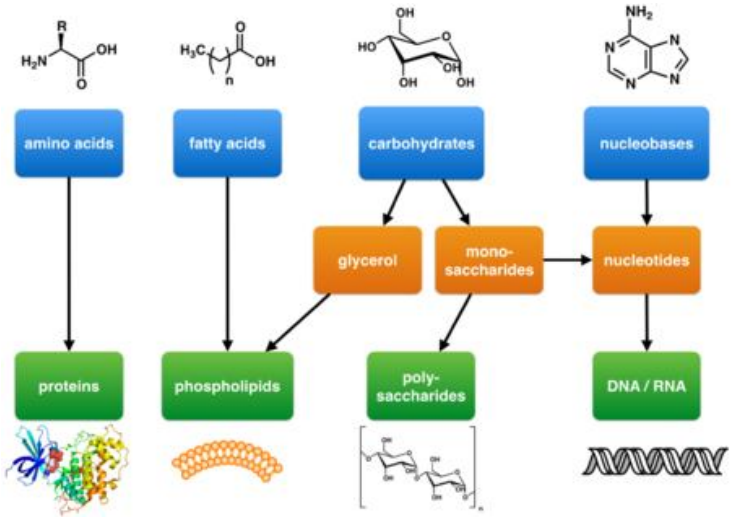
Unit-III Chemistry of Alkaloids and Terpenoids

A natural product is a chemical compound or substance produced by a living organism—that is, found in nature. Natural products can also be prepared by chemical synthesis and have played a central role in the development of the field of organic chemistry by providing challenging synthetic targets. The term natural product has also been extended for commercial purposes to refer to cosmetics, dietary supplements, and foods produced from natural sources without added artificial ingredients.

Within the field of organic chemistry, the definition of natural products is usually restricted to mean purified organic compounds isolated from natural sources that are produced by the pathways of primary or secondary metabolism. Within the field of medicinal chemistry, the definition is often further restricted to secondary metabolites. Secondary metabolites are not essential for survival, but nevertheless provide organisms that produce them an evolutionary advantage. Many secondary metabolites are cytotoxic and have been selected and optimized through evolution for use as "chemical warfare" agents against prey, predators, and competing organisms.

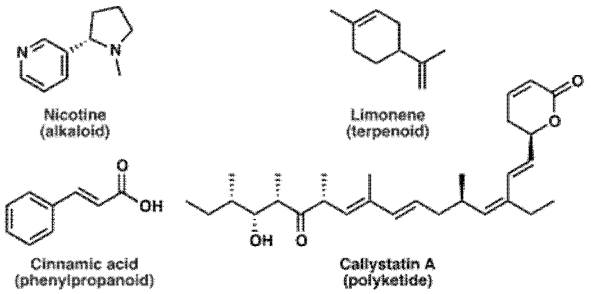
Natural products sometimes have therapeutic benefit as traditional medicines for treating diseases, yielding knowledge to derive active components as lead compounds for drug discovery. The broadest definition of natural product is anything that is produced by life and includes the likes of biotic materials (e.g. wood, silk), bio-based materials (e.g. bioplastics, cornstarch), bodily fluids (e.g. milk, plant exudates), and other natural materials (e.g. soil, coal).

Primary metabolites



Molecular building blocks of life

Secondary metabolites



Representative examples of each of the major classes of secondary metabolites

The biosynthetic pathways leading to the major classes of natural products are described below.

- Photosynthesis or gluconeogenesis → monosaccharides → polysaccharides (cellulose, chitin, glycogen etc.)
- Acetate pathway → fatty acids and polyketides
- Shikimate pathway → aromatic amino acids and phenylpropanoids
- Mevalonate pathway and methyletrythritol phosphate pathway → terpenoids and steroids
- Amino acids → alkaloids

Plants

Plants are a major source of complex and highly structurally diverse chemical compounds (phytochemicals), this structural diversity attributed in part to the natural selection of organisms producing potent compounds to deter herbivory (feeding deterrents). Major classes of phytochemical include phenols, polyphenols, tannins, terpenes, and alkaloids.

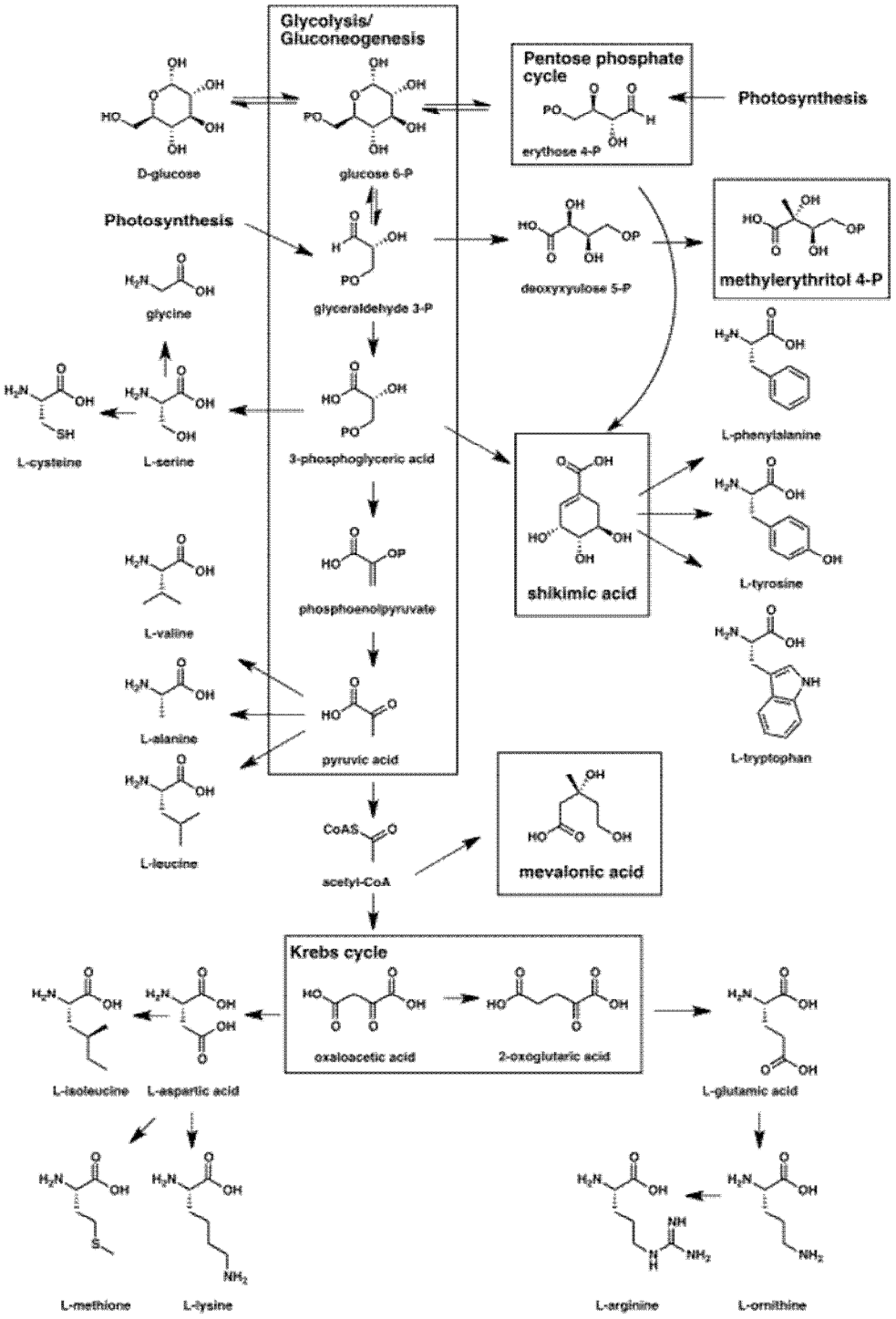
Clinically useful examples include the anticancer agents paclitaxel and omacetaxine mepesuccinate (from *Taxus brevifolia* and *Cephalotaxus harringtonii*, respectively), the antimalarial agent artemisinin (from *Artemisia annua*), and acetylcholinesterase inhibitor the galantamine (from *Galanthus* spp.), used to treat Alzheimer's disease. Other plant-derived drugs, used medicinally and/or recreationally include morphine, cocaine, quinine, tubocurarine, muscarine, and nicotine.

Animals

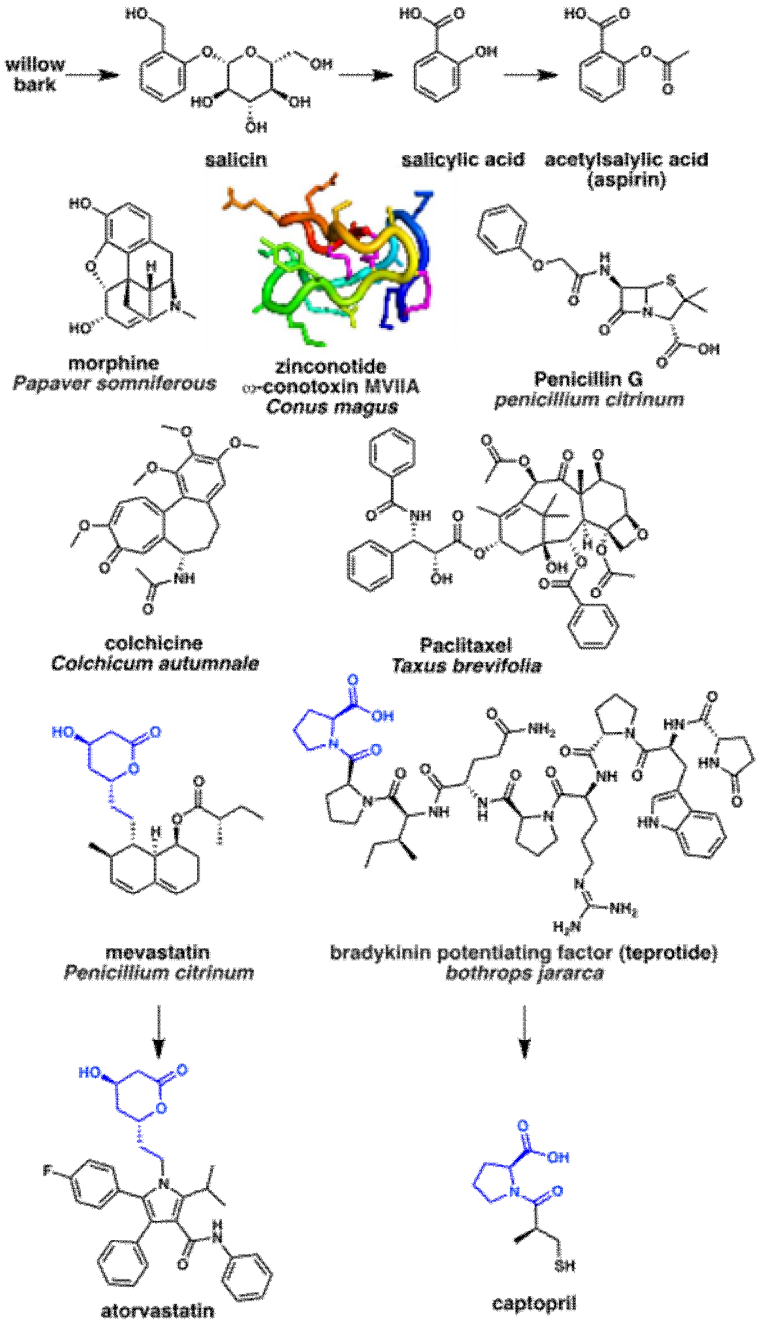
Animals also represent a source of bioactive natural products. In particular, venomous animals such as snakes, spiders, scorpions, caterpillars, bees, wasps, centipedes, ants, toads, and frogs have attracted much attention. This is because venom constituents (peptides, enzymes, nucleotides, lipids, biogenic amines etc.) often have very specific interactions with a macromolecular target in the body (e.g. α-bungarotoxin from cobras).

Medical uses

Natural products sometimes have pharmacological activity that can be of therapeutic benefit in treating diseases. As such, natural products are the active components of many traditional medicines. Moreover, synthetic analogs of natural products with improved potency and safety can be prepared and therefore natural products are often used as starting points for drug discovery.



Biosynthesis of primary and secondary metabolites



Representative examples of drugs based on natural products

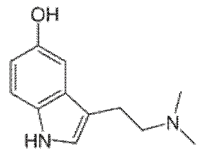
Traditional medicine

Indigenous peoples and ancient civilizations experimented with various plant and animal parts to determine what effect they might have. Through trial and error in isolated cases, traditional healers or shamans found some sources to provide therapeutic effect, representing knowledge of a crude drug that was passed down through generations in such practices as traditional Chinese medicine and Ayurveda. Extracts of some natural products led to modern discovery of their active ingredients and eventually to the development of new drugs.

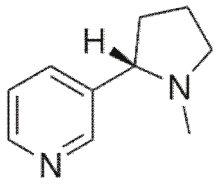
Alkaloids

Alkaloids are a class of naturally occurring organic compounds that mostly contain basic nitrogen atoms. This group also includes some related compounds with neutral and even weakly acidic properties. Some synthetic compounds of similar structure may also be termed alkaloids. In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and, more rarely, other elements such as chlorine, bromine, and phosphorus. Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals. They can be purified from crude extracts of these organisms by acid-base extraction.

Alkaloids have a wide range of pharmacological activities including antimalarial (*e.g.*quinine), antiasthma (*e.g.* ephedrine), anticancer (*e.g.* homoharring tonine), cholinomimetic (*e.g.* galantamine), vasodilatory (*e.g.*vincamine), antiarrhythmic (*e.g.* quinidine), analgesic (*e.g.* morphine), antibacterial (*e.g.* chelerythrine), and antihyperglycemi cactivities (*e.g.* piperine). Many have found use in traditional or modern medicine, or as starting points for drug discovery. Other alkaloids possess psychotropic (*e.g.* psilocin) and stimulant activities (*e.g.* cocaine, caffeine, nicotine, theobromine), and have been used in entheogenic rituals or as recreational drugs. Alkaloids can be toxic too (*e.g.* atropine, tubocurarine). Although alkaloids act on a diversity of metabolic systems in humans and other animals, they almost uniformly evoke a bitter taste.



Bufotenin, an alkaloid from some toads, contains an indole core and is produced in living organisms from the amino acid tryptophan.



The nicotine molecule contains both pyridine (left) and pyrrolidine rings (right).

Compared with most other classes of natural compounds, alkaloids are characterized by a great structural diversity. There is no uniform classification. Initially, when knowledge of chemical structures was lacking, botanical classification of the source plants was relied on. This classification is now considered obsolete. More recent classifications are based on similarity of the carbon skeleton (*e.g.*, indole-, isoquinoline-, and pyridine-like) or biochemical precursor (ornithine, lysine, tyrosine, tryptophan, etc.).[5] However, they require compromises in borderline cases; for example, nicotine contains a pyridine fragment from nicotinamide and a pyrrolidine part from ornithine and therefore can be assigned to both classes.

Alkaloids are often divided into the following major groups:

- "True alkaloids" contain nitrogen in the heterocycle and originate from amino acids. Their characteristic examples are atropine, nicotine, and morphine. This group also includes some alkaloids that besides the nitrogen heterocycle

contain terpene (*e.g.*, evonine) or peptide fragments (*e.g.* ergotamine). The piperidine alkaloids coniine and coniceine may be regarded as true alkaloids (rather than pseudoalkaloids: see below) although they do not originate from amino acids.

- "Protoalkaloids", which contain nitrogen (but not the nitrogen heterocycle) and also originate from amino acids. Examples include mescaline, adrenaline and ephedrine.
- Polyamine alkaloids – derivatives of putrescine, spermidine, and spermine.
- Peptide and cyclopeptide alkaloids.
- Pseudoalkaloids – alkaloid-like compounds that do not originate from amino acids. This group includes terpene-like and steroid-like alkaloids, as well as purine-like alkaloids such as caffeine, theobromine, theacrine and theophylline. Some authors classify as pseudoalkaloids such compounds such as ephedrine and cathinone. Those originate from the amino acid phenylalanine, but acquire their nitrogen atom not from the amino acid but through transamination.

Some alkaloids do not have the carbon skeleton characteristic of their group. So, galanthamine and homoaporphines do not contain isoquinoline fragment, but are, in general, attributed to isoquinoline alkaloids.

Properties

Most alkaloids contain oxygen in their molecular structure; those compounds are usually colorless crystals at ambient conditions. Oxygen-free alkaloids, such as nicotine or coniine, are typically volatile, colorless, oily liquids. Some alkaloids are colored, like berberine (yellow) and sanguinarine (orange). Most alkaloids are weak bases, but some, such as theobromine and theophylline, are amphoteric. Many alkaloids dissolve poorly in water but readily dissolve in organic solvents, such as diethyl ether, chloroform or 1,2- dichloroethane. Caffeine, cocaine, codeine and nicotine are slightly soluble in water (with a solubility of $\geq$1g/L), whereas others, including morphine and yohimbine are very slightly water-soluble (0.1–1 g/L). Alkaloids and acids form salts of various strengths. These salts are usually freely soluble in water and ethanol and poorly soluble in most organic solvents. Exceptions include scopolamine hydrobromide, which is soluble in organic solvents, and the water-soluble quinine sulfate.

Most alkaloids have a bitter taste or are poisonous when ingested. Alkaloid production in plants appeared to have evolved in response to feeding by herbivorous animals; however, some animals have evolved the ability to detoxify alkaloids Alkaloids are generated by various living organisms, especially by higher plants – about 10 to 25% of those contain alkaloids. Therefore, in the past the term "alkaloid" was associated with plants. The alkaloids content in plants is usually within a few percent and is inhomogeneous over the plant tissues.

Extraction

Because of the structural diversity of alkaloids, there is no single method of their extraction from natural raw materials. Most methods exploit the property of most alkaloids to be soluble in organic solvents but not in water, and the opposite tendency of their salts. Plants are thoroughly ground before extraction. Most alkaloids are present in the raw plants in the form of salts of organic acids. The extracted alkaloids may remain salts or change into bases. Base extraction is achieved by processing the raw material with alkaline solutions and extracting the alkaloid bases with organic solvents, such as 1,2-dichloroethane, chloroform, diethyl ether or benzene. Then, the impurities are dissolved by weak acids; this converts

alkaloid bases into salts that are washed away with water. If necessary, an aqueous solution of alkaloid salts is again made alkaline and treated with an organic solvent. The process is repeated until the desired purity is achieved.

In the acidic extraction, the raw plant material is processed by a weak acidic solution (*e.g.*, acetic acid in water, ethanol, or methanol). A base is then added to convert alkaloids to basic forms that are extracted with organic solvent (if the extraction was performed with alcohol, it is removed first, and the remainder is dissolved in water). The solution is purified as described above. Alkaloids are separated from their mixture using their different solubility in certain solvents and different reactivity with certain reagents or by distillation.

Isolation of Alkaloids

Suppose you know for a fact that a sea sponge sample you collected while scuba diving in Fiji contains alkaloids that are active against cancer cells. The job you have in front of you now is to extract and isolate the alkaloids from among the other thousands of organic compounds present in the sponge sample. To put things in perspective, it would be like trying to find a tiny needle among millions of pieces of straw in a barn. Fortunately there are some steps we can follow that will make things a bit easier.

Step 1

The first thing we need to do is take our sponge sample and crush it up into a very fine powder. The reason this is necessary is the finer the particles, the greater the surface area becomes and the better the extraction goes.

Step 2

The next thing we need to do is get rid of all the fats, terpenes, and other oils from the sample, because we aren't really interested in those types of compounds. This can be easily done by extracting them from the powder with hexanes or petroleum ether. Solvents like hexanes and petroleum ether work best because they are very good at solvating non-polar compounds like fats, oils, and terpenes alike. These can then be discarded since we don't need them.

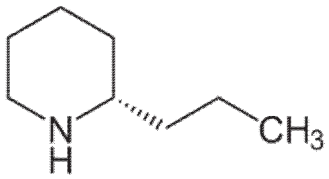
Step 3

Next, we need to extract the alkaloids that are left with a solvent. Methanol or ethanol tend to be the best solvents for extracting alkaloids. The methanol or ethanol solvent will pull all of the alkaloids out of the crude sponge material. This extraction needs to be done multiple times to make sure all of the alkaloids get isolated. An instrument called a rotary evaporator can then be used to evaporate off the solvent. At this point, we have our crude alkaloid mixture (natural sources rarely contain only one alkaloid).

Purification of Alkaloids

Now that we have our crude alkaloid mixture, we need to separate and purify each individual alkaloid from one another. This is most commonly accomplished by using an analytical separation technique called high-performance liquid chromatography (HPLC). HPLC is an excellent way to fractionate the mixture repeatedly until we have only pure individual alkaloids left.

Coniine



Coniine refers to a poisonous chemical compound, an alkaloid present in and isolable from poison hemlock (*Conium maculatum*), where its presence has been a source of significant economic, medical, and historico-cultural interest; coniine is also produced by the yellow pitcher plant (*Sarracenia flava*), and fool's parsley (*Aethusa cynapium*).

Poison hemlock

Poison hemlock (*Conium maculatum*) contains highly toxic amounts of coniine, where it contributes to hemlock's fetid smell; in addition, it contains trace amounts of other similarly poisonous alkaloids. Ingesting less than a tenth of a gram of coniine can be fatal for adult humans; this is approximately six to eight hemlock leaves. The seeds and roots are also toxic, more so than the leaves. While hemlock toxicity primarily results from consumption, poisoning can also result from inhalation, and from skin contact.

Poison hemlock grows quite tall, reaching heights of up to twelve feet. The stalk of hemlock is green with purple spots and completely lacks hair. A biennial plant, hemlock produces leaves at its base the first year but no flowers. In its second year it produces white flowers in umbrella shaped clusters. Hemlock can be confused with the wild carrot plant; however, this plant has a hairy stem without purple markings, grows less than three feet tall, and does not have clustered flowers. While the hemlock plant is native to Europe and the Mediterranean region, it has spread to every other continent excluding Antarctica.

Yellow pitcher plant

The coniine alkaloid is found in *Sarracenia flava*, the yellow pitcher plant. The yellow pitcher plant is a carnivorous plant found exclusively in the southeastern United States. The plant uses a mixture of sugar and coniine to simultaneously attract and poison insects, which then fall into a digestive tube. The naming of the plant arises from the shape of the opening to these tubes, which resembles a pitcher, which can grow up to three feet tall. The pitcher has a leaf above it that functions to prevent rain from diluting the digestive fluids deep in the tubes. There are no reports online of human poisoning via the yellow pitcher plant, perhaps because only a small portion of the plant contains coniine, or because it does not contain enough to produce toxicity. It is also not as widespread as hemlock and therefore is less likely to be encountered by humans.

Fool's parsley

Coniine is also found in *Aethusa cynapium*, commonly known as fool's parsley. While the yellow pitcher plant and fool's parsley also contain coniine, there are no reports of traditional uses for these plants.

Chemical properties

(+/–)-Coniine was first isolated by Giesecke, but the formula was suggested by Blyth and definitely established by Hoffmann. D-(*S*)-Coniine has since been determined to be a colorless alkaline liquid, with a penetrating odour and a burning taste; has D^{0° 0.8626 and D^{19° 0.8438, refractive index $n^{23^\circ}{}_D$ 1.4505, and is dextrorotatory, $[\alpha]^{19^\circ}{}_D$ +15.7°. (See

comments about the specific rotation below, under "Enantiomers".) L-(*R*)-Coniine has $[\alpha]^{21^\circ}_D$ 15° and in other respects resembles its D-isomer, but the salts have slightly different melting points; the platinichloride has mp. 160 °C (Löffler and Friedrich report 175 °C), the aurichloride mp. 59 °C.

Solubility

Coniine is slightly soluble (1 in 90) in cold water, less so in hot water, so that a clear cold solution becomes turbid when warmed. On the other hand, the base dissolves about 25% of water at room temperature. It mixes with alcohol in all proportions, is readily soluble in ether and most organic solvents. Coniine dissolves in carbon disulfide, forming a complex thiocarbamate.

Crystallization

Coniine solidifies into a soft crystalline mass at −2 °C. It slowly oxidizes in the air. The salts crystallize well and are soluble in water or alcohol. The hydrochloride, B•HCl, crystallizes from water in rhombs, mp. 220 °C, $[\alpha]^{20^\circ}_D$ +10.1°; the hydrobromide, in needles, mp. 211 °C, and the D-acid tartrate, $B{\bullet}C_4H_6O_6{\bullet}2\ H_2O$, in rhombic crystals, mp. 54 °C. The platinichloride, $(B{\bullet}HCl)_2{\bullet}PtCl_4{\bullet}H_2O$, separates from concentrated solution as an oil, which solidifies to a mass of orange-yellow crystals, mp. 175 °C (dry). The aurichloride, $B{\bullet}HAuCl_4$, crystallizes on standing, mp. 77 °C. The picrate forms small yellow needles, mp. 75 °C, from hot water. The 2,4-dinitrobenzoyl- and 3,5-dinitrobenzoyl-derivates have mps. 139.0–139.5 °C and 108–9 °C respectively. The precipitate afforded by potassium cadmium iodide solution is crystalline, mp. 118 °C, while that given by nicotine with this reagent is amorphous.

Color changes

Coniine gives no coloration with sulfuric or nitric acid. Sodium nitroprusside gives a deep red color, which disappears on warming, but reappears on cooling, and is changed to blue or violet by aldehydes.

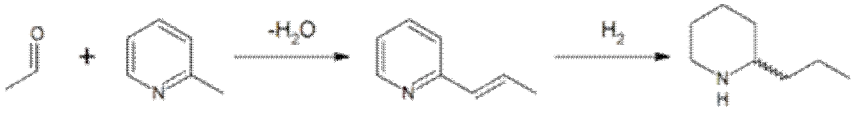
Enantiomers

Salts of given enantiomers do not necessarily have the same specific rotation as the same enantiomer of the free base. The hydrochloride salts of the (*S*)-(+) and (*R*)-(−) enantiomers of coniine have values of $[\alpha]_D$ of +4.6° and -5.2°, respectively (c = 0.5, in methanol).

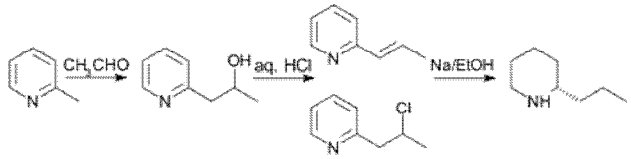
Synthesis

Many syntheses of coniine have been reported over the last 50 years; one example of a stereoselective synthesis is that of Enders and Tiebes, who cite some of the earlier preparations.

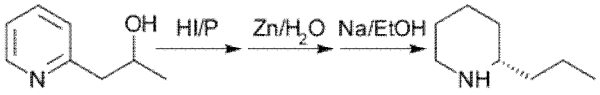
In the original synthesis of this substance by Ladenburg in 1886, N-methylpyridine, as its iodide salt, was isomerised at 250 °C to obtain 2-methylpyridine (α-picoline). Reaction of this, as shown in the scheme below, with the cyclic trimer of acetaldehyde, paraldehyde, in the presence of a base gave 2-propenylpyridine via a Knoevenagel condensation. This intermediate was reduced with metallic sodium in ethanol or by hydrogen gas to provide racemic (±) coniine. Enantiopure coniine was then obtained by a chiral resolution, specifically, fractional crystallisation of the diastereomeric (+)-tartaric acid salt.



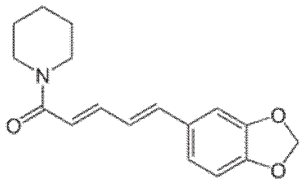
The initial reaction, however, gives a poor yield and was improved by interaction of the two reagents at 150 °C in sealed tubes to give methyl-2-picolylalkyne, which was then heated at 185 °C with hydrochloric acid for 10 hours, producing a mixture of 2-propenylpyridine and 2-chloropropylpyridine. This mixture was reduced to *rac*-coniine by sodium in ethanol.



In 1907 the process was still further improved by reducing 2-(2'-hydroxypropyl)pyridine with phosphorus and hydroiodic acid at 125 °C and treating the product with zinc dust and water, then reducing the product with sodium in ethanol.



Piperine



Piperine, along with its isomer chavicine, is the alkaloid[1] responsible for the pungency of black pepper and long pepper. It has been used in some forms of traditional medicine.

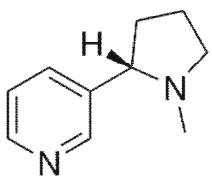
Preparation

Piperine is extracted from black pepper using dichloromethane. Aqueous hydrotropes can be used in the extraction to result in high yield and selectivity. The amount of piperine varies from 1–2% in long pepper, to 5–10% in commercial white and black peppers. Further, it may be prepared by treating the solvent-free residue from an alcoholic extract of black pepper, with a solution of potassium hydroxide to remove resin (said to contain chavicine, an isomer of piperine) and solution of the washed, insoluble residue in warm alcohol, from which the alkaloid crystallises on cooling.

Reactions

Piperine yields salts only with strong acids. The platinichloride $B_4 \cdot H_2PtCl_6$ forms orange-red needles. Iodine in potassium iodide added to an alcoholic solution of the base in the presence of a little hydrochloric acid gives a characteristic periodide, $B_2 \cdot HI \cdot I_2$, crystallising in steel-blue needles, melting point 145 °C.

Nicotine



Nicotine is an antiherbivory alkaloid and potent parasympathomimetic stimulant and found in plants, mostly those in the nightshadefamily. Nicotine acts as a receptor agonist at most nicotinic acetylcholine receptors, except at two nicotinic receptor subunits where it acts as a receptor antagonist. Nicotine is highly addictive. It is one of the most commonly abused drugs. An average cigarette yields about 2 mg of absorbed nicotine, while high amounts (30–60 mg) can be harmful. Nicotine induces both behavioral stimulation and anxiety in animals. Nicotine addiction involves drug-reinforced behavior, compulsive use, and relapse following abstinence. Nicotine dependence involves tolerance, sensitization, physical dependence, and psychological dependence. Nicotine dependency causes distress. Nicotine withdrawal symptoms include depressed mood, stress, anxiety, irritability, difficulty concentrating, and sleep disturbances.

Mild nicotine withdrawal symptoms are measurable in unrestricted smokers, who experience normal moods only as their blood nicotine levels peak, with each cigarette. On quitting, withdrawal symptoms worsen sharply, then gradually improve to a normal state. The evidence suggests that exposure to nicotine between the ages of 10 and 25 years causes lasting harm to the brain and cognitive ability. Nicotine use during pregnancy increases the child's risk of type 2 diabetes, obesity, hypertension, neurobehavioral defects, respiratory problems, and infertility.

Nicotine use as a tool for quitting smoking has a good safety history. Nicotine use in the form of nicotine replacement products poses less of a cancer risk than smoking. There is inadequate data to establish if nicotine is itself a carcinogen, but there is evidence of possible risks. The health effects of long-term nicotine replacement use were unknown as of 2014. Overdose on nicotine-containing products results in nicotine poisoning. The use of electronic cigarettes, which are designed to be refilled with nicotine-containing e-liquid, has raised concerns over nicotine overdoses, especially with regard to the possibility of young children ingesting the liquids.

Sources

Nicotine is found in the leaves of *Nicotiana rustica* (in amounts of 2–14%); in the tobacco plant, *Nicotiana tabacum* (in amounts of 1–3%); in *Duboisia hopwoodii*; and in *Asclepias syriaca*. It constitutes approximately 0.6–3.0% of the dry weight of tobacco.

Uses

Medical

The primary therapeutic use of nicotine is in treating nicotine dependence in order to eliminate smoking with the damage it does to health. Controlled levels of nicotine are given to patients through gums, dermal patches, lozenges, electronic/substitute cigarettes or nasal sprays in an effort to wean them off their dependence. Studies have found that these therapies increase the chance of success of quitting by 50 to 70%, though reductions in the population as a whole have not been demonstrated.

In contrast to recreational nicotine products, which have been designed to maximize the likelihood of addiction, nicotine replacement products (NRTs) are designed to minimize addictiveness. The more quickly a dose of nicotine is delivered and absorbed, the higher the addiction risk. Some forms of NRT deliver nicotine more quickly than others, and it is possible to become dependent on some NRTs.

Pesticide

Nicotine has been used as an insecticide since at least the 1690s, in the form of tobacco extracts (although other components of tobacco also seem to have pesticide effects). Nicotine pesticides have not been commercially available in the US since 2014, and homemade pesticides are banned on organic crops and counterrecommended for small gardeners. Nicotine pesticides have been banned in the EU since 2009. Foods are imported from countries in which nicotine pesticides are allowed, such as China, but foods may not exceed maximum nicotine levels. Neonicotinoids, which are derived from and structurally similar to nicotine, are widely used as agricultural and veterinary pesticides as of 2016. In nicotine-producing plants, nicotine functions as an antiherbivory chemical; consequently, nicotine has been widely used as an insecticide, and neonicotinoids, such as imidacloprid, are widely used.

Enhancing performance

Nicotine-containing products are sometimes used for the performance-enhancing effects of nicotine on cognition. A meta-analysis of 41 double-blind, placebo-controlled studies concluded that nicotine or smoking had significant positive effects on aspects of fine motor abilities, alerting and orienting attention, and episodic and working memory. A 2015 review noted that stimulation of the α4β2 nicotinic receptor is responsible for certain improvements in attentional performance; among the nicotinic receptor subtypes, nicotine has the highest binding affinity at the α4β2 receptor (k_i=1 nM), which is also the biological target that mediates nicotine's addictive properties. Nicotine has potential beneficial effects, but it also has paradoxical effects, which may be due to the inverted U-shape of the dose-response curve or pharmacokinetic features.

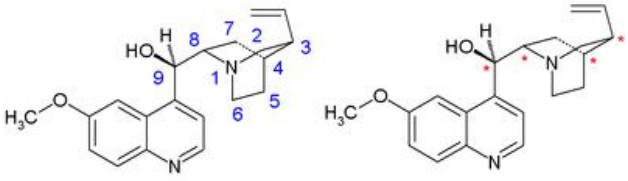
Cancer

Although there is insufficient evidence to classify nicotine as a carcinogen, there is an ongoing debate about whether it functions as a tumor promoter. *In vitro* studies have associated it with cancer, but carcinogenicity has not been demonstrated *in vivo*. There is inadequate research to demonstrate that nicotine is associated with cancer in humans, but there is evidence indicating possible oral, esophageal, or pancreatic cancer risks. Nicotine can induce inflammation in the lungs that imitates metastatic cancer.

Fetal development and breastfeeding

Nicotine is not safe to use in any amount during pregnancy. Nicotine crosses the placenta and is found in the breast milk of mothers who use nicotine replacement therapy mothers who smoke, and mothers who inhale passive smoke. Nicotine from e-cigarettes can also harm the fetus and the use of e-cigarettes in pregnancy is counter recommended.

Quinine



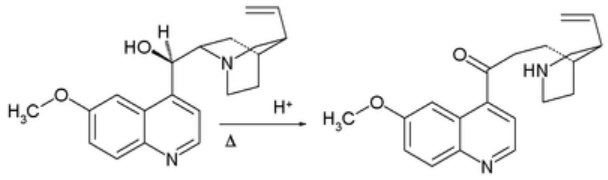
The quinine is a naturally-occurring antimalarial drug, was developed over a 150-year period. The development of synthetic quinine is considered a milestone in organic

chemistry although it has never been produced industrially as a substitute for natural occurring quinine.

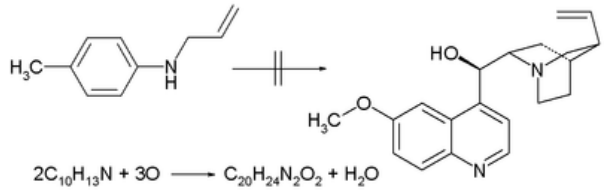
Chemical structure

The aromatic component of the quinine molecule is a quinoline with a methoxy substituent. The amine component has a quinuclidine skeleton and the methylene bridge in between the two components has a hydroxyl group. The substituent at the 3 position is a vinyl group. The molecule is optically active with five stereogenic centers (the N1 and C4 constituting a single asymmetric unit), making synthesis potentially difficult because it is one of 16 stereoisomers.

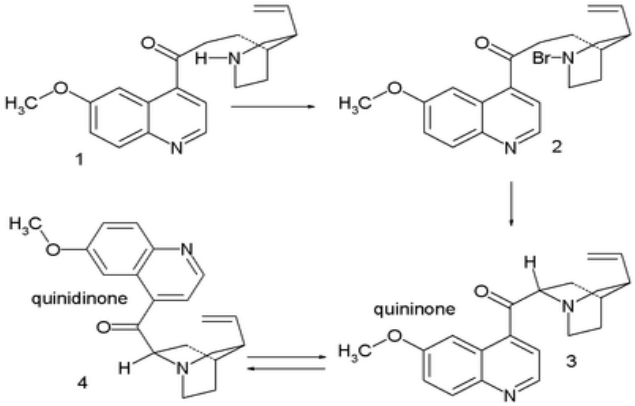
Quinotoxine (or *quinicine* in older literature) by acid-catalysed isomerization of quinine.



Quinine synthesis by oxidation of *N*-allyltoluidine based on the erroneous idea that two equivalents of this compound with chemical formula$C_{10}H_{13}N$ plus three equivalents of oxygen yield one equivalent of $C_{20}H_{24}N_2O_2$ (quinine's chemical formula) and one equivalent of water. His oxidations with other toluidines sets him on the path of mauveine which eventually leads to the birth of chemical industry.

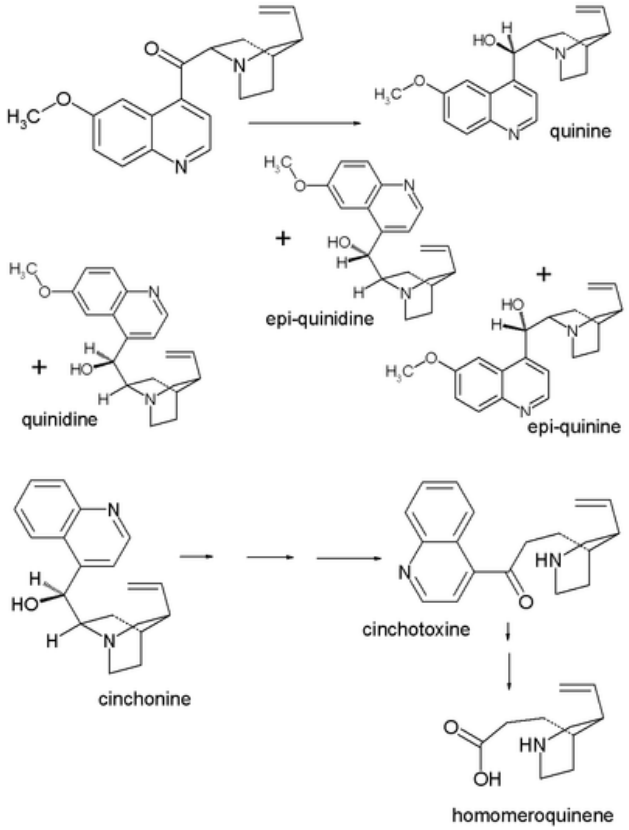


Paul Rabe and Karl Kindler synthesize quinine from quinotoxine,

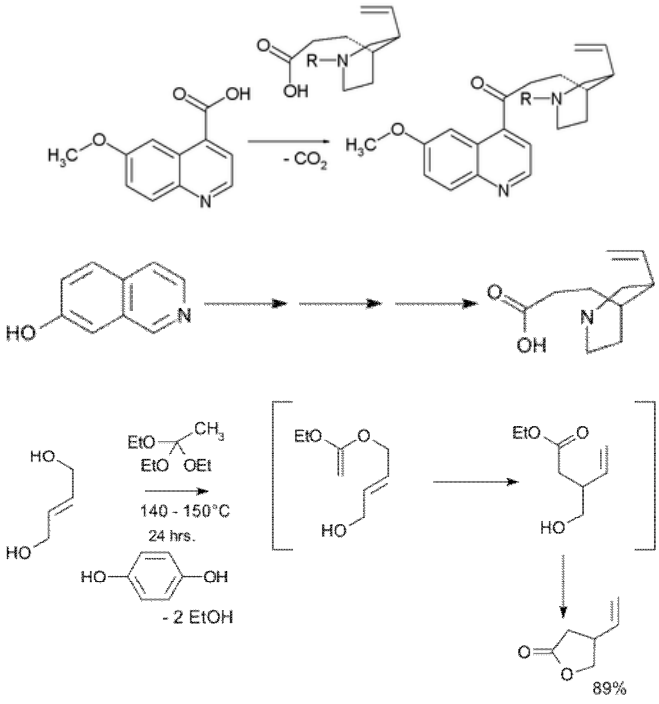


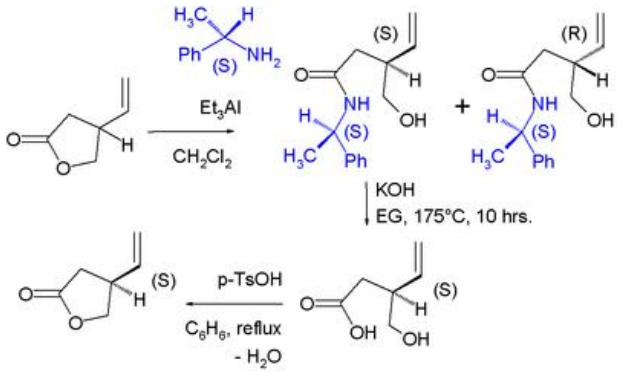
The first step in this sequence is sodium hypobromite addition to quinotoxine to an *N*-bromo intermediate possibly with structure 2. The second step is organic oxidation with sodium ethoxide in ethanol. Because of the basic conditions the initial product quininone interconverts with quinidinone via a common enol intermediate and mutarotation is observed. In the third step the ketone group is reduced

with aluminum powder and sodium ethoxide in ethanol and quinine can be identified. Quinotoxine is the first relay molecule in the Woodward/Doering claim.



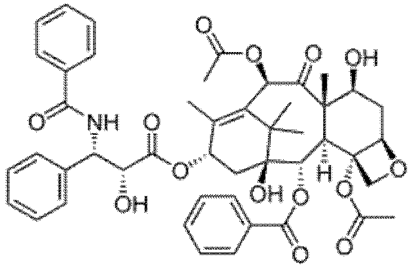
The key step in the assembly of quinotoxine is a Claisen condensation:





In this process the racemic lactone reacts in aminolysis with (*S*)-methylbenzylamine assisted by triethylaluminum to a diastereomeric pair of amides which can be separated by column chromatography. The *S*-enantiomer is converted back to the *S*-lactone in two steps by hydrolysis with potassium hydroxide and ethylene glycol followed by azeotropic ring closure.

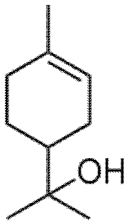
Terpenoid



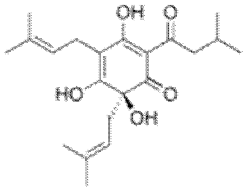
Chemical structure of the terpenoid taxol, an anticancer drug.

The terpenoids (/ˈtɜːrpɪnɔɪd/ *TUR-pin-oyd*), sometimes called isoprenoids, are a large and diverse class of naturally occurring organic chemicals derived from terpenes. Most are multicyclic structures with oxygen-containing functional groups. About 60% of known natural products are terpenoids. Although sometimes used interchangeably with "terpenes", terpenoids contain additional functional groups, usually O-containing. Terpenes are hydrocarbons.

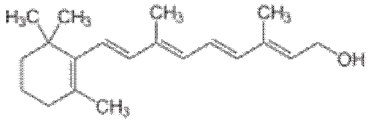
Plant terpenoids are used for their aromatic qualities and play a role in traditional herbal remedies. Terpenoids contribute to the scent of eucalyptus, the flavors of cinnamon, cloves, and ginger, the yellow color in sunflowers, and the red color in tomatoes. Well-known terpenoids include citral, menthol, camphor, salvinorin A in the plant *Salvia divinorum*, the cannabinoids found in cannabis, ginkgolide and bilobalide found in *Ginkgo biloba*, and the curcuminoids found in turmeric and mustard seed. The steroids and sterols in animals are biologically produced from terpenoid precursors. Sometimes terpenoids are added to proteins, e.g., to enhance their attachment to the cell membrane; this is known as isoprenylation.



Terpineols are monoterpenoids.



Humulones are classified as sesquiterpenoids.



Retinols is a diterpenoid.

Structure and classification

Terpenoids are modified terpenes, wherein methyl groups have been moved or removed, or oxygen atoms added. (Some authors use the term "terpene" more broadly, to include the terpenoids.) Just like terpenes, the terpenoids can be classified according to the number of isoprene units that comprise the parent terpene:

- Hemiterpenoids, 1 isoprene unit
- Monoterpenoids, 2 isoprene units
- Sesquiterpenoids, 3 isoprene units
- Diterpenoids, 4 isoprene units
- Sesterterpenoids, 5 isoprene units
- Triterpenoids, 6 isoprene units. Example: sterols.
- Tetraterpenoids, 8 isoprene units. Example: carotenoids
- Polyterpenoid with a larger number of isoprene units
- Terpenoids can also be classified according to the number of cyclic structures they contain. The Salkowski test can be used to identify the presence of terpenoids.

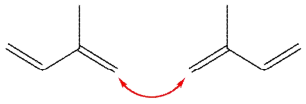
Biosynthesis

Terpenoids, at least those containing an alcohol functional group, often arise by hydrolysis of carbocationic intermediates produced from geranyl pyrophosphate. Analogously hydrolysis of intermediates from farnesyl pyrophosphate gives sesquiterpenoids, and hydrolysis of intermediates from geranylgeranyl pyrophosphate gives diterpenoids, etc.

Isoprene Rule

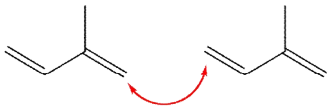
Formally, in biosynthesis of terpenes, two or more isoprene molecules are linked to one another. Linking between two isoprene molecules could occur in three ways, given that the head and the tail of the molecule are primarily involved in the linking:

1. The head of one isoprene molecule could link with the head of another isoprene molecule.



This link is called a head-to-head or 1-1 link.

2. The head of one isoprene molecule could link with the tail of another isoprene molecule.

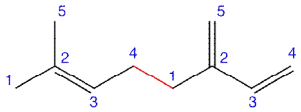


This link is called a head-to-tail or 1-4 link.

3. The tail of one isoprene molecule could link with the tail of another isoprene molecule.

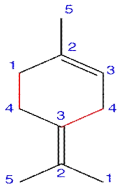
This link is called a tail-to-tail or 4-4 link.

Cyclic terpenes also contain links that are neither 1-1, 1-4, nor 4-4, which are called crosslinks.
Isoprene rule states that, in most naturally occurring terpenes, there are no 1-1 or 4-4 links.
Eg. 1:



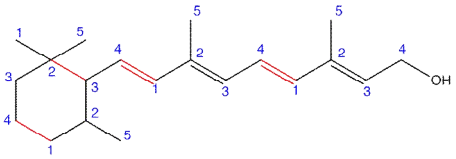
Myrcene

Eg. 2:



Limonene

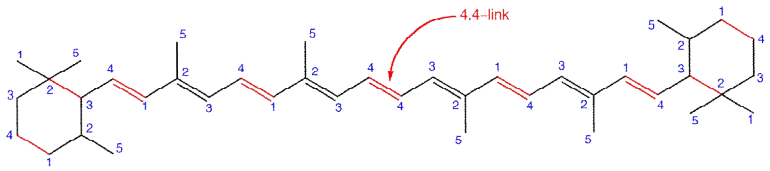
Eg. 3:



Retinol

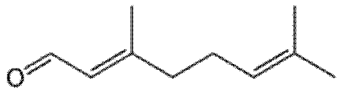
drmurugesanchemistry@gmail.com

A terpene that does not obey the isoprene rule is called an irregular terpene.
Eg:



β-Carotene

Citral



Citral or 3,7-dimethyl-2,6-octadienal or lemonal, is either a pair, or a mixture of terpenoids with the molecular formula $C_{10}H_{16}O$. The two compounds are double bond isomers. The *E*-isomer is known as geranial or citral A. The *Z*-isomer is known as neral or citral B.

Occurrence

Citral is present in the oils of several plants, including lemon myrtle (90–98%), *Litsea citrata* (90%), *Litsea cubeba* (70–85%), lemongrass(65–85%), lemon tea-tree (70–80%), *Ocimum gratissimum* (66.5%), *Lindera citriodora* (about 65%), *Calypranthes parriculata* (about 62%), petitgrain (36%), lemon verbena (30–35%), lemon ironbark (26%), lemon balm (11%), lime (6–9%), lemon (2–5%), and orange.

Uses

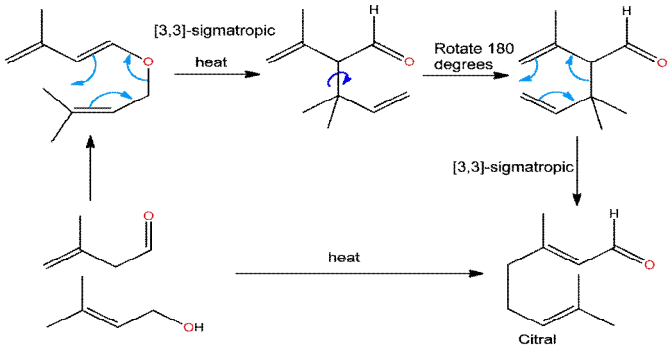
Geranial has a strong lemon (citrus) odor. Neral's lemon odor is less intense, but sweeter. Citral is therefore an aroma compound used in perfumery for its citrus effect. Citral is also used as a flavor and for fortifying lemon oil. It also has strong antimicrobial qualities, and pheromonal effects in insects. Citral is used in the synthesis of vitamin A, ionone, and methylionone, to mask the smell of smoke.

Health and safety information

Two studies showed 1–1.7% of people to be allergic to citral, with allergies frequently reported. Citral on its own is strongly sensitizing to allergies; the International Fragrance Association recommends that citral only be used in association with substances that prevent a sensitizing effect. Citral has been extensively tested, with no known genotoxicity or carcinogenic effect.

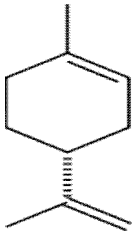
Synthesis of Citral

Citral is a compound which can be used in the synthesis of vitamin A. This industrial synthesis is made up of two different [3,3]-sigmatropic rearrangements done in sequence. The first is a Claisen rearrangement which involves oxygen in the chair-like transition state. More details of the Claisen rearrangement can be found here. The second part of the single step reaction is a Cope-rearrangement, in which only carbons are involved in the chair-like transition state. These two reactions happen in succession when the two starting materials are heated together, and the reaction is driven by formation of a conjugated carbonyl group in the product.



Limonene

IUPAC name: 1-Methyl-4-(prop-1-en-2-yl)cyclohex-1-ene
Other names: 1-Methyl-4-(1-methylethenyl)cyclohexene
4-Isopropenyl-1-methylcyclohexene
p-Menth-1,8-diene
Racemic: DL-Limonene; Dipentene



Limonene is a colorless liquid aliphatic hydrocarbon classified as a cyclic monoterpene, and is the major component in the oil of citrus fruit peels. The D-isomer, occurring more commonly in nature as the fragrance of oranges, is a flavoring agent in food manufacturing. It is also used in chemical synthesis as a precursor to carvone and as a renewables-based solvent in cleaning products. The less common L-isomer is found in mint oils and has a piny, turpentine-like odor.

Limonene takes its name from the peel of the lemon. Limonene is a chiral molecule, and biological sources produce one enantiomer: the principal industrial source, citrus fruit, contains D-limonene ((+)-limonene), which is the (*R*)-enantiomer. Racemic limonene is known as dipentene. D-Limonene is obtained commercially from citrus fruits through two primary methods: centrifugal separation or steam distillation.

Chemical reactions

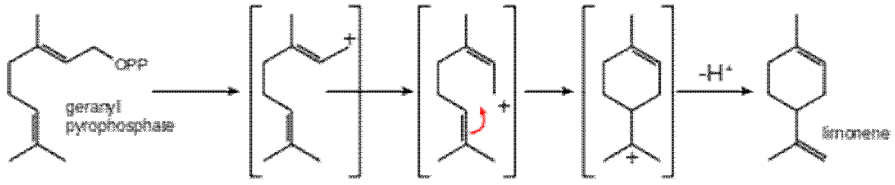
Limonene is a relatively stable monoterpene and can be distilled without decomposition, although at elevated temperatures it cracks to form isoprene.[5] It oxidizes easily in moist air to produce carveol, carvone, and limonene oxide.[6][7] With sulfur, it undergoes dehydrogenation to *p*-cymene. Limonene occurs commonly as the D- or (*R*)-enantiomer, but racemizes to dipentene at 300 °C. When warmed with mineral acid, limonene isomerizes to the conjugated diene α-terpinene (which can also easily be converted to *p*-cymene). Evidence for this isomerization includes the formation of Diels–Alder adducts between α-terpinene adducts and maleic anhydride.

It is possible to effect reaction at one of the double bonds selectively. Anhydrous hydrogen chloride reacts preferentially at the disubstituted alkene,

whereas epoxidation with mCPBA occurs at the trisubstituted alkene. In another synthetic method Markovnikov addition of trifluoroacetic acid followed by hydrolysis of the acetate gives terpineol.

Biosynthesis

In nature, limonene is formed from geranyl pyrophosphate, via cyclization of a neryl carbocation or its equivalent as shown. The final step involves loss of a proton from the cation to form the alkene.



The most widely practiced conversion of limonene is to carvone. The three-step reaction begins with the regioselective addition of nitrosyl chloride across the trisubstituted double bond. This species is then converted to the oxime with a base, and the hydroxylamine is removed to give the ketone-containing carvone.

Safety and research

D-Limonene applied to skin may cause irritation from contact dermatitis, but otherwise appears to be safe for human uses. Limonene is flammable as a liquid or vapor, and is toxic to aquatic life. There is no evidence for efficacy or regulatory approval of perillyl alcohol – the precursor for D-limonene – as a chemotherapeutic agent.

Uses

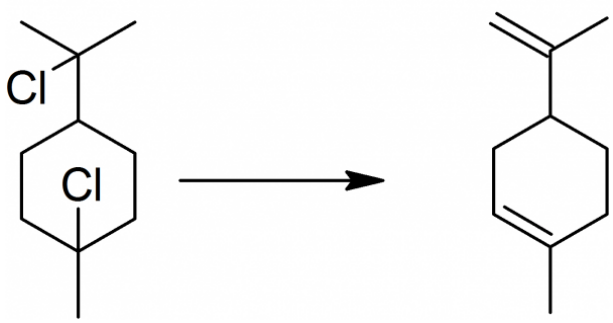
Limonene is common as a dietary supplement and as a fragrance ingredient for cosmetics products. As the main fragrance of citrus peels, D-limonene is used in food manufacturing and some medicines, such as a flavoring to mask the bitter taste of alkaloids, and as a fragrance in perfumery, aftershave lotions, bath products, and other personal care products. D-Limonene is also used as botanical insecticide. D-Limonene is used in the organic herbicide "Avenger". It is added to cleaning products, such as hand cleansers to give a lemon or orange fragrance and for its ability to dissolve oils. In contrast, L-limonene has a piny, turpentine-like odor.

Limonene is used as a solvent for cleaning purposes, such as the removal of oil from machine parts, as it is produced from a renewable source. It is used as a paint stripper and is also useful as a fragrant alternative to turpentine. Limonene is also used as a solvent in some model airplane glues and as a constituent in some paints. Commercial air fresheners, with air propellants, containing limonene are used by philatelists to remove self-adhesive postage stamps from envelope paper. Limonene is also used as a solvent for filament-fused 3D printing. Printers can print the plastic of choice for the model, but erect supports and binders from HIPS, a polystyrene plastic that is easily soluble in limonene. As it is combustible, limonene has also been considered as a biofuel.

In preparing tissues for histology or histopathology, D-limonene is often used as a less toxic substitute for xylene when clearing dehydrated specimens. Clearing agents are liquids miscible with alcohols (such as ethanol or isopropanol) and with melted paraffin wax, in which specimens are embedded to facilitate cutting of thin sections

for microscopy. In traditional medicine, D-limonene is marketed to relieve gallstones, gastroesophageal reflux disease, and heartburn, although none of these supposed effects is confirmed by high-quality clinical research.

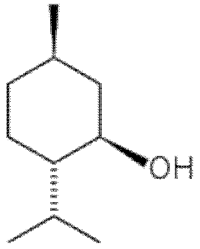
Preparation of limonene



To to round bottom flask 10 g of limonene dihydrochloride and 20 g of aniline are cautiously warmed until reaction begins. The flask is further heated for few minutes and 20 ml of glacial acetic acid is added. The reaction mixture is steam-distilled and the distillate is once more steam-distilled with oxalic acid (mineral acids must not be used), and this process repeated until no more aniline comes over. The hydrocarbon is separated from the aqueous portion of the distillate, dried over solid potassium hydroxide, and finally distilled over sodium. It forms a colorless liquid boiling at 178-180° C.

Menthol

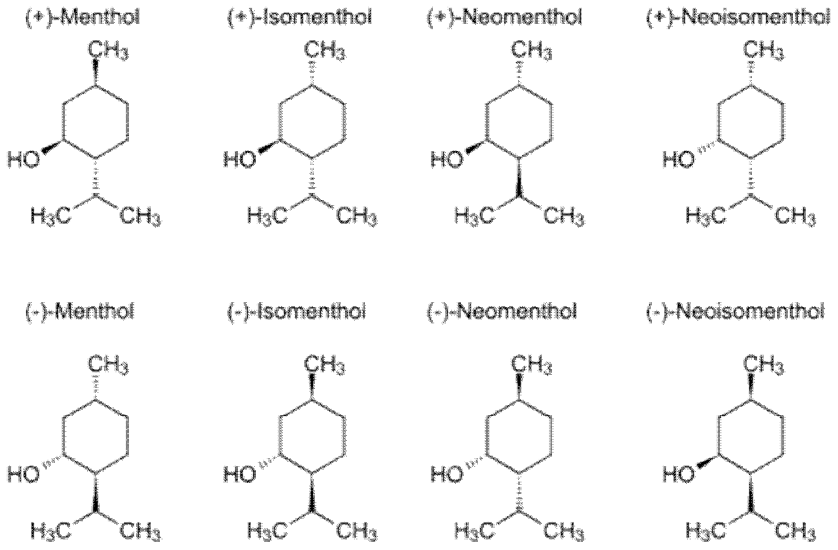
IUPAC name: 5-Methyl-2-(propan-2-yl)cyclohexan-1-ol
Other names: 2-Isopropyl-5-methylcyclohexan-1-ol



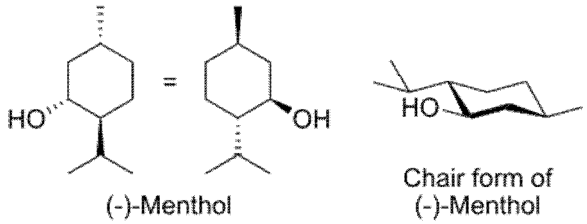
Menthol is an organic compound made synthetically or obtained from corn mint, peppermint, or other mint oils. It is a waxy, crystalline substance, clear or white in color, which is solid at room temperature and melts slightly above. The main form of menthol occurring in nature is (−)-menthol, which is assigned the (1*R*,2*S*,5*R*) configuration. Menthol has local anesthetic and counterirritant qualities, and it is widely used to relieve minor throat irritation. Menthol also acts as a weak kappa opioid receptor agonist.

Structure

Natural menthol exists as one pure stereoisomer, nearly always the (1*R*,2*S*,5*R*) form (bottom left corner of the diagram below). The eight possible stereoisomers are:



In the natural compound, the isopropyl group is in the *trans* orientation to both the methyl and hydroxyl groups. Thus, it can be drawn in any of the ways shown:



The (+)- and (–)-enantiomers of menthol are the most stable among these based on their cyclohexane conformations. With the ring itself in a chair conformation, all three bulky groups can orient in equatorial positions. The two crystal forms for racemic menthol have melting points of 28 °C and 38 °C. Pure (−)-menthol has four crystal forms, of which the most stable is the α form, the familiar broad needles.

Biological properties

Menthol's ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin is responsible for the well-known cooling sensation 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 chilis.

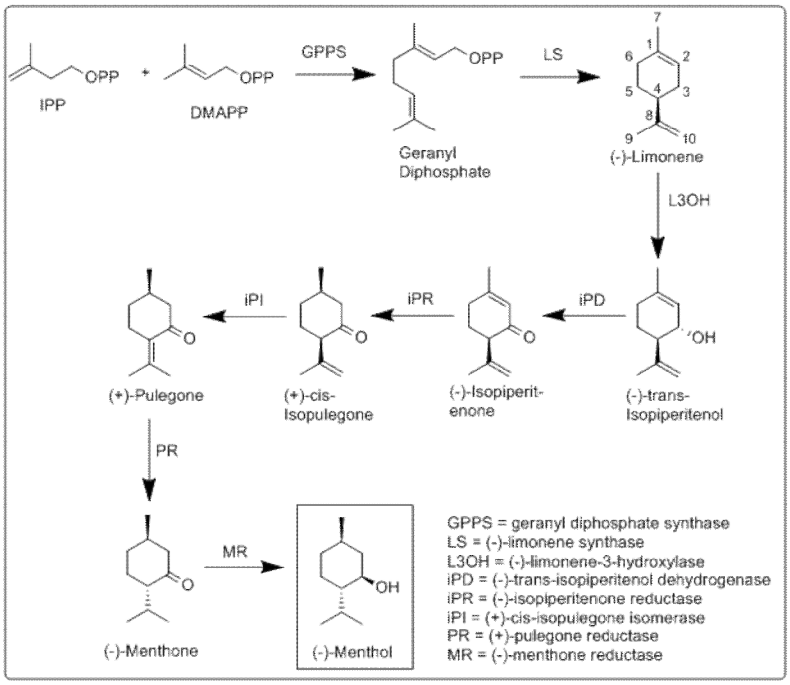
Menthol's analgesic properties are mediated through a selective activation of κ-opioid receptors. Menthol also blocks voltage-sensitive sodium channels, reducing neural activity that may stimulate muscles.[4] A study showed that topical absorption of ibuprofen is not increased by menthol, but does note the complementary effect of the menthol as a pain reliever itself. Topically applied menthol does not actually reduce inflammation of tissues or influence the cause of pain. Menthol is widely used in dental care as a topical antibacterial agent, effective against several types of streptococci and lactobacilli.

Occurrence

Mentha arvensis (wild mint) is the primary species of mint used to make natural menthol crystals and natural menthol flakes. This species is primarily grown in the Uttar Pradesh region in India. Menthol occurs naturally in peppermint oil (along with a little menthone, the ester menthyl acetate and other compounds), obtained from *Mentha* × *piperita* (peppermint). Japanese menthol also contains a small percentage of the 1-epimer, neomenthol.

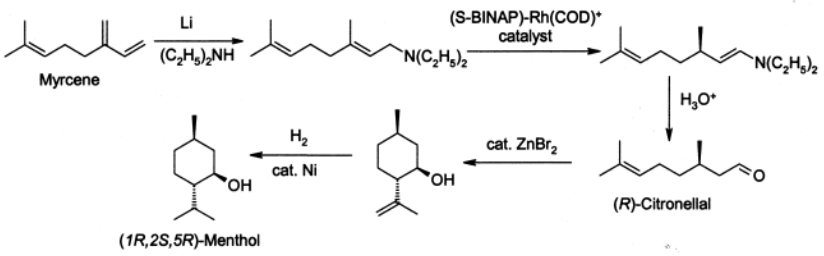
Biosynthesis

The biosynthesis of menthol has been investigated in *Mentha* × *piperita* and the enzymes involved in have been identified and characterized. It begins with the synthesis of the terpene limonene, followed by hydroxylation, and then several reduction and isomerization steps.

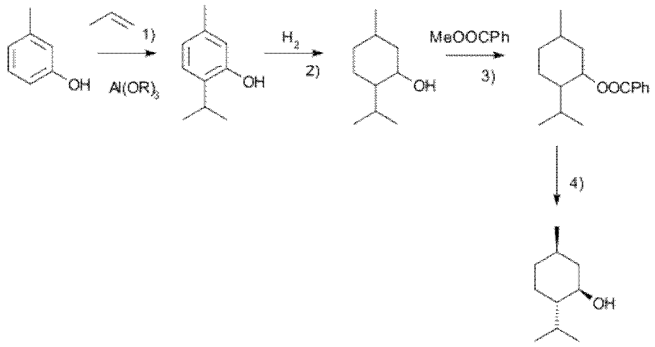


Production

Natural menthol is obtained by freezing peppermint oil. The resultant crystals of menthol are then separated by filtration. The process involves an asymmetric synthesis developed by a team led by Ryōji Noyori, who won the 2001 Nobel Prize for Chemistry in recognition of his work on this process:



The process begins by forming an allylic amine from myrcene, which undergoes asymmetric isomerisation in the presence of a BINAP rhodium complex to give (after hydrolysis) enantiomerically pure *R*-citronellal. This is cyclised by a carbonyl-ene-reaction initiated by zinc bromide to isopulegol, which is then hydrogenated to give pure (1*R*,2*S*,5*R*)-menthol. Another commercial process is the Haarmann–Reimer process. This process starts from *m*-cresol which is alkylated with propene to thymol. This compound is hydrogenated in the next step. Racemic menthol is isolated by fractional distillation. The enantiomers are separated by chiral resolution in reaction with methyl benzoate, selective crystallisation followed by hydrolysis.



Racemic menthol can also be formed by hydrogenation of pulegone. In both cases with further processing (crystallizative entrainment resolution of the menthyl benzoate conglomerate) it is possible to concentrate the L-enantiomer, however this tends to be less efficient, although the higher processing costs may be offset by lower raw material costs. A further advantage of this process is that D-menthol becomes inexpensively available for use as a chiral auxiliary, along with the more usual L-antipode.

Applications

- Menthol is included in many products for a variety of reasons. These include:
- In nonprescription products for short-term relief of minor sore throat and minor mouth or throat irritation.

Examples: lip balms and cough medicines.

- As an antipruritic to reduce itching.
- As a topical analgesic, it is used to relieve minor aches and pains, such as muscle cramps, sprains, headaches and similar conditions, alone or combined with chemicals such as camphor, eucalyptus oil or capsaicin. In Europe, it tends to appear as a gel or a cream, while in the U.S., patches and body sleeves are very frequently used.

Examples: Tiger Balm, or IcyHot patches or knee/elbow sleeves.

- As a penetration enhancer in transdermal drug delivery.
- In decongestants for chest and sinuses (cream, patch or nose inhaler).

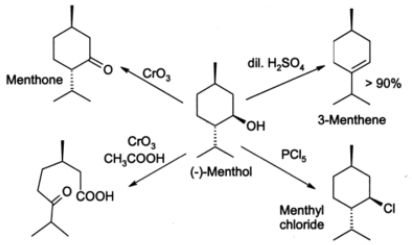
Examples: Vicks VapoRub, Mentholatum, VapoRem.

- In certain medications used to treat sunburns, as it provides a cooling sensation (then often associated with aloe).
- In aftershave products to relieve razor burn.
- As a smoking tobacco additive in some cigarette brands, for flavor, and to reduce throat and sinus irritation caused by smoking. Menthol also increases nicotine receptor density, increasing the addictive potential of tobacco products.
- Commonly used in oral hygiene products and bad-breath remedies, such as mouthwash, toothpaste, mouth and tongue sprays, and more generally as a food flavor agent; such as in chewing gum and candy.

- As a pesticide against tracheal mites of honey bees.
- In perfumery, menthol is used to prepare menthyl esters to emphasize floral notes (especially rose).
- In first aid products such as "mineral ice" to produce a cooling effect as a substitute for real ice in the absence of water or electricity (pouch, body patch/sleeve or cream).
- In various patches ranging from fever-reducing patches applied to children's foreheads to "foot patches" to relieve numerous ailments (the latter being much more frequent and elaborate in Asia, especially Japan: some varieties use "functional protrusions", or small bumps to massage one's feet as well as soothing them and cooling them down).
- In some beauty products such as hair conditioners, based on natural ingredients (e.g., St. Ives).
- As an antispasmodic and smooth muscle relaxant in upper gastrointestinal endoscopy.
- In organic chemistry, menthol is used as a chiral auxiliary in asymmetric synthesis. For example, sulfinate esters made from sulfinyl chlorides and menthol can be used to make enantiomerically pure sulfoxides by reaction with organolithium reagents or Grignard reagents. Menthol reacts with chiral carboxylic acids to give diastereomic menthyl esters, which are useful for chiral resolution.

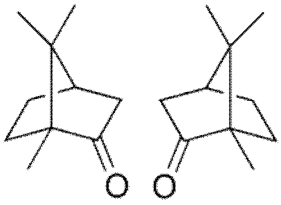
Reactions

Menthol reacts in many ways like a normal secondary alcohol. It is oxidised to menthone by oxidising agents such as chromic acid or dichromate, though under some conditions the oxidation can go further and break open the ring. Menthol is easily dehydrated to give mainly 3-menthene, by the action of 2% sulfuric acid. Phosphorus pentachloride (PCl_5) gives menthyl chloride.



Camphor

IUPAC name: 1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one
Other names: 2-Bornanone; Bornan-2-one; 2-Camphanone; Formosa



Camphor (/ˈkæmfər/) is a waxy, flammable, transparent solid with a strong aroma. It is a terpenoid with the chemical formula $C_{10}H_{16}O$. It is found in the wood of the camphor laurel (*Cinnamomum camphora*), a large evergreen tree found in Asia (particularly in Sumatraand Borneo islands, Indonesia) and also of the unrelated *kapur tree*, a tall timber tree from the same region. It also occurs in some other related trees in the laurel family, notably *Ocotea usambarensis*. The oil in rosemary leaves (*Rosmarinus officinalis*), in the

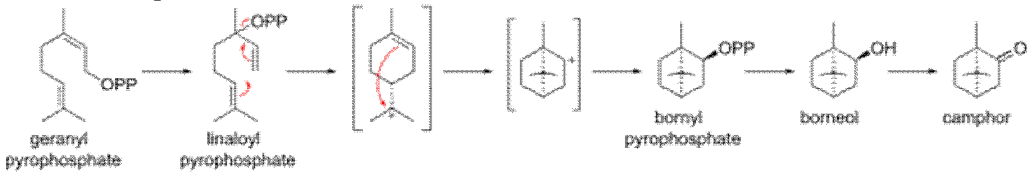
mint family, contains 10 to 20% camphor, while camphorweed (*Heterotheca*) only contains some 5%. Camphor can also be synthetically produced from oil of turpentine. It is used for its scent, as an ingredient in cooking (mainly in India), as an embalming fluid, for medicinal purposes, and in religious ceremonies. A major source of camphor in Asia is camphor basil (the parent of African blue basil). The molecule has two possible enantiomers as shown in the structural diagrams. The structure on the left is the naturally occurring (*R*)-form, while its mirror image shown on the right is the (*S*)-form.

Production

Camphor was produced as a forest product for millennia, condensed from the vapor given off by the roasting of wood chips cut from the relevant trees. When its uses in the nascent chemical industries (discussed below) greatly increased the volume of demand in the late 19th century, potential for changes in supply and in price followed. In 1911 Robert Kennedy Duncan, an industrial chemist and educator, related that the Imperial Japanese government had recently tried to monopolize the production of natural camphor as a forest product in Asia but that the monopoly was prevented by the development of the total synthesis alternatives, which began in "purely academic and wholly uncommercial" form with Gustav Komppa's first report "but it sealed the fate of the Japanese monopoly […] For no sooner was it accomplished than it excited the attention of a new army of investigators—the industrial chemists.

Biosynthesis

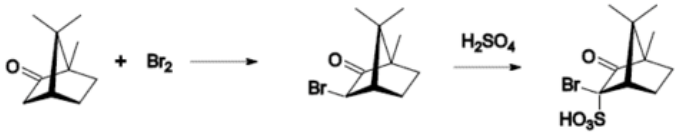
In biosynthesis, camphor is produced from geranyl pyrophosphate, via cyclisation of linaloyl pyrophosphate to bornyl pyrophosphate, followed by hydrolysis to borneol and oxidation to camphor.



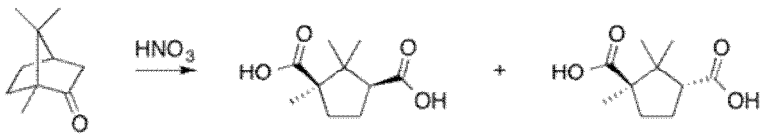
Reactions

Typical camphor reactions are

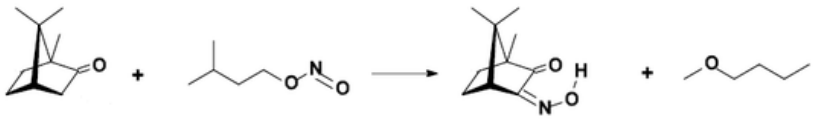
Bromination



Oxidation with nitric acid



Conversion to isonitroso camphor



Camphor can also be reduced to isoborneol using sodium borohydride.

- Prepared diamond thin film using camphor as the precursor for chemical vapor deposition.
- Carbon nanotubes were successfully synthesized using camphor in chemical vapor deposition process.

Explosives

Camphor is used as a plasticizer for nitrocellulose, an ingredient for fireworks and explosive munitions. During the late 19th Century, as Western manufacturers developed machine guns and other rapid fire ordnance, it became imperative to reduce the smoke that covered battlefields so that haze obscured hidden gun emplacements could be revealed. Camphor was an essential component in the production of smokeless gunpowder. Also, the new smokeless powder did not foul the weapons as much as conventional gunpowder.

Nitrocellulose plastics

Closely related chemically to the explosives uses are the uses in nitrocellulose plastics (pyroxylin plastics). In the early decades of the plastics industry, camphor was used in "immense quantities" (that is, by the carload) in the making of such plastics, including celluloid and pyroxylin lacquers, and of explosives. It was in this connection that the development of a synthetic source became economically important, as discussed above.

Pest deterrent and preservative

Camphor is believed to be toxic to insects and is thus sometimes used as a repellent. Camphor is used as an alternative to mothballs. Camphor crystals are sometimes used to prevent damage to insect collections by other small insects. It is kept in clothes used on special occasions and festivals, and also in cupboard corners as a cockroach repellent. The smoke of camphor crystal or camphor incense sticks can be used as an environmentally-friendly mosquito repellent.

Recent studies have indicated that camphor essential oil can be used as an effective fumigant against red fire ants, as it affects the attacking, climbing, and feeding behavior of major and minor workers. Camphor is also used as an antimicrobial substance. In embalming, camphor oil was one of the ingredients used by ancient Egyptians for mummification. Solid camphor releases fumes that form a rust-preventative coating and is therefore stored in tool chests to protect tools against rust.

Use in Perfumes

In the ancient Arab world, Camphor was one of the most popular perfume ingredients. According to the Perfume Handbook, "[Camphor] features in more than a quarter of al-Kindi's perfume recipes and in many other medieval Arabic works, including the *Arabian Nights Tales.*" The word camphor or *campheer* also appears in many translations of the biblical Song of Solomon. However, the original Hebrew word *kopher*, actually refers to *henna*, another perfume and dyestuff of the Arabic world. The Chinese referred to the best camphor as "dragon's brain perfume," due to its "pungent and portentous aroma" and "centuries of uncertainty over its provenance and mode of origin."

Medicinal Uses

Physiology

Camphor is readily absorbed through the skin, where it stimulates nerve endings sensitive to heat and cold, producing a warm sensation when vigorously applied, or a cool

sensation when applied gently. These effects are particularly noticeable in the lungs and airways if camphor is inhaled as an aerosol. The action on nerve endings also induces a slight local analgesia. The sensation of heat that camphor produces on the skin is presumably due to activation of the ion channels TRPV3 and TRPV1, while the cool sensation due to activation of TRPM8.

The global effects on the body include tachycardia (increased heart rate), vasodilation in skin (flushing), slower breathing, reduced appetite, and increased secretions and excretions such as perspiration and urination. Camphor is toxic in large doses. It produces symptoms of irritability, disorientation, lethargy, muscle spasms, vomiting, abdominal cramps, convulsions, and seizures. Lethal doses in adults are in the range 50–500 mg/kg (orally). Generally, two grams cause serious toxicity and four grams are potentially lethal.

Traditional uses

Camphor has been used in traditional medicine from time immemorial in countries where it was native. It was probably the odor of the substance and its decongestant effect that led to its use in medicine.

Camphor was used in ancient Sumatra to treat sprains, swellings, and inflammation. It has long been used as a medical substance in ancient India, where it generally goes by the name *karpūra*. It has been described in the 7th-century Āyurvedic work *Mādhavacikitsā*as being an effective drug used for the treatment of fever. The plant has also been named *hima* and has been identified with the plant *Cinnamomum camphora*. According to the *Vaidyaka-śabda-sindhu*, it is one of the "five flavours" used in betel-chewing, where it is also referred to as *candrabhasma* ('moon powder'). Camphor also was used for centuries in Chinese medicine for a variety of purposes.

Hindu religious ceremonies

Camphor is widely used in Hindu religious ceremonies. It is put on a stand called 'karpur dāni' in India. Aarti is performed after setting fire to it usually as the last step of puja.