Skeletal Rearrangements in Organic Chemistry

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This book is the only monograph that analyzes in detail and in a comprehensive manner the main issues of skeletal rearrangements, which are of exceptional importance in synthetic organic chemistry, at a high scientific level and in a concise form. Particular attention was paid to the description of the mechanisms of skeletal rearrangements leading to hard-to-reach and valuable natural bioactive compounds, the synthesis of which by other routes is extremely difficult. The description of the mechanisms of over one hundred examples of reactions occurring through skeletal rearrangements of various types is given. For chemists-researchers working in the field of organic synthesis and can also be recommended to teachers, postgraduate students and students of higher education institutions and universities.

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INTRODUCTION

In modern organic chemistry, among numerous chemical transformations, molecular and skeletal rearrangements occupy a special place. Readers can find fairly extensive information on molecular rearrangements in a number of serial books and textbooks [1-6]. For a more in-depth study, the monograph [7] is recommended. What is the difference between a skeletal rearrangement and a molecular rearrangement?

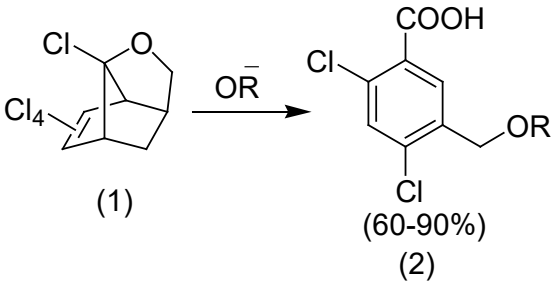
During molecular rearrangements, the mutual arrangement of atoms in a molecule, the location of multiple bonds and their multiplicity change. They can be carried out with the preservation of the atomic composition of the molecule (isomerization) or with a change in it. Reactions that result in the formation of molecules identical to the original ones are called degenerate rearrangements. Molecular rearrangements are divided into two main types:

a) intermolecular, when the migrating group of atoms or the atom is completely separated from the molecule and can be attached to any atom of another such molecule;
b) intramolecular, when the migrating group passes from one atom to another in the same molecule.

Molecular rearrangements during which intramolecular migration of a group with its pair of electrons to an electron-deficient center occurs are called nucleophilic or anionotropic, and when migrating to a carbon atom containing an unshared pair of electrons, they are called electrophilic or cationotropic.

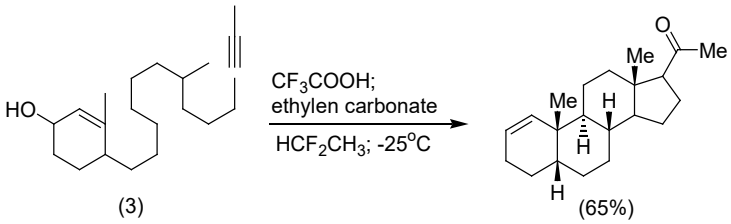
However, in skeletal rearrangement, in principle, the molecule involved in the reaction, breaking down into its constituent parts, is transformed into a different structure, different from the original configuration. The close attention of researchers on this topic is caused by its unique possibilities for obtaining complex and economically important, as well as useful substances. Indeed, in skeletal rearrangement, an exceptionally valuable and exotic product is sometimes observed, which is

very different in structure and properties from the original substrate. For example, from a tricyclic compound of the norbornene series (1), under the action of alcoholates, an aromatic ring (2) is formed in a completely unusual and tandem manner with a non-trivial distribution of substituents in the benzene ring, the synthesis of which by other methods is extremely difficult [8]:



(1) (2)

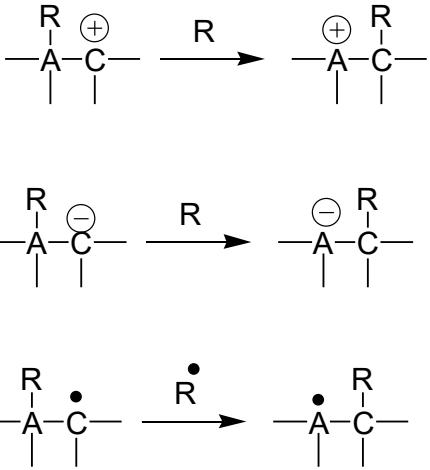
The one-step intramolecular pathway for the formation of steroid compounds (4) from simple alkenes (3) also testifies to the significance of what has been said [9]:



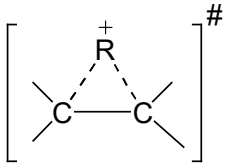
(3) (4)

Rearrangements are reactions that involve the displacement of functional groups or the reorganization of the carbon skeleton of the molecule. This monograph mainly examines rearrangements involving the reorganization (change) of the carbon skeleton. In modern organic chemistry, existing rearrangements are divided into three groups: nucleophilic, electrophilic, and radical. A rearrangement involving the transfer of a substituent to an adjacent carbon atom or heteroatom is common. Of course, in a nucleophilic rearrangement, the displacement

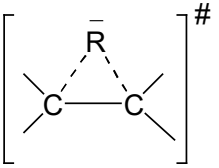
occurs with the formation of an electron sextet, in an electrophilic rearrangement, a free electron pair, and in a radical rearrangement, an unpaired electron.



Electrophilic rearrangements involving carboanionic species are rather less common than similar rearrangements involving carbocations. The difference between them can be clearly seen by comparing their transition states with a 1,2-shift of the alkyl group in the carbocation and carboanion:

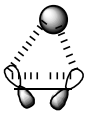


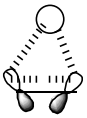
Carbocationic TS
$(2e)^-$

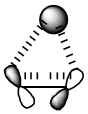


CarboanionicTS
$(4\bar{e})$

If a pair of electrons is required for delocalization and stabilization of the first transition state (TS), then 4 are needed for the second TS. In the first case, the number of electrons is Hückel, and in the second, the number of electrons is Mobius, as shown below:


(2 inversions)

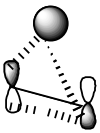

(no inversions)

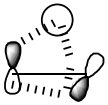

(2 inversions)


(2 inversions)

Suprasurface overlap of AOs having a Hückel topology (for any combination of three pericyclic AOs the number of phase inversions is even or zero).

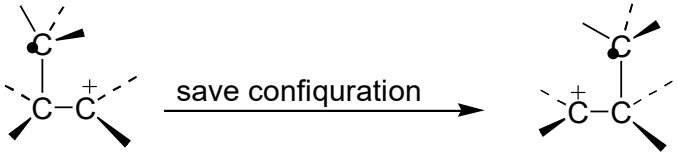

(1 inversion)


(1 inversion)


(3 inversions)

Antara-surface overlap of AOs having a Mobius topology (for any combination of AOs the phase inversion number in the cycle is odd).

And therefore, the carbocationic PS having 2 electrons is an allowed process (Huckel topology) and therefore refers to suprasurface overlaps of interacting orbitals and when the alkyl group migrates to the electron-deficient center, its configuration is preserved [2,5]:



Probably, for this reason, the usual suprasurface 1,2-shift of the alkyl group from carbon to carbon, which has a carboanionic character, is practically unknown. Although there were several examples where the anthrasurface 1,2-alkyl shift (Moebius topology) occurs from other atoms (from nitrogen or sulfur atoms to a carboanion), for example, in the case of the Stevens rearrangement [219-221]. Judging by this, in this monograph we limited ourselves only to considering reactions occurring through a carbocationic TS.

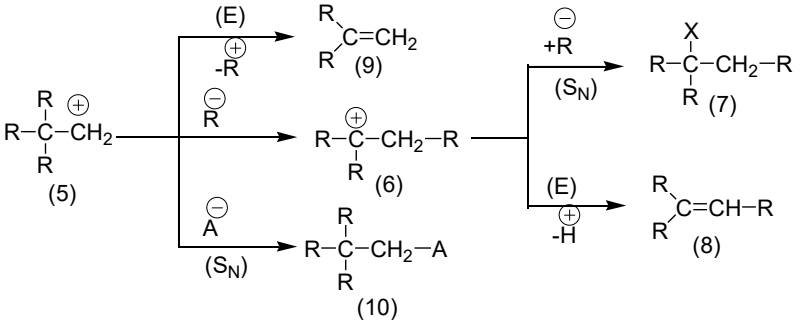
Although there are a number of review articles in the domestic and foreign literature [23,24,26,36,83] considering skeletal rearrangements, nevertheless, the issues presented in them are of a rather narrow nature, cover different topics and corresponding reactions, i.e., there were no views from a common and unified position, and they were not studied in their entirety. This monograph, the first in the periodical press, devoted to the issue of the mechanisms of skeletal rearrangements, which is offered to the attention of readers, aims to eliminate this gap.

CHAPTER ONE

NUCLEOPHILIC REARRANGEMENTS TO AN ELECTRON-DEFICIENT CARBON ATOM

Since the vast majority of intermolecular, intramolecular, and intermediate rearrangements occur via an aromatic transition state of the Huckel type and are pericyclic processes, we will first focus on these processes.

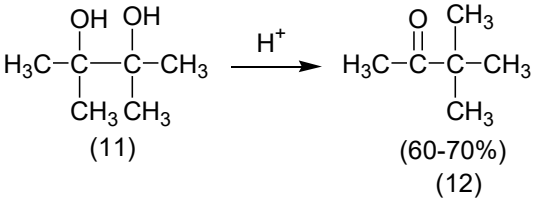
As shown above, this type of rearrangement usually occurs with the formation of a 6-electron carbocation (sextet) (5) during the reaction. The carbocation (5) formed in the gap can be stabilized by migration of the substituent from the adjacent carbon atom to the electron-withdrawing atom and the creation of a strong octet (6). The second way of stabilizing the carbocation (5) can occur by its elimination with the formation of an alkene (9) or by the addition of a nucleophile with the isolation of compound (10). The relative stability of the two carbocations (5) and (6) predetermines the regioselectivity or the ratio of the obtained regioisomers.



Let us consider separately the most important reactions in which sigmatropic migration of groups or substituents to electron-withdrawing atoms of carbon, oxygen, nitrogen, etc. occurs.

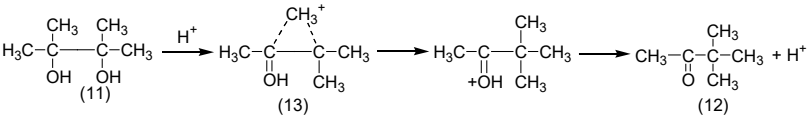
1.1 Pinacol rearrangement

The simplest representative of this type of rearrangement is the classic example of the pinacol rearrangement – the interaction of 2,3-dimethylbutanediol-2,3 (pinacol) with mineral acids to form methyl tert-butyl ketone (pinacolone) [10, 11]:

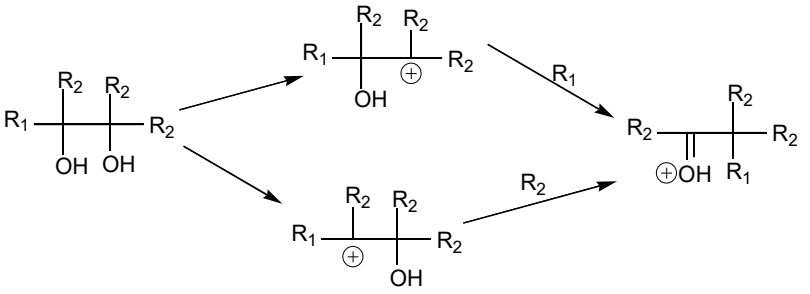


(11) (60-70%) (12)

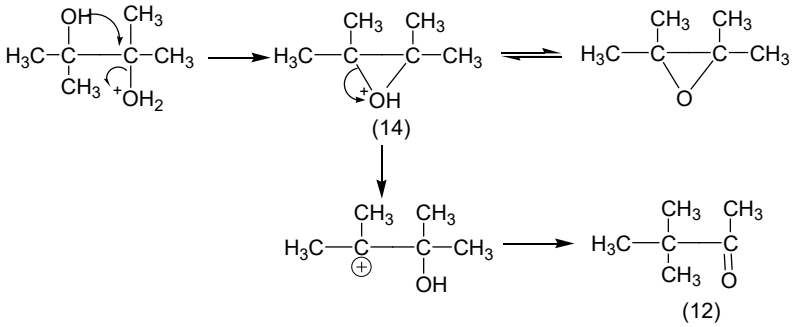
The proposed reaction mechanism involves the generation of a carbocation (13) followed by sigmatropic migration of the CH_3 substituent, which is facilitated by the electron-donating effect of the $\overline{OH}$ group.



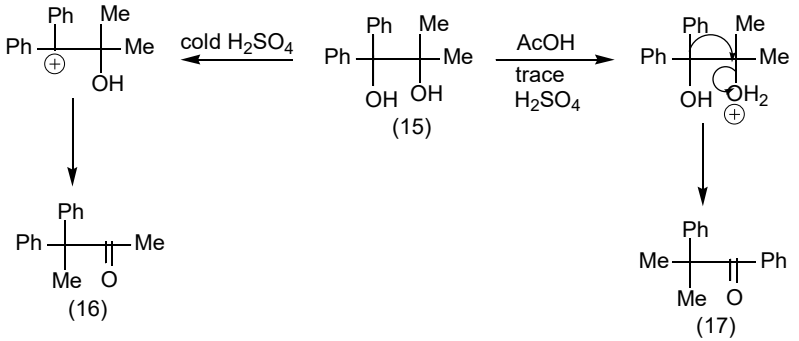
The general scheme of the pinacol rearrangement, first discovered by R. Fittig in 1860, is presented as follows:



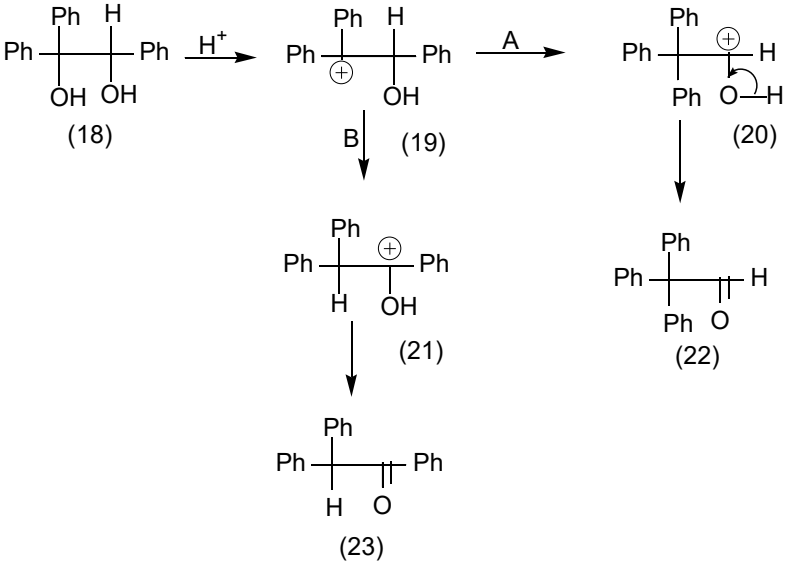
According to some literary sources [12-14], the reaction proceeds with the formation of an epoxy intermediate in situ:



Pinacol rearrangement usually occurs when treating glycol with strong acids. In this case, one of the two more easily ionized C–O bonds forms a carbocation and as a result, one of the groups migrates from the neighboring carbonyl residue. The regiospecificity of the reaction depends entirely on the conditions under which it is carried out. When taking into the reaction the initial substrate containing different substituents (in this case Me and Ph), the direction and corresponding products change greatly:

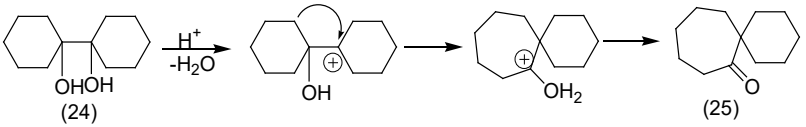


The reaction of compound (15) with cold H_2SO_4 is stereospecific and leads to the formation of product (16), and with acetic acid with traces of sulfuric acid it forms exclusively ketone (17). Let us give another example of the pinacol rearrangement of the asymmetric compound (18):

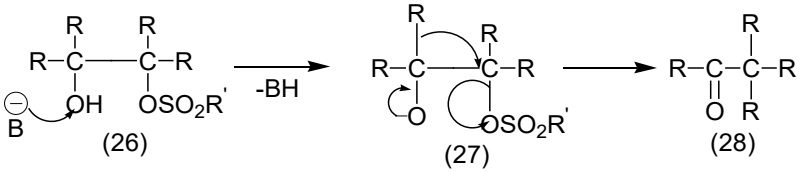


The tertiary hydroxyl in the compound (18) is more easily eliminated, as it leads to a more stable carbocation (19). The latter, in turn, can rearrange with the migration of either phenyl or hydrogen. It has been established that both products (22) and (23) are formed as a result, and in this case the regiospecificity depends on the reaction conditions.

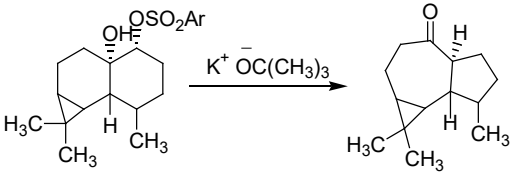
Using the pinocolin rearrangement, it is possible to obtain overloaded ketones that are difficult to obtain by other routes. In addition, using this method, it is easy to synthesize trisubstituted acetic acids, the production of which by other routes is almost impossible. A remarkable transition of cyclic pinazones (24) to spirane ketones (25) is carried out through the pinocolin rearrangement [15]:

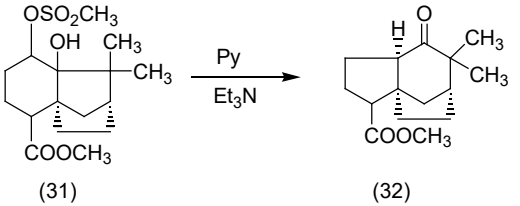


Glycol monosulfonates (26) under the action of bases generate carbon anion (27) and rearrange into ketones (28):

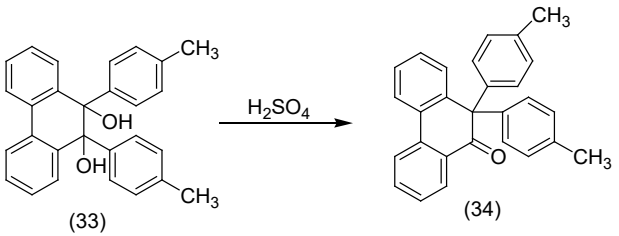


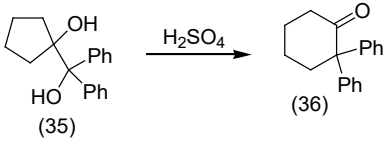
This rearrangement method is often used in the construction of cyclic compounds, especially in the synthesis of terpenes [16, 17]:





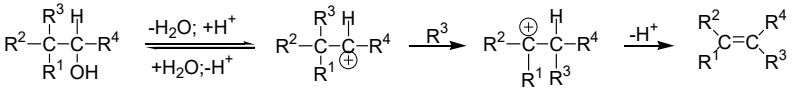
Examples of pinacol rearrangements [18, 19]:





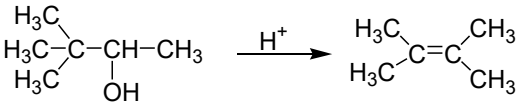
1.2 Retropinacol rearrangement

In this type of reaction, the process is also carried out by the formation of a carbocation (38) due to the splitting off of hydroxyl or halogen in the substrate (37). The carbocation (38) is stabilized as a result of the migration of groups from the neighboring carbon atom and the newly formed carbonium ion (39), throwing off a proton, is transformed into an olefin (40) [1-6]:



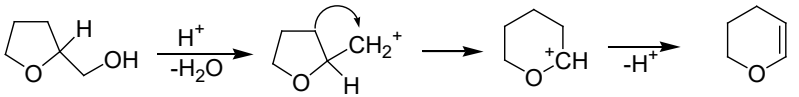
(37) (38) (39) (40)

The simplest example of such a rearrangement is the reaction of pinacol alcohol (41) with acid, accompanied by the formation of tetramethylethylene (42):



(41) (42)

Dihydropyran (44), which is widely used in directed synthesis as a hydroxyl protecting group, can be obtained by dehydration of tetrahydrofurfuryl alcohol (43) via a retropinacol rearrangement step [20, 21]:

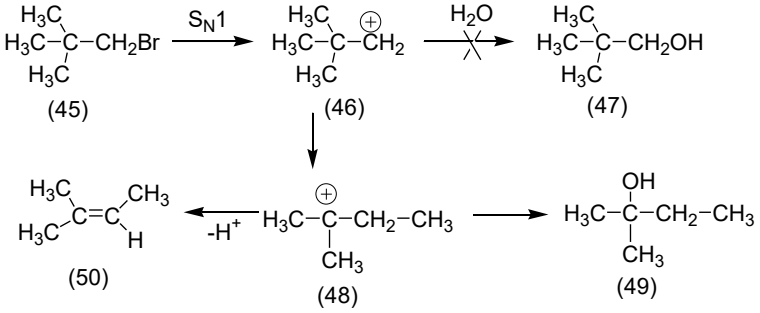


(43) (44)

1.3. Wagner-Meerwein rearrangement

The above-mentioned rearrangement was discovered in 1899 by G. Wagner during the dehydration of alcohols of the class of bicyclic native terpenes and was further studied in detail by G. Meerwein in the 1920s,

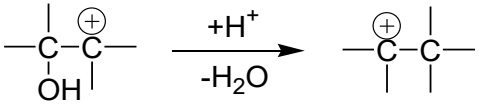
who proposed a carbocation mechanism for this reaction. It is sometimes called the neopentyl or camphene [1,2]-sigmatropic rearrangement of the first row, since the first tested reaction of hydrolysis of neopentyl bromide by the SN_1 mechanism did not give the expected product (47), but, contrary to expectations, led to the formation of compound (49) [22]:



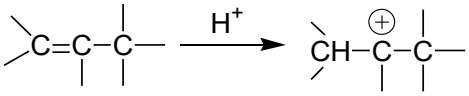
The distinctive stability of the carbocation (48) compared to the ion (46) facilitates the cleavage of the C—C bond and the migration of substituents (alkyl, aryl, etc.) from the adjacent position to the carbocation center, and hence this type of transformation is sometimes called the [1,2]-sigmatropic Wagner-Meerwein rearrangement. The presence of the carbocation (48) in this transformation is confirmed by the formation of a tiny amount of the alkene (50).

The generation of the carbocation in these reactions can occur in the following ways:

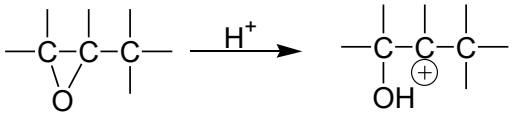
a) by the elimination of hydroxyl under the action of the anion of strong acids:



b) The addition of a proton to a double bond:



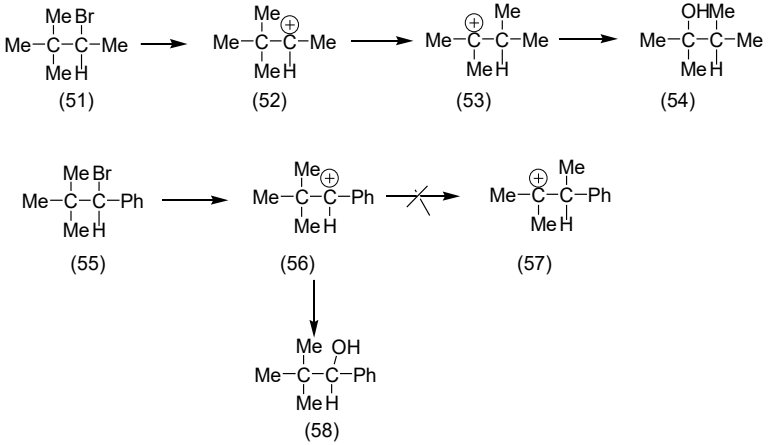
c) Opening of the epoxy ring:



In most cases, the 1,2-sigmatropic shift of substituents in these reactions depends substantially on the strength of their nucleophilicity and the migration ability is arranged in the following order:

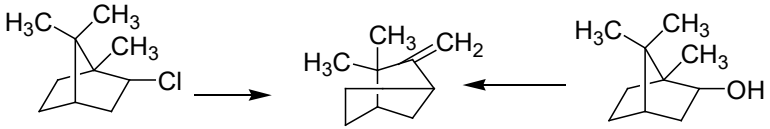
-H< -Me < -Et < -iso-Pr <-iso-Bu< -tret-Bu < -Ph

In addition, if the neopentyl bromide (51) rearranges during hydrolysis, this is not observed in its phenyl analogue (55):

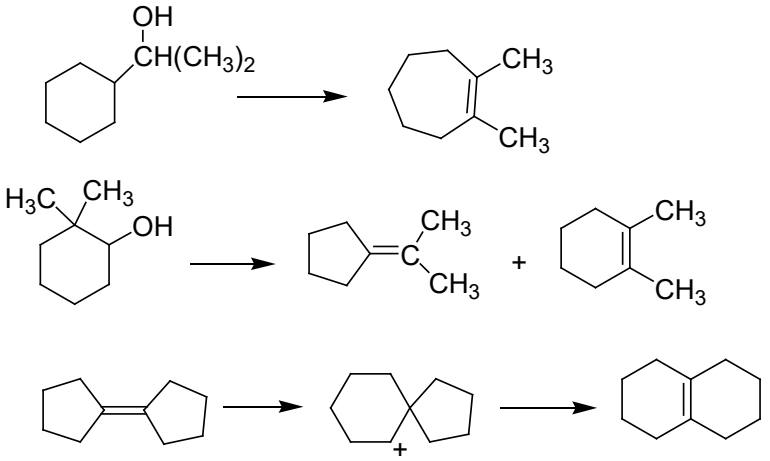


Although the benzyl cation in this case is secondary rather than tertiary, this fact indicates the dominant stability of this cation compared to the methyl one. The Wagner-Meerwein rearrangement occurs in solutions and melts and is often accompanied by expansion or contraction of the rings.

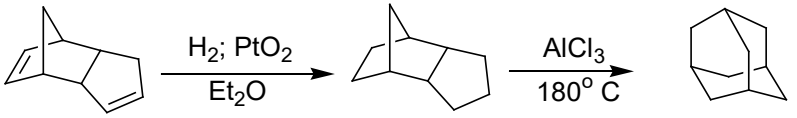
It is especially characteristic of mono- and bicyclic terpenes.



It occurs similarly in cyclic compounds:

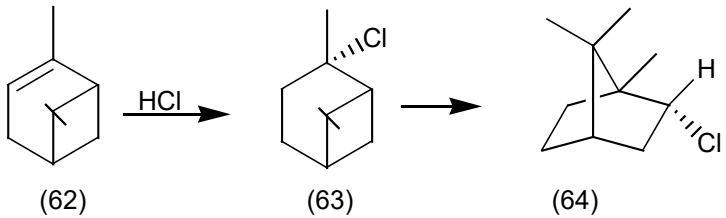


A very accessible compound, the cyclopentadiene dimer (59), undergoes catalytic hydrogenation, after which the obtained fully hydrogenated product (60) isomerizes via the Wagner-Meerwein rearrangement to adamantane (61) under the action of Lewis acids [23]:



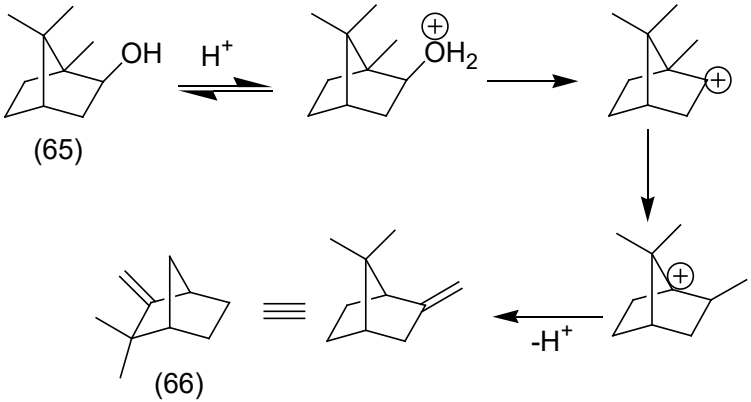
(59) (60) (61)

If the reaction of α-pinene (62) is carried out at a very low temperature and the reaction mixture is protected from moisture, pinene hydrochloride (63) can be easily obtained. The latter readily undergoes a Wagner-Meerwein rearrangement with a shift of one of the C—C bonds to obtain bornyl chloride (64) [7]:



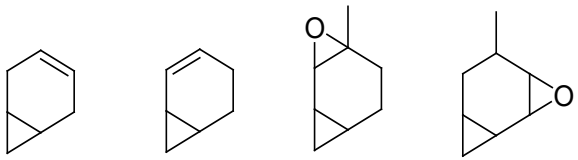
(62) (63) (64)

The monoterpenoid, the racemate of isoborneol (65), easily undergoes a Wagner-Meerwein rearrangement under the action of strong acids and, by releasing water, is converted into camphene (66) [22]:



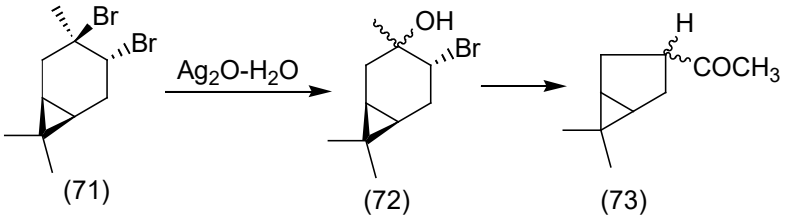
(65) (66)

In the review article [24], rearrangements of carane compounds (67-70) in addition, elimination and substitution reactions were considered, and the stereochemical features of carane derivatives were systematically studied, and some structural and spatial prerequisites determining the nature of the rearrangements were identified:



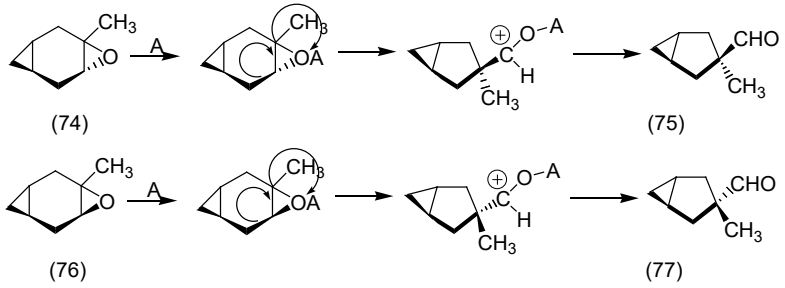
(67) (68) (69) (70)

However, in the indicated work the issues considered mainly relate to molecular rearrangements (allylic and homoallylic with the involvement of the cyclopropyl radical) of the above-mentioned compounds and therefore go beyond the scope of the main material we have provided. Nevertheless, in the last chapter the authors touched upon the Wagner-Meerwein rearrangement, which occurs through the migration of the neighboring group. Such a rearrangement in the indicated systems was first found by Kuchinsky et al. [25]. It was shown that the reaction of 3β,4α-dibromocarane (71) with aqueous Ag_2O mainly yields 3-acetyl-6,6-dimethylbicyclo[3.1.0]hexane (73). The formation of (73) from compound (71) under conditions of nucleophilic substitution is explained by assuming in situ conversion of 3-carene (72) to bromohydrin:

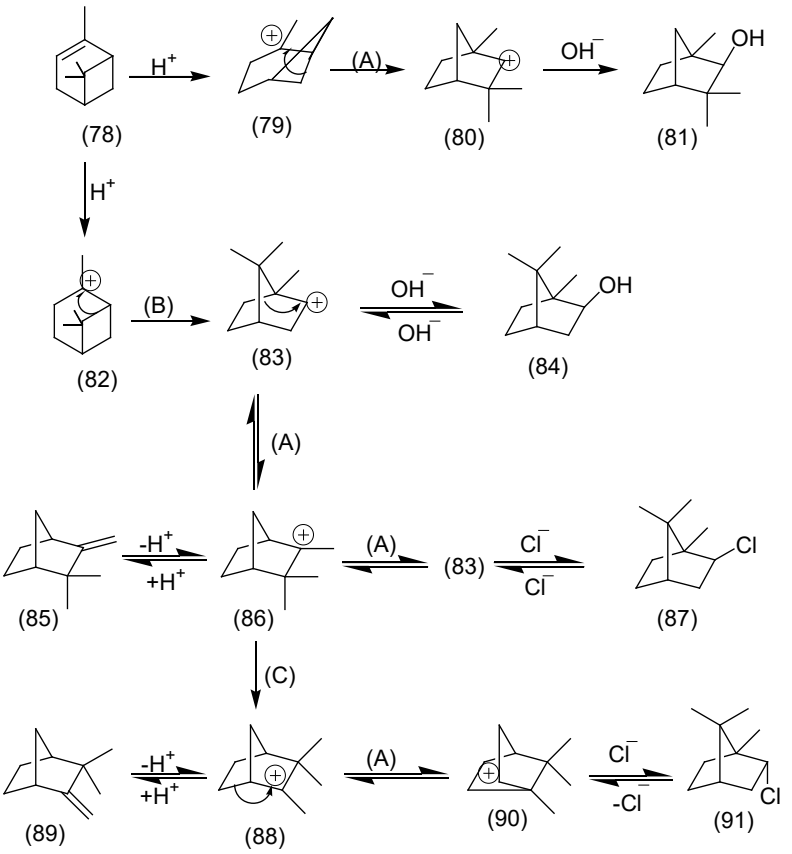


Compound (73) can be formed by a 1,2-shift of C_2 – C_3 according to Wagner-Meerwein by narrowing of the cyclohexane ring.

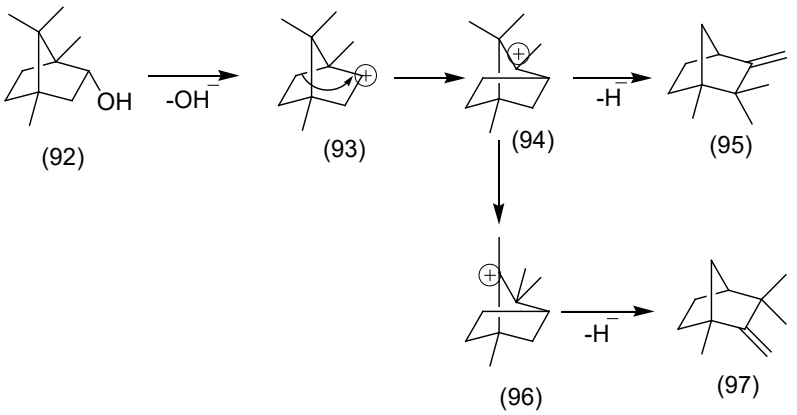
It is noteworthy that for stereoisomeric 3,4-epoxycaranes (74) and (76) a rearrangement with narrowing of the cyclohexane ring in the other direction is characteristic – with 1,2 migration of the C_4—C_5 bond:



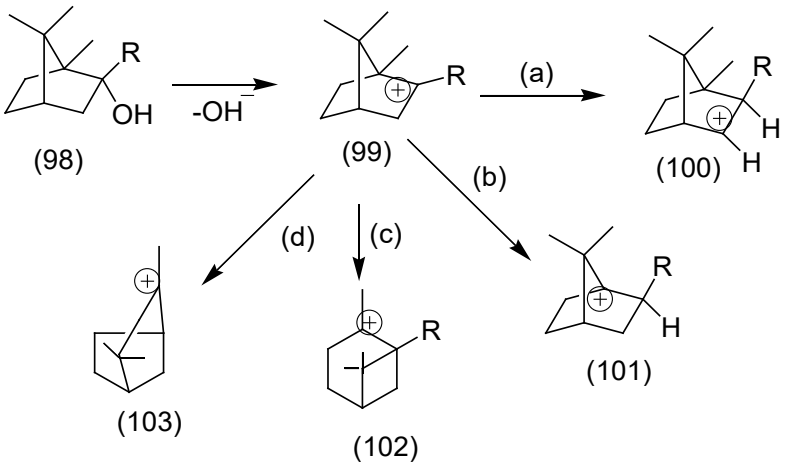
As indicated above, the Wagner-Meerwein skeletal rearrangement refers to the camphene rearrangement of the first kind and it occurs mainly in compounds of the terpene series under conditions of nucleophilic substitution, addition and elimination. In these reactions, the formation of a carbocation can lead to migration of the C—C bond in the ring (path A), bridge (B) or 1,2 – shift of the side group (C):



As can be seen from the above scheme, the rearrangement of α-pinene (78) can actually lead to: a) in the ring (path A) to the formation of fenchyl alcohol (81), b) in the bridge (path B) to borneol (84), c) 1,2-shift of the side methyl group (C) to (-)- (85) and (+) – camphenes (89). The formation of isobornyl chloride (87) and bornyl chloride (91) is also carried out by the rearrangement of the α-pinene molecule along path (A). In this scheme, the paths A and B shown, for example, the formation of (-) camphene from borneol (83→86→85) refer to the Wagner-Meerwein rearrangement. At first glance, one can assume that these paths should lead to separate enantiomers, since one of the chiral centers of the borneol molecule does not participate in this reaction. However, what is actually formed is a mixture of enantiomers or simply racemates. It turns out that in this reaction, the methyl group is simultaneously displaced (path C). This parallel competing reaction is called the camphene rearrangement of the second kind and is recognized as the Nametkin rearrangement. In this scheme: (-)-camphene → (86) → (88) → (90) → bornyl chloride (91). Geometric isomers can be formed in these reactions:



The chemoselectivity and structure of the resulting products of camphene rearrangements are determined by the relative rates of competing reactions. For borneol derivatives (98), the following types of rearrangements can be assumed:

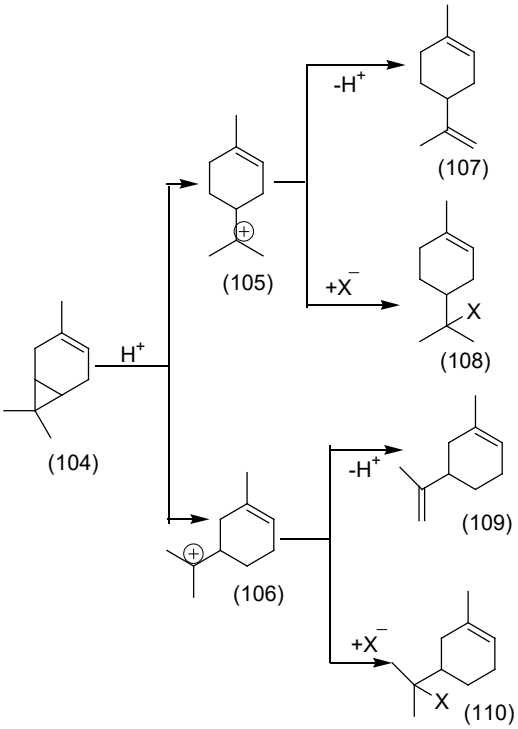


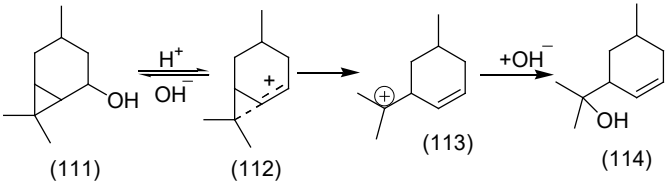
Of the four products listed in the reaction scheme, the carbocation (103) is mainly realized. In case (a), a less stable secondary carbocation (100) is formed, path (b) is forbidden by the Bredt rule, and path (c) promises a thermodynamically less favorable four-membered ring. In turn, the carbocation (103) can then split off a proton, add a nucleophile and undergo a rearrangement. A recently published review article [26] examines in more detail the chemistry of one of the widespread monoterpenoids, 3-carene (104), which is part of essential oils and turpentines. Interest in this type of terpenes is due to the presence of two reaction centers (a double bond and a cyclopropane ring), characterized by increased electron density, which makes it reactive with electrophilic agents. And from a practical point of view, 3-carene is a very useful substrate for obtaining important natural substances - pheromones, pyrethroids, sesquiterpenoids, juvenoids, fragrant compounds, etc.

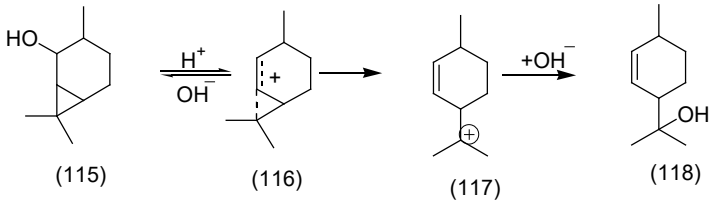
The authors of the work [26] emphasize that in the existing reviews [27, 28] and an extensive monograph [29] the factual materials on carane compounds include up to 1976, and they almost do not consider the mechanisms of the described reactions, mainly they are of a stating nature. Particular attention in the review [26] is given to the mechanisms of 3-carene rearrangements.

It was established [26] that, depending on the reaction conditions, the cyclopropane ring acts as an isolated reaction center, leading to carbocations (105) and (106).

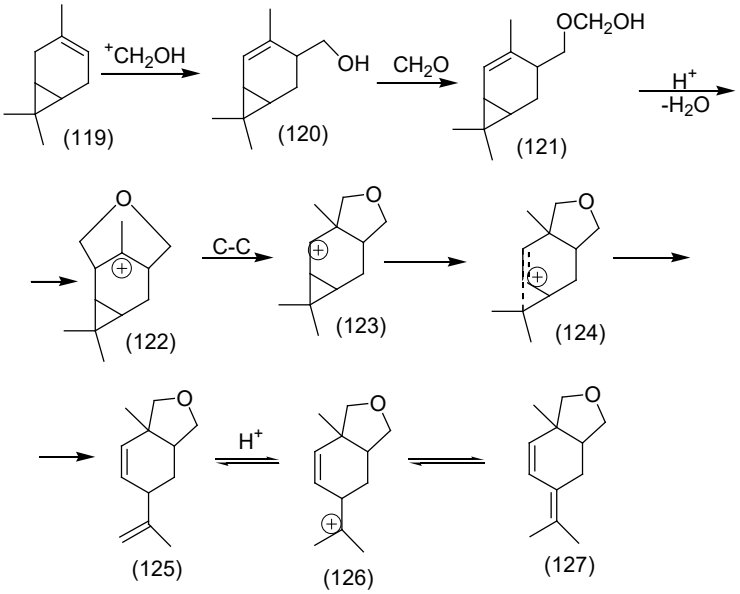
Here the double bond does not interact with the formed carbocation center; the latter is stabilized by the splitting off of a proton or the addition of a nucleophile. Classifications, ionic rearrangements of carane structures are divided into Wagner-Meerwein type rearrangement with narrowing of the six-membered ring, homoallylic rearrangement and rearrangement with transannular participation of the cyclopropane fragment. According to the authors [26], the Wagner-Meerwein rearrangement is better considered from the standpoint of concerted reactions, since they involve shifts of substituents or alkyl groups in charged systems. The reason for the dominant behavior of the cyclopropane ring compared to the double bond is explained from the standpoint of the principle of hard and soft bases (HSBP). Cyclopropane has a harder base than the double bond (ionization potentials of 10.9 and 9.3 eV, respectively). As can be seen from the above scheme, the specified rearrangement occurs by homoallylic displacement of the double bond, rather than the Wagner-Meerwein rearrangement (in the cases of carbocations 113 and 117).


-H+
(107)
(105)
+X−
X
(108)
H+
(104)
-H+
(109)
(106)
+X−
X
(110)


H+
OH−
OH
+OH−
OH
(111)
(112)
(113)
(114)


HO
H+
OH−
+OH−
OH
(115)
(116)
(117)
(118)

In the condensation of 3-carene with CH_2O according to Prins, the mechanisms of formation of esters (125) and (127) are interpreted by the sequential occurrence of the Wagner-Meerwein rearrangement and homoallyl [30, 31]:



As can be seen from the equation scheme, the Wagner-Meerwein rearrangement, occurring as an alkyl shift, does not change the structure of the carane. However, the alkyl shift is real only because in the secondary ion (123) delocalization of the carbocation with the participation of cyclopropane leads to its opening and formation of a thermodynamically more stable homoallyl cation (124), the latter, in turn, is stabilized by the release of a proton from one of the gem-dimethyl groups, giving compound (125). Cyclic ether (125) is converted into another isomer (127) via the classical carbocation (126).

1.4. Favorsky rearrangement

The well-known rearrangement of α-haloketones in synthetic organic chemistry, called the Favorsky rearrangement, was discovered in a series