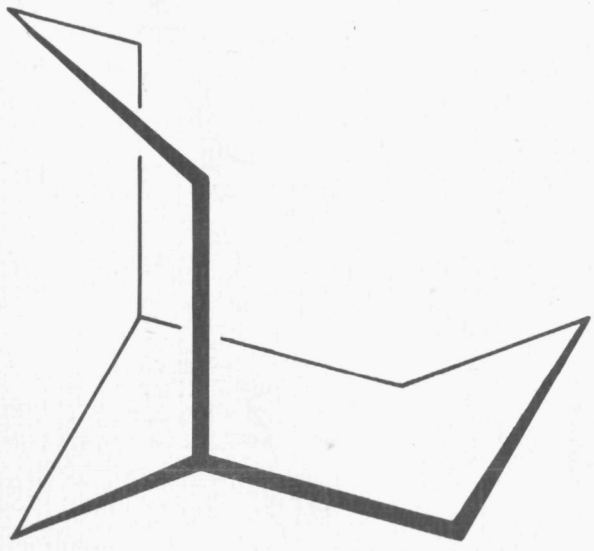
Synthesis, configurational and conformational analysis of some types of cyclohexane and bicyclo[3.3.1]nonane derivatives

J. A. Peters



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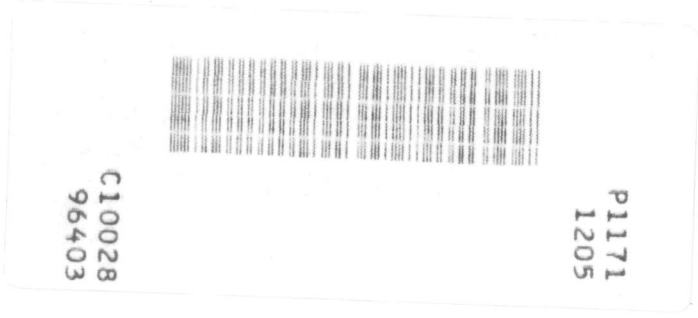

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PART I KOCH-HAAF CARBOXYLATIONS OF ALICYCLIC SYSTEMS

CHAPTER 1. INTRODUCTION TO PART I

The reaction steps involved in the *Koch-Haaf* carboxylation are briefly discussed. Some applications are given and the aims of the investigation of Chapter 2-4 are outlined.

CHAPTER 2. CARBOXYLATIONS OF *tert*-ALKYL SUBSTITUTED CYCLOALKANOLS

Contrary to literature data 1-isopropylcyclohexanol afforded both 1-isopropylcyclohexanecarboxylic acid and 2-cyclohexyl-2-methylpropanoic acid upon carboxylation by the method of *Koch*.

The *Koch-Haaf* carboxylation of a number of *tert*-alkyl substituted cycloalkane derivatives has been studied. Side reactions were suppressed by using the *Haaf* conditions with slow stirring of the reaction mixture.

tert-Butylcyclohexanols afforded 1-*tert*-butylcyclohexanecarboxylic acid accompanied by 2-methyl--2-(1-methylcyclohexyl)propanoic acid. In the *Koch-Haaf* reaction of 3-*tert*-butylcyclopentanol and 4-*tert*-butylcycloheptanol more complex rearrangements occurred. The main products were 1,2,2-trimethylcyclohexanecarboxylic acid and 2-cyclohexyl--2,3-dimethylbutanoic acid, respectively.

From the composition of the reaction products conclusions were drawn concerning the mechanisms of the rearrangements involved in these reactions. In some of the reactions protonated cyclopropane rings are proposed as intermediates.

CHAPTER 3. CARBOXYLATION OF 1-ALKYLCYCLOHEXANEMETHANOLS, 1-(1-ALKYLCYCLOHEXANE)-ETHANOLS, AND 1-METHYL SUBSTITUTED SPIRO[2.5]OCTANES

The *Koch-Haaf* carboxylation of a series of 1-alkylcyclohexanemethanols and 1-(1-alkylcyclohexane)ethanols has been studied. In the initial cation the 1-alkyl group always migrates into the side chain, yielding tertiary carboxylic acids. An exception is the carboxylation of 1-(1-adamantane)ethanol, which gives the corresponding secondary acid besides 3-ethyladamantanecarboxylic acid. The latter compound is formed probably from the initial carbonium ion after a bimolecular hydride shift.

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PART II SYNTHESIS AND CONFORMATION OF BICYCLO-[3.3.1]NONANES

CHAPTER 5. INTRODUCTION TO PART II

The conformational features of the bicyclo-[3.3.1]nonane system are discussed and a literature review on the synthesis of 3- and 3,7-substituted bicyclo[3.3.1]nonanes is given. The objectives of the investigations in this field at the Delft Laboratory of Organic Chemistry are outlined.

CHAPTER 6. SYNTHESIS AND (NON-CHAIR) CONFORMATION OF SOME 3α,7α-DISUBSTITUTED BICYCLO-[3.3.1]NONANES

A new synthetic route to 3α,7α-disubstituted bicyclo[3.3.1]nonanes *via* oxidative cleavage of homoadamantan-4-one is described.

The conformation of the resulting bicyclo-[3.3.1]nonane derivatives was investigated by means of ^1H NMR spectroscopy with the use of lanthanide shift reagents. This method was shown to be reliable for this class of compounds. The vicinal hydrogen-hydrogen coupling constants obtained showed that a bicyclo[3.3.1]nonane with the $-C(CH_3)_2OH$ group at the 3α- and 7α-positions is predominantly in the double-boat conformation. The data on bicyclo[3.3.1]nonane-3α,7α-dicarboxylic acid and its dimethyl ester can be explained by a rapid interconversion of two (identical) chair--boat conformations, of which both the chair and the boat part are flattened.

CHAPTER 7. SYNTHESIS AND CONFORMATION OF SOME 3,7-DISUBSTITUTED 9-OXOBICYCLO[3.3.1]-NONANES

Condensation of pyrrolidine enamines of 4-alkylcyclohexanones with methyl α-(bromomethyl)-acrylate affords methyl 7β- and 7α-alkyl-9-oxo-bicyclo[3.3.1]nonane-3α-carboxylates in a ratio of 3:2. The mechanism of the annelation reaction is discussed. The conformations of the reaction products and their epimers have been studied by means of PMR spectroscopy.

CHAPTER 8. SYNTHESIS AND CONFORMATION OF BICYCLO-[3.3.1]NONANE-3α,7α-DICARBOXYLIC ACID, ITS DIMETHYL ESTER AND SOME OTHER 3,7--DISUBSTITUTED BICYCLO[3.3.1]NONANES; ADAMANTANE AS AN INTEGRATED HOLDING SYSTEM

The conformation of bicyclo[3.3.1]nonane--3α,7α-dicarboxylic acid and its dimethyl ester has been studied by comparing ^1H NMR and ^{13}C NMR spectra of these compounds with those of some model 3,7-disubstituted bicyclo[3.3.1]nonanes, fixed in a single conformation by the use of

adamantane as an integrated holding group or by means of suitable substitution. It is shown that the dicarboxylic acid and its dimethyl ester exist predominantly as two rapidly interconverting (identical) chair-boat conformations with distinctly flattened rings; the population of the double-boat conformation appears to be very small.

CHAPTER 9. CHAIR-BOAT EQUILIBRIA IN BICYCLO[3.3.1]-NONANE AND SOME OF ITS 3- AND 3,7-SUBSTITUTED DERIVATIVES; THERMODYNAMIC PARAMETERS AND GEOMETRY OF THE CONFORMERS AS OBTAINED BY MOLECULAR MECHANICS

ΔG-values for conformational equilibria in 3,7-substituted bicyclo[3.3.1]nonanes have been obtained by means of epimerisation experiments (cc⇌bc) and by variable temperature ^{13}C NMR (bc⇌bb). The results of these experiments fit well with those of molecular mechanics using the Schleyer force field. In bicyclo[3.3.1]nonane and 3β-substituted derivatives the cc conformation predominates; however, bulky 3β-substituents such as t-butyl, are found to have a destabilizing effect. A 3α-substituent forces the substituted wing into the boat conformation. For the 3α,7α-disubstituted derivatives the conformational preferences depend on the size of the substituents: for 3α-methyl, 7α-t-butylbicyclo[3.3.1]nonane the cb and t-bb conformers are of approximately equal enthalpy.

The geometries, obtained by the calculations, show that the conformers of bicyclo[3.3.1]nonane (cc, bc and t-bb) are all distinctly flattened. The boat wings of bc conformers are not twisted to any extent. The t-bb is the most stable bb conformation. The influence of substitution at positions 3 or 7 is discussed in detail; in general, a bulky substituent, such as t-butyl, affects the geometry of both wings of the ring system. The calculated geometries are in good agreement with the conclusions of previous ^{1}H NMR investigations.

CHAPTER 10. ^{13}C NMR SPECTROSCOPY OF SOME 3- AND 7-SUBSTITUTED BICYCLO[3.3.1]NONANES

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CHAPTER 11. CONFORMATIONAL ANALYSIS OF 7-ALKYL-3--OXABICYCLO[3.3.1]NONANES AND COMPLEXES WITH LANTHANIDE SHIFT REAGENTS

The conformation of 3-oxabicyclo[3.3.1]-nonane and of some of its 7α- and 7β-alkyl substituted derivatives have been studied with the use of ^{13}C and ^{1}H NMR spectroscopy. A comparison is made with the carbocyclic analogues. It turns out that the replacement of the 3-methylene group by oxygen has no substantial influence on the conformational preferences. With the aid of $^{3}J_{HH}$ coupling constants it is shown that the geometry of the cyclohexane rings is about the same as in the corresponding carbocyclic compounds. The results of calculations on lanthanide induced shifts indicate that the tetrahydropyran ring is not flattened but probably somewhat puckered. The calculated location of Eu(III) in complexes of $Eu(dpm)_3$ with the 3-oxabicyclo[3.3.1]nonanes is compared with that in the complexes of the related compounds 2-oxaadamantane and 4-methyltetrahydropyran. The data indicate that the lanthanide ion coordinates "axially" to the latter compound.

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CHAPTER 13. 4-METHYLPROTOADAMANT-4-EN-2-ONE: AN UNEXPECTED PRODUCT FROM THE REACTION OF 1-METHYLADAMANTAN-2-ONE WITH SODIUM AZIDE AND METHANESULFONIC ACID

4-Methylprotoadamant-4-en-2-one was isolated from the reaction of 1-methyladamantan-2-one with sodium azide and methanesulfonic acid. A side product of this reaction is probably 4-methyleneprotoadamantan-2-one.

PART I

KOCH-HAAF CARBOXYLATIONS OF ALICYCLIC SYSTEMS

CHAPTER 1

INTRODUCTION TO PART I

The synthesis of *linear* carboxylic acids is one of the eldest branches in chemical industry. Many processes based on natural products or on petrochemicals have been developed[1]. Although several laboratory methods are known for the synthesis of *branched* carboxylic acids, there are only two routes in technical practice, namely the oxidation of branched aldehydes and the *Koch* carboxylation of olefins[1]. Moreover, some representatives of this type of acids are isolated from natural products (e.g. abietic acid, dextropimaric acid). Esters of branched carboxylic esters are difficult to hydrolyze and have a high thermostability. Therefore, these derivatives have found applications in alkyd resins and as plasticizers, paint dryers and lubricants.

In the fifties *Koch* developed a versatile carboxylation reaction, by which olefins and alcohols can be converted, in high yields, into branched carboxylic acids by the use of a two step procedure[2,3]. First, the substrate is treated with carbon monoxide (1-100 atm.) in a strongly acidic medium at temperatures between -20 and +85°. Subsequent dilution with water affords the carboxylic acids. As shown by *Eidus* et al., the use of alcohols in the second step affords esters[4].

M e c h a n i s m

The *Koch* reaction most probably proceeds by subsequent carbonylation (2) and hydratation (3) of a carbenium ion, generated from the substrate in the strongly acidic medium (1) (see Scheme 1)[19]. Since this process proceeds *via* a carbenium ion,

$$H^+ + \text{substrate} \rightleftharpoons R^+ \quad (1)$$

$$R^+ + CO \rightleftharpoons RCO^+ \quad (2)$$

$$RCO^+ + H_2O \rightleftharpoons RCOOH_2^+ \quad (3)$$

$$RCOOH_2^+ + H_2O \rightleftharpoons RCOOH + H_3O^+ \quad (4)$$

$$H_2O + R^+ \rightleftharpoons \text{alkenes} + H_3O^+ \quad (5)$$

Scheme 1

several other reactions may be involved e.g. intra- and intermolecular rearrangements of the carbenium ion, deprotonation towards isomeric alkenes (5), cyclization, oligomerization and fragmentation.

In the usual acidic media (H_2SO_4, H_3PO_4) generally tertiary carboxylic acids are obtained irrespective of the starting compound. Considering that the decarbonylation of secondary oxocarbenium ions is relatively slow[7,18] (cf. Chapter 4), this shows that the isomerization of the intermediate carbenium ion is faster than the carbonylation. Sometimes, secondary carbenium ions can be trapped by the use of the *Haaf* modification in which a

relatively high ratio of CO and substrate concentration is applied. This is particularly the case when isomerization of the cation requires an increase of branching. These rearrangements are relatively slow as has been shown by *Brouwer*[8]. The intermolecular rearrangements can be suppressed by using a low concentration of organic reactant[5] (see also Chapter 3).

Side reactions such as oligomerization and cyclization are slow with respect to the carbonylation; therefore, these reactions may also be suppressed by increasing the ratio of CO and substrate concentration.

The thermodynamics and kinetics of the various reaction steps in super acidic reaction media (e.g. $HF-BF_3$, $HF-SbF_5$ and FSO_3H-SbF_5) have been studied and reviewed by *Hogeveen*[7].

It has been shown that the stabilization of the positive charge in oxocarbenium ions is rather insensitive to the structure of the alkyl group[7,8]. Therefore, determination of the equilibrium constant of the carbonylation/decarbonylation step is an important tool in the study of stabilization of carbenium ions[7].

Recently, *Souma* and *Sano*[9] reported that the *Koch* reaction of alcohols, olefins and alkanes in H_2SO_4 is catalyzed by $Cu(I)(CO)_3^+$ and $Ag(CO)_n^+$ ions (n=1,2), prepared *in situ* from the metal salt or oxide and CO. The mechanism of this reaction is unclear up to now. Probably, substrate metal carbonyl complexes are intermediates.

The reaction medium

Strong acids, such as H_2SO_4, H_3PO_4, $H_3PO_4.BF_3$, $BF_3.H_2O$, HF, $HF-BF_3$, SbF_5-SO_2 and $SbCl_5-SO_2$ are suitable as reaction media for the *Koch* carboxylation. The nature of the acidic catalyst influences the product distribution.

In laboratory experiments H_2SO_4 is the most commonly used acidic medium. In this reaction medium CO can be generated *in situ* from formic acid[11]. Then, in some cases, slow stirring, ensuring a high CO concentration, causes trapping of secondary carbenium ions.

In industrial processes $H_3PO_4.BF_3$ (Shell) and $BF_3.2H_2O$ (Enjay) are applied as the acidic reaction media[1]. These systems have the advantage that, after dilution with equimolar amounts of water, a separation between carboxylic acids and catalyst system is achieved, allowing recycling of the acidic catalyst without intermediate purification. Recently, a convenient method of HF and H_2SO_4 catalyst recovery in the *Koch* reaction has been described[10].

Reactants

Originally, *Koch* developed the carboxylation for olefins and alcohols as the starting materials. Later on, the reaction was extended to other substrates, which are able to form carbenium ions in strongly acidic media (e.g. esters, alkyl halides). Even alkanes can be used as starting material. Then the presence is required of an alcohol or olefin, which can serve, after conversion to the carbenium ion, as hydride acceptor (see Scheme 2). Of course,

$$R_1H + R_2^+ \rightleftharpoons R_1^+ + R_2H$$
$$R_1^+ + CO + 2H_2O \longrightarrow R_1COOH + H_3O^+$$
$$R_2^+ + CO + 2H_2O \longrightarrow R_2COOH + H_3O^+$$

Scheme 2

with this method the carboxylic acid corresponding to the hydride acceptor is obtained as a side product[2]. In super acidic reaction media, alkanes can be converted into carboxylic acids without the

use of a hydride acceptor. *Hogeveen* et al. reported the synthesis of acetic acid from methane[13] (see Scheme 3). These authors also succeeded in trapping

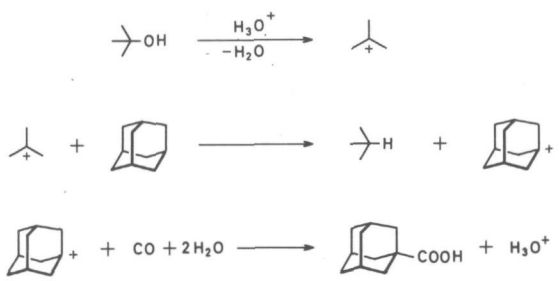
$$CH_4 + SbF_5 \longrightarrow CH_3^+ + SbF_5H^-$$

$$CH_3^+ + CO \longrightarrow CH_3CO^+ \xrightarrow{H_2O} CH_3COOH + H_3O^+$$

Scheme 3

the stable vinyl cations by the use of super acidic systems[14].

From the numerous applications of the *Koch* carboxylation[2], the use in the functionalization of adamantane and diamantane is especially worth to be mentioned[15-17] (see Scheme 4).



Scheme 4

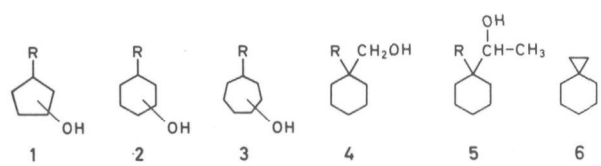
The *Koch* synthesis is applied to the manufacture of pivalic acid from isobutene and branched C_7-C_{11} carboxylic acids from diisobutene or C_6-C_{10} olefins (Shell, Enjay). Moreover, the process is used in the synthesis of glycolic acid from formaldehyde (Dupont)[1].

Scope of Part I of this thesis

At the start of this investigation the application of the *Koch-Haaf* synthesis to the field of the cycloalkane chemistry was restricted to compounds with small side chains, such as methyl, ethyl and isopropyl. The aim of the investigation, described in Part I of this thesis, was to extend this reaction to cycloalkanes with more complex side chains.

The investigation was started with some *tert*-alkyl substituted cycloalkanols (1-3) as the substrate (see Chapter 2). Since the steric requirements of CO-introduction are rather small, the *Koch-Haaf* reaction of these compounds is a potential method to synthesize sterically hindered carboxylic acids, which are difficult to synthesize otherwise. Moreover, the composition of the reaction products should be very useful for obtaining a more detailed insight in the mechanism of the rearrangements of the intermediate cations. In these compounds both the cycloalkane ring and the side chain may be involved in the rearrangements yielding several tertiary cationic centers. Another interesting question was, whether secondary carbenium ions may be intercepted by using *Haaf* conditions (high ratio of CO and substrate concentration).

The work on compounds 1-3 initiated the choice of some other substrates: 1-alkylcyclohexanemethanols (4), 1-(1-alkylcyclohexane)ethanols (5) and spiro[2.5]octanes (6) (see Chapter 3).



A second goal of our work was to elucidate the transport of charge in the intermediate carbenium ion during the *Koch-Haaf* carboxylation in sulfuric acid. Until now no studies on this subject have been reported in the literature. Since this reaction medium has a rather low acidity (with respect to super acidic media) carbenium ion/alkene equilibria may play a role in the mechanism. In Chapter 4 the use of deuterium labelling in the study of the isomerization of some cycloalkyl cations during

the *Koch-Haaf* reaction in sulfuric acid, is described.

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CHAPTER 2

CARBOXYLATIONS OF *tert*-ALKYL SUBSTITUTED CYCLOALKANOLS *

Introduction

In connection with our work on p*K*a's of cyclohexanecarboxylic acids [1], a series of 1-alkyl substituted cyclohexanecarboxylic acids was required.

As has been discovered by *Koch* tertiary carboxylic acids can be synthesized easily by treating alcohols or olefins with carbon monoxide in a strongly acidic medium [2,3]. Thus *n*-alkylcyclohexanols are converted smoothly into the corresponding 1-*n*-alkylcyclohexanecarboxylic acids [4]. According to *Koch* and *Haaf* 1-isopropylcyclohexanol, however, does not afford 1-isopropylcyclohexanecarboxylic acid but exclusively 2-cyclohexyl-2-methylpropanoic acid [4]. These authors assumed this to be due to steric hindrance of carbonylation of the intermediate cation. Comparison of the Dreiding models of the 1-isopropylcyclohexyl cation and the dimethylcyclohexyl carbonium ion shows, however, that there is little difference in steric hindrance of carbonylation between these ions. Therefore we reinvestigated this reaction.

In our hands 1-isopropylcyclohexanol yielded two compounds, *viz.* 1-isopropylcyclohexanecarboxylic acid (**1**) and 2-cyclohexyl-2-methylpropanoic acid (**2**) in varying ratios, depending on the conditions.

This result encouraged us to start an investigation of the Koch-Haaf carboxylation of a number of *tert*-alkyl substituted cyclopentane, cyclohexane, and cycloheptane derivatives in order to find out whether in this way 1-*tert*-alkylcycloalkanecarboxylic acids could be prepared. In this paper we report the results of this study.

Mainly alcohols were used as starting materials, while, in general the formic acid method, modified as described by *Haaf* [5], was the experimental technique. Thus carbon monoxide was generated *in situ* from formic acid and sulfuric acid and the reaction mixture was stirred slowly. In this way high concentrations of carbon monoxide were maintained.

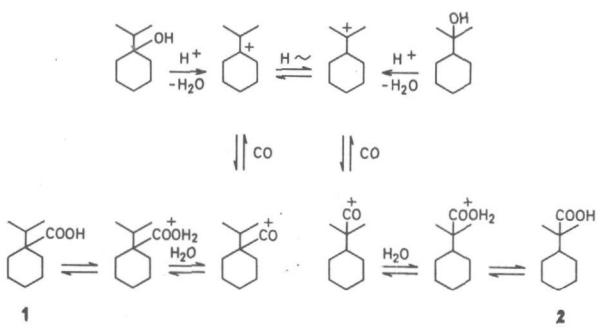
Results and discussion

Cyclohexane derivatives

Isopropylcyclohexanol

When the carboxylation of 1-isopropylcyclohexanol was performed under the conditions of *Koch* and *Haaf* [4] a mixture of **1** and **2** in a ratio of 44 : 56 was obtained. A more detailed investigation showed that the ratio of **1** and **2** was strongly dependent on the concentration of the sulfuric acid. Going from 94% sulfuric acid to 10% sulfur trioxide in sulfuric acid the ratio was found to shift from 73 : 27 to 15 : 85 (see Table I) [6].

Starting from pure **1** or pure **2** and using 96% sulfuric acid, **1** and **2** were obtained in a ratio of 14 : 86 too. Scheme 1 shows the equilibria involved. Apparently this ratio corresponds with the equilibrium of protonated **1** and **2**. Comparison of the Dreiding models of **1** and **2** shows that **2** is favorable for steric reasons.



Scheme 1

Table I

Koch-Haaf reactions of 1-isopropylcyclohexanol and related compounds

Expt. Nr.	Starting compound	Sulfuric acid	Method of stirring	Yield of acids %	Ratio of 1 and 2	Acidic side products (3), % of total yield of acids
1	1-isopropylcyclohexanol	88%	fast	13	78/22	13
2	1-isopropylcyclohexanol	94%	fast	26	73/27	19
3	1-isopropylcyclohexanol	97%	fast	47	57/43	19
4	1-isopropylcyclohexanol	99%	fast	44	44/56	16
5	1-isopropylcyclohexanol	5% SO_3	fast	52	22/78	31
6	1-isopropylcyclohexanol	10% SO_3	fast	27	15/85	27
7	1-isopropylcyclohexanol	20% SO_3	fast	26	14/86	32
8	1-isopropylcyclohexanol	99%	slow	38	55/45	8
9	1-isopropylcyclohexanol	96%	slow	50	77/23	13
10	2-isopropylcyclohexanol	96%	fast	47	70/30	15
11	2-isopropylcyclohexanol	96%	slow	42	64/36	6
12	2-cyclohexyl-2-propanol	96%	fast	33	73/27	19
13	2-cyclohexyl-2-propanol	96%	slow	36	44/56	7
14	**1**	96%	slow	100	73/27	0
15	**1**	99%	fast	100	15/85	1
16	**2**	96%	slow	99	8/92	0
17	**2**	96%	slow	94	14/86	1
18	**2**	20% SO_3	slow	70	13/87	17

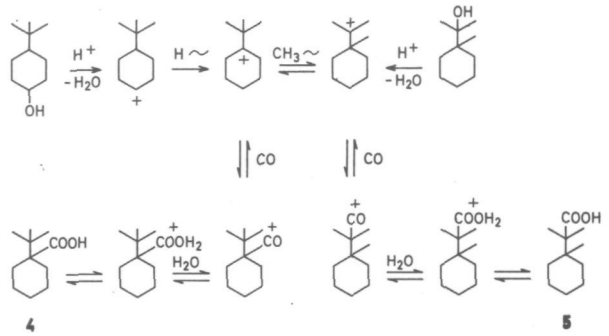
* A reprint of J.A. Peters and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas* 90, 65 (1971).

At high water contents of the reaction mixture and at high carbon monoxide concentrations (method of slow stirring) the composition of the reaction products is kinetically controlled. We assume the equilibrium between the carbonium ions to be fast [10] under all conditions applied. Apparently the carbonylation of the 1-isopropylcycolhexyl cation is somewhat faster than that of the dimethylcyclohexyl carbonium ion. Molecular models show that the changes in conformational and other strain during these reactions are rather similar.

It may be noted that the yield of acids and the amount of acidic side products (**3**) are dependent on the reaction conditions.

tert-*Butylcyclohexanols*

As reported shortly in a previous paper [11] 4-, 3-, 2-, and 1-*tert*-butylcyclohexanol as well as 2-(1-methylcyclohexyl)-2-propanol yield a mixture of 1-*tert*-butylcyclohexanecarboxylic acid (**4**) and 2-methyl-2-(1-methylcyclohexyl)propanoic acid (**5**) in a ratio of 3 : 1 upon Koch-Haaf carboxylation. The possible mechanism of this carboxylation is outlined in Scheme 2. Moreover a small amount (2%) of some other acids was found. Isolation and identification of each of the compounds separately was not accomplished, but mass- and NMR spectral data indicate that 2-methyl-1-isopropylcyclohexanecarboxylic acid and 2-methyl-2-(2-methylcyclohexyl)-propanoic acid are present.



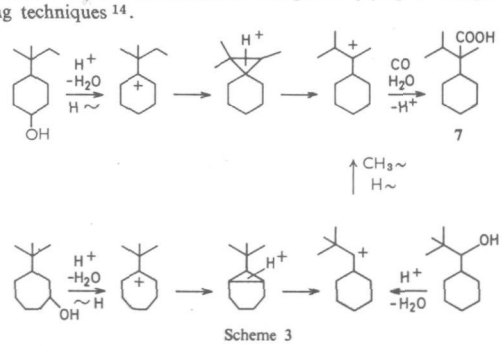
Scheme 2

The same ratio of **4** and **5** was obtained, when subjecting pure **4** or a 1 : 1 mixture of **4** and **5** to the Koch-Haaf conditions. This shows that in the reaction medium equilibrium exists between the corresponding protonated acids.

Applying the original procedure of the Koch carboxylation with fast stirring, a complex mixture of isomeric acids was formed, while the ratio of **4** and **5** still remained the same. Slow stirring of the reaction mixture causes a high carbon monoxide concentration [5] and therefore the slower isomerisation reactions are suppressed.

4-tert-*Pentylcyclohexanol*

The main product of the Koch-Haaf carboxylation of 4-*tert*-pentylcyclohexanol was 2-cyclohexyl-2,3-dimethylbutanoic acid (**7**). Formation of this acid *via* exclusively methyl and hydride shifts requires a complex reaction sequence including secondary carbonium ions. It seems more likely that a protonated cyclopropane ring is involved in the mechanism (see Scheme 3). Intermediate cyclopropane rings have been used for the explanation of several carbonium ion rearrangements [12]. In some cases the existence of these intermediates was proved by spectroscopic [12,13] or labeling techniques [14].



Scheme 3

Exactly the same mixture of acids resulted from the carboxylation of 1-cyclohexyl-2,2-dimethyl-1-propanol. The main product was also **7**. This reaction may involve a methyl and a hydrogen shift.

Di- and tri-alkylcyclohexane derivatives

In order to evaluate the effect of alkyl groups on the formation of structural and geometrical isomers the Koch-Haaf carboxylation of some di- and tri-alkylcyclohexane derivatives was investigated.

2,5-Di-*tert*-butylcyclohexanol reacted analogously to the mono-*tert*-butylcyclohexanols, yielding 1,*c*-4-di-*tert*-butyl-*r*-1-cyclohexanecarboxylic acid and 2-(*t*-4-*tert*-butyl-1-methyl-*r*-1-cyclohexyl)-2-methylpropanoic acid (in a ratio 4 : 1). In the same way 2,4-, 2,6-, and 3,5-di-*tert*-butylcyclohexanol yielded 1,*t*-3-di-*tert*-butyl-*r*-1-cyclohexanecarboxylic acid and 2-(*c*-3-*tert*-butyl-1-methyl-*r*-1-cyclohexyl)-2-methylpropanoic acid. Here, however, the ratio of these two acids is quite different (9 : 1). Apparently steric factors are involved.

Although the starting material always consisted of a mixture of *cis*/*trans* isomers, the only acids found were those with the carboxyl group in axial and the alkyl groups in equatorial positions. In the side products with an isobutyric acid group, this group was always in an equatorial position. Thus, in general the Koch synthesis gives rise to the more stable isomers.

The Koch-Haaf reaction on 2-*tert*-butyl-4-methylcyclohexanol and 4-*tert*-butyl-1-methylcyclohexanol afforded mainly *t*-3-*tert*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid and *c*-4-*tert*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid, respectively. Apparently for steric reasons the carbonylation of the *tert*-butyl-1-methylcyclohexyl cation is preferred to that of the 1-*tert*-butyl-methylcyclohexyl cation.

An exception to the normal reaction pattern was found in the reactions of 1-*tert*-butyl-2-methylcyclohexene and 2-methyl-1-isopropylcyclohexanol. Here the *tert*-butyl and the isopropyl group were split off resulting in 1-methylcyclohexanecarboxylic acid as the main reaction product. A similar phenomenon was found by *Christol* and *Solladié* [9], when carboxylating 1,2-dimethylcyclohexanol. From the present results and those of Christol and Solladié it may be concluded that the extent to which the 2-alkyl function splits off increases in the order *methyl* < *isopropyl* < tert-*butyl*.

The product of the Koch-Haaf carboxylation of 2,4,6-trimethylcyclohexanol was 1,*t*-3,*t*-5-trimethyl-*r*-1-cyclohexanecarboxylic acid.

Carboxylation of a mixture of cyclohexenes, resulting from dehydration of 2,6-di-*t*-butyl-4-methylcyclohexanol, afforded a mixture of 1,*t*-3-di-*tert*-butyl-*t*-5-methyl-*r*-1-cyclohexanecarboxylic acid and *t*-3,*t*-5-di-*tert*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid (in a ratio of 2 : 3). Again all the acids mentioned above were those with the carboxyl group in axial and the alkyl groups in equatorial positions. When crowding in the molecule increases the yield of the Koch-Haaf reaction decreases.

A surprising reaction is that of 2,4,6-tri-*tert*-butylcyclohexanol: this compound was converted quantitatively into *cis*-1,3,5-tri-*tert*-butylcyclohexene. The observed low solubility of this alkene in the reaction medium might be responsible for this phenomenon.

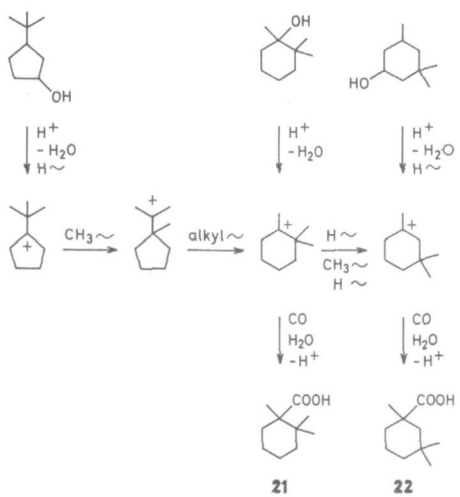
Cyclopentane derivatives

3-tert-*Butylcyclopentanol*

The Koch-Haaf carboxylation on 3-*tert*-butylcyclopentanol yielded a mixture of 73% of 1,2,2-trimethylcyclohexanecarboxylic acid (**21**), 10% of 1,3,3-trimethylcyclohexanecarboxylic acid (**22**), and small amounts of at least three other acids. An identical mixture of acids was obtained from the Koch-Haaf reaction on 1,2,2-trimethylcyclohexanol.

3,3,5-Trimethylcyclohexanol yielded upon carboxylation mainly **22** besides the same three side products as obtained from 3-*tert*-butylcyclopentanol and 1,2,2-trimethylcyclohexanol. Compound **21**, however, was absent in the reaction products. Apparently kinetic control is involved.

The proposed mechanism of the reactions, mentioned above, is represented in Scheme 4. It is likely that the first steps of the mechanism of the reaction of 3-*tert*-butylcyclopentanol are analogous to those of the carboxylation of the *tert*-butylcyclohexanols. The dimethyl-(1-methylcyclopentyl)-carbonium ion obtained is able to undergo ring enlargement towards the more stable 1,2,2-trimethylcyclohexyl cation. This ion has less ring and

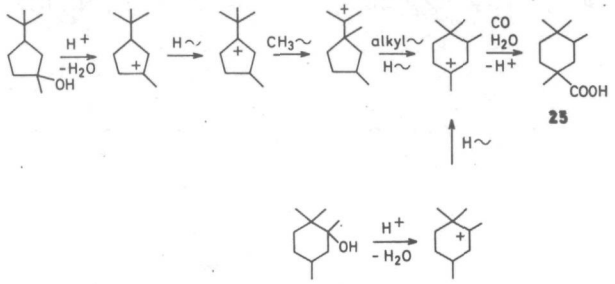


Scheme 4

steric strain than its precursor. Previous work, carried out by *Eidus* et al [15] and *Crouzet* and *Giral* [16] has shown that ring enlargement is a common feature in Koch carboxylations of cyclopentane derivatives.

3-tert-Butyl-1-methylcyclopentanol

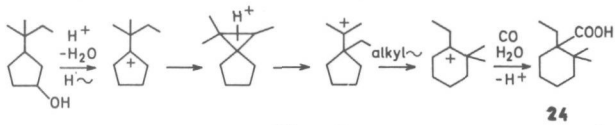
Although the exact structure of the carboxylation product of 3-*tert*-1-methylcyclopentanol could not be elucidated, there is strong evidence that this acid is a tetramethylcyclohexanecarboxylic acid, probably 1,3,4,4-tetramethylcyclohexanecarboxylic acid (**25**). Compound **25** was also obtained upon carboxylation of 1,2,2,5-tetramethylcyclohexanol. In the reaction mixture of the first mentioned carboxylation no 1-*tert*-butylcyclohexanecarboxylic acid was detected. Therefore in the reaction mechanism a direct rearrangement of the 3-*tert*-butyl-1-methylcyclopentyl ion into the 3- or 4-*tert*-butylcyclohexyl cation, which should afford 1-*tert*-butylcyclohexanecarboxylic acid upon hydride shift and carboxylation, may be excluded. Apparently the 3-*tert*-butyl-1-methylcyclopentyl cation rearranges into the 1-*tert*-butyl-3-methylcyclopentyl cation, that may rearrange by a similar mechanism to that shown in Scheme 4 into the 1,3,4,4-tetramethylcyclohexyl cation. This may be converted into *e.g.*, acid **25** (see Scheme 5).



Scheme 5

3-tert-Pentylcyclopentanol

Koch-Haaf carboxylation of 3-*tert*-pentylcyclopentanol yielded a very complex mixture of acids in which 1-ethyl-2,2-dimethylcyclohexanecarboxylic acid (**24**) was the most abundant product (40%). A possible mechanism is outlined in Scheme 6. The analogy with the reaction sequence of 4-*tert*-pentylcyclohexanol and 3-*tert*-butylcyclopentanol may be noted.



Scheme 6

Cycloheptane derivatives

Cycloheptanol afforded 1-methylcyclohexanecarboxylic acid upon Koch carboxylation [4]. We have found that, as distinct from cyclohexanol, here the ring contraction is not influenced by the use of the Haaf technique of slow stirring of the reaction mixture.

As might be expected ring contraction also occurred in the Koch-Haaf reaction of 4-*tert*-butylcycloheptanol. The main product was 2-cyclohexyl-2,3-dimethylbutanoic acid (**7**). This acid was also obtained upon Koch-Haaf carboxylation of 4-*tert*-pentylcyclohexanol and 1-cyclohexyl-2,2-dimethyl-1-propanol.

The mechanism of this reaction is outlined in Scheme 3.

Experimental part

General

The composition of the acidic reaction products of the Koch-Haaf reactions was determined by GLC of the corresponding methyl esters, obtained by reaction of the acids with an excess of diazomethane. In all cases the analyses were carried out on at least two different columns. The mass spectra were recorded with a Varian-MAT SM-1 spectrometer at 70 eV using a direct insertion probe. The NMR spectra were measured in tetra solution at 39° with a Varian A-60 apparatus. Chemical shifts (δ) are given in ppm relative to TMS. IR spectra were recorded in tetra solution on a Perkin-Elmer-521 spectrophotometer. Elemental analyses were performed by Mr. *M. van Leeuwen* and were correct within 0.2% (absolute).

Starting materials

1-Isopropylcyclohexanol [17], *2-cyclohexyl-2-propanol* [18], *1-tert-butylcyclohexanol* [11], *2-(1-methylcyclohexyl)-2-propanol* [11] and *4-tert-butyl-1-methylcyclohexanol* [19] were prepared as described in the literature.

A number of *cyclohexanols* was prepared by hydrogenation of the corresponding phenols in heptane at 200 atm and at 200° over Raney nickel. Some compounds in which a *tert*-butyl group was in the 2-position, afforded also cyclohexanones. These were reduced by an excess of lithium aluminium hydride in ether.

1-Cyclohexyl-2,2-dimethyl-1-propanol

Hydrogenation of 2,2-dimethyl-1-phenyl-1-propanol [20] over rhodium on carbon, in ethanol at 100 atm and 25°, yielded the desired alcohol; b.p. 109-110°/20 mm; $n_D^{25} = 1.4659$; NMR spectrum: singlets at $\delta = 0.93$ (9) and $\delta = 1.65$ (1), $\delta = 3.00$ (1), and a complex signal at $\delta = 1.0$-2.0 (11).

2-Methyl-1-isopropylcyclohexanol

This compound was prepared from 2-methylcyclohexanone and isopropylmagnesium bromide; b.p. 108-112°/61 mm.

1-tert-Butyl-2-methylcyclohexene and isomers

1-*tert*-Butyl-2-methylcyclohexanol was prepared from 2-*tert*-butylcyclohexanone and methylmagnesium iodide in ether. Distillation of the product in the presence of sulfuric acid yielded a mixture of cyclohexenes; b.p. 74-80°/14 mm. Hydrogenation of this mixture in *n*-heptane over palladium on carbon at 1 atm and 25° afforded exclusively 1-*tert*-butyl-2-methylcyclohexane.

Dehydration of 2,6-di-tert-butyl-4-methylcyclohexanol

A solution of the hydrogenation product of 2,6-di-*tert*-butyl-4-methylphenol in DMSO was boiled for four days. Work-up of the reaction mixture yielded a mixture of three cyclohexenes; b.p.101-103°/11 mm.

1,2,2-Trimethylcyclohexanol

2,2-Dimethylcyclohexanone, accompanied by small amounts of 2-methylcyclohexanone, 2,6-dimethylcyclohexanone, and 2,2,6-trimethylcyclohexanone [21] was treated with methylmagnesium chloride in THF. 1,2,2-Trimethylcyclohexanol was obtained by distillation in a spinning-band column; b.p. 80.5-81.5°/20 mm; NMR spectrum: singlet at $\delta = 0.93$ (6) and $\delta = 1.12$ (3) and a complex signal at $\delta = 0.85$-2.05 (9).

3-tert-Butylcyclopentanol

3-*tert*-Butylcyclopentanone [22] was reduced into 3-*tert*-butylcyclopentanol by an excess of lithium aluminium hydride in ether. The NMR spectrum showed that the product consisted of two isomers in a ratio of 1 : 1; b.p. 101.5-104°/22 mm; NMR spectrum: 2 singlets at $\delta = 0.87$ (9), a singlet at $\delta = 3.82$ (1), and a complex signal at $\delta = 1.0$-3.2 (8).

3-tert-Pentylcyclopentanol

This compound was prepared in an analogous way. Again a mixture of two isomers (in a ratio of 2 : 1) was obtained b.p. 99-104°/12 mm; NMR spectrum: singlets at $\delta = 0.85$ and $\delta = 0.87$ (6), A_2B_3-system at $\delta = 0.60$-1.40 (5), singlet at $\delta = 3.16$ (1), and a complex signal at $\delta = 1.4$-3.2 (8).

3-tert-Butyl-1-methylcyclopentanol

Reaction of 3-*tert*-butylcyclopentanone [21] with methylmagnesium chloride in THF afforded 3-*tert*-butyl-1-methylcyclopentanol; b.p. 94.0-94.5°/17 mm; m.p. 34.5-36°; NMR spectrum: singlet at $\delta = 0.90$, and a complex signal at $\delta = 1.20$-2.38.

1,2,2,5-Tetramethylcyclohexanol

This compound was prepared similarly to 1,2,2-trimethylcyclohexanol. The starting compound was 2,5-dimethylcyclohexanone. The reaction product was a mixture of the two isomers; b.p. 88-93°/20 mm.

4-tert-Butylcycloheptanol

Reduction of 4-*tert*-butylcycloheptanone [23] with an excess lithium aluminium hydride in ether yielded the desired alcohol; b.p. 128-132°/19 mm; $n_D^{25} = 1.4744$; NMR spectrum: singlet at $\delta = 0.82$ (9) and complex signals at $\delta = 0.8$-2.2 (11) and 3.7-3.9 (2).

Koch-Haaf reactions. General procedure

Sulfuric acid (96%, 270 ml) and carbon tetrachloride (40 ml) were placed in a 1-litre four-necked flask fitted with a stirrer, a thermometer, a dropping funnel, and a gas outlet. Formic acid (98%, 3 g) and then a solution or a stirred dispersion of the alcohol (0.25 mol) in formic acid (98%, 46 g) were added dropwise at 10° in the course of 1 h with slow stirring (25 r.p.m.; stirrer blade ~ 3 cm²). The mixture was stirred for 4 h at 10-25° and then poured on to 1 kg of ice.

The mixture was shaken with six 100 ml portions of hexane. The combined hexane solutions were extracted with three 200 ml portions of aqueous 2 *N*-KOH. The alkaline solutions were combined, acidified with hydrochloric acid and then shaken with 500 ml of ether. The ethereal solution was washed with water and then dried over $MgSO_4$. The ether was evaporated, yielding the acidic reaction products. The results are compiled in Tables I and II.

In expts. 32-35 and 37-39 (see Table II) a somewhat modified procedure was used. The hexane was evaporated from the hexane extract. The residue was taken up in 200 ml of aqueous KOH (20%). The resultant mixture was washed with hexane, the aqueous layer acidified with hydrochloric acid and extracted with ether.

Fast stirred reactions were performed as described by *Koch* and *Haaf* [4].

Reaction products

1-Isopropylcyclohexanecarboxylic acid (**1**)

The product from expt. 9 (see Table I) was recrystallized from aqueous ethanol; m.p. 104-5-105° (lit. [24,25] m.p. 104-105°); mass spectrum: important peaks at $m/e = 170$ and 128; NMR spectrum: doublet at $\delta = 0.97$, $J = 6$ Hz and a complex signal at $\delta = 0.8$-2.5.

The same acid was obtained on hydrogenation of 1-isopropyl-2,5-cyclohexadiene-1-carboxylic acid, prepared by reductive alkylation of benzoic acid with lithium-ammonia and isopropyl bromide [26].

Separation of **1** and **2** was achieved on a 50 m polypropylene glycol coated capillary column.

1-tert-Butylcyclohexanecarboxylic acid (**4**) and
methyl 2-methyl-2-(1-methylcyclohexyl)propanoate (**5**)

The isolation of these compounds has been described earlier [11].

Methyl 2-methyl-1-isopropylcyclohexanecarboxylate and
methyl 2-methyl-2-(2-methylcyclohexyl)propanoate (**6**)

The acidic products from expt. 23 were esterified by an excess of diazomethane in ether. By means of preparative GLC a fraction consisting of the methyl esters of **6** was obtained. From a comparison of mass and NMR spectral data and of retention times of this ester mixture and pure methyl 2-methyl-1-isopropylcyclohexanecarboxylate [26], on a polypropylene glycol column, it was concluded that **6** probably contained 2-methyl-1-isopropylcyclohexanecarboxylic acid and 2-methyl-2-(2-methylcyclohexyl)propanoic acid.

2-Cyclohexyl-2,3-dimethylbutanoic acid (**7**)

This compound was obtained by recrystallization of the crude acidic product from expt. 27; m.p. 83-83.5° (from aqueous ethanol); mass spectrum: important peaks at $m/e = 198$, 156, 116 and 101; NMR spectrum (in benzene solution): doublets at $\delta = 0.62$ and 0.77, $J = 7$ cps (6); singlet at $\delta = 0.86$ (3), and a complex signal at $\delta = 0.9$-2.1 (11); IR spectrum: characteristic band at 1450 cm^{-1}.

t-*3-tert-Butyl-1-methyl-*r-*1-cyclohexanecarboxylic acid* (**10**)

This product was obtained after recrystallization of the crude product from expt. 30 from petroleum ether 60-80; m.p. 106.5-107.5°; mass spectrum: important peaks at $m/e = 198$, 183, and 141; NMR spectrum: singlets at $\delta = 0.88$ (9) and 1.25 (3) and a complex signal at $\delta = 0.5$-2.5 (9).

Table II

Results of the *Koch-Haaf* carboxylations

Expt. nr.	Starting compound	Yield of acids, %	Composition of the reaction product
19	1-*tert*-butylcyclohexanol	58	77% 1-*tert*-butylcyclohexanecarboxylic acid (**4**); 20% 2-methyl-2-(1-methylcyclohexyl)-propanoic acid (**5**); 3% 2-methyl-1-isopropylcyclohexanecarboxylic acid and 2-methyl-2-(2-methylcyclohexyl)propanoic acid (**6**)?
20	2-*tert*-butylcyclohexanol	62	70% **4**; 24% **5**; 6% **6**
21	3-*tert*-butylcyclohexanol	80	72% **4**; 26% **5**; 2% **6**
22	4-*tert*-butylcyclohexanol	80	71% **4**; 27% **5**; 2% **6**
23	4-*tert*-butylcyclohexanol *	85	**4** : **5** : **6** = 59 : 19 : 32; 60% unidentified
24	2-(1-methylcyclohexyl)-2-propanol	71	71% **4**; 26% **5**; 3% **6**
25	pure **4**	85	66% **4**; 30% **5**; 4% **6**
26	mixture of 47% **4** and 53% **5**	91	67% **4**; 24% **5**; 9% **6**
27	4-*tert*-pentylcyclohexanol	85	86% 2-cyclohexyl-2,3-dimethylbutanoic acid (**7**); 4% 1-methylcyclohexanecarboxylic acid (**8**); 10% unidentified (**9**)
28	1-cyclohexyl-2,2-dimethyl-1-propanol	48	73% **7**; 7% **8**; 20% **9**
29	1-*tert*-butyl-2-methylcyclohexene and isomers	55	68% **8**; 32% trimethylacetic acid
30	2-*tert*-butyl-4-methylcyclohexanol	60	76% *t*-3-*tert*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid (**10**); 24% unidentified
31	4-*tert*-butyl-1-methylcyclohexanol	38	94% *c*-4-*tert*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid (**11**); 6% unidentified
32	2,6-di-*tert*-butylcyclohexanol	75	90% 1,*t*-3-di-*tert*-butyl-*r*-1-cyclohexanecarboxylic acid (**12**); 10% 2-(*c*-3-*tert*-butyl-1-methyl-*r*-1-cyclohexyl)-2-methylpropanoic acid (**13**)
33	2,4-di-*tert*-butylcyclohexanol	31	84% **12**; 8% **13**; 8% unidentified (**14**)
34	3,5-di-*tert*-butylcyclohexanol	68	88% **12**; 12% **13**
35	2,5-di-*tert*-butylcyclohexanol	67	47% 1,*c*-4-*tert*-butyl-*r*-1-cyclohexanecarboxylic acid (**15**); 13% 2-(*t*-4-*tert*-butyl-1-methyl-*r*-1-cyclohexyl)-2-methylpropanoic acid (**16**); 40% unidentified
36	2,4,6-trimethylcyclohexanol	62	100% 1,*t*-3,*t*-5-trimethyl-*r*-1-cyclohexanecarboxylic acid (**17**)
37	2,6-di-*tert*-butyl-4-methylcyclohexanol	—	mainly starting materials, besides a complex mixture of cyclohexenes
38	idem, dehydration product	26	56% *t*-3,*t*-5-di-*tert*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid (**18**); 34% 1,*t*-3-di-*tert*-butyl-*t*-5-methyl-*r*-1-cyclohexanecarboxylic acid (**19**) 10% unidentified
39	2,4,6-tri-*tert*-butylcyclohexanol	—	no acids; neutral product: 100% *cis*-1,3,5-tri-*tert*-butylcyclohexene (**20**)
40	3-*tert*-butylcyclopentanol	55	73% 1,2,2-trimethylcyclohexanecarboxylic acid (**21**); 10% 1,3,3-trimethylcyclohexanecarboxylic acid (**22**); 17% > 4 unidentified acids (**23**)
41	1,2,2-trimethylcyclohexanol	41	77% **21**; 10% **22**; 13% **23**
42	3,3,5-trimethylcyclohexanol	92	79% **22**; 21% **23**
43	3-*tert*-pentylcyclopentanol	66	45% 1-ethyl-2,2-dimethylcyclohexanecarboxylic acid (**24**); 55% > 12 unidentified acids
44	3-*tert*-butyl-1-methylcyclopentanol	46	85% 1,3,4,4-tetramethylcyclohexanecarboxylic acid (**25**)? 15% unidentified
45	1,2,2,5-tetramethylcyclohexanol	68	95% **25**; 5% unidentified
46	cycloheptanol	85	100% **8**
47	4-*tert*-butylcycloheptanol	54	56% **7**; 5% **8**; 39% **9**

* Reaction with fast stirring.

c-4-tert-*Butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid* (**11**)

The acidic products from expt. 31 were recrystallized from ethanol-water to yield **11**; m.p. 131-132°; mass spectrum: important peaks at m/e = 198, 183, 143, and 142; NMR spectrum: singlets at δ = 0.85 (9) and 1.21 (3) and a complex signal at δ = 0.7-2.5 (9).

1,t-*3-Di*-tert-butyl-r-*1-cyclohexanecarboxylic acid* (**12**)

The reaction mixture from expt. 32 was recrystallized from aqueous ethanol to yield **12**; m.p. 147-147.5°; mass spectrum: important peaks at m/e = 240, 225, 184, and 127; NMR spectrum: singlets at δ = 0.87 (9) and 0.96 (9) and a complex signal at δ = 0.7-2.3 (9); IR spectrum: characteristic band at 1450 cm^{-1}. The weak acidity (pK_a = 7.76 in 50% ethanol at 25°) is in agreement with the structure assigned.

*Methyl-2-(c-3-*tert-*butyl-1-methyl-*r*-1-cyclohexyl)-2-methylpropanoate* (**13**)

The mother liquors from the recrystallization of **12** were combined and the solvent was evaporated. The residue was esterified with an excess of diazomethane in ether. The methyl ester of **13** was isolated by preparative GLC; b.p. 219-221°/758 mm; mass spectrum: important peaks at m/e = 254, 239, 198, and 102; NMR spectrum: singlets at δ = 0.82 (9), 0.89 (3), 1.10 (6), and 3.56 (3) and a complex signal at δ = 1.2-1.8(9).

1,c-*4-Di*-tert-*butyl-r-1-cyclohexanecarboxylic acid* (**15**)

The mixture of acids from expt. 35 was treated with pentane at room temperature. The insoluble part was filtered off. From the filtrate the pentane was evaporated and the residue was recrystallized from aqueous ethanol to yield **15**; m.p. 191-191.5°; mass spectrum: important peaks at m/e = 240, 225, 184, 129, and 127; NMR spectrum: singlets at δ = 0.96 (9) and 0.82 (9), and a complex signal at δ = 1.2-1.8 (9).

*2-(*t-*4-*tert-*Butyl-1-methyl-*r*-1-cyclohexyl)-2-methylpropanoic acid* (**16**)

The pentane-insoluble part of the products from reaction 35 was recrystallized from aqueous ethanol to yield **16**; m.p. 196-196.5°; mass spectrum: important peaks at m/e = 240, 225, 184, 153, 97, and 88; NMR spectrum (in DMSO solution): singlets at δ = 0.82 (9), 0.87 (3), and 1.04 (6) and a complex signal at δ = 1.1-1.7 (9).

1,t-*3*,t-*5-Trimethyl-*r*-1-cyclohexanecarboxylic acid* (**17**)

This acid was obtained by recrystallization from aqueous ethanol of the acidic product from expt. 36; m.p. 121.5-122°; mass spectrum: important peak at m/e = 170; NMR spectrum: singlet at δ = 1.20 (1-methyl), doublet at δ = 0.86, J = 6 cps (3- and 5-methyl) and complex signals at δ = 0.28-0.70 (axial 2-, 4- and 6-H-atoms), δ = 1.40-1.90 (equatorial 2-, 4-, and 6-H-atoms), and δ = 1.93-2.31 (axial 3- and 5-H-atoms).

t-*3*,t-*5-Di*-tert-*butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid* (**18**)

Recrystallization of the acid from expt. 38 from aqueous ethanol (3 : 7) yielded **18**; m.p. 219.5-220°; mass spectrum: important peaks at m/e = 254, 197 and 151; NMR spectrum (in DMSO): singlets at δ = 0.84 (18) and 1.14 (3) and complex signals at δ = 0.15-0.9 and 1.5-2.6 (8).

1,t-*3-Di*-tert-*butyl-*t*-5-methyl-*r*-1-cyclohexanecarboxylic acid* (**19**)

The solvents were evaporated from the mother liquor from the recrystallization of **18**. The residue was recrystallized from aqueous ethanol (1 : 1) to yield a mixture of 70% of **19** and 30% of **18**. After sublimation a mixture of 80% of **19** and 20% of **18** was obtained; m.p. 136-140°; mass spectrum: important peaks at m/e = 254, 198, 143, and 141; NMR spectrum: singlets at δ = 0.86 (9) and 0.98 (9) and a complex signal at δ = 0.2-2.4 (11).

Cis-*1,3,5-tri-*t*-butylcyclohexene* (**20**)

This product, obtained from expt. 39, was identical with that synthesized by reduction of 1,3,5-tri-*t*-butylbenzene with lithium in ethylamine [27]; m.p. 67-67.5°.

1,2,2-Trimethylcyclohexanecarboxylic acid (**21**)

This compound was isolated from the acidic reaction products of expt. 40 *via* the benzylamine salt; m.p. 176.5-177° (from aqueous ethanol); mass spectrum: important peaks at m/e = 170, 155, 152, 137, and 124. NMR spectrum: singlets at δ = 1.22 (3) and 1.02 (6) and a complex signal at δ = 1.35-1.7 (8); IR spectrum: characteristic band at 1450 cm^{-1}. This acid is identical with a sample of 1,2,2-trimethylcyclohexanecarboxylic acid, prepared starting from camphor [24,28].

1,3,3-Trimethylcyclohexanecarboxylic acid (**22**)

This compound was isolated from the acidic reaction products of expt. 42; b.p. 140.5-142°/12 mm (lit. [29] b.p. 144-147°/11 mm). The methyl ester was prepared with an excess of diazomethane in ether and purified by preparative GLC; b.p. 102°/24 mm; mass spectrum: important peaks at m/e = 184, 169, 125, 109, and 101; NMR spectrum: singlets at δ = 0.73, 0.88, 1.12 and 3.64 and a complex signal at δ = 0.5-2.5.

1-Ethyl-2,2-dimethylcyclohexanecarboxylic acid (**24**)

Isolated from the reaction products of expt. 43 *via* the benzylamine salt; m.p. 87-88° (from petroleum ether 60-80); mass spectrum: important peaks at m/e = 184, 166, 155, and 101; NMR spectrum: singlets at δ = 1.02 (6), triplet at δ = 0.80, J = 7 cps (3), quartet at δ = 1.94, J = 7 cps, and a complex signal at δ = 1.25-3.2 (10).

Tetramethylcyclohexanecarboxylic acid (**25**)

Isolated from the reaction products of expt. 44 *via* the benzylamine salt; m.p. 116.5-117° (from aqueous ethanol); mass spectrum: important peaks at m/e = 184, 123, 98, and 83; NMR spectrum: signals at δ = 0.76, 0.85, 0.90, 0.97, 1.21, 1.32 and a complex signal at δ = 1.1-2.3; IR spectrum: characteristic band at 1450 cm^{-1}.

Acknowledgements

We are indebted to Mr. *B. van de Graaf* and Mr. *H. M. A. Buurmans* for measuring and interpreting the mass spectra and to Mr. *J. D. Remijnse* for taking and discussing the NMR spectra.

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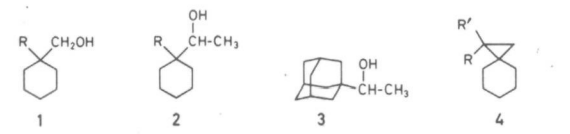
CHAPTER 3

Carboxylation of 1-alkylcyclohexanemethanols, 1-(1-alkylcyclohexane)ethanols, and 1-methyl substituted spiro[2.5]octanes *

Introduction

As has been discovered by *Koch* tertiary carboxylic acids can be synthesized by treating alcohols with carbon monoxide in a strongly acidic medium[2,3]. We have shown previously[1] that the carboxylation of *t*-alkylcycloalkanols is a convenient route to tertiary cyclohexanecarboxylic acids.

Koch and *Haaf*[4] have studied the carboxylation of some 1-*n*-alkylcyclohexanemethanols (**1a,b**). 1-*n*-Alkylcyclohexanecarboxylic acids (**6a,b**) were obtained as the sole reaction products. We have confirmed these results.

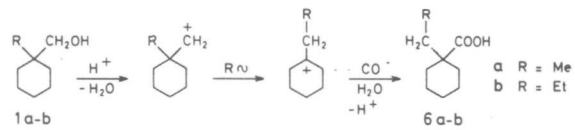


1 2 3 4

a R = Me
b R = Et
c R = i-Pr
d R = *t*-Bu

a R = R′ = H
b R = H; R′ = Me
c R = R′ = Me

These reactions proceed most likely *via* a 1,2-shift of the 1-*n*-alkyl group in the initial carbonium ion (see Scheme 1).



1a-b 6a-b

a R = Me
b R = Et

Scheme 1

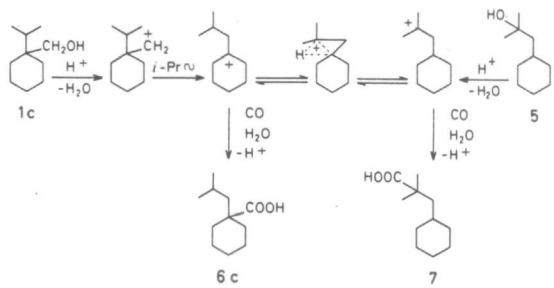
In the present work some 1-alkylcyclohexanemethanols (**1c,d**) with branched alkyl groups were subjected to carboxylation in order to find out whether Scheme 1 applies here. The experimental technique was always the formic acid method with slow stirring of the reaction mixture. *Haaf*[5] has shown that under these conditions of high CO-concentration carbonium ion rearrangements are suppressed; *e.g.* the ratio secondary: tertiary carboxylic acids, obtained from 2-pentanol or cyclohexanol, was raised by using this technique. In this connection we have studied the carboxylation of a series of 1-(1-alkylcyclohexane)ethanols (**2a-d**) and of 1-(1-adamantane)ethanol (**3**), which compounds might yield the corresponding secondary carboxylic acids or – through a 1,2-alkyl shift in the initial cation – tertiary acids.

Furthermore the Koch-Haaf carboxylation of some 1-methyl substituted spiro[2.5]octanes (**4a-c**) has been investigated. Cyclopropane rings are known to be cleaved[6,7] under the carboxylation conditions. The data on compounds **1** and **2** should enable us to determine the mode of opening of the cyclopropane rings in compounds **4a-c**.

Results and discussion

1-Isopropylcyclohexanemethanol

The carboxylation of 1-isopropylcyclohexanemethanol (**1c**) afforded 1-isobutylcyclohexanecarboxylic acid (**6c**) and 3-cyclohexyl-2,2-dimethylpropanoic acid (**7**) in a ratio of 7 : 1 (cf. Table I). A possible reaction mechanism is outlined in Scheme 2.



1c 6c 7

Scheme 2

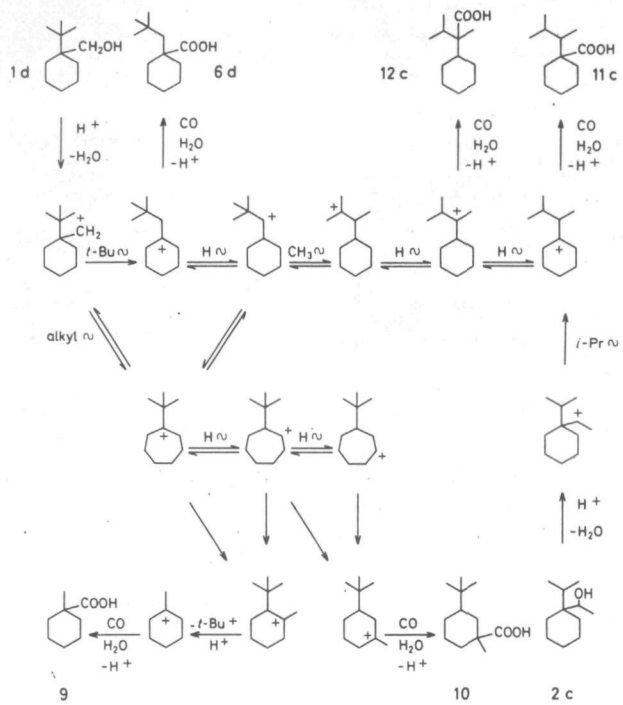
We assume that the isomerization of the 1-isobutylcyclohexyl cation into the 1-cyclohexyl-2-methyl-2-propyl cation involves a protonated cyclopropane ring. This isomerization is analogous to the degenerate 1,3-hydride shift in the 2,4-dimethylpentyl cation, which has been shown to proceed most likely *via* a protonated cyclopropane ring[8,9]. Compounds **6c** and **7** were obtained in another ratio (3 : 2) from the Koch-Haaf reaction of 1-cyclohexyl-2-methyl-2-propanol (**5**). Apparently kinetic control is involved.

1-t-Butylcyclohexanemethanol

A more complex mixture of acids was obtained from the Koch-Haaf carboxylation of 1-*t*-butylcyclohexanemethanol (**1d**). Again, a 1,2-alkyl shift is likely to occur in the initial cation. The resulting 1-neopentylcyclohexyl cation can also be generated from 1-cyclohexyl-2,2-dimethyl-1-propanol, which compound, as has been shown previously[1], gives rise to complex rearrangements. The main product obtained from **1d** was 2-cyclohexyl-2,3-dimethylbutanoic acid (**12c**) (59%). Moreover, small amounts of some other acids were formed. Of these 1-neopentylcyclohexanecarboxylic acid (**6d**) (5%), *trans*-3-*t*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid (**10**) (5%), and 1-methylcyclohexanecarboxylic acid (**9**) (5%) could be isolated and identified. Moreover, the presence of 18% of 1-(1,2-dimethylpropyl)cyclohexanecarboxylic acid (**11c**) was shown by GLC-MS. The same acids, though in a somewhat different ratio, were obtained from the carboxylations of 1-cyclohexyl-2,2-dimethyl-1-propanol[1], 4-*t*-pentylcyclohexanol[1], 4-*t*-butylcycloheptanol[1], and 1-(1-isopropylcyclohexane)ethanol (**2c**). Possible reaction sequences are compiled in Scheme 3.

The presence of compound **10** in the reaction mixture indicates that *t*-butylcycloheptyl cations play a role in the reaction mechanism. Compound **9** may be obtained *via* fragmentation of the 2-*t*-butyl-1-methylcyclohexyl cation[1], which is formed upon ring contraction in the

* A reprint of J.A. Peters and H. van Bekkum, *Recl.Trav. Chim. Pays-Bas* 92, 379 (1973).



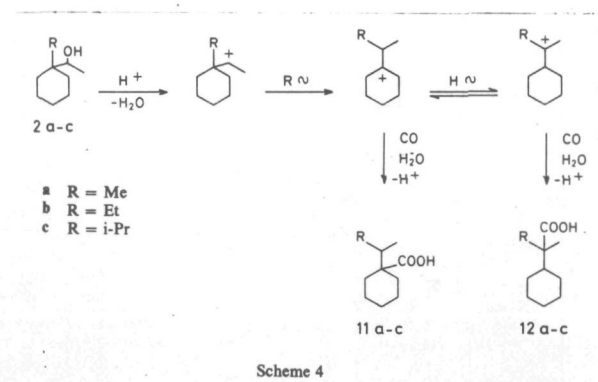
Scheme 3

t-butylcycloheptyl cation. This is supported by the relatively large amount of **10** (24%) obtained from the Koch-Haaf reaction of 4-*t*-butylcycloheptanol[1].

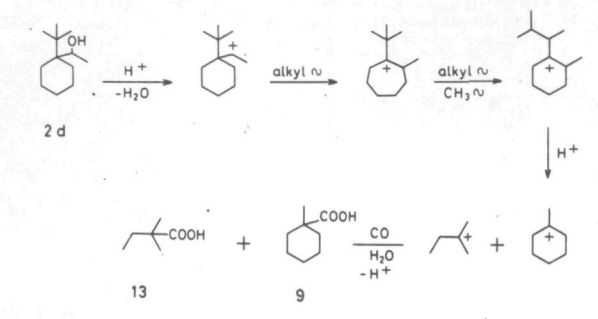
When dilution techniques[10–12] were applied to these reactions the same ratio of acids was obtained. Apparently intermolecular rearrangements are unimportant under the conditions used[13].

1-(1-Alkylcyclohexane)ethanols

The course of the reaction of compounds **2a-c** appears to be analogous to that of compounds **1a-c**. No secondary acids were identified. A 1,2-shift of the alkyl group into the side chain seems to be the key step in the rearrangement of the initial cation (see Scheme 4). Direct carbonylation affords acids **11**, whereas a hydride shift followed by carbonylation leads to acids **12**. In the case of 1-(1-isopropylcyclohexane)ethanol (**2c**) additional isomerizations take place during the reaction (cf. Scheme 3).



Scheme 4



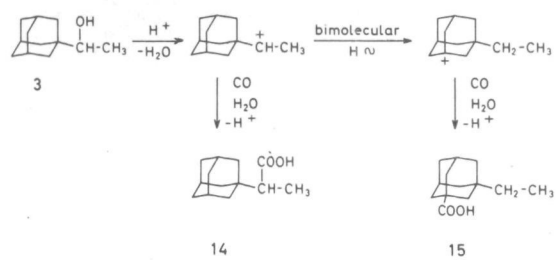
Scheme 5

As should be expected from previous results of the Koch-Haaf reaction on isopropylcyclohexanols[1] the ratio of **11** and **12** is strongly dependent on the amount of water in the reaction mixture. In more concentrated sulfuric acid the amount of the more stable carboxylic acids **12** increases.

During the Koch-Haaf carboxylation of 1-(1-*t*-butylcyclohexane)-ethanol (**2d**) extensive fragmentation occurred. Scheme 5 illustrates a mechanism. As shown previously[1], fragmentation is a normal phenomenon in 1,2-dialkylcyclohexyl cations.

1-(1-Adamantane)ethanol

From the carboxylation of 1-(1-adamantane)ethanol (**3**) a mixture of 3-ethyladamantanecarboxylic acid (**15**) and 2-(1-adamantane)propanoic acid (**14**) in a ratio 2:3 was obtained. Under diluted conditions (see experimental part) **14** appeared to be the main product (88%). Since dilution has such a strong influence on the composition of the reaction product, the former acid must be formed *via* an intermolecular hydride shift in the intermediate cation (see Scheme 6). Analogous results were obtained recently by *von Schleyer* et al. [10–12] for the Koch reaction on 2-(1-adamantane)-2-propanol. Apparently adamantane is a relatively active hydride donor (cf. note 13).

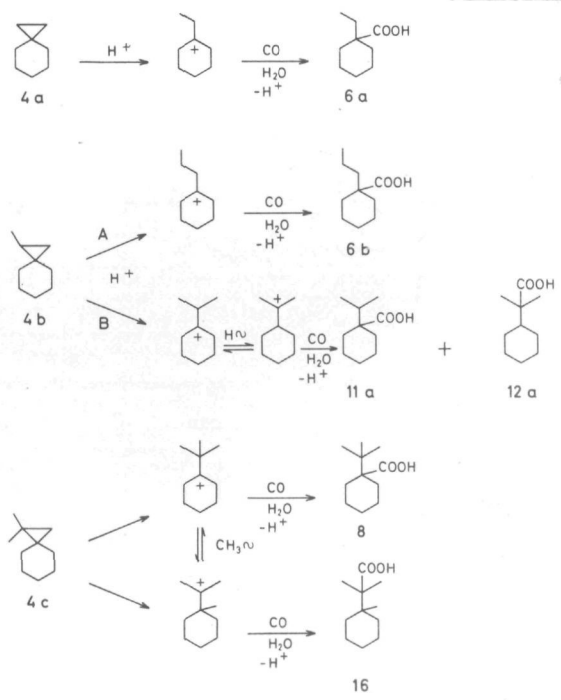


Scheme 6

No homoadamantanecarboxylic acids could be detected in the reaction products of the carboxylations of 3. As shown by *von Schleyer* et al.[11] 1-adamantanemethanol affords exclusively homoadamantanecarboxylic acids on Koch-Haaf carboxylation. Apparently the secondary 1-(1-adamantane)ethyl cation is more stable than the tertiary 4-methyl-3-homoadamantyl cation.

Spiro[2.5]octanes

As has been shown by *Haaf*[6] and by *Falbe* et al.[7] non-cyclic carboxylic acids are obtained from the Koch carboxylation of cyclopropanes. Accordingly the spiro[2.5]octanes **4a-c** are ruptured under Koch-Haaf conditions. Obviously ring opening leading to a primary or secondary ion will be more difficult than opening to a tertiary carbonium ion. The unsubstituted spiro compound (**4a**) gave, as expected, 1-ethylcyclohexanecarboxylic acid (**6a**) as the sole reaction product (see Scheme 7).



Scheme 7

The products obtained from **4b** showed that two pathways are involved: 16% opens according to route A (1,3-opening), the remainder reacts according to route B (2,3-opening):

The ratio 1,3- : 2,3-opening appears to be independent on the acidity of the reaction medium (cf. Table I). As would be expected, the ratio of 1-isopropylcyclohexanecarboxylic acid (**11a**) and 2-cyclohexyl-2-methylpropanoic acid (**12a**) depends on the acidity of the reaction medium in the same way as was observed for the Koch carboxylations of 1-isopropylcyclohexanol[1] and 1-(1-methylcyclohexane)ethanol (**2a**).

As regards compound **4c** it may be noted that 1-isobutylcyclohexanecarboxylic acid (**6c**) and 3-cyclohexyl-2,2-dimethylpropanoic acid (**7**) were absent in the reaction products, showing that 1,3-opening of the cyclopropane ring is not involved.

It can be seen that the part of the products that arise *via* 1,3-opening of the cyclopropane ring decreases, going from **4a** to **4c**. It may be concluded that protonation of the appropriate side is sterically hindered by the substituents at the 1-position.

Experimental part

General

The composition of the acidic reaction products of the Koch-Haaf reactions was determined by GLC of the corresponding methyl esters, obtained by reacting the acids with an excess of diazomethane. The mass spectra were recorded with a Varian-MAT SM-1 spectrometer at 70 eV. The NMR spectra were measured in carbon tetrachloride solution at 39° with a Varian A-60 or a Varian T-60 apparatus. Chemical shifts (δ) are given in ppm relative to TMS. The mass spectra and the NMR spectra of the starting materials were in agreement with the assigned structures. Elemental analyses were performed by Mr. *M. van Leeuwen* and were correct within 0.2% (absolute).

Starting materials

1-Alkylcyclohexanemethanols (**1**)

The 1-alkylcyclohexanemethanols were prepared in 80–95% yield by reduction of the corresponding 1-alkylcyclohexanecarboxylic acids[1,4] with an excess of lithium tetrahydridoaluminate in diethyl ether. The reductions of 1-isopropyl- and 1-*t*-butylcyclohexanecarboxylic acid were carried out in freshly purified di-*n*-butyl ether. *1-Isopropylcyclohexanemethanol* (**1c**); b.p. 113–114°/15 mm. *1-t-Butylcyclohexanemethanol* (**1d**); m.p. 66–66.5° (from aqueous ethanol).

1-(1-Methylcyclohexane)ethanol (**2a**)

1-Acetyl-1-methylcyclohexane[14] was reduced with lithium tetrahydridoaluminate in ether to yield 1-(1-methylcyclohexane)ethanol; b.p. 98–99°/21 mm. *1-(1-Ethylcyclohexane)ethanol* (**2b**) was prepared in the same way; b.p. 106–107°/14 mm.

1-(1-Isopropylcyclohexane)ethanol (**2c**)

1-Isopropylcyclohexanecarboxylic acid[1] (48 g) was boiled with thionyl chloride (80 ml) for 1 h. The excess of thionyl chloride was evaporated. After distillation, pure 1-isopropylcyclohexanecarbonyl chloride (46 g, 87%) was obtained: b.p. 106–108°/16 mm.

A solution of 1-isopropylcyclohexanecarbonyl chloride (44 g) in THF (120 ml) was added at 0° to methylmagnesium chloride (1 mole) in THF (290 ml). The mixture was heated under reflux for 3 h. After cooling, water (200 ml) and 4*N* H_2SO_4 (200 ml) were added. After the usual work-up pure 1-acetyl-1-isopropylcyclohexane (32 g, 82%) was obtained; b.p. 102–104°/16 mm.

A solution of 1-acetyl-1-isopropylcyclohexane (32 g) in di-*n*-butyl ether (30 ml) was added to a suspension of lithium tetrahydridoaluminate (5.5 g) in di-*n*-butyl ether (170 ml). Then the mixture was boiled under reflux for 3 h. After the usual work-up 1-(1-isopropylcyclohexane)ethanol (31 g, 96%) was obtained; b.p. 117–119°/16 mm.

1-(1-t-Butylcyclohexane)ethanol (**2d**)

This compound was synthesized as for **2c**. The physical constants were as follows: 1-*t*-butylcyclohexanecarbonyl chloride; b.p. 122–124°/19 mm; 1-acetyl-1-*t*-butylcyclohexane; b.p. 122–123°/17 mm; m.p. 38.5–39° (from petroleum-ether 40–60); 1-(1-*t*-butylcyclohexane)ethanol; b.p. 136–138°/20 mm.

1-(1-Adamantane)ethanol (**3**)

This compound was prepared as described by *Stetter* and *Rauscher*[15]; m.p. 75–76°.

Spiro[2.5]octane (**4a**)

1,1-Bishydroxymethylcyclohexane[16] was converted into **4a** *via* the corresponding dimesylate and dibromide, according to the procedure of *Magrill* et al.[17]; b.p. 126°/764 mm; $n_D^{20} = 1.4473$.

1-Methylspiro[2.5]octane (**4b**)

This compound was prepared as described by *Grandberg* et al.[18]; b.p. 130°/758 mm; $n_D^{20} = 1.4509$.

It should be noted that the product of the first reaction step, a condensation of cyclohexanone with ethyl acetoacetate is not cyclohexylideneacetone, as suggested by *Grandberg* et al., but cyclohexenylacetone.

1,1-Dimethylspiro[2.5]octane (**4c**)

Methylation of isopropylidenecyclohexane[19] according to the modification of *Rawson* et al.[20] of the Simmons-Smith reaction, afforded **4c**, accompanied by small amounts of some side-products. Purification *via* the thiourea inclusion compound yielded pure **4c**; b.p. 152°/760 mm.

Table I

Results of the Koch-Haaf reactions

Expt.	Starting compound	Yield of acids, %	Composition of the acidic reaction products
1	1-methylcyclohexanemethanol (**1a**)	73	100% 1-ethylcyclohexanecarboxylic acid (**6a**)
2	1-ethylcyclohexanemethanol (**1b**)	89	100% 1-*n*-propylcyclohexanecarboxylic acid (**6b**)
3	1-isopropylcyclohexanemethanol (**1c**)	88	53% 1-isobutylcyclohexanecarboxylic acid (**6c**) 8% 3-cyclohexyl-2,2-dimethylpropanoic acid (**7**) 39% unidentified acids (**17**)
4	1-cyclohexyl-2-methyl-2-propanol (**5**)	33	54% **6c**; 38% **7**; 8% **17**
5	1-*t*-butylcyclohexanemethanol (**1d**)	72	59% 2-cyclohexyl-2,3-dimethylbutanoic acid (**12c**) 18% 1-(1,2-dimethylpropyl)cyclohexanecarboxylic acid (**11c**) 5% 1-neopentylcyclohexanecarboxylic acid (**6d**) 5% *trans*-3-*t*-butyl-1-methyl-*r*-1-cyclohexanecarboxylic acid (**10**) 5% 1-methylcyclohexanecarboxylic acid (**9**) 8% unidentified $C_{12}H_{22}O_2$-acids (**18**)
6	1-(1-methylcyclohexane)ethanol (**2a**)[a]	23	73% 1-isopropylcyclohexanecarboxylic acid (**11a**) 25% 2-cyclohexyl-2-methylpropanoic acid (**12a**) 2% unidentified acids
7	**2a**[b]	48	17% **11a**; 73% **12a**; 10% unidentified acids
8	1-(1-ethylcyclohexane)ethanol (**2b**)	40	52% 2-cyclohexyl-2-methylbutanoic acid (**12b**) 43% 1-*s*-butylcyclohexanecarboxylic acid (**11b**) 5% unidentified acids (**19**)
9	product from expt. 8[c]	92	61% **12b**; 18% **11b**; 21% **19**
10	1-(1-isopropylcyclohexane)ethanol (**2c**)	53	54% **12c**; 6% **11c**; 5% **6d**; 12% **9**; 12% **10**; 11% **18**
11	1-(1-*t*-butylcyclohexane)ethanol (**2d**)	51	52% 2,2-dimethylbutanoic acid (**13**) 30% **9**; 18% unidentified acids
12	1-(1-adamantane)ethanol (**3**)	89	62% 2-(1-adamantane)propanoic acid (**14**) 36% 3-ethyladamantanecarboxylic acid (**15**) 2% unidentified acids (**20**)
13	**3**[a]	77	88% **14**; 5% **15**; 7% **20**
14	spiro[2.5]octane (**4a**)[a]	43	96% **6a**; 4% unidentified acids
15	1-methylspiro[2.5]octane (**4b**)	12	18% **6b**; 56% **11a**; 16% **12a**; 10% unidentified acids
16	**4b**[b]	29	16% **6b**; 10% **11a**; 65% **12a**; 9% unidentified acids
17	**4b**[d]	23	25% **6b**; 6% **11a**; 40% **12a**; 29% unidentified acids
18	1,1-dimethylspiro[2.5]octane (**4c**)	36	28% 1-*t*-butylcyclohexanecarboxylic acid (**8**) 8% 2-methyl-2-(1-methylcyclohexyl)propanoic acid (**16**) 64% ⩾ 12 unidentified acids

[a] in 92% H_2SO_4; [b] in min. 98% H_2SO_4 (BDH, AnalaR); [c] in 100% H_2SO_4 + 7% SO_3; [d] in 100% H_2SO_4 + 10% SO_3; [e] under diluted conditions (see experimental part).

1-Cyclohexyl-2-methyl-2-propanol (**5**)

This compound was prepared by reaction of methyl cyclohexaneacetate with methylmagnesium chloride in THF; b.p. 101–102°/19 mm.

Koch-Haaf reactions. General procedure

Sulfuric acid (96–100%, 270 ml) and carbon tetrachloride (40 ml) were placed in a 1-litre four-necked flask fitted with a stirrer, a thermometer, a dropping funnel, and a gas outlet. Formic acid (98%, 3 g) and then a solution of the alcohol (0.25 mole) in formic acid (98%, 46 g) were added at 15–20° in the course of 1 h with slow stirring (25 r.p.m.; stirrer blade ~3 cm^2). In expts. 13–15 (spiro[2.5]octanes) formic acid and a solution of the substrate in carbon tetrachloride were added separately. The mixture was stirred for 3 h at 15–20° and then poured on to 1 kg of ice. The mixture obtained was shaken with six 100 ml portions of hexane or chloroform (expts. 12–13). The combined organic solutions were extracted with three 200 ml portions of aqueous 2*N* KOH. The alkaline solutions were combined, acidified with hydrochloric acid and then shaken with five 100 ml portions of ether or chloroform (expts. 12–13). The organic solution was washed with water and then dried over $MgSO_4$. The solvent was evaporated yielding the acidic products. The results are compiled in Table I.

Reactions under diluted conditions

Sulfuric acid (96–100%, 270 ml) and carbon tetrachloride (250 ml) were placed in the apparatus described above. Formic acid (98%, 50 g) and at the same time, but separately, a solution of the alcohol (0.01 mole) in carbon tetrachloride (50 ml) were added at 10–15° in the course of 1 h with vigorous stirring. The mixture was stirred for 1 h and then poured on to 1 kg of ice. The work-up was as described above.

Reaction products

1-Isobutylcyclohexanecarboxylic acid (**6c**)

The acidic reaction products of expt. 3 were esterified with diazomethane. From the mixture of esters obtained, methyl 1-isobutylcyclohexanecarboxylate was isolated by means of preparative GLC; NMR spectrum: doublet at δ = 0.83 (6 H, *J* = 7 Hz), singlet at δ = 3.63 (3 H), and a complex signal at δ = 0.8–2.5 (13 H); mass spectrum: characteristic peaks at *m/e* = 198, 155, 142, 139, and 83.

The same ester was obtained by reductive alkylation[21] of benzoic acid with lithium-ammonia and isobutyl chloride to yield 1-isobutyl-2,5-cyclohexadiene-1-carboxylic acid; b.p. 161–162°/13 mm, followed by hydrogenation in *n*-heptane at 25° over 5% Pt/C to yield **6c**; b.p. 163–164°/13 mm, and esterification with diazomethane.

3-Cyclohexyl-2,2-dimethylpropanoic acid (**7**)

Methyl 2,2-dimethyl-3-phenylpropanoate[22] was hydrogenated in *n*-heptane over 5% Rh/C at room temperature and 200 atm to yield 7; b.p. 105°/18 mm; NMR spectrum: singlets at δ = 1.12 (6 H) and δ = 3.57 (3 H), and a complex signal at δ = 0.7–2.0 (13 H); mass spectrum: characteristic peaks at *m/e* = 198, 141, 102, and 83.

By means of GLC analysis and comparison of the NMR spectra of the methyl esters it was shown that 3-cyclohexyl-2,2-dimethylpropanoic acid was present in the reaction mixture from expt. 3.

2-Cyclohexyl-2,3-dimethylbutanoic acid (**12c**)

This compound was obtained by recrystallization of the crude acidic product of expt. 5 and shown to be identical with the authentical sample[1].

Side-products of the Koch-Haaf reaction on 1-t-butylcyclohexanemethanol and 1-(1-isopropylcyclohexane)ethanol (**6d**, **9**, **10**, and **11c**)

The methyl esters of **6d**, **9**, and **10** were obtained after subsequently spinning band distillation and preparative GLC of the methyl esters of the acidic reaction products from expt. 5. Methyl 1-neopentylcyclohexanecarboxylate (**6d**); NMR spectrum: singlets at δ = 0.90, 1.52, and 3.60 (3 H) and a complex signal at δ = 0.6–2.5; mass spectrum: characteristic peaks at *m/e* = 212, 197, 157, 156, 155, 153, and 57. Methyl *trans*-3-*t*-butyl-1-methyl-*r*-1-cyclohexanecarboxylate (**10**); NMR spectrum: singlets at δ = 0.87 (9 H), 1.14 (3 H), and 3.60 (3 H) and a complex signal at δ = 0.7–2.4 (9 H); mass spectrum: characteristic peaks at *m/e* = 212, 197, 155, 153, and 57. Compound **9** was identical with an authentic sample. The presence of **11c** was shown by GLC-MS of the methyl esters: characteristic peaks at *m/e* = 212, 180, 169, 153, 142, and 141.

1-Isopropylcyclohexanecarboxylic acid (**11a**) *and 2-cyclohexyl-2-methylpropanoic acid* (**12a**)

Recrystallization of the acidic reaction products from expt. 6 and expt. 7 from ethanol-water gave **11a** and **12a**, respectively. These compounds were identical with authentic samples[1].

1-s-Butylcyclohexanecarboxylic acid (**11b**)

Reductive alkylation of benzoic acid with lithium-ammonia and *s*-butyl bromide[21] yielded 1-*s*-butyl-2,5-cyclohexadiene-1-carboxylic acid; b.p. 163–164°/13 mm; m.p. 39–40°. Hydrogenation of this acid in *n*-heptane at 25° and 1 atm over 5% Pt/C yielded 1-*s*-butylcyclohexanecarboxylic acid; m.p. 76–77°; NMR spectrum: complex signal at δ = 0.7–2.3 (19 H) and singlet at δ = 12.35 (1 H); mass spectrum: characteristic peaks at *m/e* = 184, 155, 139, 128, and 83.

GLC analysis of the methyl esters showed that this acid was present in the reaction products of expts. 8 and 9.

2-Cyclohexyl-2-methylbutanoic acid (**12b**)

A mixture of the acidic reaction products of expt. 8 (4.60 g) and formic acid (98%, 4.60 g) was added at 0° in the course of 45 min to H_2SO_4-SO_3 (7% SO_3, 27 ml). The mixture was stirred vigorously. After 1 h the reaction mixture was poured on to 100 g of ice. After the usual work-up a mixture of 61% **12b**, 18% **11b**, and 21% unidentified acids was obtained (4.23 g, 92%). Acid **12b** was obtained by subsequent distillation and recrystallization (from pentane) of the reaction products; b.p. 161–162°/13 mm; m.p. 78–78.5°; NMR spectrum: singlets at δ = 12.30 (1 H) and δ = 1.00, triplet at δ = 0.87 (*J* = 7 Hz), and a complex signal at δ = 1.0–2.2 (19 H); mass spectrum: characteristic peaks at *m/e* = 184, 102, and 87.

GLC analysis of the methyl esters showed that this acid was present in the reaction products from expt. 8.

1-Methylcyclohexanecarboxylic acid (**9**) *and 2,2-dimethylbutanoic acid* (**13**) *from expt. 11*

The acidic reaction products were separated by spinning band distillation. The pure acids were identical with authentic samples.

2-(1-Adamantane)-2-methylpropanoic acid (**14**)

Recrystallization of the acidic reaction product of expt. 12 from petroleum-ether 60–80 afforded **14**; m.p. 158–159°; NMR spectrum: singlet at δ = 11.6 (1 H), doublet at δ = 1.11 (3 H, *J* = 7 Hz), and a complex signal at δ = 1.4–2.8 (16 H); mass spectrum: characteristic peaks at *m/e* = 208 and 135.

3-Ethyladamantanecarboxylic acid (**15**)

The acidic reaction products of expt. 12 were esterified with diazomethane. The mixture of esters obtained was separated by preparative GLC; NMR spectrum: A_2B_3-system at δ = 0.6–1.3 (5 H), singlet at δ = 3.67 (3 H) and a pattern of signals characteristic for 1,3-disubstituted adamantanes[23].

Identification of some of the acidic reaction products of expt. 18

The presence of 1-*t*-butylcyclohexanecarboxylic acid (**8**) and 2-methyl-2-(1-methylcyclohexyl)propanoic acid (**16**) was shown by GLC analysis and GLC–MS analysis of the methyl esters of the acidic reaction products.

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13 The same holds for the carboxylation of alkylcyclohexanols *e.g. t*-butylcyclohexanol. However, when the carboxylations were performed according to the original procedure of *Koch*[2] with fast stirring of the reaction mixture, in some cases substantial amounts of side-products were formed. These products may be the result of intermolecular shifts, because they disappear when the same technique is used under diluted conditions (cf. ref. 11 note 14).
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CHAPTER 4

Exchange phenomena during Koch-Haaf carboxylations in sulfuric acid-d_2 *

Introduction

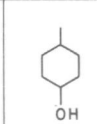
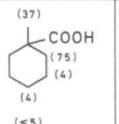
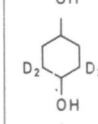
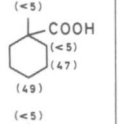
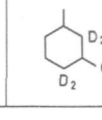
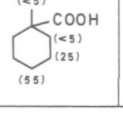
The *Koch-Haaf* reaction[2,3] most probably proceeds by subsequent carbonylation and hydration of a carbenium ion, generated from *e.g.* alkenes or alcohols. Due to carbenium ion isomerisation the reaction generally yields tertiary carboxylic acids. In the present work the transport of the positive charge in the carbenium ion intermediate of the carboxylation of 4- and 3-methylcyclohexanol (which afford 1-methylcyclohexanecarboxylic acid as the sole acidic reaction product[4]) was studied. Two mechanisms may be envisaged: (i) hydride transfer reactions and (ii) carbenium ion/alkene equilibria[5]. Operation of mechanism (i) may be detected by starting from specifically deuterated compounds. By performing the *Koch* reaction in D_2SO_4 the intermediacy of alkenes was studied. Intermolecular reactions were suppressed by using a low concentration of substrate[6]. Separately the H/D exchange of some secondary and tertiary carboxylic acids in D_2SO_4, under *Koch-Haaf* conditions, was studied. In this connection the reversibility of the carbonylation step[7,8] will be discussed.

Results and discussion

The *Koch-Haaf* reaction of 4-methylcyclohexanol in D_2SO_4 afforded 1-methylcyclohexanecarboxylic acid in which D was incorporated in the methyl group and the 2- and 6-positions (see Table 1).

When similar experiments (nos. 2 and 3) were performed with specifically deuterated methylcyclohexanols in H_2SO_4, 1-methylcyclohexanecarboxylic acid with D scrambled over the 3-, 4-, and 5-positions and practically no D present at the 2- and 6-positions was obtained.

Table 1 Koch-Haaf reactions (1 h, 10°) of methylcyclohexanols

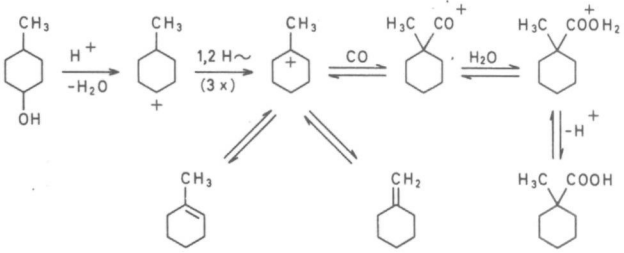
Expt.	Starting compound	Reaction medium	Labeled product [a]	D-content medium after reaction
1		D_2SO_4		77 %
2		H_2SO_4		1 %
3		H_2SO_4		1 %

[a] The D content at the different positions is given in parentheses.

During expt. 1 the D incorporation at the 2- and 6-positions appears to attain equilibrium with the reaction medium. From this observation and from the substantial H/D exchange in the methyl group it may be concluded that the isomerised carbenium ion, *viz.* the 1-methylcyclohexyl cation is in rapid interconversion with methylenecyclohexane and 1-methylcyclohexene. Practically no D is incorporated at the other ring positions of the resulting 1-methylcyclohexanecarboxylic acid, showing that alkenes are not involved to any appreciable extent in the isomerisation of the 4- and 3-methylcyclohexyl cation.

The results of expts. 2 and 3 show that the isomerisation of the 4- and 3-methylcyclohexyl cation proceeds by a series of 1,2-hydride shifts. An important contribution of 1,3- or 1,4-hydride shifts can be excluded since then the amount of D at the 4- and 3-positions respectively, of the reaction product would be negligible. Again, the absence of D at the 2- and 6-positions and in the methyl group is explained by a rapid exchange *via* alkenes.

The reaction mechanism for the carbonylation of 4-methylcyclohexanol is summarized in Scheme 1.



Scheme 1

Alkene intermediates were shown to operate also in the *Koch* carboxylation of some other compounds (Table 2, expts. 4–6). The D incorporation in the *tert*-butyl group during the carboxylation of 4-*tert*-butylcyclohexanol can be explained by a reversible methyl shift, followed by deprotonation and

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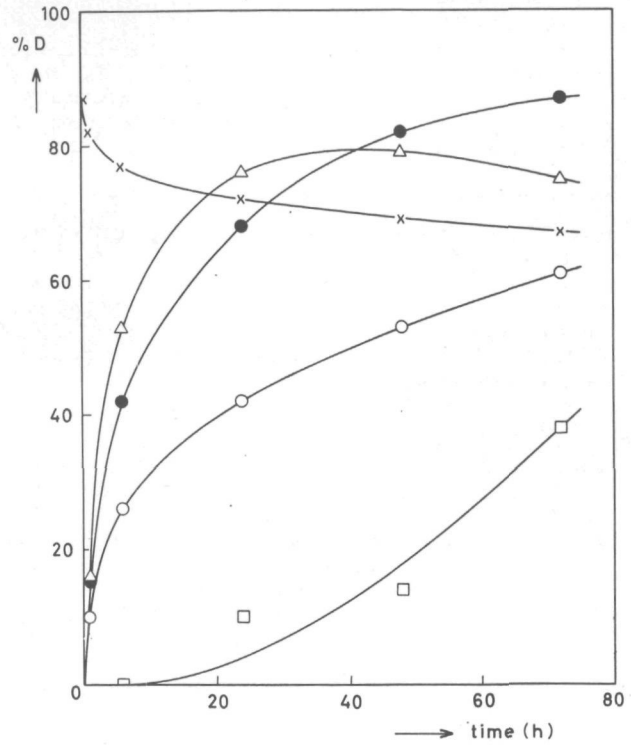


Fig. 1. H/D exchange in 1-methylcyclohexanecarboxylic acid in D_2SO_4–HCOOH, 20°;

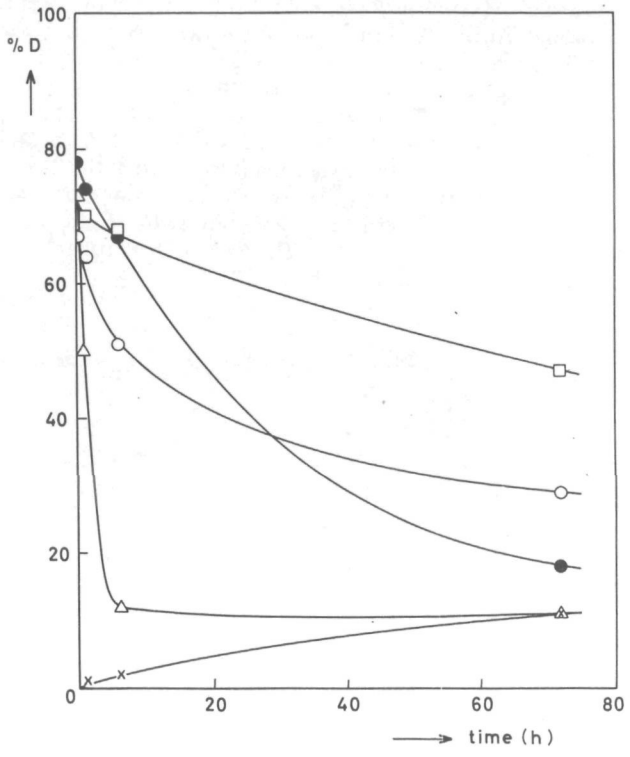


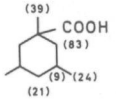
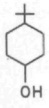
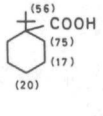
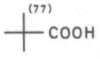
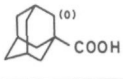
Fig. 2. H/D exchange in deuterated 1-methylcyclohexanecarboxylic acid in H_2SO_4–HCOOH, 20°;

○ *Total;* ● *1-methyl;* △ *2,6-positions;* □ *3,5-positions, 4-position;* × *reaction medium.*

deuteronation, in the 1-*tert*-butylcyclohexyl cation[9] (see Scheme 2).

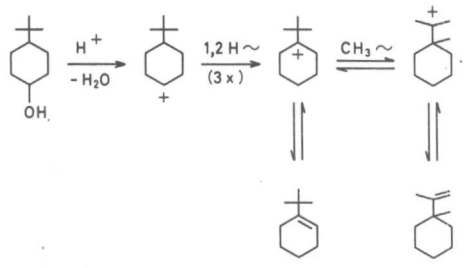
Similar results to those obtained in expt. 5 were obtained when pure 1-*tert*-butylcyclohexanecarboxylic acid was the starting compound, using identical reaction times and conditions. We therefore assume that D is introduced at the 3-, 4- and 5-positions by scrambling of D initially present at the 2- and 6-positions. Due to steric effects the carbenium ion concentration, and therefore also the rate of scrambling, might be higher than in expt. 1.

Table 2 Koch-Haaf reactions in D_2SO_4-HCOOH (1 h, 10°)

Expt.	Starting compound	Labeled product[a]	D-content medium after reaction
4			75 %
5			72 %
6			75 %
7			83 %

[a] The D content at the different positions is given in parentheses.

An exception was the carboxylation of adamantanol[10], in which case, as would be expected, the anti-Bredt alkene adamantene was not formed.



Scheme 2

The equilibrium depicted in Scheme 1, could also be attained starting from 1-methylcyclohexanecarboxylic acid. Here the formation of the intermediate carbenium ions is rather slow[8]. This enabled us to study the progress of the exchange processes in D_2SO_4 as a function of time. Fig. 1 shows the D incorporation in 1-methylcyclohexanecarboxylic acid at 20° in D_2SO_4-HCOOH. The relatively fast H/D exchange in the methyl group is noteworthy, since 1-methylcyclohexene is thermodynamically more stable than methylenecyclohexane[11]. Apparently kinetic factors are involved. In the transition state of the deprotonation of the 1-methylcyclohexyl cation a coplanar orientation of the C–H bond and the vacant *p*-orbital will be required[12,13,6].

Molecular models show that for the 2- and 6-protons this cannot be attained without deviation of the original ring geometry, whereas in the preferred conformation one of the

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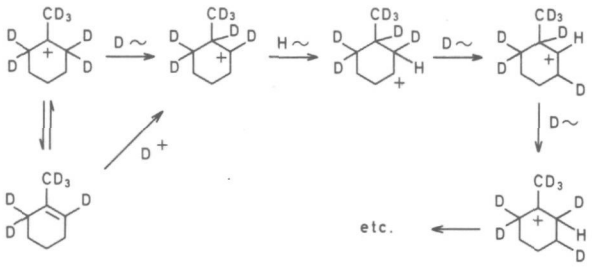
methyl C–H bonds will already be coplanar with the vacant *p*-orbital. At prolonged reaction times the D content of the methyl group and the 2- and 6-positions exceeds that of the reaction medium. This may be attributed to an isotope effect (*cf.* Fig. 2). It may be noted that the deuteronation of the 3-, 4- and 5-positions is slow compared with that of the 2- and 6-positions. Possibly the deuterium introduced at the 2- and 6-positions slowly scrambles over the other ring positions by a series of 1,2-hydride and deuteride shifts. These shifts may be preceded by an anti-Markownikow deuteronation of 1-methylcyclohexene (see Scheme 3).



Scheme 3

In secondary acids (as *e.g.*, *cis/trans*-4-methylcyclohexanecarboxylic acid, *cis*-4-*tert*-butylcyclohexanecarboxylic acid, cyclohexanecarboxylic acid, 2-cyclohexylpropanoic acid and 3-pentanecarboxylic acid) we detected no D incorporation (even after 1 week at 20°) in 98% D_2SO_4 under *Koch-Haaf* conditions. Moreover, no trace of isomerisation towards tertiary acids could be detected[14]. Apparently in the *Koch-Haaf* carboxylation the formation of secondary acids is irreversible and that of tertiary acids reversible.

As shown by *Deno*, simple aliphatic primary or secondary acids are present as protonated acids in 90–100% H_2SO_4[15]. We observed that under these conditions 1-methylcyclohexanecarboxylic acid rapidly loses carbon monoxide. Apparently, in contrast to tertiary acids, the rate of formation of carbenium ions is very low for secondary carboxylic acids under *Koch-Haaf* conditions. *Hogeveen* has shown that in HF–BF_3 the rate of dehydration of protonated carboxylic acids is almost independent of structure[16], whereas the rate of decarbonylation is lowered considerably going from tertiary to secondary oxo-carbenium ions[8]. Furthermore, there is also no substantial difference in rate of hydrolysis in H_2SO_4 between secondary and tertiary carboxylic esters[14]. Therefore, the low rate of formation of carbenium ions from secondary carboxylic acids seems to be due to a low rate of decarbonylation.

When, in Koch reactions, CO is generated *in situ* from formic acid and sulfuric acid, tertiary carboxylic acids are usually obtained[2], showing that in general isomerisation of the intermediate carbenium ion is much faster than carbonylation. Application of the modification of *Haaf* with slow stirring of the reaction mixture sometimes gives rise to a larger portion of secondary acids in the reaction products[17]. In these cases, due to the high CO concentration, the secondary carbenium ion is trapped before it can isomerise to a tertiary one. In our work on *Koch-Haaf* carboxylations of secondary *tert*-alkylcycloalkanols[1,9] we always applied the *Haaf* modification, but we never detected a secondary carboxylic acid in the reaction products. Otherwise it may be noted that in all examples given by *Haaf* the isomerisation in question would give an increase in branching. Then, according to *Brouwer*, a protonated cyclopropane ring is involved[18] in the rearrangement, requiring a relatively high free enthalpy of activation.

Experimental part

The mass spectra were measured by Dr. *P. J. W. Schuijl* and Mr. *H. M. A. Buurmans* with a Varian–MAT SM-1 spectrometer at 70 eV, by using a direct insertion probe. Proton magnetic resonance spectra were recorded with a Varian–XL-100 spectrometer by Mr. *J. M. van der Toorn.*

Starting materials

$Eu(DPM)_3$ was obtained from Merck and was purified by sublimation at 180°/0.1 mm. Dideuterosulfuric acid was obtained from Merck. 4-Methylcyclohexanol-2,2,6,6-d_4 and 3-methylcyclohexanol-2,2,6,6,-d_4 were prepared by treating the corresponding cyclohexanones with deuteroacetic acid, until a mass spectral purity of 100% was obtained, followed by $LiAlH_4$ reduction. 1-Methylcyclohexanecarboxylic acid[9] was purified *via* the benzylamine salt.

Koch-Haaf reactions

A mixture of 25 ml D_2SO_4 or H_2SO_4, 150 ml CCl_4, and 4.56 g 98% HCOOH was stirred at 10° (stirrer speed 120 r.p.m.; stirrer blade 3 cm^2). A solution of 0.01 mole of the alcohol in 50 ml CCl_4 was added dropwise in 45 min. The mixture was stirred for 1 h at 10° and then poured on to 100 g of ice. The two layers were separated. The aqueous layer was extracted with four 30 ml portions of CCl_4. The combined CCl_4 solutions were extracted with four 40 ml portions of 2 *N* KOH. The alkaline solutions were combined and washed with two 30 ml portions of hexane. After acidification with 12 *N* HCl the dispersion obtained was shaken with four 30 ml portions of ether. The organic solution was washed with two 30 ml portions of water and dried over $MgSO_4$. Evaporation of the solvent yielded the acidic products. Further purification was achieved by distillation or by recrystallisation.

Koch-Haaf reactions of carboxylic acids in D_2SO_4-HCOOH

In a thermostatted mercury sealed flask (50 ml) a solution of 0.094 mole of the acid in 1 ml HCOOH was added at once to 10 ml of D_2SO_4. The flask was closed immediately and the solution was homogenized quickly. Then stirring was stopped. After the appropriate reaction time the reaction mixture was poured on to 35 g ice. The dispersion obtained was extracted with six 15 ml portions of hexane. The hexane solution was extracted with four 15 ml portions of 2 *N* KOH. The alkaline solution was washed with two 15 ml portions of hexane, acidified with 12 *N* HCl and then extracted with five 15 ml portions of ether. The ethereal solution was washed with two 15 ml portions of water and dried over $MgSO_4$. Evaporation of the solvent afforded the acidic products. Further purification was achieved by distillation or recrystallisation.

Determination of the deuterium contents

The overall deuterium contents and the deuterium content of the methyl group in 1-methylcyclohexanecarboxylic acid were calculated from the intensities in the mass spectra with an isotope distribution computer programme, written by Dr. *P. J. W. Schuijl.* The deuterium distribution over the different positions in the molecules was determined by PMR spectroscopy of the methyl esters, using $Eu(DPM)_3$[20] to obtain separation between the different signals.

Acknowledgement

Thanks are due to Mr. *O. Misset* for experimental assistance.

[14] *Cf. H. van Bekkum, H. M. A. Buurmans, B. M. Wepster* and *A. M. van Wijk*, Recl. Trav. Chim. Pays-Bas **88**, 301 (1969).
[15] *N. C. Deno, C. U. Pittman, Jr.* and *M. J. Wisotsky*, J. Amer. Chem. Soc. **86**, 4370 (1964).
[16] *H. Hogeveen*, Recl. Trav. Chim. Pays-Bas **86**, 809 (1967).
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[18] *D. M. Brouwer*, Recl. Trav. Chim. Pays-Bas **87**, 210 (1968).
[19] *R. E. Pincock, E. Grigat* and *P. D. Bartlett*, J. Amer. Chem. Soc. **81**, 6332 (1959).
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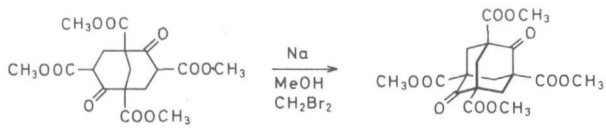
PART II

SYNTHESIS AND CONFORMATION OF BICYCLO[3.3.1]NONANES

CHAPTER 5

INTRODUCTION TO PART II

The chemistry of bicyclo[3.3.1]nonane derivatives receives much attention from a synthetic and a theoretical point of view. Until 1957 these compounds were the sole precursors accessible in the synthesis of adamantane derivatives: always an insertion of a methylene bridge in bicyclo-[3.3.1]nonane derivatives was involved[1] (see e.g. Scheme 1[2]).



1 2

Scheme 1

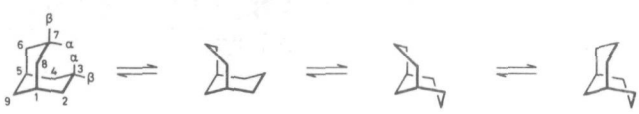
After 1957 this synthetic approach of adamantanes was superseded by *von Schleyer*'s elegant synthesis starting from the readily available cyclopentadiene dimer[3]. In the last decade the reverse route - ring cleavage of adamantane derivatives towards bicyclo[3.3.1]nonanes - has become important (cf. Chapter 6).

The discovery of the prophylactic effect of 1-adamantanamine.HCl towards influenza A virus strains and later on the discovery of the therapeutic effect of some adamantane derivatives in several other diseases, has caused an enormous increase in synthetic research on adamantane derivatives as well as on the geometrically related bicyclo[3.3.1]nonane systems. Indeed, some pharmacologically active bicyclo[3.3.1]nonanes - most of them aza analogues - have been found[4-7].

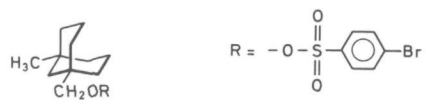
The bicyclo[3.3.1]nonane system shows interesting conformational features, which will be discussed below. Moreover, the geometry of the molecule does not allow a plane geometry around the bridgehead carbon atoms. Therefore, the "anti--Bredt" compound bicyclo[3.3.1]non-1-ene has been a great challenge for synthetic chemists[8-10].

Conformational analysis[11]

For the bicyclo[3.3.1]nonane system three groups of conformations may be envisaged: (i) the rigid double-chair (cc) conformation, in which severe interaction of $H_{3\alpha}$ and $H_{7\alpha}$ occurs, (ii) the rigid chair-boat (bc and cb) conformations and (iii) the flexible double-boat conformations (bb).



Force field calculations show that in the unsubstituted system a flattened cc is the principal conformer in the equilibrium. The free enthalpy difference between the cc and the cb conformation is calculated to be 2.5 kcal/mole; that between the cb and the bb conformation 5.7 kcal/mole[12]. The calculated free enthalpy difference between the cc and the bc conformation is in good agreement with that estimated from epimerization experiments of some 3-substituted bicyclo[3.3.1]-nonanes[13,14]. Moreover, X-ray analysis of p-bromobenzenesulphonoxymethyl-5-methylbicyclo[3.3.1]-nonan-9-ol (3) showed that this compound is indeed in a cc conformation[15,16]. Both wings of the



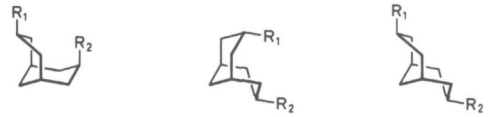
3

system are distinctly flattened: the $C_1C_2C_3$ and $C_5C_6C_7$ angles are about 114° and the C_3C_7 distance is 3.05 Å (in an ideal cc conformation this distance amounts to 2.52 Å). A comparison of the IR spectra of this compound in KBr and in CCl_4 solution indicated that the conformation of 3 in solution is the same as in the crystal. Recent electron diffraction studies on bicyclo[3.3.1]-nonane confirmed that this compound exists in a distinctly flattened cc conformation[120].

It may be anticipated that 3β(7β) substituted derivatives also occur predominantly in the cc conformation. The substituents might have influence on the extent of flattening.

Substituents at the 3α or 7α position will cause severe 3,7 interaction in the cc conformation. Therefore, in these compounds a cb conformation is preferred[13,14,17-25]. From the two possible cb conformations, that with the substituent in the boat ring will be the most favourable, since in the other cb conformation two 1,3-diaxial interactions occur.

Substitution of both the 3α and 7α positions will give rise to a more complex situation[24-26]: for these derivatives the cb, bc and the various bb conformations should be taken in consideration. It is obvious that the relative populations of these conformations will be strongly dependent on the steric requirements of R_1 and R_2.



bc cb bb

Upon replacement of the 3-methylene unit in bicyclo[3.3.1]nonane by ether oxygen several interactions in this molecule are changed. It may be anticipated that this operation affects the geometry of the wings in the different conformers as well as the relative stabilities of the conformers.

Synthesis of 3(7)-substituted bicyclo[3.3.1]-nonanes

Since the publication of the most recent review on bicyclo[3.3.1]nonanes[27], several important developments with respect to the synthesis of these compounds have been reported. Therefore, a concise review, which covers the literature until November 1977, is given here.

The literature on the synthesis of 3,7,9-substituted hetero-analogues of bicyclo[3.3.1]nonanes has been reviewed by *Zefirov* and *Rogozina*[119]. Therefore, we confine ourselves to the carbocyclic

systems, and - in view of the scope of the investigations - to the 3- and 3,7-substituted derivatives.

The synthesis of 3(7)-substituted bicyclo-[3.3.1]nonanes described in literature, can be traced back to five general types, inherent to the structure of the basis system, namely

(i) annelation reactions of cyclohexane derivatives,

(ii) annelation reactions of cyclooctane derivatives,

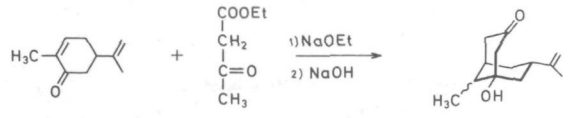
(iii) ring cleavage of adamantane derivatives,

(iv) skeleton isomerizations of other bicyclononanes,

(v) functionalization of bicyclo[3.3.1]nonanes.

(i) Annelation of cyclohexane derivatives

Probably *Rabe* was the first chemist, who described the synthesis of a bicyclo[3.3.1]nonane derivative[28,29]: base catalyzed condensation of carvone (4) with ethyl acetoacetate (5), followed by a decarboxylation afforded the bicyclic compound (6)[31-34]. *Theobald* proved the *exo* (β) configuration of the isopropenyl group[30] (Scheme 2). Several

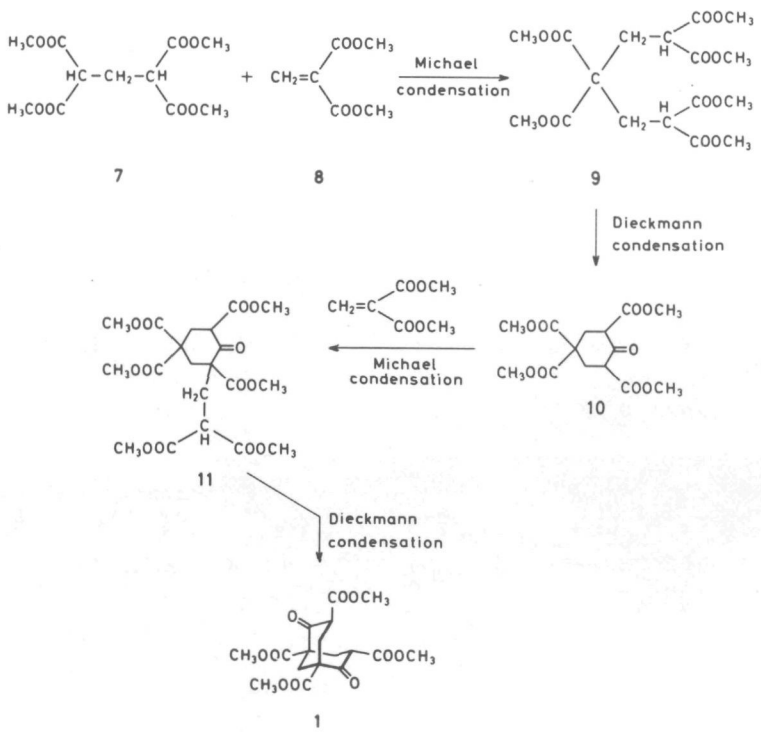


4 5 6

Scheme 2

analogous reactions have been described[29-37] and this approach was for a long period an important route to bicyclo[3.3.1]nonanes.

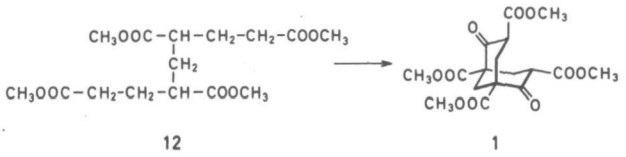
As already mentioned, *Meerweins* ester (1) has been another important starting compound in bicyclo[3.3.1]nonane and adamantane synthesis. This ester was synthesized from tetramethyl propane-1,1,3,3-tetracarboxylate (7) and dimethyl ethene-1,1-dicarboxylate (8)[38-40]. The mechanism



7 8 9 10 11 1

Scheme 3

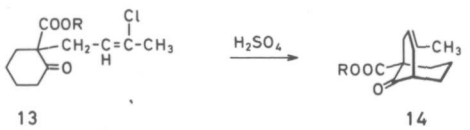
of this reaction involves a series of Michael and Dieckmann condensations (see Scheme 3). Compound 1 was also synthesized by a Dieckmann condensation of tetraethyl heptane-1,3,5,7-tetracarboxylate (12) (see Scheme 4)[41]. Dieckmann condensations are also involved in the ring closure of some 1,3-disubstituted cyclohexanecarboxylates[42,43].



12 1

Scheme 4

Prelog et al. used a modification of the *Robinson* synthesis for the preparation of unsaturated bicyclo[3.3.1]nonanes[44] (see Scheme 5). Several examples of analogous reactions are described[45-47].

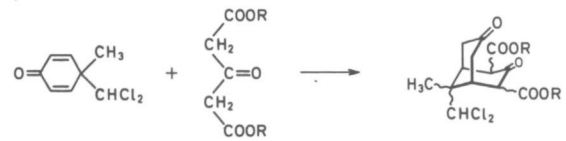


13 14

Scheme 5

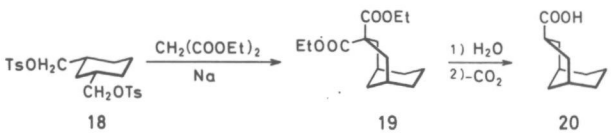
Another versatile reaction yielding bicyclo-[3.3.1]nonanes was developed by *Stetter*, who performed a double Michael condensation of 4-methyl--4-dichloromethylcyclohexa-2,5-dienone (15) with dialkyl acetonedicarboxylate (16)[48-51] (see Scheme 6).

The 3α-substituted bicyclo[3.3.1]nonanes are accessible *via* condensation of malonic ester with the ditosylate of *cis*-1,3-dihydroxymethylcyclohexane (18). Hydrolysis and decarboxylation affords selectively the 3α-carboxylic acid 20[52,53,13] (see Scheme 7).



15 16 17

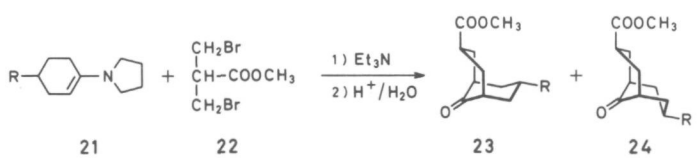
Scheme 6



18 19 20

Scheme 7

A more important route to 3α-substituted derivatives is the α,α'-annelation reaction of a



21 22 23 24

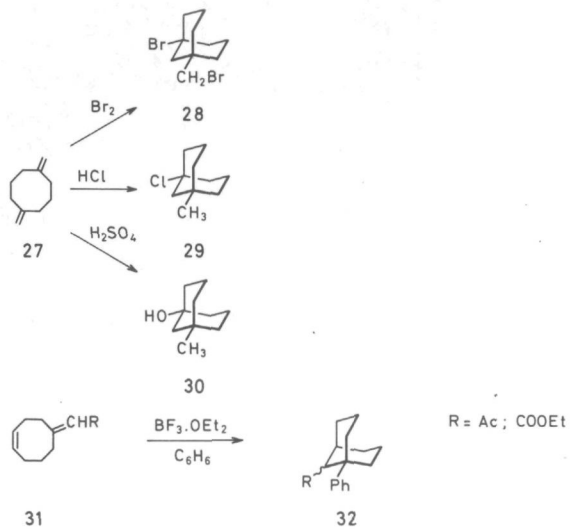
Scheme 8

cyclohexanone enamine (21) with methyl β,β-dibromo-isobutyrate (22) (Scheme 8, see also Chapter 7)[54-59]. With this reaction the 3α-carboxylate is obtained exclusively. The reaction has been extended to other α,α'-annelation reagents such as 2,2-bis(chloromethyl)acetophenone[60,61]. A related reaction involves condensation of an enamine with an α,β-unsaturated carbonyl compound to yield 2-substituted bicyclo[3.3.1]nonanes (e.g. Scheme 9)[62-70].

Scheme 9

(ii) Annelation reactions of cyclooctane derivatives

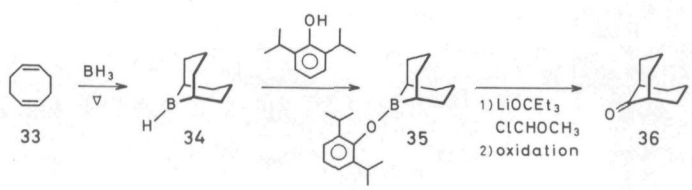
As the synthesis of substituted cyclooctane derivatives is rather difficult, the application of these compounds is restricted to the preparation of 1,5(,9)-substituted bicyclo[3.3.1]nonanes. Transannular reactions in unsaturated cyclooctane derivatives have been described (e.g. Scheme 10)[71-74].



Scheme 10

The mechanism of these reactions involves formation of a tertiary carbenium ion, followed by a transannular addition to the remaining double bond to yield a bicyclo[3.3.1]nonane derivative[118].

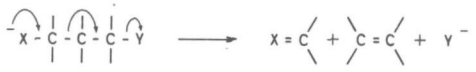
Bicyclo[3.3.1]nonan-9-one (36) can be obtained *via* 9-borabicyclo[3.3.1]nonane (34), which is easily prepared by hydroboration of 1,5-cyclooctadiene[75] (Scheme 11).



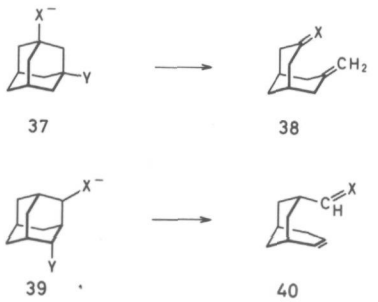
Scheme 11

(iii) Ring cleavage of adamantane derivatives

In 1955 *Grob* described a fragmentation reaction, which can be characterized by the following general reaction scheme[121]:

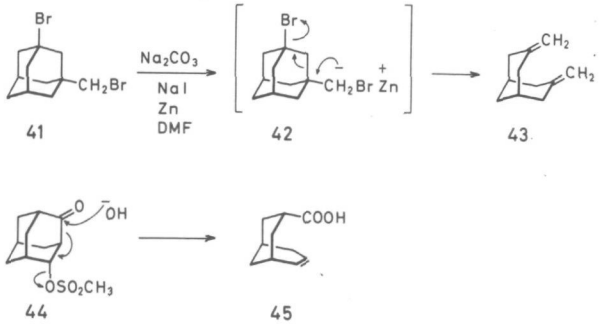


The transition state of this reaction requires an antiperiplanar conformation of the functions $^{-}X\text{-}C\diagup$ and $\diagdown C\text{-}Y$. In 1,3- and 2,4-disubstituted adamantane derivatives the conformation is fixed in this situation. Therefore, these compounds are ideal substrates for *Grob* fragmentations (see Scheme 12).



Scheme 12

Numerous applications of this type of reaction have been described[77-94]; in Scheme 13 two examples are given[79,84].

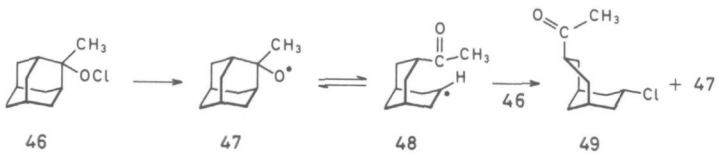


Scheme 13

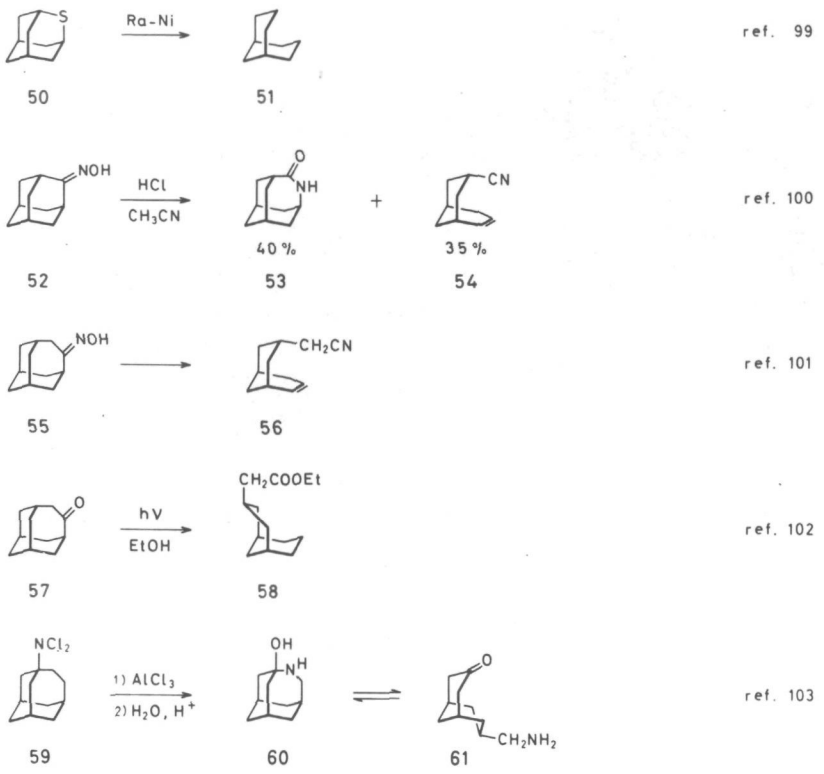
Another elegant route yielding 3α-substituted bicyclo[3.3.1]nonanes involves cleavage of t-adamantyloxy radicals, which may be conveniently generated by thermolysis or photolysis of the corresponding hypohalites[95-98] (see e.g. Scheme 14).

Some other cleavage reactions are compiled in Scheme 15[100-104]. (See also refs 104-110.)

Also reports on the cleavage of [3.3.1]propellane[111] and tricyclo[3.3.1.$0^{2,8}$]nonanes[112] to bicyclo[3.3.1]nonanes have been published.



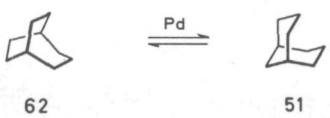
Scheme 14



Scheme 15

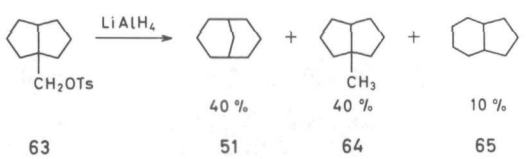
(iv) Skeleton isomerizations of other bicyclononanes

Bicyclo[3.3.1]nonane (51) can be obtained by isomerization of bicyclo[3.2.2]nonane (56) catalyzed by palladium[113] (Scheme 16).



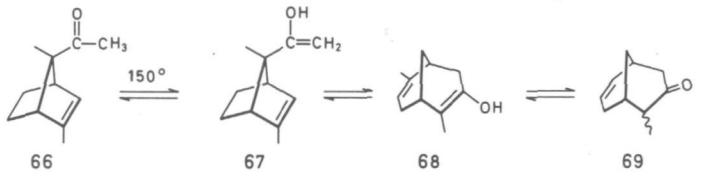
Scheme 16

During the $LiAlH_4$ reduction of the tosylate of 1-hydroxymethylbicyclo[3.3.0]octane (63) extensive rearrangements were observed. Among other products 40% bicyclo[3.3.1]nonane (51) was obtained[114] (see Scheme 17).



Scheme 17

Another isomerization involves a Cope reaction of 6-acetyl-2,3-dimethylbicyclo[2.2 1]hex-2-ene[115] (see Scheme 18).



66 67 68 69

Scheme 18

(v) Functionalization of bicyclo[3.3.1]nonanes

There are numerous examples of syntheses of 3(,7)-substituted bicyclo[3.3.1]nonanes by functionalization of other bicyclo[3.3.1]nonane derivatives. It may be noted that the geometry of the skeleton of these compounds strongly favours attack of reagents from the exo side. This phenomenon enables smooth stereoselective synthesis of 3α-substituted derivatives. In Scheme 19 an example is given[62].

70 71

Scheme 19

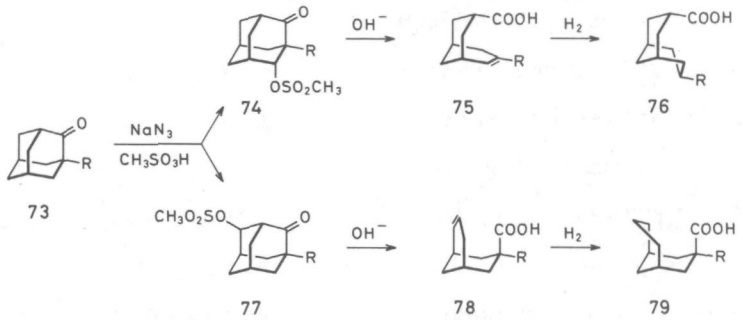
From the foregoing it may be concluded that 3α-substituted bicyclo[3.3.1]nonanes are, in general, easily accessible. These compounds can often be converted into the thermodynamic more stable 3β--substituted derivatives by means of epimerization[13,14]. With 3α,7α-substituted bicyclo[3.3.1]nonanes, however, ring closure may occur under epimerization conditions.

Scope of Part II of this thesis

In this investigation the attention was focussed on the 3,7-disubstituted bicyclo[3.3.1]nonanes. As it may be anticipated that the position (α or β) and the steric requirements of the 3,7-substituents govern the conformation, these compounds are very interesting from a conformational point of view. Until 1970 this subject was rather unexplored: compounds, which predominantly occur in a bb conformation were not known, the geometry of the cb/bc conformers was not described and data on the geometry of the cc conformation in solution were hardly available. We started our studies with bicyclo-[3.3.1]nonane 3α,7α-dicarboxylic acid (72), which

72

compound was synthesized by a new cleavage reaction of homoadamantan-4-one (Chapter 6). This compound was used in the synthesis of several other 3α,7α--substituted derivatives, including systems with bulky substituents, which may be expected to occur predominantly in a bb conformation. Moreover, ring



Scheme 20

closure of 72 yielded 2-oxoadamantane-1-carboxylic acid: a useful precursor of 1,2-disubstituted adamantanes, which are difficult to synthesize along other lines.

Until 1970 X-ray and IR spectroscopy were the most important tools in conformational analysis of bicyclo[3.3.1]nonanes. In Part II of this thesis the exploration of some other techniques in the conformational analysis of these compounds is described. ^{1}H NMR spectroscopy turns out to be, *via* the vicinal coupling constants, a powerful source of information in conformational analysis. This method is only applicable when reasonable resolution between the different proton signals is obtained. Fortunately, the start of our investigation coincided with the introduction of lanthanide shift reagents in NMR spectroscopy[116,117]. In Chapter 6 one of the first applications of shift reagents in conformational analysis is described. The vicinal coupling constants of compound 72 and its dimethyl ester did not allow unambiguous conclusions about their conformations. It was therefore necessary to compare these coupling constants with those of a series of model compounds, in which the conformation is fixed.

Two methods to lock the conformation were chosen *viz.*, (i) suitable substitution and (ii) the use of adamantane as an integrated holding system (Chapter 8).

Initially we planned the synthesis of a series of 7-alkyl-substituted bicyclo[3.3.1]nonanes *via* a cleavage reaction of adamantane derivatives (Scheme 20) on the analogy of the synthetic sequence applied by *Sasaki* et al.[84] for adamantanone itself (R = H). However, for R = methyl another product was obtained. The structure of this product was elucidated by means of ^{1}H and ^{13}C NMR spectroscopy and paramagnetic shift reagents (Chapter 13).

Since this reaction did not yield the desired products, we chose for a synthetic route *via* the corresponding 9-oxo derivatives (Chapter 8), which were conveniently accessible *via* the α,α'-annelation reaction (Chapter 7).

In Chapter 8 a detailed conformational analysis of compound 72 and its dimethyl ester is given.

One of the drawbacks of conformational analysis with the use of vicinal proton-proton coupling constants is the fact that the interpretation of the magnitudes of these coupling constants requires the assumption of an ideal tetrahedral geometry

around the carbon atoms in question. Moreover, it is rather difficult to get an impression about the contributions of the different conformers to the conformational equilibrium. As to the latter, thermodynamic parameters of chair-boat equilibria in some bicyclo[3.3.1]nonane derivatives were determined with the use of epimerization and variable temperature ^{13}C NMR experiments (Chapter 9). In addition, accurate geometries as well as thermodynamic parameters were obtained from empirical force field calculations.

With the introduction of the Pulse Fourier Transform technique ^{13}C NMR spectroscopy became easily accessible and this technique became another potential tool in the conformational analysis of bicyclo[3.3.1]nonanes. In Chapter 9 the applicability of ^{13}C chemical shifts in the conformational analysis of these compounds is investigated.

The configuration of bicyclo[3.3.1]nonanes is sometimes difficult to analyse, due to its dramatic influence on the conformation. Therefore, a search on stereoselective mass spectral fragmentations in bicyclo[3.3.1]nonanes was started. In Chapter 12, as a first example, a stereoselective fragmentation in 7-alkyl-3-oxabicyclo[3.3.1]-nonanes is described. The configuration and conformation of these compounds was established by means of ^{13}C and ^{1}H NMR spectroscopy with the use of lanthanide shift reagents (Chapter 11). Substitution of the 3-methylene group in bicyclo[3.3.1]-nonane by ether oxygen eliminates the possibility to use vicinal proton-proton coupling constants in the study of the geometry of the wing under consideration. Therefore, the fit of experimental lanthanide induced shifts with those calculated with the McConnell/Robertson relation as a function of the geometry of the tetrahydropyran ring was investigated. Also some model compounds were included in this study.

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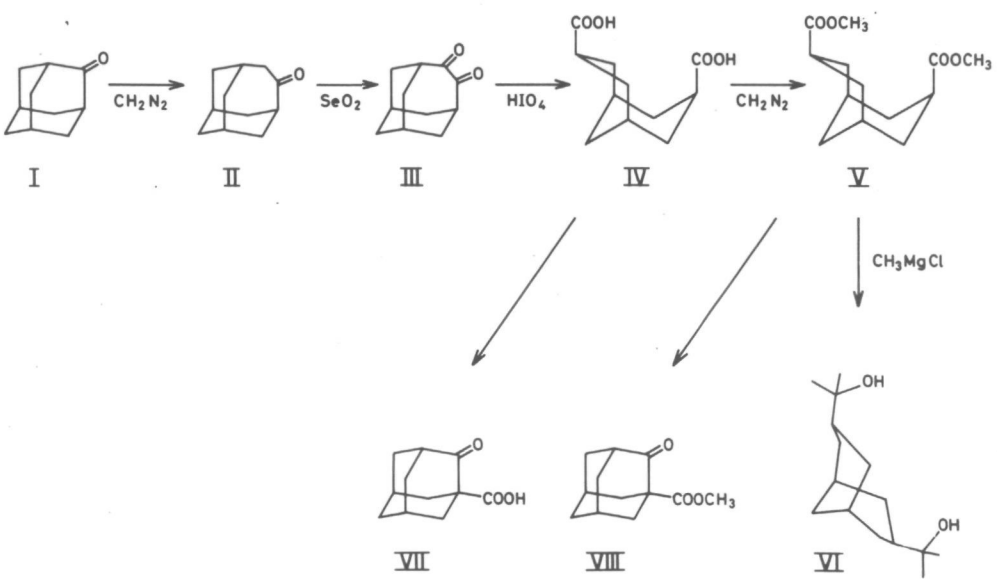
CHAPTER 6

SYNTHESIS AND (NON-CHAIR) CONFORMATION OF SOME 3α,7α-DISUBSTITUTED BICYCLO[3.3.1]NONANES*

Recent developments have made homoadamantane derivatives readily accessible[1-3]. Cleavage of these compounds would seem a convenient route to 3α,7α-disubstituted bicyclo[3.3.1]nonanes. As an example we have studied the oxidative cleavage of 4-homoadamantanone (II), which compound was prepared from adamantanone (I) and diazomethane as described by *Black* and *Gill*[1]. Compound II was oxidized with selenium dioxide into 4,5-homoadamantanedione (III)[2]. Further oxidation by heating III at 70° with periodic acid in dioxane-water (3:1) for 70 h furnished in 85% yield 3α,7α-bicyclo[3.3.1]-nonanedicarboxylic acid (IV); m.p. 180.5-181°.

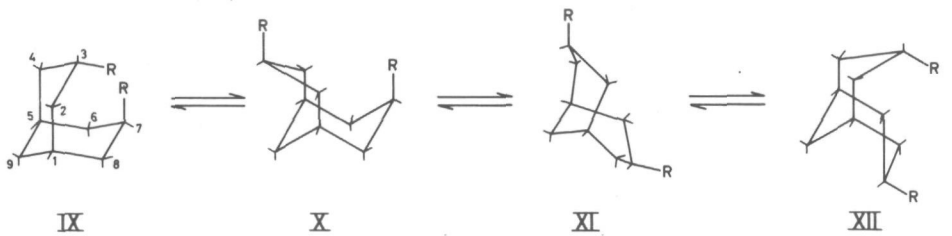
The dicarboxylic acid IV was converted with diazomethane into the corresponding dimethyl ester V. Various attempts to epimerize IV or V failed



* A reprint of J.A. Peters, J.D. Remijnse, A. van der Wiele, and H. van Bekkum, *Tetrahedron Lett.* 1971, 3065.

because ring closure towards 2-oxoadamantanecarboxylic acid (VII) or its methyl ester (VIII) occurred quantitatively. Treatment of V with a solution of methylmagnesium chloride in THF afforded 3α,7α--bis-2-(2-hydroxypropyl)bicyclo[3.3.1]nonane (VI) in 80% yield; m.p. 106-107°.

Compounds IV, V, and VI were studied with the use of ^{1}H NMR spectroscopy. The possible conformations of 3α,7α-disubstituted bicyclo[3.3.1]nonanes are outlined below. *Appleton* et al.[4] have shown that for methyl 3α-bicyclo[3.3.1]nonanecarboxylate the double chair conformation (IX) can be populated



IX X XI XII

to only a small extent. Consequently, conformation IX may be discarded for the present systems, as is also obvious from an inspection of molecular models. Thus compounds IV-VI may be considered to exist as an equilibrium of the two equivalent chair-boat conformations (X and XII) and the flexible double boat conformation (XI). Estimation of 1,3-diaxial interactions indicates that even when R is rather small, as in V, the conformation XI may play a role. Anyway, when R becomes bulkier, the contribution of XI is expected to increase as a result of unfavourable 1,3-diaxial interactions in the chair-boat conformations X and XII, which are absent in the double twist-boat conformation XI.

The 100 MHz spectrum of VI (Fig. 1A) was too complex to allow for a first-order interpretation. Therefore, spectra were recorded with increasing amounts of Eu(dpm)$_3$[5] until separation between the various multiplets was achieved. From this spectrum (Fig. 1B) chemical shifts and coupling constants were obtained by first-order analysis. More accurate data were obtained by computer iteration starting from these chemical shifts and coupling constants (see Table I). From a plot of the chemical shift of the methyl protons versus the shift of the various ring protons with increasing amounts of Eu(dpm)$_3$ (Fig. 2) the chemical shifts of the protons in the absence of Eu(dpm)$_3$ were extrapolated. Computer simulation, using these chemical

TABLE I

The coupling constants of compounds IV-VI in Hz (± 0.5 Hz)

	$J_{12\alpha}$	$J_{12\beta}$	J_{19}	$J_{2\alpha2\beta}$	$J_{2\alpha3}$	$J_{2\beta3}$
IV	3.0	7.0	3.0	-14.0	7.1	7.1
V	3.0	7.0	3.0	-14.0	7.1	7.1
VI	2.0	10.0	2.5	-12.0	12.0	6.0

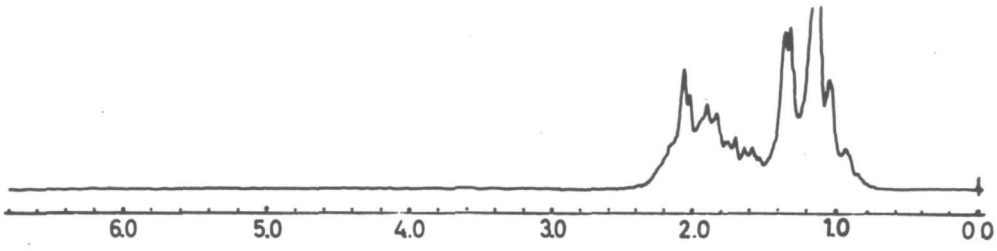


Fig. 1A. 100 MHz ^{1}H NMR spectrum of VI in $CDCl_3$ (δ-scale).

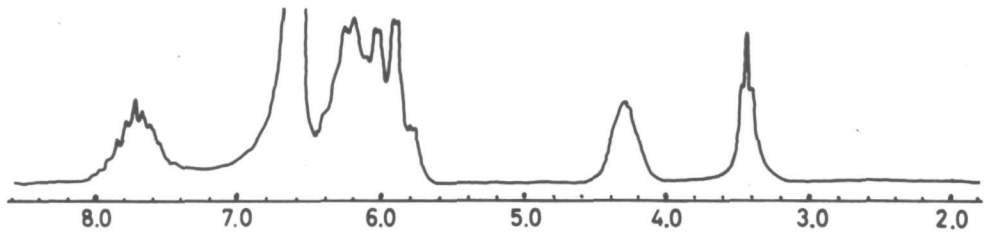


Fig. 1B. 100 MHz ^{1}H NMR spectrum of 80 mg VI in 0.5 ml $CDCl_3$ and 80 mg $Eu(dpm)_3$.

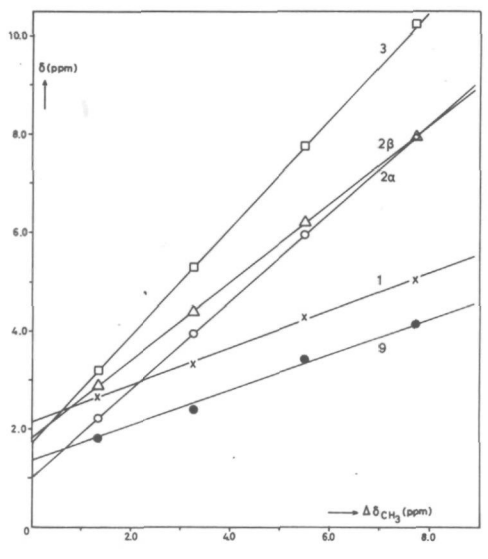


Fig. 2. The effect of $Eu(dpm)_3$ on the ^{1}H NMR of VI. The induced shift of the $C(CH_3)_2OH$-protons versus the chemical shifts of the ring protons.

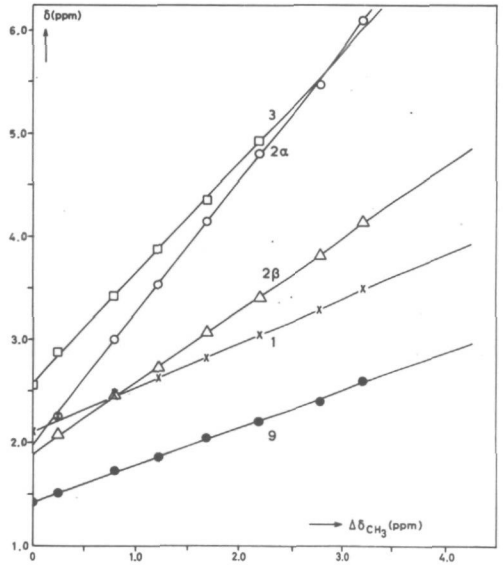


Fig. 3. The effect of $Eu(dpm)_3$ on the ^{1}H NMR spectrum of V. The induced shift of the $COOCH_3$-protons versus the chemical shifts of the ring protons.

shifts and the coupling constants from Table I, yielded a spectrum which was identical with the original one (Fig. 1A). Hence, complexation with $Eu(dpm)_3$ had no observable influence on the conformation and geometry. The splitting pattern of the signal of the 2α, 4α, 6α, and 8α-protons can

only be explained by a double twist-boat conformation. These protons are then geminally coupled (J = -12 Hz) to the corresponding β-protons, "trans diaxial" (J = 12 Hz) to the 3- and 7-protons respectively, and only weakly (J = 2 Hz) to the 1- and 5-protons, respectively. The coupling constant $J_{2\beta 3\beta}$ (6.0 Hz) has the same value as that found for the coupling between the corresponding 1- and 2-protons in *cis*-1,4-di-*t*-butylcyclohexane[6], which compound doubtless prefers the twist-boat conformation.

The 100 MHz ^{1}H NMR spectrum of compound V exhibits a sharp singlet for the protons of the two methoxycarbonyl functions, a quintet for the 3- and 7-protons (J = 7.1 Hz), and a triplet for the 9-protons (J = 3.0 Hz). The spectrum of IV is analogous to that of V. From spectra of V in the presence of various amounts of the paramagnetic shift reagent $Eu(dpm)_3$[5] all other coupling constants were derived (see Table I). The coupling constants were independent of the amount $Eu(dpm)_3$ added. Apparently the complexation with $Eu(dpm)_3$ had no observable influence on the conformation and geometry of V. As can be seen from Fig. 3, the influence of $Eu(dpm)_3$ on the 2α-protons is relatively large, showing that the distance of the Eu^{3+}-ion to these protons is rather small, especially in comparison with the 2β- and 3-protons[7]. Moreover, substantial line broadening at low temperatures (-90°) shows that these compounds exist as an equilibrium of conformations. Both facts indicate that there is an important contribution of the chair-boat conformations (X and XII) to the conformational equilibrium. The values for the coupling constants between the 2-protons and the 3-proton (both 7.1 Hz), which cannot be explained by a double twist-boat conformation (compare compound VI), also seem to be in contradiction with the X-XII equilibrium, because then these couplings are expected to be 7-9 Hz ($J_{2\alpha 3}$) and 3-5 ($J_{2\beta 3}$). The flagpole interaction in the rigid boat parts and the 1,3-diaxial repulsion in the chair parts of the conformations X and XII, however, may cause such a flattening of both the chair and the boat that these couplings become of the same magnitude. Some other bicyclo[3.3.1]-nonane derivatives are in preparation in order to verify this assumption.

A c k n o w l e d g e m e n t

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CHAPTER 7

SYNTHESIS AND CONFORMATION OF SOME 3,7-DISUBSTITUTED 9-OXOBICYCLO[3.3.1]NONANES *

INTRODUCTION

Bicyclo[3.3.1]nonane and some of its derivatives have been shown to exist in a somewhat flattened double-chair conformation (I).[2-7] Introduction of a 3β- or 7β-substituent is not expected to influence this conformation seriously. Substitution at the 3α- and/or 7α-position, however, introduces severe transannular 3,7-interactions and 1,3-diaxial interactions in the double chair conformation. Therefore in these derivatives the rigid chair-boat (II and IV) and the double-boat conformation (III) are assumed to play a major role.[8-16]

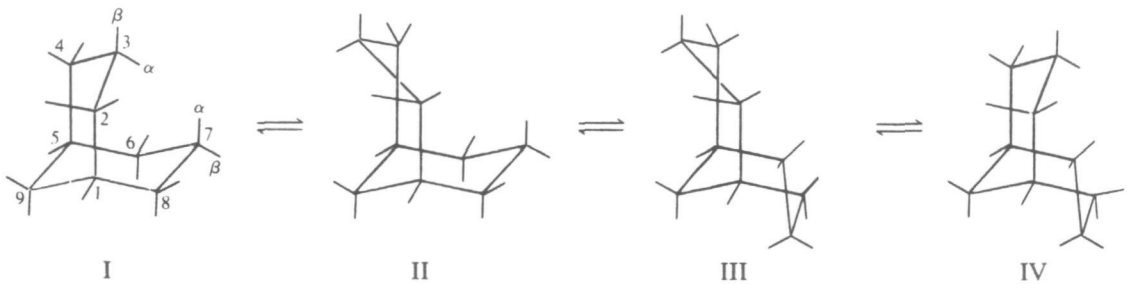
Previously we reported on the synthesis and conformation of some 3α,7α-disubstituted bicyclo[3.3.1]nonanes.[1] The present study deals with the related class of 9-oxobicyclo[3.3.1]nonanes. Here 3,9- and 7,9-hydrogen-hydrogen repulsion in the boat conformers is absent and therefore the energy difference between chair and boat conformations of the rings is expected to be smaller than in the parent ring system. We have performed a PMR conformational study of a number of methyl 7-alkyl-9-oxobicyclo [3.3.1]nonane-3-carboxylates, which were synthesized by means of α,α'-annelation of pyrrolidine enamines of 4-alkylcyclohexanones (**1**) with methyl β,β'-dibromoisobutyrate (**2**) (Scheme 1).[17-19]

In view of the results of Lawton *et al.*[19] who investigated the condensation of **1d** with dimethyl γ-bromomesaconate, one should expect methyl 7α-alkyl - 9 - oxobicyclo[3.3.1]nonane - 3α - carboxylates (**4**) to be the main products. In our hands, however, the major product was always the 3α,7β-epimer (**3**). In the present paper the mechanism of these reactions is discussed.

THE ANNELATION REACTION

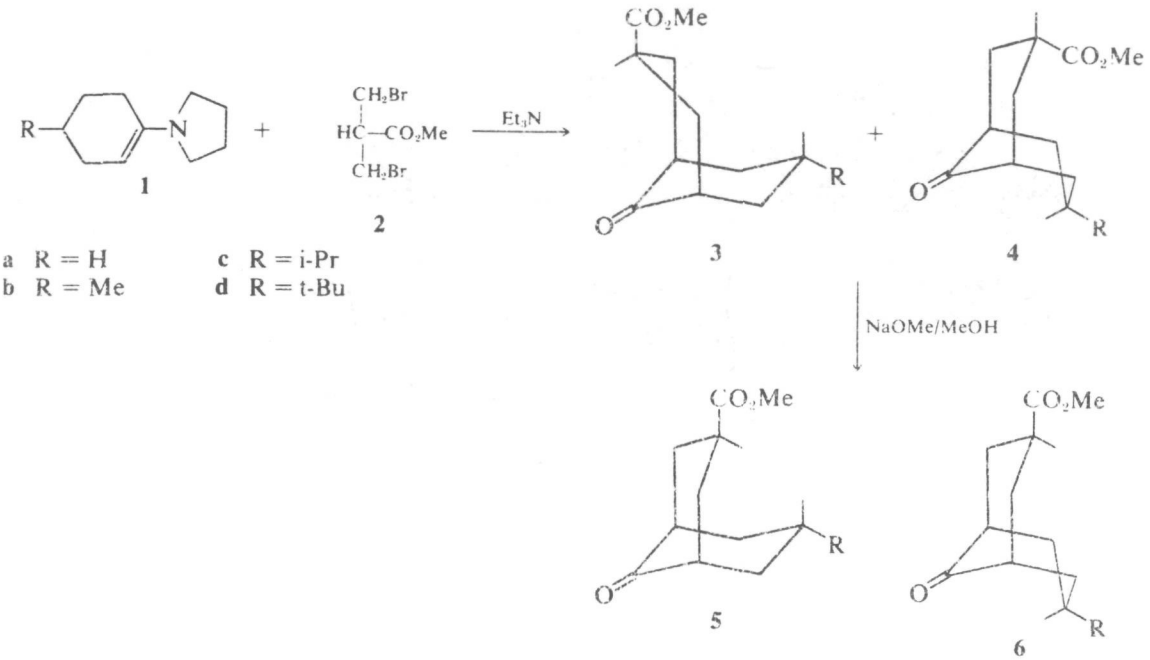
Configuration of the annelation products. Condensation of compounds **1** with methyl α-(bromomethyl)-acrylate, prepared *in situ* from **2** and Et_3N, afforded mixtures of **3** and **4**, the ratio of which appeared to be independent on the 4-alkyl group in **1** (Table 1).

Treatment of the mixtures obtained with NaOMe-MeOH gave epimerisation towards two other esters (**5** and **6**), showing that **3** and **4** differed only in the position of the alkyl group. Apparently the position of 3-CO_2Me in **3** and **4** is α: epimerisation then results in the more stable 3β-isomers. Further information on the configuration of the esters was obtained by PMR spectroscopy (100 MHz), using the shift reagents Eu(DPM)$_3$ and Eu(FOD)$_3$.[20-22] The various signals were assigned by



I II III IV

* A reprint of J.A. Peters, J.M. van der Toorn and H. van Bekkum, *Tetrahedron* 30, 633 (1974).



a R = H c R = i-Pr
b R = Me d R = t-Bu

SCHEME 1.

Table 1. Annelation of pyrrolidine enamines of 4-alkylcyclohexanones with methyl α-(bromomethyl)-acrylate

Starting compound	Reaction products Yield, %	% 3	% 4
1a (R = H)	85		
1b (R = Me)	89	63	37
1c (R = i-Pr)	81	60	40
1d (R = t-Bu)	89	59	41

the relative shifts, the splitting patterns, and by using double resonance techniques.

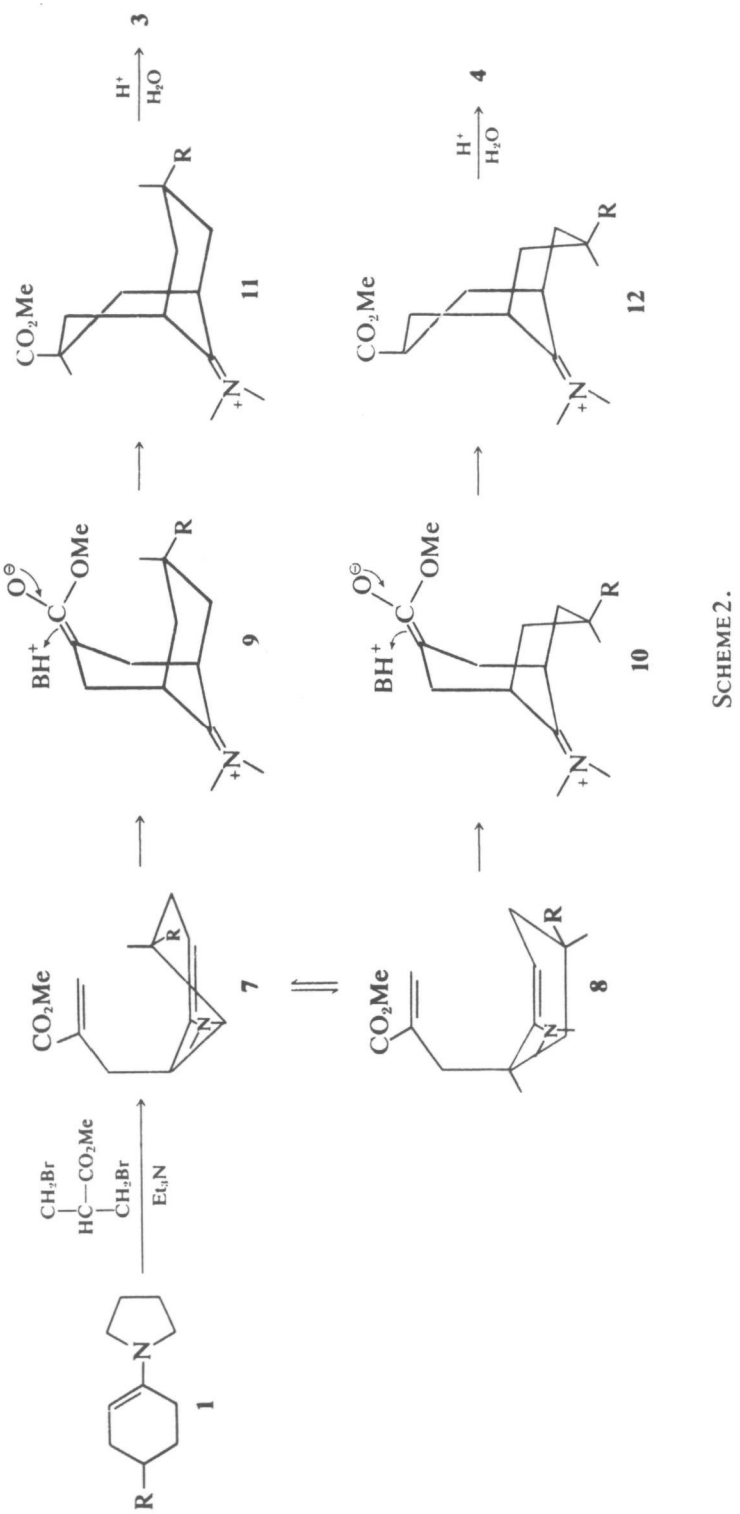
The values of the coupling constants (see Table 2) prove that the main products (**3**) are the 3α, 7β-epimers, with the ring containing the 3α-CO_2Me function in the boat conformation and the other ring in the chair conformation, while the minor products (**4**) are the 3α, 7α-epimers in a chair-boat conformation with the ring with the 7-R in the boat conformation. These assignments are in agreement with the results of the epimerisation experiments.

Mechanism. The results of the annelation reactions are not consistent with the mechanism suggested by Lawton *et al.*[19] These authors have shown that the reaction proceeds *via* a C-alkylation-proton transfer-Michael condensation path (cf. Scheme 2). After alkylation an equilibrium of both *trans* (**7**) and *cis* (**8**) position of R relative to the methylacrylate chain is possible, through a H^+ addition/elimination mechanism. For the Michael annelation to take place, it is obviously necessary that the methylacrylate chain is in a quasi-axial position. The *trans* compound (**7**) affords the 7β-R epimer (**9**), the *cis* compound (**8**) the 7α-R epimer (**10**). During the condensation of **7** a 3-CO_2Me-7-H interaction is introduced, while during the ring closure of **8** the original enamine ring will be forced into the boat conformation (to prevent severe 1,3-diaxial interactions). In view of the observed ratio of the two resulting esters there is no significant preference for one of the reaction paths. Unlike Lawton *et al.*, according to whom the reaction should proceed predominantly *via* **8**, we therefore assume that a boat-like conformation of the original enamine ring is not preferred for ring closure. Protonation of the Michael reaction products (**9**, **10**)* from the least hindered side results in the 3α-CO_2Me derivatives upon hydrolysis (**3**, **4**). During the protonation the ring containing the CO_2Me group might change from a chair into a boat conformation in order to prevent severe interactions with the other cyclohexane ring.

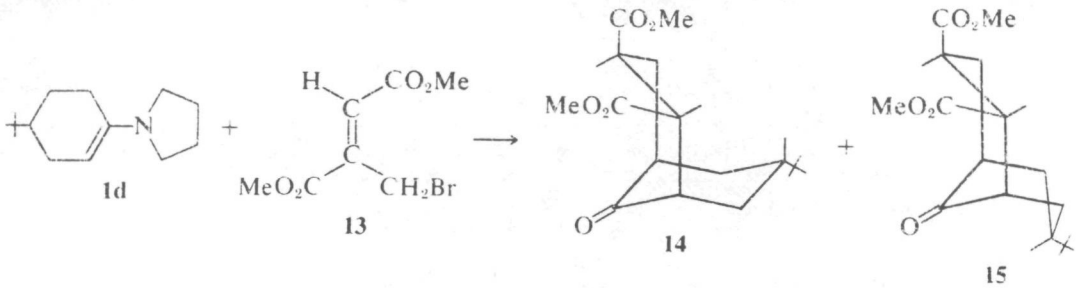
Lawton *et al.* illustrated their mechanism with the condensation of dimethyl γ-bromomesaconate (**13**) and the pyrrolidine enamine of 4-t-butylcyclohexanone (**1d**)[19] (Scheme 3).

These authors identified, by chemical means, the products to be dimethyl 7β-t-butyl-9-oxobicyclo[3.3.1]nonane-2β, 3α-dicarboxylate (**14**) and the corresponding 7α-t-Bu epimer (**15**) (**14**: **15** = 1:9). When repeating this reaction, we obtained two compounds in a ratio of about 5:1. The physical constants of the major isomer were the same as those described by Lawton *et al.*, but con-

*In contrast to Lawton *et al.*, we assume **9** to be in the double chair conformation. A PMR study of the model compound 3-isopropenyl-9-oxobicyclo[3.3.1]nonane showed that this compound is in the double-chair conformation too.



SCHEME 2.



1d 13 14 15

SCHEME 3.

trary to the assignment of these authors the structure of this product is actually **14**. This follows from the PMR spectrum, which shows singlets at δ 3·66 (6 H, 2-CO_2Me and 3-CO_2Me), and at δ 0·95 (9 H, t-Bu), a doublet of doublets at δ 3·18 (1 *H*, J = 12·0 Hz and J = 3·7 Hz, $H_{2\alpha}$), and a complex signal at δ 1·5–2·7 (10 H, other ring protons). The splitting pattern of the $H_{2\alpha}$-signal shows that the two CO_2Me groups are *trans* with respect to each other. Eu(DPM)$_3$ was added until the multiplets of H_1, $H_{2\alpha}$, $H_{3\beta}$, $H_{4\alpha}$, $H_{4\beta}$, and H_5 were separated. The signal of H_5 is a broad doublet (J = 10 Hz), which changed into a broad singlet upon irradiation of $H_{4\beta}$. Therefore the dihedral angle between H_5 and $H_{4\beta}$ will be near 0°, proving that the ring containing the CO_2Me groups is in the boat conformation. Since the couplings between H_5 and $H_{6\alpha}$ and $H_{6\beta}$ are small, the other ring is in the chair form. The signal of H_1 is a broad singlet, confirming that a chair-boat conformation is involved. This is only possible if the 7-t-Bu group is in the β-position, showing that the major isomer is **14**. With the aid of double resonance techniques the following proton-proton coupling constants were determined: $J_{2\alpha 1}$ = 3·7; $J_{2\alpha 3\beta}$ = 12·0; $J_{3\beta 4\alpha}$ = 12·0; $J_{3\beta 4\beta}$ = 5·0–5·5; $J_{4\beta 5}$ = 10; $J_{6\alpha 6\beta}$ = −12·0 Hz. All values are in agreement with the proposed configuration and conformation.

CONFORMATION OF THE ANNELATION PRODUCTS AND THEIR EPIMERISATION PRODUCTS

The conformations of the annelation products (**3** and **4**) and their epimers (**5** and **6**) were studied by means of PMR spectroscopy (100 MHz). Spectra with various amounts of the shift reagents Eu(DPM)$_3$ or Eu(FOD)$_3$[20–22] were recorded. From the spectra with optimal separation between the various multiplets the coupling constants were obtained by first-order analysis. No influence of the ratio added complex/substrate on the coupling constants could be detected. We therefore assume that in these cases the shift reagent has no significant influence on the coupling constants or on the geometry of the substrate.[23] Excellent straight lines were obtained, when the chemical shifts of the CO_2Me protons were plotted *vs* the chemical shifts of the various ring protons with increasing amounts of shift reagent.[1,24] The slope of these lines is dependent on the distance of the proton in question to the Eu^{3+}-ion which is coordinated to the 9-oxo function (and less strongly to the 3-CO_2Me group[24]). The signals were assigned by means of the splitting patterns, mutual decoupling experiments and the slopes mentioned. The coupling constants measured are given in Table 2.

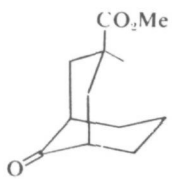
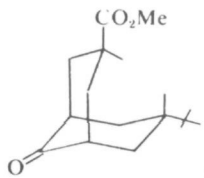
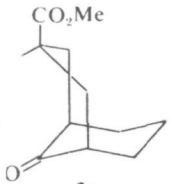
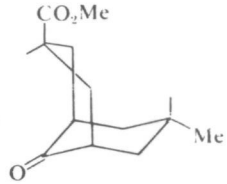
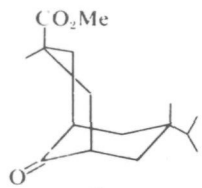
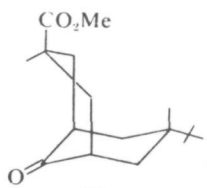
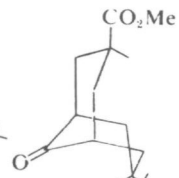
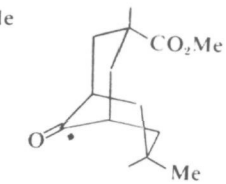
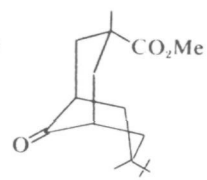
Methyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**5d**). The magnitude of the vicinal coupling constants in methyl 9-oxobicyclo-[3.3.1]nonane-3β-carboxylate (**5a**) and the corresponding 7β-t-Bu compound (**5d**) (Table 2) proves, as should be expected from literature data,[2–7] that these compounds adopt the double-chair conformation. A substantial contribution of a chair-boat conformation in **5a** can be excluded by comparison of the coupling constants of compounds **5a** and **5d**. The latter compound can be assumed, *a priori*, to exist in the double-chair conformation, since in the chair-boat conformation there would be a considerable flagpole interaction.

From the values of $J_{2\alpha 3}$ and $J_{2\beta 3}$ it can be seen that the cyclohexane ring carrying the CO_2Me group is distinctly flattened in **5a** and **5d**. The corresponding coupling constants in methyl *trans*-4-t-butylcyclohexanecarboxylate were found, with the aid of the same procedure, to be 3·7 and 12·0. About the same values have been obtained by Remijnse *et al.*[25] for t-butylcyclohexane and cyclohexane.

Assuming tetrahedral HCH angles, it can be calculated by means of the Karplus equation[26] that the dihedral angle between H_3 and $H_{2\alpha}$ is about 50°. This value was also calculated from the X-ray data of Brown *et al.*[3] for 1-*p*-bromobenzenesulphonoxymethyl-5-methylbicyclo[3.3.1]nonan-9-ol.

Methyl 7β-alkyl-9-oxobicyclo [3.3.1]*nonane-3α-carboxylates* (**3**). The coupling constants of the methyl 7β-alkyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylates (**3**) unambigiously prove that these compounds exist in the chair-boat conformation, with the ring with the 3α-CO_2Me in the boat form. Since there is no difference in coupling constants between **3a** and the corresponding 7β-alkyl derivatives (**3b-d**), the other chair-boat conformation can be ignored for **3a**. In compounds **3b-d** this conformation is unfavorable due to the flagpole interac-

Table 2. Coupling constants of 3- and 3,7-substituted 9-oxobicyclo[3.3.1]nonanes (±0·5Hz)

	 **5a**	 **5d**	 **3a**	 **3b**	 **3c**	 **3d**	 **6d**	 **4b**	 **4d**
$J_{12\alpha}$	<3	<3	<3	~2	<3	<3	3–4	<4	<4
$J_{12\beta}$	4·3	4·2	9	10	9·5	10	2–4	<5	<5
$J_{18\alpha}$	—	<3	<3	<3	2–3	2–3	—	<4	<4
$J_{18\beta}$	—	3	3	—	3	2·2	—	0·0	8–9
$J_{2\alpha 2\beta}$	−14·0	−14·0	−14·0	−14·0	−14·0	−14·0	−12·5	−15·5	~−13
$J_{2\alpha 3}$	5·2	5·5	12·5	12·7	13·0	12·5	3·7	<4	<4
$J_{2\beta 3}$	12·7	12·0	5·5	5·2	5·5	5·5	12·7	6·5	5–7
$J_{6\alpha 6\beta}$	—	−13·0	−13·0	—	−12·0	−12·0	—	−12·6	−12·0
$J_{6\alpha 7\alpha}$	—	3	3·9	—	—	3·2	—	—	—
$J_{6\alpha 7\beta}$	—	—	≤3	—	—	—	13·0	13·0	12·7
$J_{6\beta 7\alpha}$	—	13·0	14	—	13·0	13·2	—	—	—
$J_{6\beta 7\beta}$	—	—	≤3	—	—	—	4·2	~4	5·2
$J_{7\alpha 7\beta}$	—	—	−14·0	—	—	—	—	—	—

tion between the alkyl group and the 9-oxo function.

The magnitudes of the vicinal coupling constants in the ring holding the 3α-CO_2Me group differ from those expected for an ideal rigid boat cyclohexane ($J_{2\alpha3}$ = 13·0 Hz, $J_{2\beta3}$ = 3·6 Hz,[25] and $J_{12\beta}$ = 12–13 Hz[27]). Probably the boat is flattened at the 3-position.

The coupling constants of the protons in the chair ring have almost the same values as those in cyclohexanes,[25] showing that this ring has about the normal cyclohexane geometry.

Methyl 7α-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**6d**). Molecular models leave no doubt that the ring containing the 7α-t-Bu substituent should be in the boat conformation, whereas extrapolation of previous results shows that the other ring has to possess the chair conformation. This is confirmed by the PMR data. Furthermore the coupling constants show that the chair part has about the ideal geometry. The boat ring is less flattened than the boat ring in compounds **3**. Apparently non-bonding interactions between the t-Bu group and the 6- and 8-protons oppose flattening[25].*

Methyl 7α-alkyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylates* (**4**). The coupling constants of **4b** and **4d** in the presence of Eu(FOD)$_3$ (Table 2) show that these compounds exist predominantly in the chair-boat conformation with the ring containing the alkyl group in the boat form. Since we were not able to assign the signals for $H_{2\alpha}$ and $H_{2\beta}$ with certainty, the high value of one of the couplings J_{23} can be explained either by a strong flattening of the boat ring or by a contribution of other conformations *e.g.* the double-boat and in **4b** the other chair-boat.

When plotting the chemical shifts of the various protons *vs* the chemical shifts of the CO_2Me-protons at different substrate/Eu(FOD)$_3$ ratios the usual straight lines were not obtained. Therefore it is doubtful whether the shift reagent has no influence on the conformations in these cases.

The IR spectrum of **4d** showing strong absorption at 1452 cm^{-1} supports a major role of the chair-boat conformation. This band has been shown to be absent in cyclohexane derivatives which occur in a non-chair conformation.[28] Moreover the pK_a* of the corresponding carboxylic acid (Table 3) is rather high compared with the pK_a*'s of the acids corresponding to **3b** and **3d**.† This is in agreement with a contribution of the chair-boat, since in this conformation steric hindrance of the carboxylate anion will cause acid weakening.[29]

Table 3. pK_a*-Values of 7 - R - 9 - oxobicyclo [3.3.1] nonane - 3α - carboxylic acids in 50% ethanol–water at 25°

7—R	pK_a*
H	5·43
β-Me	5·38
β-i-Pr	5·43
β-t-Bu	5·42
α-t-Bu	5·78

Molecular models leave no doubt that in **4d** the ring with the 7-t-Bu group is in the boat conformation. Appleton *et al.* have estimated the enthalpy difference between double-chair and chair-boat conformers in bicyclo[3.3.1]nonane, apart from transannular ring strain, to be *ca* 5·7 kcal/mole.[11] We consider this to be a good approximation of the enthalpy difference between chair-boat and double-boat. In the 9-oxo derivatives the enthalpy of the double-boat conformer will be lowered by *ca* 1·1 kcal/mole,[30] since the flagpole interaction is absent here. Introduction of a 3α-CO_2Me group would give, according to the estimations of Appleton *et al.*[11] an increment of *ca* 3·5 kcal/mole of the enthalpy of the chair-boat conformer. Therefore the enthalpy difference between the chair-boat and the double-boat conformation in **4d** should be *ca* 1·1 kcal/mole (5·7–1·1–3·5) in favor of the former conformer.‡ In agreement with the experimental data this rough estimate shows that a slight preference for the chair-boat conformation in **4d** might be expected.

EXPERIMENTAL

The PMR spectra were obtained with a Varian XL-100-15 NMR spectrometer system equipped with a V-4415 universal probe and a V-4421 gyrocode decoupler unit.

Spectra were recorded at 39° in CCl_4 soln. Chemical shifts are given in ppm (δ) relative to TMS. CCl_4 was stored over molecular sieve 4A. The lanthanide shift reagents Eu(DPM)$_3$ and Eu(FOD)$_3$ were obtained from Merck and sublimed at 180°/0·3 mm before use.

Elemental analyses were performed by Messrs. M. van Leeuwen and M. A. Hoefnagel and were correct within 0·2% (absolute).

Annelation reactions, general procedure. To a stirred boiling soln of 0·052 mole freshly distilled pyrrolidine enamine of the cyclohexanone and 5·05 g (0·05 mole) Et_3N in 60 ml MeCN (dried over molecular sieve 3A) was added dropwise in 1 hr a soln of 13·00 g (0·050 mole) methyl β,β′-dibromoisobutyrate in 40 ml MeCN. Then the mixture was boiled under reflux for 2 hr. After addition of

*X-ray analysis even showed puckering of the boat ring in 9-benzoyl-3α-bromo-9-azabicyclo [3.3.1] nonane-2-one.[15]

†The pK_a*-value of the monocyclic parent compound 4-oxocyclohexanecarboxylic acid was found to be 5·41 suggesting an important contribution of boat conformations to the conformational equilibrium of this compound. This is supported by the magnitudes of the coupling constants measured in methyl 3, 3, 5, 5 - tetradeutero - 4 - oxocyclohexanecarboxylate (J_{12} = 9·32 Hz, $J_{12'}$ = 4·20 Hz, and $J_{22'}$ = −13·8 Hz).

‡Since twisting in the boat-rings creates a serious 2,6-interaction, it may be doubted whether the double-twist conformation is populated to any extent.

5 ml 5% HOAc the mixture was boiled for another hour. The resulting soln was diluted with 125 ml H_2O and extracted with five 60 ml portions ether. The ethereal layers were washed with three 60 ml portions 2N HCl, two 60 ml portions sat $NaHCO_3$ aq, and two 60 ml portions sat NaCl aq, and dried over $MgSO_4$. The solvents were evaporated under vacuum yielding the crude ester mixture.

The composition of the products was determined *via* integration of the CO_2Me signals in the PMR spectra and/or by GLC analysis.

It was observed that longer reaction times (*cf* Ref 20) did not influence the yield or the composition of the products.

Epimerisation experiments, general procedure. To a soln of 75 mg Na in 100 ml MeOH was added 1 g ester. After boiling for 6 hr the mixture was poured onto 100 ml 1N HCl. The dispersion obtained was extracted several times with ether. The ether soln was washed with water and dried over $MgSO_4$. After filtration the solvent was evaporated off and the ester mixture was analysed by GLC and PMR.

Methyl 9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**3a**), b.p. 165–166°/17 mm (*cf.* Ref 20); m.p. 41–42°; PMR: δ 3·62 (3H, s); 1·4–2·6 (13H). The corresponding acid was obtained by hydrolysis of **3a** in 2N KOH; m.p. 134–135° from light petroleum-EtOAc.

Methyl 7β-methyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**3b**). The crude annelation product of 4-methylcyclohexanone (9·90 g) was hydrolysed by boiling with 2N KOH to the acid; m.p. 102·5–103° (from light petroleum-EtOAc). Esterification with CH_2N_2 yielded the Me ester; PMR: δ 3·67 (3H, s), 1·00 (3H, d: J = 6·5 Hz), 1·2–2·8 (12H).

Methyl 7α-methyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**4b**). From the mother liquor of the recrystallisation of **3b** the solvent was evaporated off and the residue was recrystallised from light petroleum-EtOAc and then esterified with CH_2N_2. After evaporation of the solvent the residue was recrystallised from light petroleum to yield pure **4b**; m.p. 56·5–57·5°; PMR: δ 3·74 (3H, s), 0·86 (3H, d: J = 6 Hz), 1·2–2·8 (12H).

Methyl 7β-isopropyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**3c**). This ester was obtained analogously to compound **3b**, m.p. acid 122–123°, Ester; PMR: δ 3·60 (3H, s), 0·93 (6H, d: J = 7 Hz) 0·9–3·0 (13H).

Methyl 7α-isopropyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**4c**). The mother liquor of the recrystallisation of **3c** was recrystallised from light petroleum-EtOAc and sublimed to pure 7α-isopropyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylic acid; m.p. 91–93°. Esterification with CH_2N_2 yielded the Me ester **4c**; PMR: δ 3·70 (3H, s), 0·82 (6H, d: J = 7 Hz), 1·0–2·7 (13H).

Methyl 7α-t-butyl-9-oxobicyclo[3.3.1]*nonane-3α-carboxylate* (**4d**). The crude annelation product of 4-t-butylcyclohexanone was distilled (b.p. 128–130°/0·5 mm) and then recrystallised several times from light petroleum and sublimed to pure **4d**; m.p. 81·5–82°; PMR: δ 3·72 (3H, s), 0·83 (9H, s), 1·11 (1H, t of t: J = 12·7 and 5·0 Hz), 1·6–2·7 (11H). The corresponding acid was obtained by KOH hydrolysis of **4d**; m.p. 113–113·5° (from light petroleum).

Methyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-3α carboxylate* (**3d**). The mother liquor of the recrystallisation of **4d** was hydrolysed with 2N KOH as described. The mixture of acids obtained was recrystallised several times from light petroleum-EtOAc to yield pure 7β-t-butyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylic acid; m.p. 180·5–181°. This acid was esterified with CH_2N_2 to **3d**; PMR: δ 3·63 (3H, s), 0·93 (9H, s), 1·4–2·5 (12H).

Methyl 9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**5a**). Compound **3a** was epimerised according to the general procedure. The ester obtained was hydrolysed with 2N KOH as described. The acid was recrystallised from light petroleum-EtOAc and sublimed; m.p. 152–152·5°. Esterification of this acid with CH_2N_2 yielded pure **5a**, PMR: δ 3·63 (3H, s), 3·36 (1H, m), 2·39 (2H), 1·9–2·3 (10H).

Methyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**5d**). This compound was synthesised by epimerisation of **3d**, according to the general procedure; m.p. 96·5–97° (from light petroleum); PMR: δ 3·63 (3H, s), 0·90 (9H, s), 3·39 (1H, m), 2·36 (2H), 1·6–2·6 (9H).

Methyl 7α-t-butyl-9-oxobicyclo[3.3.1]*nonane-3β-carboxylate* (**6d**). Ester **4d** was epimerised according to the general procedure. The epimer was recrystallised from light petroleum and sublimed; m.p. 95–95·5°; PMR: δ 3·64 (3H, s), 0·93 (9H, s), 3·08 (1H, m), 1·12 (1H, m), 1·5–2·6 (10H).

Dimethyl 7β-t-butyl-9-oxobicyclo[3.3.1]*nonane-2α,-3α-dicarboxylate* (**14**). The crude annelation product of the pyrrolidine enamine of 4-t-butylcyclohexanone and dimethyl γ-bromomesaconate was titruated with ether. The solid diester was recrystallised from light petroleum-EtOAc; m.p. 128·5–129°; PMR: δ 3·66 (6H, s), 0·95 (9H, s), 3·18 (1H, d of d: J = 12·0 and 3·7 Hz), 1·5–2·7 (10H).

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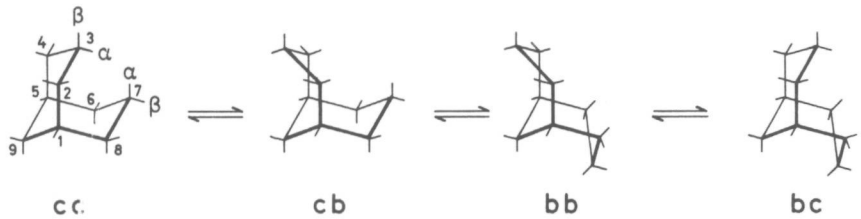
CHAPTER 8

SYNTHESIS AND CONFORMATION OF BICYCLO[3.3.1]NONANE-3α,7α-DICARBOXYLIC ACID, ITS DIMETHYL ESTER AND SOME OTHER 3,7-DISUBSTITUTED BICYCLO[3.3.1]NONANES; ADAMANTANE AS AN INTEGRATED HOLDING SYSTEM *

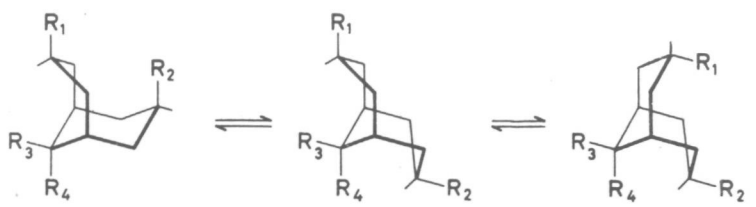
INTRODUCTION

Bicyclo[3.3.1]nonane as well as its 3β(7β)-substituted derivatives have been shown to exist in a somewhat flattened double-chair conformation (**cc**).[2] Severe transannular 3,7-interaction and 1,3-diaxial interactions destabilize the **cc** conformation in 3α(7α)-substituted bicyclo [3.3.1]nonanes. Consequently these compounds prefer a rigid chair-boat conformation (**cb**, **bc**).[2]



The enthalpy difference between the bicyclo[3.3.1]-nonane **cb** conformer and the double-boat conformer (**bb**) has been calculated to be 5·7 kcal/mole.[3] Therefore the conformational preference of 3α,7α-disubstituted bicyclo[3.3.1]nonanes will depend on the magnitude of the 1,3-diaxial interactions. The **bb** conformation will play a more important role when the bulk of the substituents increases; e.g. the diol **24** exists in the **bb** conformation,[4] whereas compound **13e** is in the **cb** conformation, with the ring containing the CO_2Me function in the boat.[1] In compounds **25** the population of the **cb** and **bb** conformers seems to depend on the size of the alkyl group.[5] The symmetrically substituted compounds bicyclo [3.3.1]nonane - 3α,7α - dicarboxylic acid (**4b**) and its dimethyl ester (**5b**) are very interesting from a conformational point of view. A previous ^1H NMR investigation[4] indicated that these compounds exist as an equilibrium of conformations, with an important contribution of the **cb** and **bc** conformations, possibly with flattening of the rings.

The present study deals with a comparison of ^1H NMR and ^{13}C NMR spectra of **4b** and **5b** with those of some other 3,7-disubstituted bicyclo[3.3.1]nonanes in order to verify these assumptions. As model compounds we used bicyclo[3.3.1]nonane derivatives constrained in a single conformation by building one of the rings into an adamantane skeleton, thus ensuring chair geometry of this ring, or by suitable substitution at the 3(7)-position.



4b $R_1 = R_2 = CO_2H$; $R_3 = R_4 = H$ **13e** $R_1 = CO_2Me$; $R_2 = t\text{-Bu}$; $R_3, R_4 = O$

5b $R_1 = R_2 = CO_2Me$; $R_3 = R_4 = H$ **25** $R_1 = OH$; $R_2 = CH_2NR_xR_y$; $R_3 = R_4 = H$

24 $R_1 = R_2 = CMe_2OH$; $R_3 = R_4 = H$

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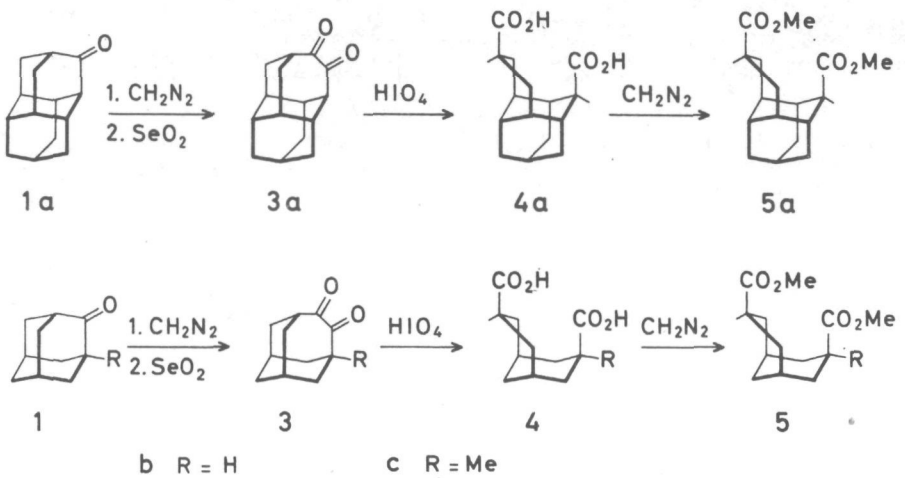
* A reprint of J.A. Peters, J.M. van der Toorn and H. van Bekkum, *Tetrahedron* 31, 2273 (1975).

Moreover a comparison was made between the 3,7-disubstituted bicyclo[3.3.1]nonanes and the previously studied 9-oxo derivatives.[1]

Synthesis

The dicarboxylic acids **4** were synthesized (Scheme 1) by means of a two step oxidative cleavage of the corresponding homoadamantanones,[4] which were obtained by ring enlargement of the adamantanones (**1**) with CH_2N_2.[7] Compounds **4** were converted into the corresponding dimethyl esters (**5**) with CH_2N_2.

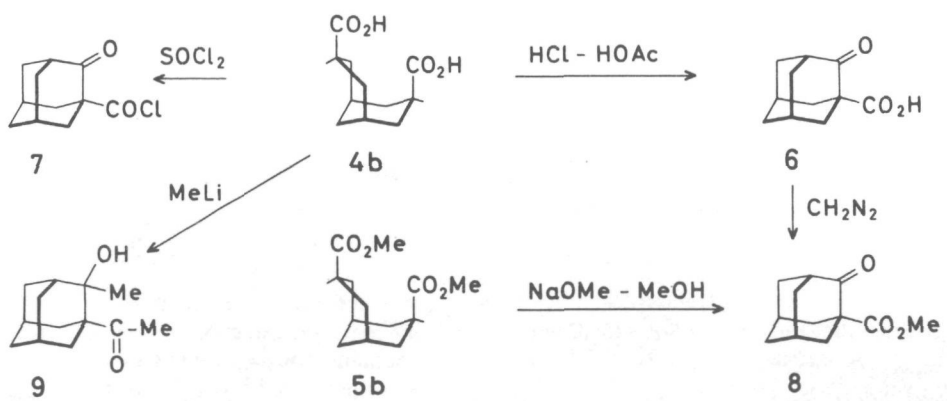
All traditional procedures to reduce the 9-oxo function in methyl 7 - alkyl - 9 - oxobicyclo[3.3.1]nonane - 3α - carboxylates (**13**)[1] failed, due to epimerisations and rearrangements. Therefore, after protection of the 9-oxo function as dimethyl acetal (**14**),[12] the 3α-CO_2Me function was reduced with LAH into the corresponding alcohol (**15**). Then the 9-oxo function was reduced by a Huang–Minlon procedure. Oxidation of the hydroxymethyl group with chromic acid in acetone, followed by esterification with CH_2N_2 afforded the methyl esters **19** (Scheme 4). It was observed that the oxidation of the



Scheme 1.

The configuration of compounds **4** and **5** allows facile ring closure in acidic as well as in alkaline medium. In Scheme 2 some examples are outlined. These procedures may serve as versatile synthetic routes towards 1,2-disubstituted adamantanes[8,9] and diamantanes.

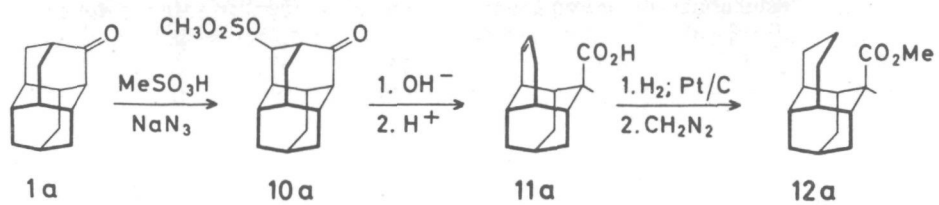
7β-alkyl derivatives (**16b, c**) produced almost quantitatively the acids **17b, c**, whereas for the 7α-alkyl derivatives (**16d,e**) the main product was the corresponding 3-oxo compound (**18**). The acid **17d** was obtained in low yield by oxidation of **16d** by O_2 with Pt as the catalyst.[13]



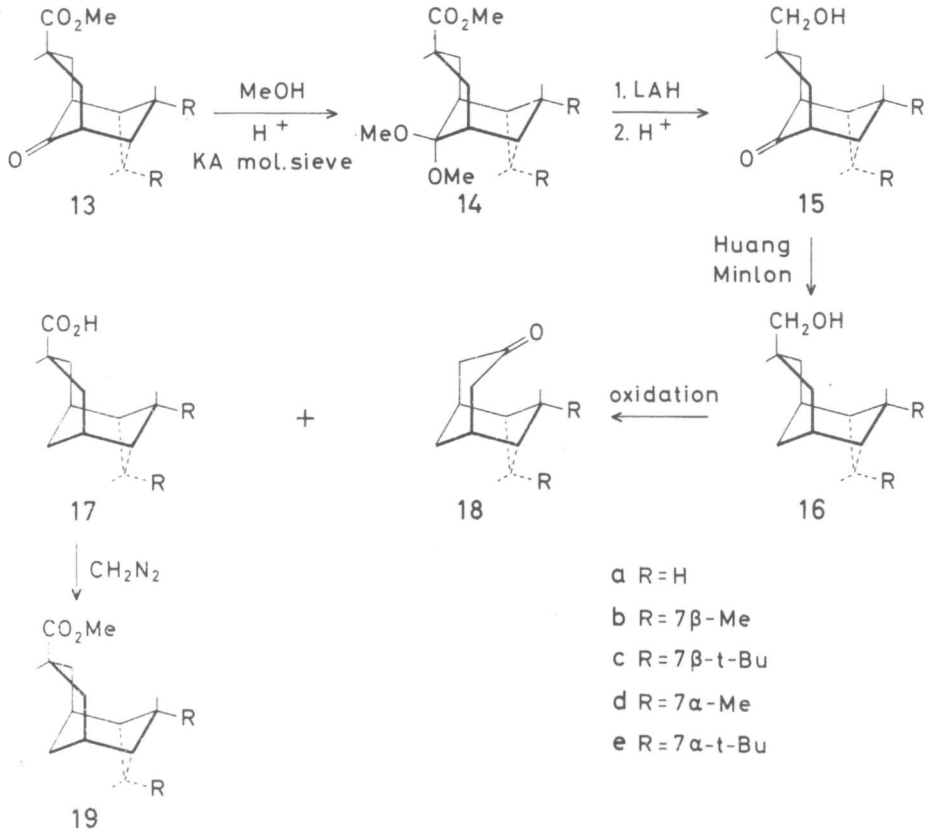
Scheme 2.

Treatment of diamantanone (**1a**) or adamantanone (**1b**) with NaN_3 in $MeSO_3H$ according to Sasaki *et al.*[10,11] yielded methanesulfonates (**10**), which, upon treatment with alkali, followed by hydrogenation and esterification gave the methyl esters **12**. In Scheme 3 this reaction sequence is outlined for compound **1a**.

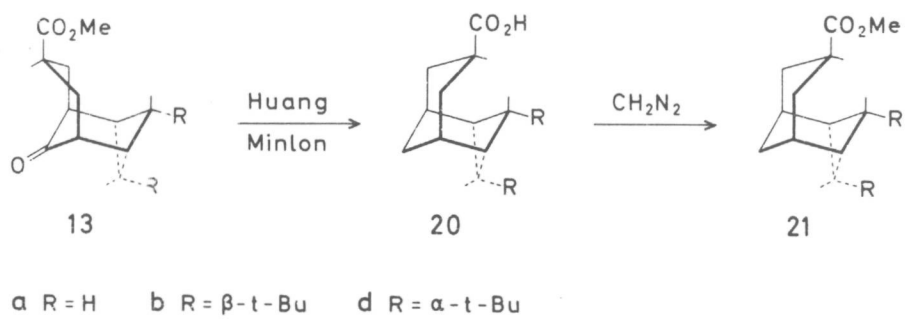
The methyl esters **21** were synthesized (Scheme 5) by means of Huang–Minlon reduction of the corresponding 9-oxo derivatives **13**, followed by esterification with CH_2N_2. The strong alkaline reaction medium caused epimerisation of the 3α-derivatives into the more stable 3β-compounds.



Scheme 3.



Scheme 4.



Scheme 5.

Reaction of compounds **19a**, **21a** and **5b** with MeMgCl gave the corresponding tertiary alcohols (**23**, **22** and **24**).

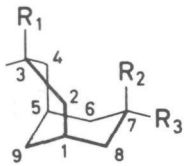
Conformational analysis

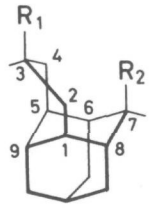
^1H NMR spectroscopy. The 100 MHz ^1H NMR spectrum of compound **5b** exhibits a sharp singlet for the protons of the two CO_2Me groups, a quintet for the 3α- and 7α-protons, a triplet for the 9-protons (J = 3·0 Hz) and a complex signal for the other ring protons. The spectrum of the corresponding dicarboxylic acid **4b** is analogous to that of **5b**. At low temperatures (−90°) substantial line broadening occurs, showing that this compound exists as an equilibrium of conformations.

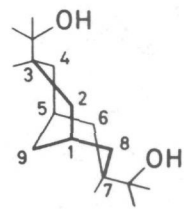
Spectra of **5b** were recorded with increasing amounts of $Eu(dpm)_3$ and $Eu(fod)_3$ until optimal separation between the various multiplets was achieved. From these spectra the coupling constants were derived by first-order analysis. The signals were assigned by the relative induced shifts, the splitting patterns, and by using double resonance techniques. These coupling constants were independent of the amount of shift reagent added, showing that the complexation had no observable influence on the conformation and geometry of **5b**. The coupling constants of **5b** and some related 3- and 3,7-substituted bicyclo[3.3.1]nonanes are listed in Table 1.

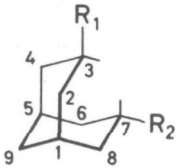
As should be expected,[1,14] the coupling constants of methyl bicyclo[3.3.1]nonane - 3α - carboxylate (**12b**) and its 7β-methyl (**19b**) and 7β - t - butyl (**19c**) derivative unambiguously prove that these compounds exist in the **cb** conformation with the ring containing the 3α-CO_2Me in the boat. Looking into more detail $J_{2\beta3\beta}$ differs from the value, that should be expected for an ideal rigid boat conformation (3·5–4 Hz). With the aid of the same procedure the corresponding coupling constant in methyl *trans* - 4 - t - butylcyclohexanecarboxylate was found to be 3·7 Hz. Apparently the boat ring in compounds **12b**, **19b** and **19c** is strongly flattened. Assuming that the HCH-angles retain the regular tetrahedral value, it can be calculated from $J_{2\beta3\beta}$ and $J_{2\alpha3\beta}$, by means of the semi-empirical version of the Pachler equations[15] as well as the Karplus equation (DAERM method[16]), that the dihedral angle between $H_{2\beta}$ and $H_{3\beta}$ is 47–50°. The

Table 1. Proton–proton coupling constants of 3- and 3,7-disubstituted bicyclo[3.3.1]nonanes (Hz)[b]









Compound No.	**5b**	**12b**	**19b**	**19c**	**5c**	**19d**	**18e**	**23**	**5a**	**12a**	**24**	**21a**	**21b**	**22**
R_1	CO_2Me	CO_2Me	CO_2Me	CO_2Me	CO_2Me	Me	t-Bu	CMe_2OH	CO_2Me	H		CO_2Me	CO_2Me	CMe_2OH
R_2	CO_2Me	H	H	H	CO_2Me	CO_2Me	} = 0	H	CO_2Me	CO_2Me		H	t-Bu	H
R_3	H	H	Me	t-Bu	Me	H		H						
$J_{12\alpha}$	≤3	1–2	<4	≤6	2·3		<4	1·5	2·5	<4	2·0	2	<3	<3
$J_{12\beta}$	8·0	10·2	10·5	11·0	11·0		~11	11·0	11·0		10·0	4·0	4·5	4·0
$J_{2\alpha2\beta}$	−14·0	−14·0	−14·0	−14·0	−14·0	~−12	−13·4	−14·0	−14·0	−12·9	−12·0	−14·0	−14·0	−13·3
$J_{2\alpha3\alpha}$	—	—	—	—	—	—	—	—	—	6·0	—	5·3–6·0	5·7	5·5
$J_{2\alpha3\beta}$	7·3	12·5	12·5	12·0	12·5	~12	13·1	13·3	12·0–13·0	<4	12·0	—	—	—
$J_{2\beta3\alpha}$	—	—	—	—	—	—	—	—	—	12·0	—	12·6	12·4	12·7
$J_{2\beta3\beta}$	6·8	6·0	6·0	6·3	6·0		4·7	5·6	6·4	~8	6·0	—	—	—
$J_{3\alpha3\beta}$	—	—	—	—	—	—	—	—	—	−14·5	—	—	—	—
$J_{18\alpha}$	≤3				2·3	<4	<3		≤4		2·0			
$J_{18\beta}$	8·0		2·3		4·0	~5	4·7		—	—	10·0			
J_{19syn}[a]	3·0				3·7		<4		≤4		2·5			2·5
J_{19anti}[a]	3·0				2·5				≤4	—	2·5			2·5
$J_{6\alpha6\beta}$	−14·0		−14·0	−12·6	−14·0	−13·5	−16·0		—	—	−12·0			~−13
$J_{6\alpha7\alpha}$	—			3·7	—	—	—	4·2	—	—	—		—	5–6
$J_{6\alpha7\beta}$	7·3		—	—	—	<3–4	—		≤3		12·0			
$J_{6\beta7\alpha}$	—			12·3	—	—	—		—	—	—			
$J_{6\beta7\beta}$	6·8		—	—	—	7	—	~12·5	—	—	6·0		—	
$J_{7\alpha7\beta}$	—		—	—	—	—	—	~−12·5	—	—	—		—	
$J_{99'}$	—				−13·0		−13·4		—	—	—			
$J_{9syn2\alpha}$					1·5–2									

[a] syn and anti with respect to the 3-position.
[b] In order to make comparison simple, an unusual numbering is used.

flattening is somewhat more pronounced than in the corresponding 9-oxo derivatives.[1] There may be two reasons for flattening: the $H_{3\beta}$–H_9 repulsion and the eclipsing between H_1 and $H_{2\beta}$ and between H_5 and $H_{4\beta}$. When the CO_2Me group is replaced by a bulkier group as in compounds **18e** and **23** the flattening is diminished. Interaction between the bulky group and $H_{2\alpha}$ and $H_{4\alpha}$ possibly opposes flattening.

The dimethyl esters **5a** and **5c** are closely related to the problem under study. These compounds are constrained in a single **cb** conformation: in **5a** one of the rings is part of the rigid all-chair adamantane skeleton, whereas for **5c** the **bb** and the other **cb** conformation can be excluded because of strong destabilization by severe Me-9H repulsions. The coupling constants of the boat part of these systems are about the same as those for compounds **12b**, **19b** and **19c**. Apparently small changes in the geometry of the chair part of the molecule have no substantial influence on the flattening of the boat.

Compound **12a** is interesting: the coupling constants show that here, in spite of a large $H_{3\alpha}$-CO_2Me interaction, a flattened chair conformation is preferred.

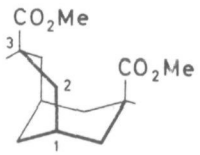
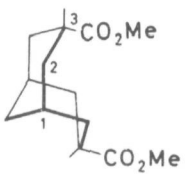
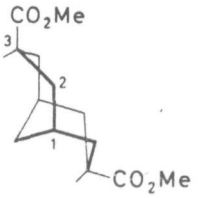
The coupling constants of the boat parts of compounds **12b**, **19b**, **19c**, **5a** and **5c** allow an estimation of the coupling constants of the boat part of the **cb** conformers of dimethyl bicyclo[3.3.1]nonane - $3\alpha,7\alpha$ - dicarboxylate (**5d**) (Table 2).

Diol **24** is the sole compound disposible, which doubtless exists in the **bb** conformation.[1] It might be expected that with a less bulky substituent (CO_2Me) at the 3α- and 7α-position, there is somewhat more flattening.†

In Table 2 estimated coupling constants of conformations of dimethyl bicyclo[3.3.1]nonane - $3\alpha,7\alpha$ - dicarboxylate (**5b**) are given. The estimated data for a rapid interconversion of the two (identical) **cb** conformations are in excellent agreement with the experimental values. A substantial contribution of the **bb** conformation can be excluded, since then $J_{2\alpha 3\beta}$ should be higher.

The lanthanide induced shift (LIS) parameters support this conclusion. In general the induced shifts are plotted versus the molar ratio shift reagent/substrate. We prefer, however, plotting the chemical shifts of the various protons versus the induced shift of one of the signals (e.g. the CO_2Me signal) with increasing amounts of shift reagent. Then for monofunctional as well as for bifunctional compounds excellent straight lines are generally obtained, which can provide-by means of extrapolation—the chemical shifts in the spectrum without shift reagent (δ_0). The slopes of these lines are dependent on the position of the proton in question *vis à vis* the coordinated Eu(III)-ion.[17] In Table 3 the slopes of these lines for several bicyclo[3.3.1]nonanes are given. For the dimethyl ester **5b** the influence of the shift reagent on the 2α-protons is relatively large, showing that the distance of

Table 2. The proton–proton coupling constants of dimethyl bicyclo[3.3.1]nonane - $3\alpha,7\alpha$ - dicarboxylate

	Estimated values				Experimental values
	 A	 B	A ⇌ B		
$J_{12\alpha}$	<2·5	<4	<3	<2·5	≤3
$J_{12\beta}$	11·0	5	8·0	10–11	8·0
$J_{2\alpha 2\beta}$	−14·0	−14·0	−14·0	−12–−14	−14·0
$J_{2\alpha 3\beta}$	12·5	<3	6·2–7·2	11·5–12·5	7·3
$J_{2\beta 3\beta}$	6·0–6·4	7·0	6·5–6·7	6·0–6·4	6·8

An estimation of the coupling constants in the chair part of these conformations can be made from the appropriate coupling constants of compound **19d** (and in part **5c**). From the low value of $J_{1\beta\beta}$ and $J_{6\alpha 7\beta}$ and from the correspondence of the coupling constants with those of compound **18e** (which doubtless exists in the **cb** conformation), it may be concluded that **19d** is indeed predominantly in a **cb** conformation with the CO_2Me group in the chair. The value of $J_{6\beta 7\beta}$ suggests strong flattening of the chair, obviously due to the 1,3-diaxial interactions of the CO_2Me group with the other ring.

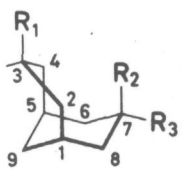
†Comparison of the coupling constants of **24**, **23**, **12b**, **19b**, **5c** and **5a** shows that the influence of this effect on the coupling constants is rather small. From a comparison of the rigid **cb 23** with the flexible **bb 24**, it may be concluded that also twisting (if present) should have rather small effects on the coupling constants. It should be noted that twisting affords a relief of $H_{3\alpha}$-H_9-strain, and a decrease of eclipsing, but on the other hand it introduces a severe interaction between $H_{2\alpha}$ and $H_{6\alpha}$ and between $H_{4\alpha}$ and $H_{8\alpha}$.

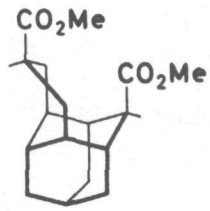
the Eu(III)-ion to these protons is rather small, especially compared to the 2β- and 3β-protons. This indicates that there has to be an important contribution of **cb** conformations (*cf.* compounds **19c**, **5c**, **5a** and **19d**).

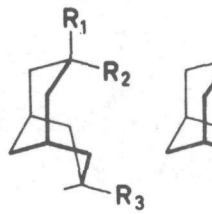
If the influence of the 7β-Me group is neglected, compound **5c** may be considered as a model for the **cb**'s in the conformational equilibrium of **5b**. The chemical shifts of two identical **cb** conformations in rapid interconversion can be estimated by averaging the chemical shifts of the corresponding protons in the chair and boat part of compound **5c** with increasing amounts of $Eu(dpm)_3$. These average chemical shifts were plotted versus the average chemical shifts of the 3- and 7-CO_2Me protons. Excellent straight lines were obtained. In Table 4 the slopes of these lines and the extrapolated (average) chemical shifts (δ_0) in the spectrum without $Eu(dpm)_3$ are given. The close agreement with the corresponding LIS-parameters of **5b** shows again that this compound exists predominantly in two rapidly interconverting **cb** conformations.

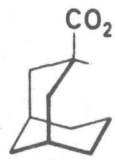
[13]*C NMR spectroscopy.* Recent results suggest that the

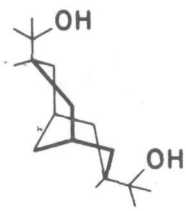
Table 3. Slopes of the lines of the chemical shifts of the various protons of 3(7)-substituted bicyclo[3.3.1]nonanes versus the induced shift of the signal of the 3-substituent with increasing amounts $Eu(fod)_3$





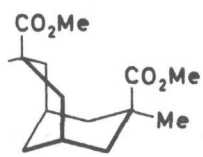




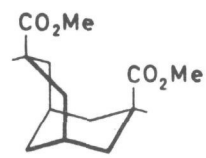


Compound No.	**5b**	**19c**	**5c**	**23**	**5a**	**19d**	**21d**	**20a**	**24**
R_1	CO_2Me	CO_2Me	CO_2Me	CMe_2OH		H	CO_2Me		
R_2	CO_2Me	H	CO_2Me	H		CO_2Me	H		
R_3	H	t-Bu	Me	H		Me	t-Bu		
H_1	0·51	0·22	0·40	0·17	0·31				0·39
$H_{2\alpha}$	1·34	0·80	2·04	0·68	1·98	0·94	0·79	1·00	0·90
$H_{2\beta}$	0·61	0·67	0·80	0·68	0·70	0·50	0·92	0·66	0·77
$H_{3\alpha}$	—	—	—	—	—	—	1·04	1·81	—
$H_{3\beta}$	1·16	1·09	1·31	0·99	1·00	1·19	—	—	1·10
$H_{6\alpha}$	1·34	0·18	0·71		0·71	0·81			0·90
$H_{6\beta}$	0·61		0·44		—				0·77
$H_{7\alpha}$	—	0·45	—	0·24	—	—	—	0·26	—
$H_{7\beta}$	1·16	—	—	0·20	1·00				1·10
H_{9syn}	0·38		0·35		0·43				0·36
H_{9anti}	0·38		0·38		—				0·36

Table 4. Comparison of LIS-parameters and extrapolated chemical shifts for compounds **5c** and **5b**



5c

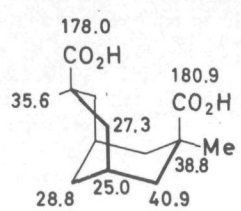


5b

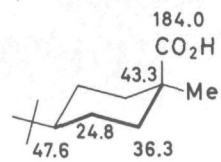
X	Y	$\Delta\delta_X+\Delta\delta_Y/\Delta\delta_{3\text{-}CO_2Me}+\Delta\delta_{7\text{-}CO_2Me}$	$\delta^\circ_X+\delta^\circ_Y/2$	$\Delta\delta_{X,Y}/\Delta\delta_{CO_2Me}$	$\delta^\circ_{X,Y}$
1	1	0.45	2.05	0.43	2.07
2 α	6 α	1.35	2.12	1.29	2.15
2 β	6 β	0.77	1.57	0.69	1.90
9syn	9anti	0.41	1.39	0.36	1.47

chemical shift of ^{13}C in a cyclohexane chair and boat conformation differs significantly.[18] A model compound for the **cb** conformation in the conformational equilibrium of **4b** is the dicarboxylic acid **4c** (Fig. 1). Supposing additivity, the influence of the methyl group on the ^{13}C chemical shifts can be computed by comparison of **26**[19] and **27**.[20]

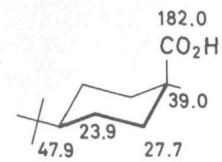
From these values and from the ^{13}C chemical shifts of **4c**, the ^{13}C chemical shifts of a **cb** conformation of **4b** were calculated. The averages of the corresponding chemical shifts for the chair- and boat-part represent calculated δ-values for a rapid interconversion of the two **cb** conformations. As shown in Table 5 excellent agreement exists with the experimental ^{13}C chemical shifts.



4 c



26



27

Fig. 1. ^{13}C chemical shifts (δ relative to TMS) of some model compounds ($CDCl_3$–DMSO-d_6 solution at 35°).

Table 5. ^{13}C chemical shifts for compound **4b** (ppm relative to TMS)

Carbon atom	1	2	3	9
Calculated	24·1	29·8	35·1	29·0
Experimental	24·0	29·8	34·7	28·5

CONCLUSIONS

The ^1H NMR, LIS- and ^{13}C NMR-data provide strong evidence that bicyclo[3.3.1]nonane - 3α,7α - dicarboxylic acid and its dimethyl ester exist predominantly as two rapidly interconverting **cb** conformers. From a comparison of the vicinal HH-coupling constants it can be concluded that both the chair- and the boat-part of these **cb** conformers are distinctly flattened.

EXPERIMENTAL

The 60 MHz ^1H NMR spectra were recorded on a Varian T-60 or a Varian A-60 apparatus. The 100 MHz ^1H NMR spectra were obtained with a Varian XL-100-15 NMR spectrometer system, equipped with a V-4415 universal probe, in the CW-mode and the 25·2 MHz ^{13}C NMR spectra with the same apparatus in the FT-mode. The ^{13}C NMR peaks were assigned by off-resonance decoupling and by the chemical shifts. The spectra were recorded at 39°. Chemical shifts of both the ^1H- and ^{13}C-resonances are given in ppm (δ) relative to TMS.

The Lanthanide shift reagents Eu(dpm)$_3$ and Eu(fod)$_3$ were obtained from Merck.

The mass spectra were recorded by Messrs B. van de Graaf, P. J. W. Schuijl and H. M. A. Buurmans with a Varian-MAT SM-1 spectrometer at 70 eV using a direct insertion probe.

Elemental analysis were performed by Messrs M. van Leeuwen, M. A. Hoefnagel and H. M. A. Buurmans and were correct within 0·2% (absolute).

Ring enlargements. According to the procedure of Black and Gill,[7] **1a**,[21,22] **1b** and **1c**[23] were converted with CH_2N_2 and BF_3 as the catalyst into the corresponding homoadamantanones (**2**). For **2a**[24] and **2c** a mixture of the two structural isomers was obtained. The crude products, which had a GLC purity of >95%, were used for the next reaction step without further purification.

SeO_2-*Oxidations.* The crude product of the preceding reaction step (0·08 mole) was boiled with 9·85 g (0·09 mole SeO_2) in 45 ml dioxane and 1·9 ml H_2O for 6 hr. After filtration of the selenium comps, the solvents were evaporated off, yielding almost quantitatively **3a**, **3b**[6] and **3c**, respectively. These compounds were used without further purification.

HIO_4-*Oxidations.* The crude **3** was heated at 70° with 31 g (0·14 mole) $HIO_4 . 2H_2O$ in 260 ml dioxane–H_2O (3:1) for 45 hr. Then most of the solvent was evaporated *in vacuo*. The residue was dissolved in 100 ml EtOAc. The soln obtained was washed with a sat thiosulfate soln (4 × 100 ml) and then extracted with 2N KOH (4 × 80 ml). The KOH soln was washed with hexane (2 × 80 ml) and then acidified with 12N HCl. The dispersion obtained was extracted with EtOAc (5 × 80 ml). The EtOAc soln was washed with H_2O (2 × 80 ml) and dried over $MgSO_4$. After evaporation of the solvent chromatographically pure **4** was obtained. Further purification was achieved by recrystallisation and sublimation *in vacuo*. When the reaction was performed starting from pure **1b**, the yield of **4b** was 85%.

The dicarboxylic acids were converted into the corresponding dimethyl esters with CH_2N_2. *Decahydro - 1,5,3 - [1,2,3] - propanetriylnaphthalene - 7α,9α - dicarboxylic acid* (**4a**); m.p. 216–217° (from EtOAc–CH_2Cl_2). *Dimethyl decahydro - 1,5,3 - [1,2,3] - propanetriylnaphthalene - 7α,9α - dicarboxylate* (**5a**); ^1H NMR (60 MHz, CCl_4): δ 3·70 (3H, s), 3·57 (3H, s), 1·6–2·35 (18H). *Bicyclo[3.3.1]nonane - 3α,7α - dicarboxylic acid* (**4b**); m.p. 180·5–181° (from light petroleum–EtOAc); ^1H NMR (100 MHz, $CDCl_3$–DMSO-d_6): δ 12·53 (2H, s), 2·51 (2H, quintet: J = 7·2 Hz), 1·7–2·3 (10H), 1·43 (2H, t: J = 3·0 Hz). *Dimethyl bicyclo[3.3.1]nonane - 3α,7α - dicarboxylate* (**5b**); ^1H NMR (100 MHz, $CDCl_3$): δ 3·63 (6H, s), 2·48 (2H, quintet: J = 7·2 Hz), 1·7–2·3 (10H), 1·42 (2H, t: J = 3·0 Hz). *3β-Methylbicyclo[3.3.1]nonane - 3α,7α - dicarboxylic acid* (**4c**); m.p. 216–218° (from light petroleum–EtOAc); ^1H NMR (60 MHz, CCl_4–DMSO-d_6): δ 11·28 (2H, s), 0·8–2·9 (14H), 1·07 (3H, s). *Methyl 3β - methylbicyclo[3.3.1]) nonane - 3α,7α - dicarboxylate* (**5c**); ^1H NMR (100 MHz, CCl_4): δ 3·68 (3H, s), 3·55 (3H, s), 1·12 (3H, s), 0·9–2·7 (13H).

2 - Oxoadamantane - 1 - carboxylic acid (**6**). In a sealed tube **4b** (508·8 mg; 2·40 mmole) was heated with 20 ml of a mixture of HOAc and 12N HCl (3:1) at 150° for 24 hr. The mixture was diluted with 30 ml H_2O and then extracted with EtOAc (5 × 20 ml). The EtOAc soln was washed with H_2O (3 × 20 ml) and dried over $MgSO_4$. After evaporation of the solvent 440·4 mg (2·23 mmole, 93%) chromatographically pure **6** was obtained. Further purification was achieved by recrystallisation from light petroleum (b.p. 40–60°) and sublimation (160°/10 mm); m.p. 166–167°; ^1H NMR (60 MHz, CCl_4–DMSO-d_6): δ 8·60 (1H, s), 1·7–2·8 (13H).

2 - Oxoadamantane - 1 - carbonyl chloride (**7**). Compound **4b** (587·5 mg, 2·77 mmole) was boiled with 15 ml $SOCl_2$ for 1 hr. Then the excess $SOCl_2$ was evaporated *in vacuo*. Dry benzene (15 ml) was added and removed again *in vacuo* to yield **7** (570·0 mg; 2·70 mmole, 97%). The pattern of the ^1H NMR signals was characteristic for 1-substituted 2-oxoadamantane derivs. The structure was confirmed by treatment of **7** with MeOH. After the usual work-up methyl 2 - oxoadamantane - 1 - carboxylate was obtained. This compound was identical with the authentic sample.

Methyl 2 - oxoadamantane - 1 - carboxylate (**8**). Acid **4b** (512·6 mg, 2·42 mmole) was esterified with CH_2N_2. The resulting methyl ester was boiled in a soln of 200 mg Na in 25 ml MeOH for 24 hr. The mixture was diluted with 25 ml H_2O. The dispersion obtained was extracted with pentane (4 × 15 ml). The pentane soln was washed with H_2O (3 × 10 ml) and dried over $MgSO_4$. After evaporation of the solvents almost pure **8** (492·9 mg; 2·37 mmole, 99%) was obtained. Further purification was achieved by recrystallisation from light petroleum; m.p. 86–86·5°; mass spectrum: important peaks at *m/e* 208, 180, 176 and 148; ^1H NMR (60 MHz, CCl_4): δ 3·68 (3H, s), 1·75–2·70 (13H).

The same ester was obtained after reaction of **6** with CH_2N_2 and after reaction of **7** with MeOH.

1 - Acetyl - 2 - methyladamantan - 2 - ol (**9**). Acid **4b** (1·01 g, 4·76 mmole) was dissolved in 20 ml THF. At 0° 40 ml of a 1·02M soln of MeLi in ether was added dropwise. The mixture was boiled for 3 hr. After cooling 50 ml H_2O was added. The layers were separated. The aqueous layer was extracted with EtOAc (4 × 30 ml). The combined organic layers were washed with 30 ml 2N KOH and with H_2O (2 × 30 ml). After drying over $MgSO_4$ and evaporation of the solvents 404·5 mg product was obtained. Recrystallisation from light petroleum and sublimation (95°/17 mm) gave pure **9**; m.p. 99–100°; mass spectrum: important peaks at *m/e* 208, 193, 190 and 165; ^1H NMR (60 MHz, CCl_4): δ 4·00 (1H, s), 2·12 (3H, s), 1·27 (3H, s), 1·1–2·5 (13H).

Work-up of the KOH-layer gave starting material (**4b**) besides **6**.

Reaction of diamantanone (**1a**) *and adamantanone* (**1b**) *with* NaN_3 *and* $MeSO_3H$.[10,11] To a suspension of the ketone in 25 ml $MeSO_3H$ 0·70 g (10·65 mmole) NaN_3 was added in the period of 1 hr. After 5 hr the mixture was poured on to 100 g ice. The suspension obtained was extracted with CH_2Cl_2 (5 × 50 ml). The CH_2Cl_2 soln was washed with H_2O (2 × 50 ml) and dried over $MgSO_4$. Evaporation of the solvent gave crude **10a**[11] (contaminated with the Beckmann rearrangement product) and **10b**[10] (which was used in the next reaction step without further purification). From the former mixture the aza products were removed by crystallisation from light petroleum (b.p. 80–110°). From the mother liquors the solvent were evaporated off. The residue was used in the next step without further purification.

Reaction of 4 - methylsulfonoxydiamantan - 2 - one (**10a**) *and - adamantan - 2 - one* (**10b**) *with alkali.*[10,11] The crude product of the preceding step was heated at 80° with 75 ml 2N KOH for 2 hr. The dispersion obtained was washed with $CHCl_3$ and acidified with 12N HCl and then extracted with $CHCl_3$ (4 × 30 ml). The $CHCl_3$ soln was washed with H_2O (2 × 30 ml) and dried over $MgSO_4$. Evaporation of the solvents gave almost pure **11b**[10] or the corresponding derivative **11a**.[11]

Hydrogenation of the unsaturated acids **11**. Crude **11** (0·50 g)

was hydrogenated in 20 ml EtOAc over 200 mg 10% Pd/C at 50° and 1 atm H_2. The catalyst was filtered off and the solvent was evaporated yielding almost pure decahydro - 1,5,3 - [1,2,3]propanetriylnaphthalene - 9α - carboxylic acid or bicyclo[3.3.1]nonane - 3α - carboxylic acid. Further purification was achieved by recrystallisation from light petroleum and sublimation. The methyl esters were obtained by reaction of the acids with CH_2N_2. *Decahydro - 1,5,3 - [1,2,3] - propanetriylnaphthalene - 9α - carboxylic acid*; m.p. 218–219°. *Methyl decahydro - 1,5,3 - [1,2,3] - propanetriylnaphthalene - 9α - carboxylate* (**12a**); ^{1}H NMR (60 MHz, CCl_4): δ 3·63 (3H, s), 2·50 (2H, broad s), 2·42 (2H, broad s), 0·9–2·1 (15H). *Bicyclo*[3.3.1]*nonane - 3α - carboxylic acid*; m.p. 127–127·5°; ^{1}H NMR (60 MHz, CCl_4): δ 12·12 (1H, s), 1·0–2·9 (15H). *Methyl bicyclo*[3.3.1]*nonane - 3α - carboxylate* (**12b**); ^{1}H NMR (100 MHz, CCl_4): δ 3·62 (3H, s), 2·49 (1H, t of t: J = 12·5 Hz and J = 6·0 Hz), 0·9–1 (4H), 0·5–0·9 (10H).

Methyl 7 - alkyl - 9,9 - dimethoxybicyclo[3.3.1]*nonane - 3α - carboxylates* (**14**). Compound **13**[1] (0·04 mole) was stirred with 10 g MeOH and 2·50 g *p*-TsOH in 100 ml dry heptane at 10°. The stirrer was stopped and 15 g molecular sieve KA was added. After 1 min the stirrer was started again. After 30 min 2·50 g *p*-TsOH and 5·0 g KA-powder were added. After another 10 min the mixture was filtered and the sieve was washed with heptane. The heptane filtrate was washed with sat $NaHCO_3$ aq (2 × 80 ml) and H_2O (2 × 80 ml) and then dried over $MgSO_4$. Evaporation of the solvents gave the dimethyl acetals. According to ^{1}H NMR the 7β-alkyl derivs were pure, while the 7α-alkyl derivs were contaminated with starting compound (24%). Distillation or recrystallisation did not improve the purity. *Methyl 9,9 - dimethoxybicyclo*[3.3.1] *- nonane - 3α - carboxylate* (**14a**); b.p. 93–94°/0·5 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·60 (3H, s), 3·13 (3H, s), 3·07 (3H, s), 1·1–2·8 (13H). *Methyl 7β - methyl - 9,9 - dimethoxybicyclo*[3.3.1]*nonane - 3α - carboxylate* (**14b**); b.p. 120–122°/0·3 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·60 (3H, s), 3·14 (3H, s), 3·07 (3H, s), 1·0–2·1 (12H), 0·88 (3H, d: J = 7 Hz). *Methyl 7β - t - butyl - 9,9 - dimethoxybicyclo*[3.3.1]*nonane - 3α - carboxylate* (**14c**); m.p. 57·5–58° (from light petroleum); ^{1}H NMR (60 MHz, CCl_4): δ 3·62 (3H, s), 3·12 (3H, s), 3·07 (3H, s), 1·1–2·2 (12H), 0·80 (9H, s). *Methyl 7α - methyl - 9,9 - dimethoxybicyclo*[3.3.1]*nonane - 3α - carboxylate* (**14d**); b.p. 173–174°/21 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·65 (3H, s), 3·12 (3H, s), 3·07 (3H, s), 1·0–2·9 (12H), 0·82 (3H, d: J = 7 Hz). *Methyl 7α - t - butyl - 9,9 - dimethoxybicyclo*[3.3.1]*nonane - 3α - carboxylate* (**14e**); b.p. 113–114°/0·3 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·63 (3H, s), 3·12 (3H, s), 3·07 (3H, s), 1·0–2·9 (12H), 0·75 (9H, s).

7 - Alkyl - 9 - oxobicyclo[3.3.1]*nonane - 3α - methanols* (**15**). The reaction product of the preceding step was dissolved in 25 ml ether and added dropwise to a suspension of LAH (3·0 g; 0·08 mole) in 90 ml ether. The mixture was boiled for 3 hr. After cooling 15 ml EtOAc, 15 ml H_2O and 200 ml 4N H_2SO_4 were added dropwise subsequently. The aqueous layer was extracted with EtOAc (3 × 70 ml). The combined organic layers were washed with H_2O (2 × 70 ml) and then dried over $MgSO_4$. Evaporation of the solvents yielded **15** (90–95%). The 7α - alkyl derivs were contaminated with the corresponding 9-OH derivs. Purification was achieved by distillation (**15d**) or by fractionated crystallisation of the impurity from light petroleum–EtOAc and subsequent evaporation of the solvents from the mother liquors (**15e**). *9 - oxobicyclo*[3.3.1]*nonane - 3α - methanol* (**15a**); b.p. 90°/0·5 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·44 (2H, broad d), 0·9–2·8 (14H). *7β - Methyl 9 - oxobicyclo*[3.3.1]*nonane - 3α - methanol* (**15b**); b.p. 120–122°/0·3 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·80 (1H, broad s), 3·37 (2H, broad d), 0·9–2·8 (12H), 0·98 (3H, d: J = 6 Hz). *7β - t - Butyl - 9 - oxobicyclo*[3.3.1]*nonane - 3α - methanol* (**15c**); m.p. 91–91·5°; ^{1}H NMR (60 MHz, CCl_4–DMSO-d_6): δ 4·00 (1H, t: J = 6·5 Hz), 3·28 (2H, d of t: J = ~4·2 Hz and J = 6·5 Hz), 1·1–2·7 (12H), 0·92 (9H, s). *7α - Methyl - 9 - oxo - bicyclo*[3.3.1]*nonane - 3α - methanol* (**15d**); b.p. 132–134°/0·5 mm; ^{1}H NMR (60 MHz, CCl_4): δ 4·2 (1H), 3·34 (2H), 1·0–2·7 (12H), 0·95 (3H). *7α - t - Butyl - 9 - oxobicyclo*[3.3.1]*nonane - 3α - methanol* (**15e**); b.p. 155–160°/1 mm; ^{1}H NMR (60 MHz, DMSO-d_6): δ 4·73 (1H, s), 3·45 (2H, broad d), 1·1–2·7 (12H), 0·90 (9H, s).

7 - Alkylbicyclo[3.3.1]*nonane - 3α - methanols* (**16**). Compound **15** (0·027 mole) was boiled with 4 ml 100% hydrazine and 5·40 g KOH in 40 ml triethyleneglycol for 1·5 hr. Then the mixture was distilled until a bottom temp. of 210° was reached. Subsequently the mixture was boiled for another 4 hr. After cooling the mixture was diluted with 70 ml H_2O and combined with the distillate. The mixture obtained was extracted with ether (5 × 30 ml). The ether soln was washed with sat NaCl aq (3 × 30 ml) and dried over $MgSO_4$. Evaporation of the solvents gave the 7 - alkylbicyclo[3.3.1]nonane - 3α - methanols in about 85% yield. Further purification was achieved by distillation or by recrystallisation. IR spectra showed the absence of a CO-function. *Bicyclo*[3.3.1]*nonane - 3α - methanol* (**16a**); b.p. 88–90°/0·2 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·90 (1H, s), 3·33 (2H, d: J = 5·2 Hz), 0·8–2·2 (15H). *7β - Methylbicyclo*[3.3.1]*nonane - 3α - methanol* (**16b**); b.p. 127–128°/8 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·75 (1H, s), 3·32 (2H, d: J = 5·5 Hz), 0·5–2·5 (14H), 0·83 (3H, d: J = 6 Hz). *7β - t - Butylbicyclo*[3.3.1]*nonane - 3α - methanol* (**16c**); m.p. 65·5–66·5°; ^{1}H NMR (60 MHz, CCl_4): δ 3·47 (1H, s), 3·33 (2H, d: J = 6 Hz), 0·5–2·4 (14H), 0·83 (9H, s). *7α - Methylbicyclo*[3.3.1]*nonane - 3α - methanol* (**16d**); b.p. 142–143°/15 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·82 (1H, s), 3·40 (2H, d: J = 5 Hz), 0·5–2·4 (14H), 0·93 (3H, d: J = 6 Hz). *7α - t - Butylbicyclo*[3.3.1]*nonane - 3α - methanol* (**16e**); b.p. 183–185°/15 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3·83 (1H, s), 3·36 (2H, d: J = 5 Hz), 0·6–2·3 (14H), 0·80 (9H, s).

7β - Alkylbicyclo[3.3.1]*nonane - 3α - carboxylic acids* (**17a, b, c**) *and methyl esters* (**19a, b, c**). At 10° 60 ml Jones reagent (26·7 g CrO_3 in 23 ml 100% H_2SO_4, diluted with H_2O to 100 ml) was added dropwise to a soln of 0·048 mole of **16** in 180 ml acetone. The mixture was then stirred at room temp. for 1 hr. After cooling until 0°, 240 ml MeOH was added. After 15 min stirring 450 ml H_2O was added. The dispersion obtained was extracted with $CHCl_3$ (5 × 100 ml). The $CHCl_3$ soln was washed with H_2O (3 × 100 ml) and dried over $MgSO_4$. After evaporation of the solvents the acids **17a–c** were obtained in about 95% yield. Further purification was achieved by recrystallisation from light petroleum. The methyl esters were synthesized by reaction of the acids with CH_2N_2. *Bicyclo*[3.3.1]*nonane - 3α - carboxylic acid* (**17a**);[14] m.p. 126·5–127°; ^{1}H NMR (60 MHz, CCl_4): δ 10·43 (1H, s), 0·9–2·7 (15H). *Methyl bicyclo*[3.3.1]*nonane - 3α - carboxylate* (**19a**); ^{1}H NMR (100 MHz, CCl_4): δ 3·62 (3H, s), 2·49 (1H), 1·0–2·2 (14H), *7β - Methylbicyclo*[3.3.1]*nonane - 3α - carboxylic acid* (**17b**); m.p. 107·5–108°; ^{1}H NMR (60 MHz, CCl_4): δ 11·73 (1H, s), 0·5–2·8 (14H), 0·85 (3H, d: J = 6 Hz). *Methyl 7β - methylbicyclo*[3.3.1]*nonane - 3α - carboxylate* (**19b**); ^{1}H NMR (60 MHz, CCl_4): δ 3·62 (3H, s), 0·7–2·8 (14H), 0·89 (3H, d: J = 6·5 Hz). *7β - t - Butylbicyclo*[3.3.1]*nonane - 3α - carboxylic acid* (**17c**); m.p. 150·5–151°; ^{1}H NMR (60 MHz, CCl_4): δ 14·63 (1H, s), 0·8–2·7 (14H), 0·83 (9H, s). *Methyl 7β - t - butylbicyclo*[3.3.1]*nonane - 3α - carboxylate* (**19c**); m.p. 36–37° (from light petroleum); ^{1}H NMR (100 MHz, CCl_4): δ 3·61 (3H, s), 2·44 (1H, t of t: J = 12·0 Hz and J = 6·3 Hz), 0·8–2·4 (13H), 0·84 (9H, s).

7α - Alkylbicyclo[3.3.1]*nonane - 3α - carboxylic acids* (**17d, e**) *and methyl esters* (**19d, e**). To a soln of **16** (3·54 mmole) in 25 ml heptane, was added 720 mg PtO_2. At 25° and 1 atm H_2 the catalyst was reduced. Then the H_2 was replaced by N_2, which was subsequently replaced by O_2. The temp. was raised until 80°. The reaction was followed by GLC. After 1 week no further conversion occurred. The catalyst was filtered off and washed with EtOAc. The filtrate was extracted with 2N KOH (3 × 15 ml). The KOH soln was washed with ether (2 × 15 ml), acidified with 12N HCl and then extracted with ether (4 × 15 ml). The ether soln was washed with H_2O (2 × 15 ml) and dried over $MgSO_4$. After evaporation of the solvent the acid **17d, e** was obtained in 15–25% yield. Compound **17d** was used without further purification. All efforts to purify compound **17e** were not successful. The esters (**19d, e**) were obtained after reaction of the acids with CH_2N_2. *7α - Methylbicyclo*[3.3.1]*nonane - 3α - carboxylic acid* (**17d**); ^{1}H NMR (60 MHz, CCl_4): δ 11·04 (1H, s), 0·5–3·0 (14H), 0·83 (3H, d: J = 6 Hz). *Methyl 7α - methylbicyclo*[3.3.1]*nonane - 3α - carboxylate* (**19d**); ^{1}H NMR (60 MHz, CCl_4): δ 3·65 (3H, s), 0·5–3·0 (14H), 0·77 (3H, d: J = 5·8 Hz).

7α - t - Butylbicyclo[3.3.1]*nonan - 3 - one* (**18e**). The neutral

organic layers of the oxidation of **17e** were combined, washed with H_2O (3 × 15 ml) and dried over $MgSO_4$. The solvents were evaporated off and the residue was crystallized from light petroleum at −80°. Further purification was achieved by sublimation at 55°/0·1 mm; mass spectrum: important peaks at *m/e* 138, 95, 80; ^{1}H NMR (60 MHz, CCl_4): δ 0·8–2·8 (13H), 0·78 (9H, s).

7 - *Alkylbicyclo*[3.3.1]*nonane* - 3β - *carboxylic acids* (**20**) *and methyl esters* (**21**). Ester **13** (0·027 mole) was boiled with 4 ml 100% hydrazine and 6·35 g KOH in 50 ml triethyleneglycol for 1·5 hr. Then the mixture was distilled until a bottom temp. of 200° was reached. Subsequently the mixture was boiled for another 4 hr. The mixture was diluted with 300 ml H_2O and acidified with 180 ml 6N HCl. The acid was filtered off, washed with H_2O, dried and recrystallized from light petroleum–EtOAc. The methyl esters were obtained by reaction of the acids with CH_2N_2. 7β - *t* - *Butylbicyclo*[3.3.1]*nonane* - 3β - *carboxylic acid* (**20b**): m.p. 136·5–137°; ^{1}H NMR (60 MHz, CCl_4): δ 12·02 (1H, s), 3·06 (1H), 1·15–2·25 (13H), 0·83 (9H, s). *Methyl* 7β - *t* - *butylbicyclo*[3.3.1]-*nonane* - 3β - *carboxylate* (**21b**): ^{1}H NMR (60 MHz, CCl_4): δ 3·68 (3H, s), 3·12 (1H), 1·15–2·20 (13H), 0·83 (9H, s). 7α - *t* - *Butylbicyclo*[3.3.1]*nonane* - 3β - *carboxylic acid* (**20d**): m.p. 152–152·5°; ^{1}H NMR (60 MHz, CCl_4): δ 11·88 (1H, s), 2·63 (1H), 0·6–2·2 (13H), 0·87 (9H, s). *Methyl* 7α - *t* - *butylbicyclo* [3.3.1]*nonane* - 3β - *carboxylate* (**21d**); ^{1}H NMR (60 MHz, CCl_4): δ 3·60 (3*H*, *s*), 2·61 (1*H*), 0·7–2·2 (13*H*), 0·86 (9*H*, *s*).

3 - [2 - (2 - *Hydroxypropyl*)]*bicyclo*[3.3.1]*nonane* (**22**, **23**). These compounds were synthesized analogously to compound **24**. 3β - [2 - (2 - *Hydroxypropyl*)]*bicyclo*[3.3.1]*nonane* (**22**): m.p. 116–118°; ^{1}H NMR (60 MHz, acetone-d_6): δ 2·87 (1H, s), 1·2–2·5 (15H), 1·08 (6H, s). 3α - [2 - (2 - *Hydroxypropyl*)]*bicyclo* [3.3.1]*nonane* (**23**); m.p. 82–83°; ^{1}H NMR (100 MHz, CCl_4): δ 0·9–2·2 (16H), 1·13 (6H, s).

3α,7α - *Bis* - 2 - (2 - *hydroxypropyl*)*bicyclo*[3.3.1]*nonane* (**24**). Dicarboxylic acid **4b** (513·4 mg, 2·42 mmole) was esterified with CH_2N_2. The ester was dissolved in 25 ml ether and added at 0° dropwise to 25 ml of a 3·2 M soln of MeMgCl in THF. The mixture was stirred at 0° for 1 hr and then boiled for 1 hr. The mixture was poured on to 200 g ice. The dispersion obtained was saturated with NH_4Cl and then extracted with EtOAc (5 × 30 ml). The EtOAc soln was washed with a sat thiosulfate soln (2 × 30 ml), with H_2O (2 × 20 ml) and dried over $MgSO_4$. Evaporation of the solvent gave 571·5 mg (2·38 mmole, 98%) **24**. Further purification was achieved by recrystallisation from light petroleum; m.p. 106–107°; mass spectrum; important peaks at *m/e* 204, 189, 164, 149, 121 and 59; ^{1}H NMR (100 MHz, $CDCl_3$): δ 1·18 (12H, s), 0·8–2·4 (16H).

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ADDITIONAL COMMENT

Recently, it has been shown that a 9-oxo function in bicyclo[3.3.1]nonanes can be reduced to methylene by means of a Clemmensen reduction[1]. Although this route was found to be very useful in the synthesis of the compounds described in the foregoing Chapter[2] its applicability is probably restricted to carbocyclic compounds; the reduction of 9-oxo-3-oxabicyclo[3.3.1]nonanes (Chapter 11) with the use of a Clemmensen reaction was found to proceed only with a low yield, presumably due to C-O ether bond rupture.

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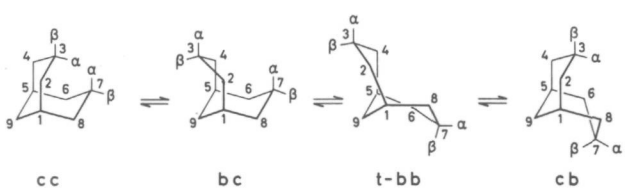
CHAPTER 9

CHAIR-BOAT EQUILIBRIA IN BICYCLO[3.3.1]NONANE AND SOME 3- AND 3,7-SUBSTITUTED DERIVATIVES; THERMODYNAMIC PARAMETERS AND GEOMETRY OF THE CONFORMERS AS OBTAINED BY MOLECULAR MECHANICS*

Introduction

For the bicyclo[3.3.1]nonane system three groups of conformations should be envisaged: (i) the rigid double chair (cc), (ii) the rigid chair--boats (bc and cb) and (iii) the double boats (bb) ranging from the eclipsed double boat (e-bb) to the double twist-boats (t-bb)[1,2]. Previously, with the aid of ^{1}H and ^{13}C NMR spectroscopy[3,4], we have



cc bc t-bb cb

shown that substituents at the 3- and 7-positions govern the conformation of these compounds. In 3β- and/or 7β-substituted systems the cc conformation predominates, whereas a substituent at the 3α- or 7α-position forces the ring involved into the boat conformation. When both the 3α- and 7α--positions are substituted, the conformational preference (bc⇌bb⇌cb) strongly depends on the size of the substituents. From vicinal proton--proton coupling constants of 3,7- substituted bicyclo[3.3.1]nonanes it was concluded that in these compounds both the chair and the boat wings of the cc, bc and cb conformers are flattened.

However, alternative explanations for the magnitudes of the coupling constants cannot be excluded completely. *E.g.*, instead of flattening of the boat part in cb and bc conformers, some twisting or contributions of other conformers could also explain the coupling constants observed. Moreover, the interpretation of coupling constants is based on the assumption that an ideal tetrahedral geometry exists around the carbon atoms.

The aim of the present investigation was to establish the conformation of 3,7-substituted bicyclo[3.3.1]nonanes with exclusion of the ambiguities cited above. Therefore, accurate geometries as well as thermodynamic parameters are required. In the present paper three approaches are used, namely epimerisation experiments, ^{13}C variable temperature experiments, and empirical force field calculations.

ΔG-values for cc/bc equilibria of 3(7)α-alkyl-

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bicyclo[3.3.1]nonanes have been obtained from epimerisation experiments with the corresponding 3-CO_2Me derivatives. A comparison is made with literature data.

So far no ΔG- or ΔH-values for bc/bb equilibria have been reported. Previously, it was shown that the chemical shifts in ^{13}C NMR spectra are very sensitive to the conformation[4,5]. Therefore, ^{13}C NMR spectroscopy at variable temperature may be a useful technique for the determination of thermodynamic parameters of bc/bb equilibria. A prerequisite is that the absolute ΔG-values are not too large. For the study of the cb/bb equilibrium some 3α,7α-substituted bicyclo[3.3.1]nonanes, in which both the cb and the bb conformers are populated to a reasonable extent, were selected.

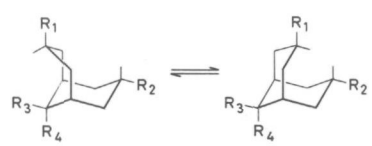
Empirical force field calculations may be an attractive approach to obtain thermodynamic parameters as well as geometries. Though calculations on bicyclo[3.3.1]nonane and some of its derivatives have been performed[6-8], a systematical study of 3,7-substituted systems is not available. In this paper the results of calculations on bicyclo-[3.3.1]nonane and a number of its 3- and 7-alkyl substituted derivatives are presented and discussed. The calculated geometries are compared with experimental data[1].

Epimerisation experiments

It has been suggested that the ΔG-values for the epimerisation equilibrium of methyl bicyclo[3.3.1]-nonane-3-carboxylates reasonably represents the difference in free enthalpy between the cc and the bc conformations of bicyclo[3.3.1]nonane[9]. Since the ΔG-value of 3α/3β-hydroxybicyclo[3.3.1]nonane is about the same, it was assumed that the influence of substituents at the 3α-position on the energy of the bc conformation is close to that of 3β-substituents on the energy of the cc conformation[10].

We have extended the above series of ΔG-values

Table 1. ΔG-values for epimerisation of 3-substituted bicyclo[3.3.1]nonanes at 25° in CH_3OH solution



Nr	Substituents	ΔG kcal/mole[a]	ref.
1	R_1=CO_2Me; R_2,R_3,R_4=H	-2.7	9
2	R_1=OH; R_2,R_3,R_4=H	-2.5[b]	10
3	R_1=CO_2Me; R_2=t-Bu; R_3,R_4=H	-1.3	c
4	R_1=CO_2Me; R_2=t-Bu; R_3/R_4=O	-1.1	c

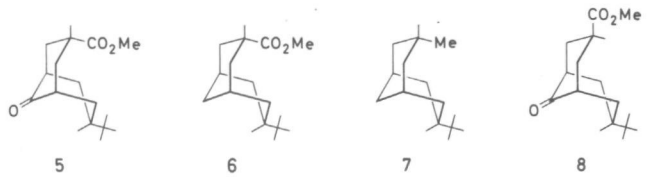
[a] ± 0.2 kcal/mole; the equilibrium was approached from both sides; [b] at 94° in isopropyl alcohol; [c] this work

for epimerisation with data on the methyl 7β-t--butylbicyclo[3.3.1]nonane-3-carboxylates and the corresponding 9-oxo derivatives (see Table 1). By this choice of substituents the intercomparison of the results of the epimerisation experiments, the ^{13}C NMR measurements and the force field calculations is facilitated. The magnitudes of the ΔG--values for the 7β-t-butyl derivatives (3,4) are distinctly lower than those of the other compounds. Apparently the t-butyl group exerts a destabilizing effect on the cc conformation (exceeding any effect of this kind on the bc conformation).

It should be noted that the difference between the ΔG-value for epimerisation of the 3-CO_2Me-7β--t-Bu derivative (3) and that of the corresponding 9-oxo derivative (4), which may be attributed to the decrease of 3,9-interaction in the bc conformation as a result of the replacement of CH_2 by CO, is unexpectedly small.

^{13}C NMR measurements

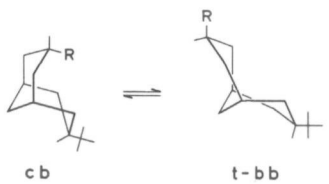
For the ^{13}C NMR spectroscopic studies at variable temperatures some 7α-t-butylbicyclo-[3.3.1]nonanes (5-7) were selected. In these com-



5 6 7 8

pounds the bulky 7α-t-butyl group fixes the ring involved in the boat conformation. The other ring may adopt the chair as well as the boat conformation. The population of the cb and bb conformers will depend on the temperature.

Some of the ^{13}C chemical shifts for compounds 5-7 were strongly dependent on temperature (in a non-linear way). In order to correct for temperature influences, which are not caused by changes in conformational populations, spectra of compound 8 were measured at variable temperature. For this conformationally homogeneous compound the temperature dependencies of the chemical shifts were linear and small (0.004 ppm/^{o}C)[11]. These temperature influences were used to correct the chemical shifts of the corresponding carbon atoms in compounds 5-7. We assume that the corrected temperature influences are due to shifts in the cb/bb equilibria of 5-7. Then, these equilibria can be



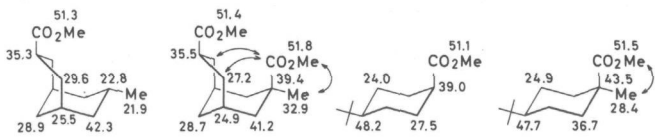
analyzed by relation (1), where δ_T is the corrected ^{13}C chemical shift measured at temperature T, δ_{cb} is the chemical shift of the carbon atom under consideration in the cb conformation and δ_{bb} its chemical shift in the bb conformation.

$$-\ln \frac{\delta_T - \delta_{cb}}{\delta_{bb} - \delta_T} = \frac{\Delta H}{RT} - \frac{\Delta S}{R} \qquad (1)$$

The value of δ_{bb} was estimated by adding substituent effects to the chemical shift of the carbon atom in the bb conformation of bicyclo[3.3.1]-nonane[4]. An analogous procedure seems not to be allowed for δ_{cb}. A substituent at the 3α-position of the chair wing experiences strong non-bonding interactions from $H_{6\alpha}$ and $H_{8\alpha}$, which might be re-

flected in the chemical shifts, in particular of C_3 and $C_{6/8}$. Therefore, increments, obtained from a study of the model compound 10 and some related compounds, were added to the initial approximations of δ_{cb} for C_3 and $C_{6/8}$.

First the deshielding effect of geminal Me-CO_2Me substitution was estimated from a comparison of the ^{13}C chemical shifts for compounds 11



9 10 11 12

Fig. 1. ^{13}C chemical shifts of some model compounds (in $CDCl_3$ solution)

and 12, taking into account the effects of an equatorial Me group along the cyclohexane ring, as reported by *Dalling* and *Grant*[12]. Moreover, the effect of the introduction of an axial CO_2Me group could be estimated from these chemical shifts. The values obtained are in accordance with those reported by *Stothers* et al.[13]. Then substraction of the chemical shifts of compound 9 from those of compound 10, followed by correction for the effects of introduction of an axial CO_2Me and geminal interaction, yielded the increments needed for the estimations of δ_{cb}.

The approximations of δ_{cb} and δ_{bb} were used as starting parameters in a non-linear regression procedure, by which the experimental ^{13}C chemical shift data were fitted to relation (1). The ΔH- and ΔS-values obtained are given in Table 2.

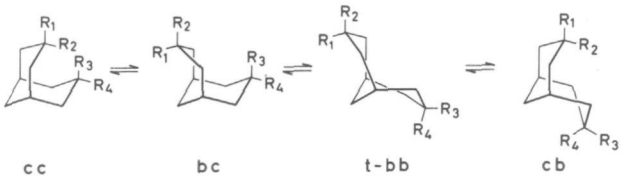
Table 2. ΔH- and ΔS-values for cb$\rightleftharpoons$bb equilibria in some bicyclo[3.3.1]nonane derivatives

Compound	ΔH kcal/mole	ΔS e.u.
5	1.0 ± 0.1	2.4 ± 0.2
6	1.8 ± 0.2	3.9 ± 1
7	0.0 ± 0.5	1 ± 2

The ΔH-value of the cb/bb equilibrium in compound 5 matches the conclusions reached from previous ^1H NMR and IR studies and from the pK_a^* of the corresponding carboxylic acid[3]. The same ΔH-value was estimated on the basis of an enthalpy difference between the bb and the cb conformation of bicyclo-[3.3.1]nonane of 5.7 kcal/mole[3]. The difference in ΔH-values between compounds 5 and 6 may be due to a difference in 7,9-interaction in these compounds. The relatively low ΔH-value of the cb/bb equilibrium in compound 7 may be explaned by the somewhat higher steric requirements of a Me group compared with a CO_2Me group. This will have a relative destabilizing effect on the cb conformation.

Calculated thermodynamic parameters

Empirical force field calculations on bicyclo-[3.3.1]nonane (13), on its 3α- and 3β-methyl and t-butyl derivatives (14-17), and on the four 3-methyl-7-t-butylbicyclo[3.3.1]nonane epimers (18-21) were performed using the "*Schleyer* 1973" force field[6,19].



cc bc t-bb cb

13 R_1,R_2,R_3,R_4=H
14 R_1=Me; R_2,R_3,R_4=H
15 R_1=t-Bu; R_2,R_3,R_4=H
16 R_2=Me; R_1,R_3,R_4=H
17 R_2=t-Bu; R_1,R_3,R_4=H
18 R_1=Me; R_4=t-Bu; R_2,R_3=H
19 R_2=Me; R_4=t-Bu; R_1,R_3=H
20 R_2=Me; R_3=t-Bu; R_1,R_4=H
21 R_1=Me; R_3=t-Bu; R_2,R_4=H

The strain energies obtained are given in Table 3. The results for the unsubstituted system (13) are identical with those reported by *Schleyer* et al.[6].

The calculations confirm the conclusions obtained from earlier experimental data[1]. Bicyclo-[3.3.1]nonane (13) as well as its 3β- (and 3β,7β-) derivatives (14,15,18) occur predominantly in the cc conformation. A 3β-t-butyl group has a small destabilizing effect on this conformation. In the 3α- (and 3α,7β- or 3β,7α-) substituted derivatives (16,17,19,21) the bc conformation predominates; the contribution of the bb conformation can be ignored. The situation in 3α,7α-substituted compounds will be somewhat more complex. From Table 3 it can be deduced that the conformational enthalpy for the cb/bb equilibrium in the 3α-Me,7α-t-Bu derivative (20) is only 0.72 kcal/mole: the cb and the bb conformer contribute to a reasonable extent to the equilibrium. We anticipate that with bulky substituents at both the 3α- and 7α-positions the t-bb conformation will predominate, whereas with a small substituent at one of the positions mentioned and a bulky one at the other the cb (bc) conformation will predominate. The rapid equili-

Table 3. Strain energies of some bicyclo[3.3.1]nonane derivatives (kcal/mole)

Nr	Substituents				Strain energies (kcal/mole)				
	3α	3β	7α	7β	cc	bc	t-bb	cb	e-bb[a]
13	H	H	H	H	9.59	12.08	17.82	12.08	20.27
14	H	Me	H	H	9.13	16.56	19.76	11.45	25.00
15	H	t-Bu	H	H	13.54			15.75	
16	Me	H	H	H		11.42	17.15	16.23	
17	t-Bu	H	H	H		15.71	21.07		24.22
18	H	Me	H	t-Bu	13.11				
19	Me	H	H	t-Bu		15.03			
20	Me	H	t-Bu	H			20.35	19.63	23.61
21	H	Me	t-Bu	H				14.99	

[a] This is not an energy minimum, as follows from the calculation of the eigenvalues of the final force constant matrix

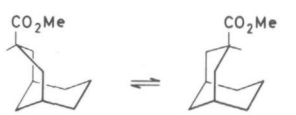
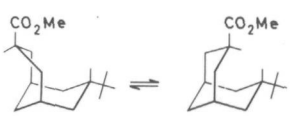
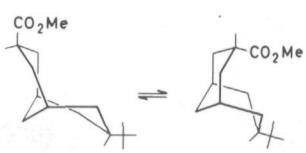
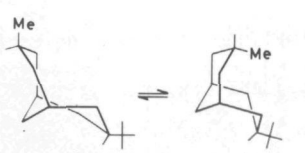
brium between the identical cb and bc conformers of the 3α,7α-di-CO_2Me substituted derivative, which was previously demonstrated[1], can be rationalized with these data too.

NMR data[1] were not conclusive with respect to the question whether the bb conformation in bicyclo[3.3.1]nonanes is twisted or not. The calculations showed that for compounds 13, 17 and 20 the double-twist boat (t-bb) is the most stable bb conformation. The strain energy of this conformation was 3-5 kcal/mole lower than that of the e-bb conformation[20].

Since the steric requirements of a methyl and a carboxymethyl group are roughly of the same order of magnitude, it may be assumed that the influence of these groups on the strain energy is about the same. Therefore, a comparison between the ΔG- and ΔH-values, obtained from the epimerisation and the ^{13}C NMR experiments, with conformational energies of related compounds as calculated from Table 3, seems of interest. Table 4 shows that a good agreement exists between these data.

From Table 3 strain energy increments for a methyl and a t-butyl group at position 3 or 7 for different conformations can be derived (see Table 5). The increments for the cc and t-bb confor-

Table 4. ΔG, ΔH, and ΔS values for chair-boat equilibria in some bicyclo[3.3.1]nonanes at 25°; a comparison between experimental and calculated values

	Experimental values			Calculated values[a]		
	ΔG[b]	ΔH[b]	ΔS[c]	ΔG[b]	ΔH[b]	ΔS[c]
	−2.7[d]			−2.4	−2.3	+0.5
	−1.3[d]			−2.3	−1.9	+1.3
	−0.6[e]	−1.8	−3.9			
	+0.3	0.0	−1.0	−0.1	−0.7	−1.8

[a] from force field calculations; [b] kcal/mole; [c] e.u.; [d] from epimerisation experiments; [e] from ^{13}C NMR at variable temperature

Table 5. Mean strain energy differences due to alkyl substitution (kcal/mole)[a]

Bicyclo[3.3.1]nonanes				
substituent	cc	bc	t-bb	cb
3β-Me	-0.45	4.48	1.94	-0.68
3α-Me		-0.64	-0.70	4.08
3β-t-Bu	3.97			3.64
3α-t-Bu		3.52	3.23	

Cyclohexanes[b]		
substituent	chair	twist-boat
equatorial Me	-0.56	
"equatorial" t-Bu	3.99	3.26

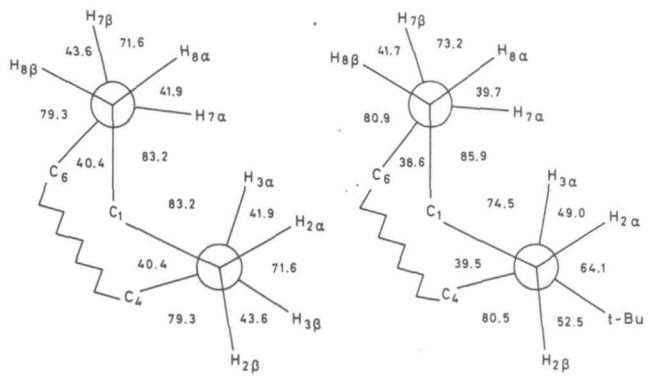
[a] Cf. ref 16; [b] ref 14

mations parallel those for the corresponding conformations in cyclohexane[14], indicating that here analogous interactions are responsible for these increments. Remarkably, the magnitudes of the increments for the 3α- (boat wing) and 7β--substituents (chair wing) for the bc conformation are about the same. As will be shown later on, the effects of introduction of a 3α-substituent resemble those of introduction of a 7β-substituent.

Calculated geometries

Systems with a double-chair conformation

The results of the force field calculations on the cc conformation of bicyclo[3.3.1]nonane (22) (see Table 6) show that the molecule has C_{2v}-symmetry. The distance between $H_{3\alpha}$ and $H_{7\alpha}$ is calculated to be 2.12 Å, whereas in a perfect cc conformation the separation is only 0.76 Å. As is shown by the internal ring torsion angles (see Fig. 3), the severe interaction between these atoms gives rise to a distinct flattening of the

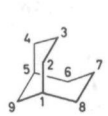
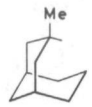
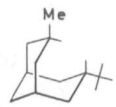


22 24

Fig. 3. cc Conformations; torsion angles around C_2C_3 (C_3C_4) and C_6C_7 (C_7C_8)

wings of the ring system. Moreover, a larger separation between the wings is achieved by increased $C_2C_1C_8$ and $C_4C_5C_6$ valency angles. The results of the calculations are in agreement with those of previous molecular mechanical studies[6,7] and with

Table 6. Selected ring torsion angles, valency angles and bond lengths of the cc conformations of bicyclo[3.3.1]nonane derivatives[a]

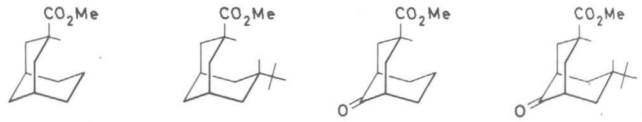
	 22	 23	 24[b]	 25[b]
ring torsion angles				
$C_1C_2C_3C_4$	40.4	40.6	39.5	38.7
$C_3C_4C_5C_9$	52.3	52.6	52.7	52.2
$C_2C_1C_9C_5$	63.5	63.4	63.6	63.9
$C_1C_8C_7C_6$	40.4	39.3	38.6	38.1
valency angles				
$C_8C_1C_2$	115.1	115.2	115.3	115.5
$C_1C_2C_3$	115.0	115.3	116.3	115.7
$C_2C_3C_4$	113.4	112.6	111.3	112.6
$C_2C_1C_9$	109.5	109.4	109.5	109.7
$C_1C_9C_5$	108.8	108.6	108.2	108.0
$C_1C_8C_7$	115.0	115.2	115.3	116.5
$C_6C_7C_8$	113.4	113.6	113.5	111.5
$R_1C_3H_{3\alpha}$	103.8	105.5	103.3	105.0
bond lengths				
C_1C_2	1.540	1.540	1.540	1.540
C_2C_3	1.537	1.539	1.545	1.539
C_1C_8	1.540	1.540	1.540	1.540
C_7C_8	1.537	1.538	1.537	1.546
C_1C_9	1.531	1.530	1.528	1.527

[a] Complete Tables of geometric parameters are available from the authors on request; [b] in compounds 24 and 25 the symmetry of the molecule is somewhat distorted. The figures given are averages of corresponding values. The maximum deviations from the values given are: 0.3^{o} (torsion angles) and 0.1^{o} (valency angles).

the results of recent electron diffraction studies[15].

Introduction of a t-butyl group on the 3β--position will cause several gauche butane interactions in the six-membered ring involved (cf. Table 5). As may be expected from previous calculations on alkylcyclohexanes[14], this results in bending of $H_{3\alpha}$ into the direction of the center of the ring (see Fig. 3), an increase of the $C_1C_2C_3$ and $C_3C_4C_5$ valency angles (see Table 6) and an increase of the C_2C_3 and C_3C_4 bond lengths. As a consequence of the displacement of $H_{3\alpha}$, its interaction with $H_{7\alpha}$ enforces, which results in analogous phenomena in the other wing. As should be expected the effects there are more pronounced than in the substituted ring. It should be noted that in the 3β-methyl compound still a plane of symmetry through C_3, C_7 and C_9 is present, whereas in the t-butyl derivatives (24, 25) the symmetry is no longer preserved: the t-butyl group has no perfectly staggered position with respect to C_3. A similar situation was calculated for t-butylcyclohexane[14].

Since the steric demands of a methyl group are roughly of the same order of magnitude as those of a methoxycarbonyl group, a comparison of the calculated geometries of 23 and 25 with the results of previous ^{1}H NMR studies on methyl bicyclo-[3.3.1]nonane-3β-carboxylate (26), its 7β-t-butyl derivative (27) and the related 9-oxo compounds (28 and 29) seems of interest[1,3]. As Table 7 shows, the magnitudes of the vicinal proton-proton coupling constants $J_{12\alpha}$, $J_{12\beta}$, $J_{2\alpha3\alpha}$ and $J_{2\beta3\alpha}$ are in accordance with the calculated dihedral angles in compounds 26-29[1,17].



26 27 28 29

Table 7. Comparison of calculated dihedral angles and vicinal proton-proton coupling constants

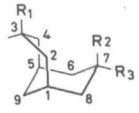
fragment	calculated dihedral angles (degrees)		coupling constants observed[a] (Hz)			
	23	25	26	27	28	29
12β/4β5	49.9	49.3	4.0	4.5	4.3	4.2
2α3α/3α4α	45.6	43.6	5.3-6.0	5.7	5.2	5.5
2β3α/3α4β	160.8	158.5	12.6	12.4	12.7	12.0

[a] ± 0.2 Hz

Systems with a boat-chair conformation

The calculations show that in the bc conformation of unsubstituted bicyclo[3.3.1]nonane a mirror plane through C_3, C_7 and C_9 is present: the boat wing is not twisted. As can be seen from the internal ring torsion angles and the valency angles (see Table 8), again both wings of the system are

Table 8. Selected ring torsion angles, valency angles and bond lengths of bc conformations of some bicyclo[3.3.1]nonanes



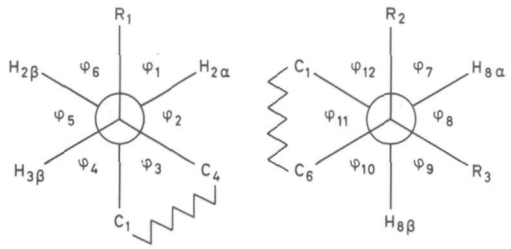
Nr	30	31	32	33	34[a]	35[a]	36[a]	37	38
R_1	H	H	H	Me	t-Bu	Me	t-Bu	H	t-Bu
R_2	H	H	H	H	H	H	H	Me	Me
R_3	H	Me	t-Bu	H	H	t-Bu	Me	H	H
internal ring torsion angles									
1234	44.3	43.8	43.2	43.9	39.9	42.6	38.9	39.6	39.1
3219	7.6	8.0	8.6	7.5	9.5	8.7	10.2	10.7	10.3
2195	60.0	60.3	60.7	59.8	60.5	60.6	60.8	61.4	61.0
1876	48.4	48.4	48.0	48.4	49.2	48.2	49.5	38.1	37.1
7819	56.2	56.5	57.0	56.3	56.8	57.2	57.1	51.8	51.8
8195	64.0	63.9	63.8	64.1	63.7	63.9	63.5	64.3	65.1
8123	114.2	113.8	113.6	114.2	112.7	113.5	112.1	112.5	113.1
7812	67.1	66.9	66.7	67.0	66.8	66.5	66.5	72.6	73.0
valency angles									
123	113.9	113.9	113.9	114.4	115.8	114.4	115.9	114.3	115.7
234	113.2	113.3	113.4	112.6	112.0	112.8	112.3	114.7	112.4
459	111.1	111.1	111.3	111.2	111.2	111.3	111.2	111.1	111.4
187	113.1	113.5	114.4	113.0	112.9	114.3	113.2	116.3	116.3
678	112.1	111.3	109.7	112.0	111.6	109.6	110.8	112.4	112.5
819	108.5	108.5	108.6	108.5	108.8	108.6	108.9	108.9	108.9
195	109.0	108.9	108.4	108.9	108.6	108.3	108.4	108.7	108.1
bond lengths									
23	1.537	1.537	1.537	1.538	1.546	1.538	1.547	1.538	1.547
67	1.536	1.538	1.545	1.536	1.535	1.545	1.537	1.543	1.542

[a] In these compounds the symmetry of the molecule is slightly distorted. Averages of two corresponding values are given. The maximum deviation from the value given is 0.4^{o} (torsion angles) and 0.1^{o} (valency angles).

distinctly flattened, although less than in the cc conformation. This flattening may be attributed to the interactions between $H_{3\beta}$ and H_9 and to those between $H_{7\alpha}$ and $H_{2\alpha}$ and $H_{4\alpha}$. Flattening of the chair moves $H_{7\alpha}$ away from $H_{2\alpha}$ and $H_{4\alpha}$, whereas flattening of the boat part results in a larger separation of $H_{2\alpha}$ and $H_{4\alpha}$ and therefore, an increase of the distances between these atoms and $H_{7\alpha}$ is achieved.

This hypothesis is supported by the influences of substitution of the 3- and/or 7-positions on the geometry of the bc conformation. The impact of a 7β-alkyl substituent again is analogous to that of such a group on the geometry of cyclohexane (see Table 9). In these compounds the displacement of $H_{7\alpha}$ towards the center of the system may be responsible for the increased flattening of the boat

Table 9. bc Conformations; torsion angles around C_2C_3 and C_7C_8



boat wing chair wing

	Nr	30	32[a]	34[a]	37
	R_1	H	H	t-Bu	H
	R_2	H	H	H	Me
	R_3	H	t-Bu	H	H
boat wing	ϕ_1	45.2	43.8	49.8	40.3
	ϕ_2	78.8	80.4	83.9	84.9
	ϕ_3	44.3	43.2	39.9	39.6
	ϕ_4	76.7	77.6	72.5	80.7
	ϕ_5	46.2	45.1	48.7	41.6
	ϕ_6	68.9	70.0	65.2	72.9
chair wing	ϕ_7	50.7	56.7	51.8	34.5
	ϕ_8	65.0	58.3	64.3	78.3
	ϕ_9	50.6	58.8	51.3	35.7
	ϕ_{10}	71.9	72.6	71.0	80.8
	ϕ_{11}	48.4	48.0	49.2	38.1
	ϕ_{12}	73.5	65.7	72.4	92.6

[a] See Table 8, note a

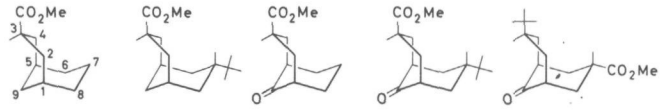
wing.

A bulky substituent at the 3α-position (pseudo--equatorial in the boat part) induces, in addition to analogous phenomena, an increased flattening of the boat part. This may be attributed to the enforcement of the 3,9-interaction, which would occur, when only the usual changes in geometry took place. The distance between $H_{2\alpha}$ and $H_{4\alpha}$ is somewhat larger than in the unsubstituted system, due to the increased flattening. This is reflected in a decreased flattening in the chair wing (see e.g. compound 32).

As should be expected, the calculations show that introduction of a 7α-methyl group (axial in the chair part) has rather dramatic consequences for the geometry of the bc conformation. The 1,3--diaxial interactions between the 7α-substituent and the other ring are decreased by a very strong flattening of the chair, accompanied by an increase of the valency anlges $C_5C_6C_7$ and $C_7C_8C_1$ and a stretching of the C_6C_7 and C_7C_8 bonds. Moreover, the other ring is flattened too and the valency angles $C_1C_2C_3$ and $C_3C_4C_5$ are enlarged, resulting in a larger separation between $H_{2\alpha}$ and $H_{4\alpha}$.

From Table 10 it can be seen that the dihedral angles calculated for the bc conformations are in agreement with the magnitudes of vicinal proton--proton coupling constants observed in the related methoxycarbonyl derivatives 39-43[1,3].

Table 10. Comparison of calculated dihedral angles and observed proton-proton coupling constants for bc conformations of some bicyclo[3.3.1]nonane derivatives



39 40 41 42 43

	calculated dihedral angles[a] (degrees)			experimental coupling constants (Hz)				
	33	35	36	39	40	41	42	43[b]
12α/4α5	110.4	109.1	106.1	1-2	<6	<3	<3	--
12β/4β5	4.6	5.6	7.4	10.2	11.0	9	10	--
2α3β/3β4α	162.4	160.7	162.5	12.5	12.0	12.5	12.5	12.7
2β3β/3β4β	48.4	47.0	47.7	6.0	6.3	5.5	5.5	4.2
6α7α/7α8α	50.7	56.8	54.6	--	3.7	3.9	3.2	3.7
6β7α/7α8β	166.3	173.9	170.3	--	12.3	14	13.2	12.7

[a] See Table 8, note a; [b] in order to make comparison simple, an unusual numbering is used.

Table 11. Selected ring torsion angles, valency angles and bond lengths of t-bb conformations of some bicyclo[3.3.1]nonane derivatives

	44	45	46	47
ring torsion angles				
1234	28.9	28.6	28.0	27.5
2345	52.1	52.1	52.4	52.0
3459	11.2	11.6	13.2	12.9
4591	49.8	49.5	48.6	48.8
5912	73.0	72.8	72.7	72.9
9123	31.1	31.3	31.9	32.3
5678	28.9	28.6	27.7	27.4
6781	52.1	51.9	51.0	51.0
7819	11.2	11.0	10.3	10.9
8195	49.8	50.0	50.5	50.0
1956	73.0	73.2	73.9	73.7
9567	31.1	31.4	32.3	32.5
valency angles				
123	113.1	113.6	114.6	114.6
345	113.6	114.0	114.6	114.6
234	112.9	112.2	110.5	110.6
219	107.8	107.9	107.8	107.8
459	111.1	111.2	111.5	111.5
195	107.8	107.6	107.3	107.1
$R_1 3 R_2$	105.7	107.0	104.7	104.7
bond lengths				
23	1.542	1.543	1.551	1.551
34	1.536	1.537	1.543	1.543

Systems with a double twist-boat conformation

The double twist-boat conformation - the most stable bb conformation - of bicyclo[3.3.1]nonane (44) has a twofold axis of symmetry through C_9 and the middle between C_1 and C_5 (see Table 11). An inspection of a *Dreiding* model shows that two "ideal" double twist-boat conformations are possible in the bicyclo[3.3.1]nonane system. In these conformations strong non-bonding interactions occur between $H_{2\alpha}$ and $H_{6\alpha}$ and $H_{4\alpha}$ and $H_{8\alpha}$, respectively, and between $H_{3\beta}$ and $H_{7\beta}$ and the H_9 atoms. The low values for the calculated internal torsion angles $C_1C_2C_3C_4$ and $C_5C_6C_7C_8$ with respect to the corresponding torsion angles in the twist-boat conformation of cyclohexane[14], reveal that the interactions are diminished by a distinct flattening of both wings. The dihedral angles show that the "twisting" is analogous to that in the twist-boat of cyclohexane.

The most characteristic effect of the introduction of a t-butyl substituent at the 3α-position is a rotation of the t-butyl group and $H_{3\beta}$ away from the $H_{2\alpha}$ and $H_{4\alpha}$ atoms (see Fig. 4). This phenomenon is accompanied by some flattening (probably due to the flagpole interaction), stretching of the C_2C_3 and C_3C_4 bonds and a decrease of the valency angle $C_2C_3C_4$. The influences of the substitution on the geometry of the unsubstituted ring are of minor importance.

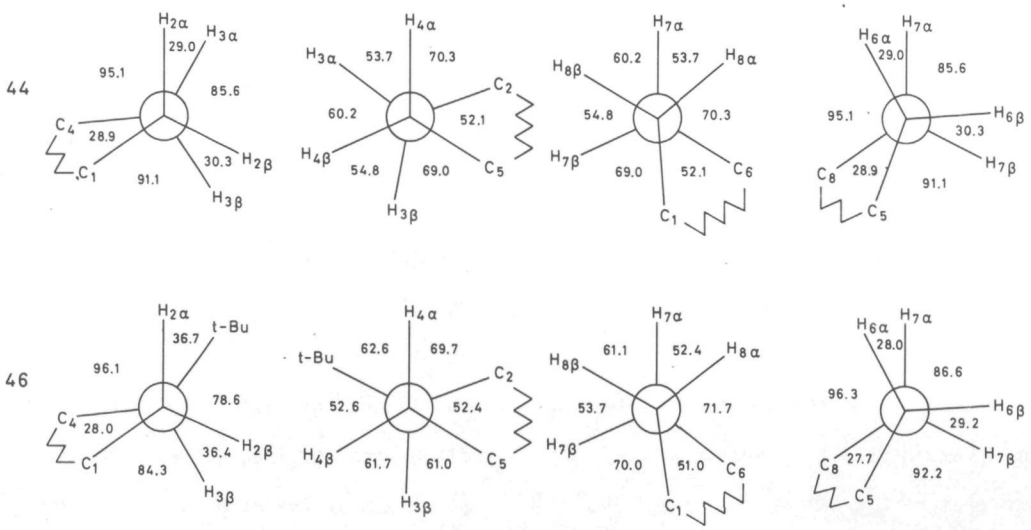


Fig. 4. Torsion angles around C_2C_3, C_3C_4, C_6C_7 and C_7C_8 of the t-bb conformations of bicyclo[3.3.1]nonane (44) and 3α-t-butylbicyclo[3.3.1]nonane (46)

Conclusions

A good agreement exists between the results of the force field calculations and those of the experimental procedures. In bicyclo[3.3.1]nonane and its 3β-substituted derivatives the cc conformation predominates. 3α-Substituents force the substituted ring into the boat conformation. In these compounds the bb conformation can be ignored. For 3α,7α-substituted derivatives the conformational preferences depend on the size of the substituents. With a 3α-methyl and a 7α-t-butyl substituent both the cb and the bb conformers contribute to the conformational equilibrium. The double-twist bb conformation is more stable than the eclipsed bb conformation.

All conformations (cc, cb, t-bb) are distinctly flattened. Substitution of the 3- (and/or 7-) position affects both wings, in particular in the cc and cb conformations. The most characteristic effect of t-butyl substitution is a rotation of the substituted carbon atom away from the nearest H-atoms, accompanied by some flattening of the corresponding ring. Dramatic changes in calculated geometry occur when the 7α-position of the chair part in a bc conformation is substituted.

Experimental

NMR spectroscopy. ^{13}C NMR spectra (20 MHz) were recorded on a Varian CFT-20 apparatus at 35°. The variable temperature ^{13}C NMR spectra (25.2 MHz) were obtained with a Varian XL-100-15 NMR spectrometer system, equipped with a V-4412 universal probe, in the PFT-mode. The chemical shifts are given in ppm relative to TMS (δ).

Calculations. The valence force field calculations were carried out using a fully analytical version of the *Boyd* 1968 minimization procedure[18] and an IBM 370/158 computer.

Epimerisations. The epimerisations were performed as described by *Appleton* et al.[8]. The analyses of the resulting mixtures were carried out by means of GC with a 3m silar-5-CP column or by integration of the CO_2Me signals in the ^1H NMR spectrum after addition of a small amount of $Eu(fod)_3$.

Syntheses. The syntheses of all compounds, with the exception of compound 3, have been described previously[1,3]. For compound 2 the procedure described by *Schneider* and *Ansorge*[5] was followed. Reduction of the Me ester with LAH, followed by conversion of the hydroxymethyl compound into the tosylate and subsequently another LAH reduction gave compound 2.

7α-t-Butylbicyclo[3.3.1]nonane-3α-carboxylic acid. HCl-gas was bubbled through a refluxing mixture of 3.05 g 7α-t-butyl-9-oxobicyclo[3.3.1]nonane-3α-carboxylic acid (12.8 mmole)[3], 80 g freshly prepared Zn-amalgame and 100 ml 37% HCl. After 3 hr the conversion was complete. The mixture was diluted with 600 ml H_2O. The aqueous layer was extracted with ether (5 x 100 ml). The combined organic layers were washed with sat NaCl aq (100 ml) and then extracted with 2 N KOH (4 x 60 ml). The KOH soln was washed with ether (2 x 70 ml) and then acidified with 37% HCl. The dispersion obtained was extracted with ether (4 x 50 ml). The ether soln was washed with H_2O (2 x 50 ml) and dried over $MgSO_4$. After evaporation of the solvents 2.68 g almost pure carboxylic acid (11.9 mmole, 93%) was obtained. Further purification was achieved by sublimation at 100°/10 mm and recrystallisation from light petroleum/EtOAc; m.p. 132-132.5°[1].

7α-t-Butyl-3α-hydroxymethylbicyclo[3.3.1]nonane. The

methyl ester of the compound obtained in the preceding reaction step was esterified with CH_2N_2 in ether. A soln of 1.10 g of the Me ester (4.8 mmole) in 10 ml ether was added dropwise to a suspension of 0.50 g LAH (13.2 mmole) in 15 ml ether. Then the reaction mixture was boiled for 3 hr. After cooling 10 ml H_2O and subsequently 20 ml 4 N H_2SO_4 were added dropwise. The aqueous layer was extracted with ether (4 x 20 ml). The combined ether solns were washed with H_2O (2 x 20 ml) and dried over $MgSO_4$. After evaporation of the solvents 1.00 g of the hydroxymethyl compound (4.8 mmole, 100%) was obtained. This product was identical with an authentic sample[1].

Tosylate of 7α-t-butyl-3α-hydroxymethylbicyclo-[3.3.1]nonane. Tosylchloride (1.00 g, 4.4 mmole) was added to a soln of the product of the preceding step in 20 ml pyridine. The soln obtained was stored at 0^o during 48 hr. Then the reaction mixture was poured onto 200 ml 2 N HCl (0^o). The precipitate was filtered, washed with ice water and dried over P_2O_5. Almost pure tosylate (1.569 g, 4.2 mmole, 87%) was obtained, which was used in the following step without further purification.

7α-t-Butyl-3α-methylbicyclo[3.3.1]nonane. A soln of 1.560 g of the product of the preceding step (4.1 mmole) in 30 ml ether was added dropwise to a suspension of 1.19 g LAH (31.3 mmole) in 30 ml ether. Then the mixture was stirred for 2 hr at room temperature and 2 hr at the boiling point. After cooling 10 ml H_2O and then 40 ml 4 N H_2SO_4 were added dropwise. The aqueous layer was extracted with ether (3 x 20 ml). The combined ethereal solns were washed with H_2O (3 x 20 ml) and dried over $MgSO_4$. The solvents were distilled off and the residue was purified by chromatography over alumina (elution with light petroleum). From the eluate the solvents were distilled off and the residue was distilled under reduced pressure to yield 0.536 g pure 3 (2.8 mmole, 67%); b.p. 130^o/70 mm; mass spectrum important peaks at *m/e* 81, 95, 121, 123, 136 and 137.

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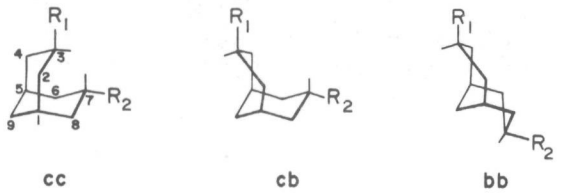
19. All calculations were also performed with the "Allinger 1971" force field[7]. The trends in the results of these calculations are in agreement with those obtained with the "Schleyer 1973" force field. In general the agreement between experimental data and calculations is better with the latter force field.

20. The e-bb conformation is not an energy minimum, as follows from the calculation of the eigenvalues of the final force constant matrix.

CHAPTER 10

^{13}C NMR SPECTROSCOPY OF SOME 3- AND 7-SUBSTITUTED BICYCLO[3.3.1]NONANES *

Due to its conformational features, the bicyclo[3.3.1]nonane system is an attractive subject of study. It has been shown that bicyclo[3.3.1]nonane and its 3-*exo* and/or 7-*exo* substituted derivatives exist in a somewhat flattened double-chair conformation (**cc**).[1] Substitution of the 3-*endo*-position causes severe 3,7-interaction. Consequently these compounds prefer a rigid



chair-boat conformation (**cb**), with the 3-*endo*-substituent (R_1) in the boat part. When both the 3-*endo* and 7-*endo*-position are substituted with bulky groups the double-boat conformation (**bb**) will be favoured.

Previously we have studied the conformation of 3,7-substituted (9-oxo-)bicyclo[3.3.1]nonanes by means of the vicinal proton-proton coupling constants. We are at present investigating some alternative tools for conformational analysis of compounds in which these coupling constants are not conclusive.

It has been shown that the ^{13}C NMR chemical shifts are sensitive to stereochemical factors. Moreover, the effects of substituents on ^{13}C shielding are often additive within a class of compounds.[2] These features make ^{13}C NMR a powerful method for conformational analysis. So far only a few papers on ^{13}C NMR spectroscopy of bicyclo[3.3.1]nonanes—all dealing with compounds in the **cc** and/or **cb** conformation—have been published.[3-5]

In this paper, the ^{13}C NMR spectra of a series of 3- and 3,7-substituted bicyclo[3.3.1]nonanes and the corresponding 9-oxo derivatives are presented and discussed. The conformations of these compounds were established earlier by means of ^{1}H NMR spectroscopy with the aid of lanthanide shift reagents.[1,6] This study includes compounds, which prefer **cc**, **cb** as well as **bb** conformations.

EXPERIMENTAL

The 25.2 MHz ^{13}C NMR spectra were recorded with a Varian XL-100-15 NMR spectrometer system, equipped with a V-4415 universal probe, in the PFT-mode. All spectra were obtained from $CDCl_3$-solutions at 39°. The chemical shifts are given in ppm relative to TMS (δ).

9-Oxobicyclo[3.3.1]nonane and its 7-*endo*- and 7-*exo*-t-butyl derivative were prepared by a Hunsdiecker reaction of the corresponding 9-oxo-bicyclo[3.3.1]nonane-3-carboxylic acid,[6] followed by hydrogenation of the resulting bromide.

Hunsdiecker reaction. To a stirred soln of 16 g dry Br_2 in 100 ml CCl_4 (dried over molecular sieve 3A) 0.088 mole of the silver salt of the carboxylic acid was added in small portions. During the addition of the salt the temp. was maintained at 20–25°. Then the temp. was raised until 50°. After 30 min the mixture was filtered and from the filtrate the solvents were evaporated. A soln of the residue in 50 ml ether was washed with $NaHSO_3$ aq and then with H_2O. After drying over $MgSO_4$ the solvents were evaporated to yield the bromide with a yield of about 70%. This product was used in the next step without further purification.

Hydrogenation. A mixture of 0.01 mole of the bromide in 20 ml EtOAc and 1.0 g NaOAc was hydrogenated at 50° with 10% Pd/C as the catalyst. After the calculated amount of hydrogen was consumed the soln was filtered. After evaporation of the solvents the residue was recrystallized from light petroleum and sublimed at 10 mm. 9-*Oxobicyclo*[3.3.1]*nonane*; m.p. 156–157°. 7-Exo-*t-butylbicyclo*[3.3.1]*nonane*; m.p. 68.5–69.5°; ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.87 (9H, s), 1.5–2.5 (13H). 7-Endo-*t-butylbicyclo*[3.3.1]*nonane*; m.p. 61.5–62.5°; ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.89 (9H, s), 0.9–2.7 (13H).

7 - Endo - *t - butyl* - 3 - endo[2 - (2 - *hydroxypropyl*)] - 9 - *oxobicyclo*[3.3.1]*nonane* was synthesized by reaction of methyl 7 - *endo* - t - butyl - 9,9 - dimethoxybicyclo[3.3.1]nonane - 3 - *endo* - carboxylate[6] with MeMgBr, followed by hydrolysis; m.p. 111–111.5°; ^{1}H NMR (60 MHz, $CDCl_3$): δ 0.87 (9H, s), 1.20 (6H, s), 1.2–2.6 (13H).

The syntheses of all other compounds have been described in previous publications.[1,6]

Spectral assignments. The ^{13}C chemical shift data of the 3,7-substituted bicyclo[3.3.1]nonane derivatives are collected in Table 1; those of the corresponding 9-oxo derivatives in Table 2. Peak assignments were made with the use of the off-resonance technique, the relative intensities and intercomparison of the chemical shifts within families of derivatives. Moreover, substituent effects, estimated from the corresponding cyclohexane derivatives, were taken into account.

DISCUSSION

In order to get an impression of conformational effects on the ^{13}C chemical shifts given in Tables 1 and 2, it is necessary to correct for substituent influences. When the δ and ϵ effects are neglected, the α, β and γ substituent effects in the **cc** system can be derived from a comparison of the data of the compounds concerned. The values obtained (see Table 3) are in good agreement with the corresponding values for cyclohexane derivatives.

For geometric reasons, the interactions, introduced by a 3-*endo* or 7-*endo*-substituent in a boat ring of a **cb** or **bb** conformation, are analogous to those introduced by a 3-*exo*- or 7-*exo*-substituent in the **cc** conformation or an equatorial substituent in cyclohexane. Therefore we

* A reprint of J.A. Peters, J.M. van der Toorn and H. van Bekkum, *Tetrahedron* 33, 349 (1977).

Table 1. ^{13}C chemical shift data for 3,7-substituted bicyclo[3.3.1]nonanes

substituents	conformation[b]	chemical shifts								
		C_1	C_2	C_3	C_6	C_7	C_9	OMe	CO_2Me	alkyl group
nil[a]	cc	27.9	31.6	22.5	31.6	22.5	35.1	--	--	--
3-exo-CO_2Me	cc	27.5	34.0	39.1	30.9	22.1	34.1	51.4	177.1	--
3-exo-CO_2Me, 7-exo-t-Bu	cc	28.1	34.0	39.2	33.3	42.3	33.8	51.4	176.9	27.0, 32.0
3-exo-CMe_2OH	cc	27.0	32.2	43.2	31.5	22.3	34.5	--	--	28.2, 73.2
3-endo-CO_2Me	cb	25.0	29.1	36.0	33.1	16.0	29.1	51.4	177.2	--
3-endo-CO_2Me, 7-exo-t-Bu	cb	25.4	29.6	35.8	34.0	36.5	29.0	51.4	177.2	27.5, 32.1
3-endo-CMe_2OH	cb	25.4	27.2	40.3	33.7	16.0	28.9	--	--	27.1, 73.1
3-endo-t-Bu, 7-exo-CO_2Me	cb	25.2	27.8	38.8	36.4	33.9	27.2	51.4	177.0	27.5, 32.5
3-endo-CMe_2OH, 7-endo-CMe_2OH	bb	24.5	32.0	41.4	32.0	41.4	23.7	--	--	27.0, 72.7

[a] Ref. 3.

[b] As indicated by ^1H-NMR spectroscopy

Table 2. ^{13}C chemical shift data for 3,7-substituted 9-oxobicyclo[3.3.1]nonanes

substituents	conformation[a]	chemical shifts								
		C_1	C_2	C_3	C_6	C_7	C_9	OMe	CO_2Me	alkyl group
nil	cc	46.5	34.3	20.6	34.3	20.6	221.4	--	--	--
3-exo-t-Bu	cc	46.1	35.9	40.7	34.2	21.3	221.3	--	--	27.2, 32.8
3-exo-CO_2Me	cc	45.4	36.4	37.4	34.0	21.0		51.8	--	--
3-exo-CO_2Me, 7-exo-t-Bu	cc	45.2	36.4	38.1	35.7	41.5		51.9		27.2, 31.0
3-endo-t-Bu	cb	44.6	30.7	41.3	36.1	15.2	222.2	--	--	27.3, 32.4
3-endo-CO_2Me	cb	43.8	32.0	37.0	35.8	15.1	219.8	51.8	174.6	--
3-endo-CO_2Me, 7-exo-t-Bu	cb	43.0	32.5	36.8	36.8	36.0	220.6	51.8	174.6	27.9, 31.9
3-endo-CO_2Me, 7-exo-i-Pr	cb	43.0	32.6	36.8	39.1	31.7	220.6	51.8	174.7	20.3, 32.3
3-endo-t-Bu, 7-exo-CO_2Me	cb	43.1	32.4	40.9	37.9	33.2	219.9	51.9	184.9	27.4, 32.4
3-endo-CMe_2OH, 7-endo-t-Bu	bb	42.4	34.4	42.7	34.8	42.2	224.7	--	--	27.0, 27.0, 32.1

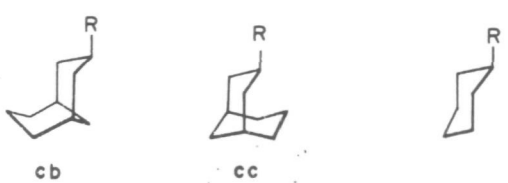
[a] As indicated by ^1H-NMR spectroscopy

Table 3. Substituent effects on ^{13}C chemical shifts in bicyclo[3.3.1]nonane derivatives[a]

	α	β	γ
CO_2Me	16.7	2.3	-0.5
	(16.2)	(1.7)	(-1.6)
CMe_2OH	21.7	0.6	-0.9
	(22.9)	(1.0)	(0.2)
t-Bu	20.0	1.7	0.0
	(21.4)	(0.7)	(0.0)

[a] Derived from cc conformations; the corresponding values for equatorial substitution in cyclohexane[7,8] are given in parenthesis

assume that substituent effects derived from **cc** conformations or from cyclohexane derivatives are in good approximation also applicable for *endo* substituents R in **cb** and **bb** conformations.



After correcting for substituent effects, the agreement of the chemical shifts of corresponding carbons within a series of compounds with the same conformation is very good with a standard deviation of less than 1 ppm. The average values are given in Tables 4 and 5.

As already mentioned by Wiseman and Krabbenhoft[4] the chemical shift of the C_7-atom in the **cb** conformation

Table 4. Average ^{13}C chemical shifts of bicyclo[3.3.1]nonane

conformation	^{13}C chemical shift					
	C_1	C_2	C_3	C_6	C_7	C_9
double-chair	28.1	31.5	22.3	31.5	22.3	34.4
chair-boat[a]	25.9	26.7	19.0	33.3	16.4	28.6
double-boat	26.3	31.4	20.7	31.4	20.7	23.7

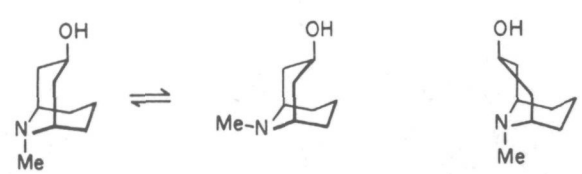
[a] C_2 and C_3 are assigned to the boat part

Table 5. Average ^{13}C chemical shifts of 9-oxobicyclo[3.3.1]nonane

conformation	^{13}C chemical shift					
	C_1	C_2	C_3	C_6	C_7	C_9
double-chair	46.0	34.2	21.0	34.2	21.0	221.4
chair-boat[a]	44.0	29.9	20.6	35.7	15.7	220.6
double-boat	43.3	33.5	21.6	33.5	21.6	224.7

[a] C_2 and C_3 are assigned to the boat part

shows appreciable shielding. This may be attributed to the γ-gauche interactions between the 7-*endo* and the 2- and 4-*endo*-hydrogens, which are operative in this conformation.[9] Probably due to this effect in the **cb** conformation, C_2 and C_4 are also shielded. This explanation would account for the observation that the ^{13}C chemical shifts of C_2 and C_7 in the **bb** conformation are more close to those in the **cc** conformation. The shielding of C_2 and C_4 in the **cb** conformation seems to be in contradiction with the investigation of Wiseman and Krabbenhoft.[4] From the similarity of the chemical shifts of C_2/C_4 in the granatols **1** and **2** these authors concluded that in this case there is no reciprocity for the chemical shifts of the sterically



1a **1b** **2**

interacting moieties. In our opinion, however, a correction should be made for steric effects caused by the N–Me function. Compound **1** occurs approximately as an 1:1 equilibrium of **1a** and **1b**, but in compound **2** the N–Me group is almost exclusively axial to the chair-ring. Consequently C_2 and C_4 in the *exo*-compound **1** experience a considerable γ-gauche effect; in *endo*-compound **2** no γ-gauche interaction between C_2/C_4 and N–Me occurs. After correction for this difference, the trends in ^{13}C chemical shifts of **1** and **2** would seem in agreement with our results.

In the **cb** and **bb** conformations, C_1 is also somewhat shielded with respect to the **cc** conformation. This might be due to eclipsing of H_1 and $H_{2\text{-exo}}$ in the former conformations. Going from the **cb** to the **bb** conformation, no further shielding is observed. This may be associated with twisting in the flexible **bb** conformation.

We did not correct for δ-substituent effects. The differences in chemical shifts of C_9 in the bicyclo[3.3.1]nonane derivatives, however, are large enough to be significant. Probably a γ-eclipsing of C_9 and C_3 and/or C_7 is responsible for the shielding of C_9 in the **cb** and **bb** conformations.

It may be concluded that, after correcting for substituent effects, the ^{13}C chemical shifts of bicyclo[3.3.1]nonane derivatives are characteristic for their conformation. The data presented prove to be useful in the estimate of the conformational preferences of these compounds and may be helpful in signal assignment in ^{13}C NMR spectra of bicyclo[3.3.1]nonane derivatives.

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CHAPTER 11

CONFORMATIONAL ANALYSIS OF 7-ALKYL-3-OXABICYCLO[3.3.1]NONANES AND COMPLEXES WITH LANTHANIDE SHIFT REAGENTS*

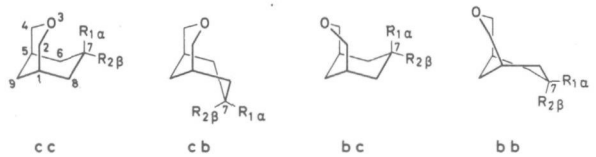
Introduction

Bicyclo[3.3.1]nonane has been shown to exist predominantly in the double-chair (cc) conformation[1,2]. In this conformation a strong repulsion occurs between $H_{3\alpha}$ and $H_{7\alpha}$, which is reflected in a substantial flattening of both wings of the system. An alkyl group at the 3β- or 7β-position enhances the preference of the substituted ring for the chair conformation. Substitution of $H_{3\alpha}$ or $H_{7\alpha}$ by an alkyl group, however, forces the substituted ring into the boat conformation. In the boat-chair (bc) and the chair-boat (cb) conformers both wings are flattened, due to $H_{3\beta}$-H_9 (or $H_{7\beta}$-H_9) and $H_{7\alpha}$-$H_{2\alpha}$/$H_{4\alpha}$ (or $H_{3\alpha}$-$H_{6\alpha}$/$H_{8\alpha}$) interactions.

Replacement of the 3-methylene unit in bicyclo-[3.3.1]nonane by ether oxygen changes the 3,7 and 3,9 interactions in the cc and bc conformation, respectively. It has been suggested that the gauche--gauche 1,5-O-CH_2 interaction is non-repulsive[3]. Therefore, the introduction of oxygen might have implications on the geometry of the wings in the various conformers and also on the relative stabilities of these conformations.

The conformation of 3-oxabicyclo[3.3.1]nonane (1) has been investigated by *Stapp* and *Randall*[4] and by *Zefirov* and *Rogozina*[5]. These authors demonstrated with the use of ^1H NMR spectroscopy that this compound predominantly occurs in the cc conformation. Unfortunately, the separation of the signals in the ^1H NMR spectrum was not large enough to allow a determination of vicinal coupling constants. So no conclusions concerning any flattening could be drawn.

The present investigation deals with a con-



1 R_1=R_2=H
2 R_1=H; R_2=Me
3 R_1=H; R_2=i-Pr
4 R_1=H; R_2=t-Bu
5 R_1=Me; R_2=H
6 R_1=i-Pr; R_2=H
7 R_1=t-Bu; R_2=H

* J.A. Peters, P.E.J. Peters-van Cranenburgh, J.M. van der Toorn, Th.M. Wortel and H. van Bekkum, *Tetrahedron*, submitted.

formational analysis of compound 1 as well as its 7α- and 7β-methyl, isopropyl and t-butyl derivatives (2-7)[6].

From the results of previous investigations[1] as well as from an inspection of *Dreiding* models it can be concluded that for compounds 1-4 the contribution of the cb and the bb conformers to the conformational equilibrium can be neglected; for compounds 5-7, the cb, bc and bb conformations should be taken into consideration.

The conformations of the compounds mentioned were investigated with the use of ^{1}H and ^{13}C NMR spectroscopy[7]. Lanthanide shift reagents (LSR) were used to obtain a separation of the signals in the ^{1}H NMR spectrum. From the $^{3}J_{HH}$ coupling constants information about the extent of flattening was obtained. The magnitudes of these coupling constants are compared with those of related carbocyclic derivatives and with the dihedral angles in these compounds obtained from empirical force field calculations[1].

The $^{3}J_{HH}$ coupling constants, however, do not give information concerning the geometry of the tetrahydropyran ring. Therfore, the agreement between calculated and experimental lanthanide induced shifts of compound 1 as a function of the extent of flattening of this ring was investigated. The results were compared with those of compound 6. For comparison, calculations on the mode of coordination of shift reagents with the somewhat related compounds 4-methyltetrahydropyran (8) and 2-oxa-adamantane (9) were included.

8

9

Results and discussion

^{13}C NMR spectroscopy

The ^{13}C chemical shift data of the 3-oxabicyclo-[3.3.1]nonanes are collected in Table 1. Peak assignments were made with the use of the off-resonance technique, the relative intensities, and intercomparison of the chemical shifts within families of derivatives, taking into account substitu-

Table 1. ^{13}C chemical shifts of 7-substituted 3-oxabicyclo[3.3.1]nonanes

compound	chemical shifts (ppm)						
	C_1	C_2	C_6	C_7	C_9	alkyl group	
1	30.0	73.4	31.2	22.5	33.3		
2	30.7	73.0	40.4	28.1	33.2	24.2	
3	30.6	73.2	35.4	38.9	33.2	19.9	35.0
4	30.5	73.2	31.9	41.9	32.9	27.0	32.8
5	27.9	74.7	35.0	24.8	26.6	22.0	
6	27.7	75.2	30.1	36.2	26.5	20.4	33.2
7	28.4	74.8	27.5	39.4	26.9	27.6	

ent effects.

In order to reveal conformational factors in the ^{13}C chemical shifts of compounds 1-7, it is primarily necessary to correct for substituent influences. Previously, we have shown that the substituent influences in cyclohexane and bicyclo[3.3.1]-nonane are about the same and independent of the ring conformation[7]. Therefore, it is assumed that the same substituent influences can be applied for 3-oxabicyclo[3.3.1]nonane too.

After correcting for the 7-substituent (only α, β, and γ substituent influences were taken into account), the chemical shifts of corresponding carbon atoms, within a series of analogously substituted compounds turn out to agree closely (standard deviation less than 1 ppm). The average values for the corrected ^{13}C chemical shifts are given in Table 2. For comparison the average ^{13}C chemical shifts for the various established conformations of the carbocyclic system[7] are included. The ^{13}C chemical shifts clearly demonstrate that 3-oxabicyclo[3.3.1]nonane (1) and its 7β-substituted derivatives (2-4) occur predominantly in the cc conformation, whereas the 7α-substituted derivatives (5-7) prefer the cb conformation. In particular the ^{13}C chemical shifts of C_6 and C_7 agree well with those of the parent system. Obviously, the shifts of the other carbon atoms are subject to the influence of the heteroatom, but the conformational influences on these shifts observed in the carbocyclic compounds can still be recognized here.

Table 2. Average ^{13}C chemical shifts for 3-oxabicyclo[3.3.1]nonane and bicyclo[3.3.1]nonane[a]

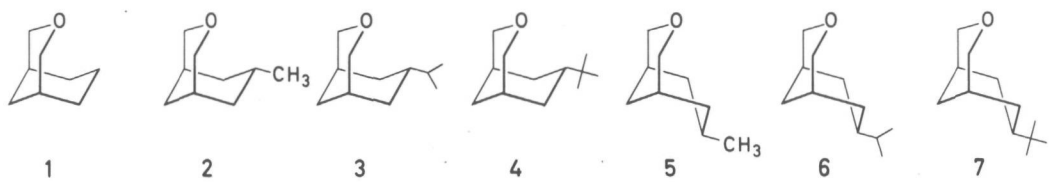
compound	^{13}C chemical shifts (ppm)					
	C_1	C_2	C_3	C_6	C_7	C_9
3-oxabicyclo[3.3.1]nonanes						
1-4	30.4	73.2	--	31.1	22.0	33.7
5-7	27.9	74.9	--	26.1	19.1	26.7
bicyclo[3.3.1]nonanes						
cc	28.1	31.5	22.3	31.5	22.3	34.4
cb	25.9	33.3	16.4	26.7	19.0	28.6
bb	26.3	31.4	20.7	31.4	20.7	23.7

[a] Substituent effects were deduced from ^{13}C chemical shifts in bicyclo[3.3.1]nonanes; Me: α 5.6, β 9.2, γ 0.7; i-Pr: α 17.6, β 3.4, γ -0.5; t-Bu: α 20.0, β 1.7, γ 0.0 ppm.

Vicinal proton-proton coupling constants

^{1}H NMR spectra (100 MHz) of compounds 1-7 were recorded with increasing amounts of $Eu(dpm)_3$ or $Eu(fod)_3$ until optimal separation of the various multiplets was achieved. The signals were assigned by the magnitude of the induced shifts, the splitting patterns, and by using double resonance techniques. From the expanded spectra the coupling constants were derived by first-order analysis. A further refinement of the values obtained was achieved by computer simulation of parts of the spectra. Line broadening, due to large amounts of shift reagent added, was sometimes a limiting factor in determining accurate coupling constants. The magnitudes of the coupling constants were independent of the amount of shift reagent added. Moreover, the relative induced shifts were constant over the whole range of measurements. Therefore, it seems safe to assume that the complexation has no important influence on the conformation of the substrates. The coupling constants obtained are listed in Table 3.

Table 3. Proton-proton coupling constants of 7-alkyl 3-oxabicyclo[3.3.1]nonanes (Hz)



	1	2	3	4	5	6	7
$J_{12\alpha}$	≤4	3-4	3-4	3-4	3-4	3-4	≤4
$J_{12\beta}$	≤4	3-4	3-4	3-4	3-4	3-4	≤4
$J_{18\alpha}$	<4	2.9	<4	<4	≤2	≤2	<5
$J_{18\beta}$	3.3	3.8	∿4	<4	11.5	11.5	10-11
$J_{6\alpha7\alpha}$	5.7	5.3	5-6	5.2	--	--	--
$J_{6\alpha7\beta}$	≤1.0	--	--	--	12.7	13.2	10-13
$J_{6\beta7\alpha}$	12.4	12.2	12-13	12.5	--	--	--
$J_{6\beta7\beta}$	5.7	--	--	--	5.3	5.2	∿5
J_{19syn}	≤4	2.7	<4.5	∿2.5	2.5		
J_{19anti}	≤4		<4.5	∿2.5			
$J_{2\alpha2\beta}$	-10.8	-10.6	-10.5	-10.6	-10.3	-10.5	-10--11
$J_{6\alpha6\beta}$	-13.5	-13.5	-13--14	-13.5	-12.5	-13.5	-12--14
$J_{7\alpha7\beta}$	-13.5	--	--	--	--	--	--
$J_{9syn9anti}$	∿-13	∿-12	-11.8	-12.0	-12.1	-12.2	-12--13

In particular $J_{12\beta}$ and $J_{18\beta}$ are diagnostic for the conformation of the bicyclo[3.3.1]nonane derivative. All values of $J_{12\beta}$ measured are small (< 4 Hz), showing that in all compounds investigated the tetrahydropyran ring predominantly (> 90%) exists in the chair conformation. For 3-oxabicyclo-[3.3.1]nonane itself (1) and its 7β-alkyl derivatives (2-4) the value of $J_{18\beta}$ is small (< 4 Hz), showing these compounds to prefer the cc conformation. From the value of $J_{18\beta}$ in the compounds with a 7α-substituent (5-7), which is about 11.5 Hz, it may be concluded that these derivatives predominantly occur in the cb conformation. Information about the extent of flattening can be obtained from an inspection of the couplings between H_6 and H_7. These coupling constants are very close to those in related carbocyclic compounds[1]; from force field calculations it may be concluded that in these compounds the angle between the $C_1C_8C_6C_5$-plane and the $C_6C_7C_8$-plane is about 145° (the angle between the $C_1C_2C_4C_5$- and $C_1C_6C_8C_5$-planes is about 116°)[2]. It may be assumed that in the 3-oxabicyclo[3.3.1]-nonanes the extent of flattening is about the same. Going from the unsubstituted compound 1 to the 7β--t-butyl derivative 4, there is a slight decrease of $J_{6\alpha7\alpha}$. This is in accordance with the results of the force field calculations[2], which showed that in bicyclo[3.3.1]nonane the strain introduced by a 3β--t-butyl group is relieved by bending $H_{3\alpha}$ into the direction of the center of the ring system, resulting in an increase of the dihedral angle between $H_{3\alpha}$ and $H_{2\alpha}$.

In conclusion: the substitution of the 3--methylene unit in 7-substituted bicyclo[3.3.1]-nonanes by ether oxygen has no substantial influence on the conformational preferences and on the geometry of the carbocyclic six-membered ring in these compounds. Because of the presence of the heteroatom, no information about the flattening of the tetrahydropyran ring could be obtained from the coupling constants.

Complexes of 3-oxabicyclo[3.3.1]nonanes and some related compounds with lanthanide shift reagents

It has been shown that in ^{1}H NMR spectroscopy the chemical shifts induced by lanthanide shift reagents are, in general, of pseudo-contact origin and obey the *McConnell-Robertson* equation (1),

$$\Delta\nu_i = K(3\cos^2\theta_i - 1)/r_i^3 \qquad (1)$$

where $\Delta\nu_i$ is the induced shift in the LSR-substrate complex, r_i the distance between the Ln-ion and the nucleus under consideration, θ_i is the angle between the principal magnetic axis of the complex and the vector r_i, and K is a constant[8]. Thus, apart from the position of the Ln-ion, the induced shift is dependent on the geometry of the substrate. Therefore, the lanthanide induced shift data of the 3-oxabicyclo[3.3.1]nonanes (see Table 4) may be useful for obtaining information about the tetrahydropyran ring in these compounds. So computer searches for the location of the Ln-ion in complexes of shift reagents with these compounds were made. The agreement between the calculated and observed induced shifts was expressed, as usual, in the crystallographic agreement factor[8].

An inspection of molecular models showed that only the *exo* lone pair of the oxygen atom in the 3-oxabicyclo[3.3.1]nonanes investigated is available for coordination with $Eu(dpm)_3$. Therefore, the LIS calculations on these compounds were performed with the assumption of a unique position of the Ln-ion.

Table 4. Relative lanthanide induced shifts

compound	shift reagent	$\Delta\nu_i$ [a]
1	$Eu(dpm)_3$	1.00($H_{2\alpha}$)[b,c]; 0.84($H_{2\beta}$)[b,c]; 0.56($H_{7\alpha}$); 0.37(H_{9syn}); 0.29(H_1,$H_{6\alpha}$,H_{9anti}); 0.22($H_{6\beta}$); 0.18($H_{7\beta}$)
1	$Pr(dpm)_3$	1.00($H_{2\alpha}$)[b,c]; 0.80($H_{2\beta}$)[b,c]; 0.55($H_{7\alpha}$); 0.38(H_{9syn}); 0.31(H_1,$H_{6\alpha}$,H_{9anti}); 0.24($H_{6\beta}$); 0.20($H_{7\beta}$)
4	$Eu(dpm)_3$	1.00($H_{2\alpha}$)[b,c]; 0.83($H_{2\beta}$)[b,c]; 0.72($H_{7\alpha}$); 0.37(H_{9syn}); 0.30(H_1,$H_{6\alpha}$,H_{9anti}); 0.25($H_{6\beta}$)
6	$Eu(dpm)_3$	1.00($H_{2\beta}$)[b]; 0.81($H_{2\alpha}$)[b]; 0.51($H_{6\alpha}$); 0.39(H_{9syn}); 0.30(H_1,H_{9anti}); 0.22($H_{6\beta}$); 0.21($H_{7\beta}$)
8	$Eu(dpm)_3$	1.00(H_{2eq}); 0.82(H_{2ax}); 0.48(H_{3ax}); 0.38(H_{4ax}); 0.31(H_{3eq}); 0.17(Me)[c]
8	$Pr(dpm)_3$	1.00(H_{2eq}); 0.81(H_{2ax}); 0.45(H_{3ax}); 0.36(H_{4ax}); 0.32(H_{3eq}); 0.16(Me)[c]
9	$Eu(dpm)_3$	1.00(H_1); 0.46(H_{4syn}); 0.29(H_{4anti}); 0.27(H_5); 0.24(H_6)
9	$Pr(dpm)_3$	1.00(H_1); 0.47(H_{4syn}); 0.32(H_{4anti}); 0.26(H_5); 0.25(H_6)

[a] The assignments are given in parentheses. Of a set of chemically equivalent atoms only the lowest numbered one is given. [b] The assignments of $H_{2\alpha}$ and $H_{2\beta}$ may be interchanged. [c] Not included in the calculations.

Table 5. The coordination of $Eu(dpm)_3$ with cyclic ethers

compound	method of averaging[a]	distance Eu-O (Å)	ϕ[b] (°)	180-θ[c] (°)	population (%)	agreement factor
1[d,e]	1	4.06	90	2.4	100	0.07
1[d,f]	1	3.09	270	43.5	100	0.06
6	1	2.57	270	63.7	100	0.04
8[g]	1	3.20	90	48.0	100	0.03
8[g]	2	3.27	90	54.6	94	} 0.02
			270	54.6	6	
9	2	3.00	90	39.0	50	} 0.03
			270	39.0	50	

[a] 1 = unique position, 2 = two-site averaging. [b] The angle between the XY-plane and the plane formed by Eu-O and the X-axis. [c] The angle between Eu-O and the positive X-axis. [d] $H_{2\alpha/4\alpha}$ and $H_{2\beta/4\beta}$ not included in the calculations. [e] Angle between C_2OC_4- and $C_1C_2C_4C_5$-planes 145°. [f] Angle between C_2OC_4- and $C_1C_2C_4C_5$-planes 107°. [g] Methyl group not included in the calculations.

Since the $^3J_{HH}$ coupling constants demonstrated that the carbocyclic ring in compound 1 has about the same geometry as that in bicyclo[3.3.1]nonane, we started our calculations with a model with both wings flattened to the same extent. Although the agreement factor obtained is satisfactory, the calculated position of the Ln-ion seems not realistic (see Table 5). Therefore, the C_2OC_4-plane was rotated stepwise around C_2C_4 into the direction of $H_{7\alpha}$ and the calculations were repeated after each step. It appeared that the agreement factor improved slightly: a minimum was reached when the angle between the planes mentioned is 107°. More significantly the calculated position of the Ln--ion for this situation (see Table 5) compares well with that in some related complexes. Although the results of these calculations must be interpreted with care, it seems safe to assume that in 3-oxabicyclo[3.3.1]nonane, the tetrahydropyran ring is less flattened than the corresponding ring in the carbocyclic system. The former ring may even be somewhat puckered. Perhaps an attractive interaction between the ether oxygen and $H_{7\alpha}$ is involved[3]. The two syn interactions between $H_{7\alpha}$ and the tetrahydropyran ring may be responsible for the flattening of the cyclohexane part of the 3-oxabicyclo[3.3.1]nonane system.

In the calculations on the coordination of shift reagents with compound 6, a model for the

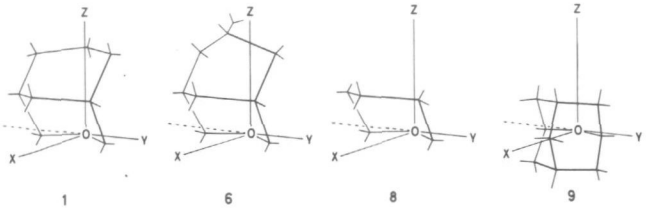


Fig. 1. Positions of the substrates in the coordinate system

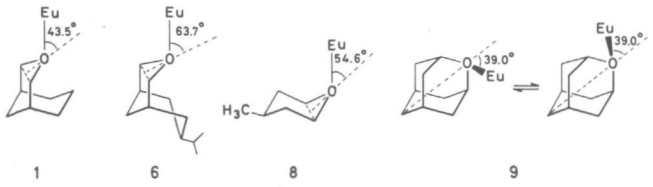


Fig. 2. Calculated Eu(III) locations in $Eu(dpm)_3$ complexes

substrate, analogous to that of the related carbocyclic compound, afforded an optimal fit between experimental and calculated induced shifts. This shows that the complexation has probably no substantial influence on the geometry of the tetrahydropyran ring. The calculated lanthanide location is in agreement with that in the other compounds investigated. Apparently, the geometry of the cb conformation of 3-oxabicyclo[3.3.1]nonanes is analogous to that of the carbocyclic compounds.

For comparison, the LIS calculations were also performed on 4-methyltetrahydropyran (8) and 2-oxaadamantane (9). In these calculations coordination at two sites was considered, situated symmetrically with respect to the plane through the oxygen atom and the two neighbouring carbon atoms (XY-plane, see Fig. 1). For compound 8 the populations of the Ln-ion at these sites were optimized. The calculated coordination sites resemble those of the 3-oxabicyclo[3.3.1]nonanes.

The complexation of 2-oxaadamantane was studied earlier by *Hájek* et al. with the use of the relaxation reagent $Gd(dpm)_3$[14]. From line broadenings of ^1H NMR signals these authors concluded that Gd(III) has a unique coordination site on the X-axis (see Fig. 1). The discrepancy between that study and our LIS calculations may be due to the relative inaccuracy of the ^1H line broadening data

with respect to LIS data.

Surprisingly, the calculated preferred coordination site of 4-methyltetrahydropyran (8) is the axial position in the six-membered ring. This conclusion is supported by the relative strong broadening of $H_{3ax/5ax}$ and $H_{2eq/6eq}$ with respect to those of $H_{3eq/5eq}$ and $H_{2ax/6ax}$ in the $Eu(dpm)_3$ expanded spectrum after the addition of a small amount of $Gd(dpm)_3$. An inspection of *Dreiding* models of the "axial" and "equatorial" complexes of 8 with $Eu(dpm)_3$ shows that it is rather unlikely that the preference for the axial position is caused by steric effects. Possibly, the stabilisation of the "axial" complex may be due to a favourable proximity of the $C_3C_4C_5$ part of the substrate to the t-butyl groups of $Eu(dpm)_3$.

Further investigations are in progress with the aim to obtain additional proof for the conformation of 3-oxabicyclo[3.3.1]nonanes and for the unexpected way of coordination of $Eu(dpm)_3$ with 4-methyltetrahydropyran.

Experimental

The 60 MHz ^1H NMR spectra were recorded on a Varian T-60 apparatus. The 100 MHz ^1H NMR spectra were obtained with a Varian XL-100-15 NMR spectrometer system. The 20 MHz ^{13}C NMR spectra were recorded with a Varian CFT-20 apparatus. All spectra were obtained from $CDCl_3$ solns. The spectra were measured at 39°. Chemical shifts of both the ^1H and ^{13}C resonances are given in ppm relative to TMS (δ).

The lanthanide shift reagents were obtained from Merck. They were sublimed at 180°/0.1 mm and after that handled in a glove box, flushed with dry nitrogen. The solvent used in LIS experiments was dried over molecular sieve 3A.

For the simulation of the ^1H NMR spectra the program LAOCOON-8 was used.

In the LIS calculations relative values of $\Delta\nu_i$ were used (see Table 4). These were obtained from plots of ν_i versus ν_j at various amounts of shift reagent. As shown by *Kelsey* the slopes of these lines give $\Delta\nu_i/\Delta\nu_j$[11,12]. For compounds 1 and 9 the ^1H NMR LIS experiments were performed with both $Eu(dpm)_3$ and $Pr(dpm)_3$. The relative $\Delta\nu_i$ values appear to be almost independent of the shift reagent used, indicating that the contributions of contact and complex formation shift may be neglected[13]. In the ^{13}C NMR experiments the values of $\Delta\nu_i$ were dependent on the shift reagent used. These data were therefore not included in the calculations. The cartesian coordinates of the substrates, required for the LIS calculations, were estimated from those of the corresponding carbocyclic compounds as obtained from empirical force field calculations[2].

The LIS calculations were performed with computer programs, based on those of *Armitage* et al.[9] and *Wing* et al.[10]. In the latter program the coordinate transformation was revised.

Dreiding models of $Eu(dpm)_3$ complexes were constructed using structural parameters of some other complexes, obtained by X-ray spectroscopy[10].

The syntheses of 3-oxabicyclo[3.3.1]nonanes (1-7) have been described previously[6]. 4-Methyltetrahydropyran (8)[16] and 2-oxaadamantane (9)[15] were synthesized according to procedures described in the literature.

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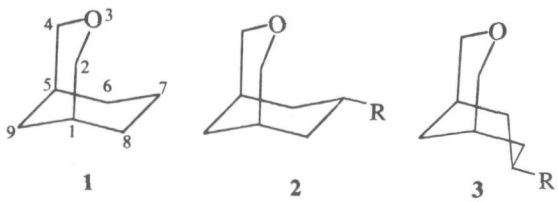
CHAPTER 12

THE ELECTRON IMPACT INDUCED FRAGMENTATIONS OF SOME 7-ALKYL-3-OXABICYCLO[3.3.1]NONANES *

INTRODUCTION

In a previous paper it was shown that for t-butylcyclohexanecarboxylic acids the electron impact induced fragmentation is dependent on the ability of the carboxyl and the t-butyl group to interact.[1] In *cis*-2-, *trans*-2-, *cis*-3- and *cis*-4-t-butylcyclohexanecarboxylic acid a transannular hydrogen transfer is observed, resulting in loss of C_4H_8 and C_4H_7. Other examples of stereoselective fragmentations in cyclohexane derivatives have been given.[2]

With the aid of other instrumental techniques we have studied the configuration and conformation of some bicyclo[3.3.1]nonane derivatives.[3] These systems have a unique structure allowing interesting transannular interactions. Therefore in the mass spectrometry of these compounds stereoselective fragmentations, which might be helpful in configurational assignments, may be operative. Until now only a few studies on the mass



1 2 3

a: R = Me
b: R = i-Pr
c: R = t-Bu

spectral fragmentation of bicyclo[3.3.1]nonanes, most of them dealing with 2-substituted derivatives, have been published.[4]

In this paper the mass spectral fragmentations of 3-oxabicyclo[3.3.1]nonane (**1**), its 7-*exo*- (**2a–c**) and its 7-*endo*-alkyl (**3a–c**) derivatives are reported. The mass spectral fragmentation pattern of these compounds was elucidated using the defocussing technique as well as direct analysis of daughter ions (DADI method).

†Large-sized copies of the fragmentation maps are available from the authors.

Synthesis of the 3-oxabicyclo[3.3.1]nonanes

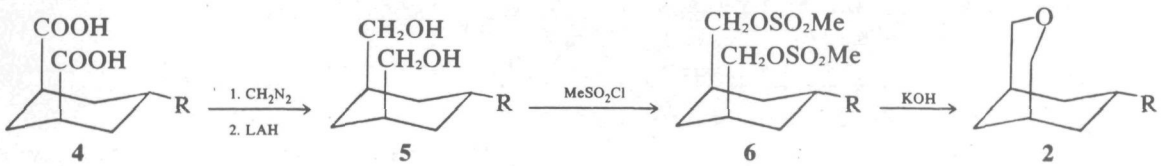
The 7-*exo*-alkyl-3-oxabicyclo[3.3.1]nonanes (**2**) were synthesized following the procedure of Haggis and Owen.[5] 5-Alkylcyclohexane-*cis*-1,3-dicarboxylic acids (**4**) were converted to the methanol derivatives (**5**). Reaction with methanesulfonyl chloride afforded the mesylates (**6**), which gave the desired 7-*exo*-alkyl-3-oxabicyclo[3.3.1]nonanes (**2**) upon reaction with aqueous KOH (Scheme 1). Application of this route to the synthesis of the 7-*endo*-alkyl compounds (**3**) afforded complex mixtures, due to epimerizations during the reaction with KOH. Only the 7-*endo*-t-butyl derivative (**3c**) could be isolated from such a reaction mixture.

The 7-*endo*-methyl- and 7-*endo*-isopropyl-3-oxabicyclo[3.3.1]nonanes (**3a,b**) were synthesized starting from 4-oxacyclohexanone (**7**). α,α'-Annelation of the pyrrolidine enamine **8** with methyl β,β'-dibromoisobutyrate[7] afforded methyl 3-oxa-9-oxobicyclo[3.3.1]nonane-7-*endo*-carboxylate (**9**). After protection of the 9-oxo-function as the dimethyl acetal reduction with LAH and acid hydrolysis gave the 7-*endo*-methanol compound (**11**). The 9-oxo-function was removed by a Huang–Minlon reduction. Tosylation of the resulting methanol compound (**12**) and subsequent reduction with LAH gave 7-*endo*-methyl-3-oxabicyclo[3.3.1]nonane (**3a**). Reaction of **10** with MeMgBr resulted in the corresponding dimethylcarbinol (**13**). Treatment with 4 N H_2SO_4–dioxane (1:1) caused hydrolysis of the acetal and dehydration to yield 7-isopropyl-9-oxo-3-oxabicyclo[3.3.1]non-6-ene (**14**). Due to its special geometry this compound could be hydrogenated selectively to 9-hydroxy-7-*endo*-isopropyl-3-oxabicyclo[3.3.1]nonane (**15**). After oxidation of the 9-hydroxy-function, a Huang–Minlon reduction afforded the desired 7-*endo*-isopropyl-3-oxa-bicyclo[3.3.1]nonane (**3b**) (Scheme 2).

The configuration of compounds **1–3** was proved by NMR spectroscopy with the use of lanthanide shift reagents.

Mass spectra

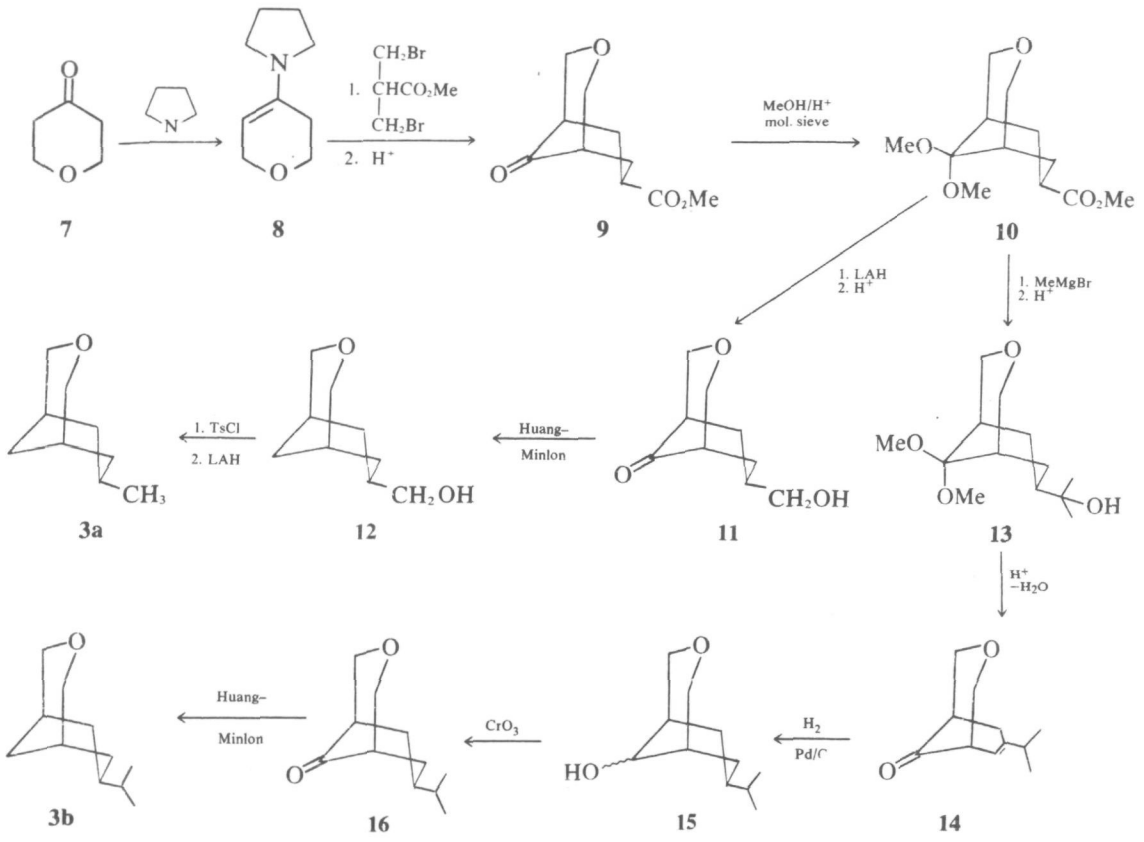
The mass spectra of the oxabicyclo[3.3.1] nonanes (Figs. 1–5)† show that in unsubstituted 3-



4 5 6 2

Scheme 1.

* A reprint of J.A. Peters, B. van de Graaf, P.J.W. Schuyl, Th.M. Wortel and H. van Bekkum, *Tetrahedron* 32, 2735 (1976).



Scheme 2.

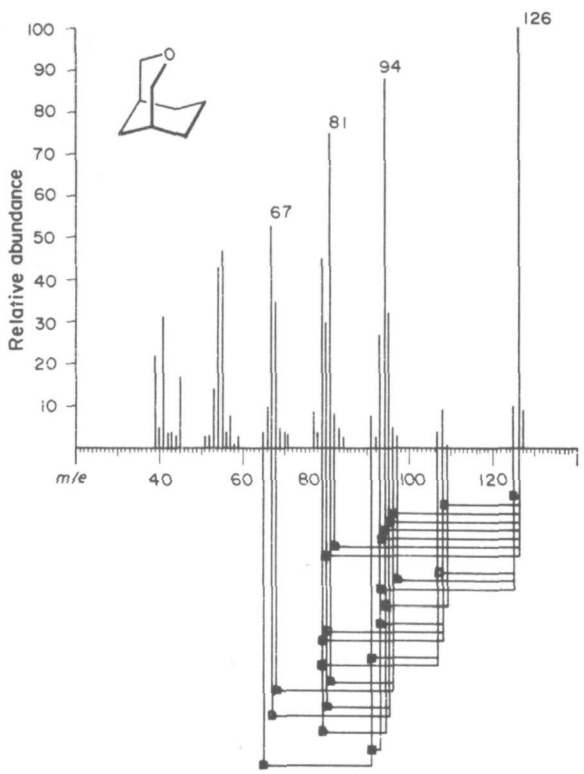


Fig. 1. Fragmentation map of 3-oxabicyclo[3.3.1]nonane.

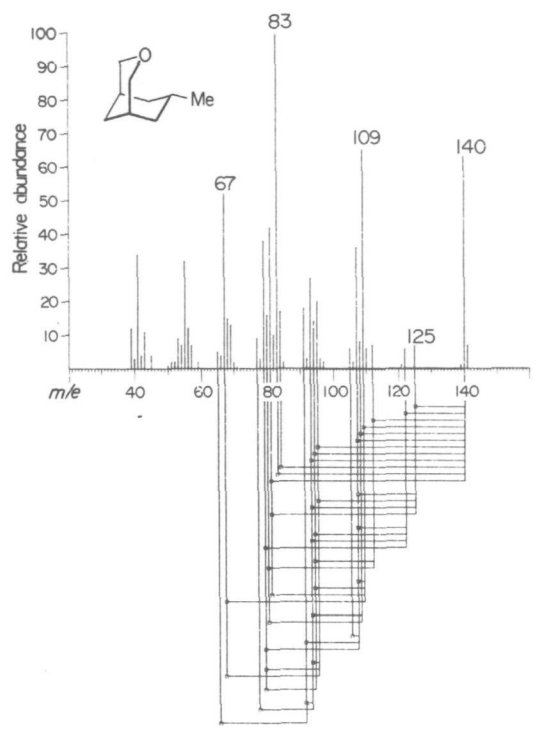


Fig. 2. Fragmentation map of 7-*exo*-methyl-3-oxabicyclo-[3.3.1]nonane.

oxabicyclo[3.3.1]nonane (**1**) the fragmentation is invoked with the expulsion of an oxygen-containing fragment (H_2O, CH_2O, $CH_3O\cdot$, CH_3OH and CH_3OCH_3), whereas in the 7-isopropyl (**2b, 3b**) and 7-t-butyl (**2c, 3c**) derivatives loss of the alkyl group dominates the fragmentation. The 7-methyl derivatives (**2a, 3a**) show both types of fragmentations.

The most important difference in mass spectral behaviour occurs between 7-*exo*-t-butyl-3-oxabicyclo-[3.3.1]nonane (**2c**) and the corresponding 7-*endo*-derivative (**3c**). In **2c** the t-Bu group is eliminated as $C_4H_9\cdot$ to yield the ion at *m/e* 125. In the spectrum of **3c**, in addition to the peak at *m/e* 125, relative intensive peaks are found at *m/e* 126 and 127 (loss of C_4H_8 and $C_4H_7\cdot$ respectively). In this compound the t-Bu group is able to

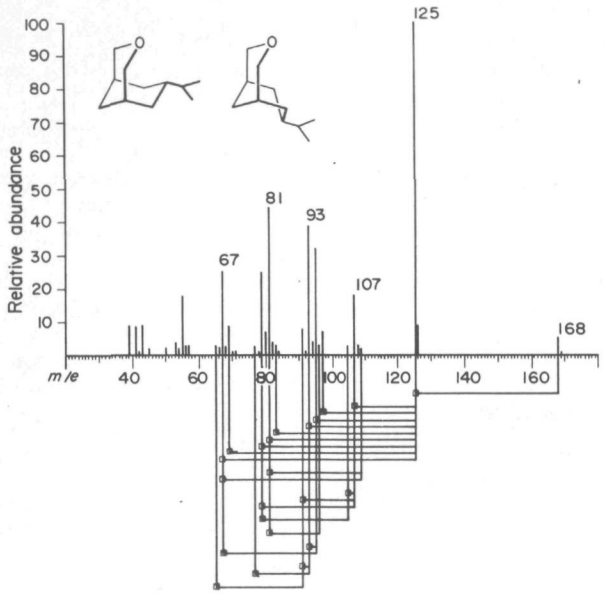


Fig. 3. Fragmentation map of 7-*exo*- and 7-*endo*-isopropyl-3-oxabicyclo[3.3.1]nonane.

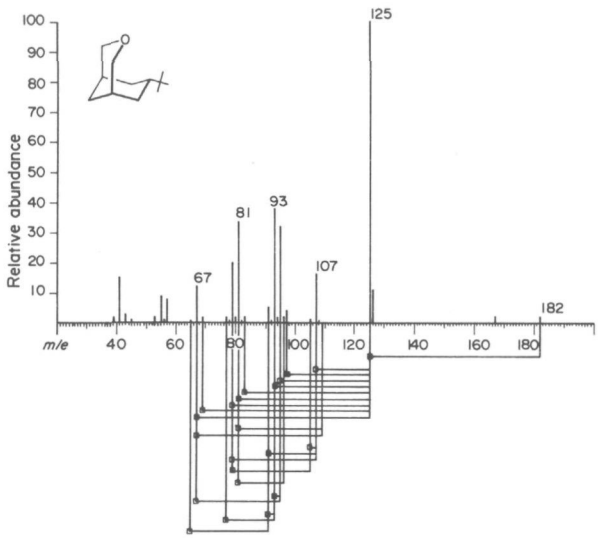


Fig. 4. Fragmentation map of 7-*exo*-t-butyl-3-oxabicyclo-[3.3.1]nonane.

approach the O atom by the conversion of the boat ring into a (flattened) chair, allowing a transannular hydrogen transfer (Scheme 3). Then elimination of C_4H_8 by a simple cleavage reaction affords the ion at *m/e* 126. Here as well

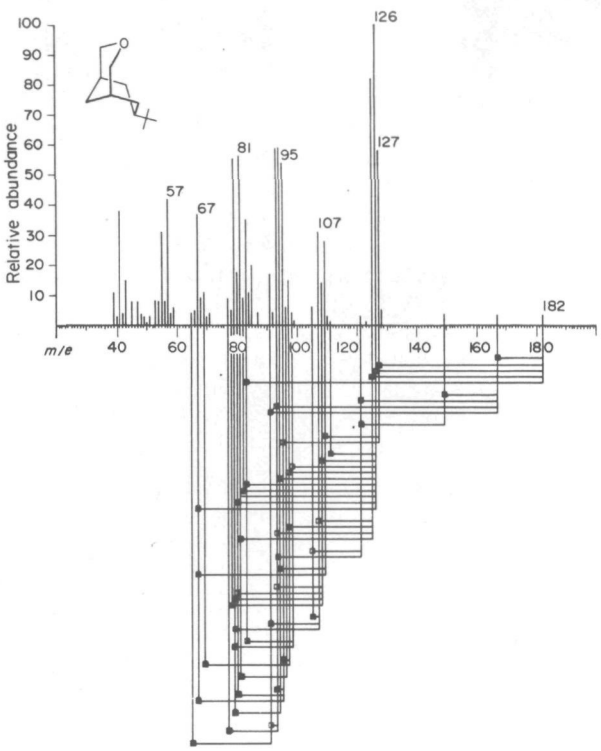
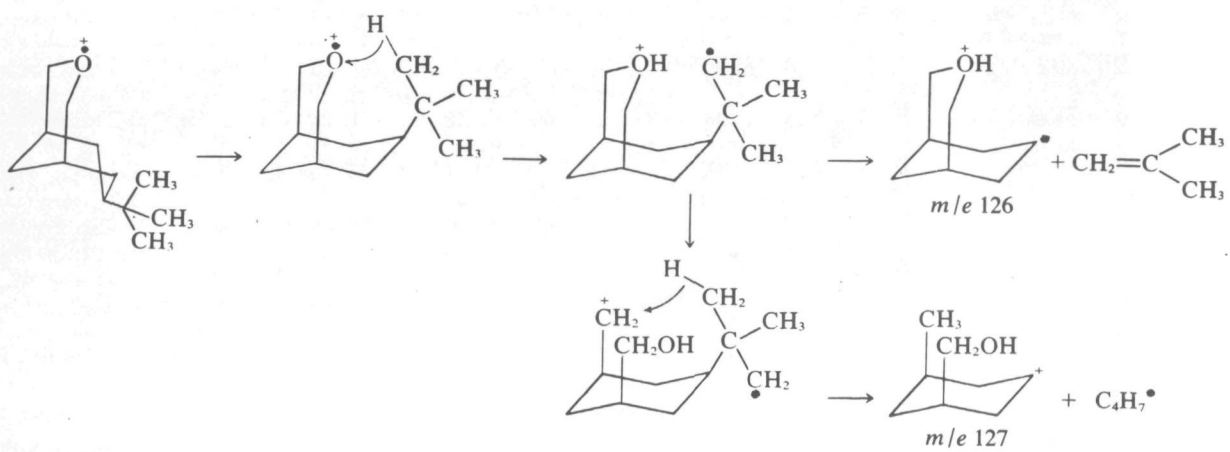


Fig. 5. Fragmentation map of 7-*endo*-t-butyl-3-oxabicyclo-[3.3.1]nonane.

as in the t-butylcyclohexanecarboxylic acids,[1] the elimination of C_4H_8 is accompanied by the loss of $C_4H_7\cdot$. Most probably the latter fragmentation also starts with a transannular hydrogen transfer. This might be followed by heterolytic cleavage and one or more hydride shift(s) with elimination of $C_4H_7\cdot$ (Scheme 3).

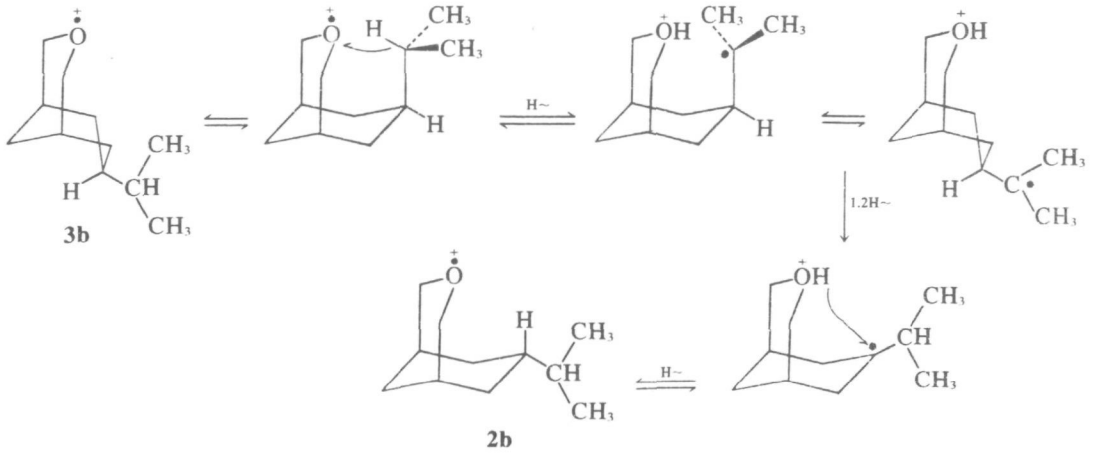
It may be noted that, in contrast to the spectra of **2c** and **3c**, the spectra of *endo* and *exo*-7-isopropyl-3-oxabicyclo[3.3.1]nonane (**2b, 3b**) are almost identical. The fragmentations producing the ions at *m/e* 126 and 127 were not observed to any extent. This similarity in mass spectral behaviour prompted us to investigate the mass spectra of *cis*- and *trans*-4-isopropylcyclohexanecarboxylic acid. Here indeed, in contrast to the corresponding t-Bu derivatives, the same similarity was observed. This does not imply that in the *endo*-compound **3b** (or *cis*-4-isopropylcyclohexanecarboxylic acid) a transannular hydrogen transfer is absent. It is well established that transfer of a tertiary hydrogen is preferred over a primary one;[9,10] both transfers would be allowed by the geometry. The first hydrogen transfer rationalizes the absence of loss of



Scheme 3.

C_3H_6 and C_3H_5·. Subsequent hydrogen transfers could result in epimerization of the *endo*-compound (**3b**) to the *exo*-compound (**2b**) (or *cis* to *trans*-4-isopropylcyclohexanecarboxylic acid). If this isomerization is relatively fast (with respect to fragmentation) the similarity of mass spectra can be explained. A possible mechanism for **3b** is outlined in Scheme 4.

From this investigation and that of the 4-alkylcyclohexanecarboxylic acids[1] it may be concluded that for t-alkyl substituted compounds, differences in mass spectral behaviour, due to presence or absence of interaction between the alkyl group and the cation radical site, may be quite helpful in configurational assignments.



Scheme 4.

EXPERIMENTAL

Mass spectra were recorded on a Varian-MAT 311A mass spectrometer, operating at 70 eV and 3 mA emission current. Samples were introduced via a heated reservoir inlet system. The metastable DADI experiments were carried out by a scan of the electrostatic analyzer voltage from 500 to 50 V. The metastable defocussing experiments were carried out by a scan of the accelerating voltage from 1–3 kV. The metastable analyses were carried out for the ions between *m/e* 65 and the parent ion.

The 7-*exo*-alkyl-3-oxabicyclo[3.3.1]nonanes (**1, 2**) and 7-*endo*-t-butyl-3-oxabicyclo[3.3.1]nonane (**3c**) were synthesized following the procedure of Haggis and Owen,[5] starting from the corresponding 5-alkylcyclohexane-*cis*-1,3-dicarboxylic acids.[6]

3-*Oxabicyclo*[3.3.1]*nonane* (**1**). Purification was achieved via the thiourea inclusion compound, followed by sublimation; m.p. 111–113°. ^{1}H NMR (CCl_4, 100 MHz); δ 3.86 (2H, broad d), 3.65 (2H, broad d), 1.4–2.8 (10H).

7-Exo-*methyl*-3-*oxabicyclo*[3.3.1]*nonane* (**2a**). Purification was achieved via the thiourea inclusion compound and distillation; b.p. 170°/760 mm. ^{1}H NMR (CCl_4, 100 MHz); δ 3.76 (2H, broad d), 3.57 (2H, broad d), 2.55 (1H, broad septet), 0.83 (3H d), 0.8–2.1 (8H).

7-Exo-*isopropyl*-3-*oxabicyclo*[3.3.1]*nonane* (**2b**). Purification was achieved via the thiourea inclusion compound followed by distillation; b.p. 103°/26 mm. ^{1}H NMR ($CDCl_3$, 100 MHz); δ 3.84 (2H, broad d), 3.66 (2H broad d), 2.20 (1H), 0.88 (6H), 1.0–2.1 (9H).

7-Exo-t-*butyl*-3-*oxabicyclo*[3.3.1]*nonane* (**2c**). Purification was achieved via the thiourea inclusion compound, followed by distillation; b.p. 104°/18 mm; ^{1}H NMR ($CDCl_3$, 100 MHz): δ 3.86 (2H, broad d), 3.70 (2H, broad d), 0.87 (9H, s), 1.1–2.0 (9H).

Pyrrolidine enamine of 4-*oxacyclohexanone* (**8**). In a nitrogen atmosphere, a mixture of 73.4 g 4-oxacyclohexanone[8] (0.73 mole), 165 ml pyrrolidine and 2 g *p*-TsCl was boiled in 750 ml benzene. Water was separated by means of a Dean–Stark trap. After 3 hr no more water was formed. The benzene was evaporated off under vacuo and the residue was used in the next reaction step without further purification.

Methyl 3 - *oxa* - 9 - *oxobicyclo*[3.3.1]*nonane* - 7 - endo - *carboxylate* (**9**). In a nitrogen atmosphere to a stirred boiling soln of the crude product of the preceding step and 70.7 g Et_3N in 530 ml MeCN was added dropwise in 1 hr a soln of 131.6 g methyl β,β'-dibromoisobutyrate (0.51 mole) in 400 ml MeCN. Then the soln was boiled under reflux for 1 hr. After addition of 50 ml 5% HOAc the mixture was boiled for another hr. From the resulting soln the greater part of the solvents were evaporated under vacuum. The residue was diluted with sat NaCl aq (1 l) and extracted with EtOAc (6 × 150 ml). The EtOAc layers were washed with sat NaCl aq (2 × 150 ml), and dried over $MgSO_4$. Evaporation of the solvents yielded 52.6 g crude **9**. After distillation 31.4 g pure **9** (0.16 mole, 31%) was obtained; b.p. 112°/0.8 mm; ^{1}H NMR (60 MHz, CCl_4): δ 3.66 (3H, s), 1.8–4.4 (11H), mass spectrum (70 eV): important peaks at *m/e* 198, 170, 169, 168, 167, 166, 165, 152, 139.

Methyl 9,9 - *dimethoxy* - 3 - *oxabicyclo*[3.3.1]*nonane* - 7 - endo *carboxylate* (**10**). Compound **9** (31.0 g, 0.16 mole) was stirred with 105 ml MeOH and 10 g *p*-TsOH in 500 ml dry hexane. The stirrer was stopped and 90 g molecular sieve KA was added. After 1 min the stirrer was started again. After 20 min 10 g *p*-TsOH and 30 g KA powder were added. After another 10 min the mixture was filtered and the sieve was washed with dry ether. The filtrate was washed with sat $NaHCO_3$ aq (2 × 100 ml). The washings were extracted with ether (2 × 100 ml). The combined organic layers were dried over $MgSO_4$–K_2CO_3. After evaporation 29.2 g **10** (0.12 mole, 76%) was obtained; ^{1}H NMR (60 MHz, CCl_4); δ 3.5–3.8 (4H), 3.55 (3H, s), 3.10 (6H, s), 0.9–2.7 (7H).

3 - *Oxa* - 9 - *oxobicyclo*[3.3.1]*nonane* - 7 - endo - *methanol* (**11**). To a stirred suspension of 8.6 g LAH (0.23 mole) in 260 ml dry ether was added dropwise a soln of 15.1 g **10** (0.062 mole) in 90 ml dry ether. Then the mixture was boiled for 3 hr. After cooling 50 ml H_2O and 200 ml 4 N H_2SO_4 were added dropwise subsequently. The aqueous layer was extracted with EtOAc (5 × 100 ml). The combined organic layers were washed with sat NaCl aq (2 × 100 ml) and dried over $MgSO_4$. After evaporation of the solvents 6.7 g **11** (0.039 mole, 64%) was obtained. This compound was used in the next step without further purification.

3 - *Oxabicyclo*[3.3.1]*nonane* - 7 - endo - *methanol* (**12**). Compound **11** (6.7 g) was boiled with 6.3 ml 100% hydrazine and 7.90 g KOH in 55 ml triethylene glycol for 1.5 hr. Then the mixture was distilled until a bottom temp of 200° was reached. The residue was boiled under reflux for another 5 hr. The residue and the destillate were combined and diluted with 150 ml sat NaCl aq. After filtration, the suspension was extracted with ether (5 × 50 ml). The ether extract was washed with sat NaCl aq and dried over $MgSO_4$. After evaporation of the solvents 3.67 g **12** (0.024 mole, 62%) was obtained, which was used in the next step without purification.

Tosylate of compound **12**. Crude **12** (3.60 g, 0.023 mole) was dissolved in 40 ml pyridine. After adding 7.0 g TsCl (0.037 mole)

the mixture was stored at 0° for 12 hr. Then the mixture was poured onto 250 ml 1 N HCl (0°). The dispersion obtained was extracted with EtOAc (6 × 50 ml). The EtOAc layers were washed with 2 N HCl (2 × 50 ml) and sat NaCl aq (2 × 50 ml) and dried over $MgSO_4$. After evaporation of the solvents 3.57 g of a tosylate mixture was obtained.

7 - Endo - *methyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**3a**). To a suspension of 2.0 g LAH (0.053 mole) in 60 ml ether, a soln of the crude product of the preceding step in 30 ml ether was added dropwise. The mixture was boiled under reflux for 4 hr. After cooling 10 ml H_2O and 90 ml 4 N H_2SO_4 were added dropwise subsequently. The aqueous layer was extracted with ether (4 × 30 ml). The combined organic layers were washed with H_2O (2 × 30 ml) and dried over $MgSO_4$. After filtration the ether was distilled off. The residue, which consisted of **3a** and small amounts of **2a**, **12** and some unidentified products, was further purified by means of preparative GLC (6 m OV-17, 115°). After that **3a** was still contaminated with a small amount of **2a**. GC–MS analysis showed no essential differences between the mass spectra of **3a** and **2a**; ^{1}H NMR (60 MHz, CCl_4): δ 3.46 (4H, AA'BB'-system), 0.88 (3H, d: J = 6 Hz), 0.8–2.1 (9H).

9,9 - *Dimethoxy* - 7 - endo - [2 - (2 - *hydroxypropyl*)] - 3 - *oxabicyclo* [3.3.1] *nonane* (**13**). A MeMgBr soln was prepared from 7.45 g Mg (0.31 mole) in 50 ml THF and a 3.50 M soln of MeBr in THF (100 ml, 0.35 mole). This soln was cooled to 0°. Then a soln of **10** (14.0 g, 0.057 mole) in 50 ml THF was added dropwise in 30 min. After that the reaction mixture was boiled under reflux for 3 hr. After cooling to 0° sat $(NH_4)_2SO_4$ (500 ml) was added dropwise. The aqueous layer was extracted with EtOAc (5 × 80 ml). The combined organic layers were washed with sat NaCl aq (3 × 80 ml) and dried over $MgSO_4$–K_2CO_3. After evaporation of the solvents 13.8 g **13** (0.057 mole, 100%) was obtained; ^{1}H NMR (60 MHz, CCl_4): δ 3.3–3.8 (4H, AA'BB'), 3.12 (3H, s), 3.15 (3H, s), 1.10 (6H, s), 1.0–2.8 (8H).

7 - *Isopropyl* - 9 - *oxo* - 3 - *oxabicyclo*[3.3.1]*non* - 6 - *ene* (**14**). The product of the preceding reaction step was boiled with 50 ml H_2O, 50 ml dioxane and 50 ml 4 N H_2SO_4 for 2 hr. Then the reaction mixture was extracted with ether (3 × 50 ml) and EtOAc (2 × 50 ml). The combined organic layers were washed with sat NaCl aq (2 × 50 ml) and dried over $MgSO_4$. Evaporation of the solvents gave 13.9 g alkenes mainly **14**; b.p. 80–110°/0.10 mm; ^{1}H NMR (60 MHz, CCl_4): δ 5.42 (1H, broad d: J = 6 Hz), 1.08 (6H, d: J = 7 Hz), 1.5–4.2 δ (11H).

9 - *Hydroxy* - 7 - endo - *isopropyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**15**). Compound **14** (4.50 g, 0.025 mole) was hydrogenated in 50 ml EtOAc with 700 mg 10% Pd/C as catalyst at 60° and 1 atm H_2. When no more H_2 was taken up, the catalyst was filtered and from the filtrate the solvents were evaporated off to yield 4.32 g almost pure **15** (2 epimers) (0.024 mole, 96%).

7 - Endo - *isopropyl* - 9 - *oxo* - 3 - *oxabicyclo*[3.3.1]*nonane* (**16**). At 0°, to a soln of the crude product of the preceding step in 25 ml acetone 6 ml of Jones reagent (26.7 g CrO_3 in 23 ml 100% H_2SO_4, diluted with H_2O to 100 ml) was added dropwise. The mixture was stirred at room temp. for 1 hr. Then 15 ml MeOH was added. After another 30 min the mixture was diluted with H_2O (50 ml) and then extracted with $CHCl_3$ (5 × 15 ml). The $CHCl_3$-layers were washed with H_2O (3 × 15 ml) and dried over $MgSO_4$. The solvents were evaporated off and the residue (3.72 g) was purified via the thiourea inclusion compound to yield 0.72 g chromatographically pure **16**; mass spectrum (70 eV): important peaks at *m/e* 184, 182, 165, 149, 121, 119, 109, 107 and 105.

7 - Endo - *isopropyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**3b**). Compound **16** (720 mg) was boiled with 0.6 ml 100% hydrazine and 770 mg KOH in 10 ml triethylene glycol for 1.5 hr. Then the mixture was distilled. In 7 hr, the bottom temp. was slowly raised to 200°. The distillate and the residue were combined and then diluted with 15 ml H_2O. The mixture obtained was extracted with ether (6 × 15 ml). The ether layers were extracted with sat NaCl aq and dried over $MgSO_4$. After filtration 40 ml of ether was distilled off. The residue was purified via preparative GLC (6 m OV-17, 150°); ^{1}H NMR (60 MHz, CCl_4): δ 3.44 (4H, AA'BB'-system), 0.88 (6H, d: J = 5.5 Hz), 1.0–2.4 (10H).

7 - Endo - t - *butyl* - 3 - *oxabicyclo*[3.3.1]*nonane* (**3c**). According to Scheme 1 a mixture was obtained, containing **3c** as well as **2c**. Rough purification was achieved by distillation. The fraction, which boiled at 90–100°/5 mm was further purified by chromatography over alumina with $CHCl_3$ as eluent, followed by distillation; b.p. 110°/5 mm. ^{1}H NMR (CCl_4, 60 MHz): δ 3.40 (4H, AA'BB'-system), 0.90 (9H, s), 1.0–2.5 (9H).

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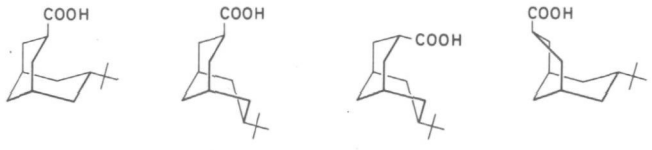
[9]M. M. Green, R. J. Cook, W. Rayle and E. Walton, *Chem. Commun.* 81 (1969).

[10]M. M. Green and R. B. Roy, *J. Am. Chem. Soc.* **92**, 6368 (1970).

ADDITIONAL COMMENT

Recently, we have studied the mass spectral fragmentation of the four epimeric 7-t-butylbicyclo-[3.3.1]nonane-3-carboxylic acids (1-4). Again the mode of the expulsion of the t-butyl group appeared to be dependent on the configuration (see Table 1).



1 2 3 4

Table 1. Relative peak intensities[a] in the mass spectra of compounds 1-4 (70 eV).

m/e	1	2	3	4
M-55	54	22	39	4
M-56	52	100	100	4
M-57	14	7	52	100
M-58	30	5	2	0

[a] Corrected for ^{13}C- and ^{18}O natural abundances.

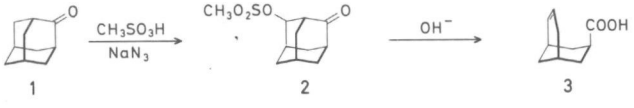
Compound 1 showed all possible modes of t-butyl expulsion in a substantial way. Moreover, the DADI spectra of the ions, given in Table 1, are almost independent on the configuration. Therefore, the fragmentation of this compound was studied in some detail. At decreasing electron energies the ratios of the intensities of the peaks at m/e M-55, M-56, and M-57 were essentially constant. Therefore, it may be assumed that in *all* fragmentations in question rearrangements are involved. Labelling studies indicated that fragmentation yielding the M-55 ion comprises multistep hydrogen shifts.

Similar complicated rearrangements may be involved in the fragmentations of the 7-t-butyl-3--oxabicyclo[3.3.1]nonanes, described in the foregoing Chapter. In order to elucidate the mass spectral fragmentation mechanisms in these and analogous compounds further work is in progress.

CHAPTER 13

4-Methylprotoadamant-4-en-2-one: an unexpected product from the reaction of 1-methyladamantan-2-one with sodium azide and methanesulfonic acid *

Some years ago *Sasaki* et al.[1] reported that adamantanone (**1**) under Schmidt conditions gave 4(e)-(methanesulfonoxy)-adamantan-2-one (**2**), accompanied by small amounts of the normal Schmidt product 4-azahomoadamantan-5-one. With dilute alkali **2** was smoothly converted into bicyclo[3.3.1]-non-6-ene-3α-carboxylic acid (**3**). Meanwhile this route has also been used with success starting from diamantanone[2,3].



1 2 3

Scheme 1

In our studies on 3,7-substituted bicyclo[3.3.1]nonanes[4] we selected this procedure to synthesize 3- and 7-methyl-substituted bicyclo[3.3.1]nonane-3α-carboxylic acids starting from 1-methyladamantan-2-one[5].

The first reaction step, however, did not yield the expected 4-methanesulfonoxy derivative as shown by the absence of sulfur and a ^{1}H-NMR signal from the CH_3SO_3-group. On treatment with alkali no reaction occurred. According to GLC analysis the reaction product consisted of two compounds in the ratio 2 : 1. These compounds were separated by preparative GLC.

For the major product combustional and mass spectral analysis (important peaks at *m/e* 162, 124, 119, 105, 93, 92, 91, 77 and 65) gave the molecular formula $C_{11}H_{14}O$. The IR spectrum (CCl_4) showed characteristic bands at 2940, 1740 and 1660 cm^{-1}. The ^{1}H-NMR spectrum (60 MHz, CCl_4) showed resonances at δ 6.12 (1H, broad doublet J = 8 Hz) and 1.1–2.8 (13H, complex signal). In the complex signal a sharp doublet (δ 1.80, J = 1–1.5 Hz) was observable, which collapsed into a singlet on irradiation at δ 6.12. Irradiation at δ 1.80 changed the signal at δ 6.12 into a sharp doublet. Upon addition of Eu(fod)$_3$ a doublet (1H, J = 7 Hz) and a broad singlet (1H) were separated from the complex signal. The ^{13}C-NMR spectrum (25.2 MHz, $CDCl_3$) consisted of 11 signals: at δ 212.2 (s), 135.0 (s), 134.4 (d), 53.7 (d), 49.5 (d), 39.4 (t), 37.1 (t), 34.8 (t), 31.4 (d), 31.2 (d) and 21.9 (q) ppm relative to TMS. From these data we conclude that the major compound is 4-methylprotoadamant-4-en-2-one (**4**).

4 5

This structure was confirmed by the Lanthanide Induced Shift (LIS) data. Table I shows the slopes of the lines obtained by plotting the chemical shifts of the protons or ^{13}C-atoms *versus* the induced chemical shifts of the H_5- or C_5-signal, respectively, for increasing amounts of Eu(fod)$_3$. If no contact shift is present these slopes are equal to the ratio of the maximally induced chemical shifts Δ^i_{max} and Δ^5_{max} (*i* is the atom under consideration)[6].

[1] *T. Sasaki, S. Eguchi* and *T. Toru*, J. Amer. Chem. Soc. **91**, 3390 (1969).
[2] *F. Blaney, D. Faulkner* and *M. A. McKervey*. Synth. Commun. **3**, 435 (1973).
[3] *J. A. Peters, J. M. van der Toorn* and *H. van Bekkum*. Tetrahedron accepted for publication.
[4] *J. A. Peters, J. M. van der Toorn* and *H. van Bekkum*. Tetrahedron **30**, 633 (1974).
[5] *D. Lenoir, R. Glaser, P. Mison* and *P. v. R. Schleyer*. J. Org. Chem. **36**, 1821 (1971).
[6] *D. R. Kelsey*. J. Amer. Chem. Soc. **94**, 1764 (1972).

* A reprint of J.A. Peters, J.M. van der Toorn and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas* 94, 122 (1975).

Table I LIS data on compound **4**.

atom position	^{13}C-NMR data		^{1}H-NMR data	
	δ_o (ppm)	Δ^i/Δ^{C_5}	δ_o (ppm)	Δ^i/Δ^{H_5}
1	49.5	1.62	2.08	2.83
2	212.2	–	–	–
3	53.7	0.63	2.25	3.26
4	135.0	1.31	–	–
5	134.4	1.00	6.12	1.00
6	31.4	0.67		
7	34.8	0.42	1.38	0.87
8	39.4	1.06		
9	37.1	0.77		
10	31.2	0.49		
Me	21.9	0.67	1.80	1.39

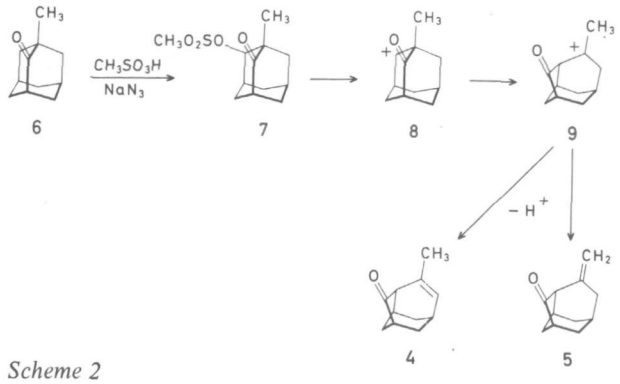
Since Δ_{max} is dependent on the position of the atom in question with respect to the coordinated Eu(III)ion according to the Roberts-McConnell equation [1], these slopes are diagnostic for the structure.

$$\Delta_{max} = K(3\cos^2\theta - 1)/R^3 \qquad [1]$$

Assuming that complexation occurs into the oxygen atom's lone pair orbitals[7], a calculation[8], using equation [1], shows that good agreement with the experimental slopes is obtained when the two possible ways of coordination (*Z* and *E* with respect to C_1) contribute in a ratio 4 : 1. Obviously this preference is caused by steric factors. The calculated slopes differ from the experimental ones for C_1, C_2, C_3, H_1 and H_3. For these atoms the proximity of Eu(III) will cause a large contribution of contact shift.

For the minor reaction product the ^{1}H-NMR spectrum (60 MHz, CCl_4) showed a broad signal at δ 4.83 (2H) and a complex signal at δ 1.4–3.2 (12H). Probably this compound is 4-methyleneprotoadamantan-2-one (**5**).

These unexpected reaction products may be explained by the following reaction sequence. The initially formed methanesulfonoxy compound **7** undergoes elimination yielding the secondary carbenium ion **8**, which rearranges towards the tertiary cation **9**. Upon deprotonation of **9**, **4** or **5** is obtained (see Scheme 2).



Scheme 2

The difference in behaviour between **2** and **7** may be connected with the stability of the cations formed upon elimination of the methanesulfonoxy group. Unlike **8**, the secondary carbenium ion obtained from **2** is unable to rearrange to a more stable tertiary carbenium ion.

Experimental part

The 60 MHz ^{1}H-NMR spectra were recorded on a Varian T-60 apparatus. The 25.2 MHz ^{13}C-NMR spectra were obtained with a Varian XL-100–15 NMR spectrometer system, equipped with a V-4415 *universal* probe, in the FT-mode. The multiplicity of the ^{13}C resonances was determined by the off-resonance technique. After addition of $Eu(fod)_3$ the relation between the ^{13}C and ^{1}H signals was established by selective proton decoupling. The spectra were recorded at 39°. Chemical shifts of both the ^{1}H and ^{13}C resonances are given in ppm (δ) relative to TMS.

The mass spectra were recorded by Messrs. *B. van de Graaf, P. J. W. Schuijl* and *H. M. A. Buurmans* with a Varian-MAT SM-1 spectrometer at 70 eV using a direct insertion probe.

The IR spectra were recorded with a Hilger-Watts Infrascan apparatus.

The elemental analysis was performed by Mr. *M. van Leeuwen* and was correct within 0.2% (absolute).

"Schmidt reaction" of 1-methyladamantan-2-one

To a suspension of 5.78 g (3.52 mmole) of 1-methyladamantan-2-one in 45 ml methanesulfonic acid was added in portions 3.57 g (0.06 mole) of sodium azide in 1 hr at 0°. The dispersion was stirred for 4 hr at 0°. The reaction mixture was then poured on to 100 g of ice. The dispersion obtained was extracted with ether (5 × 50 ml). The ethereal solution was washed with water (2 × 50 ml) and dried over $MgSO_4$. After evaporation of the solvent 3.71 g of an oil, consisting of two compounds in a ratio of 2 : 1, was obtained. Separation was achieved by preparative GLC (6 m PEG, 190°). The major product was subsequently distilled; b.p. 122°/13 mm.

[7] *D. J. Chadwick* and *D. H. Williams*, Chem. Comm. **1974**, 128.

[8] A computer programme is being designed in order to get a more precise calculation in problems of this type.

SAMENVATTING

Deel I van dit proefschrift omvat een onderzoek naar de synthetische toepasbaarheid van de *Koch–Haaf* carboxylering en een studie van de mechanismen, die een rol spelen bij omleggingen van het intermediaire kation.

Na een algemene inleiding (hoofdstuk 1) wordt in hoofdstuk 2 de *Koch–Haaf* carboxylering van een aantal *tert*-alkyl gesubstitueerde cycloalkaanderivaten besproken. Nevenreacties werden onderdrukt door het toepassen van de *Haaf* modificatie, waarbij door langzaam te roeren een hoge CO-concentratie in stand wordt gehouden.

tert-Butylcyclohexanolen leverden 1-*tert*-butylcyclohexaancarbonzuur en als nevenproduct 2-methyl-2(2-methylcyclohexyl)propaanzuur. Bij de *Koch–Haaf* reactie van 3-*tert*-butylcyclopentanol en 4-*tert*-butylcycloheptanol traden meer ingewikkelde omleggingen op. De hoofdprodukten waren resp. 1,2,2-trimethylcyclohexaancarbonzuur en 2-cyclohexyl-2,3-dimethylbutaanzuur.

Uit de samenstelling van de reactieprodukten werden conclusies getrokken aangaande het mechanisme van de omleggingen, die in deze reacties een rol spelen. In enkele reacties worden cyclopropanen als intermediairen voorgesteld.

In hoofdstuk 3 komt ter nadere bewijsvoering aan de orde: de *Koch–Haaf* carboxylering van een aantal 1-alkylcyclohexaanmethanolen, 1-(1-alkylcyclohexaan)ethanolen en 1-methyl-gesubstitueerde spiro[2.5]octanen. Er werd aangetoond dat voor de 1-alkylcyclohexaanmethanolen en de 1-(1-alkylcyclohexaan)ethanolen, in het oorspronkelijk gevormde kation de 1-alkyl groep altijd naar de zijketen verhuist, zodat tertiaire carbonzuren verkregen worden. Een uitzondering vormde de carboxylering van 1-(1-adamantaan)ethanol: hier werd naast het overeenkomstige secundaire zuur 3-ethyl-adamantaan-1-carbonzuur verkregen. De laatstgenoemde verbinding wordt waarschijnlijk via een bimoleculaire hydrideverhuizing uit het oorspronkelijk gevormde kation verkregen.

Bij de carboxylering van 1-methyl-gesubstitueerde spiro[2.5]octanen blijken sterische factoren te bepalen welke binding van de cyclopropaanring bij voorkeur wordt geopend.

In hoofdstuk 4 wordt aangetoond dat, gedurende de *Koch–Haaf* carboxylering van 3- en 4-methylcyclohexanolen, de isomerisatie van het intermediaire secundaire carbeniumion naar het tertiaire 1-methylcyclohexylkation via een aantal opeenvolgende 1,2-hydrideverhuizingen verloopt. Door D_2SO_4 als reactiemedium te gebruiken werd aangetoond dat het laatstgenoemde kation in snel evenwicht is met 1-methylcyclohexeen en methyleencyclohexaan. De

tussenkomst van alkenen in sommige andere *Koch-Haaf* reacties werd eveneens aangetoond. Aan de hand van de H/D uitwisseling van enkele carbonzuren in D_2SO_4-HCOOH kon de reversibiliteit van de *Koch* reactie onder verschillende condities beoordeeld worden.

Deel II van dit proefschrift beschrijft de synthese en de conformatieanalyse van een aantal 3,7-digesubstitueerde bicyclo[3.3.1]nonanen. In een algemene inleiding (hoofdstuk 5) worden de conformationele aspecten van het systeem besproken en wordt een literatuuroverzicht van de synthese van 3- en 3,7-gesubstitueerde bicyclo[3.3.1]nonanen gegeven.

In hoofdstuk 6 wordt een synthetische route naar 3α,7α-digesubstitueerde bicyclo[3.3.1]nonanen, via oxidatieve opensplitsing van homoadamantan-4--on, beschreven. De conformatie van de verkregen produkten werd onderzocht met behulp van ^1H NMR spectroscopie en lanthanide shiftreagentia. De betrouwbaarheid van deze methode werd gecontroleerd. De verkregen vicinale proton-proton koppelconstanten toonden aan dat het derivaat met de substituenten $-C(CH_3)_2OH$ voornamelijk in een dubbele boot conformatie verkeert. Bicyclo[3.3.1]nonaan-3α,7α--dicarbonzuur en de dimethylester daarvan komen vermoedelijk voor als twee snel in elkaar overgaande (identieke) stoel-bootconformaties, waarvan zowel het stoel- als het bootgedeelte afgevlakt is.

Teneinde deze veronderstelling te verifiëren was het noodzakelijk om een aantal modelstoffen in het onderzoek te betrekken.

In hoofdstuk 7 wordt de condensatie van pyrrolidine enamines van 4-alkylcyclohexanonen met methyl α-(broommethyl)acrylaat beschreven. Het mechanisme van de anneleringsreactie wordt besproken. De conformatie van de anneleringsprodukten en hun epimeren werd bestudeerd met behulp van ^1H NMR spectroscopie en lanthanide shiftreagentia.

Hoofdstuk 8 beschrijft een algemene synthese-route om de 9-oxo-functie in de bovengenoemde verbindingen te reduceren tot CH_2. In de meeste daarna verkregen produkten is de conformatie vastgelegd door de 3- en/of 7-substituent. Deze verbindingen waren daarom goed bruikbaar als modellen in de conformatieanalyse van bicyclo[3.3.1]nonaan-3α,7α-dicarbonzuur en zijn dimethylester. Bovendien werden, uitgaande van diamantaan, enige verbindingen gesynthetiseerd, waarin adamantaan als geïntegreerde "holding group" aanwezig was. Vergelijking van ^1H en ^{13}C NMR spectra van deze modelverbindingen met die van het dicarbonzuur en zijn dimethylester toonde aan dat de laatstgenoemde verbindingen inderdaad voornamelijk als twee snel in elkaar overgaande (identieke) stoel-boot conformaties met sterk afgevlakte ringen voorkomen; de populatie van de dubbele-boot conformatie blijkt erg klein te zijn.

In hoofdstuk 9 wordt de bepaling van ΔG-waarden voor conformationele evenwichten in 3,7-gesubstitueerde bicyclo[3.3.1]nonanen beschreven. Hierbij werd gebruik gemaakt van epimerisatie-experimenten en van ^{13}C NMR spectroscopie bij variable temperatuur, waarmee respectievelijk het dubbele--stoel/boot-stoel evenwicht en het boot-stoel/dubbele twist-boot evenwicht bestudeerd werd. Er is goede overeenstemming tussen de resultaten van deze experimenten en die van valentiekrachtveldberekeningen. Valentiekrachtveldberekeningen gaven onder meer de volgende uitkomsten: bicyclo-[3.3.1]nonaan komt voornamelijk in de dubbele--stoel conformatie voor. Een omvangrijke substituent (zoals t-butyl) op de 3β-positie heeft een

relatief destabiliserend effect op de dubbele--stoel conformatie. 3α-Substituenten dwingen de gesubstitueerde ring in de boot conformatie. Voor de 3α,7α-gesubstitueerde verbindingen hangt de populatie van de conformaties af van de grootte van de substituenten. Voor 3α-methyl-7α-t-butylbicyclo[3.3.1]nonaan bleken de ΔH-waarden voor de stoel-boot en de dubbele twist-boot conformaties ongeveer gelijk te zijn.

De krachtveldberekeningen leverden tevens geometrische gegevens voor de verschillende conformeren van een aantal bicyclo[3.3.1]nonaanverbindingen. Berekend werd dat alle conformaties van bicyclo[3.3.1]nonaan (dubbele-stoel, stoel--boot en dubbele twist-boot) aanzienlijk afgevlakt zijn. Het bootgedeelte van een stoel-boot conformatie is een starre geëclipseerde boot. De dubbele twist-boot conformatie blijkt de stabielste dubbele-boot conformatie te zijn. Er wordt een gedetailleerde beschrijving van de invloed van 3- en 7-substituenten op de geometrie gegeven. Over het algemeen beïnvloedt een omvangrijke substituent, zoals t-butyl, beide vleugels van het ringsysteem. De berekende geometrieën blijken goed overeen te stemmen met de conclusies van het in hoofdstuk 6-8 beschreven ^{1}H NMR onderzoek.

In hoofdstuk 10 worden de ^{13}C NMR spectra van een aantal 3,7-gesubstitueerde bicyclo[3.3.1]nonanen besproken. Het blijkt dat de ^{13}C chemische verschuivingen, na correctie voor substituentinvloeden, informatie kunnen verschaffen over de ringconformatie.

Hoofdstuk 11 beschrijft een onderzoek naar de conformatie van 3-oxabicyclo[3.3.1]nonaan en enkele 7α- en 7β-alkylderivaten daarvan. Hierbij werd gebruik gemaakt van ^{13}C en ^{1}H NMR spectroscopie. Er wordt een vergelijking gemaakt met carbocyclische analoga. Het blijkt dat de vervanging van de 3-methyleen groep door een zuurstofatoom geen merkbare invloed op de conformationele voorkeuren heeft. Met behulp van vicinale proton-proton koppelconstanten wordt aangetoond dat de geometrie van de cyclohexaanring vrijwel gelijk is aan die in de overeenkomstige carbocyclische verbindingen. De resultaten van de berekeningen aan lanthanide--geïnduceerde verschuivingen leveren aanwijzingen dat de tetrahydropyranring in 3-oxabicyclo[3.3.1]-nonaan niet afgevlakt is, maar integendeel misschien iets "puckered" is. De berekende positie van Eu(III) in de complexen van $Eu(dpm)_3$ met de 3-oxabicyclo[3.3.1]nonanen wordt vergeleken met die in complexen van de verwante verbindingen 2-oxaadamantaan en 4-methyltetrahydropyran. Verrassenderwijs blijkt dat in het lanthanide shiftreagens complex van de laatstgenoemde verbinding het lanthanide-ion een axiale positie inneemt.

De synthese van de onderzochte 3-oxabicyclo-[3.3.1]nonanen wordt in hoofdstuk 12 weergegeven. De gebruikte syntheseroutes zijn analoog aan die beschreven in hoofdstuk 7 en 8. De massaspectrometrische fragmentatie van deze systemen werd bestudeerd met behulp van analyse van de metastabiele pieken (DADI en defocussing techniek). De aard van de alkyl groep blijkt het fragmentatiepatroon te beïnvloeden. Bij de 7-t-butylderivaten werden stereoselectieve fragmentaties waargenomen. In de mechanismen hiervan speelt transannulaire waterstofoverdracht een rol.

In het kader van het eerder genoemde onderzoek van modelverbindingen werd een poging ondernomen om 3- en 7-methyl-gesubstitueerde bicyclo[3.3.1]-nonaan-3-carbonzuren te synthetiseren *via* reactie van 1-methyladamantan-2-on met natriumazide en methaansulfonzuur volgens de methode van *Sasaki c.s.*

Deze reactie leverde echter niet het gewenste produkt op. In hoofdstuk 13 wordt de structuuropheldering van de verkregen reactieprodukten beschreven. Met behulp van ^{1}H NMR en ^{13}C NMR spectroscopie en lanthanide shiftreagentia, werd aangetoond dat het hoofdprodukt 4-methylprotoadamant--4-en-2-on was. Een nevenprodukt van deze reactie is waarschijnlijk 4-methyleenprotoadamantan-2-on.

S T E L L I N G E N

1. De conclusies van *Anteunis* c.s. inzake de conformatie van 7,7-dimethyl-2,4--dioxabicyclo[3.3.1]nonaan zijn onjuist. Uit de door deze auteurs bepaalde proton--proton koppelingsconstanten volgt dat de genoemde verbinding voornamelijk voorkomt in de boot-stoel conformatie met de dioxaanring in de boot conformatie.

M. Anteunis, C. Bécu en F. Anteunis-de Ketelaere, *J. Acta Ciencia Indica* 1, 1 (1974).

2. De berekeningen van *Gore* en *Armitage* aan de coördinatie van $Eu(fod)_3$ aan Multistriatin (2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octaan) zouden veel aan waarde hebben gewonnen indien monofunctionele modelstoffen in het onderzoek zouden zijn betrokken.

W.E. Gore en I.M. Armitage, *J. Org. Chem.* 41, 1926 (1976).

3. De door *Dixon* c.s. gegeven interpretatie van het massaspectrum van "2-hydroxybicyclo[3.3.1]nonaan" is onjuist. Uit het massaspectrum blijkt dat de gemeten verbinding verontreinigd is met de overeenkomstige 2-oxoverbinding.

J.R. Dixon, G.J. James en I.G. Morris, *J. Chem. Eng. Data* 20, 125 (1975); J. Cable, J.K. MacLeod, M.R. Vegar en R.J. Wells, *Org. Mass Spectrom.* 7, 1137 (1973).

4. De door *Burgstahler* c.s. waargenomen gekleurde nevenproducten bij een *Rosenmund* reductie volgens de werkwijze van *Peters* en *van Bekkum* ontstaan niet, indien de katalysator onmiddellijk na de reactie - onder uitsluiting van zuurstof - afgefiltreerd wordt.

A.W. Burgstahler, L.O. Weigel en C.G. Shaefer, *Synthesis* 1976, 767.

5. De door *Vegar* en *Wells* gepubliceerde signaaltoekenning in het ^{1}H NMR spectrum van bicyclo[3.3.1]nonan-3-on in aanwezigheid van shiftreagens, is waarschijnlijk onjuist. Hierdoor komen deze auteurs, voor wat de conformatie betreft, tot conclusies die in strijd zijn met die van onderzoek aan analoge verbindingen.

M.R. Vegar en R.J. Wells, *Tetrahedron Lett.* 1971, 2847;
N.S. Zefirov, *Russ. Chem. Rev.* 44, 196 (1975).

6. Bij de schatting van het enthalpieverschil tussen de dubbele stoel en de stoel-boot conformatie van bicyclo[3.3.1]nonan-2-on hebben *Appleton* c.s. gebruik gemaakt van het enthalpieverschil tussen de stoel en de *twist*-boot conformatie van cyclohexanon. Zij hebben zich hierbij niet gerealiseerd dat de stoel-bootconformatie van de eerstgenoemde verbinding star is.

R.A. Appleton, C. Egan, J.M. Evans, S.H. Graham en J.R. Dixon, *J. Chem. Soc. (C)* 1968, 1110.

7. In het computerprogramma van *Wing* c.s. voor de berekening van de structuur van complexen met lanthanide shiftreagentia wordt een assentransformatie op onjuiste wijze uitgevoerd.

R.M. Wing, J.J. Uebel en K.K. Andersen, *J. Am. Chem. Soc.* 95, 6046 (1973), supplementary material.

8. Uit de metingen van *Reuben* aan de complexering van xylitol met lanthanideionen kunnen geen conclusies betreffende de stoichiometrie van deze complexen worden getrokken.

J. Reuben, *J. Am. Chem. Soc.* 99, 1765 (1977).

9. De verklaring van *Naccache* c.s. voor de discrepantie tussen de resultaten van waterstofchemisorptie en die van electronenmicroscopie aan een bij 500° gecalcineerde PtY-zeoliet is aan twijfel onderhevig.

C. Naccache, N. Kaufherr, M. Dufaux, J. Bandiera en B. Imelik, *Proc. 4th Congress Molecular Sieves Chicago 1977*, 538.

10. Bij schaatswedstrijden over 1000 m kan de startpositie het resultaat beïnvloeden. Dit kan vermeden worden door deze wedstrijden te vervangen door wedstrijden over 900 m.

J.A. Peters

19 april 1978