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Sesquiterpenes

By Gerhard Rücker[*]

Of the 4000 or so terpenoid natural products known today, whose carbon skeleton can be divided up into isopentane units by the "isoprene rule" (C_{10}, monoterpenes; C_{15}, sesquiterpenes; C_{20}, diterpenes; C_{25}, sesterterpenes; C_{30}, triterpenes; steroids; carotenoids; polyprenes), the sesquiterpenes, numbering about 1000, represent the largest single class. According to the well founded concepts developed in recent years for the biogenesis of their highly diverse carbon skeletons, the present report is divided into nine sections dealing respectively with farnesanes, bicyclofarnesols (drimanes, iresanes), bisabolanes, cadinanes, humulanes and caryophyllanes, germacranes, "hydroazulenes", selinanes and eremophilanes, and maalianes and aristolanes. Further groups of sesquiterpenes can be derived from each of these structural types.

1. Introduction

The chemistry of the sesquiterpenes with their 15 carbon atoms—corresponding to three isopentane units—arranged in an acyclic or mono-, bi-, tri-, or tetracyclic skeleton has undergone a period of rapid development during the past two decades following the introduction of chromatographic separation techniques and physical methods of structural analysis. In 1953 about 16 sesquiterpene skeletons were known corresponding to about 30 compounds, in 1964 the respective figures were 40 and

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300, and in 1971 100 and 1000. Sesquiterpenes having the same carbon skeleton are classified as a single group. The farnesanes, bisabolanes, cadinanes, humulanes, germacranes, selinanes number among the larger and better known groups of sesquiterpenes (cf. Fig. 1).

The sesquiterpenes, which occur primarily in higher plants—less frequently in lower plants and in the animal kingdom (*e.g.* in insects)—are often steam volatile, and comprise not only mostly unsaturated hydrocarbons (including some alkynes) but also alcohols, ketones, aldehydes, and carboxylic acids. They may also contain three- to seven-membered ether rings and furan rings. Chlorine- and bromine-substituted sesquiterpenes, as well as about 25 nitrogen-containing compounds with 15 C atoms (sesquiterpene alkaloids) isolated predominantly from *Nymphaeaceae* also deserve mention. Compounds with only 12 or 14 carbon atoms (norsesquiterpenes) can also be derived from certain sesquiterpenes.

The sesquiterpene lactones occurring in *Compositae*, and also in other plant families, have attracted particular interest. The first compound of this class, α-santonin[1], which was isolated in crystalline form in 1830, is still the object of intensive study[2]. So far about 300 sesquiterpene lactones are known; worthy of particular mention are the germacranolides[3,4], guaianolides[3-5], pseudoguaianolides[3,6,7], selinanolides (≡ eudesmanolides)[8], and eremophilanolides[4]. Most of them are saturated or α,β-unsaturated γ-lactones. Apart from a few δ-lactones, only two β-lactones (anisatin, neoanisatin)[9] have been found. A trilactone, bilabolide[10], is also known alongside about 25 dilactones.

In addition to the isolation and structural elucidation of numerous new compounds recent advances in sesquiterpene chemistry have included a better knowledge of the stereochemistry of the molecules, their reactivity and rearrangements, and their biogenesis. In this connection the outstanding successes achieved in the synthesis of sesquiterpenes should be emphasized[*]. Several earlier structural assignments have been corrected by syntheses and application of modern physical methods[4]. Thus the "vetivanes", formerly regarded as hydroazulenes, proved to be spirocyclic agarospiranes or eremophilanes with a decalin skeleton[12]. The detection of sesquiterpenes with toxic and interesting biological properties, *e.g.* cytotoxic activity[15], also deserves mention (for reviews see refs. [13—15]). In the present brief progress report most of the studies on sesquiterpenes published in the past two decades have had to go without mention; such are included as references in the publications cited below and in reviews[3-8,11,13,15-19].

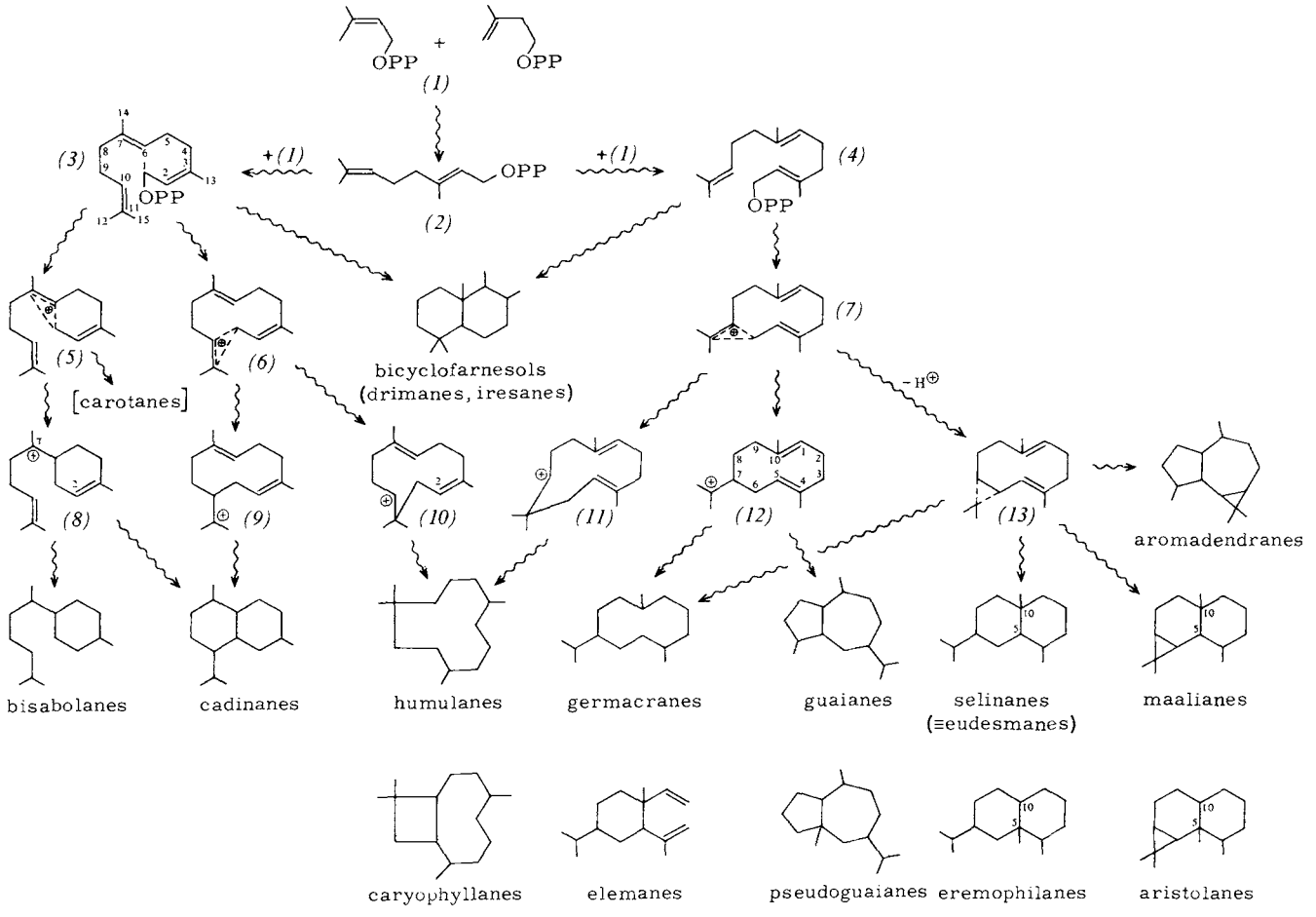


Fig. 1. Biogenesis of the sesquiterpenes. Wavy lines in this and the following figures signify biogenetic transitions. The basic skeletons are generally shown without multiple bonds.

[*] For a review see ref. [11]; for examples refs. [25, 33, 37, 38, 50, 64, 69, 82, 111, 117, 126, 130, 131, 135, 138, 145, 151, 165, 167, 173].

It was not easy to hit upon a reasonable and comprehensive scheme for a discussion of sesquiterpenes. The present report is essentially arranged in line with biogenetic considerations (Fig. 1). The nine sections deal with biogenetically related, or interconvertible, groups of sesquiterpenes. Reviews have appeared on the biogenesis of these compounds[11, 13, 17, 18, 20].

According to *Ruzicka* and *Hendrickson*, 2-*cis*-6-*trans*-farnesyl pyrophosphate *(3)* or the corresponding 2-*trans*-6-*trans* compound *(4)* is regarded as the biological precursor of almost all sesquiterpenes; it is formed from acetyl coenzyme A *via* mevalonic acid, isopentenyl pyrophosphate *(1)*, and geranyl pyrophosphate *(2)* (Fig. 1). For steric reasons, a 2-*trans*-6-*cis*-farnesyl-, a 2-*cis*-6-*cis*-farnesyl-, or a nerolidyl precursor has to be assumed for a few sesquiterpenes. Removal of the pyrophosphate group from *(3)* or *(4)* yields carbocations whose formulation as nonclassical cations *(5)* and *(6)* or *(7)* explains their cyclization to two cyclic cations each [*e.g.* *(9)* and *(10)* from *(6)*; *(11)* and *(12)* from *(7)*]. These can afford most of the sesquiterpenes by processes such as 1,2- or 1,3-hydride shifts, electronically and sterically controlled cyclizations with the two remaining double bonds ("Markownikoff" and "anti-Markownikoff cyclizations"), Wagner-Meerwein rearrangements, and 1,2-methyl shifts. Considerable significance attaches to the biogenetic formation of diastereoisomers and enantiomers. It should however be noted that many hypotheses regarding the biosynthesis of sesquiterpenes that are based on structure, stereochemistry, and reactivity still require experimental proof *in vivo*[13, 20].

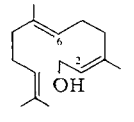
The future of terpene research will still be concerned primarily with the isolation and structural elucidation of new compounds which could be important as missing biosynthetic links, as biologically active substances, or as reactants for the study of chemical problems. The sesquiterpenes throw up problems of a largely stereochemical nature. The course of their numerous rearrangements provides information about relationships between stereochemical and electronic factors and the reactivity of the compounds. The chemistry of nonclassical carbocations has also profited from work on sesquiterpenes. The photochemistry of the sesquiterpenes is still in its infancy. Syntheses of sesquiterpenes nearly always have to be carried out stereoselectively; they can contribute to the solution of problems in preparative chemistry.

Knowledge of reactivity, photochemistry, and syntheses stimulate research into sesquiterpene biogenesis, a field that will become increasingly important in the future. The aim is to elucidate the formation of the numerous carbon skeletons and to obtain information about the reasons behind the frequently complex stereospecific biosynthetic pathways that could also be of interest for the biogenesis of other natural products. In this connection, importance also attaches the site of formation and of deposition of the sesquiterpenes in plants and to their distribution throughout the plant and animal kingdoms. The biological properties of some sesquiterpenes show that they are not merely metabolic "waste products". For instance, they are of significance as plant growth substances, growth regulators, and sex attactants of fungi. Others function as the juvenile hormones essential for normal development of insects or occur as components of insect secretions. These aspects have opened up an area of sesquiterpene research that is of potential interest, *e.g.* for the solution of practical problems of influencing the growth of cultivated plants and in plant protection.

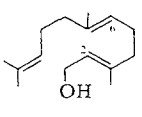
Sesquiterpenes can provide impetus to drug research too. The starting point of such work is the pharmacological effects determined so far for a relatively small number of compounds. They include cytotoxic, antibiotic, fungistatic, virostatic, anthelmintic, antiphlogistic, and sedative properties, thus covering a fairly broad spectrum. Considerable uncertainty still surrounds the extent to which the sesquiterpenes contribute to the manifold and frequently unspecific action of the essential oils in which they occur. Mention should be made here of the importance of sesquiterpene research for the chemistry of essences and of aromas and flavors.

2. Acyclic Sesquiterpenes (Farnesanes)

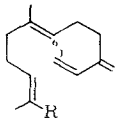
The first sesquiterpene whose structure was correctly determined (1913)[21] is the widely distributed 2-*trans*-6-*trans*-farnesol *(4a)*. The 2-*cis*-6-*trans* compound *(3a)* has also been found in essential oils[22]. Like other natural and synthetic compounds derivable from farnesane and bisabolane (Fig. 2), *(4a)* and *(3a)* have a juvenile hormone action on insects[13, 23]. The saturated parent hydrocarbon farnesane has also been found to occur in Nature, as have monounsaturated farnesenes. Essential oils frequently contain the fourfold unsaturated 6-*trans*-β-farnesene [(*E*)-β-farnesene] *(14)*[24, 25]. Of the four *cis-trans* isomeric α-farnesenes, which have all been synthesized, only two have so far been found in Nature[25], (*E*,*E*)-α-farnesene *(15)* and (*Z*,*E*)-α-farnesene *(16)*. The all-*trans* aldehydes β- *(17)* and α-sinensal *(18)* occur in *Citrus* species[26].



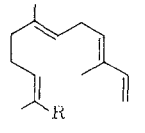
(3a)



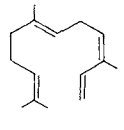
(4a)



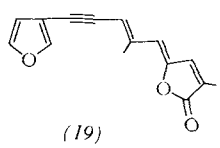
(14), R = CH_3
(17), R = CHO



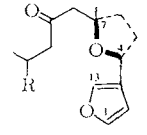
(15), R = CH_3
(18), R = CHO



(16)



(19)



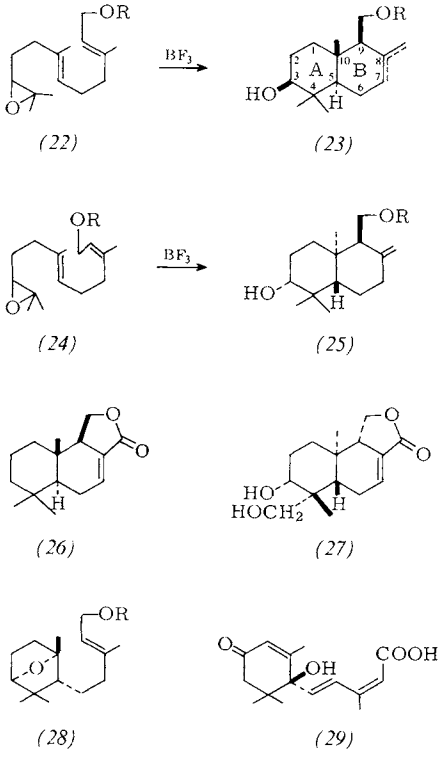
(20), R = CH_3
(21), R = CH_2OH

Only one lactone has so far been discovered in the farnesane group, *viz.* freelingyne *(19)* containing a triple bond and a furan ring[28]. The hepatotoxic substances from *Myo-*

porum species and from sweet potatoes infected with fungi [(−)-ngaione, (+)-ngaione (≡ipomeamarone) *(20)* and ipomeamaronol *(21)*], having a furan ring bridging C-1 and C-13[29] and a tetrahydrofuran ring[27] between C-4 and C-7, number among the farnesanes. Farnesanes with two furan rings are also known[30].

3. Bicyclofarnesols (Drimanes, Iresanes)

The drimanes, *e.g. (23)* and *(26)*, and iresanes, *e.g. (25)* and *(27)*, constituting the small group of the bicyclofarnesols, possess enantiomeric skeletons. Their biogenesis is assumed to involve direct *trans*-antiparallel cyclization of farnesyl pyrophosphate (Fig. 1), *(3)* possibly representing the precursor of the drimanes and *(4)* that of the iresanes[20]. Accordingly, the epoxide of *trans,trans*-farnesyl umbelliferonyl ether *(22)* cyclizes in the presence of BF_3 to give drimenol umbelliferonyl ether *(23)*[31]. Under the same conditions the epoxide of *trans,cis*-farnesyl umbelliferonyl ether *(24)* afforded a very low yield of farnesiferol A *(27)* having an iresane skeleton[31,32]. The umbelliferonyl ether of *(3)*, umbelliprenin, was isolated from *Umbelliferae* (*e.g. Ferula* species). Sterically the skeleton of the drimanes corresponds to rings A and B of most di- and triterpenes. The opposing "unusual" steric arrangement of the iresanes is found in only a few higher terpenes. Most drimanes and iresanes are unsaturated γ-lactones with the lactone ring in the 8,9 position [*e.g.* cinnamolide *(26)* and iresine *(27)*][33,34]. Farnesiferol C *(28)*[32], which has been known for some time, and the plant growth regulating abscisic acid (≡abscisin II≡dormin) *(29)*[35,36] from young cotton fruit and sycamore leaves can be derived from *(3)* or *(4)* by simple cyclization[20].



(22) *(23)* *(24)* *(25)* *(26)* *(27)* *(28)* *(29)*

R = umbelliferonyl

4. Bisabolanes and Related Sesquiterpenes

Precursors having the monocyclic skeleton of bisabolane—*(8)*, *(40)*, *(41)*, *(42)* (Figs. 1 and 2)—have to be considered for the biogenesis of many sesquiterpenes[20]. The bisabolane group is known to contain numerous hydrocarbons, alcohols, ketones, aldehydes, and carboxylic acids. Only β-bisabolene *(30)* will be mentioned as an example. The insect juvenile hormone (+)-juvabione *(35)* was found to deviate in the stereochemistry of its side chain[23,37]. Bisabolanes having aromatic or quinonoid six-membered rings and with tetrahydrofuran or lactone rings are also known.

Several small groups of sesquiterpenes representing isoprenologous monoterpenes can be derived from the cation *(8)* (Figs. 1 and 2) by deprotonation and cyclization. These include l-sirenin *(39)*, an isoprenologous carene (sesquicaranes), the sex attractant of the female gametes of several fungi[38]. α-Bergamotene [*(36)* or *(37)*] is an isoprenologous α-pinene, and β-bergamotene *(38)* an isoprenologous β-pinene. Synthetic studies[39] have shown that the isoprenoid side chain and the cyclohexene ring may be mutually "*trans*" or "*cis*" oriented [*(36)* or *(37)*] in natural α-bergamotene, while β-bergamotene occurs only as the "*trans*" compound *(38)* in Nature. The biogenesis of the antibiotic and cytostatic fumagillin *(34)* from *Aspergillus fumigatus*[13,14] is assumed to involve cleavage of the cyclobutane ring in *(38)*[20]. Cyclization, Wagner-Meerwein rearrangement, and deprotonation of the cation *(8)* can yield two isoprenologous camphenes, the bicyclic β-santalene *(31)*[40] and the tricyclic α-santalene *(32)*[7], which occur alongside other santalenes in Indian sandalwood oil[41]. Isoprenologous bornanes such as campherenol *(33)* are related to the bisabolane cation *(8)*[42].

The discovery of the diketone acorone *(44)* as the first sesquiterpene having a spirocyclic carbon skeleton by *Šorm et al.*[44] attracted acute interest and led to the isolation of further acoranes. Cyclization of the cation *(41)* [or *(40)*] is invoked to explain the biosynthesis of the [4.5]spirocyclic sesquiterpenes. Various stereoisomeric forms of the skeleton can apparently arise depending upon the steric course of the reaction: for instance, cation *(45)* which is regarded as a precursor of α-acorenol *(49)* and deviates sterically from acorone *(44)*. A differently substituted [4.5]spirocyclic ring system is found in the agarospiranes which are biogenetically related to the selinanes (Fig. 7).

Cation *(45)* can be transformed into the tricyclic cedranes, *e.g.* (−)-α-cedrane *(50)* by renewed ring closure[43] and is regarded as an intermediate of the acid-catalyzed conversion of *(49)* into *(50)*[43]. The small group of the cedranes[45,46] embraces hydrocarbons, *e.g. (50)*, alcohols, and carboxylic acids occurring in *Juniperus* species, cedarwood oils, and in the basic hydrolyzates of shellac, which is well known to be secreted by the insect *Lacifer lacca*[47].

Biogenetic precursors of the chamigranes such as *(52)*[48] having a spiro[5.5]undecene structure *(46)* and the cuparanes *(43)* can be formed from cation *(42)* by cyclization[20,46]. The chamigrane cation *(46)*, whose biogenesis by direct cyclization of *(3)* or *(4)* analogous to the formation of the bicyclofarnesols is also conceivable[49], is also

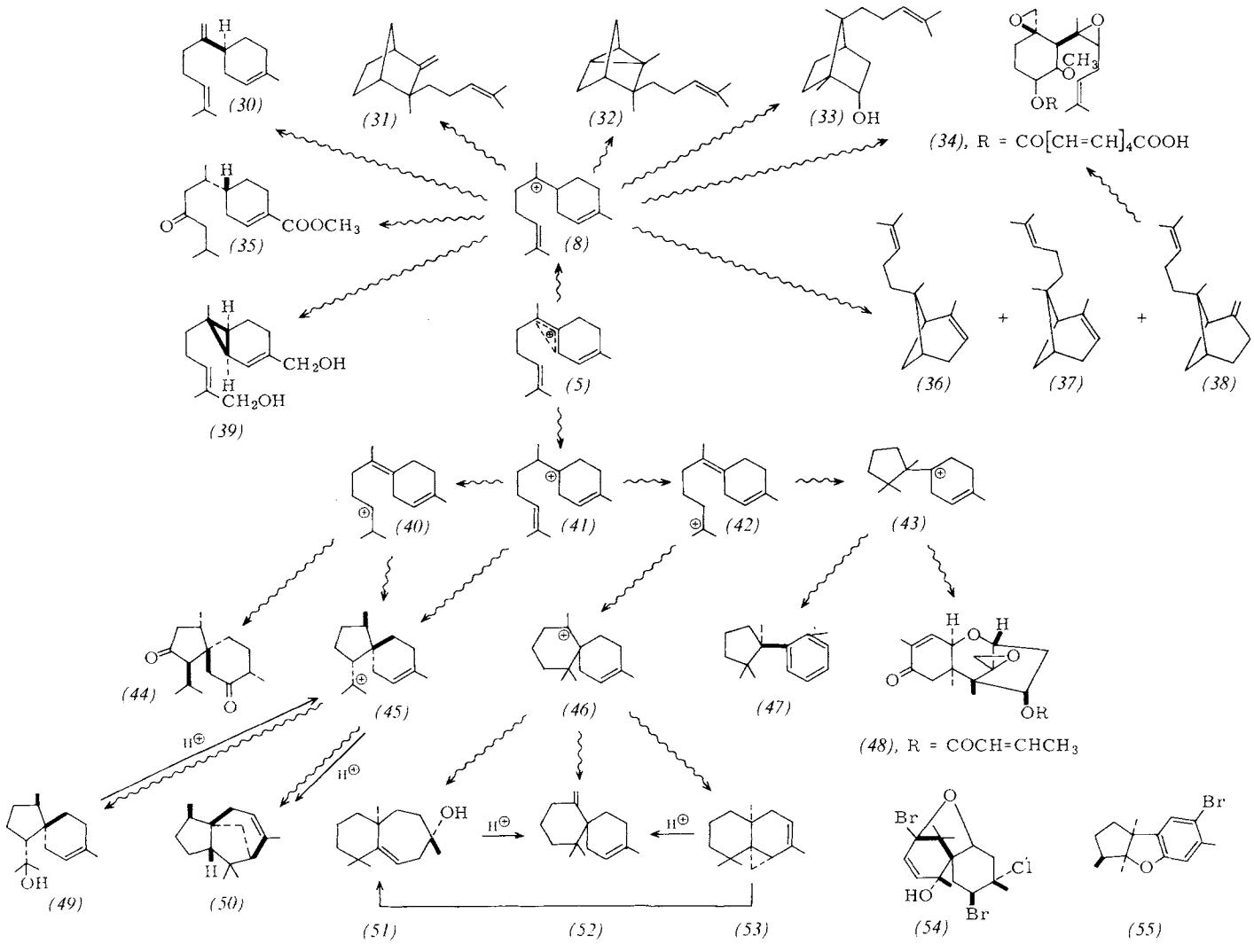


Fig. 2. Bisabolanes and related sesquiterpenes.

viewed[20] as a precursor of widdranes such as *(51)* (widdrol) and thujopsanes such as *(53)* (thujopsene)[46,50]. Acid-catalyzed transitions have been observed between these small groups of related sesquiterpenes, *e.g.* from *(51)* and *(53)* to β-chamigrene *(52)*[48] or from *(53)* to *(51)*[51]. A recent discovery was the chamigrane derivative pacifenol *(54)*, the first sesquiterpene to contain both chlorine and bromine[52]. Nearly all the cuparanes, which are mainly isolated from *Cupressaceae*, *e.g.* cuparene *(47)*, contain an aromatic ring[46]. Algae, fungi, and molluscs afforded substances such as aplysin *(55)* exhibiting a modified substitution of the parent system[53] (lauranes) which may also contain chlorine or bromine, as well as an additional ether ring, and, like *(54)*, are regarded as detoxification products of halogenated pesticides[52]. The trichothecanes, *e.g.* trichothecin *(48)*, isolated as cyclic esters (roridins, verrucarins) from microorganisms and of interest owing to their antibiotic properties[13,54], are derivable from cation *(43)*.

5. Cadinanes and Related Sesquiterpenes

Sesquiterpenes having a 1,7-dimethyl-4-isopropyldecalin skeleton (Figs. 1 and 3) are designated cadinanes, and frequently also as cadalanes, because they afford the naphthalene derivative cadalene on dehydrogenation with sulfur or selenium. The cadinanes, which all contain an α-isopropyl group, can be divided into four types according to the stereochemistry of the ring linkage (Fig. 3): the true cadinanes, *e.g. (57)* [(+)-γ-cadinene] and the bulgaranes, *e.g. (58)*[55] [(−)-ε-bulgarene], display a *trans* linkage of the two cyclohexane rings, and the muurolanes, *e.g. (59)* [(−)-α-muurolene][56], and amorphanes, *e.g. (60)* [(−)-γ-amorphene][56] a *cis* linkage.

Cyclization of the bisabolane cation *(8)* or the germacrane cation *(9)*[57] (Figs. 1 and 3) or of a 2-*cis*-6-*cis*-farnesyl precursor[20] is assumed to account for the biogenesis of these four stereochemical variants of the dimethylisopropyldecalin system. Acid treatment of bicyclogermacrene *(13)* (Fig. 1) opens the three-membered ring to give cadinanes[58]. Numerous cadinane hydrocarbons and alcohols (cadinols) have been found in higher and lower[59] plants. Either ring A or both rings of the cadinanes may be aromatic. Furans and *p*- and *o*-quinones with a cadinane skeleton have likewise been found in Nature. Biogenetic formation of the indan derivative oplopanone *(56)* may conceivably proceed *via* ring contraction of an α-cadinol[60]. Relations can also be detected between other sesquiterpenes having an indan-type carbon skeleton and

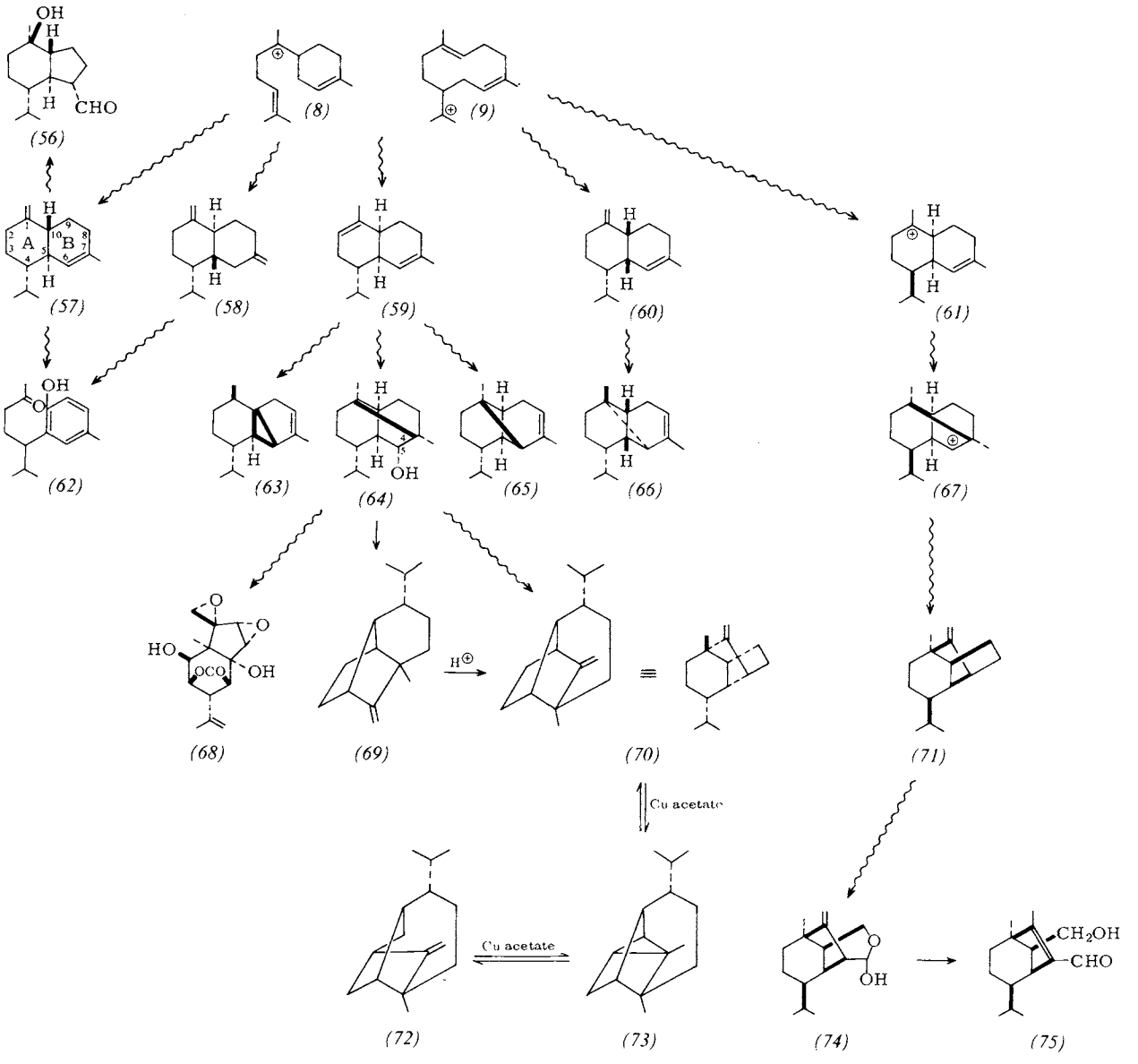


Fig. 3. Cadinanes and related sesquiterpenes.

the humulanes, germacranes, guaianes, selinanes, or eremophilanes[13,20]. Several monocyclic sesquiterpenes having carbon skeletons resembling bisabolane, *e.g.* sesquichamaenol *(62)*[61], are formed by ring cleavage from cadinanes or bulgaranes[20]. The tricyclic cubebanes, *e.g.* *(63)* (α-cubebene)[64], copabornanes *(64)*, and copaanes *(65)* can be derived biogenetically from the *cis*-fused muurolanes *(59)*, and the ylanganes *(66)*[20,62] from the amorphanes *(60)*. Model experiments also suggested that a pigment-sensitized photocyclization of germacrene D *(101)* could be operative in biogenesis of the copaanes *(65)*[63].

(+)-Sativene *(70)* can be derived from the copabornanes *(64)*; it was isolated from *Abies* species[68] and in the presence of copper acetate in acetic acid it equilibrates with cyclosativene *(73)*[68] and isosativene *(72)*[67]. The effect of acid also converts copacamphene *(69)*, which is chemically accessible[67] from *(64)*[69], into *(70)*. Derivatives of cyclocopacamphene, stereoisomeric to cyclosativene at the isopropyl group, were isolated from vetiver oil[70]. Cleavage of the 4,5 bond in *(64)* is considered a possible biogenetic route to the carbon skeleton of the poisonous picrotoxans, *e.g.* *(68)* (tutin)[71].

The grain fungus *Helminthosporium sativum* (≡*Cochliobulus sativum*) produces the helminthosporanes, unstable hemiacetals, *e.g.* *(74)* (prehelminthosporol), which display antiviral activity *in vitro*[13,65]. These compounds are partly converted into the aldehydes helminthosporol *(75)* or helminthosporal on work-up of the plant material[65]. Their biogenesis has been rationalized by invoking cyclization of the cation *(61)* to the "epicopabornane" cation *(67)*, which on deprotonation and rearrangement yields (−)-sativene *(71)*. Compound *(71)* also occurs in the same fungus and is regarded as the immediate precursor of the helminthosporanes[20,66].

6. Humulanes, Caryophyllanes, and Related Sesquiterpenes

The monocyclic humulanes, *e.g.* *(77)* (α-humulene), possess an eleven-membered ring, and the bicyclic caryophyl-

lanes, *e.g. (76)* (β-caryophyllene), a *trans* fused cyclobutane-cyclononane ring system (Figs. 1 and 4). It seemed reasonable to consider the monocyclic cation *(10)* as biological precursor for both groups of sesquiterpenes (Fig. 1)[20], particularly as *(77)* can be converted chemically by ring closure into *(76)*[74,80]. However, the assumption of a common precursor is no longer tenable since it was discovered that all three ring double bonds of α-humulene *(77)* are *trans*[72]. With the exception of caucalol *(79)*[73] which contains a *cis* double bond, the humulanes are considered to arise from the all-*trans* cation *(11)* as biogenetic precursor[20]. α-Humulene *(77)* and β-caryophyllene *(76)*[75–77], first isolated 80 years ago from clove oil, are widely distributed in Nature. In addition, epoxides and alcohols having the same basic skeleton are also known[75,78]. Both *(77)* and *(76)* readily afford tricyclic ring systems (*e.g.* tricyclohumulanes) by molecular rearrangement[74,75,77,79–81]. Starting from *(77)* and proceeding *via* the cation *(78)*[20] one obtains the antibiotically active illudins *(80)*[82,83], marasmic acid *(81)*[83], and hirsutic acid C[84].

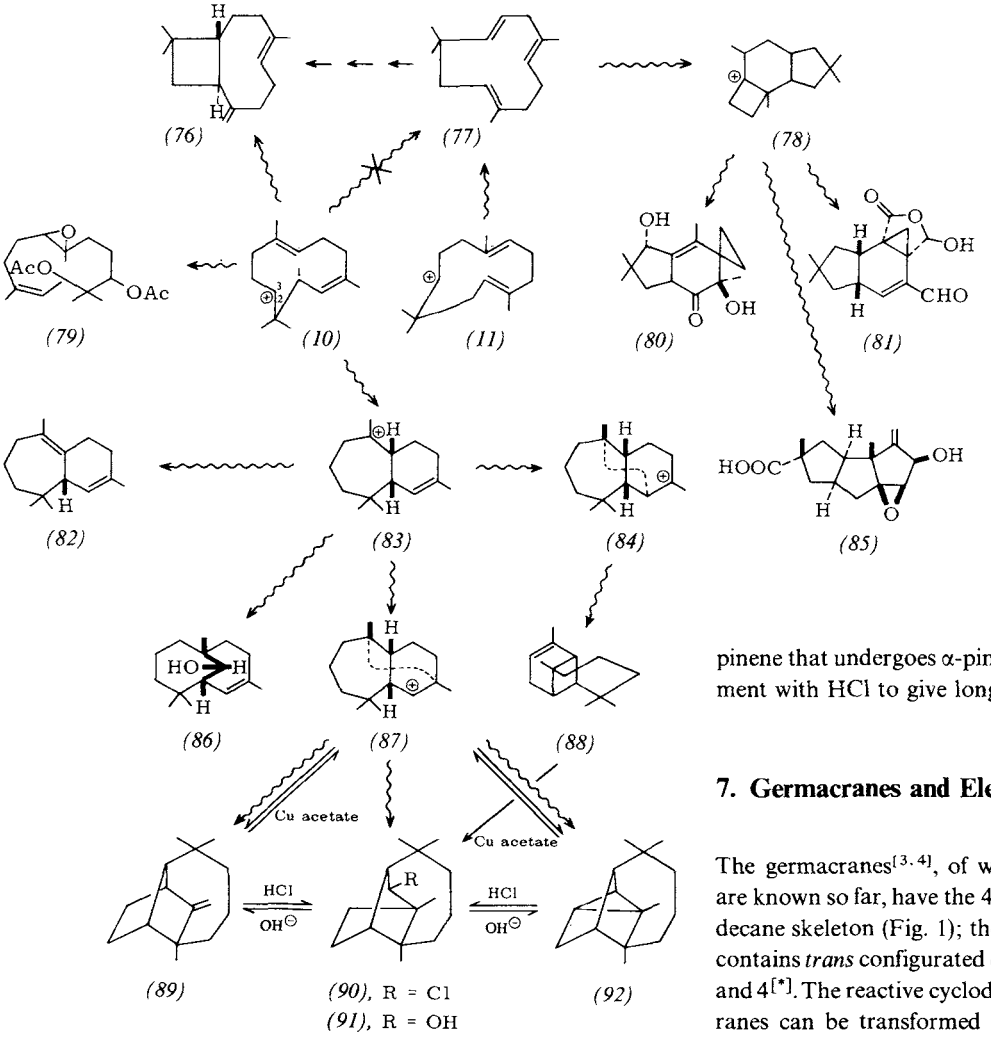


Fig. 4. Humulanes, caryophyllanes, and related sesquiterpenes.

A 1,3 hydride shift and cyclization can transform *(10)* into the cation *(83)* that is of significance as a biogenetic precursor of several small groups of sesquiterpenes[20]. The himachalanes, *e.g. (82)* (α-himachalene) and allohimachalol *(86)*[85], are representatives that have been isolated from cedar oil[86].

The biogenesis of the longifolanes is reported to proceed from *(10) via (83)* to the cation *(87)*[20], from which longifolene *(89)*, longiborneol *(91)*[85], and longicyclene *(92)* are formed. Longifolene *(89)*, which occurs in pine resins, has attracted interest on account of the Wagner-Meerwein rearrangement type reactions involving carbocations[87–89]—which are comparable with the rearrangements of sativene [*(70)*, Fig. 3][67]. In the presence of copper acetate in acetic acid, *(89)* equilibrates *via* the cation *(87)* with isolongifolene[90] and longicyclene *(92)*[67,86,88], which have likewise been isolated from pine species. It is the first naturally occurring tetracyclic sesquiterpene. Treatment with HCl transforms both *(89)* and *(92)* into (+)-longibornyl chloride *(90)*, a homolog of bornyl chloride. Solvolysis of *(90)* regenerates *(89)* and *(92)*[87].

The biogenesis of longipinene *(88)*, which similarly occurs in pine species[91], also proceeds *via* cation *(83)* involving initial cyclization to *(84)*. *(88)* is an isoprenologous α-pinene that undergoes α-pinene-bornyl chloride rearrangement with HCl to give longibornyl chloride *(90)*[87].

7. Germacranes and Elemanes

The germacranes[3,4], of which about 90 representatives are known so far, have the 4,10-dimethyl-7-isopropylcyclodecane skeleton (Fig. 1); the ten-membered ring generally contains *trans* configurated double bonds in positions 1(10) and 4[*]. The reactive cyclodecadiene system of the germacranes can be transformed into mono-, bi-, and tricyclic sesquiterpenes by thermal Cope rearrangements and acid- and light-induced cyclizations (Fig. 5). The germacranes were therefore accorded significance for the biosynthesis of other sesquiterpenes *(20)*, thus stimulating extremely

[*] The molecular skeleton was numbered by analogy with other sesquiterpenes.

intense work on this group. For the same reason relations between reactivity and stereochemistry of the cyclodecadiene system have also attracted attention. Moreover, the

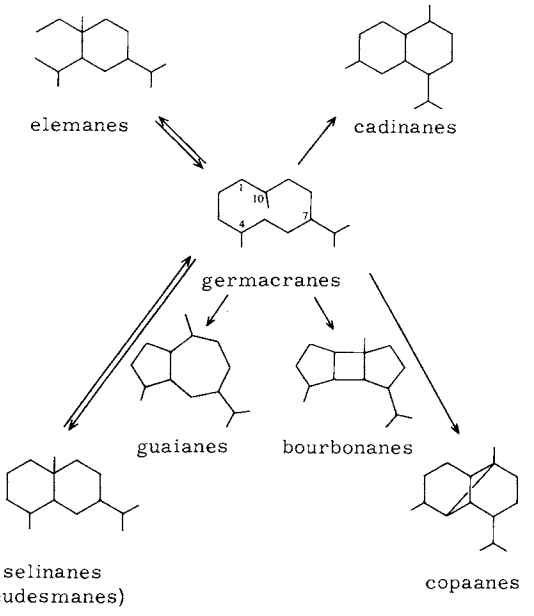


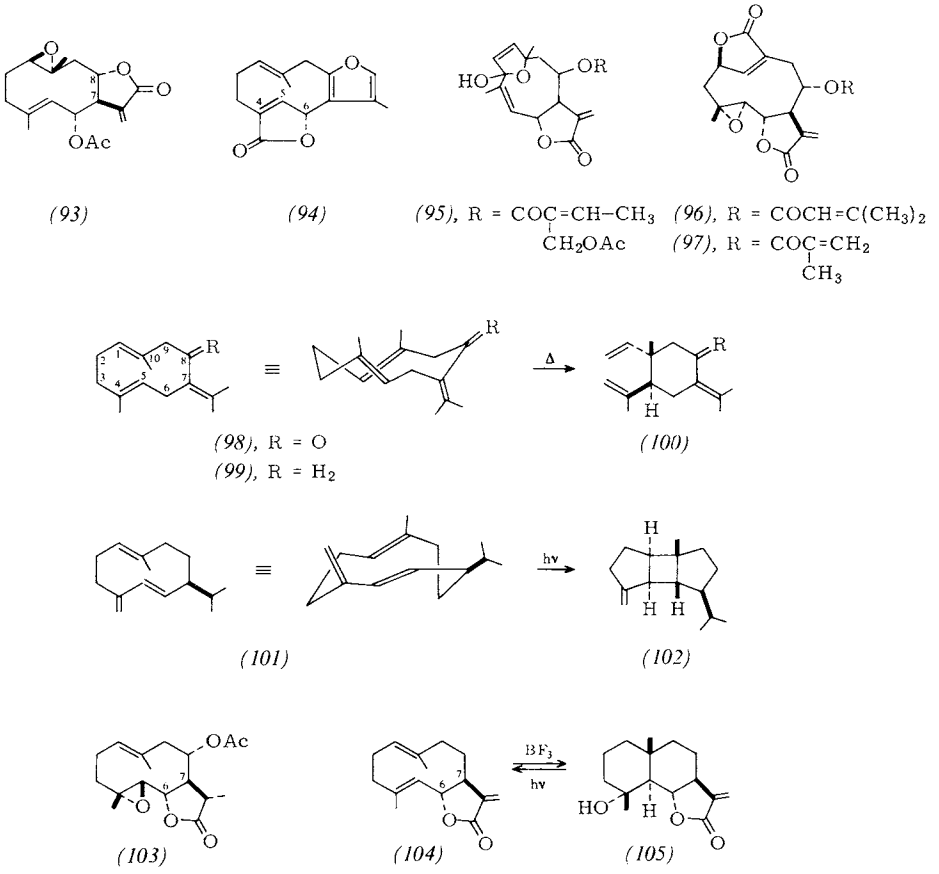
Fig. 5. Rearrangements of germacranes to other sesquiterpenes.

germacranes also include substances with interesting biological properties. Biogenetic formation[20] of the germacrane skeleton from *(4)* (Fig. 1) has been detected by *in vivo* experiments[92].

Most of the germacranes are lactones (germacranolides)[3,4]. Mention should be made of pyrethrosin *(93)*[93,94], the first germacrane derivative to be isolated (1957). In *(93)* the α,β-unsaturated γ-lactone ring is in the 8α,7β position; it can also be in the 6α,7β position, *e.g.* in *(104)*, and more rarely in the 4,6-position, *e.g.* in *(94)* (linderalactone), a representative of the furanogermacranolides. The cyclic hemiketal liatrin *(95)*, like the dilactones elephantin *(96)* and elephantopin *(97)*, possesses cytotoxic properties[13,14,96]. The ketone germacrone *(98)* was the first germacrane found to have no lactone ring[97,98]. Subsequently, the thermolabile germacrenes A to D were discovered to occur in Nature, *e.g.* *(99)* (germacrene B) and *(101)* (germacrene D). Mention should also be made of the bicyclogermacrene *(13)* (Fig. 1) containing a cyclopropane ring[58,99].

An important role is played by the stereochemistry of the cyclodecadiene ring in biogenetic transformations[20] and chemical conversions (Fig. 5) of germacranes into other sesquiterpenes. It could be established for numerous germacranes by X-ray analysis of halogenated derivatives[93] or silver nitrate complexes[98,101,102], by measurement of the nuclear Overhauser effect[103], and by low temperature NMR studies[103]. In the conformation with *syn*-methyl groups in positions 4 and 10 found for most compounds, *e.g.* *(98)*, *(99)*, and *(101)*, the π orbitals are positioned favorably for Cope rearrangements and electrocyclic reactions[100].

Thermal Cope rearrangements[100] of germacranes furnish elemanes[19,58,95,99,100,104], sesquiterpenes having a 1-methyl-1-vinyl-2-isopropenyl-4-isopropylcyclohexane skeleton (Figs. 1 and 5). Apart from a few exceptions[96], the elemanes isolated from essential oils, and also numerous elemane lactones (elemanolides), can be regarded as Cope



(93) *(94)* *(95)*, R = $COC(CH_2OAc)=CH-CH_3$ *(96)*, R = $COCH=C(CH_3)_2$ *(97)*, R = $COC(CH_3)=CH_2$

(98), R = O
(99), R = H_2

(100) *(101)* *(102)* *(103)* *(104)* *(105)*

rearrangement products of germacranes[58,95,98,104]. Under certain conditions the Cope rearrangement is reversible[19,100,105]; it proceeds stereospecifically. All-*trans*-cyclodecadienes, *e.g.* *(99)* (germacrene B)[101] are converted into *trans*-elemanes, *e.g.* *(100)*[99,100], whereas 1(10)-*cis*-4-*trans*-cyclodecadienes form *cis*-elemanes[99]. This rule has been employed in determining the stereochemistry of germacranes[99].

Of the cyclization reactions of germacranes (Fig. 5) we shall first consider the formation of cadinanes in the presence of $H^{\oplus}$ ions[57,58,105,106]. UV-irradiation of germacrane D *(101)* generated *(102)*[107] having the same skeleton as the tricyclic bourbonanes[57] occurring in *Geranium* and *Mentha* species. Under the same conditions, a cyclodecadiene employed as model substance was also transformed into ketones having copaane-type skeletons (Fig. 3)[63]. The formation of guaianes from germacranes, particularly germacrane epoxides[104], has also been reported[58,98,108,109]. Isomerizations of germacranes to guaianes also extend to germacrane lactones[108]. Reports have also appeared of stereospecific[112,113] cyclizations of germacranolides to lactones having a selinane-type skeleton (Figs. 1 and 7)[4,104,11,113,114]. For instance, costunolide *(104)*[102] is converted by the action of boron trifluoride into selinanolide *(105)*[110]; *(105)* regenerated *(104)* in a photochemical process[111].

8. Sesquiterpenes Having a Hydroazulene Skeleton (Guaianes, Pseudoguaianes, and Related Sesquiterpenes)

Several groups of sesquiterpenes possess a hydrogenated azulene[173] skeleton bearing two methyl and one isopropyl groups (Figs. 1 and 6) but differ in the positions of the substituents. The largest group of these "hydroazulenes" comprises the guaianes, with about 100 members, followed by the pseudoguaianes, with about 70. Only a few represen-

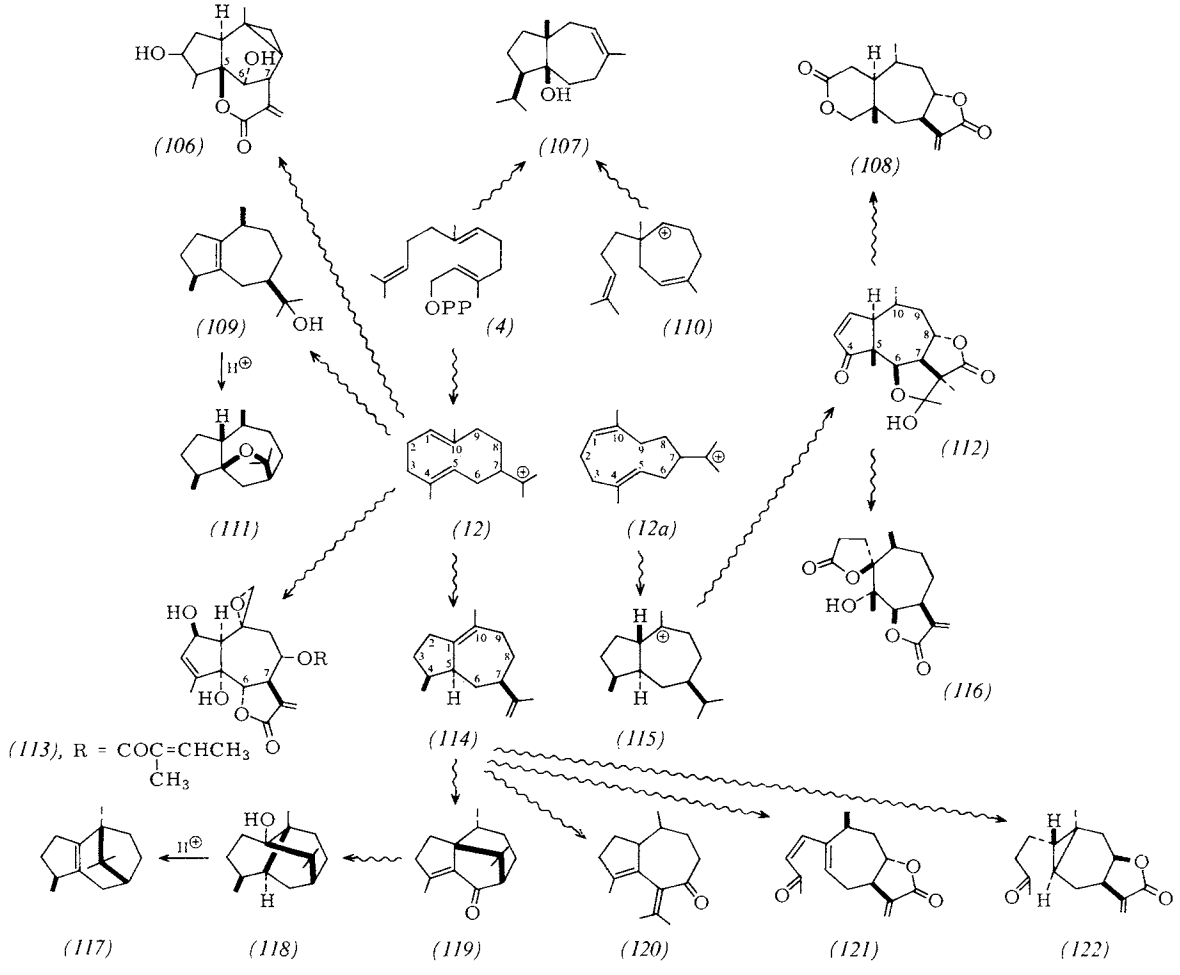


Fig. 6. Sesquiterpenes with a hydroazulene skeleton.

tatives of the carotanes, isopatchoulanes, and zieranes (Fig. 6) have so far become known.

Biogenetically[120], an "anti-Markownikoff cyclization" between C atoms 1 and 5 of cation *(12)* leads to the *cis* linked guaianes (Fig. 6). As examples of this group of sesquiterpenes we can consider α-bulnesene *(114)*[117] and guaiol *(109)*, which undergoes ready conversion into the tetrahydrofuran derivative guaioxide *(111)* by acid-catalyzed ring closure[118]. The guaiane lactones (guaianolides)[3-5] which number about 60 compounds, represent

one of the largest groups of sesquiterpene lactones[3, 5, 8, 18]. Most of them are unsaturated 6α,7β-lactones, *e.g.* euparotin *(113)*. Formation of the lactone ring in positions 7β,8α or 7β,8β is less common. Several guaianolides, *e.g. (113)*, are cytotoxic[96, 119]. Absinthin, obtained from wormwood, is a Diels-Alder adduct of two guaianolides[120]. *(106)* (zaluzanin A) comes from the small group of ivaxillaranes having a tricyclic skeleton[5, 121].

In 1962 *Herz et al.*[122] were able to show that the supposed guaianolide tenulin does not have a methyl group in position 4, but a tertiary one in position 5 *(112)*. This finding constituted the discovery of the first compound having the "pseudoguaiane" skeleton; so far only lactones are known (pseudoguaianolides). They display a pronounced structural variety and occur in *Compositae*[3, 4, 6, 7, 18, 123]. Their generally unsaturated γ-lactone ring is located at 6β,7β, at 7β,8α, or at 7β,8β. The methyl group at C-10 can be in the α or β position. Glycosides of pseudoguaianolides have also been found[124, 125]. 1,5-Cyclization of the cation *(12a)* to give *(115)* is assumed to explain the biosynthesis of the pseudoguaianolides (Fig. 6)[20] which, unlike most guaianes, exhibit *trans* linkage of the two rings. A 1,2 hydride shift and migration of the methyl group from C-4 to C-5 would account for conversion of *(115)* into the skeletons of the two pseudoguaianolides which are diastereomeric in position 10[20].

lides by cleavage of the five-membered ring[8, 15]. As examples we may consider *(121)* (xanthatin), which displays a regulating effect on plant growth[126], and *(122)* (carabrone)[126]. These "derived" sesquiterpenes also embrace dilactones, *e.g. (108)* (vermeerin)[125], and spiro-γ-lactones, *e.g. (116)* (canabrin)[127].

The guaianes are biogenetically related to the small group of isopatchoulanes, *e.g. (119)* (patchoulenone)[129, 130, 133], and the zieranes, *e.g. (120)* (zierone)[128]. Patchouli alcohol *(118)*[131, 132], a compound of unusual structure, is connected with the patchoulanes[11]; it is readily transformed into β-patchoulene *(117)* on treatment with acid. The small carotane group, *e.g. (107)* (carotol)[115, 116], represents a special case with regard to its biosynthesis (Fig. 6). Available evidence suggests either direct cyclization of *(4)*[115] or formation from *(3)* (Fig. 1) by way of *(5)* and *(110)*[20].

9. Selinanes and Eremophilanes

The bicyclic selinanes (≡eudesmanes) and eremophilanes having the basic structure of a dimethyl-7-isopropyldecalin differ only in the position of a tertiary methyl group (Figs. 1 and 7) which is bonded to C-10 in the selinanes and

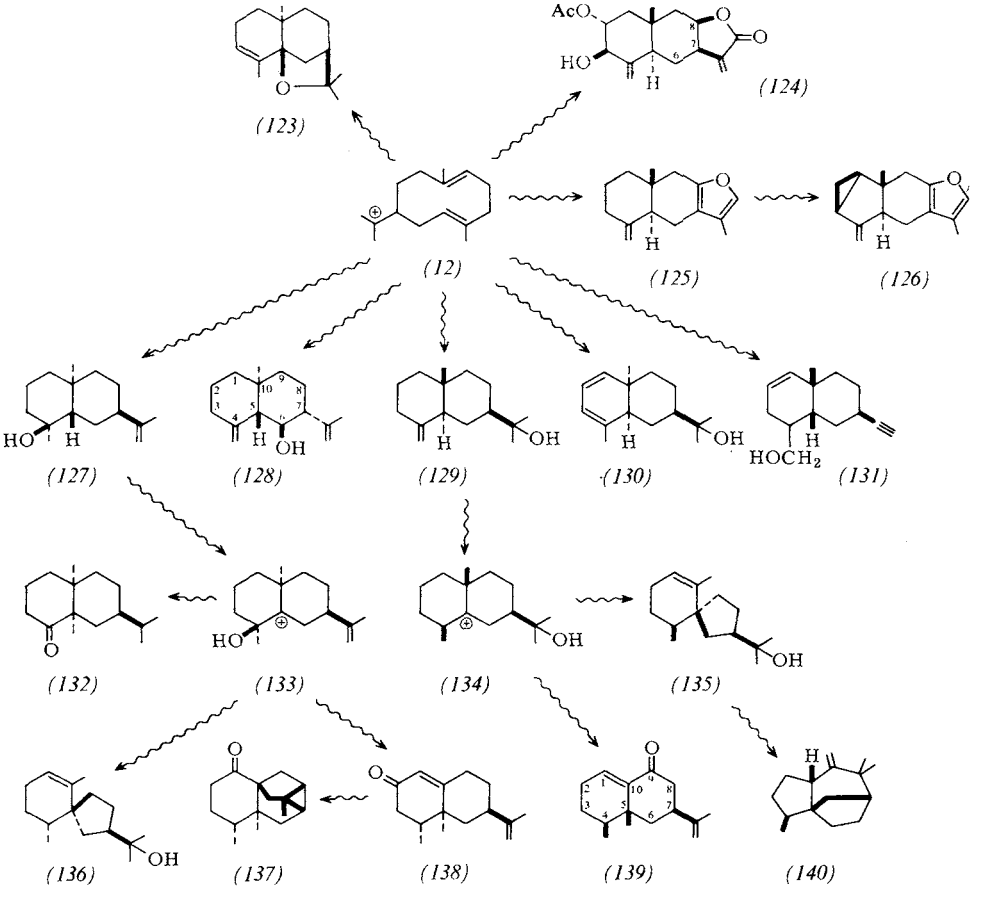


Fig. 7. Selinanes (≡eudesmanes), eremophilanes, and related sesquiterpenes.

Sesquiterpene lactones having a cycloheptane ring and which are designated as xanthinanes and carabranes (Fig. 6) can be derived from guaianolides and pseudoguaianolides to C-5 in the eremophilanes. The skeleton of the eremophilanes cannot be divided into isopentane units like that of the selinanes.

As in the case of the cadinanes (Fig. 3) the selinanes comprise four structural types[134], depending on the mode of ring fusion, whose biogenesis can proceed *via* corresponding conformers of the germacrane cation *(12)*[20, 137]. Two of them are *trans*-decalins with the basic structures of (−)-selinane, *e.g. (128)*[140], and the enantiomeric (+)-selinane, *e.g. (129)*[138, 139]. The "epi-eudesmanes", *e.g. (130)* [(+)-occidentalol][135], and the chamaecynanes [nor-eudesmanes bearing an ethynyl group, *e.g. (131)*][136] have a *cis*-decalin structure. The same ring linkage as in (−)-selinanes [*e.g. (128)*], but with an opposing steric arrangement of the isopropyl group, is encountered in the agarofurans, *e.g. (123)*[144], and the derivatives of intermedeol *(127)*[141−143].

Atractylone *(125)*[145] is a representative of the furanoselinanes, a group that also includes the lindenanes, *e.g. (126)* (lindenene), which feature a tricyclic skeleton[146]. Approximately 50 sesquiterpene lactones are known to have the selinane-type structure (selinanolides ≡ eudesmanolides)[4, 8]. In these compounds γ-lactone ring formation can occur between C-7 and either a 6α-hydroxyl group (santonins[1, 2]) or, as in *e.g. (124)* (pulchellin B)[147], an 8β-hydroxyl group.

The selinanes can be regarded as biogenetic precursors for the formation of valeranone *(132)* *via* the cation *(133)*[148]. The valeranes, which are characterized by a *cis*-decalin skeleton, have so far only been found in *Valerianaceae*[148, 149]. Two diastereomeric basic structures are known for the [4.5]spirocyclic agarospiranes which are biogenetically related to the selinanes by way of cation *(134)*; the two types are found in hinesol *(135)*[12, 151] and agarospirol *(136)*[12, 150, 152] respectively. Just as the cedranes were derived from the [4.5]spirocyclic acoranes (Fig. 2), the zizaanes (≡ tricyclovetivanes), *e.g. (140)*, can also be regarded as being related to the agarospiranes *(135)*[137], whose biogenesis has been discussed in terms of (+)-γ-curcumene as precursor[153].

The eremophilanes (Figs. 1 and 7) having the basic structure of a 4,5-dimethyl-7-isopropyldecalin have been reviewed in detail[4]. Two sterically distinct types are known: compounds of the "eremophilone type", *e.g. (139)*, have all three side chains in a β-arrangement[154], whereas eremophilanes of the "nootkatone type", *e.g. (138)*, have α-methyl groups[152, 155, 156]. Both types arise biogenetically from selinanes *via* cations such as *(134)* and *(133)* which undergo a 1,2-shift of the tertiary methyl group[4, 7, 137, 142, 143, 155]. A spirocyclic intermediate has also been invoked[157] for this biogenetic transformation. Biogenesis of the ishwaranes *(137)* may conceivably involve ring closure by way of the isopropyl group[158].

Eremophilanes, especially lactones (eremophilanolides), have frequently been found in the plants of the *Compositae* family[8]; compounds containing a furan ring (furanoeremophilanes, furanoeremophilanolides) are also encountered.

10. Maalianes and Aristolanes, Aromadendranes

The tricyclic maalianes and aristolanes (≡ calaranes)[159] (Figs. 1 and 8) possess a decalin skeleton with a fused cyclopropane ring. The aristolanes differ from the maalianes, in the same way as the eremophilanes from the selinanes, in the position of the tertiary methyl group. The maalianes (Fig. 8) are biogenetically accessible by cyclization of the cation *(7)* *via* bicyclogermacrene *(13)*

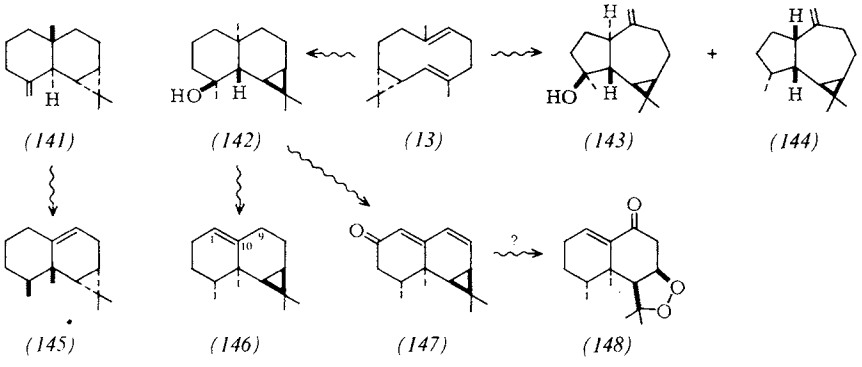


Fig. 8. Maalianes, aristolanes, and aromadendranes.

(Fig. 1)[55]. Apart from maaliol *(142)*[163], compounds are also known with an enantiomeric skeleton, *e.g. (141)* [(+)-γ-maaliene] which could be isolated from the gorgonian *Pseudopterogorgia americana*[164].

Just as the eremophilanes are formed from the selinanes, the aristolanes arise by a 1,2-methyl shift in the maalianes[20, 143]. Their biogenesis is thought to proceed from the corresponding selinanes *via* ring closure to give the cyclopropane ring and a 1,2-methyl shift[137]. In addition to 1(10)-aristolene *(146)* (≡ calarene, β-gurjunene)[165] and 9-aristolene, which always occur together[143, 159, 160, 162, 166], further aristolane sesquiterpenes were subsequently isolated[160, 161, 167, 168], including the ketone *(147)*[168] whose structure was recently discovered to apply also to the supposed selinane nardostachone[169]. The 1,2-dioxolane derivative nardosinone *(148)* from the valerian *Nardostachys chinensis*[170] is structurally and probably also biogenetically related to the aristolanes. α-Ferulene *(145)* and other enantiomeric aristolanes have likewise been found to occur naturally[164, 171].

Both *trans* [*e.g.* spathulenol *(143)*] and *cis* fused compounds [*e.g.* alloaromadendrene *(144)*] are known in the tricyclic aromadendrane series[172]. Supporting evidence for the formation of these sesquiterpenes *via* bicyclo-

germacrene *(13)* is provided by the proton-catalyzed cyclization of this hydrocarbon to give the aromadendrane ledrene[58].

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The Chemistry of Dichloromethylenammonium Salts[1] ("Phosgenimonium Salts")

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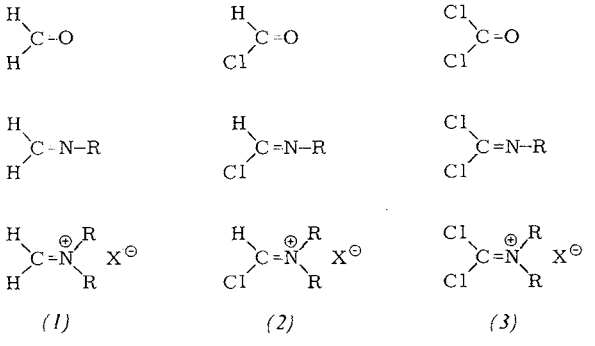
Dedicated to Professor Heinrich Hellmann

Dichloromethylenammonium salts, particularly dichloromethylenedimethylammonium chloride, occupy a unique place as stable but reactive building blocks for synthesis. They contain three mobile chlorine atoms activated by an amino group on the same carbon atom. These salts can be regarded as chlorinated Vilsmeier or Mannich reagents and are thus at a higher oxidation level. As in the Mannich or Vilsmeier reaction, the carbon condenses here as an electrophile with formation of C—C or C—hetero atom bonds in a variety that is still far from being exhausted.

1. Introduction

Whereas the chemistry of formaldehyde, the unstable formyl chloride, phosgene, and their imines[2] is well developed, the corresponding imonium salts, *i.e.* the dichloromethylenammonium salts *(3)*, were almost forgotten until the start of our investigations in 1969, though the first compound of this class, *N,N*-diethyl-*N*-dichloromethylenammonium chloride, was described as early as 1959[3].

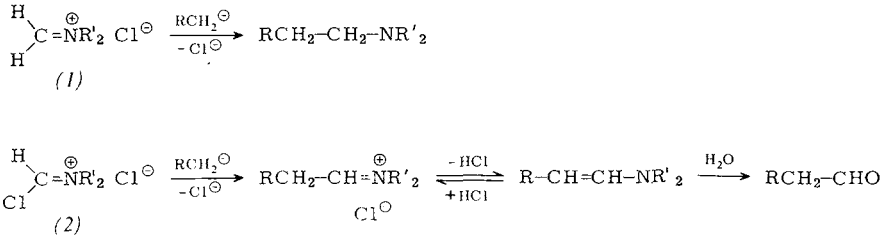


(1) *(2)* *(3)*

This neglect is the more surprising in that the high reactivity of the methylenammonium salts[4] *(1)* has been known for a long time through the Mannich reaction[5]. The chloromethylenammonium salts (Vilsmeier-Haack reagent[6a-6d] [*(2)*, $X^{\ominus}=PO_2Cl_2^{\ominus}$] and Arnold reagent[6e,6f] [*(2)*, $X^{\ominus}=Cl^{\ominus}$]) have also been in use for a long time, though the elucidation of their structures was achieved in part only a few years ago[6g,6h,7].

Mannich reagents *(1)*, as methylenammonium salts, react with nucleophiles by aminomethylation[5]. The Vilsmeier-Haack and Arnold reagents *(2)*, as chloromethylenammonium salts, give corresponding imonium compounds and particularly (by their hydrolysis) aldehydes.

Dichloromethylenammonium salts with tertiary nitrogen are relatively easily obtainable, some even commercially[14]. Dichloromethylenammonium salts with secondary and primary nitrogen can be prepared at least *in situ* from dichloromethylenamine and cyanogen chloride



(1)

(2)

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