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2-ACYLCYCLOALKANE-1,3-DIONES. OCCURRENCE IN NATURE, BIOLOGICAL ACTIVITY, BIOGENESIS, CHEMICAL SYNTHESIS

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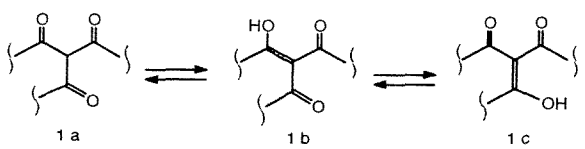
This review systematizes information on 2-acylcyclohexane-1,3-diones and 2-acylcyclopentane-1,3-diones isolated from natural sources. Questions of their biological and chemical synthesis, their natural functions, and the biological activity that they exhibit are discussed.

In one form or another,* the 2-acylcycloalkane-1,3-dione (β-triketone) fragment (**1**a-c) is present in many biologically active components of medicinal plants used in the folk medicines of various countries since the most ancient times. The history of the chemical study of natural cyclic β-triketones is therefore very closely linked with the general course of the development of organic chemistry itself. The biologically active components of the resins of the fern *Aspidium felix*, for example, were first investigated in 1826, and usnic acid was isolated from the lichens *Usnea barbata* and *Ramalina fraxinea* in 1843. An antihelminthic extract from the African plant *Hagenia abyssinica* (koso), known and used since antiquity, was subjected to its first chemical study in 1839. Investigations of the biologically active components of hops, used in brewing, were begun in 1885 [1].



1 a 1 b 1 c

Early investigations led to the isolation of various 2-acylcycloalkane-1,3-diones the structures of which were unambiguously confirmed or refined, thanks to the development of spectral methods of analysis, almost a century later — in the 1950s and 1960s of the 20th century. The chemical structures of the β-triketones proved to be extremely diverse. Widely distributed among them are 2-acylcyclopentane-1,3-diones and, in particular, 2-acylcyclohexane-1,3-diones with various alkyl, arylalkyl, and alkenyl side-chains. At the same time, the cyclic part of the molecule is frequently alkylated with one or more (up to four) methyl groups (for the cyclohexane derivatives, usually at the C_4 and C_6 atoms) and/or lower alkyls (up to C_4) with both normal and branched structures. The cycloalkane ring may bear from one to three prenyl, geranyl, or farnesyl residues. In the cyclohexane β-triketones there is very frequently an additional C_5 ketone function, which may also be present in the form of an enolic methyl ether. In many cases, the 2-acylcyclohexane-1,3-diones are constituent parts of polycyclic (polynuclear) molecules.

At the present time it has been established that cyclic β-triketones are present in various natural materials, including not only plant sources but also marine invertebrates and secretions of insect glands. In spite of the multiplicity of types of biological activity characteristic of cyclic β-triketones, and the clear inadequacy of information on their biogenesis and biotransformations *in vivo*, the protective role that these substances play in Nature may be regarded as obvious.

*All structures are shown in the form in which they are given in the original.

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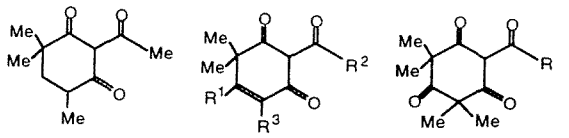
CYCLIC β-TRIKETONES FROM ESSENTIAL OILS

The compounds of the heading are found in Nature in the form of 2-acylcyclohexane-1,3-dione and 2-acylcyclopentane-1,3-dione derivatives, the latter being relatively rare. A large number of 2-acylcyclohexane-1,3-diones with simple structures have been found in the essential oils of plants of the genera *Eucalyptus, Leptospermum, Xanthostemon, Darwinia* and others from the Myrtaceae family growing in Australia and New Zealand and used in folk medicine [2]. The first of this group to be discovered were angustione (**2**) and dehydroangustione (**3a**) [3, 4], isolated from *Backhousia angustifolia*. Leptospermone (**4a**) [5-7] and its minor homolog flavesone (**4b**) [8] and also the dihydrocinnamoyl homolog grandiflorone (**4c**) [9] have been isolated from various species of the Australian tea tree, *Leptospermum*.

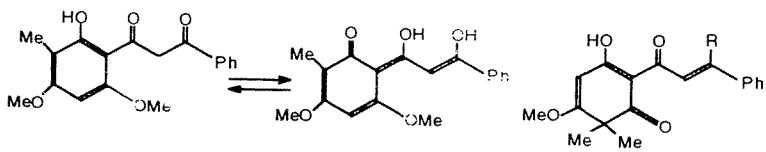


2 3 a-d 4 a-c

3 a) R^1=H, R^2=R^3=Me
b) R^1=OMe, R^2=*i*-Pr, R^3=Me
c) R^1=OMe, R^2=*i*-Pr, R^3=H
d) R^1=R^3=H, R^2=*i*-Pr

4 a) R=*i*-Bu
b) R=*i*-Pr
c) R=CH_2CH_2Ph

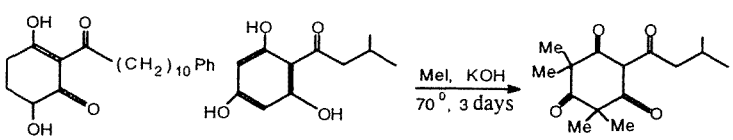
Tasmanone (**3b**) has been identified in fresh leaves of the eucalyptuses *Eucalyptus risdoni, E. linearis, E. tasmanica,* and *E. camfeldii* [10], agglomerone (**3c**) in *E. agglomerata* and *E. meckieanna* [11], and xanthostemone (**3d**) in *Xanthostemon chrysanthus* [12]. The β-hydroxychalcone (**5**) has been isolated from *Leptospermum scoparium*, which is used in the treatment of dysentery, diarrhea, and skin diseases, and, recently, in some forms of cancer; according to NMR spectroscopy, (**5**) exists in equilibrium with the tautomer (**6**), which is the methyl ether of a dienolic form of a cyclohexane β-triketone [13].



5 6 7 a-b a) R=OH, b) R=H

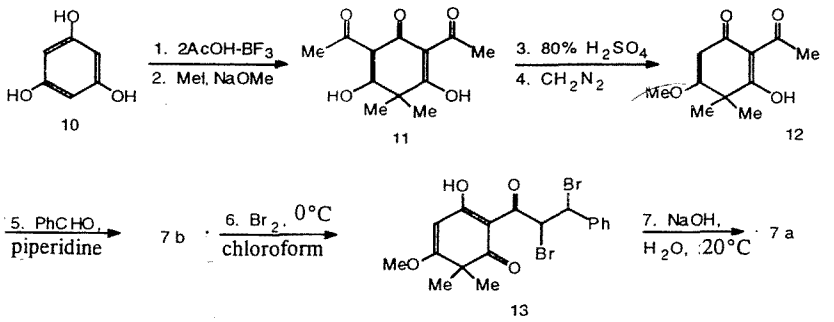
A triketone of similar structure, syzygiol (**7a**), in which the nonaromatic nature of the ring is fixed by its gem-dimethylation, has recently been isolated from the Indonesian plant *Syzygium polycephaloides* (also of the Myrtaceae family) [14]. Syzygiol (**7a**) possesses the property of inhibiting the development of skin cancer [15].

The triketone (**8**), having an extremely simple structure but bearing an unusually long arylalkyl side-chain, has been isolated from some Brazilian plant species *Virola ssp.* [16, 17]. This compound has also been isolated from *Horsfeldia glabra* [18].

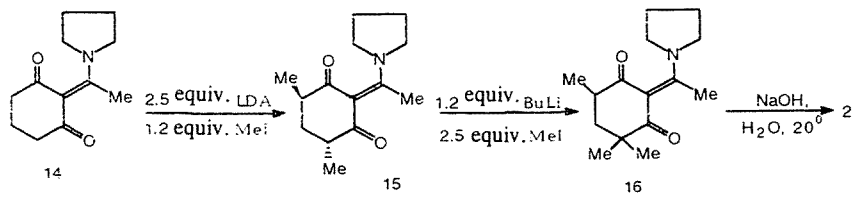


8 4a

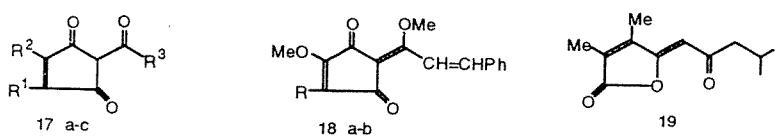
Syntheses of some of these natural compounds have been described in the literature. The synthesis of leptospermone (**4a**) by the methylation of phloroisovalerophenone (**9**) with methyl iodide in an alkaline medium has served to confirm its structure [7]. A scheme including the methylation of a 2-acylbenzene-1,3,5-triol (**11**) has likewise been used in a seven-stage synthesis of syzygiol (**7a**) [15]:



Several syntheses of the angustiones (**2**) and (**3a**) have been described [3, 19, 20]. The simplest synthesis of angustione (**2**) [20] was achieved by the successive introduction of three methyl groups into the molecule of the enaminodiketone (**14**).



The cyclopentane β-triketone calythrone (**17a**) has been found in the essential oil of the Australian plant *Calythrix tetragona* [3, 21]. In addition to calythrone, this group of extremely rare 2-acylcyclopentane-1,3-diones includes the orange pigment linderone (**17b**) isolated from the roots of the Malaysian tree *Lindera pipericarpa* [22-24] and also the yellow pigment lucidone (**17c**), isolated from a variety of *L. lucida* [23, 25]. The corresponding methyl ethers methyllinderone (**18a**) [22, 24] and methyllucidone (**18b**) [23, 25] have also been detected in these plants, which are used by the aborigines for cosmetic and medicinal purposes.



17 a-c

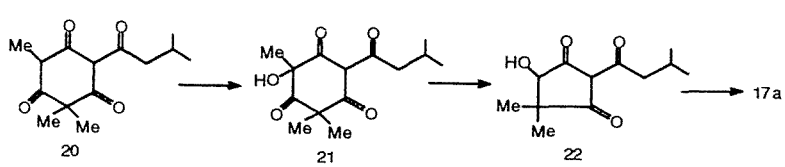
a) $R^1=R^2=Me$, $R^3=i$-Bu
b) $R^1=R^2=OMe$, $R^3=CH=CHPh$
c) $R^1=H$, $R^2=OMe$, $R^3=CH=CHPh$

18 a-b

a) R=OMe; b) R=H

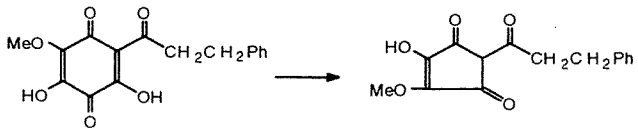
19

Calythrone (**17a**) has been synthesized in low yields by condensing acyclic ketones with dimethyl maleate [26] and also isopropylene acetate with maleic anhydride [27]. The rearrangement of the Z-butenolide (**19**) under the action of sodium methanolate in hot methanol has given good yields [23], and the ease of the rearrangement forced the authors to doubt the β-triketone structure of calythrone (**17a**) and actually to admit the possibility of the butenolide structure (**19**) for the natural compound, giving the triketone (**17a**) in the process of alkaline treatment during isolation.



20 21 22

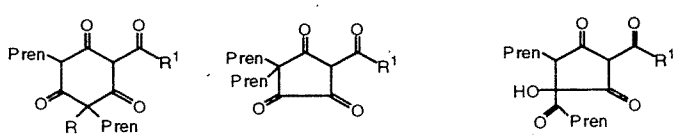
An extremely plausible scheme has been proposed for the biosynthesis of calythrone (**17a**) which includes a stage of oxidizing derivative (**20**), followed by contraction of the ring and dehydration of the gem-dimethylhydroxytriketone (**21**) [1], which correlates well with the possibility of chemical synthesis of the structurally close demethyllinderone (**24**) through contraction of the ring of the 2,6-dihydroxyquinone (**23**) under the action of aqueous alkali [24].



23 24

PRENYLATED 2-ACYLCYCLOALKANE-1,3-DIONES FORMING COMPONENTS OF HOP RESINS

Even at the dawn of the history of the use of hops (*Humulus lupulus*, Cannabinaceae) in brewing it had become clear that their value was due not only to their effect on the taste of the beer but also to their antibiotic action, thanks to which, while yeast grows freely, the development of putrefying bacteria is suppressed [1]. It has been established that the antibiotic properties of hops are connected with the so-called "soft resin" fraction in hop extracts, the main components of which are cyclic β-triketones [28]. This fraction contains hop α-acids [29] — humulone (**25**a) [30], cohumulone (**25**b) [31, 32], adhumulone (**25**c) [33]) and posthumulone (**25**d) [29], and also hop β-acids [34, 45] — lupulone (**26**a) [36], colupulone (**26**b) [36, 37], and adlupulone (**26**c) [36]. A common structural feature of these compounds is the presence in them of two (humulones (**25**)) or three (lupulones (**26**)) prenyl substituents in the ring. In addition to the β-triketones, aromatic compounds of related structure have also been isolated — for example, 4-deoxyhumulones (**27**) [38-40], these also being mixtures of homologs with respect to the acyl chain.

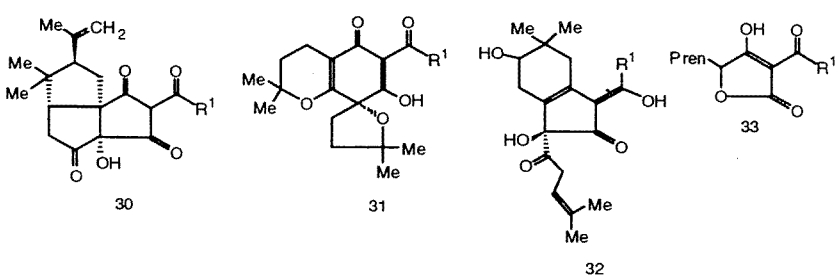


25 a-d — 27 a-d 28 a-d 29 a-d

25 R=OH
26 R=Pren
27 R=H

a) R^1=*i*-Bu, b) R^1=*i*-Pr,
c) R^1=sec-Bu, d) R^1=Et, everywhere Pren=$CH_2CH{=}CMe_2$

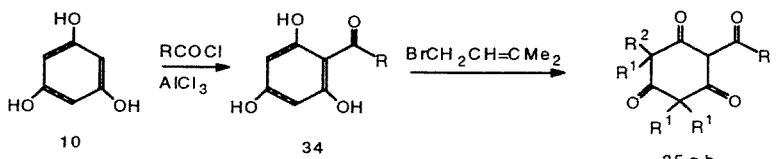
When hop and hop extracts are stored, a multiplicity of isomerization and oxidation reactions of the substances that they contain take place, the lupulones (**26**) being oxidized faster than the humulones (**25**) [41, 42]. The oxidation products of the lupulones (**26**) are the hulupones (**28**a-c), which are 5,5-gem-diprenylated 2-acylcycloalkane-1,3,4-triones and have been named, in accordance with the rules adopted in this series, hulupone (**28**a), cohulupone (**28b**), and adhulupone (**28**c) [43, 44].



30 31 32 33

The transformations of the humulones (**25**) in aqueous solutions in the air — i.e., under the conditions of brewing beer — are more complex, but, in the main, the products of these transformations retain a β-triketone nature. Thus, the humulones (**25**a-d) isomerize into the corresponding *iso*-α-humulones (**29**a-d) [29, 45]. The oxidation of the humulones forms compounds that are the products of side-chain cyclization: tricyclodehydroisohumulone (**30**) [46-49], the dihydropyrans (**31**) and (**32**) [50], and 2-acyltetronic acids (**33**) [51]. The oxidation products impart to the beer specific bitter nuances, and therefore the problem of controlling the quality of the beer is closely linked with the possibility of rapidly evaluating the

depth of the chemical transformations of the hop acids. In view of this, the main attention of researchers in this field has recently been directed to the development of chromatographic methods of analyzing mixtures of hop acids and their degradation products [52-54].



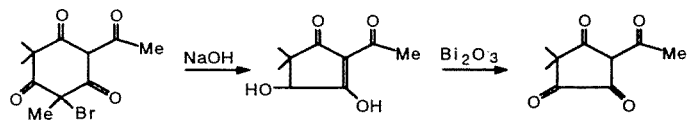
10 34 35 a,b

R^1=Pren a) R^2=H, b) R^2=R^1

The synthesis of the hop acids involves the acylation of phloroglucinol (**10**) with the appropriate acid chloride in the presence of aluminum chloride [55], followed by the prenylation of the acyl derivative (**34**) under the action of 1-bromo-3-methylbut-2-ene in the presence of sodium ethanolate [55, 36] (with a yield of the desired product (**35a**) of 10-20%) or of ion-exchange resins [40] (with a yield of 30-40%). The use of strongly basic ion-exchange resins has given the tetrasubstituted derivatives (**35b**). The lupulones (**26**) have also been obtained by the alkenylation of 2-acylcyclohexane-1,3,5-triones with alkenyl bromides in ether under the action of liquid ammonia, the yields here being 60-70% [56].

The humulones (**25**) have been synthesized by roughly the same scheme, using 2 equivalents of alkenyl bromide in the alkenylation stage and with an additional stage of hydroxylation at C_4 by the action of lead tetraacetate in methanol containing $PdCl_2$ activated by oxygen [32].

The cyclopentane hulupones (**28**) [41-44] and their gem-dimethyl analogs (**38**) have been synthesized by the oxidation of the corresponding lupulones (**26**) with oxygen in the presence of sodium sulfite, lead tetraacetate, or bismuth oxide, which, apparently, models their biogenesis [57], and also by contracting the rings of halogenated cyclohexane-1,3-diones such as (**36**) [58-60].

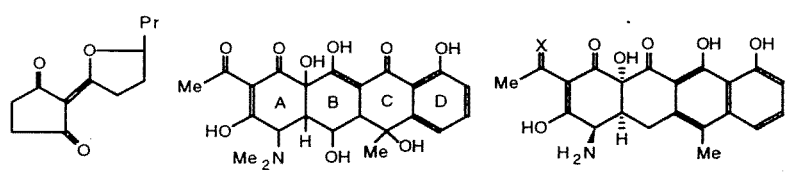


36 37 38

In addition to the above-mentioned antibiotic properties of the hop acids, we may note here an antidiabetic activity found for the humulones (**25**) and lupulones (**26**) [61] and also a fungicidal action of the humulones in relation to various *Trichophytom, Candida, Fusarium, Mucor*, and *Staphylococcus* species [62].

2-ACYLCYCLOALKANE-1,3-DIONES AS PRODUCTS OF LOWER PLANTS

Oudenone (**39**), produced by *Oudemansiella radicata* cells and possessing a hypertensive activity and an inhibiting action on tyrosine hydroxylase, may be regarded as an internal enol ether of a 2-acylcyclopentane-1,3-dione [63].



39 40 41 a-e

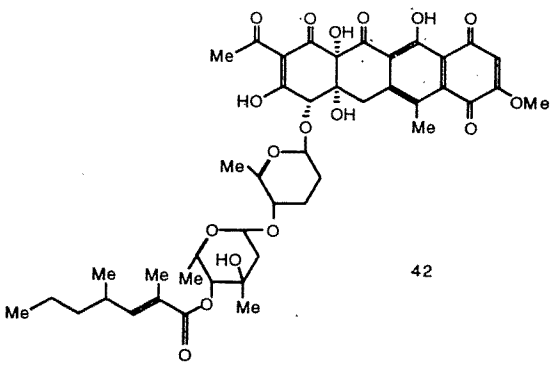
a) X=O, b) X=NC$_6$H$_4$p-SO$_2$NH$_2$, c) X=NC$_6$H$_4$p-SO$_2$NHAc

d) X=N-N(CH$_2$CH$_2$)$_2$NMe, e) X=N-N(CH$_2$CH$_2$)$_2$NCH$_2$CH$_2$OH

At the beginning of the 1960s, 2-acetyl-2-decarboxamidooxytetracycline (**40**), exhibiting from 5 to 50% of the activity of tetracycline in relation to various pathogenic microorganisms, was identified as the main component among the tetracyclic antibiotics produced by the vital activity of some *Streptomyces* species (*S. rimosus* [64, 65] and *S. psammoticus* [66]). Later, in the 1970s, the structure of the antibiotic chelocardin (**41**a), produced by *Nocardia sulphurea* from the same order of actinomycetes was established and was also found to contain a cyclohexane triketone fragment [67, 68]. Chelocardin (**41**a) differs from natural tetracyclines by a primary amino group at C-4 in place of an α-dimethylamino group, and also by the aromatic nature of ring *C*. However, in spite of this it retains an antimicrobial activity resembling that of chloramphenicol, while its 4-epimer, having the configuration of natural tetracycline, is totally inactive. The action spectrum of chelocardin (**41**a), active against Gram-negative bacteria, differs considerably from that of tetracycline, which acts on Gram-positive microorganisms [69]. A number of derivatives of chelocardin (products of its condensation with hydrazines, hydrazides, anilines) have been synthesized. In the majority of cases their activity was retained at the level of chelocardin (**41**a), and only derivatives (**41**b-e) were more active.

We may note here that the biological activity of the tetracyclines themselves is shown in an inhibition of protein synthesis, of oxidative phosphorylation, and of electron transport in bacterial and mammalian cells [68].

Recently, an anthracycline antibiotic with a 2-acylcyclohexane structural element — dutomycin (**42**) — exhibiting a high cytotoxic activity *in vitro* against leukemia P388 has been isolated from a soil *Streptomyces* [70].



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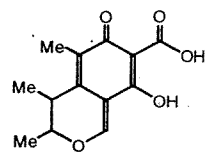
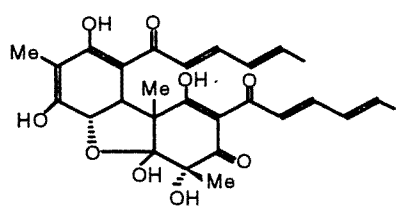


43

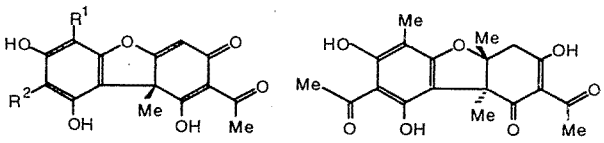
The antibiotic (−)-citrinin (**43**), the triacylmethane fragment of which includes a side-chain carboxyl and not an acyl chain as in all the substances described above, is an interesting example of a fungal metabolite produced by certain strains of the molds *Penicillium citrinum* and *Aspergilli*, and it has also been detected in the leaves of the Australian plant *Crotolaria crispata* [1, 71, 72]. It is interesting that the synthetic (+)-isomer of citrinin possesses the same activity as the natural isomer. It suppresses the activities of carboxylase, *D*-aminooxidase, and succindehydrogenase, and activates cytochrome oxidase, while at high concentrations it lowers the activity of urease. The hypothesis has been expressed that the inhibition of *Staphylococcus aureus* by citrinin is connected with its suppression of the absorption of oxygen by this microorganism [72].

Relatively recently, in 1986, the cyclohexane β-triketone bisvertinolone (**44**) was isolated from the products of the metabolism of a fungus of the order hyphomycetes, *Verticillium intertextum*, which damages the vessels of higher plants (fruit trees, Solanaceae family, cotton plant) [73].



44

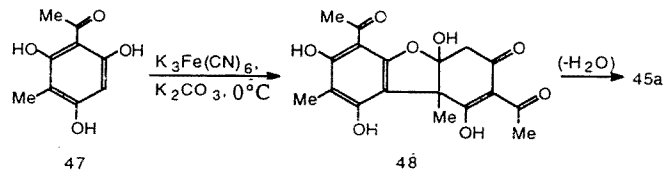
One of the best-studied natural β-triketones — usnic acid (**45**a) [74], isolated from *Usnea barbata* and *Ramalina fraxinea* as early as 1843 [71] — is an object of particular interest, thanks to its wide distribution in the lichens of 75 species [1] and its extremely high toxicity. Lichen fungi are capable of synthesizing usnic acid (**45**a) even when isolated from the algae symbiotically linked with them [75]. An isomethoxide of usnic acid, which has been called placodiolic acid (**46**), has been isolated from the lichen *Lecanora rubina* (Lecanoraceae, subspecies *Placodium*) [76].



45 a-c 46

a) R^1=Ac, R^2=Me; b) R^1=Me, R^2=Ac; c) R^1=$CONH_2$, R^2=Me

The determination of the chemical structure of usnic acid (**45**a) required considerable efforts, and structural formulas proposed for it were repeatedly rejected. Only in 1955 did Barton et al. achieve an elegant synthesis. This synthesis made use of the radical dimerization of the cresol (**47**) under the action of mild oxidizing agents [77, 78]. Its performance permitted the development of a theory according to which the oxidative duplication of simple phenol radicals is one of the stages in the biosynthesis of polycyclic phenols [72, 75, 79]. It is interesting that a scheme including a stage of the oxidation of phenol derivatives followed by doubling has also been proposed for the synthesis of bisvertinolone (**44**) [73].



47 48

The absolute configurations of usnic acid (**45**a) and placodiolic acid (**46**) and their isomers have been established by x-ray structural analysis [80, 81].

Usnic and isousnic acids (**45**a and **45**b) have recently been isolated from the lichens *Ramalina hierrensis* [82] and *Parmelia vagans* [83], while the amide of usnic acid, which possesses fungicidal activity and inhibits protein kinase C, has been detected in *Cercosporidium henningsii* [84]. Usnic acid (**45**a), itself, is a weak antibiotic. It is considered that since lichens grow very slowly, the lichen acids fulfill a protective function, preserving them from being eaten by animals and insects [85] and from attack by other fungi [75]. It is known that lichens were used for medical purposes as long ago as 2000 B.C. in ancient Egypt, especially in the treatment of tuberculosis and diarrhea, for disinfection, and for accelerating the healing of wounds. An obstacle to the medical use of usnic acid (**45**a) was its exhibition of lipophilic properties in spite of the large number of oxygen atoms in its molecule: it is practically insoluble in water and lower alcohols, while being soluble in chloroform and, slightly, in benzene. It has been possible to overcome these properties, resulting from strong hydrogen bonds [86], by converting the acid into a salt. The drugs binan, which is sodium usnate [85], and usno, which is benzyldimethyl-(2-[2-p-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl)ammonium usnate [75], possess the nature of salts. These drugs are active against Gram-positive bacteria (*Bacillus subtilis, Sarcinia lutea, Staphylococcus ssp.*, and others) [87]. They are used for treating fresh and suppurating wounds, burns, trophic and varicose ulcers, acute suppurative inflammatory processes of the soft tissues, dermatoses, and pyoderma, and in the fight against tuberculosis, tetanus, and diphtheria, and also in gynecology for treating erosions of the neck of the uterus and mastitises. In this connection it has been established that usnic acid possesses a bacteriostatic, rather than a bactericidal, effect; i.e., it inhibits the multiplication of the microorganisms and changes the general course of the biophysical processes in them, but the bacterial flora does not disappear and continues to exist up to the end of complete epithelialization.

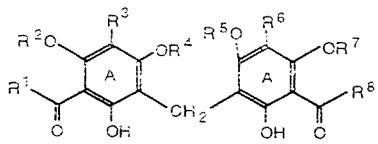
We may note that usnic acid (**45**a) is found in Nature equally frequently in the dextro- and the levororatory forms and sometimes in the form of the racemate, all three forms possessing approximately the same biological activity. The majority of structural changes in the usnic acid (**45**a) molecule, with the exception of acetylation of the phenolic hydroxyl at C-6, lead to its almost complete inactivation [71].

The mechanism of the action of usnic acid (**45**a) has not been definitively elucidated; however, it is considered that it suppresses some enzyme systems such as the oxidative phosphorylation of citrate, succinate, fumarate, and pyruvate [75] and suppresses depolymerization processes in the synthesis of RNA [72]. It is assumed that it acts in some way on the system of terminal electron transfer, blocking the transformation of energy in terminal respiration and uncoupling the process of oxidative phosphorylation [87].

COMPONENTS OF FERNS — FILICINS

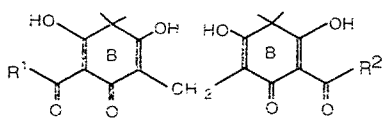
Antihelminthic preparations from the fern *Aspidium felix mas* have been known since the time of Theophrastus and they have retained their therapeutic value up to the present, since they are components of many pharmaceutical preparations [1, 88, 89]. The chemical composition of ferns of the class Pterophyta or Filicinae is diverse. They contain higher aliphatic (C_{19}-C_{33}) alkanes, alcohols, ketones, fatty acids, sugars, glycosides, aromatic compounds, etc. [90].

The most uniform and best-studied group of compounds isolated from ferns is the polymethylated acylphloroglucinols (**49-56**). These derivatives, united under the name filicins, are found only in ferns of the family Aspidaceae (subfamilies Dryopterioideae and Tectarioideae) [91]. The majority of Dryopteris and Arachinoides species contain filicins consisting structurally of residues of acylphloroglucinols (rings of type *A*) and of acylfilicinic acid (rings of type *B*). Sometimes 6-alkyl-2H-pyran-2,4(3H)-dione rings (type *C*) are found. All the rings in various combinations are linked with one another through methylene bridges. Two aromatic residues *A* are present in the molecule of phloraspin (**49**a) [92] and in those of pseudoaspidin (**49**b) [90], and margaspidin (**49**c) [93-95].



49 a-c

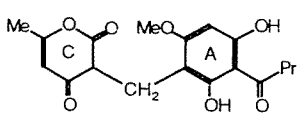
R^1,R^6=C_1-C_3 unbranched alkyls
a) R^2=R^4=R^6=R^7=H, R^3=R^5=Me
b) R^2=R^3=R^6=R^7=Me, R^4=R^5=H
c) R^2=R^4=R^7=H, R^3=R^5=R^6=Me



50 a,b

a) R^1,R^2=C_1-C_3 unbranched alkyls
b) R^1=R^2=*i*-Pr

The structural skeleton of albaspidin (**50**) is composed of two cyclohexadienone rings of type *B* [96, 97]. Phloraspiron (**51**) [98] and phloropyron (**52**) [99] combine in their molecules residues of pyrandione rings *C* with rings of types *A* and *B*, respectively. The combination of rings *A* and *B* is widespread in filicin structures. Such are the molecules of aspidin (**53**a) [97, 100], paraaspidin (**53**b) [100], desaspidin (**53**c) [101], orthodeaspidin (**53**d) [90], flavaspidiic acid (**53**e) [96, 102] and norflavaspidic acid (**53**f) [95]. Only structures (**50**, **52**, and **53**) can formally be assigned to the cyclohexane β-triketones proper. However, it is not difficult to see the relationship of rings *A* and *B* since the phloroglucinol residue *A* may, with a certain degree of approximation be considered as an enolic form of the cyclohexane ring *B* in which aromaticity is fixed by the O-methylation of an enolic hydroxyl. The inverse statement that the cyclohexane ring *B* is a product of the destruction of the aromatic ring *A* as the result of gem-dimethylation is equally permissible.



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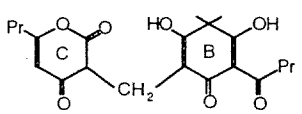

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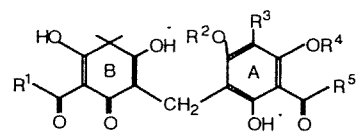
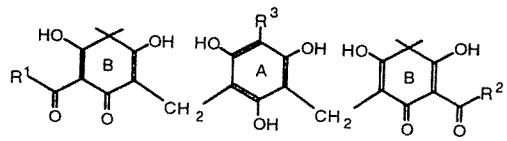


53 a-f

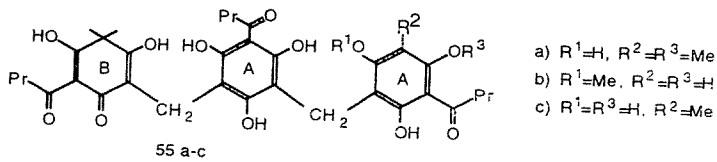
R^1,R^5=C_1-C_3 inorg. acid
a) R^2=H, R^3=R^4=Me
b) R^2=R^3=Me; R^4=H
c) R^2=Me, R^3=R^4=H
d) R^2=R^3=H, R^4=Me
e) R^2=R^4=H, R^3=Me
f) R^2=R^3=R^4=H

Rings *A* and *B* can be linked in threes, as, for example, in filixic acid (**54**) (*B*−*A*−*B* type) [103, 104], trisaspidin (**55**a), trisdesaspidin (**55**b), and trisflavaspidiic acid (**55**c) (*B*−*A*−*A* type) [104], and even in fours — in methylene-bis-norflavaspidic acid (**56**a) [105] and dryocrassin (**56**b) [106] (*B*−*A*−*A*−*B* type).

The use of mild methods of isolation excluding alkaline treatment of the plant extracts has permitted the identification of tetra-, penta-, and hexaalbaspidin and tetra- and hexaflavaspidic acids, which are extremely unstable and undergo degradation in the course of isolation when severe methods of alkaline treatment are used [107]. With the development of the

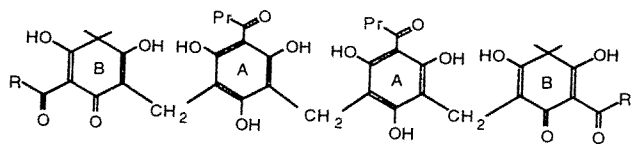


54



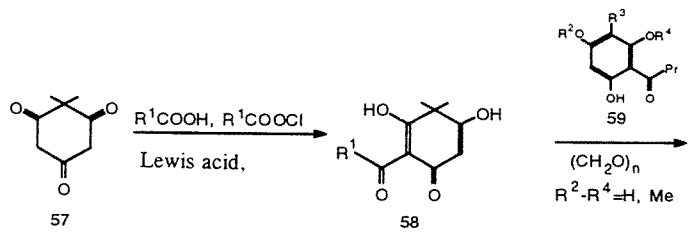
55 a-c

a) R^1=H, R^2=R^3=Me
b) R^1=Me, R^2=R^3=H
c) R^1=R^3=H, R^2=Me

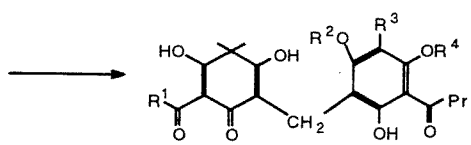


56 a,b a) R=Pr; b) R=Me

technique of chromatographic separation it has been established that albaspidin (**50**) and desaspidin (**53**c) [108], and flavaspidic (**53**e) [108, 109, 110] and filixic (**54**) [103, 109, 110] acids are not chemically homogeneous but consist of mixtures of homologs at the acyl groups, while in all cases the aromatic ring bears a butyryl substituent and the cyclohexane ring — together with the butyryl group of the main components — may also have propionyl and acetyl groups.



57 58 59



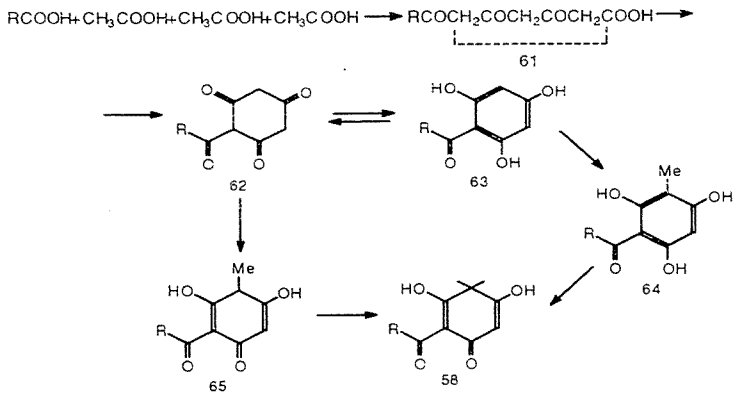
60

The structures of the polycyclic filicins have been confirmed by their synthesis. The synthesis of filicins of type (**60**) has been achieved through the acylation [111] of filicinic acid (**57**) [112, 113] followed by the condensation of the acylfilicinic acid (**58**) with butyrylphloroglucinol (**59**) and formaldehyde in the presence of sulfuric acid [96], piperidine [114], or alkali [97]. The acylfilicinic acid (**58**) may also be obtained by the iodomethylation of phloroacetophenone [115] (see also the synthesis of leptospermone (**4**a)). Analogous condensations have been used for the synthesis of tri- [103, 104] and tetranuclear [105] alkylphloroglucinols (**54-56**).

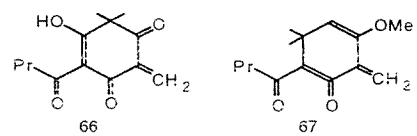
The results of biotrials of individual components of ferns are extremely ambiguous, but the most active antihelminthics must apparently be considered to be aspidin (**53**a) and flavaspidic acid (**53**e) the molecules of which include 2-acylcyclohexane fragments [90]. Synthetic substances of type (**60**) have been patented as antihelminthics [88, 89]. However, the filicins do not exhibit only antihelminthic activity. Acylfilicinic acid derivatives (**58**) and various aspidinols (**59**) are rodent repellants [116] and are also used for impregnating wood with the aim of protecting it from rot caused by bacteria and fungi [117]. An antiinflammatory action of these substances in experiments on mice infected with *Staphylococcus aureus* has also been reported [118].

Regardless of the number of rings in filicin derivatives, they all reveal an obvious structural unity, which may be connected with their biogenetic relationship. There are no direct proofs of this, but some interesting hypotheses have been expressed on the mechanism of the biosynthesis of 2-acylcyclohexane-1,3-diones [1] and the related 2-acylphloroglucinols [90, 108]. They are all based on Birch's postulate presuming the biosynthesis of phenolic compounds through the addition of

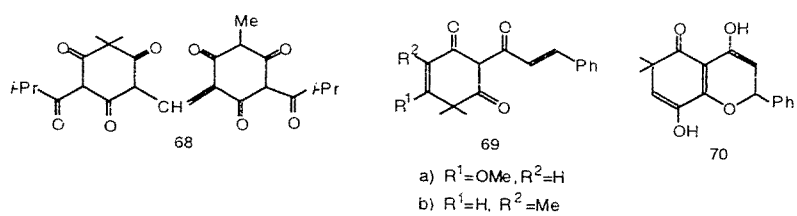
acetate residues in the "head to tail" manner, followed by the cyclization, probably in the form of esters of coenzyme *A* [90], of a polyketide intermediate (**61**) with the formation of a 2-acylcyclohexane-1,3,5-trione (**62**). The tautomeric transformation of (**62**) into the phloroglucinol (**63**) takes place so readily that it is difficult to state whether a structure of the type of an acylfilicinic acid (**58**) arises on the subsequent dimethylation of the phenol ring of (**63**) or on the methylation of (**62**).



However, the fact that methylation of the monomeric residues precedes their oxidative doubling has been unambiguously confirmed by *in vivo* experiments using ^{14}C-labeled methylmethionine [120]. It is considered that quinone methide intermediates (**66**, **67**) are first formed and are then condensed under the action of a peroxidase. Such condensation of (**66**) and (**67**) has been demonstrated *in vitro* using horseradish peroxidase [121].

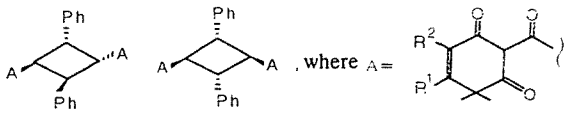


In the 1960s it was considered that monocyclic products of the type of aspidinol (**59**) are not present in the actual plants but are products of the degradation taking place during extraction with alkaline reagents [94, 98]. At the same time, because of the high tendency to tautomeric transformations of groups of the (**62**) ⇄ (**63**) type even within a given polycyclic compound, the hypothesis has been expressed that polynuclear products of the type of aspidin (**53**a) [107] and flavaspidic acid (**53**e) [90] may also be artefacts. In any case, aspidin (**53**a) has never been isolated from fresh plants but only after their storage for 2-3 months, and for flavaspidic acid — together with structure (**53**e) — structure (**68**), combining two cyclohexane fragments, has been proposed [3]. However, at the end of the 1970s and beginning of the 1980s, the structures of polynuclear filicins containing up to six rings in the molecule were confirmed by ^{13}C NMR spectroscopy [122, 123] and mass spectrometry [124].



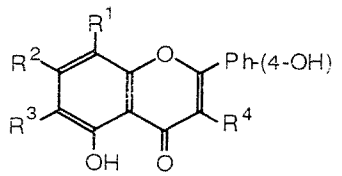
Ferns of other species have reliably yielded mononuclear cyclohexane β-triketones capable of being photodimerized to structures differing fundamentally from the filicins. Thus, the wax coating of the Californian "golden back" fern *Pityrogramma triangularis* (known formerly as *Ceropteris triangularis*), cultivated for decorative purposes, has yielded the yellow pigment ceroptene (**69**a) having the structure of a cyclohexane β-triketone with a cinnamoyl side-chain [125, 126]. At the same time, isoceroptene was identified in trace amounts [119, 127, 128], and this was first ascribed structure (**70**) [129]. Later, it was established that isoceroptene is a photodimer of ceroptene (**71**), formed from the latter under the action of sunlight or UV radiation [130], and consists of two isomers, which have been called α-diceroptene (**71**a) and ε-diceroptene

(71b). Substituted cyclobutane structures (**71**) were ascribed to these dimers on the basis of the methods of x-ray structural analysis [131, 132]. An analogous compound ohobanin (**69**b) and its centrosymmetrical photodimer (**71**a) has been isolated from the fern *Oreopteris quelpaertensis* [133].



The ceroptene coating of the "ceraceous" ferns has been ascribed the role of protectant in the initial stages of growth, since young shoots are almost completely coated with the pigment, while in mature plants it is found only on the dorsal (under) surface of the leaves [125].

As well as ceroptene (**69**a), numerous flavonoids of the type of (**72**) [133, 134], showing an extremely close structural relationship with the triketones under consideration have been identified among the components of the waxy coating of ferns. A biosynthetic relationship of flavonoids of type (**72**) with acylphloroglucinols and acylcyclohexanetriones is also quite probable [135].



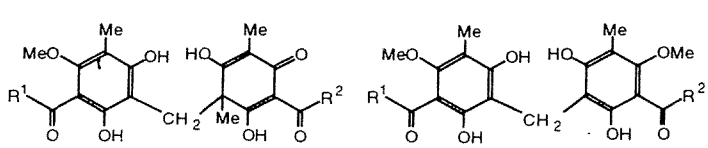
72

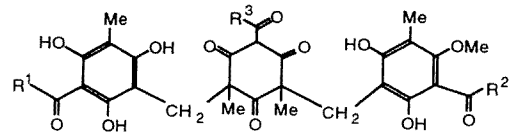
R^1=OH, OMe, Me.
R^2-R^4=H, OH, OMe, Me

SUBSTANCES STRUCTURALLY RELATED TO THE FILICINS FROM OTHER PLANTS

Preparations from male flowers of the so-called "koso" (or kusso, kusso, kausso, etc.) tree *Hagenia abyssinica* (Rosaceae) growing in the mountains of Ethiopia and East Africa — have long been known and used as antihelminthic agents in Africa and the Near East and currently appear in the European pharmacopeia [1]. It has been shown that extracts from koso leaves contain acylphloroglucinol derivatives (**73-75**) analogous to the filicins and differing from them practically only in the branching nature of the acyl side-chains [136-139]. Like the filicins, kosotoxin (**73**), kosin (**74**) [28, 138], and protokosin (**75**) [138, 139] are mixtures of homologs [140].

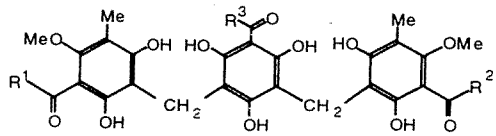
The antihelminthic agent agrimophol has been isolated from the Chinese plant *Agrimonia pilosa*, belonging to the same family, Rosaceae. On the basis of spectral [141] and x-ray structural [142] studies and also of its synthesis [143] from aspidinol (**59**), methylated isovalerophenone (**9**), and formaldehyde, it has been ascribed the structure of one of the homologs of kosotoxin (**73**, R^1 = Pr, R^2 = sec-Bu). This compound has been tested by Chinese workers as a component of an active antitumoral composition [144]. In its natural source, agrimophol is accompanied by trinuclear resorcinols called agrimols (**76**) [145, 146].





R^1-R^3=*i*-Pr, *i*-Bu, sec-Bu

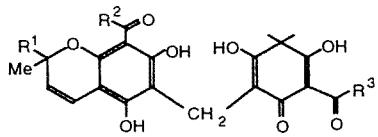
75



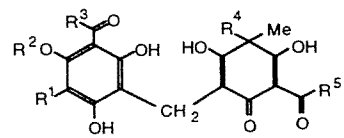
R^1=Me, Pr, *i*-Pr
R^2=Pr, *i*-Pr, sec-Bu
R^3=Pr, *i*-Pr

76

Filicin-like compounds that have acquired the names of japonicins A (**53**b), B (**77**a), C(**78**a), and D (**54**, R^1–R^3 = *i*-Pr)have been identified among the antimalarial components of *Hypericum japonicum* of the Hypericaceae family (synonym *Sarotra japonica*) [147]. From the same plant, widely used by Chinese folk medicine for the treatment of various bacterial diseases, infectious hepatitides, gastro-intestinal disorders, and tumors, has been isolated the antibiotic sarothralin, to which, on the basis of spectral and crystallographic results, the same structure as japonicin C (**78**a) has been assigned [148].



77 a-d



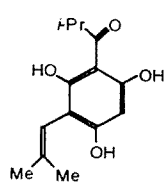
78 a-g

a) R^1=CH_2CH_2CH=CMe_2, R^2=R^3=*i*-Pr
b) R^1=Me, R^2=R^3=Et
c) R^1=R^2=Me, R^3=Et
d) R^1=R^2=R^3Me

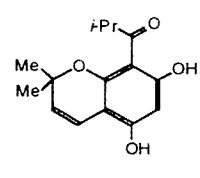
a) R^1=H, R^2=*i*-C_5H_{11}, R^3=Ph, R^4=Me, R^5=*i*-Pr
b) R^1=R^4=Me, R^2=H, R^3=R^5=*i*-Pr
c) R^1=R^4=Me, R^2=H, R^3=*i*-Pr, R^5=sec-Bu
d) R^1=R^4=Me, R^2=H, R^3=R^5=sec-Bu
e) R^1=CH_2CH=$CMeCH_2CH_2CH$=CMe_2, R^2=H, R^3=R^5=*i*-Pr, R^4=Me
f) R^1=R^4=Pren, R^2=H, R^3=R^5=Me
g) R^1=Pren, R^2=H, R^3=R^5=*i*-Pr, R^4=Me

Later, the antibiotics saroaspidins A (**78**b), B (**78**c), and C (**78**d) [149] were isolated from this plant, and so was sarotralin G (**78**e) [150], bearing in the phloroglucinol ring an alkadienyl (geranyl) substituent unusual for this group of substances.

Drummondins A (**77**b), B (**77**c), and C (**77**d), analogous in structure to japonicin B, and drummondin F (**78**f), all possessing antimicrobial and cytotoxic properties, have been isolated from the variety *Hypericum drummondii*. Two homologs of aspidin (**53**) have also been isolated [151, 152].

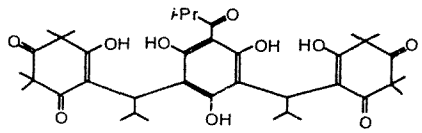


79



80

As early as the 1960s, from extracts of the so-called "rabbit plant" *Hypericum uliginosum*, which is used in Mexico for the treatment of diarrhea, were isolated the antibiotics uliginoside A, the structure of which coincides with that ascribed to japonicin B (**77**a), and uliginoside B (**78**g) [153, 154]. Their structures have been confirmed by synthesis, which used methods analogous to those for the synthesis of albaspidin (**50**) [155, 156]. Uliginoside A (**77**a) was synthesized by the condensation of 2-methylbut-2-enyl bromide with isobutyrylphloroglucinol (**9**), giving 54% of derivative (**79**), which takes part in so-called rottlerone exchange with the isobutyryl homolog of albaspidin (**50**), to form 50% of (**77**a) [155]. For the synthesis of uglinoside B (**78**g), intermediate (**79**) was first subjected to cyclodehydrogenation to the corresponding chromene (**80**) [156].



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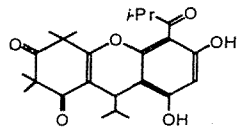
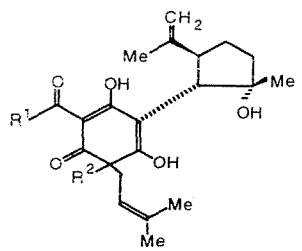


82

Compounds consisting of residues of acylated phloroglucinol and syncarpic acid linked through an isobutyl bridge have been isolated from the shrubby plant *Myrtus communis*, which is widely distributed in the Mediterranean area [157]. Although these compounds, called myrtucommulones A (**81**) and B (**82**) and possessing an antibacterial activity against Gram-positive bacteria similar to that of the filicins, have no pure β-triketone fragment in their molecule it is possible to see in their structures a quite definite affinity with the filicins. The authors concerned [157] also put forward the hypothesis that the biosynthesis of (**81**) and (**82**) follows the route suggested for the fern acylphloroglucinols [75]. However, the absence of an acyl substituent in the cyclohexane fragments of (**81**) and (**82**) and the presence of a gem-dimethyl grouping in its place enables ideas on the biosynthesis of the filicins to be corrected and forces us to assume that an acyl group is not an obligatory substituent in the molecule of the polyketide (**61**) before its cyclization but can be introduced through the acylation of an already cyclized molecule of the type of (**62**) or (**63**) after its methylation — which proves to be impossible for the myrtucommulones where the exhaustive C-methylation of the ring takes place before such acetylation.

OTHER CYCLIC B-TRIKETONES FROM HIGHER PLANTS

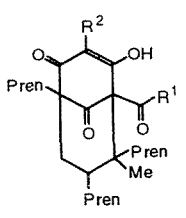
Extracts of plants from the above-mentioned family Hypericaceae have given a broad spectrum of cyclohexane β-triketones. A Chinese variety, *Hypericum chinese*, has yielded two chinesins (**83**a) and (**83**b) which, in addition to antimicrobial activity, have also exhibited a cytostatic effect in *in vitro* tests with HeLa cells [158].



83 a-f

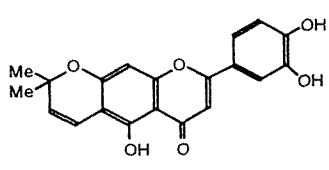
a) R^1=sec-Bu, R^2=Me
b) R^1=*i*-Pr, R^2=Me
c) R^1=*i*-Bu, R^2=Me
d) R^1=*i*-Pr, R^2=Pren
e) R^1=*i*-Bu, R^2=Pren
f) R^1=Ph, R^2=Pren

On the basis of spectral and x-ray structural results, an analogous structure has been ascribed to components of the European St. John's wort *H. calycinum*, hypercalins (**83**c-f), which have shown an inhibiting action close in magnitude to the action of 5-fluorouracil on the growth of Co-115 human carcinoma cells [159, 160]. The antibiotic hyperforin, consisting of a quadruple isoprenylated tetraketone (**84**a), has been isolated from common St. John's wort [161-163]. Like many of the compounds considered above, hyperforin (**84**) exists as a mixture of homologs: recently, a minor higher homolog of hyperforin at the acyl chain (**84**b) called adhyperforin by analogy with the humulones, has been detected in this variety of St. John's wort [164]. A triply isoprenylated analog of hyperforin (**84**c), isolated from the African variety *H. revolutum*, and the above-mentioned *H. calycinum* have proved to be cytotoxic [165].

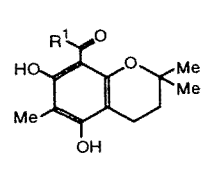


84 a-c

a) R^1=*i*-Pr, R^2=Pren, b) R^1=sec-Bu, R^2=Pren, c) R^1=*i*-Pr, R^2=H



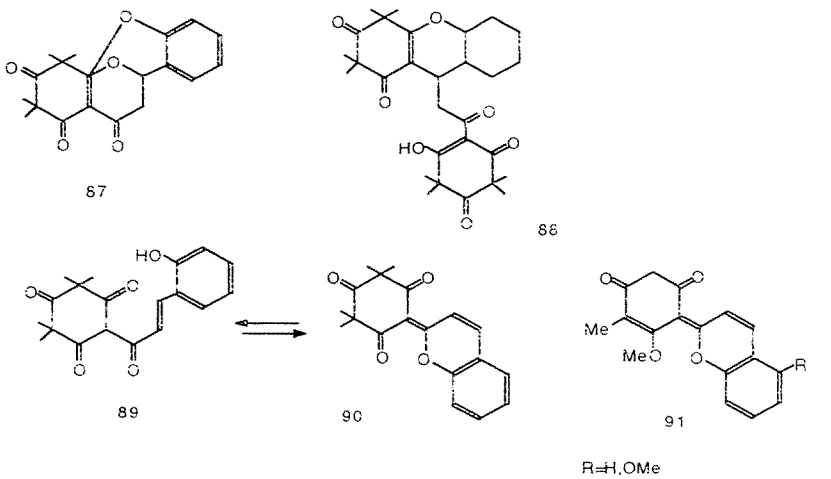
85



86

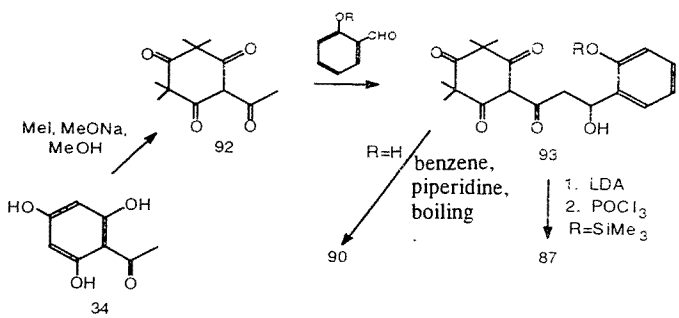
R^1=*i*-Pr, sec-Bu

The above-mentioned cyclohexane derivatives in extracts from various *Hypericum* species are accompanied by aromatic compounds of the type of the flavonol (**85**) [166] and fungicidal chromenyl ketones (**86**) [167] biogenetically related to them.

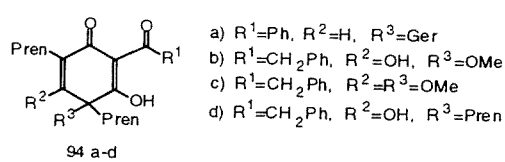


An analogous pattern of chemical composition, combining cyclohexane β-triketones as the main components with flavonoids, coumarins, and chalcones close in structure [168, 169] can be observed in extracts of the edible fruit of the African plant *Uvaria afzelii* (Annonaceae), which have revealed the presence of the triketones vafzelin (**87**), uvafzelin (**88**) [170], and the interconverting 2-hydroxy-7,8-dehydrograndiflorone (**89**) and emorydone (**90**), the latter compound being called syncarpin by other authors [171] and representing an intramolecular enol ether of a cyclohexanone β-triketone system. Also extremely close in structure to emorydone (**90**) are the dalrubones, dienol ethers isolated from the legumes *Dalea ssp* (Leguminosae) [172].

The synthesis of varfzelin (**87**) and syncarpin (**90**) [171] has been achieved, starting from 2-acetylsyncarpic acid (**92**), obtained by the exhaustive C-methylation of phloroacetophenone (**34**) [173].

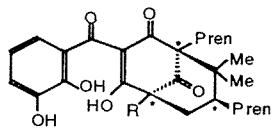


Various 2-acylcyclohexane-1,3-diones have been isolated from the fruit of some *Garcinia* species (family Guttiferae or Clusiaceae, order Theaceae). The polyisoprenylated β-triketone kolanone (**94**a), possessing antimicrobial activity, has been detected in the fruit of *G. kola* [174].



Derivatives similar in structure to hyperforin (**84**) have been isolated from *G. xanthochymus* [175, 176]. On the basis of spectral and x-ray structural results, they have been ascribed the structures of (+)-xanthochymol (**95**a) [177, 178] and (+)-isoxanthochymol (**96**a) [178]. Extracts of *G. hombroniana* contain bronianone (**95**b) [178], and extracts of *G. cambogia* con-

tain camboginol (**95**c) and cambogin (**96**b) [179, 180]. Garcinol, isolated from *G. indica*, has the same structure as camboginol (**95**c), while isogarcinol (**97**) is an isomer of isoxanthochymol (**96**a) [180, 181].

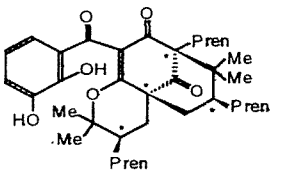


95 a-c

a) R=$CH_2CH(CMe{=}CH_2)CH_2CH_2CMe{=}CH_2$

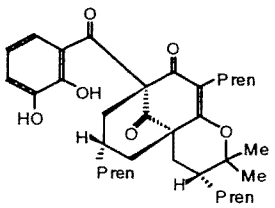
b) R=$(CH_2CH{=}CMeCH_2)_2CH_2CH{=}CMe_2$

c) R as in a), opposite orientation of the bonds at *

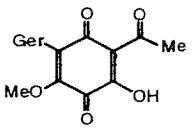


96a,

96b - opposite orientation of the bonds at *



97



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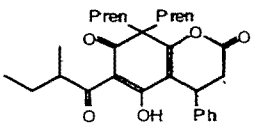
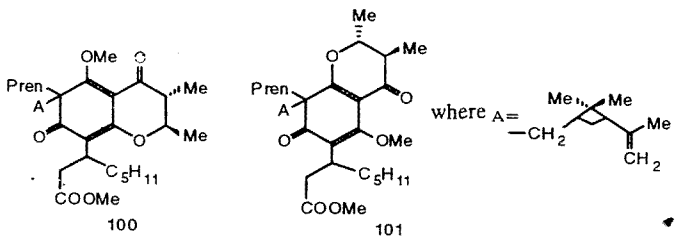


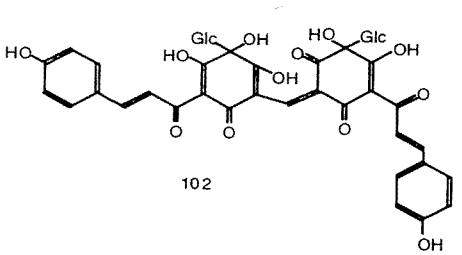
99

Prenylated triketones (**94**b-d) having structures close to kolanone (**94**a) [182] and also the geranyl-substituted polyketone (**98**) [183] have been identified in South African species of the everlasting genus *Helichrysum ssp.*

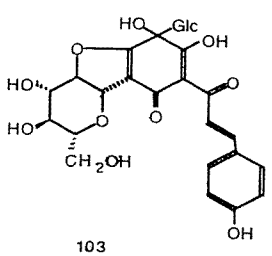


100 101

Calofloride (**99**) and methyl esters of caloverticillic acids (**100**) and (**101**), all with molluskicidal properties, have been isolated from *Calophyllum verticillatum* (family Clusiaceae) growing in Madagascar; in the latter two compounds, the cyclohexane part of the molecule bears cyclobutane and ester substituents, unusual in this series, and the β-tricarbonyl system itself is concealed by double enolization of the carbonyl groups, fixed by the formation of internal and methyl ethers [184].



102



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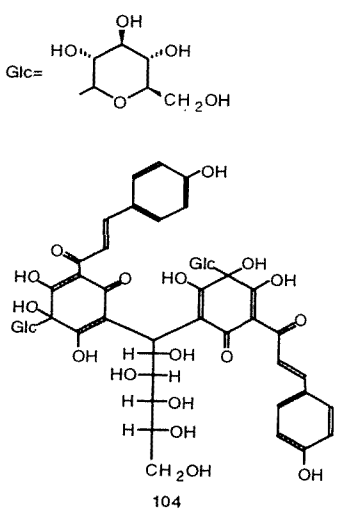
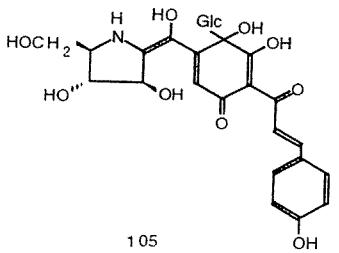


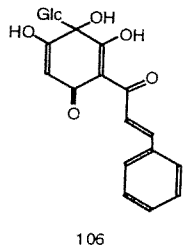
104

An acetone extract of the dry leaves of the herbaceous plant safflower (*Carthamus tinctorius*, Compositae), used in Chinese medicine for the treatment of gynecological and cardiac diseases, and also as a sedative and antiinflammatory agent,

has yielded pigments with extremely complicated structures: carthamin (**102**), safflor yellow A (**103**) [185], safflor yellow B (**104**) [186], tinctormine I (**105**), and safflor-metabolin (**106**) [187]. They are all C-glycosides of cyclohexane β-triketones, carthamin (**102**) and safflower yellow B (**104**) being symmetrically substituted dimers. Extracts containing carthamin (**102**) are used in cosmetics as harmless pigments for preparing eye shadows [188-190], while tinctormin (**105**) has proved to be a Ca^{2+} ion antagonist [187]. It has recently been shown that on anaerobic incubation with human intestinal bacteria, including *Peptostreptococcus anaerobius*, safflower yellow B (**104**) is transformed into carthamin (**102**), hydroxysafflower yellow A, and safflower-metabolin (**106**) [191].



105



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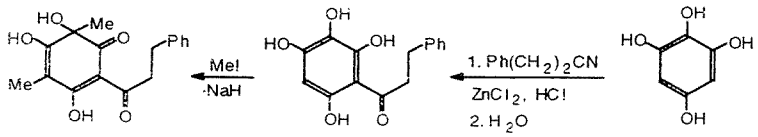
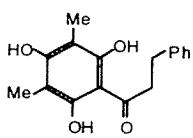


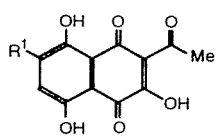
107

108

The β-triketone (**107**), which has been given the name of ceratiolin, has been isolated from an aqueous extract of fresh leaves of the plant *Ceratiola ericoides* (Empetraceae), endemic for Florida [192]. Ceratiolin (**107**) has been synthesized by the methylation of the tetrahydroxychalcone (**108**) which, in its turn, was obtained from benzene-1,2,3,5-tetrol by the Hoesch reaction [193]. Ceratiolin (**107**) exhibits an allopathic (growth-suppressing) action on other plants [192, 193]. It is assumed that, biogenetically, it is an oxidized derivative of the dihydrochalcone (**109**) [192]. This hypothesis is well supported by the fact that ceratiolin (**107**) is readily formed on the oxidation of the dihydrochalcone (**109**) by atmospheric oxygen [193].



109



110 a,b

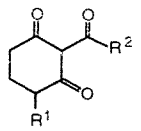
a) R^1=H; b) R^1=OH

In the mid-1960s about 30 pigments were isolated from the spines and tests of the Hawaian echinoderms *Echinothrix diadema* and *E. calamaris*; these have been called spinochromes, and among them it has been possible to isolate compounds (**110**a and b) having a cyclohexane β-triketone fragment in their structures [194, 195]. This was the first report of cyclic β-triacylmethanes from other than plant sources.

2-ACYLCYCLOHEXANE-1,3-DIONES AS COMPONENTS OF INSECT SECRETIONS

In 1978, 2-acylcyclohexane-1,3-diones (**111**a, b) were first identified as the main components of secretions of the mandibular glands of larvae of the Mediterranean flour moth *Euphestia kuchniella* (order Lepidoptera) [196]. Later, cyclohexane β-triketones (**113-120**a, b) [197-199] containing long (C_{14}-C_{18}) unbranched mono- and diunsaturated 2-acyl substituents were detected in secretions of the larvae of this species. Cyclohexane β-triketones with saturated side-chains and

having no 4-hydroxy groups (**111-113**a) have been detected in other pyralid species, *Cadra cautella* and *Plodia interpunctella* [200]. It has been shown that these triketones possess pheromonal properties, acting on the egg-laying behavior of butterflies and on the distribution of pyralid larvae [201-203], and also exhibit kairomonal activity, attracting their parasites — the wasps *Ventura* (*Nemeretis*) *canescens* [197, 203] and *Bracon hebetor* (Hymenoptera: Braconidae) [204] — and, thus, are natural regulators of the population densities of the above-mentioned Lepidoptera species.



111-126

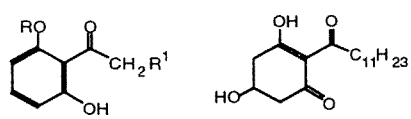
a) R^1=H

b) R^1=OH

	R^2	
111	$(CH_2)_7(Z)CH=CH(CH_2)_7CH_3$	[196,199]
112	$(CH_2)_8(E)CH=CH(CH_2)_4CH_3$	[197]
113	$(CH_2)_{10}(Z)CH=CH(E)CH=CHCH_3$	[197-199]
114	$(CH_2)_9(Z)CH=CH(CH_2)_3CH_3$	[199]
115	$(CH_2)_7(Z)CH=CH(CH_2)_5CH_3$	[199]
116	$(CH_2)_5(Z)CH=CH(CH_2)_7CH_3$	[199]
117	$(CH_2)_{12}(E)CH=CHCH_3$	[199]
118	$(CH_2)_7(Z)CH=CHCH_2(Z)CH=CHC_5H_{11}$	[199]
119	$(CH_2)_5(E)CH=CH(Z)CH=CH(CH_2)_7CH_3$	[199]
120	$(CH_2)_5(Z)CH=CH(Z)CH=CH(CH_2)_7CH_3$	[199]
121	$(CH_2)_{14}CH_3$	[200]
122	$(CH_2)_{16}CH_3$	[200]
123	$(CH_2)_{18}CH_3$	[200]
124	$(CH_2)_{10}CH_3$	[200]
125	$(CH_2)_{12}CH_3$	[200]
126	$(CH_2)_8(E)CH=CH(CH_2)_2CH_3$	[205]

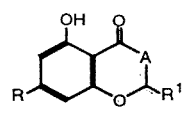
Like other kairomones, the 2-acylcyclohexane-1,3-diones are active at the nanogram level, i.e., in far higher concentrations than the sex pheromones. The highest activity in relation to the wasp *Ventura canescens* is possessed by the 4-hydroxy derivatives [199, 206]. The low volatility of the 2-acylcyclohexane-1,3-diones resulting from their high polarity and relatively large molecular mass leads to their "recognition" both by the host insects and by their parasites at fairly short distances, which ensures fine biological control of the numbers of insects. Since the "responsiveness" of the parasites to the presence of 2-acylcyclohexane-1,3-diones does not decrease and does not reach saturation with a rise in the concentration of the triketones [206], this property may have great applied value for the fight against pyralid crop pests.

The triketones (**121**a), (**124**a), (**125**a), and (**126**b) are the main components of the setal exudates of various species of lace bugs *Stephanitis ssp.* and *Corythucha ssp.* (Heteroptera or Hemiptera: Tingidae) [205, 207]. 2-Acylresorcinols with saturated and unsaturated side-chains (**127-136**) extremely close in structure to the β-triketones considered have been found in the larval secretions of *S. rhodendri, S. pyrioides,* and *S. takeyai* [207-209]. The ready dehydration of the 5-hydroxylated derivative (**137**) detected in *S. takeyai* to the corresponding aromatic compound (**136**) permits the assumption of a biogenetic relationship between the 2-acylcyclohexane-1,3-diones and the 2-acylresorcinols [207]. The triketones (**121**) and (**124-126**) and the chromones (**138, 139**) and chromanones (**140**), which are products of the intramolecular cyclization of the triketones, are also, apparently, linked biogenetically with one another [207-209]. The chromones (**138, 139**) and chromanones (**140**) are the first representatives of this class of substances to have been isolated from insects.



127-136

137



138-140

127 R=R^1=H

128 R=H, R^1=COC_9H_{19}

129 R=CH_2Ph, R^1=H

130 R=CH_2Ph, R^1=COC_9H_{19}

131 R=H, R^1=COC_7H_{15}

132 R=H, R^1=$COC_{11}H_{23}$

133 R=H, R^1=$COC_{13}H_{27}$

134 R=H, R^1=$COC_{15}H_{31}$

135 R=H, R^1=$CH(OH)C_9H_{19}$

136 R=H, R^1=$C_{11}H_{23}$

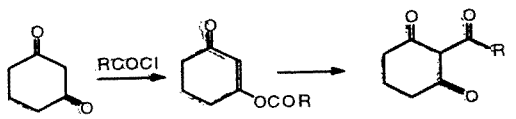
R^1= H or C_9H_{19}-$C_{15}H_{31}$ alkyl

138 R=H, A - double bond

139 R=OH, A - double bond

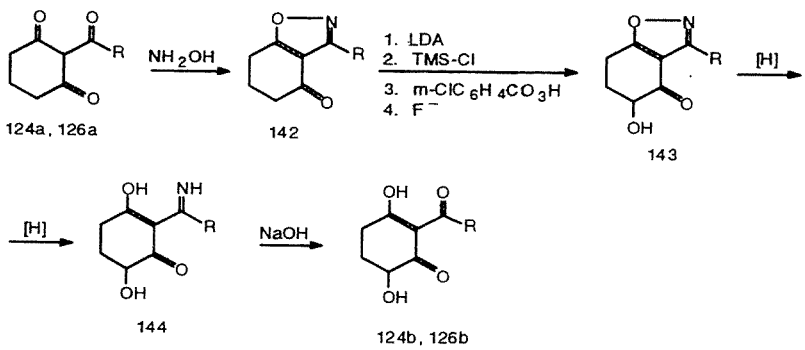
140 R=H, A - single bond

The synthesis of β-triketones of the type of (**111-126**a) is relatively simple and includes the reaction of cyclohexane-1,3-dione with the appropriate acid chlorides, followed by the O−C isomerization of the resulting enolic ester (**141**) to the desired triketone by boiling in toluene with a 4-dialkylaminopyridine [203].



141 111a, 113a, 118a

In the synthesis of the 4-hydroxylated 2-acylcyclohexane-1,3-diones (**124**b, **126**b) [210], the key stage is the conversion of the readily accessible corresponding triketones (**124**a, **126**a) into dihydrobenzoxazolone derivatives (**142**). This procedure binds two of the three oxygen atoms of the triketone, preventing competitive enolization and thereby ensuring regioselectivity on hydroxylation to derivatives (**143**), which are then reduced by catalytic hydrogenation or reduction with $NaBH_4/NiCl_2$ in dimethylformamide to the iminoenols (**144**). Alkaline hydrolysis of the iminoenols leads to the desired β-triketones (**124**b, **126**b).



124a, 126a 142 143 144 124b, 126b

The same principle of the isoxazole protection of the β-triketone system during hydroxylation has been used in the synthesis of the triketones (**111**), (**118**) and (**121**) [211] and (**137**) [212].

At the present time the biological properties of exudates of *Stephanitis ssp.* have not been well studied; only a strong inhibition of PGH synthetase by the aromatic derivatives (**127**) and (**138**) has been detected [213], and there is a report [205, 213] of the presumed protective function of the triketones that, as shown above, is also characteristic for cyclic β-triketones of plant origin.

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