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Skeletal transformations of heterocage compounds involving the hetero-function

B M Lerman

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Abstract. Published data on the skeletal transformations of oxa-, aza-, bora- and polythia-cage compounds accompanied by replacement of one heteroatom by another, of a heteroatom by a carbon atom or of a carbon atom by a heteroatom are surveyed. Skeletal transformations of compounds with oxacage structures leading to compounds with carbocage structures are considered. The bibliography includes 65 references.

I. Introduction

Synthtic methods based on skeletal rearrangements occupy a prominent place in the chemistry of cage and heterocage compounds. The types of these rearrangements are quite diverse; rearrangements typical of cage compounds do not necessarily occur in their hetero-analogues. The most famous skeletal rearrangement of carbopolycyclanes, namely, the thermodynamically controlled isomerisation induced by strong Lewis acids, the discovery of which has opened up the way to adamantane, its homologues, polymantanes and many other cage compounds, provides an example of 'non-universal' processes. This rearrangement has found no use in the synthesis of heteroorganic derivatives, because their skeletons are unstable in strongly acidic media. However, a large number of rearrangements occur successfully in reactions of both cage and heterocage compounds. This group includes the rearrangement of (hetero)cubanes into (hetero)snowtanes, photoisomerisation of (hetero)polycyclodienes, skeletal interconversions of functionally substituted (2,4,6,8-tetrathia)adamantanes and (2,4,6,8-tetrathia)protoadamantanes, *etc*. These rearrangements have been considered in the monographs by Fort [1] and Bagrii,[2] in the well known reviews dealing with the chemistry of cage and heterocage compounds [3 – 5] and in a number of reviews specially devoted to skeletal rearrangements of this type of compound.[6 – 9]

In addition to rearrangements that are common to cage compounds and their hetero-analogues and to those peculiar only to cage compounds, there exist skeletal rearrangements, which are typical only of heterocage derivatives, because they involve the hetero-function. The picture of skeletal rearrangements of (hetero)cage compounds is not complete without this type of rearrangements. However, they have not been considered in the monographs and reviews mentioned above. The purpose of the present review is to fill this gap. We survey the available data on the skeletal transformations of functionally substituted heteropolycyclanes in which a heteroatom is replaced by another heteroatom or by a carbon atom, or a carbon atom is replaced by a heteroatom, the initial heteroanalogous framework being retained. The skeletal rearrangements of oxacage compounds giving rise to derivatives with a related oxacage or a stabilomer carbocage structure are also considered.

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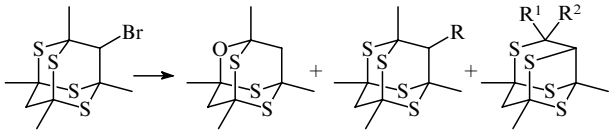
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II. Skeletal transformations with replacement of one heteroatom by another

Transformations of this type accompany some reactions of functional derivatives of 1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane and compounds with the 'bird-cage' structure containing a heteroatom, *i.e*. with the structure of 4-heterohexacyclo-[5.4.1.$0^{2,6}0^{3,10}0^{5,9}0^{8,11}$]dodecane. These transformations give rise to compounds with the same cage structure but with a different heteroatom. Some functional derivatives of the 'bird-cage' series isomerise under the action of appropriate reagents. The initial number of heteroatoms in the cage as well as the initial carboanalogous structure are retained in all the transformations under consideration.

1. S → O transformations

Solvolysis of 9-bromo-1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane **1** in 50% – 92% aqueous acetic acid affords a debromination product, 2-oxa-4,6,8-trithiaadamantane **2** with a different system of heteroatoms. In addition to **2**, the reaction yields a number of compounds in which the initial structure is retained, namely, debromination product **3** and solvolysis product **4**, and derivatives with the protoisomer structure, namely, hydrolysis product **5** and dehydrobromination product **6**.



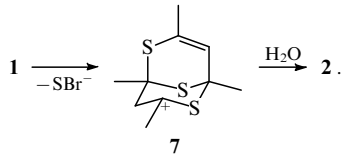
1 **2** **3**: R = H; **4**: R = OH **5**: R^1 = Me, R^2 = OH; **6**: $R^1 + R^2 = CH_2$

The proportion of the compound **2** in the product mixture depends on the concentration of acetic acid, the highest content (56%) being attained in 90% acid (Table 1). It is noteworthy that solvolysis of the bromide **1** in 50% – 90% formic acid also yields **2**; however, in this case, the proportion of **2** in the product mixture does not exceed 5%.[10,11]

Table 1. Acid solvolysis of the bromide **1** under various conditions.

Acid concentration (%)	Composition of the reaction products (%)			
	2	**3**	**4**	**5**, **6**
MeCOOH				
92	54	37	9	–
90	56	34	6	–
80	40	34	26	–
70	18	46	33	–
60	10	42	27	18
50	2	22	15	45
HCOOH				
92	2	37	62	–
85	5	37	58	–
60	4	37	59	–
50	2	36	55	–

A probable scheme for this transformation includes fragmentation with the abstraction of SBr^- and subsequent cyclisation of the unsaturated bicyclic intermediate **7** induced by H_2O and leading to the incorporation of oxygen into the skeleton.



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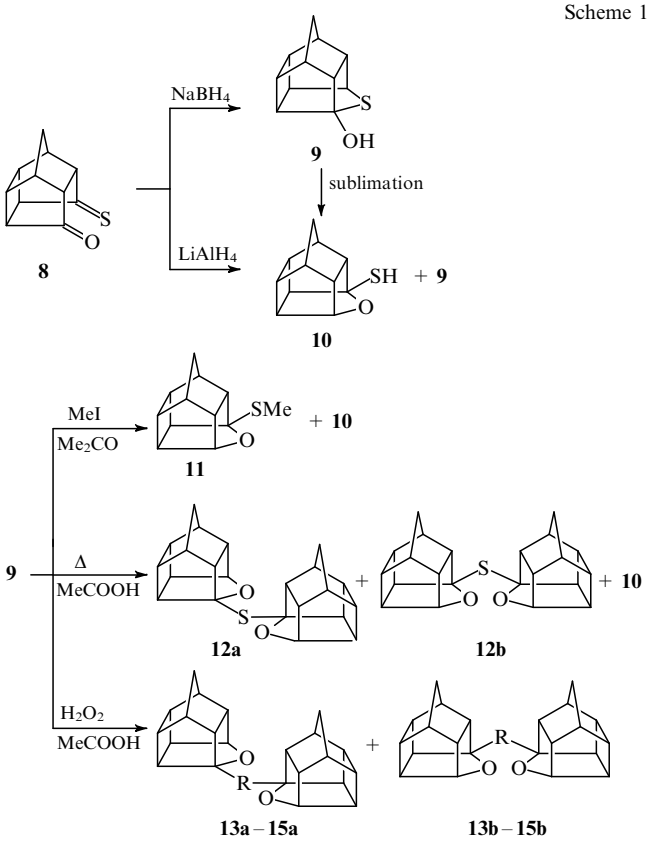
It should be noted that the compound **2** is formed as a side product in the synthesis of 1,3,5,7-tetramethyl-2,4,6,8-tetrathiaadamantane **3** by condensation of acetylacetone with hydrogen sulfide in concentrated HCl. Condensation of these compounds in glacial acetic acid affords **3** as the only product.[12]

Transformations of 4-hydroxy-derivative **9** are also accompanied by skeletal rearrangements in which the sulfur atom is replaced by oxygen (Scheme 1). The compound **9** is prepared from thioketone **8** having a pentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]un-decane structure by reduction with $NaBH_4$, which is accompanied by transannular cyclisation. When $LiALH_4$ is used instead of $NaBH_4$, the reaction gives isomeric thiol **10**, in addition to **9**. The compound **9** does not isomerise to **10** under the action of $LiAlH_4$; however, this isomerisation easily occurs upon sublimation of **9** and upon treatment of **9** with methyl iodide in acetone. In the latter case, thiomethylation product **11** is formed together with the thiol **10**. This isomerisation also occurs during the thermolysis of **9** in acetic acid; this gives a mixture of the thiol **10** and bicage sulfides **12a** and **12b** in a ratio of 2 : 1.

The same skeletal transformation accompanies oxidation of the compound **9** with H_2O_2 (1 – 10 mol) in MeCOOH leading to bicage disulfide **13**, disulfoxide **14** and sulfone **15**. It is noteworthy that each of these compounds is formed as a mixture of two diastereomers **a** and **b** (Scheme 1).[13]

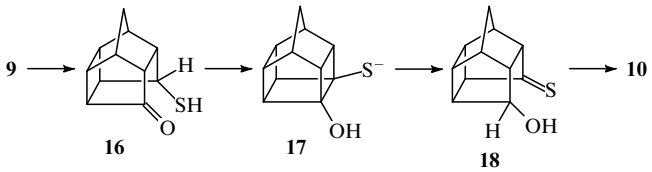
A possible scheme for the above transformation includes the intermediate formation of an open (with respect to the internal thioacetal **9**) form **16**, which is followed by transfer of the chelating proton from sulfur to oxygen, which might lead to

Scheme 1



13: R = SS; **14**: R = SOSO; **15**: R = SO_2.

intermediate **17**. The 'open' hydroxy-thione **18** thus formed is then converted into the corresponding cyclic form, the thiol **10**.

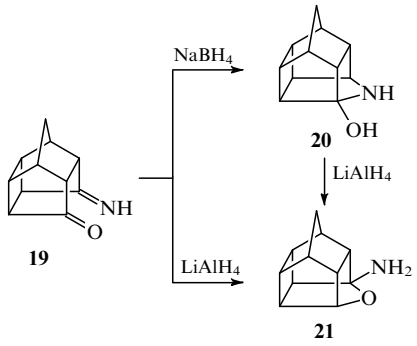


The bicage sulfide **12** results most likely from the interaction of the intermediate **18** with the thiol **10** accompanied by elimination of H_2S. The formation of the compounds **13** – **15** can be rationalised, in turn, in terms of a scheme including isomerisation of **9** to **10** followed by a series of consecutive oxidation stages, **10** → **13** → **14** → **15**. The formation of the latter compound is accompanied by the abstraction of SO_2.

2. N → O transformations

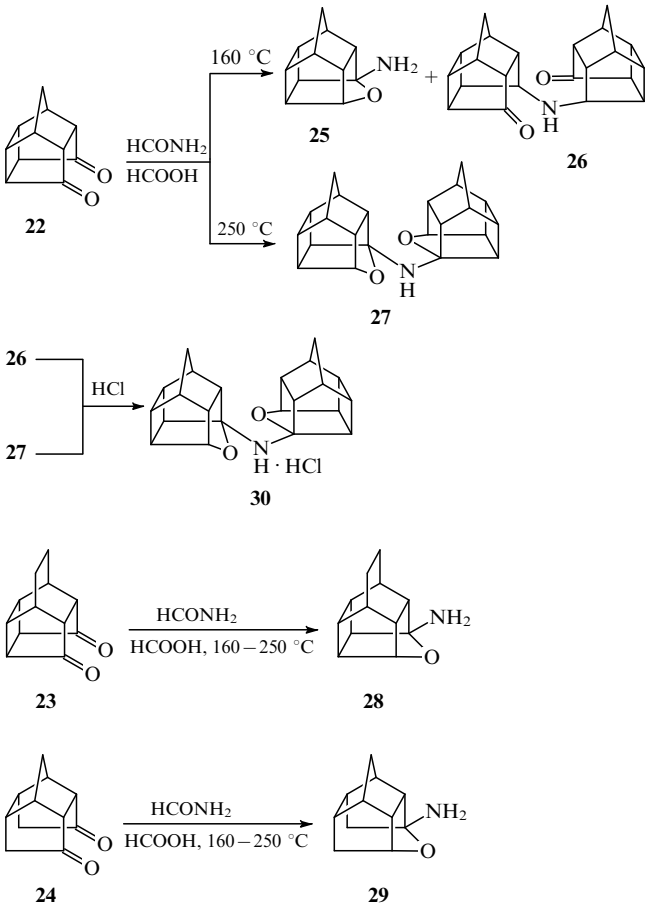
Skeletal transformations with replacement of heteroatoms are also typical of compounds with a bird-cage structure containing a nitrogen atom in the cage. For example, isomerisation of hydroxy-derivative **20** into amino-derivative **21** readily occurs in the presence of $LiAlH_4$. When the same reagent is used to reduce imino ketone **19**, the reaction is accompanied by transannular cyclisation and also gives rise to the compound **21**, whereas reduction of the imino ketone **19** with $NaBH_4$ yields only **20** (Scheme 2).[14–16] Apparently, a transformation of this sort also occurs during reductive amination of some cage diketones (3,6-diones **22** – **24**) under the action of formamide in formic acid, which is accompanied by transannular cyclisation (Scheme 3).[17] These reactions involve one carbonyl group and afford the corresponding bird-cage primary and secondary amines **25**, **27** – **29** with an oxygen atom in the cage. Secondary amine **26**, which contains fragments of the initial structure and which is formed from the diketone **22** when the reaction is conducted under mild

Scheme 2

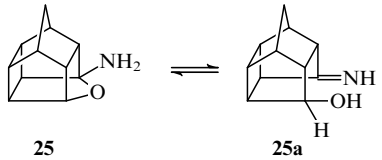


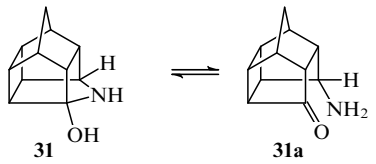
conditions, provides an exception. The fact that the amines **26** and **27** give rise to the same hydrochloride **30** implies that hydrochlorination of the former compound is accompanied by transannular cyclisation and isomerisation.

Scheme 3



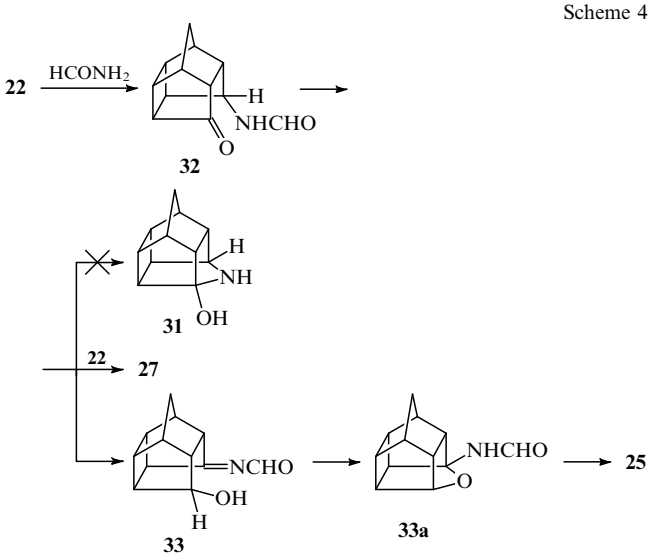
The compounds **25** and **27**–**29** are internal hemiacetals; the corresponding open derivatives are imino alcohols **25a** rather than amino ketones like **31a**, the formation of which should have been expected in the above reactions.





Using the formation of **25** and **27** as an example, it has been shown that the reductive amination of the 3,6-dione **22** is accompanied by isomerisation; most likely, formamido ketone **32** isomerises to give formimino alcohol **33** (Scheme 4). Apparently, the transformation **32** → **33** occurs similarly to the corresponding isomerisation of sulfur-and-oxygen-containing analogues described above.[17]

Scheme 4



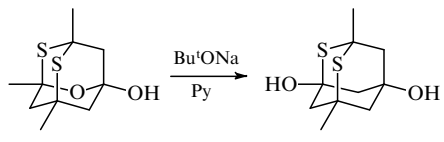
The data presented here indicate that cage compounds with an oxa-bridge are formed preferentially under these conditions. Probably, this is due to the fact that oxygen endows lesser strain to the rigid bird-cage structure than sulfur or nitrogen. Hence, the S → O and N → O type transformations discussed here result in the formation of compounds with a less strained heteroanalogous structure.

III. Skeletal transformations with replacement of oxygen by carbon or of carbon by oxygen

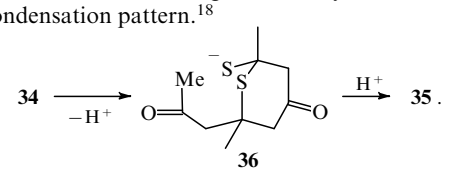
Some transformations of heterocage compounds of the O → C and C → O types have been described; these processes give rise to derivatives with carboanalogous structures containing one oxygen atom more or less in the cage than the initial compound.

1. 'Oxadithiaadamantane → dithiaadamantane' transformation

Treatment of 1-hydroxy-3,5,7-trimethyl-2-oxa-4,6-dithiaadamantane **34** with Bu^{t}ONa in pyridine and then with an acid results in its partial isomerisation to give the dihydroxy-derivative of 3,5-dimethyl-2,4-dithiaadamantane **35**. The proportion of this compound in the mixture of reaction products amounts to 20% – 25%.



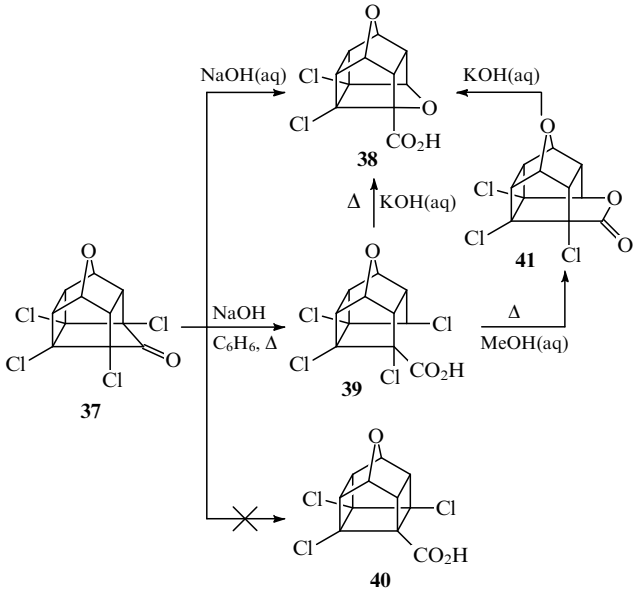
A possible mechanism of this isomerisation includes base-induced ionisation of the compound **34** and subsequent rupture of two bonds; the resulting anion **36** cyclises according to the aldol condensation pattern.[18]



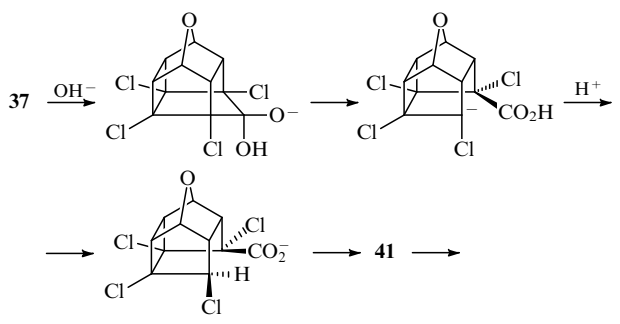
2. C → O transformation

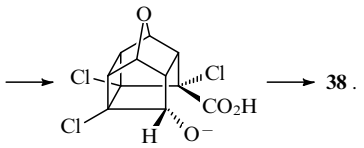
The conversion of the C → O type accompanies the transformation of 1,7,8,11-tetrachloro-ketone **37** having the bird-cage structure and containing one oxygen atom in the cage induced by 25% aqueous NaOH into acid **38** having the bird-cage structure with two oxygen atoms in the cage (yield 66.5%). This acid can be regarded as an abnormal product of the Favorsky rearrangement. If the reaction is carried out in an organic solvent (benzene, toluene, THF), it gives rise to another abnormal product, namely, tetrachloro-substituted carboxylic acid **39** with the 11-oxapentacyclo[6.2.1.$0^{2,7}$.$0^{4,10}$.$0^{5,9}$]undecane structure (yield 80.2%). The normal product of the Favorsky rearrangement, acid **40** having a substituted bishomocubane structure, is not formed under the conditions studied. When the acid **39** is refluxed in aqueous KOH, it is converted into the acid **38**, while heating of **39** in aqueous methanol gives rise to lactone **41**. When the latter is kept in aqueous KOH, it is also converted into the compound **38** (Scheme 5).

Scheme 5



The **37** → **38** transformation occurs most likely by a mechanism that includes formation of the lactone **41**.[19]

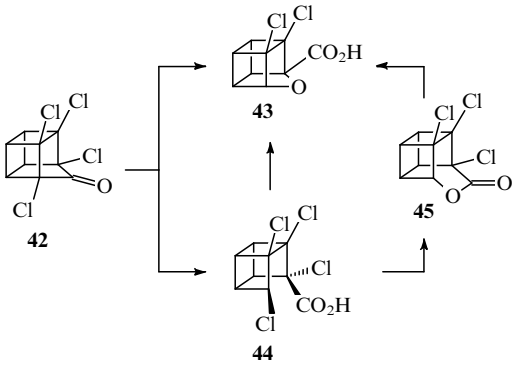




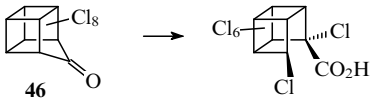
Presumably, the C → O transformation under discussion results in the formation of a less strained structure, because the –O– bridge imparts lesser strain to the rigid bird-cage framework than a carbonyl group incorporated into its 'wing'. At the same time, the resulting structure with two oxygen atoms is certainly less strained than the structure of the bishomocubane oxa-derivative.

According to the above mechanism, the product **38** is formed without participation of the oxygen bridge already present in the cage. This is confirmed by the occurrence of a similar transformation in the series of carbocage α-halo-ketones. For example, ketone **42** with a homocubane, pentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]-nonanone, structure was converted, depending on the reaction conditions, into chloro-derivative of oxacubanecarboxylic acid **43** or chloro-derivative of secocubanecarboxylic acid **44** (Scheme 6). The **44** → **45** → **43** transformations were also accomplished. In this case, too, no normal Favorsky rearrangement product was obtained.[20]

Scheme 6

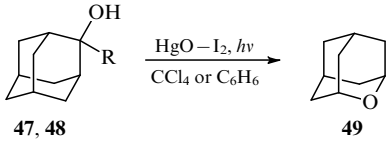


Unlike the tetrachloro-ketone **42**, octachloro-ketone **46** with the same structure is converted under similar conditions only into the octachloro-derivative of secocubanecarboxylic acid.[21]



In many other reactions of cage α-halo-ketones, α-halo-diketones and corresponding ketals, no C → O transformation products have also been obtained.[21–24] The results presented here make it possible to conclude that the C → O type transformation is peculiar only to those pentacyclic α-halo-ketones in which the structure of the cage and the number and arrangement of halogen atoms ensure additional stabilisation of the corresponding anion.

In addition to the cage (oxa)pentacyclanes discussed above, some 2-substituted adamantanes also undergo this type of transformation. For example, when adamantan-2-ol **47** and its 2-methyl-derivative **48** are exposed to UV radiation in CCl_4 or benzene in the presence of an HgO – I_2 mixture, 2-oxaadamantane **49** is formed in a yield of 43% – 47%.[25,26]



R = H (**47**), Me (**48**).

Reactions of these compounds with other oxidants are not accompanied by a skeletal transformation of this type and yield mostly oxahomoadamantane, 4-oxatricyclo[4.3.1.1^{3,8}]undecane, derivatives.[27–29]

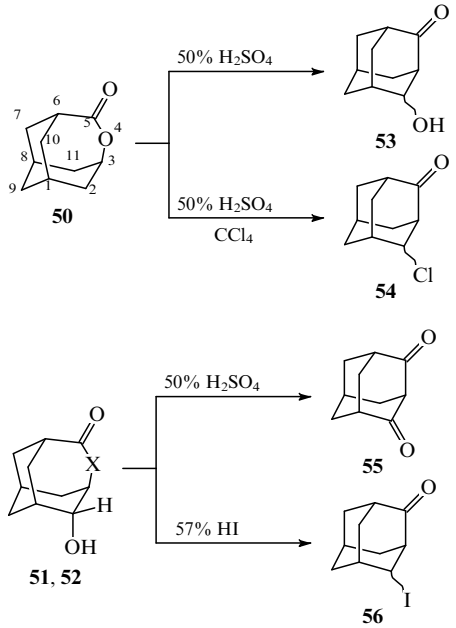
IV. Skeletal transformations of oxacage compounds accompanied by the loss of oxygen and a change in the carbon skeleton

In this Section, we consider reactions of oxacage compounds with electrophiles accompanied by extensive rearrangement of the skeleton. This rearrangement includes opening of the oxygen bridge, loss of the hetero-function and further skeletal transformations resulting in the formation of the corresponding carbocage stabilomer structure.

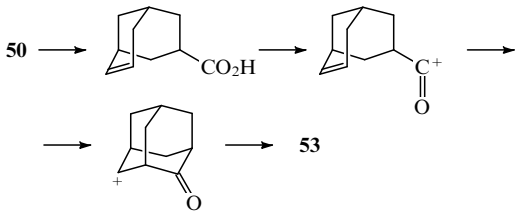
1. Transformations of the 'oxahomoadamantane → adamantane' type

On treatment with H_2SO_4 or hydrohalic acids, compounds of the oxahomoadamantane series with oxygen-containing substituents undergo a skeletal transformation yielding functional-substituted adamantane derivatives: C_{10}-tricyclane stabilomers. This transformation is typical of lactone **50**, 2-hydroxy-lactone **51**, 2-hydroxy-lactam **52** and some other compounds. For example, at 90–100 °C in the presence of 50%–80% H_2SO_4, the lactone **50** isomerises into 2-hydroxyadamantan-4-one **53**, which is formed as a mixture of *syn*- and *anti*-isomers in a ratio of 5 : 1.[30–33] When this reaction is carried out in CCl_4, it gives the product of isomerisation and chlorination, 2-chloroadamantan-4-one **54** (Scheme 7).[30] By treatment with 50% H_2SO_4, the hydroxy-derivative **51** has been converted into adamantane-2,4-dione **55** in 22% yield; the reaction of **51** with 57% HI gives 2-iodoadamantan-4-one **56**.[33] The hydroxy lactam **52** reacts with the above reagents to give the same products but in lower yields than the compound **51**; in addition, compounds with non-rearranged structures are formed.[34]

Scheme 7

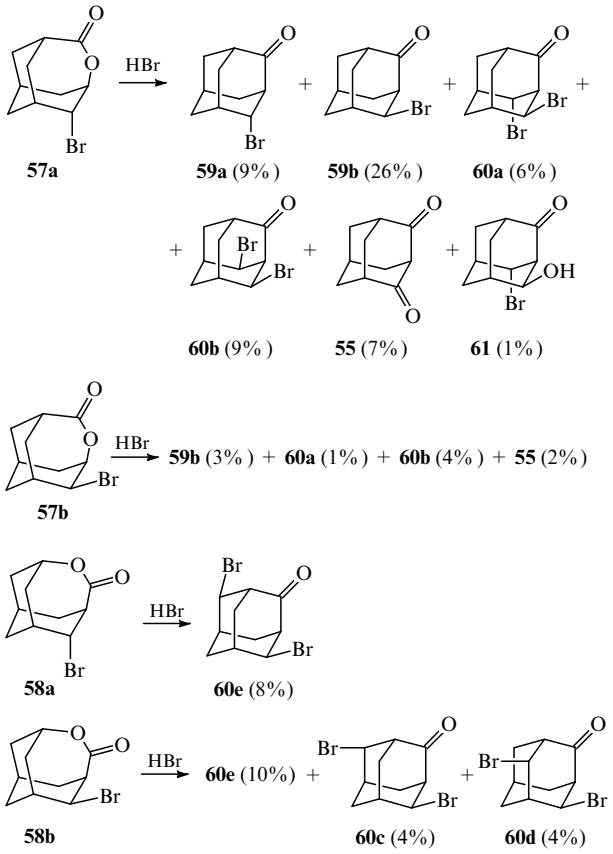


The mechanism of these transformations presumably includes fragmentation and cyclisation stages.

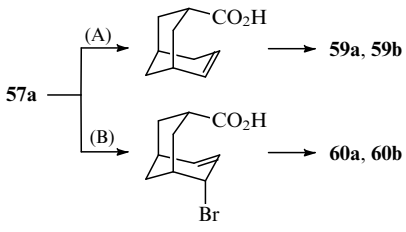


The reactions of individual stereoisomeric 2- and 7-bromolactones **57a**,**b** and **58a**,**b** with 48% HBr give rise to adamantanone derivatives including stereoisomeric 4-bromides **59a**,**b**, 4,10-dibromides **60a**,**b**, 4,8-dibromides **60c**,**d**, 4*a*,9*e*-dibromide **60e**, adamantane-2,4-dione **55** and 4*a*-hydroxy-10*e*-bromide **61**. The selectivity of the reaction, the array of reaction products and their proportions in the mixture depend substantially on the positions and spatial arrangement of the substituent in the starting bromolactones (Scheme 8).

Scheme 8

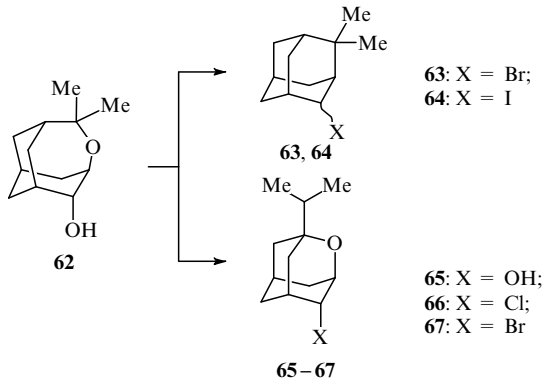


These results are due to the fact that fragmentation can follow either a reductive (type A) or non-reductive (type B) pathway as shown for the bromo-lactone **57**. In this case, pathway A predominates. In the case of the bromo lactones **58a**,**b**, the fragmentation occurs only by pathway B.[35]

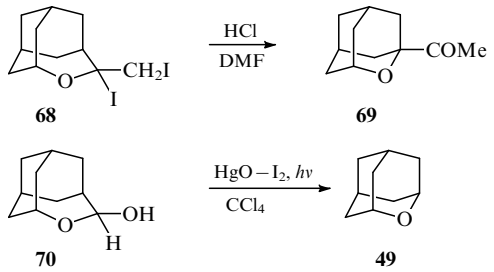


It should be mentioned that the isomeric bromoadamantanones are able to undergo interconversions.[36]

The transformations under consideration also accompany the reactions of 2-hydroxy-5,5-dimethyl-4-oxahomoadamantane **62** with HBr and HI, which lead to the corresponding 2-halo-4,4-dimethyladamantanes **63** and **64** formed as mixtures of *syn*- and *anti*-isomers.[33]

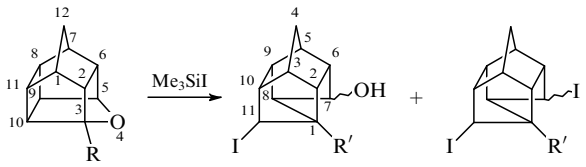


It is noteworthy that the compound **62** undergoes this type of transformation with the loss of oxygen from the cage only under the action of 'hard' reagents. The reactions with 'softer' reagents are accompanied by another skeletal transformation, namely, oxahomoadamantane → oxaadamantane rearrangement. Thus on treatment with 60% H_2SO_4, the compound **62** isomerises into *anti*-4-hydroxy-1-isopropyl-2-oxaadamantane **65**, while the reaction with hydrochloric acid yields a mixture of isomeric chlorides **66** in a ratio of 1 : 1, and the reaction with thionyl bromide gives bromide **67**.[33] This rearrangement also accompanies the reaction of 2-iodo-2-iodomethyloxahomoadamantane **68** with HCl in DMF resulting in the formation of methyl 2-oxaadamantyl ketone **69**[25 – 28] and the oxidation of hemiacetal **70** having an oxahomoadamantane structure with the $HgO-I_2$ system under UV radiation, which gives rise to 2-oxaadamantane.[25]



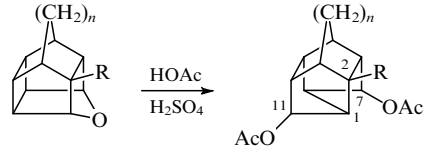
2. 'Bird-cage → trishomocubane' skeletal transformation

Treatment of bird-cage compounds containing an oxygen atom in the cage or their homologues with some electrophilic reagents results in an extensive skeletal rearrangement leading to compounds with the structure of trishomocubane, *i.e.* pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane. This compound is the stabilomer in the series of cage C_{11}-pentacyclanes.[9] Compound **71** and its 3-substituted derivatives **72** – **74** were converted into polyiodo- and hydroxyiodo-derivatives of trishomocubane by the reaction with Me_3SiI. The reaction affords one of the above derivatives or their mixture depending on the nature of the substituent and the duration of the process. For example, after 12 h, the compound **71** was converted into 7-hydroxy-11-iodo-derivative **75** in a 48% yield, whereas after 150 h, 7,11-diiodo-derivative **76** was obtained in a yield of 73%.[37] The same reaction of methyl-substituted compound **72** gave rise to a mixture of 7-hydroxy-11-iodo-1-methyl-substituted product **77** and 7,11-diiodo-1-methyl-substituted derivative **78**; the compound **73** containing a phenyl group was converted only into 7-hydroxy-11-iodo-1-phenyl derivative **79** under the same conditions. Finally, the 2-hydroxyethyl-substituted compound **74** gave 1-(2-iodoethyl)-7,11-diiodo-derivative **80** in 30% yield.[38]



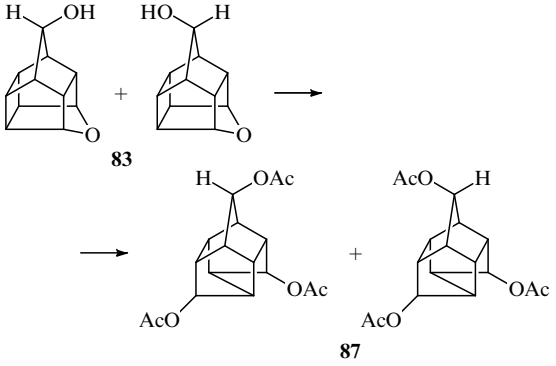
71, **75**, **76**: R = R′ = H;
72, **77**, **78**: R = R′ = Me;
73, **79**: R = R′ = Ph;
74: R = $(CH_2)_2OH$; **80**: R′ = $(CH_2)_2I$.

The compounds **71**, **81** and **82** undergo a similar skeletal rearrangement under the action of glacial acetic acid in the presence of a catalytic amount of 98% H_2SO_4. In the case of **71**, 7,11-diacetoxytrishomocubane **84** is formed in 15% yield,[39] while **81** has been converted into diacetate **85** with the structure of bismethanotwistane, pentacyclo[7.3.0.0^{2,7}.0^{3,11}.0^{6,10}]dodecane, in 24% yield.[40] The same transformation of the (−)-6-carboxymethyl derivative **82** leads to (−)-2-carboxymethyl-7,11-diacetoxytrishomocubane **86**.[41, 42]



71, **84**: R = H, *n* = 1;
81, **85**: R = H, *n* = 2;
(−)-**82**, (−)-**86**: R = CH_2CO_2H, *n* = 1.

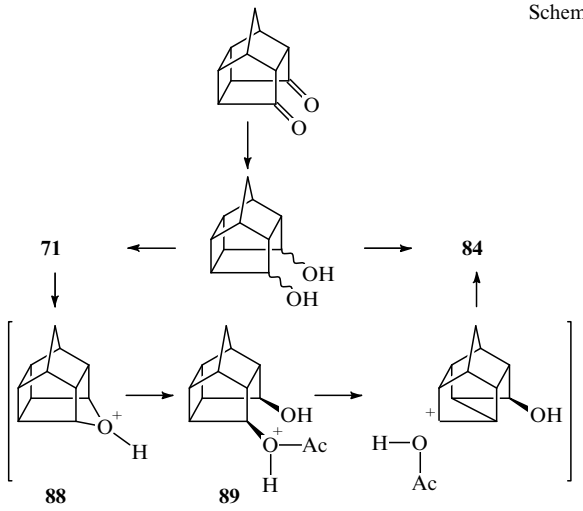
Under similar conditions, a mixture of *syn*- and *anti*-epimers of 12-hydroxy-derivative **83** has been converted into a mixture of epimeric 7,11,12-triacetoxytrishomocubanes **87**.[43]



The mechanism of this rearrangement, which has been discussed in relation to **71**, includes the formation of the protonated ether **88**, which undergoes a nucleophilic attack by MeCOOH to give intermediate **89**. The latter undergoes a skeletal rearrangement with opening of the four-membered ring, similar to the corresponding rearrangement in the series of the carbo-analogue, which results in the formation of the trishomocubane structure (Scheme 9).[39]

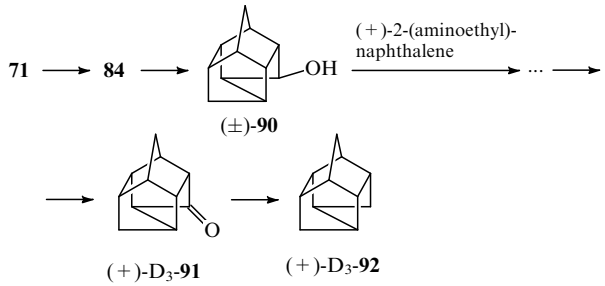
Compounds with the bird-cage structure containing an oxygen atom in the cage and related compounds are formed from derivatives of pentacyclo[6.2.1.0^{2,7}.0^{4,10}.0^{5,9}]undecane and its homologues, as has been shown for the compound **71**. Thermodynamically controlled isomerisation of bird-cage derivatives makes it possible to prepare di- and tri-substituted trishomocubanes the syntheses of which are described in this Section.[44 – 50] Of the two alternative routes mentioned above, it is the synthesis based on bird-cage compounds with an oxygen atom in the cage

Scheme 9

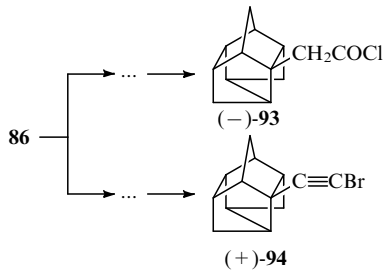


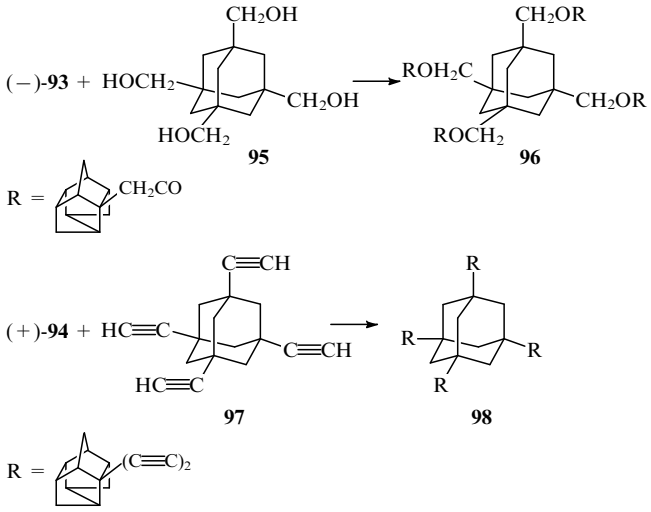
(the so-called modified Barborac method) that proved to be more convenient from the preparative viewpoint, because none of its steps yields side products or mixtures of isomers. Therefore, this method has found application in the preparation of key synthons for the syntheses of optically active organic molecules with *T*-symmetry and a known absolute configuration.

For example, by a series of transformations of bird-cage compounds, including preparation of (±)-hydroxytrishomocubane **90**, the synthesis of (+)-D_3-trishomocubanone **91** and (+)-D_3-trishomocubane **92** has been accomplished.[51, 52]

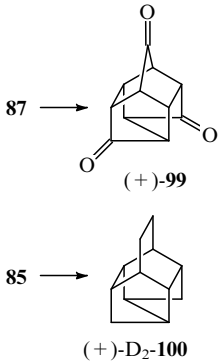


The compound **86** obtained by this skeletal rearrangement has served as a key intermediate in the synthesis of 2-substituted trishomocubane derivatives, namely, acid chloride (−)-**93** and ethynyl bromide (+)-**94**. The reaction of the former with 1,3,5,7-tetrakis(hydroxymethyl)adamantane **95** has given rise to compound (−)-**96**,[42] whereas the latter reacts with 1,3,5,7-tetra(ethynyl)adamantane **97** to give compound (+)-**98**.[53, 54]





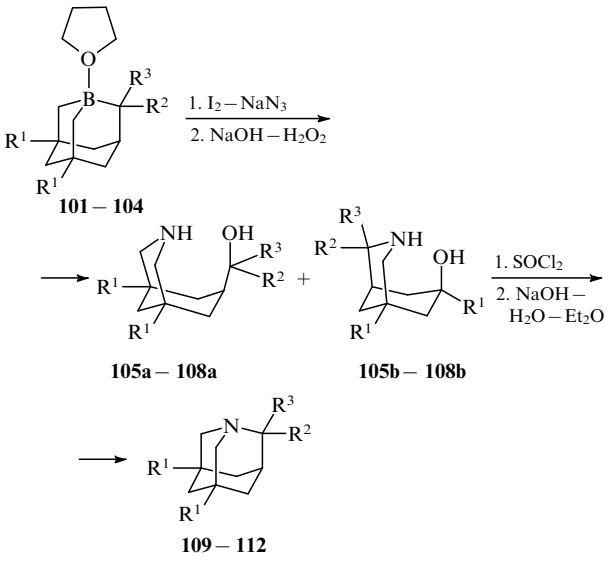
Optically active (+)-triketone **99** with the trishomocubane structure was synthesised from a mixture of epimeric 7,11,12-triacetates **87**,[51] while the diacetate **85** was converted into (+)-D_2-bismethanotwistane **100**.[40]



V. Syntheses based on boraadamantanes accompanied by rearrangements involving the boron atom

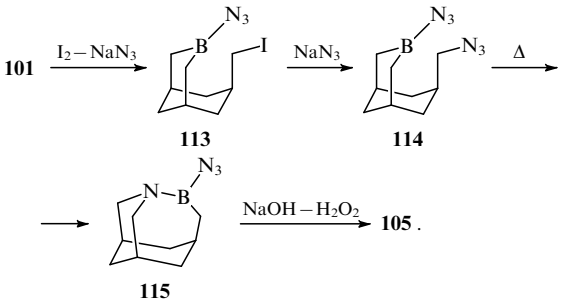
Cage derivatives of boron can be used as key intermediates in the syntheses of compounds of the adamantane series including aza- and oxa-derivatives.[55, 56] The transition from bora-containing compounds to other structures is accomplished *via* skeletal rearrangements. Various types of transformations are known, including those in which the boron atom is replaced by a nitrogen or carbon atom or in which the bridging boron atom is displaced from the cage.

The skeletal rearrangement of the B → N type is the key stage in the transformation of compounds **101**–**104** of the 1-boraadamantane series into 1-azaadamantane **109** and its alkyl derivatives **110**–**112**, which are difficult to prepare by any other method. For example, iodination of the tetrahydrofuran complexes **101**–**104** in the presence of NaN_3 followed by oxidation of intermediate compounds by the $NaOH-H_2O_2$ system gives rise to mixtures of isomeric amino alcohols **105**–**108** with the 3-azabicyclo[3.3.1]nonane structure; cyclisation of these products in the presence of $SOCl_2$ affords the corresponding compounds **109**–**112** in an overall yield of 15%–40%.[57–59]

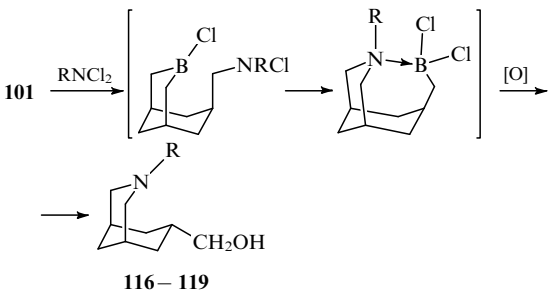


101, **105**, **109**: $R^1 = R^2 = R^3 = H$;
102, **106**, **110**: $R^1 = Me$, $R^2 = R^3 = H$;
103, **107**, **111**: $R^1 = R^2 = H$, $R^3 = Me$;
104, **108**, **112**: $R^1 = H$, $R^2 = R^3 = Me$.

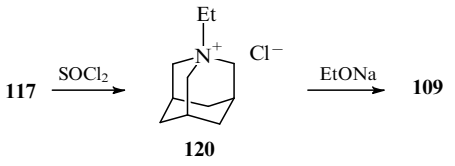
A possible mechanism for this reaction accompanied by a skeletal rearrangement, which is considered in relation to the compound **101**, includes fragmentation with cleavage of one of the B–C bonds and formation of 3-azido-7-iodomethyl-3-borabicyclo[3.3.1]nonane **113**. The latter reacts with excess NaN_3 to give diazide **114**, which undergoes thermal 1,2-anionotropic rearrangement and subsequent cyclisation to give 2-azido-1-aza-2-borahomoadamantane **115**. This is followed by fragmentation accompanied by the loss of boron and yielding the compound **105**.



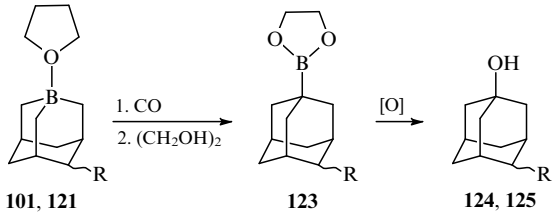
The B → N transformation has also been observed in the amination of 1-boraadamantane with alkyldichloroamines. *N*-Alkyl-derivatives of 3-azabicyclo[3.3.1]nonane (**116**–**119**) were obtained in this way. On treatment with $SOCl_2$, the *N*-ethyl-substituted compound **117** cyclises to give quaternary salt **120**; its subsequent fragmentation leads to the 1-azaadamantane **109**.[60,61]



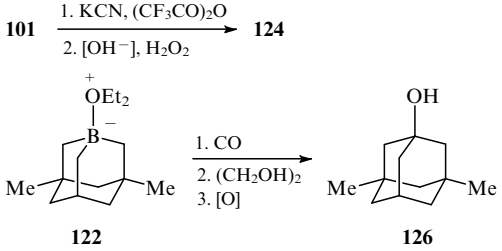
R = Me (**116**), Et (**117**), Pr (**118**), Bu (**119**).



Carbonylation of 1-boraadamantane derivatives **101**, **121** and **122** in the presence of ethylene glycol is accompanied by skeletal transformation in which the boron atom is replaced by a carbon atom. The oxidation of the resulting ethylene glycol ester of 1-adamantylboronic acid **123** (or the corresponding derivatives) affords compounds of the adamantane series. Thus the compound **101** was converted into adamantan-1-ol **124** in 78% yield, the 4-chloro-derivative **121** gave the 4-chloro-1-hydroxy-derivative **125** (in a low yield) and the reaction of etherate **122** resulted in the formation of 1-hydroxy-3,5-dimethyladamantane **126** (yield 95%).[62,63] It should be noted that the **101** → **124** transformation can also be accomplished using the $KCN-(CF_3CO)_2O$ system.[62]

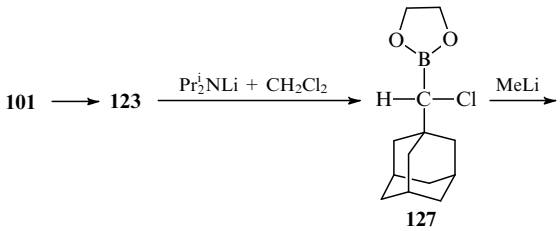


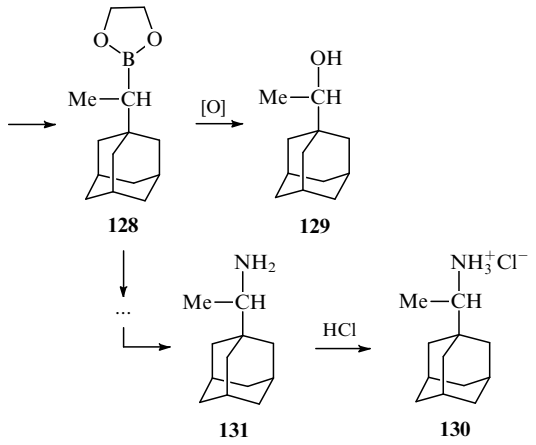
R = H (**101**, **124**), Cl (**121**, **125**).



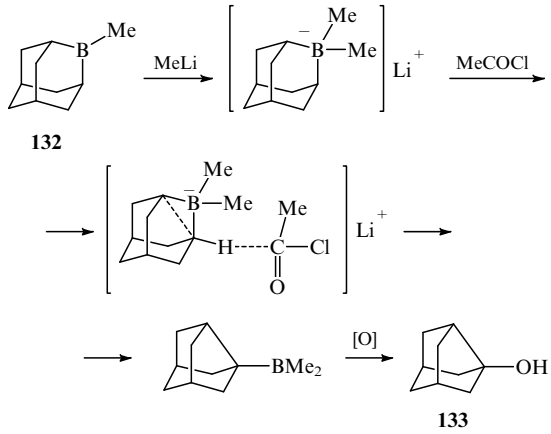
Treatment of the carbonylation products **123** with dichloromethyllithium affords chloride **127**. When this product is treated, without isolation, with methyllithium, it is converted into compound **128**, oxidation of which yields 1-(1-hydroxyethyl)adamantane **129**.[64]

Based on this skeletal transformation of 1-boraadamantane **101**, a new method for the synthesis of remantadine **130**, a known antiviral drug, has been developed. 1-(1-Aminoethyl)adamantane **131** was obtained in a yield of 38% with respect to the initial boraadamantane **101**. The salt **130** was prepared by treating the free base **131** with HCl in ether.[64]





Complexes of cage boratricyclanes with lithiumalkyls are capable of reducing (by hydride transfer) some types of organic compounds; this reaction is accompanied by rearrangement of the boratricyclane cage. This rearrangement in which the boron atom is removed from the cage makes it possible to proceed from 2-methyl-2-boraadamantane **132** to 1-hydroxynoradamantane **133**.[65]



VI. Conclusion

It follows from the reactions considered above that skeletal transformations typical of functionally substituted cage heterotricyclanes and heterohexacyclanes are quite diverse and can be induced by various reagents under mild conditions. The reactions of functionally substituted thia- or aza-cage compounds accompanied by cage rearrangements and by replacement of the sulfur or nitrogen atom by oxygen give rise to compounds with the oxacage skeleton, which is less strained than the initial structures. Oxacage derivatives, in turn, can be converted under certain conditions into the corresponding stabilomer carbocage structures.

Thus, the information presented in this review not only considerably supplements the general scheme of known skeletal modifications of cage compounds, but also markedly extends the views about the synthetic potential of the rearrangements of hetero(poly)cyclanes leading to the replacement, introduction or removal of the hetero-function.

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