THE CHEMISTRY OF CARYOPHYLLENE AND RELATED COMPOUNDS

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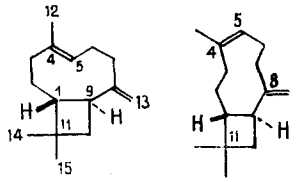
A review is given of the literature over the period from the middle of the 1950s to the beginning of the 1980s on the distribution in nature, the biological activity, the conformation, and the chemical transformations of sesquiterpenes of the caryophyllene type.

Of all the multiplicity of sesquiterpene hydrocarbons found in the vegetable kingdom, caryophyllene (I) – 1R,4E,9S-4,11,11-trimethyl-8-methylenebicyclo[7.2.0]undec-4-ene – is one of the most widespread. It is found in many essential oils, including the oil of the clove tree Eugenia caryophyllata (Syzygium caromaticum), which contains caryophyllene in considerable amount and serves as a preparative source for the isolation of this compound. Caryophyllene (I) is present in many resins and extracts of plant origin, and also in the oleoresins of the majority of conifers of the Pinaceae family growing on the territory of the USSR [1]. The cis isomer of caryophyllene at the endocyclic double bond – isocaryophyllene (II) – is found in nature in insignificant amounts, in spite of its high stability, and only rarely accompanies caryophyllene.



I II

The study of the chemistry of compounds of the caryophyllene groups now dates back more than 150 years, although structure (I) was definitely established only at the beginning of the 1950s, when the brilliant work of Barton et al. [2] showed the structures and absolute configurations of caryophyllene and some tricyclic products of its cyclization. The absolute configurations of caryophyllene derivatives have also been discussed by Horeau and Sutherland [3], and their results are in agreement with the conclusions of Barton et al. that (–)-caryophyllene from clove oil has the 1R,9S-configuration illustrated by formula I. The bicyclic structure has been confirmed by the total synthesis of DL-caryophyllene and of DL-isocaryophyllene by various methods [4].

The undiminishing attention of chemists to caryophyllene over many years now, is due to the unusual structure of this hydrocarbon: the presence of trans-linked butane and nonane carbon rings and of a trans-substituted double bond in the nine-membered ring. Such a structure is considerably strained and undergoes rearrangements with extreme readiness, giving a whole set of more stable bi- and tricyclic systems. As Paul de Mayo [5] has written "caryophyllene is one of the most remarkable and versatile of terpenoids of any class in its variety of skeletal transformations."

Interest in caryophyllene compounds is also caused by the fact that some bicyclo[7.2.0]-undecane derivatives found in nature possess interesting biological properties. Furthermore, synthetic derivatives of caryophyllene are used in perfumery as odoriferous substances and odor fixatives [6], and also as aromatic additives for tobacco and food products [7]. There are review papers on the use of caryophyllene and its derivatives in perfumery [8].

CARYOPHYLLENE DERIVATIVES IN NATURE

For a long time, caryophyllene (I) remained the only representative of natural medium-ring olefins containing a nine-membered ring. The first caryophyllene derivative found in

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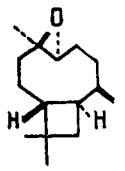
nature was caryophyllene 4β,5α-epoxide (III), which was isolated from lavender oil [9] and was subsequently obtained by the oxidation of caryophyllene [10]. The structure of the epoxide (III) was established from the products of its acid-catalyzed cyclization [2] and was confirmed almost 30 years later by direct x-ray structural studies [11]. The surfur analogue of the epoxide (III) – caryophyllene 4,5-episulfide (IV) – has also been found in nature, being isolated in the distillation of hop oil [12]. Although the configuration of the episulfide groups has not been established, there is every reason to assume in its stereochemical plan that the episulfide (IV) is similar to the epoxide (III), since the episulfide is formed as the main product on the addition of sulfur to caryophyllene [13].



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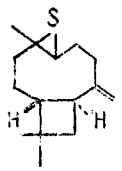

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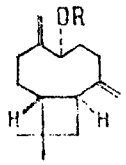
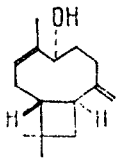


V a,b
a. R = H
b. R = Ac



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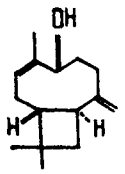

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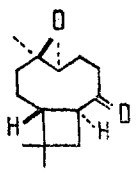

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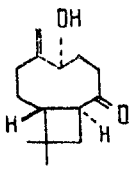

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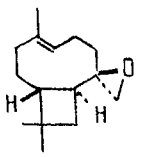
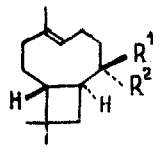
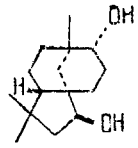


X



XI a,b
a. R^1 = H, R^2 = CHO
b. R^1 = CHO, R^2 = H



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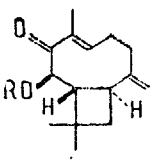
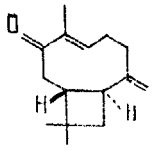
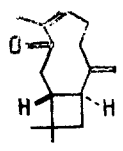


XIII a, b
a. R = Ac
b. R = H



XIV

In the middle of the fifties, Czech workers found in buds of the birch Betula alba caryophyllene alcohols – betulenols – the structures of which were the subject of discussion for a long time [14] until one of these alcohols – α-betulenol (Va) – was obtained by the isomerization of the epoxide (III) [15]. α-Betulenol acetate (Vb) was detected among the growth inhibitors present in the buds of another species of birch – Betula verrucosa [16]. In a study of the composition of the resin Dipterocarpus pilosus, Indian workers detected two other compounds close in structure – caryophyllenol-I (VI) and caryophyllenol-II (VII) [17]. Simultaneously, a group of Italian authors reported on the isolation from the oil of Copaifera multijuga of a new compound with a caryophyllene carbon skeleton – the alcohol α-multijugenol [18] and observed that the alcohol isolated was identical with one of the products of the isomerization of the epoxide (III). A comparison of the physicochemical characteristics given in publications [17] and [18] showed that α-multijugenol was very similar with respect to its angle of optical rotation and spectral characteristics to the alcohol (VII), but not to alcohol (VI) – the minor product of the isomerization of the epoxide (III) [17].



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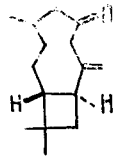
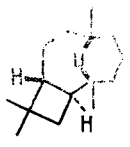
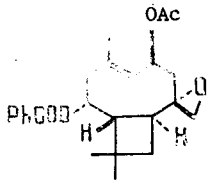


XVI



XVII

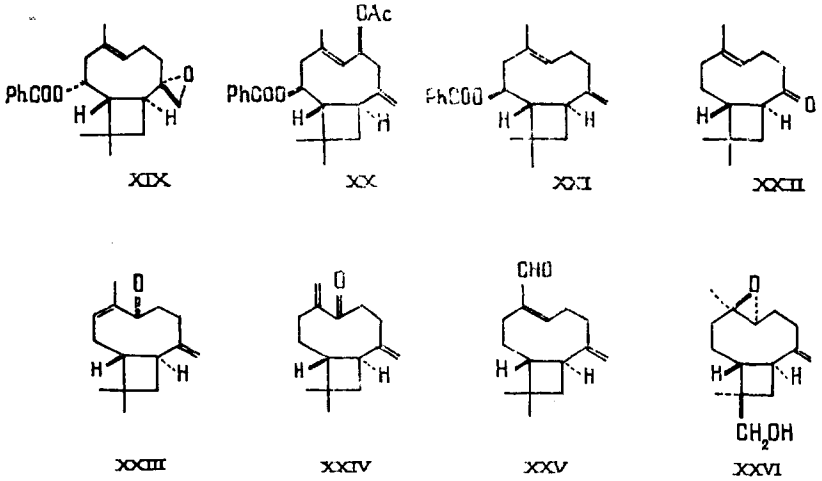


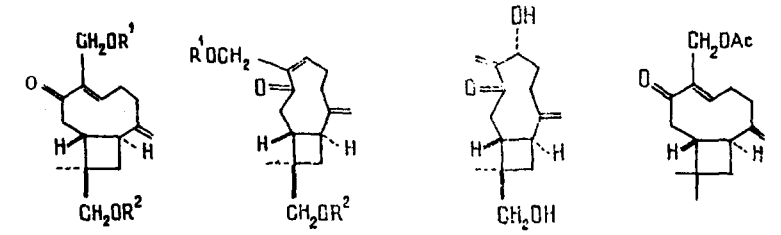
XVIII

A carbonyl analogue of the epoxide (III) the norsesquiterpene compound kobusone (VIII), accompanied by isokobusone (IX), has been found in the oil of Cyperus rotundus [19]. The epoxide (X) has been detected in the essential oil of sage, Salvia sclarea, being present in a mixture with the aldehydes (XIa) and (XIb) epimeric at the C^8 atom [20]. The ease of in vitro conversion of kobusone (VIII) into isokobusone (IX) [19] and of the epoxide (X) into aldehydes (XI) [20] permits the assumption that compounds (IX) and (XI) may not be native but are formed in the course of secondary, nonenzymatic processes in the treatment of the natural raw material. The same applies to the alcohols (Va) and (VI), which can be obtained by the isomerization of the epoxide (III) on sorbents. Furthermore, the formation of the epoxide (III), itself, if it is present in small amounts against a background of a considerable amount of caryophyllene, can be assigned to secondary processes, since the epoxide (III) is readily obtained on the oxidation of caryophyllene by atmospheric oxygen [10].

Nonenzymatic cyclization in the treatment of the raw material could also explain the formation of clovane-1,9-diol (XII), which has been isolated from the epigeal part of the plant Viguiera hypargyrea, because this oil is known as a product of the acid-catalyzed rearrangement of the epoxide (III) [2]. But the diol (XII) is, nevertheless, a native product since the formation of the diol (XII) from the epoxide (III) by a nonenzymatic route requires fairly severe conditions: heating with sulfuric acid in aqueous acetone solution [2].

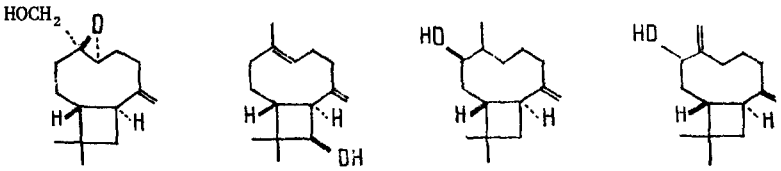
Progress in instrumental methods of analysis has led to the situation that in the last 10 years a large number of natural caryophyllene compounds have been described that had been detected in the high-boiling fractions of essential oils and of extracts of plant and animal origin. Buddledins A (XIIIa) and B, (XIIIb) [22] and C (XIV), D (XV), and E (XVI) [23] have been isolated from the plant Buddleia davidii. An interesting intracyclic ether – caryophyllane 4,8-β-oxide (XVII) has been detected in the oil of Lippia citridiora [24]. Four benzoates of the caryophyllene series (XVIII)-(XXI) have been isolated from the roots and epigeal part of the plant Solidago nemoralis [25]. In the high-boiling fraction of lavender oil, together with kobusone (VIII) and buddledin C (XIV), other carbonyl compounds (XXII-XXV) have been found [26]. An unusual derivative (XXVI) – the product of the oxidation of the epoxide (III) at one of the geminal methyl groups – is present in the body of the fungus Lactarius camphoratus [27]. The same epoxy alcohols have been isolated from the urine of rabbits that have been given caryophyllene [28]. A number of derivatives oxidized at the β-methyl group of the geminal center of derivatives (XXVII-XXIX) is formed in the plant Pulicaria dysenterica, together with compound (XXX) [29], which is also, apparently, a precursor of the 14-β-hydroxymethyl and 14-β-acetoxymethyl derivatives mentioned above. Compound (XXVII) has also been detected in the plant Inula spiraefolia [30]. A 12-hydroxy derivative of the epoxide (III) – the epoxyalcohol (XXXI) – has been found in the epigeal part of Lychnophora salicifolia [31] and as a component of an extract from the birch Betula pubescens [32].





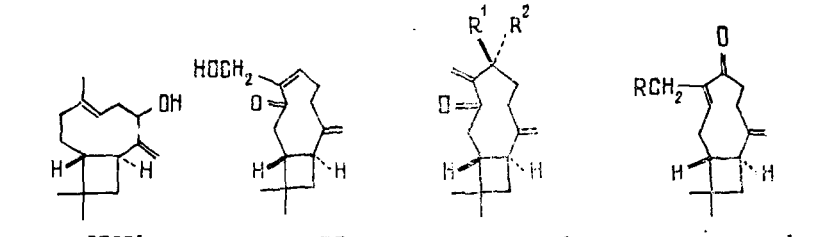
XXVII a,b,c
a R^1=Ac, R^2=H
b R^1=H, R^2=Ac
c R^1=R^2=Ac

XXVIII a,b,c
a. R^1=R^2=H
b. R^1=H, R^2=Ac
c. R^1=Ac, R^2=H



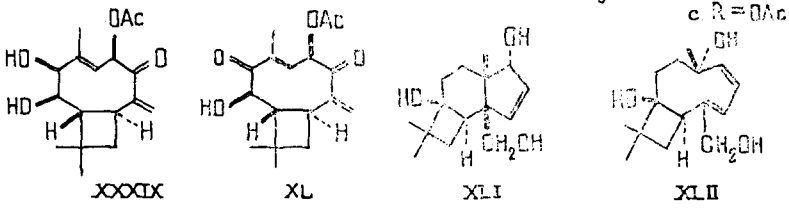
XXXI XXXII XXXIII XXXIV

Several monohydroxy derivatives of caryophyllene and of dihydrocaryophyllene are known. In addition to the 5-hydroxy derivatives (Va), (VI), and (VII), mentioned above, such are 10β-hydroxycaryophyllene (XXXII) isolated from the epigeal part of the plant Leucanthenum maximum [33], the 3-hydroxy derivatives (XXXIII) and (XXXIV), obtained from the high-boiling fraction of turpentine [34], and 7-hydroxycaryophyllene (XXXV), which is present in the mixture of high-boiling components of clove oil and of the oil of the hop Humulus lupulus [35].

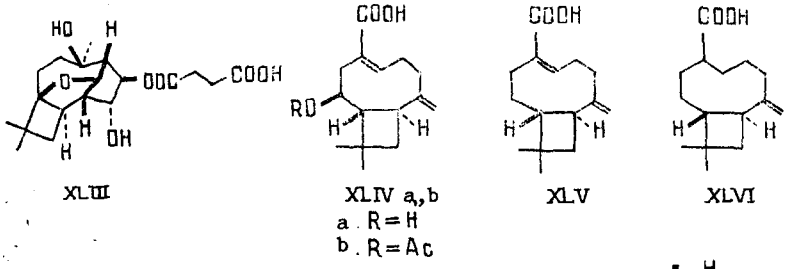


XXXV XXXVI XXXVII a, b
a. R^1=OCH$_3$, R^2=H
b. R^1=H, R^2=OCH$_3$

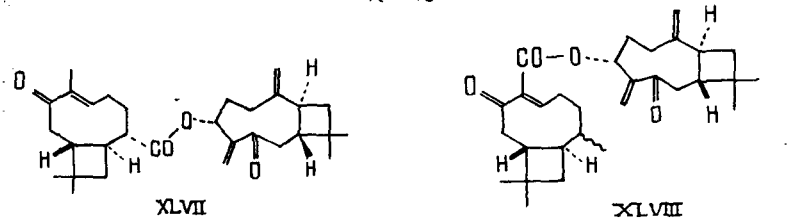
XXXVIII a, b, c
a R=H
b R=OH
c R=OAc



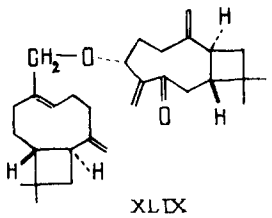
XXXIX XL XLI XLII



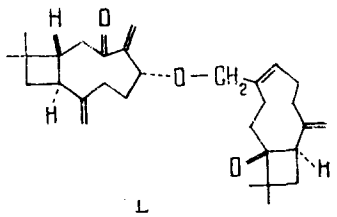
XLIII XLIV a,b
a. R=H
b. R=Ac XLV XLVI



XLVII XLVIII



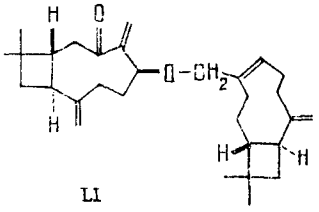
XLIX



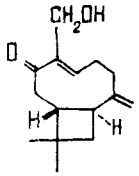
L

In a study of an extract of the plant Jasonia glutinosa, the 3-keto derivatives (XXXVI), (XXXVIIa), and (XXXVIIb) were isolated [36], (XXXVIIa) and (XXXVIIb) having at the C^5 atom a small substituent unusual for oxidized terpenoids – a methoxy group. The 5-keto derivatives (XXXVIIIa) and (XXXVIIIb), each having a trans-double bond in the nine-membered ring between the C^3 and C^4 atoms, have been found in an extract of Fleischmannia viscidipes [37], and the corresponding acetate (XXXVIIIc) in an extract of F. pycnocephaloides [38]. Cultures of some species of fungus of the genus Hyphaloma produce highly oxidized caryophyllene compounds – naematolin (XXXIX) and naematolone (XL) [39]. Another fungus – Poronia punctata – also synthesizes polyfunctional oxidized derivatives: punctatin A (XLI) [40] and punctatins B (XLII), and C (XLIII) [41].

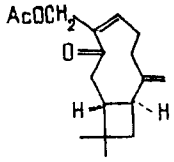
The first carboxylic acid of the caryophyllene series – lychnopholic acid (XLIVa) – was first isolated from the plant Lychnophora affinis, which is known for its cytotoxic properties [42], and then from a plant of the same genus L. martiana, in which it is present together with the acetate (XLIVb) [43]. The epigeal part of L. salicifolia contains, together with lychnopholic acid and its acetate, two other compounds of the same series – the acids (XLV) and (XLVI) [44]. From the plant Pulicaria dysenterica, together with the 3-keto derivatives that have been mentioned above, the ester (XLVII), the acid and alcohol components of which are both oxidized caryophyllene fragments has also been isolated [29]. A biscaryophyllene ester with a different structure (XLVIII) has been detected in an extract of Pulicaria scabra, where it is present in a mixture with the biscaryophyllene ethers (XLIX)-(LI) and the monocaryophyllene compounds (XXX), (XXXVI), (LII), and (LIII) [45]. Two epimeric ε-lactones – lychnosalicifolide (LIV) and epilychnosalicifolide (LV) – have been isolated from the plant Lychnophora salicifolia [46].



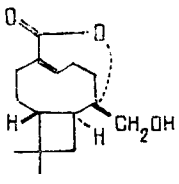
LI



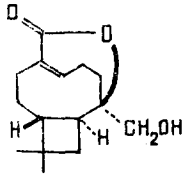
LII



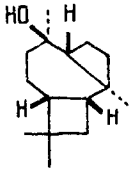
LIII



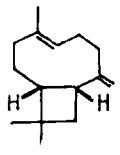
LIV



LV



LVI



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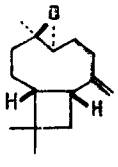
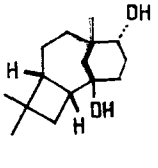
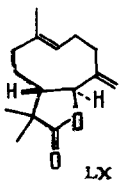


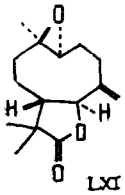
LVIII



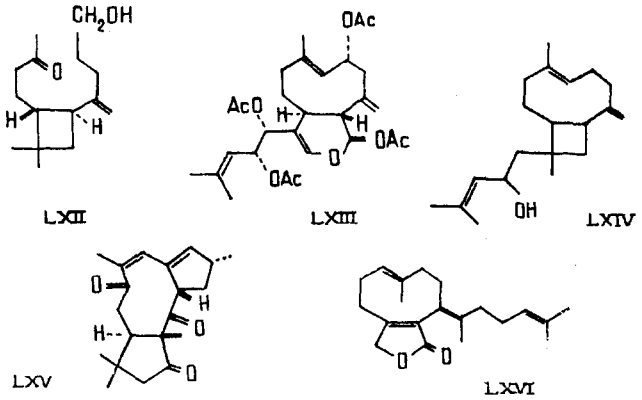
LIX



LX



LXI



LXII LXIII LXIV

LXV LXVI

A characteristic structural feature of compounds of the caryophyllene group is the trans-linkage of the nonane and butane carbon rings. The trans-linkage of the rings for the bicyclo[7.2.0]undecane system is more stable than the cis-linkage, and this circumstance is made use of in the course of the total synthesis of caryophyllene and isocaryophyllene [4]. In natural sources, however, caryophyllene derivatives with the cis linkage of the carbon rings are found: the alcohol koraiol (LVI), isolated from the oleoresin of the Korean pine Pinus koraiensis [47], cis-caryophyllene (LVII), found in the plant Euryps brevipapposus [48], cis-caryophyllene 4,5-epoxide (LVIII), isolated from the roots of Senecio crassissimus, and senecrassane-5,8-diol (LIX), obtained on extracting the epigeal part of a plant of the same species [49].

Natural sesquiterpenes of the caryophyllene type are, thus, oxidized derivatives of caryophyllene the majority of which retain the bicyclic carbon skeleton of caryophyllene. In addition to this type of compound, and the few cyclocaryophyllene compounds mentioned above, sesquiterpene compounds containing only one carbon ring but, undoubtedly, biogenetically very close to caryophyllene compounds have been detected in nature. Such derivatives include parvinolide (LI) [50] and epoxyparvinolide (LXI) [51], isolated from the plant Pogostremon parviflorus and the ketoalcohol (LXII), which has been found in an extract of Monactis macbridei [52].

Compounds of the caryophyllene type represent a unique group of natural compounds in the sense that they have a nine-membered carbon ring in their molecules. It is true that diterpenoids isolated from soft corals exist which also have a nine-membered carbon ring in their molecules, but these diterpenoids are so close structurally to ordinary caryophyllene compounds that they are even called caryophyllene diterpenoids. At the present time, caryophyllene diterpenoids of two types are known: of the xenicin type (LXIII) [53] with an opened cyclobutane fragment, and of the xeniaphyllenol type (LXIV) [54], in which the cyclobutane fragment is retained.* A number of caryophyllene diterpenoids related to those mentioned above has been described in references [57, 58].

BIOLOGICAL ACTIVITY OF CARYOPHYLLENE COMPOUNDS

There is no information in the literature on a systematic study of the biological properties of caryophyllene compounds. This state of affairs is apparently due to the fact that the majority of the caryophyllene derivatives mentioned above have been isolated from natural sources in small amounts insufficient for wide biological trials, and as yet have no practical application. So far as concerns the caryophyllene compounds most widely distributed in nature – caryophyllene (I) itself, caryophyllene epoxide (III), and the alcohols (Va) and (VI) that are derivatives of this epoxide, there have been a number of interesting observations on their biological properties.

In the first place, investigations connected with the study of the action of these compounds on various tests of the cotton plant must be mentioned. It has been reported [59] that caryophyllene (I) attracts the green lacewing Chrysopa carnea and the epoxide (III) attracts the rove beetle Collops vittatus; it has been established that caryophyllene and also caryophyllene epoxide are attractants for males of the pink bollworm Pectinophora gossypiella. In the

*There are also nine-membered carbon rings in some other diterpenoids such as jatrophatrione (LXV) [55] or neodictyolactone (XLVI) [56], but these diterpenoids are few in number and belong to other structural types.

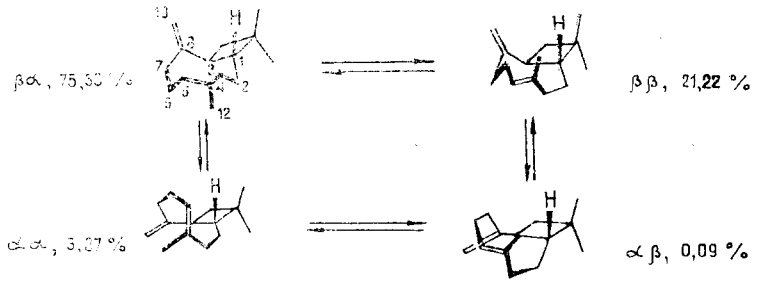
course of further investigations it was found that caryophyllenol-I attracts male individuals of Collops vittatus ten times more strongly than the epoxide (III) [60]. Caryophyllene epoxide (III) isolated from the essential oil of the cotton plant also attracts Campoletis sonorensis individuals. It is striking that caryophyllene (I), which is the main component of the oil, does not possess attractant activity [61]. Caryophyllene epoxide exhibits repellent activity with respect to some arthropods: in trials of various substance as repellents for the ants Lasius niger and Crematogaster matsumurai it was found that among terpenoids the epoxide (III) stood out by its considerable activity [62]. The epoxide (III) possesses a high toxicity in relation to the turbellarian Dugesia tigrina [63].

Caryophyllene 4β,5α-epoxide (III) is thus, at the present time the most interesting derivative of the caryophyllene type. There is a review paper on the properties, distribution in nature, toxicology, and use in the foodstuffs and perfumery industries of the epoxide (III) [64].

Of the other biological properties of caryophyllene compounds attention is merited by the growth-inhibiting activity of α-betulenol acetate (Vb) [16], the toxicity for fish of the buddledins (XIII)-(XVI) [22, 23], and the antimicrobial activity of naematolone (XL) and naematolin (XXXIX) [39] and the punctatins (XLI)-(XLIII) [40, 41].

THE CONFORMATION OF THE NINE-MEMBERED RING IN CARYOPHYLLENE COMPOUNDS

The nine-membered ring of the caryophyllene (I) molecule retains considerably conformational mobility. Of all the conformational motions of the caryophyllene skeleton it is possible to single out two main ones which substantially change the mutual positions of the atoms of the nine-membered rings: the intramolecular rotation of the C^3—C^4—C^5—C^6 fragment with a change of the orientation of the methyl groups at the C^4 atom (in the endo conformer the methyl groups is on the same side as the H^1 atom; in the exo conformer the methyl group is on the opposite side to that of the H^1 atom), and a change in the orientation of the exomethylene group (Scheme 1).

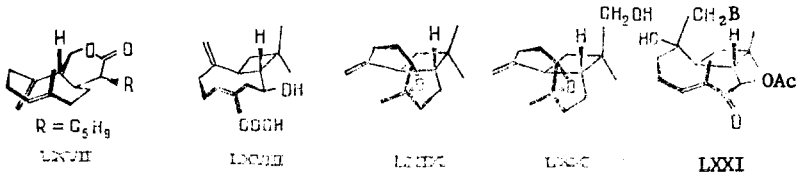


Scheme 1

The magnitude of the rotation barrier of the fragment containing the endocyclic double bond (i.e., the barrier to the rotations βα ⇄ ββ and αα ⇄ αβ) has been determined from the temperature dependence of the ^{13}C NMR spectra and is 16.25 kcal/mole, which is somewhat lower than in trans-cyclononene [65]. The ratio of the conformational isomers of caryophyllene (I) has been studied by various methods: the ^1H NMR spectra has been obtained in the temperature interval of from −90°C to +30°C [6] but it was impossible to interpret the results obtained; from the ^{13}C NMR spectra an endo:exo [(βα + αα):(ββ + αβ)] ratio of 76:24 was found, approximately corresponding to that calculated by the method of molecular mechanics (the calculated values of the populations of the conformations are given in Scheme 1) and in good agreement with the ratios determined from the composition of products of various reactions of caryophyllene: epoxidation, hydroboration, and photooxidation [65]. A close ratio of the conformers (80:20) was found from the ^1H NMR spectrum for 8-norcaryophyllen-13-one (XXII) [67].

A conformation analogous to the βα-conformation of caryophyllene has been found in the crystalline state for the caryophyllenic diterpenoid coraxeniolide-A (LXVII) [58] and lychnopholic acid (XLIVa, LXVIII), [42]. It is striking that the 4,5-epoxy derivatives (III) and (XXVI), which from the stereochemical point of view are similar to exo-caryophyllene, exist in the solid phase in the conformations (LXIX) [11] and (LXX) [27], corresponding to the αα-conformer and not to the more stable βx-conformer of caryophyllene. Conformation (LXXI) of the bromohydrin of buddledin A (XIIIa) has, in the crystal, a conformation similar to the

endo conformation of caryophyllene with respect to the nature of the orientation of C^3–C^4–C^5–C^6 fragment.

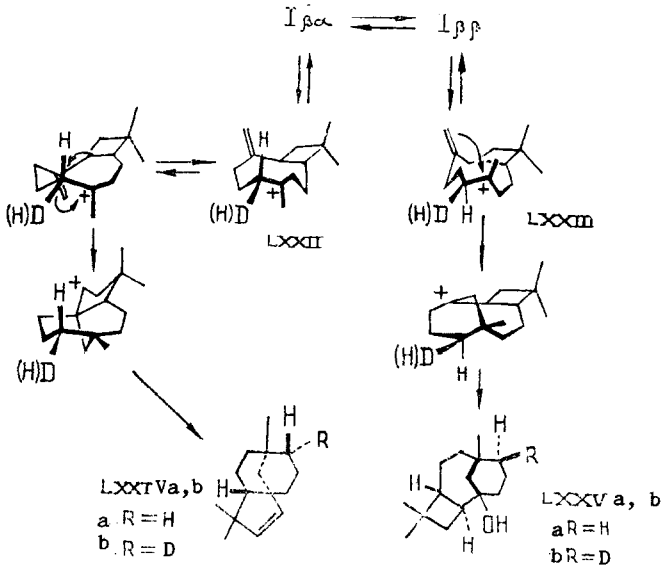


LXXVII LXXVIII LXXIX LXXX LXXI

Equilibria analogous to those shown in Scheme 1 may also exist in the case of isocaryophyllene (II). The conformers of isocaryophyllene apparently differ little in energy, as is shown by the formation of equal amounts of the 4,5-monoepoxides [68]. On the basis of the result of a study of the photooxidation reaction, the hypothesis has been put forward that for isocaryophyllene the endo:exo ratio is 55:45 [69]. The endo ⇄ exo rotation barrier in isocaryophyllene is, in all probability, lower than in caryophyllene [66].

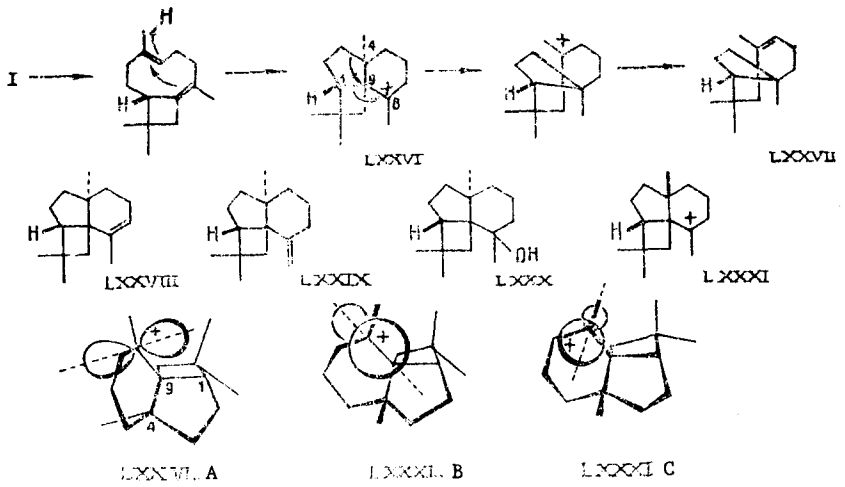
ELECTROPHILIC CYCLIZATION

Caryophyllene. After the treatment of caryophyllene (I) with sulfuric acid in ethereal solution at 0°C, initially two products were isolated: caryolan-1-ol (LXXVa) and clovene (LXXIVa) [2]. The total synthesis of clovene (LXXIVa) has been described [70]. The stereochemistries of the caryolane and clovane series of caryophyllene derivatives differ by the spatial position of the bridge methylene group [71]. This difference is due to the fact that caryolane and clovene are preceded by cationoid particles (LXXIII) and (LXXII) with different orientations of the methyl group at the C^4 atom, these particles being formed from different conformers, as is confirmed by the cyclization of caryophyllene (I) under the action of deuterated sulfuric acid [72], which gives two products: 9βD(>97%)-caryolan-1-ol (LXXVb) and 9αD(>96%)-clovene (LXXIVb). When caryophyllene was treated with acid the yield of caryolan-1-ol (LXXVa) sometimes reached 50% [73, 74], which, calculated on the ββ-conformer amounts to 250%. Such a high yield can be explained by the assumption that the protonation of the main βα-conformer leads to a cation incapable of cyclization because of the unfavorable orientation of the exomethylene group (Scheme 2), and therefore the cyclization of the βα-conformer into clovene (LXXIVa) takes place more slowly than the cyclization of the ββ-conformer into caryolan-1-ol, and, as the result of back-protonation, "pumping over" in the direction of the minor conformation is possible.



Scheme 2

The formation of caryolan-1-ol (LXXVa) with a high yield (61%) has been described for the oxymercuration-demercuration reaction [75], but in the same reaction with a different ratio of the reactants the cyclic ether (LXXXV) was obtained [24].

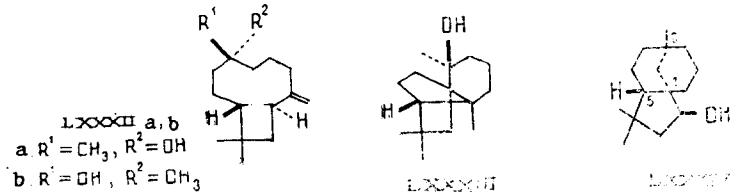


Scheme 3

Clovene (LXXIVa) is not the only hydrocarbon formed in the acid-catalyzed cyclization of caryophyllene (I) [76]. With the aid of GLC not less than 13 hydrocarbons have been found in the crude product, two of which make up 90% of the hydrocarbon fraction, one of these being clovene (LXXVa) while the other has been called neoclovene (LXXVII) [77]. For the formation of neoclovene (LXXVII), a scheme has been proposed which includes a migration of the double bond from the 8,13- to the 8,9-position (Scheme 3). Such a sequence of transformations is largely confirmed by the fact that the hydrocarbons α- and β-panasinsenes (LXXVIII) and (LXXIX) corresponding to the intermediate cation (LXXVI), which have been isolated from the essential oil of ginseng Panax ginseng are very sensitive to the action of acids and are readily converted under such action into neoclovene (LXXVII) [78]. The alcohol (LXXX) behaves similarly [79].

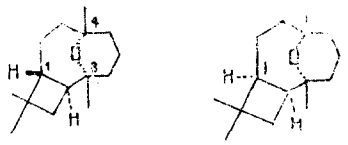
Because of the ease of their isomerization into neoclovene, it is not possible to obtain panasinsenes by the acid cyclization of caryophyllene. The β-isomer (LXXIX) has been synthesized by an indirect route through a norsesquiterpene derivative [78] and has been obtained directly from caryophyllene as the result of biomimetic cyclization under mercuration–demercuration conditions [80]. The total synthesis of β-panasinsenes (LXXIX) has been described in [81]. The possibility of the cyclization (I) → (LXXIX) and the ease of isomerization of the latter into neoclovene (LXXVII) is, nevertheless, a proof of the fact that in the conversion of caryophyllene (I) into neoclovene (LXXVII) it is just the cation (LXXVI) with the α-configuration of the angular methyl group, and not the epimer (LXXXI), that is obtained as an intermediate. But the formation of (LXXVI) appears more probable since the spatial arrangement of the bonds in (LXXVI) is more favorable for rearrangement into neoclovene (LXXVII): the magnitude of the dihedral angle between the vacant orbital of the cation and the migrating C^1–C^9 is ~0° for conformation (LXXXI.A and (LXXXI.B).

The ratio of the products of the acid-catalyzed cyclization of caryophyllene can vary according to the solvent [73] and to the catalyst [82]. When caryophyllene [I] was treated with aqueous solutions of chloroacetic acids, the main products were alcohols, which, with the exception of caryolan-1-ol (LXXVa), corresponded to the hydrocarbons found in the reaction mixture: dihydrocaryophyllen-4-ol (LXXXII), dihydroneocloven-9β-ol (LXXXIII), and dihydrocloven-2β-ol (LXXXIV) [74]; hydration by means of chloroacetic acids can take place effectively in the presence of synthetic zeolites [83] and ion-exchange resins [84]. The cyclization of caryophyllene (I) in formic and acetic acids gives formates and acetates of the alcohols (LXXVa) and (LXXXIV) [85].



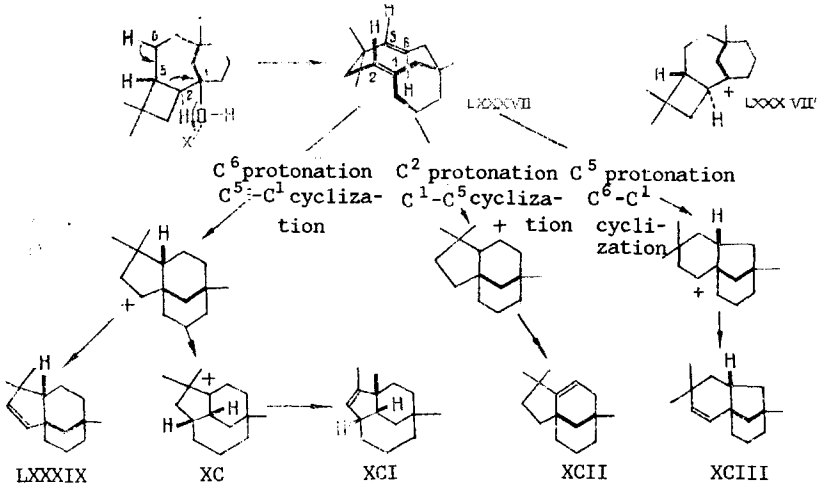
Oxygen-containing derivatives produced by the hydration of caryophyllene (I) are also obtained under oxymercuration–demercuration conditions [24, 75, 86] when, together with the

usual products – caryolan-1-ol (LXXVa), dihydrocaryophyllene-4-ol (LXXXIIa), and caryophyllane 4,8-oxide (LXXXV) – 1-epicaryophyllane 4,8α-oxide (LXXXVI), having the cis-linkage of the nonane and butane carbon rings, is formed [86]. The formation of such unusual products is connected with the occurrence of a side reaction of the reduction of the organomercury compounds [87].



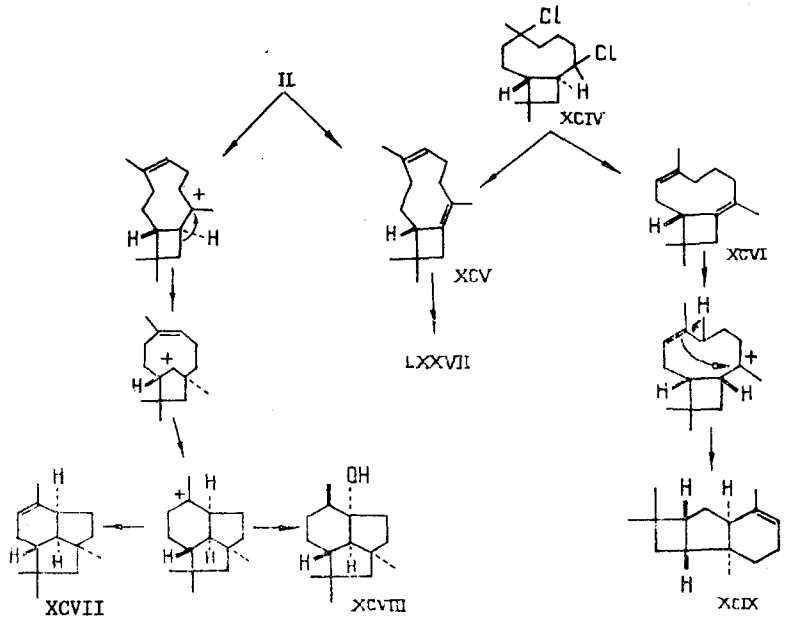
LXXXV LXXXVI

Caryolan-1-ol. It is a striking fact that caryophyllene, on treatment with acids, gives a tertiary alcohol – caryolan-1-ol (LXXVa) which proves to be stable to the action of concentrated sulfuric acid; the hydroxy groups in this compound can be replaced by a chlorine or a bromine atom [88] and is eliminated only with difficulty. The dehydration of caryolan-1-ol, as was initially assumed [76], leads to the formation of two hydrocarbons: pseudoclovene and isoclovene (XCI), the synthesis of the latter having been described in the literature [89]. Later, however, it was found that pseudoclovene was a mixture of two hydrocarbons – pseudoclovene A (XCII) [90] and B (XCIII) [91]. Another hydrocarbon isolated from the products of the dehydration of caryolan-1-ol has acquired the name of epiclovene (LXXXIX) [92]. The structure of the products of the rearrangement of the caryolane skeleton has been established by x-ray structural analysis, and there is a review paper on these investigations [93]. The formation of all the products of the dehydration of caryolan-1-ol (LXXVa) is shown in general Scheme 4 [91, 92], which assumes the intermediate formation of the bicyclic hydrocarbon (LXXXVII). It is quite likely that all the dehydration products are formed from one and the same bicyclic precursor. This is indicated by results [94] showing that on the dehydration of caryolan-1-ol (LXXVa) in superacids at low temperatures the ion (XC) is obtained from the 1-caryolyl cation (LXXXVIII) as the result of successive 1,2-shifts. There is every ground for assuming that the hydrocarbons (LXXXIX) and (XCI) are formed in the course of rearrangement without recyclization of the tricyclic skeleton.



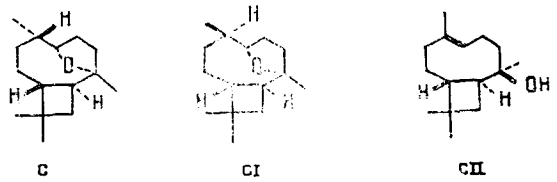
Scheme 4

Isocaryophyllene, Caryophyllene Dihydrochloride. Isocaryophyllene (II) cyclizes under the action of acids just as readily as caryophyllene (I), but the composition of the products is different. In the isocaryophyllene (II) molecule, in contrast to caryophyllene (I), there is practically no strain of the 4,5-double bond, and therefore the protonation of the exocyclic double bond takes place initially leading either to an isomerization product (XCV) giving neoclovene (LXXVII) or to the hydrocarbon (XCVII) (Scheme 5) [95]. The rearrangement of isocaryophyllene (II) in a superacid can take place more profoundly with the formation of the alcohol (XCVIII) [96]. One of the two main products of the cyclization of caryophyllene dihydrochloride (XCIV) is neoclovene (LXXVII) [97]. The formation of another product – the hydrocarbon (XCIX) – is due to the fact that the splitting out of hydrogen chloride preceding cyclization gives both $\Delta^{4,5}$ and $\Delta^{3,4}$ products (XCV and XCVI, respectively) (Scheme 5).



Scheme 5

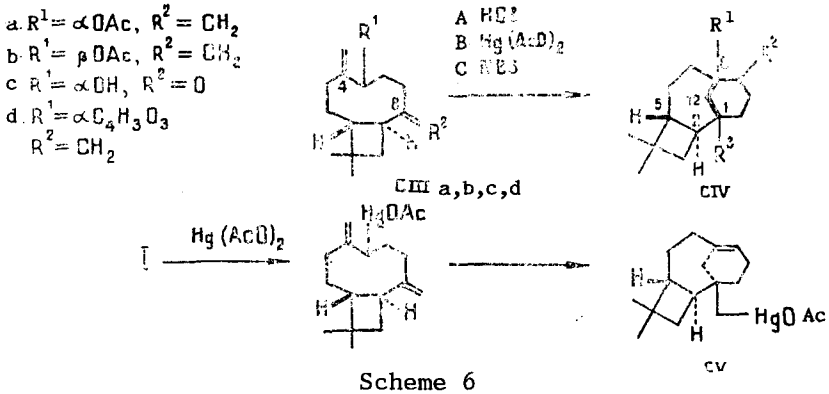
The hydration of isocaryophyllene (II) under oxymercuration–demercuration conditions leads to intracyclic ethers while, in contrast to caryophyllene (I), in addition to the 4,8-oxides (XVII) and (LXXXV), products of the hydration of the 4,5-double bond contrary to Markovnikov's rule are also formed – the epimeric caryophyllane 5,8-oxides (C) and (CI) [98].



C CI CII

Hydroxy Derivatives. In the nine-membered ring of caryophyllene derivatives transannular cyclizations with the participation of the oxygen atom of the alcohol group induced by bivalent mercury salts readily take place. As an example of such a reaction we may give the transformation of dihydrocaryophyllene-8β-ol (CII) into caryophyllane 4,8β-oxide (XVII) [24]. The formation of cyclic ethers has also been described for the reactions of caryophyllan-5Z,8(13)-dien-4α- and -4β-ols (CXVIIIa) and (CXVIIIb) [24], of dihydrocaryophyllen-4α- and -4β-ols (LXXXIIa) and (LXXXIIb) [86], and of dihydrocaryophyllen-5-ols with different configurations [98, 99].

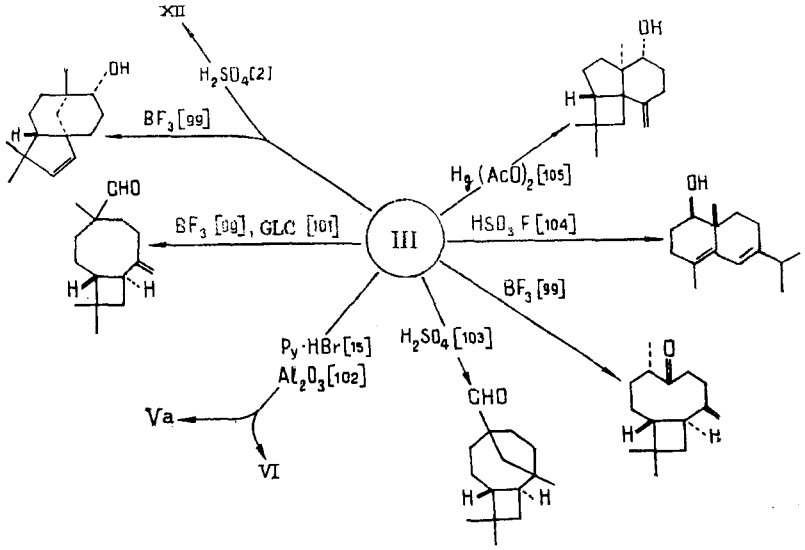
4,8-Bismethylene Compounds. Characteristic for the series of 4,8-bismethylene derivatives of caryophyllene (CIII) is cyclization under the action of various electrophilic reagents with the formation of compounds of the tricyclo[6.3.1.$0^{2,5}$]dodecane series (CIV) with a 12β-methylene bridge. A stereochemically unusual cyclization of the type taking place under the action of a mercury salt on caryophyllene (I) and giving a derivative (CV) with a 12α-methylene bridge is also known [100] (Scheme 6).



Scheme 6

REACTIONS OF 4,5-EPOXY DERIVATIVES

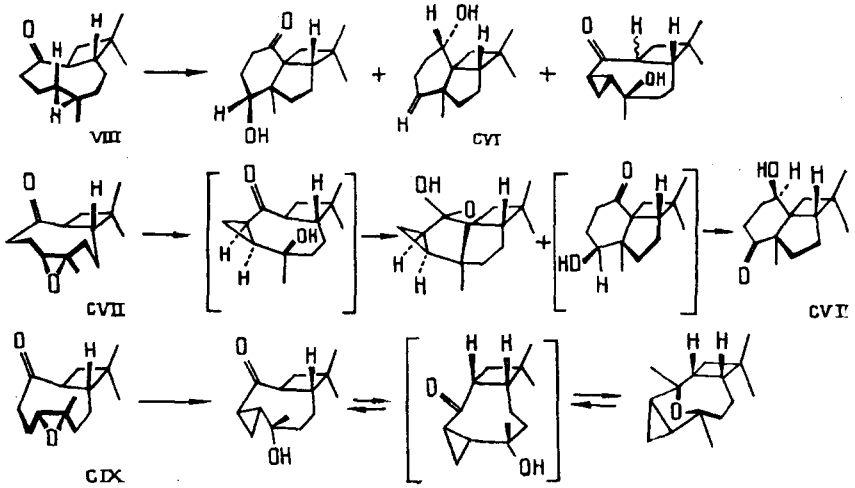
When caryophyllene (I) is treated over acids, the crystalline monoepoxide (III) is formed [10], and for a long time this was considered the only monoepoxide. Although it has not been possible to isolate a second epoxide – caryophyllene 4α,5β-oxide (CX) – in the individual state, its formation has been shown by the ^1H NMR method [66]. The oxide (III) is very sensitive to the action of electrophilic reagents, in reactions with which it isomerizes in seven different directions (Scheme 7).



Scheme 7

The epoxide ring in the epoxyketone (VIII) also readily opens on electrophilic attack: treatment with hydrogen chloride converts kobusone (VIII) into the chlorohydrin (CIV), R^1 = Cl; R^2, R^3 = OH [106]; the reaction takes place with the intermediate formation of isokobusone (IX), which is also obtained in the reverse reaction on the elimination of hydrogen chloride from the chlorohydrin [107].

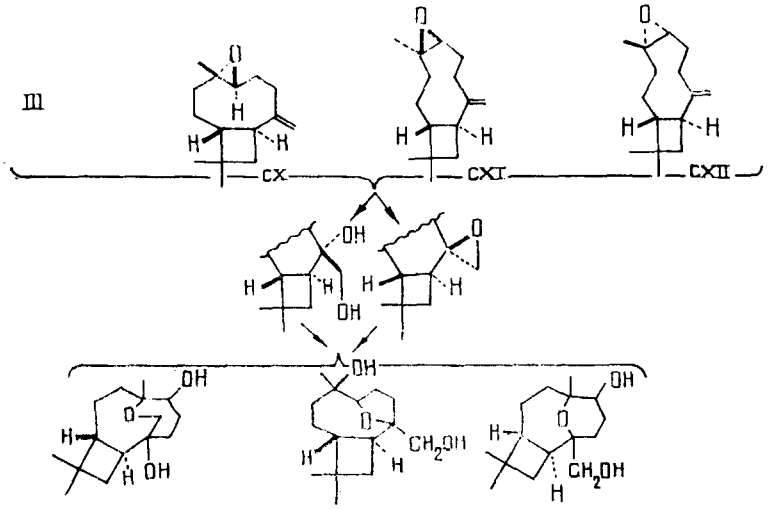
The epoxide (III) is exceptionally stable in relation to alkalies: the epoxide ring is not opened on heating with caustic soda at 150°C [108], which is explained by the impossibility of the approach of an external nucleophilic particle from the rear side of the epoxide ring. At the same time, the intramolecular opening of the epoxide ring takes place very readily in kobusone (VIII) and its epimers (CVII) and (CIX), giving tricyclic derivatives by a reaction catalyzed by alkali-metal alcoholates [109] (Scheme 8). The transformations represent an intramolecular nucleophilic opening of the epoxide ring under the action of an enolate anion or – which is the same thing – an intramolecular alkylation in the α-position of the keto group. Alkylation is possible at two positions (C^7 and C^9), but for each



Scheme 8

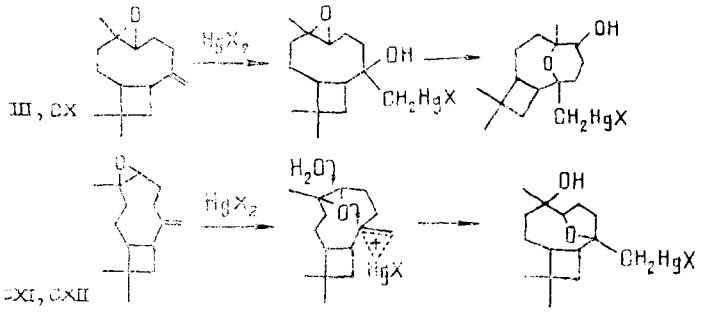
ketoepoxide there is a predominant direction of attack. The isomerization of the epoxyketones (VIII) and (CVII) gives the unusual products (CVI) and (CVIII), which are formed from 5-hydroxy-8-keto precursors by a 1,4-hydride shift in the cyclohexane fragment [110].

The intramolecular opening of the oxide ring takes place readily with the formation of cyclic ethers in the 8,13-dihydroxy derivatives of the 4,5-epoxides, which are obtained from the epoxides (III) and (CX) [(CXI) and (CXII)] on oxidation with osmium tetroxide and by the Prilezhaev reaction, epoxidation taking place predominantly from the β-side, and hydroxylation from the α-side, of the double bond (Scheme 9) [108, 111]. The opening of the epoxide ring takes place under the action of an alcoholate anion as an intramolecular nucleophilic substitution by an S_N2 mechanism, the intramolecular reaction being regiospecific in each compound.



Scheme 9

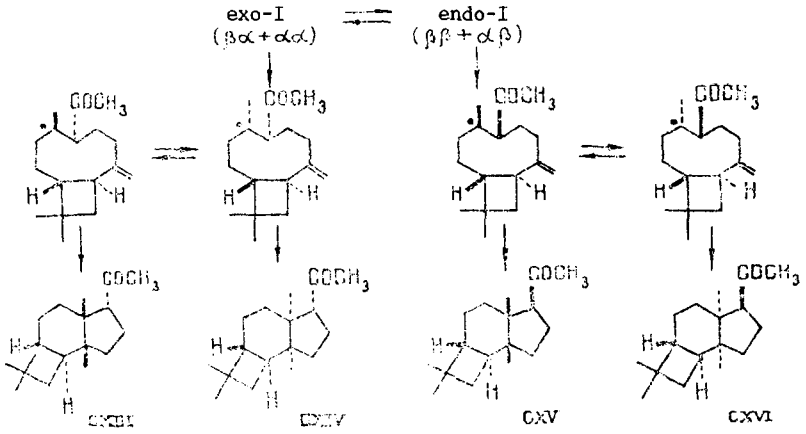
The opening of the epoxide ring with the formation of intracyclic ethers on oxymercuration–demercuration takes place dissimilarly for the 4,5-epoxides of caryophyllene (III), (CX) and of isocaryophyllene (CXI), (CXII): while in the reaction of the caryophyllene derivative hydration of the 8,13-double bond takes place initially, and the hydroxy group at the C^8 atom attacks the epoxide group from the rear side; in the case of the isocaryophyllene derivatives the oxygen atom of the oxide group, as early as the mercuration stage, acts as the nucleophile in the opening of the 8,13-mercurinium ion (Scheme 10) [112].



Scheme 10

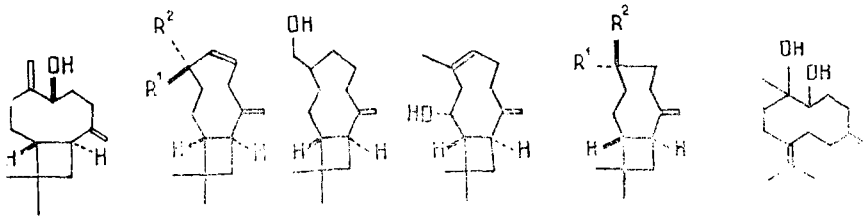
OTHER REACTIONS AT THE 4,5-DOUBLE BOND

Together with various transformations under the action of electrophilic reagents, the radical cyclization of the caryophyllene skeleton is known: the acetyl radical causes the cyclization of caryophyllene with the formation of a mixture of four epimeric ketones (CXIII), (CXIV), (CXV), and (CXVI) in a ratio of 5:2:1:1 (Scheme 11) [113]. The ratio of the yields of the reaction products permits the conclusion that the addition of the $CH_3CO^{\bullet}$ radical to caryophyllene proceeds considerably faster than the endo ⇄ exo transition (the CXII + CXIV): (CXV + CXVI) ratio of 7:2 corresponds approximately to the ratio of the exo- and endo-conformers of caryophyllene).



Scheme 11

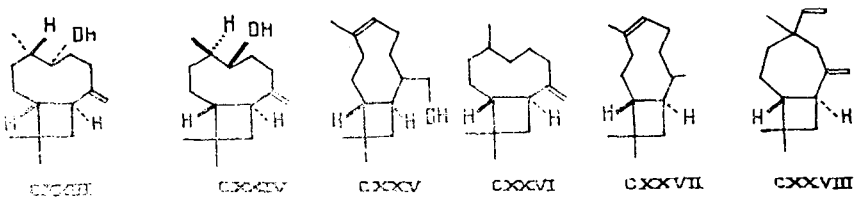
The reactivity of the trisubstituted double bond in caryophyllene (I) is higher than that of the exocyclic double bond and higher than that of the trisubstituted double bond in isocaryophyllene (II). Monoepoxidation [66, 68] can be performed selectively at the 4,5-double bond, and the oxidation of caryophyllene takes place far faster than that of isocaryophyllene [114]; however, the introduction of an 8,13-epoxy group with retention of the endocyclic double bond is possible only when the former is previously protected [20]. The attack of singlet oxygen in photooxidation is directed to the 4,5-double bonds in caryophyllene and isocaryophyllene and leads to a mixture of the allyl alcohols (Va, VI, and VII) (CXVII, CXVIIIa, and CXVIIIb) [69, 115]. Among the products of the oxidation of caryophyllene by lead tetraacetate [116] are the epoxide (III), the ketones (CXXIa and CXXIb), and the alcohols (Va, VI, VII, XXXV, LXXXII, CXVII, CXVIIIa, CXVIIIb, CXIX, CXX, and CXXII) – again, the products obtained on the attack of the oxidant at the endocyclic double bond predominate.



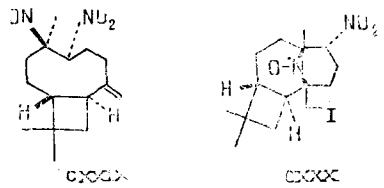
a R^1= OH, R^2= CH_3
b R^1= CH_3, R^2= OH

a R^1= H, R^2= $COCH_3$
b R^1= $COCH_3$, R^2= H

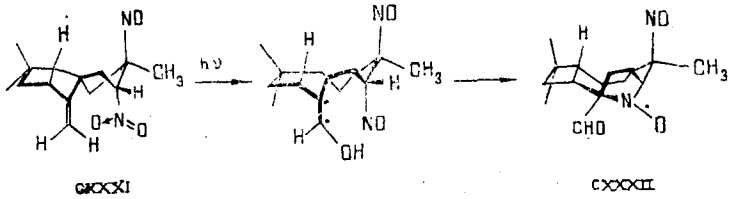
In the case of caryophyllene (I), hydroboration with biscyclohexylborane takes place exclusively at the 4,5-double bond and, after the oxidation of the organoboron compounds, the alcohols (CXXIII and CXXIV) are obtained in a ratio close to the ratio of the exo- and endo-conformers of caryophyllene [117]. Under these conditions, isocaryophyllene (II) forms only the product of addition at the 8,13-double bond (CXXV). The reduction of caryophyllene and that of isocaryophyllene with diimide also takes place differently: caryophyllene gives 4,5-dihydrocaryophyllene (CXXVI), and isocaryophyllene gives 8,13-dihydroisocaryophyllene (CXXVII) [117]. The catalytic hydrogenation of the two hydrocarbons – caryophyllene and isocaryophyllene – forms the same product (CXXVII) [114]. The cis-double bond of the nine-membered ring of caryophyllene compounds is more stable than the trans-double bond: caryophyllene (I) is smoothly converted into isocaryophyllene (II) by irradiation with UV light [118] or on heating to 175°C in the presence of selenium [119]. At higher temperatures (>240°C), the caryophyllene skeleton is unstable and isomerizes with the ejection of two carbon atoms from the ring, giving the hydrocarbon (CSSVIII) [20].



Caryophyllene (I) readily forms crystalline derivatives – nitrosite, nitrosite monohydrochloride, nitrosochloride, dihydrochloride – which have long been used for the identification of this hydrocarbon [121]. The structure of one of these products – the blue nitrosite – has been widely studied [122] and has been definitely established as the result of an x-ray structural investigation of the iodonitrosite (CXXX) – a stable nitroxyl radical formed under the action of iodine on the nitrosite [123]. On the basis of the formula of (CXXX), caryophyllene nitrosite can be assigned the structure (CXXIX), which has also been confirmed by the results of NMR spectroscopy [124]. From the nitrosite (CXXIX) a number of nitrogen-containing compounds with the caryophyllene carbon skeleton have been synthesized [122, 124, 125].

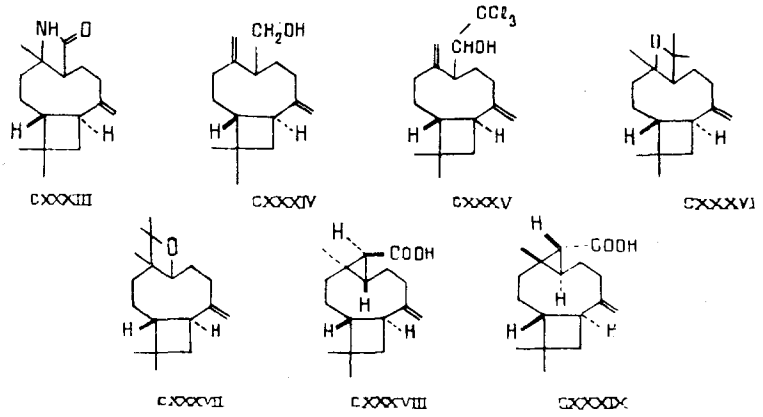


The iodonitrosite (CXXX) is not the only stable radical formed from the nitrosite (CXXIX). The existence of at least eight nitrogen-containing radicals generated from compounds (CXXIX) under various conditions has been established by the ESR method [126]. Of the reactions described in this last-mentioned paper, attention is merited by the conversion of the nitrosite (CXXIX) into a tricyclic product (CXXXII) which takes place in the solid phase on irradiation with UV light. The formation of compound (CXXXII) makes it possible to conclude that in the crystalline state the nitrosite (CXXIX) has the conformation (CXXXI), since only with this orientation of the exomethylene and nitro groups is an intramolecular reaction at the exocyclic double bond possible (Scheme 12).



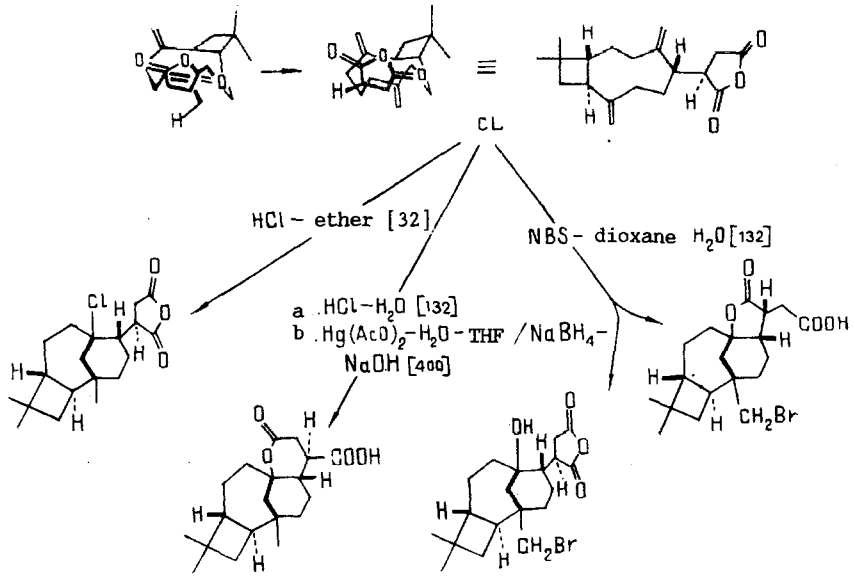
Scheme 12

The high reactivity of the endocyclic double bond in caryophyllene (I) permits reactions of selective addition at the C^4–C^5 double bond to be performed under milder conditions: the reaction with chlorosulfonyl isocyanate gives the azacyclobutanol derivative (CXXXIII) [127]; condensation with formaldehyde leads to the primary alcohol (CXXXIV) [128]; on treatment with chloral in the presence of aluminum chloride compound (CXXXV) is obtained [129]; the photoaddition of acetone takes place with the formation of a mixture of the adducts (CXXXVI) and (CXXXVII) [130]; in the reaction with diazoacetic ester the cyclopropanecarboxylic acids (CXXXVIII) and (CXXXIX) are formed [131]; and the reaction with sulfur with irradiation gives the episulfide (IV) [13].



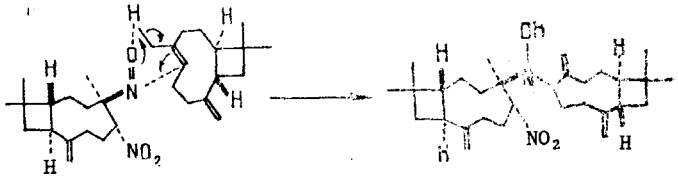
Caryophyllene (I), unlike the majority of other nonconjugated dienic hydrocarbons, readily reacts with maleic anhydride to form an "adduct" (CL), as shown in Scheme 13. The

structure and stereochemistry of the "adduct" (CL) were suggested on the basis of a study of the cyclization products [132] and were established accurately by x-ray structural analysis [133]. The "adduct" (CL), like other bis-exomethylene derivatives of caryophyllene (Scheme 6) cyclizes under the action of electrophilic reagents (Scheme 13).



Scheme 13

The formation of a bis-exomethylene adduct also takes place in the reaction of caryophyllene (I) with the nitrosite (CXXIX) in chloroform solution in the dark (Scheme 14) [134].



Scheme 14

The endocylcic trans-double bond and the 4,5-trans-epoxide group which is analogous to it in the stereochemical respect are the main factors that are responsible for the strain of the nine-membered ring. As can be seen from some of the reactions given above, for caryophyllene and some of its derivatives reactions are characteristic that cause a substantial decrease in this strain by the allyl shift of the double bond into the $\Delta^{3,4}$ and $\Delta^{4,12}$ positions with the retention of the bicyclic carbon skeleton, the main products being compounds with an exocyclic 4,12-double bond.

As has been correctly observed by Greenwood et al. [107] with reference to [135], "this type of elimination to form an exocyclic, rather than endocyclic, double bond appears to be characteristic of the caryophyllene and humulene ring systems." The tendency of the caryophyllene skeleton to form predominantly products with a 4,12-double bond must, however, be connected with the completely definite conformation of the nine-membered ring. In actual fact, the photooxidation of caryophyllene (I), which was considered above, gives a mixture of the allyl alcohols (Va, VI, VII, and CXVII) in a ratio of 68:4:10:13 [115], i.e., from exo-caryophyllene is formed predominantly the $\Delta^{4,12}$-product (Va), and from endo-caryophyllene almost equal amounts of the $\Delta^{3,4}$- and $\Delta^{4,12}$-products (VII and CXVII), respectively.

The same alcohols are formed on the isomerization of the epoxides (III) and (CX) under the action of n-butyllithium: the oxide (III) gives a mixture of the alcohols (Va) and (VI) in a ratio of 58:8 [115], and epoxide (CX) leads to a mixture of (VII) and (CXVII) in a ratio of 4:1. Furthermore, the isomerization of the epoxide (III) on acidic alumina gives practically equal amounts of the alcohols (Va) and (VI), while the alcohols (VII) and (CXVII) in a ratio of 3:1 are obtained from the epoxide (CX) under these conditions.

Thus, it may be assumed that elimination with the predominant formation of a 4,12-exocyclic double bond is characteristic for those caryophyllene compounds with conformation (or configuration) of the C^3–C^4–C^5–C^6 fragment of which is close to the conformation of this fragment in exo-caryophyllene.

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