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Skeletal rearrangements of monoterpenoids of the carane series

V A Chuiko, O G Vyglazov

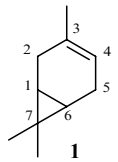
Contents

I.	Introduction	49
II.	Rearrangements of carane monoterpenoids occurring by the ionic mechanism	49
III.	Rearrangements occurring by the radical mechanism	52
IV.	Concerted reactions	54

Abstract. Data on rearrangements of monoterpenoids with the bicyclo[4.1.0]heptane skeleton occurring by ionic, radical and concerted mechanisms are generalised and analysed. The bibliography includes 135 references.

I. Introduction

One of the most widespread monoterpene hydrocarbons is 3-carene, or 3,7,7-trimethylbicyclo[4.1.0]hept-3-ene (**1**), which is a constituent of many essential oils and turpentines.[1,2]



1

The interest in 3-carene stems from the presence in its molecule of a *gem*-dimethylcyclopropane ring, a unique fragment, which is an important structural unit of many biologically active compounds. These include, for example, natural and synthetic pyrethroids, sterculic acid and its esters, aminocyclopropanecarboxylic acid derivatives, *etc*. In addition, 3-carene and related compounds, like other bicyclic terpenoids, can undergo various skeletal rearrangements. As a result, they are very promising models for studies in fundamental organic chemistry and are useful starting compounds for the synthesis of valuable products: sesquiterpenoids,[3] pheromones,[4] juvenoids,[5] pyrethroids[6,7] and fragrance compounds.[7–9]

The currently known skeletal rearrangements of compounds of the carane series result in several types of structure, namely, with bicyclo[3.1.0]hexane, bicyclo[3.2.0]heptane, *p*- and *m*-menthane and 1,1,4-trimethylcycloheptane skeletons. According to their mechanisms, these rearrangements are classified as ionic, radical and concerted.

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The available reviews on carane-type monoterpenoids were mainly written more than 25 years ago. They do not reflect the diversity of skeletal rearrangements studied over the past decades. A detailed review by Arbuzov and Isaeva[10] dealt with rearrangements that occur by the ionic mechanism. Yet another review[11] mainly describes rearrangements of carane monoterpenoids in which the cyclopropane ring opening affects the 'external' bonds to give compounds of the *p*- and *m*- menthane series.

The extensive monograph 'Chemistry of Monoterpenes' by Erman[12] provides an excellent and systematic description of data on reactions of monoterpenes and on the mechanisms of these reactions; however, the experimental data on the transformations of terpenoids belonging to the carane series only includes literature data published before 1976. Since then, new results have been obtained, and new concepts on the mechanisms of certain reactions discussed in the monograph cited have appeared. The reviews that are published from time to time[13,14] just state the facts rather than analyse them, therefore they generally do not consider or discuss the mechanisms of the transformations described. The most recent reviews dealing with the rearrangements of terpenoids[3,15,16] give almost no consideration of the transformations of compounds with the carane skeleton.

The purpose of the present review is to generalise data on the skeletal rearrangements of terpenoids belonging to the carane series accumulated over the time period since the publication of reviews by Arbuzov and Isaeva[10] and by Erman.[12] Earlier publications are only considered if the history of the problem is of interest or if a new understanding of the known facts has appeared. The rearrangements are discussed according to their mechanisms. The most thorough attention is given to concerted rearrangements, because these data have not been generalised or discussed so far.

II. Rearrangements of carane monoterpenoids occurring by the ionic mechanism

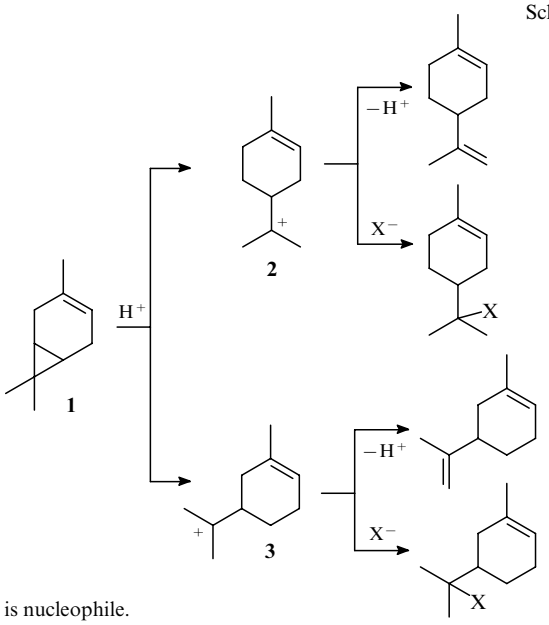
The realisation of the ionic mechanism in molecular rearrangements of carane monoterpenoids is due to the interaction of the cyclopropane ring with the electron-deficient carbenium centre at the α- or β-position with respect to the ring. Rearrangements of this type are of interest because they can provide intermediates with a delocalised charge. According to the classification suggested in the review by Arbuzov and Isaeva,[10] ionic rearrangements of carane structures are divided into homoallylic rearrangements, rearrangements with the transannular involvement of the cyclopropane ring (CPR) and the Wagner – Meerwein rearrangements with contraction of the six-membered ring. However, this classification does not reflect the diversity of ionic

rearrangements of carane structures and is arbitrary. The homoallylic rearrangement is not the only one of the possible skeletal transformations *via* a carbocation with a delocalised charge: carane structures containing double bonds can also contain a pentadienyl-type cation; the latter may be formed in different ways from different compounds. In addition, we believe that it is more correct to consider rearrangements with transannular involvement of the CPR and the Wagner – Meerwein rearrangements together with concerted reactions because they involve alkyl shifts in charged systems.

1. Carbenium-ion rearrangements

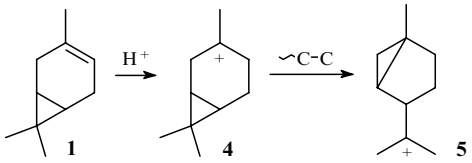
A molecule of 3-carene contains two reactive fragments: a double bond and a cyclopropane ring. Both of these fragments have enhanced electron density, which makes the molecule reactive with respect to electrophilic agents. The rearrangement of 3-carene which occurs under the action of acids to give compounds of the *p*- and *m*-menthane series is well known.[12] It is likely that in this case the cyclopropane ring acts as an isolated reaction centre to form carbenium ions **2** or **3** (Scheme 1). The double bond is remote and does not interact with the carbon atom which carries a positive charge. The ions are stabilised by elimination of a proton or by capture of a nucleophile.

Scheme 1



X^- is nucleophile.

This transformation occurs in those cases where the CPR is initially protonated. Obviously, the addition of a proton to the double bond of the hydrocarbon **1** should give a tertiary ion **4**.

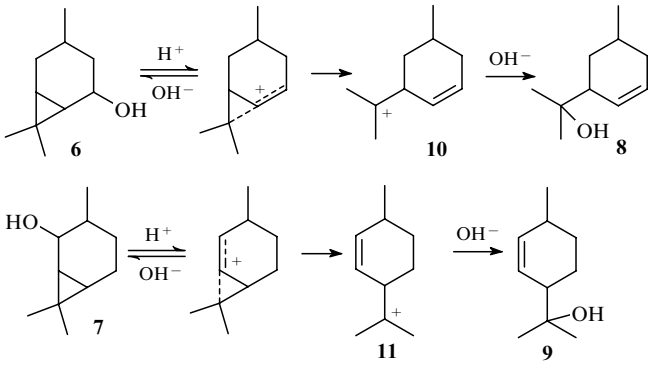


Ions of this type can undergo a rearrangement due to the so-called 'transannular cyclopropyl participation'[10] (see Section IV.4), but this would result in an ion **5** and other products.

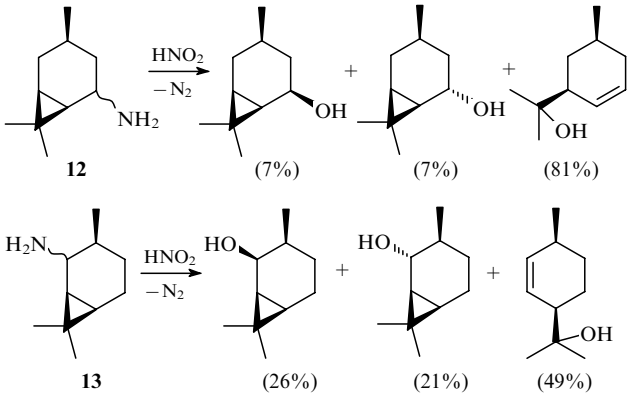
The fact that it is the CPR rather than the double bond that is protonated in the case of 3-carene can be rationalised in terms of the HSAB (Hard – Soft Acid – Base) principle. Cyclopropane is a harder base than the double bond (the ionisation potentials are 10.9 and 9.3 eV, respectively). In a molecule of 3-carene, the difference between the energies of the highest occupied molecular orbitals (HOMO) of the corresponding fragments is somewhat smaller but still rather high (9.16 and 8.61 eV).[17] A hard acid, *viz*., a proton, is first added to the hard base, *viz*., the CPR. In fact, the reaction between equimolar amounts of 3-carene and hydrogen chloride gives derivatives with *p*- and *m*-menthane skeletons.[18] The similarity of the electronic structures of the double bond and the CPR [19] predetermines the similarity of their reactivities.[20] The existence of a cationoid site at the α-position with respect to the cyclopropane ring results in their conjugation and formation of a homoallylic ion. The direction of the reaction of this ion with a nucleophile depends on spatial factors, on the nature of the leaving group and on the degree of solvation of the molecule (in solvolysis reactions), *etc*.

If the subject of the attack in the homoallylic ion is the CPR, the latter is opened; in carane derivatives, a skeletal rearrangement occurs.

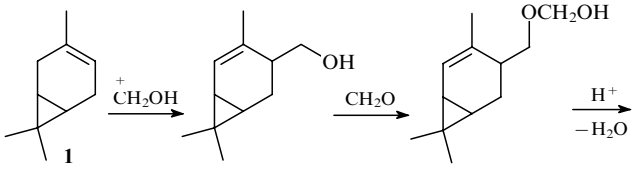
For example, under conditions of acid catalysis, caran-5-ol (**6**) and caran-2-ol (**7**) are isomerised to *m*- (**8**) and *p*-menthen-8-ols (**9**), respectively, as a result of a hydroxide attack on the C(8) atom in homoallylic ions **10** and **11**.[21, 22] These reactions can be considered as regiospecific.

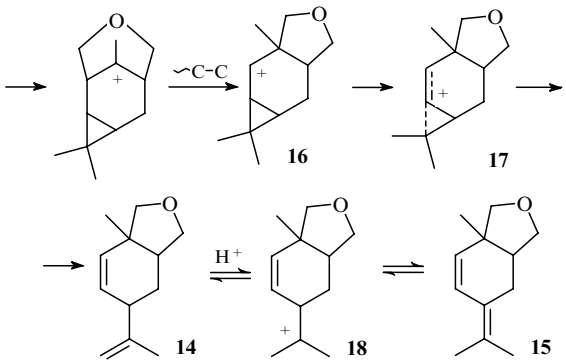


Deamination of 5- (**12**)- and 2-aminocaranes (**13**) occurs in a similar way; however, the presence of bicyclic alcohols among the products shows that the reaction was not completed in this case.[23]



Homoallylic rearrangements can occur along with other ionic rearrangements. For example, the Prins condensation of 3-carene with formaldehyde gives, among other reaction products, two cyclic ethers **14** and **15**. Their formation is explained by the occurrence of the Wagner – Meerwein rearrangement followed by a homoallylic rearrangement.[24, 25]

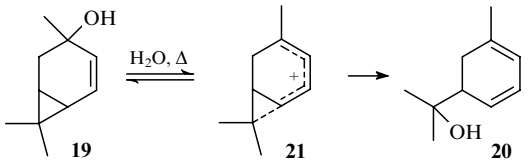




In this case, the Wagner–Meerwein rearrangement, which occurs as an alkyl shift, does not change the carane structure. However, the alkyl shift is only possible because the charge delocalisation in the secondary ion **16** with involvement of the cyclopropane ring results in ring opening to give the homoallylic ion **17** which has a lower energy. The ion **17** is stabilised by elimination of a proton from one of the geminal methyl groups giving the ether **14**. In an acidic medium, this ether isomerises to the ether **15** *via* the classical cation **18**.

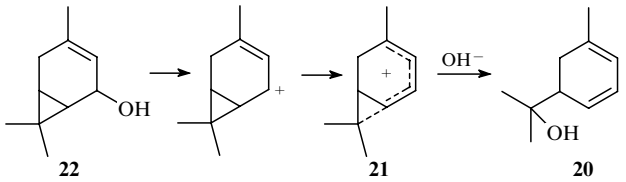
2. Rearrangements that occur *via* ions with a high degree of charge delocalisation

Obviously, the system CPR–charged carbon atom can comprise one or more double bonds. The resulting homopentadienyl ion has a higher degree of charge delocalisation, and hence a lower energy, than the homoallyl ion. Therefore, reactions involving homopentadienyl ions occur more readily than those involving homoallyl ions. The isomerisation of 4-caren-3-ol (**19**) to hydroxydiene **20** occurs upon boiling in water, even in the absence of acid catalysts:[26]

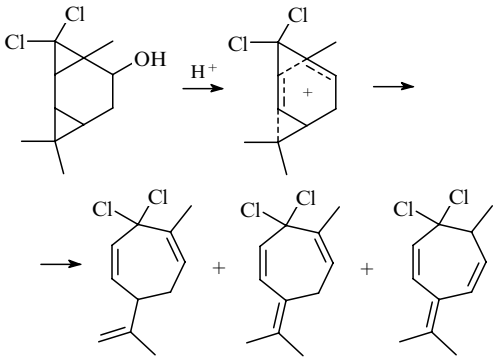


As in the isomerisation of compounds **6** and **7**, the irreversibility of the attack on the cyclopropane fragment of the ion **21** makes the reaction regiospecific.

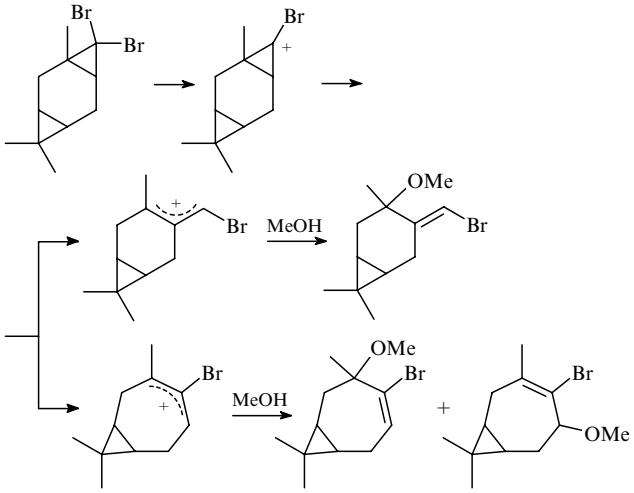
It should be noted that the neighbourhood (and, possibly, conjugation) of the double bond and CPR in a neutral molecule is not prerequisite for the formation of a homopentadienyl ion and hence, for a skeletal rearrangement. From the viewpoint of the reaction mechanism, the selective isomerisation of car-3-en-5-ol (**22**) to *m*-mentha-1,3-dien-8-ol (**20**) is of interest: the double bond and the CPR are united in a conjugated system by a carbocationic centre that is formed between them.[27]



The conjugated system cationoid centre–CPR can involve not only the adjacent double bond but also the second three-membered carbocycle. The involvement of such an intermediate in the reaction results in the rearrangement of the tricyclooctane skeleton into a substituted cycloheptadiene.[28] This rearrangement is interesting because in this case it is the internal bond of the *gem*-dichlorocyclopropane ring that cleaved, whereas it is the external bond that cleaved in the *gem*-dimethylcyclopropane ring.

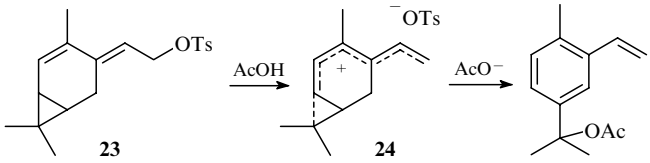


It is evident from the examples of ionic rearrangements presented above that the cleavage of the 'external' bond is a rule, which has almost no exceptions, for the *gem*-dimethylcyclopropane ring. On the contrary, the three-membered ring with two halogen atoms behaves in different ways. In the methanolysis of the adduct of 3-carene with dibromocarbene, the CPR opens in two ways, giving rise to both products with the retention of the carane structure and to rearrangement products.[29]



The fact that different bonds of the three-membered rings are cleaved in ionic reactions may be due to the nature of geminal substituents. The *gem*-dimethyl group shortens (and strengthens) the opposite cyclopropane bond,[30] whereas two geminal chlorine atoms lengthen and weaken this bond. The effect of geminal bromine atoms has the same direction but is weaker.[31]

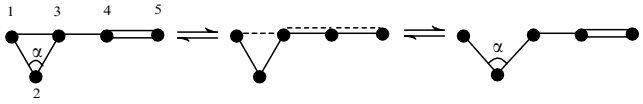
Acetolysis of toluene-*p*-sulfonate **23** occurs extremely readily;[32] in this case, the degree of charge delocalisation in the intermediate (homoheptatrienyl ion **24**) is even higher than that in the homopentadienyl ion.



Ts = $SO_2C_6H_4Me$-4.

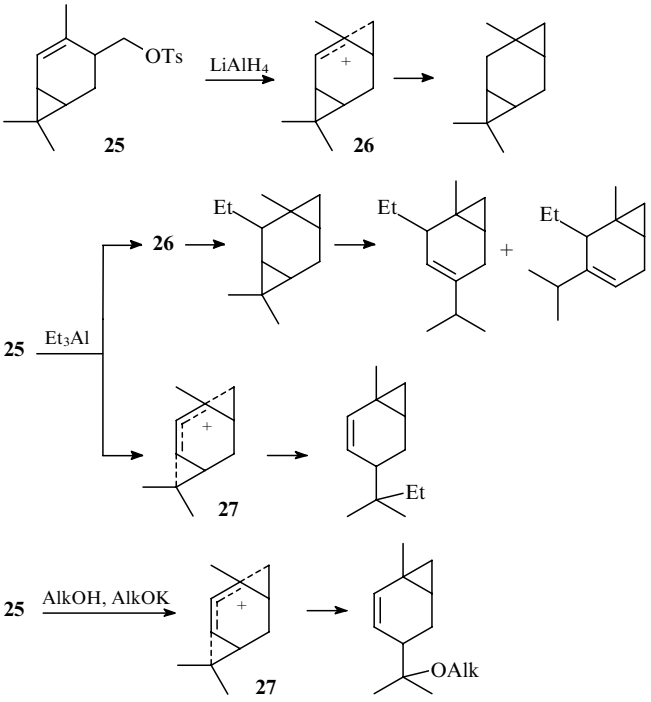
It was mentioned above that homoallylic and homopentadienyl rearrangements are irreversible; however, this statement is not quite correct. In fact, such transformations of carane derivatives can be carried out with a 100% degree of conversion. This is due to the geometry of the ion and the resulting molecule. The C(2) atom of the CPR, which is not involved in the conjugation chain, changes its hybridisation from sp^2 to sp^3 in the process of stabilisation of the homoallyl ion. As a result, the C(1)–C(2)–C(3) angle, which equals 60° in the cyclopropane molecule, increases to 109° in the molecule formed; in turn, this increases the distance between C(1) and C(3). However, if these

atoms are brought closer in some way, the formation of a homoallyl ion becomes possible again.



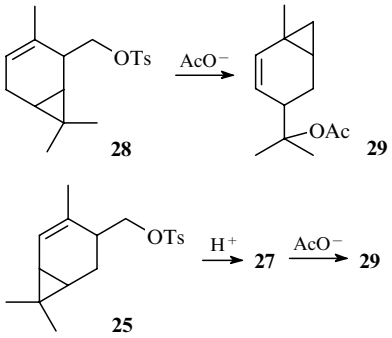
α = 60° α = 109°

In practice, compounds with the menthane skeleton are never transformed into carane-type compounds. However, it was in the carane structures (owing to their specific features) that it was possible to observe the retro-homoallylic rearrangement, in which a homoallyl ion is formed from a linear fragment of the molecule and the three-membered ring is closed. Such an effect was observed in the reaction of toluene-*p*-sulfonate **25** with lithium aluminium hydride [33] or triethylaluminium,[34] as well as upon its solvolysis.[35]

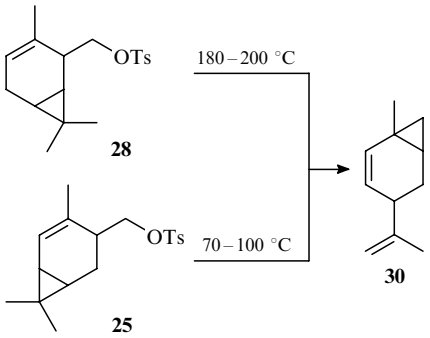


Obviously, in an ideal case, this reaction should occur according to the S_N1 mechanism. However, it is likely that the reaction involves contact ion pairs: very strong polarisation of the substrate occurs, with an almost complete charge separation; however, the resulting cation is stabilised by the counter-ion. Elimination of the toluene-*p*-sulfonate group from compound **25** gives a cation with a charge on the primary carbon atom; it is much less stable than the tertiary ions formed upon protonation of the CPR. The ion can be stabilised due to conjugation of the charged atom with the double bond; in this case, the p-orbitals overlap through space rather than through the σ-bond. The tight solvate environment favours the approach of these fragments, because the process is likely to be fast. This pathway gives the homoallyl ion **26** and/or the dihomopentadienyl ion **27**. If the reaction occurs *via* the intermediate ion **27**, quite an unusual rearrangement occurs: in fact, one molecule undergoes two rearrangements in different directions simultaneously, *viz*., a homoallylic rearrangement, which results in the cyclopropane ring opening, and a retro-homoallylic rearrangement where a new three-membered carbocycle is closed.

It is appropriate here to note a very interesting fact: both 2-tosyloxymethyl-3-carene (**28**) and 4-tosyloxymethyl-2-carene (**25**) give the same ether **29** upon acetolysis.[36]



The mechanism of the formation of the acetate **29** remains obscure so far. It is also of note that no products are formed which might be expected based on the data on the transformations of the ester **25**. The authors of the present review have observed yet another, rather unusual transformation of the toluene-*p*-sulfonate **28**: its pyrolysis results in the same hydrocarbon as that formed from the toluene-*p*-sulfonate **25**, *viz*., 1-methyl-4-isopropenylbicyclo[4.1.0]hept-2-ene (**30**).[36]



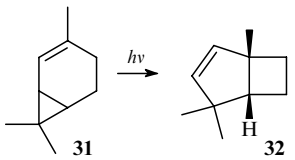
The pyrolysis mechanism of the ester **25** [37] will be discussed below, along with the possible mechanism of the pyrolysis of the toluene-*p*-sulfonate **28**.

Certainly, the mechanisms of ionic rearrangements involving ions with charge delocalised along the conjugation chain are hypothetical and are based on the structures of the final products. It is still unclear whether conjugation in such systems is really possible. As shown below when discussing hydrogenation of 2-carene (**31**), the neighbourhood of a double bond and the CPR by no means ensures their conjugation, at least for a neutral molecule in the ground state.[17, 38] It would be highly important to use modern quantum-chemical calculation methods in order to check whether charge delocalisation is possible in a conjugation system, which involves a CPR as an element, in rearrangements of compounds belonging to the carane series.

III. Rearrangements occurring by the radical mechanism

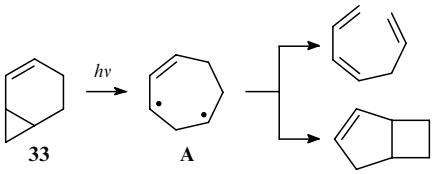
Generally, radical rearrangements of monoterpenoids belonging to the carane series occur in photochemical reactions. The photochemical transformations of such compounds have been reviewed in detail.[12] Here we consider only those which involve radicals, with emphasis on non-trivial skeletal rearrangements.

For 3-carene, no rearrangements under irradiation have been observed. Only its photochemical oxidation to give three hydroperoxides has been reported.[39] Upon irradiation in the presence of a sensitiser, the isomeric 2-carene is rearranged into 1,4,4-trimethylbicyclo[3.2.0]hept-2-ene (**32**), which has been employed in the synthesis of grandisole.[4]



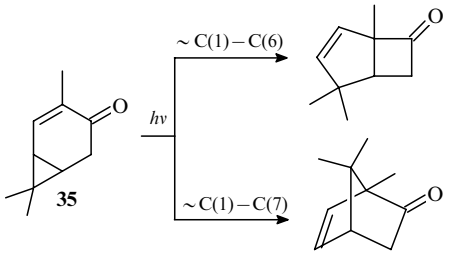
31 **32**

The rearrangement mechanism was not studied in this case; however, the mechanism for a related compound, *viz*., 2-norcarene (**33**), has been reported.[40] Irradiation of compound **33** resulted in *cis*-hepta-1,3,6-triene as the main product, *i.e*., the $[2\pi + 2\omega + 2\sigma]$-process predominated. The formation of a small amount of bicyclo[3.2.0]hept-2-ene (**34**) allowed the authors to assume a common biradical intermediate **A** with a seven-membered ring:



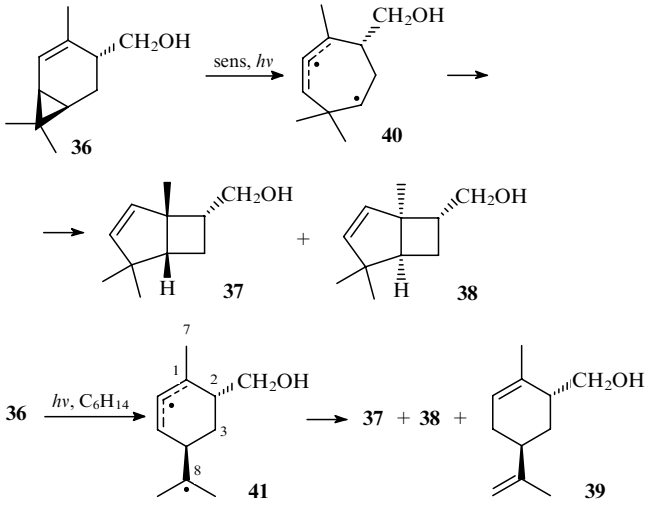
33 **A** **34**

There is a viewpoint [12, 41] that the formation of compounds with the bicyclo[3.2.0]heptane skeleton from certain carane terpenoids upon irradiation can occur as a photo-induced sigmatropic rearrangement. This assumption is supported by the fact that a bornene structure is formed in parallel from ketone **35**.



35

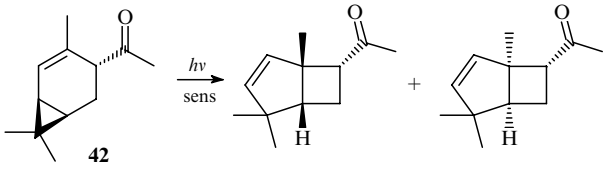
The concerted mechanism of rearrangement of ketone **35** is indirectly supported by the results of irradiation of 4-hydroxymethyl-2-carene (**36**) with a high-pressure mercury lamp:[42] if a sensitiser is present, only stereoisomeric bicyclic alcohols **37** and **38** are formed, whereas direct irradiation in hexane gives rise to a monocyclic alcohol, *viz*., compound **39**, in addition.



36 **40** **37** **38** **41** **39**

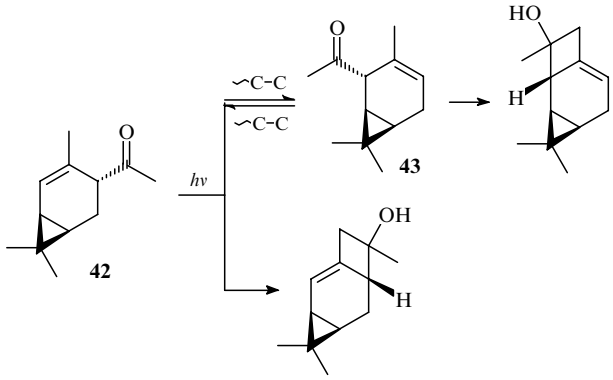
Kropp, who studied this reaction,[42] drew an analogy with a 1,3-conjugated system and postulated the formation of allyl radicals. In this case, the CPR can undergo homolytic opening with cleavage of an internal and of one of the external bonds. Probably, if a sensitiser is present, the molecule is transformed to biradical **40** from the triplet state: in this case, the weakest bond in the CPR is cleaved. In the singlet excited state, the molecule has higher energy, resulting in the cleavage of both possible bonds in the CPR. In this case, cleavage of the C(1)−C(7) bond occurs rather than its shift. Obviously, recombination and formation of a new bond between the C(1) and C(8) atoms in radical **41** (which would result in a bornane skeleton) are impossible because the distance between these atoms is larger than that between the atoms with unpaired electrons in biradical **40**.

Irradiation of 4-acetyl-2-carene (**42**) in the presence of a sensitiser gives products with the bicyclo[3.2.0]heptane structure,[43] *i.e*., replacement of a hydroxymethyl group by an acyl group does not alter the mechanism.



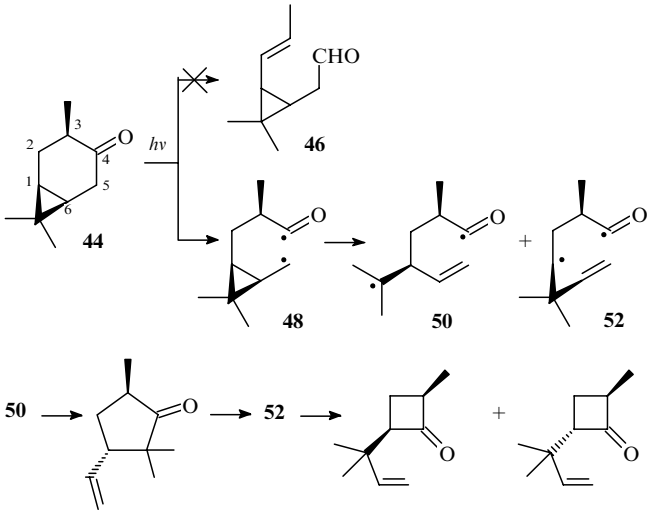
42

However, irradiation of the ketone **42** in the absence of sensitisers results in a fundamentally different rearrangement leading to the product of a 1,3-acyl shift [2-acetyl-3-carene (**43**)] and to tricyclic alcohols, *i.e*., the Norrish type II cyclisation products of both ketones present in the reaction medium.[43]

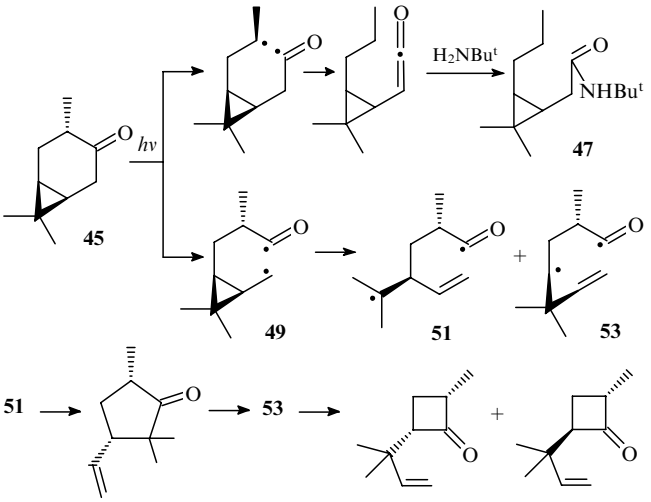


42 **43**

A somewhat unusual behaviour of *cis*- (**44**) and *trans*-4-caranone (**45**) is observed in their irradiation. Although the structures of these molecules enable the Norrish type II cleavage of two bonds, *viz*., C(3)−C(4) and C(4)−C(5), the phototransformation products of *cis*-caranone (**44**) only contained compounds formed as a result of the C(4)−C(5) bond cleavage.[44]



44 **46** **48** **50** **52**



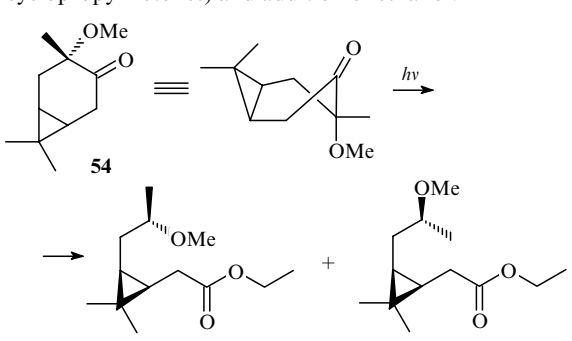
Contrary to expectations, no formation of aldehyde **46** or epimerisation of the ketone **45** was observed. However, upon irradiation of the latter in the presence of *tert*-butylamine, the reaction products contained a small amount (> 1%) of amide **47**, which indicated that homolytic cleavage of the C(3) – C(4) bond does occur but quite insignificantly.

Formally, the photochemical behaviour of ketones **44** and **45** is very similar to the allylic rearrangements of β,γ-unsaturated ketones.[45] Kropp *et al.*[44] believed that the photochemical rearrangement of caranones **44** and **45** is the first example of the cyclopropyl analogue of the photochemical allylic rearrangement. However, the reaction is reversible for β,γ-unsaturated ketones and irreversible for ketones **44** and **45**.

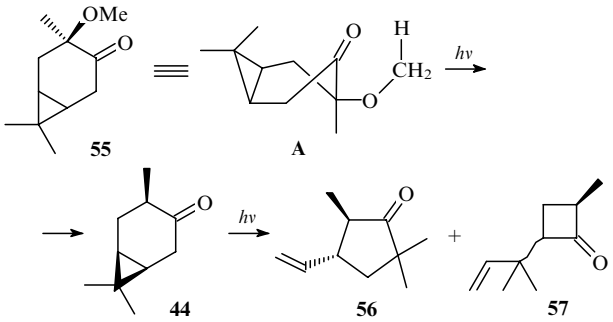
By analogy with β,γ-unsaturated ketones, the direction of α-cleavage of carbon – carbon bonds is presumably determined by the 'allylic' effect of the CPR, which weakens the C(4) – C(5) bond owing to either the conjugation or inductive effect. In the radicals **48** and **49** formed, the C(1) – C(6) or C(1) – C(7) bonds should be cleaved. The ratio of cyclopentanones and cyclobutanones in the reaction products (3 : 1) reflects the preferential cleavage of the more substituted C(6) – C(7) bond and the comparative stability of the tertiary (**50**, **51**) and secondary (**52**, **53**) radicals.

There is yet another difference between allylic photochemical rearrangements of β,γ-unsaturated ketones and similar rearrangements of cyclopropyl ketones. The allylic rearrangement is believed to be a concerted process.[45] However, Heckert and Kropp [44] consider that the transformations of caranones **44** and **45** cannot be a concerted reaction, at least as judged by the formation of epimeric cyclobutanones.

The direction of the skeletal photochemical rearrangement of terpenoids belonging to the carane series depends on the orientation of substituents: direct irradiation of *trans*-3-methoxy-4-caranone (**54**) in ethanol occurs with opening of the six-membered ring with cleavage of the C(3) – C(4) bond (which is non-typical of β,γ-cyclopropyl ketones) and addition of ethanol.[39]



In the case of *cis*-3-methoxy-4-caranone (**55**) with an equatorial methoxy group, the only reaction observed is the Norrish type II elimination, resulting in the caranone **44**; the required planar six-membered transition state (TS) **A** is formed readily, and the formation of the ketone **44** competes successfully with the cleavage of the C(3) – C(4) bond.[39]



When exposed to light, the ketone **44** undergoes homolytic cleavage of the C(4) – C(5) bond and homoallylic rearrangement, which is typical of β,γ-cyclopropyl ketones.[44,46] This reaction gives cyclopentanone **56** and cyclobutanone **57**.

Thus, the photochemical rearrangements of carane monoterpenoids may be divided in two groups, *viz.*, those where the cyclopropane part of the carbon skeleton and the double bond serve as the chromophores, and those where this role is played by a functional substituent. In the presence of sensitisers, rearrangements of the former type occur, giving rise to bicyclo[3.2.0]heptane derivatives. Irradiation in the absence of sensitisers generally results in rearrangements of the latter type; in this case, the following reactions are possible: opening of the large or small ring, contraction of the large ring or formation of a tricyclic structure. In each specific case, the direction of the reaction depends on the nature and position of the substituent which acts as the chromophore.

IV. Concerted reactions

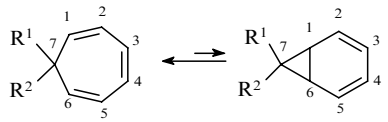
Ionic reactions of carane compounds are dealt with in numerous publications and these works have repeatedly been systematised, whereas concerted transformations have been studied to a much lesser extent, and the results have not been generalised so far. To be fair, it should be noted that not all reactions attributed to the concerted type actually correspond to this type. For example, in the case of 2,4-caradiene (**58**), the 1,5-thermal shift is formally a concerted sigmatropic reaction. However, first, this occurs *via* a biradical intermediate rather than *via* a cyclic TS (with simultaneous cleavage and formation of C – C bonds); second, it is not a sigmatropic process in essence. In certain cases, the concerted mechanism involves a strongly polarised TS or is coupled with the ionic mechanism. However, the reaction classification would be overcomplicated if these features were taken into account; therefore, in this section we shall discuss the transformations which are traditionally attributed to concerted reactions.

We believe that a survey of such reactions of carane monoterpenoids is especially interesting because it is these that sometimes result in unique transformations that are characteristic only of these compounds (for example, the Berson – Willcott rearrangement [47]). Studies of concerted reactions expand substantially our knowledge about the mechanisms of chemical reactions in general.

1. Norcaradiene – cycloheptatriene interconversion

One of the most interesting skeletal transformations of carane structures, *viz.*, rearrangements which relate terpenoids of the carane and 1,1,4-trimethylcycloheptane series, attracted the attention of researchers; this resulted in the discovery of such a remarkable phenomenon in organic chemistry as the norcaradiene – cycloheptatriene 'rapid' equilibrium. Many studies on this subject have been carried out in the last third of the twentieth century.[47–55] The fast equilibrium of the valence tautomers of norcara-2,4-diene (**59**) and cyclohepta-1,3,5-triene (**60**) is caused

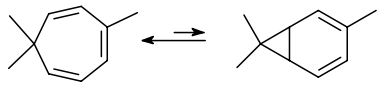
by a typical concerted reaction, *viz*., disrotatory opening and closure of the three-membered carbocycle; this process obeys the conservation of orbital symmetry rules formulated by Woodward and Hoffmann.[56]



60 **59**

For the unsubstituted hydrocarbon ($R^1 = R^2 = H$), this equilibrium is so much shifted to the monocyclic tautomer **60** that norcaradiene could not be detected by any physical method. Its existence was postulated on the basis of the behaviour of substituted analogues ($R^1 = CN$, $R^2 = CF_3$; $R^1 = CO_2Me$, $R^2 = Ph$; $R^1 = CO_2Me$, $R^2 = C_6H_4OMe$-4), which were found as equilibrium mixtures with the corresponding cycloheptatrienes in low-temperature NMR studies of the latter.[55] It was only in 1981, a quarter of a century after the hypothesis about the valence tautomerism of cycloheptatriene appeared, that unsubstituted norcaradiene was detected during the low-temperature (77 K) photolysis of tricyclo[3.2.2.$0^{2,4}$]non-6-ene-8,9-dione.[57]

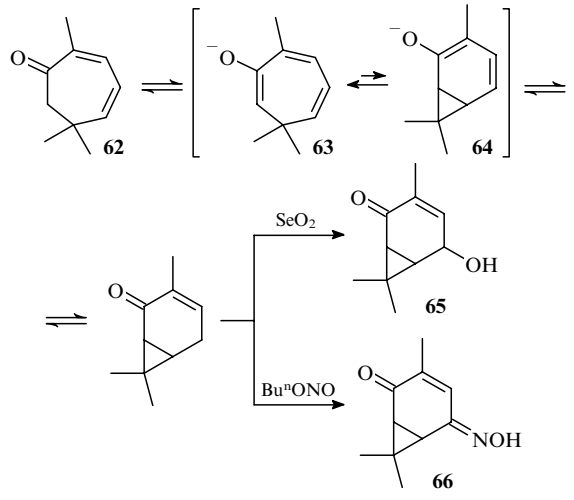
It was found experimentally that the bicyclic structure can be stabilised by π-accepting substituents at position 7.[55] An elegant explanation of the nature of this stabilisation was given by R Hoffmann within the framework of the frontier MO method.[53] Obviously, methyl substituents cannot serve as stabilisers; therefore, the equilibrium for the system 2,4-caradiene (**58**) – 3,7,7-trimethylcyclohepta-1,3,5-triene (**61**) is always shifted towards the monocyclic partner. However, these valence tautomers are different compounds that really exist. They possess different reactivities, which should be reflected (and is actually reflected, as will be shown below) in chemical reactions.



61 **58**

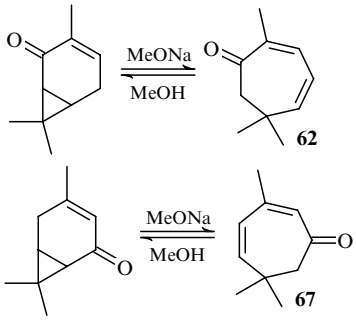
Rearrangements caused by valence tautomerism described above will be discussed in more detail than ionic rearrangements, because the tautomerism of norcaradiene has almost not been considered in Russian scientific literature. Unfortunately, even researchers who work in the field of terpenoid chemistry employ insufficiently substantiated hypotheses to explain the expansion of the carane skeleton to the cycloheptane one.[12, 58]

The cycloheptatriene – norcaradiene rearrangement has been discovered in a study of the chemical transformations of eucarvone [2,6,6-trimethylcyclohepta-2,4-dienone (**62**)], a terpenoid first synthesised by Baeyer [59] and then discovered in the essential oils of various plants.[60]



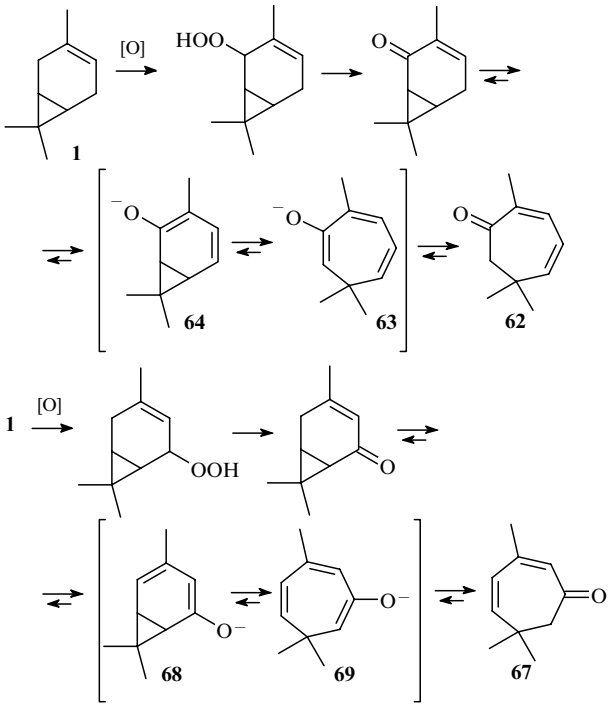
62 **63** **64** **65** **66**

The hypothesis about the valence tautomerism of mono- and bicyclic enols **63** and **64** as a possible explanation of the skeletal rearrangement of the ketone **62** during the formation of 3,7,7-trimethyl-5-hydroxy-3-caren-2-one (**65**) and 3,7,7-trimethyl-5-oxyimino-3-caren-2-one (**66**) was put forward in 1956.[61, 62] It was then found that rearrangements of carane derivatives into trimethylcycloheptane ones are much more common, because the equilibrium in the dynamic interconversion of the two tautomers is strongly shifted toward the monocyclic partner.[63]



62 **67**

2,5,5-Trimethylcyclohepta-2,4-dienone (**67**), like the ketone **62**, has been found in the turpentines obtained from *Pinus silvestris L.*[64] Probably, the presence of these ketones in turpentine oil is explained by the formation, during plant growth, of carane-type unsaturated ketones from 3-carene (one of the major turpentine components); these are then transformed into monocyclic dienones in a concerted electrocyclic reaction. This is supported by the results of liquid-phase oxidation of 3-carene: the percentage of ketones **62** and **67** in the reaction products was 20% and 28%, respectively.[65]



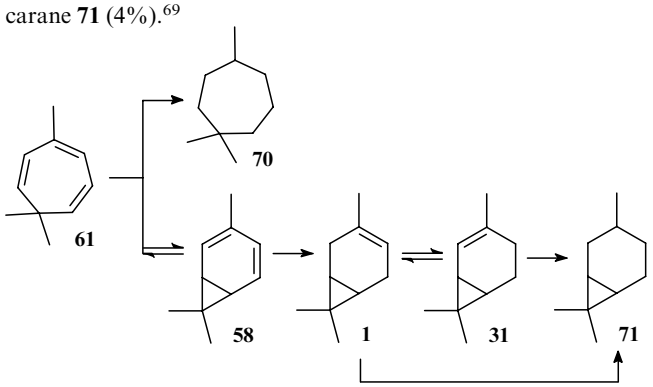
1 **64** **63** **62** **1** **68** **69** **67**

It should be noted that the **64** → **63** and **68** → **69** rearrangements represent the only currently feasible explanation of the presence of seven-membered ketones in essential oils. The general scheme of the biogenesis of terpenes [66, 67] does not envisage any formation of such compounds at all. However, the widespread occurrence of 3-carene and its derivatives in nature and also the fact that trimethylcycloheptanes are only present in those essential oils which contain carane-type terpenoids, may be considered as indirect evidence in favour of the assumption about the formation of terpenoids with a seven-membered ring. We believe that the assumption that eucarvone (**62**) can be formed during biosyn-

thesis [12] in the same way as Baeyer [59] had synthesised it, *viz*., by hydrobromination of carvone followed by dehydrobromination of the resulting 8-bromo-1-menthen-6-one, is much less likely.

Finally, a serious argument in favour of the **58** → **61** rearrangement as the reason for the formation of cycloheptane terpenoids both *in vitro* and *in vivo* is the detection of triene **61** in pine turpentine oil and in oleo-resin from certain pine (*Pinus silvestris*) trees.[68] Since this triene coexists with cara-2,4-diene, which is present in turpentine and in oleo-resin, it may be concluded that 2-carene, which is also present in turpentine, can undergo catalytic (enzymic) dehydrogenation.

The dual nature of triene **61** is very evident in its hydrogenation: reaction products of incomplete hydrogenation contain not only trimethylcycloheptadienes and trimethylcycloheptenes but also 3-carene (**1**) and 2-carene (**31**). Exhaustive hydrogenation results in a mixture of 1,1,4-trimethylcycloheptane (**70**, 96%) and carane **71** (4%).[69]



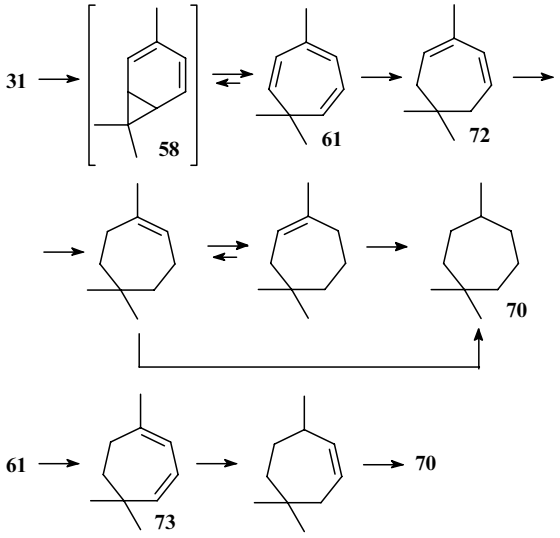
Certainly, the ratio of the final hydrogenation products (**70** : **71** = 96 : 4) does not reflect the content of the tautomers in the original equilibrium mixture. A comparatively large percentage of carane **71** may be due to the fact that the planar diene system of caradiene **58** competes successfully with non-planar diene parts of the triene **61** in the 1,4-addition of hydrogen.

3-Carene is hydrogenated in an unusual way. Cocker *et al*.[70] discovered in 1966 that hydrogenation of 3-carene over platinum results in a mixture of compounds **71** (98%) and **70** (2%), whereas hydrogenation over palladium gives rise to the hydrocarbon **70** as the major product (74%).[70] It was found later that hydrogenation of 3-carene on a copper–nickel catalyst results exclusively in 1,1,4-trimethylcycloheptane (**70**).[58] The authors of both studies believed that this reaction pattern was due to the isomerisation of 3-carene (**1**) to 2-carene (**31**) and 1,4-addition of hydrogen to the vinylcyclopropane system of the latter to give a hydrocarbon with a seven-membered ring.

It was implied that the possibility (or impossibility) of 1,4-addition, which is the key step of the rearrangement, depends on the nature of the catalyst. However, 1,4-addition is only possible if there is conjugation in the diene fragment (or a homodiene fragment in the hydrocarbon **31**). However, the molecule of terpene **31** is in the planar chair-like conformation,[38] which casts doubts that such conjugation is possible. The photoelectron spectrum shows that the π-orbital and the HOMO of the dimethylcyclopropane ring in the molecule of compound **31** essentially do not interact.[17] The impossibility of 1,4-addition for the 2-carene molecule (**31**) has been confirmed experimentally.[71] It was shown that the reaction of singlet oxygen, which is an extraordinarily reactive dienophile, with this terpene gives only allylic hydroperoxides, whereas its other reactions, *e.g*., with α-phellandrene and α-terpinene, give endoperoxides, which are 1,4-addition products.

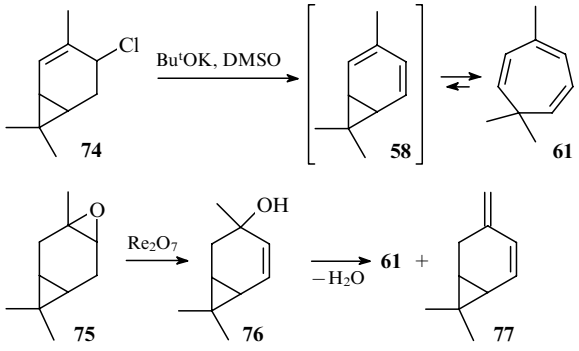
In their discussion of the reaction mechanism, Cocker *et al*.[70] did not take their own results into account: if palladium was used as the catalyst, the content of hydrocarbon **70** increased with the increase in the hydrogenation temperature and was 100% at temperatures above 70 °C, *i.e*., the ratio of the reaction products is primarily affected by temperature. A similar temperature dependence was established later for hydrogenation over platinum: at 20 °C, the percentage of hydrocarbon **70** is 2%–3%, whereas at 70 and 90 °C, it is 37% and 46%, respectively.[72]

The rationale for the skeletal rearrangement of 3-carene during hydrogenation is that both platinum and palladium catalyse both the direct and reverse reactions and can fulfil dehydrogenation in the presence of free hydrogen.[73] Hydrogenation of 3-carene upon addition of hydrogen to the double bond gives rise to carane; dehydrogenation of 2-carene, which always exists in the reaction medium (due to isomerisation of 3-carene, which occurs on the catalyst in the presence of hydrogen), results in the diene **58**, triene **61** and other compounds with modified skeletons.[74] An increase in temperature favours endothermic dehydrogenation and hence increases the content of rearranged products. It should be noted that hydrogenation on a copper–nickel catalyst carried out at high temperatures (180 °C) gave the hydrocarbon **71** as the only product.[58]



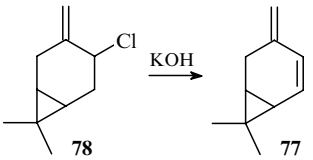
The direct proof that it is this mechanism that is actually realised is that 2- and 3-carenes undergo disproportionation over palladium and platinum in the absence of free hydrogen. In this case, the triene **61** was identified among the products, which confirms the assumption that dehydrogenation of 2-carene (**31**) is a step which is responsible for the formation of rearranged products.[75] In addition, the reaction mixture contained trimethylcycloheptadienes **72** and **73**. However, none of the known pathways of the isomerisation of terpenes **1** and **31** (including catalytic reactions) results in such ring expansion.

Based on the above considerations, it may be concluded that rearrangement of carane structures into trimethylcycloheptane structures occurs if the formation of the diene **58** (or its derivatives) is possible during the reaction. The simplest way to caradiene **58** is that from 2- and 4-carene derivatives with a functional group in the allylic position. Thus, dehydrochlorination of 4-chloro-2-carene (**74**) results in the triene **61**.[76] The transformation products of epoxide (**75**) in the presence of

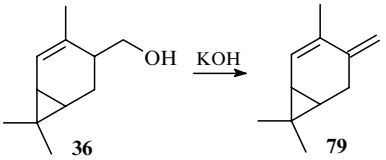


rhenium catalysts contained 4-caren-3-ol (**76**), which also gives the hydrocarbon **61** upon dehydration.[77]

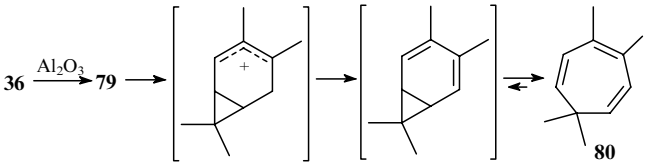
Theoretically, dehydration of the alcohol **76** can also follow another direction, *viz*., with the formation of a terminal methylidene group. The corresponding hydrocarbon, 3(10),4-caradiene (**77**), was in fact detected among the reaction products formed from the epoxide **75**.[77] Hydrocarbon **77**, which was originally obtained by dehydrochlorination of 4-chloro-3(10)-carene (**78**),[78] is the first stable diene with the carane skeleton.



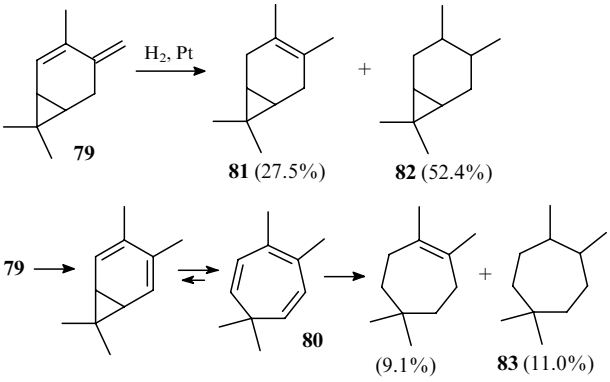
Dehydration of the alcohol **36** in the presence of potassium hydroxide resulted in the second compound of this series, *viz*., 4-methyl-3(10),4-caradiene (**79**).[79]



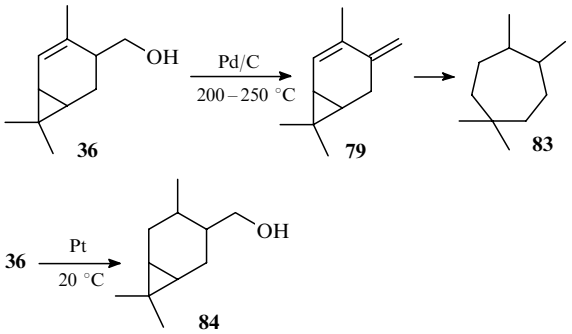
Dienes **78** and **79** are stable (*i.e*., they do not undergo tautomeric transformations), as, unlike compound **58**, they have a transoid diene system, which cannot undergo electrocyclic closure, and hence, concerted rearrangement. However, these compounds are highly reactive: even weak acids, such as salicylic and benzoic acid, isomerise the transoid diene system into a cisoid system; after that, a concerted rearrangement into cycloheptatrienes occurs.[80] The dehydration products of the alcohol **36** with Al_2O_3 (Lewis acid) were found not to contain even traces of the diene **79** (unlike its alkaline dehydration[79]); however, 3,4,7,7-tetramethylcyclohepta-1,3,5-triene (**80**) was present.[81]



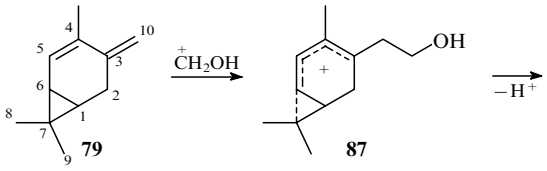
Hydrogenation of the diene **79** over platinum black at 20 °C also occurs with a rearrangement, which obviously results from its isomerisation on the catalyst.[80] In this case, of note is that the exhaustive hydrogenation products contain a rather high percentage of compounds **81** and **82** with a bicyclo[4.1.0]heptane skeleton. This means that the rate of hydrogen addition to the diene **79** is higher than the rate of its isomerisation, which is a side process (at least, at room temperature).

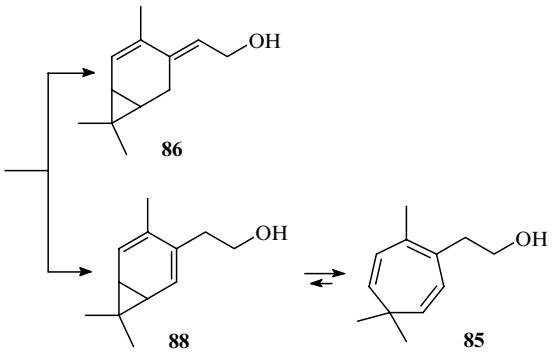


As a result of the three reactions altogether, *i.e*., dehydration, isomerisation and hydrogenation, the catalytic hydrogenation of the alcohol **36** under drastic conditions yields 1,1,4,5-tetramethylcycloheptane (**83**).[82] Over platinum at 20 °C, the reaction does not involve isomerisation; it occurs by simple hydrogen addition to the double bond and gives rise to 4-hydroxymethylcarane (**84**).[83]



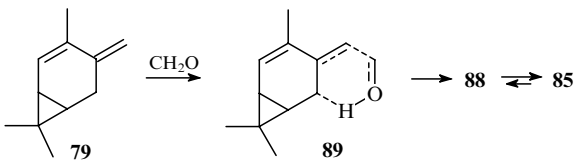
The rearrangement which occurs due to the valence tautomerism makes it possible to obtain functional derivatives of cycloheptatriene. For example, the diene **79** undergoes the Prins reaction to give two hydroxymethylation products, *viz*., a mono- (**85**) and bicyclic one (**86**).[84]





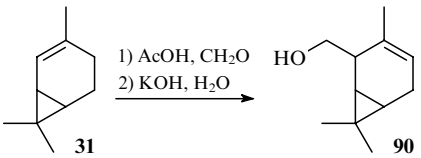
Electrophilic attack on the terminal double bond in compound **79** by a protonated formaldehyde molecule results in homodienyl ion **87**, which is stabilised by deprotonation (i) from C(5) to give the alcohol **88**, or (ii) from C(10) to give the allylic alcohol **86**. The alcohol **86**, when treated with an acid, is isomerised to caradiene alcohol **88**, which then rearranges into the alcohol **85**.

The monocyclic alcohol **85** can also be formed by yet another mechanism. If the initial hydrocarbon adds a formaldehyde molecule, the first reaction step occurs as a concerted process *via* a six-membered polarised TS (**89**)[85] to give the bicyclic alcohol **88**. Subsequent rearrangement yields the reaction product **85**. Thus, the transformation of the diene **79** into the trienic alcohol **85** can occur as a sequence of two concerted reactions.

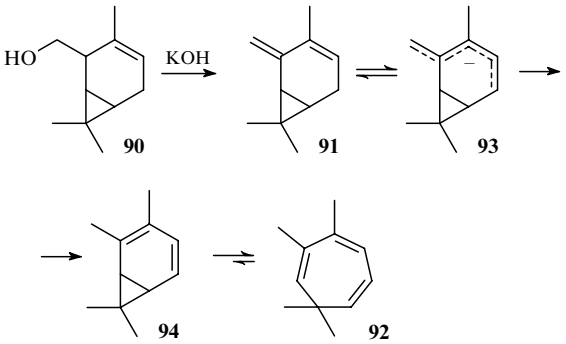


It should be noted that the attack of an electrophilic agent (a charged molecule or a dipole) is directed to the C(10) atom in compound **79**, *i.e*., to one end of the conjugated homotrienyl system, which is more accessible spatially. However, in the reaction with 2-carene (**31**), the protonated formaldehyde mole-

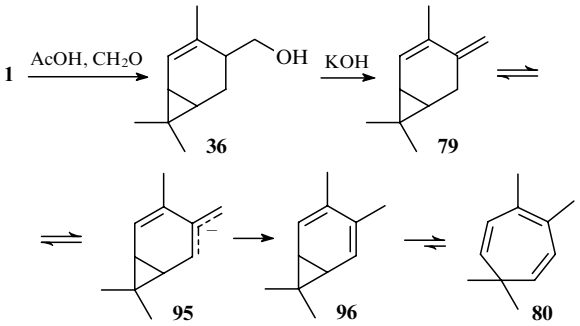
cule adds to the least substituted end of the double bond to give homoallylic alcohol **90**,[86] which is additional evidence for the absence of conjugation in the 2-carene molecule.



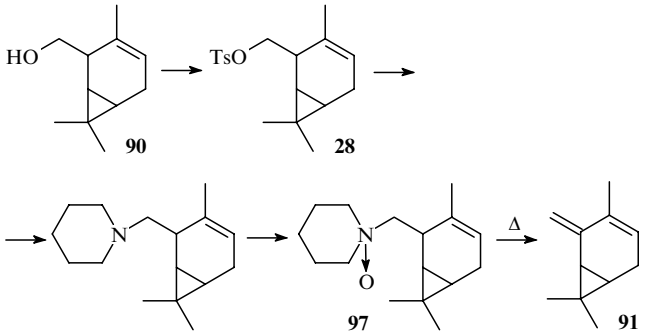
It should be noted that dehydration of 2-hydroxymethyl-3-carene (**90**) with potassium hydroxide does not give a caradiene with an exocyclic double bond (**91**) as the main product; instead, this yields 2,3,7,7-tetramethylcyclohepta-1,3,5-triene (**92**), which is obviously formed *via* intermediates **93** and **94**.[86]



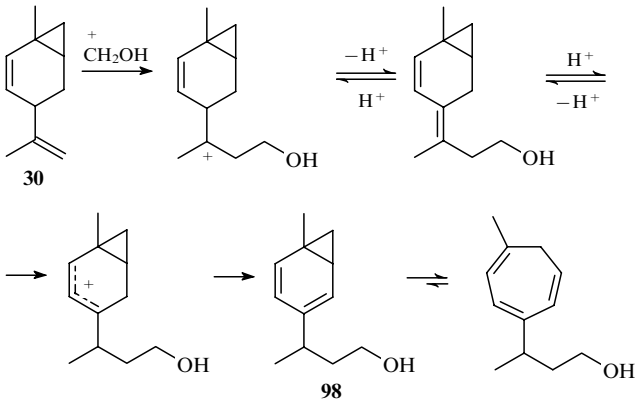
Dehydration of the alcohol **36** gave not only the triene **80** but also the diene **79** as the reaction products.[84] Charge is delocalised to a greater extent in the pentadienyl anion **93** than in the allylic anion **95**; therefore, the transformation of the diene **91** into the final product **92** occurs more readily than the transformation of the diene **79** into the diene **96** and further into cycloheptatriene **80**.



Generally, concerted rearrangements of transoid caradienes occur very readily, therefore special measures are to be taken to avoid this reaction and obtain very labile non-rearranged dienes. For example, thermal decomposition of *N*-oxide **97** was the only approach that allowed hydrocarbon **91** to be prepared from the alcohol **90**.[86]



Turning back to the Prins reaction, it may be noted that when a hydrocarbon molecule that has the bycyclo[4.1.0]hept-2-ene system contains an additional isolated double bond (as in compound **30**), the initial attack of formaldehyde is directed at this bond. However, under conditions of acid catalysis, the bicyclic alcohol formed initially readily isomerises to give a bicyclo[4.1.0]-hepta-2,4-diene system (*e.g.*, compound **98**), in which a concerted rearrangement occurs.[86]

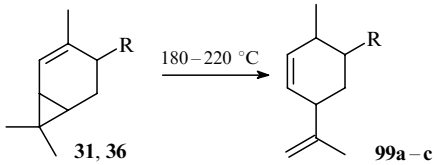


2. Sigmatropic rearrangements

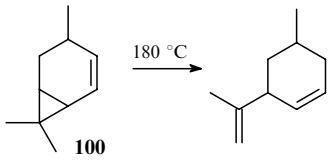
Thermal rearrangement of 2-carene (**31**) and its derivatives was the first example of the transformations which were later called the 1,5-homodienyl shift.[87]

It is well known that vinylcyclopropane is transformed into cyclopentene at temperatures above 330 °C; the reaction occurs as a homolytic bond cleavage followed by isomerisation of the biradical formed and subsequent recombination.[88] The activation energy of this rearrangement is rather high and equals 208 kJ mol^{-1} (see Ref. 89).

However, 2-carene and its derivatives, whose molecules contain the vinylcyclopropane moiety, undergo a rearrangement at a temperature as low as 180 °C to give the corresponding derivatives of *trans*-isolimonene **99a–c**.[90,91] 4-Carene (**100**) reacts similarly.[92]



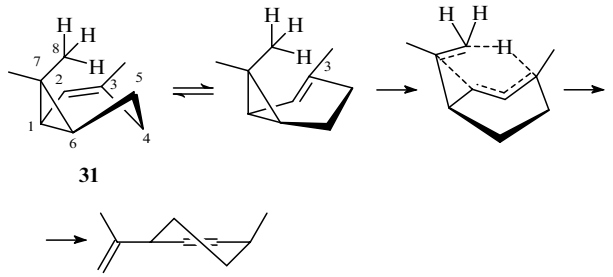
R = H (**99a**), OH (**99b**), CH_2OH (**99c**).



This transformation is determined by specific features of the structure of 2- and 4-carene derivatives: just as the 1,5-dienyl shift of hydrogen is possible in *cis*-1,3-diene systems, a 1,5-homodienyl shift is possible in carane compounds which have a vinylcyclopropane fragment. The reaction occurs *via* a six-electron transition state and obeys the selection rules for thermal hydrogen shifts.[56] No homolytic cleavage of the carbon–carbon bond occurs, since the activation energy of the 1,5-homodienyl shift is much lower than the energy of the vinylcyclopropane rearrangement; in the case of 2-carene, it equals 118 kJ mol^{-1} (see Ref. 91).

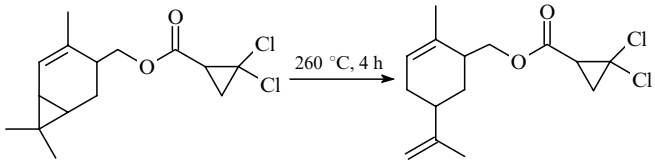
The prerequisite for the 1,5-shift is the *endo*-orientation of the C–H bond and the vinyl group involved in the formation of the transition state.[93] This is the only stereochemical requirement for the thermal rearrangement of *cis*-1-methyl-2-vinylcyclopropane; the positions of the substituents in its molecule do not cause any additional strain. This requirement is also met for the 2-carene (**31**) molecule; however, the double bond is part of the six-membered ring and therefore it deviates from the direction

which is optimal for conjugation with the CPR and formation of the TS. The distance between C(3) and the hydrogen atom at C(8) is ~ 3.1 Å in the planar chair-like conformation.[38] This means that the molecule of 2-carene (**31**) on heating should first change its conformation [as a result, the C(3)—H(8) distance decreases to 2.3 Å], and only then undergoes the 1,5-homodienyl shift.

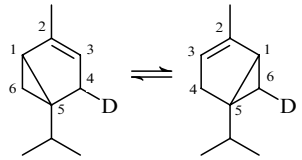


31

The nature of the substituent at position 4 can affect the activation energy of the conformation transition, but even bulky substituents do not prevent the 1,5-shift; however, the thermal rearrangement of such compounds requires higher temperatures.[94]



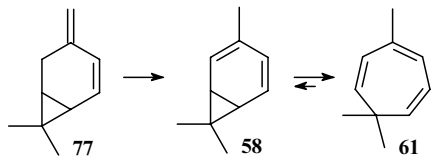
α-Thujene (**101**), whose molecule also contains a vinylcyclopropane fragment, remains unchanged when heated above 300 °C. However, experiments using a deuterium label showed that a degenerate vinylcyclopropane rearrangement actually occurs. In this case, the TS required for the 1,5-homodienyl shift is hard to access: the distance between D(4) and C(5) or C(3) is ~ 2.8 Å.[95]



101-D(4) **101**-D(6)

It should be noted that, owing to the geometry of their molecules, it is the carane structures that turned out to be suitable models for studying the 1,5-homodienyl shift. In the thermal isomerisation of terpenoids with the bicyclo[4.1.0]hept-2-ene skeleton, the 1,5-homodienyl shift occurs regio- and stereospecifically; this makes it possible, *e.g.*, to synthesise new oxygen-containing terpenoids from 2-carene derivatives.[96]

The presence of an *endo*-oriented vinylcyclopropane fragment and an appropriate C—H bond in compounds of the carane series does not necessarily mean that thermal 1,5-hydrogen shift is possible. For example, heating of caradiene **77** at 120 °C gave the triene **61** as the major (or the only one, at relatively low temperatures) transformation product.[97] At higher temperatures (170–190 °C), small amounts of *p*- and *m*-cymenes (up to 3%) formed as well.



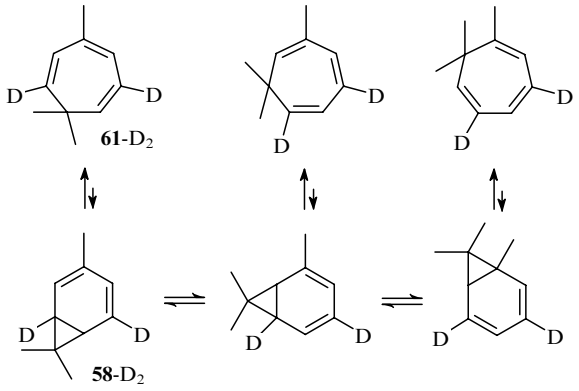
77 **58** **61**

It might seem that the 1,5-homodienyl shift should be the most likely process under these conditions: the vinyl group and one of the C(8)—H bonds have an *endo*-orientation; the C(4)—H(8) distance is ~ 2.2 Å, *i.e.*, it is easy to attain the ideal TS for the 1,5-shift calculated theoretically.[93] However, such a transformation should give *m*-mentha-1(7),4,8-triene, which is not formed in reality. A vinylcyclopropane rearrangement is also impossible at these temperatures, as they are not high enough for a radical reaction. It might be assumed that valence tautomerism is responsible for skeletal rearrangement. Then the thermal isomerisation **77** → **61** is actually reduced to the transformation of the transoid diene **77** to the cisoid diene **58**. This is formally a 1,3-sigmatropic shift.

It is generally believed that the non-catalysed hydrogen 1,3-shift does not occur in thermal reactions, since the transition state of the allowed antarafacial shift is hardly accessible because of the high angular strain in the propene fragment.[98] The suprafacial shift, which is quite possible as regards spatial aspects, is forbidden due to the orbital symmetry conservation rules. However, an *ab initio* calculation of the 1,3-shift in propene showed that the forbidden suprafacial hydrogen transfer requires a lower activation energy than the allowed antarafacial transfer.[99] This unexpected result was explained using a hypothesis about the subjacent orbital control.[100] This hypothesis underlies the assumption that a 1,3-shift occurs in the molecule of the diene **77**.

The mechanism of the thermal isomerisation of caradiene **77** was also studied by kinetic methods.[97] The transformation of the hydrocarbon **77** into the triene **61** is a sequence of two concerted reactions; for quite obvious reasons, the first one (the assumed 1,3-shift) is the limiting step. Kinetic studies showed that this step is described by a first-order equation. The activation energy determined from experimental data is 112 kJ mol^{-1}, which is close to the calculated activation energy of the antarafacial 1,3-shift (115 kJ mol^{-1}).[99] The high negative activation entropy, which equals 96 kJ mol^{-1} deg^{-1} (−23 eu), suggests that a 1,3-shift is possible in this reaction. Comparison of this value with the corresponding parameter for the 1,5-shift (−8 to −16 eu) shows that the transition state of the thermal rearrangement of caradiene **77** is highly ordered and that the participating atoms are bound very strongly. The activation energy of 1,5-shift in 2-carene (**31**) (118 kJ mol^{-1})[91] is somewhat higher than the activation energy of the thermal isomerisation of the diene **78**; this may explain why the 1,5-shift does not occur in this case.

Of special interest is the thermal rearrangement discovered by Berson and Willcott.[47] Formally, it is migration of the methyl group over all the possible positions of the triene system in the molecule of the hydrocarbon **61**. Nevertheless, this should be considered in the series of carane rearrangements, because, in fact, it is a 1,5-shift of the dimethylmethylene group rather than a 1,3- or 1,5-alkyl shift that occurs in the caradiene tautomer **58**, as shown using deuterium labelling.



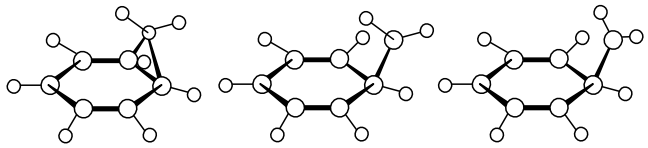
61-D_2 **58**-D_2

This specific reaction served as the impetus for the development of experimental and theoretical studies, which expanded considerably, and changed somewhat, the classical concepts of sigmatropic reactions. The triene **61** turned out to be an excellent model for these studies, since the rearrangement only occurs if a *gem*-dimethyl group is present: in the absence of geminal sub-

stituents, cycloheptatriene undergoes 1,5-hydrogen shift at temperatures above 100 °C.[101] The presence of the third methyl group, which 'walks' along the triene system of the seven-membered ring, made it possible to detect this rearrangement ('walk rearrangement').

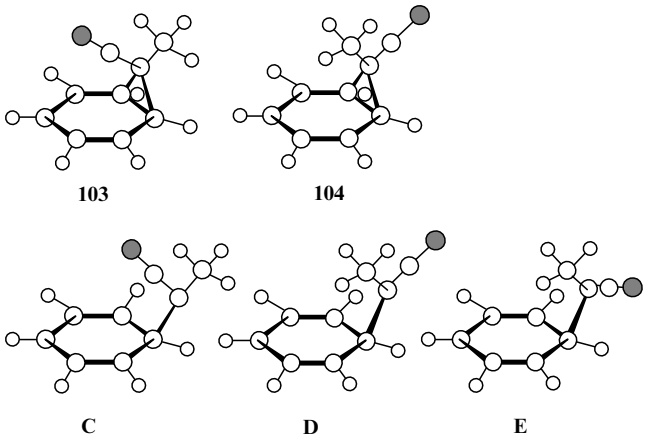
It should be noted that the mechanism of this shift does not allow the rearrangement of the heptatriene **61** to be considered completely concerted, because it occurs *via* a biradical intermediate at temperatures ~ 400 °C. This rearrangement involves a shift of the cyclopropane bond, which is not a σ-bond in the original molecule; this does not allow this rearrangement to be considered sigmatropic. Still, it was considered for a rather long time that the rearrangement of the triene **61** meets completely the selection rules for concerted sigmatropic migrations of alkyl groups, *i.e.*, it occurs as a suprafacial rearrangement with retention of the configuration of the migrating group. Elegant studies by Klärner *et al.*[102–104] rebutted these concepts completely: they replaced one methyl group by an alkoxycarbonyl, nitrile or alkoxyalkyl group and proved that the rearrangement occurs with retention of the configuration, *i.e.*, by a 'forbidden' pathway.

Recently, this phenomenon was explained on the basis of *ab initio* calculations in two theoretical papers issued almost simultaneously.[105, 106] In the case of non-substituted norcaradiene **102**, the methylene group with an unpaired electron is somewhat more remote from the six-membered ring in the biradical TS **A** for the forbidden thermal 1,5-alkyl shift than in the TS **B** of the allowed shift, which decreases the energy of the TS for the forbidden shift by ~4 kJ mol^{-1} (see Ref. 105).



102 **A** **B**

The transition states **C** and **D** for the 1,5-shift in *cis*- (**103**) and *trans*-7-cyano-7-methylnorcaradienes (**104**), which occurs with reversal of the configuration (and is therefore forbidden), is 12 and 13 kJ mol^{-1}, respectively, more favourable than the TS **E** of a similar shift with retention of the configuration (which is therefore allowed). The distance between the hydrogen atoms of the methyl group and the ring in the forbidden TS **C** and **D** is by 0.12 and 0.37 Å shorter than that in the allowed TS **E**.[106]



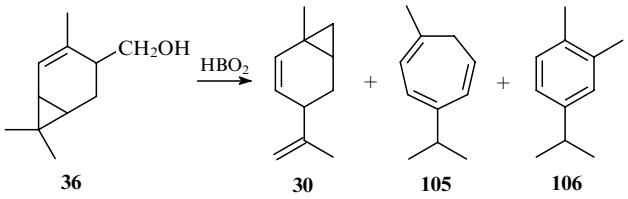
103 **104**

C **D** **E**

On these grounds, Houk *et al.*[106] conclude that when sigmatropic rearrangement occurs *via* a biradical intermediate, steric factors can dominate over electronic factors, resulting in a violation of the fundamental orbital symmetry conservation rules. It is appropriate to remind here that the studies which have led to this amazing result started with an investigation of terpenoids, *viz.*, the triene **61** and its valence tautomer, the diene **58**.

3. Thermal elimination

Attempts to dehydrate the alcohol **36** with boric acid gave a mixture of hydrocarbons **30**, **105** and **106**, instead of the expected diene **79**.[107]



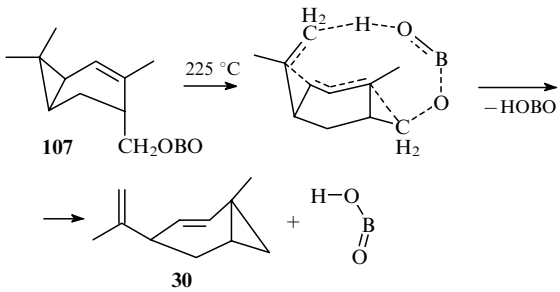
36 **30** **105** **106**

It was later found that these hydrocarbons are also formed upon thermal decomposition of mono-, di- and triesters of boric acid and the alcohol **36** (*i.e.*, intermediates of the dehydration described above), and that bicyclic hydrocarbon **30** is formed initially; other transformation products were identified as well.[108] Toluene-*p*-sulfonate and chloroacetate of the alcohol **36** reacted similarly; the corresponding acetate and aminoacetate underwent the 1,5-homodienyl shift.[109]

Thermolysis of esters is a well-studied reaction, which is used as a route to olefins by elimination of an acid residue and a hydrogen atom bound with the β-carbon atom. Elimination occurs *via* a six-electron (aromatic) TS. However, pyrolysis of the alcohol **36** and its derivatives results not in the formation of a double bond but rather in cleavage of one of the bonds in the *gem*-dimethylcyclopropane ring with simultaneous closure of a new three-membered carbocycle. Additional studies were carried out in order to study the mechanism of this unusual rearrangement: the kinetics of the thermal decomposition of the toluene-*p*-sulfonate **25** in pyridine [37] and its solvolysis [35] were studied.

These studies made it possible to propose the mechanism of this rearrangement.[37] This occurs as a concerted rearrangement *via* an aromatic ten-electron transition state, unlike the classical six-electron TS. Although the hypothesis about a ten-electron TS has not been used before in organic chemistry, it does not suffer fundamental self-inconsistencies. Recently, a ten-membered TS was calculated for the Cope [5,5]-sigmatropic rearrangement using the B3LYP/6-31G* method.[110] A calculation using the density functional shows that a ten-membered TS may be non-planar but maintains aromaticity.[111]

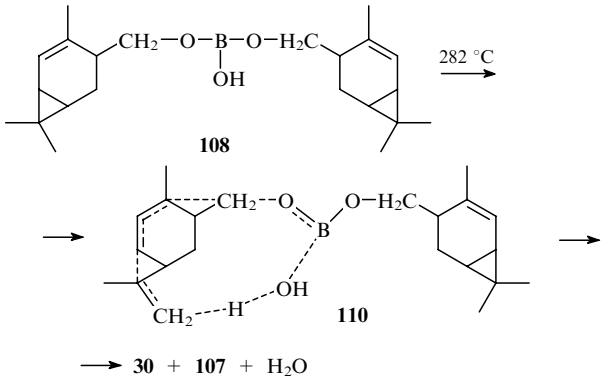
We believe that the spatial factor is responsible for this unusual reaction pathway. The formation of a six-membered TS upon elimination of acid fragments requires that the acid residue in ester **107** have an eclipsed conformation with respect to the H(4) atom. This allows the oxygen atom of the acid residue and a hydrogen atom of the *endo*-methyl group, which is linked with the cyclopropane ring, to approach each other and ensures that the vinylcyclopropane fragment is involved in the transition state. The aromaticity criterion (*i.e.*, fulfillment of the Hückel rule) requires that the p-orbitals of non-neighbouring atoms [C(3), C(11)] overlap. The formation of the cyclopropane ring and simultaneous transformation of the vinylcyclopropane fragment into the 1,4-diene system occur as a result of such through-space overlap.



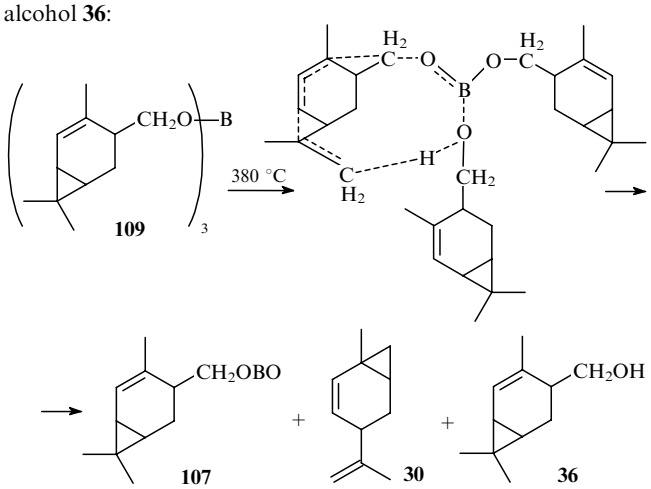
107 **30**

This viewpoint was confirmed experimentally.[37] A detailed study of the decomposition of esters **107**–**109** showed that these

reactions result in various products. For example, the pyrolysis products of the ester **108** also contained water (3% – 5%):



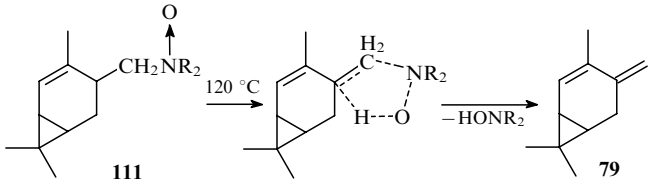
The first pyrolysis step occurs as the fragmentation of the molecule of the diester **108** *via* a ten-membered TS **110**, which includes a hydroxy group. This results in the bicyclic hydrocarbon **30**, water and ester **107**. Further, the ester **107** decomposes according to the scheme described above to give boric acid and a second molecule of the hydrocarbon **30**. The pyrolysis products of the ester **109** contained (in addition to the hydrocarbon **30** and its transformation products) 2- and 3-carenes, menthadienes and the alcohol **36**:



The first stage gives the hydrocarbon **30** and also the ester **107** (which decomposes according to the scheme described above) and the alcohol **36**. The latter undergoes partial deformylation under the reaction conditions (380 °C) to give 3-carene (**1**).[91] As a result of acid isomerisation of this terpene, 2-carene and menthadienes appear among the products.

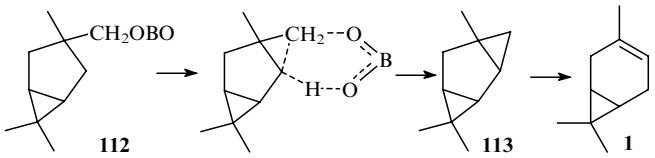
It should be noted that pyrolysis of *N*-oxide **111**, whose structure is similar to that of esters **107** – **109**, gave quantitatively the hydrocarbon **79** containing an exocyclic double bond.[112] This result may be considered as an indirect proof that the spatial factor plays a decisive role in such rearrangements.

In the oxide **111**, the functional group has one member less than that in esters **107** – **109**; as a result, the formation of a five-membered (but six-electron, *i.e.*, still aromatic) transition state becomes possible; this is smaller in size and its C(4) atom has a *gauche*-conformation.



Undoubtedly, the TS in the thermal decomposition of esters is highly polarised; its structure depends on the nature of its constituent atoms. Therefore, the acetate, borate and toluene-*p*-sulfonate of the alcohol **36** manifest different reactivities in this reaction. The reactivity even depends on the secondary effects of the heteroatoms: acetate and aminoacetate undergo a 1,5-homodienyl shift; thermolysis of the toluene-*p*-sulfonate occurs at 90 °C, that of chloroacetate at 180 °C, and that of mono-, di- and triborates at 225, 282 and 380 °C, respectively.[113]

Pyrolysis of borate **112**, in which 1,2-elimination is impossible *a priori*, gives rise to 3-carene (**1**), formed presumably upon acid isomerisation of the initial pyrolysis product, *i.e.*, tricyclic hydrocarbon **113**. None of the esters of 3,6,6-trimethylbicyclo[3.1.0]-hexan-3-ylmethanol tested in this reaction (toluene-*p*-sulfonate, acetate, amino- and chloroacetates) behaved in this way.



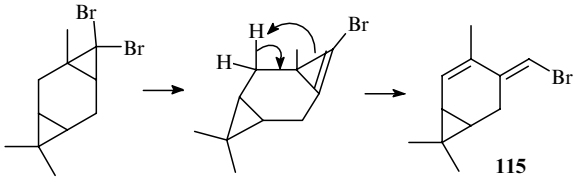
As we noted in Section II.2, the solvolysis of toluene-*p*-sulfonates **25** and **28** results in the same product **29**.[36] Pyrolysis of these compounds also affords a single reaction product **30**, although the pyrolysis of the ester **28** requires a higher temperature (180 – 200 °C) than that of the ester **25** (70 – 100 °C). We assume that this can be explained by preliminary 1,3-shift of the tosyloxymethyl group, which occurs at high temperature. A similar shift of the acyl group was observed in the photolysis of the ketone **42**[43] (see Section III).

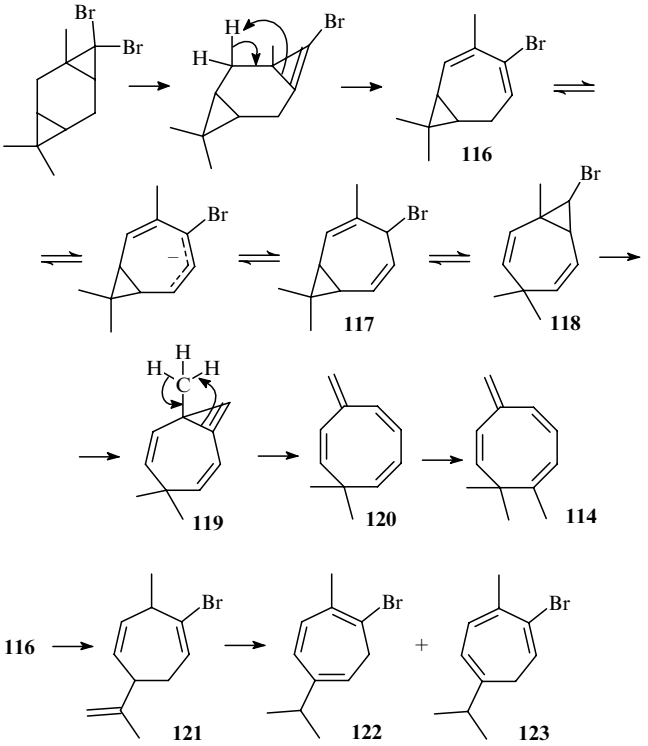
4. Ionic reactions and valence tautomerism

We have already mentioned the ionic transformations of carane monoterpenoids (*e.g.*, compounds **74** and **76**) to give a 2,4-caradiene structure, which underwent electrocyclic opening of the three-membered ring with rearrangement into a trimethylcycloheptatriene structure. In such cases, the skeletal rearrangement occurs due to valence tautomerism. Compounds of the carane series, which have a more complex carbon skeleton, can undergo ionic rearrangements of another type, giving rise to structures that are prone to tautomeric transformations.

For example, the adduct of 3-carene with dibromocarbene undergoes dehydrobromination on treatment with a superbasic system KOR – DMSO (R = H, Bu^t) with selective formation of 1,8,8-trimethyl-5-methylidenecycloocta-1,3,6-triene (**114**).[114] When the concentration of the dehydrobrominating agent was decreased, additional products were isolated from the reaction mixture; this allowed a scheme of the rearrangement to be proposed.[115]

Elimination of the first molecule of hydrogen bromide is accompanied by the isomerisation of the three-membered ring to give bromides **115** and **116**. Bromide **115** with an intact carane skeleton is formed by opening of the three-membered ring with cleavage of the external bond and does not undergo further transformations on treatment with the KOH – DMSO system. Compound **116** isomerises to give bromide **117**, which contains a *cis*-divinylcyclopropane system. This undergoes the Cope rearrangement[116] by concerted opening of the CPR to give a valence tautomer **118**. Dehydrobromination of compound **118** results in cyclopropene **119**, which isomerises to a more stable cyclooctatriene derivative **120**. The latter is methylated by the dimsyl anion under the reaction conditions.





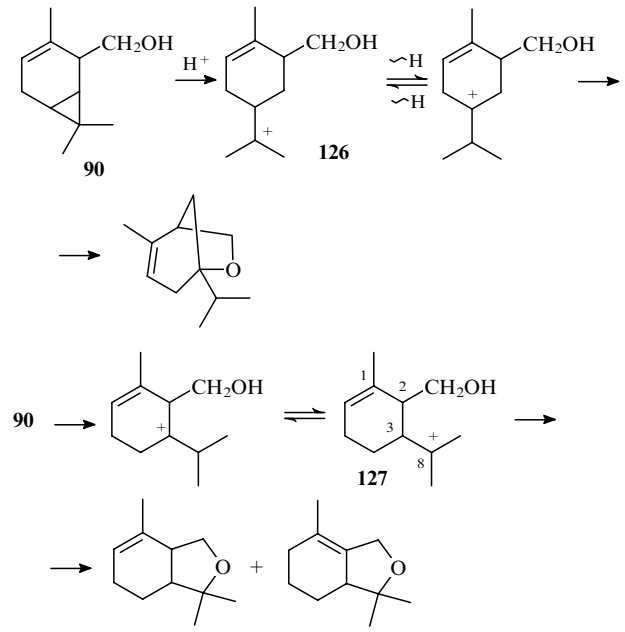
This reaction involves yet another concerted rearrangement. Bromide **121** is formed due to a 1,5-homodienyl shift; subsequent ionic isomerisation of this compound results in bromides **122** and **123**.

5. Sigmatropic shifts in charged systems

The transformations of carane structures on treatment with superacids are of considerable interest. In superacidic media, the life time of carbocations increases, enabling their more profound secondary transformations and involves all the possible reaction centres (CPR, double bonds if any, functional groups) in rearrangements. One of these possibilities comprises the sigmatropic shifts of hydrogen or alkyl groups. This gives new cations, each with its own destiny. Certainly, the diversity of the intermediates involved in these rearrangements predetermines the diversity of the reaction products.

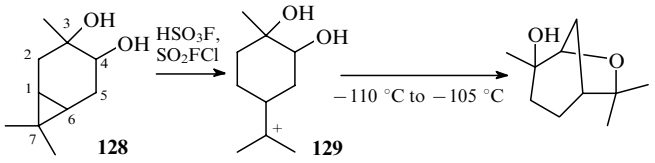
The reaction of the alcohol **36** or its derivatives with the superacid system HSO_3F-SO_2FCl affords a mixture of products, the formation of which is explained by sigmatropic shifts in the ions **124** and **125** formed initially (Scheme 2).[36]

The rearrangement of the isomeric alcohol **90** occurs similarly.[36]



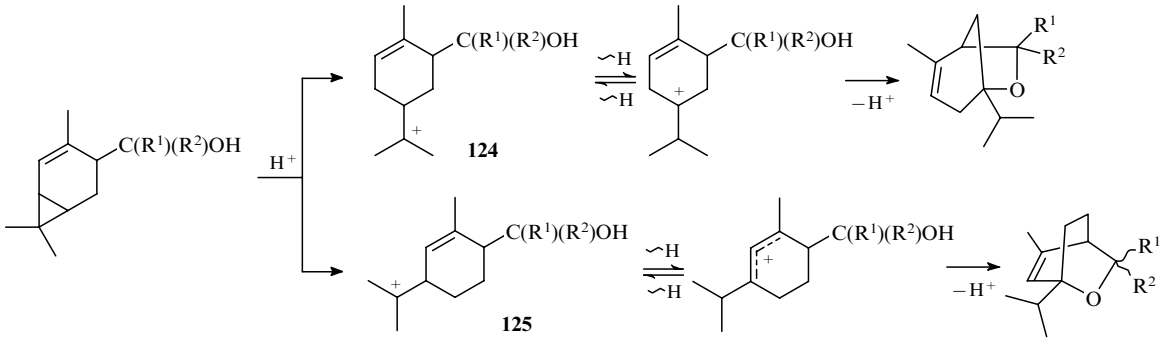
This type of cyclisation requires a 1,2-hydrogen shift in the *p*-menthene ion **126**, since the oxygen atom of the hydroxymethyl group is remote from the C(8) atom where the initial charge appears. In systems where the oxygen atom of the hydroxymethyl group is closer to the C(8) atom, cyclisation occurs *via* the *m*-menthene ion **127** formed initially. Certainly, the 1,2-shift occurs in the ion **127** as well, but the oxygen atom and the C(3) atom (where positive charge is localised after the shift) are too close, therefore cyclisation cannot occur because of the steric strain.

Cyclisation of diol **128** occurs, without initial hydrogen shift, *via* the *p*-menthane ion **129**, in which the oxygen atom is closer to the charged carbon atom than in ion **126**. This reaction involves selective opening of the cyclopropane ring with cleavage of the C(1)–C(7) bond; the reason for such selectivity has not been elucidated yet.[36]

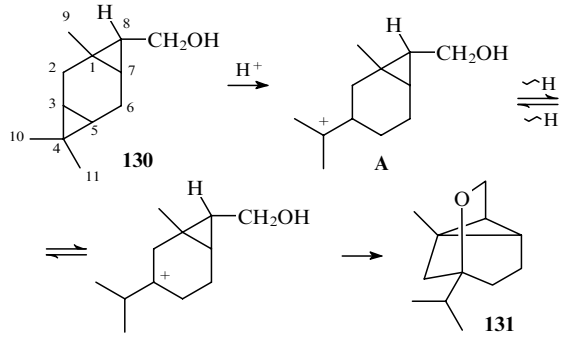


Tricyclic alcohol **130** rearranges in superacidic media with cleavage of the C(4)–C(5) bond, giving rise to compound **131**. The cyclisation occurs due to the 1,2-hydrogen shift in cation **A**.[36]

Scheme 2

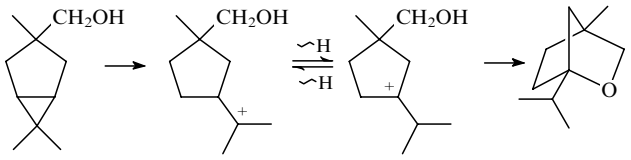


R^1 = H, Me; R^2 = H, Me, $CH_2CH=CH_2$.



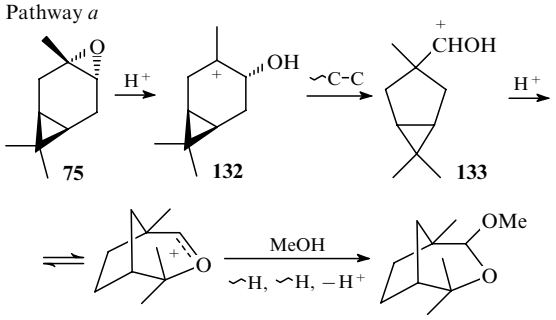
A characteristic feature of the rearrangement of the alcohol **130** is that its molecule has two three-membered rings, but only one of them opens on treatment with a superacid. This may be due to the difference between the HOMO energies of both cyclopropane fragments having different substituents, although the electrostatic effect of the hydroxymethyl group on the process, which is charge-controlled, seems unexpectedly strong.

Rearrangements accompanied by cyclisation occur in superacidic media for secocarane structures as well.[36] In this case, the positive charge should approach the oxygen atom in order that a bond can be formed:

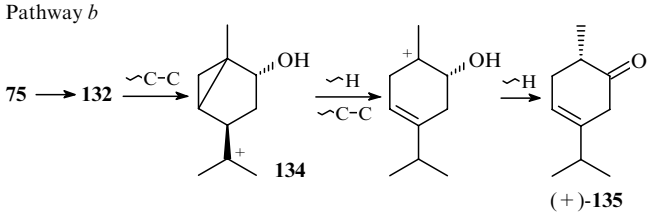


In the rearrangements of α-*trans*-3,4-epoxycarane† (**75**) in superacidic media, the intermediate ions undergo not only hydrogen but also alkyl shifts; these shifts are responsible for the transformation of the carane skeleton.[117]

Pathway *a*



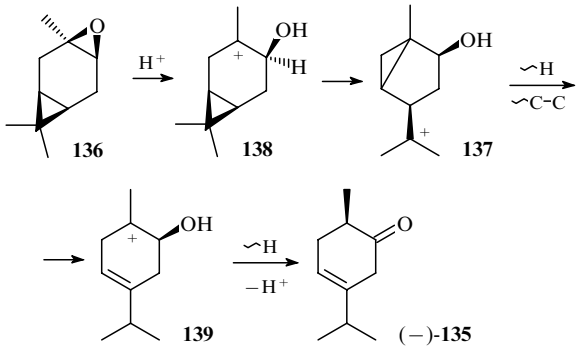
Pathway *b*



The 4-hydroxycarane-derived ion **132** should undergo a 1,2-alkyl shift with contraction of the six-membered ring to give ion **133**; elimination of a proton and ionisation of the CPR make cyclisation possible (pathway *a*).

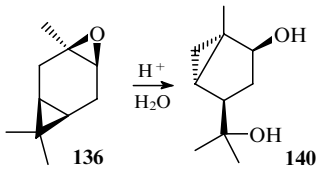
The second pathway of the transformation of ion **132**, which formally occurs as a 1,3-alkyl shift and results in ion **134** (pathway *b*), is more interesting. However, 1,3-alkyl shifts cannot occur in charged systems: the C(2) atom lacks an appropriate p-orbital. Thus, a 1,2-alkyl shift actually occurs, but the formation of the TS involves non-adjacent carbon atoms [C(1) and C(3)]. Through-space rather than through-σ-bond overlap occurs; this shift may be called homoenylic. This eventually results in the closure of the three-membered ring and gives ion **134** (β-cyclopropyl rearrangement[118]), which successively undergoes a hydrogen shift and an alkyl shift to give the final ketone (+)-**135**.[117]

In order to explain the rearrangements of β-*cis*-3,4-epoxycarane (**136**) in superacidic media, a mechanism was suggested which involves bicyclic ion **137** isomeric to ion **134**.[118] This results in the stereospecific formation of the ketone (−)-**135**; the latter is not only a stereoisomer but also an enantiomer of the ketone (+)-**135**, which is formed due to rearrangements of the epoxide **75**.

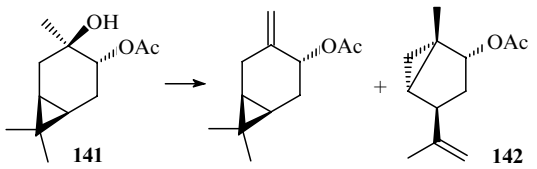


The different reactivities of epoxides **75** and **136** are explained[118] by thermodynamic and orbital factors: the orientation of the migrating bond and the vacant orbital in ions **132** and **138** is favourable for ring contraction. For ion **132**, ring contraction is more energetically favourable, whereas β-cyclopropyl rearrangement (*via* cations **137** and **139**) is favourable for ion **138**, since the orientation of the vacant orbital in this cation is more favourable for the rearrangement than that in **132**.

The above transformation schemes of epoxides **75** and **136** only cover the most probable ways for the formation of the final products. No compounds with the 4-isopropyl-1-methylbicyclo[3.1.0]hexane skeleton, which might have formed from ions **134** and **137**, were found in the transformation products of epoxycaranes in superacidic media. However, diol **140** with the same skeleton was obtained in 1962 by acid-catalysed hydration of *cis*-epoxide **136**,[119] and its structure was confirmed in 1972.[120]



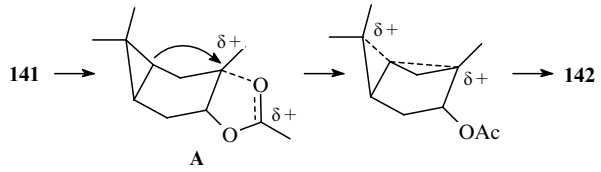
As shown in 1966, dehydration of 3β,4α-caranediol monoacetate **141** gives rise to *trans*-4-isopropenyl-1-methylbicyclo[3.1.0]hexan-2-ol acetate (**142**) as one of the products.[121]



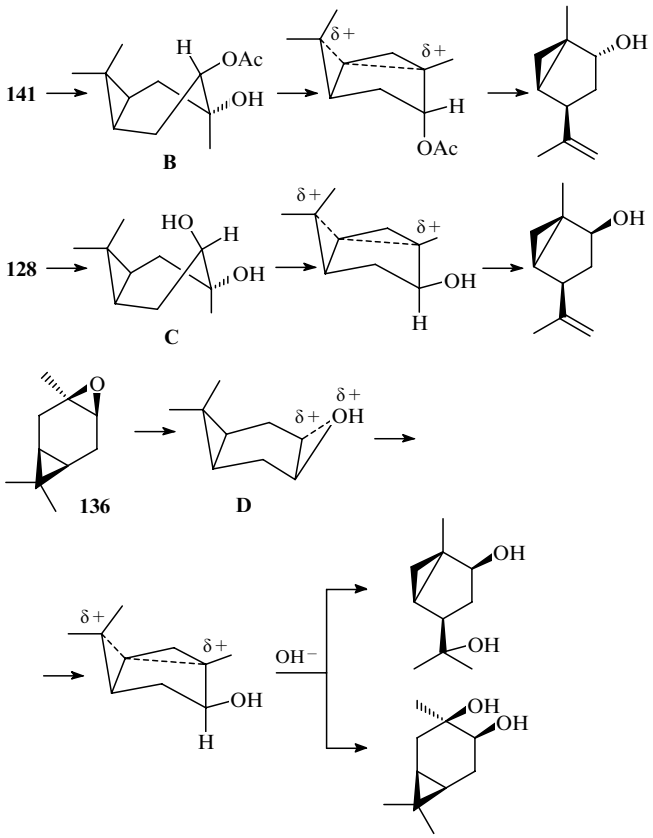
Kropp who studied this reaction[121] regarded it as the first documented example of rearrangement with transannular cyclopropyl participation.[10] He believed that CPR in nucleophilic substitution reactions acts as an internal nucleophile and the role of stereochemical factors is very high in such reactions: it is required that there is a spatial possibility for the dimethylcyclopropane ring to attack the C(3) atom, which carries a β-substituent. Also of importance is the existence of an α-sub-

† In the chemistry of terpenoids, the α and β symbols traditionally designate the spatial arrangement of functional groups in carane derivatives: α substituents and the three-membered ring are located on different sides of the cyclohexane ring (*trans*), whereas β substituents are located on the same side as the CPR (*cis*).

stituent at the C(4) atom, required for fixing the six-membered ring in the '*syn*-boat' conformation **A**.[121]

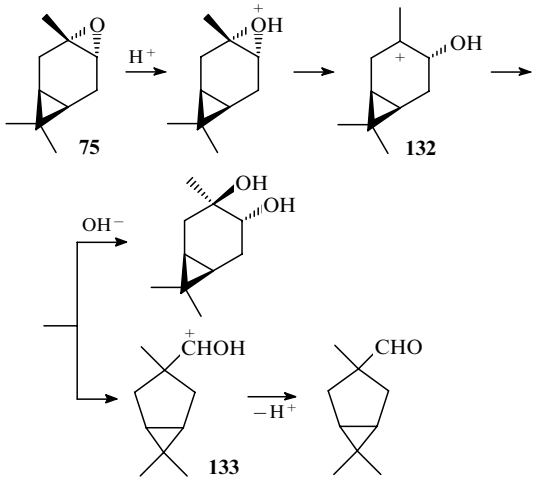


Different opinions existed regarding the stereochemical conditions of 'cyclopropyl participation' stated by Kropp. For some time, his interpretation of the spatial features of such reactions was considered generally accepted and was cited in special literature.[12] However, subsequent studies [10, 122–128] made it possible to put forward a statement (and confirm it experimentally) that the molecules of the reacting carane compounds have the '*anti*-boat' conformation (**B**–**D**) in the transition state; the orientation of the substituent at C(4) does not matter.[122, 123, 129]



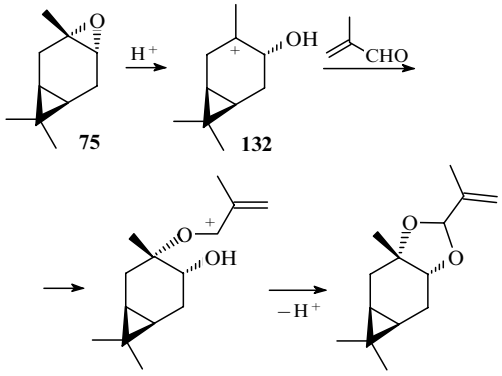
In fact, the 'transannular participation of CPR' is reduced to the 1,2-homoenyl shift, which can occur (and does occur) in charged systems. The absence of 'transannular cyclopropyl participation' products upon rearrangement in superacids is caused by the fact that, owing to the very low nucleophilicity of the medium and low temperatures, ionic processes occur to a greater extent and are highly selective. Therefore, transformations in superacids do not stop in ion **137**, but proceed further to give ion **139**, which leads to the final reaction product.

This approach explains the similarity of transformations of the epoxide **136** under the conditions of usual acid catalysis and in superacids, but new questions arise. The transformation of the epoxide **75** in superacids gives products which imply the intermediate formation of ion **134**, whereas solvolysis of compound **75** does not yield 4-isopropyl-1-methylbicyclo[3.1.0]heptane structures. As a side process, ring contraction occurs due to an alkyl shift in the ion **132** giving the ion **133**, which is stabilised by elimination of a proton; in a superacid, the ion **133** rearranges.[125, 130]

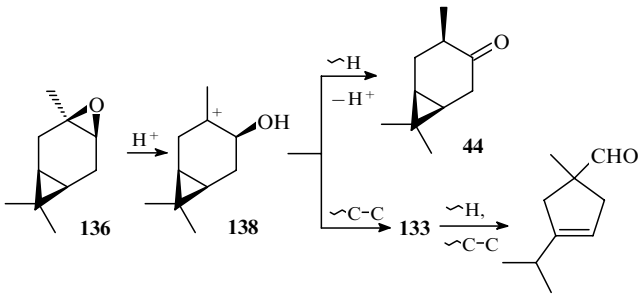


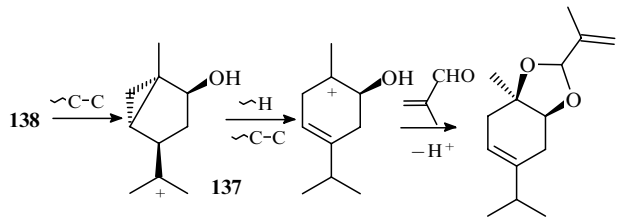
Undoubtedly, epoxides **75** and **136** react differently under usual conditions due to differences in their spatial structures. However, in superacids this difference is insignificant with respect to 'transannular cyclopropyl participation', or at least this does not play an important role. It may be assumed that charges are separated more deeply in superacids, which alters the geometry of the carane skeleton and enables the 1,2-shift. In usual acids, only partial charge is located on the involved atoms,[121] therefore the geometry of the carane skeleton is changed insignificantly. However, it should be noted that the ion **133** is formed under conditions of usual acid catalysis, which at present cannot be explained in terms of the above argumentation.

The reactions of α-epoxycarane with aldehydes over ascanite-bentonite clay (an alumosilicate catalyst) do not give any products which would imply that the ion **134** is involved in the reaction.[131]



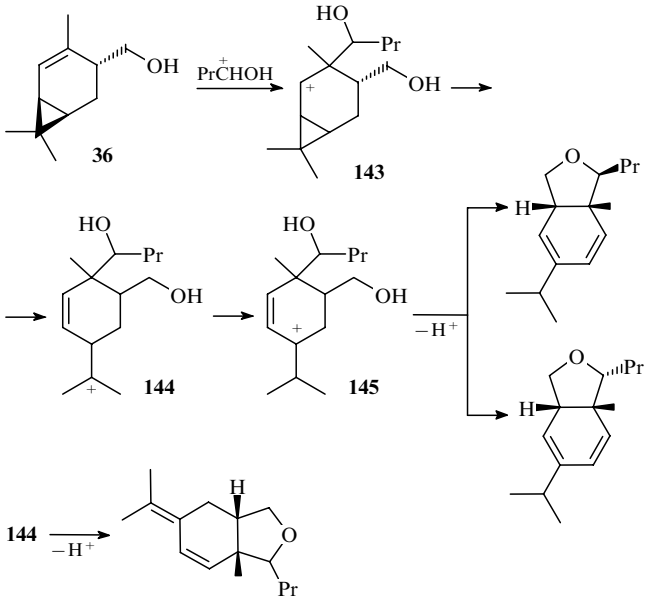
In this case, no profound transformations of ions occur, as the aldehyde traps the ion **132**, and the reaction follows a different pathway. On the other hand, under similar conditions the epoxide **136** gives products which imply that ion **138** undergoes not only a 1,2-homoenyl but also a 1,2-alkyl shift to give the ion **133** (which was not observed in superacids [118]), which is then rearranged.





As a result of the specific features of catalytic transformations on solid surfaces, the reaction of the epoxide **136** does not give an acetal with a carane skeleton; instead, it yields the ketone **44**, which is absent in the products of the reaction starting from the epoxide **75**.

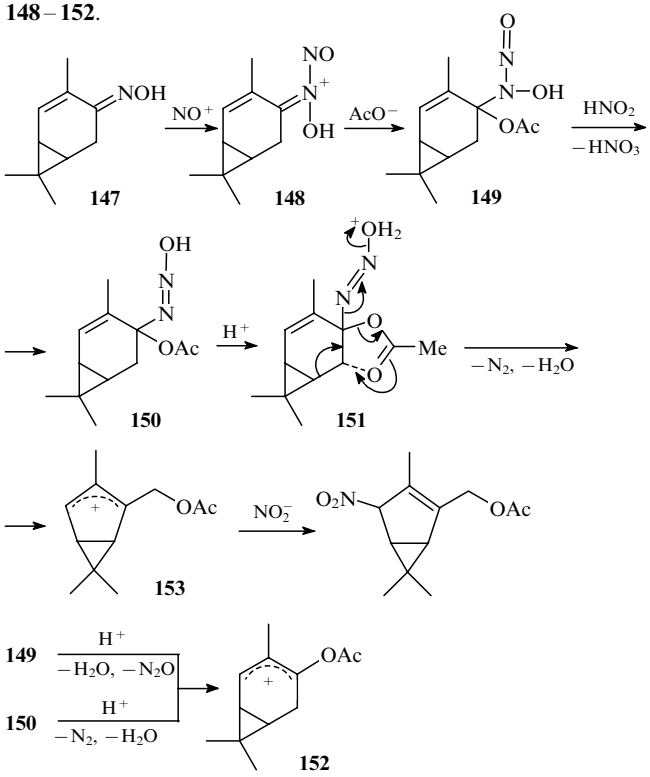
3-Carene does not react with aldehydes on ascanite-bentonite clay,[131] but under these conditions the alcohol **36** yields a series of rearranged products, the structure of which depends on the aldehyde used.[132]



The suggested reaction mechanism [132] involves the attack of protonated butyraldehyde on the more substituted end of the double bond to give a secondary cation **143** rather than a more stable tertiary cation. Rearrangement of the former with opening of the CPR gives ions **144**, **145** and then the reaction products. Section II.1 gives a different viewpoint on the formation of products with a similar skeleton.[24, 25] The mechanism proposed by Barkhash *et al.*[132] is supported by the formation of tricyclic products in the reaction of the alcohol **36** with α-methylacrolein (Scheme 3).

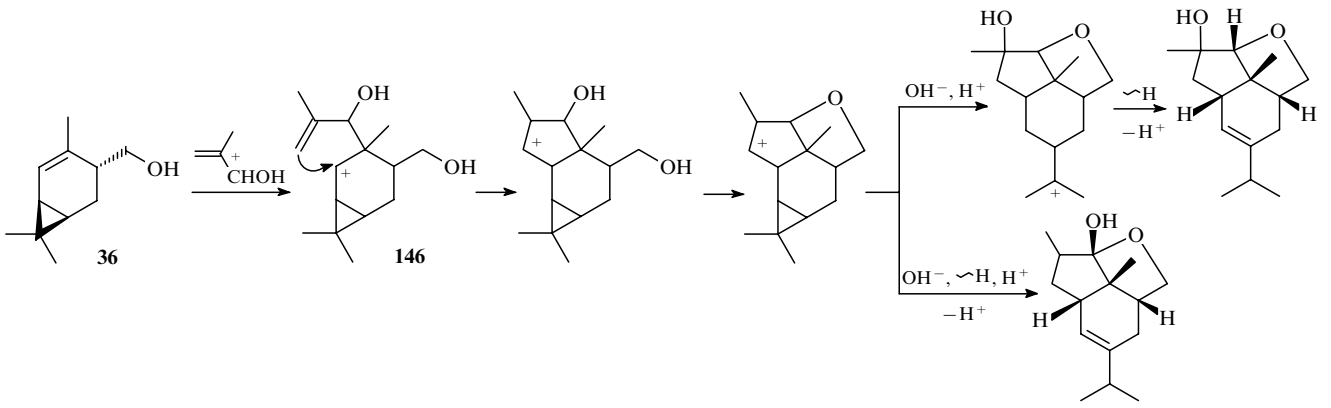
The proximity of the double bond to the cationic centre in ion **146** can result in cyclisation, which is believed to be due to the presence of a methyl group at the α-position of methylacrolein.

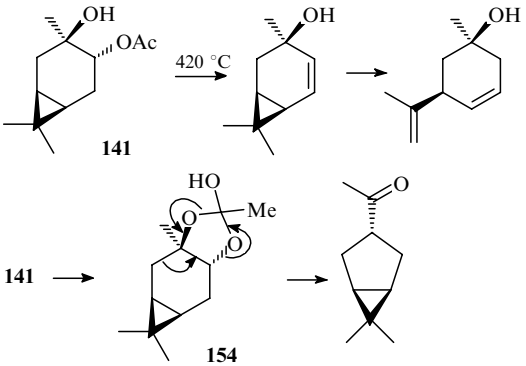
We have already described the rearrangements of the carane skeleton into the bicyclo[3.1.0]hexane one, for epoxycaranes as examples. A formally similar rearrangement of the carane skeleton is observed during the transformation of car-2-en-4-one oxime (**147**) on treatment with nitrous acid.[133] Considering the nature of the functional substituent, the most probable pathway for the transformation of oxime **147** involves intermediates **148**–**152**.



Obviously, it is the shift of the alkyl group in the charged system that is responsible for the rearrangement of the carane skeleton. Using quantum-chemical calculations, it was concluded [133] that the 1,2-alkyl shift in ion **152** is impossible from the viewpoint of its spatial structure and from thermodynamical considerations. As regards ion **151**, it is assumed that concerted elimination of nitrogen occurs in it, with simultaneous attack of the acetate group and migration of the C(5)–C(6) bond. Cation **153** is stabilised by capturing a NO_2^- anion. A transition state of the type **151** has been postulated earlier [130, 134] in order to explain the pyrolysis of caranediol monoacetate **141**.

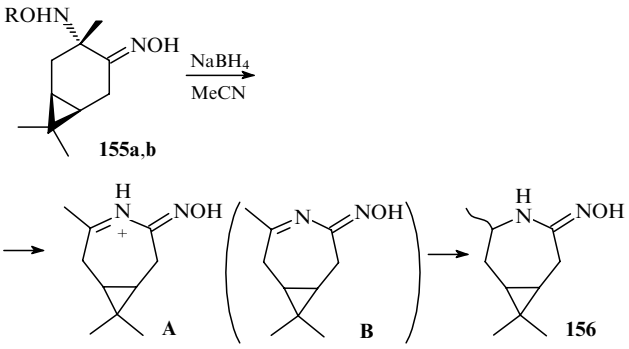
Scheme 3





However, the suggested cyclic intermediate **154** accounts for the rearrangement of bonds but formally and schematically. It is obvious that the thermal shift of the C(2)—C(3) bond can only occur in an ion. Probably, acetic acid that has already been eliminated (by a concerted mechanism) and is present in the reaction mixture favours the formation of intermediate ions.

An even more surprising example of skeletal rearrangements caused by the participation of the oxyimine group has been reported.[135] 3α-Hydroxyaminocaran-4-one oxime (**155a**) and 3α-(*O*-acetyl)hydroxyaminocaran-4-one oxime (**155b**) react with sodium borohydride in acetonitrile resulting in reaction product **156** with a fused seven-membered ring.



R = H (**a**), Ac (**b**).

In this case, acetonitrile is probably not only a solvent but also a reagent, because rearrangement does not occur when it is absent. The authors postulate two possible intermediates of this reaction (**A** or **B**) but note that the mechanism of their formation is not clear yet.

* * *

The vast material considered in this paper indicates that studies of the chemical transformations of carane derivatives goes far beyond the scope of the area of organic chemistry which is customary to regard the chemistry of terpenoids. 3-Carene is a really unique natural compound that offers wide opportunities to scientists. Owing to the accessibility of this compound, a lot of new compounds are being obtained from it; these are interesting both by themselves and as excellent models for studying reaction mechanisms. We believe that only benzene can compare with 3-carene as regards its contribution to theoretical and synthetic chemistry. The authors are far from thinking that nature has deliberately taken care of organic chemists, but it is hard to overestimate the generosity of this natural gift. We do hope that our readers feel the same way.

Although we attempted to consider the mechanisms of the known rearrangements, attentive readers have surely noticed that these mechanisms are often hypothetical and sometimes questionable. There is no doubt that studies in this field will be continued and will not only provide answers for the today's questions but also raise new ones.

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