

Volatile Oils

Volatile oils are the odorous principles found in various plant parts. Because they evaporate when exposed to the air at ordinary temperatures, they are called **volatile oils, ethereal oils, or essential oils**. The last term is applied because volatile oils represent the "essences" or odoriferous constituents of the plants. Volatile oils are colorless as a rule, particularly when they are fresh, but on long standing they may oxidize and resinify, thus darkening in color. To prevent this darkening, they should be stored in a cool, dry place in tightly stoppered, preferably full (not half-emptied), amber glass containers.

Depending on the plant family, volatile oils may occur in specialized secretory structures such as glandular hairs (Labiatae), modified parenchymal cells (Piperaceae), oil-tubes called vittae (Umbelliferae), or in lysigenous or schizogenous passages (Pinaceae, Rutaceae). They may be formed directly by the protoplasm, by decomposition of the resinogenous layer of the cell wall, or by the hydrolysis of certain glycosides. In the conifers, volatile oils may occur in all tissues; in the rose, they appear in appreciable quantities only in the petals; in cinnamon, only in the bark and the leaves; in the umbelliferous fruits, only in the pericarp; in the mints, only in the glandular hairs of the stems and leaves; and in the orange, one kind of oil occurs only in the flower petals and another kind only in the rind. Volatile oils may act as repellents

to insects, thus preventing the destruction of the flowers and leaves; or they may serve as insect attractants, thus aiding in cross-fertilization of the flowers.

*Chemical constituents of volatile oils may be divided into 2 broad classes, based on their biosynthetic origin: (1) terpene derivatives formed via the acetate-mevalonic acid pathway, and (2) aromatic compounds formed via the shikimic acid-phenylpropanoid route. The biosynthesis of relatively few of these compounds has been investigated in any detail. Most experimental studies have merely demonstrated that a particular precursor, e.g., acetate, is incorporated into a terpene molecule in a particular pattern, and little attention has been devoted to the interconversion of the numerous terpene derivatives themselves. Selected examples of biosyntheses that have been demonstrated experimentally with labeled precursors follow in the appropriate sections.

Although volatile oils differ greatly in their chemical constitution, they have a number of physical properties in common. They possess characteristic odors, they are characterized by high refractive indices, most of them are optically active, and their specific rotation is often a valuable diagnostic property. As a rule, volatile oils are immiscible with water, but they are sufficiently soluble to impart their odor to water. The aromatic waters are dependent on this slight solubility. Volatile oils, how-

ever, are soluble in ether, alcohol, and most organic solvents.

Several points of differentiation exist between volatile oils and fixed oils. Volatile oils can be distilled from their natural sources; they do not consist of glyceryl esters of fatty acids. Hence, they do not leave a permanent grease spot on paper and cannot be saponified with alkalis. Volatile oils do not become rancid as do the fixed oils, but instead, on exposure to light and air, they oxidize and resinify.

Practically all volatile oils consist of chemical mixtures that are often quite complex; they vary widely in chemical composition. Almost any type of organic compound may be found in volatile oils (hydrocarbons, alcohols, ketones, aldehydes, ethers, oxides, esters, and others), and only a few possess a single component in a high percentage (volatile mustard oil yields not less than 93% of allylisothiocyanate; clove oil contains not less than 85% of phenolic substances, chiefly eugenol). However, it is not uncommon for a volatile oil to contain over 200 components, and often the trace constituents are essential to the odor and flavor. The absence of even one component may change the aroma. Plants of the same species grown in different parts of the world usually have the same components, but the percentages that are present may differ.

Methods of Obtaining Volatile Oils

Volatile oils are usually obtained by distillation of the plant parts containing the oil. The method of distillation depends on the condition of the plant material. Three types of distillation are used by industrial firms: (1) water, (2) water and steam, and (3) direct steam.

Water distillation is applied to plant material that is dried and not subject to injury by boiling. Turpentine oil is obtained in this manner. The crude turpentine oleoresin, composed of plant exudate, rainwater, wood chips, pine needles, and other components (see page 147), is introduced

into the distilling chamber and subjected to heat until all volatile matter, both oil and water, is condensed in the condensing chamber. Turpentine oil, consisting almost entirely of terpenes, is not affected by this amount of heat.

Water and steam distillation is employed for either dried or fresh substances that may be injured by boiling. In the case of dried material (cinnamon, clove), the drug is ground and then covered with a layer of water. Steam is passed through the macerated mixture. Because the oil could be impaired by direct boiling, the steam is generated elsewhere and is piped into the container holding the drug. The oily layer of the condensed distillate is separated from the aqueous layer, and the oil may be marketed with or without further processing.

In the method of **direct steam distillation**, applicable to fresh plant drugs (peppermint, spearmint), the crop is cut and placed directly into a metal distilling tank on a truck bed. The truck is driven to a distilling shed, where steam lines are attached to the bottom of the distilling tank. The plant material is still green and contains considerable natural moisture; therefore, maceration is unnecessary. Steam is forced through the fresh herb and carries the oil droplets through a vapor pipe attached at the top of the tank to the condensing chamber.

During steam distillation (Fig. 5-1) certain components of a volatile oil tend to hydrolyze, whereas other constituents are decomposed by the high temperatures. Ideal distillation methods utilizing steam should provide for the highest possible diffusion rate of steam and water through plant membranes and should thus keep the hydrolysis and decomposition at a minimum.

Glycosidic volatile oils (mustard oil) are obtained by enzymatic hydrolysis of the glycosides. In black mustard seeds, the glycoside, sinigrin, is hydrolyzed by myrosin

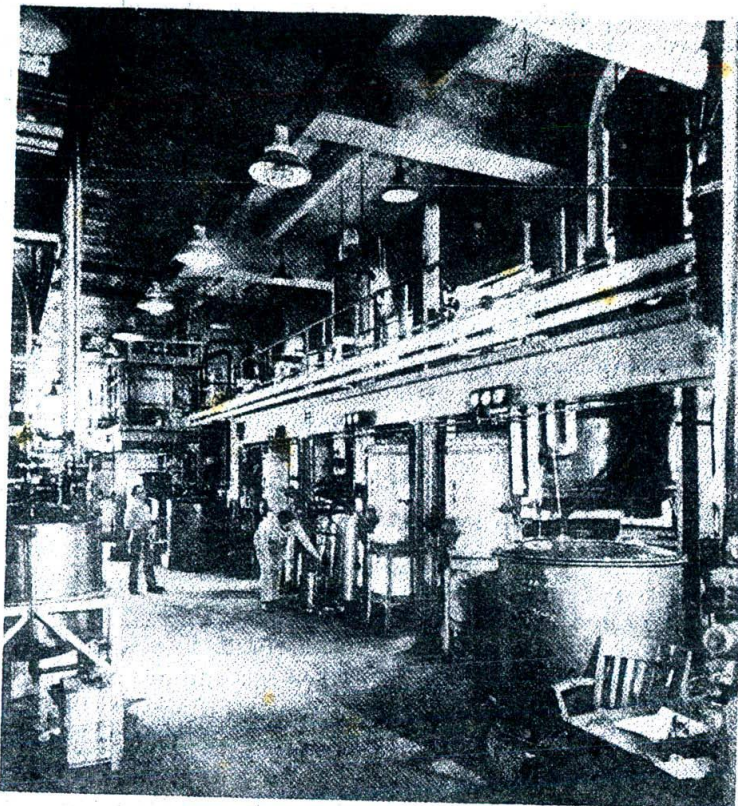


Fig. 5-1. Large-scale steam distillation equipment for the production of essential oils. (Photo courtesy of Fritzsche Brothers, Inc., New York.)

with the production of volatile mustard oil (see page 72).

Some volatile oils cannot be distilled without decomposition and are usually obtained by **expression** (lemon oil, orange oil) or possibly by other mechanical means. In the United States, the general method for obtaining citrus oils involves puncturing the oil glands by rolling the fruit over a trough lined with sharp projections that are long enough to penetrate the epidermis and pierce the oil glands located in the outer portion of the peel (**ecuelle** method). A pressing action on the fruit removes the oil from the glands, and a fine spray of water washes the oil from the mashed peel while the juice is extracted through a center tube that cores the fruit. The resulting oil-water emulsion is separated by centrifu-

gation. A variation in this process is to remove the peel from the fruit before the oil is extracted.

Often the volatile oil content of fresh plant parts (flower petals) is so small that oil removal is not commercially feasible by the aforementioned methods. In such instances, an odorless, bland, fixed oil or fat is spread in a thin layer on glass plates. The flower petals are placed on the fat for a few hours; then, repeatedly, the old petals are removed, and a new layer of petals is introduced. After the fat has absorbed as much fragrance as possible, the oil may be removed by extraction with alcohol. This process is known as **enfleurage** and was formerly used extensively in the production of perfumes and pomades.

In the perfume industry, most of the

modern essential oil production is accomplished by **extraction**, using solvent systems based on such volatile solvents as petroleum ether or benzene. The chief advantage of extraction over distillation is that uniform temperatures (usually 50° C) can be maintained during most of the process. As a result, extracted oils have a more natural odor that is unmatched by distilled oils, which may have undergone altered chemical constitution by the high temperatures. This feature is of considerable importance to the perfume industry; however, the established distillation method is a low-cost operation compared to the cost of the extraction process.

Destructive distillation is a means of obtaining **empyreumatic** oils. When the wood or resin of members of the Pinaceae or Cupressaceae is heated without access of air, a decomposition takes place, and a number of volatile compounds are driven off. The resultant mass is charcoal. The condensed volatile matter usually separates into 2 layers: an aqueous layer containing wood naphtha (methyl alcohol) and pyroligneous acid (crude acetic), and a tarry liquid in the form of pine tar, juniper tar, or other tars, depending on the wood introduced. This dry distillation is usually conducted in retorts, and if the wood is chipped or coarsely ground and the heat applied rapidly, the yield of tar represents about 10% of the wood used.

Medicinal and Commercial Uses

Many crude drugs are used medicinally because of their volatile oil content; however, in numerous cases, the volatile oils separated from the drugs are used as drugs themselves. Similarly, various crude drugs are powdered and are employed as spices and condiments (anise, clove, nutmeg). The volatile oil drugs and the separated oils are most commonly used for flavoring purposes. They may possess a carminative action, but a few (eucalyptus oil, wintergreen oil) possess additional therapeutic properties. In addition to their pharmaceutic

uses, the volatile oils are employed widely as flavors for foods and confections and in the spice, perfume, and cosmetic trades. In 1979, the United States imported over 9000 metric tons of essential oils valued at \$106 million.

The fabrication of **perfumes** is a multi-million dollar industry. Perfumery materials such as volatile oils are used directly not only for perfumes and cosmetics but also are essential for the manufacture of soaps, toiletries, and deodorizers and for masking or providing odor to household cleaners, polishes, and insecticides.

Fine perfumes are considered works of art. They have been defined as judicious blends of odorants, each having its own particular odor but whose combined odor is itself characteristically unique. The formulas for these perfumes are generally well-guarded secrets, and the perfumer must have an intimate knowledge of perhaps 1000 aromatic substances when formulating a perfume. Perfume formulation has been compared to the creation of a musical composition; the various odorants can be classified like musical notes into top, medium, and base notes. Most perfumes contain elements of all 3 categories, which are blended to provide a unique, harmonious odor. The top notes are the most volatile products. They leave the skin rapidly and include lemon, lavender, and anise oils. Odorants with intermediate volatility and tenacity are classified as middle notes and include thyme, neroli, and rose oils. Base notes are products with low volatility and high tenacity and are also described as fixatives because they provide staying power for the perfume. Common examples are vanillin (see page 74); musk, the dried secretion from the preputial follicles of the male musk deer of Asia; civet, a glandular secretion appearing in an outwardly discharging pocket underneath the posterior appendage of both the male and female civet cats; and ambergris, one of the most valuable materials used by the perfumer and a pathologic product formed in the

stomach of the sperm whale when it is feeding on squid or cuttlefish. It is thought that the indigestible beaks of these animals irritate the whale's stomach, which in turn stimulates the formation of the ambergris.

Because volatile oils are mixtures of a number of constituents, one may assume that more than one constituent possesses physiologic activity. Volatile oils generally consist of an **eleoptene**, the hydrocarbon portion of the oil, which is liquid, and one or more **stearoptenes**, the oxidized hydrocarbon portions of the oil, which are usually solid (although exceptions to this are not rare). Thus, peppermint herb owes its activity to the volatile oil; the oil in turn owes its properties to the stearoptene, menthol. Menthol is not the only constituent present; menthyl acetate, limonene, menthone, cineol, and several others have been isolated and identified. Nevertheless, peppermint oil is used for different purposes than is menthol. Stearoptenes are generally obtained by freezing the oil or by other methods. Menthol, thymol, and anethole are solid stearoptenes, whereas, eucalyptol, eugenol, and methyl salicylate are liquids.

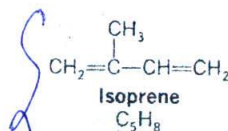
CHEMISTRY OF VOLATILE OILS

In only a few cases, as previously noted, do volatile oils consist of a single chemical compound in a state of comparative purity. In most cases, they are mixtures containing compounds of diverse types. These compounds may be separated in various ways: (1) low temperatures, which crystallize out the stearoptenes, (2) fractional distillation, (3) fractional crystallization from poor solvents, (4) different forms of chromatography, and (5) removal by chemical action. In the last group, compounds with free acidic groups may be removed from the oil with sodium carbonate, basic compounds may be removed with hydrochloric acid, phenols with sodium hydroxide, aldehydes with sodium bisulfite, and so forth.

In recent years, advances in analytic in-

strumentation, particularly in the area of chemical separation techniques based on capillary-column gas chromatography and high-pressure liquid chromatography, coupled with computerized instruments that combine gas chromatography with mass spectrometry, have led to the precise identification of the components of volatile oils, including trace constituents.

Many volatile oils consist largely of **terpenes**. Terpenes are defined as natural products whose structures may be divided into isoprene units. These units arise from acetate via mevalonic acid and are branched-chain, 5-carbon units containing 2 unsaturated bonds.



During the formation of terpenes, the isoprene units are linked in a head-to-tail fashion, and the number of units incorporated into a particular terpene serves as a basis for the classification of these compounds (Fig. 5-2). Monoterpenes are composed of 2 isoprene units and have the molecular formula, $\text{C}_{10}\text{H}_{16}$. Sesquiterpenes, $\text{C}_{15}\text{H}_{24}$, contain 3 isoprene units. Diterpenes, $\text{C}_{20}\text{H}_{32}$, have 4 isoprene units, and triterpenes, $\text{C}_{30}\text{H}_{48}$, are composed of 6 isoprene units. The terpenes found most often in volatile oils are monoterpenes. They can occur in acyclic, monocyclic, and bicyclic forms as hydrocarbons and as oxygenated derivatives, such as alcohols, aldehydes, ketones, phenols, oxides, and esters.

Another major group of volatile-oil constituents are the **phenylpropanoids**. These compounds contain the C_6 phenyl ring with an attached C_3 propane side chain. Figure 5-3 illustrates examples of these natural products. Many of the phenylpropanoids found in volatile oils are phenols or phenol ethers. In some cases, the propane side chain has been abridged to give a $\text{C}_6\text{-C}_1$ structure, such as in methyl salicylate and vanillin.

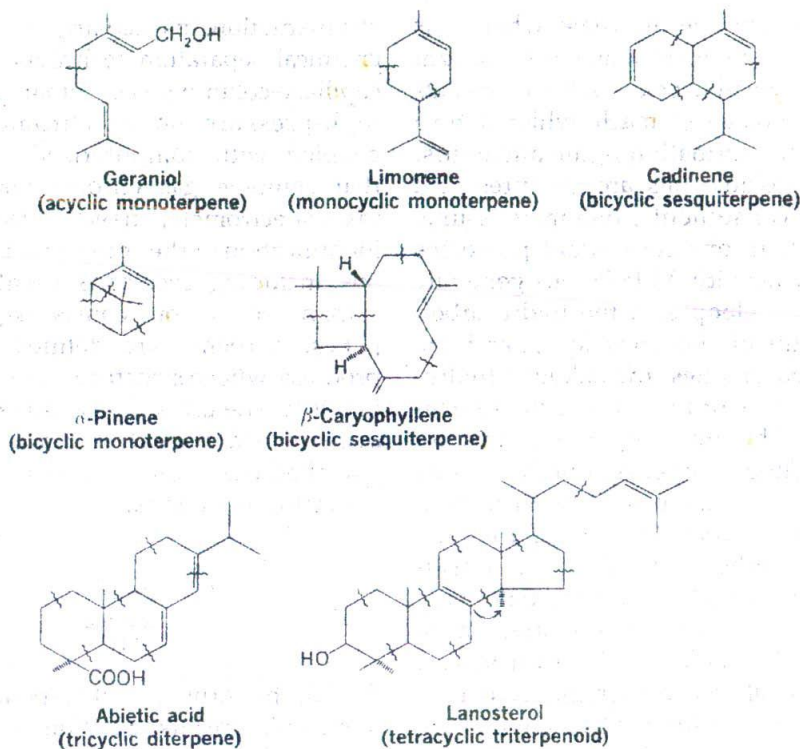


Fig. 5-2. Representative terpenes showing the isoprene units in each molecule.

Because the various constituents of volatile oils are responsible for the characteristic odors, flavors, and therapeutic properties of the oils, a chemical classification of the oils should be based on their principal chemical constituents. However, because the types of constituents are so diverse and so numerous, the assignment of the oil or the oil-bearing drug to a definitive place in such a classification is often difficult. For example, unoxygenated terpenes sometimes account for a large percentage of the oil. The stearoptene, which is present in smaller quantities, represents the constituent that is chiefly responsible for imparting the characteristic odor or flavor. The following are the divisions in which volatile oils and volatile-oil-containing drugs are placed: (1) hydrocarbons, (2) alcohols, (3) aldehydes, (4) ketones, (5) phenols, (6) phenolic ethers, (7) oxides, and (8) esters.

In addition to the molecular structure, the **stereochemistry** of the constituents of volatile oils markedly determines the type of olfactory response evoked by the compounds. Geometric isomers, whether *ortho/meta/para* or *cis/trans*, are in most cases readily distinguished both as to quality and strength of odor. An interesting stereochemical feature of many terpenes is the fact that both **enantiomers** (optically active isomers) exist in nature. In some cases, a plant species produces only one of the enantiomers, whereas a different species may produce both. Among the monoterpenes that occur as the (+) form in certain species and as the (-) enantiomeric form in others are limonene, α -terpineol, α -fenchol, borneol, menthone, carvone, and linalool. In addition, limonene, α -terpinol, α -fenchol, carvone, and camphor, as well as many others, can be found in plants as the racemic mixture.

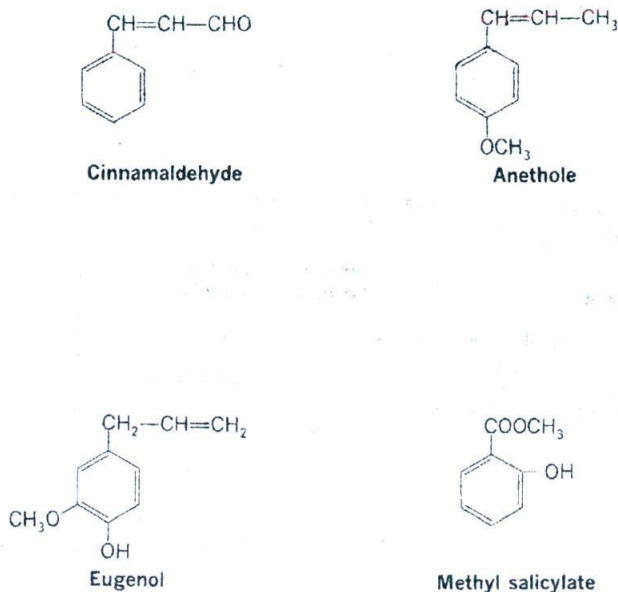


Fig. 5-3. Representative phenylpropanoids and abridged phenylpropanoids found as constituents of volatile oils.

As with many other natural product compounds that exist in enantiomeric forms, such as alkaloids and amino acids, the physiologic responses elicited by each isomer can differ. For example, (+)-carvone has an odor of caraway, whereas (-)-carvone produces a spearmint odor. These observations lend support to the stereochemical theory of olfaction which proposes that different kinds of olfactory receptor sites are in the nose. Odorant molecules could lodge on these sites and would have shapes and sizes (varying stereochemistry) that were complementary to the shape and size of the particular receptor. A proper fit at the receptor would be required to initiate a nerve impulse that would register in the brain the perception of the odor.

BIOSYNTHESIS OF VOLATILE OIL CONSTITUENTS

The biosynthetic building blocks for **terpenes** are isoprene units. The so-called bio-

synthetically active isoprene units are isopentenyl pyrophosphate and dimethylallyl pyrophosphate, compounds that arise from acetate via mevalonic acid (see page 159). Geranyl pyrophosphate is the C-10 precursor of the terpenes and is believed to play a key role in the formation of monoterpenes. It is formed by the condensation of one unit each of isopentenyl pyrophosphate and dimethylallyl pyrophosphate. As seen from Figure 5-4, geranyl pyrophosphate is believed to be the direct precursor to acyclic monoterpenes. However, it must be isomerized to neryl pyrophosphate before the cyclic monoterpenes can be formed because the *trans* isomer does not have the correct stereochemistry for cyclization. Another possibility is the formation of neryl pyrophosphate from isopentenyl pyrophosphate and dimethylallyl pyrophosphate independent of a geranyl pyrophosphate step. The intermediates in the formation of the cyclic terpenes are shown as carbonium ions; however, the

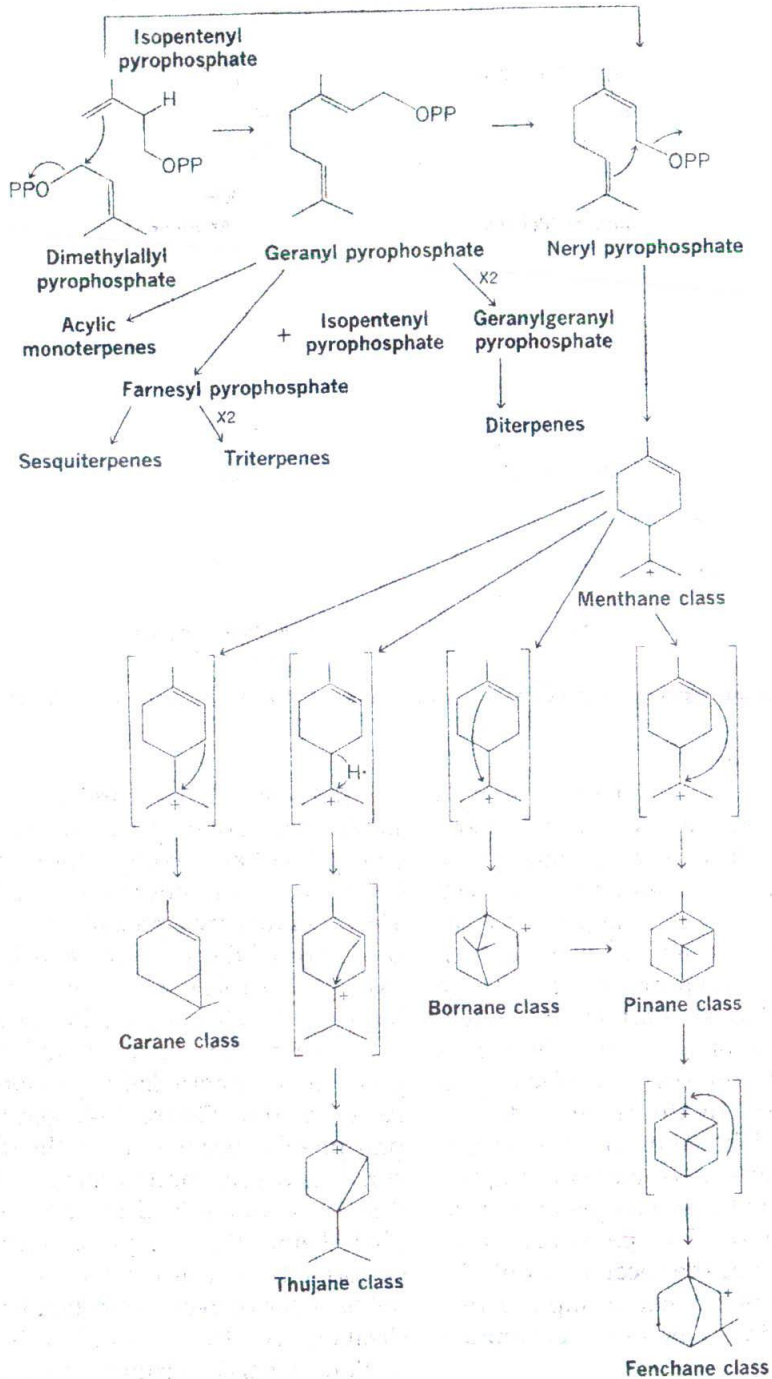


Fig. 5-4. Hypothetic mechanism for biosynthetic formation of terpenes.

true species are probably pyrophosphate esters or enzyme-bound intermediates.

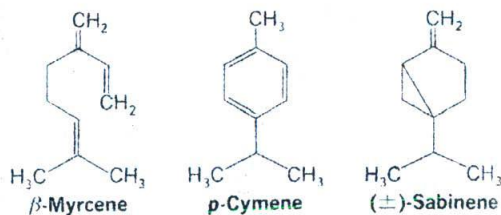
The principal precursors for **phenylpropanoid** compounds, which are found in volatile oils, are cinnamic acid and *p*-hydroxycinnamic acid, also known as *p*-coumaric acid. In plants, these compounds arise from the aromatic amino acids phenylalanine and tyrosine, respectively, which in turn are synthesized via the shikimic acid pathway (Fig. 5-5). This biosynthetic pathway has been elucidated in microorganisms by using auxotrophic mutants of *Escherichia coli* and *Enterobacter aerogenes* that require the aromatic amino acids for growth. In the biosynthesis, 2 glucose metabolites, erythrose 4-phosphate and phosphoenolpyruvate, react to yield a phosphorylated 7-carbon keto sugar, DAHP. This compound cyclizes to 5-dehydroquinic acid, which is then converted to shikimic acid. Shikimic acid, through a series of phosphorylated intermediates, yields chorismic acid, which is an important branch-point intermediate. One branch leads to anthranilic acid and then to tryptophan. The other leads to prephenic acid, the last nonaromatic compound in the sequence. Prephenic acid can be aromatized in 2 ways. The first proceeds by dehydration and simultaneous decarboxylation to yield phenylpyruvic acid, the direct precursor of phenylalanine. The second occurs by dehydrogenation and decarboxylation to yield *p*-hydroxyphenylpyruvic acid, the precursor of tyrosine.

The phenylpropanoid precursor, cinnamic acid, is formed by the direct enzymatic deamination of phenylalanine, and *p*-coumaric acid can originate in an analogous way from tyrosine or by hydroxylation of cinnamic acid at the *para* position.

HYDROCARBON VOLATILE OILS

Hydrocarbons occur in practically all volatile oils. Limonene is probably the most widely distributed of the monocyclic terpenes (see Fig. 5-2). It occurs in citrus,

mint, myristica, **caraway**, **thyme**, cardamom, coriander, and many other oils. Another important monocyclic hydrocarbon monoterpene is *p*-cymene, which is found in coriander, **thyme**, **cinnamon**, and myristica oils. Pinene (see Fig. 5-2), a dicyclic monoterpene, is also widely distributed. It is found in many conifer oils as well as in lemon, anise, eucalyptus, thyme, fennel, coriander, orange flower, and myristica oils. Sabinene, a dicyclic monoterpene of the thujane class, is distributed in cardamom and lemon oils. Acyclic monoterpene hydrocarbons are rather rare, but myrcene from myrica, lemon, and myristica oils may be cited as an example. Cadinene (see Fig. 5-2), occurring in juniper tar, is a typical sesquiterpene hydrocarbon. β -Caryophyllene (see Fig. 5-2), which is found in wormwood, peppermint, cinnamon, and clove oils, is an example of a sesquiterpene with a more unusual chemical structure.



A volatile oil drug composed chiefly of hydrocarbons is turpentine oil.

Turpentine Oil

Turpentine oil or spirits of turpentine is the volatile oil distilled from the oleoresin obtained from *Pinus palustris* Miller and from other species of *Pinus* Linné (Fam. Pinaceae) that yield terpene oils exclusively. Turpentine oil is the largest volume essential oil in commerce; little, however, is used by the essential oil and pharmaceutical industry since it is primarily a raw material for chemical manufacture.

Turpentine oil is a colorless liquid having a characteristic odor and taste, both of which become stronger and more disa-

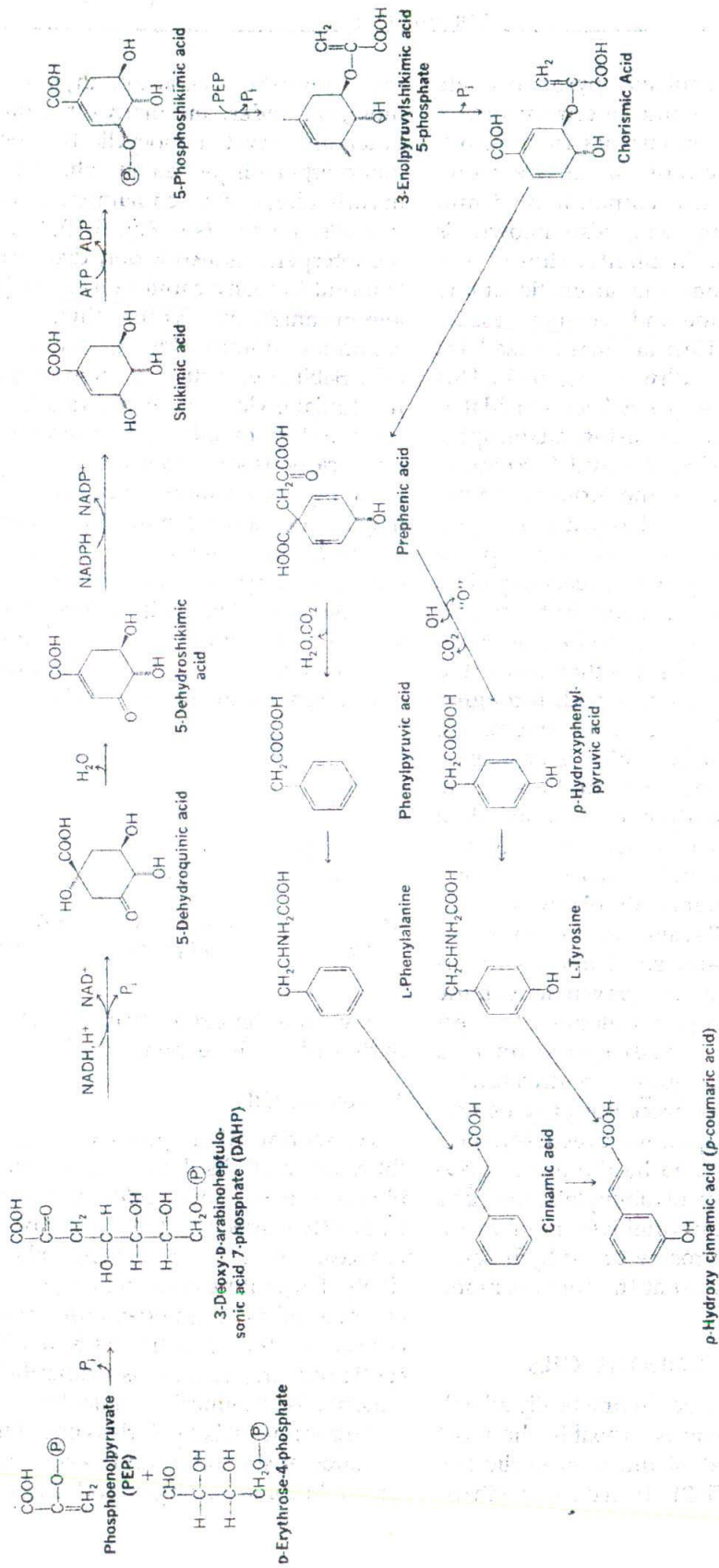


Fig. 5-5. Biosynthesis of phenylpropanoid compounds.

greeable as the oil ages or is exposed to air. Spirits of turpentine from the southeastern United States contains approximately 65% α -pinene, 30% β -pinene, and 5% other terpenes.

NONPRESCRIPTION PRODUCTS. Turpentine oil is used as a counterirritant in Vicks Vaporub®, Mentholatum Deep Heating®, and Sloan's Liniment®.

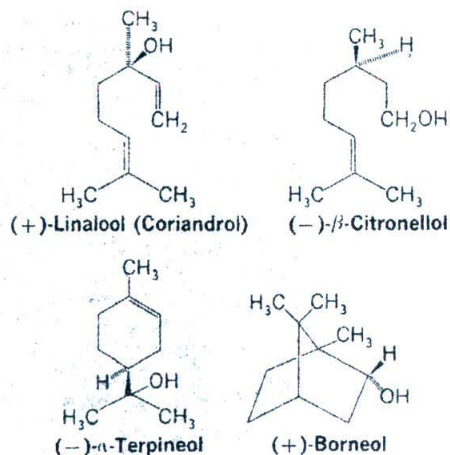
Rectified turpentine oil is turpentine oil rectified by distillation from an aqueous solution of sodium hydroxide. It is dispensed when turpentine oil is required for internal use. It has been used as an expectorant.

Terpin hydrate or terpinol is formed by the action of nitric acid on rectified turpentine oil in the presence of alcohol. It is *cis-p*-menthane-1,8-diol hydrate.

Terpin hydrate is a stimulant to mucous membranes; therefore, it is used as an expectorant in the form of terpin hydrate elixir. The usual dose of terpin hydrate is 85 mg.

ALCOHOL VOLATILE OILS

Alcohols found in volatile oils may be classified into (1) acyclic alcohols, (2) monocyclic alcohols, and (3) dicyclic alcohols. Methyl, ethyl, isobutyl, isoamyl, hexyl, and the higher aliphatic alcohols occur in volatile oils but, because they are soluble in water, they are washed away in the process of steam distillation. Many natural oils, however, contain acyclic alcohols that are terpene derivatives. Among the more important of these are geraniol (see Fig. 5-2), linalool, and citronellol. Among the more important monocyclic alcohols are menthol (from peppermint) and α -terpineol; borneol is a dicyclic terpene alcohol from Borneo camphor. Sesquiterpene alcohols include zingiberol (see page 150).



Among the important alcohol volatile oil drugs are peppermint, cardamom oil, coriander oil, rose oil, orange flower oil, juniper oil, and pine oil (Table 5-1).

Peppermint

Peppermint consists of the dried leaf and flowering top of *Mentha piperita* Linné (Fam. Labiatae). *Mentha* is from the Greek *Mintha*, the name of a mythical nymph metamorphosed into this plant; *piperita* is from the Latin *piper*, meaning pepper, and alludes to the aromatic and pungent taste of peppermint.

The plant is a perennial herb indigenous to Europe and naturalized in the northern United States and Canada. It is extensively cultivated in areas where the fertile soil has high water-holding capacity. If rainfall is not sufficient, an irrigation system is essential. Peppermint requires a daytime length of 15 to 16 hours and as much sunlight as possible. To obtain good field crops, clean planting stock must be used because disease control measures have not yet been fully developed. The plants are propagated by rhizome cuttings. When in flower, they are cut with a mowing machine, raked into windrows, dried for a few hours in the sun, and hauled to the still house. If the plant is to be used as a drug, it is carefully dried and preserved. Several varieties of peppermint are cultivated in the United States; but, whereas the Amer-

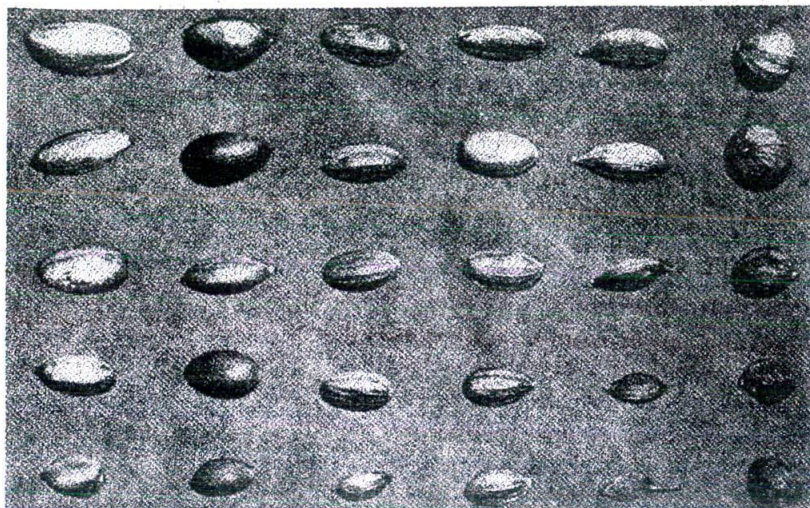


Fig. 5-6. Commercial cardamoms: from top to bottom, "longs," "short-longs," "mediums," "shorts," "tiny."

ican peppermint oil is all derived from *M. piperita*, the Japanese peppermint oil is obtained from *M. arvensis* Linné var. *piperascens*. Peppermint was described by John Ray in his *Historia Plantarum* (1704). It was extensively cultivated in England as early as 1750.

Peppermint contains volatile oil (about 1%), resin, and tannin.

Commercial dried peppermint usually consists of the dried herb, though it should contain not more than 2% of stems over 3 mm in diameter. It loses some volatile oil during drying and more during storage; the usual commercial sample has suffered

95% deterioration and yields no volatile oil upon steam distillation. However, the distillate water may be aromatic.

Peppermint oil is the volatile oil distilled with steam from the fresh overground parts of the flowering plant of *Mentha piperita* Linné (Fam. Labiatae) (Fig. 5-8), rectified by distillation and neither partially nor wholly dementholized. It yields not less than 5% of esters, calculated as menthyl acetate, and not less than 50% of total menthol, free and as esters.

The American production of peppermint oil has increased tremendously in the past century; in 1844, 88,000 lb were produced,



Fig. 5-7. Coriander fruit, magnified 6 times.

Table 5-1. Alcohol Volatile Oil Drugs

Name	Part Used	Botanical Origin	Production Areas	Important Constituents	Use
Cardamom oil (Fig. 5-6)	volatile oil distilled from the dried, ripe seed	a perennial herb, <i>Elettaria cardamomum</i> (Zingiberaceae)	Malabar Coast of India, Sri Lanka, Laos, Guatemala, El Salvador	26-40% cineole, 28-34% α -terpinyl acetate, 2-14% limonene, 3-5% sabinene, 2-8% linalyl acetate	flavor, carminative
Coriander oil (Fig. 5-7)	volatile oil distilled with steam from the dried, ripe fruit	an annual herb, <i>Coriandrum sativum</i> (Umbelliferae)	India, Morocco, eastern Europe, Mexico, United States, Argentina	60-70% (+)-linalool, limonene, α -pinene, γ -terpinene, <i>p</i> -cymene, camphor	flavor, carminative
Rose oil (otto of rose)	volatile oil distilled with steam from the fresh flowers	perennial herbs or shrubs, <i>Rosa gallica</i> , <i>R. damascena</i> , <i>R. alba</i> , <i>R. centifolia</i> , and varieties of these species (Rosaceae)	Bulgaria, southern France, Turkey, Egypt	geraniol, (-)-citronellol, nerol	perfume
Orange flower oil (neroli oil)	volatile oil distilled from the fresh flowers	a tree, <i>Citrus aurantium</i> (Rutaceae)	southern France, Algeria, Sicily, Spain, Tunisia, Morocco, Haiti, Comoro Islands, Guinea	30% (-)-linalool, (+)- α -terpineol, geraniol, geranyl acetate, β -pinene, 7% linalyl acetate, limonene	perfume, flavor
Juniper oil	volatile oil distilled with steam from the dried, ripe fruit	small evergreens, <i>Juniperus communis</i> and its variety <i>depressa</i> (Cupressaceae)	Italy, Yugoslavia	70% α -pinene, β -pinene, α -terpineol, borneol, geraniol	flavor, diuretic in the OTC drug, Odrinil®
Pine oil	volatile oil obtained by extraction and fractionation or by steam distillation of the wood	the tree, <i>Pinus palustris</i> and other species of <i>Pinus</i> (Pinaceae)	southeastern United States	65% α -terpineol, 10% methyl chavicol and related phenol ethers, 9% borneol, 8% fenchol, 4% menthols	disinfectant, deodorant

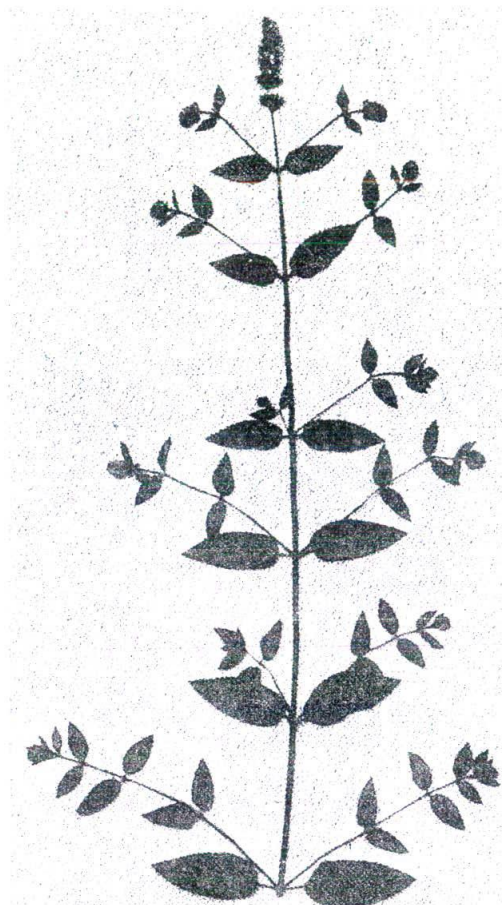


Fig. 5-8. *Mentha piperita* (peppermint) showing opposite, petiolate leaves and dense, terminal inflorescences. (Photo courtesy of A. M. Todd Company, Kalamazoo, Michigan.)

in 1944, 867,000 lb were produced, and, in 1977, 4,400,000 lb were produced and valued at \$63 million; \$32 million of this total represented the value of exported oil. About 90% of the oil is obtained from Washington, Oregon, and Idaho, principally from the Willamette river valley and Madras areas of Oregon, the Columbia river basin of Washington, and portions of the Snake river valley in Idaho. The remainder of the oil is produced in Wisconsin and Indiana. A few years ago, southern Michigan was the major area of mint cultivation in the United States, but a fungus blight (*Verticillium* wilt) infected crops and

caused abandonment of thousands of acres of formerly productive land. In recent years, wilt-resistant strains of peppermint have been developed by using the technique of irradiation-induced mutations, thereby eliminating the threat to the industry of fungal blight. In 1978, approximately 17,000 acres were under cultivation in Washington and yielded an average of 70 lb of oil to the acre.

Peppermint oil is a colorless or pale yellow liquid that has a strong, penetrating odor of peppermint and a pungent taste that is followed by a sensation of cold when air is drawn into the mouth.

American peppermint oil contains from 50 to 78% of free (-)-menthol and from 5 to 20% combined in various esters such as the acetate. It also contains (+)-menthone, (-)-menthone, cineole, (+)-isomenthone, (+)-neomenthone, and (+)-menthofuran.

Because of the commercial importance of the mint oils, the interconversions of the various terpene constituents of the oils have been studied more extensively than those of other volatile oil plants. Incorporation of $^{14}\text{CO}_2$ into the various menthane derivatives that characterize different *Mentha* species has allowed precursor relationships to be deduced (Fig. 5-9). Several of the proposed steps were directly demonstrated by isolating radioactively labeled monoterpenes and feeding them back to leaf slices or foliage. Cell-free extracts from *Mentha* leaves with pulegone- ^{14}C have confirmed the pulegone \rightarrow menthone \rightarrow menthol portion of the pathway and have established that NADPH_2 is an essential cofactor in these reduction reactions. An enzyme preparation from *Mentha* leaves has also been shown to reduce the isopropylidene double bond of piperitenone to yield piperitone. Small amounts of menthone and menthol were also formed with piperitenone as the substrate, indicating that the cyclohexene double bond of the precursor was reduced.

A key step in the biosynthesis of the *p*-menthane monoterpenes appears to be

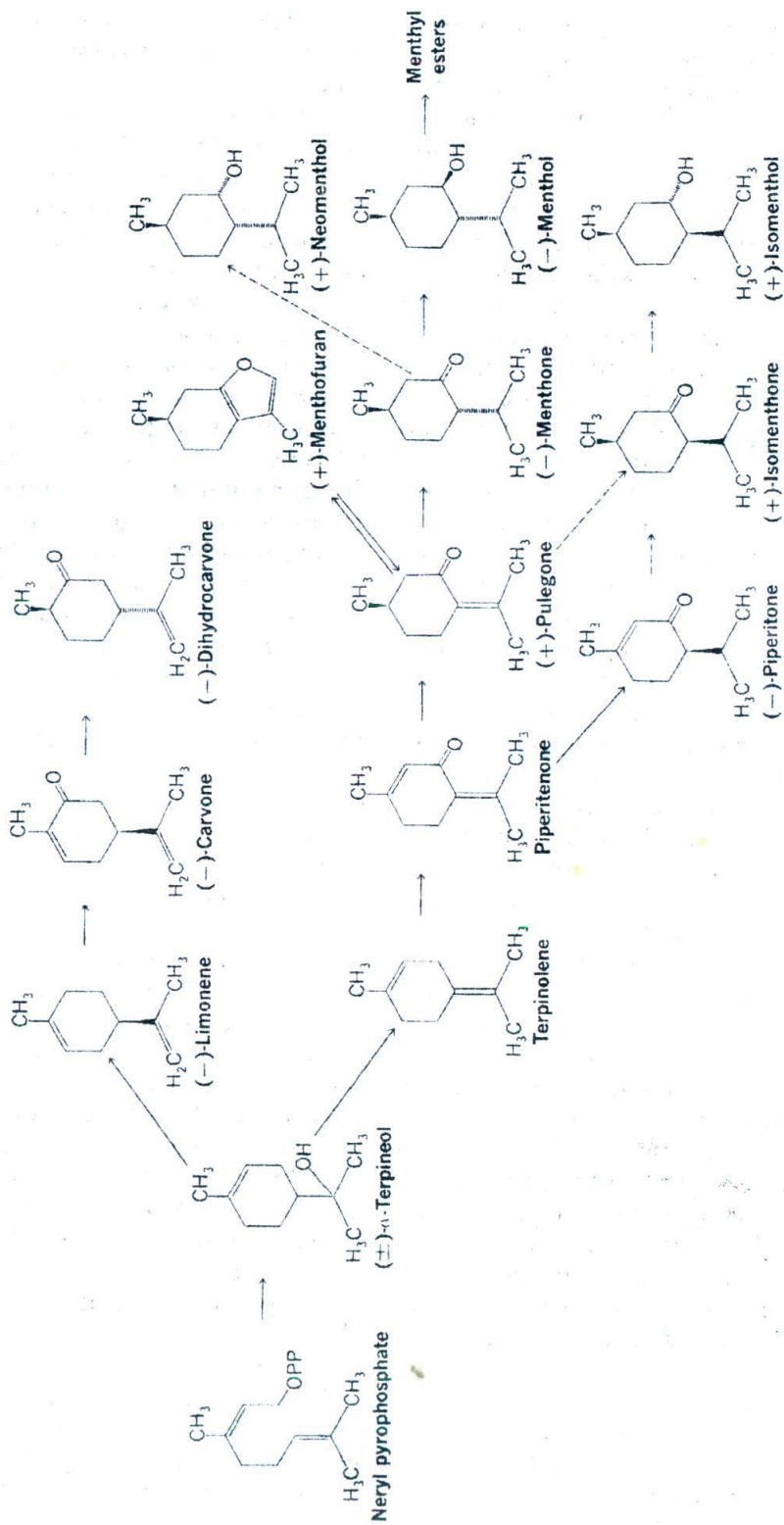


Fig. 5-9. Pathways of monoterpene biosynthesis in *Mentha* species.

the dehydration of α -terpineol to terpinolene and limonene (see Fig. 5-9). The steps leading to the formation of α -terpineol from mevalonic acid are common to several different species of mints. The pathways then diverge where α -terpineol is dehydrated to limonene in spearmint and to terpinolene in peppermint. The next step in the sequence is hydroxylation and subsequent dehydrogenation to produce either the carvone series of monoterpenes found in spearmint or the piperitenone series of monoterpenes found in peppermint. Breeding experiments with the mints indicate that a single dominant gene produces the carvone series, whereas the homozygous recessive genotype produces the piperitenone series. Apparently, the gene that differentiates between these series may be the gene that governs the enzyme that dehydrates α -terpineol to either limonene or terpinolene.

The influence of environmental factors on essential oil composition has been apparent to commercial producers for many years. Plants of the same species and genotype may produce oils of different quality when grown in different areas. The long days of northern latitudes favor the production of a peppermint oil that contains relatively small amounts of menthone and menthofuran and large amounts of menthol, whereas plants subjected to short day illumination produce an oil that contains small amounts of menthol and relatively large amounts of menthofuran.

Sequential studies with $^{14}\text{CO}_2$ have suggested that pulegone is the predominant terpene in young tissues of peppermint, where it is accompanied by menthofuran. Menthone, which is found in older tissues, also gradually disappears while menthol accumulates and is replaced, in turn, by menthyl acetate.

This sequence of biogenetic events helps to explain why peppermint oils obtained from plants containing relatively large amounts of young tissue are inferior. High concentrations (up to 30% in some cases)

of menthofuran in such oils impart a disagreeable cloying odor to products in which they may be incorporated. The reaction pulegone \rightarrow menthofuran is apparently reversible, and the concentration of both of these compounds decreases in favor of menthone, menthol, and menthyl acetate as the plant ages. Consequently, oils of good quality can be obtained only from plants containing a high percentage of mature tissues.

The problem of obtaining mature tissues is particularly acute in the Yakima valley of central Washington where environmental conditions favor early and luxuriant flowering of mint plants with concomitant production of a large proportion of relatively young tissues. Careful control of the time of harvest enables growers in that area to produce oils of satisfactory quality.

USES. Peppermint oil is a pharmaceutical aid (flavor). It has been used as a carminative, a stimulant, and a counterirritant. Its chief commercial importance is as a flavor for confections, especially for chewing gum.

It was estimated in 1972 that the domestic use of peppermint oil was as follows: chewing gum, 55%; toothpaste, mouthwash, and pharmaceuticals, 34%; confectionary products, 10%; and other products, 1%. In recent years, about one third of our national production has found its way into export trade, which has increased more than 400% since the 1940s.

NONPRESCRIPTION PRODUCTS. Peppermint oil is used as a flavoring agent in Listerine Mouthwash® and as a carminative and flavoring agent in the antacid products BiSoDol®, Gelusil®, Phillips' Milk of Magnesia®, and Tums®.

Japanese peppermint oil or mentha arvensis oil is obtained by steam distillation from *Mentha arvensis* Linné var. *piperascens*. This oil is considerably higher in menthol content but is inferior in flavor to peppermint oil. It is, therefore, solely employed as a source of menthol. The plant is indigenous to Japan and is the source of Japa-

nese menthol. Some years ago the plant was introduced into southern California and Brazil; both areas now produce considerable amounts of menthol.

Menthol or menthan-3-ol is an alcohol obtained from diverse mint oils or prepared synthetically. Menthol may be levorotatory [(-)-menthol], from natural or synthetic sources, or racemic [(±)-menthol], produced synthetically.

Menthol is usually prepared from Japanese peppermint oil by refrigeration (-22° C), during which the menthol crystallizes. The liquid portion is poured off, and the crystallized menthol is pressed between filter papers and subsequently purified by recrystallization. Synthetic racemic menthol is produced by hydrogenation of thymol. Menthol may also be prepared from pinene.

Menthol occurs as colorless, hexagonal crystals that are usually needlelike, as fused masses, or as a crystalline powder. It has a pleasant, peppermintlike odor.

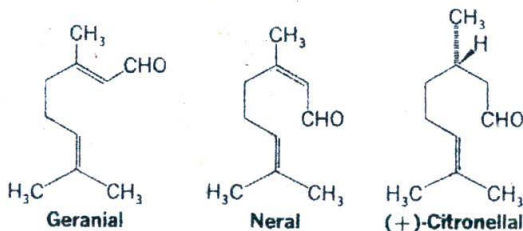
USES. Menthol is a topical antipruritic. It has been used on the skin or mucous membranes as a counterirritant, an antiseptic, and a stimulant; internally, menthol has a depressant effect on the heart. Menthol is topically applied as 0.1 to 2% preparations for use on the skin.

NONPRESCRIPTION PRODUCTS. Menthol is used as an antipruritic in such burn and sunburn preparations as Noxzema Medicated Cream®, Solarcaine®, and Unguentine®; in preparations to treat poison ivy rash, Ivy Dry Cream® and Rhulicream®; in douche powders, Zonite®; and in preparations to treat athlete's foot, NP27 Powder®. It is used as a counterirritant in external analgesic preparations that include Absorbine Jr.®, Ben-Gay®, Mentholatum®, Minit-Rub®, and Vicks Vaporub®.

ALDEHYDE VOLATILE OILS

Aldehydes occurring in volatile oils may be divided into acyclic and cyclic. Included among the former are citral, which is a 3:1

mixture of geranial to neral, and citronellal, the aldehyde corresponding to citronellol. The aromatic aldehydes include cinnamaldehyde (see Fig. 5-3) and vanillin (vanilla, benzoin, tolu and Peru balsams).



Biosynthesis of such aromatic aldehydes as benzaldehyde and vanillin takes place from phenylpropanoid precursors. Because these compounds constitute the aglycones of certain glycosides, their formation was discussed under that heading.

The terpene aldehydes derive from acetate metabolism, as illustrated in Figure 5-4.

Among the important drugs in this class are cinnamon, cinnamon oil, orange oil, lemon peel, lemon oil, hamamelis water, and citronella oil (Table 5-2).

CINNAMON

Cinnamon or Saigon cinnamon is the dried bark of *Cinnamomum loureirii* Nees (Fam. Lauraceae).

An important cinnamon in U.S. commerce is **Ceylon cinnamon**, the dried inner bark of shoots of coppiced trees of *C. zeylanicum* Nees (Fam. Lauraceae) (Fig. 5-10).

Cassia cinnamon is the dried bark of *C. cassia* (Nees) Nees ex Blume.

Cinnamon may be from the Arabic, *kinnamon*; the Malay, *kayu manis*, sweet wood; or the Hebrew, *ginnamon*, *Loureirii* is in honor of the French botanist Loureiro; *zeylanicum* signifies Ceylon; *Cassia* is from the Greek *kassia*, meaning to strip off the bark.

Cinnamon is named as a spice in the books of Moses, by the ancient Greek and Latin historians, and in Chinese herbals as early as 2700 B.C. Its cultivation in Ceylon probably dates from 1200 A.D.

The wild cinnamon trees seldom exceed

Table 5-2. Aldehyde Volatile Oil Drugs

Name	Part	Botanical Origin	Production Areas	Important Constituents	Use
Orange oil	volatile oil obtained by expression from the fresh peel of the ripe fruit	a tree, <i>Citrus sinensis</i> (Rutaceae)	California, Florida, Sicily, Brazil, West Indies	1-2% decanal, more than 90% limonene	flavor
Citronella oil	volatile oil distilled with steam from freshly cut or partially dried leaves	the grass, <i>Cymbopogon winterianus</i> and <i>C. nardus</i> (Gramineae)	Sri Lanka, Indonesia, China, Taiwan, Central America	5-55% (+)-citronellal 25-40% geraniol 11-15% (+)-citronellol	perfume insect repellent
Hamamelis water (distilled witch hazel extract)	hydroalcoholic solution of the volatile oil prepared by steam distillation of the recently cut and partially dried dormant twigs	the tree, <i>Hamamelis virginiana</i> (Hamamelidaceae)	eastern United States and Canada	9.7% 2-hexen-1-ol, 3.2% acetaldehyde, 3.5% α -ionone, 1.0% β -ionone, 0.2% safrole	astringent in the OTC hemorrhoid preparations, Tucks [®] , Rantex [®] , Mediconet [®] , Hazel-Balm [®] and Gentz-Wipes [®]

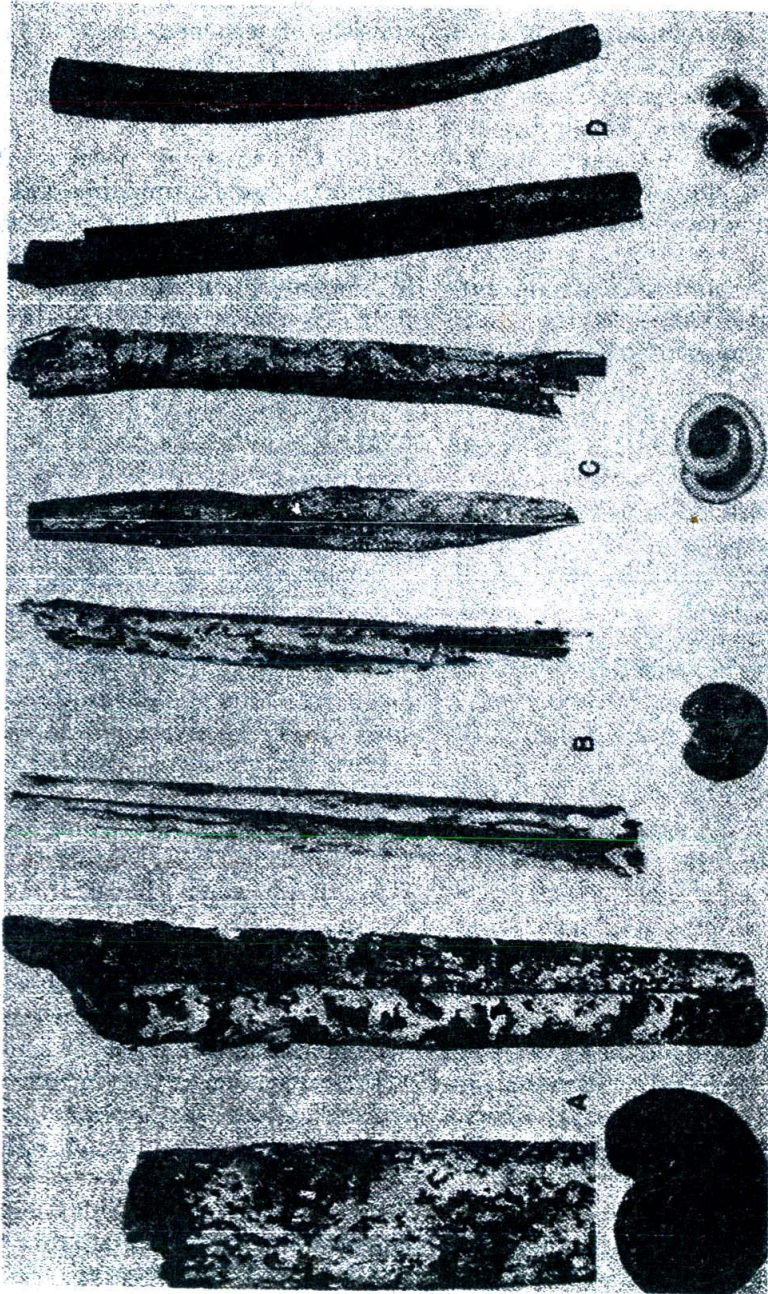


Fig. 5-10. Cinnamon bark quills in longitudinal and transverse views: A, Saigon; B, Ceylon; C, Cassia; and D, Djakarta.

9 meters in height. The leaves are coriaceous, green, and glossy; the flowers are in terminal panicles; and the fruit is fleshy and ovoid.

Practically all commercial cinnamon is now obtained from cultivated trees in Sri Lanka (Ceylon), southeastern China, Vietnam, Laos, Indonesia, the West Indies, the Seychelles, Malagasy, and many other localities. However, cinnamon from southeastern Asia and adjacent islands is superior in quality.

The bark is gathered from young trees usually less than 6 years old and, in Sri Lanka, mostly from coppice shoots 18 to 36 months old. The leaves, branches, and stem tips are distilled with steam for the volatile oil. The bark is cut transversely and longitudinally and peeled. In Sri Lanka and Indonesia, the bark is scraped while fresh to remove epidermis and cork; in China, it is planed to remove partially the cork. In Sri Lanka, many layers of the thin inner bark are rolled into one quill; in Indonesia, several layers may be quilled together; and in China and Vietnam, each layer is quilled separately or only 2 or 3 layers are quilled together.

Saigon cinnamon yields from 2 to 6% of volatile oil; cassia cinnamon, 0.5 to 1.5%; and Ceylon cinnamon, 0.5 to 1%. Other constituents are mannitol, which causes the sweetness of the bark, and tannin, which is abundant in cassia cinnamon.

USES. Saigon, Ceylon, and cassia cinnamon are carminatives and flavors.

The powdered cinnamon found in the grocery trade is frequently a blend of several kinds of cinnamon. The blending is done either to improve the aromatic quality or to cheapen the product.

Cinnamon oil is the volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia* (Nees) Nees ex Blume (Fam. Lauraceae) and rectified by distillation. It is also known as **cassia oil**.

Cinnamon oil is a yellowish to brownish liquid that becomes darker and thicker by age or by exposure to air; it possesses the

characteristic odor and taste of cassia cinnamon.

The principal constituent of the oil is cinnamic aldehyde, 80 to 95%; the remainder consists of terpenes, such as limonene, *p*-cymene, (-)-linalool and β -caryophyllene, and other compounds such as eugenol.

USES. Cinnamon oil is used as a flavoring agent; it is also a carminative and pungent aromatic. It has antiseptic properties.

Cinnamaldehyde, cinnamic aldehyde, or cinnamyl aldehyde is obtained naturally from cassia oil or synthetically from a mixture of benzaldehyde and acetaldehyde by the action of sodium hydroxide.

It should be stored in well-filled, tight, light-resistant containers and protected from excessive heat.

Lemon Peel

Lemon is the fruit of *Citrus limon* (Linné) Burmann filius (Fam. Rutaceae).

Lemon peel is the outer yellow rind of the fresh ripe fruit of *C. limon*. *Limon* is from *limun*, the name of the fruit. The plant is a small evergreen tree with shining leaves and is indigenous to northern India but cultivated to a considerable extent in such subtropical regions as southern Spain, southern Italy, Sicily, southern California, Florida, Argentina, Cyprus, Brazil, Tunisia, Israel, Mexico, India, South Africa, and Australia. The history of the lemon parallels that of the orange; it has been known since the beginning of the written history of India, its native land.

The cultivation of lemon trees and the picking, selecting, and storing of lemon fruits constitute an important industry.

The outer, lemon-yellow or dark yellow layer (peel) is removed by grating or paring. It has a highly fragrant, distinctive odor and an aromatic taste.

Lemon peel contains a volatile oil, a small quantity of hesperidin, bitter principles, a principle resembling tannin, and calcium oxalate.

USES. Lemon peel is a flavoring agent, a

stimulant, and a stomachic. It is employed chiefly in combination with other drugs.

Lemon oil is the volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *C. limon*, with or without the previous separation of the pulp and the peel. Six processes are utilized in the recovery of oil of lemon; five of these processes yield an oil meeting pharmaceutical requirements.

1. The outer portion of the rind, which contains the volatile oil, is removed by grating; the resultant raspings are placed in canvas bags and subjected to pressure. The resultant turbid oil is allowed to stand until the sediment separates, after which the oil is decanted.
2. The sponge process is employed to a considerable extent in Sicily and along the Riviera. The lemon is peeled and pieces of the peel are pressed flat so that they flex and rupture the oil cells. The oil is absorbed by a sponge which, when it becomes saturated, is squeezed out, and the process is repeated.
3. The entire fruit is rotated in a saucer-shaped container that has several rows of sharp metal pins and is called an *écuellé à piquer*. The pins rupture the oil cells, and the exuding oil collects in a long narrow depression in the bottom of the saucer, which also serves as the handle. This method is now used in the West Indies.
4. During the machine process used in Italy, the oil is separated mechanically using a principle similar to that of the *écuellé à piquer*. Only the peel is subjected to this method.
5. Cold-pressed California oil is obtained by the application of extremely high pressure to the lemons and the rapid removal of the juice and oil. The juice-and-oil mixture is then separated by high-speed centrifugal separation at the lowest feasible temper-

ature and in the shortest possible time.

6. Some lemon oil is obtained by distillation. Such oil is not comparable with the expressed oil and does not conform to pharmaceutical standards. Distilled oil is usually used for the preparation of terpeneless oil of lemon.

Lemon oil contains about 90% of terpenes consisting chiefly of (+)-limonene, the main hydrocarbon present in a range of 70 to 80%, and other monoterpene hydrocarbons, especially β -pinene and γ -terpinene (approximately 8 to 10% of each). The most important contributors to lemon-oil flavor are neral and geranial (together called citral). Some lemon oils contain up to 13% of citral, but a range of 2 to 4% is optimum for a high-quality oil. The primary esters in lemon oil are neryl and geranyl acetates, and they are believed to be important in providing a full-bodied lemon flavor.

Lemon oil that has a terebinthinate odor must not be used or dispensed; such an odor indicates decomposed terpenes or added turpentine oil.

USES. Lemon oil is a flavoring agent. It has stimulant, carminative, and stomachic properties. It is a valuable commodity used not only in food flavorings but also in cosmetics and liquid cleansers because the aroma and flavor are widely accepted by consumers. In 1967, the dollar value of lemon oil consumed in the United States was \$11 million, making it the number one volatile oil in dollar value and representing 2.5 million lb of oil.

Turpentine oil was formerly used as an adulterant but has been replaced by terpenes obtained in the preparation of terpeneless oils. California-type lemon oil should contain between 2.2 and 3.8% of total aldehydes (principally citral) and Italian-type lemon oil between 3.0 and 5.5%. Yet, even such a citral content is no criterion of purity because citral from a cheaper source (lemongrass oil obtained from *Cym-*

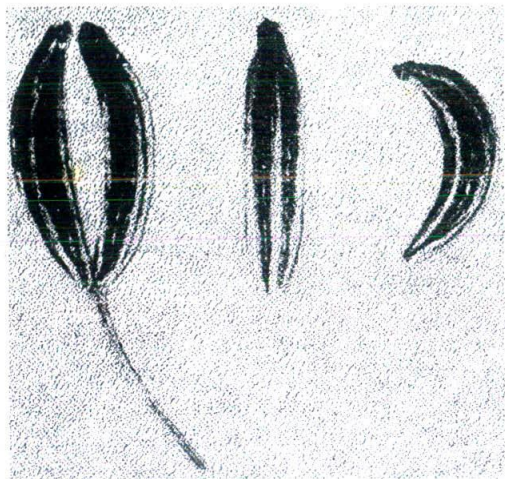


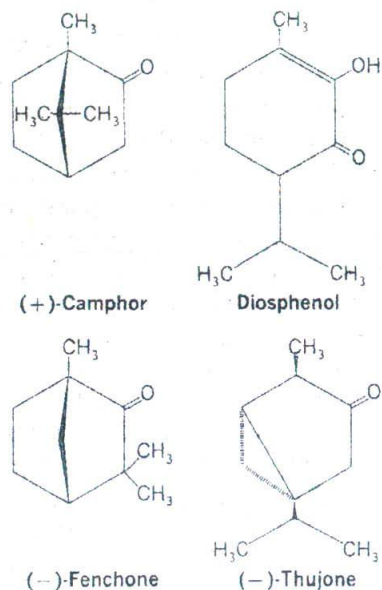
Fig. 5-11. Caraway fruits, magnified 6 times.

bopogon citratus [D.C.] Staph. [Fam. Gramineae], which contains about 80% citral) may be added. Only a careful check of the physical and chemical constants of the oil can determine its purity.

Terpeneless oils. Lemon oil and orange oil, by virtue of their high terpene content, often develop a terebinthinate odor during storage. A considerable amount of these terpenes may be removed by distillation under reduced pressure. A terpeneless lemon oil with a citral content of 40 to 50% may be prepared. In terpeneless orange oil, about 95% of the terpenes have been removed. Such oils are not subject to deterioration and may be employed in smaller quantities to obtain the same organoleptic effect. They are, however, considerably higher in price than the natural oils.

KETONE VOLATILE OILS

Ketones occurring in volatile oils may be divided into (1) monocyclic terpene ketones, including menthone, carvone, piperitone, pulegone (see Fig. 5-9), and diosphenol (a crystalline ketone in buchu); and (2) dicyclic ketones, including camphor, fenchone, and thujone.



The more important drugs in this category are camphor, spearmint, and caraway (Table 5-3).

Camphor

Camphor is a ketone obtained from *Cinnamomum camphora* (Linné) Nees et Ebermaier (Fam. Lauraceae) (natural camphor) or produced synthetically (synthetic camphor). *Camphora* is from the Arabic *kafur*, meaning chalk. The plant is a large evergreen tree indigenous to eastern Asia but naturalized in the Mediterranean region, Sri Lanka, Egypt, South Africa, Brazil, Jamaica, Florida, and California. Early references to camphor do not pertain to the laurel camphor but rather to the Borneo camphor (borneol, see page 113), which reached Arabia in the 6th century and Europe in the 12th. Laurel camphor appeared in Europe in the 17th century. When Japan annexed Taiwan, a government monopoly was created (1900). From that time until World War II, about 80% of the world's supply of natural camphor (about 4 million kg per year) was produced in Taiwan, where the tree occurs naturally in abundance and is also extensively cultivated; the remaining 20% was produced largely in Japan and southern China. Since 1945,

Table 5-3. Ketone Volatile Oil Drugs

Name	Part Used	Botanical Origin	Production Areas	Important Constituents	Use
Caraway (Fig. 5-11)	the dried, ripe fruit	the biennial herb, <i>Carum carvi</i> (Umbelliferae)	Netherlands, Soviet Union, northern Africa, India, Pakistan	3-6% volatile oil	flavor
Caraway oil	volatile oil distilled with steam from the dried, ripe fruit	the biennial herb, <i>Carum carvi</i> (Umbelliferae)	Netherlands, Soviet Union, northern Africa, India, Pakistan	50-85% (+)-carvone, 40-50% (+)-limonene	flavor, carminative
Buchu	the dried leaf	the low shrub, <i>Barosma betulina</i> , <i>B. crenulata</i> , or <i>B. serratifolia</i> (Rutaceae)	South Africa	volatile oil containing about 30% diosphenol	diuretic in OTC drugs for menstrual problems, Fluidex [®] , Odrinil [®]
Wormwood oil (absinthe oil)	volatile oil distilled with steam from the dried leaves and flowering tops	a shrubby perennial herb, <i>Artemisia absinthium</i> (Compositae)	United States, southern Europe, northern Africa	(+)-thujone, camphene, phellandrene, β -caryophyllene	counterirritant in OTC drug, Absorbine Jr. [®]
Cedar leaf oil	volatile oil distilled with steam from the fresh leaves	the tree, <i>Thuja occidentalis</i> (Cupressaceae)	eastern United States, Canada	(+)-thujone, (-)-fenchone, α -pinene	counterirritant in OTC drug, Vicks Vaporub [®]

the production of synthetic camphor has gradually lessened the demand for the natural product; nevertheless, Japanese and Taiwan camphors still are found on the market.

Natural camphor occurs as a crystalline product in clefts in the woody stems and roots and, to a greater extent, dissolved in the volatile oil. The wood is chipped and distilled with steam, and 1 lb of crude camphor is obtained from 20 to 40 lb of chips. The crude camphor is then freed of oil by centrifugation and pressing and finally resublimed and pressed into the familiar cakes.

Before World War II, about 6.5 million kg of synthetic camphor were produced annually in Europe and the United States. During the war, the production of synthetic camphor practically replaced the natural derivative. Since the war, production of natural camphor has been resumed, but it will never attain its former prominence.

Synthetic camphor is made from pinene, the principal constituent of turpentine oil. The starting point is the stumps of felled pine trees previously used in turpentine. A number of complex methods have been used for producing synthetic camphor, but all are based on (1) converting pinene into bornyl esters, which are (2) hydrolyzed to isoborneol, and (3) finally oxidized to camphor.

The specific rotation of natural camphor is between $+41^\circ$ and $+43^\circ$. Synthetic camphor is the optically inactive racemic form.

USES. Camphor is a topical antipruritic, rubefacient, and anti-infective employed at 1 to 3% in preparations for use on the skin. Commercially it is used in the manufacture of certain plastics.

NONPRESCRIPTION PRODUCTS. Camphor is used as an antipruritic in Hist-A-Balm Medicated Lotion[®], Rhulicream[®], and Noxzema Medicated Cream[®] and as a rubefacient in external analgesic preparations, such as Heet[®], Mentholatum[®], Minit-Rub[®], Sloan's Liniment[®], and Vicks Vaporub[®]. It is also an ingredient of Cam-

pho-Phenique[®] for athlete's foot and Blis-tex[®] for cold sores.

NOTE. Camphor must be labeled to indicate whether it is obtained from natural sources or is prepared synthetically.

Spearmint

Spearmint consists of the dried leaf and flowering top of *Mentha spicata* Linné (*M. viridis* Linné) (common spearmint) or of *M. cardiaca* Gerard ex Baker (Scotch spearmint) (Fam. Labiatae). *Spicata* is from the Latin *spica*, meaning a spike, and refers to the arrangement of the flowers. The plant is a perennial herb that closely resembles peppermint, is indigenous to Europe, and is naturalized and cultivated in various parts of North America. Spearmint is extensively cultivated in Washington, Idaho, Wisconsin, Michigan, and Indiana. More than 25,000 acres are presently devoted to spearmint cultivation in the state of Washington, and the average yield is 90 lb per acre. Total production of spearmint oil amounts to about 3 million lb annually. The plant appears in many of the old herbals, and its mention in early medieval lists demonstrates that it was cultivated in the convent gardens of the 9th century.

Spearmint closely resembles peppermint, but the stems are usually more purple. The leaves are sessile or nearly so, inflorescence is either in slender, interrupted cylindrical spikes or crowded lanceolate spikes, and the bracts are 7 to 10 mm in length (Fig. 5-12). Odor and taste are aromatic and characteristic; the taste is not followed by a cooling sensation.

Spearmint is composed of resin, tannin, and a volatile oil (about 0.5%) that contains carvone.

USES. Spearmint is classed as a flavor. It possesses carminative properties.

Spearmint oil is distilled with steam from the fresh, overground parts of the flowering plant of *Mentha spicata* or of *M. cardiaca*. It contains not less than 55%, by volume, of carvone. Most of the supply of

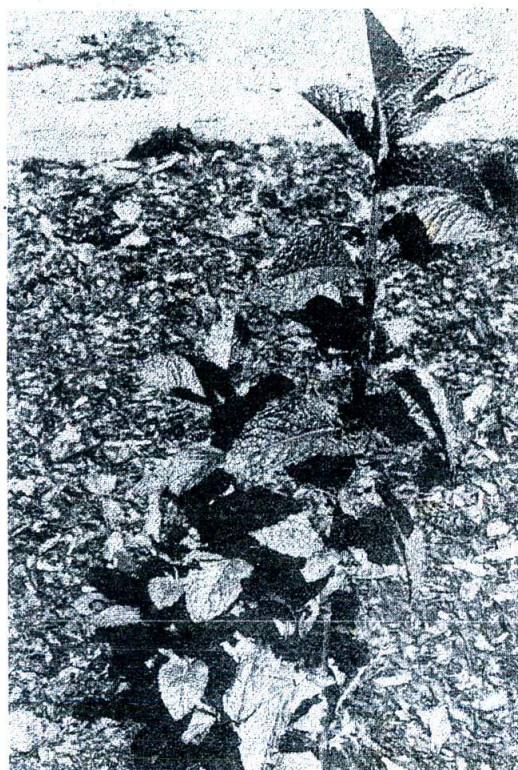


Fig. 5-12. *Mentha spicata* (spearmint) plant showing typical opposite, sessile leaves.

spearmint oil is produced in the same area as peppermint oil.

Spearmint oil is a colorless, yellow or greenish yellow liquid that has the characteristic odor and taste of spearmint.

Spearmint oil contains from 45 to 60% of (-)-carvone, 6 to 20% of alcohols, and 4 to 20% of esters and terpenes, chiefly (-)-limonene and cineole. The carvone is optically isomeric with the (+)-carvone found in oil of caraway and oil of dill.

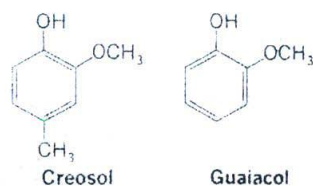
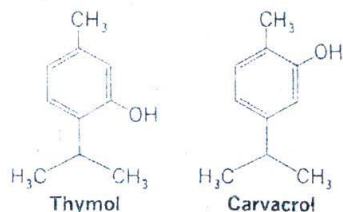
USES. Spearmint oil is a flavor. It possesses carminative properties and is used to a considerable extent in the chewing gum industry. A 1972 government survey showed that the estimated domestic use of spearmint oil was 50% toothpaste and

mouthwash, 47% chewing gum, and 3% other.

PHENOL VOLATILE OILS

Two kinds of phenols occur in volatile oils: those that are present naturally and those that are produced as the result of destructive distillation of certain plant products.

Eugenol (see Fig. 5-3), thymol, and carvacrol are the most important phenols occurring in volatile oils. Eugenol occurs in clove oil, myrcia oil, and other oils; thymol and carvacrol occur in thyme oil and others; and creosol and guaiacol occur in creosote and pine tar.



The more important drugs containing phenol volatile oils are thyme, clove, myrcia oil, creosote, pine tar, and juniper tar (Table 5-4).

Thymol is a phenol obtained from thyme oil (*Thymus vulgaris* Linné), from horsemint oil (*Monarda punctata* Linné), from *Monarda didyma* Linné oil, from ajowan oil (*Carum copticum* Benthams et Hooker), or it may be prepared synthetically from *m*-cresol or *p*-cymene. The oil may be treated in 2 ways to obtain thymol crystals: (1) it may be subjected to freezing temperatures causing the thymol to crystallize, or (2) it may be treated with sodium hydroxide solution, the aqueous solution of sodium thymol

Table 5-4. Phenol Volatile Oil Drugs

Name	Part Used	Botanical Origin	Production Areas	Important Constituents	Use
Thyme oil	volatile oil distilled with steam from the flowering plant	an evergreen herbaceous shrub, <i>Thymus vulgaris</i> , <i>T. zygis</i> , and its variety <i>guttifera</i> (Labiatae)	Spain, Italy, France, Yugoslavia, Greece	thymol, carvacrol, <i>p</i> -cymene, camphene, limonene	antiseptic in the OTC drugs, Unguentine Cream®, Dewitt's Oil for Ear Use®
Myrcia oil (bay oil)	volatile oil distilled with steam from the leaves	the tree, <i>Pimenta racemosa</i> (Myrtaceae)	West Indies	55-65% eugenol, myrcene, chavicol	perfume
Creosote (beechwood creosote)	mixture of phenols obtained from wood tar produced by destructive distillation of wood	the tree, <i>Fagus grandifolia</i> (Fagaceae) and other trees	United States	guaiacol, creosol	disinfectant in the OTC drug, Dewitt's Toothache Drops®; expectorant in the OTC drugs, Creomulsin®, Creoterpin®
Juniper tar (sade oil)	empyreumatic volatile oil distilled from the heartwood	the shrub, <i>Juniperus oxycedrus</i> (Cupressaceae)	France, other Mediterranean countries	cadinene	local antieczematic in the OTC drug Polytar®
Pine tar	empyreumatic product obtained by the destructive distillation of the wood	the tree, <i>Pinus palustris</i> or other species of <i>Pinus</i> (Pinaceae)	southeastern United States	10-20% aqueous distillate, 10-15% light oily distillate, phenol, creosol, naphthalene	local antieczematic and anti-psoriasis drug in Packer's Pine Tar®, Polytar®, expectorant in Pinex® Cough Syrup

being separated and decomposed with acid, thus liberating the thymol, which is subsequently purified.

Thymol occurs as large colorless crystals or as a white crystalline powder. It has an aromatic thymelike odor and a pungent taste. Thymol may be readily microsublimed.

USES AND DOSE. Thymol is an antifungal and antibacterial agent. It is employed topically in lotions, creams, and ointments in concentrations ranging from 0.1 to 1%.

NONPRESCRIPTION PRODUCTS. Thymol is used in the feminine hygiene products PMC Hygienic Douche Powder® and Zonite®; in the otic products Auro Ear Drops®, in the external analgesics Vicks Vaporub® and Zemo Liquid®; and in Listerine® mouthwash.

Clove

Clove or cloves is the dried flower bud of *Eugenia caryophyllus* (Sprengel) Bullock et Harrison (*E. caryophyllata* Thunberg) (Fam. Myrtaceae) (Fig. 5-13). *Eugenia*, which is Latin, and *caryophyllus*, which is Greek, mean "nut-leaf" and refer to the nutlike flower buds; "clove" is from the Latin *clavus*, meaning a nail, and refers to the shape of the whole spice.

The plant is a tree that grows to 15 meters in height and is indigenous to the Molucca Islands but cultivated on the islands of Penang, Ambon, Pemba, Zanzibar, Sumatra, Madagascar, and Mauritius as well as in the Seychelles and the West Indies. The buds are gathered when they change from green to crimson and are carefully dried in the sun.

The average yield of dried cloves per tree approximates 7 lb, although a large tree in a favorable year may produce as much as 40 lb.

Buds are separated from their individual stems by hand and spread out on coconut mats to dry. In sunny weather, drying requires 4 or 5 days; in cloudy weather, a longer time is required. When rain threatens, the buds must be covered and pro-

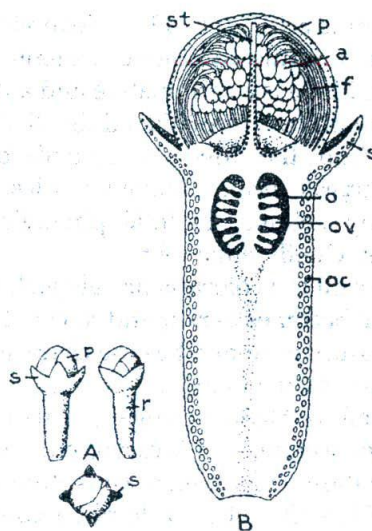


Fig. 5-13. *Eugenia caryophyllus*: A, Entire flower buds in side and upper views showing the cylindrical receptacle (*r*), the 4 calyx teeth (*s*), and the globular closed corolla consisting of 4 petals (*p*). B, Longitudinal section through the flower bud showing petals (*p*), anthers (*a*), filaments (*f*), style (*st*), ovary (*o*), ovules (*ov*), and oil cells (*oc*).

ected. During proper drying, the buds lose about two thirds of their original weight.

The best cloves come from Pemba, but four fifths of the world's supply comes from Tanzania. Clove was known to the Chinese before 266 B.C. The Dutch, who won possession of the Spice Islands in 1605, endeavored to create a monopoly and destroyed all the trees except those on the islands of Ambon and Ternate. In 1770, however, the French succeeded in introducing the tree onto Mauritius and Réunion. From there, its cultivation spread to other clove-growing areas. Almost 65% of the world's supply of cloves is ground and mixed with tobacco in cigarettes and consequently smoked. The largest consumer is Indonesia, which imports more than half of Tanzania's cloves each year.

Clove contains a volatile oil, 14 to 20%;

gallotannic acid, 10 to 13%; oleanolic acid; vanillin; and the chromone, eugenin.

USES. Clove is a carminative and a flavor.

Clove oil is the volatile oil distilled with steam from the dried flower buds of *Eugenia caryophyllus*. It contains not less than 85%, by volume, of total phenolic substances, chiefly eugenol.

Clove oil is a colorless or pale yellow liquid that becomes darker and thicker by age or exposure to air and has the characteristic odor and taste of clove.

The oil contains free eugenol (70 to 95%), eugenol acetate, and β -caryophyllene. Together these constituents constitute about 99% of the oil, but they do not account for the characteristic, fresh, fruity note of clove oil. This is produced by several minor constituents, especially methyl-*n*-amyl ketone.

USES. Clove oil is classed as a flavor. It is commonly employed as a toothache remedy that is applied topically to dental cavities as required. Clove oil also possesses antiseptic, counterirritant, and carminative properties. Oils with a particularly high content of eugenol are used in the commercial production of vanillin (see page 74).

Approximately 1 million lb of clove oil are imported into the United States annually.

NONPRESCRIPTION PRODUCTS. Clove oil is used in Noxzema Medicated Cream® and Lavis® mouthwash.

Eugenol or 4-allyl-2-methoxyphenol is a phenol obtained from clove oil and from other sources. It is usually prepared from clove oil by shaking with a 10% solution of sodium hydroxide to form sodium eugenolate. The mixture is washed with ether, and the sodium eugenolate is then decomposed with sulfuric acid. The eugenol is separated by steam distillation. It is a colorless or pale yellow, thin liquid that has a strongly aromatic odor of clove and a pungent spicy taste.

USES. Eugenol is classed as a dental analgesic. It is applied topically to dental cav-

ities and is incorporated in dental protectives.

NONPRESCRIPTION PRODUCTS. Eugenol is an ingredient in the toothache preparations Benzodent®, Jiffy Toothache Drops®, and Numzident®.

PHENOLIC ETHER VOLATILE OILS

A number of phenolic ethers occur in volatile oils. The following are the more important examples: anethole (see Fig. 5-3) from anise and fennel (Table 5-5), safrole from sassafras (see page 486) and nutmeg.



Derivatives of safrole are also often found in volatile oils. Notable among these is myristicin (methoxysafrole) from nutmeg.

Biosynthesis of Phenolic Ethers. Studies of anethole biosynthesis in *Foeniculum vulgare* have revealed that formation takes place from phenylalanine (shikimic acid-phenylpropanoid pathway, see Fig. 5-5) via a number of intermediates (Fig. 5-14). A cell-free enzyme system capable of effecting the conversion has been prepared. Methionine serves as a methyl donor for the methoxylation reaction. Other structurally related phenolic ethers are presumably formed by similar pathways.

Some of the drugs containing phenolic ether volatile oil are anise, fennel, and myristica.

Nutmeg

Nutmeg or myristica is the dried, ripe seed of *Myristica fragrans* Houlttuyn (Fam. Myristicaceae) deprived of its seed coat and arillode and with or without a thin coating of lime (Fig. 5-16). The tree is indigenous to the Molucca and neighboring islands

Table 5-5. Phenolic Ether Volatile Oil Drug

Name	Part Used	Botanical Origin	Production Areas	Important Constituents	Use
Fennel oil	volatile oil distilled with steam from the dried, ripe fruit	the perennial herb, <i>Foeniculum vulgare</i> (Umbelliferae)	central and eastern Europe, Japan, Argentina, China, United States	50-60% <i>trans</i> -anethole, (+)-fenchone, (+)- α -pinene	flavor, carminative
Anise (aniseed) (Fig. 5-15)	the dried, ripe fruit	the annual herb, <i>Pimpinella anisum</i> (Umbelliferae)	Spain, Turkey, Egypt, Poland, Soviet Union	1-3% volatile oil	flavor
Chinese anise (star anise)	the dried, ripe fruit	the tree, <i>Illicium verum</i> (Magnoliaceae)	southwestern China, Vietnam	2.5-3% volatile oil	flavor
Anise oil	volatile oil distilled with steam from the dried, ripe fruit	the annual herb, <i>Pimpinella anisum</i> (Umbelliferae), or the tree, <i>Illicium verum</i> (Magnoliaceae)	Spain, Turkey, Egypt, Poland, Soviet Union, southwestern China, Vietnam	80-90% <i>trans</i> -anethole, estragole, anisaldehyde	flavor, carminative

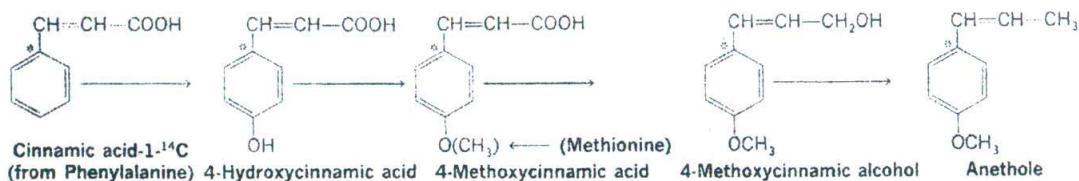


Fig. 5-14. Biosynthesis of anethole.

and is now extensively cultivated in other tropical regions, including the West Indies. The botanical name, *Myristica fragrans*, refers to the fragrance of the nutmeg. The commercial supply is largely derived from the Malay Archipelago. The trees bear continuously. Two or three crops are collected yearly. First the fleshy pericarp is removed and then the arillode, which constitutes mace when dried, is removed. The seeds are dried, requiring from 3 to 6 weeks, and then the brittle testa is cracked off.

With the exception of those from Penang, nutmegs are partially coated with lime to protect them from attack by insects. Over 5 million lb of whole nutmegs are imported into the United States annually; over 80% of this amount comes from Indonesia.

Nutmegs were introduced into Europe by the Arabs about the middle of the 12th century but were not a prevailing article of commerce until the sea routes to the Indies were opened in the 16th century. They played an important part in the Dutch spice monopoly until the tree began to be cultivated in other parts of the world (1800).

Nutmeg contains fixed oil, 25 to 40%,

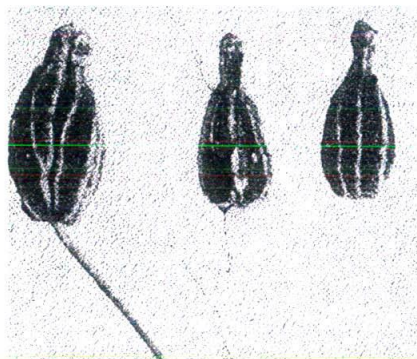
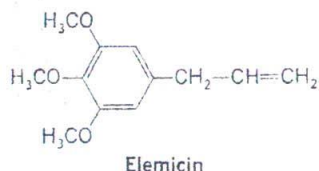


Fig. 5-15. Italian anise, magnified 6 times.

that is solid at ordinary temperatures, sometimes occurs in prismatic crystals, and is known as "nutmeg butter"; volatile oil, 8 to 15%, that contains myristicin and safrole; proteins in considerable amounts; and starch.

USES. Myristica is a flavor and a condiment. Recently, it has attracted attention as a useful agent for controlling diarrhea associated with certain carcinomas.

In recent years, nutmeg has gained a reputation, especially among prison inmates, as a hallucinogenic agent. However, the relatively large amount (up to 15 g) that must be ingested to cause the desired intoxication also produces flushing of the skin, tachycardia, absence of salivation, and other undesirable side effects. The active principle(s) responsible for the effects on the central nervous system have not been identified with certainty, but elemicin and myristicin are believed to be involved. Some theories involve the *in vivo* biotransformation of these nutmeg constituents into amphetaminelike, nitrogen-containing metabolites.



Nutmeg oil or myristica oil is the volatile oil distilled with steam from the dried kernels of the ripe seeds of *Myristica fragrans*. The oil is a colorless or pale yellow liquid that has the characteristic odor and taste of nutmeg.

East Indian nutmeg oil possesses differ-



Fig. 5-16. Nutmeg (*Myristica fragrans*) showing the one-seeded fruits (called nutmeg apples), the exposed seeds that are partially covered by the arillode (mace), and the characteristic leaves. The arillode has been partly peeled from a nutmeg seed (right center) to show how it can be removed. (Photo courtesy of Dr. Julia F. Morton, Director, Morton Collectanea, University of Miami.)

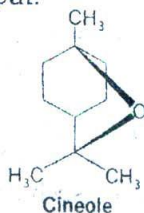
ent properties than those of West Indian nutmeg oil. The label of the container must indicate whether the oil is of East Indian or West Indian origin.

The oil contains safrole, myristicin (methoxysafrole), methoxyeugenol, (+)-camphene, β -terpineol, α - and β -pinene, myrcene, (\pm)-limonene, and sabinene.

USES. Nutmeg oil is a flavoring agent. It possesses carminative properties.

OXIDE VOLATILE OILS

Cineole (eucalyptol) is found in eucalyptus and several other volatile-oil-yielding drugs. It is also called cajuputol because it occurs in cajuput.



Eucalyptus Oil

Eucalyptus is the dried, scythe-shaped leaf of *Eucalyptus globulus* Labillardière or of other species of *Eucalyptus* (Fam. Myrtaceae) (Fig. 5-17). This tree is indigenous to eastern Australia and Tasmania and is cultivated in southern Europe and in California. *Eucalyptus* is Greek and means well-covered, alluding to the lidlike cover of the buds, and *globulus* is Latin and refers to the form of the fruit. The commercial supply of the drug is largely from Australia, Brazil, Spain, Portugal, Angola, and South Africa. The tree requires much water and has been used to dry up marsh land.

Eucalyptus contains volatile oil, 3 to 6%, several resins, and tannic acid.

Eucalyptus oil is the volatile oil distilled with steam from the fresh leaf of *E. globulus* or from other species of *Eucalyptus*. The oil is a colorless or pale yellow liquid that has a characteristic, aromatic, somewhat cam-



Fig. 5-17. Branch of eucalyptus tree showing fruits and scythe-shaped leaves.

phoraceous odor and a pungent, spicy, cooling taste.

Useful eucalyptus oil contains not less than 70% of cineole. It must be free from eucalyptus oils containing large amounts of phellandrene.

More than 300 species of *Eucalyptus* are recognized by botanists, and several different chemical races of a single species may exist. For this reason, the chemistry of the various eucalyptus oils is an extremely complex subject.

Eucalyptus oils intended for medicinal use contain about 70 to 85% cineole, plus lesser amounts of volatile aldehydes, terpenes, sesquiterpenes, aromatic aldehydes and alcohols, and phenols. Many of these minor components have irritant properties and are removed by redistillation of the oil. Oils intended for industrial purposes have piperitone and/or phellandrene as their principal components. Other eucalyptus oils used in perfumery are rich in geraniol and its esters and citronellal.

Over 450,000 lb of eucalyptus oil are imported into the United States annually.

USES. Eucalyptus oil is classed as a flavor. It is frequently used as an antiseptic, diaphoretic, and expectorant.

Cineole or eucalyptol is obtained from eucalyptus oil and from other sources. It is a colorless liquid that has a characteristic, aromatic, camphoraceous odor and a pungent, cooling, spicy taste. Cineole may be obtained (1) from eucalyptus oils by fractional distillation and subsequent freezing of the distillate or by treating eucalyptus oil with phosphoric acid and subsequently decomposing the cineole-phosphoric acid with water, or (2) from terpin hydrate as a dehydration product on treatment with acids.

USE. Cineole is classed as a flavor. It has properties similar to those of eucalyptus oil.

NONPRESCRIPTION PRODUCTS. Cineole and eucalyptus oil are employed in a wide variety of products, such as nasal inhalers

and sprays (Dristan[®], Sine-Off Once-A-Day[®], Vicks Sinex[®]); external analgesics (Antiphlogistine[®], Mentholatum Deep Heating[®], Minit-Rub[®], and Vicks Vaporub[®]); and mouthwashes (Listerine[®] and Odara[®]).

ESTER VOLATILE OILS

A wide variety of esters occurs in volatile oils. The most common are the acetates of terpineol, borneol, and geraniol. It is common practice to age perfumes to permit esterification, thus improving bouquet. Other examples of esters in volatile oils are allyl isothiocyanate in mustard oil and methyl salicylate in wintergreen oil (Table 5-6).

Biosynthesis of Esters. Terpene esters are generally formed from the respective alcohols by reaction with aliphatic acid moieties (commonly acetic acid), as was indicated for menthyl acetate. Formation of aromatic esters, at least in the case of methyl salicylate, involves the reverse process; that is, the aromatic acid reacts with an aliphatic alcohol (commonly methanol) to form the ester.

Labeled cinnamic acid has been incorporated into methyl salicylate by *Gaultheria procumbens*. The reactive form of cinnamic acid is presumably an ester of coenzyme A. The biosynthetic pathway (Fig. 5-18) involves *o*-hydroxylation of the cinnamic acid and subsequent side-chain degradation.

Among the drugs in this section are lavender oil, dwarf pine needle oil, mustard oil, and gaultheria oil.

Gaultheria Oil

Gaultheria, wintergreen, teaberry, or checkerberry consists of the dried leaves of *Gaultheria procumbens* Linné (Fam. Ericaceae), a low shrublike perennial with slender creeping or subterranean stems and branches that ascend from 5 to 15 cm in height. The leaves are alternate and evergreen, the flowers are white and axillary,

and the fruit is a bright red, globular, aromatic berry. The plant is common in coniferous woods throughout the eastern United States and Canada. The leaves are coriaceous, the upper surface is dark green and shining, and the under surface is pale green. The odor is distinct and aromatic, and the taste is aromatic and astringent.

Methyl salicylate (see Fig. 5-3) is produced synthetically or is obtained by maceration and subsequent distillation with steam from the leaves of *G. procumbens* Linné (Fam. Ericaceae) or from the bark of *Betula lenta* Linné (Fam. Betulaceae). The product must be labeled to indicate whether it was made synthetically or was distilled from either of the plants mentioned. This oil is also known as **gaultheria oil, wintergreen oil, betula oil, or sweet birch oil**.

In several eastern states the oil is obtained by distilling wintergreen plants that have been chopped into small pieces and allowed to stand in water for about 12 hours. The oil may be purified by rectification with steam. When the oil is distilled from birch bark, the process is much the same. Methyl salicylate is made synthetically by distilling a mixture of salicylic acid and methyl alcohol.

Methyl salicylate is a colorless, yellow or red liquid that has the characteristic odor and taste of wintergreen. Synthetic oil and that obtained from *Betula* are optically inactive, but the oil obtained from *Gaultheria* is slightly levorotatory.

Methyl salicylate, the chief constituent of this oil, is formed when the glycoside, gaultherin, is hydrolyzed by the naturally occurring enzyme, gaultherase, in the presence of water.

In addition to methyl salicylate, wintergreen oil contains an ester that splits into enanthic alcohol and an acid. Enanthic alcohol and its ester possess the characteristic odor that distinguishes natural wintergreen oil from synthetic methyl salicylate.

USES. Methyl salicylate is a pharmaceutical

Table 5-6. Ester Volatile Oil Drugs

Name	Part Used	Botanical Origin	Production Areas	Important Constituents	Use
Lavender oil	volatile oil distilled with steam from the fresh flowering tops	the dwarf shrub, <i>Lavandula angustifolia</i> (Labiatae)	Europe, United States, northern Africa, Tasmania	30-60% (-)-linalyl acetate, (-)-linalool, cineole, terpinen-4-ol	perfume
Pine needle oil (dwarf pine needle oil)	volatile oil distilled with steam from the fresh leaf	the tree, <i>Pinus mugo</i> and its variety <i>pumilio</i> (Pinaceae)	central Europe	3-10% bornyl acetate, α -pinene, β -pinene, Δ^3 -carene, camphene	perfume, flavor
Mustard oil (allyl isothiocyanate)	volatile oil obtained by maceration with water of the dried, ripe seed with subsequent steam distillation	the annual herb, <i>Brassica nigra</i> or <i>B. juncea</i> (Cruciferae)	temperate climates worldwide	not less than 93% allyl isothiocyanate	rubefacient in the OTC drug, Musterole®

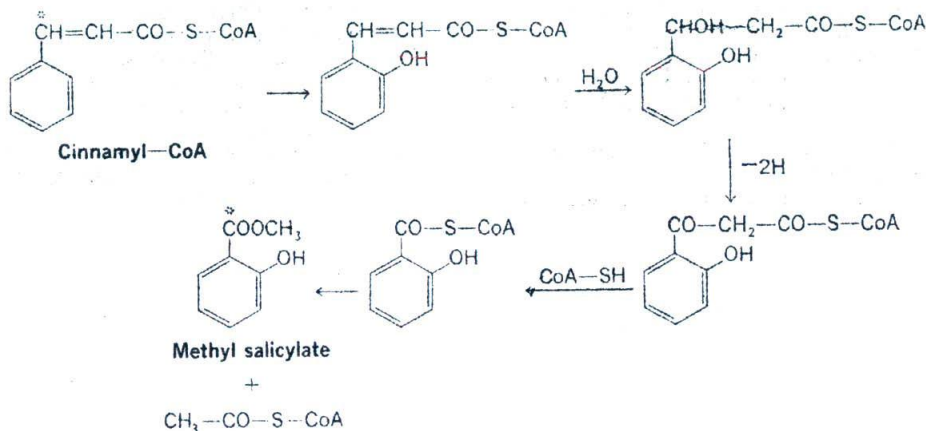


Fig. 5-18. Proposed biosynthetic pathway leading to methyl salicylate.

aid (flavor) for aromatic cascara sagrada fluidextract. In addition, it has local irritant, antiseptic, and antirheumatic properties. For topical use, 10 to 25% concentrations in lotions and solutions are employed. Wintergreen oil has been used as a flavor for many years; however, large doses of this drug have produced toxic symptoms. Ingestion of 10 ml by children has caused death. Symptoms of poisoning include nausea, vomiting, pulmonary edema, and convulsions.

The principal adulterant of natural wintergreen oil is synthetic methyl salicylate.

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