Sesquiterpenes with Ten-Membered Carbon Rings.   A Review

Frantisek Sorm

The history of sesquiterpene compounds with ten-membered carbon rings falls into the period of the discovery of natural products with medium-size carbon rings and actually starts with the determination of the structure of germacrone and pyrethrosin. Since that time a number of compounds of the latter type have been obtained from plants, especially compounds of lactone character, the so-called germacranolides. Structural and stereochemical studies on these compounds did not avoid certain errors. This paper presents a survey of the present state of our knowledge of this group of products, their mutual relations and peculiarities, and their chemical transformations, and also gives information on certain new compounds identified recently.

One of the most interesting results of recent investigations on terpenoids is the finding that some sesquiterpenoids possess medium carbon rings. The existence of such rings has been formerly assumed as highly improbable, if not impossible. In 1950 we demonstrated in our laboratories (Sorm et al., 1950) that the well-known and intensively studied sesquiterpenoid hydrocarbon caryophyllene possesses a carbon skeleton consisting of a nine-membered ring annelated to the cyclobutane ring, the existence of which was established earlier. In the next year, it was established by us (Sorm et al., 1951), and independently by Clemo in England (Clemo and Harris, 1951), that the sesquiterpenoid hydrocarbon humulene (recently shown to be a mixture of isomeric α- and β-humulene) possesses an 11-membered ring and that the structure of humulene is closely related to caryophyllene. Subsequent investigations have shown that the occurrence of the latter medium rings in nature is very rare, obviously due to the unusual ring closure of isoprene units. In fact, very few naturally occurring substances of this type were later discovered, e.g., the alcoholic butulenols in the caryophyllane series, some humulene epoxides, and some ketones (zerumbone) in the humulane series.

On the other hand, the sesquiterpenoid compounds possessing a ten-membered carbon ring appear to be widely distributed in plant material, especially in Compositae. Since the number of representatives of this group of substances is rapidly growing, it was felt desirable to present a survey, particularly from the standpoint of structural features. Our investigations were sometimes accompanied by errors. This paper offers occasion to make the corresponding corrections and reformulations. The substances mentioned in the present survey are also interesting from the standpoint of their chemical and physical properties.

All ten-membered ring sesquiterpenoids contain the same carbon skeleton which is built up of isoprene units in the sense of the Wallach–Ruzicka rule. We refer to this skeleton as the germacrane type. The name is derived from the sesquiterpenoid compound germacrone, which has been isolated

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from the essential oil of *Geranium macrorhizum.* Germacrone was the first ten-membered ring sesquiterpenoid whose structure was definitely established in our laboratories (Ognajanov et al., 1957, 1958). At about the same time Barton, in England, investigated the structure of pyrethrosine (Barton and de Mayo, 1957), a ten-membered ring sesquiterpenoid containing an annelated five-membered lactone ring.
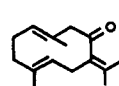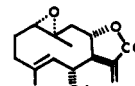

GERMACRONE   PYRETHROSINE

The 1,5-cyclodecadiene system occurring in the germacrone molecule is characteristic of many compounds of this series. The geometry has been recently unambiguously established with the use of X-ray techniques, both with the hydrocarbon germacratriene (germacrene B) and with the lactone costunolide, which was investigated in our laboratories. In both cases addition compounds with silver nitrate were used. The
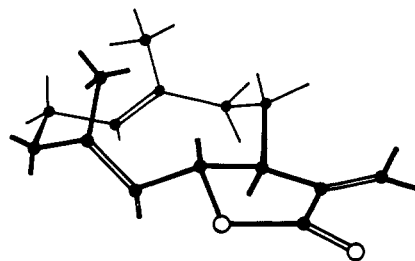
COSTUNOLIDE

structure proposed by us on the basis of chemical evidence, namely, the trans position of both endocyclic double bonds has been confirmed in this manner. Furthermore, it has been shown that in crystals of both addition compounds the parallel methyl groups are oriented practically perpendicular to the plane of the ten-membered ring and that the methyl groups are in the so-called syn position. In some compounds, however, one double bond is cis and the other trans, e.g., in neolinderalactone (Takeda et al., 1969) and in one of the stereoisomeric furanodienones (Hikino et al., 1969).

Both the parent hydrocarbons of the germacrane type and the various products of their oxidation occur in nature. The double bonds are frequently epoxidized. As it will be shown later, the oxidation can practically take place on every carbon atom of the germacrane skeleton. The various types of lactones whose carboxylic function was formed by oxidation of one or two methyl groups are also very frequent and were given the name germacranolides.

The germacrane hydrocarbons have been recently obtained from plant material. These hydrocarbons are highly unstable and their isolation requires especially mild conditions. Some hydrocarbons of the germacrane type are, namely, germacrene A from *Eunica mamosa*, germacrene B from the leaves of *Hedera helix*, germacrene C from *Kadsura japonica*, germacrene D from *Pseudotsuga japonica*, and cyclogermacrene from the essential oil of *Citrus junos*. In the second part of this paper, dealing with biogenetic relations of sesquiterpenoids, the germacrane hydrocarbons will be mentioned once more.

GERMACRENE A   GERMACRENE B   GERMACRENE C

GERMACRENE D   CYCLOGERMACRENE
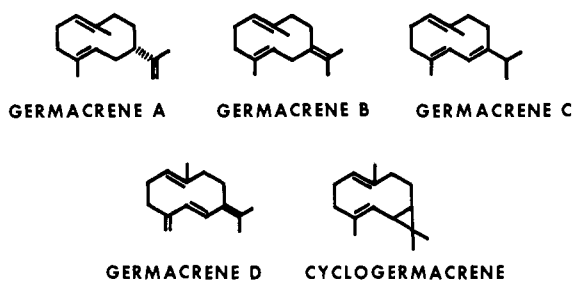
The germacrane-type alcohol, hedycaryol, was isolated by Hellyer (1962) from the essential oil of *Hedycarya angustifolia*. The plant *Parabenzoin trilobum* contains two compounds, namely, shiromodiol monoacetate and diacetate, which exhibit an antifeeding activity on some insect species. Their structure was determined with the use of X-ray techniques. Germacrone has already been mentioned. Preisocalamenediol from *Acorus calamus* is closely related to germacrone. Curdione is a diketone isolated from *Curcuma* species.
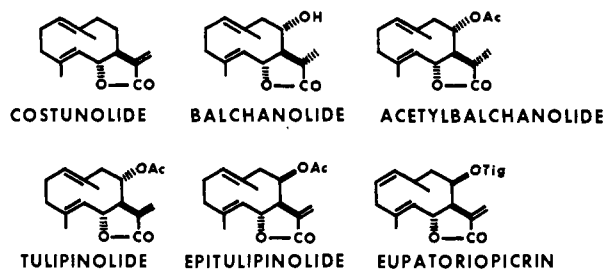

HEDYCARYOL   SHIROMODIOL
MONOACETATE   DIACETATE

GERMACRONE   PREISOCALAMENDIOL   CURDIONE
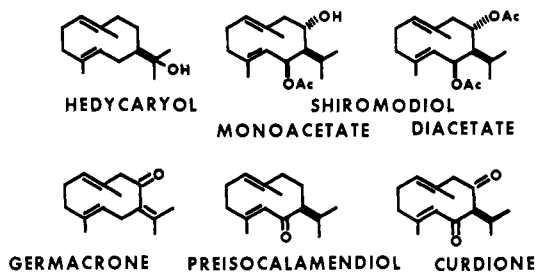
Some compounds of the germacrane series contain an annealted furan ring, e.g., the simple furanodiene and the ketone furanodienone from *Curcuma zedoaria*, and sericenine from *Neolitsea sericea*. It is highly probable that the furano-

FURANODIENE   FURANODIENONE   SERICENINE
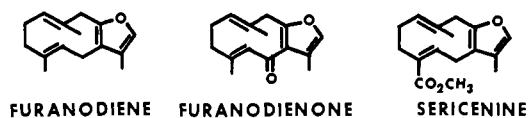
germacrane derivatives are biogenic precursors of some germacranolides. On the other hand, some germacranolides contain an additional furan ring.

The 6,12-germacranolides with a carboxylic function at position 12 are the most frequent lactones of this group. The simplest representative, costunolide, was obtained by Bhattacharyya and his school (Rao *et al.*, 1958) from the Indian plant *Saussurea lappa* and is present in various other plants; e.g., *Artemisia balchanorum* (Herout and Sorm, 1959). As

COSTUNOLIDE   BALCHANOLIDE   ACETYLBALCHANOLIDE

TULIPINOLIDE   EPITULIPINOLIDE   EUPATORIOPICRIN

already mentioned, we have recently confirmed the structure of costunolide, proposed by us earlier with the use of X-ray techniques (Sorm *et al.*, 1970). New information has been simultaneously obtained on the mutual position of the endocyclic double bond $C_{(4)}:C_{(5)}$ and the annelation of the lactone ring. The hydrogen atom at position 5 and the hydrogen atom at position 6 are in trans position to each other. As indicated by nmr data, this configuration appears usual with most germacranolides of this type.

The typical double bond in conjugation to the carbonyl group, and characteristic of most germacranolides, is also present in costunolide.

In addition to an esterified hydroxylic function, the most frequent 6,12-germacranolides possess another hydroxylic function at position 8; this function is either free or esterified.

Balchanolide which accompanies costunolide in *Artemisia balchanorum*, the wormwood from Central Asia, and the acetyl derivative of balchanolide, present in *Achillea millefolium*, belong to the first substances of the last type investigated in our laboratories. Both substances lack the double bond in conjugation to the carbonyl group. The α configuration of the $C_{(11)}$-methyl group has been established from correlation with dihydrotulipinolide.

Tulipinolide and epitulipinolide from *Liliodendron tulipifera* (*Magnoliaceae*) represent according to Doskotch (Doskotch and El-Feraly, 1970) epimeric 8-acetoxycostunolides. Eupatoriopicrin also belongs to this group of substances. Some time ago we proposed the structure with a cis annelated lactone ring. Correlation of our data with those of epitulipinolides led Doskotch to the conclusion that eupatoriopicrin is analogous to the latter compounds. The 8-hydroxylic function of eupatoriopicrin is not acetylated but rather acylated with dihydroxytiglic acid. The presence of this acid was established earlier in our laboratories. Our independent reinvestigations on eupatoriopicrin led to the same conclusions. In addition to eupatoriopicrin, we have isolated the unesterified lactone eupatolide from the plant *Eupatorium cannabium*. Because of some discrepancies in structural determinations of eupatoriopicrin, we have reinvestigated the crude fractions of this substance and observed that eupatoriopicrin is accompanied by an additional lactone which is difficult to remove. This lactone has not been obtained in the pure state but its molecule reliably contains a cis lactone system at positions 6 and 12 in addition to the acetoxy group at position 2 or 3. In my opinion it was the hydrogenolytical products of this lactone which were the cause of some erroneous conclusions on the structure of eupatoriopicrin.

The hydroxy derivatives of costunolide, the so-called tamaulipin A and tamaulipin B, were isolated by Fischer *et al.* (1968) from the Mexican vegetations of *Ambrosia confertiflora*. Costunolide epoxide, known under the name

TAMAULIPIN A TAMAULIPIN B

PARTHENOLIDE LASEROLIDE
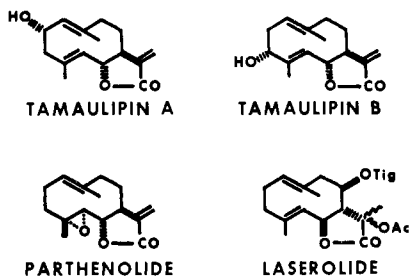
parthenolide, is present in the plant *Chrysanthemum parthnium*. The original proposal of the structure has been revised.

Laserolide is one of the few germacranolides which do not originate from plants of the family *Compositae* and *Magnoliaceae* but from the plant *Laser trilobum* of the family *Umbeliferae*. As shown by our investigations, laserolide is a 6,12-germacranolide carrying an acetoxy group at position 11 and a hydroxylic function esterified with angelic acid at position 8. The configuration of the methyl group has not been determined thus far. It is noteworthy that laserolide most probably belongs in the enantiomeric (antipode) series in contrast to other sesquiterpenoid lactones of this type, as shown by determination of the absolute configuration at $C_{(6)}$ and $C_{(8)}$.

Some time ago we isolated from the wormwood (*Artemisia absinthium*) another interesting group of germacranolides, namely, the palenolides. The geometry of the molecule of hydroxypelenolide and ketopelenolides has been recently determined by Bates *et al.* (1970).

HYDROXYPELENOLIDE KETOPELENOLIDE A KETOPELENOLIDE B
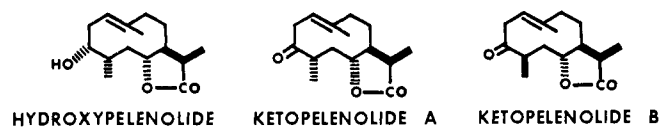
As mentioned above, the higher-oxidized compounds of the germacrane group occur frequently in nature. Notable is the rich occurrence of polyhydroxy-6,12-germacranolides, the hydroxylic functions of which are partially or completely esterified. Chihuahuin from *Ambrosia confertiflora* is a 3-hydroxy derivative of tulipinolide. Heliangin from *Helianthus tuberosus* is a 1,10-epoxy derivative related closely to chihuahuin.
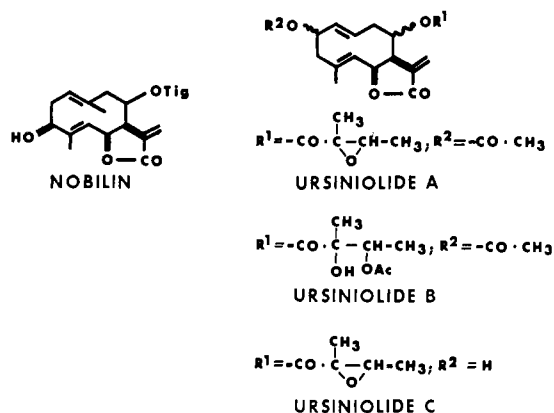

CHIHUAHUIN HELIANGIN
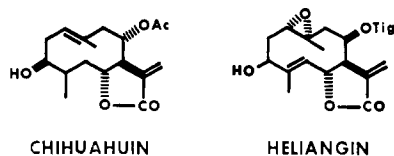
Verlotin, anhydroverlotin, and artemarin, obtained by Geissman (1970) from the plant *Artemisia verlotum*, are 6,12-germacranolides possessing an exomethylene double bond.

VERLOTIN ARTEMARIN ANHYDROVERLOTIN
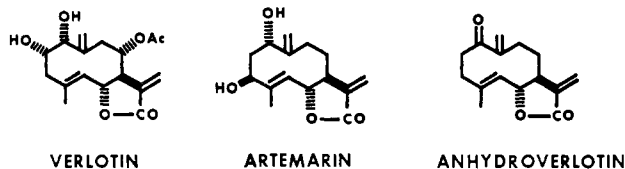
Their formation from ordinary germacranolides might be explained *via* the 1,10-epoxide.

Recently we have demonstrated in our laboratories the presence of a cis annelation between the γ lactone system and the cyclodecadiene ring in some 6,12-germacranolides, es-

pecially in the case of nobilin from *Anthemis nobilis*. Shown are the structure of nobilin and the structures of the ursiniolides from *Ursinia anthemoides*, which has been recently in-

NOBILIN URSINIOLIDE A

$R^1 = -CO \cdot C - CH - CH_3; R^2 = -CO \cdot CH_3$
| |
O

URSINIOLIDE A

$R^1 = -CO \cdot C - CH - CH_3; R^2 = -CO \cdot CH_3$
| |
OH OAc

URSINIOLIDE B

$R^1 = -CO \cdot C - CH - CH_3; R^2 = H$
|
O

URSINIOLIDE C

vestigated in our laboratories. It is noteworthy that the complex acid which esterifies position 8 of ursiniolide A is also present in the germacranolide from *Polymnia uvedalia*, as shown by Herz and Bhat (1970).

Many 6,12-germacranolides possess oxidized methyl groups at positions 14 and 15. Some of these substances occurring as bitter principles of plants of the family *Compositae* belong to the first germacranolides which were investigated in our laboratories. Some structures were reformulated. The parent substance is represented by the salonitenolide from

SALONITENOLIDE ARCTIOPICRIN

CNICIN ONOPORDOPICRIN

HOCH₂ OH
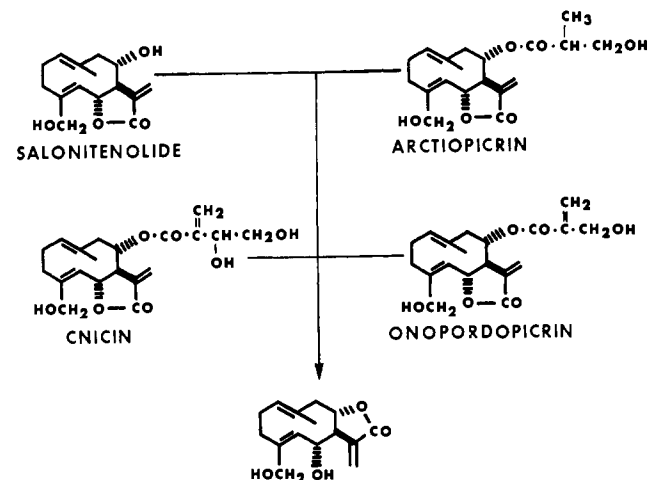
Centaurea salonitana. Salonitenolide is a 8,14-dihydroxycostunolide. Variously esterified salonitenolides may be exemplified by arctiopicrin from *Arctius minus*, cnicin from *Cnicus benedictus*, and onopordopicrin from *Onopordon acanthium*. The saponification of all three substances is accompanied by relactonization and the formation of a single product, an 8,12-germacranolide. Eriophyllin B, eriophyllin, and eriophyllin C carry an aldehydic group at position 14 and

ERIOPHYLLIN ERIOPHYLLIN B ERIOPHYLLIN C
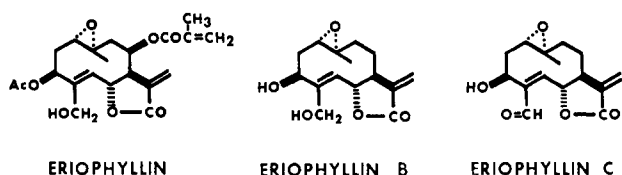
were isolated from *Eriophyllum confertiflorum* by Geissman and his school (Torrance *et al.*, 1969). The stereochemistry of these substances was determined with the use of X-ray techniques.

As demonstrated by Herz (Herz and Bhat, 1970), polydalin and uvedalin from *Polymnia uvedalin* contain a carboxylic function at position 15 and esterified hydroxylic functions at positions 8 and 9. I should like to mention that some authors prefer to write the structures of germacrone derivatives in a different form, which is also used in some publications.

POLYDALIN

UVEDALIN

R=—CO·C·COCH₃
OH

R= —CO·C—CH·CH₃
CH₃
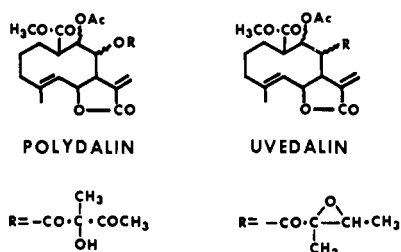
Albicolide and jurineolide obtained in our laboratories from *Jurinea* plants and urospermal A from *Urospermum dolechampii* are 6,12-germacranolides, both methyl groups of which occur in the oxidized form.

ALBICOLIDE **JURINEOLIDE** **UROSPERMAL-A**
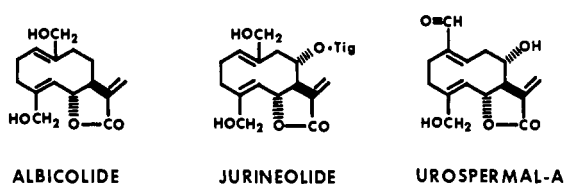
I should like now to pass to 8,12-germacranolides, which are closely related to 6,12-germacranolides. As mentioned above, the trans annelated 8,12-germacranolides are most probably more advantageous from the stereochemical point of view since they are formed by relactionization of saponified 6,12 derivatives. Unambiguous structures were assigned to chamissonin (isolated by Geissman from *Ambrosia chamissonis*) and pyrethrosin from *Chrysanthemum cinnerariaefolium*. Pyrethrosin was the first lactone which was shown by Barton to possess the germacrane skeleton. In the case of salonitolide, artemisifolin, and scabiolide, the bitter principle of *Centaurea scabiosa*, the methyl group at position 14 also occurs in the oxidized form.

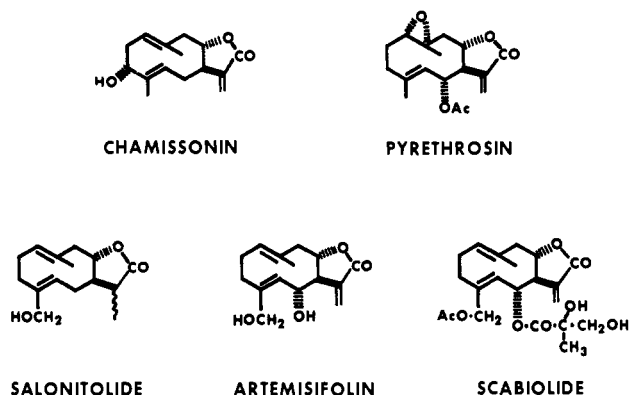**CHAMISSONIN** **PYRETHROSIN**

SALONITOLIDE **ARTEMISIFOLIN** **SCABIOLIDE**

Another type of compound of the germacrane series is exemplified by the 6,14 germacranolides. The configuration of the oldest member of this series, aristolactone from *Aristolochia reticulata*, has not been fully determined.

The series of 14,15 germacranolides, investigated by Japanese authors, exhibits, in addition to the lactone ring, a furan ring annelated to the ten-membered ring at position 8,12. The representatives of this series are linderalactone from *Lindera strychnyfolia*, neolinderan, litsealactone, zeylanicine and zeylanidine.

ARISTOLACTONE **LINDERALACTONE** **NEOLINDERAN**

LITSEALACTONE **ZEYLANICINE** **ZEYLANIDINE**
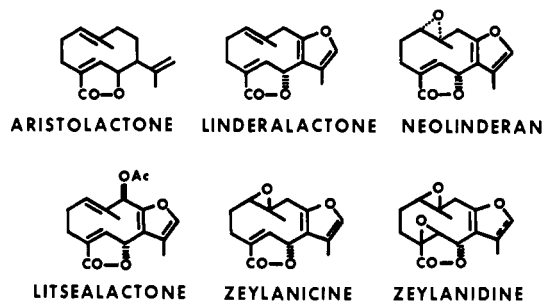
Furanogermacranolides are most probably biogenetic precursors of 8,12–6,14 dilactones of the germacrane group. Isabelin, deoxymicanolide, micanolide, and scandenolide may be mentioned as representatives of this group. Isabelin,

ISABELIN **DEOXYMICANOLIDE**

MICANOLIDE **SCANDENOLIDE**
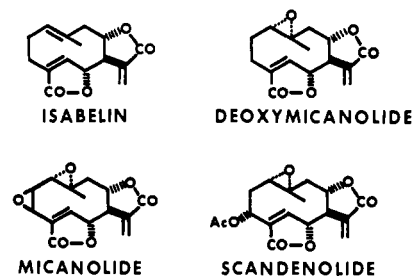
isolated from *Ambrosia psilostachya* by Yoshioka *et al.* (1968), forms two conformers in solution which differ in the geometry of the ten-membered ring.

Elephantin and elephantophin from *Elephantophus elatus*, investigated by Kupchan *et al.* (1966), belong to the 2,15–6,12 dilactones. Their structures have been decided with the use of X-ray techniques.

R=—CO·CH═C⟨CH₃/CH₃

ELEPHANTIN

R=—CO·C═CH₂
CH₃

ELEPHANTOPHIN
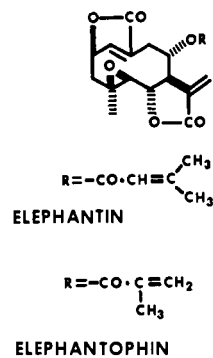
In the present review, it was not possible to mention all members of the germacrane group but I hope that I have at least shown and illustrated their wide variety.

In the second part of my paper, I should like to sum up the results on chemical transformations of compounds of the germacrane group.

Almost all transformations of the germacrane skeleton into other sesquiterpenoid compounds were observed and identified more than 10 years ago during our investigations on germacrone itself. Since considerable attention has been paid in the present time to these transformations, I should like to give a brief account of our earlier contributions.

Germacrone had been previously given a different name—germacrol. Under this name it was studied by Treibs (1952), who proposed the structure of a cyclic ether possessing the guaiane skeleton. When we began to investigate this compound, we noted that the infrared spectra are quite incompat-

S-GUAIAZULENE   ELEMANE   GERMACRONE   CADALENE   SELINANE

ible with this structure; the spectra suggested an unsaturated monocyclic ketone and not an ether (Ognjanov *et al.*, 1957, 1958). The first thing we did after this observation was to change its name to germacrone. We then tried to convert germacrone into the saturated hydrocarbon possessing the same carbon skeleton as the parent compound. The results we obtained were surprising and seemed to be contradictory. Thus, hydrogenation of germacrone in glacial acetic acid afforded as the principal product a saturated bicyclic hydrocarbon $C_{15}H_{28}$, identified as selinane by infrared spectroscopy. The lithium aluminum hydride reduction of germacrone gave an alcohol in which the carbon skeleton remained intact, as shown by the fact that the alcohol could be reconverted into germacrone on oxidation. Dehydration of the alcohol gave a mixture of hydrocarbons, the hydrogenation of which led to elemane as the main product. On dehydrogenation, germacrone gave a considerable amount of guaiazulene. The formation of cadalene from germacrane by a forced dehydrogenation is already known.

Germacrone can be thus converted into no less than four different sesquiterpenoid types, only one of which, namely elemane, is in accordance with the monocyclic nature of germacrone. Some other findings, particularly the spectroscopic evidence, indicated the improbability that germacrone could be derived from the elemane type. We have therefore concluded that germacrone represents a derivative of a novel structural type and, more particularly, that this type must undergo skeletal rearrangements with a great readiness.

These requirements would be best fulfilled by an isoprenoid system including a ten-membered carbon ring. The presence of such a cyclodecane skeleton in germacrone was unequivocally established by the synthesis of germacrane, the parent fully saturated hydrocarbon of this group.

The transannular cyclizations leading to sesquiterpenoids of the selinane group are especially characteristic of compounds of the germacrane series. The reactions of such a type might be exemplified by cyclization of pyrethrosin into the so-called isopyrethrosin, as observed by Barton and de Mayo (1957). During our investigations on the structure of costunolide we have similarly observed that its hydrogenation in acidic media leads to a mixture of santanolide A and C,

which were earlier identified as reduction products of santonine. The cyclization of dihydrocostunolide in acidic media affords 3-santenolide which has been reported in papers of McMurry and Cocker (Cocker and McMurry, 1960). Cyclization of tulipinolide leads to three theoretically possible santenolides. These cyclizations are most probably of biogenetic significance since they are stereospecific and occur under very mild conditions. The resulting santenolides possess the same configurations at the corresponding positions of the carbon skeleton. This assumption is corroborated by the circumstance that all the three santenolides, the formation of which might be expected in the transannular cyclization of costunolide, were isolated from the plant material.

PYRETHROSINE

COSTUNOLIDE

DIHYDROCOSTUNOLIDE

Recently the hydrocarbons of the germacrane series have been observed to transform readily into compounds of the cadinane, amorphane, and muurolane type. Thus, for example, as shown by Yoshihara (Yoshihara *et al.*, 1969) and his school, germacrane D rearranges thermally or by the action of silica gel to a mixture of hydrocarbons identified as α-cadinene and γ-cadinene, α-amorphene, α-muurolene, and γ-muurolene.

γ-CADINENE δ-CADINENE   GERMACRENE D α-MUUROLENE γ-MUUROLENE α-AMORPHENE β-BOURBONENE

Photoisomerization of germacrane D leads to α- and β-bourbonenes. The latter hydrocarbons were isolated some time ago in our laboratories from the essential oil of *Geranium Bourbon*.

The direct correlation between the germacrane and aromadendrane skeleton was performed by Nishimura (Shinoda *et al.*, 1969). The aromadendrane skeleton is closely related to the guaiane system. Thus, in weakly acidic media, bicyclogermacrene afforded a mixture of ledene and δ-cadinene.
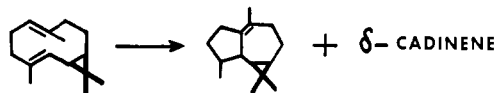
One of the most remarkable reactions of the *trans,trans*-1,5-cyclodecadiene system is the Cope reaction. The first
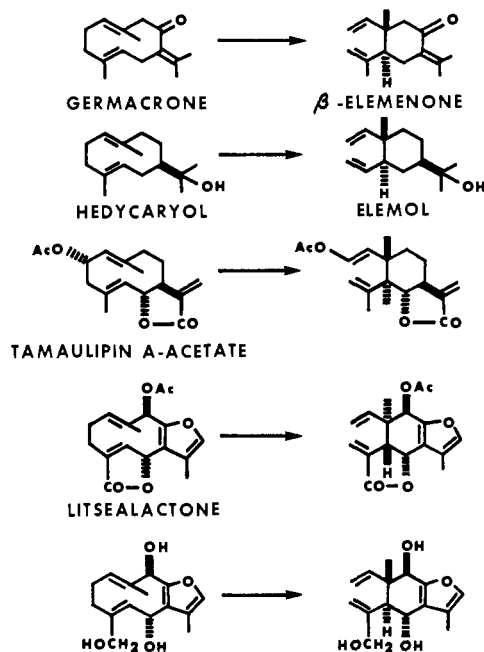
conversion of this type and the first occurrence of the Cope reaction in natural material was observed in our laboratories in the case of germacrone. Thus, pyrolysis afforded β-elemenone, the course of the rearrangement being stereospecific as characteristic of the Cope reaction. The same observation was made independently by Ohloff (1959). The Cope reaction also occurs with some other compounds of the germacrane series. Thus, germacrene C is thermally converted into β-elemene; the well-known elemol is obtained from the alcohol hedycaryol. Also the germacranolides easily undergo the Cope reaction. Thus, for example, the acetate of dihydrotamaulipin A or of the isomeric tamaulipin B affords lactones of the elemane type. The specific conformation of the cyclodecadiene ring is of great importance for the steric course of the Cope rearrangement. Compounds of the ordinary elemane series are obtained from cyclodecadiene derivatives possessing the trans,trans double bonds in syn position, *e.g.*, from such derivatives, in which the parallel methyl groups are oriented perpendicular to the plane of the ring. Any change in the geometry leads to enantiomeric derivatives. As shown by Takeda (Takeda *et al.*, 1970) and his school, linderalactone and litsealactone afford isolinderalactone and isolitsealactone, respectively, while the triol prepared from litsealactone is rearranged to a triol belonging to the ordinary elemene series.

It is well known that the Cope reaction is a reversible process and that the equilibrium between the cyclodecadiene and

the divinylcyclohexane system depends on the nature and configuration of substituents. In the system linderalactone–isolinderalactone, the components equilibrate in the ratio of 2:3.

The readiness of the conversion of some compounds of the germacrane series into compounds of the elemene type indicates that sesquiterpenoids of the latter type, possessing a quite irregular arrangement of isoprene units contradictory to the Wallach–Ruzicka rule, are artifacts originating from compounds of the germacrane type.

Both the transannular cyclization of medium rings and the Cope reaction require a specific geometry in respect to the position of double bonds or systems engaged in these reactions. In the case of compounds of the germacrane type, it is the geometry of both endocyclic double bonds in the 1,5-cyclodecadiene system which is of great importance. I should like to mention that the special features of the geometry of these double bonds were observed in our laboratories at an early stage of our investigations on compounds of the germacrane type. Thus, the ultraviolet spectra of some of these compounds exhibited maxima which were not in accordance with established structures but which rather suggested a conjugated system of double bonds. Germacrone, costunolide, dihydrogermacrone, and dihydrocostunolide may be mentioned as representatives of numerous compounds which exhibited short wavelength maxima in the 215–220 nm region. At that time we formulated an assumption on the transannular interaction of double bonds.

As confirmed by quantum chemical calculations of Koutecky and Paldus (1970), this interaction is possible. Moreover, in the case of the special geometry of both double bonds, the calculated values expressed in wavelengths of absorption maxima are in close accordance with experimental data. The correctness of these considerations and calculations was confirmed by an exact determination of the geometry of germacratriene, costunolide, and some other substances with the use of X-ray techniques. Measurements of the syn conformation of the *trans,trans*-cyclodecadiene system have shown that the distances of both double bonds correspond very closely to the calculated values (these measurements were performed on crystalline addition compounds with silver nitrate but their results may also be applied to solutions as indicated by the steric course of cyclizations). The moderately crossed position of transannular double bonds fully explains the possibility of exciton splitting.

The transannular reaction of both endocyclic double bonds is also reflected in further optical properties of the germacrane type compounds. As shown by circular dichroism measurements performed together with Snatzke, the germacrane type compounds exhibit short wavelength maxima at about 220 and 200 nm which are characteristic of the syn,trans,trans configuration of both double bonds and which are mainly due to exciton splitting of the bond consisting of the chiral overlap of the two conjugated double bonds in the ten-membered ring. They are highly characteristic of this type of interaction and their sign reflects the chirality of the unsaturated system.

The unsaturated lactones, such as costunolide and albicolide, exhibit an additional negative band at 263 nm ($\Delta\epsilon$ -1.14) which corresponds to the N $\rightarrow$ π^* transition of the unsaturated lactone

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