Monoterpenes

1. INTRODUCTION

The most simple constituents in the terpene series (except for the rare hemiterpenes), monoterpenes arise from the coupling of two "isoprene" units. Over one thousand are known: "regular" structures that are common elements of essential oils; "irregular" structures that participate in the formation of pyrethrins, and in the composition of certain essential oils of Asteraceae; cyclized into methyl-cyclopentanes, they constitute iridoids. Most monoterpenoids occur in the free state (see essential oils), but in the last few years, glycosidic structures have been characterized fairly often (some are known in melissa and in hyssop*). In the particular case of iridoids, on the contrary, the glycosidic forms are the common ones.

* Those present in fruits are also undergoing studies: they play an important role as precursors of the aroma (peach, grape, cherry, raspberry); see, among others, Krammer, G., Winterhalter, P., Schwab, M. and Schreier, P. (1991). Glycosidically Bound Aroma Compounds in the Fruits of *Prunus* Species: Apricot (*P. armeniaca* L.), Peach (*P. persica* L.), Yellow Plum (*P. domestica* L. ssp. *syriaca*), *J. Agric. Food Chem.*, **39**, 778-781, and references therein.

Exceptional in the animal kingdom (except in a few insects), rare in Fungi, they exist as halogenated compounds in Algae, and are widely distributed in higher plants, especially in certain orders or families: essential oils of the Lamiales, Asterales, Laurales, iridoids of the Gentianales, Scrophulariales, Cornales, and more.

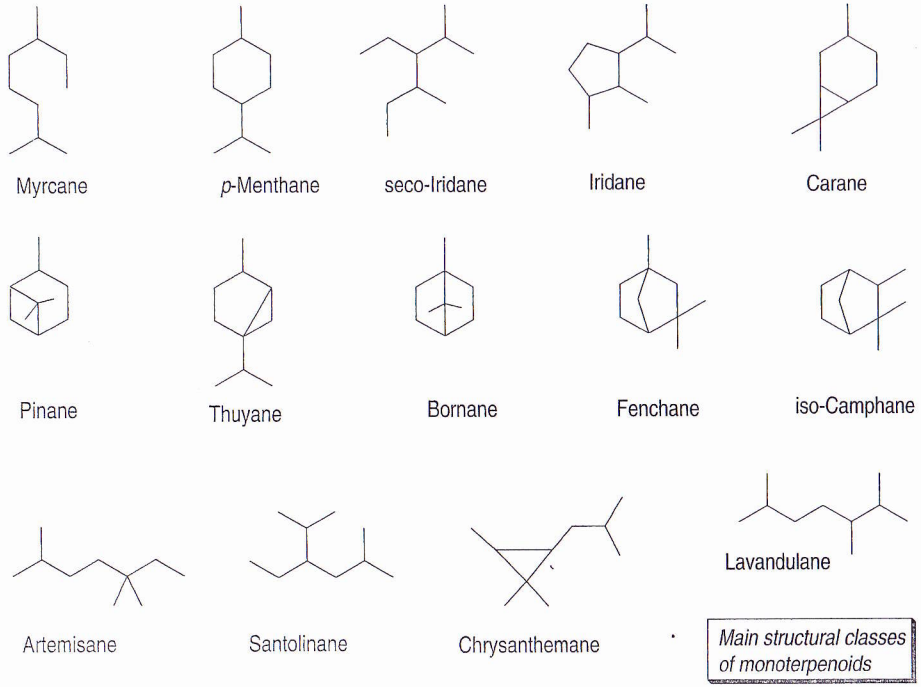
We shall present here only some structural and biogenetic generalities, to attempt to define the concept of monoterpene globally. On the other hand, the production methods, physico-chemical, biological, and pharmacological properties, quality control procedures as well as the therapeutic or economic implications differ greatly. Thus we shall cover successively:

- essential oils and oleoresins;
- irregular monoterpenes (insecticidal pyrethrins);
- iridoids.

2. STRUCTURE

Although some forty monoterpenoid skeletons are known, the vast majority of the structures reported boil down to a small number of basic features arising from the *head-to-tail* coupling of two C_5 GPP units (geranyl pyrophosphate, see the general introduction), and may be:

- acyclic (myrcane or 2,6-dimethyloctane, secoiridane);
- monocyclic (e.g., *p*-menthane, iridane);
- bi- and tricyclic (e.g., carane, pinane, bornane, thuyane).



Main structural classes of monoterpenoids

Next to these "regular" monoterpenes, more than just a few irregular structures are known that arise from:

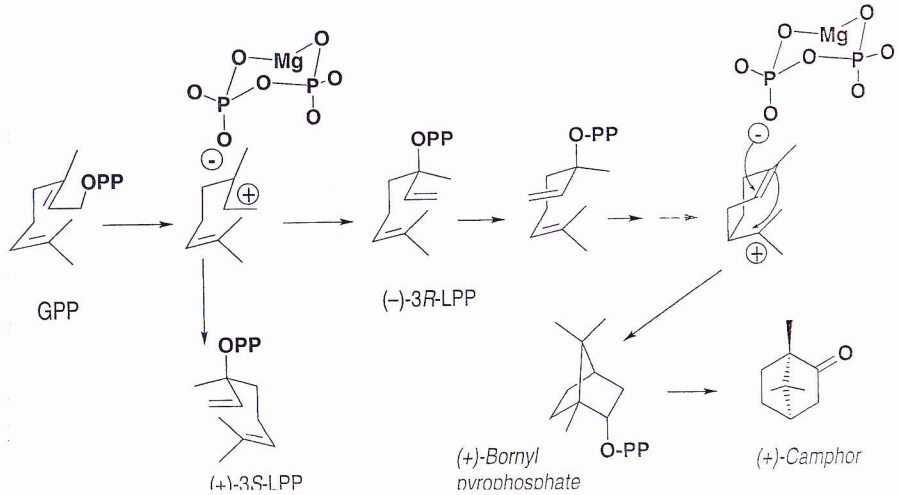
- either the rearrangement of "regular" precursors: for example isocamphane or fenchane, from the rearrangement of pinane and bornane;
- or indeed a non-conventional biogenesis: for example derivatives arising directly from chrysamthemyl pyrophosphate (chrysanthemane), or from its rearrangement (artemisane, santolinane, lavandulane, or rothrockane).

3. BIOSYNTHETIC ORIGIN

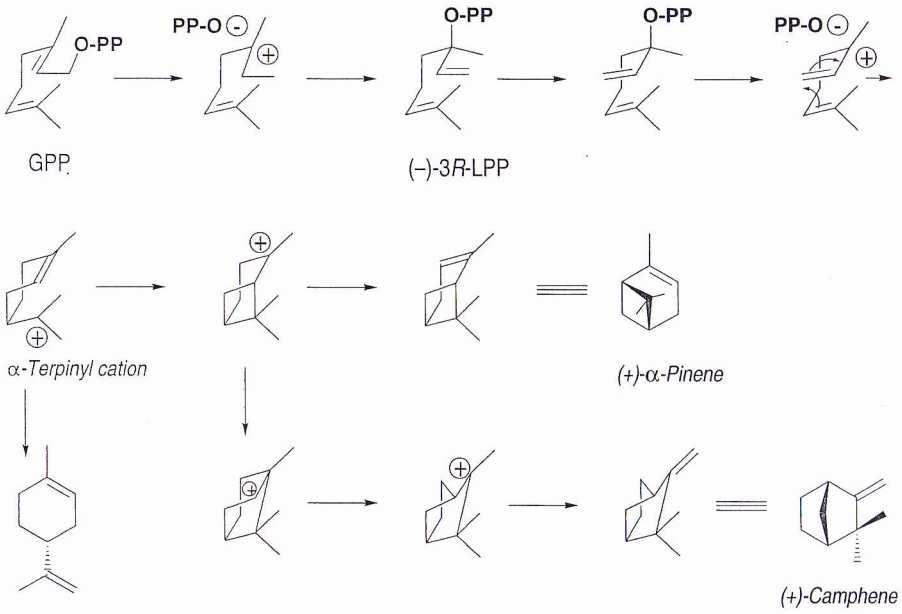
A. Regular Monoterpenes

GPP formation has been covered in the previous chapter. It is the starting point of regular monoterpenes. If the formation of alcohols and acyclic hydrocarbons from GPP is obvious, that of cyclic monoterpenes involves *in theory* the intramolecular nucleophilic attack of the C-1 of the neryl cation by the distal double bond, an attack which leads to the formation of the intermediate α-terpinyl cation.

In fact, experiments show that the reaction takes place without any *free* neryl or linalyl intermediate appearing in the medium: it has now been proved that the formation of mono- and bicyclic compounds from GPP involves monoterpene cyclases, which operate according to an isomerization-cyclization mechanism. During this process, geranyl pyrophosphate is first ionized to an ion pair, with the reaction probably being assisted by a divalent metal cation (Mn^{2+} or Mg^{2+}). Next, the allylic cation isomerizes to (3*R*)- or (3*S*)-*linalyl pyrophosphate* (LPP), which remains bonded and which, after rotation about the C-2-C-3 bond (to the *cisoid* form), ionizes again and cyclizes to the (4*R*)- or (4*S*)-α-terpinyl cation. Most known cyclases are capable of catalyzing the formation of hydrocarbons, and do so stereospecifically (e.g., (4*S*)-(–)-limonene in *Mentha spicata*, (4*R*)-(+)-limonene in *Citrus sinensis*).



The figure below illustrates how the α-terpinyl cation may lead, *via* additional cyclizations onto the residual cyclohexene double bond, proton shifts, and other classic rearrangements (Wagner-Meerwein), to the chief monoterpenoid skeletons. The study of a specific example such as the biosynthesis of (+)-camphor (in official sage) or (–)-camphor (in tansy or rosemary) shows that GPP is converted to LPP, then to bornyl pyrophosphate *via* the α-terpinyl cation; borneol is formed upon hydrolysis of the pyrophosphoryl ester, then oxidized (NAD-dependent dehydrogenase).



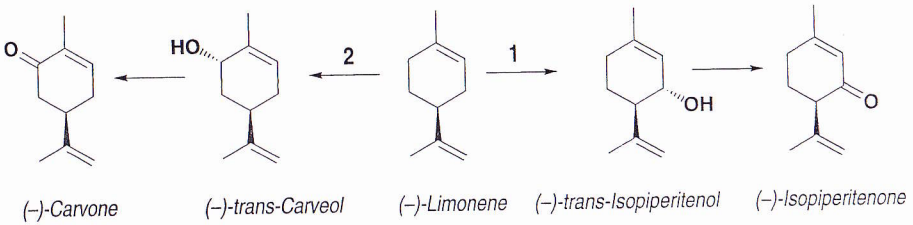
Conversion of GPP to LPP.
Formation of the α-terpinyl cation and of the principal monoterpenoid skeletons

Only the series formed from (–)-3*R*-LPP (pinenecyclase I) is represented here. In the same fashion, pinenecyclase II mediates, from (+)-3*S*-LPP, the formation of (–)-α-pinene, (–)-β-pinene, (–)-limonene, (–)-camphene, and more.

The reactions (cyclizations and rearrangements) end with either the loss of a proton and formation of a hydrocarbon, or with nucleophilic addition, for example of water, and therefore the formation of an alcohol.

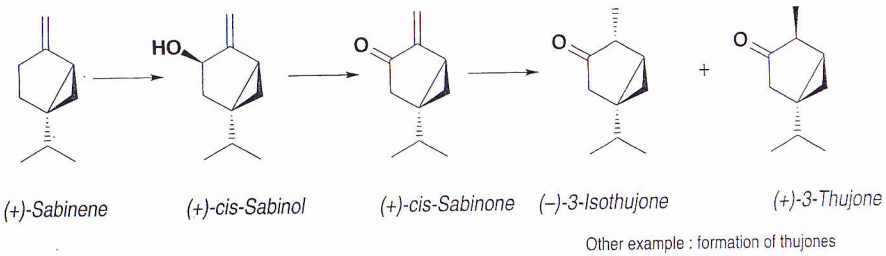
Except for the case of alcohols formed upon trapping of carbocations by water, the introduction of oxygen is rarely concomitant with cyclization: the numerous oxygenated derivatives described are frequently formed from hydrocarbons, by oxidation reactions catalyzed by classic oxidases according to a pathway which seems very general: allylic hydroxylation, oxidation of the alcohol to the corresponding β-unsaturated ketone, and possible reduction of the conjugated double bond. It appears that the enzymes involved in the reaction schemes are most often specific. Thus, in *Mentha piperita*, (–)-limonene is hydroxylated to (–)-*trans*-isopiperitenol, which is oxidized to (–)-isopiperitenone, which is reduced to (+)-*cis*-pulegone. Subsequently

isomerizations and reductions lead to (–)-menthone and menthols. In *Mentha spicata*, the reaction is of the same type, but the regiospecificity is different: the hydroxylation yields (–)-*trans*-carveol, which is oxidized to (–)-carvone (later very partially reduced). An identical mechanism explains the formation of (+)-*cis*-sabinol and (+)-sabinone from (+)-sabinene; the stereoselective reduction of (+)-sabinone leads next to (+)-3-thujone or (–)-3-isothujone.



Oxidation of monoterpenes :
allylic hydroxylation and oxidation to an α-β-insaturated ketone

Example of regioselectivity (mints):
1 = *Mentha piperita*
2 = *Mentha spicata*



Other example : formation of thujones

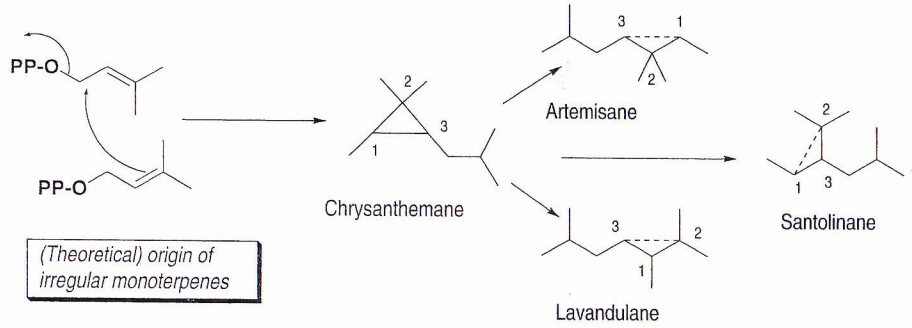
B. Irregular Monoterpenes

They arise from chrysanthemyl pyrophosphate, which in all likelihood comes from the coupling of two molecules of DMAPP, according to a mechanism analogous to that which leads from FPP to presqualene pyrophosphate (see the previous chapter). The occurrence of the other irregular terpenes would be explained by a mechanism involving the cleavage of the cyclopropane ring bonds of chrysanthemane, to form santolinanes (C-1-C-2 cleavage), or artemisanes (C-1-C-3 cleavage). Lavandulanes, theoretically formed by the cleavage of the C-2-C-3 bond, probably arise from the direct coupling of two DMAPPs. Chrysanthemic acid and its derivatives are very commonly found in Asteraceae-Anthemideae (e.g., *Tanacetum*, *Artemisia*, *Chrysanthemum*, *Santolina*).

C. Iridoids

The formation of the cyclopentapyran nucleus characteristic of iridanes goes through the C-10 hydroxylation of geraniol (or nerol), and the oxidation to the

aldehyde (10-oxogeranial), which cyclizes (iridodial, epi-iridodial) before the formation of the pyran cycle, which is stabilized by glucosylation. In some cases the precursor may be citronellol (see the chapter on iridoids, p. 589).



D. Monoterpene containing-drugs

Drugs containing essential oils, iridoids, and irregular monoterpenes are the subject of the next three chapters. The following is an oriental drug containing monoterpenoid glycosides: the peony.

- **Peony**, *Pæonia* spp., Paeoniaceae

The genus *Pæonia* is scarcely represented in Europe (*P. officinalis* L., *P. mascula* [L.] Miller); on the other hand, it is well known for the ornamental value of several of its species and their hybrids, characterized by their majestic pink, white, or red flowers, whose diameter can exceed 20 cm. Peony root is one of the most important constituents of traditional Chinese and Japanese (*kampo*) prescriptions. According to the Chinese Pharmacopoeia, the drug consists of the dried roots of *P. lactiflora* Pallas and *P. veitchii* Lynch (= *chishao*, the red peony). When the root is peeled, cooked in water, and dried, it is referred to as white peony (= *baishao*). *Mudanpi* (= *moutan cortex*), the root bark of *P. suffruticosa* Andrews is also used in traditional medicine.

The major constituent (0.5-0.6%) of the root of *P. lactiflora* is paeoniflorin, a monoterpene glucoside with a cage-like pinane skeleton. The minor constituents are also of monoterpenoid origin (oxypaeoniflorin, paeflorigenone, paeonilactones...). The most important constituents of *P. suffruticosa* root bark are paeonol (2'-hydroxy-4'-methoxyacetophenone) and its glycosides. The drug also contains monoterpene glycosides which occur as gallates (suffruticosides), like the acetophenones.

Pharmacologically, paeoniflorin is an antispasmodic and a sedative, and like paeonol, it is an anti-inflammatory agent and an inhibitor of platelet aggregation. *In vitro*, paeonol is an antibacterial agent. The drug apparently has little toxicity, and is traditionally used as an antispasmodic and analgesic agent (it is thought to have a myorelaxant activity). It is also an ingredient in prescriptions recommended for the treatment of atopic eczema.

4. BIBLIOGRAPHY (follows generalities on sesquiterpenes, p. 492)

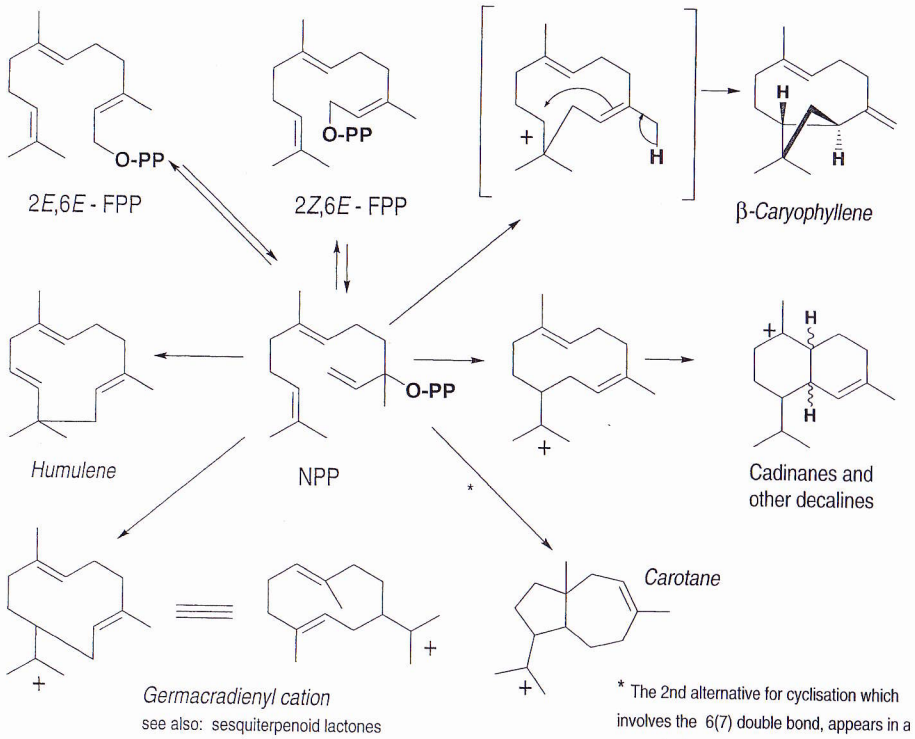
Sesquiterpenes

Since the isolation of cadinene and caryophyllene by Wallach at the end of the nineteenth century, and the first description of a sesquiterpene structure (farnesol, 1913), the number of known molecules has continually grown: the compounds described to date represent more than 100 different skeletons. We shall see that this diversity is a consequence of the rich chemical reaction potential of the common precursor: *farnesyl pyrophosphate* (FPP).

The precursor of the entire series, 2*E*,6*E*-FPP, results from the addition of a molecule of IPP onto GPP. The cyclization of FPP, or of its geometrical isomer at C-2 (2*Z*,6*E*-FPP), or of nerolidyl pyrophosphate, by nucleophilic attack on the distal double bond, leads to the most widespread sesquiterpenoid hydrocarbons: humulene and caryophyllene. It can also lead to the germacradienyl cation, from which may arise multiple compounds with bicyclic skeletons found in essential oils (e.g., germacrene D), and found as lactones with various biological activities. The electrophilic attack can involve the central double bond of FPP, and thereby induce the formation of compounds comprising a six-membered ring (bisabolane and derivatives) or, less frequently, a seven-membered ring (carotanes).

As in the case of monoterpenes, additional intramolecular cyclizations, rearrangements, and oxidations lead to a very large number of structures. The figures on the few next pages provide a glimpse into the mechanistic possibilities, a number of which remain hypothetical in the absence of experimental proof and despite their high plausibility.

In a few cases, the initial cyclization takes place with no involvement of the pyrophosphate group. It is then initiated, as for diterpenes and some triterpenes, by a protonation of the distal double bond. Examples are drimanes such as polygodial (*Polygonum hydropiper* L., Polygonaceae), or warburganal (*Warburgia salutaris* [Bertol. *f.*] Chiov., Canellaceae); this type of compound has also been described in various animal organisms.



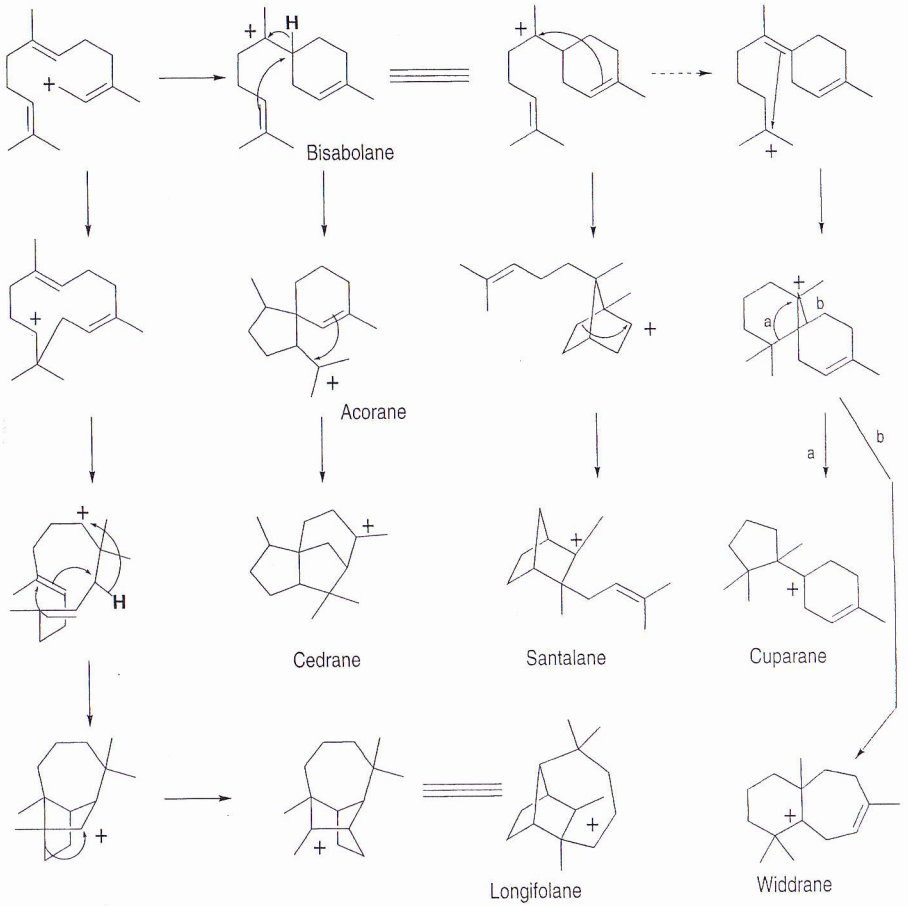
INTEREST IN SESQUITERPENES

A very large number of sesquiterpenes are common constituents of the essential oils of higher plants, and therefore may contribute to the pharmacological properties attributed to these volatile fractions (see the next chapter). One example is bisabolol and its derivatives, found in matricaria oil.

Another group of sesquiterpenes is characterized by the presence of a γ-lactone: the structural diversity and the pharmacological activity of these sesquiterpenoid lactones will be covered in a later chapter (p. 619).

Biologically, a fair number of sesquiterpenoid structures are phytoalexins (this is particularly true in the Solanaceae); others—except for abscisic acid which, *biogenetically*, is not a sesquiterpene—seem to act as growth regulators; yet others attract insects (germacrene D, (+)-αcopaene) or act against them as antifeedants (warburganal): in fact, their potential applications have inspired the synthesis of structural analogs. Finally, more than just a few sesquiterpenes isolated from marine organisms display potentially interesting pharmacological activities, and several mycotoxins are sesquiterpenoid in nature (e.g., ipomeamarone, trichothecenes).

The chief sesquiterpene with potential activity (other than sesquiterpenoid lactones and constituents of essential oils) is gossypol.



Examples of interconversions among sesquiterpenoids

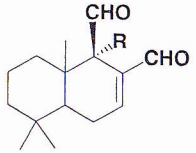
• GOSSYPOL

The seeds of cotton plants (*Gossypium* sp.) have scattered ovoid or spherical glands containing various pigments, including gossypol, which is clearly the major component. This pigment is found in all of the varieties of cotton plants, and its level ranges from 0.3 to 2% of the weight of the seed.

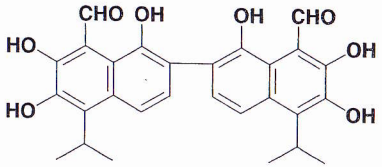
A bisnaphthalene-type and multifunctional compound, (±)-gossypol is very reactive: it reacts with the terminal amine groups of lysine-containing proteins, and this substantially decreases the nutritional value of cotton oil cattle cake. It is relatively toxic, but can be eliminated from the cattle cake by taking advantage of its thermolability.

When administered to various animal species, (±)-gossypol causes, in males,

due to the (–) isomer. In China, it has been administered to male volunteers. After two months of treatment, oligospermia is observed, as well as a high frequency of spermatozoid abnormalities. Gossypol acts by destroying the seminiferous tubules, and it is efficacious, but it has non-trivial side effects: hypokalemia, gastrointestinal distress, altered libido, and prolonged sterility. The toxic symptoms are linked mainly to the (+)-isomer, and might be diminished by decreasing the daily dose. Studies in the rat tend to demonstrate the benefits of combining with gossypol the total, anti-inflammatory, and immunosuppressive glycosides of the bark-free root of *Tripterygium wilfordii* Hook., Celastraceae.



R = H : *Polygodial*
R = OH : *Warburganal*



Gossypol

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Monoterpenes and Sesquiterpenes

Essential Oils