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Conformational Analysis of Bicyclo[3,3,1]nonanes

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The development of the principle of conformational analysis is associated mainly with the employment of cyclohexane and its heteroanalogues as model compounds. The present review surveys data on the conformational analysis of another system containing six-membered rings—bicyclo[3,3,1] nonane. A set of conformational problems, which have been successfully solved using the above bicyclic system, are discussed, the fundamental principles are formulated, and the great scope of the applications of this model in conformational research is demonstrated.
The bibliography includes 213 references.

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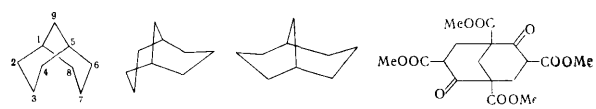
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I. INTRODUCTION

The concepts of conformational analysis constitute an extremely effective tool in the hands of the chemist whereby it is possible to understand more deeply the mechanisms of a wide variety of processes. Hence there is clearly an urgent need for a deeper understanding of the concepts and theories of dynamic stereochemistry. The general postulates of conformational analysis are based to a large extent on data for cyclohexane derivatives, its polycyclic derivatives, and its heteroanalogues such as, for example, monosaccharide derivatives, six-membered heterocycles, etc. Nevertheless the employment of cyclohexane derivatives is not always most useful. For example, one of the fundamental problems involves the study of factors which determine the possibility of the existence and the energy of flexible forms (boat, "twist-form"); problems of the reactivity of the functional groups in these conformations are also fundamental. However, there are no convenient model compounds of the cyclohexane series with the boat conformation and with a sufficiently large set of functional groups suitable for the investigation of problems of this kind. Indeed the majority of compounds of this type assume the form of a somewhat deformed (usually flattened[1]) chair and the difference between the free energies of the boat and chair forms is fairly large (5—7 kcal mole^{-1}).[2,3] Therefore many approaches to this problem are associated with the synthesis of cyclic structures (frequently containing heteroatoms), which might exist in a flexible conformation or contain individual fragments which might simulate the geometrical relations in the flexible conformation of cyclohexane (see, for example, Whitlock[4] and Adachi et al.[5]).

The study of derivatives of bicyclo[3,3,1]nonane is of great interest in this connection. We emphasise that at the beginning of the present century Rabe et al.[6] already used the bicyclo[3,3,1]nonane system for the solution of certain problems in theoretical chemistry.

Three conformations free from angular strain can be postulated for bicyclo[3,3,1]nonane itself: dichair (I), chair-boat (II), and diboat (III). In 1922 Meerwein and Schürmann[7] proposed on the basis of intuitive considerations the double chair conformation for the so called "Meerwein's ester" (IV).



(I) (II) (III) (IV)

However, systematic studies on this conformational problem began little more than ten years ago and significant progress was achieved literally in the last few years. The bibliography on this question has been steadily expanding and considerable advances have now been achieved in the understanding of the general problems of the conformational analysis of bicyclononanes. In the present review an attempt is made to examine the present state of the subject, to formulate the fundamental conformational problems which might be solved by resorting to model bicyclononane systems, and to assess the prospects of research in this field. The data are treated on a logical and not a historical basis. Apart from a greater theoretical rigour, this is justified by the considerable development of this field in recent times, which makes it difficult and sometimes simply impossible to follow the historical genesis of the ideas and the questions of priority.

II. GENERAL PROBLEMS OF THE CONFORMATIONAL ANALYSIS OF BICYCLO]3,3,1]NONANES

Although conformations (I)—(III) are free from angular strain, nevertheless none is free from a strong destabilising interaction between the non-bonded atoms. The destabilisation of the boat conformations (II) and (III) is due to the same factors which operate in the case of the boat conformation of cyclohexane, namely the presence of eclipsed ethane conformations and the flagpole—flagpole repulsion between the hydrogen atoms[2]. In the chair-boat

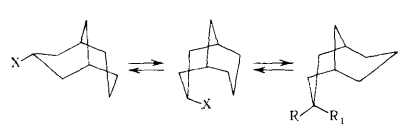
structure (II) the ring in the boat form cannot be appreciably deformed to give the twist-form owing to the rigidity of its junction with the second ring. One can probably imagine only a moderate twisting. However, since for each chair-chair conformation (I) one obtains in the inversion process two chair-boat conformations (II), the latter conformation is twice as likely to be produced. In other words the formation of form (II) is preferred on entropy grounds to the extent of $R \ln 2$. On the other hand, the diboat conformation (III) should correspond to the maximum on the energy curve. A twisted conformation, which can be called the ditwist-form, corresponds to the minimum. In this conformation the flagpole and eclipsed interactions, which are characteristic of the undistorted form (III), are appreciably diminished. This conformation is the only flexible form and is therefore more favourable from the standpoint of the entropy factor.

The chair conformation is usually greatly stabilised by the enthalpy factor (see, for example, Zefirov and Kazimirchik[8]). However there is a specific destabilising factor for the dichair conformation (I), namely the extremely powerful attraction of the *endo*-hydrogen atoms in the 3- and 7-positions. Simple calculations using the normal angles and bond lengths show that the difference between the 3-*endo*- and 7-*endo*-hydrogen atoms should be only 0.81 Å![3] We may recall that the van der Waals radius of hydrogen is 1.2 Å.[9] Therefore in the initial studies the authors gave preference to the chair-boat conformation (II) (for example in the investigations of de la Mare et al.[10] and Leonard and Morrow[11]; however, see Hall[12]) and this view has been reflected in textbooks[13].

However, one must emphasise that the above structures are limiting and one can imagine that in specific instances these ideal forms will suffer greater or smaller distortions, which will lead to a decrease of strain. For example, the flattening of the six-membered rings in conformation (I) and the bending of the C—H bonds in the 3- and 7-positions (i.e. the decrease of the $H-C_{(3)}-H$ or $H-C_{(7)}-H$ angle) can reduce the internal energy. Below it will be shown that such changes in geometry do indeed occur, as a result of which the double chair conformation is usually the most stable.

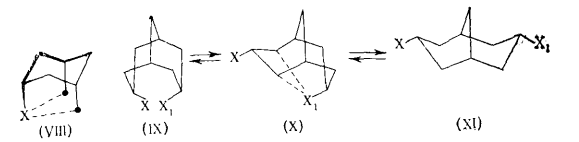
Furthermore, one can determine fairly reliably certain conformational trends arising on passing to functional derivatives and associated with the introduction of substituents, heteroatoms, etc.

Firstly, it is quite evident that the introduction of a 3-*endo*- or 7-*endo*-substituent more bulky than the hydrogen atom will cause a sharp increase of the steric repulsion in the dichair conformation (V) and its sharp destabilisation. Of the two alternative chair-boat conformations, (VI) and (VII), conformation (VI), which has a substituent in the bowsprit position [which is approximately equivalent to the position of the substituent in the equatorial conformation (VIIa)], should be more stable.



(VI) (V) (VII, R = H, R_1 = X; VIIa, R = X, R_1 = H)

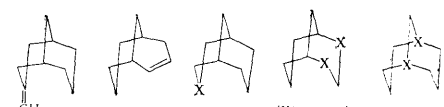
Secondly, the 3-*endo*- and 7-*endo*-positions in conformation (I) are equivalent to the axial position for cyclohexane derivatives of type (VIII). Therefore a functional derivative of type (V) or (VII) is subjected to two additional 1,3-axial interactions, analogous to those in (VIII).



(VIII) (IX) (X) (XI)

Although the extent of such interaction should be different from that observed in cyclohexane by virtue of the differences in geometry, nevertheless one can imagine that in the presence of a very bulky group X in compound (V) such interaction should lead to the destabilisation of the dichair form. For a monofunctional derivative of type (V), this factor is indistinguishable from the previous factor associated with the 3—7 repulsion factor [it will evidently effect the relative stabilities of forms (VI) and (VII), hindering strongly conformation (VI)]. However, in 3—7 disubstituted derivatives (IX) this factor can stabilise the diboat conformation (XI), but not the chair-boat conformation (X).

Thirdly, it is possible to trace certain tendencies associated with the introduction of trigonal carbon atoms into the bicyclononane skeleton. Thus it is evident that the introduction of a trigonal atom in the 9-position should lead to some stabilisation of the boat conformations (II) and (III) owing to the elimination of the flagpole—flagpole interaction, although it is difficult to predict *a priori* the extent of such stabilisation. Furthermore, the introduction of a trigonal atom in the 3-position, for example in compound (XII), leads to a decrease of the 3—7 repulsion and hence to the stabilisation of the dichair form. The introduction of a double bond in the 2,3-positions, as in compound (XIII), should also result in a marked flattening of the cyclohexene ring and a sharp diminution of the 3—7 repulsion.



(XII) (XIII) (XIV) (XV, X = O) (XVII, X = S) (XVI)

In conclusion of this section one should note particularly that many problems in the conformational analysis of bicyclo[3,3,1]nonanes have been studied in relation to heteroanalogues of this system. In broad outline, the geometry of bicyclic molecules containing the "usual" heteroatoms (oxygen, nitrogen, and even sulphur) simulates fairly satisfactorily the geometry of the carbon analogue. For example, it is not fortuitous that the conformational analysis of six-membered heterocycles reveals in broad outline the same fundamental conformational characteristics as were discovered for cyclohexane derivatives[8,14,15]. Therefore in this case one can preduct beforehand certain conformational features. Thus the introduction of a heteroatom in the 3-position, as in compound (XIV), should lead to the stabilisation of the dichair conformation by virtue of the decrease of the 3—7 repulsion. Furthermore, the introduction of heteroatoms into the bicyclononane skeleton leads to changes in the geometry which largely depend on the relative lengths of the C—C and C—heteroatom bonds. If the latter is appreciably shorter, the introduction of heteroatoms in the 2- and 4-positions, as in compound (XV), or in the 1- and 5-positions, as in compound (XVI), should lead to an enhancement of the 3—7 repulsion. The converse should also

probably be true, namely a decrease of the 3—7 repulsion with increase in the length of the C—heteroatom bond, as in compound (XVII).

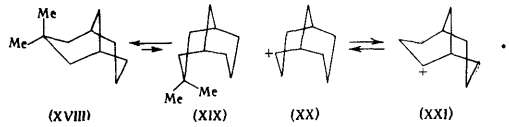
However, many "anomalies", "effects" specific to heterocyclic compounds, due to the electrostatic interactions of the heteroatoms, the interactions of the lone electron pairs, etc. are now known[8,9,16-27]. Therefore it is necessary to examine critically data on the heteroanalogues, bearing in mind the specific features of the model compounds investigated. On the other hand, the use of heteroanalogues significantly extends the range of problems which can be solved with the aid of the bicyclic model.

III. CALCULATIONS OF THE GEOMETRY AND ENERGY

To calculate the geometry and relative energy of molecules, either semiempirical quantum-chemical methods or Westheimer's classical approach are used nowadays[28,29]. The latter is widely employed in its current modifications for the calculation of the geometries of fairly complex compounds[3,30-36]. The first calculation on the bicyclo[3,3,1]nonane molecule by this method was carried out by Gleicher and von R. Schleyer[37], who calculated the geometry for the dichair conformation only. The $C_{(3)}\ldots C_{(7)}$ distance was estimated as 2.96 Å (cf. 2.56 Å for the ideal form[3,38]) and the $C_{(1)}C_{(2)}C_{(3)}$ angle was estimated as 113°. These data indicate a considerable flattening of the "wings" of the molecule. A more rigorous calculation was performed by Allinger and coworkers[3,38]. In this case too the dichair conformation differed fairly appreciably from the ideal conformation. In the first place the $C_{(3)}\ldots C_{(7)}$ distance increased to 3.18 Å and the $H_{(3)}C_{(3)}H_{(3)}$ and $H_{(7)}C_{(7)}H_{(7)}$ angles decreased to 95.2°. This resulted in an increase of the *endo*-$H_{(3)}\ldots$*endo*-$H_{(7)}$ distance from 0.81 Å for the ideal structure to 2.25 Å. Nevertheless, despite the considerable distortion of the structure and the strong non-bonding interaction, the dichair conformation (I) is more stable than the chair-boat conformation (II). Calculation of the enthalpy difference yielded 2.73 kcal mole^{-1} in favour of conformation (I).[3,38] Another calculation gave 3.7 kcal mole^{-1} for this difference[39]. However, the authors point out that this value may be too high.

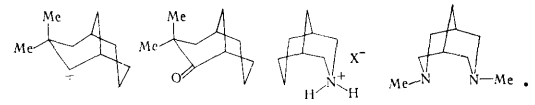
In another instance the calculated ΔH was appreciably less than 5.9 kcal mole^{-1} adopted for the enthalpy difference between the flexible and chair forms of cyclohexane[2,8,40]. Evidently this difference is caused by the appreciable relative destabilisation of the dichair.

The situation for 3,3-dimethylbicyclo[3,3,1]nonane differs significantly. A calculation has shown[39] that conformation (XVIII) is more stable to the extent of 3.9 kcal mole^{-1} than (XIX):



(XVIII) (XIX) (XX) (XXI)

The geometries of certain carbenium ions, incorporated in the bicyclo[3,3,1]nonane skeleton, have also been calculated by this method[37,39]. Thus it has been found that the dichair conformation (XX) of the 2-bicyclo[3,3,1]nonyl cation is more stable than conformation (XXI) to the extent of 2.7 kcal mole^{-1}.[39] The chair-boat conformation of the cation (XXII) is more stable than the dichair conformation, the difference between the energies being 4.4 kcal mole^{-1}.[39] Data for the carbonium ions are not only of intrinsic interest but also as model data for compounds with a trigonal carbon atom; for example, the above calculation confirms the greater stability of the chair-boat conformation of the ketone (XXIII):[39]

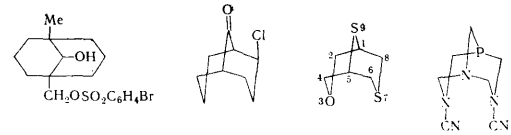


(XXII) (XXIII) [XXIV, (a) X = Br; (b) X = Cl] (XXV)

Semi-empirical quantum-chemical methods—the extended Hückel and CNDO/2 methods—have been used in calculations on the conformations of the aza-analogues of bicyclo[3,3,1]nonane[41]. Thus the hydrobromide (XXIVa) has an energy minimum in the dichair conformation with a $C_{(7)}\ldots N_{(3)}$ distance of 2.9 Å. Dimethylbispidine (XXV) also has a minimum for the dichair conformation, but the $N_{(3)}\ldots N_{(7)}$ distance is 2.5 Å, which is close to the corresponding distance in the ideal conformation. Evidently the main difference is associated with the presence of the 3- and 7-*endo*-hydrogen atoms in compound (XXIV). We may also note that the problem of the conformations of the 3,7-diheteroanalogues is of special interest in connection with the problem of the dipole—dipole or orbital interaction between the heteroatoms (see Section VI, 5).

IV. EXPERIMENTAL DATA ON THE GEOMETRY OF BICYCLO[3,3,1]NONANE DERIVATIVES

The first X-ray diffraction studies showed that the double chair conformation is characteristic of the majority of carbocyclic and heterocyclic bicyclo[3,3,1]nonane derivatives. Dobler and Dunitz[42] were the first to show that the hydrobromide (XXIVa) of 3-azabicyclononane has a flattened dichair conformation. The $N_{(3)}\ldots C_{(7)}$ distance is increased to 3.02 Å owing to the flattening (see the calculation of Chakrabarty et al.[41]). The $H_{(3)}\ldots H_{(7)}$ distance between the *endo*-hydrogen atoms can be estimated as 1.8 Å.[43,44] The molecular structure of a carbocyclic compound—the *p*-bromobenzenesulphonate (XXVI)—has been determined[43,44]. Both rings in (XXVI) have a distinct chair conformation, but the structure deviates appreciably from ideality and the two rings are appreciably flattened.



(XXVI) (XXVII) (XXVIII) (XXIX)

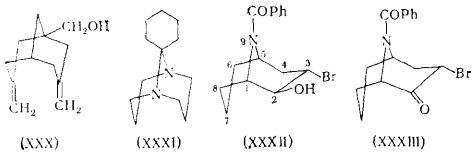
The $C_{(2)}C_{(3)}C_{(4)}$ and $C_{(6)}C_{(7)}C_{(8)}$ angles are on average 114° and the $C_{(3)}\ldots C_{(7)}$ distance is 3.05 Å. The structure of the chloroketone (XXVII) has been determined[45]. The steric repulsion of the methylene groups also leads to the flattening of the molecule and the $C_{(3)}\ldots C_{(7)}$ distance is 3.11 Å, which is much more than 2.1 Å expected for the ideal bicyclononon-9-one. We must emphasise that neither the presence of a trigonal atom in the 9-position nor the presence of the 2-*exo*-substitute in the ketone (XXVII) leads to the destabilisation of the dichair conformation. We may also recall the data concerning

the structure of the 3,7-diheteroanalogues of bicyclononane. It has been found[46,47] that 3-oxa-7,9-dithiabicyclo[3,3,1]nonane (XXVIII) exists in the dichair conformation. It is interesting that the plane passing through the $C_{(1)}$, $S_{(9)}$, and $C_{(5)}$ atoms intersects the $C_{(2)}O_{(3)}C_{(4)}$ plane at an angle of 2° and the $C_{(6)}S_{(7)}C_{(8)}$ plane at an angle of 32°45′. The appreciable flattening of the dithiane ring is evidently associated with the smaller barrier to rotation about the C—S bond compared with the C—O bond (see the relevant discussion in the author's earlier review[8]). A dichair conformation was also found for compound (XXIX), the angles $N_{(1)}C_{(2)}N_{(3)}$ and $N_{(1)}C_{(8)}N_{(7)}$ being 133—136°.[48]

There are literature data for the geometry of bicyclo[3,3,1]nonane itself[49]. It too has the dichair conformation, since it forms mixed crystals with adamantane in which this "conformation" is rigidly fixed. The lattice parameters led to the conclusion that the molecule is flattened; unfortunately the parameters of the molecular structure were not determined (for other X-ray diffraction data, see Sections VI, 5 and VI, 6).

Thus X-ray diffraction results have shown that in the crystal the dichair conformation is preferred, with an appreciable flattening of the wings of the molecule, which leads to an increase of the valence angles in the 2-, 3-, 4-, 6-, 7-, and 8-positions by 4° relative to the normal value.

There are certain data on the geometry of compounds of the above type in solution. Thus the identity of the infrared spectra in solution and in the solid phase for compounds (XXVI) and (XXVII) [43,44,50] makes it possible to extend the X-ray diffraction data also to the geometry of the molecule in solution. The development of studies on molecular geometry in solution is associated mainly with two modifications of the NMR method. Firstly, this involves the use of shift reagents[51,52]. Thus a study has been made[53] on the chemical shifts induced in the presence of $Eu(DPM)_3$ † for 1-hydroxymethyl-3,7-dimethylenebicyclo[3,3,1]nonane (XXX).



(XXX) (XXXI) (XXXII) (XXXIII)

The $C_{(3)}\cdots C_{(7)}$ distance was estimated as 3.1 Å, in agreement with the dichair structure (for the limitations of the method, see Section VI, 6).

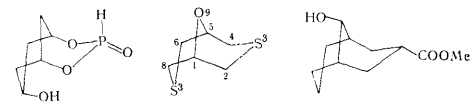
Secondly, a convenient means of investigating the geometry of six-membered systems is provided by the so called NMR "*R*-method".[54-57] In particular, this method has been used to investigate 1,5-diazabicyclo[3,3,1]nonane (XVI, X = N) and its pentamethylene derivative (XXXI).[53] The spin—spin coupling constants for the fragment $-CH_2-CH_2-$ in these compounds indicate an appreciable flattening, which leads to a decrease of the $N_{(1)}C_{(2)}C_{(3)}C_{(4)}$ dihedral angle to 48° and 45° respectively (cf. the 54.5° angle for cyclohexane[1]). This is satisfactorily correlated with the X-ray diffraction studies: the analogous dihedral angles of compounds (XXVI) are in the range 43.6—45.2°;[44-58] in compound (XXIVa) the dihedral angles are 43.0° in the cyclohexane ring and 50.2° in the piperidine ring[42,58].

†DPM = dipivaloylmethane.

As shown in Section II, the appearance of the boat conformations (II) and (III) may be expected when there is a sharp enhancement of the non-bonding interactions, which usually takes place after the introduction of bulky substituents in the 3-*endo*-position. The first compound investigated in this series was 9-benzoyl-3-*endo*-bromo-2-*exo*-hydroxy-9-azabicyclo[3,3,1]nonane (XXXII).[59,60]

As was to be expected, the substituted ring assumes the boat form. The amide nitrogen atom $N_{(9)}$ is planar, so that the geometry of the molecule of (XXXII) resembles that of bicyclo[3,3,1]nonan-9-one [for example, compound (XXVII)]. The $C_{(3)}\cdots N_{(9)}$ distance is 2.56 Å. The displacements of the $C_{(3)}$ and $C_{(7)}$ atoms from the $C_{(1)}C_{(2)}C_{(4)}C_{(5)}$ and $C_{(5)}C_{(6)}C_{(8)}C_{(1)}$ planes are respectively 0.64 and −0.63 Å, which is more than in the dichair conformation [0.51 Å for the ketone (XXVII) [45]], but less than for the ideal cyclohexane conformation (0.73 Å). Thus the ring having the chair form in the chair-boat conformation is distorted much less than in the dichair conformation. These data were confirmed by a study of the structure of the ketone (XXXIII).[61] The molecule of (XXXIII) also assumes the chair-boat conformation with a $C_{(3)}\cdots N_{(9)}$ distance of 2.61 Å and with displacements of the $C_{(3)}$ and $C_{(7)}$ atoms from the $C_{(1)}C_{(2)}C_{(4)}C_{(5)}$ and $C_{(5)}C_{(6)}C_{(8)}C_{(1)}$ planes of 0.64 and −0.65 Å.

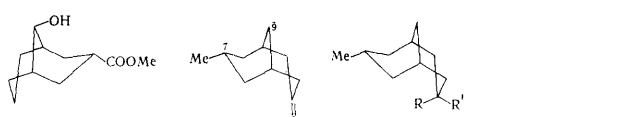
There are literature data for the boat conformations of the heteroanalogues of bicyclo[3,3,1]nonane. Thus it has been found[62,63] that one of the isomeric alcohols (XXXIV), obtained in the acid cleavage of phosphatrioxa-adamantane derivatives has the chair-boat conformation, the heterocyclic ring being in the boat form (see Section VI, 3).



(XXXIV) (XXXV) (XXXVI)

It has been shown[46,47] that 9-oxa-3,7-dithiabicyclo[3,3,1]nonane (XXXV) has the chair-boat configuration; the $C_{(2)}S_{(3)}C_{(4)}$ and $C_{(6)}S_{(7)}C_{(8)}$ planes intersect the $C_{(1)}C_{(5)}O_{(9)}$ plane at angles of 76°9′ and 11°45′ respectively. The $S_{(3)}\cdots O_{(9)}$ distance is 2.84 Å (for the relevant discussion and other data, see Section VI, 5).

Only isolated data are available for the geometry of conformation (II). The chair-boat conformation has been demonstrated[64] by the shift reagent method for the epimeric hydroxyesters (XXXVI) and (XXXVII), but the geometrical parameters were not determined (see also Vegar and Wells[65]).



(XXXVII) (XXXVIII) (XXXIX, R = OH, R′ = Me)

[XL, (a) R = OH, R′ = H; (b) R = H, R′ = OH]

A study of the induced chemical shifts established that compounds (XXXVIII), (XXXIX), and (XLa) have the chair-boat conformation with $C_{(7)}-C_{(9)}$ distances of 2.8, 2.65, and 2.65 Å respectively[66] (cf. Kimoto et al.[52]).

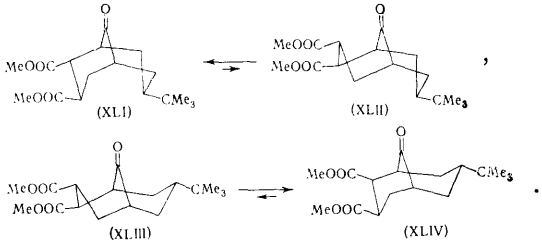
Thus X-ray diffraction data confirm the conclusion reached in Section II that the introduction of a 3-*endo*-substituent stabilises the chair-boat conformation. Despite the small number of experimental results, one may conclude that the geometry of the ring in the chair

form in this conformation is closer to that of the usual cyclohexane derivatives. The smallest intramolecular contact in conformation (II) obtains for the $C_{(3)}\ldots C_{(9)}$ distance (or $C_{(7)}\ldots C_{(9)}$ depending on the numbering system).

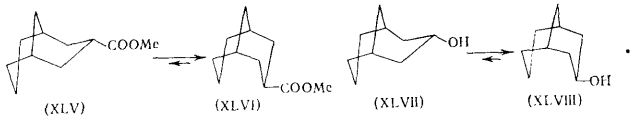
There are no literature data for conformation (III).

V. EXPERIMENTAL VALUES OF THE THERMODYNAMIC PARAMETERS OF THE CONFORMATIONAL EQUILIBRIA IN THE SYSTEM

As already mentioned in Sections II and III, one of the main problems in the conformational analysis of bicyclononanes is the determination of the relative stabilities of different conformations and the derivation of energy relations between them. Qualitative data can be obtained from results on the epimerisation of the corresponding functional derivatives. For example, the overall isomerisation of the methoxycarbonyl derivatives takes place on a preparative scale in the direction (XLII) → (XLI) and also (XLIII) → (XLIV).[67]‡ Bearing in mind the configurations of the compounds (see Sections VI, 3 and VI, 4) and hence the fact that epimerisation in controlled by the change in the conformation of the skeleton, these data make it possible to establish a qualitative sequence corresponding to the decrease of the energies of the conformations: diboat > chair-boat > dichair[67].



The first quantitative data were probably obtained in a study of the epimerisation of the esters (XLV) and (XLVI).[68] The equilibrium position was achieved starting from both isomers and the observed equilibrium constant corresponds to $\Delta G_{20^\circ} = -2.7$ kcal mole^{-1}. On the basis of the foregoing (see Sections II and IV), this value was assumed to be the difference between the free energies of conformations (I) and (II).

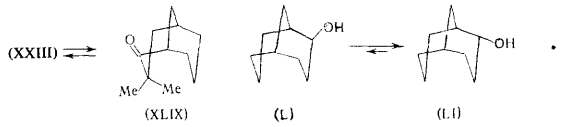


The analogous epimerisation of the isomeric alcohols (XLVII) and (XLVIII) gives rise to an equilibrium mixture containing 96.4% of the *exo*-isomer (XLVIII). Hence $\Delta G_{94^\circ} = -2.51$ kcal mole^{-1}.[69] This value is satisfactorily correlated with that observed by Appleton et al.[68] Since ΔG is independent of the nature of the substituent, this shows clearly that the difference between the free energies can be attributed solely to the different conformations of the skeleton.

‡ The paper of McEuen et al.[67] should also be referred to for the definitions of the terms adopted in the present review to designate different positions (bowsprit, gunnel, etc.).

If it is assumed that the entropies of the two conformers are the same§, then ΔH is 2.5–2.7 kcal mole^{-1} and can be compared with the energy difference calculated theoretically (see Section III). It is readily seen that the agreement between the experimental and calculated values is fairly satisfactory.

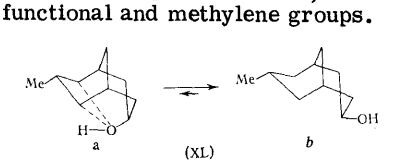
It has been found[39] that the ^{1}H NMR spectrum of the ketone (XLIX) depends on temperature. If it is assumed that this is related to the conformational equilibrium, ΔH can be estimated as 1 kcal mole^{-1}. The authors believe that this is also associated with an equilibrium of the type (I) ⇌ (II) and postulate a greater stability of conformation (XXIII) (see Section VI, 2).



There are no quantitative data on the conformational equilibrium (II) ⇌ (III).

There are also isolated literature values of ΔG_R for the substituents in the bicyclononane fragment. Thus epimerisation of bicyclo[3,3,1]nonan-2-ols (L) and (LI) yields values of ΔG_{OH} equal to −0.56 kcal mole^{-1} [69] and −0.559 kcal mole^{-1} [70] in isopropyl alcohol and −0.25 kcal mole^{-1} [69] in cyclohexane. It is interesting to compare these values with those found for cyclohexanol: 0.52 kcal mole^{-1} in aprotic media and 0.87 kcal mole^{-1} in protic solvents[71]. The equilibrium epimerisation of 2-methylbicyclo[3,3,1]nonanes at 230°C leads similarly to a mixture containing 72% of the equatorial isomer[72]. Hence it is possible to estimate $\Delta G^{230^\circ C}_{Me}$ as approximately 1 kcal mole^{-1}. This value is also much lower than that observed for methylcyclohexane (1.70 kcal mole^{-1}).[71] The decrease of ΔG_R for the 2-position in the bicyclo[3,3,1]nonane system can be attributed to the occurrence of the equatorial *endo*-$R_2\ldots$*endo*-$H_{(8)}$ interaction[39,69].

Interesting data on the epimerisation of the alcohols (XL, a and b) have been obtained[52]. The authors found that the free energy difference $\Delta G_{OH} = -2.18$ kcal mole^{-1} when equilibrium is established in isopropyl alcohol at 110°C. Evidently this difference cannot be attributed to an equilibrium of the type (I) ⇌ (II), but in fact represents the conformational energy of the substituent (cf. Hirsch[71]). The difference between the conformational energies must therefore be due to the occurrence of two unfavourable 1,3-axial–axial $CH_2\ldots OH$ interactions in conformation (XLa) compared with the analogous $CH_2\ldots H$ interactions in conformation (XLb). Assuming that the energy of the first is 1.9 kcal mole^{-1} [2] and that of the second −0.85 kcal mole^{-1},[2,71] it is possible to estimate the difference between the conformational energies as 2.1 kcal mole^{-1}. This agrees very well with the experimental value. It is also evident that the bicyclo[3,3,1]nonane system may be convenient for the investigation of the 1,3-interaction between the functional and methylene groups.

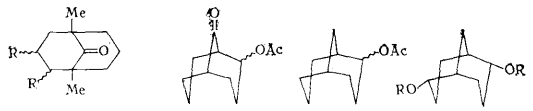


§ This hypothesis implies the neglect of the contribution of the alternative chair-boat conformation and hence of the entropy of mixing $R(x_1 \ln x_1 + x_2 \ln x_2)$.

VI. CONFORMATIONS OF FUNCTIONAL DERIVATIVES AND HETEROANALOGUES OF BICYCLO[3,3,1]NONANE

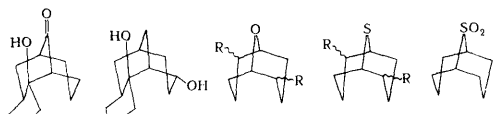
1. Determination of the Conformations of Bicyclo-[3,3,1]nonanes by Infrared Spectroscopy and ^{1}H NMR

The characteristic features of the application of infrared spectroscopy for a qualitative assignment of the conformations in the bicyclo[3,3,1]nonane series are based on the following factor. The spectra of polycyclic and skeletal compounds, in which two or more methylene groups are sterically in very close proximity, are known to contain anomalous infrared absorption bands due to C—H bonds in the region of 1490 and 2990 cm^{-1}. The infrared spectra of many bicyclo[3,3,1]nonane derivatives also contain these bands, which has been attributed to the $C_{(3)}H_2 \ldots C_{(7)}H_2$ interaction in the double chair conformation[43,44,73,74]. The proof is based on the following data[43,73]. Compound (LIIa) has an absorption band at 1490 cm^{-1}, whence it follows that the possible $C_{(3)}—C_{(9)}$ or $C_{(7)}—C_{(9)}$ interactions are not the cause of this anomaly. The intensity of this band in the infrared spectrum of the deuteriated compound (LIIb) is approximately halved. We may note that in the adamantane infrared spectrum there is no absorption in this region[75].



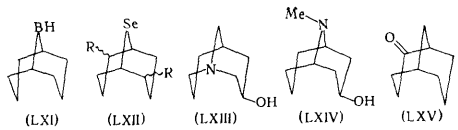
[LII, (a) R = H; (b) R = D] (LIII) (LIV) (LV, R = MeCO; LVa, R = H)

The high-frequency stretching vibration band at 2990 cm^{-1} and the deformation vibration band at 1490 cm^{-1} indicate the existence of the dichair conformation. The conformations of the ketone (XXVII) and its equatorial epimer[50], of the acetates (LIII),[76] (LIV),[77] and (LV),[78] of the alcohol (XLVIII)[69] and its 1,5-dimethyl analogue[79], of the condensed systems (LVI) and (LVII),[80] etc. were elucidated in this way. We emphasise that the dichair conformation of many 9-heteroanalogues of the bicyclo-[3,3,1]nonane system, for example of compounds (LVIII),[81-83] (LIX),[84,85] (LX),[85] (LXI),[86] and (LXII),[87] was in fact demonstrated by infrared spectroscopy.



(LVI) (LVII) R = Br, I, OAc, HgX (LVIII) R = H, Cl (LIX) (LX)

Infrared spectroscopy makes it possible to distinguish reliably bicyclo[3,3,1]nonane derivatives from the isomeric bicyclo[4,2,1]nonane derivatives[77,82,83,85,87], which are frequently obtained as a mixture in syntheses bases on cyclo-octadiene[88].

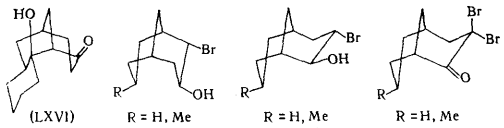


(LXI) (LXII) (LXIII) (LXIV) (LXV)

However, in many cases it was noted that the above absorption bands are not shown in the infrared spectrum even if the compound is known to exist in the double chair conformation. As an example, we may mention the aminoalcohols (LXIII) and (LXIV).[89] These bands are absent from the infrared spectra of the ketones (LXV)[77] and (LXVI).[80] In the latter case the presence of the trigonal carbon atom is responsible for the more planar ring conformation and hence for the significant separation of the transannular methylene groups (see Section VI, 2).

The application of ^{1}H NMR in this series of compounds is based on the familiar characteristics of the changes in the chemical shifts of the *a*- and *e*-protons and, what is more important, on the relation between the constant $^3J_{HH}$ and the dihedral angle (the Karplus equation). In conformation (I), the vicinal constants for the $H_{(1)}H_{(2)}$ and $H_{(2e)}H_{(3)}$ protons correspond to the *ae*- or *ee*-constant (2—4 Hz) and the constants of the $H_{(2a)}H_{(3a)}$ protons correspond to the *aa*-constant (9—12 Hz) for cyclohexane derivatives. Two larger $H_{(1)}H_{(2e)}$ (approximately 10 Hz) and $H_{(2a)}H_{(3)}$ (approximately 10—12 Hz) proton coupling constants should be observed for the boat conformation. The greatest difficulty is associated with the following factor: in conformational analysis there exist two alternative chair-boat conformations, as a result of which there is no sharp change in the hyperfine coupling constants. Furthermore, the flattening of the wings of the molecule in conformation (I) also increases the constant $J_{H_{(1)}H_{(2a)}}$ (for a detailed discussion of this problem, see Zefirov and Rogovina[90]). For the monosubstituted derivatives of type (VI), (V), (L), (LI), (LIV), (LV), (LVIII), etc., a clear-cut assignment can be achieved when a large (in excess of 9 Hz) vicinal hyperfine coupling constant is observed. All these features have been widely used to elucidate the configurations of the substituents and also for conformational assignments[52,77,91-100].

In particular, the conformation of the alcohol (XLVIII)[69,99] and its 1,5-dimethyl analogue[79], of the epimeric alcohols (XL, a and b),[52,53] of the epimeric chloroketones of the type (XXVII),[50] of the isomeric bromohydrins (LXVII) and (LXVIII),[68] and of the dibromoketone (LXIX)[68] were demonstrated by ^{1}H NMR.

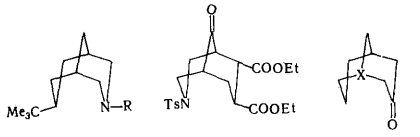


(LXVI) R = H, Me (LXVII) R = H, Me (LXVIII) R = H, Me (LXIX)

2. Conformations of Carbonyl Derivatives of Bicyclo-[3,3,1]nonane and its Monoheteroanalogues

In the first place it is necessary to consider the conformational analysis of monoheterobicyclo[3,3,1]nonanes. From the foregoing data, it is already clear that a wide variety of 2-*endo*-, 2-*exo*-, and 3-*endo*-monosubstituted derivatives of bicyclo[3,3,1]nonane and also 9-heterobicyclo[3,3,1]nonanes exist preferentially in the double chair conformation. The introduction of heteroatoms in the 1-, 2-, and 3-positions also should not apparently alter qualitatively the relative stabilities of the conformations. Although there are no data for 1-azabicyclo-[3,3,1]nonane, the existence of the 1,5-diaza-derivatives (XVI, X = N) and (XXXI) in the dichair conformation[58] confirms this view. There are literature data showing that 3-azabicyclononanes also exist in the dichair conformation for a wide variety of substituents at the nitrogen

atom. The amine (LXX),[93] *N*-benzoyl-3-azabicyclo-[3,3,1]nonane (XIV, X = $NCOC_6H_5$),[92] the toluene-*p*-sulphonate (LXXI),[101] and the hydriodide of *N*-methyl-3-azabicyclo[3,3,1]nonane[91] may be quoted as examples. It has been found by ^1H NMR that derivatives of 3-oxabicyclo-[3,3,1]nonane (XIV, X = 0) [102,103] and even of 3-thiabicyclo-[3,3,1]nonane (XIV, X = S) [90] exist in the dichair conformation. The latter example shows that even the introduction of a bulky hexoatom such as sulphur does not lead to qualitative changes in the relative energetic stabilities of conformations (I) and (II).

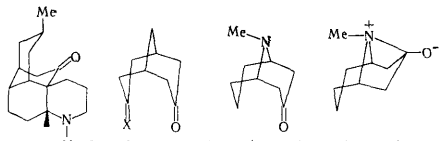


(LXX) (LXXI) (LXXII, X = CH) (LXXIII, X = N)

We shall now consider the problem of the conformational analysis of carbonyl compounds. The introduction of a carbonyl group in the six-membered ring is known to decrease appreciably the difference between the enthalpies of the boat and chair conformations; for example, the enthalpy of the boat–chair conformational transition of cyclohexanone is only 3.9 kcal $mole^{-1}$.[36,39,68] Therefore the introduction of the carbonyl group should decrease the difference between the energies of conformations (II) and (I). On the other hand, the introduction of a trigonal atom should cause some flattening and hence some stabilisation of form (I) as a result of the diminution of the 3–7 repulsion. When the C=O group is introduced into the 3-position, the repulsion of hydrogen atoms is altogether eliminated and only the *endo*-$H_{(7)} \ldots C_{(3)}$=O interaction remains. It is difficult to predict the balance of these factors, particularly for 2-oxo-derivatives[39,68].

The experimental data for 9-oxo-derivatives show that these compounds exist in the dichair conformation [compounds (XXVII),[45,50] (LII),[43,73] (LIII),[76] and (LVI) [80]]. This was to be expected, since the fragment with the carbonyl group is part of the rigid bridge system and a decrease in the barrier to rotation about the CO–C bond cannot affect the conformational energy. However, the data for 3-oxo-derivatives are contradictory. The conformation of bicyclo[3,3,1]nonan-3-one (LXXII) itself was investigated by ^1H NMR using a shift reagent[65]. It follows from the variation of the proton chemical shift with the concentration of the shift reagent that the carbonyl-containing ring must be planar. This was interpreted as indicating a conformational equilibrium between the dichair and chair-boat forms with a 1 : 1 conformer ratio. However, ultraviolet spectroscopic and ^1H NMR data for the 1-aza-analogue (LXXIII) indicate a pronounced flattening in the dichair conformation[104]. Detailed study of the conformation of the parent ketone (LXXII) should probably be continued.

We may note that X-ray diffraction analysis led to the determination of the geometry of the product obtained by the cleavage of the methiodide of lycopodine (LXXIV).[105] The bicyclononanone fragment is forced to adopt the dichair conformation, because the cyclohexane ring forms part of the rigid polycyclic system and the methyl group fixes the conformation of the second ring.

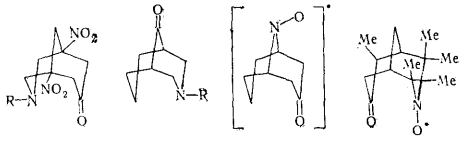


(LXXIV) [LXXV (a) X = CH_2; (b) X = O] (LXXVI) (LXXVII)

There are no data for the conformation of 3-methylenebicyclo[3,3,1]nonane (XII). Bearing in mind that 3,7-dimethylenebicyclononanes of type (XXX) exist in the dichair conformation[53], presumably the same conformation will be preferred also for ketones of type (LXXV).

In analysing the conformational equilibria of aminoketones, it is necessary to take into account an additional factor, namely the interaction of these groups in the direction $R_3\overset{+}{N} + C{=}O \rightarrow R_3\overset{+}{N}{-}C{-}O^-$. Transannular interactions of this type have been studied fairly thoroughly[106–109]. In the bicyclononane series this problem was encountered in a study of pseudopelletierine (LXXVI). The infrared spectrum of this compound indicates the absence of a transannular interaction between the amino- and carbonyl fragments of type (LXXVII), which supports the dichair conformation[108]. This was also confirmed by dipole moment data[108] and measurements of the Kerr constants[110]. The ^1H NMR spectra led to the conclusion that pseudopelletierine is in the conformation (LXXVI) with pronounced distortion of the piperidinone ring[98]. Possibly the marked flattening prevents the transannular interaction between the amino- and carbonyl groups in compounds of type (LXXVIII).[107] Similarly the aminoketone (LXXIX) also exists in the dichair conformation. The absence of an interaction between amino- and carbonyl fragments in the chair-boat conformation follows from dipole moment data and infrared spectra[111]. The infrared spectra do not contain bands in the range 2600–2800 cm^{-1}.[112,113]

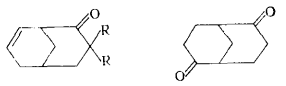
X-Ray diffraction analysis of the free radical (LXXX), which exists in a dimeric form, showed that it has the dichair conformation[114]. However, it is possible that the assumption of a tetracoordinate configuration by nitrogen on formation of the dimer is responsible for the destabilisation of the chair-boat conformation. Judging from the ESR spectrum and the dipole moment, another nitroxy-radical (LXXXI) also exists in the dichair conformation[115].



(LXXVIII) (LXXIX) (LXXX) (LXXXI)

Only isolated data are available for 2-oxo-derivatives. There are no experimental results for the ketone (LXV), although (see Section III) a number of investigators tend to give preference to the chair-boat conformation on the basis of indirect evidence[39,68]. The equilibrium (XXIII) ⇌ (XLIX) has been observed for the 3,3-dimethyl-2-oxo-derivative (see Section V). However, the conformation of the more stable isomer has not been demonstrated experimentally[39]. As stated in Section II (see also Section VI, 7), the introduction of a double bond leads to a flattening of the ring, which tends to reduce the strain in conformation (I). Therefore the chair-half-chair conformation has been postulated for the ketone (LXXXIIa)[39].

The authors assume the same conformation also for the dimethyl derivative (LXXXIIIb) on the basis of the similarity of its ultraviolet spectrum to that of the unsubstituted ketone, which naturally cannot be regarded as very reliable evidence.



[LXXXII, (a) R = H; (b) R = Me] (LXXXIII)

The dichair conformation has been assumed for the diketone (LXXXIII) on the basis of circular dichroic data[116]. In a number of studies[117,118] the dichair conformation was assumed for carbonyl derivatives of bicyclo[3,3,1]nonane without proof. There is no doubt that the problem of the conformations of 2-oxo-derivatives requires additional research. It is desirable to use for this purpose simple models, such as the ketone (LXV).

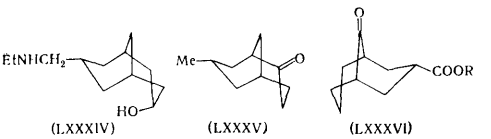
3. The Chair-Boat Conformation

We shall now consider the equilibrium (V) $\rightleftharpoons$ (VI) $\rightleftharpoons$ (VII) involving monosubstituted bicyclononanes (Section II). As stated in Section II, the introduction of a 3- (or 7-) *endo*-substituent destabilises conformation (V) and stabilises boat conformations. The problem arises of the ratio of conformations (VI) and (VII). The equilibrium position between them should be determined by two strongly destabilising 1,3-*aa*-interaction of type X... CH_2 in conformation (VII). On the other hand, in conformation (VI) the substituent occupies the bowsprit position and therefore the difference between energies of conformations (VI) and (VII) is associated with the energy of the X-*endo* $\rightleftharpoons$ X-bowsprit transition. Since the bowsprit position in conformation (VI) can be regarded as approximately equivalent to the equatorial position in conformation (VIIa), the energy difference for the (VII) $\rightleftharpoons$ (VI) transition can be estimated approximately from the energy of the (VIIa) $\rightleftharpoons$ (VI) transition. Data on the epimerisation of alcohols (XL) ($\Delta G_{OH} \simeq 2.18$ kcal mole^{-1})[52] were presented above. Thus conformer (VI) will predominate to a large extent in the conformational equilibrium; according to the data presented in Section V, the energy difference can be estimated from the energy of the X... CH_2 interaction for 1,3-disubstituted cyclohexanes.

The foregoing considerations are also valid when a choice is to be made between alternative conformations of type (X). The bowsprit position will be occupied by a substituent with more pronounced X... CH_2 repulsion. The preferred conformations of alcohols (XL)[52] and (LXXXIV)[119] confirm this postulate.

However, the above conclusion is valid only for equivalent rings in the bicyclo[3,3,1]nonane fragment. In principle, the introduction of heteroatoms can alter appreciably the energy difference between the boat and chair forms and hence disturb the above ratio of conformations (VI) and (VII). For simple mono- and di-heteroanalogues of cyclohexane, very sharp differences in this ratio are not usually observed[8,40], but in more complex cases this factor has to be taken into account.

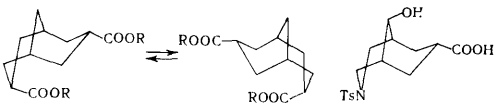
We shall consider next the influence of the nature of the 3-*endo*-substituent on the existence of this conformation. Evidently a bulky substituent such as the t-butyl group should appreciably destabilise conformation (I) and should exhibit a pronounced tendency to occupy the bowsprit position in the chair-boat conformation (II). As an example, one may compare the diester (XLIV)[67] with the epimeric ester (XLI). The 3-*endo*-methyl group also stabilises the chair-boat conformation [see compounds (XXXVIII),[66] (XXXIX),[66] and (XL).[52,66]]. It is interesting that ^{1}H NMR data for the ketone (LXXXV) indicate the existence of the normal form of the carbonyl-containing ring[68]. Furthermore, the introduction of the 3-*endo*-carboxy- or 3-*endo*-alkoxycarbonyl group also leads to conformation (II) [see compounds (XXXVI) and (XXXVII),[64] (XLII),[67] (XLV),[68] and (LXXXVI)[67]].



(LXXXIV) (LXXXV) (LXXXVI)

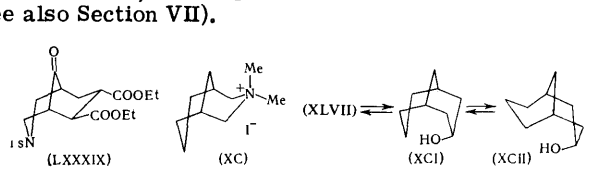
A more complex situation is observed for the dibasic acid (LXXXVIIa) and its diester (LXXXVIIb). The significant broadening of the ^{1}H NMR line at −90°C indicates the occurrence of a conformational equilibrium. However, the presence of two averaged hyperfine coupling constants J_{2a3} and J_{2e3}, both equal to 7.1 Hz, shows that the contribution of the chair-boat conformation predominates[120]. This is probably true also of other *cis*-3,7-disubstituted bicyclononanes of type (X). It has been shown for compounds (XXXII),[59,60] (XXXIII),[61] (LXVIII), and (LXIX)[68] that the introduction of a bromine atom also stabilises the chair-boat form. In the cyclohexane series the bromine atom is not regarded as a "large" substituent ($\Delta G_{Br} \simeq$ 0.38 kcal mole^{-1}),[71] since the effects of the bulk of bromine and of the length of its bond cancel out. However, in the series of bicyclo[3,3,1]nonane the bromine atom does behave as a "large" substituent.

This is true of simple heteroanalogues (see Section VI, 2). For example, the chair-boat conformation has been found for the azabicyclononanes (XXXII),[59,60] (XXXIII),[61] (LXXXVIII),[121] and (XXXIX).[101] Although the hydriodide of 3-methyl-3-azabicyclo[3,3,1]nonane[91] and the hydrochloride[91] and hydrobromide[42] of compound (XXIV) have the dichair conformation, the methiodide (XC) exists in the chair-boat conformation[91].



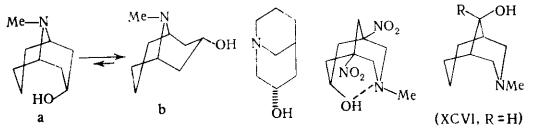
[LXXXVII, (a) R = H; (b) R = Me] (LXXXVIII)

The problem of the influence of the 3-*endo*-hydroxy-group on the preferred conformation is interesting. Firstly, this is a moderately large substituent and, secondly, the hydroxy-group can form hydrogen bonds, which can influence appreciably the position of the conformational equilibrium (see, for example, Baggett et al.[122] and Barker et al.[123]). It has been shown by ^{1}H NMR that the chair-boat conformers of 3-*endo*-bicyclo-[3,3,1]-nonanol (XLVII)[65,69,99] and of its 1,5-dimethyl derivative[79] predominate greatly. However, a study of the temperature variation of the hyperfine coupling constants and the application of shift reagents indicate the occurrence of an equilibrium[65,79,99]. However, it is not clear which form, (XCI) or (XCII), is in equilibrium with the main conformer (see also Section VII).

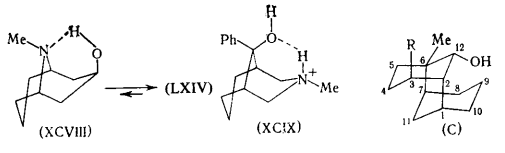


(LXXXIX) (XC) (XLVII) (XCI) (XCII)

The same problem was investigated in detail for 3α-granatanol (XCIII). Aaron et al.[89] used the method of conformational assignment based on the study of the shape of the fundamental OH stretching vibration bands in the infrared spectra. They concluded that the amines (XCIII) and (XCIV) exist in the dichair conformation. However, a detailed study of this problem showed that 3α-granatanol exists mainly in the chair-boat conformation (XCIIIb).[97-99] This is probably also true of the amine (XCIV). We may note that analysis of the band shapes in the infrared spectrum should be used with caution (see the discussion in the paper of Joris et al.[124]).



Interesting data were obtained in a study of the aminoalcohol (XCV). The infrared spectrum indicates the presence of an intramolecular hydrogen bond in this compound; thus the stabilisation of the double chair conformation by the hydrogen bond predominates over the steric repulsion due to the *endo*-functional group. This result is probably general (see Section VI, 6). It is appropriate to consider here data on the conformational equilibrium of 3β-granatanol (LXIV) and the aminoalcohol (XCVI). The infrared spectrum of the aminoalcohol (XCVI) fails to show the presence of an intramolecular hydrogen bond, which rules out the alternative chair-boat conformation[93,125]. According to ^{1}H NMR data, 3β-granatanol has the preferred dichair conformation (LXIV). However, the infrared spectrum demonstrates the presence of an intramolecular hydrogen bond, which indicates the presence of a small amount (about 11 %) of the conformation (XCVIII).[89,91] It is noteworthy that a change in conformation can occur when bicyclic amines and their derivatives are protonated (see also Section VI, 6). For example, the conformation (XCIX) has been adopted for the protonated form of the amine (XCVII), which exists in the dichair conformation[126].



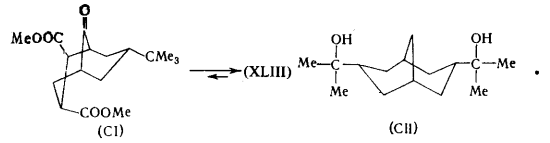
In complex polycyclic compounds the 3-*endo*-group can be constrained to form part of a dichair conformation. For example, X-ray diffraction analysis of a tricyclo-[5,3,1,1^{2,6}]dodecane (C) derivative showed that the hydroxy-group is in the *endo*-position[127]. The $C_{(9)}\ldots O$ and $C_{(4)}\ldots C_{(11)}$ distances are 2.90 and 3.09 Å respectively. Comparison of the angles shows that the hydroxy-group at $C_{(12)}$ actually causes a smaller flattening of the $C_{(8)}C_{(9)}C_{(10)}$ fragment than the $C_{(11)}$ methylene group of the $C_{(3)}C_{(4)}C_{(5)}$ fragment.

As shown in Section IV, the phosphorus-containing alcohol (XXXIV) assumes the chair-boat conformation. This conformation is determined by the strong repulsion of the two 3,7-*endo*-substituents in the dichair conformation. It is interesting that the dioxaphosphorinane ring assumes the boat form[62], probably owing to the general tendency by the P=O group to occupy the equatorial position[63].

In conclusion we may note that the problem of the conformations of bicyclo[3,3,1]nonane derivatives with a small substituent in the 3-*endo*-position is of great interest and merits a detailed study.

4. The Diboat Conformation

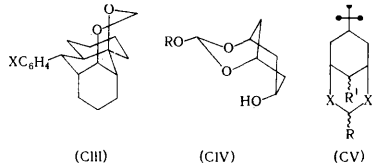
According to the discussion in Section II, the diboat conformation is to be expected for 3,7-disubstituted derivatives of type (IX). For a fairly bulky substituent X, the diboat conformation (XI) should be preferred rather than the chair-boat conformation (X). The ratios of forms (X) and (XI) depends on the ratio of the 1,3-*aa*-repulsion energy in the $X\ldots CH_2$ fragment and the energy difference for the chair-boat conformations, which should be of the same order of magnitude in the (X) → (XI) transition as for unsubstituted cyclohexane. It has been shown for compounds (XLa),[52] (LXXXIV),[119] and (LXXXVII)[120] that the hydroxy-, carboxy-, and methoxycarbonyl groups cannot destabilise the conformation (X). However, the presence of two axial methoxycarbonyl groups in the 2- and 3-positions in the ester (CI) leads to appreciable destabilisation of the chair-boat conformation[67]. Therefore the diboat conformation (XLIII) is preferred and the methoxycarbonyl groups occupy the bowsprit and gunnel positions. It is noteworthy that the presence of the trigonal atom in the 9-position should tend to decrease the strain in the boat conformation.



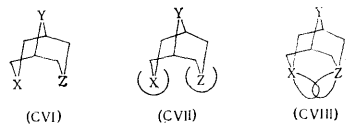
^{1}H NMR showed that the diol (CII) exists in the diboat conformation[120], which is undoubtedly related to the great bulk of the substituents.

5. The Conformations of Di- and Poly-heteroanalogues of Bicyclo[3,3,1]nonane. The Problem of the Steric and Orbital Interactions of the Heteroatoms

As mentioned above (Section II), the introduction of heteroatoms into compounds of type (XV) or (XVI) can intensify the non-bonding interactions by virtue of the shortening of the C–heteroatom bond. Measurements of the dipole moments of a series of compounds of type (CIII) showed that the 1,3-dioxan ring is in the chair-boat conformation[128]. An analogous conformation was attributed to compound (CIV),[129] probably owing to the presence of the *endo*-substituent [see also compound (XXXIV)[62,63]]. The diamines (XVI, X = nitrogen) and (XXXI)[58] have the conformation of a strongly flattened dichair. Thus the problem under consideration is far from having been solved and its investigation will have to be continued in relation to simpler examples of type (CV).

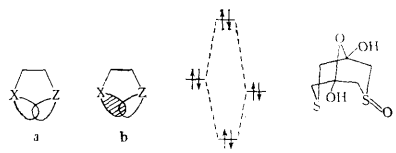


An extremely interesting conformational problem arises for 3,7-diheterobicyclo[3,3,1]nonanes of type (CVI). There is no steric repulsion of the hydrogen atoms in these compounds (X and Z are nitrogen, oxygen, or sulphur).



(CVI) (CVII) (CVIII)

However, three other types of interaction can be envisaged here. Firstly a dipole–dipole (or a charge–charge) interaction. For the usual heteroatoms, this factor should lead to repulsion and its extent should diminish down the Group of elements in the Periodic System. Secondly, we have purely steric repulsion, which at short distances is associated with the repulsion of the filled electron shells as in formula (CVII). This interaction is usually described satisfactorily by Hill's formula[130,131] or by another similar expression for the interaction potential[30,132]. An interaction of this kind presupposes a spherical symmetry of the electron shells of the type present in compound (CVII) [3] (for a discussion of the "bulkiness" of the electron pair, see Robb et al.[133]). Thirdly, we have the orbital interaction called the "hockey stick effect"[16,22,134,135], illustrated in formula (CVIII). We shall consider the last problem in greater detail. For the eclipsed (or *gauche*) conformation of a disubstituted ethane fragment of type (CIX), the overlapping of orbitals leads to the formation of the bonding (CIXa) and antibonding (CIXb) combinations and the consequent splitting of the levels [formula (CX)]. Such interaction of the orbitals "through space"[22,134,136-141] leads to the destabilisation of conformation (CIX) (antibonding predominates over bonding[137,142]). An alternative conformation (for example *trans*) should arise, provided that it is allowed by structural factors. The alternative conformation for the situation illustrated in formula (CVIII) is of the chair-boat type. The degree of repulsion should be proportional to the overlapping and should increase down the Group in the Periodic System[22].



(CIX) (CX) (CXI)

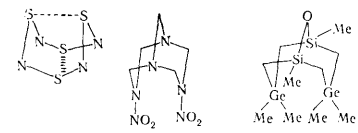
However, as shown for the first time by Hoffmann[136, 137,139], the groups X and Z can interact not only "through space" but also "through the bond", which can alter sharply the relative stabilities of the conformations[143,144]. Model compounds of the bicyclononane series can be used conveniently to isolate the orbital repulsion effect, since we can neglect the interaction between the heteratoms via four bonds.

We shall now consider experimental data on the conformations of compounds of type (CVI). Derivatives of 3,7-diazabicyclo[3,3,1]nonane (bispidine) have been studied most (see Section VI, 6). The calculated[41] and experimental[145] data for 3,7-dimethylbispidine (XXV) show that the dichair conformation predominates.

A large series of compounds of type (CVI) has been investigated[46,47,90]. In all cases where two oxygen atoms or an oxygen and a sulphur atom are present in the 3- and 7-positions [compounds (XXVIII) and (CVI) with X = Y = Z = O or X = S and Y = Z = O] the dichair conformation is preferred [for the geometry of (XXVIII), see Section IV]. However, the situation changes sharply when there are two sulphur atoms (or sulphur and selenium atoms[90]) in the 3- and 7-positions. Compound (XXXV) and compounds of type (CVI, X = Z = S, Y = CH_2; X = S, Y = O, Z = Se) exist in the chair-boat conformation[46,47,90].

It is interesting to consider the problem of the causes of such destabilisation of conformation (I). The $S_{(3)}...S_{(7)}$ distance for the hypothetical dichair conformation of (XXXV) can be calculated from the geometry of compound (XXVIII) and is found to be approximately 4.6 Å. This distance is much greater than the sums of the van der Waals radii of two sulphur atoms (3.6–3.8 Å).[146]. The experimental S...S distances are in the range 3.6–4.0 Å.[147-150] Thus the study of the geometry of molecules of type (XXVIII) and (XXXV) makes it possible to attribute the destabilisation of the dichair form to orbital repulsion.

In this connection the data of Abrahamsson and Rehnberg[147] require consideration. They found that the sulphoxide (CXI) has the dichair conformation with an extremely short $S_{(3)}...S_{(7)}$ distance of 3.17 Å. Attraction forces apparently operate between the sulphur atoms, possibly due to the positive charge on the sulphoxide sulphur atom. Examples of the stabilisation of sulphoxides and sulphones by dipole–charge attraction have been described in the literature[30,135]. We may also note that in the S_4N_4 molecule (CXII), which consists of an eight-membered ring simulating the geometry of the perimeter of the bicyclo[3,3,1]nonane molecule, there is strong attraction between two sulphur atoms, as a result of which the distance between them is 2.69 Å.[151,152]



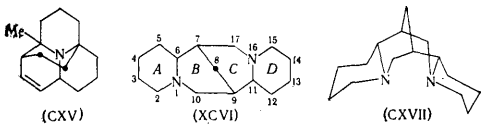
(CXII) (CXIII) (CXIV)

In conclusion of this section we may mention the conformations of polyheteroanalogues of bicyclo[3,3,1]nonane, for which only isolated and non-systematic data are available. Thus it is known that derivatives of triazaphosphabicyclononane (XXIX) [48] and tetraazabicyclononane (CXIII) [153] exist in the dichair conformation. The authors observed in the ^1H NMR spectrum of compound (CXIV) the signal of the *AB* system of the methylene protons and two signals of the methyl groups at the germanium atoms, which was used as evidence in support of the absence of an asymmetric conformation of type (II).[154] However, this reasoning is controversial and the solution of the problem requires ^1H NMR measurements at low temperatures.

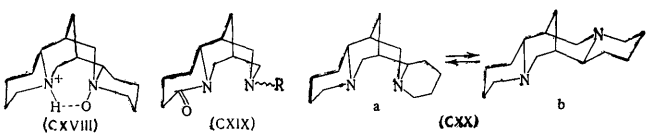
6. Conformations of Alkaloids Containing the Azabicyclo[3,3,1]nonane Fragment

The azabicyclo[3,3,1]nonane skeleton is a component of the structures of many alkaloids. Thus the 3-azabicyclononane fragment is part of the compositions of certain diterpene alkaloids[155]; many alkaloids are also based on 9-azabicyclononane derivatives[117,156,157]. As an example, one may quote porantherine (CXV); X-ray diffraction analysis of its hydrobromide shows the presence of the 9-azabicyclononane fragment in the dichair conformation[157].

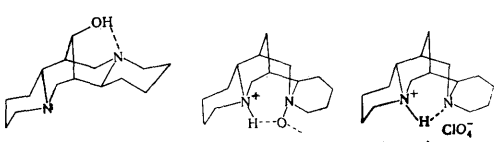
However, alkaloids of the Lupin family probably constitute the most important class. In the present section we shall consider the problem of their structures, but only in so far as this concerns the subject of the present review as a whole. Alkaloids of this group have the structure (CXVI) and as regards conformations can be divided into three groups depending on the configurations of the $C_{(11)}$ and $C_{(6)}$ centres. The dichair conformation (CXVII) should be the most stable for α-isosparteine, which has *endo*-substituents at these centres. X-Ray diffraction analysis of α-isosparteine hydrate shows that this compound does indeed have the conformation (CXVII) with an $N_{(1)} \ldots N_{(16)}$ distance of 3 Å.[158]


(CXV) (XCVI) (CXVII)

Next it was found that this conformation should be attributed to the cation of isosparteine *N*-oxide (CXVIII).[159,160] Despite the presence of the *endo*-substitute in (CXVIII), the dichair configuration is stabilised by the intramolecular hydrogen bond (see Section VI, 3). This is responsible for the enhanced basicity of the *N*-oxide itself, for which the dichair conformation has also been adopted[159,160]. We may also note that the dichair conformation has been attributed to various lactam structures with related configurations[156,159-163]. As an example, one may quote the tricyclic lactam (CXIX).[163] The study of the influence of the anisotropy of the nitrogen atom on the chemical shifts of the methylene protons enabled the authors to reach a conclusion about the conformation of the substituent at the nitrogen atom. The hydrogen atom occupies the axial position (CXIX, R = H), while the ethyl group occupies the equatorial position. It is not clear whether the stabilisation of the axial position of the hydrogen atom is a consequence of its small bulk or of the presence of the intramolecular hydrogen bond.


(CXVIII) (CXIX) a ⇌ b (CXX)

We shall now formulate the conformational problem which arises for alkaloids of the sparteine series (we believe that in a number of studies it was artificially made more complicated[164,165]). On the basis of the foregoing considerations, two conformations (CXX, a and b) can be postulated for sparteine (CXX). One of them includes a bicyclononane fragment in the dichair conformation but has an axial substituent at $C_{(11)}$ and therefore a *cis*-junction of the *C* and *D* rings of the quinolizidine fragment. *A priori* estimates of the stabilities of these conformations are difficult owing to the lack of data on conformational equilibria in model quinolizidine systems. It is known only that *trans*-quinolizidine is more stable than the *cis*-isomer, but the available quantitative data are subject to a scatter of 2.1—4.6 kcal mole^{-1}.[166-169]

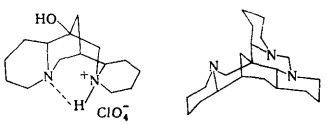

(CXXI) (CXXII) (CXXIII)

Infrared spectroscopic and ^{1}H NMR studies on compounds with the sparteine skeleton[161,162,164,170,171] showed that the *C* ring has the preferred boat conformation (CXXb). This is shown particularly clearly by the hyperfine coupling constant $J_{H_{(7)}H_{(17)}} = 10$ Hz.[164] The chair-boat conformation has also been demonstrated for 8-hydroxysparteine (CXXI)[170] by the presence of the intramolecular hydrogen bond.

However, the difference between the free energies of conformations (CXXa) and (CXXb) is probably relatively small. At any rate the formation of complexes via the two nitrogen atoms, which is possible only in the dichair conformation, may alter appreciably the position of the conformational equilibrium. Such coordination takes place, for example, when sparteine reacts as a bidentate ligand with organolithium[172] or organoaluminium compounds[173], which permits asymmetric syntheses. Incidentally, this indicates the necessity for caution in the employment of shift reagents in ^{1}H NMR conformational studies on compounds of this series.

The hydrogen bond has a similar effect. Thus the sesquiperchlorate of sparteine *N*-oxide (CXXII) exists, like compound (CXVIII), in the dichair conformation owing to the presence of the intramolecular hydrogen bond[174,175]. Borovyak et al.[176] obtained an extremely interesting result. They showed by X-ray diffraction of sparteine monoperchlorate (CXXIII) that this salt assumes the dichair conformation with a distance between the nitrogen atoms of only 2.79 Å. The sharp difference between the conformations of sparteine (in solution) and of its salt (in the crystalline state) can be attributed either to the difference between the states of aggregation or to the stabilisation of the dichair conformation by the intramolecular hydrogen bond on protonation of one nitrogen atom. It would be useful to undertake a study of the conformations of sparteine salts in solution.

There are few data on the conformations of β-isosparteine. The dichair conformation has been adopted for this compound[170]. The same conformation has been found for the monoperchlorate of the 7-hydroxy-derivative of (CXXIV) in the crystalline state[177]. However, it is possible that the presence of the hydrogen bond alters in this case too the conformational pattern characteristic of the free base.


(CXXIV) (CXXV)

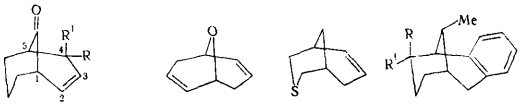
The chair-boat conformation has been found for the azabicyclononane fragment of compound (CXXV).[178] These data were obtained for the free bases and all complicating factors (for example, hydrogen bonds) are absent. Therefore the *trans*-junction of the quinolizidine fragment is probably a more important factor for conformational specificity than the dichair conformation.

7. Conformations of Unsaturated Derivatives of Bicyclo-[3,3,1]nonane and Its Heteroanalogues

The introduction of a double bond into the bicyclo[3,3,1]-nonane skeleton leads to a fairly marked distortion of the geometry. The presence of the 2,3-double bond [compound (XIII)] leads to a sharp decrease of the 3—7 repulsion owing to the flattening of the cyclohexene ring.

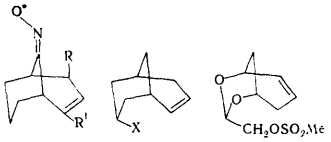
Evidently the saturated ring will have the chair conformation. By virtue of the rigid junction between the rings and the requirement that the $C_{(1)}C_{(2)}C_{(3)}C_{(4)}$ fragment must be planar, the cyclohexene ring in compound (XIII) should be rigid and incapable of inversion.

Experimental data confirmed this hypothesis. A marked flattening of the unsaturated ring in the epimeric ketones (CXXVI) and (CXXVII) has been indicated by J_{45}(CXXVI) = 6.4 Hz and J_{45}(CXXVII) = 0 [179] (cf. Zefirov and Rogovina[90], Section VI, 1).



(CXXVI, R = Ph, R' = H) (CXXVII, R = H, R' = Ph) (CXXVIII) (CXXIX) (CXXX)

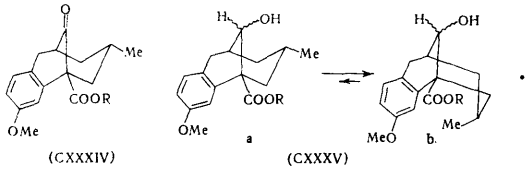
A similar flattening has been observed also in the diene (CXXVIII).[90] A conformation of type (XIII) has also been found for heteroanalogues [the sulphide (CXXIX)[90]], benzo-derivatives [compounds of type (CXXX)[180]], and stable free radicals of type (CXXXI)[181] [cf. compounds (LXXX) and (LXXXI), Section VI, 2].



(CXXXI) (CXXXII) (CXXXIII)

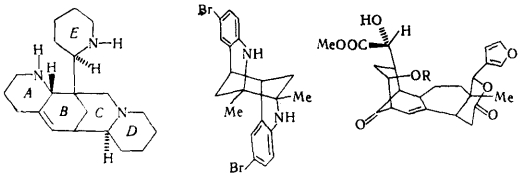
However, the conformational problem specific to the unsaturated compounds of the series under consideration is of greatest interest. It can be formulated as follows: since the unsaturated ring is appreciably flattened, it is interesting to discover whether the chair conformation of the saturated ring is retained in the presence of a 7-*endo*-substituent in compounds of type (CXXXII).

There are few available literature data but they nevertheless lead to the definite conclusion that there is a sharp decrease of 3—7 repulsion in systems of type (CXXXII). For example, the chair conformation has been attributed to the methanesulphonate (CXXXIII).[129] Interesting data have been obtained by Colvin et al.[182] The methyl group in compounds (CXXXIV) and (CXXXV) gives rise to a doublet in the ^{1}H NMR spectrum with δ = 0.8 and 0.4 p.p.m. respectively. The difference of 0.4 p.p.m. can be accounted for as follows. The methyl group in compounds (CXXXIV) is remote from the benzene ring, because the saturated ring assumes the boat conformation. Reduction of the carbonyl group leads to the appearance of flagpole—flagpole repulsion in the boat conformation, which results in an equilibrium between (CXXXVa) and (CXXXVb) and a shift of the methyl group signal owing to the steric proximity of the benzene ring. This is confirmed by the chemical shift of the compounds epimeric with respect to the methyl group, which evidently have the chair conformation in both cases[182].



(CXXXIV) (CXXXV)

The chair conformation has been found for the nitrogen-containing ring in the azabicyclononane fragment in podopetaline hydrobromide (CXXXVI).[183] The *A*, *D*, and *E* rings also have the chair form, but the *B* ring assumes the "sofa" conformation[183-186]. Thus there is a *cis*-junction between the *C* and *D* rings of the quinolizidine fragment of this compound, while in the saturated alkaloid (CXXV) there is a *trans*-junction[178] (see Section VI, 6). This example clearly demonstrates a decrease of the 3—7 repulsion for unsaturated systems of the type under consideration. There are data for the geometries of other complex compounds, for example the diamine (CXXXVII)[187] or the *p*-iodobenzoate of destigloylswietenine (CXXXVIII).[188,189] We may note that compounds of type (CXXXII) have recently become relatively readily available[190,191], so that it would be desirable to investigate the problem under consideration quantitatively on simple models.



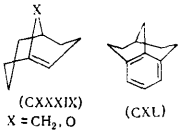
(CXXXVI) (CXXXVII) (CXXXVIII)

The syntheses of compounds of type (CXXXIX) containing a double bond at the bridgehead were described recently[192-196] and the limitations of Bredt's rule were thus demonstrated. The unsaturated ring in these structures should be a rigid half-boat in which the requirement of minimum twisting of the double bond is met. The saturated ring should have the chair form. We may note an interesting aromatic hydrocarbon (CXL).[197] Although the authors postulate the existence of several possible conformers, this does not appear to be a realistic assumption, because (CXL) should have a unique rigidly fixed structure.

VII. CONFORMATIONS AND REACTIVITIES OF BICYCLO-[3,3,1]NONANE DERIVATIVES

In this section we shall consider briefly the possibility of applying chemical methods of bicyclo[3,3,1]nonanes and their reactions will be discussed.

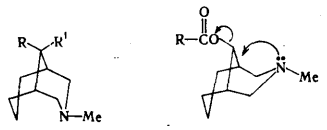
Information about the preferred conformations can be obtained from kinetic and stereochemical data. For example, the similarity of the relative rates of solvolysis of the epimeric *p*-nitrobenzoates (CXLI) and (CXLII) confirms that the dichair conformation is preferred, because in the chair-boat conformation one might expect a synartetic acceleration of solvolysis for the *anti*-epimer (CXLIII).[125,126,198]



(CXXXIX) X = CH_2, O (CXL)

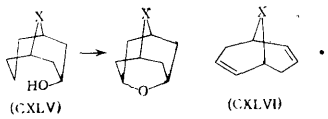
A similar addition of organomagnesium compounds to the ketone (LXXIX) leads to almost equal fractions of the

epimeric alcohols (CXLIV), a and b, which is also logical for the dichair conformation[126].



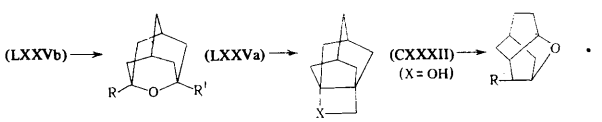
(CXLI, R = *p*-$NO_2C_6H_4COO$; R^1 = H)
(CXLII, R = H; R^1 = *p*-$NO_2C_6H_4COO$)
(CXLIII)
[CXLIV, (a) R' = OH; (b) R = OH]

Bearing in mind the non-bonding $H_{(3)} \ldots H_{(7)}$ interaction, compounds of the bicyclo[3,3,1]nonane series will presumably be converted into derivatives with adamantane-like structures. Evidently such conversion takes place in the dichair conformation. For example, the oxidation of alcohols of type (CXLV) by lead tetra-acetate is accompanied by cyclisation to oxa-adamantane derivatives[99,199].

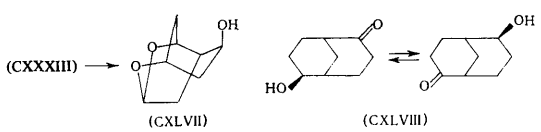


(CXLV) (CXLVI)

A wide variety of numerous transformations of 3,7-functional derivatives of bicyclo[3,3,1]nonanes into derivatives with an adamantane structure are known[200-207]. We may quote, for example, the cyclisation of dienes of type (CXLVI) and the diketone (LXXVb) to oxa-adamantane derivatives, of the methylene derivative (LXXVa) to noradamantane derivatives, and of the enol (CXXXII, X = OH) to isoadamantane derivatives[201-207].

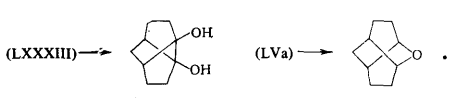


We may also note that the cyclisation of the methanesulphonate (CXXXIII) to the tricyclic compound (CXLVII) is one of the stages in the total synthesis of prostaglandin $F_{2\alpha}$.[129]



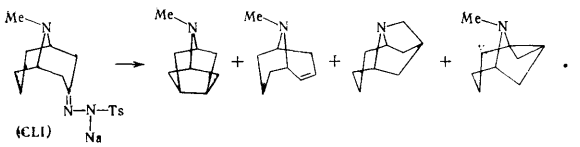
(CXLVII) (CXLVIII)

The steric proximity of the 3,7-positions makes hydride transfer possible[191,207,208]. Deuterium exchange involving the ketol (CXLVIII) indicates the occurrence of an intramolecular stereospecific 2—6 hydride shift[210]. The transition state in this reaction should include the diboat twist-conformation. We may also note the cyclisation of the diketone (LXXXIII) to a pinacol[7], which has the nortwistane skeleton, and also the cyclisation of the diol (LVa) to oxatwistane (CL).[211] These are not exhaustive examples, showing merely how the bicyclo[3,3,1]nonane fragment can react.



(CXLIX) (CL)

Naturally, conformational assignments on the basis of the structure of the products obtained must be made with caution, because the energies of conformational transitions are usually small compared with activation energies. We may point out, for example, that the decomposition of the tosylhydrazone (CLI) leads to a complex mixture of products, including some with a fixed chair-boat conformation[212,213].



(CLI)

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It follows from the foregoing data that the bicyclo-[3,3,1]nonane system is a convenient model for the solution of a large set of problems in conformational analysis. In particular, the possibilities provided by this model for the investigation of the reactivities of functional groups in the boat conformation or of problems concerning the transannular interactions of heteroatoms and functional groups are frequently completely unique. There is no doubt that the great possibilities of this system in relation to problems of conformational analysis will be ultilised in the future.

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