ALANTO- AND ISOALANTOLACTONES

I. A. Milman

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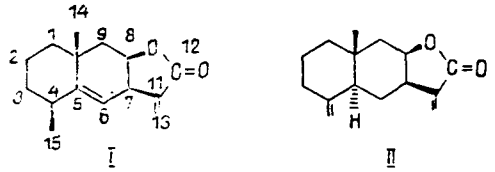
Literature information (up to 1989) on two typical representatives of the eudesmane series of sesquiterpene lactones – alanto- and isoalantolactones – has been generalized for the first time. Questions of their occurrence in nature, their ecological role, isolation, and synthesis, and also their chemical and biological properties, are considered. The possibility has been shown of passing by a series of successive chemical transformations to other natural sesquiterpene lactones with the same or a different type of skeleton.

OCCURRENCE IN NATURE, ISOLATION, CHEMICAL PROPERTIES

Alantolactone (I) and isoalantolactone (II) are typical representatives of the sesquiterpene lactones found in a number of plants of the family Compositae.



I II

A mixture containing both lactones and called helenin (or inula camphor) has long been known. In antiquity, elecampane (Inula helenium), which contains (I) and (II), was added to food as a seasoning, and in the Middle Ages it began to be used for medical purposes. At the present time, this mixture serves as the active principle of the antiulcer drug Alanton. The use of (I) and (II) will be considered in more detail below. Table 1 gives the species of plants in which (I) or (II) has been detected.

The composition of I. helenium has been studied in most detail. Together with (I) and (II), from elecampane collected from various geographical sites have been isolated unbelliferone and scopoletin (from the epigeal part) [33], dammaradienol acetate [34], and a number of lactones of the eudesmane type [35]. Elecampane is a rich source of the polysaccharide insulin (containing about 45% of it).

The USSR has a good raw materials base for the isolation of (I) and (II). Thus, every year without damage to the brushwood in the Trans-Ili Ala-Tau (Tien Shan mountains) it is possible to collect 18-20 tons of useful root mass of I. helenium and about 60 tons of I. grandis [36]. The largest amount of (I) and (II) is found in the budding phase, then it falls up to the period of flowering and almost disappears in the fruit-bearing phase. It has been shown that the quantitative composition of elecampane roots cultivated under the conditions of southern Kazakhstan is basically identical with the composition of the wild-growing material. However, in the cultivated species a larger amount of lactones and the absence of the microelements Sr and Ni have been observed.

The study of the seasonal dynamics of the accumulation of a mixture of sesquiterpene lactones by I. grandis of the Kirghizia flora has shown that the amount of essential oil depends on the phase of development, the organ, and the age of the plant [10]. Thus, up to the flowering period in the hypogeal parts the amount of lactones falls to one half, while in the epigeal part it doubles as compared with the sprouting period.

Cultivated roots of I. racemosa (India) contain a larger amount of essential oil than the European species I. helenium [17]. The petroleum ether extraction of the roots of I. racemosa grown in the Lahaul Valley in the northwestern Himalyas gives 8.5% of essential oil

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TABLE 1. Species of Plants in Which Alanto- and Isocalantolactones Have Been Found

Plant species	Lactone	Literature
Ambrosia camphorata (Greene) Payne	II	1,2
Aucklandia lappa Decne=Saussurea costus (Falc.) Lipsch.	II	3
Cronquistianthus, bishopii K. et R.	II	4
Eupatorium quadrangulatae DC	II	5, 6
Flourensia macrophylla Blake	I	7
Geigeria aspera Harvey	I	8
G. brevifolia Harvey	I	8
Hypochoeris cretensis Benth. et Hock. f.	II	9
Inula grandis Schrenk.	I, II	10, 11
I. helenium L.	I, II	12—14, 141
I. magnifica Lipsky	I, II	15
I. obtusifolia A. Kerner	I, II	16
I. racemosa Hook. f.	I, II	17—19, 142
I. royleana DC.	I, II	14, 20
I. salicina L.	I, II	14
Liatris cylindracea Michx.	II	21
Ratibida columnifera (Nutt.) Woot. et Standl.	II	22
Rudbeckia laciniata L.	I, II	23, 24
Saussurea lappa C. B. Clarke	I, II	25
Serratula latifolia	I	143
Silphium perfoliatum L.	II	26
Smallanthus reparius	II	27
Spilanthes leiocarpa DC.	I	28
Telekia speciosa (Schreb.) Baumg.	II	29—31
Xanthium canadense Mill.	II	32

containing 83% of lactones. Compounds (I) and (II) in a ratio of 40:60 predominate in the mixture.

The question arises of the importance of the sesquiterpene lactones and, in particular, (I) and (II), which are secondary metabolites and have no obvious functions in the basic metabolic processes, play an important role in protecting the plants from phytophagous pests. It has been shown that (I) [37-39], (II), and ent-isoalantolactone [38] are antifeedants for the three granary pests studied – the confused flour beetle Tribolium confusum, the larvae of the khapra beetle Trogoderma granarium, and the grain weevil Sitophilus granarius.

In a study of the influence of helenin on the tundra redback vole Clethrionomys rutilus it was found that this substance also acts as a deterrent to feeding [40]. If there was a choice between normal food and that treated with the preparation, the animals rejected the food containing at least 0.05% of helenin. However, if food with only different amounts of helenin was offered, the rate of feeding and, correspondingly, the body weight of the voles fell sharply at concentrations of the additive of 1.5% and above. Voles that received food with higher levels of helenin (3-7%) died after 3-5 days.

An investigation performed on the phytophagous ant Atta cephalotes showed the presence of some repellent properties in (I) and (II) isolated from E. quadrangulatae [5]. However, the greatest repellent action was possessed by an isomer of alantolactone with the C4-C5 position of the double bond.

The action of six sesquiterpene lactones, including (I) and (II) on the growth and development of the mosquito Aedes atropalpus has been studied [41]. Among the lactone investigated, (I) and (II) showed a pronounced toxicity in relation A. atropalpus.

Examples of the influence of (I) and (II) on the growth and development of plants has been described. Thus, in a concentration of 15-20 mg/liter, (I) and (II) produce an increase in the number of rootlets of Phaseolus aureus by a factor of 2-2.5 as compared with a control experiment [42-44]. A considerable enhancement of the effect was achieved on the use of modified lactones; for example, on the introduction of the OH group in the C-5 position with the formation of 5-hydroxyisoalantolactone (for 4-fold increase in the initiation of root formation at a concentration of 5 mg/liter) [45] and also when a trisubstituted double bond conjugated with the lactone carbonyl was present (an approximately 8-fold increase at a concentration of 15 mg/liter) [42].

Allelopathic properties are also characteristic of isoalantolactone [46, 144-146]. The action of (II) on the germination and growth of two species of weeds, Amaranthus retro-

flexus and Chenopodium strictum has been studied. A number of hypotheses has been put forward relative to the herbicidal effect observed. The acting principle is apparently the dissolved form of (II), while insoluble (II) supplements the required lactone, maintaining a constant concentration of it. An important role is also played by the lipophilicity of (II). But the majority of herbicides have log $P_{octanol/water}$ = 1-3 (log P for (II) is 3.42 [41]). More hydrophilic compounds cannot penetrate through the cell membrane, while excessively lipophilic compounds are incorporated into the membrane and do not pass into the other parts of the plant. It was concluded that the use of (I) and (II) as pesticides is potentially possible [144].

There have been a number of studies on the influence of (I) and (II) on the respiration of plants [47-52].

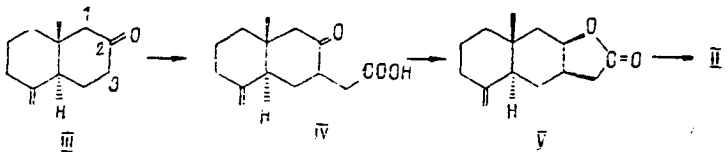
Thus, the, as yet few, examples given above show an important ecological role of (I) and (II).

Lactones (I) and (II) are usually isolated from plant raw material by extraction with various organic solvents – 85% ethanol [53], acetone [12, 54], chloroform [1, 2, 11, 15, 22], benzene [35], or petroleum ether [19, 20]. It has been proposed to use ultrasound as a supplementary measure in the treatment of the roots with an extractant [62]. As a rule, in these cases a mixture containing both compounds (I) and (II) is obtained which, to give the individual substances, are separated in some way or other. Compounds (I) and (II) are isomers with respect to the position of the double bond, and this governs approaches to the separation of the mixture. TLC and column chromatography on Al_2O_3 [10-12], on silica gel [1, 15, 20, 22], and on silica gel previously treated with 15% $AgNO_3$ [55] are widely used. Methods have been described for separating a mixture of (I) and (II) through the formation of intermediate compounds differing more widely in their properties and correspondingly easier to separate than the initial lactones. For example, use is made of the addition of dimethylamine [56], morpholine [18], and an amino-polymer [57-60] to the α-methylene group of the lactone ring. The products of the addition of morpholine to (I) and (II) are readily separated on the basis of their solubilities in ethanol. After separation, the regeneration of the initial lactone includes quaternization (the formation of a salt with MeI) followed by hydrolysis with a 5% solution of $NaHCO_3$ [61].

The possibility has been shown of the selective isolation of (I) by treating the residue after the evaporation of an acetone extract with a mixture of benzene and petroleum ether taken in definite proportions [54].

Together with isolation from plant raw material, the possibility has been studied of the chemical synthesis of (I) and (II), but this route to their production usually leads to the the formation of a racemate.

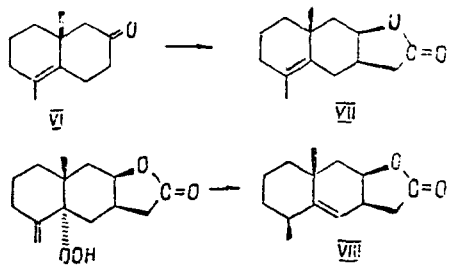
The key compound in the total synthesis of (II) is trans-9-methyl-5-methylene-2-decalone (III), the synthesis of which has been described in a number of publications [63-66]. The main stages of the conversion of (III) in (II) are shown in Scheme 1.



Scheme 1

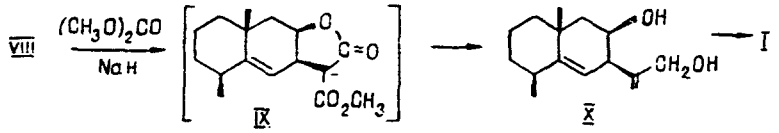
The introduction of an acetyl fragment into the C-3 position by the use of an ester of bromoacetic acid presupposes preliminary activation, which can be effected in various ways – for example, by the formation of an enamine [67, 68]. A more general method of alkylation includes preliminary methoxycarbonylation – with sodium hydride in dimethyl carbonate [69]. In this case, compound (IV) is obtained in better yield. After the reduction of the keto group ($NaBH_4$ in methanol [67, 68]; potassium Selectride in tetrahydrofuran [69]), the cis-lactone (V) is formed. The last stage is the introduction of an α-methylene group into the lactone ring. Methods of obtaining α-methylene-γ-lactones have been generalized in a review [70].

The main stages of the synthesis of (I) from 4, 10-dimethyl-4-octal-8-one (VI) are shown in Scheme 2 [71, 72]



Scheme 2

Possible routes for the synthesis of (VI) have been described [73, 72]. The production of lactone (VII) is carried out by analogy with the synthesis of lactone (V). Lactone (VIII) is obtained from (VII) by successive stereoselective photooxidation, the conversion of the resulting hydroperoxide into an alcohol, and the subsequent splitting out of water.



Scheme 3

Scheme 3 demonstrates one of the possibilities of introducing an α-methylene group into the lactone ring. This route includes the intermediate formation of the enolate (IX), the reduction of this with $LiAlH_4$, and the subsequent oxidation of the diol (X) with activated MnO_2 in benzene.

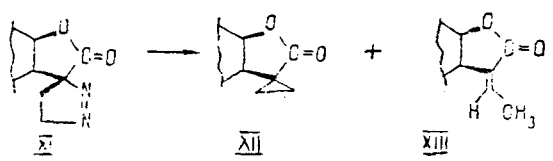
The possibility has been shown of converting (II) into (V) [74] and (VII) [75]. The aim of such conversions is the use of the compounds obtained for the synthesis of (I) and (II) labeled at C-13.

Although the first studies on the chemistry of the elecampane lactones appeared more than a century ago, their definitive structure was established with the use of the NMR method only in the middle of 60s [76]. In earlier studies, having historical value, the question was discussed of the position of linkage of the decalin system with the lactone ring, and also the position of the double bond [77, 78].

There are generalizing publications on the IR [79] and NMR [80] spectroscopy of a number of sesquiterpene lactones, including (I) and (II). The CD spectra of (I) and (II) have been discussed. An x-ray study of (I) has been made [81]. Methods have been described for the qualitative and quantitative analysis of (I) and (II) in various materials: polarography [82], titration of the mixture [83], TLC [84, 85, 10, 13], GLC [72, 86, 87, 147], and HPLC [88]. A paper has appeared on the study by TLC of the products of the addition of various amines to the C11-C13 bond in (I) and (II) [89].

The chemical transformations of lactones (I) and (II) that have been described can be subdivided into reactions at the α-methylene group of the lactone ring and those in the decalin part of the molecule (isomerization, hydroxylation, epoxidation).

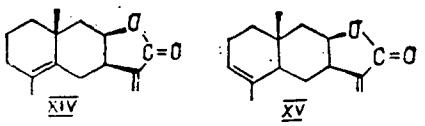
The high reactivity of the conjugated methylene group in the lactone moiety has been responsible for the ease of addition at the C11-C13 bond of various nucleophilic reagents such as ammonia, methylamine, methanol [19], various secondary amine [89, 90], and a number of amino acids [91]. A characteristic reaction of sesquiterpene lactones with an α-methylene group in the lactone ring is the addition of diazomethane, with the formation of a pyrazoline derivative (XII). The pyrolysis of the latter forms a mixture of the spirocyclopropyl derivative (XII) and a lactone with a methyl group at C13 (XIII) (the Z-isomer is formed) [42]. In the presence of diethylamine, Z,E-isomerization with the formation of a mixture of the two isomers is possible.



The α-methylene group in lactone (II) is capable of participating as the dienophilic component in the Diels–Alder reaction [92]. α-Phellandene has been used as the dienic component. The reaction was performed by autoclaving a mixture in molten biphenyl at 190°C for 2 h. The yield of addition product was 60.7%. Similar compounds have also been observed for (I) and (II) in plants [92, 23].

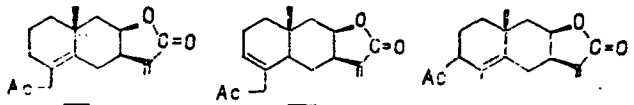
In view of the necessity for investigating the mechanism of allergic contact dermatitis with the aid of a labeled substrate, work has been carried out on introducing a hydrogen isotope into the molecule of (I) [93]. It has been possible to obtain a compound with deuterium at the C13 atom with a yield of 55-65%.

The difference in the positions of the C=C double bond (exo, endo) in the decalin moieties of the (I) and (II) molecules is responsible for a number of specific properties characteristic of only one of the two isomeric compounds. As an example we can give the acid-catalyzed shift of the C4-C15 double bond into endo- positions with the formation of the isomers (XIV) and (XV) [55, 94, 97].



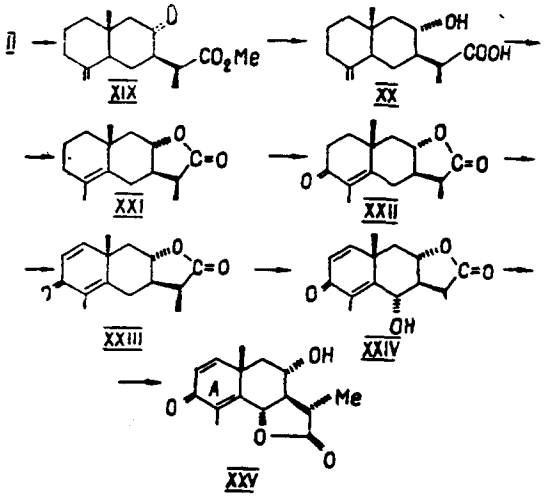
XIV XV

It has been found that the formation of compounds (XIV) and (XV) is possible on the brief treatment of (II) with a dilute solution of CH_3SO_3H in trichloroethanol. Lactone (I) does not react under the conditions described. A similar inertness of the 5,6-olefinic bond has been observed in the hydrogenation of a mixture of lactones (I) and (II) [55]. A shift of the exo- double bond also takes place under the action of formic acid on the lactone (II) [94]. If 11,13-dihydroisoalantolactone is used as the initial compound, the yield of the C4-C5 isomer amounts to 85% [97].



XVI XVII XVIII

When lactone (II) is acylated with acetic anhydride in the presence of the catalyst $ZnCl_2$, three isomers are formed – (XVI), (XVII), and (XVIII). Compounds (XVI) and (XVII) are formed by analogy with the acylation of methylenecyclohexane. The synthesis of product (XVIII) is due to the isomerization of the double bond with subsequent acylation at C-3 [95]. The hydroxylation of (II) with SeO_2 in aqueous ethanol also takes place in the C-3 position with the formation of isotelekin [96, 97].

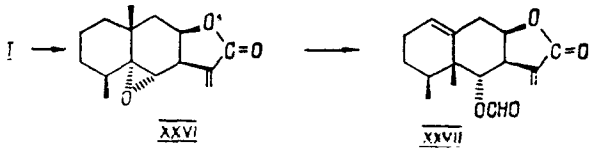


Scheme 4

Scheme 4 gives the main stages of the conversion of isoalantolactone into artemisin (XXV). Compound (XIX) is obtained by the successive selective hydrogenation of the C11-C13 bond followed by alkaline hydrolysis with the opening of the lactone ring, treatment with diazomethane, and oxidation of 8-OH group (CrO_3 in acetone). Compound (XX) is formed after

the hydrolysis of (XIX) and the reduction of the 8-keto group (Na in isopropanol). This is followed by lactonization with the trans-linkage of the ring and the migration of the C4-C15 double bond into the endo position. The formation of ring A includes the hydroxylation of the C3 position (SeO_2 in ethanol) and oxidation of the OH group (compound (XXII)). The dienone (XXIII) is obtained by dehydrogenation by boiling with dichlorodicyanobenzoquinone in dioxane. The oxidation of (XXIII) (SeO_2 in acetic acid) gives compound (XXIV), treatment of which with aqueous potassium carbonate enables the desired lactone – artemisin – to be obtained.

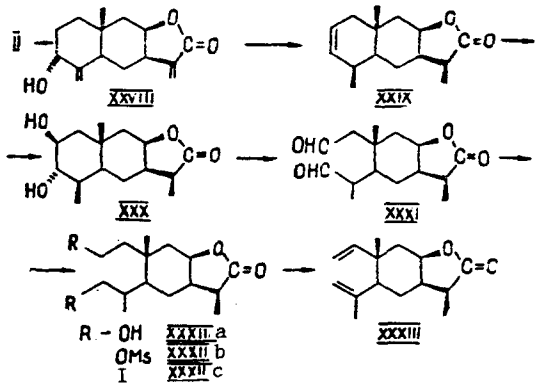
Alantolactone can serve as the initial lactone for the construction of eremophilanolides (Scheme 5). The rearrangement is achieved by treating the epoxide (XXVI) with formic acid in acetone.



XXVI XXVII

Scheme 5

Scheme 6 shows the pathway of the conversion of isoalantolactone into dihydroigalan. Isotelekin (XXVIII) is obtained by oxidation by SeO_2 in ethanol. This is followed by the hydrogenation of the exomethylene double bond in the lactone ring and dehydration with the formation of (XXIX). Treatment with H_2O_2 in acetic acid and then with a 5% solution of KOH in ethanol gives the lactone (XXX). When the latter is oxidized with periodic acid the dialdehyde (XXXI) is formed. This is followed by the successive reduction of the aldehyde groups ($NaBH_4$ in methanol) and treatment with mesyl chloride in pyridine and with sodium periodate in methyl ethyl ketone. The desired product (XXXIII) is formed after the splitting out of HI (yield in the last stage less than 10%).



XXVIII XXIX XXX XXXI XXXIIIa XXXIIb XXXIIc XXXIII

Scheme 6

BIOLOGICAL ACTION

The combined lactones (I) and (II) form the active principle of the drug Alanton, which is used in the treatment of gastric and duodenal ulcers [101-103]. The drug exhibits an antiinflammatory action, decreases the proteolytic activity of the gastric juice, and raises a lowered acid-forming function of the stomach without appreciably affecting a normal or raised function. Alanton stimulates the formation of mucin and intensifies the regenerative capacity of the gastric mucosa. A collection of medicinal plants including the roots and rhizomes of elecampane can be used as an effective antiulcer agent [104].

As early as the 1930s the toxicity of lactones (I) and (II) was studied on mice with subcutaneous injection. The minimum lethal does for both compounds was 2000 mg/kg [105]. It has been shown that helenin possesses a pronounced hemostatic action. The results of experiments on animals with multiple injections have shown that helenin greatly shortened the clotting time (at a dose of 3 mg/kg, by 75%) and considerably decreased the volume of blood loss (by 48-87%, depending on the dose) [106-108].

It has been shown in experiments on mice that, in doses of 100-200 mg/kg, lactones (I) and (II) lead to an increase in the antioxidant activity of lipids, their action considerably exceeding the activity of such natural antioxidants as α-tocopherol and ubiquinone [109].

It has been found in experiments on guinea-pigs that helenin possesses an antitussive activity, but this is only half that of codeine [110].

In spite of the antiinflammatory action exhibited by helenin, isoalantolactone in a concentration of 37 μM in an in vitro experiment did not inhibit the biosynthesis of prostaglandins [111]. It has been shown that lactone (I) inhibits the microsomal enzymes of the liver [112].

The antibacterial properties of (I) and (II) against a number of Gram-positive bacteria (Staphylococcus albus, Bacillus subtilis, Streptococcus faecalis) and Gram-negative bacteria (E. coli, Proteus vularis or P. mirabilis, and Ps. fluorescens) have been studied [113]. Complete inhibition of growth was observed only in the action of (I) on B. subtilis. Compound (II) exhibited a weak activity in relation to B. subtilis and B. vulgaris, and (I) in relation to St. albus. No inhibition of growth was observed for the other cultures mentioned above. Compound (I) and also helenin possessed a pronounced inhibiting effect against such pathogenic bacteria as St. aureus and Mycobacterium tuberculosis in concentrations of 31.2-62.5 and 31.2 μg/ml, respectively [114].

Amino derivatives of (I) and (II) had a more pronounced bactericidal effect than the initial lactones [89, 90].

The antifungal activity of (I) and (II) has been studied in relation to more than 16 different cultures [115-120]. Both lactones inhibited the growth of all the fungi studied, but the effects for each individual culture differed greatly. Both (I) and (II) exhibited their greatest inhibiting effect on the growth of the zoophilic fungi Microsporum cookei and Trichophyton mentagrophytes (complete inhibition of growth at a concentration of either lactone of 10 μg/ml) [115]. A comparable effect was obtained for the fungus M. lanosum – 15.6 μg/ml [114] – and also for T. mentagrophytes and M. canis – 3.96 μg/ml [120]. Compounds (I) and (II) were not active in relation to the yeasts S. cerevisiae and C. albicans [116], while (I) showed a greater influence on the growth of fungi than (II). The difference in the activities of (I) and (II) permits the assumption that two lactones act by their own specific routes.

In order to evaluate the significance of structure in antibacterial and antifungal activities, investigation have been made with the use of several tens of different sesquiterpene lactones [113, 116]. The main conclusion of the authors concerned is that the reason for the activity of the sesquiterpene lactones is multivalent and cannot be explained by a structural factor such as, for example, the presence or absence of an α-methylene group in the lactone ring, alone. A no small important role is also played by differences in the accessibility of the SH groups of proteins of microorganisms and their affinity for the corresponding lactones.

The antiprotozoal properties of (I) and (II) in relation to the dysentery ameba Entamoeba histolytica [121] and a number of strains of Trichomonas vaginalis [121, 122] have also been studied in vitro. Out of the 82 sesquiterpene lactones investigated, (I) and (II) were among the ten most active compounds [121]. The addition of various secondary amines to C-13 with the aim of increasing water solubility permitted some increase in activity as compared with the initial lactones. The products of the addition of morpholine, hydroxyethylpiperazine, and diethanolamine showed the greatest effect. Various strains of Tr. vaginalis possessed different sensitivities to the actions of the compounds studied. The greatest suppressing effect on the growth and development of Tr. vaginalis was exhibited by a concentration of 2.5 μg/ml [122], which is considerably inferior to that of drugs used in clinical medicine (for example, Niridazole, the minimum inhibiting concentration of which is $7.5 \cdot 10^{-3}$ mg/liter [123]).

Lactones (I) and (II) possess antihelminthic activity [17, 148]. The action of twelve N-containing derivatives of (I) and (II) has been studied in vitro in relation to Hirudo medicinalis (leech), Lumbricus terrestris (earthworm), and Ascaris suum (helminth) [124]. The most active were the products of the addition of pyrrolidine to (II) and of 4-methylpiperidine to (I).

Analysis of the activity of a number of sesquiterpene lactones in relation to the nematode Meloidogyne incognita has shown that the activity exhibited is connected with the presence of the α-methylene-γ-lactone group in the molecule. The result of the action of lactone I on nematodes was a 97% mortality [125].

It is known that compounds possessing antihelminthic properties frequently also exhibit anticarcinogenic activity [126]. An investigation of the cytotoxic properties of helenin in comparison with the individual lactones (I) and (II) showed that the activity of helenin is connected with the presence of (II) in it [55]. The model used was a culture of human epidermal carcinoma cells. The cytotoxicities of (I) and (II) have also been determined in in vitro experiments on lines of human lung carcinoma cells [127]. ID_{50} for (I) was 4.6 μg/ml; and for (II), 16 μg/ml. A dose of 50 μg/ml completely suppressed the growth of the cells. The modification of (I) by the addition of 5-fluorouracil did not lower its toxic properties and did not improve its therapeutic properties [128]. A compound obtained by the addition of hexamethyleneimine to (I) exhibited an activity in relation to leukemia L 1210 – the lives of experimental animals were lengthened by approximately 40%.

The majority of authors consider the presence of the reactive grouping $-CH=C-C=O$ as one
of the main conditions for the biological activity of sesquiterpene lactones and, in particular, (I) and (II). The mechanism of their cytotoxic action is also treated as a Michael addition reaction between this grouping and the SH groups of enzymes and proteins [129].

For example, the inhibition of such enzymes as DNA polymerase, thymidylate synthetase, and inosine phosphate dehydrogenase leads to the inhibition of the synthesis of DNA.

An alternative mechanism that has been proposed for the action of sesquiterpene lactones is their capacity for alkylating DNA. It has been shown [130] that helenalin, parthenin, coronopilin, damsin, ivasperin, and, to a smaller degree, (II) cause chromosomal aberrations in Chinese hamster ovary (CHO) cells. This has served as an indication of the fact that sesquiterpene lactones and, in particular, (II) are capable of attacking DNA directly.

The role of lipophilicity in the biological activity of the sesquiterpene lactones has been shown in a number of cases [41, 129]. For example, for (II), ivalin (2-hydroxyisoalantolactone), and ivasperin (1,2-dihydroxyisoalantolactone), cytotoxicity increases with an increase in lipophilicity [130].

Many natural sesquiterpene lactones containing an α-methylene-γ-butyrolactone grouping cause allergic contact dermatitis. The importance of the reactivity of the lactone grouping has been shown in model experiments using as examples the interaction of (I) with a number of amino acids (cysteine, tryptophan, histidine, lysine), as a result of which (I) lost its immunological reactivity [91]. At the same time, there is information on the toxicity of both (I) and 11,13-dihydro alantolactone in relation to a culture of leukocytes in vitro [131]. The authors concerned put forward a hypothesis that the toxicity of (I) is not connected with the α-methylene-γ-lactone grouping.

In order to obtain information on the hapten-carrier interaction, a series of investigations has been made with the use of various procedures [132-136].

It is assumed that sensitization by isoalantolactone is somewhat weaker than by alantolactone [99]. In earlier publications it was assumed that (II) does not possess allergic properties [137, 138].

In connection with the contradictory results obtained in relation to the sensitizing capacity of (I) and (II), an investigation has been undertaken using various methods of sensitization and different lines of animals [139]. The results showed that both helenin and the two lactones separately are potential sensitizers of guinea-pigs. There is no difference in the sensitizing capacities of (I) and (II) on intracutaneous injection into guinea-pigs. When the application test is employed, the concentration used is apparently the deciding factor for the rate of sensitization with (I) and (II). Since both lactones can induce hypersensitivity on intracutaneous injection, there are grounds for assuming that the capacity for penetrating through the skin differs greatly for the two isomers.

In order to understand the mechanism of allergic contact dermatitis better, the synthesis was undertaken of a number of compounds containing a lactone grouping [99, 140]. It was shown that (I) was the strongest allergen among 30 compounds containing this grouping.

Thus, the broad spectrum of the biological activity of alantolactone and isoalantolactone completely justifies the Russian name of the compound from which these compounds were isolated – devyasil [~ nine powers]. The analysis of the literature that has been performed shows that, in spite of their fairly long history, the elecampane lactones remain the object

of active investigation both in relation to chemical properties and in relation to biological activity.

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