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RECENT ADVANCES IN THE CHEMISTRY OF THE SESQUITERPENES

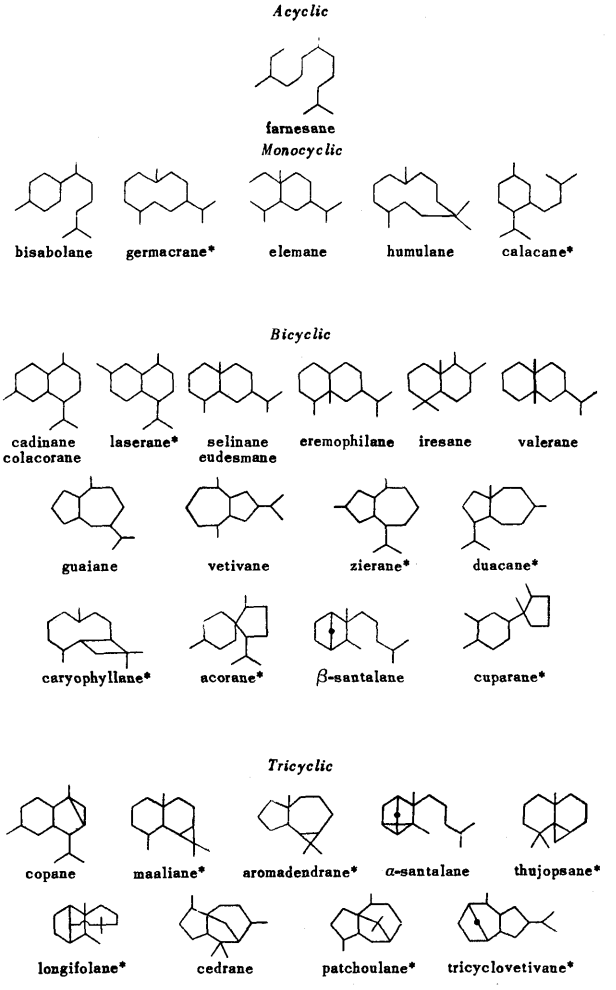
M. Suchý, V. Herout, and F. Šorm

The general study of living matter provides a constant source of information and is of great theoretical and practical value. The very origin of organic chemistry lay in the urge to investigate products of the metabolism of living organisms. Since that time the study of natural products has always formed an important part of organic chemistry. The study of substances contained in plants, which represent the major part (more than 99.9%) of living matter on the earth, has been of especial value in the development of our science. All the types of compound which make up the world of living organisms are produced in plant metabolism; this process is the source of characteristic groups of organic compounds, including especially terpenes, alkaloids, and glycosides. The thorough study of the chemical structure of numerous, genetically interrelated compounds of these groups was stimulated by their biological activity, and sometimes also by their practical importance. Their systematic study contributed to the creation of the best traditions in organic chemistry and to its present diversity.

The study of terpenes and steroids was undoubtedly of great value in the development of organic chemistry. Both groups are restricted by their simple composition, limited by containing only three principal elements, and by the individual structural regularities in each group. However, their great structural diversity and wide distribution was led to the study of terpenes and steroids becoming a subject of deep interest to many laboratories in the world. The principal methods for determining the structure of organic compounds, especially degradation, were discovered and tested in the investigation of compounds of both groups; this simultaneously stimulated the development of synthetic methods. The study of terpenes and steroids laid the foundations of stereochemistry, and constituted the starting points for modern concepts of the spatial structure of organic compounds. Chemistry was simultaneously enriched with very valuable methods for isolating pure organic substances from complex mixtures, and for their determination and identification by means of physical constants or the relations between chemical structure and physical, especially spectroscopic properties, without which modern organic chemistry cannot be imagined.

In our first review paper, published in this journal in 1953,[1] we surveyed the work carried out up to 1952 in the Institute of Organic Chemistry of the Czechoslovak Academy of Sciences. The present paper reviews some later results obtained in the Institute of Organic Chemistry and Biochemistry of the Czechoslovak Academy of Sciences in Prague, especially on terpenoid compounds of the sesquiterpene group which had been little studied previously.

Scheme 1
Survey of types of sesquiterpene hydrocarbons



These compounds, in the study of which great interest has been shown, are very varied. This can be seen from Scheme 1, on which are represented all the hydrocarbon skeletons which have now been established in this group. The asterisks indicate formulae corresponding to structures which have been discovered and proved beyond doubt during the past fifteen years; the remaining structures were investigated earlier. The names of the structural types derive from those of some important sesquiterpenoid hydrocarbons containing the given hydrocarbon skeleton.

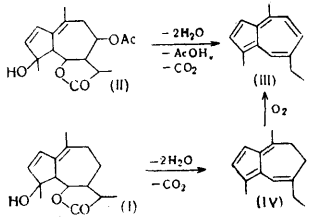
The infra-red spectra of the sesquiterpenes and the spectra of their derivatives have been collected in a new volume, which has recently been published by the German Academy of Sciences in Berlin[2].

Those natural products which are sesquiterpene derivatives having a bicyclic five- or seven-membered carbon skeleton and containing a γ-lactone group are worthy of

more detailed study. A large group of these substances are structurally related to guaiane, since their fundamantal skeleton is the carbon skeleton of guaiane, and we therefore term them *guaianolides*. They are found in many plants of the *Compositae* family. The discovery of this group of substances is associated with the study of the chamazulenogenic substances in wormwood and camomile[3,4], and with the study of the structure of chamzulene[5-7]. During 1951-1952 the problem of the structure of chamazulene and of substances, present in both plants of the *Compositae* family, which form chamazulene on distribution in steam, was solved. Since azulene is absent from the plant extract, it can be assumed to have been formed only as a result of changes occurring on distillation of the vegetable material in steam. We therefore turned our attention to the isolation of these new substances, precursors of chamazulene.

Our first result was the isolation of two crystalline hydroxylactones from bitter wormwood and pharmaceutical camomile. We determined the chemical structure of both substances, and termed them *artabsin* (I)[8] (from wormwood) and *matricin* (II)[9] (from camomile) (see Scheme 2).

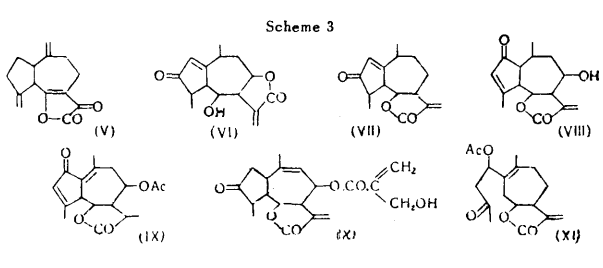
Scheme 2



These compounds are unstable: when heated in weakly acid solution they are converted into chamazulene (III) as a result of dehydration and decarboxylation. In the case of artabsin an unstable orange hydrocarbon of fulvene type is formed at first. This readily polymerisable substance had previously been obtained and identified by us in the essential oil of wormwood. It had then been named *chamazulenogen* (IV),[10] and its structure determined, being found to correspond to a dihydrochamazulene. This substance is converted into chamazulene by oxidation in the air. These reactions of artabsin, as also of matricin, which is an acetoxy-derivative of artabsin, led to the correct formula for chamazulene and at the same time enabled its composition to be established as $C_{14}H_{16}$, which is unusual for a sesquiterpenoid compound. We confirmed the structure of chamazulene by a complete synthesis.

The discovery of this new type of compound in nature stimulated further study of products extracted from plants of the *Compositae* family. This opened the way to the establishment of the structure of several similar compounds, some of which had already been known for a long time, although their structure had not been determined (Scheme 3).

Scheme 3



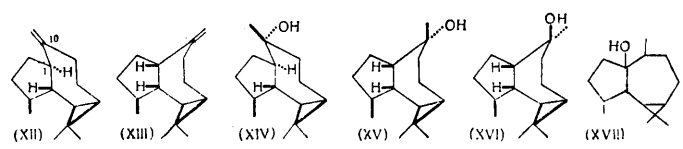
In this way structures were established for dehydrocostus lactone (V)[11,12] from the essential oil of the roots of *Saussurea lappa*, helenalin (VI)[13,14] from several species of *Helenium*, ambrosin (VII)[15,16] from *Ambrosia maritima* (a plant growing in the Nile Delta), lactucin (VIII)[17,18] from *Cichorium intybus* and several *Lactuca* species, matricarin (IX),[19] a lactone from *Matricaria chamomilla*, absinthin and anabsinthin from wormwood[20-22] cynaropicrin (X)[23,24] from *Cynara scolymus* and *Cynara cardunculus*, xanthinin (XI)[25,26] from *Xanthium pensylvanicum*, and globicin from *Matricaria globifera*[27].

All these compounds confer a bitter taste on plants containing them. Recently the structures of other guaianolides have been determined, for example arborescin[28] from *Artemisia arborescens*, carpesia lactone[29] from *Carpesium abrotanoides*, isohelenalin[30], tenulin, and isotenulin[31] from different *Helenium* species, and geigerin[32] from the South African plant *Geigeria aspera*.

We shall not give a complete catalogue of these substances: new papers are constantly appearing on the structure of new guaianolides. The number of derivatives studied so far shows that we are dealing with substances which occur very often in plants of the *Compositae* family.

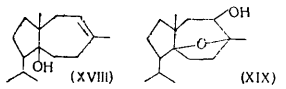
Another interesting group of compounds with a similar structure are those of the aromadendrane type, which are distinguished from the guaiane type by containing an additional three-membered carbon ring. We have discovered the hydrocarbon alloaromadendrene, which is an isomer of the already known aromadendrene. The two hydrocarbons differ in configuration at $C_{(1)}$. We established the precise structure of aromadendrene, *i.e.* the position of the three-membered ring[33], by degradation. Spatial structures were determined for both hydrocarbons, and are represented by the formulae (XII) for aromadendrene and (XIII) for alloaromadendrene[34]. Globulol (XIV), which contains the same skeleton, had been known previously. This group was extended to the following sesquiterpenoid alcohols: ledol (XV), viridiflorol (XVI), and palustrol (XVII). All these sesquiterpenoid alcohols yield the same diol on dehydration followed by hydroxylation[35-37], so that they differ only in the position of the hydroxyl group or in their spatial structure. However, the differences between them extend only to the carbon atoms $C_{(1)}$ and $C_{(10)}$. We have found that ledol corresponds to the spatial formula (XV), viridiflorol to (XVI), and globulol to (XIV). Palustrol was established as a position isomer with the hydroxyl group attached to $C_{(1)}$, as can be seen from the formula (XVII) (Scheme 4). Büchi *et al.*[38] reached the same conclusions, independently of us, in a study of the structure of aromadendrene, ledol, viridiflorol, and globulol.

Scheme 4



The azulane skeleton is also present in two sesquiterpenoid alcohols, carotol (XVIII) and daucol (XIX), which are found in the carrot, *Daucus carrota* L. In contrast to other

workers, we have suggested the formulae (XVIII) and (XIX),[39] based on identification of the oxidation products. They are confirmed by the work of Shoolery *et al.*[40] using nuclear magnetic resonance data. We obtained further interesting results in a study of a group of substances containing medium carbon rings (by this we imply rings containing 8–11 carbon atoms).

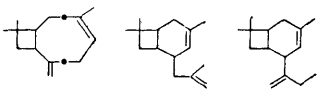


(XVIII) (XIX)

Compounds containing nine-, ten-, or eleven-membered rings have been found among natural products. The discovery of these compounds in plants was somewhat unexpected, since it was only recently that the existence of large rings in nature was rigorously proved in macrocyclic aromatic ketones which were also products of animal metabolism. The difficulties involved in the synthesis of medium-ring alicyclic compounds, which were surmounted only a few years ago by means of the acyloin condensation, together with certain theoretical aspects of their conformation, supported the previously accepted view that substances of this type were unknown in nature.

The existence in nature of a medium-sized alicyclic ring was first demonstrated by us in an investigation of the structure of caryophyllene[41]. Much work had been done on this hydrocarbon, and the two alternative structural formulae (XXa) and (XXb) were regarded as the most probable. Perhaps the major proportion of the work in the field of sesquiterpenoid compounds in general has been devoted to elucidating the structure of this hydrocarbon. It was known long ago that caryophyllene (XXI) is a bicyclic hydrocarbon containing two double bonds and a characteristic four-membered ring with two geminal methyl groups. At first we wanted to know which of the two possible formulae then proposed[42-45], (XXa) (Ruzicka) or (XXb) (Treibs), corresponded to this substance (Scheme 5).

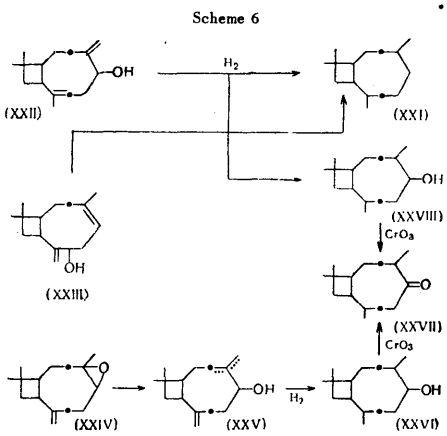
Scheme 5


(XXI) (XXa) (XXb)

However, the cleavage reactions which we carried out[48] permitted four new formulae to be ascribed to caryophyllene, according to which the molecule contains a nine-membered carbon ring. Two of them were then excluded on the basis of the structure of homocaryophyllenic acid (one of the oxidation products of caryophyllene) determined by Dawson and Ramage[46]. Simultaneously, Barton *et al.*[47] proved one of the two remaining formulae to be correct, and determined the absolute configuration of caryophyllene. The structure of the main skeleton of caryophyllene (XXI) was later confirmed by us by the partial synthesis of tetrahydrocaryophyllenic acid.

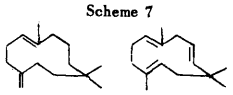
We subsequently demonstrated the presence of a caryophyllene skeleton in two sesquiterpenoid alcohols, the so-called α-betulenol (XXII) and β-betulenol (XXIII),[49] which are found in the essential oil of birch buds. Both are secondary alcohols. Scheme 6 shows the correlation of these two substances with a caryophyllene derivative, and monoepoxide (XXIV).

Scheme 6



The hydrocarbon humulene was the next compound in which it was possible to demonstrate the presence of a medium-sized, in this case an eleven-membered, ring. This hydrocarbon is supposed to be closely related genetically to caryophyllene, as is indicated by its structure and by the fact that it is often found in essential oils, for example, oil of cloves and oil of hops. Humulene[50,51] is a monocyclic compound containing three double bonds. We suggested a structure for it, which was soon confirmed by Clemo[52] on the basis that oxidative cleavage of the hydrocarbon yields only formaldehyde and acetic acid apart from 2,3-dimethylsuccinic acid: no higher monofunctional cleavage products are formed. Only the complete synthesis of hexahydrohumulene (humulane)[53] finally confirmed the humulene skeleton. The synthetic hydrocarbon which we obtained was identical with the product of complete hydrogenation of natural humulene (as established by an examination of the infra-red spectra). The question of the position of the double bonds was completely solved only recently, when we discovered that two humulenes, α (XXIX) and β (XXX),[54] occur in nature. In the first of these compounds one double bond is exocyclic and methylenic; in the other compound it is located in a carbocyclic ring (Scheme 7).

Scheme 7

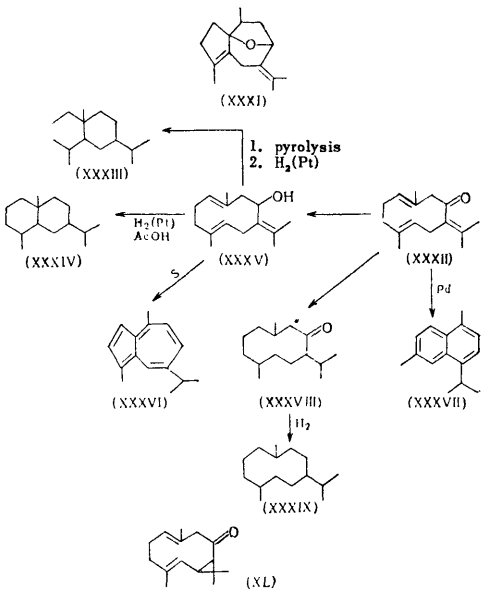

(XXIX) (XXX)

Recently Dev[55] discovered, from a comparison of the infra-red spectra of a saturated hydrocarbon obtained from the sesquiterpenoid ketone zerumbone and of humulane, that zerumbone possesses a humulane skeleton. It is probable that humulene and caryophyllene are interrelated genetically in the sense that the latter is a product of the cyclisation of the former. However, it has not yet proved possible to effect this cyclisation by chemical means because of the comparative instability of humulene.

The next constantly increasing group of sesquiterpenoid compounds comprise substances containing a ten-membered ring. These compounds, in the form of their oxygen derivatives, are probably frequent metabolic products, especially of plants of the *Compositae* family; they are of great importance in the biogenesis of several other bicyclic sesquiterpenoid compounds, as will be shown later.

The first natural product in which the presence of a ten-membered ring was suggested was the lactone pyrethrosin, studied by Barton[56,57]; the first compound in which the presence of this ring was precisely demonstrated was the ketone germacrone[58], the main constituent of "health" oil. It is interesting to recall the history of the investigation of this substance, which had already been known earlier under the name "germacrol" and investigated in detail by Treibs, who suggested the formula (XXXI) for it (Scheme 8).

Scheme 8

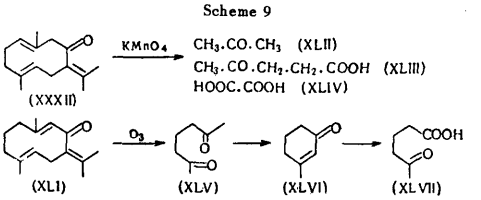


According to Treibs, germacrol was an internal ether having a guaiane skeleton. In collaboration with Bulgarian colleagues, we initiated work to check the structure of this compound, and found from the infra-red spectrum of germacrol that it is not an ether but an unsaturated ketone (absorption band for the carbonyl group at 1675 cm^{-1}).[58] When we tried to obtain hydrogenation and dehydrogenation products of germacrone (XXXII) (as we renamed the substance in conformity with the nature of the oxygen function), we obtained surprising and contradictory results. After hydrogenation in acetic acid in the presence of a platinum catalyst, we isolated two pure hydrocarbons. One of them had the composition $C_{15}H_{30}$, and according to its infra-red spectrum was elemane (XXXIII). The other, $C_{15}H_{28}$, was identical with selinane (XXXIV). Reduction of germacrone with aluminium isopropoxide yielded an alcohol (XXXV), which could be reconverted into crystalline germacrone by oxidation. Dehydration yielded a mixture of hydrocarbons, dehydrogenation of which gave a considerable quantity of guaiazulene (XXXVI). It was known that the dehydrogenation of germacrone under severe conditions will lead to the production of cadalene (XXXVII).

Thus from germacrome and its derivatives it is possible to obtain, under mild or severe conditions, derivatives of four different types of sesquiterpenes, of which only the elemane type (XXXIII) corresponds to the suggested monocyclic character of germacrone. Since it was difficult to assume the formation of other bicyclic sesquiterpenoid compounds from those of the elemane type, we concluded that germacrone is not a derivative of known types of sesquiterpenes. This was demonstrated by hydrogenation, which yielded a saturated ketone, hexahydrogermacrone $C_{15}H_{28}O$ (XXXVIII) and a hydrocarbon $C_{15}H_{30}$ (XXXIX). The infra-red spectrum of the latter showed it to represent a then unknown type of sesquiterpene, which we termed the germacrane type. All the reactions described so far can be explained if it is assumed that a ten-membered ring is present in germacrone and in germacrane (XXXIX). This is indicated also by the physical properties of hexahydrogermacrone (XXXVIII), whose infra-red spectrum showed a ketone peak (1704 cm^{-1}) characteristic of medium rings. The final proof of this was our synthesis of one of the cleavage products of germacrone[59], and especially the complete synthesis of germacrane (XXXIX). The synthetic hydrocarbon[60] was completely identical with the substance obtained from germacrone. It was extremely difficult to prove the location of the double bonds in germacrone, especially in view of the anomalous character of the infra-red and ultra-violet spectra of this compound[61]. New formulae were therefore proposed for germacrone, one of which was, for example, the formula of the maaliol type (XL) suggested by Ohloff *et al.*[62]

It has recently proved possible[63] to demonstrate the location of the double bonds from a study of the products of the alkaline oxidation of germacrone (XXXII) and its isomer, the so-called isogermacrone (XLI). On ozonolysis or oxidation with alkaline potassium permanganate, germacrone yields, apart from 1.5 moles of acetone, laevulinic acid (XLIII) and oxalic acid (Scheme 9).

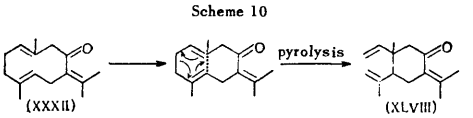
Scheme 9



Only 0.6 mole of acetone is formed by the ozonolysis of isogermacrone under similar conditions. When the heptane-2,6-dione (XLV) obtained at first was oxidised under analogous conditions, 3-methylcyclohex-2-enone (XLVI) was isolated, and this oxidised to homolaevulinic acid (XLVII). In view of this, we suggest that germacrone has the formula (XXXII), while isogermacrone is (XLI). It follows that (XLI) arises from germacrone by the displacement of one double bond; the nature of its ultra-violet spectrum also changes in conformity with this.

Our proposed formulae for germacrone are consistent also with reactions leading to other types of sesquiterpenes. The transition to the elemane group is especially interesting. Simply heating germacrone yields β-elemenone (XLVIII), involving the formation and rupture of carbon–carbon bonds. This particular reaction is favoured by the arrangement of double bonds in germacrone (Scheme 10).

Scheme 10



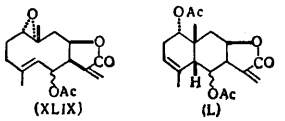
Owing to the change in position of the double bonds involved in the reaction under such conditions, isogermacrone does not pass into β-elemenone. In contrast to natural elemane derivatives, β-elemenone obtained from germacrone is optically inactive. If the natural elemane derivatives which do not possess a regular isoprene structure are formed by the above mechanism, it must be supposed that this process involves the participation of specific biocatalysts.

The transformation of germacrone into other sesquiterpenoid types on hydrogenation or dehydrogenation, and especially its conversion into compounds of the selinane type (XXXIV), can be explained by transannular cyclisations, which have been observed also in other cases[64-66].

Many compounds having a ten-membered ring have been found in a detailed study of sesquiterpenoid lactones obtained from plants of the *Compositae* family. The investigation was made after the discovery of the guaianolides, a huge new group of sesquiterpenoid compounds having a guaiane skeleton, which are closely related to the santonin group.

At the beginning of 1957 Barton published his first paper on pyrethrosin, a sesquiterpenoid lactone from *Chrysanthemum cinerariaefolium*[56] having the composition $C_{17}H_{22}O_3$ (Scheme 11).

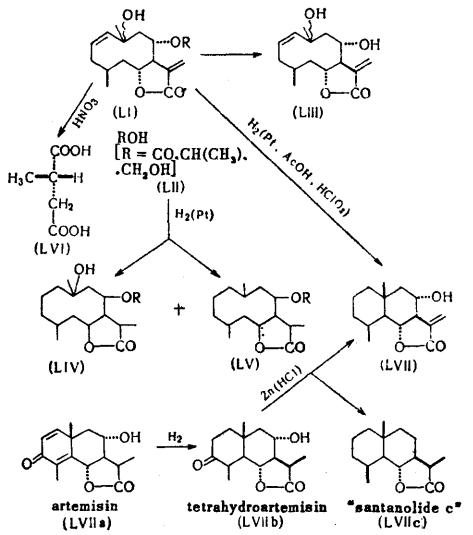
Scheme 11



On the basis of a detailed study of the reactions of cyclopyrethrosin and of the physical properties of the derivatives obtained, Barton[57] has recently proposed a final structure for pyrethrosin (XLIX) and its cyclisation product (L), and at the same time has almost completely established its configuration.

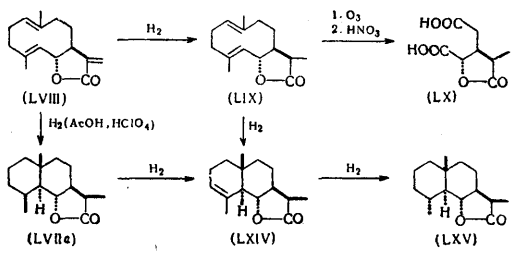
At the same time we discovered, in a study of arctiopicrin (LI),[67,68] the lactonic bitter principle of the plant *Arctium minus*, that the formula previously assigned to it was incorrect, it being actually an ester of 3-hydroxy-2-methylpropionic acid (LII) and a sesquiterpenoid lactone, which we called *arctiolide* (LIII). Since the empirical formula of (LIII) was $C_{15}H_{22}O_4$ and it contained two double bonds, its main carbon skeleton was clearly monocyclic. Further study of arctiolide by the hydrogenation of arctiopicrin proved that it was a secondary hydroxyl group which had been esterified. Reduction also involved hydrogenation of a tertiary hydroxyl, and so the ester-lactone (LV) was isolated in addition to the hydroxy-ester-lactone (LIV). The position of the double bond in the ring was then confirmed by oxidising arctiopicrin with nitric acid, the ensuing isolation of *L*(-)-methylsuccinic acid indicating the absolute configuration of the tertiary methyl group. The main proof of the structure of arctiopicrin was the direct correlation with compounds of the santonin group[64]. Here, the first observation was made of a stereospecific conversion from the germacrone group by transannular cyclisation into the selinane group. Hydrogenation of arctiopicrin in glacial acetic acid in the presence of a small amount of perchloric acid yielded a bicyclic product which after hydrolysis proved to be identical with deoxytetrahydroartemisin (LVII); this last compound was also prepared synthetically by Clemmensen reduction from artemisin (LVIIa). "Santanolide c" (LVIIc) and tetrahydroartemisin (LVIIb) were obtained as byproducts (Scheme 12).

Scheme 12



Recently the Indian workers Somasekar Rao *et al.*[69] have studied a monocyclic sesquiterpenoid lactone from the Himalayan plant *Saussurea lappa*, which they termed *costunolide* (LVIII) and showed it to contain also a germacrane cyclodecane skeleton. At the same time we were studying substances present in the Asian species of wormwood *Artemisia balchanorum*, and isolated a lactone identical with costunolide, as the main constituent of this plant. We were able[70] to prove that it corresponds to the formula (LVIII) suggested by the Indian workers (Scheme 13).

Scheme 13

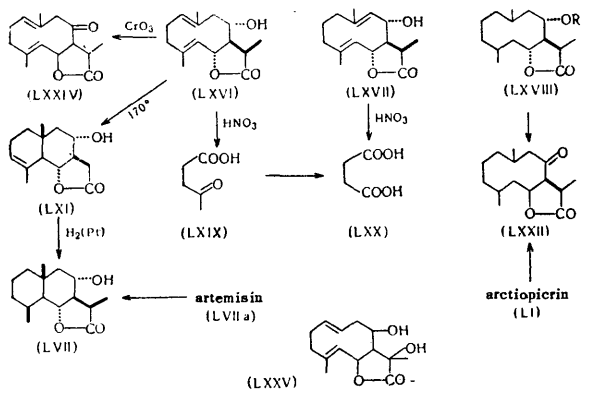


In this proof, we were assisted by the fact that among the products of the ozonolysis and further oxidation of dihydrocostunolide (LIX) was a lactone-dicarboxylic acid $C_8H_{10}O_6$ (LX) which we had already isolated earlier and identified as an oxidation product of santonin, artabsin, and absinthin[20-22]. We were also able to demonstrate rigorously the absolute configuration of costunolide. In this we were again helped by transannular cyclisations, which could now be carried out in several ways. Thus the product of the hydrogenation of costunolide in acid medium was identical with santanolide c (LVIIc), one of the reduction products of santonin (LXII). By being boiled with a mixture of acetic acid and acetic anhydride, dihydrocostunolide (LIX) could be converted into an unsaturated bicyclic lactone, which was identified as 3-santenolide (LXIV), described by Cocker and McMurry[71]. Further hydrogenation of this

initial product of cyclisation yielded a mixture of santanolide a (LXV) and santanolide c (LVIIc), already described earlier[72]. In conformity with the known configuration of santonin (LXII) all these reactions show that costunolide possesses the configuration indicated in Scheme 13. The configuration which we proposed for costunolide (LVIII) was later confirmed also by the Bhattacharyya school[73].

Costunolide is not the only lactone from *Artemisia balchanorum*. Paper chromatography of the plant extracts showed the presence of at least four lactones, three of which we were able to isolate in crystalline form. They all contain a cyclodecane ring[66]. Two of the lactones have the composition $C_{15}H_{22}O_3$, and they both contain two double bonds and one hydroxyl group. We named them *balchanolide* (LXVI) and *isobalchanolide* (LXVII). The two compounds differ only in the position of the double bonds, since hydrogenation and acetylation yield the acetyltetrahydrolactone (LXVIII) (Scheme 14). The location of the double bonds in the two lactones was determined by oxidative cleavage, which in the case of balchanolide (LXVI) yielded laevulinic acid (LXIX) and succinic acid (LXX). After cyclisation of balchanolide by the usual method in acid medium or by heating at 170° and hydrogenation of the cyclisation product (LXI), deoxytetrahydroartemisin (LVII) was obtained, a compound which we had already obtained in our work with arctiopicrin (LI). Thus the structure and the absolute configuration of both lactones were determined, and were then confirmed by correlation with derivatives prepared from arctiopicrin (LI). After oxidation of the hydroxyl group in tetrahydroisobalchanolide (LXVIII: R = H) the ketolactone (LXXII) was isolated and found to be identical with a known compound obtained from arctiopicrin (LI) and cnicin (LXXIII). The proposed structure (LXVI) is also confirmed by the fact that oxidation yields an unsaturated ketolactone (LXXIV) with a non-conjugated keto-group (Scheme 14).

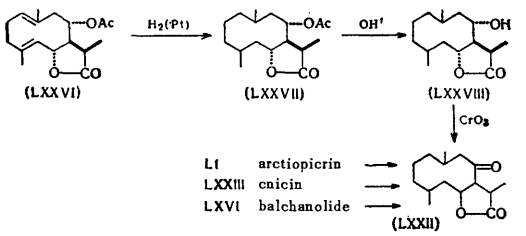
Scheme 14



The third of the substances which we isolated from *Artemisia balchanorum* had the composition $C_{15}H_{22}O_4$ (LXXV). We were able to demonstrate, by a series of reactions, that the position of the double bonds in this compound is the same as in balchanolide, and to determine the position of the tertiary hydroxyl group.

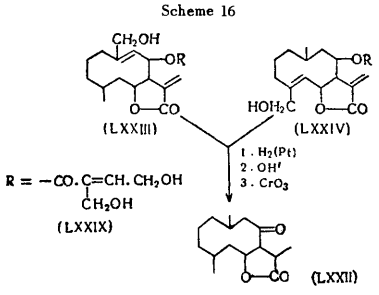
We have recently discovered[74] that one of the lactones isolated from yarrow, *Achillea millefolium*, is very closely related to balchanolide (LXVI). Chamazulene can be isolated from this plant, as also from camomile, by distillation in steam. This implies that *Achillea millefolium* contains its lactone precursors of the guaianolide group. It has not yet proved possible to isolate the original lactone in a pure form because of its instability. From yarrow itself, however, we have isolated three other crystalline lactones. One of them, having the empirical formula $C_{17}H_{24}O_4$ (LXXVI), gave acetic acid on hydrolysis. The lactone contained two double bonds in the molecule, and hydrogenation yielded a tetrahydro-derivative (LXXVII), which on hydrolysis gave a hydroxylactone (LXXVIII) (Scheme 15).

Scheme 15



When it was oxidised with chromium trioxide, we obtained a ketolactone (LXXII), which was identical with the known ketolactone prepared from arctiopicrin (LI) and cnicin (LXXIII). These facts give grounds for assuming that the new lactone from yarrow might be acetylbalchanolide (LXXVI), as was confirmed by the mixed melting-point method with acetylated balchanolide and from a comparison of the infra-red spectra.

Scheme 16

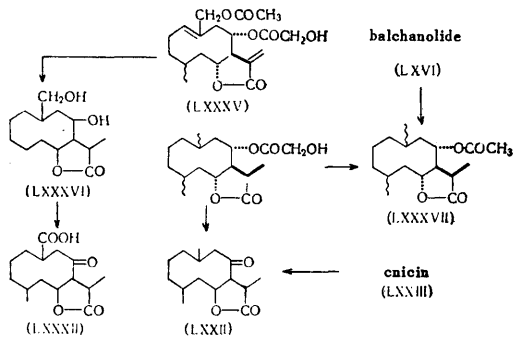


The germacrane group includes the bitter principle of *Cnicus benedictus*, which has been known for a century. This compound was assigned an incorrect formula[75], and only recently[76,77] has it been demonstrated that cnicin (LXXIII) is an unsaturated monocyclic sesquiterpenoid lactone esterified with the unusual 2,3-di(hydroxymethyl)acrylic acid (LXXIX). The free lactone has the composition $C_{15}H_{22}O_4$ and contains two hydroxyl groups and two double bonds (Scheme 16), one of the latter being conjugated with the carbonyl group of the lactone. The properties of the hydrogenation products of cnicin indicate that the esterified hydroxyl group is secondary, whereas the other hydroxyl is primary, since oxidation of the diol (LXXXI), obtained by saponification of the completely hydrogenated cnicin, yielded a ketolactonecarboxylic acid (LXXXII). The position of the esterified hydroxyl was determined from the fact that hydrogenolysis and saponification of cnicin gave a product which after oxidation with chromium trioxide yielded a ketolactone (LXXII) identical with a known compound obtained from arctiopicrin (LI). This indicates that a double bond must be located near the primary hydroxyl group (hydrogenolysis occurring readily). Hydrogenation of cnicin results in partial elimination of 2-methylbutyric acid, *i.e.* to further hydrogenolysis, indicating that cnicin

probably has the structure (LXXIII). However, the structure (LXXIV), although less probable, is not excluded. The proposed formulae are supported also by the oxidation products of hydrogenated cnicin, from which were isolated succinic, methylsuccinic, α-methylglutaric, and α-methyladipic acids. The configuration of the lactone group follows from the correlation with scabiolide (LXXXV), the configuration of the esterified hydroxyl group probably being analogous to that of the corresponding hydroxyl in scabiolide.

Cnicin, which we have recently found also in the plant *Centaurea rhenana*, is very closely related to another germacranolide, scabiolide (LXXXV), the main constituent of the oil of the cornflower species *Centaurea scabiosa*[78]. This crystalline substance is a diester of a sesquiterpenoid lactone, the esterifying acids being acetic and glycollic. The pure lactone contains two double bonds, one of which is as usual conjugated with the lactone carbonyl. One of the hydroxyl groups in scabiolide is primary, as in cnicin, the other is secondary. It has also proved possible to elucidate the relation between scabiolide (LXXXV) and cnicin (LXXIII). For this purpose the products of the complete hydrogenation of scabiolide and cnicin were saponified, and the resulting tetrahydro-derivative of the free dihydroxygermacranolide (LXXXVI) was oxidised with chromium trioxide. The same ketolactonecarboxylic acid (LXXXII) was obtained in this way. Hydrogenation of scabiolide yielded a monoester of glycollic acid (involving the carboxyl group) with the deoxytetrahydrolactone (LXXXVII), which after hydrolysis and oxidation yielded the already known ketogermacranolide (LXXII). In this way the germacrane skeleton of scabiolide was again confirmed, and the structure of its lactone ring proved (Scheme 17).

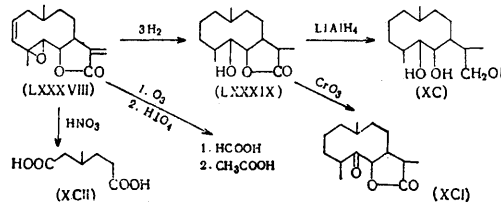
Scheme 17



The configuration of most of the centres of asymmetry in the scabiolide molecule, like that of most of the other germacranolides, was determined[79] by preparing acetyltetrahydrobalchanolide (LXXVII) from the deoxytetrahydrolactone after selective hydrolysis and acetylation with acetic anhydride.

Parthenolide[80], which we have isolated from the plant *Chrysanthemum parthenium*, is also a monocyclic lactone of the germacrane type having the composition $C_{15}H_{20}O_3$ (Scheme 18). It contains two double bonds, one of which is conjugated with the lactone carbonyl. The third oxygen atom forms an ether group, as follows from the chemical reactions and the physical constants of parthenolide. The position of one double bond was determined by ozonolysis: formic acid was produced, whereas acetic acid was obtained from the volatile residues after oxidation with periodic acid. The course of oxidation is shown in Scheme 18.

Scheme 18

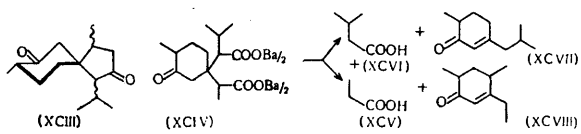


Parthenolide (LXXXVIII) is converted on catalytic hydrogenation into a hydroxylactone (LXXXIX), and on further reduction with lithium tetrahydroaluminate into a triol (XC) in which two secondary hydroxyl groups are linked to neighbouring carbon atoms. After oxidation of the hydroxylactone (LXXXIX) with chromium trioxide, a ketolactone (XCI) was isolated. The isolation of β-methyladipic acid (XCII) after oxidation of parthenolide with nitric acid enabled the position of the cyclic double bond to be determined.

The ease with which transannular cyclisations occur in sesquiterpenoids of the germacrane type, especially those resulting in compounds of the selinane type, *i.e.* in lactones of the santonin group, indicates that these reactions may be of great significance in biogenesis. It may be supposed that in nature lactones containing a cyclodecane ring are formed initially, and that substances of the santonin or guaianolide group are only formed from them by secondary reactions, analogous to the stereospecific transannular reactions which have been described. This possibility is suggested not only by the smoothness of the transannular reactions but also by the very wide distribution of the germacrane type of lactones in plants of the *Compositae* family, which contain also substances of the santonin group. Eleven very closely related lactones of the germacrane type, whose structures have been completely proved, have already been isolated within a short period. However, there is as yet no direct proof of the occurrence of such cyclisations in nature.

Many other interesting sesquiterpenoid derivatives are found in nature. An unusual structure predicted theoretically by Ružicka[81] in his paper on the biosynthesis of terpenes is shown by the diketone acorone (XCIII). This crystalline substance, obtained from *Acorus calamus*, was identified on further investigation[82-84] as a spiro-diketone having one six-membered and one five-membered ring (Scheme 19).

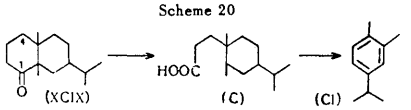
Scheme 19



The main evidence for the structure of acorone was provided by pyrolysis of the barium salt of the dicarboxylic acid (XCIV).[82] In this way propionic acid (XCV) and isovaleric acid (XCVI) were obtained together with two unsaturated ketones, isopropylmethylcyclohexenone (XCVII) and ethylmethylcyclohexenone (XCVIII). The proportions of the individual diketones were determined from the difference in optical rotation and the rotatory dispersion curves, and conclusions concerning their relative configurations were published[85].

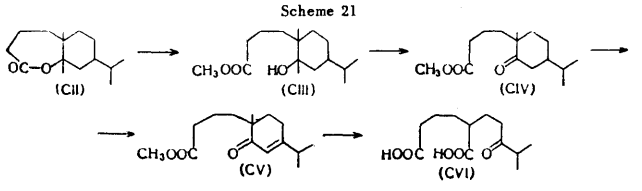
The saturated bicyclic sesquiterpenoid ketone valeranone (XCIX), which was found in *Valeriana officinalis*[86], gave rise to great difficulties in the determination of its structure. The latter was proved by the following series of reactions[87]. On photolytic cleavage valeranone gives a monocyclic acid (C), which on undergoing Barbier–Wieland degradation three times with subsequent dehydrogenation forms 1-isopropyl-3,4-dimethylbenzene (CI)(Scheme 20).

Scheme 20



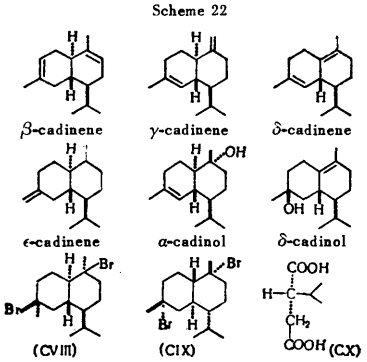
It has thus been proved that valeranone has a 7-isopropyl-9,10-dimethyldecalin hydrocarbon skeleton in which an oxo-group occupies position 1 or 4. The following series of reactions enables us to select[88] 7-isopropyl-9,10--dimethyldecalone from the two alternative formulae. Valeranone (XCIX) was oxidised with perbenzoic acid, yielding a lactone (CII). The methyl ester (CIII) obtained from it after hydrolysis was then dehydrated and ozonised. The keto-ester (CIV) after successive bromination and dehydrobromination gave an $\alpha\beta$-unsaturated keto-ester (CV), oxidative cleavage of which yielded a keto-dicarboxylic acid (CVI). From this it can be concluded that the oxo--group in valeranone is in position 1, since if it were in position 4, a tricarboxylic acid should be formed by the above reactions. This work corrected the erroneous conclusions of Indian workers[89,90], who call this substance "jatamansone".

Scheme 21



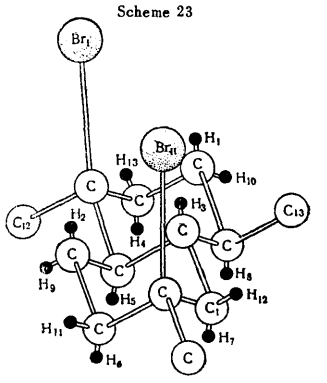
In conclusion we must mention the solution of a complicated problem, the establishment of the absolute configuration of compounds of the cadinane type. Physical methods have been of particular value in solving the structure of these natural products.

Scheme 22



We had investigated cadinane derivatives previously[91–93] as their presence had been discovered in natural materials. The structures suggested by ourselves and other investigators are indicated in Scheme 22. A common derivative of all these compounds is cadinene dihydrochloride (CVII) or even cadinene dihydrobromide (CVIII). Both derivatives contain the relatively heavy halogen atom in the molecule, and therefore are particularly easy to analyse by means of X-ray diffraction. From measurements on the X-ray patterns and calculations made by Hanic[94] it was clear that cadinene dihydrobromide (CVII) corresponds to the configuration represented diagrammatically in Scheme 23, which is equivalent to the formula (CVIII) or its mirror image (CIX).

Scheme 23



The configuration of the centres 1, 6, and 7, which are unaffected in the preparation of the halogeno-derivatives, should be identical in all these compounds. In order to determine the absolute configuration of the molecule, it was sufficient to determine the absolute configuration merely of one of these centres. On oxidative degradation of β-cadinene we obtained $D(+)$-isopropylsuccinic acid (CX), a compound whose absolute configuration has long been known. Hence the formula (CVIII) represents the absolute configuration of cadinene dihydrobromide, and consequently of other cadinene derivatives as well.

Note. Some of the formulae designated by Roman numerals are not given in the Russian original. (Ed. of Translation).

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