TERPENIC COMPOUNDS WITH MEDIUM-SIZED RINGS

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The study of all aspects of living matter is a constant source of information and stimulation of the greatest theoretical and practical importance. The very origins of organic chemistry are rooted in a desire for knowledge of the composition of living bodies and the products of their metabolism, and, ever since the birth of our science, the study of natural products has always remained one of its important concerns. The investigation of plant constituents has been of particular significance for the development of organic chemistry; it should be borne in mind that the plant kingdom accounts for much the greatest part of living matter on our earth—more than 99·9 per cent, in fact! Moreover, plants not only produce all the types of compounds found in the animal kingdom but also a number of special groups of organic substances, especially terpenoids, alkaloids, and glycosides. The varied chemical structure of the numerous, genetically related compounds of these groups, and the biological activity and practical importance of many of them have ever invited their closer investigation, and it may be said fairly that the systematic researches in these fields have contributed greatly to the finest traditions of organic chemistry, and to the present extent and variety of this science.

In my opinion, it is the work on terpenes and steroids which was of the greatest importance in the development and shaping of organic chemistry. On the one hand, there is the classical unity of each of these groups, given by their simple composition, limited to the three basic organogenic elements, and by the uniformity of rules governing their structure; on the other hand, we have the great structural diversity and ubiquity of occurrence—it is these features which have made the terpene and steroid field an arena in which many minds active in our science have tried their strength. It was in research on substances of these two groups that the principal methods of structural analysis of organic compounds were devised and put to the test, especially the methods of controlled degradation; at the same time, it provided a powerful stimulus to the development of synthetic methods. Studies on the alicyclic terpenes, and on the whole steroid group, have been the source of our present ideas on the spatial structure of organic compounds. The whole of chemistry has profited from the valuable techniques developed in these fields for the isolation of individual substances from complex mixtures, their characterization and identification by physical constants. Let me recall particularly the determination of relations between chemical structure and physical properties, especially spectroscopic properties, which form such an essential part of organic chemistry today.

I must confess to a great love for these two groups of natural substances. In today's talk I should like to review for you some results from the chemistry of the sesquiterpenes—a group of terpenoids which has only been studied in detail rather recently. Today, we know this group to be varied and rich in structural types; this is clearly illustrated by *Figure 1*, which shows the
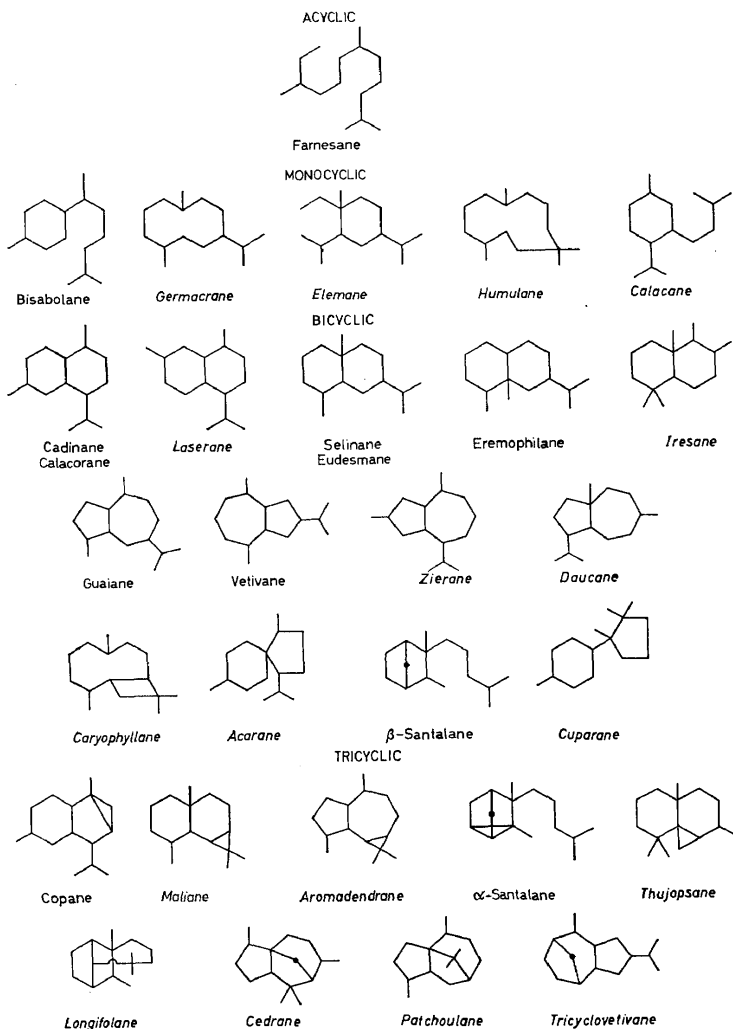

Figure 1. Types of sesquiterpenes

carbon skeletons known at present to occur in sesquiterpenes. The formulae with names printed *in italic* show structures which have been detected or firmly established within the last fifteen years, the others are older. The names of the various structural types are derived from the names of important hydrocarbons containing the appropriate carbon skeleton.

The size of the list in *Figure 1* shows clearly why it is impossible within the compass of a single lecture to summarize all our recent knowledge of
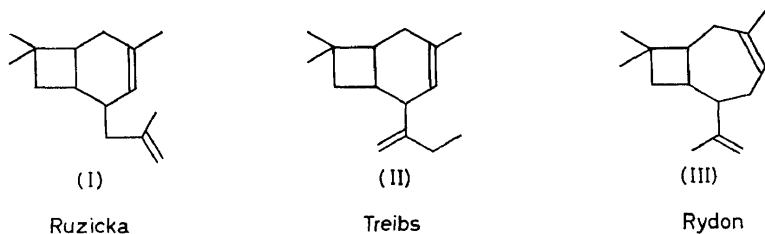
(I) (II) (III)

Ruzicka   Treibs   Rydon

Figure 2

sesquiterpene chemistry; and, with your permission, I should like, therefore, to confine myself to a discussion of compounds known to contain medium-sized rings—I have in mind nine-, ten- and eleven-membered carbon rings. The discovery of such rings in common plant constituents was somewhat surprising, since until recently the existence of larger carbon rings had been established in Nature only in the macrocyclic fragrant ketones, and these, moreover, were products of animal metabolism. The difficulty of access by synthetic means to alicyclic compounds with medium-sized rings (which has only fairly recently been overcome by use of the acyloin condensation), as well as certain theoretical considerations concerned with their steric properties, only tended to confirm the view that compounds of this type were purely products of human thought and human labour.

The first proof of the occurrence of a medium-sized alicyclic ring in Nature was obtained in our Laboratory in 1949 in the course of our studies on caryophyllene[1].

Probably more work had been devoted to the elucidation of the structure of this compound than to any single other in sesquiterpene chemistry. It had been known for a long time that caryophyllene was a bicyclic hydro-
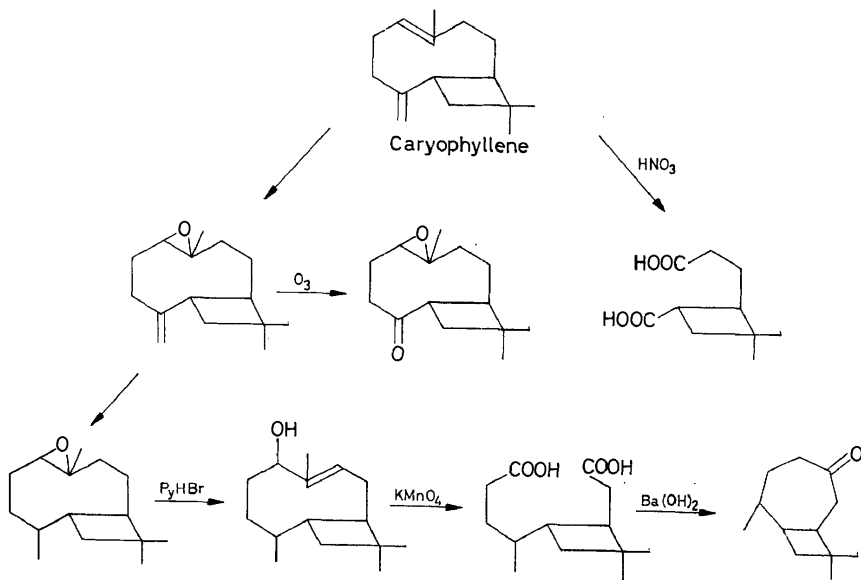

Figure 3

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carbon containing two double bonds and a characteristic four-membered ring carrying *gem*-methyl groups. Originally, it had been our aim to decide between the three structures (I) proposed by Ruzicka, and (II), proposed by Treibs, and (III), proposed by Rydon[2] (*Figure 2*). As our starting-point, we chose the readily accessible oxido-ketone described by Treibs (*Figure 3*). Greatly to our surprise, the infra-red absorption spectrum of this compound showed a carbonyl frequency typical for a ketonic group situated on a medium-sized ring. To obtain further information about the size of the second ring, we carried out a degradation of this ring in dihydro-caryophyllene oxide by unambiguous steps involving the loss of two carbon atoms, one of them from the ring. Cyclization of the resulting dicarboxylic acid gave a ketone with a ring smaller by two members than the original
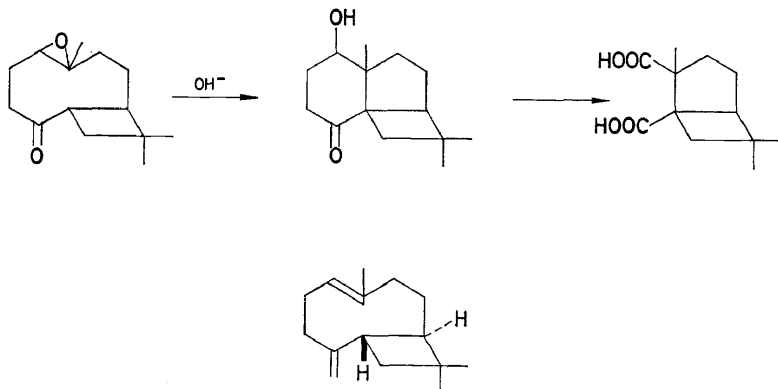

Figure 4

ring. This ketone still had an abnormally low carbonyl absorption in the infra-red (1705 cm^{-1}), corresponding to the presence of a seven-membered or, less probably, of a six-membered ring. Since tetrahydrocaryophyllene itself did not exhibit the infra-red absorption of an ethyl group, which is normally easily distinguished in saturated hydrocarbons and which would be expected to occur if the second ring were eight-membered, we considered the reaction sequence I have described to prove the presence of a nine-membered ring in caryophyllene. The C_{12}-ketone obtained in this degradation, and later prepared by partial synthesis[3], accordingly contained a seven-membered ring. I have discussed these reactions, by which the occurrence of a medium-sized ring in Nature was for the first time established, in some detail, since this work has often been reported as if we had based our conclusion, concerning the presence of a nine-membered ring, tentatively on the carbonyl frequency of Treibs' oxido-ketone alone.

Our degradative experiments permitted four formulations for caryophyllene. Two of these could be eliminated on consideration of the structure of homocaryophyllenic acid, an oxidation product of caryophyllene, as determined by Dawson and Ramage[4]. The carbon skeleton of caryophyllene was further confirmed by our partial synthesis of tetrahydrocaryophyllene[5]. The final decision between the remaining two formulae, differing in the position of the double bonds, and information about the stereochemistry of caryophyllene followed from the elegant work[6] of Barton, which

established the structure shown in *Figure 4*. The evidence was based first on the alkaline cyclization of Treibs' oxido-ketone to a tricyclic keto-alcohol and the further oxidation of this compound to the dicarboxylic acid. The annelation of the two rings is *trans-* and the double bond also has the *trans-* configuration in caryophyllene, but has the *cis*-configuration in the isomeric isocaryophyllene.

Recently, we have once more encountered the caryophyllene skeleton in two sesquiterpenic alcohols, the betulenols, isolated from the oil of birch buds (*Figure 5*)[7]. Treibs had already suggested some time ago that these compounds were related to caryophyllene. α-Betulenol is a bicyclic alcohol with two double bonds. Hydrogenation yields the saturated alcohol
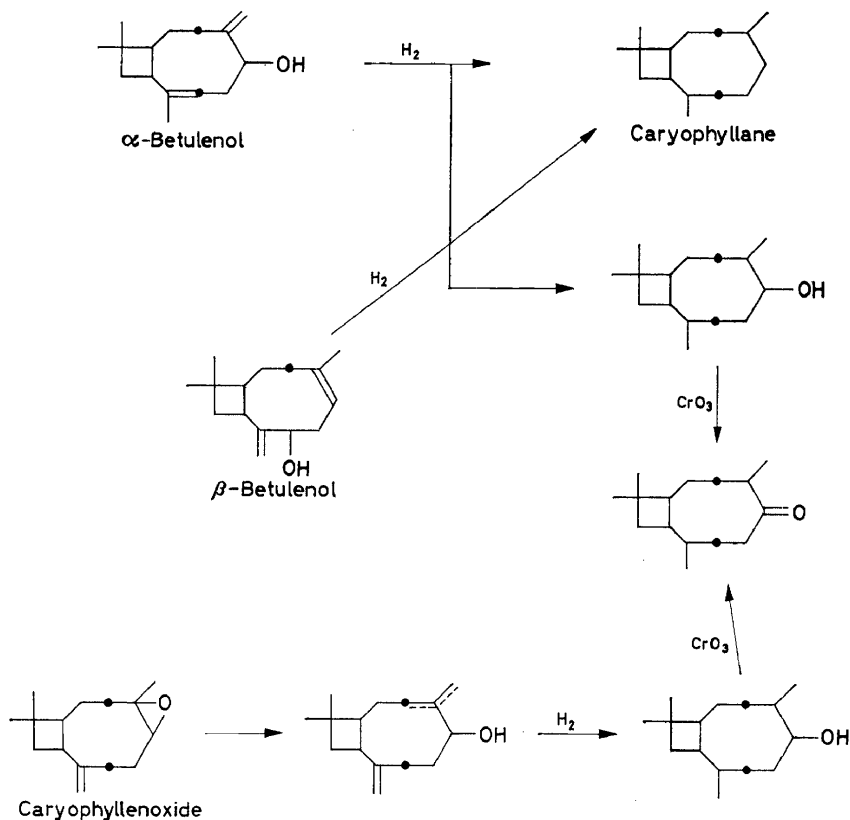
Figure 5

together with a hydrocarbon which has an infra-red absorption spectrum fully identical with that of tetrahydrocaryophyllene. This clearly demonstrates that α-betulenol belongs to the caryophyllane series. Oxidation of tetrahydrobetulenol with chromic acid gave a ketone which proved to be identical with a compound obtained from caryophyllene monoxide by an unambiguous reaction sequence; this establishes the position of the hydroxyl group. The crystalline β-betulenol is isomeric with α-betulenol, and the

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chemical reactions and physical constants permitted us to allot the structure shown in *Figure 5* to this alcohol.

The hydrocarbon humulene was a further compound in which we were able to establish the presence of a medium-sized ring—in this case, an eleven-membered ring. Humulene is monocyclic and has three double bonds. Its structure was tentatively derived by us[8] and, shortly afterwards, by Clemo and his co-workers[9] from the fact that on oxidation it gives, in addition to α,α-dimethylsuccinic acid, only formaldehyde and acetic acid, and no higher monofunctional degradation products. A proper confirmation of the suggested skeleton was given by our total synthesis of hexahydrohumulene[10].

The position of the double bonds in humulene remained unsettled for some time. We first suggested the arrangement shown in *Figure 6* (*a*) on
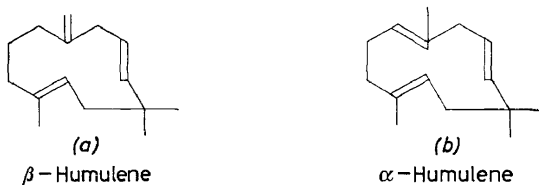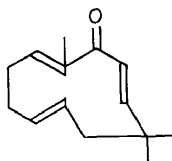
(a)
β – Humulene

(b)
α – Humulene

Figure 6

the basis of the ozonisation products and physical constants, especially the infra-red absorption at 890 cm^{-1} characteristic of vinylidene-type double bonds. Recently, Sutherland[11] and, independently, Dev[12] have come to the conclusion that pure humulene contains no exocyclic double bond and that the structure must be modified as shown in *Figure 6* (*b*). For this reason, we have recently returned to the study of humulene, after we had obtained a good supply of the hydrocarbon from the essential oil of the leaves of *Lindera strychnifolia*. Fractionation on a highly efficient column showed that with rising boiling-point there was a slight decrease in the content of exocyclic methylene groups. The highest content of exomethylene groups found was 0·36 per mole. When the distillation fractions were purified by Sutherland's method through the silver nitrate adduct, the resulting humulene contained only traces of exocyclic methylene; however, when the purified hydrocarbon was percolated through active alumina, material with a very high vinylidene content, about 83 mole per cent, was obtained. This material no longer forms a crystalline adduct with silver nitrate. Therefore, we conclude that the natural material contains two humulenes, which we call α- and β-humulene, in variable proportions. The α-isomer, without the exocyclic double bond, forms an adduct with

Zerumbone

Figure 7

silver nitrate, while the more stable β-humulene, which contains the exocyclic methylene group, forms no such adduct[13].

Some time ago, Bhattacharyya[14] and, independently, Dev[15] found that the sesquiterpene ketone zerumbone (*Figure 7*) also has the humulane skeleton; the chief evidence was again identification of the corresponding hydrocarbon with hexahydrohumulene by infra-red spectroscopy.

Sesquiterpenes containing a ten-membered carbon ring, especially oxygenated compounds, seem to be frequent products of plant metabolism, particularly in the Compositae. As I hope to show later, they are probably of some importance in the biogenesis of some other, bicyclic sesquiterpenes.

The first natural product for which a ten-membered ring structure was proposed was the lactone, pyrethrosine[16]. However, the first compound in which such a ring was definitely established was the ketone germacrone, the chief component of Bulgarian zdravets oil[17]. I think it will be instructive to recall the history of this interesting compound. It had been known for

Figure 8

some time under the name germacrol, and studied in some detail by Treibs, who also proposed the first formula for it (*Figure 8*)[18]; as you see, he regarded it as a cyclic ether with a guaiane skeleton. When we set out to check this

structure, in co-operation with our Bulgarian colleagues, we found immediately, from the infra-red absorption spectrum, that we were dealing, not with an epoxide, but with a monocyclic unsaturated ketone. However, when we tried to hydrogenate or dehydrogenate germacrone (as we renamed it) we obtained surprising and contradictory results. After hydrogenation of germacrone (and germacrol) over platinum in acetic acid we isolated two hydrocarbons, both formed by hydrogenolysis. One was identified as monocyclic elemane by its infra-red absorption spectrum; the second was similarly identified as bicyclic selinane. Further, reduction of germacrone with aluminium isopropoxide or lithium aluminium hydride gave an alcohol, " germacrol ", which was converted back into crystalline germacrone by oxidation, and, on dehydration, gave a mixture of hydrocarbons which yielded considerable amounts of guaiazulene on dehydrogenation. Furthermore, it had already been shown previously that germacrone yields cadalene on dehydrogenation under fairly drastic conditions.

We see, then, that under various conditions, germacrone or its derivatives can be converted into derivatives of no less than four sesquiterpene types; of these, only the elemane-type corresponded to the presumed monocyclic nature of germacrone. Since it was difficult to visualize the formation of the other three types of skeletons from a compound based on the elemane skeleton, we concluded that germacrone was in fact derived from none of the four sesquiterpene types. We were able to confirm this as follows. Germacrone was first partially hydrogenated in ethanol (to prevent any
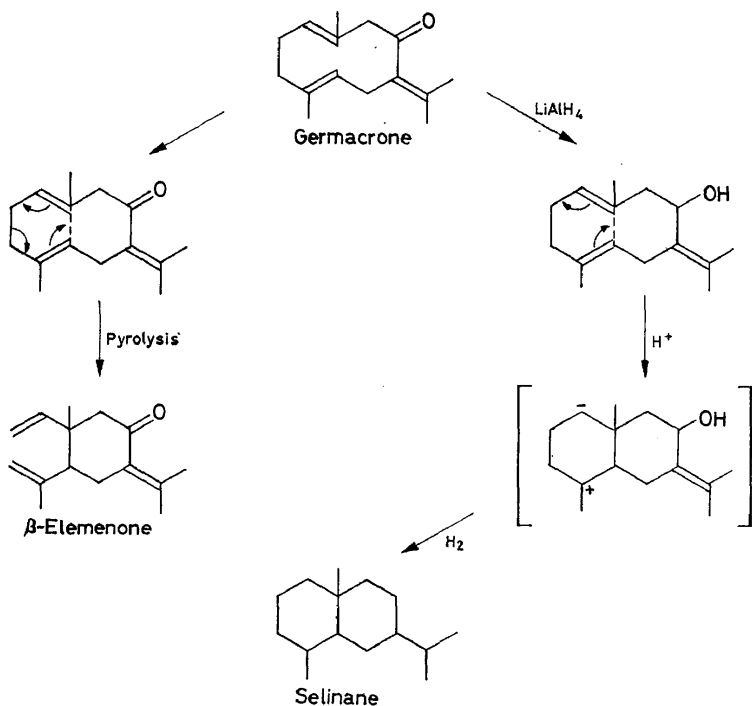

Figure 9

acid-catalysed cyclization reactions), and then further reduced in several steps.   In this way we obtained a saturated alcohol—hexahydrogermacrol—and a hydrocarbon, whose infra-red absorption spectrum showed it to belong to a new sesquiterpene-type.   We have called this the germacrane-type.   All the reactions I have spoken of can be interpreted without difficulty if we assume that germacrone contains a ten-membered ring.

The location of the double bonds in germacrone proved somewhat difficult, especially because of its anomalous infra-red and ultra-violet absorption spectra.   This difficulty even led to speculation on alternative formulae for germacrone.   A structure based on the maaliane skeleton was suggested by Ohloff[19].   In fact, the explanation of the anomalous spectral properties of germacrone and some other ten-membered ring compounds such as costunolide lies elsewhere, as I hope to show later.   Very recently, we have been able to fix the position of the double bonds in germacrone. Definite proof of the skeleton of germacrone was obtained by the total synthesis of germacrane[20].

Figure 10

The reactions by which germacrone passes into compounds with other carbon skeletons are also readily interpreted on the basis of its structure (*Figure 9*). The transition into the elemane series is especially remarkable[21, 22]. Mere heating converts germacrone to the so-called β-elemenone. The position of the double bonds in germacrone is favourable for just this sort of reaction.

The conversions of germacrone into products of other sesquiterpene types, particularly of the selinane series, by hydrogenation and dehydrogenation can be interpreted as transannular cyclization reactions, and, as we shall see, such reactions have been encountered in a number of other cases.

Some years ago, the discovery of the guaianolides, a new group of sesquiterpene lactones somewhat similar to the santonin group but containing a guaiane skeleton, prompted us to undertake a detailed examination of the sesquiterpene lactones of the Compositae, and this search revealed a number of further compounds with ten-membered rings.

As I have already mentioned, Barton published his first paper on pyrethrosin[16], a lactone from *Chrysanthemum cinerariaefolium*, early in 1957, a few months before our publication on germacrone appeared (*Figure 10*). A key experiment in the structure determination proved to be an attempt at acetylation in acid solution which led to opening of the oxide ring, and formation of a bicyclic product named cyclopyrethrosin. The skeleton of this product was established by its conversion into an unsaturated diketoacid which could be correlated with an oxidation product of pseudo-santonin. Recently, further studies on the reactions of cyclopyrethrosin and the physical properties of various derivatives have enabled Barton to establish the full structure of pyrethrosin and its cyclization product, and, in addition, to determine the configurations at most of the asymmetric centres[23].

During our investigations on the lactone arctiopicrin, the bitter principle of *Arctium minus*, we found that the molecular formula[24] which had been

Arctiopicrin $H_2(Pt, AcOH, HClO_4)$ Deoxotetrahydro-artemisin   Artemisin

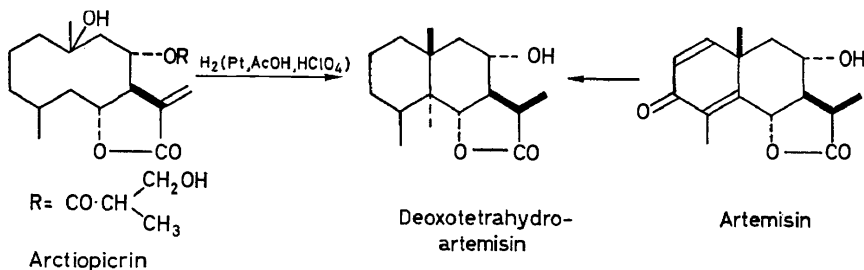$R = CO \cdot CH \begin{array}{c} CH_2OH \\ CH_3 \end{array}$

Figure 11

allotted to this compound was wrong, and that we were in fact dealing with the β-hydroxy-iso-butyric acid ester of a monocyclic sesquiterpenic hydroxylactone which we have called arctiolide[25, 26] (*Figure 11*). The most important evidence for its structure was derived by its relation to the santonin series. Hydrogenation of arctiopicrin in acid solution, followed by hydrolysis, gave a bicyclic compound which proved to be identical with deoxotetrahydroartemisin.

Some time ago, the Indian authors Rao, Kelkar, and Bhattacharyya[27] studied a sesquiterpene lactone, which they have called costunolide, from

Costunolide

(i) O$_3$
(ii) HNO$_3$

Santanolide C

Santanolide A

Figure 12

Balchanolide

H$_2$(Pt,H$^+$)

Isobalchanolide

Deoxotetrahydroartemisin

Arctiopicrin
Cnicin

11-Hydroxybalchanolide

Figure 13

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the Himalayan plant, *Saussurea lappa*. They showed that this lactone also contains a cyclodecane ring, and were able to propose two alternative formulae *a* and *b*. At about the same time, we were investigating the extractives of an Asian species of wormwood, *Artemisia balchanorum*; the main constituent proved to be a lactone which was evidently identical with costunolide. We were soon able to settle its structure and to show that it corresponded to formula *a* of the Indian authors, and to determine the absolute configuration of costunolide (*Figure 12*)[28]. Here again, stereospecific transannular cyclization reactions provided the key. Hydrogenation of costunolide in acid solution gave a product identified with santanolide C, one of the reduction products of santonin. Alternatively, dihydrocostunolide could be converted into an unsaturated bicyclic lactone; this proved identical with the 3-santenolide described by Cocker and McMurry[29], and, on hydrogenation, gave a mixture of santanolides A and C, compounds we had encountered earlier during our work on santonin. Since the absolute configuration of santonin is known, these reactions establish the configuration of costunolide. This was also confirmed later by Bhattacharyya and his co-workers[30].
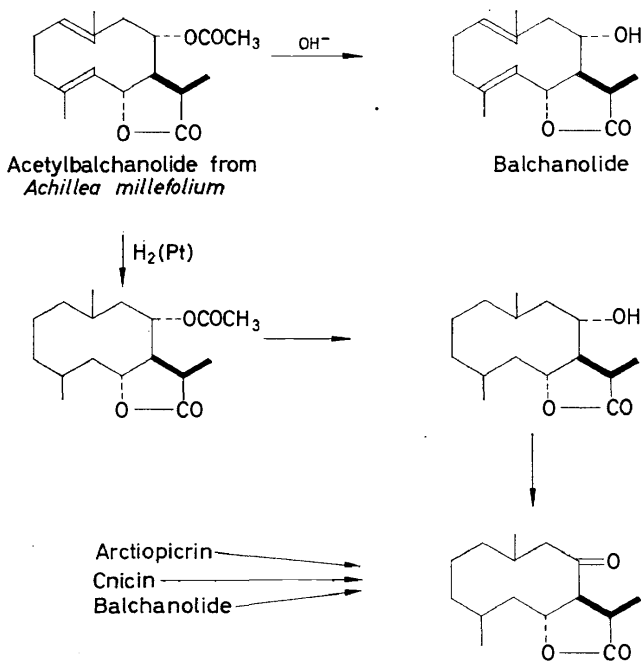

Figure 14

Costunolide is not the only lactone of *Artemisia balchanorum*. Paper chromatography of the extracts revealed at least four further compounds of this group, and three of these we have already obtained in crystalline form[31]. Each of them contains a cyclodecane ring. Two have identical compositions, and both contain two double bonds and one hydroxyl group; we have called them balchanolide and isobalchanolide (*Figure 13*). The

double bonds were located by oxidative degradation and, in the case of balchanolide, by transannular cyclization. Balchanolide can be cyclized under acid conditions in the usual way, or merely by heating it to about 170°. Hydrogenation of the product gave the same deoxotetrahydro-artemisin as we had already encountered in our work on arctiopicrin. The constitution and configuration of isobalchanolide were confirmed by correlation with compounds derived from arctiopicrin. Oxidation of the hydroxyl group of tetrahydroisobalchanolide gave two isomeric keto-lactones identical with products we had earlier obtained from arctiopicrin and cnicin. The detailed relation between balchanolide and isobalchanolide and their full stereochemistry remains to be settled.

The third crystalline lactone from *Artemisia balchanorum* is related to balchanolide—it is 11-hydroxybalchanolide.
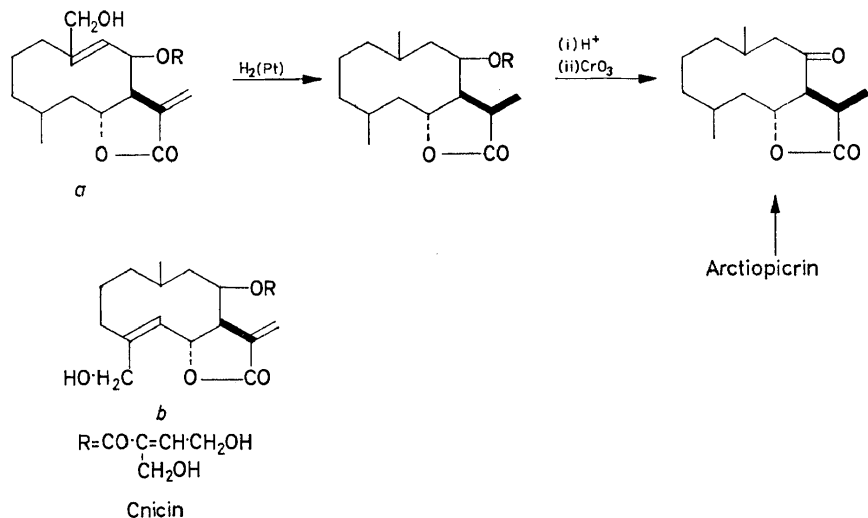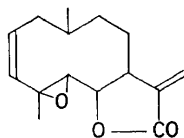

Figure 15

Recently we have found that a lactone isolated from the common milfoil (*Achillea millefolium*) is closely related to balchanolide[32]. It is the acetate of a doubly unsaturated hydroxy-lactone (*Figure 14*). Oxidation of the tetrahydro-derivative of the parent lactone obtained by hydrolysis led once more to the familar keto-lactone first prepared from arctiopicrin and cnicin. This suggested that our new lactone might be acetylbalchanolide; and, in fact, this was confirmed by a direct comparison of this compound with acetylated authentic balchanolide.

Another compound based on the germacrane skeleton is the bitter principle of *Cnicus benedictus*, a substance which has been known for more than a century, but again formulated erroneously until recently. We have shown that this compound, cnicin, is a monocyclic sesquiterpene hydroxy-lactone esterified with a rather uncommon carboxylic acid—1,4-dihydroxy-but-2-ene-2-carboxylic acid. The parent lactone has two hydroxyl groups and two double bonds, one of them in conjugation with the lactone carbonyl group (*Figure 15*). Oxidation of the monohydroxylactone resulting from

hydrogenolysis and hydrolysis once more gave our well-known keto-lactone, and this establishes the position of the secondary hydroxyl group; the ready hydrogenolysis of the primary hydroxyl incidentally locates it in the allyl position to one of the double bonds, and, since some methylethylacetic acid is also split off hydrogenolytically, the esterified hydroxyl group also appears to be next to a double bond. These facts make it likely that cnicin has the structure *a*, or, less probably, *b*[33, 34].

Yet another compound of the germacrane group was found in parthenolide, a lactone isolated in our laboratories from *Chrysanthemum parthenium*[35]. Parthenolide contains two double bonds, one of them conjugated with the carbonyl group, and a third oxygen atom present as an ether bridge (*Figure 16*).

I should now like to come back to some of the special features of these ten-membered ring compounds. The great ease with which unsaturated derivatives of germacrane undergo stereospecific transannular cyclization, most generally to compounds with a selinane skeleton—that is, in the case of the lactones, into relatives of santonin—suggests a biogenetic significance of such reactions. It appears likely that the cyclodecane-type lactones are the primary products in Nature, and that lactones of the santonin and guaianolide series are formed from them by secondary processes analogous to the stereospecific transannular reactions. A further pointer in the same direction is the frequent occurrence of lactones of the germacrane series in the Compositae in which santonin derivatives commonly occur. Within a brief space of time, nine closely-related lactones of the germacrane-type have been isolated from plants of this Family, and fully characterized. Nonetheless, actual proof of the occurrence of such cyclization reactions in Nature is still lacking.

Parthenolide

Figure 16

Some of the unusual reactions observed with medium-sized ring compounds, especially the ready transannular cyclizations of the cyclodecane derivatives, are without doubt the result of specific steric conditions in these compounds. The same cause lies at the root of the spectroscopic anomalies which have been noted with some compounds of this series, and which have a precedent in the anomalous spectrum of cyclodecenone recorded by Leonard[36]. I should like to discuss this point in a little more detail.

Germacrone (*Figure 8*) shows three maxima in the ultra-violet absorption spectrum at 213, 240, and 315 mμ. The second and third may be allotted to the unsaturated ketone grouping; but the short-wave maximum is difficult to interpret on the basis of the classical relations between structural and spectral properties. The same maximum is also found in the alcohol, germacrol, and in a number of the natural unsaturated lactones such as

costunolide, balchanolide, isobalchanolide and acetylbalchanolide. Therefore, this feature is not bound up with the carbonyl group of germacrone, but is evidently related to the character of the two endocyclic double bonds in the cyclodecane ring.

The anomalies in the ultra-violet absorption spectra of the cyclodecadiene derivatives I have discussed suggested to us the possibility of " non-classical " interactions of the endocyclic double bonds, which might well be expected to affect the spectra. Therefore, we asked Dr Koutecký, of the Institute of Physical Chemistry of our Academy, to verify this possibility by the appropriate quantum-mechanical calculations. From a consideration of models, Dr Koutecký and his co-workers, Dr Zahradník and Dr Paldus, concluded that in all three geometrical isomers of cyclodeca-1,5-diene— that is, the *cis,cis-*, *cis,trans-*, and *trans,trans*-isomers—conformations could be set up in which the double bonds were roughly parallel. *Figure 17* shows
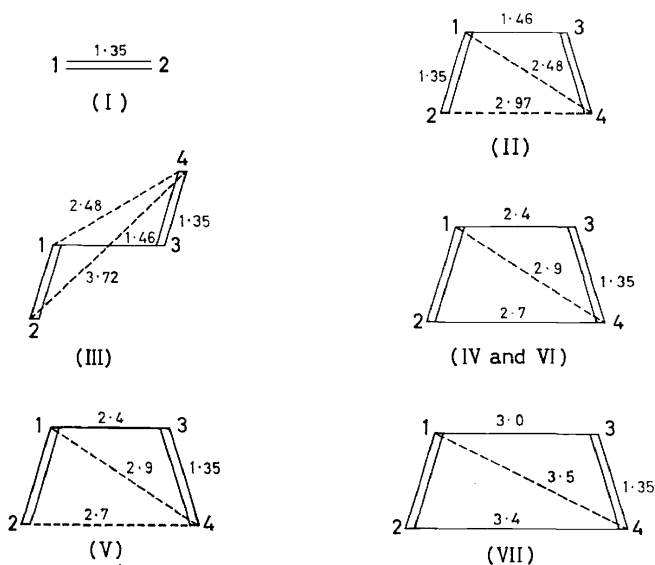

Figure 17.
(Broken lines: distances between non-bonded atoms ($\beta_{ij} = 0$))

the four spatial arrangements of the relevant four carbon atoms of the cyclodecadiene molecule for which calculations were made, together with ethylene and *cis*- and *trans*-butadiene. The energies of transition from the highest occupied to the lowest vacant energy level were calculated by a self-consistent molecular orbital method; the results for ethylene and *cis*- and *trans*-butadiene were used to check the suitability of the chosen parameters. As *Table 1* shows that the delocalization energies for three of the models are negligible, and only for model (V), with a decreased β_{24} integral, is its value appreciable. *Table 1* also shows the results of calculations of the absorption frequencies in Clar's classification. From our point of view, the most important is the highest wavelength singlet *p*-band. The calculated values for ethylene and the butadienes are in good agreement with experimental values; all the cyclodecadiene models considered show a relatively

Table 1. Delocalization energy and frequency of singlet p-bands
for models (I)–(VII)

Model	Delocalization energy (kcal/mol)	p^*
(I)	—	7·38 (170)
(II)	13·2	5·18 (239)
(III)	12·2	5·39 (230)
(IV)	0·6	4·47 (277)
(V)	5·5	5·68 (218)
(VI)	0·2	5·65 (219)
(VII)	0·2	6·30 (197)

* Frequencies in eV; for singlet p-bands also in mμ (in brackets).

marked interaction, and in particular, models (V) and (VI) give values for the singlet p-band very close to the observed absorption maxima of germacrone, costunolide and dihydrocostunolide. Therefore, the results of these calculations show that transannular interaction of the double bonds in our cyclodecadiene derivatives is not only theoretically possible, but in fact very probable.

Now let us consider the infra-red absorption spectrum of germacrone. This shows the expected absorption associated with a conjugated carbonyl and trisubstituted double bonds; however, the spectra of ketones containing a tetrasubstituted double bond in conjugation with the carbonyl bond generally show a very strong maximum at about 1620 cm^{-1}, and this is absent from the absorption spectrum of germacrone. Originally, this fact led us, and later Ohloff, to consider the possibility that germacrone might contain a reactive cyclopropane ring; but it appears now that the true cause of this anomaly is very probably once more the specific geometry of the ten-membered ring in germacrone. An inspection of models shows that some conformations in particular force the carbon–oxygen double bond out of the plane of the tetrasubstituted ethylenic double bond, and this presumably leads to the observed change in the spectral properties.

I have dealt with these spectroscopic anomalies in some detail because they show how the investigation of novel types of compounds can be complicated by lack of experience even when well-tried methods are used.

On this note I should like to close my talk, in which I have tried briefly to recall the history of research on medium-sized ring terpenes, and to present some recent results from this field.

I should like to mention the colleagues who were especially active in this work. They were Drs V. Herout, L. Dolejš, M. Suchý, M. Streibl, V. Jarolím and M. Souček.

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