ADVANCES IN TERPENE CHEMISTRY

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ABSTRACT

In the first part of the lecture some new advances in the chemistry of sesquiterpenic lactones are discussed and the revised structures of some guaianolides and germacranolides are presented.

The second part is devoted to the chemistry of sesquiterpenic compounds of eremophilane type, met by the author and his collaborators repeatedly during the study of the plants of Petasites species and related plants. In addition to the basic hydrocarbon eremophilene a series of lactonic compounds was also isolated from the mentioned plants, to which the name eremophilanolides was given and which represent a new group of sesquiterpenic lactones. The most common natural derivatives of the eremophilane series are however furoeremophilanes. In addition to the free furoeremophilane an appreciable number of hydroxy- and keto-derivatives substituted predominantly in positions 3, 6 and 9 of the eremophilane nucleus, saturated and unsaturated and containing free or esterified hydroxy groups, has been isolated from plants. In the lecture the chemistry of these compounds is discussed, mainly those isolated recently, as for example adenostylone, neoadenostylone, isoadenostylone and kablicin.

Finally, possible biogenetical pathways of the sesquiterpenic lactones from the corresponding furan derivatives are also discussed.

INTRODUCTION

It is more than fifteen years ago, during a systematic study of sesquiterpenic compounds, that our attention was drawn to the problem of the origin of natural azulenes, especially chamazulene. It is well known that this azulene causes the dark blue coloration of essential oils from certain plants of the Compositae family, mainly wormwood and camomile. At that time we elucidated and proved by synthesis the unusual structure of chamazulene, which is 1,4-dimethyl-7-ethylazulene[1], and we also isolated the precursors of chamazulene in the form of beautifully crystalline substances, to which we gave the names artabsin[2] for the substance isolated from wormwood, and matricin[3] for that isolated from camomile. These compounds were the first representatives of a new group of sesquiterpenic lactones with a guaiane skeleton to which we gave the name guaianolides, and which—as was demonstrated later on—are quite widespread in Nature and can be compared with the long known santanolides.

GUAIANOLIDES

As can be seen from *Figure 1* chamazulene is formed from matricin by a

series of reactions on mere boiling with water, while artabsin gives first the yellow-orange dihydrochamazulene which is then oxidized by air oxidation to the blue hydrocarbon. At the time we were studying the structures of matricin[4] and artabsin[5, 6], we used predominantly chemical methods which led us sometimes (as also happened in other cases and in other laboratories) to wrong conclusions. During the revision of the structures of both guaianolides by modern physical methods, mainly n.m.r., it was found that the

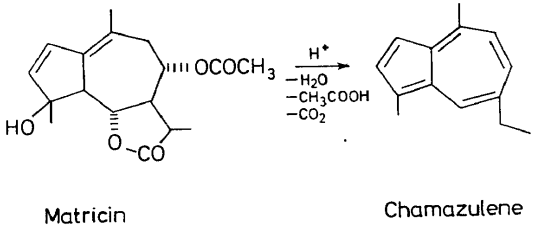


Figure 1

proposed structure of matricin was correct, while in the case of artabsin we had not determined the position of the double bonds correctly[7–9]. *Figure 2* represents the revised structure of artabsin and also the structures of two carboxylic acids of dihydrochamazulenes[10] which are formed—as we have now shown—as primary products of artabsin degradation and which we have succeeded in isolating in pure form. The acids undergo spontaneous decarboxylation to give two dihydrochamazulenes which by air oxidation give chamazulene.

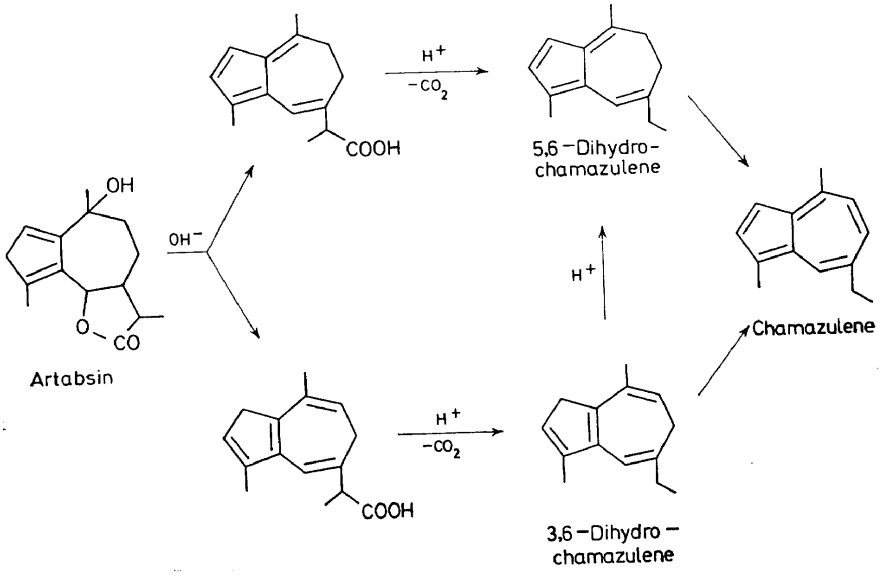


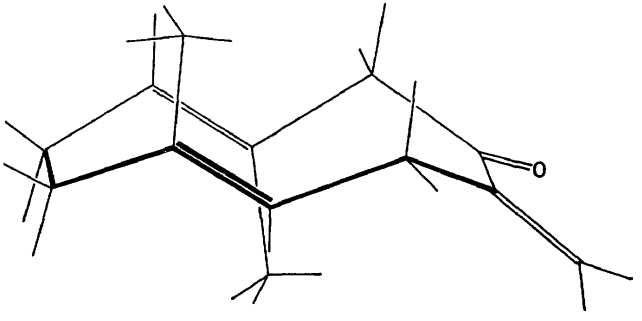
Figure 2

In our laboratory as well as in others a series of other guaianolides was isolated from different plants which are not the true precursors of chamazulene. This group of sesquiterpenic lactones is now quite numerous, comprising more than 40 substances.

When studying some sesquiterpenic lactones which were supposed to belong to the group of guaianolides Herz was able to show that they possess structures with an isomeric carbon skeleton containing an angular methyl group. This group too, named pseudoguaianolides is quite numerous to-day.

Approximately at the time when we studied the chemistry of chamazulene precursors and when we discovered a number of novel guaianolides, we also began to take an interest in the crystalline germacrone from the 'zdravets' oil of Bulgarian origin. We were able to demonstrate that the structure proposed for it by Treibs is not correct and that in actual fact the compound is a monocyclic ketone containing a ten-membered ring in the molecule and three double bonds, two of them endocyclic. Hence, following caryophyllene and humulene, germacrone provided another example of a terpenic compound containing in the molecule a medium size carbon ring. We were able to propose the correct structure for germacrone even though we only used methods available at that time. Only the steric arrangement of both endocyclic double bonds remained unclear. From the course of the transanular cyclization leading to bicyclic derivatives of the selinane series we judged that both double bonds must be *trans* which well explains their mutual interaction causing the anomalous character of the u.v. spectrum of germacrone. This has now been corroborated by x-ray analysis carried out by Rogers on germacratriene.

The sterical arrangement of germacrone is represented in *Figure 3*. The molecule of germacrone is sterically asymmetric, and in accord with this fact, this compound can be separated into two optical antipodes.



Germacrone

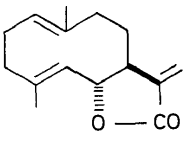
Figure 3

The germacrone skeleton was also proved later on in the molecules of certain previously known or newly isolated sesquiterpenic lactones. Thus a new, relatively frequently occurring group of terpenic lactones was discovered in Nature, to which we gave the name germacranolides. The first compounds

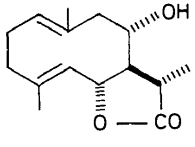
of this type were Barton's pyrethrosin and our arctiopicrin from *Arctium minus*. The majority of representatives of this group of lactones has been isolated and studied in our laboratories, mainly by Dr Suchý. The majority of germacranolides contain a double bond conjugated with the bound carboxyl which make them rather sensitive and unstable. When determining their structures by chemical methods we committed errors in some cases, but we corrected them gradually by applying modern physical methods to their study.

I should like to mention that we have determined by a detailed study of germacranolides that these compounds can be classified into two groups. Both have two endocyclic double bonds localised as in germacrone. However, one group easily undergoes a transannular cyclization, affording bicyclic lactones of the santanolide type, while the other does not cyclize in this manner. The cause of such differing behaviour lies probably in differing closure of the lactone ring the stereochemistry of which is *regularly trans* in relation to the ten-membered ring. If the lactone ring is formed between the carboxyl and the hydroxyl group in position 8 which is not close to the double bond, cyclization takes place and we must suppose—in spite of the fact that this was not directly proved—that both endocyclic double bonds have the *trans* configuration. The closure of the lactone ring with the hydroxyl group in position 6, next to one endocyclic double bond, probably has as a consequence the distortion of the medium size ring and the prevention of the transannular reaction. However, the possibility of a different configuration of the double bonds in these compounds cannot be excluded either. Also the group of germacranolides is now quite numerous.

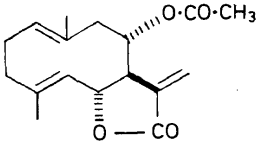
In *Figure 4* some germacranolides are shown which undergo transannular cyclization and of which costunolide is a typical example. In *Figure 5* germacranolides are given, which do not undergo cyclization, usually having more complicated structures, some of which we have recently revised. The great variety of germacranolides with other structures is shown in *Figure 6*.



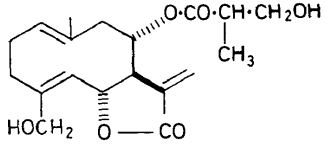
Costunolide



Balchanolide

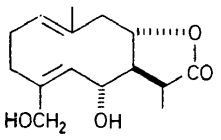


Acetylbalchanolide

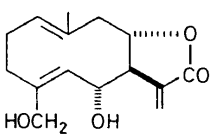


Arctiopicrin

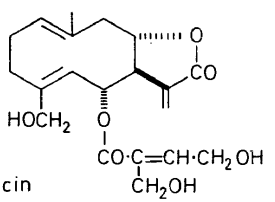
Figure 4



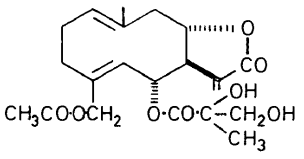
Salonitolide



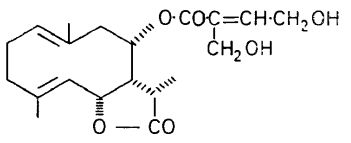
Artemisiifolin



Cnicin

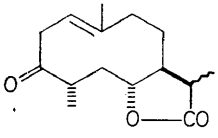


Scabiolide

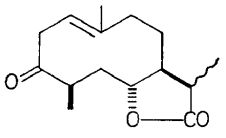


Eupatoriopicrin

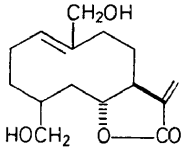
Figure 5



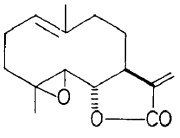
Pelenolide A



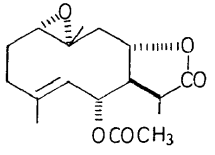
Pelenolide B



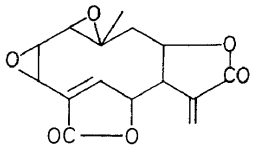
Albicolide



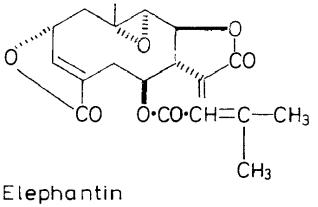
Parthenolide



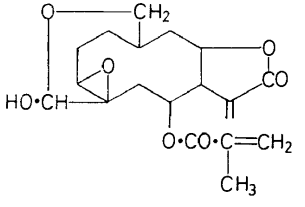
Pyrethrosine



Micanolide



Elephantin



Vernolide

Figure 6

Permit me with this to close the introductory part of my lecture, in which I endeavoured to give a picture of the present knowledge of new types of sesquiterpenic lactones with which the activity of our terpene laboratory is closely linked.

EREMOPHILANOLIDES

In the following part of my talk I should like to make you acquainted with some of our results from the chemistry of the eremophilane type. We have recently repeatedly come across these substances during the study of the components of plants of the Petasites and related species. The roots of the plants studied by us contain predominantly only higher oxidized sesquiterpenic compounds, mainly those containing a furan ring, and also sesquiterpenic lactones of the eremophilane type. Thus the continuation of my lecture will represent a sequel to the introductory part, because eremophilanolides—as we named this group of substances—are another group of natural sesquiterpenic lactones.

It is well known that the ketones eremophilone, hydroxyeremophilone and hydroxydihydroeremophilone which were isolated from an Australian tree *Eremophila mitchelli* and the carbon skeleton of which was determined by Penfold and Simonsen[11], were the first and for a long time the only known compounds of this type. The elucidation of the absolute configurations of these compounds, as represented in *Figure 7*, is due predominantly to Djerassi's school[12].

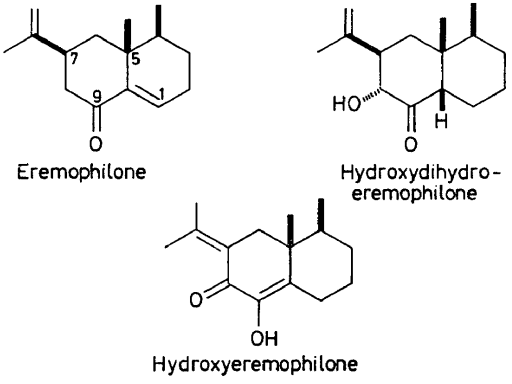


Figure 7

The components of the roots of *Petassites officinalis* were studied some years ago by Professor Stoll and his collaborators[13]. From vegetable material of Swiss origin they obtained three compounds—petasin, isopetasin and S-petasin. Additional three representatives of eremophilane type sesquiterpenes were also found in these compounds. The structures of these compounds are given in *Figure 8*. When studying the vegetable material of Czechoslovak origin we were unable to detect any of the above mentioned compounds in them, but we succeeded in the isolation of a mixture of other compounds, which belonged—as we have proved in the past few years—almost exclusively to the eremophilane type.

In all Petasites species studied the parent hydrocarbon eremophilene was present primarily. The determination of the correct structure[14] of this compound was not simple, although we were able to prove easily by correlation of its tetrahydro-derivative with the product of total reduction of

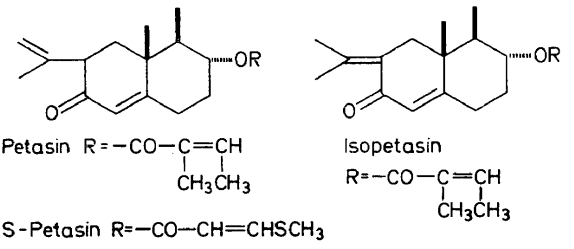


Figure 8

hydroxydihydroeremophilone that it belongs to the eremophilane type (*Figure 9*). The position of double bonds in eremophilene (I) followed both from an analysis of its n.m.r. spectrum and on the basis of chemical transformations of dihydroeremophilene (II) which can be prepared from eremophilene by partial hydrogenation on Raney nickel. This compound

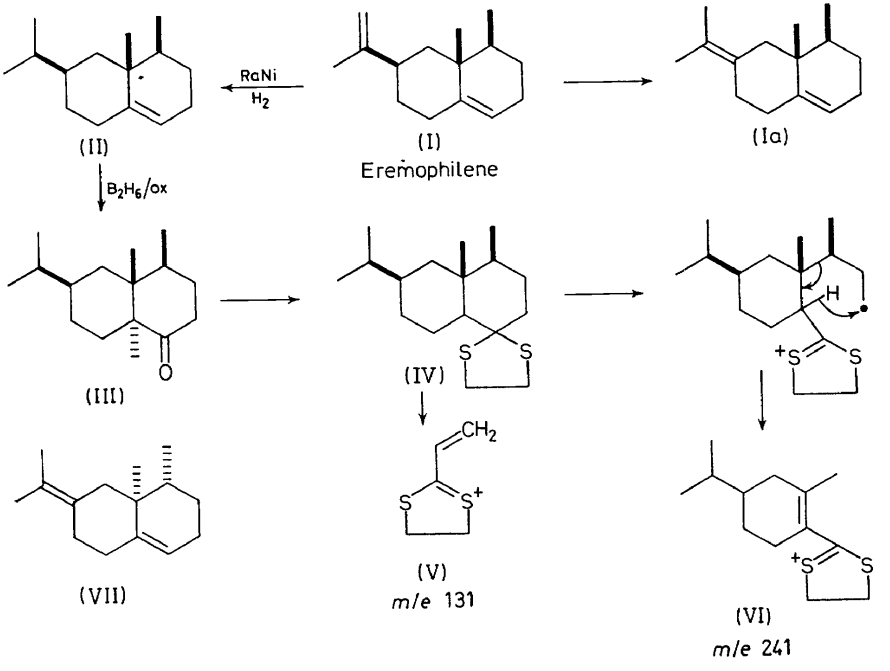
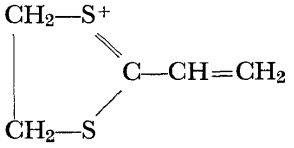


Figure 9

gave a saturated ketone (III) on reaction with B_2H_6 and subsequent oxidation. The mass spectrum of its thioketal (IV) gave for *m/e* (V) the value 131 corresponding to the structural fragment



which could have been formed only if the second double bond was in position 10,1. The mass *m/e* 241 (M-57) which can be explained by a fragmentation to (VI) as represented in *Figure 9* agrees well with this view. Another fact that accords with the proposed structure is that the hydrocarbon (VII) prepared recently in our laboratories from valerianol, has an i.r. spectrum identical with the hydrocarbon (Ia) prepared by acid isomerization from eremophilene. Both hydrocarbons have identical optical rotations but with opposite signs. All this proves that they are enantiomers.

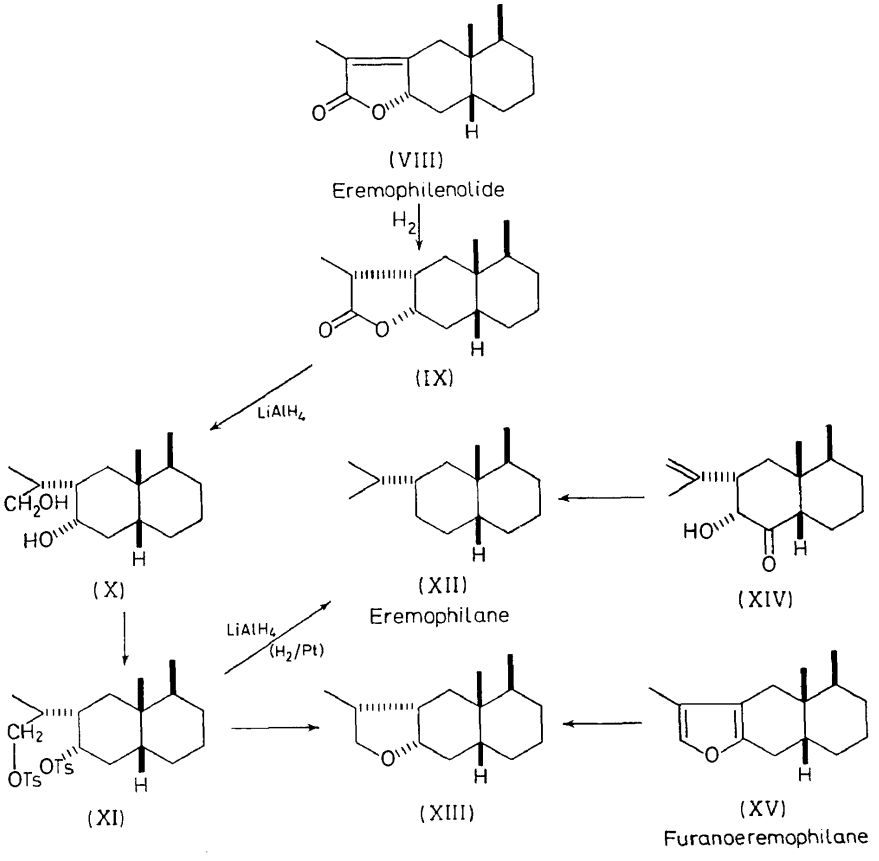


Figure 10

One of the main components of *Petasites officinalis* root is a simple α,β-unsaturated lactone of the eremophilane series to which we gave the name eremophilenolide (VIII). Its structure was determined predominantly on the basis of chemical transformations represented in *Figure 10*. Hydrogenation and further reduction of eremophilenolide gave a mixture of fully saturated hydrocarbon eremophilane (XII) and of an ether (XIII) which was identical with the product of hydrogenation of furoeremophilane (XV). The latter is also a component of *Petasites officinalis* root and we shall return to it later on. The position of the hydroxyl bond in lactone ring was considered unambiguously to be in position 8, and its configuration was determined on the basis of the Klyne–Hudson rule. The total steric structure of eremophilenolide and its dihydro-derivative followed from the correlations with eremophilane derivatives known earlier. Eremophilenolide possesses the stable all-chair steroid like conformation[15] shown in *Figure 11*.

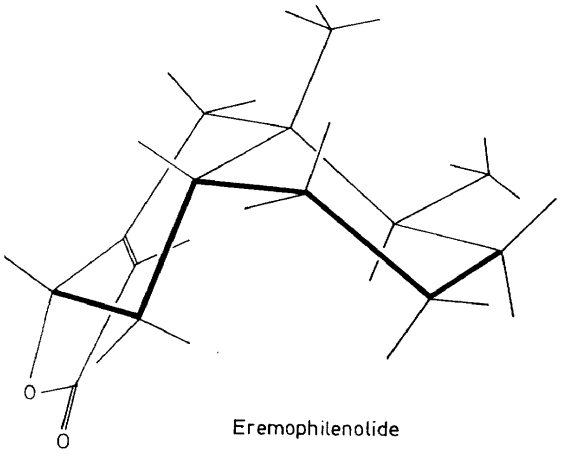


Figure 11

From the extracts of the rhizomes of coltsfoot we have been able to isolate a further four lactones, all closely related to eremophilenolide. These compounds, which are represented in *Figure 12* are all closely related to eremophilenolide. As you can see, all four are esters; the alcoholic component is 3ξ-hydroxyeremophilenolide (XVI) and the acids are in turn: angelic acid (petasolide A) (XVII), tiglic acid (petasolide B) (XVIII), *cis*-methylthioacryclic acid (XIX) (S-petasolide A) and *trans*-β-methylthioacrylic acid (S-petasolide B) B. On hydrolysis of the ester group all these compounds afford one and the same lactone characterized by a crystalline dihydro-derivative (XXI). Chromic acid oxidation of this dihydro-derivative led to a ketone (XXII). Removal of the keto group by the thioketal procedure was found to give rise to dihydroeremophilenolide (XXIII) and this establishes the structure of the carbon skeleton of the four compounds. The location of the hydroxyl could be determined from the n.m.r. spectrum of the ketone. Finally, we isolated from the roots of *Petasites*

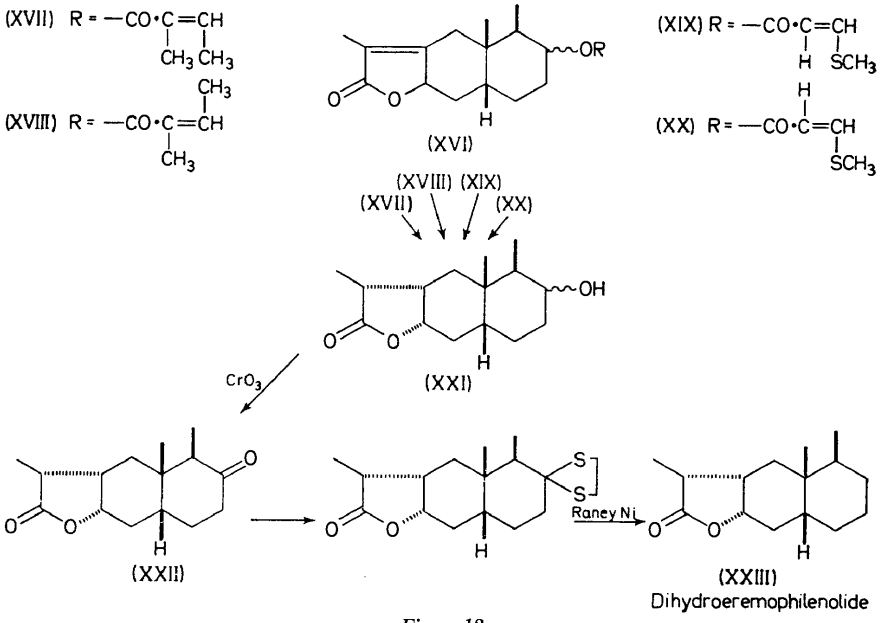


Figure 12

albus 6β-hydroxyeremophilenolide. Its structure followed from its relationship with the so-called petasalbin to which I shall return later on, and from the fact that during its hydrogenation accompanied by simultaneous hydrogenolysis the known dihydroeremophilenolide (*Figure 13*) is also formed.

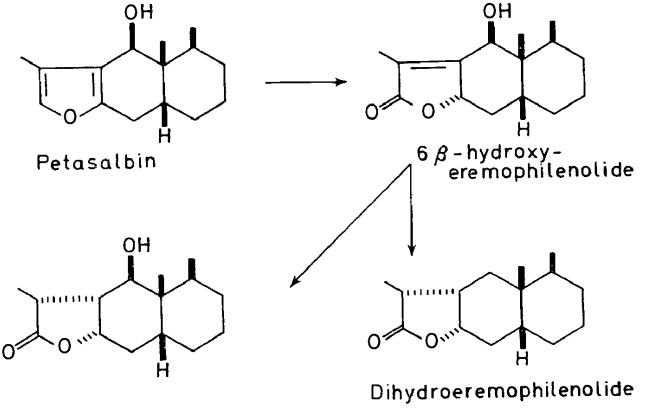
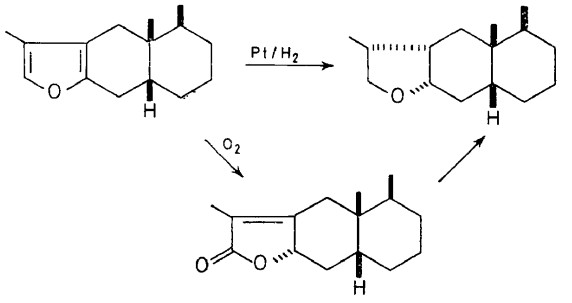


Figure 13

FURANO-EREMOPHILANOLIDES

Now, I would like to discuss in greater detail the furan derivatives of the eremophilane series which are relatively common in Nature as our latest studies and also studies in other laboratories have shown.

The simplest compound of this type is furoeremophilane itself. We isolated it for the first time from the *Petasites albus* root. Its structure and sterical arrangement was deduced both from its physical properties and from our studies on eremophilenolide (*Figure 14*). The product of hydrogenation of furoeremophilane was, as you probably may remember, identical with the ether which we obtained by reductive procedures from eremophilenolide. As these procedures could not have disturbed the active centre of furoeremophilane, its steric arrangement is thus also determined.



Eremophilenolide

Figure 14

From various Petasites species and related plants an appreciable number of hydroxy- and keto-derivatives of furoeremophilane was isolated partly in the form of various esters. Positions 3,6,9 of the eremophilane skeleton are most often substituted. This substitution seems specific for certain types of plants. For example in *Petasites albus* derivatives substituents at C_6 prevail, while in *Petasites hybridus* derivatives substitutents at C_9 are more common. Furanopetasin from *Petasites hybridus* is substituted also in position C_2.

Among monohydroxy-derivatives of furoeremophilane 6β-hydroxyeremophilane, so-called petasalbin (XXIV), is present in the roots of *Petasites albus* (*Figure 15*). This compound was also isolated by Minato and coworkers from *Ligularia sibirica*[13] and they gave it the name ligularol. Its structure was inferred from its oxidation during which the ketone ligularone (XXV) is formed which was also isolated from natural sources, and also from the physical properties of petasalbin and ligularone. In both compounds both 6-membered rings are *cis*-annelated and 6-ketofuroeremophilone (ligularone) gives a characteristic maximum at 269 nm in the u.v. spectrum belonging to the conjugated carbonyl group.

9α-Hydroxyfuroeremophilane (XXVI) is a component of the root of *Petasites hybridus*. In this compound too both rings are in *cis*-configuration. Its oxidation by manganese dioxide gives rise to 10β,H9-ketofuroeremophilane (XXVII) which is very unstable and epimerises rapidly to the stable *trans* ketone 10α,H9-ketofuroeremophilane (XXVIII). In agreement with this we have isolated this compound only from the roots of *Petasites hybridus*, although it is probable that originally its *cis* form was present in it. The proof of the

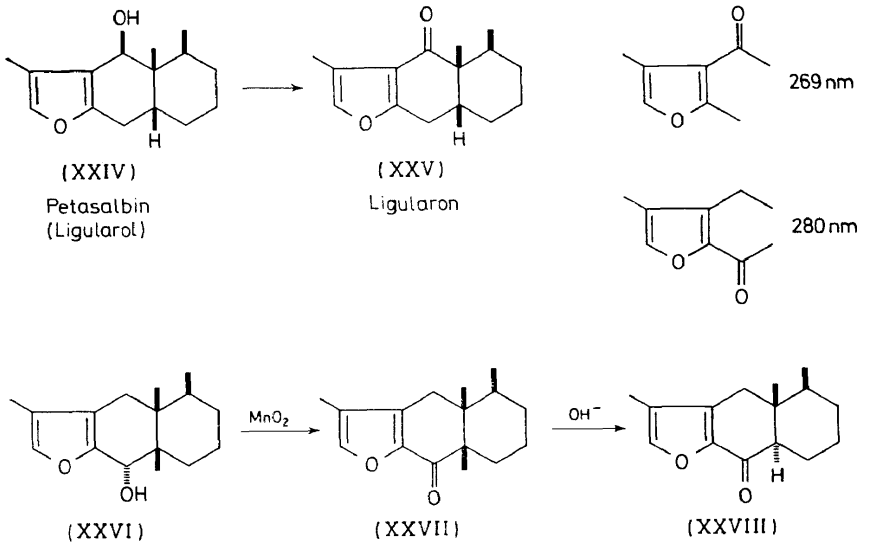


Figure 15

structure of this compound was carried out by the correlation with material prepared from so-called furanopetasin. The maximum of its u.v. spectrum differs characteristically for the 6-keto compound, because it is placed at 280 nm.

The most important disubstituted furoeremophilane is furanopetasin (XXIX), a nicely crystalline major component of *Petassites officinalis* root[13]. We proved the structure of this compound some time ago predominantly by classical methods. In view of the fact that its structure served for the deduction of other compounds of the eremophilane type, let us discuss these methods in somewhat greater detail (*Figure 16*).

Furanopetasin is a monoester of angelic acid and dihydroxy-furoeremophilane to which we gave the name furanopetasol (XXX) and which we isolated by a mild hydrolysis of the natural compound. The presence of the furan ring in furanopetasol was readily established on the basis of both spectroscopic and chemical evidence. The skeleton of furano-petasin was established by converting it to tetrahydrofuroeremophilane which, as you may recall, was obtained earlier as the product of hydrogena-tion of furoeremophilane and eremophilenolide. Hydrogenation of furano-petasin gave the hexahydro-derivative (XXXI), thus, the reaction, involved reduction of both the furan ring and the double bond in angelic acid. Tosylation of (XXXI) afforded tosylate (XXXII) and this, on treatment with lithium aluminium hydride, gave the tosylate (XXXIII).

Further oxidation with chromic acid gave rise to a keto derivative (XXXIV). This reaction sequence proves that the originally esterified hydroxyl group is secondary. The absence of a characteristic conjugation in the ultraviolet spectrum of the ketone (XXXIV) indicated that the keto group cannot be located in ring B and hence must be in ring A. Reduction of the keto group—via the thioketal (XXXV)—in the ketone (XXXIV)

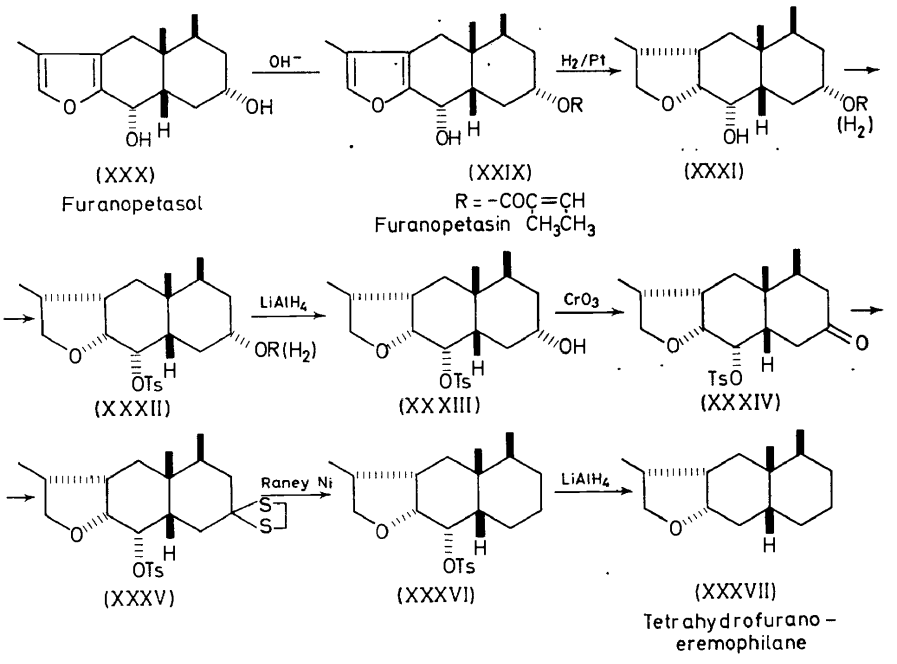


Figure 16

and subsequent reduction of the monotosylate (XXXVI) afforded tetrahydro-eremophilane (XXXVII) in low yield. This fact shows that the stereochemistry of ring annelation and of the methyl group on C-4 and C-5 in furanopetasin is the same as in tetrahydrofuroeremophilane.

There then remained the task of determining the position of both hydroxyl groups. Some of the reactions on which the assignment of the position of the hydroxyl is based are shown in *Figure 17.*

We had found early on in the work on furanopetasin that the oxidation of tetrahydrofuranopetasol (XXXVIII) with chromic acid gives a lactone keto acid (XXXIX) in good yield. From the outcome of the oxidation reaction it is also possible to assign the position of the free hydroxyl group in furanopetasin as being in ring B, conjugated with the furan ring. This assignment is in agreement with the fact that the ketone (XL), prepared by oxidation of furanopetasol with manganese dioxide, exhibits a maximum at 280 nm with log ϵ 4·3, which is characteristic of a carbonyl group conjugated with the furan ring in the α-position. Hence the hydroxyl group must be located at C-9.

The position of the other hydroxyl, that is the esterified one, follows from the fact that the lactone hydroxy-acid (XLI), obtained from the ester of the lactone keto acid by reduction with tri-t-butoxy lithium aluminium hydride, gives rise to the dilactone (XLII). The presence of two γ-lactone groupings in this compound was confirmed by analysis of the infrared spectrum. Finally, the mutual steric position of the two hydroxyl groups could be

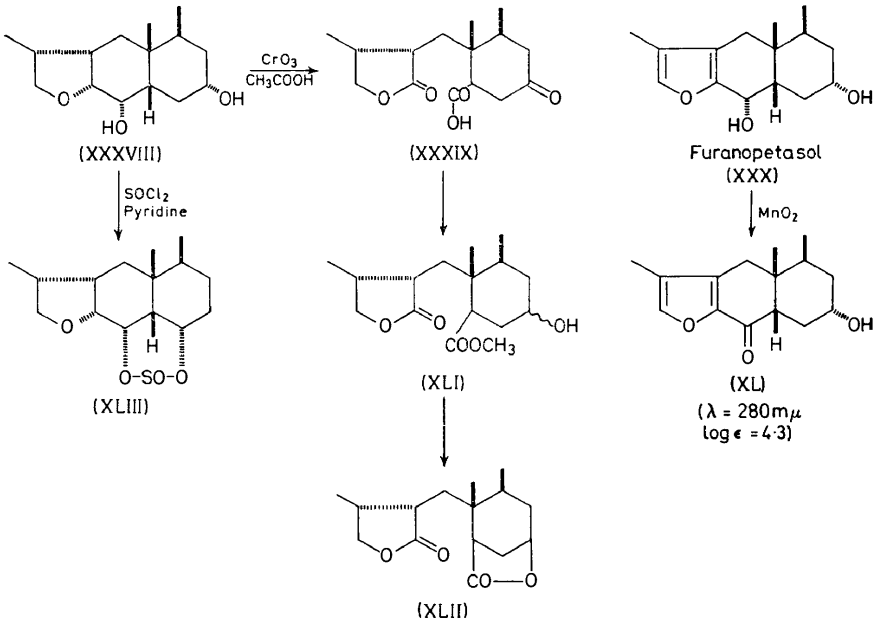
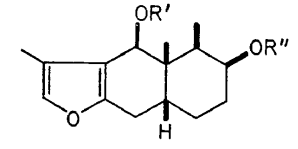


Figure 17

deduced from the finding that tetrahydrofuranopetasol (XXXVIII) on reaction with thionyl chloride affords a cyclic sulphite (XLIII). An inspection of models reveals that a cyclic sulphite can be formed only if both hydroxyl groups have the α-configuration. These facts make it possible to assign furanopetasin the configuration shown in the formula (XXIX).

A simple dihydroxy-derivative of furanopetasol is albopetasol which we isolated from the roots of *Petasites albus* (*Figure 18*). As its physical properties,



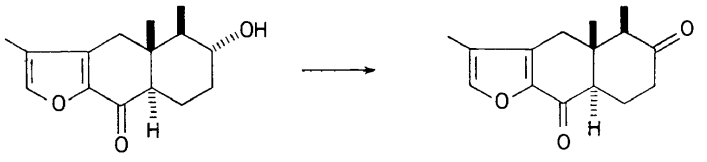
R' = R" = H	Albopetasol
R' = H, R" = angelyl	Angelyljaponicin
R' = R" = angelyl	Diangelyljaponicin

Figure 18

chemical transformations and correlation with other derivatives of furoeremophilane have shown, albopetasin is most probably 3β,6β-dihydroxyfuroeremophilane with a standard *cis* annelation of the alicyclic rings.

From the roots of *Petasites japonicus* we isolated mono-and diangelyl esters of albopetasol.

Euryopsonol[16], isolated from a South African plant *Euryops floribundus*, also belongs among disubstituted derivatives of furoeremophilane (*Figure 19*). As Rivett and Woolard[16] have shown, euryopsonol has the structure of 3α-9-ketofuroeremophilane. The annelation of both alicyclic rings is in this case *trans*, i.e. 10Hα, but it is very probable that the original component of the plants is a standard 10Hβ compound and that a rearrangement of the



Euryopsonol (XLIV)

Figure 19

unstable *cis* ketone to the *trans* ketone took place during the isolation which was not carried out under specially mild conditions. The structure of euryopsonol was proved on the basis of physical properties as well as on the basis of chemical transformations and the correlation with kablicin. The diketone (XLIV) prepared by the oxidation of the *trans* ketoalcohol obtained from kablicin was identical with a specimen prepared by the oxidation of euryopsonol.

The components of the *Adenostyles alliariae* roots[17], a plant related to the Petasites genus are closely connected with euryopsonol. These compounds are also 6-hydroxy-9-ketofuro-eremophilane derivatives, but they contain an additional double bond. They are: adenostylone, neoadenostylone and isoadenostylone (*Figure 20*).

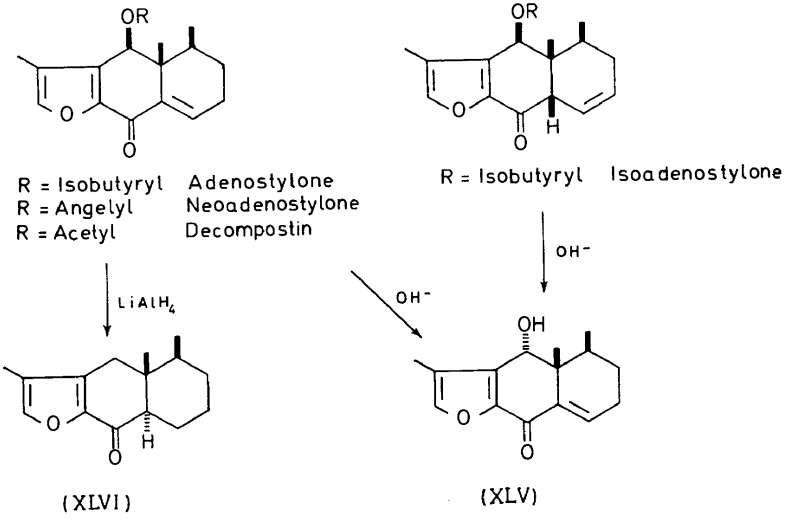


Figure 20

Very closely related with these compounds is decompostin obtained from the roots of *Cacalia decomposites* by Mexican scientists Romo and coworkers. Chemical and physical research has shown that adenostylone, neoadenostylone and decompostin are esters of 6β-9-keto-$\Delta^{10,1}$-furoeremophilane. Adenostylone is esterified with isobutyric acid, neoadenostylone with angelic acid and decompostin with acetic acid. Isoadenostylone, an isomer of adenostylone, is also an ester of isobutyric acid and the parent sesquiterpenic derivative, but it is a compound with a shifted double bond, i.e. 6β-9-keto-$\Delta^{1,2}$-10βH-furoeremophilene. The position of double bonds and especially the difference between adenostylone and isoadenostylone follow from the physical properties of the investigated substances—mainly u.v., i.r. and n.m.r. spectra. On alkaline hydrolysis all the mentioned compounds afford 6α-hydroxy-9-keto-$\Delta^{10,1}$-furoeremophilene (XLVI). In the case of isoadenostylone isomerization of the double bond takes place which shifts into conjugation with the carbonyl group. On reduction of adenostylone with lithium aluminium hydride, accompanied also by the reduction of the conjugated double bond and the elimination of the esterified hydroxy group in position 6, the known 9-keto-furo-10αH-eremophilane (XLVI) is formed. We have isolated this compound, as you may remember, from the roots of *Petasites hybridus* (where it is probably present in the standard 10βH-form), but we have also prepared it by chemical changes from furanopetasin or furanopetasol. 6α-Configuration of the hydroxy group followed from the analysis of n.m.r. spectra and from the analyses of o.r.d. and circular dichroism measurements[18]. Compounds with a carbonyl group in position 9 display a Cotton effect at about 240 nm which is appreciably influenced by the character of the substitution in position 6. In the case of 6β-configuration it is negative, in the case of 6α-configuration positive. This method, as well as its n.m.r. spectrum enabled us also to solve the configuration of isoadenostylone, which has, as I have mentioned already, the configuration 10βH.

The most complex furoeremophilane derivative is kablicin[19], isolated in our laboratories from the roots of Petasites *kablikianus* and *Petasites paradoxus*, of which it is the main component. The elucidation of the structure of kablicin was relatively difficult, and we were compelled to utilize both chemical methods and all modern physical methods. It was of great advantage that we were also studying at roughly the same time the chemistry of substances related to adenostylone, because the results of both studies were complementary.

Kablicin (XLVII) (*Figure 21*) is a derivative of a trihydroxylated furoeremophilane esterified on two hydroxy groups, both with angelic and dimethylacrylic (senecionic) acids. The parent trihydroxyfuroeremophilane (XLVIII) can be obtained on reaction with lithium aluminium hydride. Alkaline hydrolysis of kablicin gives a mixture of neutral compounds from which we isolated on the one hand the monoacyl derivative (XLIX) containing esterified senecio acid, and on the other hand a mixture of two hydroxyketofuroeremophilanes (L) and (LI), which are, according to their characteristic u.v. spectra (maxima at 280 and 282 nm), C_{10}-*cis* and *trans* isomers of the hydroxy derivative of 9-keto-furoeremophilane. By this we also determined the position of one of the hydroxy groups in the parent

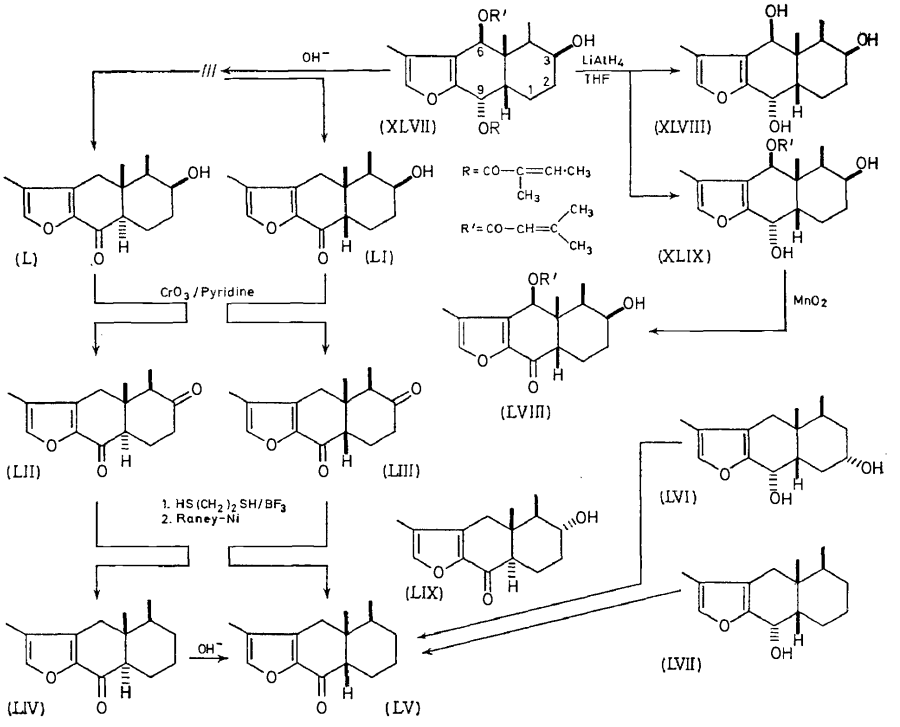


Figure 21

triol kablicin. The peculiar elimination of the second hydroxy group, free or esterified, could be explained on the basis of our previous knowledge. Such a reaction can take place only if this group is in position 6. This assumption of ours was corroborated by the fact that the mentioned monoacyl derivative of the furoeremophilane triol, isolated after alkaline hydrolysis of kablicin, changed in alkaline medium to the known mixture of *cis–trans* isomeric hydroxy-9-ketofuroeremophilanes. As trihydroxyfuroeremophilane does not react in this manner, it is evident that its monoester with the esterified senecio acid in position 6, must be an intermediary product of this elimination reaction. From this it is clear that the second hydroxy group esterified with senecio acid must be located at position 6 of the eremophilane skeleton of kablicin. The third free hydroxy group is in position 3 as was deduced from the n.m.r. spectrum of the deuterated diketones (LII) and (LIV). The protonmagnetic resonance spectra of kablicin show that the free hydroxy group is equatorial, while in 10αH-3-hydroxy-9-ketofuranoeremophilane (LII) it is axial. From this it is clear that the configuration of the hydroxy group in position 3 is beta The configuration of the esterified hydroxy groups in position 6 has been determined on the basis of n.m.r. and circular dichroism of 10βH-3β-hydroxy-6β-acyloxy-9-ketofuroeremophilane (LVIII) the configuration of the esterified C_9-hydroxyl was inferred from the p.m.r. spectrum of kablicin and a distinct interaction of the hydrogen

atoms on carbons 9 and 10, which showed clearly that the configuration of hydrogen atoms bound to C_9 and C_{10} is *cis*.

A very interesting compound of the eremophilane series, of a completely new type, was isolated from the non-crystalline chromatographic fractions of the light petroleum extracts of *Petasites officinalis* root[20]. Its formula is $C_{17}H_{28}O_3$ and it gives an intense colour reaction typical of furanoid compounds (*Figure 22*). Interestingly enough neither the u.v. nor the i.r. spectra

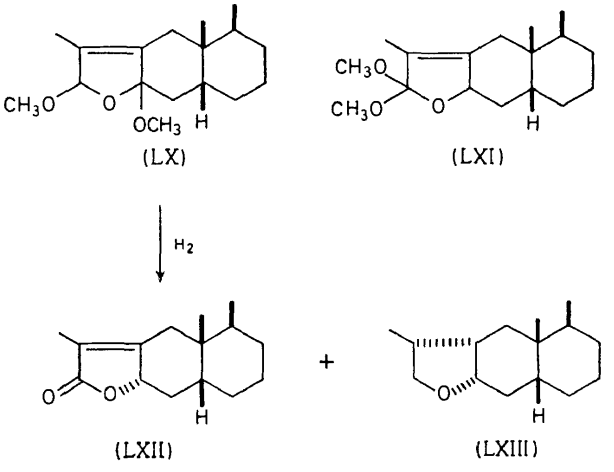
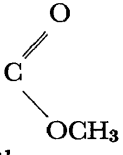


Figure 22

indicate the presence of this moiety. The i.r. spectrum also shows that the compound contains neither a carbonyl nor a hydroxyl group demonstrating thus that the oxygen atoms are present in the form of ethers. The structural assignment was eventually made on the basis of physical methods. The mass spectrum exhibits an intense fragmentation giving particles of mass 31 and mass 32, indicating the presence of methoxyl group and a particle of mass 59 corresponding to the grouping



The n.m.r spectrum confirmed the presence of two methoxyl groups and of two biquaternary double bonds with a methyl and a methylene group in the alpha positions. Hydrogenation of this compound in glacial acetic acid on platinum afforded a mixture of tetrahydroeremophilane (LX) and eremophilenolide (LXIII). All this evidence points to the two alternative formulae (LX) or (LXI). In order to distinguish between the two alternatives, we determined the n.m.r. spectrum of the compound in question and eremophylenolide. An analysis of the spectra unambiguously established the structure (LX). The formation of eremophilenolide on hydrolysis of our compound may be rationalized as shown in *Figure 23*. This compound

cannot be an artifact, because during its isolation we avoided the use of methanol. Hence, it is evident that its formation in which the peroxides of methanol must have played a role takes place in the plant.

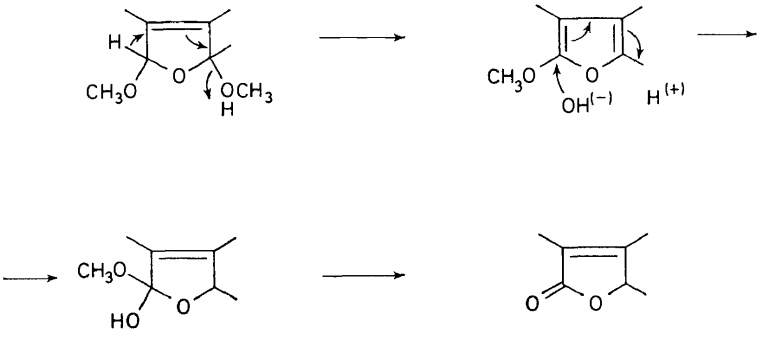


Figure 23

BIOGENESIS OF FURANO-EREMOPHILANOLIDES

Let me now make a brief mention of the biogenesis of the lactones of the eremophilane type. There is experimental evidence indicating that the furanoeremophilanes are direct precursors of these lactones. This is shown in *Figure 24*. Thus, we have been able to show that petasalbin on auto-oxidation gives rise to 6β-hydroxyeremophilanolide. This reaction, incidentally, was of great help in elucidating the structure of petasalbin which, as you may recall, has the structure of 6β-hydroxyfuranoeremophilane.

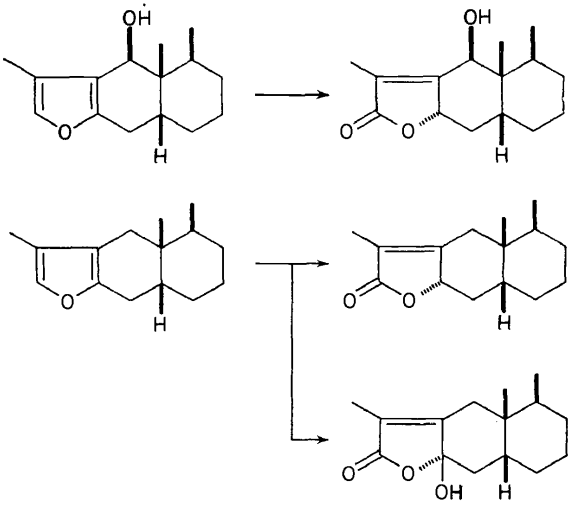


Figure 24

The auto-oxidation of furanoeremophilane gives rise to two products: the compound, shown to be identical in all respects with naturally occuring eremophilenolide and the compound, containing an additional hydroxyl group on the carbon 8. I should like you to note that the course of the auto-oxidation is stereospecific.

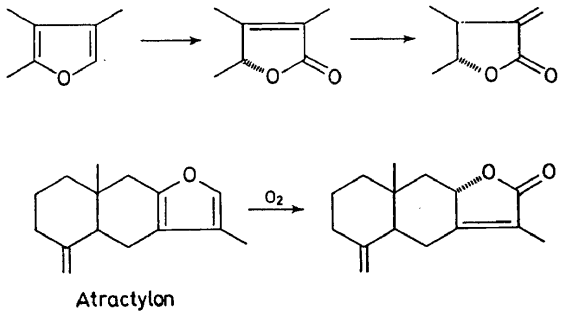


Figure 25

It is attractive to speculate whether analogous oxidation reactions of furan ring containing sesquiterpenes, possibly due to specific enzyme systems, could not also be responsible for the formation of sesquiterpenic lactones in Nature. This hypothesis is also supported by the fact that the majority of sesquiterpenic lactones has the α-configuration and contains the characteristic vinylidene double bond conjugated with the lactonic carbonyl group. It seems plausible to assume that this double bond could arise by a 1,2-shift from the isopropylidene position. This assumption, incidentally, is confirmed by some results of the Japanese authors Hikino, Hikino and Yosioka which are shown in *Figure 25.* These authors found that the auto-oxidation of atractylon, a furane derivative possessing the santalane skeleton, leads to compounds of the santanolide series.

Acknowledgement

I should like to thank my collaborators, and in particular Dr L. Novotný who is the principal author of the work on eremophilane type compounds.

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