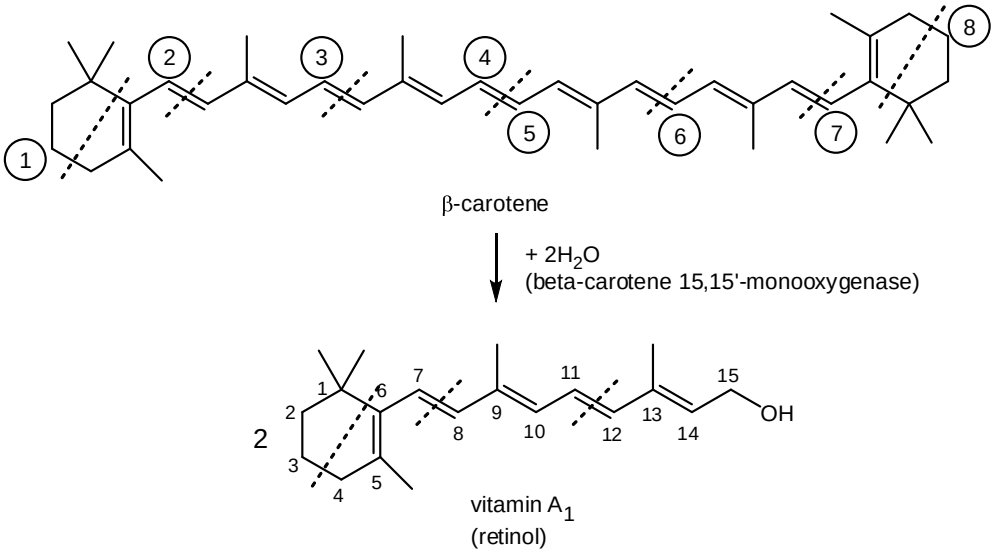

**Vitamin $A_1$** is also a diterpene. When the primary hydroxyl group ($CH_2OH$) of retinol is oxidized to aldehyde (CHO), the compound is **retinal**; and to carboxylic acid (COOH) – it is retinoic acid.




The $C_{30}$ compounds - triterpenes are abundant. An example is **squalene** which is high-boiling viscous oil that is found in large quantities in shark liver oil and can be isolated from olive oil. Squalene is common intermediate in the biosynthesis of steroids.

**Carotenoids** are examples of tetraterpenes, isoprenoids with 40 carbon atoms which are biosynthesized following the isoprene biogenetic rule and have eight isoprene units. They are integral and essential components of the photosynthetic membranes in all plants. Carotenoids that function within the photosynthetic machinery are commonly referred to as primary carotenoids, because they are essential. Their common structural feature (difference from terpenes like menthol and camphor) is the presence of conjugated double bonds with *trans* configuration. Thus created chromophore absorbs light in the visible, blue range and therefore carotenoids are colored in the complementary range compounds. They are easily oxidized by air. After hydrogenation they lose color and are stable towards air. They are nonpolar (long hydrocarbon chains) and soluble in lipids but insoluble in water.

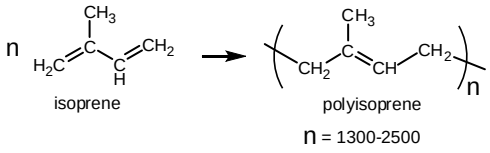
Structurally carotenoids are in the form of a polyene chain (many *conjugated* double bonds) which is sometimes terminated by rings. Therefore they are subdivided into: olephinic carotenoids and cyclic carotenoids. The carotenoids are classified as xanthophylls and carotenes. **Xanthophills**, such as lutein and zeaxanthin, contain oxygen (in OH, CO, COOH groups). The unoxygenated (oxygen free) carotenoids such as $\alpha$-carotene, $\beta$-carotene and lycopene are known as carotenes. **Carotenes** typically contain only carbon and hydrogen. Their color, ranging from pale yellow through bright orange to deep red, is directly linked to their structure. Xanthophylls are often yellow, hence their class name. Probably the most well-known carotenoid is the one that gives this second group its name, carotene, found in carrots (also apricots, tomatoes, squash, and they give the pleasant color of tree leaves in autumn) and is responsible for their bright orange color. Crude palm oil, however, is the richest source of carotenoids in nature in terms of retinol equivalent (provitamin A).




**β-Carotene** is a cyclic carotenoid with formula $C_{40}H_{56}$. It contains two end cycles (related to β-ionone) and 11 conjugated double bonds. It is a red-orange pigment abundant in plants and fruits. It is found also in milk, butter, serum and retina. Natural carotene is a mixture of α-, β-, and γ- isomers, the most common form of carotene is β-. It is a precursor (inactive form) of vitamin A (the oldest discovered vitamin in cod liver oil – 1909). Being highly conjugated, β-carotene is deeply colored, and as a hydrocarbon lacking functional groups, it is very lipophilic. Each "vitamin" may refer to several *vitamer* compounds that all show the biological activity associated with a particular vitamin. Such a set of chemicals are grouped under an alphabetized vitamin "generic descriptor" title, such as "vitamin A" which includes the compounds retinal, retinol, and many carotenoids. Vitamers are often inter-converted in the body.

**Retinol**, the animal form of vitamin A, is a fat-soluble vitamin important in vision and bone growth. Retinol is among the most useable forms of vitamin A, which also include **retinal** (aldehyde form), **retinoic acid** (acid form) and **retinyl ester** (ester form). The 11-*cis*-retinal isomer is the chromophore of rhodopsin, the vertebrate photoreceptor molecule. Rhodopsin is comprised of the 11-*cis*-retinal covalently linked via a Schiff base to the opsin protein (either rod opsin or blue, red or green cone opsins). The process of vision relies on the light-induced isomerization of the chromophore from 11-*cis* to all-*trans* resulting in a change of the conformation and activation of the photoreceptor molecule. One of the earliest signs of vitamin A deficiency is night-blindness followed by decreased visual acuity.

**Polyterpenes** consist of long chains of *many isoprene* units. Natural rubber consists of polyisoprene in which the double bonds are *cis*. Some plants produce a polyisoprene with *trans* double bonds, known as gutta-percha.




The term terpenoids is used to describe compounds which are derived from terpenes, even though their skeleton is not composed exclusively of $C_5$ isoprene units. The alterations in terpenoids include rearrangements, loss of carbon atoms or introduction of additional carbon atoms. Cholesterol, a steroid, is an example of a terpenoid that has lost some of the isoprenoid carbon atoms. Cholesterol is formed from squalene − a triterpene. Squalene cyclizes in an acid catalyzed reaction to lanosterol and this precursor of cholesterol loses three carbon atoms and is additionally modified in enzyme catalyzed reactions to cholesterol.