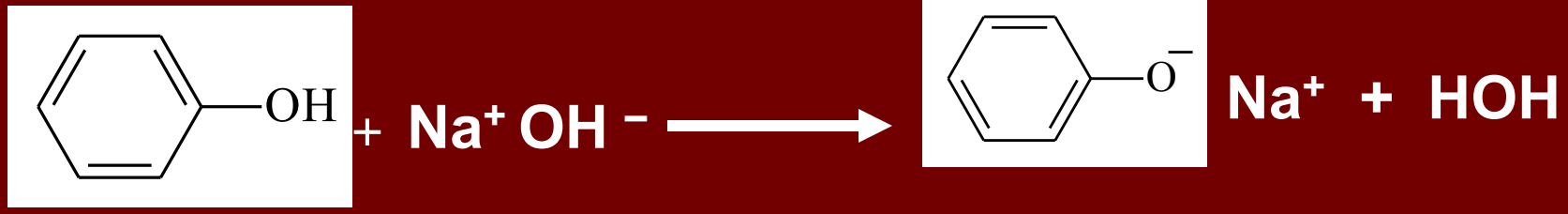
Phenols and phenolic ethers

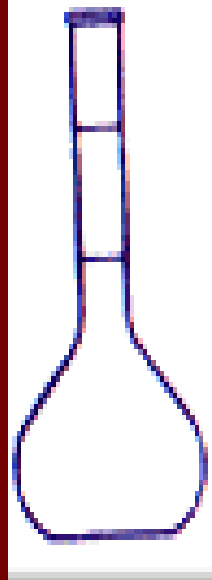
- They are among the most important constituents of volatile oils.

- **General methods of isolation:**
- Phenols (weak acids) form water soluble salts with dilute alkali solutions (3-5%). Therefore the oil containing phenols is shaken with dilute aqueous solution of alkalis;



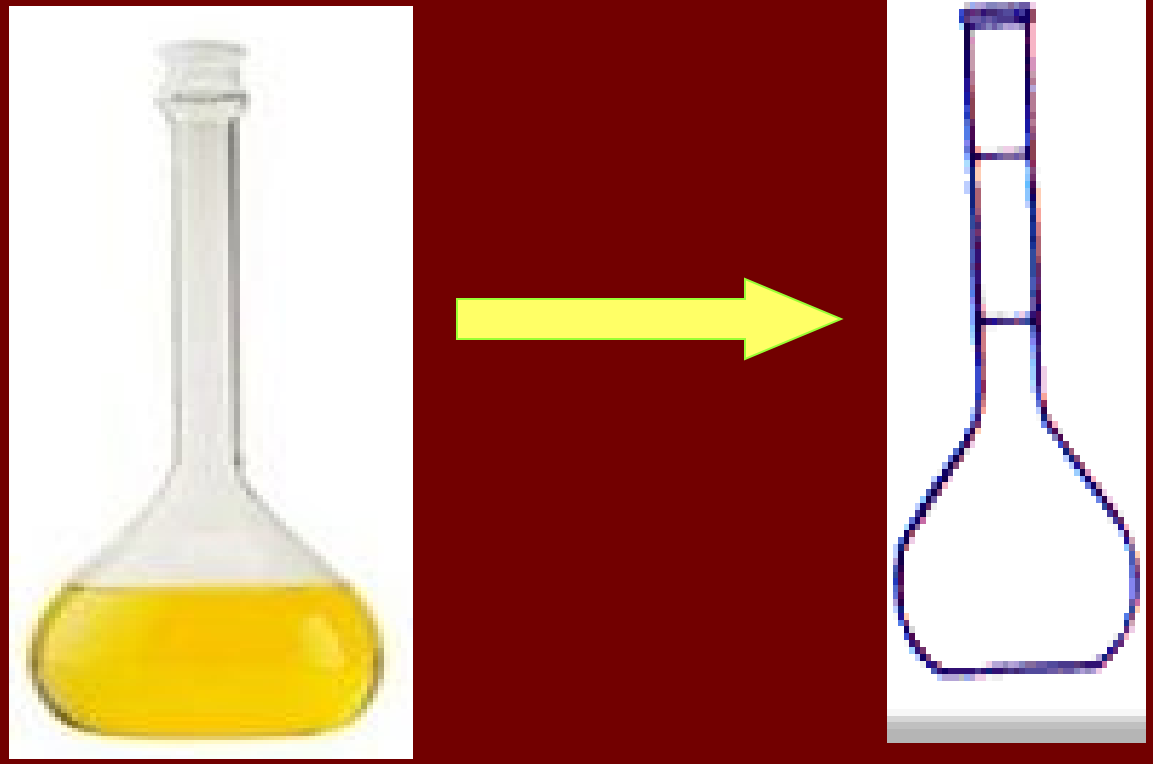
Phenol

Sodium phenoxide

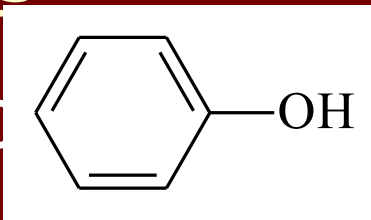


General methods of isolation of phenols

- The aqueous layer is separated then acidified (to liberate the phenol) and either steam distilled or extracted with ether.



General methods of isolation Phenols and phenolic ethers



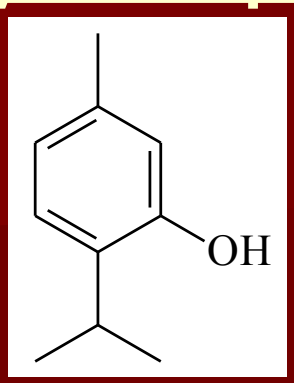
- By cooling the oil or the suitable fracti some phenols and phenolic ethers can be separated in crystalline form.
- General characters of terpene phenols :
- With $FeCl_3$ ⟶ colored iron compounds.
- Undergo some reactions characteristic of alcohols; as reactions with acetic anhydride, phenyl isocyanate,…

Classification

Phenols and phenolic ethers may be grouped into:

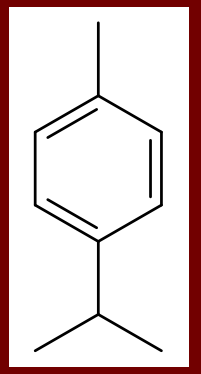
- - Monohydric (thymol)
- - Dihydric (eugenol, safrole,..)
- - Trihydric (myristicin)
- - Tetrahydric (apiole)

Monohydric phenols



Thymol

3-Hydroxy-p-cymene

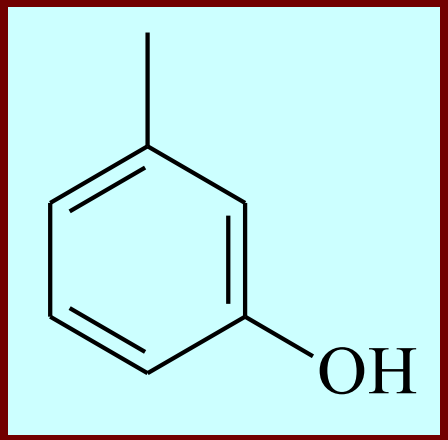


p-Cymene

- Oil of Thyme, *Thymus vulgaris*, F Labiatae (Lamiaceae)

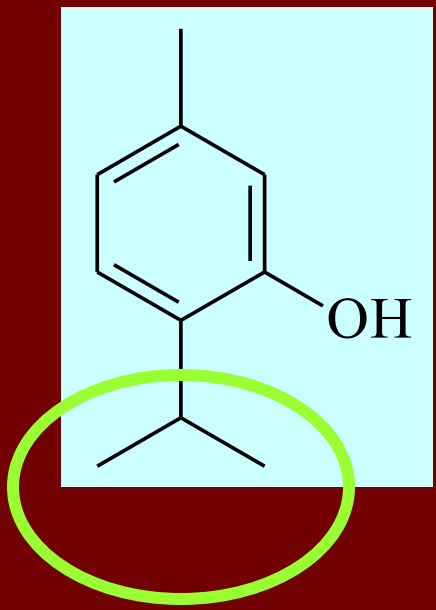
Thymol

- Isolation:
- Fractional distillation
- Cooling the oil ⟶ crystals
- Using KOH (5%)
- Synthesis



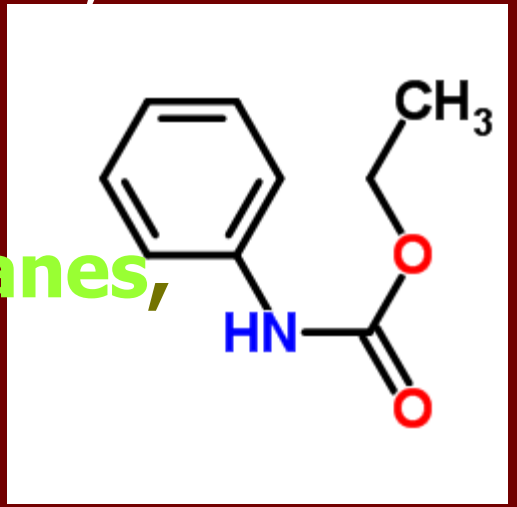
m-cresol

-Isopropyl alcohol
-Catalyst



Thymol

- Properties:
- Large crystals with a thyme-like odour and a pungent taste.
- Soluble (1:1200) in water, (1:1) in alcohol, soluble in ether, chloroform,….
- Identification:
- Through derivatives: as **phenyl urethanes**, dinitrobenzoate,….
- Color reactions:
- Thymol+ gl. Acetic acid + 3 drops conc. H_2SO_4 + 1 drop conc. HNO_3 ⟶ **greenish-blue colour.**



Thymol

- Thymol+ conc. H_2SO_4 ⟶ thymol sulfonic acid +$FeCl_3$ ⟶ violet colour.
- **Uses:**

  Thymol has disinfectant and antibacterial properties; employed in some antiseptic mixtures as gargles, mouthwashes and dental preparations.

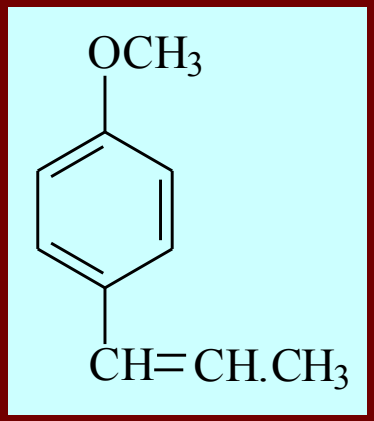
- Anti-anxiety activity of thymol ***(Journal of Acute Disease, November 2014)***

- Thymol inhibits bladder cancer cell proliferation via inducing cell cycle arrest and apoptosis (novel treatment)

Biochemical and Biophysical Research Communications
Volume 491, Issue 2, 16 September 2017, Pages 530–536

- **Thymol** and eugenol were chosen to be starting compounds to synthesize acetyl and benzoyl derivatives and to test their antileishmanial activity in vitro and in vivo.
- **Acetyl-thymol** was more active than thymol and the positive control drug amphotericin B.
- **The thymol** derivatives demonstrated the greater activity than the eugenol derivatives.

Anethole



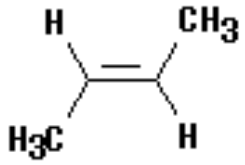
p-propenyl-methyl phenol

Anise camphor

- Aniseed oil 84-93% E-anethole
- Bitter Fennel oil 50-80%
- Sweet Fennel oil 80%

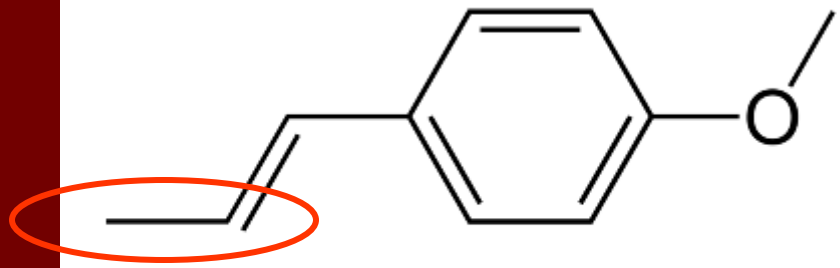
F. Umbellifarae (Apiaceae)

(E)- : the higher priority groups are on opposite sides of the double bond.

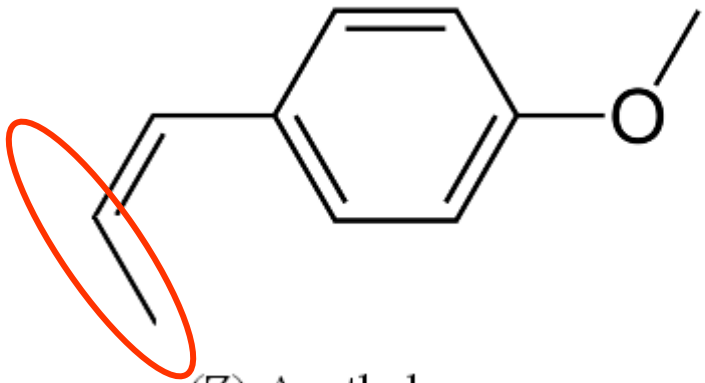


trans-2-butene

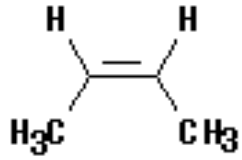
(E)-2-butene



(E)-Anethole



(Z)-Anethole



cis-2-butene

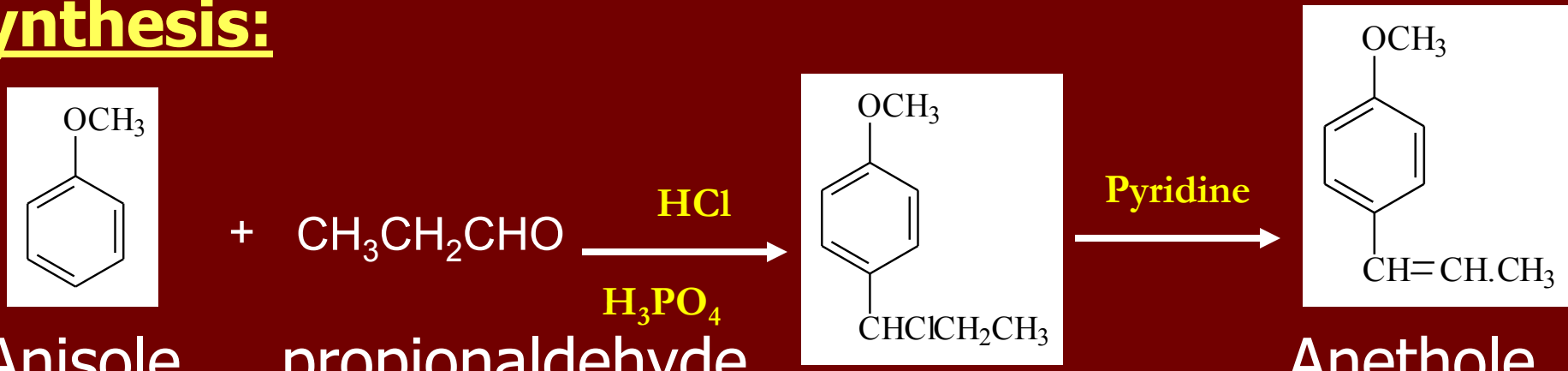
(Z)-2-butene

Anethole

Isolation:

- Cooling oil or fraction rich in anethole ⟶ crystals

Synthesis:



Anisole propionaldehyde Anethole

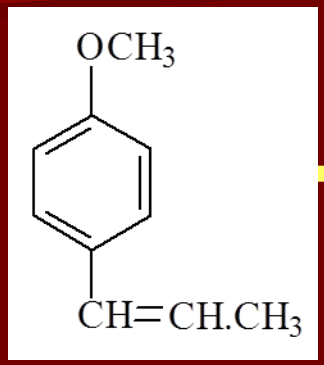
Properties:

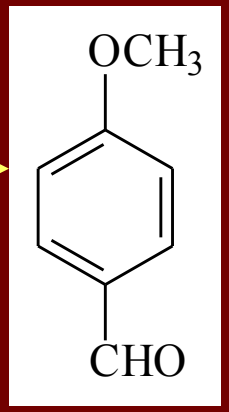
White crystalline mass of intensely sweet odour and taste (anise fruit).

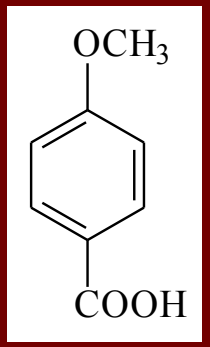
Insoluble in water and soluble in organic solvents.

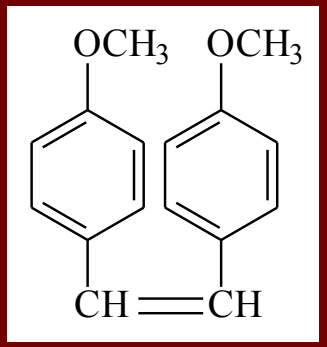
Anethole

- Unstable under the influence of light, air or heat









Anisaldehyde Anisic acid p-p-Dimethoxy stilbene

Photoanethole

- **Identification:**
- By oxidation → anisaldehyde, on further oxidation → anisic acid.

Anethole

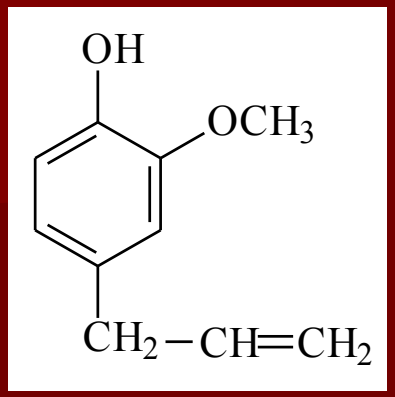
Uses:

- Anethole is widely used as a palatable flavour in confectionary and beverages, also in pharmaceutical preparations as dentifrices, mouthwashes and gargles.
- Anethole suppressed cell survival and induced apoptosis in human breast cancer cells *(June 2012, Phytomedicine)*

** The fruits extract of ***Foeniculum vulgare*** and its active constituent, **TA,** provide a possible novel approach for treating and preventing UV-induced melanogenesis.

Journal of Dermatological Science-2016

Dihydric phenols

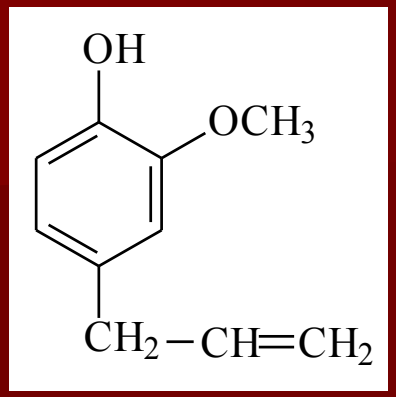


Eugenol

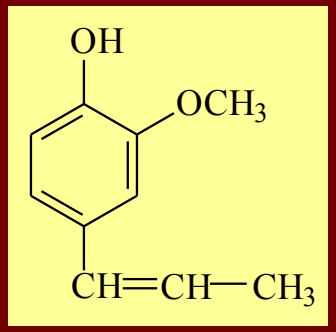
4-allyl-2-methoxy phenol

- Oil of clove (F. Myrtaceae)
- Oil of Cinnamon leaves (F. Lauraceae)
- As glycoside, **gein** *Geum urbanum* (F. Rosaceae)

Eugenol



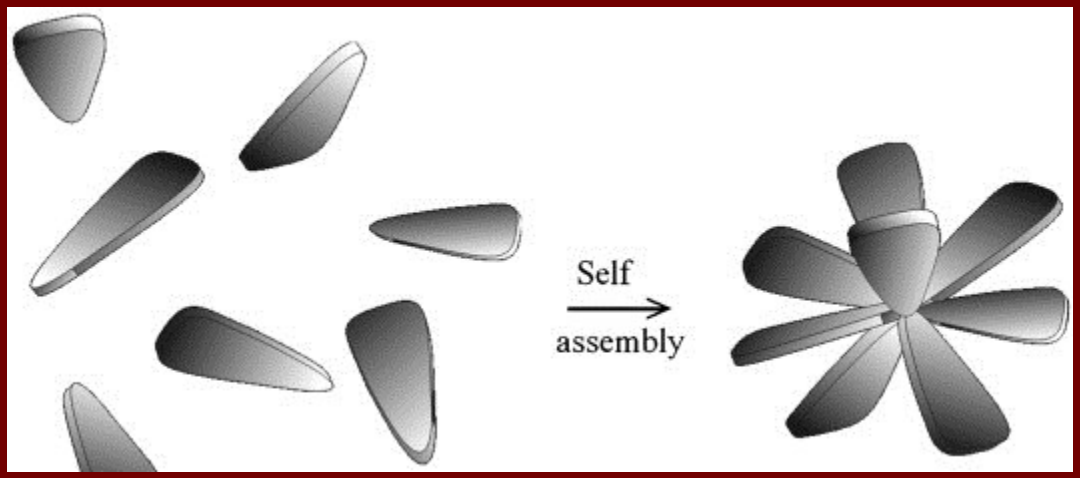
- **Isolation:**
- Using KOH (5%)
- **Properties:**
- Yellowish, viscous liquid with burning taste and clove-like odor.
- Heavier than water, sparingly soluble in water, soluble in alcohol and caustic alkalis.
- By heating with KOH → isoeugenol



Eugenol

- **Identification:**

- **Formation of derivatives as benzoate, phenyl urethane,…**
- **Microchemical test: a drop of oil + a drop of 3% NaOH saturated with NaBr → crystals of sodium eugenate (needle and pear-like forms arranged in rosette-like bunches).**
- **Color reactions with $FeCl_3$**

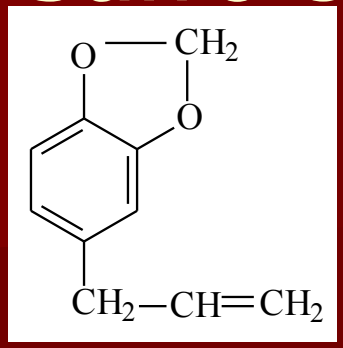


Uses:

- Eugenol is used in toothache remedies; has local anesthetic properties (inhibits nerve conduction), also an anti-inflammatory. It is bactericidal at law concentration; used in formulation of mouthwashes.
- In vivo, eugenol inhibited rat paw oedema (**5 times more potent than aspirin**). The results provide evidence that eugenol acts as a dual antagonist of AA and PAF (*Phytomedicine, 1995)*.
- Preparation of vanillin

PAF Platelet-activating factor (AA) arachidonic acid

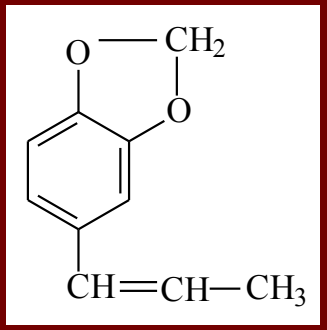
Safrole



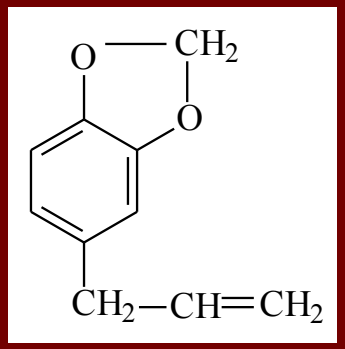
Allyl catechol methylene ether

- Oil of Sassafras: 80% safrole
- Oils of **star anise**, nutmeg and Cinnamon leaf.
- Isolation:
- By cooling the oil or safrole containing fraction to about –10°C.
- Properties:
- Colorless liquid, insoluble in water, soluble in alcohol or ether, by cooling → crystalline mass.

Safrole

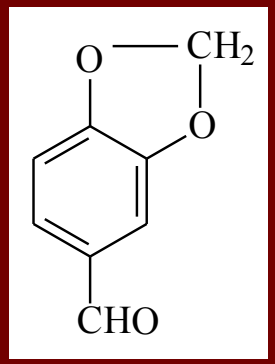


- By heating with alkali ⟶ Isosafrole
- **Identification:**
- Formation of derivatives as pentabromosafrole, pictate
- Safrole or isosafrole + conc. H_2SO_4 ⟶ intense red color.



Safrole

Oxidation ⟶



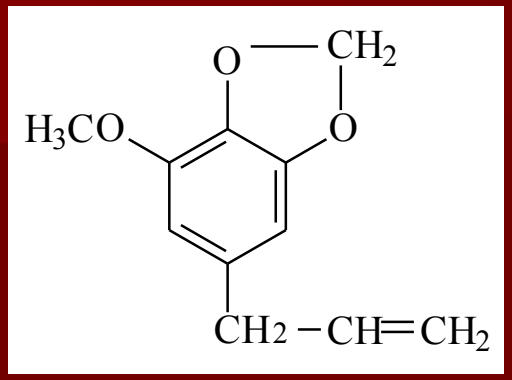
Piperonal

Uses of Safrole

- Was widely used as flavour before it was banned; safrole induces the formation of hepatic tumours in rodents (carcinogen).
- Safrole is an important raw material for the chemical industry because of two derivatives: (Piperonal), which is widely used as a fragrance and flavoring agent, and piperonyl butoxide (PBO), a vital ingredient of pyrethroid insecticides.

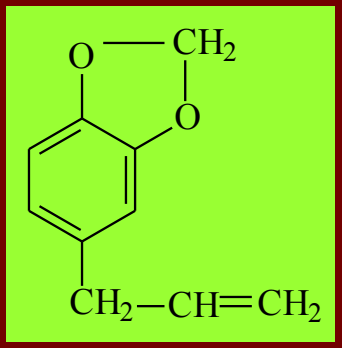
Safrole should be handled as a carcinogen with extreme caution. ***Encyclopedia of Toxicology (Third Edition), 2014, Pages 205-207***

Trihydric phenolic ether



Myristicin

6-methoxy safrole



Safrole

- Oil of nutmeg (*Myristica fragrance, F.* Myristicaceae*)*
- Oil of **mace** *(*dried arillus of *Myristica Fragrance*)

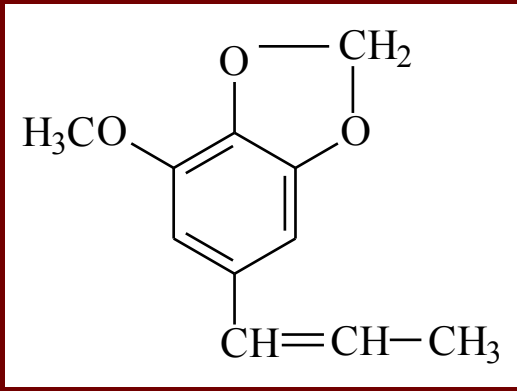
❖ Isolation:

- -Fractional distillation

** The expressed oil, known as nutmeg butter, is composed principally of a lipid called trimyristin

Myristicin

- Properties:
  - Oily liquid with faint aromatic odor, does not congeal at low temperature, heavier than water.

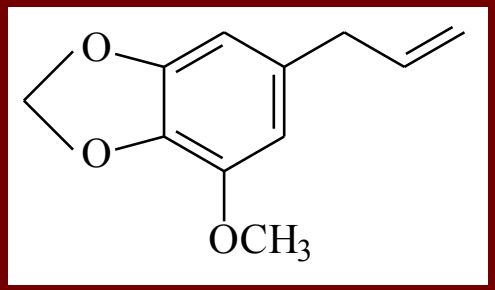


  - On boiling with alcoholic KOH ⟶ isomyristicin
- Identification:

On oxidation with $KMnO_4$ gives the corresponding aldehyde/acid.

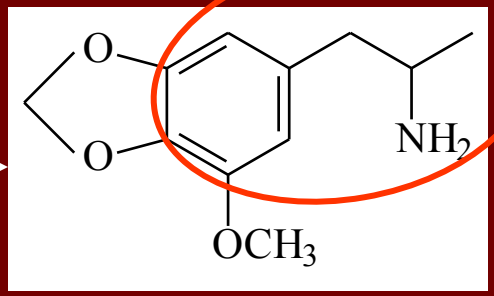
Nutmeg and Myristicin

- Nutmeg is used as stomachic, stimulant and carminative (spice).
- The psychotropic activity of nutmeg (euphoria, hallucination) seems linked to myristicin and closely related products: **MMDA** is thought to be formed in the body after ingestion of nutmeg by **amination** process on **myristicin** and may be the agent responsible for the euphoric and hallucinogenic effects of high doses of nutmeg.

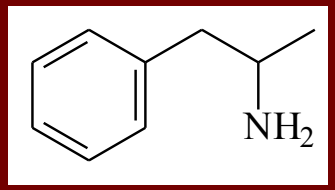


Myristicin

In the body



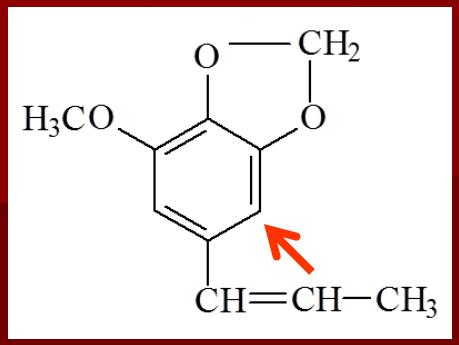
3-methoxy-4,5-methylene dioxy-amphetamine (MMDA)

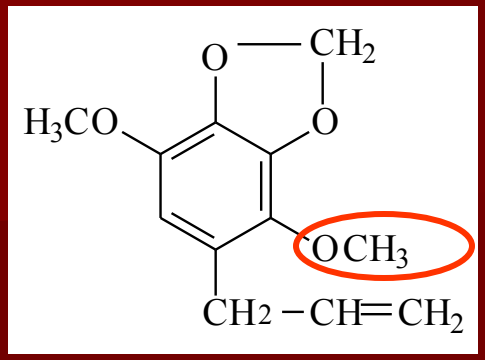


Amphetamine

- Myristicin cause apoptosis in human **leukaemia cells**. ***Chemico-Biological Interactions, Volume 218, 25 July 2014, Pages 1-9***
- Antihelmintic **(against** *Anisakis simplex)*

Tetrahydric phenolic ether

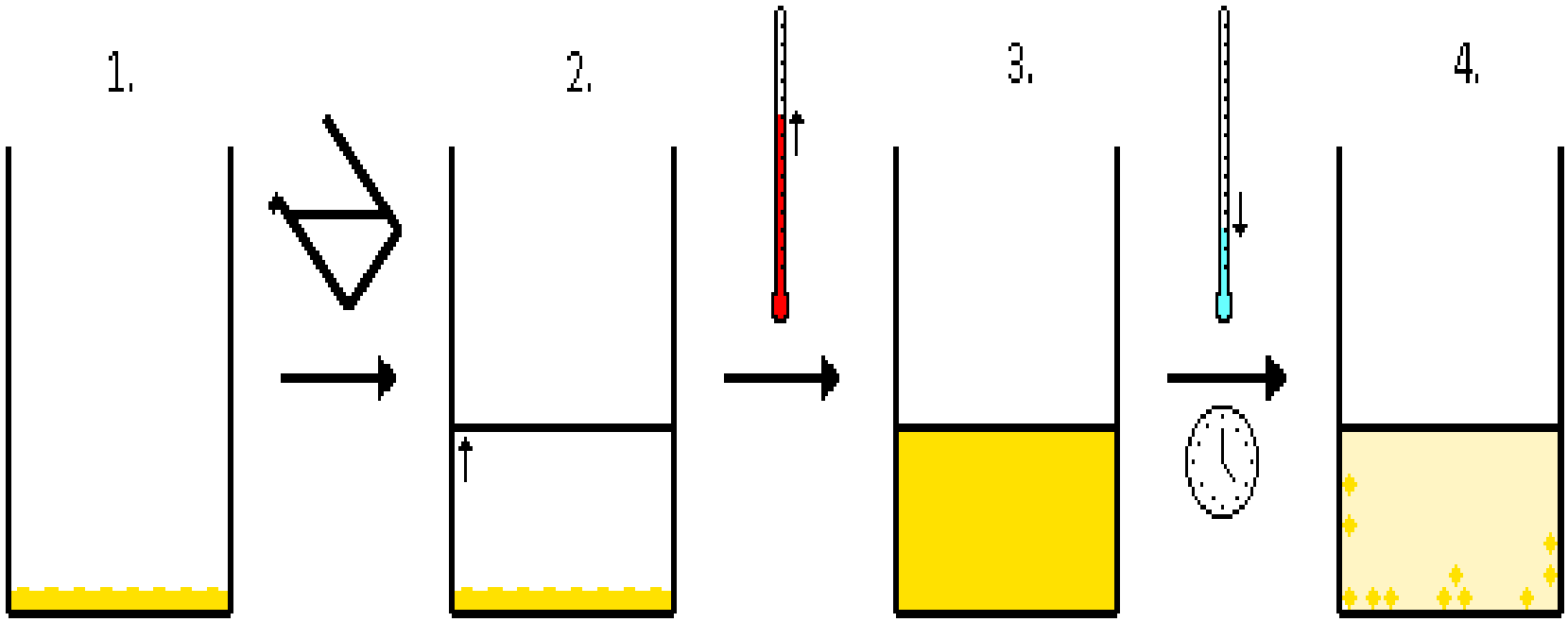




Apiole, Parsley camphor

3-methoxy myristicin

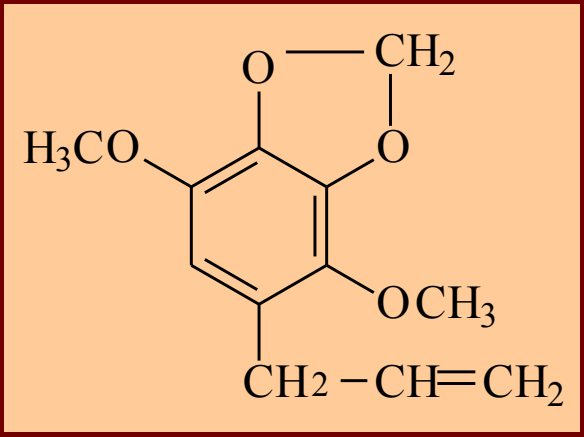
- Parsley seed oil (بقدونس)
- ❖ Isolation:
- By cooling the oil and **recrystallization** from alcohol and pet. ether.
- ❖ Properties:
- Long colourless needles with faint parsley odour, insoluble in water, soluble in alcohol and ether.
- On boiling with alcoholic KOH ⟶ isoapiole


1.
2.
3.
4.

Apiol

- Identification:
- By oxidation with $KMnO_4$ ⟶ apiolaldehyde and apiolic acid.
- By preparation of apiole tribromide.

- Apiole has carminative, diuretic and **uterine stimulant** properties **(abortifacients)** , not used now because of intoxication of high doses.



Determination of Phenols

- The general method is based on the fact that phenols react with alkali hydroxides to form phenolates, KOH is preferred; more soluble.
- Disadvantages of this method
- Water-soluble materials (as alcohols,…) will go into solution and calculated as phenols.
- Aqueous solution of phenolates is a better solvent for the non-phenolic portion of the oil ⟶ apparent higher content of phenols.

HI method for ethers

- Conversion of ethers into phenols by treating the oil with HI and the resulted phenol determined as above.
- Determination of free phenols (before HI)
- Treatment with HI and determine the total phenols and phenolic ethers.
- Phenolic ethers are estimated by difference.
- Chromatographic method
- Gas chromatography ⟶
- - Retention time (R_t) ⟶ **identification.**
- Area under the peak **quantitative determination.**

Bonds Formed	Bonds Broken
A O–H	B H–I
C C–I	D C–OH

Step 1: protonation