MOLECULAR REARRANGEMENTS OF TETRA- AND PENTACYCLIC DITERPENOIDS FORMED WITH THE PARTICIPATION OF PIMARANE INTERMEDIATES

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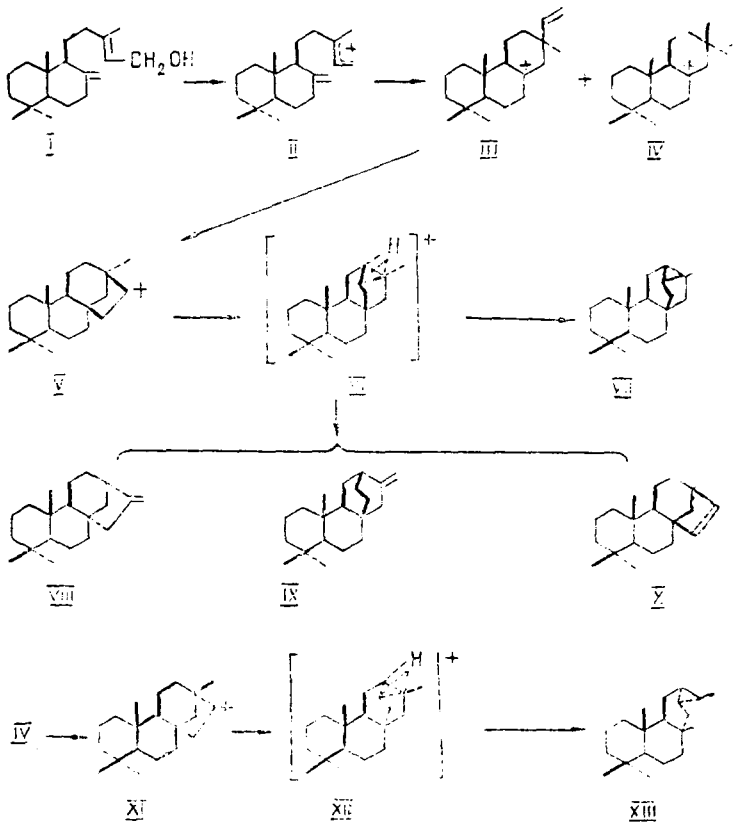
The molecular rearrangements of tetra- and pentacyclic diterpenoids formed with the participation of pimarane intermediates are considered.

In the development of the chemistry of terpenoids in general and of diterpenoids in particular the isoprene biogenetic rule formulated by L. Ruzicka [1, 2] has played a very fruitful role. He proposed one of the most important biogenetic schemes for diterpene compounds, including the cyclization of aliphatic diterpenoids into bicyclic labdane compounds and their subsequent transformation into tricyclic pimarane compounds (the transition (I) → (III) + (IV). The isoprene biogenetic rule received further development in the work of Wenkert [3], who put forward a hypothesis according to which tetracyclic diterpenoids with the kaurane (VIII), atisane (IX), and hibane (X) structures are formed from one and the same nonclassical carbocation (VI), obtained, in its turn, from the tricyclic intermediate (III). The formation of the diterpenoids of the phyllocladane (XIV), neoatisane (XV), and isohibane (XVI) series from one and the same tricyclic carbocation (IV), epimeric with the carbocation (III) at C-13, can be represented analogously. At the present time, representatives of all the types mentioned, with the exception of the neoatisane type (XV), have been detected in natural sources. It stands to reason that similar biogenetic links exist in the series of enantiomeric diterpenoids [4].



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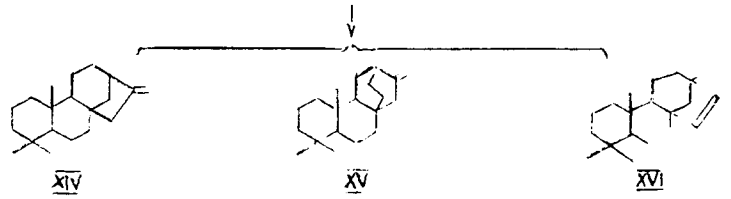


The biogenetic schemes of the transformation of diterpenoids were subsequently confirmed by biosynthetic investigations [5]. Another argument in their favor was the detection in natural sources of ent-trachylobane (VII), which is nothing other than the product of the deprotonation of the nonclassical carbocation (VI) [6], and its derivatives [7]. Finally, to confirm the scheme of the formation of tetra- and pentacyclic diterpenoids proposed by Wenkert, numerous investigations were undertaken of the acid isomerization in vitro of kaurane, hibane, atisane, and phyllocladane and, then, also of trachylobane diterpenoids. In view of the fact that availabilities of these substances are different, some of such transformations are also of definite synthetic interest.

It must be mentioned that there is only one review [8] in which the mutual isomerization of tetra- and pentacyclic diterpenoids is reported, but it was published long ago and naturally does not reflect the current state of the question.

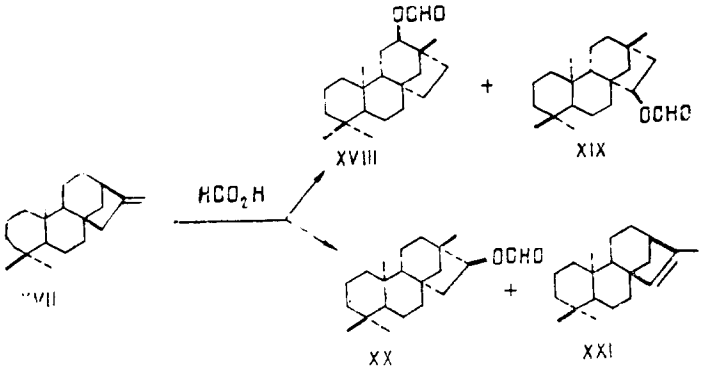
In the present review we have generalized studies in which the isomerization and rearrangement of tetra- and pentacyclic diterpenoids containing functional groups at the C-12–C-16 atoms have been investigated, since only such compounds can undergo the transformations reflected in the scheme given above.

The rearrangements are considered separately for each group of tetracyclic diterpenoids and for the pentacyclic diterpenoids.

The literature published up to and including 1989 is generalized in the review.

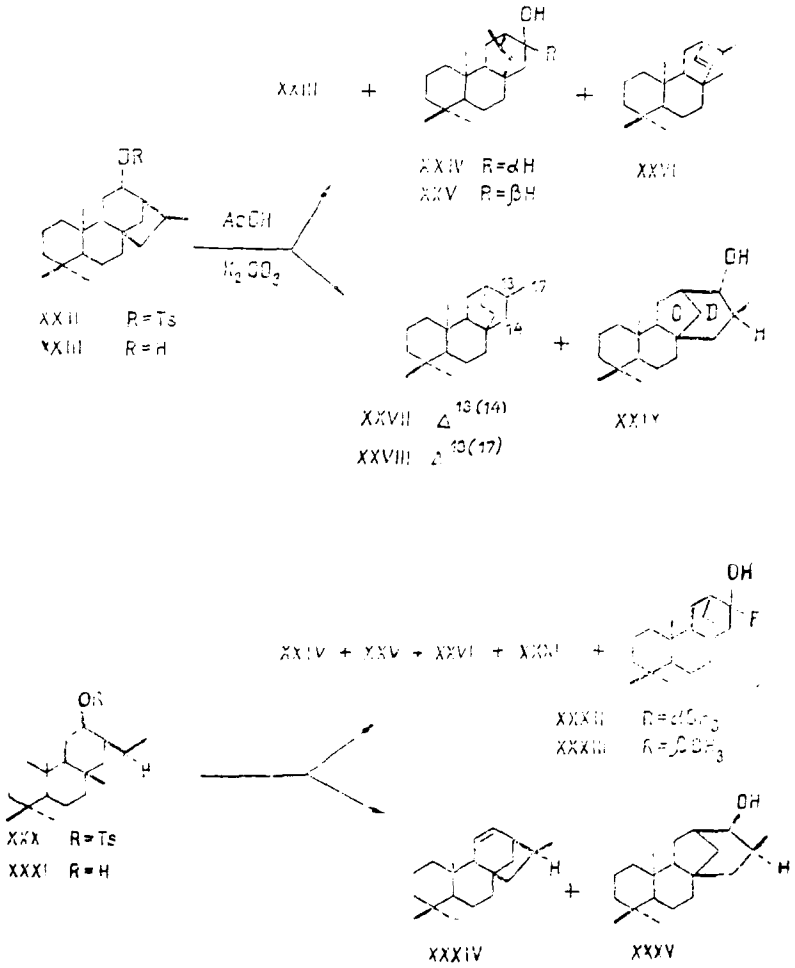
REARRANGEMENT OF KAURANE DITERPENOIDS

On the interaction of ent-kaurene (XVII) with 98% formic acid, together with its isomerization into ent-isokaurene (XXI), a rearrangement of the carbon skeleton takes place with the formation of a mixture of the isomeric stachanol formates (XVIII)-(XX) [9].

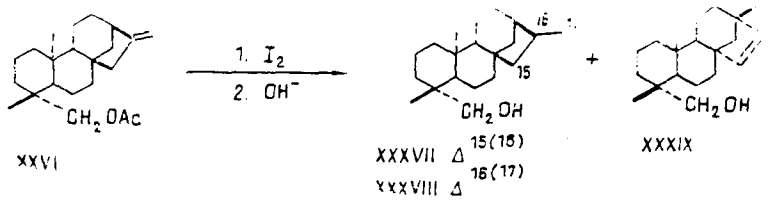


The solvolysis of the tosylate (XXII) of the alcohol (XXIII) in acetic acid in the presence of potassium carbonate [10] leads to a product in which the atisane derivatives (XXIII)-(XXVIII) predominate, while substance (XXIX) with a rearranged structural fragment involving rings C and D has been isolated in small amount (see scheme on following page).

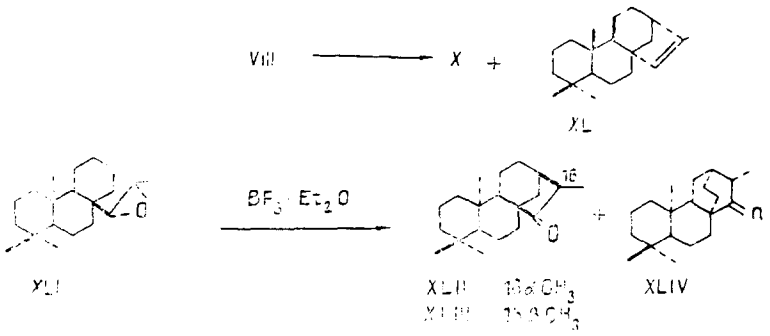
Compounds of the same structural types (XXIV)-(XXVI) and (XXXI)-(XXXIV) have also been detected in the product of the solvolysis of the tosylate (XXX) of the epimeric alcohol (XXXI) [11] (see scheme on following page).



On being boiled with iodine in benzene, ent-kaurene (XVII) undergoes isomerization into ent-isokaurene (XXI) [12]; however, under the same conditions (followed by saponification) the acetate of ent-kaurene gives a product containing, in addition to the isomeric alcohols of the ent-kaurane series (XXXVII) and (XXXVIII), a small amount of monogynol (XXXIX) [13], which belongs to the stachane series.



When kaurene (VIII) is isomerized under more severe conditions (boiling with iodine in xylene), in addition to isomerizing into isokaurene (XL) it also rearranges into hibaene (X) [14].

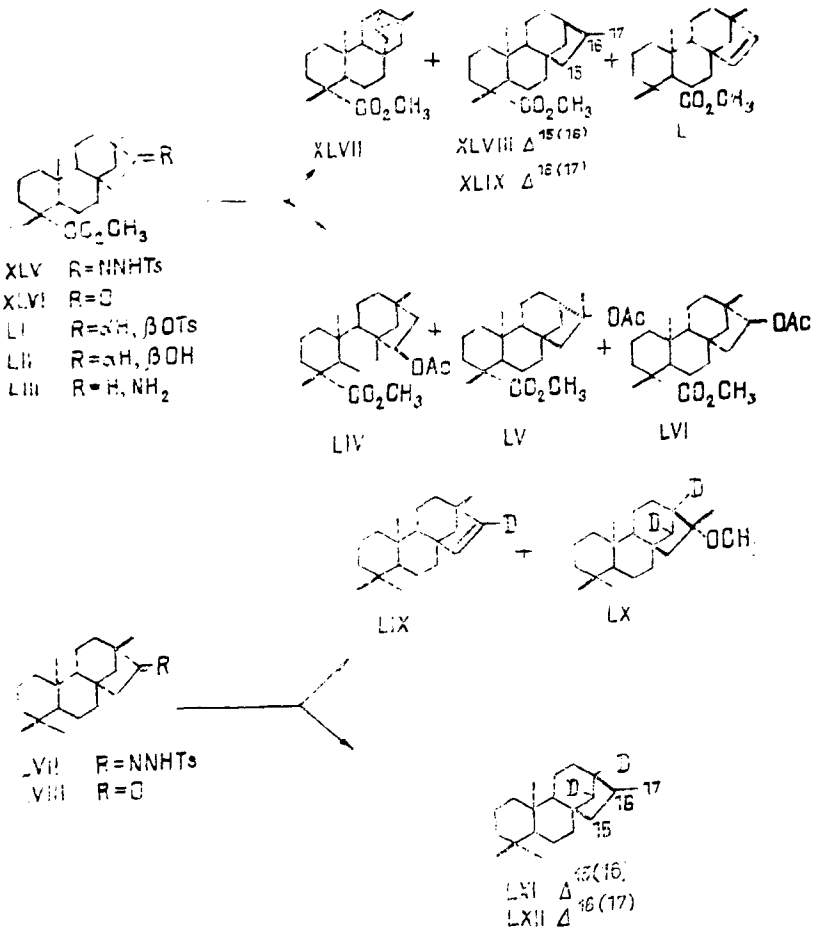


15α,16α-Epoxy-ent-kaurene (XLI) has been isomerized with boron trifluoride etherate into a mixture of the ketones (XLII)-(XLIV) in which compound (XLIV), belonging to the ent-atisane series, considerably predominated [15].

It follows from the facts given that isomerization into atisane and stachane (hibane) compounds is the usual process for kaurane diterpenoids with functional groups at C-14, C-15, and C-16. If, however, the functional group is located at C-12, compounds with a pentacyclic ring C that do not fall within Wenkert's scheme are also formed.

REARRANGEMENT OF STACHANE (BEYERANE, HIBANE) DITERPENOIDS

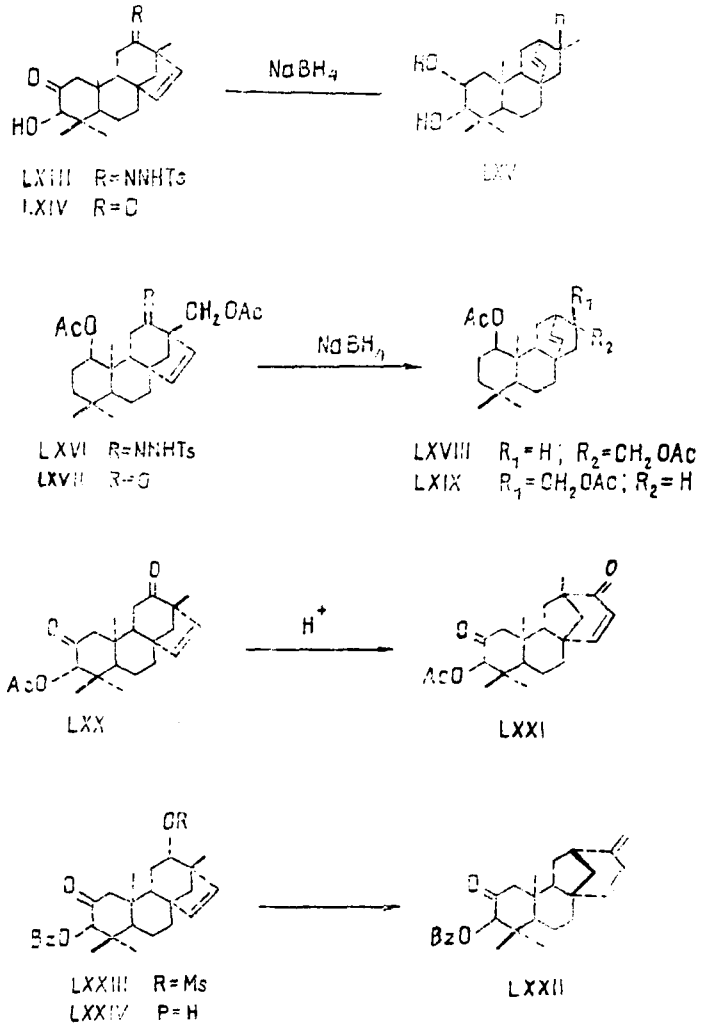
One of the interesting reactions causing a rearrangement of the stachane system has proved to be the decomposition of the tosyl hydrazone (XLV) of the ketone (XLVI) by metallic sodium in glyme, giving a mixture of esters with trachylobane (XLVII), ent-kaurane (XLVIII and XLIX), and stachane (L) structures [16]. The same authors have shown that the solvolysis of the tosylate (LI) of the alcohol (LII) forms a mixture of unsaturated esters with ent-kaurane (XLVIII and XLIX) and stachana (L) structures, while the deamination of the amine (LIII) forms a mixture of the same compounds and of the acetoxy esters (LIV)-(LVI). However, in this case the acetoxy esters (LIV)-(LVI) predominate in the product [17].



The cleavage of the tosylhydrazone (LVII) of stachan-15-one (LVIII) by sodium methanolate in deuterated methanol has been described [18]. The reaction products proved to be the deuterated stachene (LIX) and the deuterated kaurane compounds (LX)-(LXII). These facts have thrown light on the mechanism of the isomerization reaction.

The sole product from the action of sodium tetrahydroborate on the monotosylhydrazone (LXIII) of 3β-hydroxystach-15-ene-2,12-dione (LXIV) is a diol (LXV) of the atisane series [19], the structure of which has been confirmed by x-ray structural analysis [20]. Under the same conditions, the tosylhydrazone (LXVI) of ketone (LXVII) gives a mixture of the acetoxyatisanes (LXVIII) and (LXIX) [21].

Under the action of acids, 3-acetoxystach-15-ene-2,12-dione (LXX) is converted into the diketo acetate (LXXI) with a rearranged skeleton [22]. The solvolysis of the mesylate (LXXIII) of the alcohol (LXXIV) leads to compounds with the same carbon skeleton (LXXII) [23, 24].



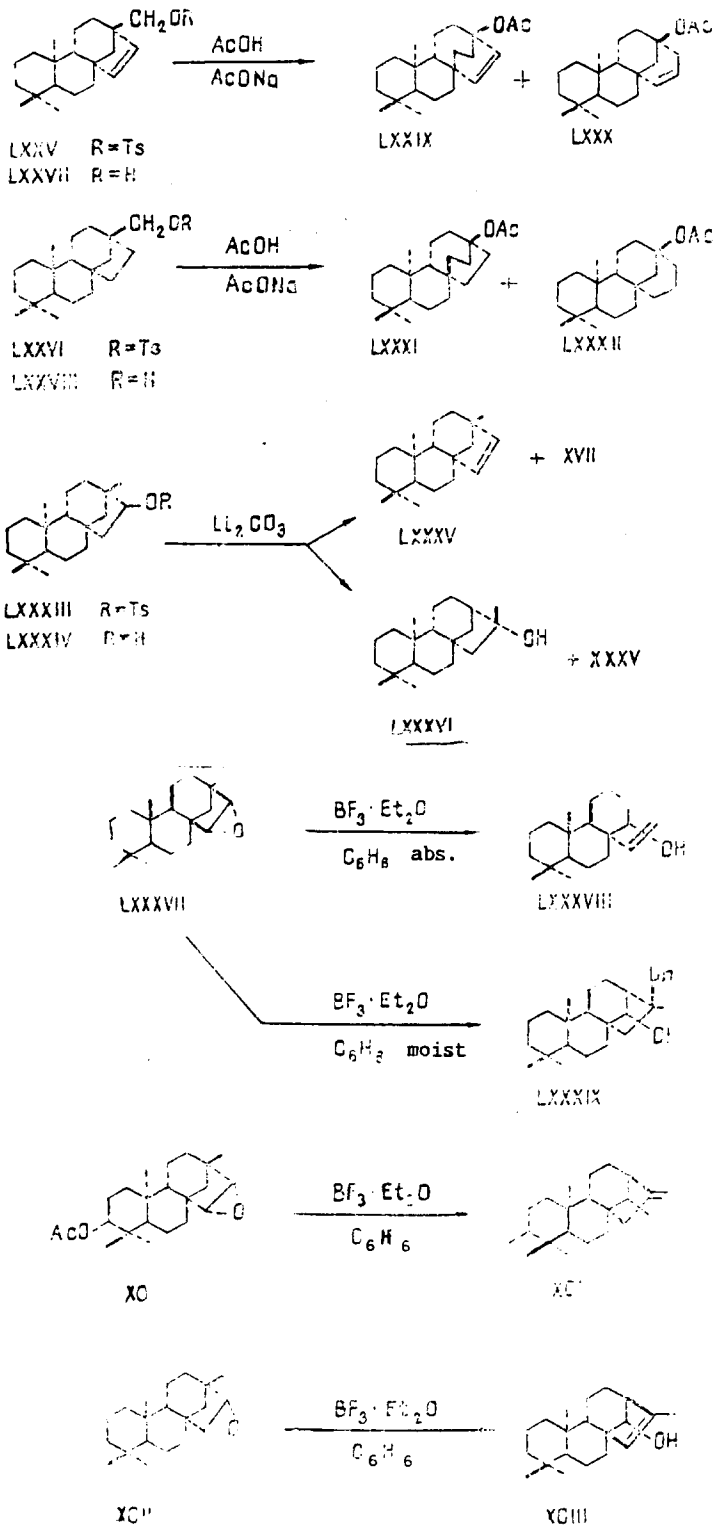
The solvolysis of the tosylates (LXXV) and (LXXVI) of the alcohols (LXXVII) and (LXXVIII) by acetic acid in the presence of sodium acetate has been studied [25]. The reaction products proved to be, respectively, the acetates (LXXIX) and (LXXX) and the dihydro acetates (LXXXI) and (LXXXII), based on a new carbon skeleton.

The solvolysis of the tosylate (LXXXIII) of stachan-16-ol (LXXXIV) in the presence of lithium carbonate in dioxane forms a mixture of substances (XVII), (XXI), (LXXXV), and (LXXXVI) in which the kaurane derivatives predominate [26] (see scheme on following page).

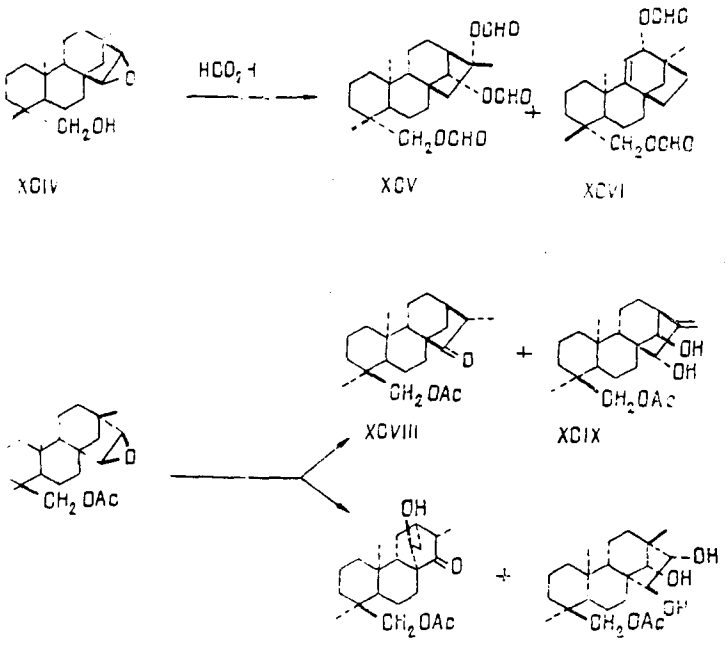
Under the action of hydrogen chloride in chloroform, stachene (LXXXV) isomerizes into an equilibrium mixture of the ent-kaurenes (XVII) and (XXI) [27].

Japanese chemists [28] have investigated the isomerization of 15α,16α-epoxyhibane (LXXXVII) under the action of boron trifluoride etherate and have shown that in dry benzene kauren-14α-ol (LXXXVIII) and in moist benzene kaurane-14,16-diol (LXXXIX) are formed. In contrast to these results, 3α-acetoxy-14α,15α-epoxystachane (XC) is isomerized by the same reagent in dry benzene into the unsaturated hydroxy acetate (XCI) with a semicyclic double bond [29], and 14α,15α-epoxystachane (XCII) into kaur-15-en-14α-ol (XCIII) [30].

The interaction of 19-hydroxy-15β,16β-epoxystachane (XCIV) with formic acid has been studied [31, 32]. In addition to the ester (XCV) with a rearranged kaurane skeleton, compound (XCVI) of the stachane series, containing a double bond in the C-9–C-11 position



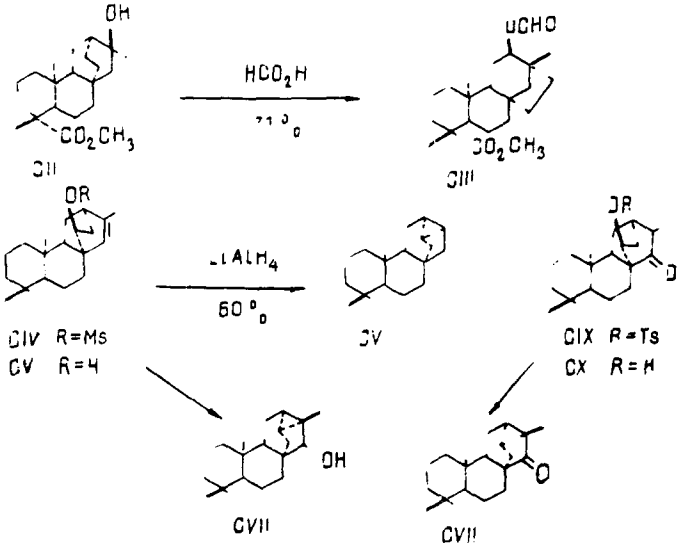
was obtained. An interesting paper [33] has recently appeared in which the rearrangement of the epoxy acetate (XCVII) under the action of ruthenium acetoacetonate is described. This gave a complex mixture of products among which were substances with kaurane structures, (XCVIII) and (XCIX), and with atisane (C) and stachane (CI) structures.



It follows from the facts given above that rearrangements of stachane (hibane) diterpenoids take place mainly with the formation of kaurane and atisane compounds.

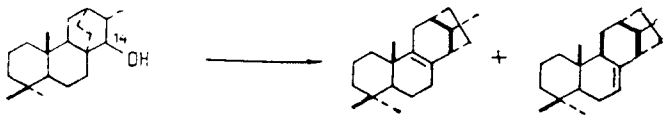
REARRANGEMENTS OF ATISANE DITERPENOIDS

A rearrangement of atisane diterpenoids was first described in [34]. The formolysis of the methyl ester of 13-hydroxy-ent-atisan-19-oic acid (CII) takes place fairly unambiguously and gives a high yield (71%) of a diester with a stachane structure (CIII) [17, 34].



An interesting and fairly rarely encountered rearrangement takes place on the reduction of the mesylate (CIV) of the ent-atian-13-en=15-ol (CV) with lithium tetrahydroaluminate [35]. In this case the ent-trachylobane (CVI) was obtained with a 60% yield. On the interaction of the same mesylate (CIV) with the methylsulfinylmethyl carbanion in dimethyl sulfoxide, a mixture of the ent-trachylobane compounds (CVII) (yield 30%) and CVIII (yield 60%) is formed [35]. The latter is the only product of the reaction of the tosylate (CIX) of the alcohol (CX) [36] under the same conditions.

Under the action of boron trifluoride etherate, atisan-14α-ol (CXI) isomerizes into a mixture of olefins with a new carbon skeleton, (CXII) and (CXIII) [37]. The latter has also been obtained in the interaction of the alcohol (CXI) with thionyl chloride.



CXI 14α-OH
CXIV 14α-OH

CXII CXIII

The dehydration of an epimer of the alcohol (CXI) [atisan-14β-ol (CXIV)] with phosphorous oxychloride also takes place with a rearrangement of the carbon skeleton and gives only the hydrocarbon (CXIII) [38].

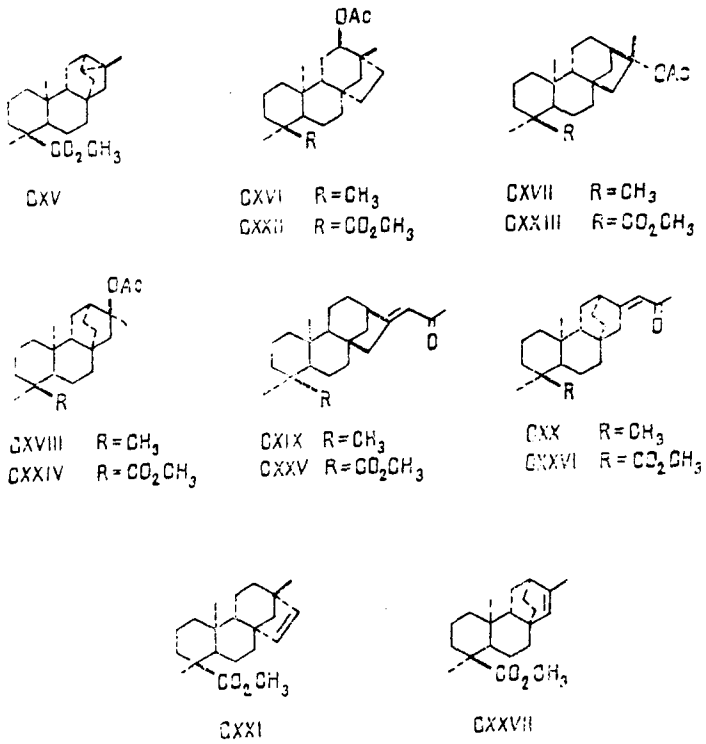
As has been shown [27], under the action of hydrogen chloride in chloroform atisene (XXVIII) is converted into an equilibrium mixture of the starting material and isoatisene (XXVII).

It can be seen from the information given that atisane diterpenoids containing functional groups at C-13 and C-14 isomerize with the formation of trachylobane, kaurane, and hibane structures or else give compounds with new carbon skeletons that have not so far been detected in natural sources.

REARRANGEMENTS OF TRACHYLOBANE DITERPENOIDS

As was to be expected, the most characteristic rearrangements for compounds of this unique class of pentacyclic diterpenoids, the molecule of which contains the structural fragment of the A/B rings that is typical for the labdanoid cyclic system, are those connected with the opening of the cyclopropane ring.

The acid-catalyzed rearrangement of trachylobane diterpenoids, and, namely, of ent-trachylobane (CVI) itself and of methyl ent-trachylobanoate (CXV) in acetic acid and acetic anhydride was first studied by French chemists [39]. As a result, from ent-trachylobane (CVI) were obtained compounds of the ent-atisane (XXVII), ent-beyerane (LXXXV), and ent-kaurane (CXVI)-(CXX) series, and from methyl ent-trachyloban-18-oate (CXV) the corresponding esters of the same structural series (CXXI)-(CXXVII).



CXV

CXVI R=CH$_3$
CXXII R=CO$_2$CH$_3$

CXVII R=CH$_3$
CXXIII R=CO$_2$CH$_3$

CXVIII R=CH$_3$
CXXIV R=CO$_2$CH$_3$

CXIX R=CH$_3$
CXXV R=CO$_2$CH$_3$

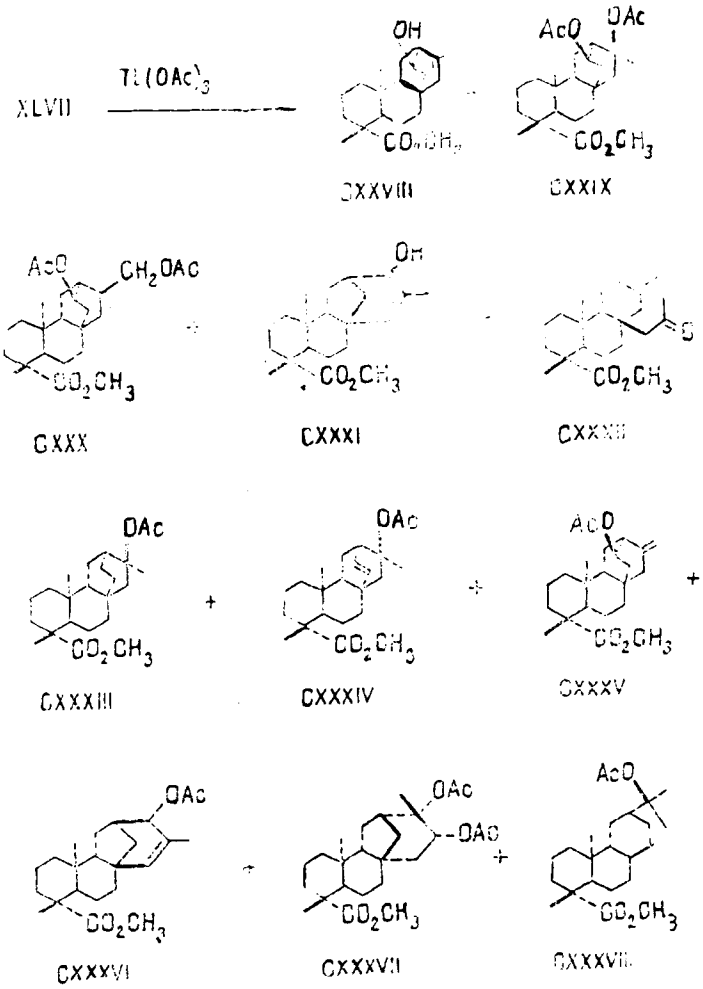
CXX R=CH$_3$
CXXVI R=CO$_2$CH$_3$

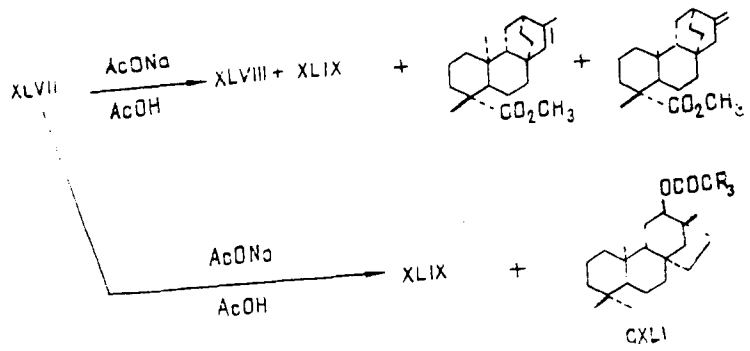
CXXI CXXVII

Thus, under the conditions described, cleavage of the carbon—carbon bonds of the cyclopropane ring take place in all three possible directions.

The isomerization of ent-trachylobane (CVI) under the action of hydrogen chloride takes place analogously, leading to a mixture of ent-kaurene (XVII), ent-isokaurene (XXI), ent-atisene (XXVIII), and ent-isoatisene (XXVII) [27].

Canadian chemists [40] have investigated the oxidative cleavage of methyl ent-trachyloban-19-oate (XLVII) under the action of thallium acetate and have obtained mixture of substances (CXXVIII)-(CXXX) with the atisane structure and compound (CXXXI) with a new carbon skeleton formed on the further rearrangement of the atisane system. Later [41], the minor products formed in this reaction (CXXII)-(CXXXVIII) were also isolated. Three compounds from this group, (CXXXVI)-(CXXXVIII), possess new carbon skeletons.





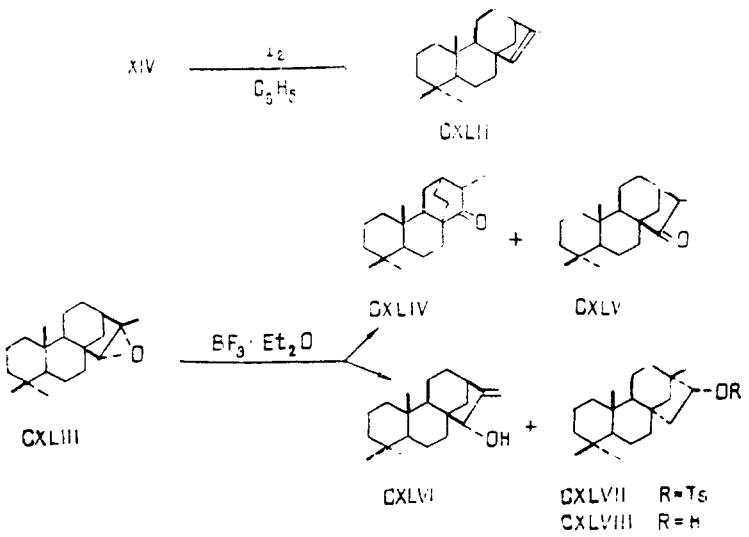
The solvolysis of the ester (XLVII) in acetic acid in the presence of sodium acetate leads to a mixture of the unsaturated esters (XLVIII), (XLIX), (CXXIX), and (CXL), while in trifluoroacetic acid the products are compounds (XLIX) and (CXLI) [9].

Thus, trachylobane derivatives rearrange under the action of acidic agents mainly into atisane, kaurane, and hibane compounds.

On the whole, however, only a few publications devoted to the study of the rearrangements of trachylobane diterpenoids are known.

REARRANGEMENTS OF PHYLLOCLADANE AND ISOHIBANE DITERPENOIDS

There are very few publications in the literature devoted to the isomerization of phyllocladane diterpenoids. Phyllocladane (XIV) itself is readily isomerized by iodine in boiling benzene into an equilibrium mixture with isophyllocladene (CXLII) [12].



The interaction of 15α,16α-epoxyphyllocladane (CXLIII) with boron trifluoride etherate in benzene has been studied in a number of investigations [37, 38, 43]. This interaction gave a mixture of neoisoatisan-14-one (CXLIV) and isokauran-15-one (CXLV). Performance of the reaction in ether leads to a mixture of the ketone (CXLVI) and the allyl alcohol (CXLVI), but in dimethyl sulfoxide only to the alcohol (CXLVI) [43].

On being boiled in collidine, the tosylate (CXLVII) of the isohibanol (CXLVIII) gives an equilibrium mixture of phyllocladene (XIV), isophyllocladene (CXLII), and isohibaene (XVI) [44]. The last-mentioned compound is isomerized by iodine in xylene into a mixture of the phyllocladenes (XIV) and (CXLII).

On generalizing the literature information on the isomerization of the kaurane (VIII), atisane (IX), hibane (X), and trachylobane (VII) diterpenoids that has accumulated in the literature at the present time it may be concluded that it completely confirms Wenkert's hypothesis. Compounds of each of these compounds functionalized at C-12—C16 under rearrangements into compounds of the other three structural types, while those with functional groups at C-12 may give (in addition to the "normal" rearrangement products according to Wenkert's scheme) compounds with a different carbon skeleton including five-membered rings C and D.

Judging from the as yet limited information existing in the literature, analogous transformations take place in the diastereomeric series of diterpenoids including the phyllocladane (XIV), neoatisane (XV), isohibane (XVI), and isotrachylobane (XIII) diterpenoids, although at the present time there are only a few publications devoted to this series of substances and by no means all their possible transformations have been confirmed in vitro.

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STEREOSELECTIVE SYNTHESIS OF A β-D-PHOSPHATIDYLGALACTOSE

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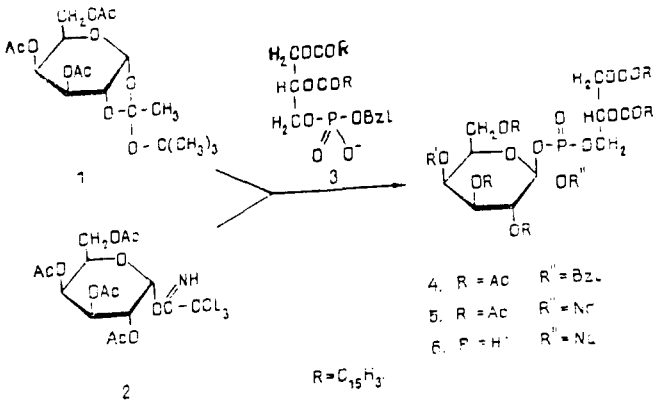
The stereoselective synthesis of a β-D-phosphatidylgalactose has been achieved by the interaction of a benzyl phosphatidate with D-galactose tert-butyl orthoacetate or trichloroacetimidate.

We have previously performed the synthesis of a β-D-phosphatidyl-glucose on the basis of the stereoselective phosphorylation of an orthoester or the trichloroacetimidate of D-glucose with a benzyl phosphatidate [1]. In a continuation of structural-functional investigations of glycophospholipids, in the present paper we describe the synthesis of a galactose-containing analogue of natural glycerophospholipids with the β-configuration of the glycosidic bond (6).

In the scheme developed, the starting compounds were D-galactose tert-butyl orthoacetate (1) and trichloroacetimidate (2) and a benzyl phosphatidate (3). The D-galactose orthoester (1) was obtained by the method of [2] from acetobromogalactose via a stage of the formation of the corresponding β-nitrate. D-Galactose trichloroacetimidate (2) was synthesized from acetobromogalactose by the saponification of the bromine [3] and treatment of the resulting 2,3,4,6-tetra-O-acetyl-D-galactopyranose with trichloroacetonitrile in the presence of sodium hydride [4]. The benzyl phosphatidate (3) was obtained by a known scheme [5].

The glycosylation of the benzyl phosphatidate (3) by the action of the D-galactose orthoester (1) and trichloroacetimidate (2) was performed at 18-20°C in anhydrous C_6H_6 and anhydrous CH_2Cl_2, respectively, with the use of a 10% excess of the phospholipid (3).



The pattern of the change in the composition of the reaction mixture was similar to that observed previously for the gluco analogue. However, the galactose derivatives (1 and 2) showed a somewhat lower reactivity on glycosylation by the benzyl phosphatidate (3) than the corresponding glucose derivatives. This was expressed in some increase in the reaction

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