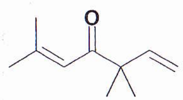
GENTIANA LUTEA L.

Irregular Monoterpenes

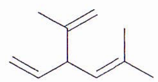
Pyrethrins

Of the "irregular" monoterpenes arising from the non-classic coupling of IPP and DMAPP (see generalities), some are found in essential oils: artemisia ketone in some Asteraceae, lavandulyl acetate in lavenders, santolinatriene, rothrockene, and more.

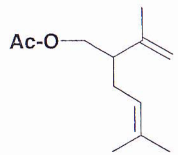
The only irregular monoterpenes truly used are the pyrethrins, which are esters of cyclopropanoic acids, have a chrysanthemane skeleton, and are isolated from an Asteraceae, pyrethrum. These compounds are insecticides, are non-toxic for humans and other mammals, and have given rise to a series of synthetic compounds, the pyrethrinoids.



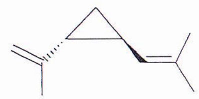
Artemisia-ketone



Santolinatriene



Lavandulyl acetate



Rothrokene

- **PYRETHRUM,**
  Tanacetum cinerariifolium (Trev.) Schultz Bip.
  = *Chrysanthemum cinerariaefolium* (Trev.) Vis., Asteraceae

The use of pyrethrums against insects goes back to antiquity: the Caucasian pyrethrum (*Chrysanthemum coccineum* Willd. and *C. marshalii* Aschers) was used against lice. Although the use of the pyrethrum of Dalmatia (also known as "insect flower") is more recent (probably from the beginning of the nineteenth century), it has inspired a lot of research: selection of productive clones, separation and identification of the active substances (1920-1960), and, since 1950, synthesis of pyrethrins and of their analogs, the pyrethrinoids (or pyrethroids). These synthetic esters are more efficacious and more stable than their natural counterparts, but they do retain their key characteristics, namely they are biodegradable and virtually innocuous for warmblooded creatures.

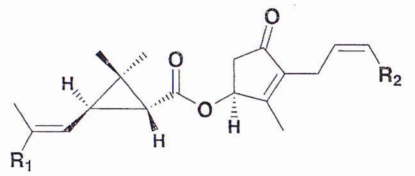
The Plant, the Drug. Pyrethrum grows in tufts, has erect stems (50-80 cm), is perennial by a rhizome, and is characterized by deeply divided leaves that are covered on both sides by a dense wooly material. The capitulums are solitary, surrounded by two to three rows of scaly and pubescent bracts, reminiscent of those of *Leucanthemum* (daisies): pistillate ligulate white ray-flowers at the periphery of a nearly flat receptacle, and multiple bisexual, tubular, yellow disk-flowers in the center.

Probably originally indigenous to Iran, and initially produced in the coastal mountains of the Balkans, where it grows wild, pyrethrum was soon cultivated, first in Japan, then in several African countries: high plateaus of Kenya and Tanzania, South America (Ecuador), and Tasmania, where highly productive clones with synchronized floration are cultivated and multiplied by *in vitro* micropropagation. Although pyrethrum production has sharply decreased in the last ten years, the demand for natural products remain substantial, particularly for household insecticidal preparations.

The drug consists of the capitulums in full bloom, because the young akenes have the highest level of pyrethrins. The capitulums can easily be distinguished from those of *Leucanthemum* by the morphology of the peripheral flowers, in that the tridentate ligule of *Tanacetum* has more prominent veins.

Chemical Composition. The weak aromatic odor of the drug is due to a small quantity of essential oil. Like many Asteraceae, the plant contains sesquiterpenoid lactones. The active constituents are monoterpenoid esters: the pyrethrins. Their concentration ranges from 0.5% in wild pyrethrums to 2% and more in selected clones. In fact, the general term pyrethrin designates a mixture of six esters (pyrethrins I and II, cinerins I and II, and jasmolins I and II) which result from the esterification of two acids and three alcohols of similar structure. The pyrethrins are clearly dominant, and represent more than two thirds of the total esters.

General formula of pyrethrins



$R_1 = CH_3$ (pyrethric acid): *series I*
$R_1 = CO_2CH_3$ (chrysanthemic acid): *series II*

$R_2 = CH\text{-}CH_2$: *Pyrethrins I and II*
$R_2 = CH_3$: *Cinerins I and II*
$R_2 = CH2CH_3$: *Jasmolins I and II*

The two constituent acids of the different esters have a key structural element: a substituted cyclopropane nucleus. In both cases, the configuration of C-1 is (*R*) and the orientation of the isobutenyl moiety is *trans* relative to the carboxyl group [C-3 is (*S*)]. In the I series, the acid is pyrethric acid, and in the II series, there is a functionalization of the isobutenyl moiety by a carbomethoxyl group: the result is chrysanthemic acid.

The alcohols or rethrolones are secondary alcohols, have in common a methyl-cyclopentenolone nucleus, and differ by the nature of their side chain: a (2'-*Z*)-2',4'-pentadienyl residue (pyrethrolone), a (2'-*Z*)-2'-pentenyl residue (cinerolone), or a (2'-*Z*)-2'-butenyl residue (jasmolone). All of these esters are oily liquids, water-insoluble, and unstable. They are mono- and diesters, and they are readily hydrolyzed. When unsaturated they are readily photoisomerized and oxidized on the isobutenyl residue of the acid, or on the mono- or di-unsaturated alcohol residue: the half-life of natural pyrethrins under daylight is estimated at no more than about ten minutes.

Biological Properties of Pyrethrins. Pyrethrins are toxic for coldblooded animals: fish, amphibians, and insects. These "contact" insecticides are characterized by a powerful knock down effect (literally, their ability to knock the insect down to the ground), but their lethal effect is less pronounced. This statement deserves to be qualified: the methyl ester of the compounds of the II series is rapidly degraded by the nervous cells of the insect, and as a consequence, the lethal effect is weak whereas the paralyzing effect is great. In contrast, the knock down effect of the esters of the I series is less pronounced, but their greater stability increases their lethal effect. Pyrethrins are also insect repellents.

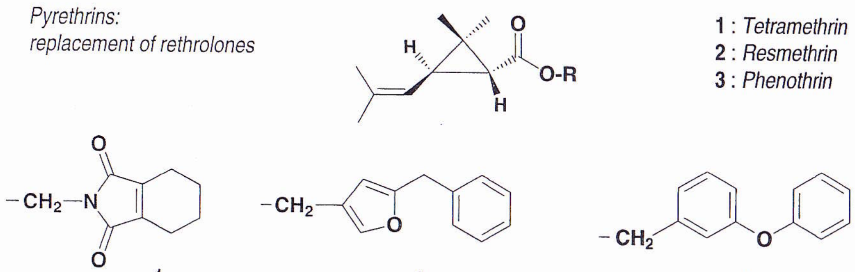
Pyrethrins are nerve poisons which act on sensory, as well as motor fibers, and cause loss of coordination, hyperactivity, and paralysis and death of the insect. Experiments on the giant axon of the cockroach shows that they keep calcium channels open, thus causing a continuous series of action potentials, and inducing an loss of excitability that may become irreversible. The instability of pyrethrins to light precludes the design of lasting insecticidal preparations, and their efficacy is limited in time. Their acute toxicity for humans and domestic animals is negligible by the oral route (DL50 around 2 g/kg), and their lability excludes the possibility of cumulative effects. The natural esters do not appear to induce resistance. To increase the activity and to delay the detoxification by the insect, it is customary to use pyrethrins in association with so-called "synergistic" molecules, such as piperonyl butoxide.

Uses. Although supercritical extraction with carbon dioxide allows the highly selective obtention of extracts enriched in active substances, the form most frequently used is a solvent extract (hexane, petroleum ether), which contains 25 to 50% pyrethrins; the capitulum powder is also used. Commercial extracts are used alone or in combination with synergists or other insecticides, after dilution in an appropriate solvent as a solution, emulsion, or aerosol. These various preparations are mostly marketed as household insecticides against flies, fleas, cockroaches, and other insects. They are also used in veterinary medicine, to protect pets against external parasites. The phytopharmaceutical use of pyrethrins is limited by their instability to light and their rapid metabolism.

SYNTHETIC PYRETHRINOIDS (PYRETHROIDS)

The efficacy and lack of toxicity of pyrethrins make them an interesting model for the synthesis of structural analogs. This field of research has proved very productive, and has resulted in the marketing of a wide range of very active synthetic products, many of which can be used in agriculture, since they are more stable to light and stable for a longer time.

The first synthetic direction is to modify the alcohol moiety. The shortening of the pentadienyl side chain of pyrethrolone leads to allethrin's eight stereoisomers, one of which, (*S*)-bioallethrin, is widely used. Other modifications are more substantial and consist of replacing the alcohol by a cyclic structure: a 5-benzyl-3-furylmethyl residue (resmethrin), a 3-phenoxybenzyl residue (phenothrin), or a tetrahydrophthalimidomethyl residue (tetramethrin). Later on, it was shown that the activity could be increased substantially by introducing a chiral center at the benzylic carbon of the alcohol; in this case, only one enantiomer is active [see the esters of the (2*S*)-2-hydroxy-2-(3-phenoxymethyl) acetonitrile (= deltamethrin) type below].



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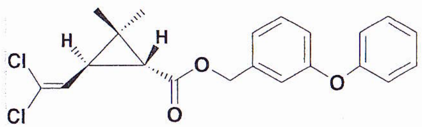
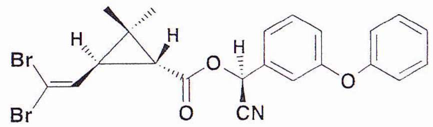
The other route to structural analogs entails modifications of the cyclopropanoic acid. Although the configuration of C-1 may not be altered (it must remain *R*), it is possible to modify the isobutenyl residue: inversion of orientation relative to the carboxyl group (*trans* instead of *cis*), replacement by a dichlorovinyl group (as in permethrin, cypermethrin), or by a dibromovinyl groups (as in deltamethrin). The geometry of the double bond (in non-symmetrical compounds) also has an influence on the activity (*E* in the case of chrysanthemic acid, but *Z* in norpyrethric diesters more recently developed). This unsaturation may actually be removed; the same comment applies to the chain itself (absent in fenpropathrin). Other series, devoid of the cyclopropane ring, have also been developed (e.g. fenvalerate).



Permethrin



Deltamethrin

The world consumption of synthetic pyrethrinoids is steadily increasing and their field of application greatly exceeds that of their natural counterparts: they are used under various forms as household insecticides against flies, cockroaches, and mosquitoes (bioallethrin), as well as for the protection of crops (against bruchus, calandra) and for crop dusting (against Colorado beetles, altica, caterpillars).

BIBLIOGRAPHY

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