ADVANCES IN THE CHEMISTRY OF SESQUITERPENE LACTONES

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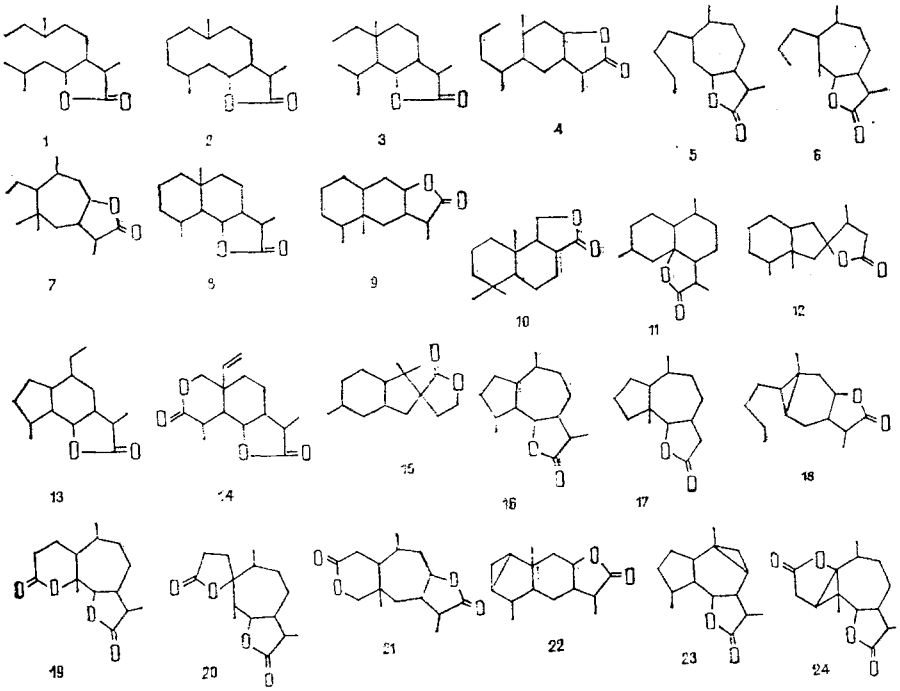
UDC 547.314

The paper gives a review of the chemistry of natural sesquiterpene lactones.

The chemistry of natural sesquiterpene lactones began to develop very quickly after 1950, following the appearance of the results of investigations by Czech scientists F. Šorm, V. Herout and their colleagues [1-3]. In the Soviet Union, the sesquiterpene lactones of the wild flora have been studied by K. S. Rybalko [4]. Since 1967, the sesquiterpene lactones of the flora of Central Asia have been studied systematically in the Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Uzbek SSR [5, 6]. This class of terpenoids is being intensively studied in many countries of the world, since the lactones possess a broad spectrum of biological activity: antihelminthic, cardiotonic, anti-inflammatory, analgesic, antitumoral, antimalarial, etc. [10].

More than 1200 lactones of various types (scheme 1) have been isolated from plant sources. A large part of these types is represented by the germacranolides, eudesmanolides, and guaianolides isolated from plants of the families *Asteraceae* [10], and *Apiaceae* [4] and biogenetically related to one another.



Scheme 1. Typical Natural Sesquiterpene Lactones: 1) seco-germacranolides; 2) germacranolides; 3) elemanolides; 4) seco-eudesmanolides; 5) xanthanolides; 6, 7) seco-ambrasanolides A and B; 8) eudesmanolides; 9) eremophyllanolides; 10) iresanolides; 11) cadinanolides; 12) bakkenolides; 13) chrymanolides; 14) vernolepinolides; 15) herbadysidolides [16]; 16) guaianolides; 17) ambrasanolides; 18) carabranolides; 19, 20) psilostachanolides A and B; 21) vermeeranolides; 22) linderanolides; 23) ivaxillarinolides; 24) confertdiolides [17].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 551-569, September-October, 1982. Original article submitted September 18, 1981.

0009-3130/82/1805-0519$07.50

The aim of the present review is a generalization of literature information that has recently appeared and an acquaintanceship with the characteristic and general reactions of the interconversions of the types of lactones listed.

The basic skeleton of the sesquiterpene lactones includes fifteen carbon atoms and is characterized by the presence of one or two γ-lactone or a γ- and a δ-lactone ring. From the structure of the hydrocarbon skeleton, these compounds can be classified as acyclic (1), monocyclic (2-7), bicylic (8-21), and tricylic (22-24).

In recent years, a series of lactones of complex structure has been isolated the skeleton of which consists of 30 carbon atoms. These lactones must be called disesquiterpenoids, and they are also considered in the present review.

It has been established for a number of plants [11-15], as examples, that the qualitative and quantitative composition of the lactones depends on the vegetation period, the growth site, and the plant organ.

GERMACRANOLIDES

Germacranolides are sesquiterpene lactones the carbon skeleton of which consists of cyclodecane condensed with a γ-lactone ring (scheme 2).

Germacranolides with different degrees of saturation are known. Their double bonds are usually located at C_1—C_{10}, C_4—C_5, and C_7—C_{11} (25, 26). Germacranolides have been found in which one of the double bonds is located at C_9—C_{10}, as, for example, in tatridin C (29).

It can be seen from the structures of germacranolides (25, 26) that the three carbon atoms C_{13}, C_{14}, and C_{15} are represented in the form of methyl or methylene groups. In salonitenolide (43), albicolide (44), urospermal (46), and germanin B (47), these methyl groups are oxidized to alcohol, aldehyde, and carboxy groups, respectively. In their turn, the alcohol and carboxy groups may be esterified or glucosidated, as in the germacranolides 45 and 48.

Deoxyelephantopin (30), melampodin B (31), and isabelin (32) each contain two γ-lactone rings. The formation of one of them can be explained by the presence of a carboxy group at C_4 or C_{10} and of hydroxy groups present in the γ position relative to one another. In addition, germacranolides with a furan ring are known such as, for example, neolinderlactone (33).

The epoxide group is frequently found in the germacranolides, and lactones with one and with two epoxide rings (34-36) have been isolated. The precursors of these lactones are compounds with double bonds.

Germacranolides with ether and ester groups (38-42), and carbonyl (49) and peroxide (50) groups, which may be present on various carbon atoms, have been found. The lactone acanthamolide (51), containing nitrogen in its molecule, has also been isolated.

The large number of lactones with the germacrane skeleton is due to the diversity of the functional groups and their position and association.

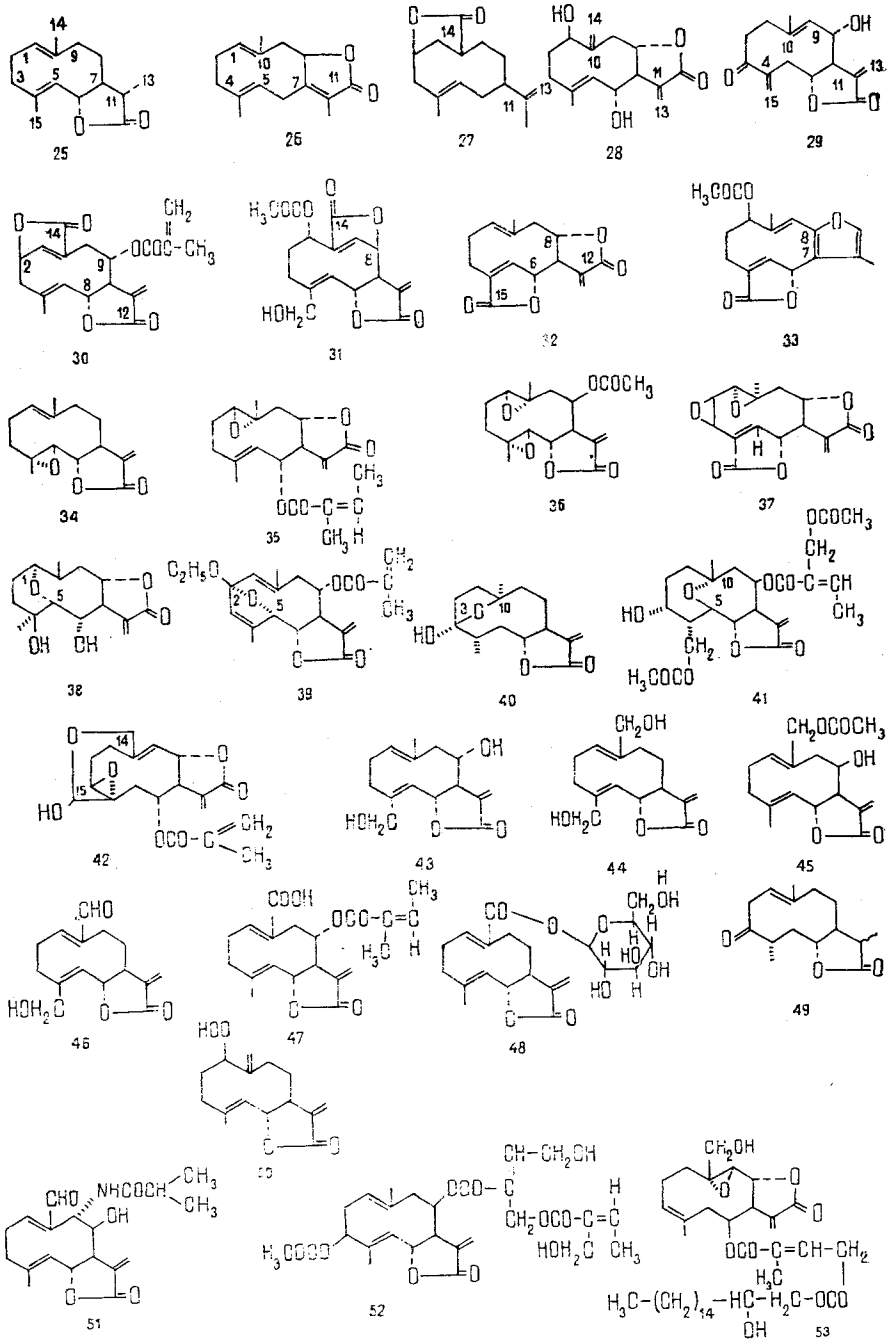
Cope Rearrangement. When the germacranolides are subjected to thermolysis, a Cope rearrangement takes place (scheme 3). It is characteristic for compounds including diallyl groupings, and takes place through a transitional cyclohexane state with the participation of six centers. The stereochemistry of the Cope rearrangement has been discussed by Doering and Roth [52].

For the successful performance of this reaction with a germacranolide having an exomethylene group conjugated with the lactone carbonyl, it must previously be hydrogenated and the reaction be carried out with the dihydro derivative [18].

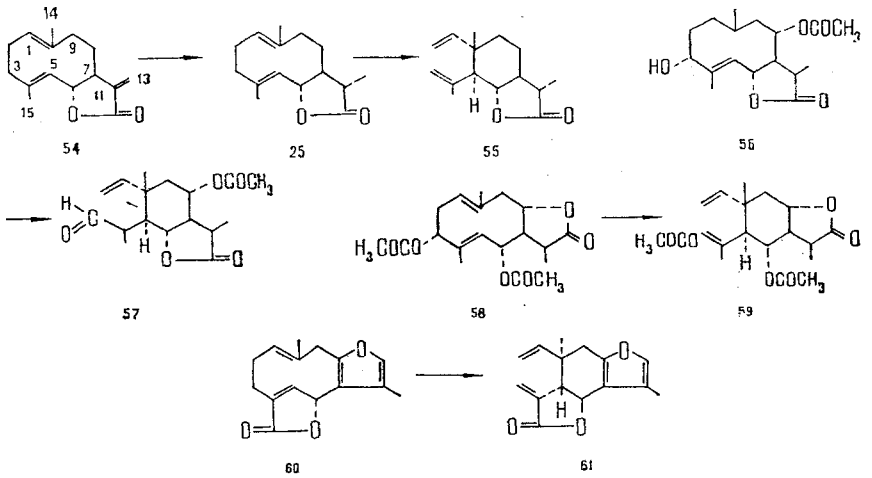
The Cope rearrangement of a number of germacranolides (25, 56, 58, 60) leads to the formation of elemanolides (55, 57, 59, 61).

The cyclization of the germacranolides is widely used to prove the structures of germacranolides with double bonds at C_1—C_{10} and C_4—C_5, and also of compounds having a double bond and an epoxide group at the same carbon atoms (25, 34, 35).

This reaction belongs to the transannular type and takes place through an approach of the C_1 and C_5 or C_1 and C_{10} carbon atoms present on opposite sides of a cyclodecane ring



Scheme 2. Germacranolides: 25) dihydrocostunolide [18]; 26) glechomanolide [19]; 27) aristolactone [20, 21]; 28) tanachin [22]; 29) tatridin C [10]; 30) deoxyelephantopin [29]; 31) melampodin B [30]; 32) isabelin [31, 32]; 33) neolinderlactone [33, 34]; 34) parthenolide [35, 36]; 35) tanacin [37], 36) epitulipinolide diepoxide [38]; 37) mikanolide [32. 39, 40]; 38) badgerin [40]; 39) phantomolin [42]; 40) tirotundin [43]; 41) chapliatrin [44]; 42) vernolide [45, 46]; 43) salonitenolide [23]; 44) albicolide [24]; 45) ovatifolin [27]; 46) urospermal [25]; 47) germanin B [26]; 48) a glucogermacranolide [28]; 49) ketopelenonide A [47]; 50) peroxycostunolide [48]; 51) acanthamolide [51]; 52) provincialin [49]; 53) eupassofilin [50].



Scheme 3. 25) Dihydrocostunolide [18]; 54) costunolide [18]; 56) dihydrochihuahuin [53]; 58) dihydrochamissonin [54]; 60) linderalactone [55]; 61) isolinderalactone [55].

having the "two chair" conformation and double bonds spatially close and arranged in a cruciform manner.

The cyclization of costunolide (54) (scheme 4) has been performed with the aid of various reagents — boron trifluoride etherate [56], N-bromosuccinimide [56], and m-chloroperbenzoic acid [58] — and also by catalytic hydrogenation in an acid medium with the formation of santanolide C (69). It can also be performed by a microbiological method [60].

The cyclization of costunolide (54) by the reagents mentioned formed the eudesmanolides (62-69). The photolysis of costunolide (54) also led to cyclization, but with the formation of the guaianolide (78) [61]. A similar cyclization leading to lumidihydroisabelin (83) is observed in the photolysis of dihydroisabelin (82) [62].

The acetylation and oxidation of pyrethrosin (70) leads to the eudesmanolides (71-73). Apparently, in these reactions cyclization first takes place and then the cyclization products undergo acetylation and oxidation [63]. The cyclization of artabin (84) with 50% sulfuric acid has given tetrahydro-β-santonin (85). The cyclization of tanacin (35) has been carried out under the same conditions [65].

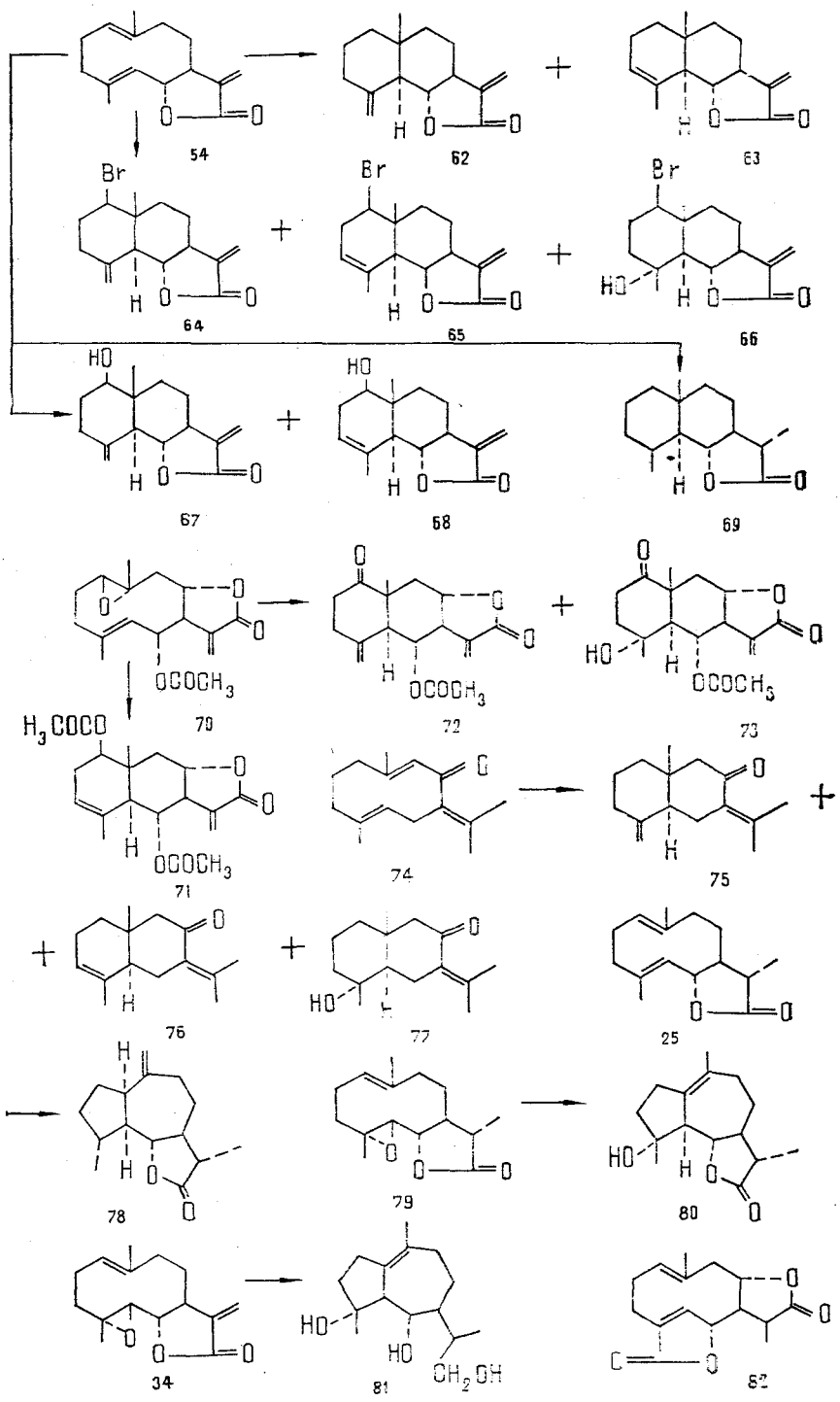
When parthenolide (34) was subjected to catalytic hydrogenation in the presence of Pd/C, cyclization and the reduction of the exomethylene group were observed [67]; its reduction with lithium tetrahydroaluminate also led to cyclization and the reduction of the γ-lactone ring [66]. The cyclization of dihydroparthenolide (79) took place when it was treated with boron trifluoride etherate [68]. The action of mercury salts on isogermacrone (74) formed the eudesmanes (75-77) [69].

Cyclization is also possible when the double bonds in the germacrane nucleus are located at C_4—C_5 and C_9—C_{10}. The presence of an epoxide group in the germacrane nucleus at C_1—C_{10} and of a double bond at C_4—C_5 (70) leads on cyclization to the formation of eudesmanolides, and a double bond at C_1—C_{10} and an epoxide group at C_4—C_5 (34) to guaianolides.

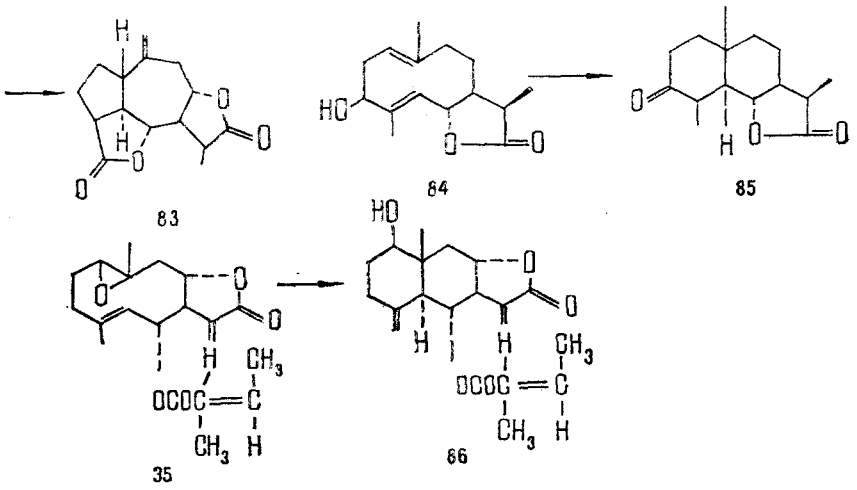
The cyclization of costunolide (54) in a nonaqueous medium forms two products (62, 63), and in water three (64-66). The formation of the third product (66) can be explained by the addition of a molecule of water to compound (64) in accordance with the Markovnikov rule.

Reactions Due to Functional Groups. The presence of a γ-lactone ring is a general characteristic of the sesquiterpene lactones. On treatment with solutions of alkalis, this ring opens with the formation of salts of γ-hydroxy acids (e.g., 87), and on acidification the initial lactone (e.g., 25) is re-formed (scheme 5).

The action of solutions of alkalis on salonitenolide (43) opens the γ-lactone ring but on acidification artemisifolin (88), having a different position of the γ-lactone ring, is formed. This reaction is known in the chemistry of sesquiterpene lactones as the relactonization reaction, and it is observed when there is a hydroxy group with the α orientation in the γ position relative to the lactone carbonyl. When there is a group with the β orienta-



Scheme 4



Scheme 4 (continued). 54) costunolide [56]; 62) β-cyclocostunolide; 63) α-cyclocostunolide; 64, 65, 66) bromoeudesmanolides; 67) reynosin; 68) santamarin; 69) santanolide C [59]; 70) pyrethrosin [63]; 71) acetylcyclopyrethrosin [63]; 72, 73) ketocyclopyrethrosins; 74) isogermacrone [69]; 75, 76, 77) products of the cyclization of isogermacrone; 25) dihydrocostunolide [61]; 78) guaianolide; 79) dihydroparthenolide [68]; 80) cyclization products [67]; 34) parthenolide [67]; 81) guaiane alcohol; 82) dihydroisabelin [62]; 83) lumidihydroisabelin; 84) artabin [64]; 85) tetrahydro-β-santonin; 35) tanacin [65]; 86) chrysanin.

tion in the same position, no relactonization takes place; this applies, for example, to eupatolide (90).

The γ-lactone ring in costunolide (54) opens under the action of sodium tetrahydroaluminate and is reduced to an alcohol group with the formation of compound (91).

Let us consider the oxidation and acetylation reactions of the hydroxy group. The oxidation of artemisifolin (96) with chromium trioxide gives isabelin (97), i.e., a new γ-lactone ring is formed [73]. The acetylation of goyazensolide (98) with acetic anhydride in pyridine leads not only to acetylation but also to the allyl rearrangement with the formation of product (99) [74].

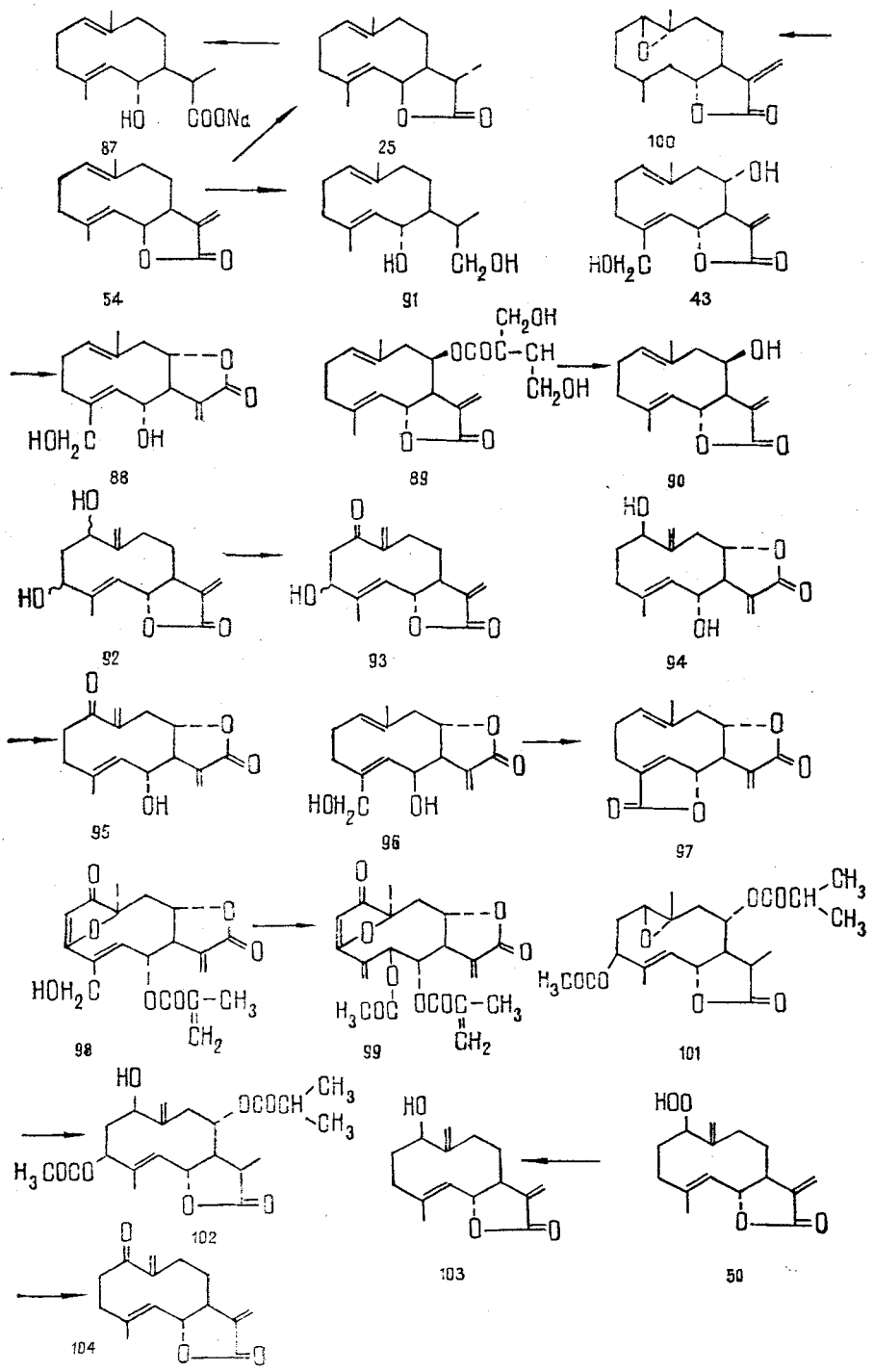
The oxidation of isoridentin (92) with chromium trioxide in pyridine gives ketoisoridentin (93) [75], and the oxidation of tanachin (94) gives tamirin (95) [22]. These results indicate that a hydroxy group present in the α position relative to an exocyclic double bond is more reactive than the hydroxy group in the same position relative to an endocyclic double bond.

Usually, double bonds in sesquiterpene lactones are oxidized by peracids to epoxide compounds. Thus, for example, the oxidation of costunolide (54) with perbenzoic acid forms epoxycostunolide (100) [76]. The epoxy group in erioflorin (101) can be opened in an acid medium with the formation of hydroxy and exomethylene groups (102) [77].

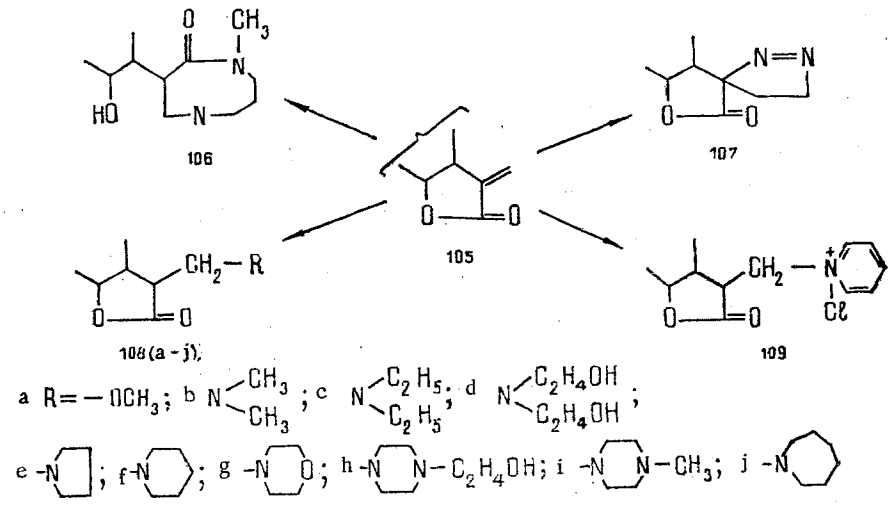
The selective reduction of an exomethylene group conjugated with a lactone carbonyl takes place under the action of sodium tetrahydroborate in an alcoholic medium. It has been reported that in the case of the trans linkage of the γ-lactone ring with the germacrane skeleton a dihydro product with the α orientation of the methyl group formed is the predominant product. Thus, dihydrocostunolide (25) is obtained from costunolide.

The treatment of peroxycostunolide (50) [42] with triphenylphosphine gives artemorin (103), and its acetylation gives anhydroverlotorin (104).

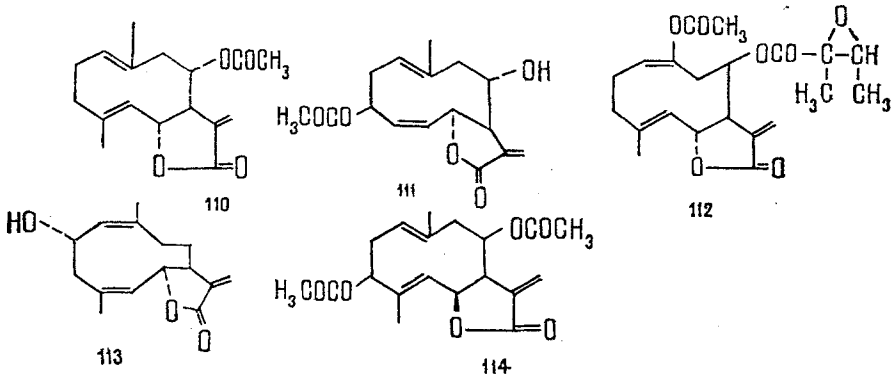
The high reactivity of an exomethylene group conjugated with the lactone carbonyl is characteristic for all groups of sesquiterpene lactones. It is precisely the presence of this grouping that explains the antitumoral and antimicrobial activity of the sesquiterpene lactones. It readily takes part in various reactions; for example, with diazomethane a pyrazoline derivative (107) is formed [78]; with pyridine, a quaternary compound (109) [79];



Scheme 5. 25) dihydrocostunolide; 87) Na salt of a hydroxy acid; 100) epoxycostunolide [76]; 54) costunolide [72]; 91) reduction product of costunolide; 43) salonitenolide; 88) artemisifolin [70]; 89) eupatoriopicrin; 90) eupatolide [71]; 92) isoridentin [75]; 93) ketoisoridentin; 94) tanachin [22]; 95) tamirin; 96) artemisifolin [73]; 97) isabelin; 98) goyazensolide [74]; 99) acetylgoyazensolide; 101) erioflorin [77]; 102) reaction product from erioflorin; 103) artemorin; 50) peroxycostunolide [42]; 104) anhydroverlotorin.



Scheme 6. 105) Lactone with an exomethylene group; 106) product of the addition of sym-dimethylethylenediamine; 107) pyrazoline derivative [78]; 108) (a-j)) products of the addition of methanol and secondary amines [81]; 109) quaternary compound with pyridine [79].



Scheme 7. 110) epitulipinolide [87]; 111) eupaformonin [88]; 112) melampodin [87]; 113) cis,cis-2α-hydroxycostunolide [87]; 114) ursiniolide A [87].

and with symmetrical dimethylethylenediamine a nitrogen-containing base (106) [80]; and it also adds methanol and combines with secondary amines forming products (108a-j) (scheme 6).

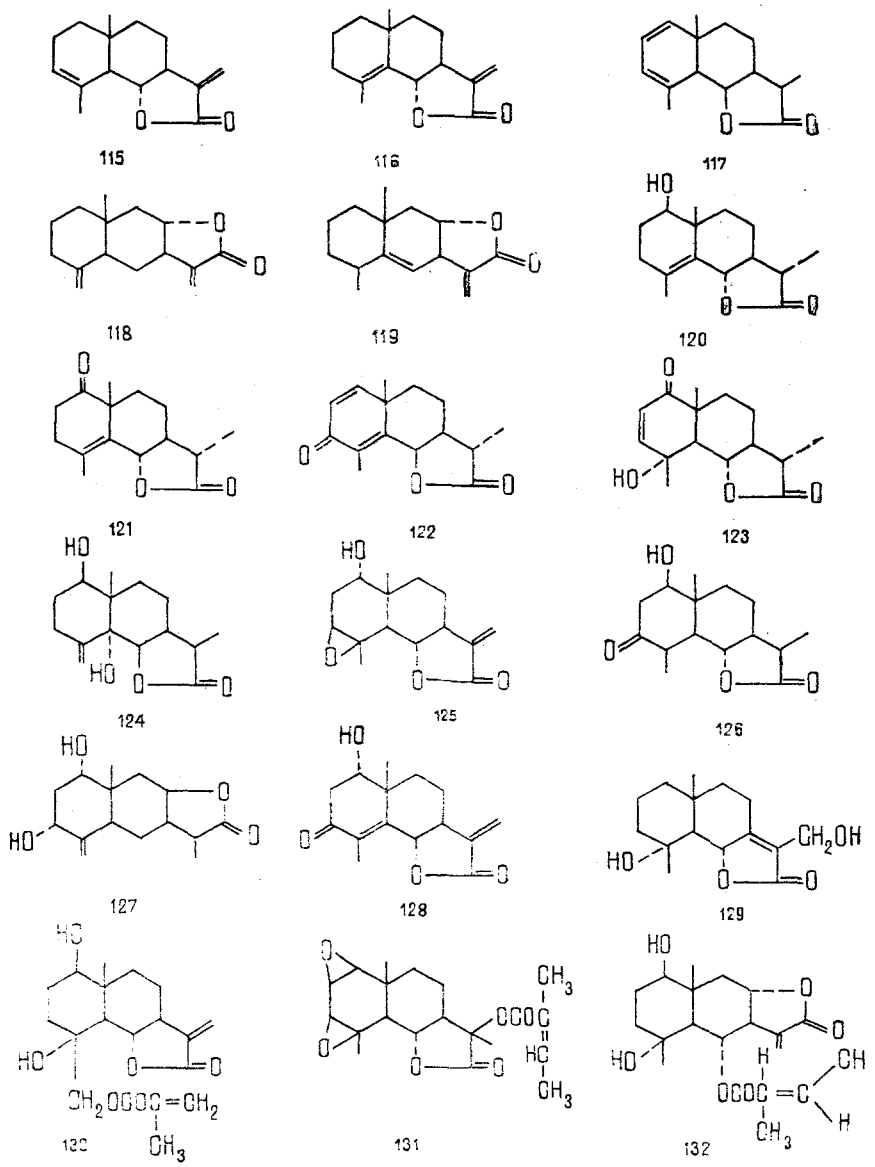
Stereochemistry of the Germacranolides. The germacrane ring in each of the compounds under consideration may have different conformations: two chairs, two boats, chair-boat, and boat-chair. This is due to the presence of two double bonds and γ-lactone ring, which is usually trans-linked with the germacrane skeleton. Compounds have also been isolated with the cis linkage of the γ-lactone ring, for example, ursiniolide A (114) [87].

Four spatial isomers of germacranolide are known as a result of the geometry of the double bonds, which may be trans-trans-substituted, as in epitulipinolide (110) [87], trans-cis, as in eupaformonin (111) [88], cis-trans, as in melampodin (112) [87], or cis-cis, as in 2α-hydroxycostunolide (113) [87] (scheme 7).

EUDESMANOLIDES

Eudesmanolides are sesquiterpene lactones the carbon skeleton of which consists of a decalin nucleus having a γ-lactone ring at the C_6—C_7 or C_7—C_8 atoms (see scheme 9). The lactone ring may be cis- or trans-linked. The eudesmanolides usually contain three methyl groups, at C_4, C_{10}, and C_{11}, one of them being angular.

Lactones are known with exomethylene groups at the C_4 and C_{11} atoms (113, 115, 128). The eudesmanolides differ from one another in their degree of saturation, and the double



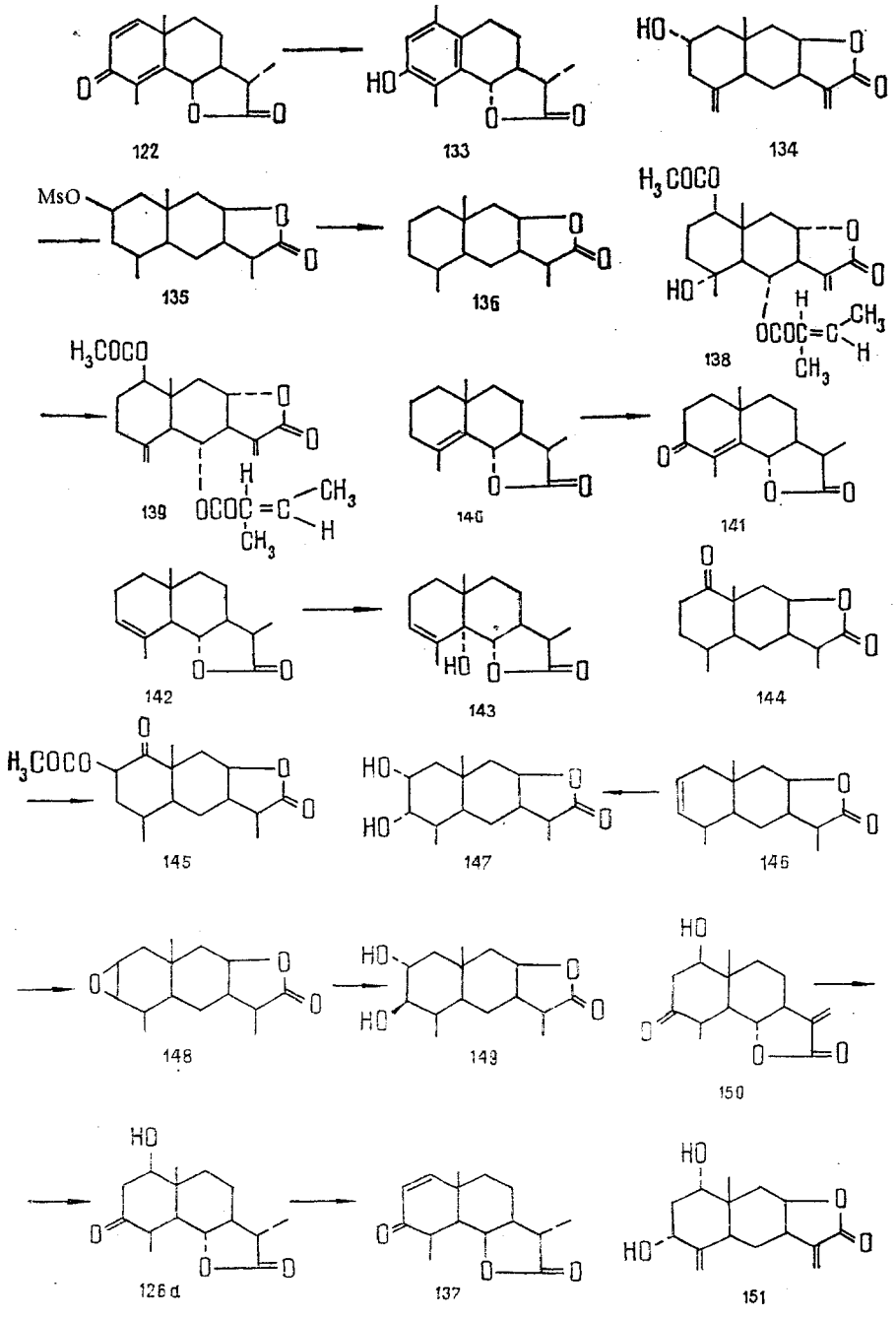
Scheme 8. 115) α-Cyclocostunolide [89, 90]; 116) arbusculin B [89, 91]; 117) feropodin [92]; 118) isoalantolactone [93]; 119) alantolactone [83, 94]; 120) artesin [95]; 121) taurin [26]; 122) α-santonin [97, 98]; 123) tauremisin [99, 100]; 124) arsubin [101]; 125) ludovicin [102]; 126) arabsin [103]; 127) ashurbin [103]; 128) picridin [104]; 129) arbusculin D [105]; 130) vahlenin [106]; 131) decipienin [107]; 132) tanapsin [108].

bonds may be present in very different positions (115-119). Furthermore, they include various functional groups: hydroxy (124-126), ketone (121), epoxy (125), and ester (130, 132). Eudesmanolides also differ in the positions of these functional groups and their combination.

Lactones have been isolated with diene (117) and dienone (122) systems of double bonds and with an α,β-unsaturated carbonyl group (123) (scheme 8).

Reactions Used in Elucidating the Structures of the Eudesmanolides. Whether a sesquiterpenoid belongs to the eudesmanolide group is revealed by the dehydrogenation reaction in the presence of selenium, sulfur, or palladium on various supports with the production of 7-ethyl-1-methylnaphthalene. In this reaction, the angular methyl group is split off and decarboxylation takes place, but there is no change in the carbon skeleton.

One of the first natural eudesmanolides is α-santonin (122). When it is treated with concentrated hydrochloric acid, desmotropsantonin (133) is formed, in which, in addition to aromatization, migration of the angular methyl group has taken place (scheme 9).


122
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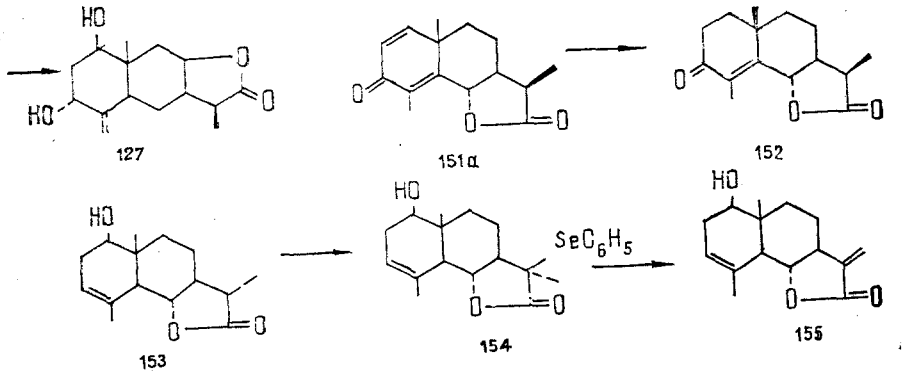
Scheme 9



Scheme 9 (continued). 133) desmotropsantonin; 134) ivalin [109]; 135) mesyl ester; 136) reduction product; 126a) arsanin [110]; 137) anhydroarsanin; 138) acetyltanapsin [111]; 139) chrysanin; 140) dihydrofrullanolide [112]; 141) oxidation product; 142) α-cyclodihydrocostunolide [113]; 143) hydroxyeudesmanolide; 144) dehydrotetrahydroasperilin [114]; 145) 2-acetyl-1-oxo-tetrahydroalantolactone; 146) anhydrotetrahydroivalin [115]; 147) cis-diol; 148) epoxy compound [116]; 149) trans-diol; 150) artecalin [117]; 151) granilin [103]; 127) ashurbin; 151a) β-santonin [118]; 152) dihydro-β-santonin; 153) dihydrosantamarin [119]; 154) phenylselenylated derivative; 155) santamarin.

The elimination of a hydroxy group in a eudesmanolide is carried out by various methods. For example, in ivalin (134) the hydroxy group is mesylated (135) and is then reduced with the formation of a product (136) containing no hydroxy group. In acetyltanapsin (138), the tertiary hydroxy group is eliminated by thionyl chloride with the formation of acetylchrysanin (139).

The allyl methylene group in dihydrofrullanolide (140) is oxidized by sodium chromate to a carbonyl group (141), and the methine group in α-cyclodihydrocostunolide (142) is oxidized by selenium oxide to a hydroxy group (143).

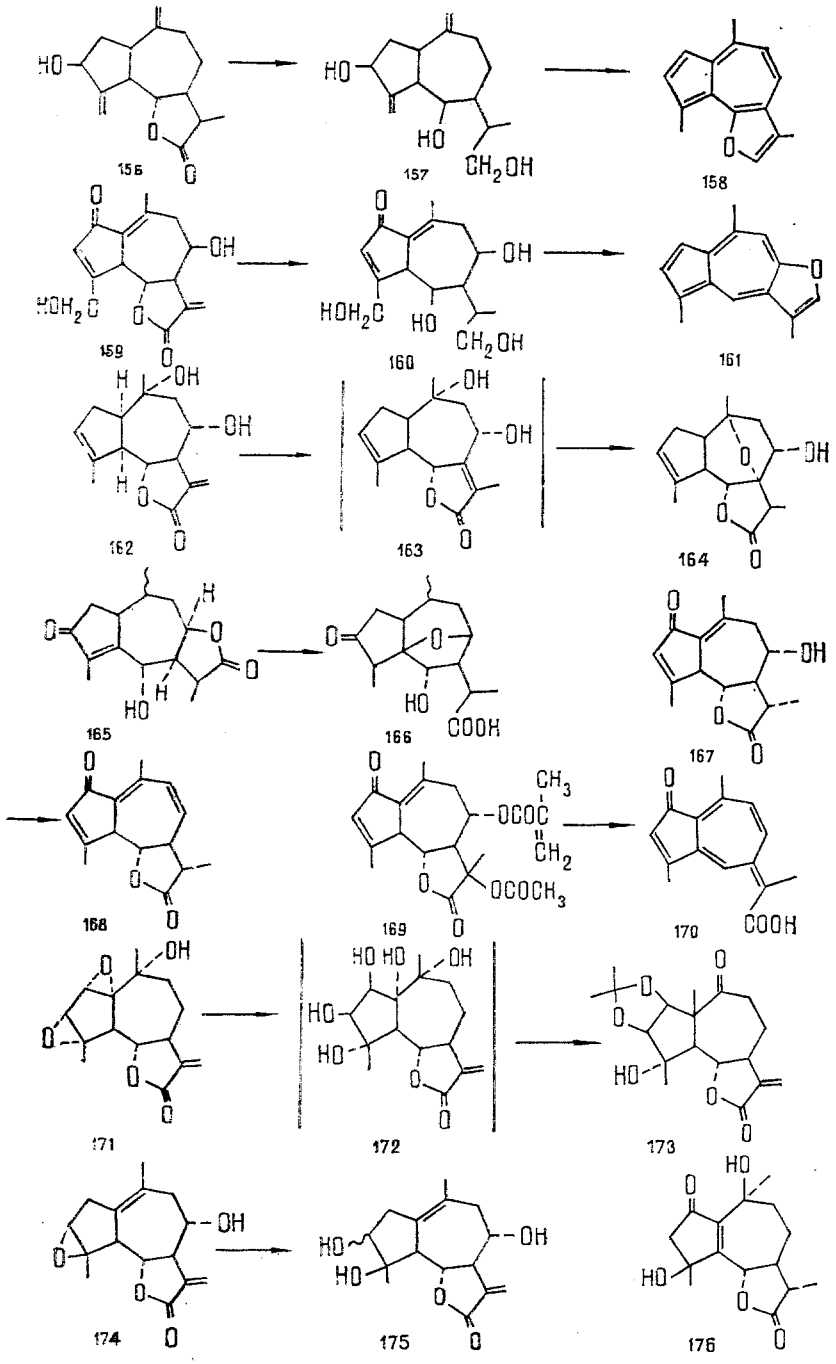
When dehydrotetrahydroasperilin (144) is treated with lead tetraacetate, an acetyl derivative (145) is obtained at the expense of the allyl methylene group. The oxidation of a eudesmanolide containing a disubstituted double bond (146) with osmium dioxide usually gives a compound with a cis-diol system and α-oriented hydroxy groups (147). On the other hand, oxidation with peracids leads to a lactone with a trans-diol system of hydroxy groups (149) via an epoxy compound (148).

The selective reduction of an exomethylene double bond conjugated with a γ-lactone carbonyl group is carried out with sodium tetrahydroborate in an alcoholic medium with the predominant formation of a single isomer. In the case of the trans linkage of the γ-lactone ring with the nucleus, the dihydro product formed has the α orientation and in the case of cis linkage it has the β orientation. Thus, for example, the reduction of artecalin (150) with sodium tetrahydroborate gives arsanin (126), and the reduction of granilin (151) gives ashurbin (127).

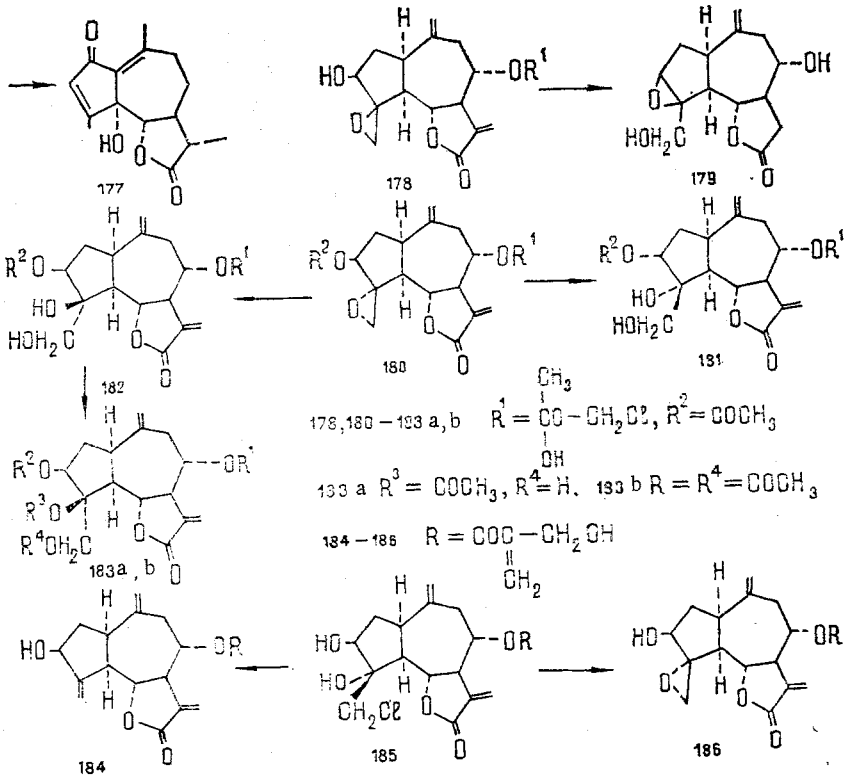
Catalytic hydrogenation on the presence of platinum oxide in benzene has been used for the selective hydrogenation of β-santonin (122). This forms dihydro-β-santonin (152).

In recent years, to prove the structures of eudesmanolides use been made of a selective dehydrogenation reaction consisting in the formation of α-methylene-γ-lactones from the corresponding methyl analogs [112]. A phenylselenylated derivative (154) is obtained, and this is treated with hydrogen peroxide in an acid medium to give a lactone with an exomethylene group. Thus, santamarin (155) is obtained from dihydrosantamarin (153).

A large amount of information relative to the configuration of a methyl group attached to a γ-lactone ring absorbing in the 225-230-nm region is given by a study of the circular dichroism (CD) curves. The sign of the Cotton effect depends both on the position of the γ-lactone ring and on its linkage with the nucleus and the configuration of the methyl group.



Scheme 10



Scheme 10 (continued). 156) dihydrozaluzanin C [120]; 157) reduction product; 158) artemazulene; 159) lactucin [121, 123]; 160) reduction products; 161) linderazulene; 162) cumambrin B [124]; 163) intermediate compound; 164) isocumambrin B; 165) geigerin [125]; 166) hydroxy acid; 167) austricin (deacetylmatricarin) [126, 127]; 168) anhydroaustricin (anhydrodeacetylmatricarin); 169) laferin [128, 129]; 171) canin [130]; 172) intermediate compound; 173) canin acetonide; 174) ajadin [131]; 175) ajanin; 176) artemolin [132]; 177) parishin C; 178) acroptilin [133, 134], 179) saponification product; 180) acroptilin acetate [135]; 181) linichlorin C; 182) isomer of linichlorin C; 184) cynaropicrin; 185) chlorojanerin [136]; 186) janerin.

We have studied the CD spectra of a number of eudesmanolide in which the lactone ring is present at the C_6 and C_7 atoms and is trans-linked with the eudesmane skeleton. When the methyl group has the α orientation, a positive Cotton effect is observed in the 230-nm region, and when it has the β orientation there is a negative Cotton effect in the same region [152].

GUAIANOLIDES

Guaianolides are sesquiterpene lactones the carbon skeleton of which consists of a guaiane nucleus condensed with a γ-lactone ring at C_6—C_7 or C_7—C_8 in trans- or cis-linkage (156, 165).

Guaianolides are known with the cis linkage of the cyclopentane and cycloheptane rings and the α orientation of substituents (162) and with the trans linkage of these rings and the β orientation of a substituent at C_1. Three carbon atoms in these compounds are represented by methyl or hydroxymethyl groups at C_4, C_{10}, and C_{11}. In this type of sesquiterpenoids, lactones have been found with exomethylene (180) and chloromethyl (185) groups at C_4 and C_{10} (scheme 10).

The guaianolides differ from one another by the nature and positions of their functional groups and by their degree of saturation. The double bonds are frequently conjugated with the formation of diene and dienone groupings that may be present in the most diverse positions.

The carbon skeleton of the guaianolides is revealed by the dehydrogenation reaction in the presence of selenium, palladium, carbon, or sulfur. This reaction involves aromatization, the opening of the γ-lactone ring, and decarboxylation with the formation of chamazulene. The dehydration of the reduction product of dihydrozaluzanin C (157) gives artemazulene (158), and the product of the reduction of lactucin (160) is a mixture of artemazulene (158) and linderazulene (161). Consequently, linderazulene is formed from guaianolides having a hydroxy group at C_8 and also from guaianolides with the γ-lactone ring at the C_7—C_8 atoms.

The treatment of cumambrin B (162) with sodium acetate in dimethyl sulfoxide leads to the formation of isocumambrin B (164). The formation of an ether bond between C_7 and C_{10} in isocumambrin B takes place through the intermediate compound (163). The reaction of caustic soda on geigerin (165) opens the γ-lactone ring with the formation of the sodium salt of a γ-hydroxy acid, and on acidification (166) is obtained. In this case, an ether bond arises between C_5 and C_8 which hinders the formation of a γ-lactone ring.

Boiling austricin (167) in toluene in the presence of potassium carbonate gives anhydroaustricin (168). When laferin (169) is saponified with alkali, deacetylation, the opening of the γ-lactone ring, and the elimination of the hydroxy groups formed is observed with the production of an acid having a conjugated system of double bonds (170).

With acetone in sulfuric acid, canin (171) forms the acetonide (173) via an intermediate compound (172). The opening of the epoxide ring in ajadin (174) takes place when it is heated with oxalic acid, the product being ajanin (175).

Artemolin (176) is not acetylated by acetyl chloride but is converted into parishin C (177), i.e., elimination of the hydroxy group and an allyl rearrangement take place.

When acroptilin (178) is treated with caustic soda, in addition to the saponification of the ester group a product with a new epoxide ring (179) is formed. As is well known, an epoxymethylene group is readily opened under the action of nucleophilic reagents. This reaction takes place in accordance with Krasuskii's rule, i.e., the bond between the oxygen atom and the less substituted carbon atom is cleaved. For example, the reaction of acroptilin acetate (180) with perchloric acid in tetrahydrofuran forms linichlorin C (181) and its isomer (182). This isomer is readily isolated at room temperature with acetic anhydride in pyridine to mono- and diacetyl derivatives (183a, b), or in one of the hydroxy groups it has a tertiary nature.

The action of hydrogen chloride on guaianolides with epoxy groups leads to their opening and, as a rule, the halogen atom adds to the less substituted carbon atom. The initial compound can be recovered by treating the chlorine-containing guaianolide with silver nitrate. In this way the passage from chlorojanerin (185) to janerin (186) has been performed, and the reduction of chlorojanerin by the zinc-copper couple in absolute ethanol has led to cynaropicrin (184).

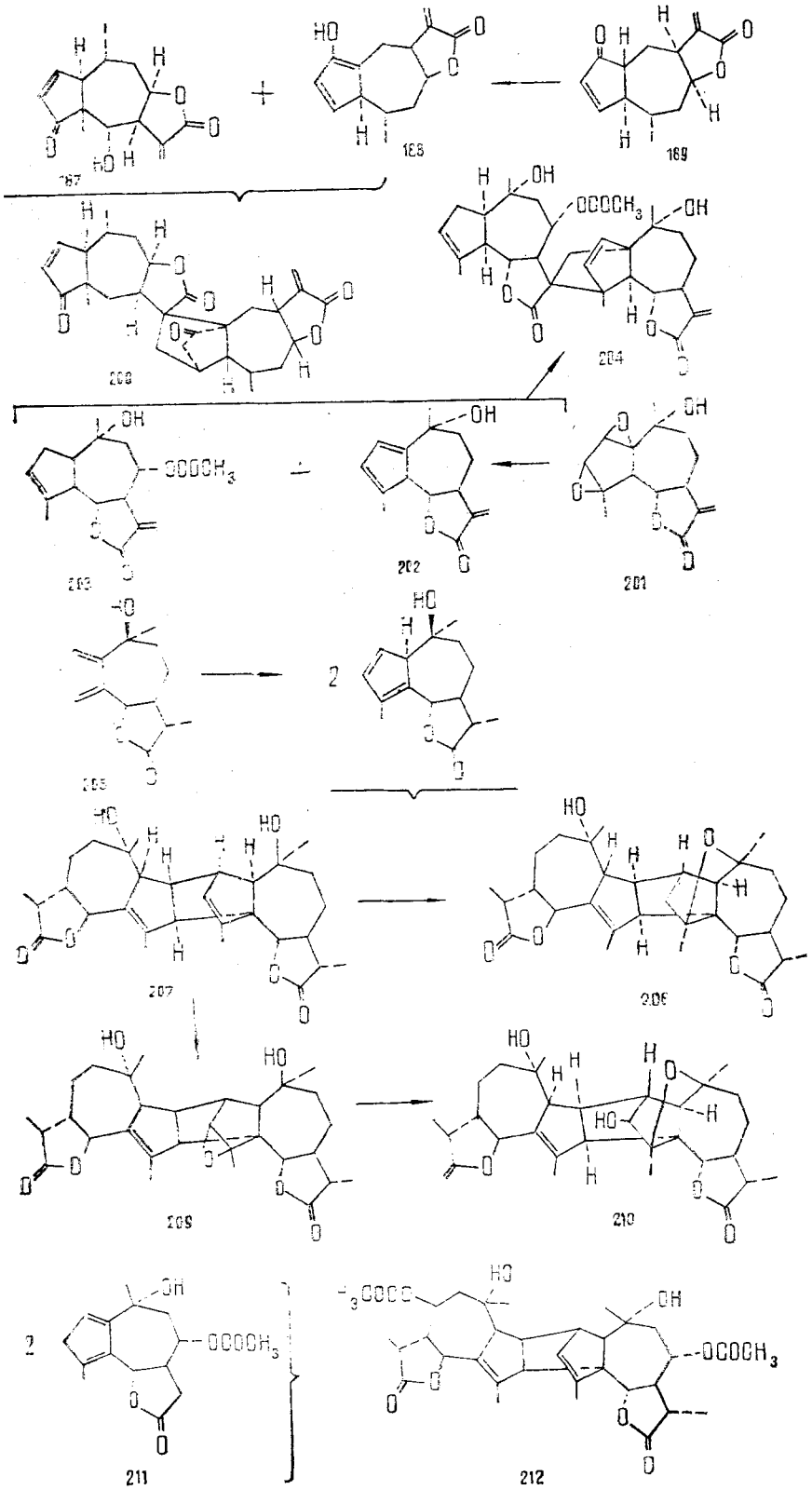
DISESQUITERPENOIDS

The structure of the disesquiterpenoids, the carbon skeleton of which consists of 30 carbon atoms, must be considered as the product of the diene synthesis of two sesquiterpenoid molecules. The sesquiterpenoid fragments of these compounds may relate to the same or different types of terpenoids.

The first natural dimeric guaianolide, absinthin (207), was isolated in 1956 by Herout et al. [137]. On being boiled in decalin, absinthin decomposes into two guaianolides, one of which was identified as artabsin (205). In 1968, the structure of artabsin was reconsidered. In view of this, the structure of absinthin was corrected [138]; it is now considered as a natural product of the diene synthesis of two artabsin molecules.

It is known that in an acid medium absinthin is readily converted into anabsinthin (208) [137]. Our results have confirmed that absinthin is a diguaianolide which is probably synthesized in the plant from the guaianolide (206) [140].

The lactone anabsin (210), which we isolated from *Artemisia absinthium* L. [139, [140], is also a diguaianolide. In differs from anabsinthin by the presence of a second hydroxy group in a cyclopentane ring. In the plant, anabsin is apparently formed as the result of the oxidation of absinthin via the epoxy compound (209). The structures of absinthin and anabsin were determined on the basis of the results of a study of the NMR spectra of the lactones and their derivatives and have been confirmed by x-ray structural analysis [140]. In 1980 French scientists came to similar conclusions [141].



Scheme 11. 187) halenalin [149, 150]; 188) enolic form of mexicanin E; 189) mexicanin E [151]; 200) microlenin [148]; 201) cumambrin A [145, 146]; 202) guaianolide; 203) chrysartemin B [147]; 204) handelin [143, 144]; 205) artabsin [138]; 206) isomerization product of artabsin; 207) absinthin [139, 141]; 208) anabsinthin [137]; 209) product of the oxidation of absinthin; 210) anabsin [139, 140]; 211) achillicin [142]; 212) diguaianolide.

Artemisia absinthium possibly also contains disesquiterpenoids the sesquiterpene fragments of which belong to different types of terpenoids, since guaianolides, germacranolides, and eudesmanolides have now been isolated from these plants [64, 103].

Recently, from *Achillea millefolium* L. has been isolated the guaianolide achillicin (211) [142], which suggests the possibility of the presence of the diguaianolide (212) in this plant.

From *Handelia trichophylla* (Schrenk) Heimerl, we have isolated the diguaianolide handelin (204) [143, 144]. It may be assumed that in the plant it is formed as the result of the diene synthesis between cumambrin A (201) [145, 146] and the guaianolide (202), which is apparently a precursor of chrysartemin B (203) [147]. Such hypotheses are confirmed by the isolation from the same plant of cumambrin A and chrysartemin B, but it has not yet been possible to isolate the guaianolide (202). In handelin the sesquiterpene fragments are connected via a spiro center, i.e., an exomethylenic double bond conjugated with a γ-lactone carbonyl participates in one sesquiterpene fragment. A similar bond between two sesquiterpene fragments has been reported in the disesquiterpenoid microlenin (200) [148] (scheme 11).

In the plant, microlenin is apparently formed in the process of the diene synthesis from the pseudoguaianolide helenalin (187) [149, 150] and the norpseudoguaianolide mexicanin E (189) [151] (scheme 11).

Thus, the search for disesquiterpenoids must be performed in those plants from which sesquiterpenoids with diene groupings or their oxidation products, diepoxy compounds, and also lactones with α,β-unsaturated carbonyl groups, which can isomerize into enolic groups, have been isolated.

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