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Isoprenoids as natural products with a wide variety of functions†

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ABSTRACT. The available information about certain biological properties of isoprenoid is surveyed. Their role in the regulation of the vital activity of plants and insects as well as their ecological importance, consisting in ensuring the coexistence of organisms of different classes, are demonstrated. Certain structural elements essential for the manifestation of antifeedant activity are indicated.

The bibliography includes 47 references.

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I. Introduction

The enormous strides which isoprenoid chemistry and biology have made in the recent decades necessitate a survey of the present state of our knowledge of the importance of isoprenoids as biologically active compounds. The information explosion resulting from the current vigorous research into this topic can be illustrated by two examples: (1) the Glasby Encyclopaedia of Terpenoids (edited in 1982) which still contains not less than 10 000 compounds after the exclusion of all data on natural steroids. (2) The present author's illustration by a graph of the enormous rise of the number of natural sesquiterpenoids found hitherto (Fig. 1). Fig. 1 shows the number of compounds of this single class of terpenoids, which was more than 7500 by the end of 1987, over half being sesquiterpene lactones. The curve has a consistently exponential shape. During 1970 and 1971,[1] the author attempted to summarise the data available at the time on the biological activities of (1) all isoprenoids[1] (one chapter comprising 50 pages of concentrated information) and (2) all data concerning sesquiterpenoids[2] (a 37 page chapter). However, it was already evident that we obtain information about the structures of newly described natural products much faster than data on different types of their biological activity. The latter are often combined nowadays with data on their ecological importance.

† Lecture delivered by Prof Herout at the Czechoslovak-Polish Meeting on Isoprenoids (1987), the relevant data being presented at the Zelinskii Institute of Organic Chemistry, Moscow, in 1988.

The version printed here is based largely on the English text kindly supplied by the author and partly on the Russian translation by N Ya Grigor'eva (edited by A M Moiseenkov) (Ed. of Translation).

II. Secondary isoprenoid metabolites as biologically important compounds

The question which the author put as early as 1970, namely "are secondary metabolites (in our case isoprenoids) present in plants only as waste products?", is being solved nowadays more or less unambiguously. Of course they are biosynthesised as "secondary" metabolites, but many (if not all) are essential for the life and/or survival of plants. It is now known that similar "secondary products" are not produced exclusively by the plant kingdom but are used in a wide variety of different ways also in other domains: insects and diverse marine organisms are producers of typical isoprenoids and steroids. They are not only important regulators of life functions but their presence in intracellular membranes is essential for the complex functions of living cells. This is typical, with some differences, for all classes of organisms, for example, the most primitive of the existing micro-organisms, the so called archeobacteria, have the membranes in their unicellular bodies "fixed" or "reinforced" with the aid of α,ω-bisphytanol ethers (I). The more advanced "true bacteria" contain in their membrane triterpene derivatives, for example, of the hopane type (II) (cf. Ourisson[3]). At present most advanced organisms, such as plants, fungi, and animals, make use exclusively of sterols. These are phytosterols, such as sito-, stigma-, or campe-sterols for plants and ergosterol, for example, in the case of fungi, and cholesterol (III) for animals.

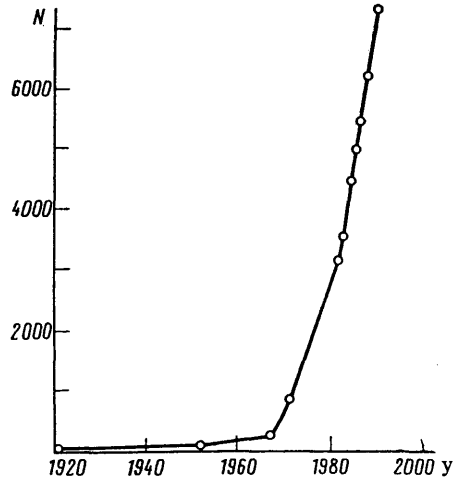
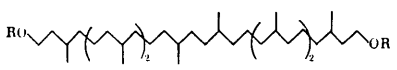
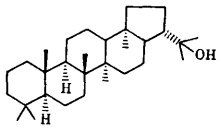


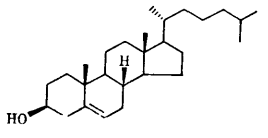
Figure 1. Growth as a function of time of the number of sesquiterpenoids (N) discovered in natural sources.



(I)

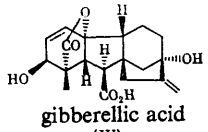


hopanol (II)



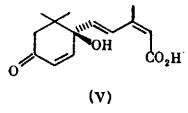
(III)

Djerassi's recent work[4] on the widely differing side chains in the sterols of marine organisms demonstrates that our knowlege of these facts remain far from perfect. The important place which hormones and vitamins as well as a number of other regulators and transferring agents occupy among secondary metabolites and which is closely related to the regulatory functions is noteworthy. Such substances have to be examined in greater detail. Certain vitamins are typical products derived from isoprenoids or steroids (A, D, E, K). Carotenoids, which are tetraterpene derivatives, have in addition important functions participating together with the chlorophylls in photosynthesis; phytol is an important component of the molecules of different chlorophylls. Steroid hormones are typical hormonal regulators in vertebrates, functioning as sexual hormones, corticoids, etc. We now have a deeper understanding of the function of ecdysteroids and juvenile hormones in the class of Arthropoda (insects, crustaceans) and probably worms (Annelida) as well. In the plant kingdom other isoprenoids function as hormones, for example, diterpenoids such as gibberellins (IV) (about 70 naturally occuring compounds of this type are known)[5] and the sesquiterpenoid abscisic acids (V) together with some of its metabolites.



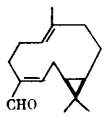
gibberellic acid

(IV)

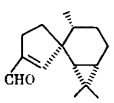


(V)

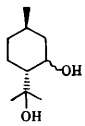
The function of the "prolongation factor" has been discovered, in addition to gibberellins, also in other compounds, especially brassinoids[6,7] during recent decades. The list of compounds of isoprenoid character able to influence the germination or growth of plants is also large. This influence, mostly in a negative sense, represents the known "allellopathic activity" of many plants in their fight against competing plants belonging to other species. Here mention will be made only of some components of liverworts discovered quite recently, for example, (–)-lepidozenal (VI) [8] and (+)-vitrenal (VII).[9] Monoterpene derivatives with the same mode of action are known in certain higher plants, such as the eucalyptus, for example *p*-menthane-3,8-diols (VIII) and (IX).[10]



(VI)



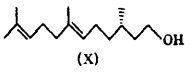
(VII)



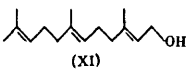
(VIII), (IX)

The important role of "secondary metabolites" in the coexistence with organisms belonging to different domains and hence their ecological importance have been traced during recent decades. In view of the manifold activity of isoprenoids, the above studies were concentrated on the latter. The activity of isoprenoids is frequently encountered in the interactions of different organisms belonging to all existing domains: Mabry and Gill[11] attempted to list the different types of activity of terpenoids in 1979 but today the list would have to be much larger. Only certain striking examples will be selected, since a detailed description would require several books. For example, the relatively recently discovered group of sesterpenoids (with 25 carbon atoms in their molecules)—not yet mentioned by Mabry and Gill—includes, according to a more recent review,[12] more than 160 compounds, mostly with functions of a defensive character. They are not restricted to plants but occur as metabolites of insects and especially of diverse marine organisms.

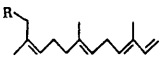
Isoprenoids do not by any means serve solely as deterrent substances. On the contrary, they frequently possess attractant properties. The scent of flowers has its value in attracting pollinators and many simple derivatives of the monoterpene series are generally known. Some of them have been adopted by insects as their own "pheromones", which is particularly interesting: a single example may be quoted: orchid (*Ophrys* sp.) pollinators are attracted from a distance to orchid flowers (and to flowers of similar, mainly tropical species) by scents of a sesquiterpene character (the name of the Swedish entomologist Kullenberg[13,14] may be mentioned in this connection), which are identical with the sexual pheromones of their females (such pollinators may be, for example, the solitary bees *Aculeate Hymenoptera*). The spectrum of the activity of simple aliphatic sesquiterpenoids is broad—for example, the dihydrofarnesol derivative terrestrol (X) [15] is a "territory marker" for the male bumble bee. Farnesol (XI) is a typical scent of certain flowers, while the basic hydrocarbon farnesene (XII) and its geometrical isomers are known "alarm"pheromones in certain Aphids.[16] Homo-derivatives of this series, for example homofarnesene (XIII) constitute[17] a "trail marker" for an ant (*Solenopsis invicta*).



(X)

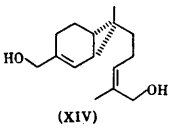


(XI)

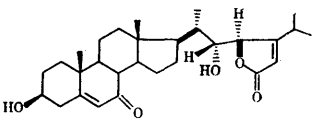


R = H (XII), R = CH_3 (XIII)

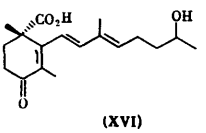
The sesquiterpenoid derivative sirenin (XIV) is known as a "sperm attractant" in the water-mould *Allomyces* sp., a fairly primitive organism on the evolutionary scale. Other examples where isoprenoids play a similar role in the sexual reproduction of fungi[18] are the steroid antheridiol (XV) and the nor-carotenoid derivative trisporic acid (XVI).



(XIV)

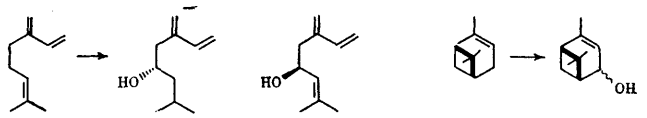


(XV)



(XVI)

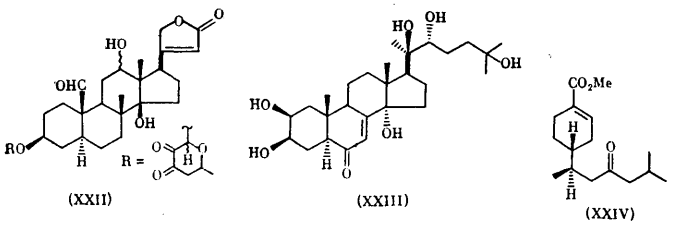
Certain compounds ingested with food and modified somewhat during their assimilation are frequently converted into derivatives with a new property, which is an entirely normal process. For example, the aggregation pheromones of certain bark beetles (*Ips* sp., *Dendroctonus*, etc.) convert some of the terpenoid derivatives in their food [for example, myrcene (XVII), α-pinene (XX)] into their own aggregation pheromone ipsenol (XVIII), ipsdienol (XIX), and/or *cis*- and *trans*-verbenols (XXI)—cf. Fergusson and Metcalf;[19] naturally, they usually contribute "another component", arising from their own biosynthetic capacity, to the mixtures of their pheromones.



(XVII) (XVIII) (XIX) (XX) (XXI)

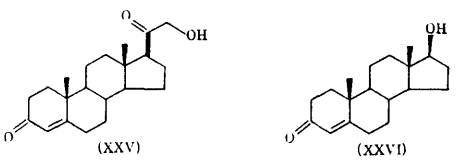
Our "human" interest is concerned at present mainly with "deterrent" activities and we are therefore much more familiar with the latter. Individual monoterpene compounds, contained in most of the essential oils of the needles or barks of conifers, play, according to their quantity or concentrations, a decisive role in determining whether these plants will or will not be resistant to the attack of herbivores. The influence of myrcene, limonene, Δ^3-carene, α- and β-pinenes, and α-phellandrene has been frequently found to be a decisive factor in the animals' choice of food. They are probably not "toxic" in the narrow sense but are unpleasant and therefore deter. This is exemplified by the fact, discovered some years ago in our laboratories, that a mixture of this kind, resembling "turpentine oil", is used by the soldiers of certain *Nasutitermes* as a deterrent against their usual natural enemies—ants.[20] In this case the terpenoids do not originate from their food but are biosynthesised in their bodies.

If we follow the activities of secondary metabolites, we can conclude that their function can often vary. The necessity to limit the active potential of any "secondary product" results in its being sequestered in some place in the body (for example, in the case of plants, in vacuoles, glandular trichomes, and resin- or milk-ducts) in such a way that it cannot disturb the vital functions of the organism producing it. It can of course be present in the form of a harmless precursor as well. By possessing such a "latent" active principle, organisms have secured a weapon against their enemies. Consider cardenolides as an example. The plants producing them are protected against many phytophages (as well as vertebrates, molluscs, and insects), since these compounds are toxic in the true sense—can be regarded as "antifeedants", since they deter most enemies. These compounds (or at least many of them), applied in appropriate doses, are used in human medicine as valuable stimulators of the heart's activity. Some insect species have discovered, during their coevolution with plants, how to "sequester" these noxious compounds in their own body, usually in the larval stage; however, cardenolides [for example, uzaridin (XXII)] are also maintained in pupae and later in adults. They thus gain a double advantage: firstly they secure a competitive advantage in being able to feed on plants with cardenolides in their tissues and, secondly, they are now toxic to their natural enemies such as lizards, birds, and others.[21] This is a rare but by no means a unique case, as we have recently discovered in a series of similar adaptations (not only for isoprenoids but also for alkaloids, cyanogens, etc.). A similar situation can be traced in other seemingly non-toxic compounds—hormones. Plants which were able to develop during their phylogeny the production of insect hormones [ecdysteroids, for example, ecdysterone (XXIII), or juvenile hormone simulators, for example, juvabione (XXI)], whose only importance according to present knowledge involves their ecological function, are protected from any insect phytophages, since the presence of their hormones in their food or in contact with their food can disturb the normal evolution of these organisms.



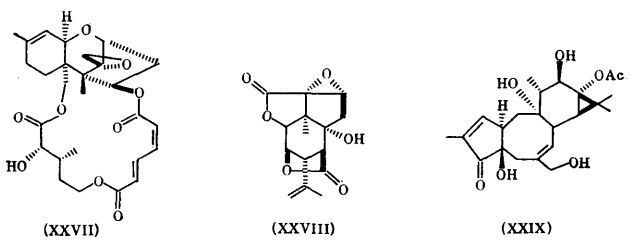
(XXII) (XXIII) (XXIV)

On the other hand, some insects produce relatively large quantities of vertebrate steroid hormones for their defense (for a series of these studies, we are indebted to Schildknecht[22]). Certain water beetles produce, for example, cortexone (XXV), testosterone (XXVI), etc. which protect them against vertebrates such as predatory frogs, fish, etc. The vertebrate hormones are probably useless against insects.



(XXV) (XXVI)

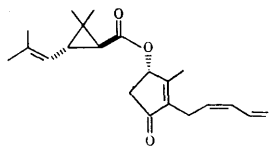
If we attempt to follow the complexity of compounds produced in nature as "secondary products", we encounter a distinct tendency—during the phylogeny of many taxa (especially in the plant kingdom), many complicated structures are biosynthesised successively and many "elaborate" molecules are also the most active. The author does not wish to develop a definition of the "toxic" principle in these terms, since very simple compounds such as HCN are toxic enough, but the isoprenoids which can be designated as "truly toxic" usually have a more complex structure. Trichothecenes are a good example[23] [see, for example, verrucarin A (XXVII)] of typically very active but very toxic antibiotics with a sesquiterpenoid moiety. Here one may include picrotoxinin (XXVIII), a compound isolated for its toxic properties, and phorbol (XXIX), a well known toxic component of plants belonging to the family *Euphorbiaceae* (cf. Evans and Taylor[24]).



(XXVII) (XXVIII) (XXIX)

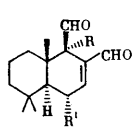
Other also relatively complex molecules, protecting their parent organisms, need not be toxic in the usual sense. We know of compounds which we simply designate as insecticidal, since they are relatively harmless to classes of organisms other than insects. It may be that they simply penetrate the special sort of chitin cuticle

which is important for arthropods. We shall mention as the only example pyrethrins (XXX) [25] with an isoprenoid component (chrysanthemic acid) in their molecules.



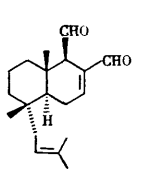
pyrethrin A (XXX)

We find that the physiological activity of secondary products is mostly not so specialised and their activity is then expressed in different ways—we speak of their bactericidal, fungistatic, and molluscicidal activities. As a result of the coevolution of plants (as the main source of food, directly or indirectly, of most other classes of organisms), their secondary metabolites represent a broad array of components with similar activities. Their phytophagous enemies have to develop sensory systems to protect themselves against feeding on noxious food. Such compounds are classified nowadays as deterrent compounds or antifeedants. These apparently include the vast majority of the known isoprenoids (naturally on the basis of the data published hitherto, although only a limited fraction of the compounds indicated have been investigated on these lines). However, certain rules concerning the structural prerequisites for "deterrents" can be derived from the limited number of examples available. The author's favourite examples are certain groups[26] which are found repeatedly in isoprenoid structures, in the first place a vicinal dialdehyde group, usually conjugated with a double bond, as in polygodial (XXXI) and in the related drimanes [warburganal (XXXII), ugadensidial (XXXIII)]. They are all very pungent to the human tongue and are deterrent to many insect herbivores. Polygodial was first encountered in *Polygonaceae* (*P. hydropiper*) and later in *Magnoliales* and independently in some liverworts (*Marchantiopsida*).

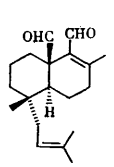


R = R' = H (XXXI)
R = OH, R' = H (XXXII)
R = R' = OH (XXXIII)

To complete the list, it also occurs in animals—molluscs (certain nudibranchs[27]). All these organisms are protected against their predators, although the latter are very different. For nudibranchs, it represents a unique weapon against fish. The same "model" is repeated in the diterpenoid series in liverworts, for example, in sacculatal (XXXIV) [28] and in perottetianal (XXXV).[29]

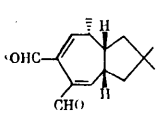


(XXXIV)

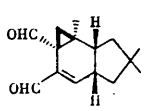


(XXXV)

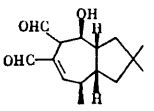
A similar pungent taste and protecting properties are known for the fruit bodies of many fungi which contain, for example, velleral (XXXVI), isovelleral (XXXVII), piperdial (XXXVIII), and merulidial (XXXIX).[30]



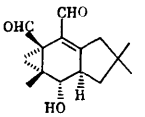
(XXXVI)



(XXXVII)

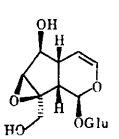


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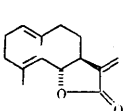


(XXXIX)

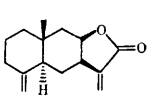
In the case of velleral, an interesting aspect of its deterrent activity was noted: in the fruit body, only a precursor (velutinol) is present. After mechanical damage to the fruit body's cells, it gives rise to the pungent velleral as a result of an enzyme reaction. Velleral, being unstable, later changes into another more stable compound. The idea of a parallel effect—the interaction with receptors on the human tongue and deterrent activity—was originally proposed by Kubo.[31] This is probably a much wider phenomenon and we believe that not only compounds giving rise to a "hot" or "pungent" perception but all bitter compounds act similarly. This concerns, for example, alkaloids, since the latter are mostly quite bitter, as well as other classes of compounds. Among isoprenoids, we know very many groups of bitter derivatives, for example, all iridoids[32] and especially their glycosides [for example, catalpol (XL)]. There is at present much evidence that they exhibit a common antifeedant activity. Furthermore, this concept agrees well with the properties of the large group of sesquiterpene lactones which have been investigated in the author's Prague laboratories for more than 40 years. In the author's research, the principal indication of their presence in a plant belonging to the family Compositae was a "sensory" one: the pungent taste indicated the presence of certain simple γ-lactones having a typical structure usually with an exocyclic methylene group and the lactone ring formed as a result of the oxidation of the methyl component of the isopropyl residue of the acyclic precursor and the subsequent ring closure at the hydroxyl in the α-position relative to this residue; typical examples are costunolide (XLI), isoalantolactone (XLII); for more information, see one of the latest reviews.[33]



(XL)



(XLI)

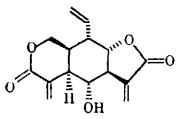


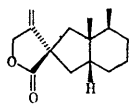
(XLII)

Compounds with a large number of oxygen-containing functional groups are usually bitter. The typical α,β-unsaturated γ-lactone group is believed to constitute the active principle, since it is capable of interacting with cysteine and of inducing cytotoxicity—a typical property in many kinds of biological activity.[34,35] This is the reason why many of these compounds were studied as possible anticancer agents. Vernolepin (XLIII) [36] was found to be the most active; its molecule contains two such lactone groups at once. More than 20 syntheses of this compound or its simplified derivatives have been described.

Dozens of the more than 3700 sesquiterpene lactones known at present have now been tested and found active in many respects (as antifeedants, not only for insects but also for mammals, bacteriostatic agents, fungicides, vermifuges, etc.). In many cases they induce human dermatitis. They are not in practical use and α-santonin is very obsolete today as a vermifuge. Nevertheless, in the plant kingdom they represent a good example of an antifeedant group which occurs repeatedly in classes which are distant on the evolutionary scale—mostly in *Compositae* (nearly 3500), *Umbeliferae* (more than 100), Magnoliales, and finally liverworts (more than 50

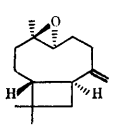
compounds). In our experiment, we demonstrated together with Dr Nawrot that the antifeeding effect for some insects **is not** necessarily combined with the α,β-unsaturation in the lactone ring [cf. the activity of bakkenolide (XLIV); cf. Harmatha and Nawrot[37]].

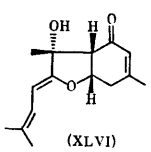

(XLIII)


(XLIV)

The antifeeding activity is not limited to lactones, since many other active sesquiterpene compounds are known. An interesting compound is caryophyllene epoxide (XLV), which has been repeatedly identified as the antifeedant for leaf-cutting ants (*Atta* sp.); because of its fungistatic properties, caryophyllene epoxide stops the growth of a special fungus which is cultivated by these ants as food.[38]

Compound (XLVI), a very potent antifeedant which is the main component of the seeds of *Angelica sylvestris*,[39] was discovered during our studies on bisabolangelone.

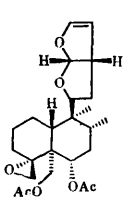

(XLV)

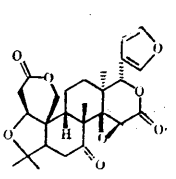

(XLVI)

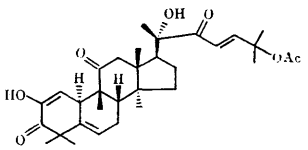
Diterpenoid derivatives are feeding deterrents as well. This concerns not only the many relatively simple diterpenic acids but especially two groups of bitter compounds—quassinoids[40] and clerodanes [as an example, see clerodin (XLVII)]. Clerodanes are the largest group of compounds tested hitherto for their antifeedant activities—more than 100 compounds (see the recent review of Van Beek and de Groot[41]).

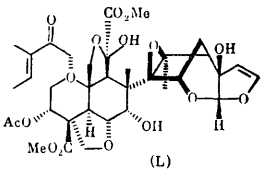
In the triterpene series, the same situation is repeated as in diterpenoids: apart from the relatively simple triterpenoids, certain groups of bitter compounds of this class are known, for example, cucurbitacins, limonoids, and/or meliacins. All their names are derived from the names of plant families [*Cucurbitaceae*; limonoids from the lemon; *Meliaceae*; for example, see limonin (XLVIII) and cucurbitacin E (XLIX)].

The most thoroughly studied compound until now, namely the tetranortriterpenoid azadirachtin, is a meliacin. It is the characteristic compound found in the neem tree (*Azadirachte indica*) and its very complex final structure (L) was established only recently by Kraus et al.[42] Three symposia and several books[43,44] have been devoted to this special antifeedant—still probably the only one in practical use in the form of alcoholic seed extracts. Rembold called it a "blessing for the developing countries", since in tropical areas it is readily available even to simple farmers.

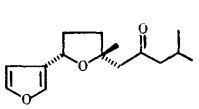

(XLVII)

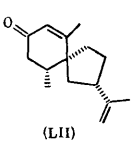

(XLVIII)


(XLIX)


(L)

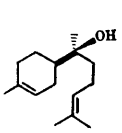
This is a brief resumé of the antifeedant history. It is incomplete since new groups with deterrent activity are being discovered, for example, saponins of triterpenoid and/or steroid origin. Whole books have been devoted to phytoalexins—compounds which are produced by plants only after they have been damanged, for example, by pathogenic fungi.[45] One fact must be emphasised as remarkable, namely plants of the family *Solanaceae*, which contain no sesquiterpenoids when in a healthy condition, produce exclusively the sesquiterpene derivatives ipomeamarone (LI) and solavetivone (LII) as phytoalexins for their protection.

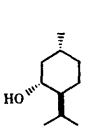

(LI)


(LII)

III. Conclusion

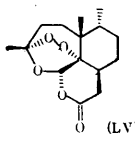
An attempt has been made to comment very briefly on the broad spectrum of the biological activities of isoprenoids known at the present time. Owing to their important functions, they are used in many branches of human activity. Their importance in medicine is well known. They serve as medicaments in the form of natural products (hormones, vitamins, etc.) or as products of organic synthesis as well. They have retained their importance in perfumery and in the cosmetic industry at the time when synthetic materials have clearly come to the fore. However, as models, natural products remain irreplaceable. We shall consider two characteristic examples as an illustration. The author's studies of the common European medicinal plant camomile in the early 1950s led to the discovery of *l*-α-bisabolol (LIII)—its most important component with anti-inflammatory properties. At the present time, tonnes of synthetic dl-α-bisabolol are being produced by the BASF company, since it is one of the five most valued components of cosmetics. (–)-Menthol (LIV), an important product of the food industry (sweets, chewing gum, and, of course, cigarettes) is also made synthetically.


(LIII)

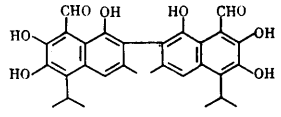

(LIV)

New compounds are being added to the contemporary medicinal preparations on the basis of recent studies on substances listed in the old "Materia Medica", i.e. traditional drugs of different nations. In China, where this is a very old tradition and recent research has been very active and fruitful, two preparations of isoprenoid origin have been discovered. Qinghaousu (LV) and its derivatives have been found[46] in *Artemisia annuua L.* They are also known as arteannuins or artemisimins. They are rare sesquiterpene lactones

with a cadinane carbon skeleton. These compounds constitute a very useful remedy against some forms of malaria—also in cases where the classical drug quinine is not successful. Furthermore, gossypol (LVI), a cadinane type of dimeric sesquiterpenoid, is now undergoing clinical experimental tests[47] as a chemosterilant for men (but not for women, since steroid derivatives are still normally employed for the latter).



(LV)



(LVI)

In agriculture and forestry novel means for the integrated fight against insect pests may be expected to be added to the hitherto most effective pyrethrin and the insecticides derived from this model substance, known as pyrethroids and constituting at the present time a major proportion of the agents used in practice. However, hitherto azadirachtin, mentioned above, is the only substance suitable for practical application; none of the others meet the rigorous criteria imposed on compounds of this kind. However, certain new (non-isoprenoid) natural products may prove to be more promising. I therefore end with a hopeful thesis: "Nature possesses much more potent means than we, humans, have been able to discover hitherto".

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