STEREOCHEMICAL STUDIES OF HETEROCYCLIC ANALOGUES OF DECALINS

A thesis submitted to the University of Keele in part fulfilment of the requirement for the Degree of Doctor of Philosophy.

by

G. Wilcox

Department of Chemistry
University of Keele
Staffordshire

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The work in this thesis was carried out by the author under the supervision of Dr. D.V. Griffiths.

G. Wilson.

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Abstract

This dissertation is concerned with the synthesis of the octahydro-1-benzopyran and octahydro-1,4-benzoxazine systems and the application of ^{1}H and ^{13}C n.m.r. spectroscopy to determine the stereochemistry and major conformation adopted by the isomers of these systems.

A synthetic route has been developed for the synthesis of isomerically pure samples of both the cis and trans isomers of the heterocyclic analogue of decalin, octahydro-1-benzopyran.

The position of the conformational equilibrium in the cis isomer has been established by low temperature ^{13}C n.m.r. spectroscopy and the result is compared with that previously reported for the analogous nitrogen system, decahydroquinoline. High field ^{1}H n.m.r. spectroscopy has enabled vicinal coupling data to be obtained for the C2-C3 bond in both the cis and trans isomers. This is used to assess the degree of distortion in the pyran portion of the ring system.

A route for the production of octahydro-1,4-benzoxazine has been developed together with a chromatographic procedure for obtaining samples of the pure cis and trans isomers. This synthetic route has also been extended to produce pure samples of many of the isomers of the 2,3,6 and 7 methyl-substituted derivatives.

The stereochemistry of these isomers has been determined from their ^{1}H and ^{13}C n.m.r. spectra. The proton-proton vicinal coupling constants for the C2-C3 bond in these isomers is used to assess the degree of distortion in the oxazine portion of the ring system. The position of the conformational equilibria in the cis isomers of these systems has been assessed by low temperature ^{13}C n.m.r. spectroscopy and is interpreted in terms of the interactions present in the major conformations.

INTRODUCTION

1. Stereochemical Considerations

This dissertation is concerned with the synthesis and subsequent stereochemical investigations of some heterocyclic analogues of decalin, and in particular, the octahydro-1-benzopyran and octahydro-1,4-benzoxazine systems. The effect of methyl substitution on these systems has also been studied. Before discussing this work in detail, however, it is worth considering the historical background leading to our present study.

It is now more than one hundred years since van't Hoff[1] and Le Bel[2] laid the foundations of stereochemistry when, in 1874, they independently proposed that the four valencies of carbon were orientated towards the vertices of a regular tetrahedron. This in turn, gave rise to the concept of three-dimensional molecules and in 1890 Sachse[3] suggested that the cyclohexane molecule could exist in two puckered (i.e. non-planar) forms which possessed this tetrahedral arrangement for the bonding around the carbon atoms. These were later called the chair (1) and boat (2) conformations.

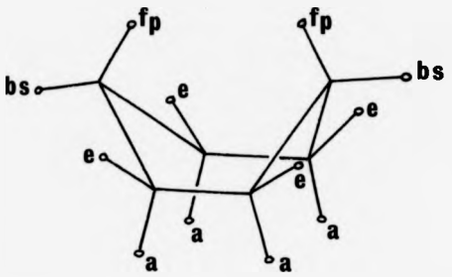
(1)

(2)

It should be noted at this point that, strictly speaking, the term conformation applies to any "stereoisomer that can be interconverted either by rotation about bonds of order approximately one (with any concomitant small distortions of bond lengths and angles) or by inversion at a three-coordinate centre in the molecule"[4]. This definition means that most molecules can exist in an infinite number of possible conformations. In most stereochemical studies, however, we are usually largely concerned with those "stable" conformations which are significantly populated under normal conditions. The term conformation has therefore been used in this dissertation to describe those 3-dimensional structures of the molecule which are significantly populated under the conditions used to investigate the system.

The subsequent development of Sachse's ideas about the structure of the cyclohexane molecule to those currently accepted have been well documented[5] and therefore only a summary of the currently accepted ideas about the structure of cyclohexane will be discussed here.

It is now known that the boat conformation (3) of the cyclohexane molecule is much less favourable than the "strain-free" chair form due to unfavourable steric interactions between the flag-pole hydrogens and torsional strain along the sides of the boat.

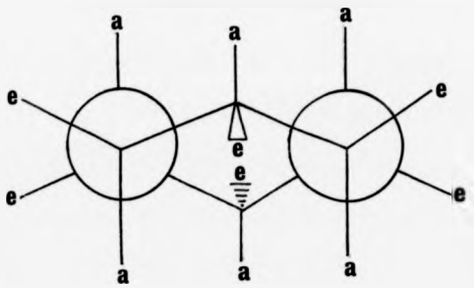


(3)

fp = flag-pole hydrogens
bs = bowsprit hydrogens
e = equatorial hydrogens
a = axial hydrogens

It is also known that this boat form of cyclohexane is not a "stable" conformation since twisting[6] leads to a less strained system known as the twist-boat conformation. However, even this twist-boat form suffers from significantly more torsional and steric strain than the chair form and, therefore, with very few exceptions, the cyclohexane molecule adopts the chair conformation in solution. Thus, it is this chair conformation which will now be considered in detail.

Examination of the hydrogen atoms in the chair form of cyclohexane by a consideration of the Newman projection[7] (4) shows that they adopt one of two environments.

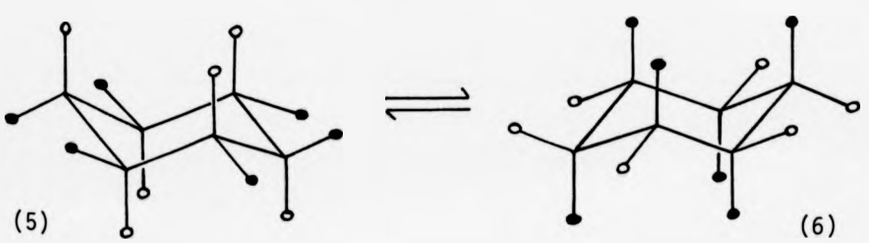


(4)

a = axially orientated hydrogen
e = equatorially orientated hydrogen

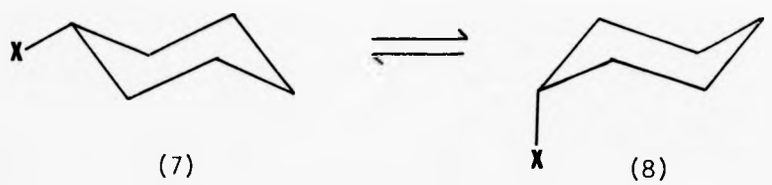
Those which lie in the plane of the ring are referred to as being equatorially disposed while those whose C-H bonds are perpendicular to the plane of the ring are said to be axially disposed. However, it was not until 1950, when the work of D.H. Barton[8] indicated the chemical consequences of having an axial or equatorial substituent on the cyclohexane ring, that the true significance of this distinction was realised.

A further complication which arises in the case of the cyclohexane system is that it is possible to invert the ring (5 $\rightleftharpoons$ 6) so that those hydrogens previously occupying an axial position become equatorially disposed and vice versa. This process, known as ring inversion, has only a relatively low energy barrier[9] which means that the interconversion (5 $\rightleftharpoons$ 6) occurs rapidly under normal conditions.



(5) (6)

For cyclohexane there is no difference between these two interconverting structures since they are identical. However, replacement of one of the hydrogens by a substituent will result in different interactions being present in the two chair forms. Since in general the axial positions are more sterically crowded than the equatorial positions, the substituent usually prefers to adopt an equatorial orientation. The position of the conformational equilibrium (7 $\rightleftharpoons$ 8) will therefore usually favour (7) although the extent to which (7) is favoured will depend on the relative free energies of the two chair conformations.



(7) (8)

The conformational ratio (7:8) can be used to calculate the conformational free energy difference for the system using equation (1). The value of $-\Delta G^{o}$ is a characteristic of the particular substituent and is conventionally taken to have a positive value.

$$-\Delta G^{o} = RT\ln \frac{PA}{PB} \qquad (1)$$

ΔG^{o} = Potential energy difference of the two conformations

R = Gas constant (8.314 J K^{-1} mol^{-1})[10]

T = Absolute temperature (°K)

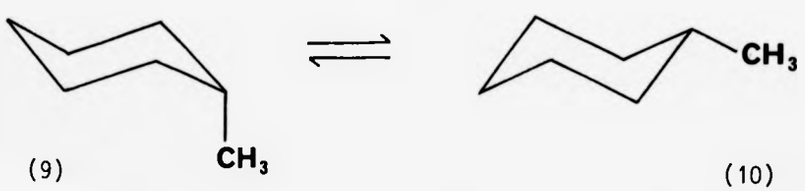
PA = Mole fraction of conformation A

PB = Mole fraction of conformation B

A consideration of the effects of $-\Delta G^{o}$ on the position of the resulting conformational equilibrium, as indicated by PA, (Fig. 1) shows that ideally it is desirable to study systems in which the conformational ratio (PA:PB) is no more extreme than about 95:5. If systems are studied having a more extreme ratio then small errors made when measuring the position of the conformational equilibrium will cause large errors in the $-\Delta G^{o}$ values obtained.

In some cases a less extreme ratio can be obtained by using a disubstituted cyclohexane system where the effects of one group can be offset against the effects of another whose $-\Delta G^{o}$ value is known. Such an approach can prove very valuable but it involves making an assumption that the $-\Delta G^{o}$ values for the two substituents are additive[11]. Such an assumption is only valid if there is no interaction between the two substituents. This assumption is not always valid[12] and caution must be exercised when using this approach.

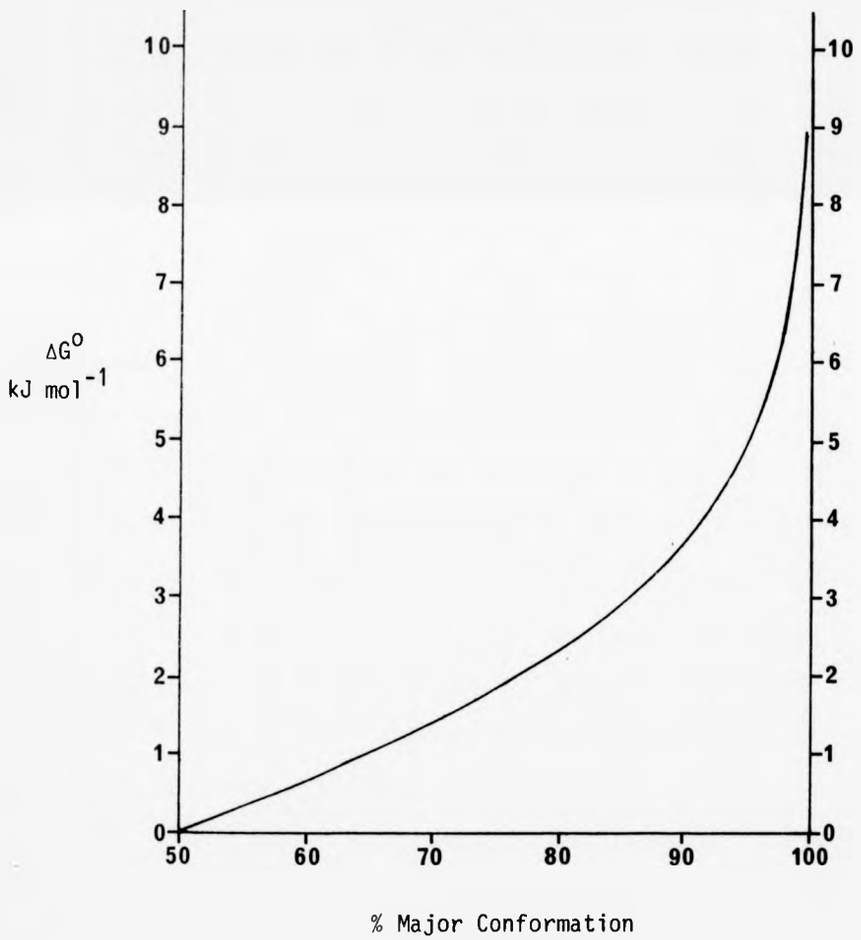
Let us now consider methylcyclohexane, the monosubstituted cyclohexane system which is most relevant to the work described later in this dissertation. Methylcyclohexane adopts one of two major conformations in solution. In both of these the cyclohexane ring adopts a chair conformation, but in one the methyl is axially disposed (9) and in the other it is equatorially disposed (10).



(9) (10)

Fig. 1.

Graph showing the Effect of ΔG^{o} on the Position of Conformational Equilibrium for Two Interconverting Conformations at 25 °C

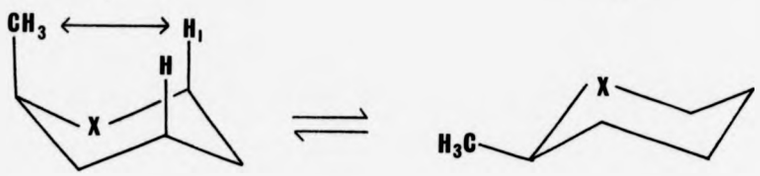


For (9) we have an increase in steric strain relative to the unsubstituted cyclohexane molecule due to the introduction of two methyl/hydrogen 1,3-diaxial interactions. Such interactions are, however, absent when the system undergoes ring inversion to give (10) where the methyl group is equatorially disposed. It is not surprising, therefore, that the dominant conformation in methylcyclohexane is that having the methyl substituent equatorially disposed (10). The position of the conformational equilibrium (9 $\rightleftharpoons$ 10) has been obtained directly by spectroscopic methods[13,14] and this in turn has been used to calculate the $-\Delta G^{o}$ value for the methyl substituent. The generally accepted value for $-\Delta G^{o}_{Me}$ is 7.1 kJ mol^{-1} (1.7 kcal mol^{-1}).

Let us now consider the situation where a substituent is placed in the ring rather than on the ring. Thus, for example, let us consider the effect of replacing one of the methylene units in cyclohexane by a heteroatom (X), such as oxygen or nitrogen. Fortunately, these systems still adopt chair conformations since the C-X-C bond angle and C-X bond length are not significantly different from the corresponding parameters observed in the unsubstituted cyclohexane molecule[15]. Nevertheless, introduction of a heteroatom does produce a distortion in the ring which has an impact when other substituents are present on the ring system.

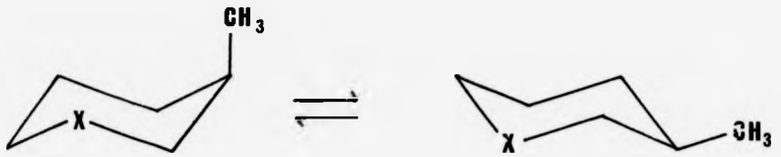
Thus, for example, let us consider the heterocyclic analogue of cyclohexane having a methyl group situated α to the heteroatom (11 $\rightleftharpoons$ 12).

(11) (12)



As the C-X bond lengths for oxygen and nitrogen (142 and 148 pm respectively)[4] are shorter than the C-C bond length (153 pm)[4] in cyclohexane the distance between the axially disposed methyl and the axial proton H1 in (11) is smaller than in the methylcyclohexane conformation (9) thus increasing the magnitude of this steric interaction. On the other hand the smaller C-X bond length has little effect on the interactions in the corresponding equatorially substituted system (12) so that the $-\Delta G^{o}$ value for the methyl group would be expected to be larger in the piperidine and tetrahydropyran systems than in methylcyclohexane.

The opposite situation occurs in the case where the methyl substituent is β to the heteroatom. In this case (13 ⇌ 14, X = O) we must again consider the effects of the shorter C-O bond length but in addition we must also note that one of the axially disposed protons has been replaced by one of the lone pairs of electrons on the oxygen atom. Since a lone pair/methyl 1,3-diaxial interaction is less than that of the corresponding proton/methyl diaxial interaction in methylcyclohexane the $-\Delta G^{o}$ value for (13 ⇌ 14) should also be less than that found in methylcyclohexane. This is confirmed by the $-\Delta G^{o}$ value of 5.3 kJ mol^{-1} obtained for the 3-methyl substituent on tetrahydropyran by Anderson and Sepp[16].



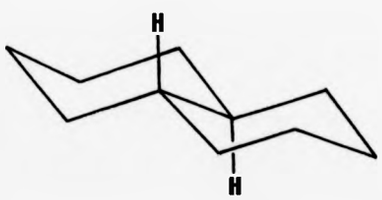
(13) (14)

In the case of (13 ⇌ 14, X = NH) the situation is further complicated by the presence of both a lone pair of electrons and a proton on the nitrogen. This means that before the interactions can be assessed in this system it is necessary to know whether it is the proton or the lone pair of electrons which occupies the axial position. This assessment is further complicated by the phenomenon of nitrogen inversion which enables the lone pair of electrons and the proton on the nitrogen to exchange their positions without the process of ring inversion occurring. Fortunately this problem has received considerable attention and in recent years it has been indicated that, for the parent piperidine system, the N-H proton prefers to adopt an equatorial orientation both in the gas phase[17] and in solution[18,19]. The situation for (13 ⇌ 14, X = NH) can therefore be considered to be similar to that in the corresponding oxygen system in that the lone pair of electrons on the heteroatom is axially disposed. However, because of the larger van der Waals radius for nitrogen the "lone pair"/methyl 1,3-diaxial interaction will be larger than that observed in the oxygen system. This is confirmed by the $-\Delta G^{o}$ value of 6.3 kJ mol^{-1} obtained from a C-3 methyl substituent on a piperidine ring[20].

Although many heterocyclic systems have been studied[21,22] in the recent past, it is those based on the decalin system with which

our studies are concerned and it is these systems which will now be considered. The decalin system itself can in some ways be regarded as a disubstituted cyclohexane system and historically it proved to be important in the development of our understanding of the cyclohexane system. As previously mentioned, Sache had postulated that cyclohexane could exist in a chair arrangement as early as 1890 but it had been left to Mohr[23] in 1918 to resurrect these ideas when he considered the stereochemistry of the decalin system. Sachse's suggestion that cyclohexane could exist in either a boat or chair conformation, led Mohr to postulate that decalin could exist in two different isomeric forms, a twin chair form having a trans-fused ring junction and a twin boat form having a cis-fused ring junction. Although the existence of the cis and trans isomers of decalin was confirmed experimentally by Huckel[24] in 1925 it is now known that the cis isomer of decalin does not exist in a twin boat conformation but that it too exists in a twin chair arrangement.

The trans-decalin system may be regarded as consisting of two cyclohexane rings which are fused in an equatorial-equatorial manner (15).

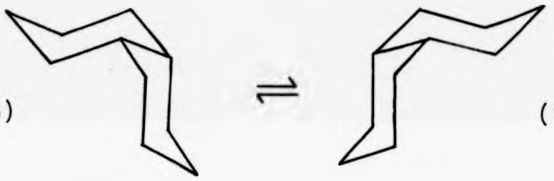


(15)

Since this ring system is unable to undergo ring inversion into the corresponding diaxially fused conformation it can be regarded as being conformationally rigid. For this reason any substituent placed in an

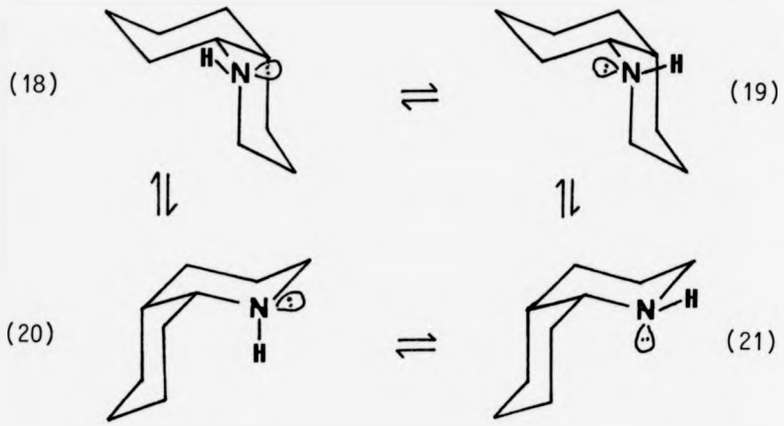
axial position on the ring will remain in this orientation. Such systems are therefore extremely useful for studying the extent to which the ring will distort as a result of the strain introduced by an axial substituent.

Unlike the trans isomer, cis-decalin is a conformationally mobile system in that two conformations can be drawn (16 ⇌ 17) which are interconvertable by the process of ring inversion.

(16)  (17)

For cis-decalin these two conformations are of equal energy since they are indistinguishable from each other. However, for substituted cis-decalins such as when the C1 methylene is replaced by a heteroatom this situation no longer applies.

Although both thiadecalin[25,26] and decahydroquinoline[27,28] are examples of 1-substituted heterocyclic analogues of decalin which have been studied in recent years, it is from the study of the nitrogen system, decahydroquinoline[28], that this work originates. In the case of the cis-decahydroquinoline system there is not only the possibility of ring inversion but also the complication of nitrogen inversion, previously discussed, which gives rise to the possibility of four conformations of cis-decahydroquinoline (18, 19, 20 and 21).

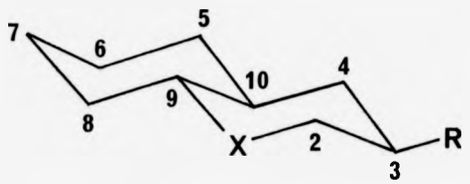


^{1}H and ^{13}C n.m.r. spectroscopy have been used to demonstrate that the conformational preference is strongly in favour of (21) and/or (20). However, it was concluded that since (19) and (20) would be expected to be equivalent or nearly so, in energy terms, then the exclusion of (19) implies the exclusion of (20). Hence, cis-decahydroquinoline has been stated to exist in largely conformation (21) under the conditions employed for the study. However, the presence of small proportions of the remaining conformations cannot be excluded.

The corresponding oxygen analogue, cis-octahydro-1-benzopyran has not been studied. In cis-octahydro-1-benzopyran, where there is no complication arising from nitrogen inversion, we have only two twin--chair conformations, interconvertable by the process of ring inversion. Furthermore, there is no ambiguity as to the position of the oxygen's lone pairs of electrons so that an assessment of the interactions present in the two conformations can be made.

At this point it is convenient to give the conventions used throughout this dissertation for describing these heterocyclic decalin analogues.

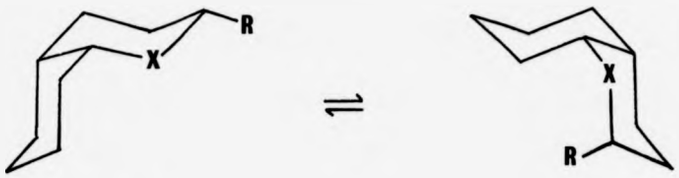
For the trans-decalin analogue (22) having a heteroatom (X), the system will be numbered from the heteroatom in the usual way, as indicated in the structure.



(22)

The numbering of the bridgehead positions as 9 and 10 rather than 4a and 8a avoids any confusion arising from the use of the symbol 'a' which is used in this dissertation to denote an axial orientation. (The suffix 'e' is used to represent an equatorially disposed substituent). When a methyl substituent is added, for example at C3, then the relationship of the hydrogen atom at C3 is quoted as being cis or trans relative to the nearest bridgehead position. Thus, for example, structure (22, X = O and R = Me) would be referred to as trans-(9H,10H)-cis--(3H,10H)-octahydro-3-methyl-1-benzopyran, where trans-(9H,10H) defines the ring junction and cis-(3H,10H) defines the relationship of the methyl substituent with respect to the H10 ring junction proton.

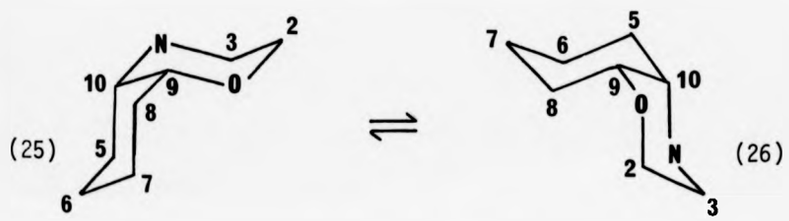
In the case of the cis-fused ring system of the type indicated in structure (23 $\rightleftharpoons$ 24) the nomenclature used is the same. For example, if the structure has a C2 methyl substituent (23 $\rightleftharpoons$ 24, R = CH_3 and X = O) then such a structure would be called, cis-(9H,10H)-cis-(2H,9H)--octahydro-2-methyl-1-benzopyran.



(23) (24)

In this way all the methyl isomers of these systems can be uniquely defined. For the cis isomers such as (23 ⇌ 24) it is also useful to be able to refer to a particular conformation. The convention used in this work is such that if the heteroatom is attached axially, relative to the cyclohexane ring (as in 23), then this will be referred to as a Type A conformation. Conversely, (24) will be referred to as a Type B conformation.

A further complication arises when we have a disubstituted system. In this dissertation we are only concerned with the oxygen and nitrogen heteroatoms. When both of these are present the structures will be numbered from the oxygen atom and the conformational arrangement will be referred to by the orientation of the oxygen atom. Thus, for example, the numbering system used for the cis-octahydro-1,4-benzoazine system (25 ⇌ 26) will be that indicated on the structures. Furthermore conformation (25), where the oxygen atom is axially disposed with respect to the cyclohexane ring, will be denoted the Type A conformation.



2. Nuclear Magnetic Resonance Spectroscopy

Nuclear magnetic resonance spectroscopy is one of the most useful techniques available for studying the stereochemistry adopted by organic molecules in solution. Furthermore, this usefulness has increased significantly in recent years with the advent of "very high field" spectrometers which operate at fields of 8 T or more. These spectrometers are capable of giving much more interpretable (more first order) ^{1}H n.m.r. spectra than was previously possible. This in turn has meant that a lot of information can now be obtained about systems which previously would have been difficult to study due to the highly second order nature of their spectra.

From a conformational point of view one of the most valuable parameters that can be obtained from the ^{1}H n.m.r. spectrum is the $^{3}J_{HH}$ vicinal coupling constant. The size of this coupling is related to the dihedral angle between the coupled protons and can therefore often be used to obtain detailed information about the relative orientations of the protons within the molecule being studied. The relationship between the dihedral angle and the $^{3}J_{HH}$ vicinal coupling is given by the Karplus equation[29,30] (2) and typical values for a substituted ethane are given in Fig. 2.

$$^{3}J_{HH} = A\cos^{2}\theta + C \qquad (2)$$

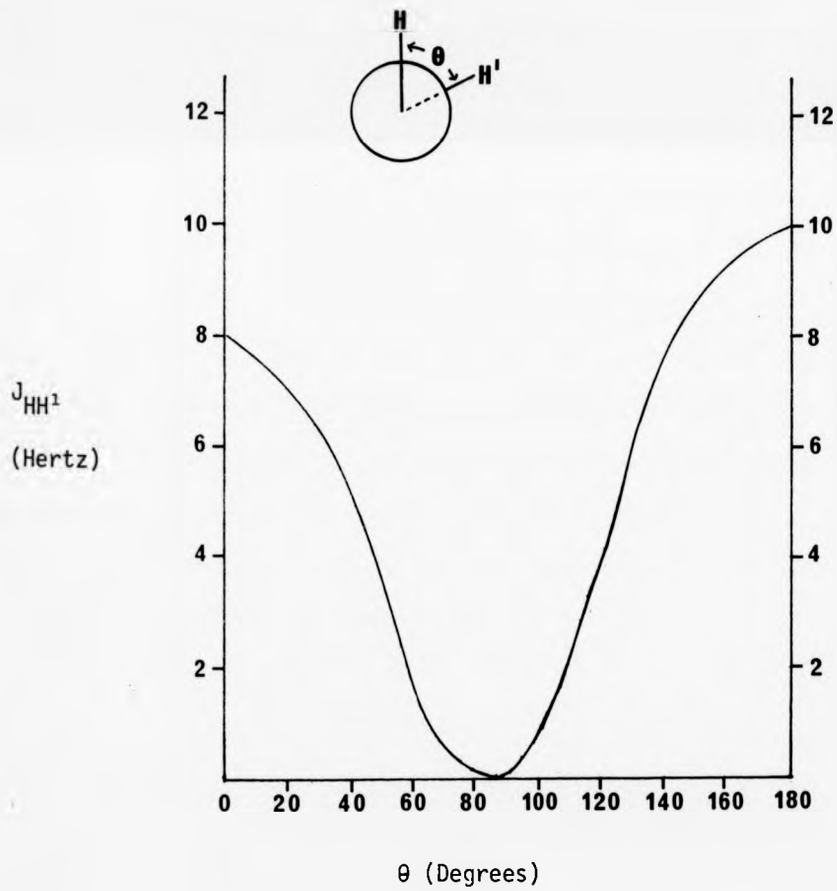
Where A and C are constants for a particular system.

It can be seen that the $^{3}J_{HH}$ vicinal coupling is very sensitive to the dihedral angle between the coupled protons. Thus, for example, the coupling between two adjacent axial protons in a cyclohexane ring

Fig. 2.

The Vicinal H-C-C-H Coupling Constant

as a Function of the Dihedral Angle θ



system ($^3J_{aa}$), where $\theta = 180°$, will have a larger value than when one or both the protons are equatorially disposed ($^3J_{ae}$ and $^3J_{ee}$), where $\theta = 60°$. This is also found experimentally. Thus, typically $^3J_{aa}$ = 8-12 Hz, while $^3J_{ae}$ = 2-5Hz and $^3J_{ee}$ = 1-3Hz.

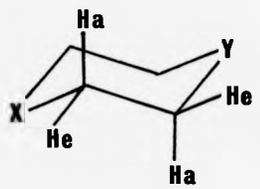
(c.f. J geminal = 10-12Hz)

Although the Karplus expression has a potentially wide application there are however a number of problems which do arise and which therefore limit its use. For example, although the value of $^3J_{HH}$ depends on the dihedral angle between the protons one cannot automatically obtain a value for the dihedral angle from a knowledge of $^3J_{HH}$ alone. This is because $^3J_{HH}$ is also affected by other factors such as the carbon-carbon bond length, the H-C-C valence angle and the electronegativity and orientation of the substituents on the carbon atoms. Fortunately, although for a given dihedral angle the value of $^3J_{HH}$ decreases with decreasing C-C bond length and increasing H-C-C valence angle, these problems can be overcome by obtaining information from other systems having similar values for these parameters. The substituent effects are, however, more difficult to deal with. It is known that for a system of the type XYHC-CHWZ the general form for the dependence is given by equation (3),

$$^3J = {}^3J^o(1-M\Sigma\Delta E) \qquad (3)$$

where $^3J^o$ is the coupling parameter with no dependence on electronegativity, M is a constant for geometrically related couplings and ΔE is the sum of the differences between the electronegativity of hydrogen and those of the substituents W, X, Y and Z. Therefore, only if the values of $^3J^o$, M and ΔE are known for a given series can

quantitative information be obtained. In certain systems, such as (27), Lambert[31,32,33] has shown that these unknown factors can be eliminated enabling the dihedral angle for the system to be determined from a knowledge of the appropriate $^3J_{HH}$ vicinal couplings.



(27)

Thus, for example, the value of R (equation 4), which is independent of the electronegativities of X and Y,

$$R = \frac{Jtrans}{Jcis} = \frac{^oJtrans(1-M\Sigma\Delta E)}{^oJcis\ (1-M\Sigma\Delta E)} = \frac{^oJtrans}{^oJcis} \qquad (4)$$

Where $Jtrans = \frac{1}{2}(Jaa + Jee)$

$Jcis = \frac{1}{2}(Jae + Jea)$

can be shown to be directly related to the dihedral angle θ by equation (5).

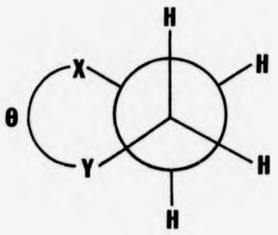
$$\cos\theta = \left(\frac{3}{2 + 4R}\right)^{\frac{1}{2}} \qquad (5)$$

This means that the dihedral angle between X and Y in systems such as (27) can be determined from a knowledge of the appropriate $^3J_{HH}$ vicinal coupling constants alone.

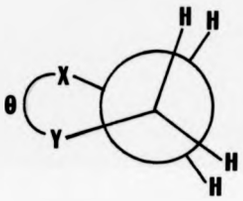
It has been found that in general the R value for an undistorted chair conformation (28) lies in the range 1.9-2.2. Thus, for example,

in cyclohexane, piperidine and 1,4-dioxane R is close to 2.2.

(28)



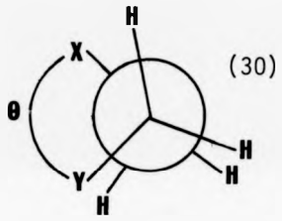
Undistorted
R ∿ 1.9-2.2



(29)

Flattened
R < 1.8

(30)



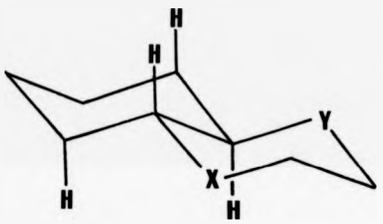
Puckered
R > 2.3

Flattening of this chair arrangement (29) lowers the value of R, so that, for example, the analysis of the C2-C3 portion of cyclohexanone gives a value of R ∿ 1.7. Conversely, increased puckering of the ring (30) raises the R values. This effect is observed in thiane where R is found to be about 2.6. Thus, in principle, it should be possible to detect distortion from the normal chair arrangement in the heterocyclic analogues of decalin by analysis of their R values from the appropriate fragments of the molecules.

For the heterocyclic analogues of decalin studied in this dissertation the vicinal coupling data can also be used to identify whether the system has a cis- or trans-fused ring junction. Additionally, the preferred conformation of the cis isomers can be determined. To do this the vicinal coupling data is used in a more qualitative manner and

relies on the observation that in similar systems to those considered, the $^3J_{aa}$ coupling is considerably larger than the other vicinal couplings, but is of similar magnitude to the ^2J geminal coupling.

On consideration of the trans-fused ring system (31) it can be seen that both ring junction protons will experience two large $^3J_{aa}$ couplings since they are both coupled to two axially disposed protons.

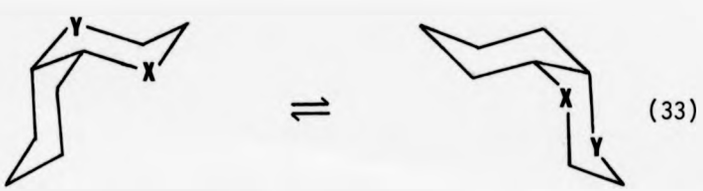


(31)

Typically, therefore, the bridgehead protons will give rise to a signal showing triplet character. Hence, where X and Y are heteroatoms, the trans-fused nature of the ring junction can be deduced from the multiplicity of the bridgehead protons. In the case of a mono-substituted system (e.g. 31 where X = O, Y = CH_2) the trans stereo-chemistry of the ring junction could be deduced from the multiplicity of the bridgehead proton adjacent to the heteroatom, alone.

For the cis-fused system the situation is more complex due to the two possible conformations (32 and 33).

(32)



(33)

In (32) where the heteroatom (X) is axially orientated, relative to the cyclohexane ring, the ring junction proton (H9) next to this heteroatom will possess no large couplings, but it will possess a number of smaller couplings. Consequently the H9 resonance will therefore be observed as a broad singlet in the ^{1}H n.m.r. spectrum. On the other hand the H10 proton will have a large J_{aa} coupling to H5a and will therefore have doublet character.

These multiplicities are reversed in the other cis conformation (33). For this conformation the H9 resonance now has a large J_{aa} coupling to the H8a proton and appears as a large doublet, while H10, with no large couplings, appears as a broad singlet. Thus the multiplicity of the bridgehead proton resonances can be used to deduce not only the cis-fused nature of the system (32 $\rightleftharpoons$ 33) but also the particular conformation. For a disubstituted system (e.g. 32 where X = O, Y = NH) the multiplicity of the bridgehead proton H9 can again be used to deduce the stereochemistry of the isomer.

The above assignments of the conformation can, however, only be made if the bridgehead proton resonances are visible. Fortunately, the presence of an electronegative heteroatom substituent in the decalin ring ensures that the protons on the adjacent carbons are shifted downfield of the other protons in the molecule. The ring junction protons adjacent to a heteroatom such as oxygen should therefore be easy to identify and their multiplicities determined. This also applies in the case of a nitrogen heteroatom substituent, though the downfield shift would not be expected to be as great as that observed for oxygen.

^{13}C n.m.r. spectroscopy has also been applied successfully to identify the stereochemistry adopted by some heterocyclic analogues

of decalin[28]. This is usually achieved by comparing the experimentally produced proton decoupled spectrum with that predicted for a particular stereochemistry from a consideration of model compounds. To obtain the predicted spectra for heterocyclic analogues of decalin it is necessary to determine the chemical shifts of the carbons in the appropriate isomer of decalin and to then apply corrections to these values to allow for the effects of introducing a heteroatom or a substituent into the system. These substituent parameters can be obtained from model systems so that, for example, a comparison of the chemical shifts in piperidine and cyclohexane enabled nitrogen substituent parameters to be obtained which were then subsequently applied to the decahydroquinoline system[34].

When obtaining the ^{13}C n.m.r. specta of cis-decalin analogues it is often necessary to use low temperatures to ensure that problems associated with ring inversion are avoided. At room temperature the cis isomers are rapidly interconverting between the two possible twin--chair conformations. This means that the magnetic environment of a nucleus at a site within the molecule may change many times during the transition of the nucleus from one energy level to another. The apparent magnetic environment of the nucleus will therefore be a weighted average of the environments experienced by it during the transition. This in turn will mean that the spectrum obtained for the cis isomers will also be a weighted average of the two component spectra. Clearly, if the position of the conformational equilibrium (32 $\rightleftharpoons$ 33) in these cis isomers is extreme there will be little error in using the room temperature spectrum. However, if the minor conformation is significantly populated this could have a substantial effect on the room temperature spectrum. Under these circumstances

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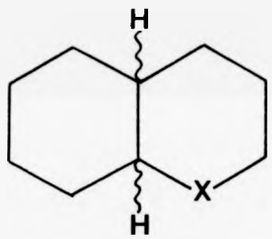
cooling the sample slows the rate of interconversion sufficiently to allow sets of signals from both cis-conformations to be observed. These two sets of signals can then be compared with calculated values enabling an assignment of both the major and minor conformations to be made with some confidence.

The ratio of the two cis conformations, as previously discussed, is related to the difference in the interactions present in the two conformations. It is therefore a useful parameter to know if the effects of introducing a substituent or a heteroatom into the decalin system are to be better understood. The conformational ratio can be obtained by taking measurements from the ^{13}C n.m.r. spectrum. This can be done by obtaining the spectrum under conditions where the system is 'frozen out' and where sets of signals from both interconverting conformations can be seen. By comparing the integrated area of a particular signal from one conformation with that of the signal produced by the structurally identical carbon nucleus in the other conformation a ratio can be estimated. This ratio can then be used to calculate the $-\Delta G^{o}$ value, under these conditions. It should be noted that the signals from structurally identical carbons are usually compared so as to minimise the effects of any distortions in the integrated signals which arise as a result of differing T1 values within the molecule. Nevertheless, caution should be exercised when considering systems where the position of the conformational equilibrium is extreme.

In conclusion, therefore, it can be seen that both ^{13}C and ^{1}H n.m.r. spectroscopy can provide useful information when analysing the conformations adopted by the heterocyclic analogues of decalins.

1. The Synthesis of Octahydro-1-benzopyrans

The 1-substituted heterocyclic analogues of decalin, particularly the cis ring-fused isomers, provide useful information about the effects of incorporating heteroatoms into carbocyclic ring systems. The nitrogen system (34, X = NH), decahydroquinoline[27,28], has been extensively studied and the sulphur analogue[26,35] has also been investigated.



(34)

It is somewhat surprising, therefore, to find that no similar studies have been carried out on the comparable oxygen system, octahydro-1--benzopyran.† In fact, there are no reported preparations of cis--octahydro-1-benzopyran and only limited reports of the trans isomer. Nevertheless, in many ways the results from the cis-octahydro-1-benzopyran isomer should be easier to interpret than those from the decahydroquinoline system where, due to the phenomenon of nitrogen inversion, the assessment of the interactions present in the two cis conformations is difficult.

Although the stereochemical aspects of the octahydro-1-benzopyran system have been little studied the system has been known for over 40 years. It was first reported in 1940 by de Benneville and Connor[36,37] during their investigations of the hydrogenation of

†See appendix

2H-1-benzopyran-2-one (coumarin) and related compounds. Since that time various substituted octahydro-1-benzopyrans have been reported[38,39]. In general these have not been studied from a stereochemical point of view. However, some aspects of the stereochemistry of the cis and trans isomers of the 10-methyl system have been reported[40]. More recently the trans isomer of the unsubstituted parent system has been reported as one of the products in the intramolecular oxymercuration of trans-2-allylcyclohexanols[41] and also in the reductive demercuration of a perhydrobenzofuran[42].

In order to study the stereochemistry of the octahydro-1--benzopyran system we wished to prepare isomerically pure samples of the cis and trans forms of the parent system together with a number of methyl substituted analogues. Work previously reported for the decahydroquinoline system[28] suggested that the most efficient approach would be to prepare isomeric mixtures of the octahydro-1--benzopyrans which could then be separated chromatographically to give small quantities of the pure isomers for further study. The first reported synthesis of the octahydro-1-benzopyran system by the reduction of 2H-1-benzopyran-2-one (coumarin)[36] therefore seemed attractive in this respect. The 2H-1-benzopyran-2-ones (coumarins) were well known and the preparations of a variety of methyl derivatives have been reported[43]. Furthermore, the parent system (coumarin) was commercially available in large quantities. However, although a number of catalytic reductions of 2H-1-benzopyran-2-one were attempted under a variety of conditions, attempts to repeat the original work of de Benneville and Connor to produce octahydro-1--benzopyran using a high pressure autoclave proved difficult. Although 2H-1-benzopyran-2-one could be hydrogenated at high temperatures

and pressures no significant quantities of octahydro-1-benzopyran were produced. In most cases a considerable amount of polymeric material was obtained. In view of this a more refined approach was used based on 2H-3,4-dihydro-1-benzopyran (chroman).

A. Investigation of the Synthesis of cis- and trans-Octahydro--1-benzopyran by Reduction of 2H-3,4-Dihydro-1-benzopyran

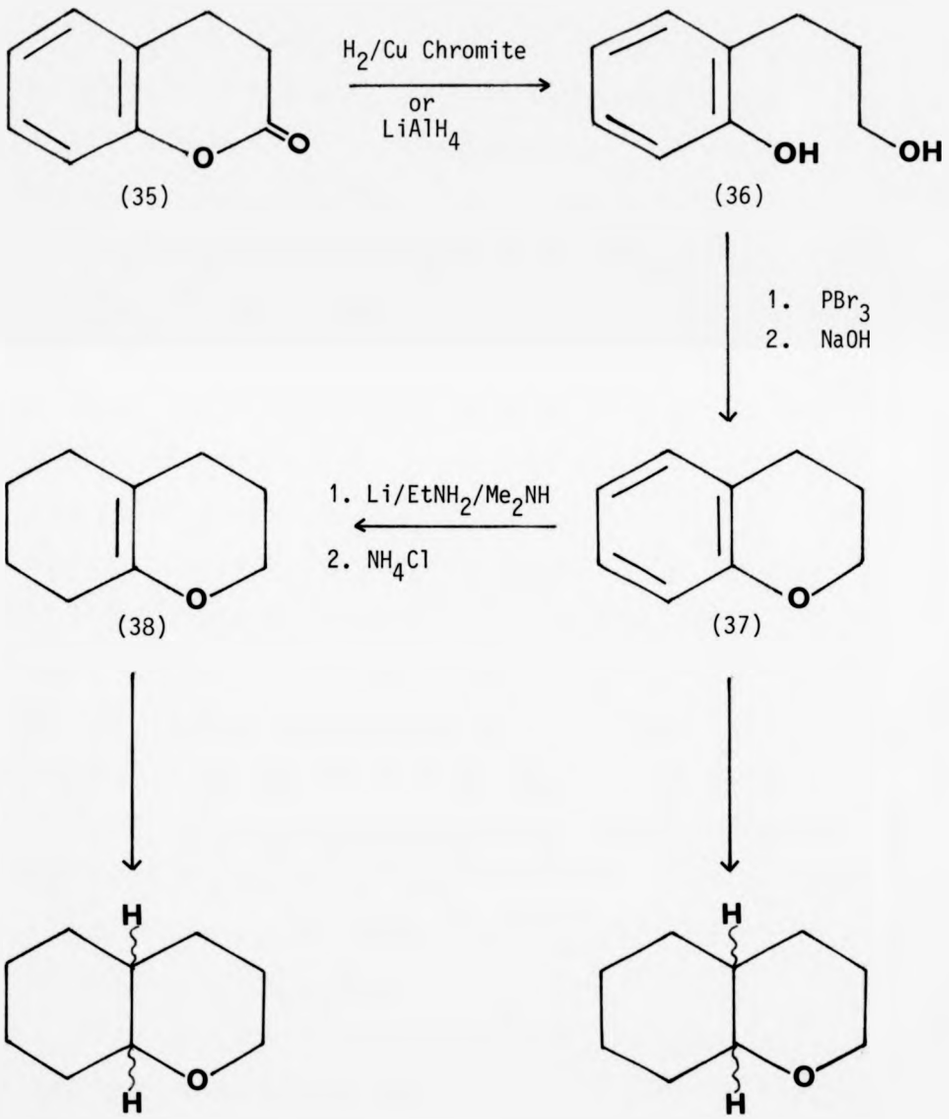
It has been reported that 2H-3,4-dihydro-1-benzopyran is reduced to octahydro-1-benzopyran in excellent yield under vigorous catalytic hydrogenation conditions[36]. Although the stereochemistry of this product was not reported it is known that the reduction of quinoline under similar conditions gives almost entirely trans-decahydroquinoline[28]. It would therefore seem reasonable to assume that the hydrogenation of 2H-3,4-dihydro-1-benzopyran gives largely trans--octahydro-1-benzopyran.

2H-3,4-Dihydro-1-benzopyran can also be reduced by lithium in ethylamine and dimethylamine[44] to give 2H-3,4,5,6,7,8-hexahydro--1-benzopyran (tetrahydrochroman) which can then be reduced catalytically to octahydro-1-benzopyran[45]. Once again the stereochemistry of the octahydro-1-benzopyran produced in this way was not reported but one might expect catalytic hydrogenation of the 2H-3,4,5,6,7,8-hexahydro--1-benzopyran (38) to give largely cis-octahydro-1-benzopyran.

It was hoped that these two different methods (Fig. 3) for reducing 2H-3,4-dihydro-1-benzopyran might therefore enable both the cis and trans isomers of octahydro-1-benzopyran to be produced separately.

Fig. 3.

Proposed Route for the Synthesis of cis- and trans-Octahydro-1-benzopyran



The initial step for both routes involved the reduction of 2H-3,4-dihydro-1-benzopyran-2-one (35) to 3-(2'-hydroxyphenyl)-propanol, (36). This was originally carried out by hydrogenation using freshly prepared copper chromite catalyst under vigorous conditions in an autoclave, as previously reported[36]. The diol (36) was then cyclised using phosphorus tribromide and sodium hydroxide to 2H-3,4-dihydro-1-benzopyran (37). Although this proved to be a satisfactory route giving overall yields of around 65% the initial autoclave reaction proved to be inconvenient and very time consuming. A superior method for the production of 3-(2'-hydroxy-phenyl)propanol was found to be the reduction of 2H-3,4-dihydro-1--benzopyran-2-one with lithium aluminium hydride. This method gave excellent yields and the diol produced was in a sufficiently pure enough state to be used in the subsequent cyclization step without further purification. With this improvement large quantities of 2H-3,4-dihydro-1-benzopyran were produced in high yield ($\sim$ 86%). A number of methods for reducing this material to the fully saturated octahydro-1-benzopyran system were then investigated. In view of the absence of previous reports of the cis isomer of octahydro-1--benzopyran the route which was expected to give this isomer was investigated first.

(i) Reduction of 2H-3,4-dihydro-1-benzopyran via 2H-3,4,5,6,7,8--hexahydro-1-benzopyran

2H-3,4,5,6,7,8-Hexahydro-1-benzopyran, prepared by the reduction of 2H-3,4-dihydro-1-benzopyran using the lithium-amine method previously reported[44] was subjected to a variety of hydrogenation conditions using T1 Raney nickel as the catalyst. Quite vigorous conditions were necessary for this reduction. Analytical gas liquid

chromatography indicated the formation of only one hydrogenation component which was then isolated by preparative gas liquid chromatography. This component gave a ^{1}H n.m.r. spectrum (Plate 4, Table 6) consistent with that expected for cis-octahydro-1-benzopyran (see later discussion). Further analysis by ^{13}C n.m.r. spectroscopy confirmed that the cis isomer was the major product, but also indicated the presence of a small amount of a second component later identified as trans-octahydro-1-benzopyran (calculated as 9% by peak height). The stereochemistry of the major product was thus as predicted, although the reduction conditions required were somewhat higher than anticipated from our study of 3,4-dihydropyran. Thus, for example, 3,4-dihydropyran was completely hydrogenated to the saturated tetrahydropyran within 6 hours at atmospheric pressure and room temperature using 10% Pd on charcoal as catalyst. In contrast 2H-3,4,5,6,7,8-hexahydro-1-benzopyran required about 21 hours at 6.3 atmospheres and a temperature of 148 °C with the same catalyst.

The reduction product of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran contained sufficient of the cis-octahydro-1-benzopyran isomer to enable the ^{1}H and ^{13}C n.m.r. parameters of this isomer to be obtained without removing the small amount of trans isomer. However, there was insufficient trans material present to obtain any significant amount of data about the ^{1}H n.m.r. spectrum of this isomer. Attempts to isolate a small sample of the trans isomer by chromatography were unsuccessful and for this reason an attempt to prepare a sample of largely trans-octahydro-1-benzopyran was made by reducing 2H-3,4--dihyhdro-1-benzopyran directly.

(ii) Catalytic hydrogenation of 2H-3,4-dihydro-1-benzopyran to octahydro-1-benzopyran

Hydrogenation of 2H-3,4-dihydro-1-benzopyran in cyclohexane using a Raney nickel catalyst gave largely one product which when analysed by gas liquid chromatography had the same retention time as the octahydro-1-benzopyran sample previously prepared. ^{13}C n.m.r. spectroscopy confirmed that the product was octahydro-1-benzopyran but also showed the isomeric ratio to be cis 91% : trans 9%, the same ratio as that previously obtained from the reduction of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran.

This result was rather unexpected since under similar conditions quinoline is reduced to give almost exclusively trans--decahydroquinoline. We would not expect the similarity in the isomeric composition of the two octahydro-1-benzopyran samples to be due to equilibration between the two isomers since any process of equilibration between the cis and trans isomers would be expected to favour the more thermodynamically stable trans isomer over the cis isomer. However, an attempt to equilibrate this isomeric mixture under a variety of conditions failed to alter the initial cis and trans ratio observed.

The most logical explanation for the above observations was that the direct reduction of 2H-3,4-dihydro-1-benzopyran to the fully saturated system proceeded via the enol ether, 2H-3,4,5,6,7,8-hexahydro-1-benzopyran. Such a reaction pathway would limit the suitability of this approach for producing the trans isomer. Although this was not too serious for the parent system where other methods were available for the production of this isomer, it would have seriously affected the planned studies of the methyl substituted systems.

For this reason the reaction pathway for the reduction of 2H-3,4--dihydro-1-benzopyran to octahydro-1-benzopyran was investigated further.

B. Investigation of the Reduction Pathway in the Catalytic Hydrogenation of 2H-3,4-Dihydro-1-benzopyran

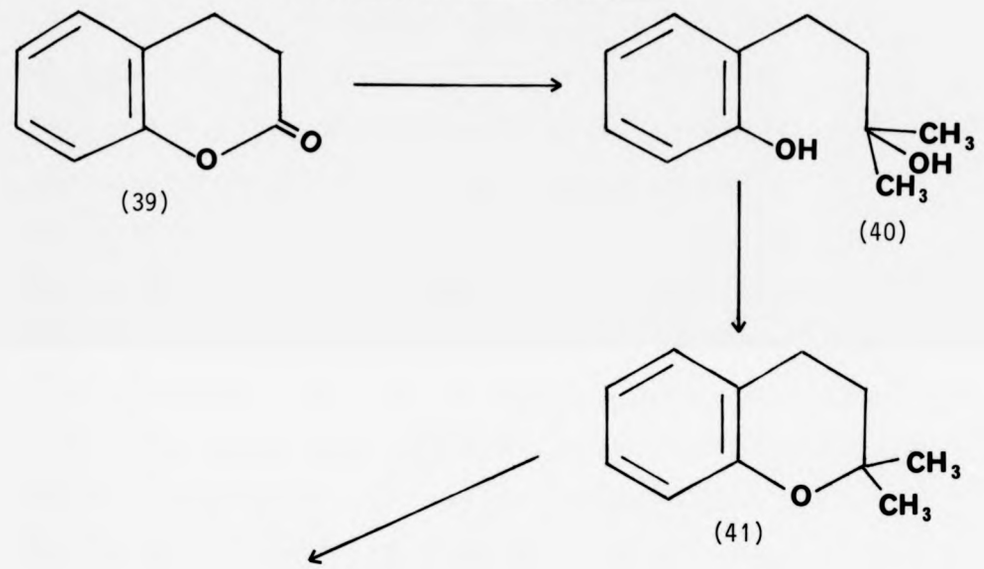
To maximise the chances of observing intermediates in the reduction pathway a large scale reduction of 2H-3,4-dihydro-1--benzopyran was carried out. This reaction was stopped before the catalytic hydrogenation was complete and the products analysed by gas liquid chromatography. This indicated that about one third of the starting material had been fully reduced and that no significant quantities of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran had been produced. However, after fractional distillation, a fraction was obtained which contained a component having the same retention time as that of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran. This component was calculated to be only about 0.1% of the total product.

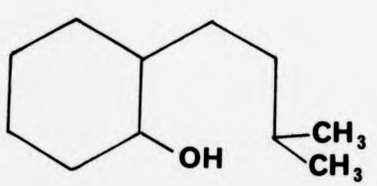
One possible explanation for the low concentration of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran could be that it is readily reduced once formed. To increase the concentration of this intermediate in the hydrogenation products it was therefore necessary to try and modify the system so as to reduce its ease of reduction without affecting the course of the reaction.

It was felt that 2H-3,4-dihydro-2,2-dimethyl-1-benzopyran (Fig. 4) might provide a suitably modified system. Furthermore, this material could be readily prepared in high yield by the action of methyl magnesium iodide on 2H-3,4-dihydro-1-benzopyran-2-one (39)

Fig. 4.

The Synthetic Route for the Preparation of 2H-3,4-Dihydro-2,2-dimethyl-1-benzopyran and the Result of Catalytic Hydrogenation

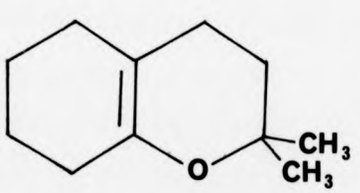


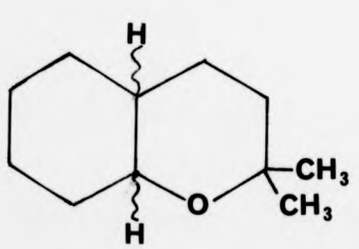


(43)

32% cis
68% trans

(42)





(44)

84% cis
16% trans

to give 4-(2'-hydroxyphenyl)-2-methylbutan-2-ol (40), which could then be cyclized to the desired material using the method indicated by Smith and Ruoff[46]. The presence of the geminal dimethyl group in 2H-3,4-dihydro-2,2-dimethyl-1-benzopyran (41) should not significantly affect the ease of formation of any 2H-3,4,5,6,7,8--hexahydro-2,2-dimethyl-1-benzopyran (42), but it would increase the strain in the octahydro-2,2-dimethyl-1-benzopyran system (44) by ensuring all conformations possessed an axially disposed methyl group. The increased strain should therefore reduce its ease of formation from 2H-3,4,5,6,7,8-hexahydro-2,2-dimethyl-1-benzopyran. If 2H-3,4-dihydro-2,2-dimethyl-1-benzopyran is reduced to cis-octahydro-2,2-dimethyl-1-benzopyran via the 2H-3,4,5,6,7,8-hexahydro-2,2--dimethyl-1-benzopyran intermediate, the amount of this intermediate present during the course of the reduction should therefore be increased relative to that in the parent system.

After a number of experiments the minimum conditions required to reduce the 2H-3,4-dihydro-2,2-dimethyl-1-benzopyran to the corresponding octahydro-2,2-methyl-1-benzopyran system were established. A reaction using these conditions was therefore carried out but stopped before complete reduction had occurred. Analysis of the product by gas liquid chromatography showed the presence of three components in approximately equal quantities and the absence of any 2H-3,4-dihydro--2,2-dimethyl-1-benzopyran. These three components were separated by spinning band distillation under reduced pressure and then identified by ^{1}H and ^{13}C n.m.r. spectroscopy.

The highest boiling component was identified as the ring cleaved product 2-(3'-methylbutyl)cyclohexanol (43). Both cis and trans isomers were present in this component in the proportion of

32% to 68% respectively. The substantial amount of ring cleaved product is probably due to the increased strain introduced by the geminal dimethyl group into the octahydro-2,2-dimethyl-1-benzopyran structure in comparison with the unsubstituted parent system where no ring-cleaved material was observed.

The lowest boiling component was identified as octahydro--2,2-dimethyl-1-benzopyran (44). As with the parent system the cis isomer was the major product (∿ 84%) but some trans isomer (∿ 16%) was also present. The slightly lower proportion of the cis isomer in this system (∿ 84%) relative to that observed in the unsubstituted parent system (∿ 91%) probably indicating a smaller difference in the free energies of the cis and trans isomers in the dimethyl system.

The component with its boiling point between those of the other two components could not be readily isolated in a completely pure form due to contamination with octahydro-2,2-dimethyl-1-benzopyran. Nevertheless, it could be readily identified as 2H-3,4,5,6,7,8-hexahydro--2,2-dimethyl-1-benzopyran (42). The ^{13}C n.m.r. spectrum of this material was similar to that predicted with the chemical shifts of the two lowest field signals (144.5 and 102.2 p.p.m.) comparing favourably with those observed for the unsubstituted analogue (C9 = 146.7 and C9 = 104.5 p.p.m.). Furthermore, this material also possessed the characteristic infra-red absorption around 1700 cm^{-1} arising from the presence of the enolic double bond. However, to confirm the identity of this component an authentic sample was prepared by the lithium-amine reduction of 2H-3,4-dihydro-2,2-dimethyl-1-benzopyran. The required hexahydro material was obtained in excellent yield and gave data in agreement with that of the material produced in the catalytic hydrogenation reaction (see experimental section).

The reduction pathway for 2H-3,4-dihydro-2,2-dimethyl-1-benzopyran was thus confirmed as proceeding via a hexahydro intermediate.

In view of the results for the 2,2-dimethyl system there is therefore strong evidence to suggest that direct catalytic hydrogenation of 2H-3,4-dihydro-1-benzopyran type systems will proceed via a hexahydro intermediate to give largely cis products. Modifications to the originally proposed route to avoid passing through a hexahydro intermediate were therefore investigated to try to increase the proportion of trans isomer in the octahydro-1-benzopyran system. These modifications are now discussed.

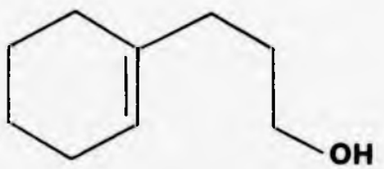
C. Investigations into the Preparation of trans-Octahydro--1-benzopyran

(i) By the attempted reduction of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran.

In the preparation of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran by the lithium-amine reduction of 2H-3,4-dihydro-1-benzopyran it has been reported[44] that two unidentified minor products were also formed. One of these minor components, observed as a forepeak (12-13%) in the gas liquid chromatograph of the reaction product, was suggested as being due to one or both isomers of the octahydro-1-benzopyran system. If this were the case it seemed possible that the octahydro-1-benzopyran was being produced by reduction of the 2H-3,4,5,6,7,8-hexahydro-1--benzopyran. Although isolated double bonds of this type do not normally reduce under the lithium-amine reduction conditions used[47], if it did reduce we would expect it to give predominantly the trans--octahydro-1-benzopyran isomer. Lithium-amine reductions are believed to occur via the formation of an anionic intermediate which

then protonates to give the most stable reduction product.

The reduction of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran by the lithium-amine method was therefore investigated. Unfortunately neither this nor a sodium-ammonia reduction succeeded in producing any octahydro-1-benzopyran. In view of this, the originally reported lithium-amine reduction of 2H-3,4-dihydro-1-benzopyran was investigated. Only one minor component was observed in addition to the 2H-3,4,5,6,7,8-hexahydro-1-benzopyran and furthermore this was shown to have a molecular composition consistent with that of the octahydro-1-benzopyran system. However, the ^{13}C n.m.r. spectrum and the ^{1}H n.m.r. spectrum (in the presence and absence of the shift reagent $Eu(FOD)_3$[48]) were consistent with the component being the ring opened product, 1-(3'-hydroxypropyl)cyclohexene (45). It is interesting to note that in the original paper[44] one of the reported minor components was said to be a double-bond isomer.

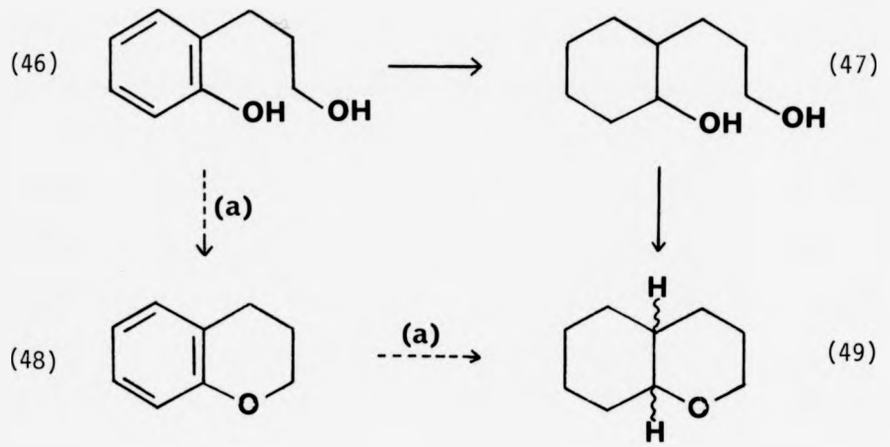


(45)

(ii) By the catalytic hydrogenation of 3-(2'-hydroxyphenyl)propanol.

In their studies of the hydrogenation of 2H-1-benzopyran-2-one, de Benneville and Connor had shown that 3-(2'-hydroxyphenyl)propanol could be hydrogenated to the diol, 2-(3'-hydroxypropyl)cyclohexanol. If this diol could be cyclized to give the octahydro-1-benzopyran system by use of hydrogenation conditions then such a route would avoid the intermediacy of 2H-3,4,5,6,7,8-hexahydro-1-benzopyran. As 3-(2'-hydroxyphenyl)propanol was readily available from our earlier preparation of 2H-3,4-dihydro-1-benzopyran, this reaction was investigated further as a possible route to trans-octahydro-1-benzopyran.

Initial investigations showed that the use of temperatures above 100 °C during the hydrogenation of 3-(2'-hydroxyphenyl)propanol (46) caused a significant amount of cyclisation of this material to occur prior to reduction. Under these circumstances the reduction step involved the hydrogenation of 2H-3,4-dihydro-1-benzopyran (48), the very reaction we were trying to avoid. However, by careful control of the hydrogenation conditions it was found to be possible to reduce the 3-(2'-hydroxyphenyl)propanol to 2-(3'-hydroxypropyl)-cyclohexanol (47) without any significant formation of 2H-3,4-dihydro--1-benzopyran. If 2H-3,4-dihydro-1-benzopyran had been formed under these conditions it would have been present in the final reaction mixture because it is resistant to further hydrogenation under these conditions. The formation of any octahydro-1-benzopyran (49) therefore arises from the cyclization of 2-(3'-hydroxypropyl)cyclohexanol rather than by reduction of 2H-3,4-dihydro-1-benzopyran.



(a) This route is not followed under minimum hydrogenation conditions.

When 2-(3'-hydroxypropyl)cyclohexanol was reduced so as to give only the diol (47) and octahydro-1-benzopyran, analysis of the diol showed the presence of approximately equal quantities of both the cis and trans isomers, whereas analysis of the octahydro-1-benzopyran showed a slightly greater preference for the cis isomer (66% cis, 34% trans). Unfortunately, it did not prove possible to separate the cis and trans diols despite considerable efforts and it was therefore not possible to investigate the feasibility of being able to cyclize the trans diol stereospecifically to give trans-octahydro-1--benzopyran at this time. Later in our investigations it was possible to produce a pure sample of trans-2-(3'-hydroxypropyl)cyclohexanol by the lithium aluminium hydride reduction of trans-octahydro-1-benzopyran-2-one (see later section). However, the trans diol when cyclized

under hydrogenation conditions over Raney nickel gave a mixture of the cis and trans isomers of octahydro-1-benzopyran (33% cis, 67% trans).

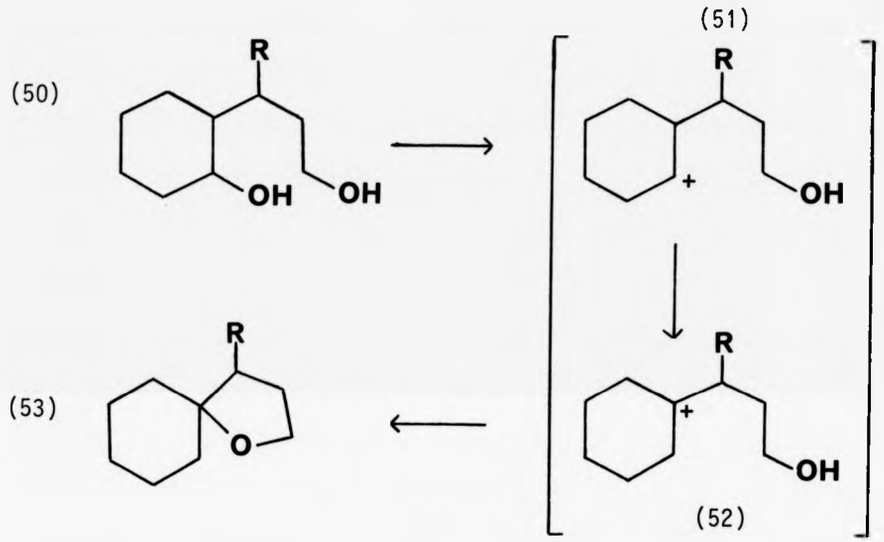
(iii) By cyclization of 2-(3'-hydroxypropyl)cyclohexanol using phosphoric acid.

It has been reported[49] that 2-(3'-hydroxy-1-methylpropyl)-cyclohexanol (50, R = Me) can be cyclized in the presence of 85% phosphoric acid to give the octahydro-4-methyl-1-benzopyran system. Although the isomeric composition was not specified the most likely reaction mechanism would seem to involve an initial protonation of the diol at the ring hydroxyl group and for this then to be followed by loss of water to give the secondary carbenium ion (51, R = Me). At this point the original cis/trans stereochemistry of the diol has been lost and subsequent cyclization would therefore be expected to give the more stable isomers.

If the same logic is applied to the cyclization of the 2-(3'--hydroxypropyl)cyclohexanol system then it should be possible to cyclize the cis and trans mixture of 2-(3'-hydroxypropyl)cyclohexanol (50, R = H), previously prepared, to give trans-octahydro-1-benzopyran.

The cis and trans mixture of 2-(3'-hydroxypropyl)cyclohexanol was therefore heated under vacuum with 85% phosphoric acid and the distillate collected. Examination of the reaction product revealed that although it had a molecular composition in accord with that expected for octahydro-1-benzopyran it did not give the expected spectral data. For example, the ^{13}C n.m.r. spectrum showed the presence of one quarternary carbon and eight methylene carbons. Furthermore, the ^{13}C n.m.r. spectrum showed a marked temperature dependence with a coalescence of the signals being observed at about -49 °C. This data was consistent with the product being the spiro

ether, 1-oxa[4,5]decane (53, R = H), the observed temperature dependence arising from the possibility of ring inversion occurring in the cyclohexane ring.



This product can be readily explained from a consideration of the mechanism if the secondary carbenium ion (51, R = H) rearranges to the more stable tertiary carbenium ion (52, R = H) prior to cyclization. In view of the ready formation of the spiro ether (53, R = H) and the absence of any sign of octahydro-1-benzopyran this must cast some doubt on the validity of the previously reported cyclization of 2-(3'-hydroxy-1'-methylpropyl)cyclohexanol to the octahydro-4-methyl-1-benzopyran system. However, it should be noted that in a subsequent cyclization reaction of 2-(3'-hydroxypropyl)cyclohexanol some octahydro-1-benzopyran was produced. This product was shown to have the same cis/trans ratio (50:50) as that in the starting material which suggests it is formed via a cyclization route which does not involve the carbenium ion (51, R = H).

D. Alternative Approach to the Synthesis of cis- and trans--Octahydro-1-benzopyran

In view of the lack of success of the synthetic routes using 2H-3,4-dihydro-1-benzopyran as a starting material for the preparation of pure samples of both cis- and trans-octahydro-1-benzopyran an entirely different approach was developed. Since we had not found it possible to separate the cis and trans isomers of octahydro-1-benzopyran it was clear that a stereospecific synthesis for both isomers was required. Furthermore, the proposed route should ideally be capable of being extended to produce pure isomers of a number of the methyl substituted octahydro-1-benzopyrans which were of interest.

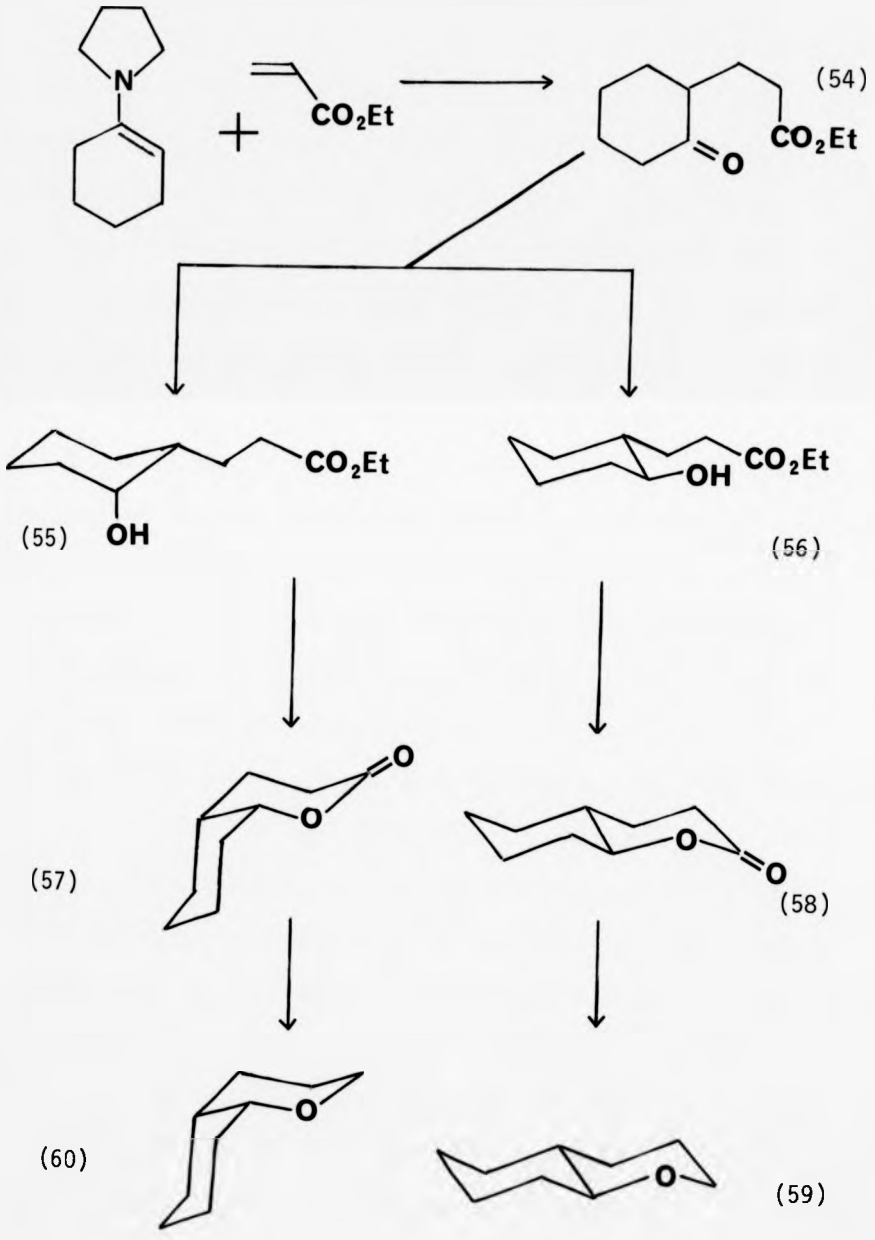
The method developed is shown in Fig. 5. This involved the initial formation of 2-(2'-carbethoxyethyl)cyclohexanone (54) by the reaction of the pyrrolidine enamine of cyclohexanone with ethyl acrylate. This was then reduced to give a cis and trans mixture of 2-(2'-carbethoxyethyl)cyclohexanol (55 and 56). These isomers could be cyclized to give the corresponding lactones (58 and 57) which, it was hoped, could then be reduced to the appropriate octahydro-1-benzopyran isomers (59 and 60). This route has the advantage that separation of the cis and trans isomers can be attempted at several points in the synthesis, although clearly it would be advantageous to be able to leave this until the last possible point in the synthesis.

(i) Preparation of 2-(2'-carbethoxyethyl)cyclohexanone

The preparation of 2-(2'-carbethoxyethyl)cyclohexanone by the reaction of the pyrrolidine enamine of cyclohexanone with ethyl acrylate has been previously reported[50] and proved to be a satisfactory method giving a good yield of the desired product.

Fig. 5

The Synthetic Route for the Preparation of cis- and trans-Octahydro-1-benzopyran



(ii) Preparation of 2-(2'-carbethoxyethyl)cyclohexanol

(a) Attempted preparation by reduction of 2-(2'-carbethoxyethyl)-cyclohexanone with sodium borohydride

The reduction of the cyclohexanone (54) with sodium borohydride in isopropanol led to the formation of a viscous liquid which was shown by n.m.r. spectroscopy to be a mixture of the cis and trans isomers of 2-(3'-hydroxypropyl)cyclohexanol in approximately equal quantities. Although ester functions are not normally reduced under these conditions H.O. House et. al.,[51] have also observed that the corresponding methyl ester is reduced to give the diol using sodium borohydride. These workers suggested that the hydroxy esters initially formed on reduction of the keto ester were converted to the corresponding lactones which then underwent further reduction. Furthermore, they found that reaction of the isomeric lactone mixture (57 and 58) with sodium borohydride also produced the diol, 2-(3'-hydroxy-propyl)cyclohexanol. In view of this result an alternative method of selective reduction of the keto function was investigated.

(b) Catalytic hydrogenation of 2-(2'-carbethoxyethyl)cyclohexanone

As the keto function of 2-(2'-carbethoxyethyl)cyclohexanone should be more susceptable to reduction by hydrogenation than the ester function the necessary conditions to achieve this were investigated. As expected, on hydrogenation of this material using a platinum black catalyst the keto function was found to be reduced without affecting the ester function. This reduction was also found to occur reasonably well with a 10% palladium on charcoal catalyst, though more vigorous conditions and a longer reaction time were required. The reduction material in these hydrogenation reactions was found to consist of equal proportions of cis- and trans-2-(2'-carbethoxyethyl)cyclohexanol.

(iii) Separation of the cis and trans isomers of 2-(2'-carbethoxyethyl)cyclohexanol

Initial investigations using thin layer chromatography revealed that these cyclohexanol isomers could be separated to a limited extent. Preparative thin layer chromatography, therefore, allowed samples of the less retentive cis isomer to be obtained in a pure state whereas samples of trans isomer were contaminated with quantities of the cis isomer. Medium pressure chromatography, however, allowed pure samples of each isomer to be obtained. The samples of the cis and trans cyclohexanols were readily identified by their characteristic ^1H n.m.r. spectra (see experimental section). A problem which arose following the separation of the isomers was due to the ease at which the trans cyclohexanol would cyclise to the corresponding trans lactone. Fortunately, this cyclization seemed only to occur significantly when the fractions were warmed to remove the solvent at the end of the chromatographic separation. Nevertheless, the cyclohexanols were separated as soon as possible after their preparation to avoid the possibility of cyclization occuring prior to their separation.

(iv) Preparation of the cis and trans isomers of octahydro-1-benzopyran-2-one

Both the cis and trans isomers of 2-(2'-carbethoxyethyl)cyclohexanol were observed to cyclize readily in either acid or base catalysed conditions. However, the method chosen involved heating the cyclohexanols under reflux in benzene with a trace of p-toluenesulphonic acid. The trans cyclohexanol (55) was observed to cyclize readily, while the cis cyclohexanol (56) took slightly longer.

Separation of the isomeric mixture of the cis (57) and trans (58) lactones was also investigated but no separation was observed. Previous workers[51] have also reported that they could not achieve a chromatographic separation of the lactone mixture. However, as the pure cis and trans isomers of octahydro-1-benzopyran-2-one could be prepared by the previously described route, this was not a serious problem. Only the final step of the proposed route, the reduction of the lactones to the corresponding octahydro-1-benzopyrans, therefore remained.

(v) Reduction of octahydro-1-benzopyran-2-one to octahydro-1-benzopyran

Several potential methods for reducing δ-lactones to cyclic ethers have been reported which could be applied to our system. Firstly, previous workers[36] had reported that octahydro-1-benzopyran-2-one can be reduced in a high pressure autoclave to octahydro-1-benzopyran. Secondly, several δ-lactones have been reported[52] to be rapidly hydrogenated in high yields to ether derivatives under relatively mild conditions. Thirdly, Pettit et al.[53] have indicated that δ-lactones may, in certain circumstances, be reduced to ethers by reaction with a mixture of boron trifluoride and sodium borohydride. These methods were therefore investigated.

(a) Attempted catalytic hydrogenation of octahydro-1-benzopyran-2-one

In the first instance high pressure and temperature hydrogenation conditions were applied to a mixture of the cis and trans isomers of octahydro-1-benzopyran-2-one. However, the reaction did not produce any observable amount of the required products and this route was therefore abandoned without further work.

(b) Attempted atmospheric hydrogenation of octahydro-1-benzopyran-2-one

Edward and Ferland have reported[52] that the 10-methyl analogue of octahydro-1-benzopyran-2-one (cis and trans mixture) can be reduced in high yield to the corresponding octahydro-1-benzopyran system. Their method involved the use of atmospheric hydrogenation conditions with a platinum oxide catalyst in glacial acetic acid containing precisely regulated amounts of 70% perchloric acid. However, when this method was applied to the unsubstituted octahydro-1-benzopyran--2-one system no uptake of hydrogen was observed and examination of the reaction mixture confirmed that no reduction had taken place.

(c) Preparation of octahydro-1-benzopyran from octahydro-1-benzopyran-2-one using a borane complex

The boron trifluoride-sodium borohydride reaction mixture reported by Pettit et al.[53] to reduce certain δ-lactones suggested that the reducing species in this case might be the boron hydride, borane. Since this reagent was available to us in the form of a 1:1 borane--dimethyl sulphide complex it was decided to investigate the possibility of using this reagent rather than the less convenient method used by Pettit et al. The addition of a quantity (∿ 28% excess) of the borane-dimethyl sulphide complex to a portion of pure trans-octahydro--1-benzopyran-2-one led to the formation of a white solid after a period of about 5 minutes. This solid then subsequently disappeared as the reaction proceeded. After several hours the reaction was worked up (see experimental section) and the product analysed by n.m.r. spectroscopy. This showed that the only product formed was the isomerically pure trans-octahydro-1-benzopyran, the desired product. It became clear later, however, that we were fortunate to have used a freshly

opened bottle of the borane complex for this reaction. Thus when the reaction was repeated later on a larger scale a different product was observed. This product was subsequently identified as the lactanol, trans-octahydro-1-benzopyran-2-ol.

In view of the fact that the original reaction had produced the desired cyclic ether in such an excellent yield it was therefore of considerable importance to establish conditions that would consistently give the desired product. As the addition of a trace of boron trifluoride-diethyl etherate has been reported[54] to assist reductions using the borane-dimethyl sulphide complex this modification was investigated using cis-octahydro-1-benzopyran-2-one. On using an excess of the borane-dimethyl sulphide complex together with a quantity of boron trifluoride-diethyl etherate (1 molar equivalent) the cis-lactone was reduced to the desired isomerically pure cis--octahydro-1-benzopyran. This would suggest that the formation of the lactonal is at least partly related to the borane-lactone ratio. Although the yields obtained from this reaction ($\sim$ 55%) were lower than from the first reaction with the trans-lactone, the reaction was nevertheless reproducable.

The route indicated in Fig. 5 was therefore shown to be convenient for the production of pure isomers of both cis- and trans--octahydro-1-benzopyran. Furthermore, the method had the potential of being extended for the study of a number of interesting methyl analogues of octahydro-1-benzopyran. These aspects are discussed later.

E. Stereochemical Aspects

(i) trans-Octahydro-1-benzopyran

The trans isomer of octahydro-1-benzopyran could be readily identified as that isomer having a temperature independent n.m.r. spectrum. Its 100 MHz ^{1}H n.m.r. spectrum (Plate 1, Table 1) consisted of a complex envelope of overlapping resonances between ∿ 0.8 and 1.9 p.p.m. together with three lower field resonances. These lower field resonances could be readily assigned to those protons nearest the oxygen (i.e. H2a, H2e and H9). From a consideration of the multiplicities predicted for these three protons it was possible to assign the doublet at lowest field to the H2e proton. Although the two remaining resonances both possessed triplet character, it was possible to assign the lower field signal at 3.44 p.p.m. to H2a since it was distorted towards the H2e signal indicating the presence of a mutual coupling.

Although the 400 MHz ^{1}H n.m.r. spectrum (Table 1) of trans--octahydro-1-benzopyran still produced a complex envelope of resonances at high field the three lower field signals were simplified significantly. Irradiation of the multiplet at 3.44 p.p.m. resulted in the loss of the large coupling from the resonance at 3.96 p.p.m. confirming the assignment of these two lowest field signals as H2a and H2e respectively. The observation that the H2a proton resonance is at higher field than that of the H2e proton is in accord with the general observation that the axial protons resonate at higher field than the equatorially disposed protons in cyclohexane and pyran systems[9,55]. Furthermore, the chemical shift difference between the H2e and H2a resonances of 0.52 p.p.m. observed for trans-octahydro-1-benzopyran compares favourably with the 0.55 p.p.m. difference observed in the α-methylene

Plate 1.

The 100 MHz ^{1}H N.M.R. Spectrum of trans-Octahydro-1-benzopyran

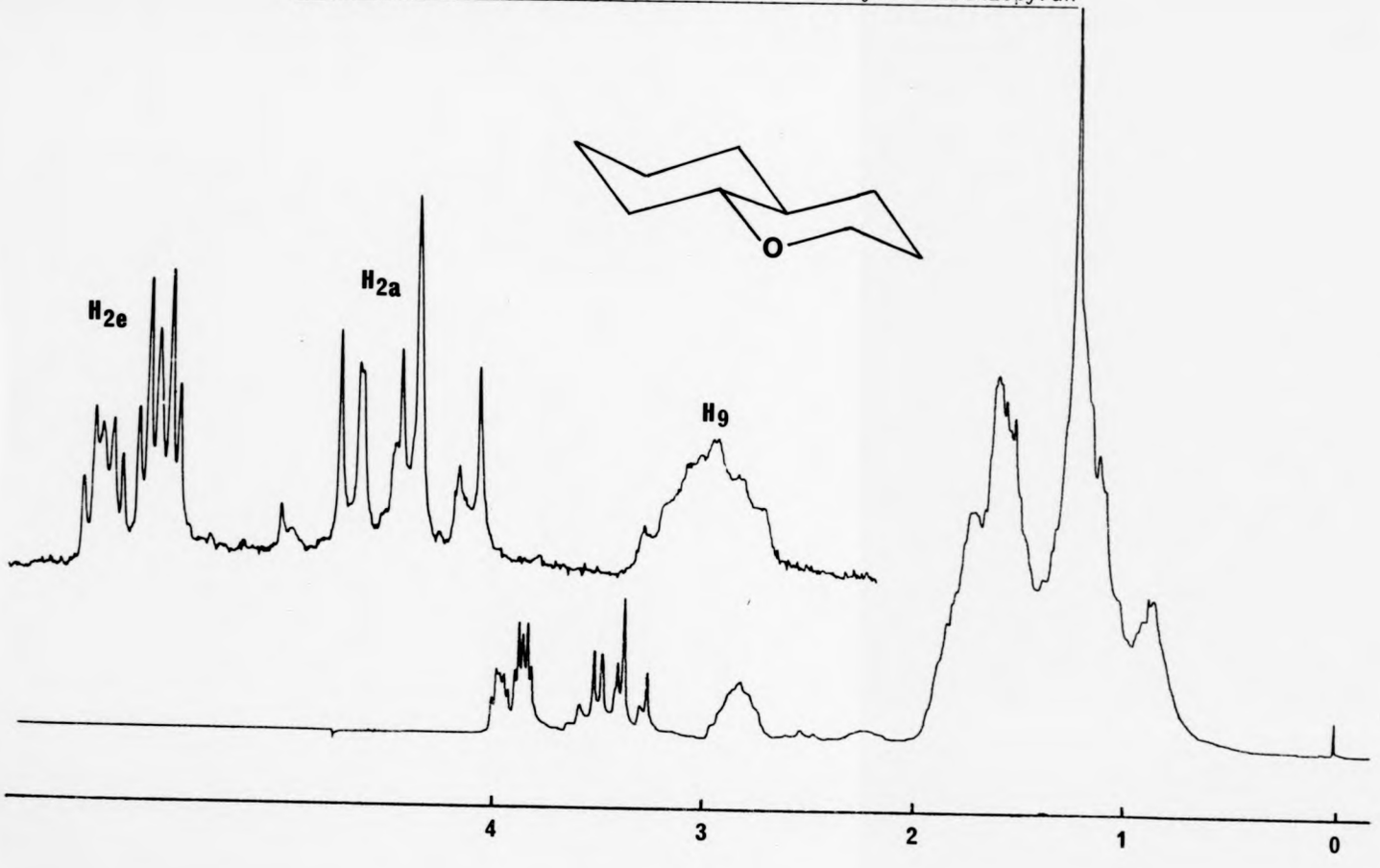


Table 1

^{1}H n.m.r. Spectral Data

trans-Octahydro-1-benzopyran

Proton	Shift(δ)	Description of Resonance
(100 MHz Spectrum)*		
2e	3.97	Distorted multiplet (band width ∿ 20 Hz) showing doublet character.
2a	3.44	Distorted multiplet with triplet of doublet character (band width ∿ 30 Hz)
9	2.89	Poorly resolved signal of triplet character (band width ∿ 31 Hz).
Remaining Protons	∿ 0.8-1.9	Complex envelope of overlapping resonances.
(400 MHz Spectrum)		
2e	3.96	Multiplet with doublet of doublet of triplet character. ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 4.6 Hz; $J_{2e,3e} \sim J_{2e,4e}$ = 1.7 Hz)
2a	3.44	Multiplet with doublet of doublet of doublet character ($J_{2a,3a}$ = 12.3 Hz; $J_{2a,2e}$ = 11.3 Hz; $J_{2a,3e}$ = 2.7 Hz).
9	2.89	Multiplet with triplet of doublet character (band width ∿ 27 Hz).
Remaining Protons	0.83-1.89	Complex envelope of overlapping resonances.

* $CDCl_3$ Solvent at 25 °C

group in tetrahydropyran[9]. It is interesting to note that the 400 MHz ^{1}H n.m.r. spectrum of trans-octahydro-1-benzopyran showed an additional small coupling (J = 1.7 Hz) in the H2e resonance besides those expected. This additional coupling was assigned as the $J_{2e,4e}$ coupling in view of the 'W' relationship[56] between H2e and H4e.

As previously mentioned (see Introduction) the vicinal ^{1}H couplings for the C2-C3 portion of the molecule can be used to obtain the R value[31] which is a measure of ring distortion. Although in the 400 MHz ^{1}H n.m.r. spectrum of trans-octahydro-1-benzopyran only the protons on the C2 position of the molecule are clearly visible, the necessary coupling information can be obtained from the H2e and H2a signals alone. If these values are used (i.e. $J_{2a,3a}$ = 12.3 Hz; $J_{2e,3e}$ = 1.7 Hz; $J_{2e,3a}$ = 4.6 Hz and $J_{2a,3e}$ = 2.7 Hz) a value of R = 1.9 is obtained and corresponds to a dihedral angle of 56°. Although this value is smaller than that expected for the undistorted decalin system (cf. cyclohexane R = 2.2) it is consistent with the expected effect of incorporating the oxygen atom (cf. tetrahydropyran R = 1.9)[33].

The ^{13}C n.m.r. spectrum of trans-octahydro-1-benzopyran (Table 2, Plate 2) compared very well with that predicted from a consideration of the shifts for trans-decalin (Table 3) together with oxygen substituent effects obtained from a comparison of the shifts in tetrahydropyran and cyclohexane (Table 4). It should be noted, however, that only the assignments of C2, C9 and C10 could be made unambiguously. The remaining six carbon resonances are all methylene carbons and also have similar chemical shifts. They have therefore been assigned by obtaining the closest fit with the calculated values. Nevertheless, the ^{1}H and ^{13}C n.m.r. data proved conclusively that this material was trans-octahydro-1-benzopyran.

Plate 2.

The ^{13}C N.M.R. Spectrum of trans-Octahydro-1-benzopyran

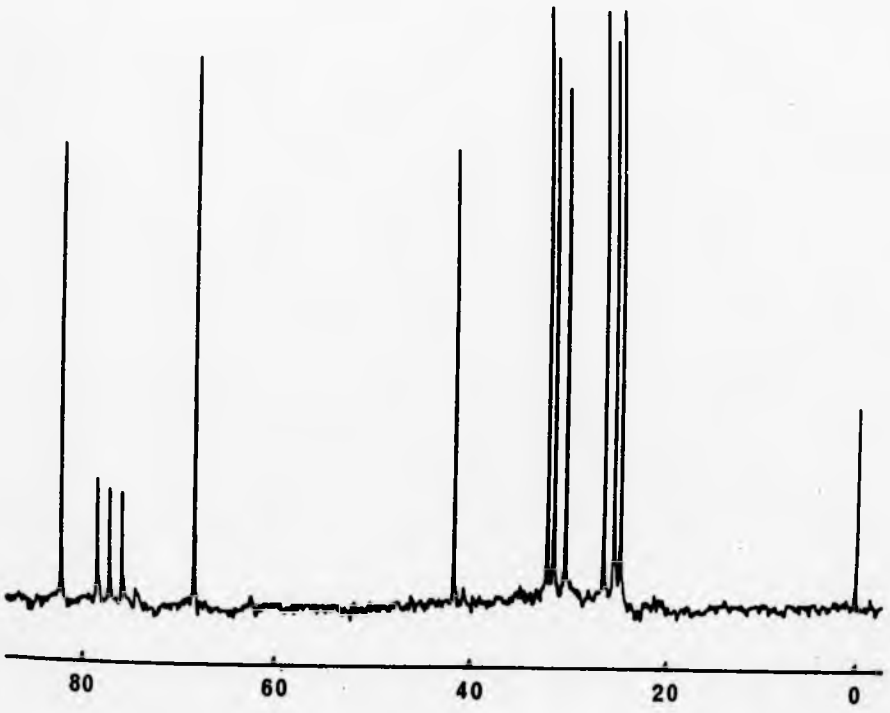
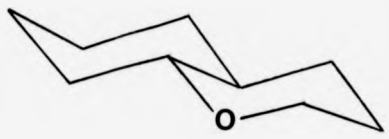


Table 2

^{13}C n.m.r. Spectral Data

trans-Octahydro-1-benzopyran



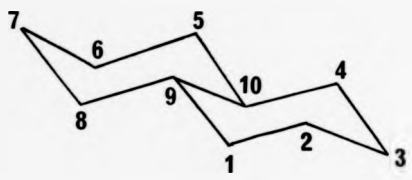
Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.0	T	68.28	T
3	25.7	T	25.78	T
4	30.2	T	31.90	T
5	30.2	T	30.71	T
6	27.1	T	26.82	T
7	22.7	T	25.07	T
8	33.2	T	32.56	T
9	84.8	D	82.02	D
10	42.5	D	42.14	D

*Calculations based on trans-decalin with modifications for the effect of oxygen from our studies on tetrahydropyran.

†$CDCl_3$ Solvent at 25 °C.

Table 3

^{13}C N.M.R. Chemical Shifts of cis- and trans-Decalin



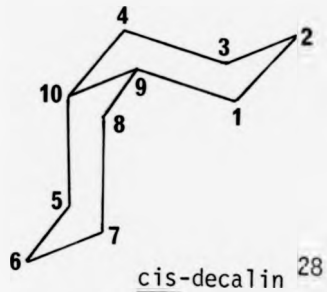
trans-decalin [28]

Solvent: C_6D_6

C9 = C10 = 43.88

C1 = C4 = C5 = C8 = 34.63

C2 = C3 = C6 = C7 = 27.10



cis-decalin [28]

Neat Liquid (-50 °C)

C9 = C10 = 36.3

C4 = C8 = 32.7

C3 = C7 = 21.2

C2 = C6 = 27.2

C1 = C5 = 25.8

All the above chemical shifts are quoted in p.p.m. downfield from Me_4Si.

Table 4

The ^{13}C N.M.R. Chemical Shifts of Tetrahydropyran and Cyclohexane and the Effect of Oxygen Substitution

Tetrahydropyran

Solvent: $CDCl_3$ + $CFCl_3$ (50:50 at -70 °C)

C2 = C6 = 68.57

C3 = C5 = 26.31

C4 = 23.25

Effect of Oxygen Substitution†

α = +40.87

β = - 1.39

γ = - 4.45

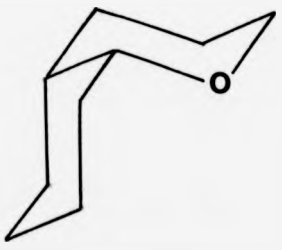
†The effect of oxygen substitution is calculated from tetrahydropyran on the basis that the ^{13}C n.m.r. chemical shift of cyclohexane is 27.7 p.p.m.[57]

All the above chemical shifts are quoted in p.p.m. downfield from Me_4Si.

(ii) cis-Octahydro-1-benzopyran

This component could be readily identified as the cis isomer of the octahydro-1-benzopyran system since its ^{13}C n.m.r. spectrum was temperature dependent showing the presence of an exchange process. At room temperature the ^{13}C n.m.r. spectrum of this isomer showed nine sharp lines (Plate 3). However, as the sample was cooled a significant amount of line broadening was observed. At -20 °C this broadening was most marked, with all but two signals significantly broadened. These two signals were identified by an "off-resonance" decoupling experiment as the C9 and C10 positions in the ring system and they remained sharp throughout the experiment. However, even those signals which were broad at -20 °C had sharpened by -50 °C indicating that the system had been "frozen out" at this temperature. Unfortunately, no small signals corresponding to the minor conformation of the cis-octahydro-1-benzopyran could be observed indicating that the position of the conformational equilibrium Type A $\rightleftharpoons$ Type B was obviously extreme. Nevertheless, the ^{13}C chemical shifts for the major conformation of cis-octahydro-1-benzopyran (Table 5) compared well with those calculated for the Type A conformation (61) from cis-decalin chemical shift values (Table 3), together with the appropriate oxygen substituent parameters (Table 4).

(61)



Conformation
Type A

Plate 3.

^{13}C N.M.R. Spectra from the Variable Temperature Study of cis-Octahydro-1-benzopyran

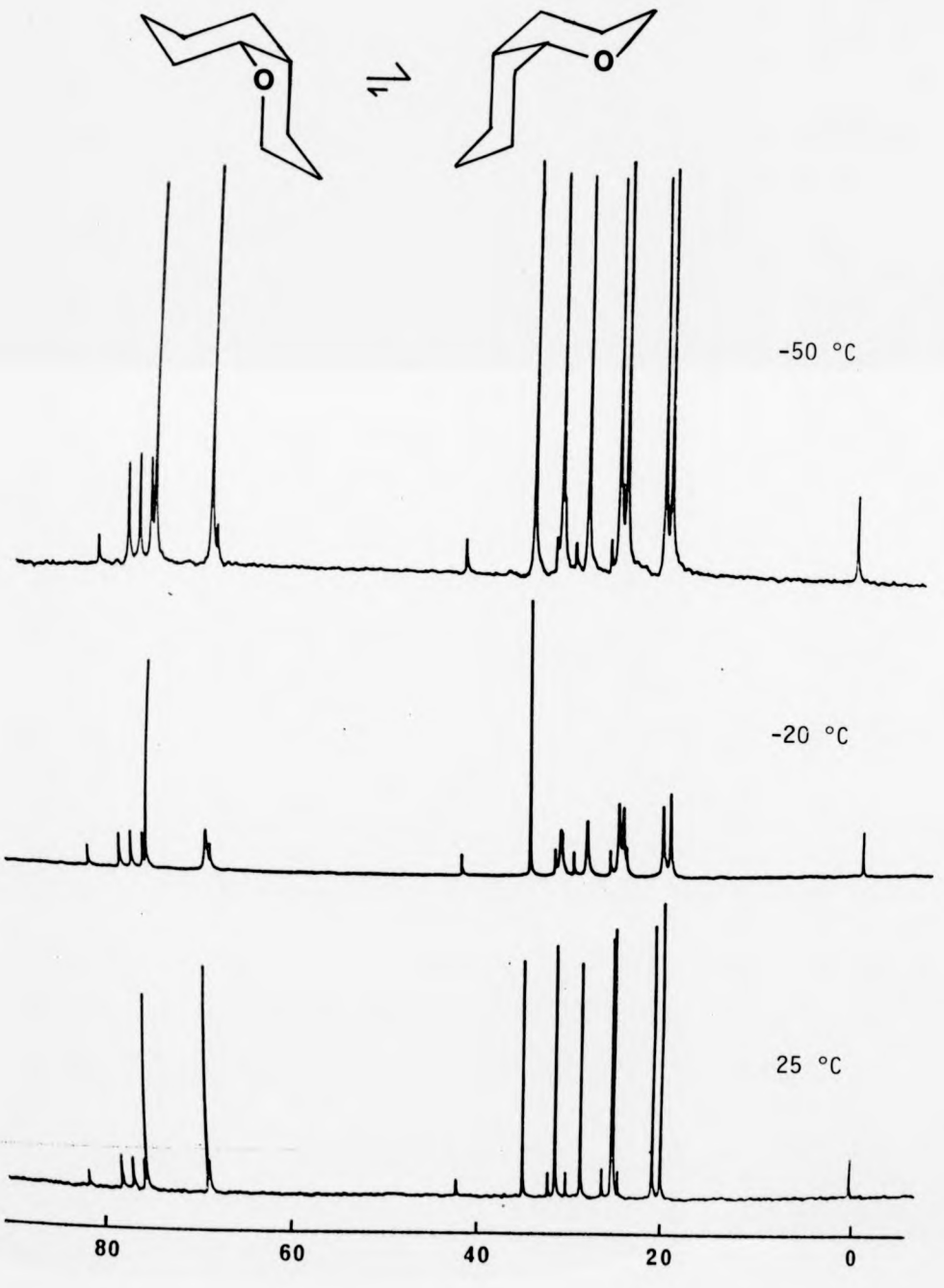
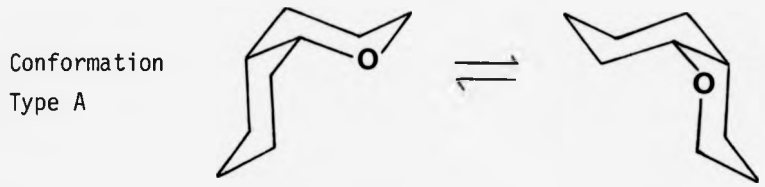


Table 5

^{13}C n.m.r. Spectral Data

cis-Octahydro-1-benzopyran



Carbon No.	Calculated Values*			Experimental Values†	
	Shift(δ)		Mult.	Shift(δ)	Mult.
	Type A	Type B			
2	68.1	62.1	T	68.91	T
3	19.8	25.8	T	20.92	T
4	28.3	21.4	T	29.05	T
5	21.4	28.3	T	24.97	T
6	27.2	21.2	T	25.73	T
7	16.8	22.8	T	20.21	T
8	31.3	24.4	T	31.83	T
9	77.2	77.2	D	75.21	D
10	34.9	34.9	D	34.70	D

*Calculations based on cis-decalin with modifications for the effect of oxygen from our studies on tetrahydropyran.

†Experimental values from sample in $CDCl_3$ + $CFCl_3$ (50:50) at -50 °C.

This showed the position of the conformational equilibrium (Type A ⇌ Type B) to be strongly in favour of Type A, as previously observed for the cis isomer of the decahydroquinoline system[28]. This interpretation was confirmed by a consideration of the ^1H n.m.r. spectrum of this material.

Examination of the room temperature 100 MHz ^1H n.m.r. spectrum of this isomer revealed a complex envelope of signals at high field (Plate 4, Table 6) together with signals at lower field arising from the three protons nearest to the oxygen. Analysis of this lower field region was complicated by the partial overlap of two of these signals, those from H2a and H9. This was particularly unfortunate because the stereochemistry of such systems can be identified from the shape of the bridgehead proton H9. For this reason cis-2,2--dideutero-octahydro-1-benzopyran was synthesised to simply the low field region of the ^1H n.m.r. spectrum. Deuteration of the methylene protons on C2 simplified the ^1H n.m.r. spectrum by removing the H2a and H2e signals, thereby exposing the bridgehead proton, H9, as a broad singlet resonating at 3.54 p.p.m. (Plate 5). This broad singlet (half-band width = 7 Hz) indicated that the H9 proton had no large couplings and therefore that it must be equatorially orientated relative to the cyclohexane ring. This, therefore, not only indicated the ring junction to be cis but it also showed the major conformation was that of Type A.

Subsequent examination by 400 MHz ^1H n.m.r. spectroscopy (Table 6) of the non-deuterated material demonstrated that the use of high field spectrometers can greatly simplify complex spectra without the need for deuteration. Thus at 400 MHz the broad singlet (from H9) at 3.54 p.p.m. was clearly visible. The signal at 3.98

Plate 4.

The 100 MHz ^{1}H N.M.R. Spectrum

of cis-Octahydro-1-benzopyran

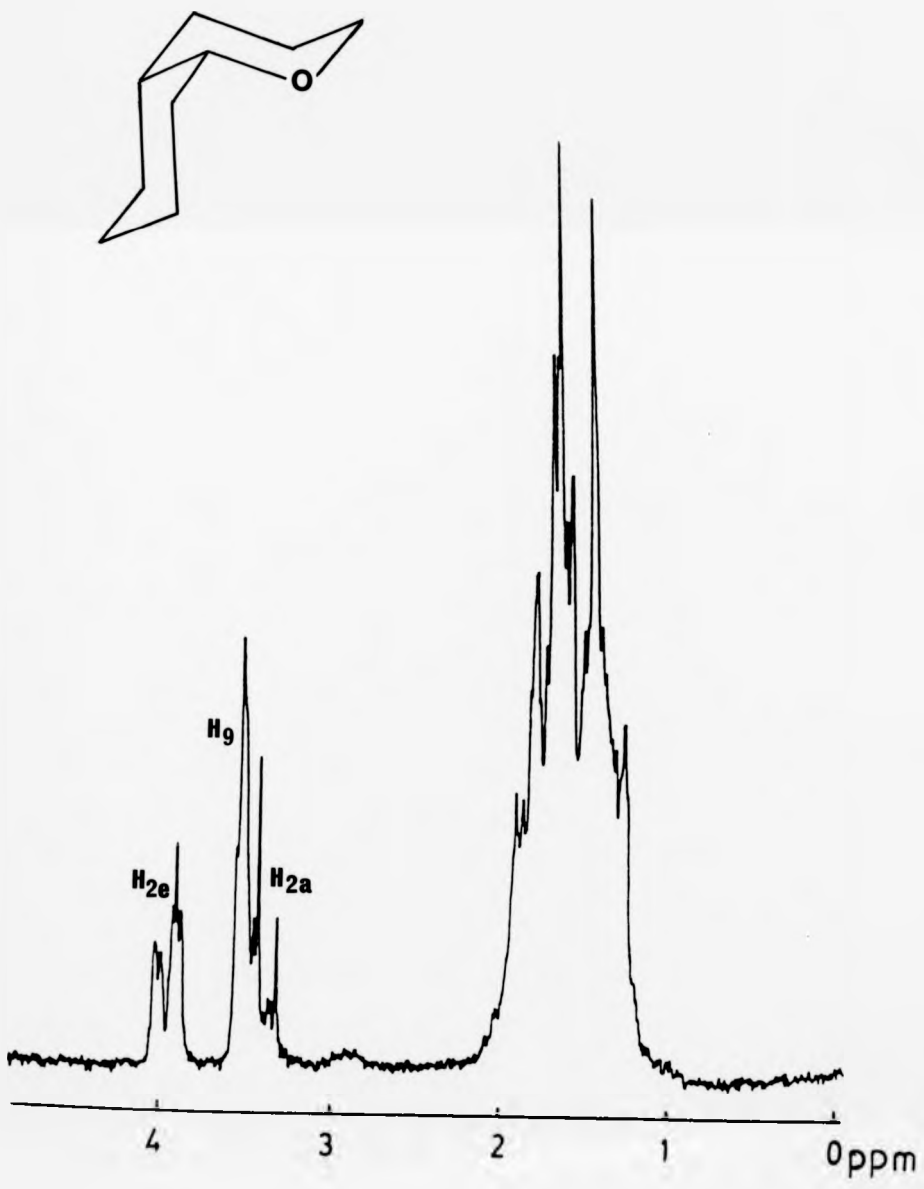


Plate 5.

The 100 MHz ^{1}H N.M.R. Spectrum of cis-2,2-Dideutero-octahydro-1-benzopyran

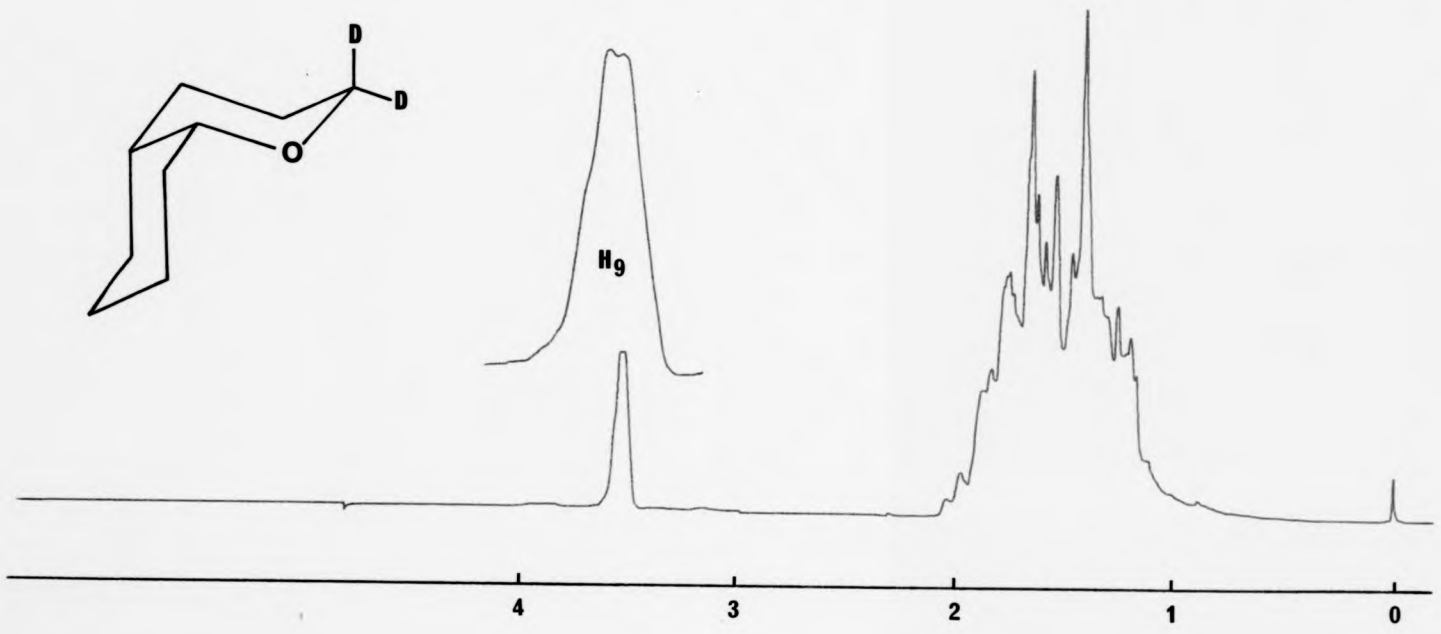
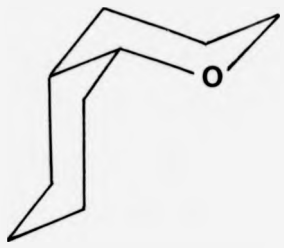


Table 6

^{1}H n.m.r. Spectral Data

cis-Octahydro-1-benzopyran



Conformation
Type A

Proton	Shift(δ)	Description of Resonance
(100 MHz Spectrum)*		
2e	3.98	Distorted doublet (observed splitting = 11.5 Hz) showing further couplings.
9	3.54	Broad singlet (half band width = 7 Hz) partially overlapping H2a.
2a	3.43	Multiplet with triplet character (band width ∿ 25 Hz) partially overlapped by H9.
Remaining Protons	∿ 1.0-2.0	Complex envelope of overlapping resonances.
(400 MHz Spectrum)*		
2e	3.98	Doublet of doublet of triplets ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 4.9 Hz; $J_{2e,3e} \sim J_{2e,4e}$ = 2.0 Hz).
9	3.54	Poorly resolved signal showing quartet character (half-band width = 6 Hz).
2a	3.45	Multiplet with doublet of doublet of doublet character. ($J_{2a,2e}$ = 11.3 Hz; $J_{2a,3a}$ = 12.0 Hz: $J_{2a,3e}$ = 2.6 Hz).
Remaining Protons	1.18-1.87	Complex envelope of overlapping resonances.

* $CDCl_3$ Solvent at 25 °C.

p.p.m., of doublet character, was assigned to the H2e proton, while the remaining signal at 3.45 p.p.m., having two large couplings, was assigned to the H2a proton. Once again, as observed for trans-octahydro-1-benzopyran, the 400 MHz ^{1}H n.m.r. spectrum of cis-octahydro--1-benzopyran also showed the presence of a small coupling (J = 2.0 Hz), besides those expected for the H2e resonance. This small coupling was also assigned as the $J_{2e,4e}$ coupling in view of the "W" relationship between the H2e and H4e protons.

Although care should be exercised when using coupling data from the room temperature spectrum of cis-octahydro-1-benzopyran a value for R could be calculated. From the vicinal couplings obtained from those protons on C2 (i.e. $J_{2a,3a}$ = 12.0 Hz; $J_{2e,3e}$ = 2.0 Hz; $J_{2e,3a}$ = 4.9 Hz and $J_{3e,2a}$ = 2.6 Hz) a value of R = 1.9 was obtained. It is interesting to note that the R values for both the cis and trans isomers are alike showing there is a similar degree of distortion in the tetrahydropyran rings in these two isomers. Furthermore, the value of R = 1.9 shows that the oxygen substituent has caused some flattening of the ring containing the oxygen (cf. cyclohexane, R = 2.2). This is consistent with previously reported studies on tetrahydropyran which indicated that the chair conformation[58] of tetrahydropyran also has an R value[33] of 1.9.

Since one of the aims of this work had been to compare the relative effects of introducing an oxygen or nitrogen atom into the decalin ring system it was disappointing that no signals could be observed initially for the Type B conformation of cis-octahydro-1--benzopyran in the low temperature ^{13}C n.m.r. spectrum. Although it could be seen that the position of the conformation equilibrium (Type A $\rightleftharpoons$ Type B) was more extreme than previously observed for the

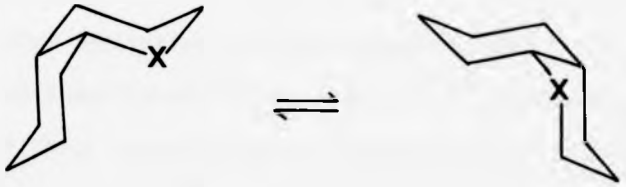
cis-decahydroquinoline system, it had been hoped that a more quantitative measure of the difference might be obtained.

Considerable efforts were therefore made to try to observe signals in the ^{13}C n.m.r. spectrum arising from the minor conformation of cis-octahydro-1-benzopyran. To do this the low temperature ^{13}C n.m.r. spectrum was studied again, but this time the data was accumulated using a "block averaging" technique to maximise the chances of observing any small resonances for the Type B conformation. On consideration of the calculated ^{13}C chemical shifts (Table 5) for the Type B conformation a signal would be expected in the region of 62 p.p.m. for the C2 carbon. For this reason this region in the "block averaged" spectrum was carefully examined. After accumulating data for several hours at -70 °C a distinct but small signal was observed at 60.10 p.p.m. in the resulting spectrum. Although this signal was very small it was significant in that it only appeared in the low temperature spectrum. The absence of the signal at higher temperature indicated that it did not arise from a conformationally rigid impurity. For this reason the small signal at 60.10 p.p.m. was assigned to the C2 carbon in the Type B conformation of cis-octahydro-1-benzopyran. Although caution must be exercised when trying to obtain conformational ratios from such spectra our best estimate for the ratio was 99.5:0.5 in favour of the Type A conformation.

In view of the estimated ratio (at -70 °C) of 99.5% to 0.5%, the conformational free energy difference was calculated to be in the order of 8.9 kJ mol^{-1}. For the corresponding nitrogen analogue, cis-decahydroquinoline, the proportion of Type A $\rightleftharpoons$ Type B has been reported[34] as 93.5% to 6.5% (at -74 °C) respectively. The conform-

ational free energy difference in the decahydroquinoline system is therefore 4.4 kJ mol^{-1} in favour of a Type A conformation.

The increase in population of the Type A conformation at the expense of Type B for cis-octahydro-1-benzopyran (62 ⇌ 63, X = O) relative to cis-decahydroquinoline (62 ⇌ 63, X = NH) can be explained by consideration of the interactions involved. For the Type A conformation (62, X = O) the oxygen would be expected to have less of an interaction with the H5a and H7a protons than the nitrogen analogue (62, X = NH). This is because the oxygen atom has a smaller van der Waals radius than the nitrogen[4]. This would be enhanced by the increase in the interaction between the H8a and H2a protons in the Type B conformation of cis-octahydro-1-benzopyran (63, X = O) relative to cis-decahydroquinoline (63, X = NH). It is therefore not too surprising that the Type A ⇌ Type B conformational equilibrium is more extreme, in favour of the Type A conformation, for cis-octahydro-1-benzopyran than for cis-decahydroquinoline.



(62) (63)

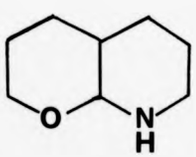
ational free energy difference in the decahydroquinoline system is therefore 4.4 kJ mol^{-1} in favour of a Type A conformation.

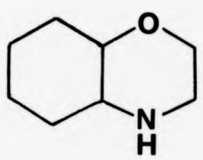
The increase in population of the Type A conformation at the expense of Type B for cis-octahydro-1-benzopyran (62 ⇌ 63, X = O) relative to cis-decahydroquinoline (62 ⇌ 63, X = NH) can be explained by consideration of the interactions involved. For the Type A conformation (62, X = O) the oxygen would be expected to have less of an interaction with the H5a and H7a protons than the nitrogen analogue (62, X = NH). This is because the oxygen atom has a smaller van der Waals radius than the nitrogen[4]. This would be enhanced by the increase in the interaction between the H8a and H2a protons in the Type B conformation of cis-octahydro-1-benzopyran (63, X = O) relative to cis-decahydroquinoline (63, X = NH). It is therefore not too surprising that the Type A ⇌ Type B conformational equilibrium is more extreme, in favour of the Type A conformation, for cis-octahydro-1-benzopyran than for cis-decahydroquinoline.

(62) (63)

2. Synthesis and Stereochemistry of Octahydro-1,4-benzoxazine

One of the aims of the work described in this thesis was to compare the relative effects of nitrogen and oxygen substitution in the decalin system. Unfortunately, the rather extreme position of the conformation equilibrium (Type A ⇌ Type B) in the octahydro--1-benzopyran system (discussed previously) makes it difficult to do this accurately from a consideration of the mono-substituted decalins alone. For this reason it was decided to try and compare their relative effects more directly by offsetting the effects of one heteroatom substitution with that of the other in a disubstituted decalin system. Two possible structures should provide the desired effect. These are the octahydropyranno[2,3-b]-pyridine (64) and octahydro-1,4-benzoxazine (65) systems.

(64) 



(65)

The reduced pyrannopyridine system (64) has not been reported, but the 2-methyl derivative of the octahydro-1,4-benzoxazine system has been briefly mentioned in the literature.[59] Furthermore, during the course of these investigations the parent trans-octahydro-1,4--benzoxazine was reported[60] as part of a study of the absolute configuration adopted by some morpholine type systems. For both the octahydro-1,4-benzoxazine and octahydropyranno[2,3-b]pyridine systems possible aromatic precursors have been reported.[61,62] It was therefore decided to prepare the aromatic precursors,

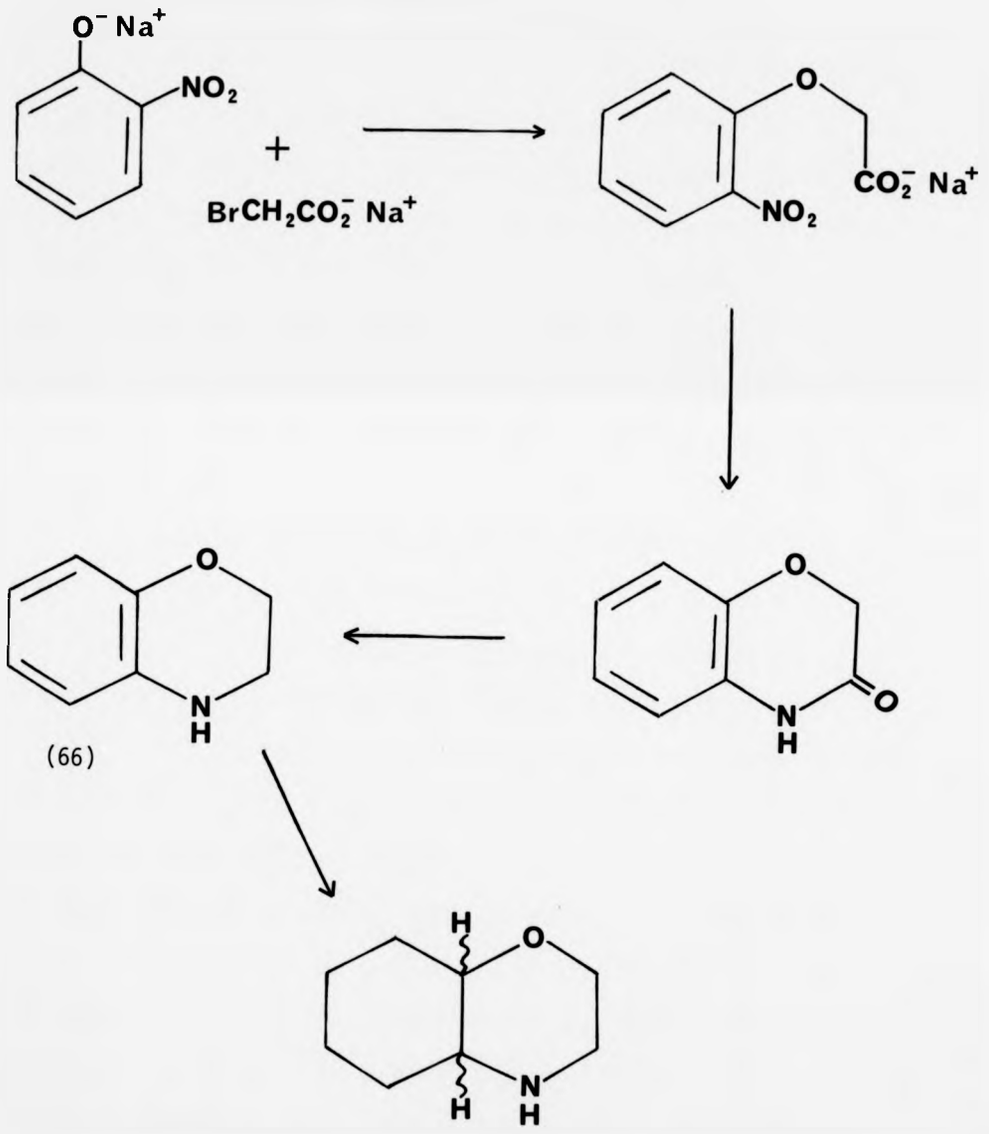
2H-3,4-dihydro-1,4-benzoxazine and 2H-3,4-dihydropyranno[2,3-b]-pyridine with the intention of subjecting them to high pressure catalytic hydrogenation. Previous experience of the hydrogenation of quinoline[28] has shown that such treatment should produce a mixture of the required isomers. Although difficulty had been experienced in separating the octahydro-1-benzopyran isomers it was felt that the presence of the basic nitrogen atom in the disubstituted decalins should make the separation problem more similar to that experienced in the decahydroquinoline system where chromatography had been used successfully in a number of cases.[28]

The syntheses of both 2H-3,4-dihydropyranno[2,3-b]pyridine and 2H-3,4-dihydro-1,4-benzoxazine were therefore investigated. Unfortunately for the 2H-3,4-dihydropyranno[2,3-b]pyridine system difficulty was experienced in the final reduction stage to give the fully saturated system. High pressure catalytic hydrogenation did not produce any material identifiable as the desired product. The only reduction products appeared to be ring cleaved compounds and polymeric material. In view of this our effort was therefore concentrated on the 2H-3,4-dihydro-1,4-benzoxazine system which could be hydrogenated to the corresponding fully reduced system.

Although 2H-3,4-dihydro-1,4-benzoxazine was prepared as indicated in Fig. 6 the method of Shirai *et al.*[63] was also investigated as a route to this material. However, we found this method which involved the reaction of the potassium salt of 2-aminophenoxide with 1,2-dibromoethane in ethanol gave only a poor yield (∿ 10%) of the desired product.

Fig. 6.

The Synthetic Route for the Preparation of cis- and trans-Octahydro-1,4-benzoxazine



(66)

(67)

As has been previously mentioned the catalytic hydrogenation of 2H-3,4-dihydro-1,4-benzoxazine (66) led for the formation of the fully reduced octahydro-1,4-benzoxazine system (67). As with other decalin systems both cis- and trans-fused systems are possible and both were formed during the hydrogenation. ^{13}C n.m.r. spectroscopy indicated that both isomers were present in approximately equal quantities. This ratio is interesting since it should be noted that under similar conditions quinoline was reduced to give almost entirely trans-decahydroquinoline[28] and 2H-3,4-dihydro-1-benzopyran was reduced to give predominantly cis-octahydro-1-benzopyran. In the case of the hydrogenation of 2H-3,4-dihydro-1,4-benzoxazine it appears that two different reduction routes seem to be equally preferred.

Although it was found possible to obtain a separation of these isomers by gas liquid chromatography it was decided to investigate the possibility of using preparative thin layer chromatography as a possibly more efficient alternative. Initial investigations using silica coated thin layer chromatography plates indicated that a partial separation could be obtained using an appropriate methanol:ethyl acetate mixture as eluent. However, the isomer with the larger R_f value tended to tail into the second isomer on the plate making a complete separation difficult. To improve the quality of the separation and to increase the quantity of material which could be handled, a medium pressure chromatography system was developed. By using a "Whatman" column packed with "Kieselgel 60" and by eluting with a methanol:ethyl acetate mixture a satisfactory separation was produced. Nevertheless, some overlapping of the two isomeric Components (A and B) was still

present and therefore the isomeric composition of the fractions had to be determined before the isomerically pure fractions could be combined. Although analytical gas liquid chromatography could be used in this particular case it was found necessary to use ^{13}C and ^{1}H n.m.r. spectroscopy to do this in some of the methyl analogues which will be described later. The first isomer (Component A) to be eluted from the column was later shown to be the trans-fused isomer.

A. Stereochemical Aspects

(i) Component A (trans-Octahydro-1,4-benzoxazine)

The 100 MHz ^{1}H n.m.r. spectrum (Plate 6, Table 7) of this material consisted of a complex envelope of overlapping resonances with the lowest field signal resonating at 3.87 p.p.m. Fortunately, however, the presence of the two heteroatoms caused downfield shifts on those protons on carbons 2,3,9 and 10 so that these were observed separately. On comparing the shifts and apparent multiplicities of these low field signals with those in the decahydroquinoline and octahydro-1-benzopyran systems it was possible to make a preliminary assignment of these signals. In particular the triplet at 2.39 p.p.m. was assigned to the proton on C10 in the trans-fused isomer. Nevertheless, the spectrum was still rather second order and difficult to analyse. For this reason a 400 MHz ^{1}H n.m.r. spectrum of this material was obtained. This spectrum (Plate 7, Table 8) was much more first order, particularly from the low field region of the spectrum. The lowest field signal at 3.86 p.p.m. was assigned as the H2e resonance since it had only one large coupling, as expected for an equatorially disposed proton, and since it had a

Plate 6.

The 100 MHz ^{1}H N.M.R. Spectrum of trans-Octahydro-1,4-benzoxazine

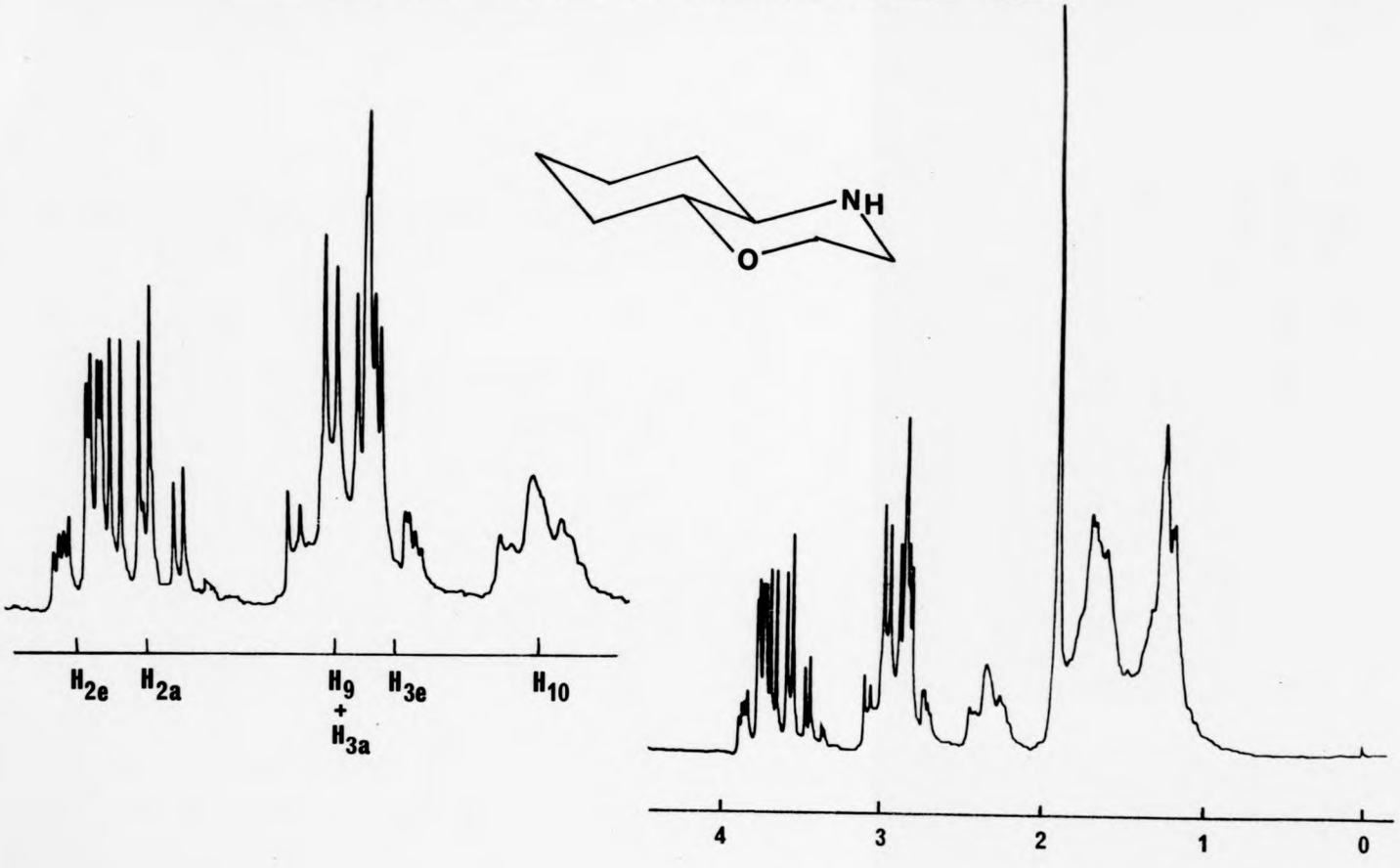


Table 7

^{1}H n.m.r. Spectral Data

trans-Octahydro-1,4-benzoxazine

Proton	Shift(δ)	Description of Resonance
(100 MHz Spectrum)*		
2e	3.87	Multiplet (band width ∿ 22 Hz) distorted due to coupling to H2a.
2a	3.63	Multiplet (band width ∿ 29 Hz) showing triplet of doublet character.
9	∿ 3.03	Multiplet obscured by H3a.
3a	3.03	Multiplet (band width ∿ 29 Hz) distorted due to coupling to H3e.
3e	2.84	Multiplet (band width ∿ 21 Hz) distorted due to coupling with H3a.
10	2.39	Poorly resolved multiplet (band width ∿ 29 Hz) showing triplet of doublet character.
N-H	2.04	Singlet
Remaining Protons	∿ 1.1-2.0	Complex envelope of overlapping resonances.

*$CDCl_3$ Solvent at 25 °C.

Plate 7.

The 400 MHz ^{1}H N.M.R. Spectrum of trans-Octahydro-1,4-benzoxazine

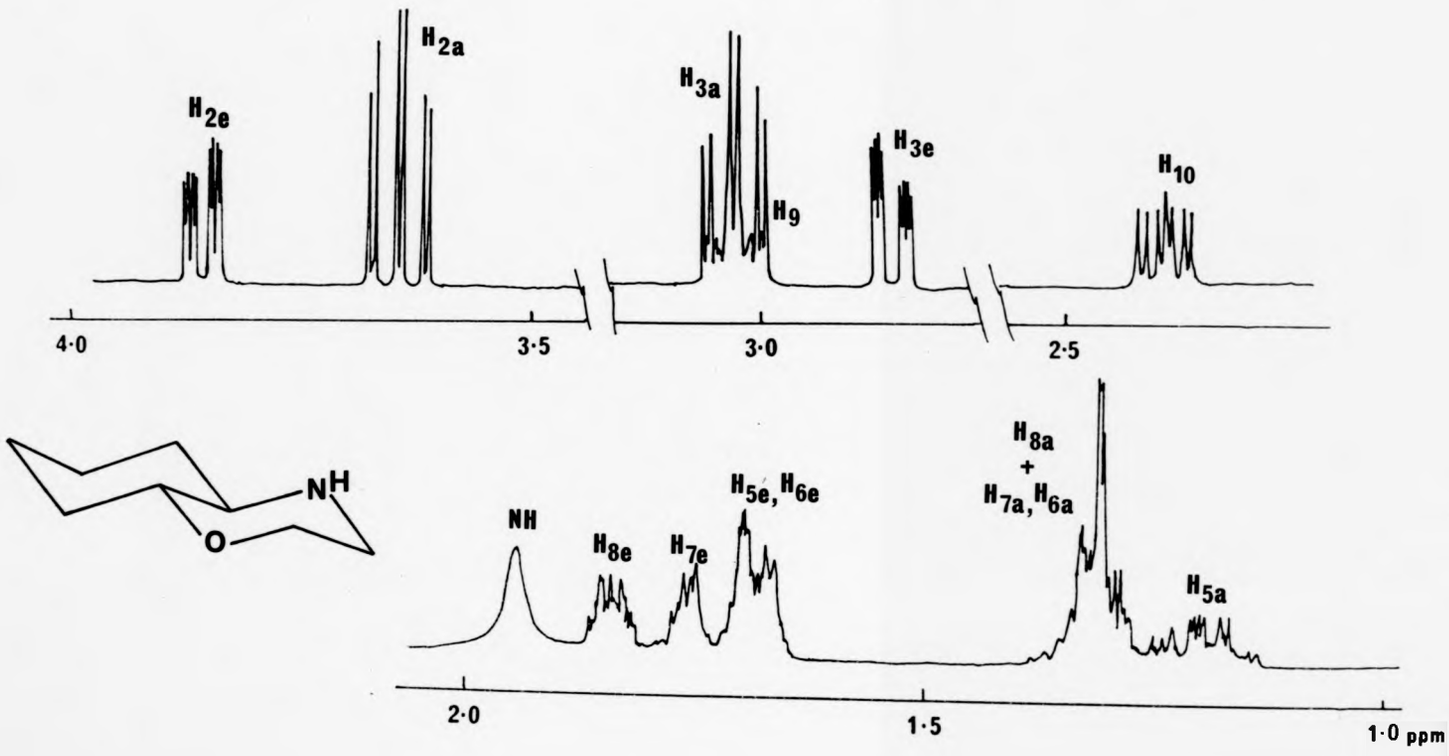
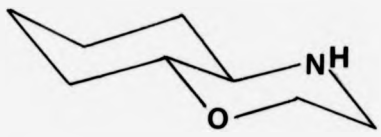


Table 8

^{1}H n.m.r. Spectral Data

trans-Octahydro-1,4-benzoxazine



Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.85	Doublet of doublet of doublets ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 3.4 Hz; $J_{2e,3e}$ = 1.3 Hz).
2a	3.64	Multiplet with triplet of doublet character. ($J_{2a,2e}$ + $J_{2a,3a}$ = 23.0 Hz; $J_{2a,3e}$ = 2.8 Hz).
9	3.03	Multiplet (band width $\sim$ 30 Hz) obscured by H3a.
3a	3.03	Multiplet with triplet of doublet character ($J_{3a,3e}$ + $J_{3a,2a}$ = 23.9 Hz: $J_{3a,2e}$ = 3.4 Hz).
3e	2.86	Doublet of doublet of doublets ($J_{3e,3a}$ = 12.2 Hz; $J_{3e,2a}$ = 2.7 Hz; $J_{3e,2e}$ = 1.2 Hz).
10	2.39	Multiplet with doublet of doublet of double character (band width $\sim$ 29 Hz).
N-H	1.94	Broad singlet.
8e	1.84	Poorly resolved multiplet (band width $\sim$ 23 Hz).

/continued

Table 8 - continued

Proton	Shift(δ)	Description of Resonance
7e	1.76	Poorly resolved multiplet (band width $\sim$ 20 Hz).
5e, 6e	1.64-1.72	Complex envelope of resonances
8a, 7a, 6a	1.27-1.39	Complex envelope of resonances
5a	1.20	Multiplet (band width $\sim$ 45Hz).

*$CDCl_3$ Solvent at 25 °C

shift comparable to that of the 2e proton in trans-octahydro-1--benzopyran (3.97 p.p.m.). The distortion of this signal towards the adjacent resonance (more noticeable in the 100 MHz spectrum) implied that the signal at 3.64 p.p.m. was due to the 2a proton, this being further supported by the chemical shift and multiplicity of the signal.

The signals for the H3a and H3e protons were assigned in a similar way, the coupling pattern indicating the orientation (axial or equatorial) and their distortion indicating that they were coupled to each other. It is interesting to note that the chemical shifts of the H3a and H3e resonances (3.03 and 2.85 p.p.m. respectively) have been reversed in comparison to the analogous H2a and H2e resonances (2.65 and 3.06 p.p.m.) in the corresponding decahydroquinoline analogue. It should also be noted that the downfield shift (0.39 p.p.m.) observed for the H3a resonance relative to the analogous resonance of the decahydroquinoline system was also observed (0.30 p.p.m.) for the H10 resonance. Irradiation of the H3a resonance in a spin decoupling experiment confirmed these assignments by simplifying the signals in the expected manner.

The assignment of the remaining H9 and H10 signals could be made by a consideration of their chemical shifts. The signal for H9 was almost completely obscured by overlap with the H3a resonance but nevertheless it was still possible to see that both the H9 and H10 resonances had triplet character, confirming the trans-fused nature of the ring junction.

Irradiation of the H9 resonance at 3.03 p.p.m. caused the signal at 1.84 p.p.m. to simplify. This latter signal, due to an equatorially disposed proton, must therefore be the H8e resonance.

A change was also observed in the region 1.27 to 1.39 p.p.m., arising from three overlapping axially orientated protons, and was thus assigned as containing the H8a resonance.

The high field resonance at 1.20 p.p.m. was assigned to the H5a proton since irradiation at this site caused the H10 proton resonance to lose a large $^{3}J_{aa}$ coupling. Since irradiation of the H5a proton caused no effect on the equatorially disposed proton at 1.76 p.p.m. this signal was assigned to the H7e proton. An effect was observed, however, on the two overlapping signals between 1.64 and 1.72 p.p.m. and these were therefore identified as the H5e and H6e resonances. The only unassigned signals, those from the H6a and H7a protons, were therefore assigned to the complex envelope of three overlapping resonances between 1.27 and 1.39 p.p.m. Later studies on methyl substituted derivatives of trans-octahydro--1,4-benzoxazines (described later) provided further support for these assignments.

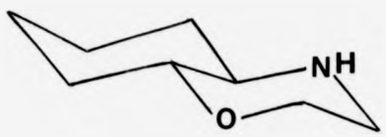
Analysis of the proton couplings for the C2-C3 portion of the molecule allowed the R value (see introduction) of the oxazine ring to be determined. From the vicinal couplings obtained (Table 8) the R value for trans-octahydro-1,4-benzoxazine was calculated as being in the range R = 2.2 - 2.3. This is as expected in view of the value reported for morpholine[33] (R = 2.2).

It is interesting to note that the ^{13}C n.m.r. spectrum of trans-octahydro-1,4-benzoxazine (Table 9) is in good agreement with those values calculated by modifying the shifts observed for trans-decalin with parameters for the effects of heteroatom substitution (see Tables 3 and 10), the latter being obtained from trans-decahydroquinoline. This adds further support for the assignment of this material as the trans-fused isomer.

Table 9

^{13}C n.m.r. Spectral Data

trans-Octahydro-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.8	T	67.89	T
3	46.3	T	46.69	T
5	30.2	T	30.88	T
6	25.6	T	24.58	T
7	24.5	T	24.58	T
8	30.8	T	31.51	T
9	81.6	D	81.19	D
10	60.8	D	60.28	D

*Calculations based on trans-decalin with modifications for the effect of oxygen and nitrogen obtained from trans-octahydro-1--benzopyran and trans-decahydroquinoline.

†$CDCl_3$ Solvent at 25 °C.

Table 10

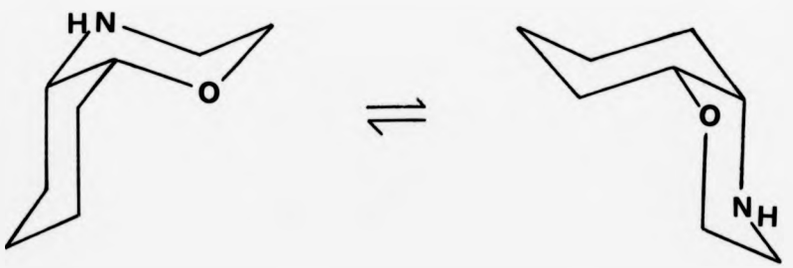
The Effects of Heteroatom Substitution on the ^{13}C n.m.r Chemical Shifts of trans-Decalin

Carbon No.	Effect(δ)*	
	X = O	X = NH
2	41.2	20.5
3	- 1.3	0.5
4	- 2.7	- 1.7
5	- 3.9	- 1.7
6	- 0.3	- 0.6
7	- 2.0	- 1.2
8	- 2.1	- 0.5
9	38.1	18.6
10	- 1.7	- 0.4

*These effects were calculated from a knowledge of the ^{13}C n.m.r. chemical shifts of trans-decalin (Table 3) together with the experimentally observed values for trans-octahydro-1-benzopyran (Table 2) and trans-decahydroquinoline[28].

(ii) Component B (cis-Octahydro-1,4-benzoxazine)

The n.m.r. spectrum of this component was temperature dependent, hence Component B was therefore readily identified as the cis-fused isomer. In view of the observation that the n.m.r. spectrum of Component A (trans isomer) was temperature independent, in the same temperature range, the temperature dependent nature of Component B was interpreted as resulting from ring inversion rather than nitrogen inversion. The temperature dependence in the n.m.r. spectrum of Component B thus reflects the fact that this cis isomer exists in two conformational forms (68 ⇌ 69) which are constantly interconverting by the process of ring inversion. Fortunately, at room temperature, the spectrum could be interpreted sufficiently to give an indication of the predominant conformation. Thus, although the 100 MHz ^{1}H n.m.r. spectrum (Plate 8, Table 12) gave an uninterpretable envelope of resonances at high field (1.7 - 2.2 p.p.m.), the six protons next to the heteroatoms gave a set of low field signals which could be assigned in terms of a Type A conformation (68).



(68)
Conformation
Type A

(69)
Conformation
Type B

Plate 8.

The 100 MHz ^{1}H N.M.R. Spectrum of cis-Octahydro-1,4-benzoxazine

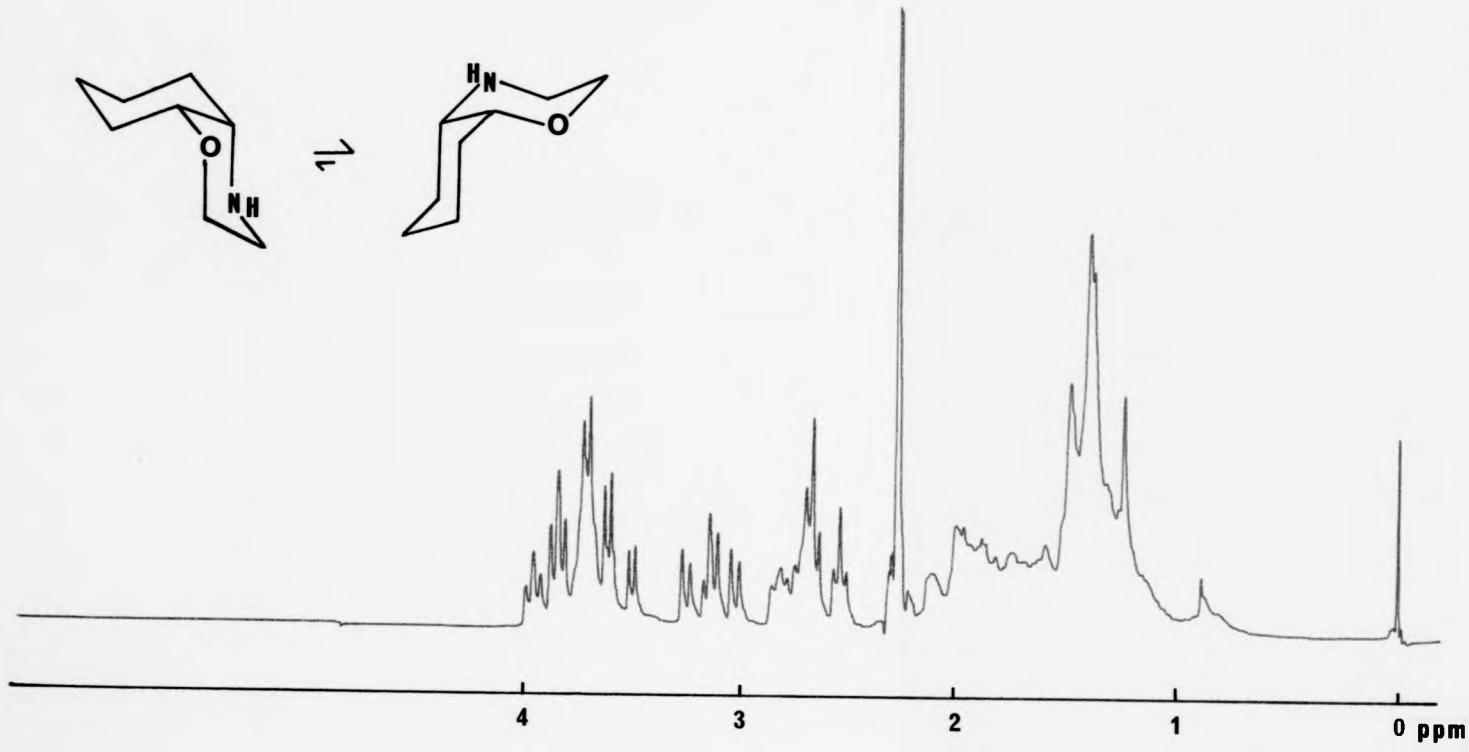
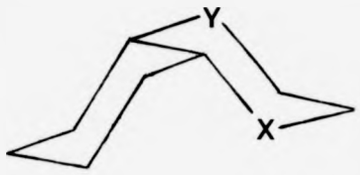


Table 11

The Effects of Heteroatom Substitution on the ^{13}C n.m.r. Chemical Shifts of cis-Decalin



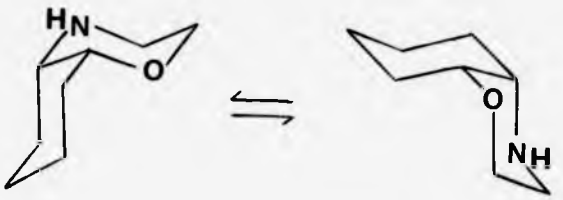
Carbon No.	Effects(δ)*			
	X = O, Y = CH_2	Y = O, X = CH_2	X = NH, Y = CH_2	Y = NH, X = CH_2
2	41.7	40.9	20.0	18.8
3	- 0.3	- 1.4	1.5	1.2
4	- 3.7	- 4.5	- 2.1	- 1.6
5	- 0.8	- 4.5	0.6	- 0.9
6	- 1.5	0.0	- 0.8	0.0
7	- 1.0	- 4.5	- 0.4	- 0.6
8	- 0.9	- 1.4	0.1	1.2
9	38.9	40.9	19.0	17.0
10	- 1.6	- 1.4	0.0	- 0.4

*These effects were calculated from a knowledge of the ^{13}C n.m.r. chemical shifts of cis-decalin (Table 3) together with the calculated values or, where possible, the experimentally observed values for cis-octahydro-1-benzopyran (Table 5) and cis-decahydroquinoline[28].

Table 12

^{1}H n.m.r. Spectral Data

cis-Octahydro-1,4-benzoxazine



Proton	Shift(δ)	Description of Resonance
(100 MHz Spectrum)*		
2e	3.91	Distorted doublet of triplets (band width ∿ 21 Hz).
9	3.70	Broad singlet (half-band width ∿ 6 Hz) overlapped with H2a.
2a	3.61	Distorted multiplet showing triplet of doublet character (band width ∿ 29 Hz).
3a	3.14	Multiplet (band width ∿ 30 Hz) showing doublet of doublet of doublet character.
10	2.77	Multiplet (band width ∿ 20 Hz) partially obscured by overlap with H3e.
3e	2.61	Multiplet (band width ∿ 20 Hz) showing doublet of triplet character.
N-H	2.29	Singlet
Remaining Protons	∿ 1.7-2.2	Complex envelope of overlapping resonances.

*$CDCl_3$ Solvent at 25 °C.

Since the protons next to the oxygen resonated at lowest field then the signal at 3.91 p.p.m. (having only one large Jgem coupling) was assigned to the H2e proton. The signal at 3.61 p.p.m. (with two large couplings), severely distorted towards the H2e resonance, was assigned to H2a and the broad singlet at 3.70 p.p.m., overlapping the H2a resonance, was assigned to the H9 proton. It should be noted that the multiplicity of the H9 signal corresponds to that expected for the Type A conformation. The three remaining low field signals were therefore assigned to those protons next to the nitrogen in the following way. Irradiation of the signal at 2.61 p.p.m. caused the loss of one of the two major couplings to the signal at 3.14 p.p.m., indicating that the former signal corresponded to the H3e proton and the latter to the H3a resonance. Consequently, the remaining signal at 2.77 p.p.m. was assigned to the H10 bridgehead position, its multiplicity also being consistent with the Type A conformation. The irradiation of the signal at 2.61 p.p.m. also caused changes in the multiplicities of the H2e and H2a signals which were consistent with the assignment previously described.

The above interpretation of the room temperature spectrum thus points to a situation in which the position of the conformational equilibrium (Type A $\rightleftharpoons$ Type B) lies well towards the Type A conformation.

To obtain accurate coupling data for the predominant conformation in this system the low temperature ^{1}H n.m.r. spectrum was therefore studied. In order for the spectrum to be analysed more easily a high field 400 MHz ^{1}H n.m.r. spectrum was obtained. As the temperature of the sample was lowered the spectrum broadened so that at about -10 °C a rather featureless spectrum was observed. However, on further cooling (-60 °C) the spectrum sharpened allowing signals from both Type A and Type B conformations to be observed.

A comparison of this spectrum with that of the room temperature spectrum is shown in Plate 9.

At low temperature the low field signals for the major conformation could be readily assigned by comparison with the room temperature spectrum. Several higher field signals could also be assigned in the low temperature spectrum. For example, the quartet of doublets at 2.15 p.p.m. could be assigned to the H5a proton in a Type A conformation because of its characteristic multiplicity and because irradiation of this signal caused the loss of the major coupling to the H10 resonance. Irradiation of the H5a signal also caused the loss of a large coupling on a signal at 1.25 p.p.m.. Since this signal originally appeared as a multiplet with quartet of triplet character it was assigned to the adjacent axially orientated proton, H6a. The remaining signals have been assigned (Table 13) by comparison of their chemical shifts with those signals unambiguously assigned in the corresponding methyl substituted derivatives (described later).

As previously mentioned, several signals associated with the minor conformation (Type B) were also observed in the low temperature 400 MHz ^{1}H n.m.r. spectrum (Table 14). Of the expected six low field resonances, five were either completely or partially visible and these were readily assigned by comparison with analogous methyl substituted derivatives (discussed later). The only low field signal to be totally obscured, that assigned to the H10 proton, is probably under the H3a signal from the major conformation.
A further signal from the minor conformation was also observed at 2.27 p.p.m.. Since this signal was observed as having quartet of doublet character it could be assigned as the H8a resonance. The chemical shift of this signal also compared favourably with those

Plate 9.

400 MHz ^{1}H N.M.R. Spectra from the Variable Temperature Study of cis-Octahydro-1,4-benzoxazine

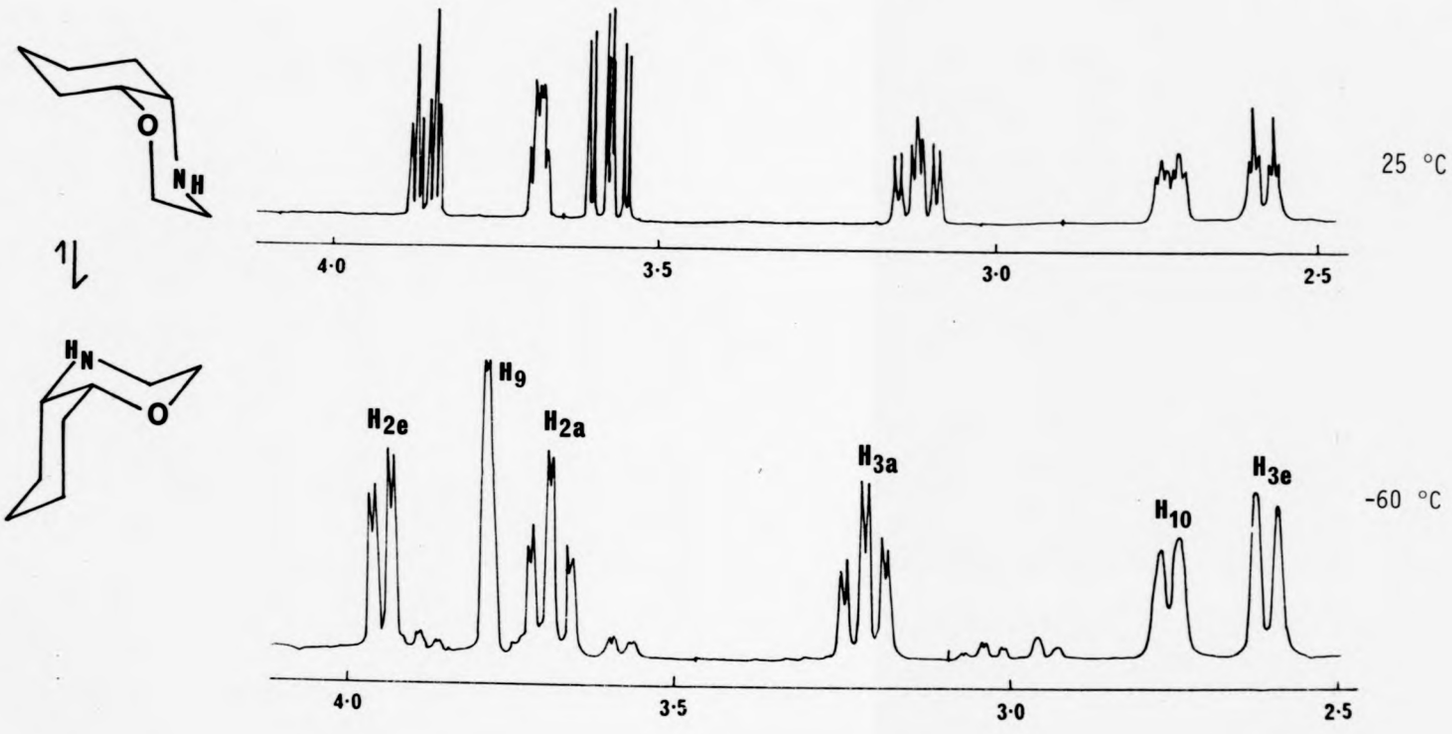
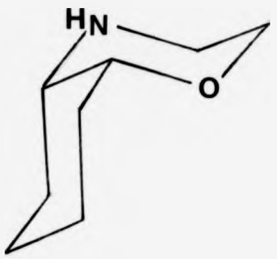


Table 13

^{1}H n.m.r. Spectral Data

cis-Octahydro-1,4-benzoxazine



Conformation
Type A

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.95	Doublet of doublets ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 3.2 Hz).
9	3.79	Broad singlet (half-band width = 7 Hz).
2a	3.69	Triplet of doublets ($J_{2a,2e}$ + $J_{2a,3a}$ = 23.3 Hz; $J_{2a,3e}$ = 2.6 Hz).
3a	3.22	Triplet of doublets ($J_{3a,3e}$ + $J_{3a,2a}$ = 24.8 Hz; $J_{3a,2e}$ = 3.4 Hz).
10	2.78	Poorly resolved signal of doublet of triplet character (band width ∿ 29 Hz).
3e	2.61	Poorly resolved doublet ($J_{3e,3a}$ = 12.5 Hz).
5a	2.15	Quartet of doublets ($J_{5a,5e}$ ∿ $J_{5a,6a}$ ∿ $J_{5a,10}$ = 12.8 Hz; $J_{5a,6e}$ = 3.8 Hz).
8e	1.86	Poorly resolved signal of doublet character (band width ∿ 30 Hz).
NH	∿ 1.84	Obscured due to overlap with other resonances.

/continued

Table 13 - continued

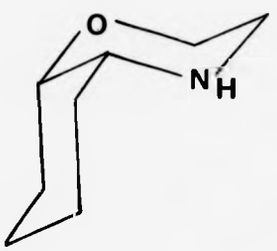
Proton	Shift(δ)	Description of Resonance
6e	1.79	Poorly resolved signal of doublet character (band width ∿ 30 Hz).
7e, 7a, 5e, 5a.	1.32-1.53	Complex envelope of overlapping resonances.
6a	1.25	Multiplet (band width ∿ 50 Hz) with quartet of triplet character.

*$CDCl_3$ Solvent at -60 °C.

Table 14

^{1}H n.m.r. Spectral Data

cis-Octahydro-1,4-benzoxazine



Conformation
Type B

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2a	3.89	Poorly resolved multiplet (band width ∿ 30 Hz) showing triplet of doublet character, partially obscured by H2e signal from major conformation.
9	∿ 3.7	Poorly resolved signal almost completely obscured by H2a signal from major conformation.
2e	3.58	Poorly resolved signal (band width ∿ 23 Hz) showing doublet of doublet character.
10	-	Not observed, possibly overlapped with H3a signal of major conformation.
3a	3.04	Poorly resolved signal (band width ∿ 32 Hz) showing triplet of doublet character.
3e	2.95	Poorly resolved signal (band width ∿ 21 Hz) showing doublet character.
8a	2.27	Poorly resolved multiplet (band width ∿ 45 Hz) showing quartet of doublet character.
Remaining Protons	-	Not observed due to overlap with signals from the major conformation.

*$CDCl_3$ Solvent at -60 °C.

in similar methyl substituted systems. It is interesting to note that the H8a resonances (for Type B conformations) and the H5a resonances for Type A conformations), were generally observed at lower field than those of the other protons on C5,6,7 and 8.

As with the trans isomer previously described, couplings from the C2-C3 portion of the molecule were used to obtain the R value for the major conformation of the cis isomer. However, due to the poor resolution of the low temperature 400 MHz ^{1}H n.m.r. spectra, not all the required vicinal couplings could be obtained by direct measurement. This applied particularly to the small $^{3}J_{e,e}$ coupling. However, this could be estimated (i.e. $^{3}J_{e,e} \sim 1.3$ Hz) with some confidence in view of the value obtained for the corresponding trans isomer. From the vicinal couplings (Table 13) the R value was therefore calculated as being within the range R = 2.2 - 2.3. This value compares well with that obtained for the trans isomer and with that of morpholine[33] (R = 2.2). In view of this result the octahydro-1,4-benzoxazine system appears to be more similar to cyclohexane (R = 2.2) than the octahydro-1-benzopyran system (R = 1.9).

Although an approximate conformational ratio (Type A $\rightleftharpoons$ Type B) could be obtained from the low temperature 400 MHz ^{1}H n.m.r. spectrum, this ratio was investigated by low temperature ^{13}C n.m.r. spectroscopy. As with the ^{1}H n.m.r. spectra the room temperature ^{13}C n.m.r. spectrum largely reflected that of the major conformation (Type A). However, as the temperature was lowered the spectrum broadened and then sharpened, so that at -67 °C signals arising from both major and minor conformers could be clearly seen (Plate 10). The chemical shifts for the two sets of signals (Tables 15 and 16) compared favourably with the calculated values (obtained from the appropriate

Plate 10.

^{13}C N.M.R. Spectra from the Variable Temperature Study of cis-Octahydro-1,4-benzoxazine

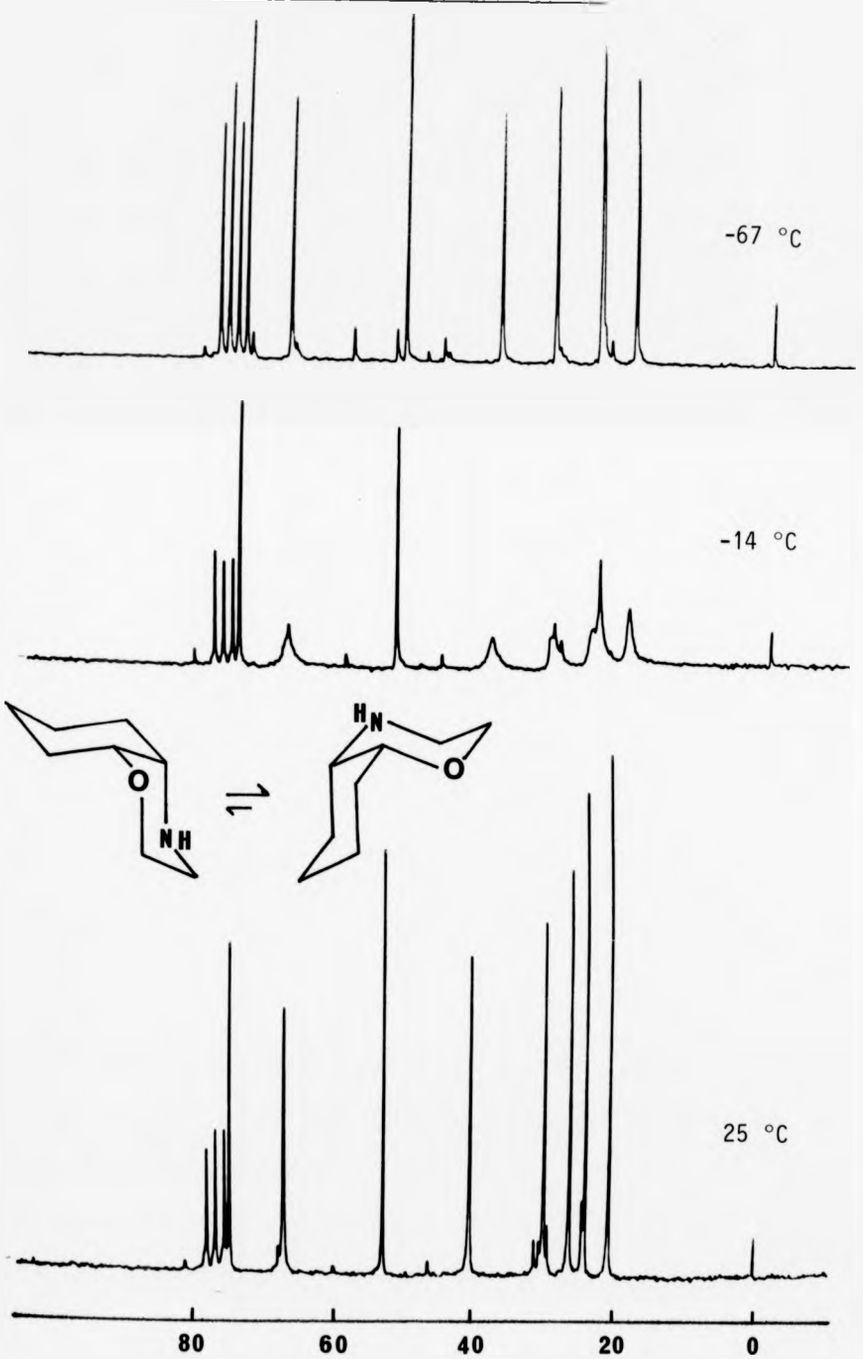
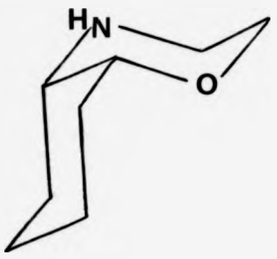


Table 15

^{13}C n.m.r. Spectral Data

cis-Octahydro-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	70.1	T	68.56	T
3	39.7	T	39.27	T
5	26.2	T	25.04	T
6	25.1	T	24.82	T
7	20.2	T	19.80	T
8	30.9	T	31.39	T
9	74.8	D	74.81	D
10	52.6	D	52.72	D

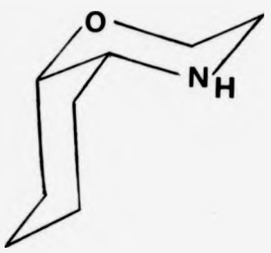
*Calculations based on cis-decalin with modifications for the effect of oxygen and nitrogen from cis-octahydro-1-benzopyran and cis-decahydroquinoline.

†Experimental values from sample in $CDCl_3$ + $CFCl_3$ solvent (50:50) at -67 °C.

Table 16

^{13}C n.m.r. Spectral Data

cis-Octahydro-1,4-benzoxazine



Conformation
Type B

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	63.6	T	60.07	-
3	45.8	T	47.12	-
5	28.4	T	31.54	-
6	21.6	T	(a)	-
7	22.0	T	(a)	-
8	25.0	T	23.23	-
9	77.2	D	73.90	-
10	53.9	D	53.95	-

*Calculations based on cis-decalin with modifications for the effect of oxygen and nitrogen obtained from cis-octahydro-1--benzopyran and cis-decahydroquinoline.

†Experimental values from sample in $CDCl_3$ + $CFCl_3$ (50:50) at -67 °C.

(a) Signals obscured by those of major conformation.

substitution parameters as indicated in Tables 3 and 11) and give further support for the assignment of the conformations. By measuring the relative integrals of the C9 and C10 carbon resonances in both Type A and Type B conformations a ratio of 91% to 9% was established indicating a conformational free energy difference of 4.0 kJ mol^{-1} (at -67 °C).

Assuming a simple additivity relationship between the effects of oxygen and nitrogen atoms in cis-octahydro-1,4-benzoxazine, it is possible to use the value of this conformational free energy difference together with that reported for cis-decahydroquinoline[34] (4.4 kJ mol^{-1} at -74 °C) to obtain a value for cis-octahydro-1--benzopyran of about 8.4 kJ mol^{-1}. This would imply that the conformational ratio in cis-octahydro-1-benzopyran is 99.3% to 0.7% (calculated at -70 °C) in favour of the Type A conformational arrangement. This compares well with the best estimate of 99.5% to 0.5% obtained from the low temperature ^{13}C n.m.r. spectrum of cis-octahydro-1-benzopyran and lends further support for our assignment of the small signal at 60.1 p.p.m. (previously discussed) to C9 in the minor conformation of this material.

In order to investigate the effects of methyl substitution on octahydro-1,4-benzoxazine several methyl derivatives were prepared and studied. It was hoped that methyl substitution into the cyclohexane part of the system would give interesting results. For example, any resulting distortion of the oxazine part of the molecule would be reflected in the R value for the system which could be calculated in the same manner as for the parent octahydro-1,4--benzoxazines. In addition to this it was hoped that the methyl substituted cis-fused systems would give interesting data about the position of the conformation equilibrium (Type A $\rightleftharpoons$ Type B), and

hence an idea of the amount of strain introduced into such systems by a methyl group. The conformational aspects of the cis-fused systems were also studied further by preparing systems substituted with methyl groups at the C2 and C3 positions of the molecule. The preparations and results of these methyl derivatives are discussed individually in the following sections.

3. Octahydro-6-methyl-1,4-benzoxazine

As previously mentioned, the purpose of introducing methyl groups into the octahydro-1,4-benzoxazine ring system was to investigate how this would effect the conformations adopted by the system. These changes, if they occurred, would be evident in the n.m.r. spectra. For example, analysis of the $^{3}J_{HH}$ vicinal coupling constants, for the C2 - C3 portion of the molecule, could be used to monitor for possible distortion of the oxazine ring, while low temperature ^{13}C n.m.r. spectroscopy could be used to monitor changes in the position of the conformational equilibrium (Type A $\rightleftharpoons$ Type B) in the cis isomers.

The octahydro-6-methyl-1,4-benzoxazine system was therefore synthesised for this purpose. This system can exist in four isomeric forms because not only can it adopt a cis- or trans-fused ring junction but it also possesses an additional asymmetric centre at C6. Thus, for example, in the trans-fused isomers, the methyl group at C6 can be either axially or equatorially disposed.

All four octahydro isomers were prepared in the form of an isomeric mixture by the catalytic hydrogenation of the aromatic precursor, 2H-3,4-dihydro-6-methyl-1,4-benzoxazine. This precursor was prepared in a manner similar to that previously described for the unsubstituted system, 2H-3,4-dihydro-1,4-benzoxazine (Fig. 6), except that the 2-nitrophenol previously used was replaced by 4-methyl-2-nitrophenol. This was used to produce 4-methyl-2--nitrophenoxyacetic acid which on hydrogenation gave the lactamide, 6-methyl-1,4-benzoxazine-3(4H)-one. Further reduction with lithium aluminium hydride gave the required aromatic precursor, 2H-3,4-dihydro--6-methyl-1,4-benzoxazine.

Initial investigations allowed the minimum reduction conditions for catalytic hydrogenation to be found. However, with cyclohexane as the solvent and 10% palladium on charcoal as catalyst, a hydrogenation time in excess of 20 hours was required (at 158 °C and 42 atm.). Although a reasonable ratio of the four isomers of octahydro-6-methyl-1,4-benzoxazine was obtained (40% Component A, 40% B, 8% C and 12% D), the results were difficult to reproduce. A hydrogenation under more vigorous conditions (167 °C) gave an increase in the amount of Component B at the expense of the others, particularly Component A (e.g. 27% Component A, 56% B, 6% C and 11% D). This lack of consistency between the isomeric ratios was regarded as being the consequence of partial equilibration. This view was later substantiated by results obtained from the 3-methyl system (discussed later). The problem of equilibration was overcome by using water as the hydrogenation solvent, allowing a lower hydrogenation temperature (152 °C) to be used for shorter periods of time ($\sim$ 12 hours). These conditions produced consistent isomeric ratios for the reduction products (40% Component A, 40% B, 8% C and 12% D).

During the catalytic hydrogenation reaction the uptake of hydrogen gas was used to monitor the progress of the reduction. In this way any deviation from the normal rate of hydrogen uptake (e.g. due to catalyst poisoning) could be quickly detected and the reaction stopped before any unnecessary equilibration of the "octahydro" isomers had occurred. It is interesting to note that although a steady hydrogen uptake was observed during the hydrogenation of the 6-methyl system, it was consistently slower than the 2-methyl and 3-methyl derivatives (discussed later), under similar conditions.

Although the ^{13}C n.m.r. spectrum of a sample of the hydrogenation products showed four distinct sets of signals corresponding to the four isomers of octahydro-6-methyl-1,4--benzoxazine, analysis by gas liquid chromatography showed only two components, while thin layer chromatography (silica plates) allowed three components to be partially resolved. However, medium pressure chromatography enabled separation of three of the isomers (Components A, B and D), while the fourth, Component C, was obtained in an enriched form. This sample of Component C was subjected to a further chromatographic separation enabling a sample of $\sim$ 62% isomeric purity to be obtained, (a quantity of Component B was also present).

Although samples of high isomeric purity were used for the ^{1}H n.m.r. studies it was necessary to be less selective in the choice of material for the variable temperature ^{13}C n.m.r. studies, where larger quantities of material were required. As a result the samples used for the ^{13}C n.m.r. studies of Component A contained traces of Component B. The stereochemical aspects of each component are discussed in order of their elution from the chromatography column.

A. Stereochemical Aspects

(i) Component A (cis-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl--1,4-benzoxazine

This isomer was the least retentive of the four isomers obtained by medium pressure chromatography. Initial investigations using both ^{13}C and ^{1}H n.m.r. spectroscopy showed this component

to have a temperature dependent n.m.r. spectrum, indicating that it was one of the two cis-fused ring junction isomers.

At room temperature the 400 MHz ^{1}H n.m.r. spectrum of Component A therefore reflected only an averaged spectrum resulting from the rapid interconversion of the Type A and Type B conformations of this molecule (Plate 11). However, on lowering the temperature to -50 °C the rate of interconversion of these two conformations could be slowed sufficiently to enable signals from the two "frozen out" conformations to be observed (Plate 11). Unfortunately, the few small signals associated with the minor conformation could only be observed as poorly resolved humps and therefore could not be used to provide accurate coupling data. However, the signals for the major conformation were reasonably well resolved allowing the sterochemistry of the system to be ascertained (Table 17).

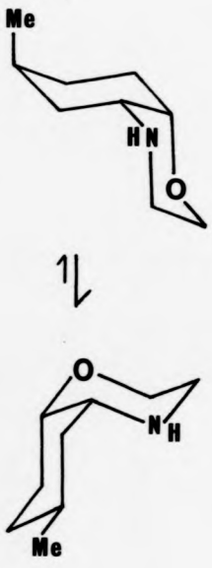
The lower field signals associated with the oxazine portion of the molecule were readily assigned by their multiplicities and by comparison with other methyl analogues (Fig. 7). Thus the multiplet resonating at lowest field (3.87 p.p.m.) was assigned to the H2a proton while the signals at 3.57, 3.03 and 2.94 p.p.m. were assigned to the H2e, H3a and H3e protons respectively. Their multiplicities were consistent with these assignments and their chemical shifts compared well with those of the parent system (Table 14). The H9 and H10 bridgehead protons were assigned similarly. The H9 resonance contained one large coupling while the H10 resonance appeared as a broad singlet. Hence, from the multiplicity of the bridgehead protons, a cis-fused ring system in a Type B conformation was indicated.

In the case of the higher field resonances, those associated with the cyclohexane portion of the molecule, several signals could

Plate 11.

400 MHz ^{1}H N.M.R. Spectra from the Variable Temperature Study

of cis-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



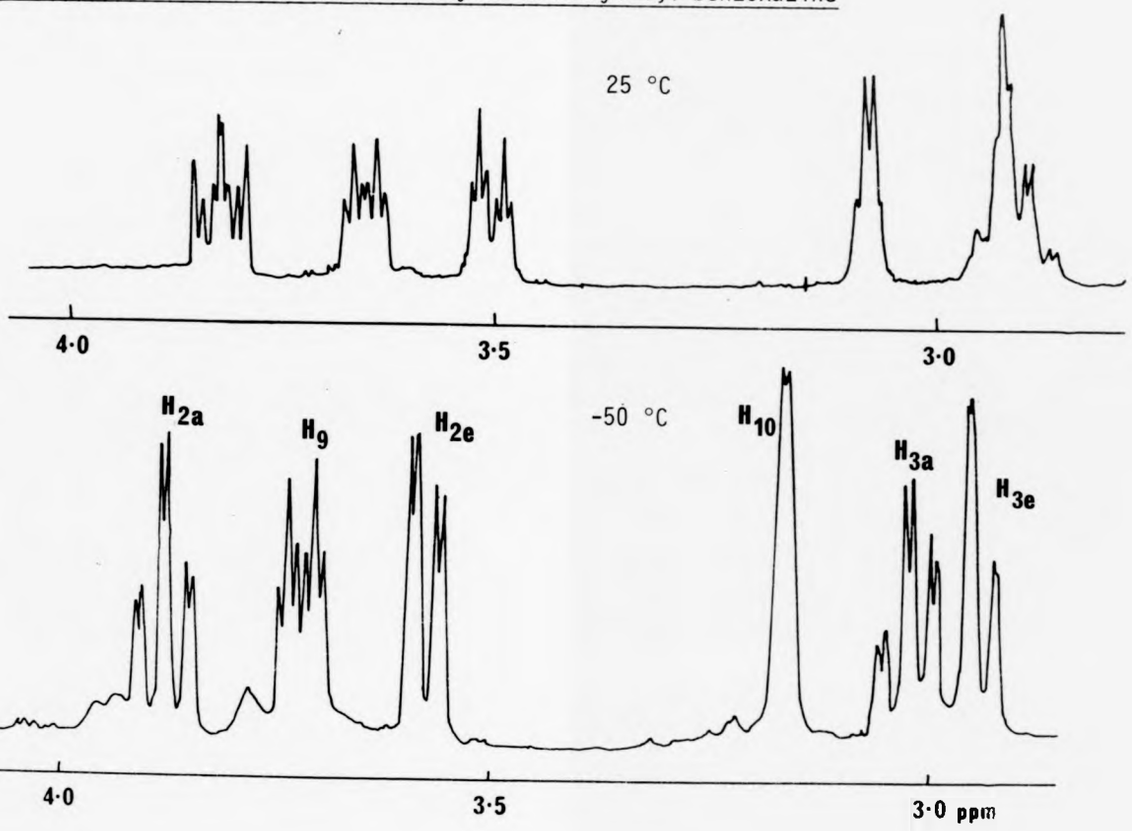
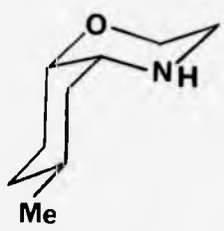


Table 17

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



Conformation
Type B

Proton (400 MHz Spectrum)*	Shift(δ)	Description of Resonance
2a	3.87	Multiplet with triplet of doublet character ($J_{2a,2e} + J_{2a,3a}$ = 23.5 Hz; $J_{2a,3e}$ = 2.8 Hz).
9	3.71	Multiplet (band width ∿ 31 Hz) with doublet of triplet character.
2e	3.57	Poorly resolved doublet of doublets ($J_{2e,2a}$ = 11.6 Hz; $J_{2e,3a}$ = 3.0 Hz)
10	3.17	Broad singlet (half-band width = 8 Hz) showing further couplings.
3a	3.03	Multiplet with triplet of doublet character ($J_{3a,3e} + J_{3a,2a}$ = 23.8 Hz; $J_{3a,2e}$ = 3.2 Hz).
3e	2.94	Poorly resolved doublet (band width ∿ 27 Hz) showing further small couplings.
8a	2.32	Poorly resolved quartet of doublets ($J_{8a,8e} \sim J_{8a,7a} \sim J_{8a,9}$ = 12.7 Hz; $J_{8a,7e}$ = 3.4 Hz).
7e	1.77	Poorly resolved multiplet (band width ∿ 36 Hz) with doublet character.

/ continued

Table 17 - continued

Proton	Shift(δ)	Description of Resonance
6a, 5e	1.57-1.72	Complex envelope of overlapping resonances.
8e	1.53	Poorly resolved multiplet (band width $\sim$ 33 Hz) of doublet character.
5a	1.24	Poorly resolved multiplet (band width $\sim$ 45 Hz) with triplet of doublet character.
7a	0.97	Poorly resolved multiplet (band width $\sim$ 50 Hz).
Me	0.86	Doublet ($J_{Me,6a}$ = 6.2 Hz)
N-H	-	Obscured by other resonances.

*$CDCl_3$ Solvent at -50 °C.

be identified by their characteristic multiplicities. The quartet of doublets at 2.32 p.p.m. was identified as the H8a resonance while the multiplet with triplet of doublet character at 1.24 p.p.m. was assigned to the H5a proton. The multiplicity of the H5a proton also indicated that the 6-methyl substituent was equatorially disposed, thus identifying the component as being cis-(9H,10H)--trans-(6H,10H)-octahydro-6-methyl-1,4-benzoxazine.

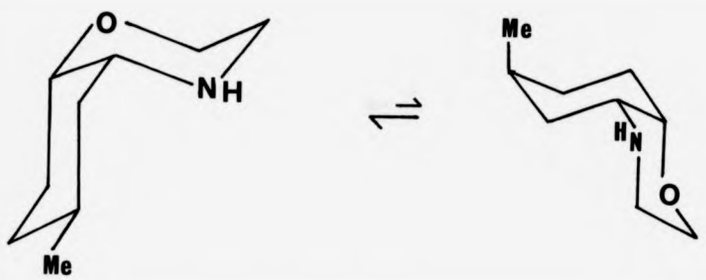
However, apart from the characteristic signals due to the H7a and methyl protons the remaining H8e, H7e, H5e and H6a resonances could only be tentatively assigned. The resonances at 1.77 and 1.53 p.p.m. both arising from equatorial protons were tentatively assigned to the H7e and H8e protons respectively. The resonance at 1.53 p.p.m. was only slightly distorted indicating it to be geminally coupled to a proton at much lower field. While the H8a resonance at 2.32 p.p.m. would fit this requirement for the geminally coupled proton the complex envelope of resonances (1.57 to 1.72 p.p.m.) certainly would not. For the resonance at 1.77 p.p.m., which was slightly distorted towards high field, the assignment to the H7e proton was based on comparisons with other methyl analogues (Fig. 7) of similar conformation. The two remaining resonances, due to the H5e and H6a protons were therefore attributed to the complex two proton multiplet between 1.57 and 1.72 p.p.m. These assignments therefore show that this component has a ^{1}H n.m.r. spectrum consistent with cis-(9H,10H)-trans-(6H,10H)--octahydro-6-methyl-1,4-benzoxazine in its Type B conformation.

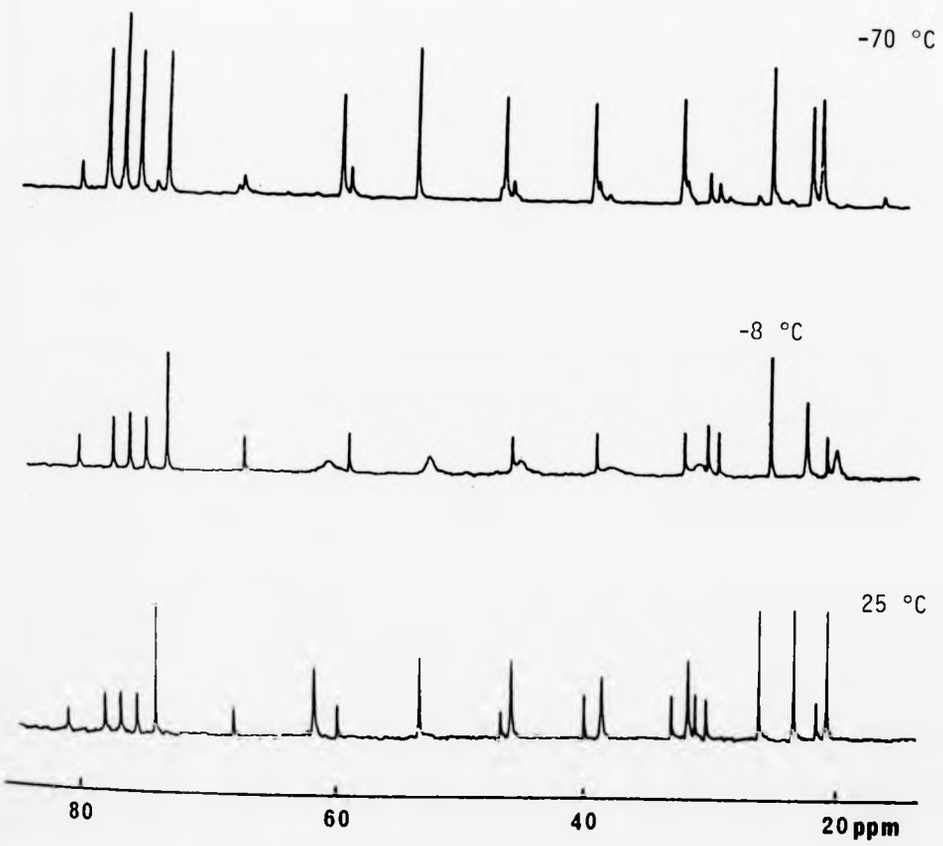
Low temperature ^{13}C n.m.r. spectroscopy was also used to confirm the major and minor conformations of Component A. Once again at room temperature only an averaged spectrum was observed (Plate 12) but on cooling to -70 °C the rate of interconversion was

Plate 12.

^{13}C N.M.R. Spectra from the Variable Temperature Study of

cis-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine





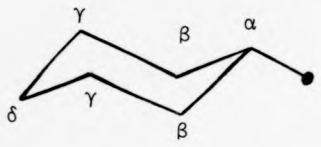
sufficiently slow to enable signals from both conformations to be observed. Using parameters obtained from cis-octahydro-1,4--benzoxazine (Tables 15 and 16) together with substituent parameters for the effects of axially or equatorially substituted methyl groups (Table 18), enabled chemical shifts to be calculated for both conformations of Component A. These calculated values for the Type A (Table 19) and Type B (Table 20) conformations can be seen to correspond well with those values determined experimentally and provide further support for the proposed assignment of Component A.

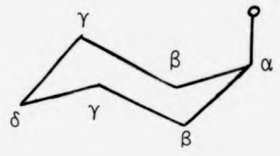
The relative intensities of the ^{13}C signals arising from the two conformations also allowed the position of the conformational equilibrium (Type A $\rightleftharpoons$ Type B) to be determined. Fortunately, the signals arising from the C9 position in both conformations were clearly visible allowing a ratio of 92:8 in favour of the Type B conformation to be determined. From this ratio a conformational free energy difference of 4.1 kJ mol^{-1} (at -70 °C) was calculated. Using the conformational free energy values, previously determined for the unsubstituted parent system (4.0 kJ mol^{-1}) and methyl-cyclohexane (7.1 kJ mol^{-1})[14], a value of 3.1 kJ mol^{-1} in favour of a Type B conformation (70) would be predicted, assuming a simple additivity relationship between these effects. The preference for the Type B conformation can thus be seen to be due to the greater preference of the methyl group for an equatorial orientation than that of the ring system for a Type A conformation.

Although the 6-methyl isomer does not have the added complications produced by an "inside" axial methyl substituent for its Type A conformation (71) there is still a discrepancy between the predicted and experimentally obtained values. Nevertheless,

Table 18

The Effect of a Methyl Substituent on the ^{13}C N.M.R. Chemical Shifts of Cyclohexane





Effect of an equatorial methyl substituent[66]

α_e = +5.64 p.p.m.

β_e = +8.90 p.p.m.

γ_e = 0.00 p.p.m.

δ_e = -0.28 p.p.m.

Effect of an axial methyl substituent[66]

α_a = +1.08 p.p.m.

β_a = +5.17 p.p.m.

γ_a = -5.39 p.p.m.

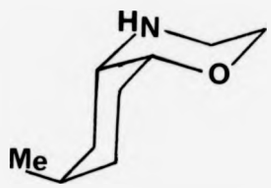
δ_a = -0.14 p.p.m.

A positive value for the effect of the methyl substituent represents a shift to lower field.

Table 19

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



Conformation
Type A

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.6	T	68.12	-
3	39.3	T	38.72	-
5	30.2	T	29.57	-
6	25.9	D	25.74	-
7	25.0	T	24.55	-
8	26.0	T	27.23	-
9	74.7	D	74.57	-
10	47.3	D	47.32	-
Me	-	Q	17.21	Q

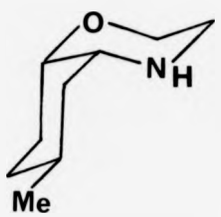
*Calculations based on the experimental values observed for the Type A conformation of cis-octahydro-1,4-benzoxazine (Table 15) with modifications for the effect of the methyl substituent (Table 18).

†Experimental values from sample in $CDCl_3$ + $CFCl_3$ (2:1) at -70 °C.

Table 20

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



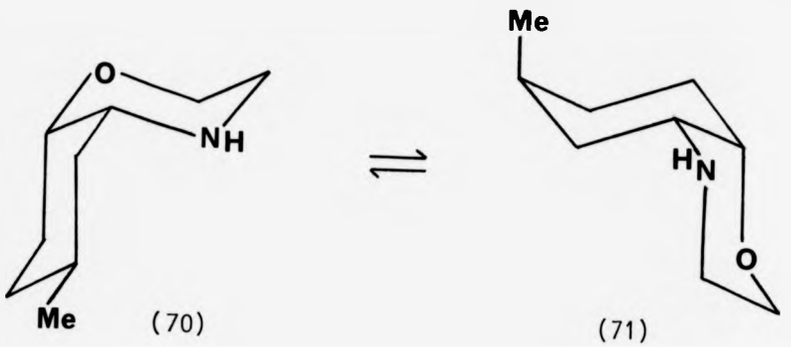
Conformation
Type B

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	60.1	T	59.97	T
3	47.1	T	47.01	T
5	40.4	T	39.95	T
6	27.2	D	26.06	D
7	30.9	T	33.06	T
8	23.2	T	22.91	T
9	73.6	D	73.76	D
10	54.0	D	53.95	D
Me	-	Q	22.14	Q

*Calculations based on the experimental values, where possible, or calculated values for the Type B conformation of cis-octahydro--1,4-benzoxazine (Table 16) with modifications for the effect of the methyl substituent (Table 18).

†Experimental values from sample in $CDCl_3$ + $CFCl_3$ (2:1) at -70 °C.

the predicted value was closer to that observed than in the case of some other derivatives (cf. 2-methyl analogue, discussed later).



(70) (71)

(ii) Component B (trans-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl--1,4-benzoxazine)

The stereochemistry of this component was readily deduced from its spectral data. Analysis of the 400 MHz ^{1}H n.m.r. spectrum (Plate 13, Table 21) with the aid of a "spin decoupling" experiment allowed all the resonances to be assigned. For those resonances associated with the oxazine portion of the molecule an excellent match with those of the unsubstituted trans-fused system was observed (cf. Plates 7 and 13, Fig. 8). This not only indicated the trans-fused nature of this component but also showed that the 6-methyl substituent had little or no effect on the ^{1}H n.m.r. chemical shifts for this part of the molecule. This latter point would be consistent with an equatorially disposed methyl group on C6. However, for the cyclohexane portion of the system, a

Plate 13.

The 400 MHz ^{1}H N.M.R. Spectrum of trans-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine

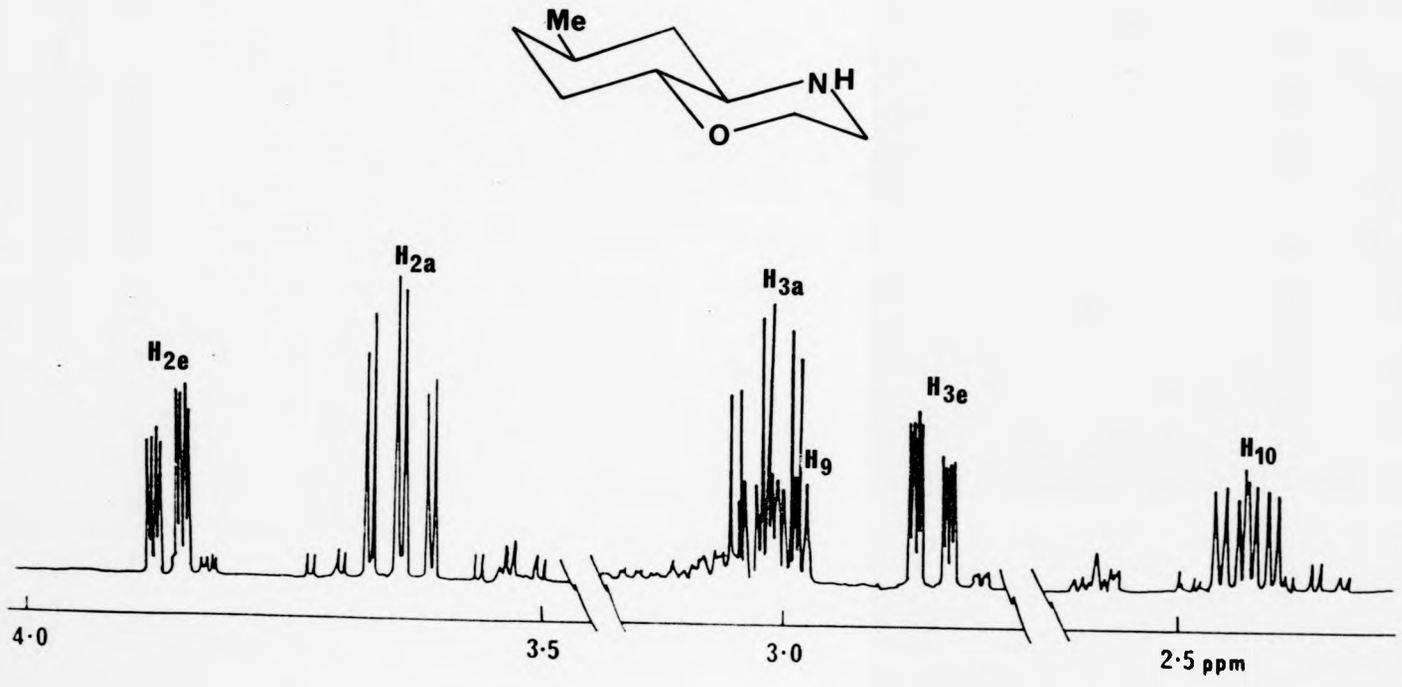


Table 21

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.86	Doublet of doublet of doublets ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 3.4 Hz; $J_{2e,3e}$ = 1.3 Hz).
2a	3.64	Multiplet with triplet of doublet character ($J_{2a,2e} + J_{2a,3a}$ = 23.0 Hz; $J_{2a,3e}$ = 2.6 Hz).
3a	3.02	Multiplet with triplet of doublet character ($J_{3a,3e} + J_{3a,2a}$ = 23.9 Hz; $J_{3a,2e}$ = 3.4 Hz).
9	3.01	Multiplet (band width ∿ 27 Hz) overlapped with H3a.
3e	2.86	Doublet of doublet of doublets ($J_{3e,3a}$ = 12.1 Hz; $J_{3e,2a}$ = 2.6 Hz; $J_{3e,2e}$ = 1.3 Hz).
10	2.43	Multiplet (band width ∿ 27 Hz).
8e	1.82	Multiplet (band width ∿ 26 Hz) with doublet character.
N-H	1.79	Broad singlet.
7e	1.71	Multiplet (band width ∿ 28 Hz) with doublet character.

/continued

Table 21 - continued

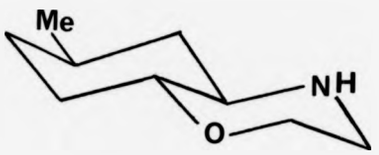
Proton	Shift(δ)	Description of Resonance
5e	1.64	Multiplet (band width $\sim$ 28 Hz) with doublet character.
6a	1.56	Complex multiplet (band width $\sim$ 44 Hz).
8a	1.38	Multiplet (band width $\sim$ 44 Hz) with quartet of doublet character.
7a	1.04	Multiplet (band width $\sim$ 45 Hz) with quartet of doublet character.
5a	0.94	Multiplet (band width $\sim$ 40 Hz) with quartet character.
Me	0.91	Doublet ($J_{Me,6a}$ = 6.6 Hz).

*$CDCl_3$ Solvent at 25 °C.

Table 22

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	67.9	T	67.97	T
3	46.7	T	46.63	T
5	39.8	T	40.01	T
6	30.2	D	31.25	D
7	33.5	T	33.13	T
8	31.5	T	30.50	T
9	80.9	D	81.17	D
10	60.3	D	59.62	D
Me	-	Q	21.89	Q

*Calculations based on the experimental values of trans-octahydro--1,4-benzoxazine (Table 9) with modifications for the effect of the methyl substituent (Table 18).

†$CDCl_3$ Solvent at 25 °C.

noticeable change in the chemical shifts was observed relative to the parent trans-fused molecule. This was particularly noticeable for the H5a and H7a protons which experienced upfield shifts relative to the corresponding parent analogue, also consistent with an equatorial methyl group[9] at C6.

As previously stated the protons from the oxazine portion of the system were readily assigned from their chemical shifts and multiplicites by comparison with those in trans-octahydro-1,4--benzoxazine. As with the parent system the H9 and H3a resonances were overlapping. However, the H10 proton gave a clearly visible multiplet at 2.43 p.p.m. which was characteristic of a trans-fused system.

Apart from the distinctive methyl doublet at 0.91 p.p.m. the other higher field signals could only be assigned with the aid of a "spin decoupling" experiment involving the irradiation of the multiplet, with quartet character, at 1.38 p.p.m.. Irradiation of this multiplet caused a noticeable effect on the H9 bridgehead resonance, indicating that the irradiated multiplet was due to the H8a proton. Further effects of this irradiation were also observed on the resonances at 1.04 and 0.94 p.p.m., both of which lost one major coupling. The signal at 1.04 p.p.m., previously with quartet of doublet character, was assigned to the H7a proton, while the quartet type resonance at 0.94 p.p.m. was consistent with that expected for the H5a proton, if one assumes an equatorial methyl group on C6. The only remaining unassigned axially orientated proton, H6a, gave a complex multiplet centred at 1.56 p.p.m. and was unaffected by the irradiation of H8a. The remaining equatorial proton resonances were also readily assigned. The signal at 1.82 p.p.m.

lost its only large coupling and was therefore attributed to the H8e proton. At 1.71 p.p.m. the doublet type signal lost a small coupling consistent with that expected for the H7e proton. The remaining signal at 1.64 p.p.m. was unaffected by the irradiation of H8a and hence assigned to the H5e proton.

Comparison of the calculated ^{13}C n.m.r. chemical shifts with those experimental observed (Table 22) also confirmed the stereochemistry of this component as being consistent with that of trans-(9H,10H)-cis-(6H,10H)-octahydro-6-methyl-1,4-benzoxazine.

(iii) Component C (trans-(9H,10H)-trans-(6H,10H)-Octahydro-6--methyl-1,4-benzoxazine)

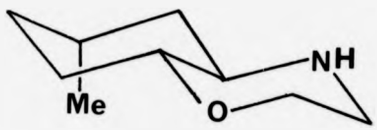
This component could not be obtained in an isomerically pure state and consequently the 400 MHz ^{1}H n.m.r. spectral data (Table 23) had to be obtained from an enriched sample ($\sim$ 62% isomeric purity) which also contained an amount of the isomeric Component B ($\sim$ 38%).

In general the lower field signals for Component C compared well with those chemical shifts and multiplicities observed for the unsubstituted parent trans-fused system. It was therefore assigned as having a trans-fused ring junction, this being further supported by the temperature independent nature of the spectrum. The H2e, H2a, H3a and H3e resonances were therefore readily assigned by comparison with the parent system (Fig. 9). In the case of the bridgehead protons the H9 proton resonated at 3.02 p.p.m. and compared well with the position observed in the parent system (3.03 p.p.m.). This was not unexpected since, irrespective of whether the 6-methyl substituent was axial or equatorial, the chemical shift of the H9 resonance would not be expected to be significantly altered, relative to the corresponding unsubstituted system. However, the

Table 23

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



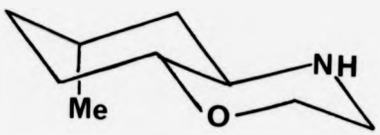
Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*†		
2e	3.87	Doublet of doublets ($J_{2e,2a}$ ∿ 11.4 Hz; $J_{2e,3a}$ ∿ 3.4 Hz).
2a	3.65	Multiplet with triplet of doublet character ($J_{2a,2e}$ + $J_{2a,3a}$ ∿ 23.1 Hz; $J_{2a,3e}$ ∿ 2.7 Hz).
3a	3.05	Multiplet with triplet doublet character ($J_{3a,3e}$ + $J_{3a,2a}$ ∿ 24.1 Hz; $J_{3a,2e}$ = 3.4 Hz).
9	∿ 3.02	Multiplet (band width ∿ 30 Hz) partially obscured by H3a and contaminant resonances.
3e	2.89	Poorly resolved multiplet (band width ∿ 23 Hz) with doublet character.
10	2.66	Multiplet (band width ∿ 29 Hz) with doublet of doublet of doublet character.
N-H	2.23	Broad singlet.
Remaining Protons	0.87-1.77	Complex envelope of overlapping resonances.
Me	1.04	Doublet ($J_{Me,6e}$ = 7.3 Hz).

*This sample contained the isomeric impurity, Component B (∿ 38%), which further complicated the interpretation of this spectrum.
† $CDCl_3$ Solvent at 25 °C.

Table 24

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-trans-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	67.9	T	68.02	T
3	46.7	T	46.75	T
5	36.05	T	37.11	T
6	25.7	D	27.40	D
7	29.8	T	29.89	T
8	26.1	T	25.64	T
9	81.1	D	82.10	D
10	54.9	D	54.94	D
Me	-	Q	18.49	Q

*Calculations based on the experimental values of trans-octahydro--1,4-benzoxazine (Table 9) with modifications for the effect of the methyl substituent (Table 18).

†$CDCl_3$ Solvent at 25 °C.

chemical shift of the H10 proton would be expected to be altered by the presence of an axial 6-methyl substituent since an axial proton resonance with a 1,3 relationship to an axial methyl group experiences a downfield shift.[65] It is therefore not surprising that the H10 resonance at 2.66 p.p.m. has a downfield shift of 0.27 p.p.m. relative to that in the parent system. An axial methyl substituent at C6 was therefore inferred. Apart from the methyl resonance at 1.04 p.p.m., no further resonances could be distinguished clearly, due to the presence of the isomeric impurity.

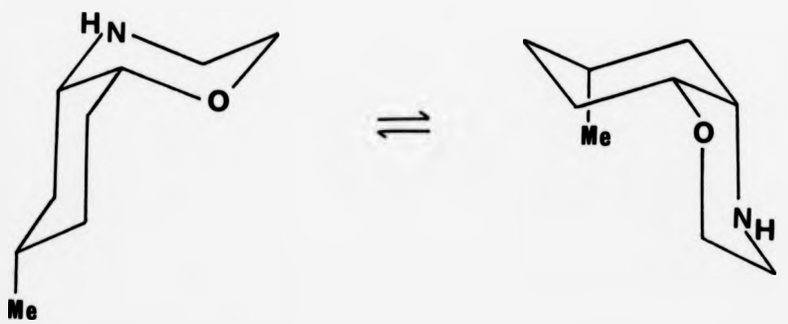
Confirmation of the stereochemical assignment of this component was also obtained from the ^{13}C n.m.r. spectral data (Table 24). Using parameters for the effect of an axial methyl substituent[66] (Table 18) and the experimentally observed shifts for trans-octahydro-1,4-benzoxazine the expected ^{13}C n.m.r. chemical shifts could be calculated for Component C. Apart from the excellent match between the calculated and experimentally observed values it is also worth noting that the C10 resonance has been subjected to an upfield shift of 5.34 p.p.m. relative to that observed in the parent system. This shift compares well with the expected upfield shift arising from a γ-axial methyl group (5.39 p.p.m.) based on reported results from methylcyclohexane.[66] The spectroscopic evidence thus clearly indicated that Component C is trans-(9H,10H)-trans-(6H,10H)--octahydro-6-methyl-1,4-benzoxazine.

(iv) Component D (cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine)

This component was the most retentive of the four isomers of octahydro-6-methyl-1,4-benzoxazine on the medium pressure chromatography column. Analysis by ^{1}H and ^{13}C n.m.r. spectroscopy

once again enabled the sterochemistry of the system to be determined. The 400 MHz ^{1}H n.m.r. spectrum (Plate 14, Table 25) gave a readily interpretable low field set of signals but a complex higher field region. The resonances associated with the protons near the heteroatoms compared well with those previously observed for cis-octahydro-1,4-benzoxazine in its Type A conformation. The signals assigned to the H2e, H2a, H3e and H3a protons gave the appropriate multiplicities and the chemical shifts differed by not more than 0.07 p.p.m. from those observed in the analogous parent system (Table 13). Furthermore, the H9 and H10 bridgehead protons gave rise to resonances that were typical of a cis-fused isomer with a Type A conformation (cf. Plates 9 and 14). Component D was therefore clearly shown to be a cis-fused isomer in the Type A conformation.

It is interesting to note at this point that although Component D was clearly a cis-fused isomer it did not show the expected temperature dependence in its ^{1}H and ^{13}C n.m.r. spectra. These two properties are not inconsistent, providing that the position of the conformational equilibrium (72 $\rightleftharpoons$ 73) is very extreme.



(72) (73)

Plate 14.

The 400 MHz ^{1}H N.M.R. Spectrum of cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine

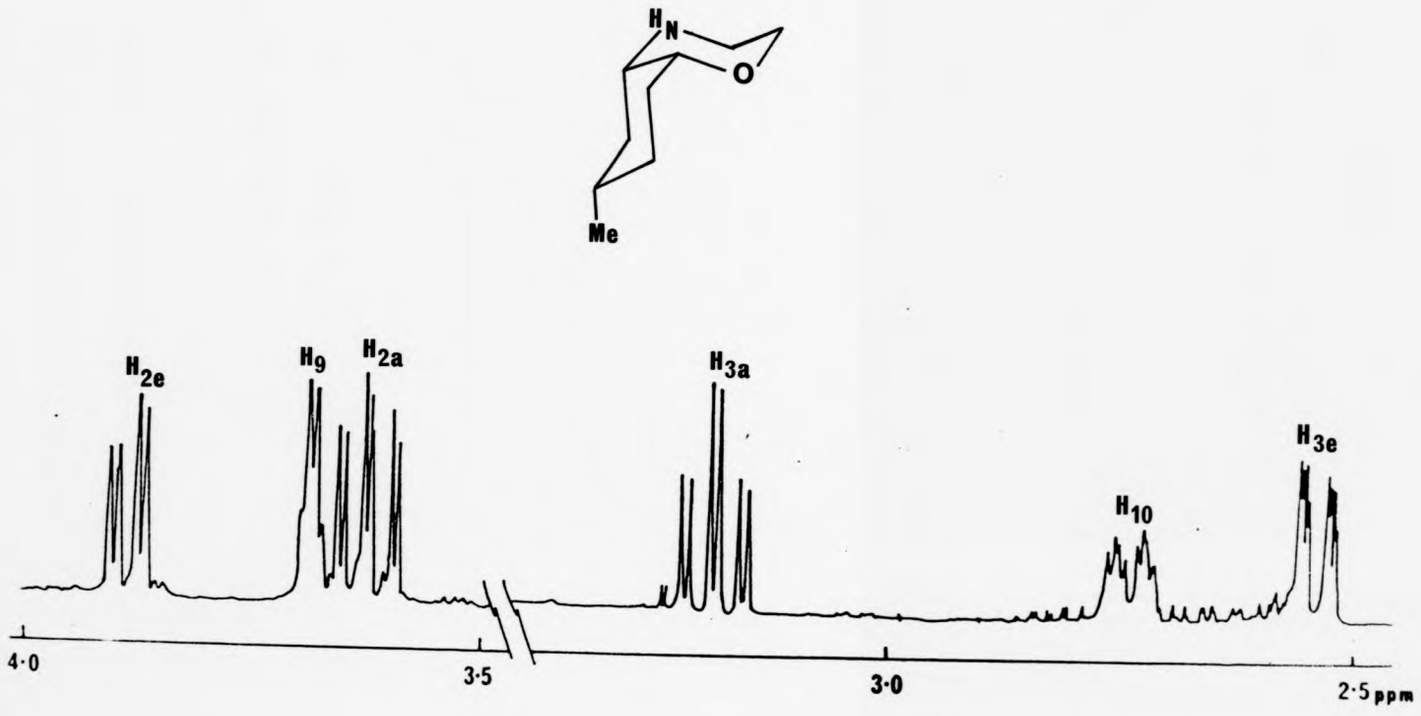
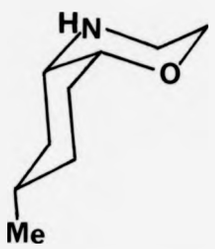


Table 25

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



Conformation
Type A

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.89	Doublet of doublets ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 3.6 Hz).
9	3.69	Multiplet (half-band width = 6 Hz).
2a	3.63	Multiplet with doublet of doublet of doublet character ($J_{2a,2e}$ + $J_{2a,3a}$ = 23.3 Hz; $J_{2a,3e}$ = 2.8 Hz).
3a	3.19	Multiplet with triplet of doublet character ($J_{3a,3e}$ + $J_{3a,2a}$ = 24.6 Hz; $J_{3a,2e}$ = 3.6 Hz).
10	2.74	Multiplet (band width ∿ 26 Hz) with doublet character.
3e	2.54	Multiplet with doublet of doublet of doublet character ($J_{3e,3a}$ = 12.6 Hz; $J_{3e,2a}$ = 2.8 Hz; $J_{3e,2e}$ = 1.1 Hz).
N-H	2.16	Broad singlet
8e	1.86	Multiplet (band width ∿ 25 Hz), partially overlapped with H5a.
5a	1.84	Multiplet with quartet character ($J_{5a,5e}$ ∿ $J_{5a,6a}$ ∿ $J_{5a,10}$ ∿ 12.0 Hz).

/continued

Table 25 - continued

Proton	Shift(δ)	Description of Resonance
7e, 5e, 6a, 8a.	1.33-1.52	Complex envelope of overlapping resonances.
7a	1.14	Multiplet (band width $\sim$ 47 Hz) with quartet of doublet character.
Me	0.95	Doublet ($J_{Me,6a}$ = 6.4 Hz).

*$CDCl_3$ Solvent at 25 °C.

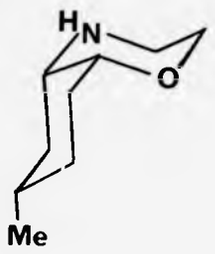
However, it does show that we must exercise caution when using the temperature independence of the n.m.r. spectra to assist in distinguishing between the cis-fused and trans-fused isomers in these studies.

While the lower field resonances in the ^{1}H n.m.r. spectrum of Component D were apparently unaffected by the 6-methyl substituent, a significant shift in certain higher field resonances was observed. In comparison with the parent system the H5a signal was noticeably moved to higher field (0.31 p.p.m.), appearing as a distinct quartet at 1.84 p.p.m.. Furthermore, the absence of the normal small coupling ($J_{5a,6e}$) from the adjacent 6e position indicated that this position was occupied by the methyl group and hence that the isomer was cis-(9H,10H)-cis-(6H,10H)-octahydro-6-methyl-1,4-benzoxazine. Partly obscured by the H5a resonance was a signal of doublet character (1.86 p.pm.) due to an equatorially disposed proton. This signal was assigned to the H8e proton on the basis of comparisons with other methyl analogues (Fig. 10). The H7a resonance appeared as a characteristic multiplet with quartet character at 1.14 p.p.m.. It is interesting to note that this signal has experienced an upfield shift similar to that observed for H5a as a result of the equatorial methyl group on C6. Apart from the methyl signal at 0.95 p.p.m. the remaining protons (i.e. H7e, H5e, H6a and H8a) could only be assigned to the complex envelope of overlapping resonances between 1.33 and 1.52 p.p.m.. Nevertheless, sufficient ^{1}H n.m.r. spectral data had been obtained to confirm the assignment of Component D to cis-(9H,10H)-cis--(6H,10H)-octahydro-6-methyl-1,4-benzoxazine in its Type A conformation. A comparison of the calculated ^{13}C n.m.r. chemical shifts for this isomer with those observed experimentally for Component D (Table 26) provided further support for this assignment.

Table 26

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1,4-benzoxazine



Conformation
Type A

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.6	T	68.58	T
3	39.3	T	39.48	T
5	33.9	T	33.92	T
6	30.5	D	31.61	D
7	28.7	T	28.47	T
8	31.4	T	31.13	T
9	74.5	D	74.21	D
10	52.7	D	53.01	D
Me	-	Q	22.33	Q

*Calculations based on the experimental values for the Type A conformation of cis-octahydro-1,4-benzoxazine (Table 15) with modifications for the effect of the methyl substituent (Table 18).

†$CDCl_3$ Solvent at -25 °C.

The very extreme position of the conformational equilibrium (Type A ⇌ Type B) in this cis-fused isomer, as shown by the temperature independent nature of the ^{13}C n.m.r. spectrum is due to the fact that the Type A conformation (72) not only has the ring system in its preferred conformation but it also has the methyl group in the more stable equatorial orientation. In the Type B conformation (73) the heteroatoms are in their least preferred arrangement and, in addition, the methyl group is in an axial orientation. Furthermore, the Type B conformation also has the methyl group in an "inside" position resulting in severe steric interactions between itself and the N4 position. As a consequence of these interactions the expected preference of Component D for a Type A conformation would thus be large. Even without considering the substantial interactions between the methyl at C6 and the N4 position we would predict a free energy difference of about 11.1 kJ mol^{-1} which corresponds to an equilibrium ratio of 99.85:0.15 (at-67 °C) in favour of the Type A conformation (72). Hence, it is not too surprising that Component D did not give temperature dependent n.m.r. spectra.

B. Summary

Having identified the four isomers of the octahydro-6-methyl--1,4-benzoxazine system it was of interest to analyse the ^{1}H n.m.r. spectral data more closely to see if information about the degree of distortion of the ring system could be obtained. For this reason the vicinal couplings for the C2-C3 portion of the molecule were obtained, as far as possible, and used to calculate the R value[31].

The poor resolution in the low temperature ^{1}H n.m.r. spectrum of Component A and the isomeric impurities in the spectrum of Component C caused difficulties in obtaining some coupling information, such as the value of the small vicinal coupling $^{3}J_{2e,3e}$. However, this difficulty was overcome by estimating this value as 1.3 Hz, this being the value in the least distorted parent trans-fused system. Fortunately, small variations in $^{3}J_{2e,3e}$ were shown to have little effect on the value of R determined for the isomers. The R values obtained for Components A,B,C and D in this way were 2.2 - 2.3, 2.2, 2.1 and 2.0 respectively which correspond to a dihedral angle range of only about 57 - 59 °C. These R values are not significantly different from the 2.2 - 2.3 range observed for the octahydro-1,4--benzoxazine parent isomers and show clearly that the presence of the methyl group on C6 has little effect on the distortion in the oxazine ring as monitored by the dihedral angle along C2 - C3. Even in Component C, which possesses a strained axially disposed methyl group, the R value is not significantly different from that in the parent system.

Finally, now that the identity of Components A,B,C and D are known we can assess the isomeric ratios produced during the catalytic hydrogenation of 2H-3,4-dihydro-6-methyl-1,4-benzoxazine. Interestingly it can now be seen that with water as the solvent the total amount (52%) of the cis-fused isomers (Components A and D) produced in the catalytic hydrogenation was similar to the total amount (48%) of trans-fused material (Components B and C). This is similar to the cis:trans ratio produced during the catalytic hydrogenation of 2H-3,4-dihydro-1,4-benzoxazine to give the parent system (previously discussed).

However, it is interesting to note that while it was the more stable trans-isomer (Component B) which was the major trans isomer produced it was the less stable cis isomer (Component A) which was the major cis isomer formed. Unfortunately there appears to be no simple explanation as to why such large quantities of Component A are produced.

However, it is interesting to note that while it was the more stable trans-isomer (Component B) which was the major trans isomer produced it was the less stable cis isomer (Component A) which was the major cis isomer formed. Unfortunately there appears to be no simple explanation as to why such large quantities of Component A are produced.

4. Octahydro-7-methyl-1,4-benzoxazine

As with the 6-methyl system previously discussed, the octahydro-7-methyl-1,4-benzoxazine system was prepared to investigate the effects of introducing a methyl substituent into the cyclohexane portion of the molecule. Although all four isomers were successfully prepared in the form of an isomeric mixture, the separation of this mixture proved very difficult. Nevertheless, samples of three of the isomers were obtained in a reasonably pure state by medium pressure chromatography and the fourth isomer, although highly contaminated with two other isomers, was obtained in a sufficiently pure enough state to enable some stereochemical information to be obtained.

Once again the "octahydro" isomers were prepared by catalytic hydrogenation of an appropriate aromatic precursor. The precursor used, 2H-3,4-dihydro-7-methyl-1,4-benzoxazine, was prepared by the method previously described for the parent system (Fig. 6), except that 5-methyl-2-nitrophenol was used in place of 2-nitrophenol as the starting material.

As expected, the ratio of the four isomers of octahydro-7--methyl-1,4-benzoxazine, produced on reduction of the aromatic precursor, varied with the catalytic hydrogenation conditions used. For example, in a hydrogenation using cyclohexane as solvent and palladium on charcoal as catalyst an isomeric ratio of 38:7:42:13 was obtained (for Components A, B, C and D respectively). However, it was found to be difficult to reproduce this ratio consistently using this solvent. As with the 6-methyl system, previously considered, it was found considerably easier to obtain reproducible

results using water as solvent. This solvent also allowed slightly lower hydrogenation temperatures to be used. Using water as the solvent and conditions similar to those applied to the 6-methyl system enabled the octahydro-7-methyl-1,4-benzoaxazine system to be prepared with an isomeric ratio of 42:6:42:10 (for Components A, B, C and D respectively).

Although ^{13}C n.m.r. spectroscopy showed the presence of all four isomers in the isomeric mixtures, it was difficult to separate all these isomers chromatographically. Analytical gas liquid chromatography indicated the presence of only two components, while thin layer chromatography (silica plates) allowed three of the isomers to be partially resolved. Nevertheless, the careful application of medium pressure chromatography enabled three of the isomers to be obtained in an isomerically pure state. Analysis of the fractions from a chromatographic run, which lasted several days, enabled one fraction to be identified containing about 40% of the fourth isomer (Component B). The fraction prior to this was found to contain largely Component A, while the fraction immediately after was found to contain largely Component C. In view of this similarity in retention times of these three components it was felt that further efforts to purify Component B were likely to be unproductive. The stereochemical information obtained for Component B was therefore obtained from the enriched sample previously mentioned. The isomers are discussed below in order of their elution from the chromatography column.

A. Stereochemical Aspects

(i) Component A (cis-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl--1,4-benzoxazine)

This component was the first to be eluted from the medium pressure chromatography column and exhibited a temperature dependent n.m.r. spectrum. Since work on the parent and 6-methyl systems had indicated that this type of temperature dependence was due to ring inversion rather than nitrogen inversion, Component A was assigned to one of the cis-fused isomers.

Although the n.m.r. spectra were temperature dependent the 400 MHz ^{1}H n.m.r. spectrum at -50 °C (Plate 15, Table 27) did not differ significantly from that observed at room temperature. No signals associated with a minor conformation were observed, indicating that the position of the conformation equilibrium (Type A $\rightleftharpoons$ Type B) was extreme.

The low field signals from the major conformation, those associated with the protons on the oxazine ring, were readily assigned in the 400 MHz ^{1}H n.m.r. spectrum at -50 °C. The protons on C2, 3, 9 and 10 gave resonances which had multiplicities and chemical shifts which compared well with those observed for cis-octahydro-1,4-benzoxazine in its Type B conformation (Table 14, Fig. 7). These signals were therefore assigned by comparison with cis-octahydro-1,4-benoxazine.

The spectrum at higher field ($\sim$ 1-2 p.p.m.) was more complex and only a few individual signals could be assigned. The signal resonating as a quartet at 1.99 p.p.m. was assigned to the H8a proton, its multiplicity implying an equatorial orientation for the adjacent 7-methyl substituent. Similarly, the resonance at 1.15 p.p.m., showing quartet of doublet character, was attributed to the H6a proton

Plate 15

The 400 MHz ^{1}H N.M.R. Spectrum of cis-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine

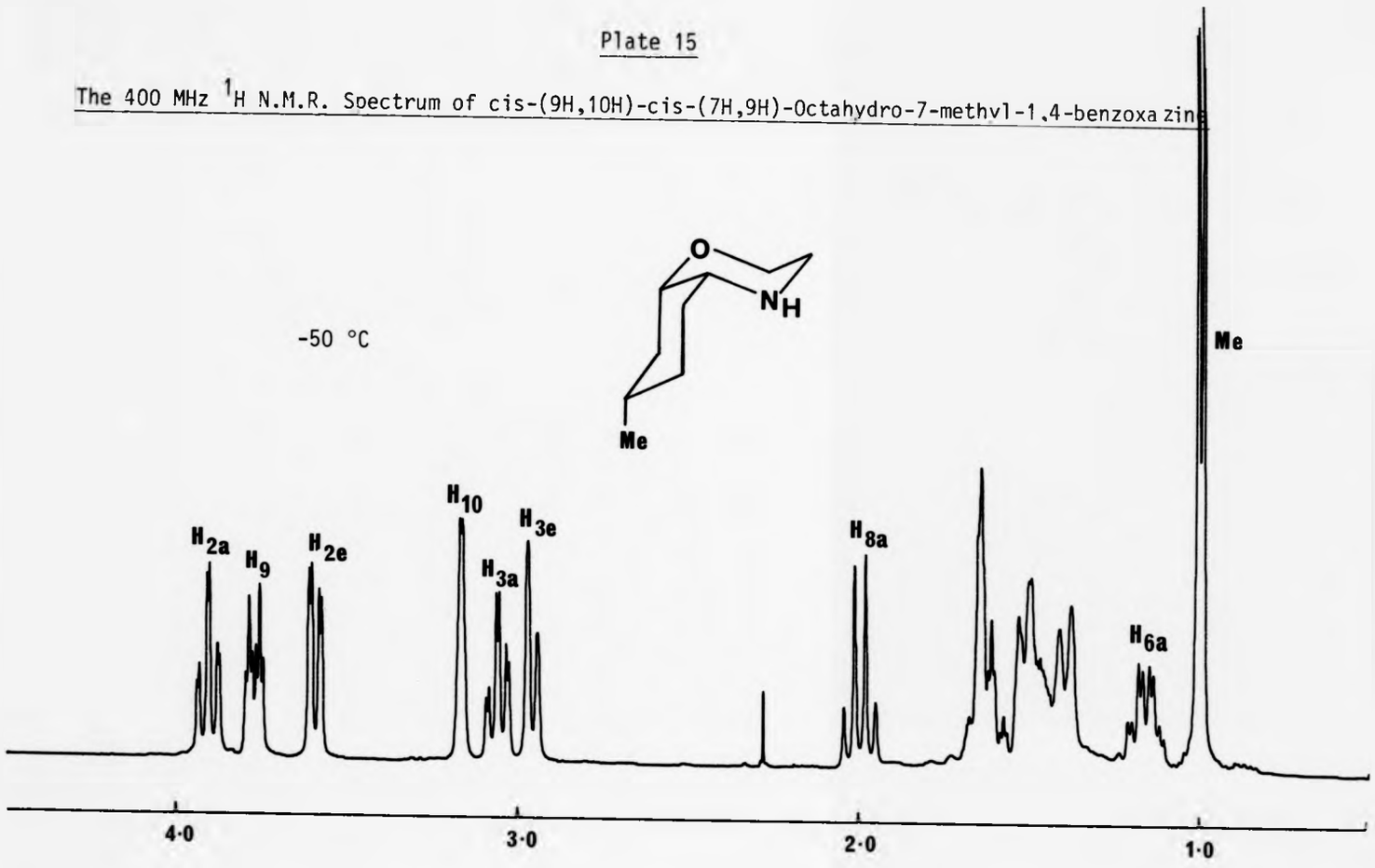
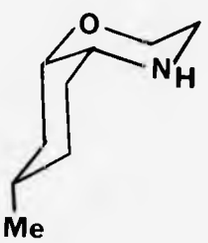


Table 27

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine



Conformation
Type B

Proton (400 MHz Spectrum)*	Shift(δ)	Description of Resonance
2a	3.90	Multiplet with triplet of doublet character ($J_{2a,2e} + J_{2a,3a}$ = 23.4 Hz; $J_{2a,3e}$ = 2.6 Hz).
9	3.77	Multiplet (band width ∿ 26 Hz) with doublet of triplet character.
2e	3.59	Doublet of doublets ($J_{2e,2a}$ = 11.5 Hz; $J_{2e,3a}$ = 3.4 Hz).
10	3.17	Broad singlet (half band width = 7 Hz) show small couplings.
3a	3.06	Multiplet with triplet of doublet character ($J_{3a,3e} + J_{3a,2a}$ = 23.8 Hz; $J_{3a,2e}$ = 3.4 Hz).
3e	2.95	Poorly resolved signal with doublet character (band width ∿ 23 Hz).
8a	1.99	Multiplet with quartet character ($J_{8a,8e} \sim J_{8a,7a} \sim J_{7a,9}$ = 12.2 Hz).
5e, 6e, 8e, 5a, 7a, N-H.	∿ 1.43-1.70	Complex envelope of overlapping resonances.

/ continued

Table 27 - continued

Proton	Shift(δ)	Description of Resonance
6a	1.15	Poorly resolved multiplet (band width ∿ 48 Hz) with quartet of doublet character.
Me	0.99	Doublet ($J_{Me,7a}$ = 6.4 Hz).

*$CDCl_3$ + 25% $CFCl_3$ Solvent at -50 °C.

due to its characteristic multiplicity. It is interesting to note that both the H8a and H6a protons resonate at higher field (0.23 and 0.28 p.p.m. respectively) in this isomer than was observed in cis-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine (discussed later), due to the effect of the equatorial 7-methyl substituent. These shifts are in agreement with those observed in the 6-methyl analogue (previously discussed), where the equatorial methyl group on C6 was found to affect the chemical shifts of the axial proton resonances on C5 and C7 by similar amounts (0.23 and 0.25 p.p.m. respectively). These results are consistent with the reported upfield shift (0.25 p.p.m.) caused by an equatorial methyl group on axial β-proton resonances[9].

The only remaining signal that could be assigned was the methyl doublet at 0.99 p.p.m. Nevertheless, although the remaining signals appeared as a complex envelope of overlapping resonances, the portion of the spectrum which could be assigned clearly indicated that Component A was cis-(9H,10H)-cis-(7H,9H)-octahydro-7-methyl-1,4-benzoxazine and that it adopted the Type B conformation.

Due to the poor resolution of the ^{1}H n.m.r. spectrum at -50 °C not all the required vicinal coupling data could be obtained directly. However, by estimating the $J_{2e,3e}$ coupling as 1.3 Hz (in view of the value obtained from trans-octahydro-1,4-benzoxazine) the R value[31] could be calculated. The value calculated for this system (R = 2.2) was similar to that observed for the parent and 6-methyl systems previously discussed. This once again indicates that an equatorial methyl group on the cyclohexane portion of the ring has little effect on the distortion of the oxazine portion of the molecule.

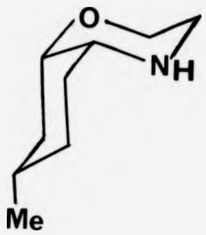
Further information about the position of the conformational equilibrium was obtained from ^{13}C n.m.r. spectroscopy. Although cooling the sample caused the ^{13}C n.m.r. spectrum to broaden (at about -30 °C) and then resharpen at lower temperatures (-63 °C), no signals associated with a minor conformation could be observed under these conditions. Nevertheless, the shifts observed for the dominant conformation could be compared with those calculated for this system, the latter being obtained from parameters for the Type B conformation of cis-octahydro-1,4-benzoxazine and for the effects of an equatorially disposed methyl substituent (Table 18). This comparison (Table 28) provided further support for the assignment of Component A.

It is interesting that the position of the conformational equilibrium is so extreme when one considers that the ring system is adopting the less preferred Type B conformation (cf. cis-octahydro--1,4-benzoxazine). From the parent system we have seen that the Type B conformation is about 4.0 kJ mol^{-1} less stable than the Type A conformation. On the other hand the methyl group has a $-\Delta G^{o}$ value of about 7.1 kJ mol^{-1}. Assuming an additivity relationship this would predict the Type B conformation of cis-(9H,10H)-cis-(7H,9H)--octahydro-7-methyl-1,4-benzoxazine to be only about 3.1 kJ mol^{-1} more stable than the corresponding Type A conformation. However, if one examines the Type A conformation (74) it can be seen that a severe steric interaction between the methyl group and the oxygen occurs which is absent in the Type B conformation (75).

Table 28

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine



Conformation
Type B

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	60.1	T	59.92	T
3	47.1	T	47.12	T
5	31.5	T	30.98	T
6	30.5	T	28.32	T
7	27.6	D	31.66	D
8	32.1	T	31.66	T
9	73.6	D	73.67	D
10	53.7	D	53.13	D
Me	-	Q	22.38	Q

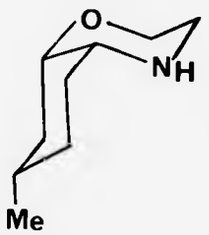
*The calculated values were obtained from the experimentally observed values, where possible, or calculated values for the Type B conformation of cis-octahydro-1,4-benzoxazine (Table 16), with modifications for the effect of an equatorial methyl substituent (Table 18).

†50% $CDCl_3$ + 50% $CFCl_3$ Solvent at -63 °C.

Table 28

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine

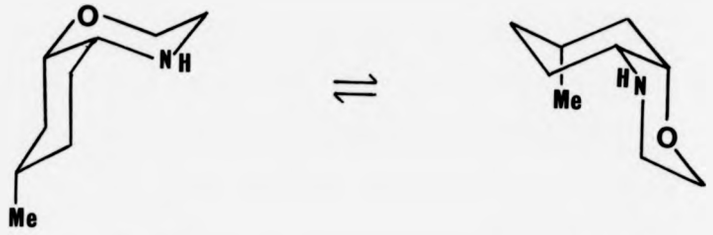


Conformation
Type B

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	60.1	T	59.92	T
3	47.1	T	47.12	T
5	31.5	T	30.98	T
6	30.5	T	28.32	T
7	27.6	D	31.66	D
8	32.1	T	31.66	T
9	73.6	D	73.67	D
10	53.7	D	53.13	D
Me	-	Q	22.38	Q

*The calculated values were obtained from the experimentally observed values, where possible, or calculated values for the Type B conformation of cis-octahydro-1,4-benzoxazine (Table 16), with modifications for the effect of an equatorial methyl substituent (Table 18).

†50% $CDCl_3$ + 50% $CFCl_3$ Solvent at -63 °C.



(75) (74)

The results of such an interaction must therefore be taken into account when assessing the relative energies of these two conformations. The extreme position of the conformational equilibrium (74 ⇌ 75) observed clearly shows that this methyl/oxygen interaction has a significant impact on the system.

(ii) Component B (trans-(9H,10H)-trans-(7H,9H)-Octahydro-7--methyl-1,4-benzoxazine)

Unfortunately, as previously mentioned, this component proved very difficult to isolate in an isomerically pure form. The best sample obtained was an enriched sample containing about 40% of Component B with the remainder being isomeric contaminants (∿ 20% Component A and ∿ 40% Component C). As a consequence of this contamination only a few resonances in the 400 MHz ^{1}H n.m.r. spectrum could be identified as arising from Component B (Table 29). Resonating at 3.88 p.p.m. was a poorly resolved signal with doublet character which was identified by comparison with trans-octahydro--1,4-benzoxazine (Fig. 9) as being due to the H2e proton in a trans--fused system. Although the signal at about 3.74 p.p.m. was complicated by overlap with contaminant resonances its band width (∿ 29 Hz) was consistent with that of an axial proton. Furthermore, since its chemical shift compared well with that of the H2a proton

Table 29

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-trans-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine

Proton (400 MHz Spectrum)*†	Shift(δ)	Description of Resonance
2e	3.88	Poorly resolved doublet (band width ∿ 23 Hz)
2a	∿ 3.74	Multiplet (band width ∿ 29 Hz)
9	3.39	Multiplet (band width ∿ 29 Hz) with doublet of doublet of doublet character.
Me	1.03	Doublet ($J_{Me,7e}$ = 7.4 Hz)

*$CDCl_3$ Solvent at 25 °C.

†This sample contained isomeric impurities (Components A and C) which complicated the interpretation and obscured the remaining resonances.

in the parent trans-fused system it was assigned as the H2a signal. The only other low field signal to be distinguished was a multiplet centred at 3.39 p.p.m. (band width ~ 29 Hz) which contained two large couplings and one small coupling. This multiplicity compared well with that observed for the H9 resonance in the parent trans--fused system. The resonance at 3.39 p.p.m. was therefore assigned to the H9 proton in Component B. It should be noted that this H9 resonance is at lower field (0.36 p.p.m.) than that observed in the parent system. Interestingly, in the case of the trans-fused analogue with an axial 2-methyl group (discussed later), a similar low field shift (0.30 p.p.m.) on the H9 resonance has been observed, caused by an axial γ-methyl substituent. The low field shift of the H9 resonance in Component B was therefore regarded as indicative of an axial 7-methyl group which identifies Component B as trans-(9H,10H)--trans-(7H,9H)-octahydro-7-methyl-1,4-benzoxazine. Apart from the methyl doublet at 1.03 p.p.m. no other resonances could be analysed due to the isomeric impurities.

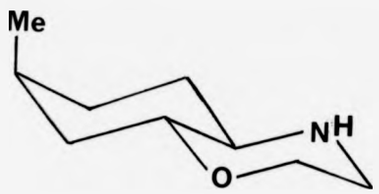
As a result of the limited ^{1}H n.m.r. spectral data on Component B no R value could be calculated. However, in view of the result for the corresponding 6-methyl system, this 7-methyl analogue would not be expected to have any significant distortion produced in the oxazine portion of molecule by the presence of the axial 7-methyl substituent.

Analysis by ^{13}C n.m.r. spectroscopy confirmed the nature of the stereochemistry. Using the appropriate parameters (Tables 9 and 18) the calculated values produced were found to be comparable with those experimentally observed (Table 30). Of particular interest was the chemical shift of the bridgehead carbon, C9. The chemical shift of this carbon has been moved to higher field by 4.38 p.p.m. relative

Table 30

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-trans-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift (δ)	Mult.	Shift(δ)	Mult.
2	67.9	T	67.70	-
3	46.7	T	46.47	-
5	25.5	T	26.17	-
6	29.8	T	29.89	-
7	25.7	D	28.01	-
8	36.7	T	36.34	-
9	75.8	D	76.81	-
10	60.14	D	61.01	-
Me	-	Q	18.56	-

*The calculated values were obtained from the experimentally observed values for trans-octahydro-1,4-benzoxazine (Table 9) with modifications for the effect of an axial methyl substituent (Table 18).

†$CDCl_3$ Solvent at 25 °C.

to the parent trans-fused system. Although this observed shift was not quite as large as expected for an axial γ-methyl group (5.39 p.p.m.)[66], an axial methyl could nevertheless be inferred. The n.m.r. spectral data for Component B was thus consistent with that expected for trans--(9H,10H)-trans-(7H,9H)-octahydro-7-methyl-1,4-benzoxazine.

(iii) Component C (trans-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl--1,4-benzoxazine)

This component produced a 400 MHz ^{1}H n.m.r. spectrum (Plate 16, Table 31) that had a good spread of resonances. This meant that all the resonances could be assigned with the aid of a "decoupling" experiment. For the lower field region of the spectrum i.e. those resonances from protons on carbons adjacent to the heteroatoms, an excellent match was obtained, both from the point of view of their chemical shifts and multiplicities, with those observed in trans-octahydro-1,4-benzoxazine (cf. Plates 7 and 16, Fig. 8). Hence, a trans--fused ring junction was inferred for Component C. The similarity of the shifts of the H9 and H10 bridgehead resonances also indicated that they have not been affected by the 7-methyl substituent. This in turn suggests that the methyl group on C7 is equatorially orientated (cf. H9 resonance of Component B).

The signals associated with the cyclohexane portion of the molecule were assigned by analysis of the effects caused by the irradiation of the multiplet with quartet of doublet character centred at 1.24 p.p.m.. This signal, in view of its multiplicity, could have arisen from either the H5a or H6a protons. However, irradiation of this multiplet resulted in the loss of a large coupling from the H10 resonance and clearly indicated the irradiated resonance to be due to the H5a proton. The quartet at 1.05 p.p.m. was unaffected by

Plate 16

The 400 MHz ^{1}H N.M.R. Spectrum of trans-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine

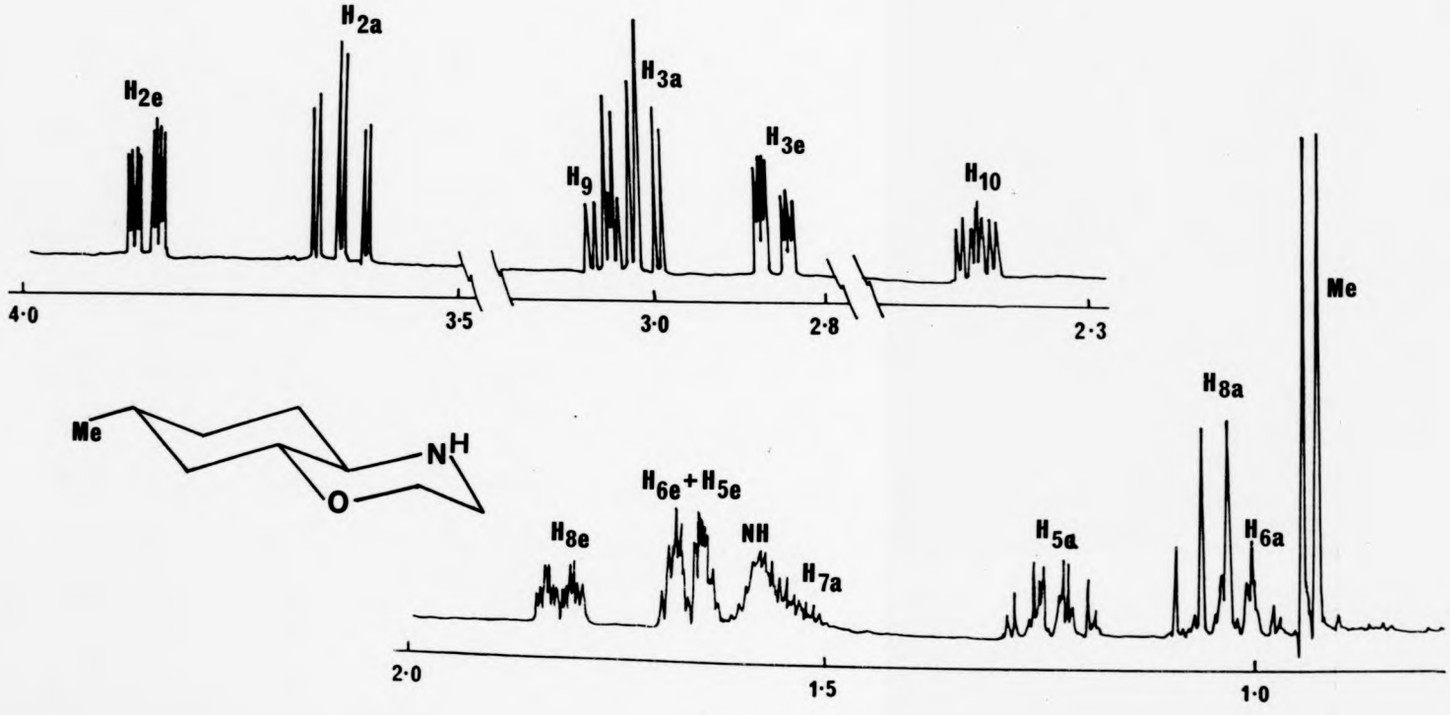


Table 31

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.86	Doublet of doublet of doublets ($J_{2e,2a}$ = 11.3 Hz; $J_{2e,3a}$ = 3.4 Hz; $J_{2e,3e}$ = 1.1 Hz).
2a	3.63	Multiplet with triplet of doublet character ($J_{2a,2e} + J_{2a,3a}$ = 23.0 Hz; $J_{2a,3e}$ = 2.6 Hz).
9	3.05	Multiplet (band width ~ 27 Hz) partially overlapping with H3a.
3a	3.03	Multiplet with triplet of doublet character ($J_{3a,3e} + J_{3a,2a}$ = 23.8 Hz; $J_{3a,2e}$ = 3.5 Hz).
3e	2.86	Doublet of doublet of doublets ($J_{3e,3a}$ =12.2 Hz; $J_{3e,2a}$ = 2.6 Hz; $J_{3e,2e}$ = 1.3 Hz).
10	2.36	Multiplet (band width ~ 27 Hz) with doublet of doublet of doublet character.
8e	1.81	Multiplet (band width ~ 25 Hz) with doublet of triplet of doublet character.

/continued

Table 31 - continued

Proton	Shift(δ)	Description of Resonance
6e, 5e	1.66	Two overlapping multiplets (band width $\sim$ 27 Hz) with doublet character.
N-H	$\sim$ 1.5	Broad signal obscured by overlap with H7a.
7a	1.56	Complex multiplet (band width $\sim$ 45 Hz).
5a	1.24	Multiplet (band width $\sim$ 45 Hz) with quartet of doublet character.
8a	1.05	Quartet ($J_{8a,8e} \sim J_{8a,7a} \sim J_{8a,9}$ = 12.2 Hz).
6a	1.02	Multiplet (band width $\sim$ 45 Hz) with quartet of doublet character, partially overlapped with H8a.
Me	0.94	Doublet ($J_{Me,7a}$ = 6.6 Hz).

*$CDCl_3$ Solvent at 25 °C.

irradiation of H5a and, in view of its multiplicity, was assigned to the H8a proton. A further multiplet at 1.02 p.p.m., with quartet of doublet character, which partially overlapped the H8a resonance simplified with the loss of one large coupling on irradiation of H5a indicating this resonance to be due to the H6a proton. The remaining axially orientated H7a proton was assigned to the complex multiplet centred at 1.56 p.p.m.. This resonance was distorted due to overlap with the broadened N-H resonance, but its multiplicity was unaffected by the "decoupling" experiment. In the case of the three equatorial protons the resonance at 1.81 p.p.m. was unaffected by irradiation of the H5a signal and was therefore assigned to the H8e proton. The remaining H6e and H5a resonances, which overlapped each other, were centred at 1.66 p.p.m.. The irradiation experiment caused the collapse of these signals to a broadened resonance, presumably due to the loss of a major coupling from the H5e signal and a minor coupling from the H6e signal. The methyl resonance occurred as a distinct doublet centred at 0.94 p.p.m.. Thus the ^{1}H n.m.r. spectral data was consistent with the assignment of Component C to trans-(9H,10H)-cis--(7H,9H)-octahydro-7-methyl-1,4-benzoxazine.

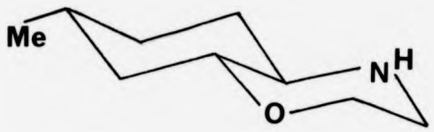
Analysis of the ^{1}H n.m.r. vicinal coupling data from the C2-C3 portion of the molecule gave an R value[31] in the range 2.1-2.2. This value was again similar to those observed for the other octahydro-1,4--benzoxazine systems previously discussed. This component would be expected to be the least distorted of the 7-methyl analogues since it is the most thermodynamically stable isomer in that it has a trans--fused ring junction and an equatorial methyl group.

Using the appropriate parameters (from Tables 9 and 18) the expected ^{13}C n.m.r. chemical shifts for this isomer were calculated.

Table 32

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-cis-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	67.9	T	67.86	T
3	46.7	T	46.69	T
5	30.9	T	31.04	T
6	33.5	T	33.20	T
7	30.2	D	31.33	D
8	40.4	T	39.27	T
9	81.2	D	80.65	D
10	60.0	D	60.00	D
Me	-	Q	22.02	Q

*The calculated values were obtained from the experimentally observed values for trans-octahydro-1,4-benzoxazine (Table 9), with modifications for the effect of an equatorial methyl substituent (Table 18).

†$CDCl_3$ Solvent at 25 °C.

These values showed an excellent fit with those obtained experimentally (Table 32). This data also confirmed the assignment of Component C.

(iv) Component D (cis-(9H,10H)-trans-(7H,9H)-Octahydro-7-methyl--1,4-benzoxazine)

The 400 MHz ^{1}H n.m.r. spectrum of Component D (Table 33) gave a low field region which corresponded well with that of cis-octahydro--1,4-benzoxazine in its Type A conformation. Component D was therefore confidently assigned as a cis isomer in the Type A conformation. It should be noted that despite a cis-fused ring junction no temperature dependence was observed in the n.m.r. spectra, indicating a very extreme position for the conformational equilibrium.

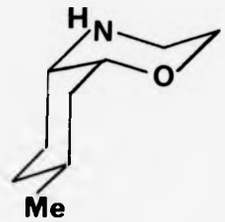
With the aid of a decoupling experiment and by comparison with similar analogues (Fig. 10) all the resonances were assigned in the 400 MHz ^{1}H n.m.r. spectrum. The lower field resonances, those arising from the H2e, H9, H2a, H3a, H10 and H3e protons, were all assigned by comparison with the multiplicities and chemical shifts of those protons in the Type A conformation of cis-octahydro-1,4-benzoxazine. These resonances compared well with the parent system with a deviation in chemical shifts of not more than 0.08 p.p.m..

Since the lower field resonances implied a Type A conformation the quartet of doublets at 2.15 p.p.m. was assigned to the H5a proton by comparison with similar systems. Irradiation of the quartet of doublet type signal at 0.97 p.p.m. resulted in the partial simplification of a number of resonances. The H5a resonance lost one major coupling indicating the irradiated resonance to be due to the H6a proton. The multiplicity of the H6a signal indicated the equatorial nature of the 7-methyl group thus defining the system as cis-(9H,10H)--trans-(7H,9H)-octahydro-7-methyl-1,4-benzoxazine. The complex

Table 33

^{1}H n.m.r. Spectra Data

cis-(9H,10H)-trans-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine



Conformation
Type A

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.91	Doublet of doublets ($J_{2e,2a}$ = 11.6 Hz; $J_{2e,3a}$ = 3.8 Hz).
9	3.80	Broad singlet (half-band width = 6 Hz) showing further small couplings.
2a	3.71	Multiplet with triplet of doublet character ($J_{2a,2e} + J_{2a,3a}$ = 23.9 Hz; $J_{2a,3e}$ = 2.8 Hz).
3a	3.17	Multiplet with triplet of doublet character ($J_{3a,3e} + J_{3a,2a}$ = 24.9 Hz; $J_{3a,2e}$ = 3.8 Hz),
10	2.86	Multiplet (band width $\sim$ 25 Hz) with doublet character.
3e	2.69	Poorly resolved doublet ($J_{3e,3a} \sim$ 12.7 Hz) showing further small couplings.
5a	2.15	Quartet of doublets ($J_{5a,5e} \sim J_{5a,6a} \sim J_{5a,10}$ = 12.7 Hz; $J_{5a,6e}$ = 3.7 Hz).
N-H	1.97	Broad singlet

/continued

Table 33 - continued

Proton	Shift(δ)	Description of Resonance
8e	1.86	Multiplet (band width $\sim$ 27 Hz) with doublet character.
6e	1.75	Multiplet (band width $\sim$ 30 Hz) with doublet character.
7a	1.68	Complex multiplet (band width $\sim$ 44 Hz), partially overlapped with H6e.
5e	1.55	Multiplet (band width $\sim$ 27 Hz) with doublet character.
8a	1.14	Multiplet (band width $\sim$ 31 Hz) with triplet of doublet character.
6a	0.97	Multiplet (band width $\sim$ 45 Hz) with quartet of doublet character.
Me	0.86	Doublet ($J_{Me,7a}$ = 6.6 Hz).

*$CDCl_3$ Solvent at 25 °C.

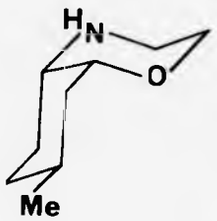
resonance centred at 1.68 p.p.m. was also observed to be partially simplified due to the irradiation of the H6a resonance, hence the complex multiplet was assigned to the H7a proton. The only remaining axial proton resonance, a multiplet with triplet of doublet character centred at 1.14 p.p.m., was unaffected by the decoupling experiment and was therefore attributed to the H8a proton. Of the three equatorial protons the doublet type resonance at 1.86 p.p.m. was also unaffected by the irradiation of H6a resonance, indicating the resonance to be due to the H8e proton. However, the resonances at 1.75 p.p.m. and 1.55 p.p.m. were simplified and lost a major and a minor coupling respectively. This result indicated these resonances to be due to the H6e and H5e protons respectively. The methyl resonance appeared as a doublet centred at 0.86 p.p.m. and was the highest field methyl resonance observed for the 7-methyl isomers. The spectral data was thus consistent with Component D corresponding to cis-(9H,10H)-trans-(7H,9H)-octahydro-7-methyl-1,4-benzoxazine. A comparison of the ^{13}C n.m.r. chemical shift data for both the expected and observed shifts (Table 34) also supported this assignment.

In view of the results previously obtained for the R values of these systems it was not surprising that the R value for Component D (assuming an estimated value of about 1.3 Hz for $J_{2e,3e}$) was found to be in the range 2.0-2.1. The R value[31] for this component, and for those previously discussed, indicates that the introduction of a methyl substituent at C6 or C7 in the molecule has virtually no effect on the distortion observed in the C2-C3 portion of the molecule, regardless of the orientation of the methyl substituent and the conformation of the ring system.

Table 34

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-trans-(7H,9H)-Octahydro-7-methyl-1,4-benzoxazine



Conformation
Type A

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.6	T	66.96	T
3	39.3	T	38.44	T
5	25.0	T	23.92	T
6	33.7	T	33.20	T
7	25.4	D	25.95	D
8	40.3	T	39.60	T
9	74.8	D	74.08	D
10	52.4	D	52.36	D
Me	-	Q	21.82	Q

*The calculated values were obtained from the experimentally observed values for the Type A conformation of cis-octahydro-1,4-benzoxazine (Table 15), with modifications for the effect of an equatorial methyl substituent (Table 18).

†$CDCl_3$ Solvent at 25 °C.

Due to the cis-fused nature of Component D there are two possible conformation types. However, the spectral data clearly indicated that an extreme equilibrium existed in favour of the Type A arrangement. The extreme nature of the equilibrium can be explained in view of the interactions present in the Type A (76) and Type B (77) conformations. For conformation Type B the oxygen and nitrogen heteroatoms are in the least preferred arrangement, as indicated by the parent system, to the extent of about 4.0 kJ mol^{-1}.

(76) (77)

Additionally, the Type B conformation (77) has an axial methyl substituent, which if likened to methylcyclohexane would be unfavoured by a further about 7.1 kJ mol^{-1}. Hence the Type B conformation would be less favoured to the extent of about 11.1 kJ mol^{-1}, assuming a simple addivity relationship for these two effects. The extent of the conformational equilibrium would therefore be expected to be 99.85% for Type A and 0.15% for Type B (calculated at -67 °C) which would explain why the n.m.r. spectra were not observed to be temperature dependent.

5. Octahydro-2-methyl-1,4-benzoxazine

The analysis of the ^{1}H n.m.r. spectra of the 6 and 7-methyl derivatives of octahydro-1,4-benzoxazine (previously discussed) showed that the introduction of a methyl group into the cyclohexane portion of the molecule had little effect on the degree of puckering in the oxazine ring, as measured by the dihedral angle along the C2-C3 bond. It was therefore of interest to see if distortion of the oxazine portion of the ring system would occur if the methyl group was introduced directly into this portion of the molecule.

The first example of this type to be investigated was the octahydro-2-methyl-1,4-benzoxazine system. The approach used to synthesize the isomers of this system was similar to that previously described for octahydro-1,4-benzoxazine (Fig. 6) with the exception that the sodium salt of bromoacetic acid was replaced by the sodium salt of 2-bromopropionic acid. Originally the sodium salt of 2-chloropropionic acid was used in the synthesis, but this was found to give only a low yield ($\sim$4%) of the required 2-(2'-nitrophenoxy)-propionic acid.

In order to try and produce an isomeric mixture containing reasonable quantities of all four isomers of octahydro-2-methyl--1-4-benzoxazine, a number of different reaction conditions were investigated for the catalytic hydrogenation of the aromatic precursor, 2H-3,4-dihydro-2-methyl-1,4-benzoxazine. An investigation, by ^{13}C n.m.r. spectroscopy, of the isomeric ratios in these hydrogenation products gave some interesting results. For example, with cyclohexane as the solvent and 10% palladium on charcoal as catalyst, it was found that the isomeric ratio in the product depended not only on the temperature but also on the period of the hydrogenation.

For instance, if the hydrogenation was carried out at 50 atmospheres pressure and 158 °C for 9.5 hours the observed isomeric ratio was 32:5:51:12 (for Components A,B,C and D respectively), whereas in a similar reduction lasting 17 hours the ratio was 24:6:56:14. This was shown to be due to equilibration of the isomeric mixture following reduction. Fortunately the use of water as the hydrogenation solvent allowed the reduction of the aromatic system to be achieved under milder conditions where equilibration could be largely avoided. This approach consistently gave an isomeric ratio of 44:6:44:6 (for Components A,B,C and D respectively).

Interestingly, the isomeric ratio was also changed if the hydrochloride of 2H-3,4-dihydro-2-methyl-1,4-benzoxazine in water was hydrogenated rather than the free base in water, an effect which has also been reported in the synthesis of the decahydro-4-methyl-quinoline system[28]. Under these more acidic conditions the isomeric ratio produced was 67:3:23:7 (for Components A,B,C and D respectively). However, since this did not give a larger proportion of the minor isomers it offered no significant advantage over the method using the free base.

In order to try and obtain pure samples of each isomer a sample of the isomeric mixture produced by reduction of the free base (having an isomeric composition of 44:6:44:6 for Components A,B,C and D respectively) was investigated by thin layer and gas liquid chromatography. Unfortunately, in both cases, only three separate components could be observed, indicating that two of the isomers had similar retention times. Medium pressure chromatography was therefore used to give a large number of fractions in the hope that some might contain pure samples of the desired isomers. Analysis

of these fractions by ^{1}H and ^{13}C n.m.r. spectroscopy enabled pure samples of three of the isomers (Components A,C and D) to be identified but there was considerable contamination of those fractions containing Component B by either Component A or C. For this reason, it was necessary to combine those fractions containing significant quantities of Component B and to then subject this material to a second chromatographic separation. A number of fractions from this second run, although still contaminated with Components A and C, were sufficiently enriched to enable the stereochemistry of Component B to be studied by ^{1}H and ^{13}C n.m.r. spectroscopy. The four isomers are now discussed in order of their elution from the chromatography column.

A. Sterochemical Aspects

(i) Component A (cis-(9H,10H)-trans-(2H,9H)-Octahydro--2-methyl-1,4-benzoxazine).

Component A exhibited a temperature dependent ^{13}C n.m.r. spectrum such that at -28 °C a significant amount of line broadening was observed, indicating the presence of an exchange process. In view of the results from the systems previously discussed this exchange process was interpreted as being indicative of a cis-fused isomer. Although this exchange process could be "frozen out" by cooling the sample to -62 °C, the ^{13}C n.m.r. spectrum under these conditions showed signals for only one conformation indicating that the position of the conformation equilibrium (Type A $\rightleftharpoons$ Type B) was relatively extreme. In view of the temperature dependent nature of the ^{13}C n.m.r. spectrum of Component A, the 400 MHz ^{1}H n.m.r. spectrum was also investigated at a variety of temperatures. However, no significant differences were observed between the ^{1}H

n.m.r. spectrum obtained at -60 °C and that obtained at room temperature. Although there was a significant loss of resolution in the lower temperature spectrum, only slight changes in chemical shifts were apparent and no signals associated with a minor conformation could be observed. In view of this, the data from the better resolved room temperature spectrum was taken as being representative of the major conformation of Component A.

At room temperature the 400 MHz ^{1}H n.m.r. spectrum (Plate 17, Table 35) of Component A showed the five resonances due to the protons near to the heteroatoms quite clearly. These signals were readily assigned by comparison with other methyl analogues (Fig. 7). In particular the resonances at 3.69 and 3.06 p.p.m. were assigned to the H9 and H10 bridgehead protons respectively, their multiplicities clearly indicating that Component A was a cis-fused isomer in a Type B conformation.

The orientation of the methyl group was determined by a consideration of the multiplicities of those protons on C2 and C3. For example, the presence of two large couplings in the H3a resonance clearly indicated the presence of a $^{3}J_{aa}$ vicinal coupling which in turn implied that the methyl group on C2 was equatorially disposed. Component A was therefore shown to be cis-(9H,10H)-trans-(2H,9H)--octahydro-2-methyl-1,4-benzoxazine.

At higher field in the ^{1}H n.m.r. spectrum (2.21 p.p.m.) the distinct quartet of doublets characteristic of the H8a resonance was observed, but apart from the methyl doublet at 1.07 p.p.m. only three further signals could be assigned. Irradiation of the multiplet with quartet of triplet character at 1.23 p.p.m. resulted in the loss of one large coupling in the H8a resonance and hence the irradiated

Plate 17

The 400 MHz ^{1}H N.M.R. Spectrum of cis-(9H,10H)-trans-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine

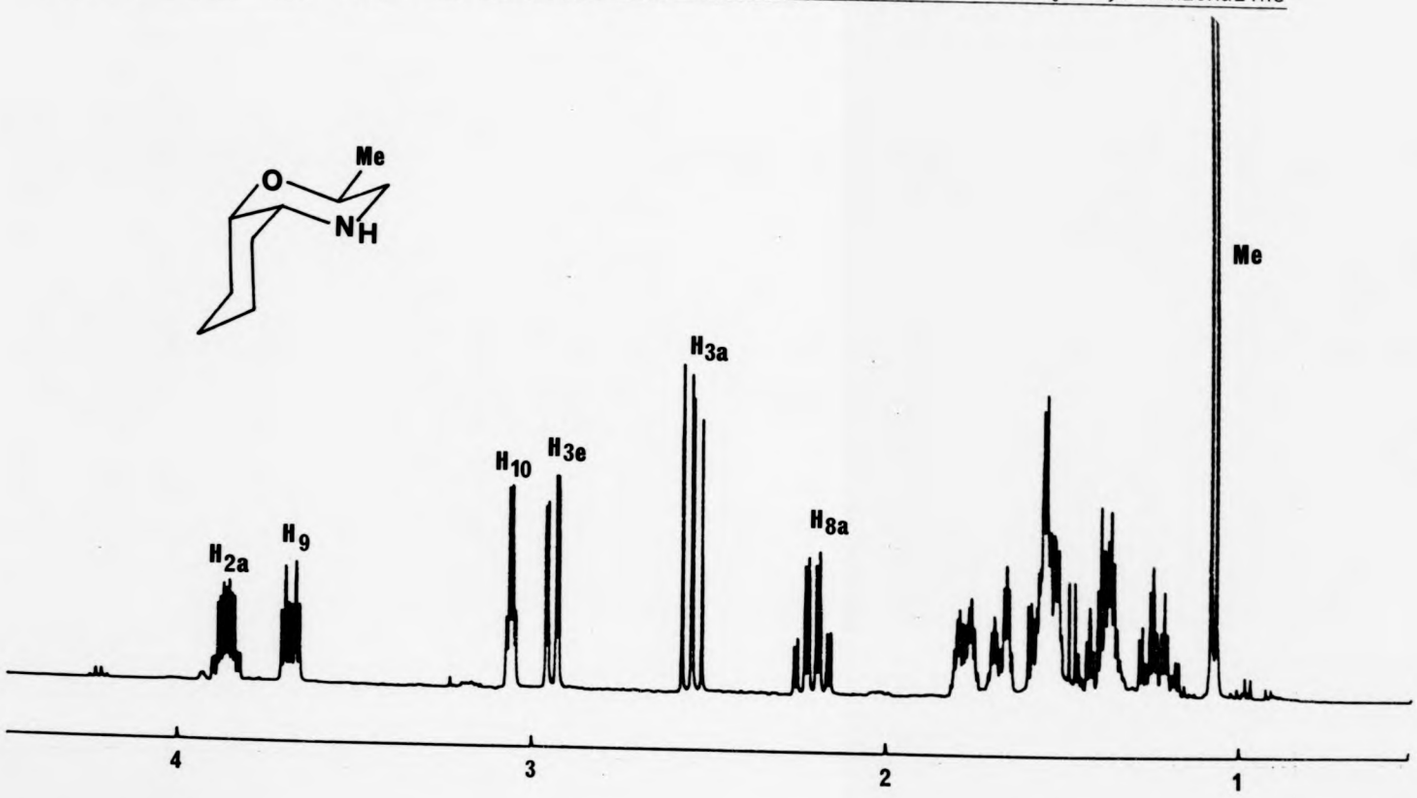
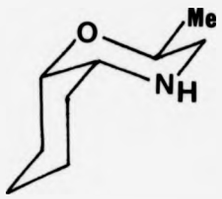


Table 35

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-trans-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Conformation

Type B

Proton (400 MHz Spectrum)*	Shift(δ)	Description of Resonance
2a	3.87	Symmetrical multiplet (band width ∿ 34 Hz).
9	3.69	Multiplet (band width ∿ 24 Hz) with doublet of triplet character.
10	3.06	Narrow multiplet (band width ∿ 15 Hz) with quartet character.
3e	2.94	Doublet of doublets ($J_{3e,3a}$ = 12.1 Hz; $J_{3e,2a}$ = 2.7 Hz).
3a	2.55	Doublet of doublets ($J_{3a,3e}$ = 12.0 Hz; $J_{3a,2a}$ = 10.0 Hz).
8a	2.21	Quartet of doubets ($J_{8a,8e} \sim J_{8a,7a} \sim J_{8a,9}$ = 12.4 Hz; $J_{8a,7e}$ = 3.8 Hz).
7e	1.78	Multiplet (band width ∿ 32 Hz) with doublet character.
5e	1.68	Multiplet (band width ∿ 31 Hz) with doublet character.
6e, 8e 5a, 6a, NH	∿1.33-1.60	Complex envelope of overlapping resonances.
7a	1.23	Multiplet (band width ∿ 47 Hz) with quartet of triplet character.
Me	1.07	Doublet ($J_{Me,2a}$ = 6.2 Hz).

*$CDCl_3$ Solvent at 25 °C.

resonance was assigned to the H7a proton. The irradiation of the H7a resonance also caused the multiplet at 1.78 p.p.m. to simplify due to the loss of its only large coupling and this was therefore assigned as the H7e resonance. In contrast, the multiplet with doublet character at 1.68 p.p.m. was unaffected by irradiation of H7a and it was therefore assigned to the H5e proton. The remaining resonances appeared as a complex envelope of overlapping signals and could not be identified further.

The ^{13}C n.m.r. spectral data observed for Component A compared well with the shifts predicted for cis-(9H,10H)-trans-(9H,10H)--octahydro-2-methyl-1,4-benzoxazine in its Type B conformation (Table 36) and provided further support for the assignment. These predicted shifts were based on either the values calculated for the Type B conformation of cis-octahydro-1,4-benzoxazine or, where possible, those observed experimentally (Table 16). The values for the parent ring system were then modified to allow for the effects of methyl substitution[67] (Table 37).

As previously mentioned, the low temperature ^{13}C n.m.r. spectrum of Component A did not reveal any signals associated with a minor conformation indicating that the position of the conformational equilibrium (78 ⇌ 79) was extreme in favour of (78).

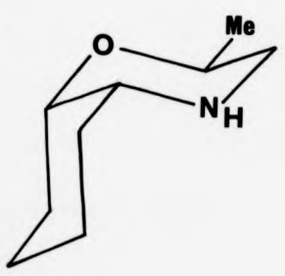
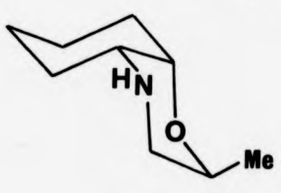
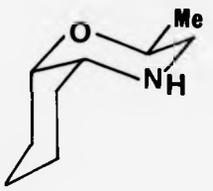
(78)  ⇌  (79)

Table 36

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-trans-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Conformation

Type B

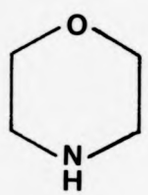
Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	65.2	D	64.10	D
3	52.6	T	53.38	T
5	31.5	T	31.02	T
6	21.6	T	19.76	T
7	22.0	T	23.88	T
8	23.2	T	24.69	T
9	73.9	D	74.20	D
10	54.0	D	52.97	D
Me	-	Q	19.23	Q

*Calculations based on the experimental values, where possible, or the calculated values for the Type B conformation of cis--octahydro-1,4-benzoxazine with modifications for the effect of the methyl substituent (see Tables 16 and 37).

†Experimental values from sample in $CDCl_3$ + $CFCl_3$ (50:50) at -62 °C.

Table 37

The Effect of Methyl Substitution on the ^{13}C n.m.r. Chemical Shifts of Morpholine[67].



Substituent	Effect of substitution*/p.p.m.					
	α_e	α_a	β_e	β_a	γ_e	γ_a
C(2) - CH_3	5.1	-2.3	5.5	3.7	-	-5.9
C(3) - CH_3	4.4	1.5	6.8	3.5	-	-6.0

A positive value for the above effects represents a shift to lower field.

*The subscripts 'a' and 'e' refer to axial and equatorial methyl substitution respectively.

If the relative stabilities of the Type A and Type B conformations of Component A are considered it can be seen that there are two competing factors. Firstly, we know from our studies of cis-octahydro-1,4-benzoxazine that the Type A conformation is favoured by about 4.0 kJ mol^{-1} relative to the Type B conformation. On the other hand, we might expect, from a consideration of the 3-methylpiperidine system[20], that the equatorially disposed methyl group in (78) would be preferred by about 6.3 kJ mol^{-1} over the axially orientated one in (79). If we assume these two effects are additive we would predict a free energy difference between (78) and (79) of about 2.3 kJ mol^{-1} in favour of (78), which would correspond to a conformational ratio of 79:21 at -67 °C. The observed conformational free energy difference of at least 6.0 kJ mol^{-1} (calculated for a ratio of 97:3 at -65 °C) was, therefore, larger than expected. This implies that either the $-\Delta G°$ value for the C2 methyl group is much larger (at least about 10 kJ mol^{-1}) than that observed in 3-methylpiperidine or the assumption that one can use a simple additivity relationship to predict the conformational free energy difference between (78) and (79) is not valid.

The increase in the preference for (78) may be a consequence of increased ring puckering in the vicinity of the oxygen causing (79) to be less favoured due to the increase in the diaxial repulsion between the C2 methyl group and the H9 proton. A similar explanation has been used for the analogous nitrogen system, cis-(9H,10H)-trans--(2H,9H)-decahydro-2-methylquinoline[68], where a similar unexpectedly extreme conformational equilibrium was also observed.

As previously mentioned, it was also of interest to see if the introduction of a methyl group on the C2 position would cause

any significant distortion of the oxazine portion of the ring system. Unfortunately, it is not possible to use the R-value method[33] for the isomers of octahydro-2-methyl-1,4-benzoxazine since not all the required vicinal couplings can be obtained. However, the available data can be used to obtain an indication of whether or not a methyl group at C2 is producing significant distortion.

Thus, for example, T.P. Forrest[69] has shown that it is possible to estimate the dihedral angle along the C2-C3 bond in systems containing an oxazine ring by using equations (6), (7) and (8).

$$(6) \quad J = (4.1 + 0.63\Sigma\Delta X)(1 - 0.462\Delta X_1)(1 - 0.462\Delta X_2)$$

Where J = the expected value of a vicinal coupling constant with a dihedral angle of 60°.

ΔX = the electronegativity difference between the substituent and hydrogen.

$\Delta\Sigma X$ = the sum of the ΔX values for all substituents on the ethane framework.

ΔX_1 and ΔX_2 = the ΔX values for the two substituents antiperiplanar to the coupled protons.

In this approach the calculated 60° vicinal coupling constant (J) obtained from equation (6) is compared with the observed coupling constant and the difference taken to indicate a divergence of the dihedral angle from the normal 60° angle. Using electronegativity parameters previously reported by Huggins,[70] Forrest used equation (6) to calculate the expected value of $^3J_{a,e}$. He then used this value in equation (7) to determine the value of the constant A.

(7) $J_{calc'd} = A\cos^2 60 - 0.3$

The calculated value of the constant A was then used in equation (8) together with the observed vicinal coupling constant to calculate a value for the dihedral angle θ.

(8) $\cos\theta = [(J_{obs'd} + 0.3)/A]^{\frac{1}{2}}$

Thus, for example, in morpholine itself Forrest was able to calculate the dihedral angle along C2-C3 using the average $^3J_{a,e}$ vicinal coupling as being 58°, the same value as that determined by the R-value approach. In addition he was able to calculate the dihedral angle along the C2-C3 bond in a N-methyl substituted morpholine system with an axial methyl group on C3 as being 55°.

Although caution should be exercised when using vicinal coupling data to assess dihedral angles it is interesting to note that if Forrest's approach is applied to cis-(9H,10H)-trans--(2H,9H)-octahydro-2-methyl-1,4-benzoxazine the vicinal coupling $J_{2a,3e}$ = 2.7 Hz ± 0.2 Hz gives a dihedral angle of 57.4° ± 1.2°. This value is in close agreement with the average value of 58.5° (obtained via the R-value method) for cis-octahydro-1,4-benzoxazine which is not unreasonable since we would not expect the presence of the equatorial methyl group on C2 in Component A to result in a significant distortion of the ring system.

(ii) Component B (trans-(9H,10H)-trans-(2H,9H)-Octahydro-2--methyl-1,4-benzoxazine.

As previously mentioned, this component could only be obtained in an enriched form. Nevertheless, sufficient spectroscopic data could be obtained from this enriched sample for its identity to be deduced and its stereochemistry studied.

The interpretation of the 400 MHz ^{1}H n.m.r. spectrum (Table 38) of Component B was complicated by the presence of signals from isomeric impurities (Components A and C). However, several signals from Component B could be distinguished, especially those arising from the protons near to the heteroatoms. The signals at 3.21 and 2.72 p.p.m. were readily assigned to the H3a and H3e resonances respectively, in view of their multiplicities and by comparison with other methyl analogues (Fig. 9). Furthermore the absence of a large coupling in the H3a signal from a H2a proton indicated that the axial position on C2 was occupied by the methyl substituent. Hence, the complex multiplet at 4.02 p.p.m. was therefore assigned as the H2e resonance. The two remaining lower field resonances, those at 3.33 and 2.34 p.p.m. were assigned as the H9 and H10 bridgehead resonance by comparison with similar analogues, their multiplicites clearly indicating that Component B had a trans-fused ring junction. Component B was therefore identified as trans-(9H,10H)-trans-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine. No other resonances from Component B could be identified at higher field, apart from the methyl doublet at 1.38 p.p.m., due to the presence of the signals from the isomeric impurities.

The calculated ^{13}C n.m.r. spectral data for trans-(9H,10H)-trans-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine compared well with the experimentally observed values for Component B (Table 39) and provided further support for the assignment. It is interesting to note that the effect of an axial methyl substituent on a α-carbon has been reported[67] to result in a shift of 6.0 p.p.m. to higher field. In accord with this observation, an upfield shift of 7.91 p.p.m. was observed for the C9 position in Component B, relative to that observed in trans-octahydro-

Table 38

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-trans-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine

Proton (400 MHz Spectrum)*	Shift(δ)	Description of Resonance
2e	4.02	Symmetrical multiplet (band width ∿ 28Hz) with quartet of doublet character.
9	3.33	Multiplet (band width ∿ 26 Hz) with doublet of doublet of doublet character.
3a	3.21	Doublet of doublets ($J_{3a,3e}$ = 12.1 Hz; $J_{3a,2e}$ = 4.3 Hz)
3e	2.72	Doublet of doublets ($J_{3e,3a}$ = 12.1 Hz; $J_{3e,2e}$ = 0.8 Hz).
10	2.34	Multiplet (band width ∿ 26 Hz) with doublet of doublet of doublet character.
Remaining Protons	∿ 1.15-1.80	Complex envelope of overlapping resonances.
Me	1.38	Doublet ($J_{Me,2e}$ = 6.8 Hz).

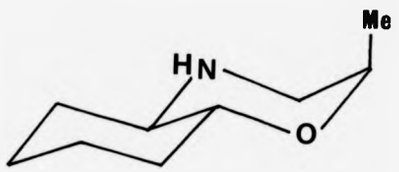
*$CDCl_3$ Solvent at 25 °C.

This spectrum was complicated by the presence of isomeric impurities (Components A and C) which limited the amount of data which could be obtained.

Table 39

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-trans-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	65.6	D	68.72	D
3	50.4	T	50.22	T
5	30.9	T	31.19	T
6	24.6	T	24.83	T
7	24.6	T	24.75	T
8	31.5	T	31.48	T
9	75.3	D	73.28	D
10	60.3	D	61.11	D
Me	-	Q	16.12	Q

*Calculated values based on the experimental values from trans-octahydro-1,4-benzoxazine (Table 9) with modifications for the effect of methyl substitution (Table 37).

†$CDCl_3$ Solvent at 25 °C.

-1,4-benzoxazine.

If the approach of Forrest[69], previously applied to Component A, is used to determine the dihedral angle along C2-C3 in Component B, two vicinal couplings are available for the calculations. The vicinal coupling $J_{2e,3a}$ = 4.3 Hz ± 0.2 Hz gives a value of 52.7° ± 1.0°, while the vicinal coupling $J_{2e,3e}$ = 0.8 Hz ± 0.2 Hz gives a value of 53.7° ± 2.3°. These values are in good agreement and indicate that the presence of an axial methyl group on C2 in trans-(9H,10H)-trans-(2H,9H)-octahydro-2-methyl--1,4-benzoxazine is resulting in some distortion of the oxazine ring relative to the unsubstituted parent system.

It is interesting to note that Forrest also found that the presence of an axial methyl group at C3 on a morpholine ring significantly reduced the dihedral angle along C2-C3[69]. However, when dealing with distorted systems it is important to realise that equation (6) implies that the constant (0.462) is independent of the dihedral angle (120 + θ) between the "coupled proton" and the substituent antiperiplanar to it. Theoretical considerations would suggest that this is unlikely. However, when Forrest attempted to allow for expected angular dependence by assuming a $\cos^2$ relationship between the constant for the substituent effect (0.462) and the dihedral angle (120 + θ) he found that the effect on the calculated dihedral angle θ was only small. Thus, for a dihedral angle of θ = 50° he found the likely error incurred by assuming equation (6) to be valid was only about 0.3°.

(iii) Component C (trans-(9H,10H)-cis-(2H,9H)-Octahydro-2--methyl-1,4-benzoxazine).

The lower field region of the 400 MHz ^{1}H n.m.r. spectrum of Component C (Plate 18, Table 40) was readily interpreted from a

Plate 18

The 400 MHz ^{1}H N.M.R. Spectrum of trans-(9H,10H)-cis-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine

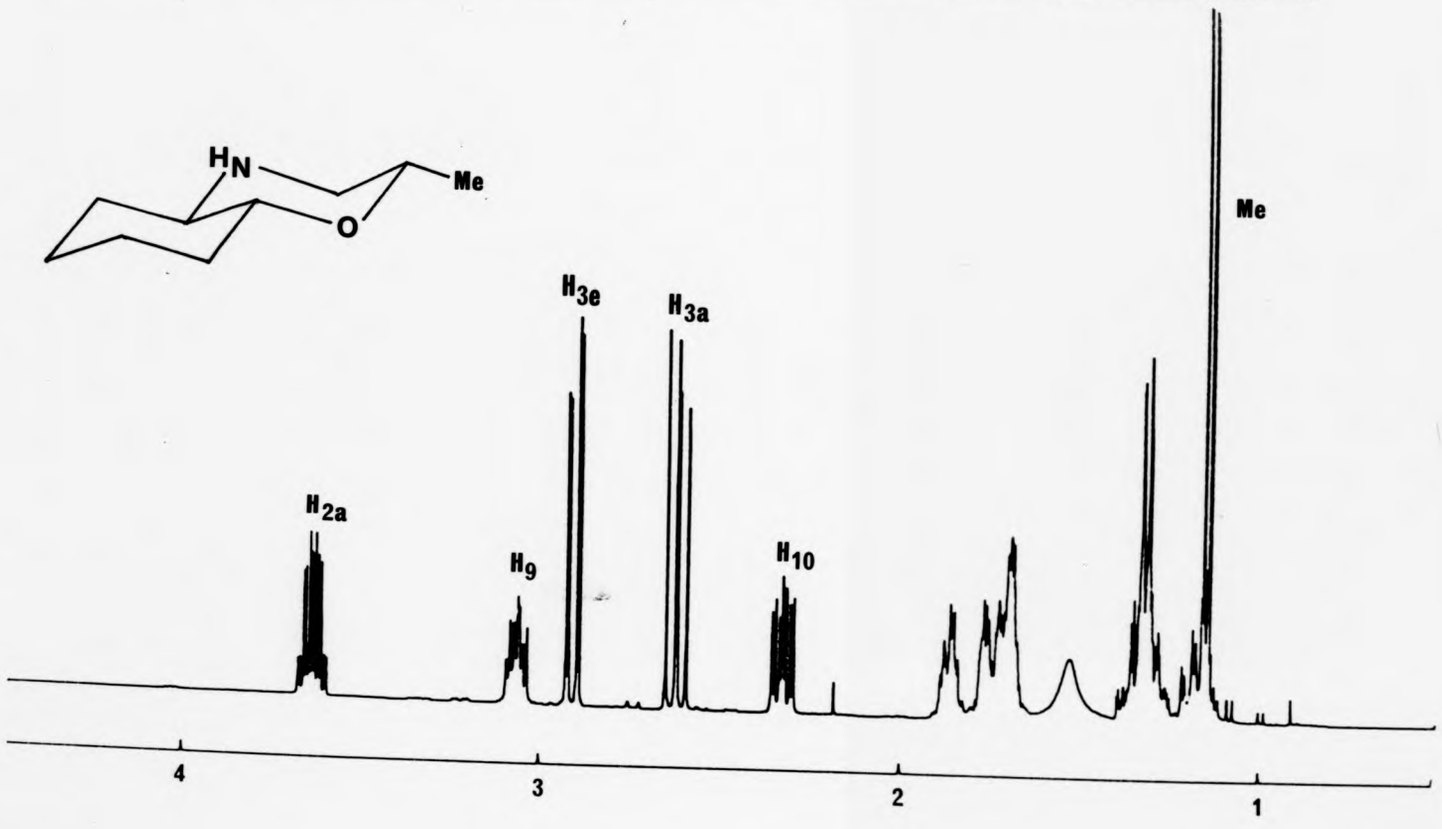
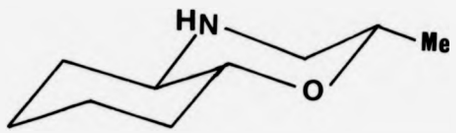


Table 40

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-cis-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2a	3.63	Multiplet (band width ∿ 33 Hz) with doublet of quartet of doublet character.
9	3.06	Poorly resolved multiplet (band width ∿ 27 Hz) with doublet of doublet of doublet character.
3e	2.90	Doublet of doublets ($J_{3e,3a}$ = 12.1 Hz; $J_{3e,2a}$ = 2.5 Hz).
3a	2.61	Doublet of doublets ($J_{3a,3e}$ = 12.2 Hz; $J_{3a,2a}$ = 10.2 Hz).
10	2.31	Multiplet (band width ∿ 27 Hz) with doublet of doublet of doublet character.
8e	1.85	Multiplet (band width ∿ 23 Hz).
5e, 6e, 7e	∿1.65-1.79	Complex envelope of overlapping resonances.
N-H	1.53	Broad singlet.
6a, 7a, 8a	∿1.24-1.39	Complex envelope of overlapping resonances.
5a	1.16	Multiplet (band width ∿ 42 Hz) with quartet of doublet character.
Me	1.14	Doublet ($J_{Me,2a}$ = 6.2 Hz).

*$CDCl_3$ Solvent at 25 °C.

consideration of the multiplicities of the resonances and a knowledge of the shifts found for protons in similar systems (Fig. 8). In this way the signals at 2.90 and 2.61 p.p.m. were assigned to the H3e and H3a protons respectively. The presence of two large couplings in the resonance of the H3a proton showed clearly the presence of an axial proton on C2 which in turn indicated that the C2 methyl group was equatorially disposed. This also implied that the complex multiplet at 3.63 p.p.m., showing coupling to the methyl doublet, was due to the H2a proton. The two remaining lower field resonances at 3.06 and 2.31 p.p.m. compared well, both in terms of their chemical shifts and multiplicities, with those observed for the H9 and H10 bridgehead protons in trans-octahydro-1,4-benzoxazine. Hence, it was concluded that Component C had a trans-fused ring junction. From the above data Component C was therefore identified as trans-(9H,10H)-cis-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine.

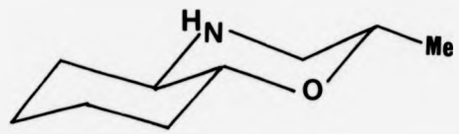
At higher field the resonances at 1.85 and ∿1.16 p.p.m. were assigned to the H8e and H5a protons respectively by comparison with similar systems (Fig. 8), but apart from these only the distinct doublet at 1.14 p.p.m., due to the methyl substituent, could be assigned unambiguously. The remaining resonances, those due to the equatorially disposed protons (H5e, H6e and H7e) and the axially orientated protons (H6a, H7a and H8a) could only be assigned to the two complex envelopes of overlapping resonances at ∿1.65 - 1.79 p.p.m. and ∿1.24 - 1.39 p.p.m. respectively.

In support of the assignment of Component C the experimentally observed ^{13}C n.m.r. data was found to be in good agreement with the calculated values (Table 41) for trans-(9H,10H)-cis-(2H,9H)--octahydro-2-methyl-1,4-benzoxazine.

Table 41

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-cis- (2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	73.0	D	72.95	D
3	52.2	T	53.14	T
5	30.9	T	30.98	T
6	24.6	T	24.62	T
7	24.6	T	24.62	T
8	31.5	T	31.39	T
9	81.2	D	81.17	D
10	60.3	D	59.46	D
Me	-	Q	19.06	Q

*Calculations based on the experimental values from trans-octahydro-1,4-benzoxazine (Table 9) with modifications for the effect of methyl substitution (Table 37).

†$CDCl_3$ Solvent at 25 °C.

Once again the degree of distortion in the oxazine portion of the molecule was assessed by a consideration of the values of the $^{3}J_{2a,3e}$ proton vicinal coupling constant. Although no signification distortion would be expected in trans-(9H,10H)-cis--(2H,9H)-octahydro-2-methyl-1,4-benzoxazine relative to trans--octahydro-1,4-benzoxazine the methyl substituted system gives an ideal opportunity to check the validity of Forrest's approach. It is therefore interesting to note that the value of $^{3}J_{2a,3e}$ (2.5 Hz ± 0.2 Hz) corresponds to a dihedral angle along C2-C3 of 58.7° ± 1.3°, in excellent agreement with that calculated for the parent system using the R-value method. This therefore gives further support for the use of Forrest's approach in these systems.

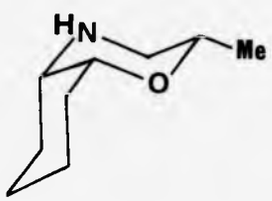
(iv) Component D (cis-(9H,10H)-cis-(2H,9H)-Octahydro-2-methyl--1,4-benzoxazine).

Component D was the most retentive of the 2-methyl isomers on the medium pressure chromatography column. Examination of its 400 MHz ^{1}H n.m.r. spectrum (Table 42) revealed two resonances at 2.73 and 2.56 p.p.m. which, in view of their multiplicities and chemical shifts (see Fig. 10), were assigned to the H3a and H3e resonances respectively. The presence of two large couplings to the H3a proton (i.e. $^{3}J_{aa} + {}^{2}J_{gem}$) indicated that the methyl group on C2 was equatorially orientated and hence the complex multiplet at 3.59 p.p.m. was assigned as the H2a resonance. The resonances at 3.75 and 2.62 p.p.m. which were readily assigned to the H9 and H10 ring junction protons compared well with those observed for the Type A conformation of cis-octahydro-1,4-benzoxazine. The ^{1}H n.m.r. spectrum of Component D was therefore consistent with a cis-fused isomer in a Type A conformation having an equatorially

Table 42

^{1}H n.m.r. Spectra Data

cis-(9H,10H)-cis-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Conformation Type A

Proton (400 MHz Spectrum)*	Shift(δ)	Description of Resonance
9	3.75	Broad singlet (half-band width = 6 Hz) showing further small couplings.
2a	3.59	Complex multiplet (band width ∿ 34 Hz) with doublet of quartet of doublet character.
3a	2.73	Multiplet with doublet of doublet character ($J_{3a,3e}$ = 12.5 Hz; $J_{3a,2a}$ = 10.5 Hz).
10	2.62	Multiplet (band width ∿ 24 Hz) with doublet of doublet of doublet character.
3e	2.56	Multiplet with doublet of doublet character ($J_{3e,3a}$ = 12.6 Hz; $J_{3e,2a}$ = 2.8 Hz).
5a	2.08	Multiplet with quartet of doublet character ($J_{5a,5e} \sim J_{5a,6a} \sim J_{5a,10} \sim$ 12.6 Hz; $J_{5a,6e} \sim$ 12.6 Hz; $J_{5a,6e}$ = 3.8 Hz).
N-H	1.97	Broad singlet.
8e	1.87	Multiplet (band width ∿ 24 Hz).
6e	1.77	Multiplet (band width ∿ 29 Hz) with doublet character.
7e,5e,8a,7a	1.31-1.51	Complex envelope of overlapping resonances.

/Table continued over ...

Table 42 - continued

Proton	Shift(δ)	Description of Resonance
6a	1.24	Multiplet (band width $\sim$ 51 Hz) with quartet of triplet character.
Me	1.14	Doublet ($J_{Me,2a}$ = 6.2 Hz)

*$CDCl_3$ Solvent at 25 °C.

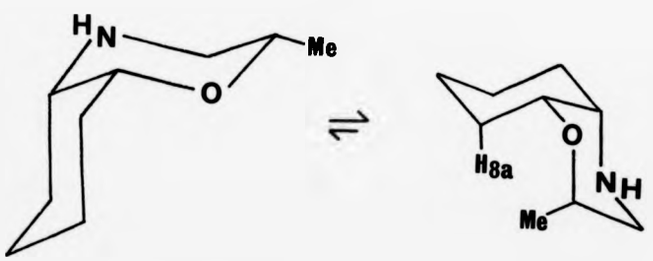
disposed methyl group on C2. Consequently, Component D was assigned as cis-(9H,10H)-cis-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine. It is interesting to note that only the chemical shift of the H3a resonance was appreciably affected by the presence of the methyl group, this being shifted upfield by 0.40 p.p.m. relative to that observed in the Type A conformation of cis-octahydro-1,4-benzoxazine. Similar effects were also observed for the H3a resonances in Components A and C which were also shifted upfield by similar amounts (0.49 and 0.42 p.p.m. respectively) relative to the corresponding parent isomers.

The assignment of the higher field resonances was aided by irradiation of the multiplet with quartet of triplet character at 1.24 p.p.m. As a result of this irradiation the quartet of doublets at 2.08 p.p.m., observed to be characteristic of the H5a resonance for Type A conformations, was partially simplified due to the loss of a large coupling. The irradiated signal was, therefore, assigned as the H6a resonance. Effects of the irradiation of H6a were also observed on the doublet type resonance at 1.77 p.p.m. which lost its only large coupling, identifying it as the H6e resonance. The doublet type signal at 1.87 p.p.m. was unaffected by the irradiation of H6a and was therefore attributed to the H8e resonance. Apart from the distinct methyl doublet at 1.14 p.p.m. the remaining signals (H7e, H5e, H8a and H7a) were observed only as a complex envelope of overlapping resonances.

Once again the value (2.8 Hz ± 0.2 Hz) of the vicinal coupling constant $^{3}J_{2a,3e}$ could be used to estimate the extent of distortion in the oxazine portion of the ring system. The value of 56.8° ± 1.2° obtained for the dihedral angle along C2-C3, as

expected, is not dissimilar to that observed for the other cis-fused isomer (Component A). The results for Components A, C and D therefore suggest that the presence of an equatorially disposed methyl group at C2 produces no significant distortion of the ring system.

The experimentally obtained ^{13}C n.m.r. spectral data compared well with the calculated values (Table 43) for cis-(9H,10H)-cis--(2H,9H)-octahydro-2-methyl-1,4-benzoxazine and provided further support for the assignment of Component D. It is interesting to note that the ^{13}C n.m.r. spectrum of Component D was not observed to be temperature dependent, even though this component was identified as a cis-fused isomer which could potentially adopt two different twin-chair conformations (80 and 81). This lack of temperature dependence implied that the position of the conformational equilibrium was extreme. If the relative free energies of (80) and (81) are considered this is not too surprising.

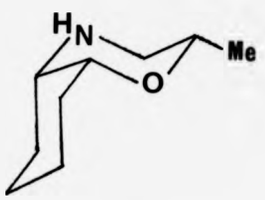


(80) (81)

Table 43

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-cis-(2H,9H)-Octahydro-2-methyl-1,4-benzoxazine



Conformation

Type A

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	73.7	D	73.53	D
3	44.8	T	46.10	T
5	25.0	T	25.28	T
6	24.8	T	25.15	T
7	19.8	T	19.99	T
8	31.4	T	31.60	T
9	74.8	D	74.83	D
10	52.7	D	52.17	D
Me	-	Q	19.21	Q

*Calculations based on the experimental values from the Type A conformation of cis-octahydro-1,4-benzoxazine (Table 15) with modifications for the effect of methyl substitution (Table 37).

†$CDCl_3$ Solvent at 25 °C.

In (81) not only do we have the ring system in its less favoured Type B conformation and an axially orientated methyl group but we also have an unfavourable interaction between the methyl group and H8a. If we assume that the $-\Delta G°$ value for the methyl substituent is similar to that reported for 3-methylpiperidine[20] (6.3 kJ mol^{-1}) and that the Type A conformation of the ring system is favoured by about 4.0 kJ mol^{-1} then, from a consideration of these two factors alone, we would predict a conformational free energy difference of about 10.3 kJ mol^{-1} in favour of the Type A conformation. The inclusion of the unfavourable interaction between the methyl group and H8a in (81) in these calculations would increase the conformational free energy difference significantly and hence we would expect to observe a ratio greater than the 99.8:0.2 calculated (at -67 °C) assuming a free energy difference of only 10.3 kJ mol^{-1}. The extreme position of the conformational equilibrium observed is therefore consistent with that predicted and explains why the ^{13}C n.m.r. spectrum was temperature independent over the temperature range studied.

6. Octahydro-3-methyl-1,4-benzoxazine

The octahydro-3-methyl-1,4-benzoxazine system was also examined in order to assess the effect of introducing a methyl substituent into the oxazine portion of the ring system. It was also of interest to investigate the effect of a C3 methyl substituent on the position of the conformational equilibrium (Type A $\rightleftharpoons$ Type B) in the cis-fused isomers of octahydro-3-methyl-1,4-benzoxazine.

The approach used for the synthesis of the octahydro-3-methyl--1,4-benzoxazine isomers, as with those isomers of the other methyl substituted systems previously discussed, involved the catalytic hydrogenation of the appropriate aromatic precursor. However, unlike those previously discussed, the aromatic precursor for the 3-methyl system, 2H-3,4-dihydro-3-methyl-1,4-benzoxazine, could not be prepared by the route indicated in Fig. 6. Instead, this material was prepared via the synthesis of 2-nitrophenoxypropanone by the reaction of the sodium salt of 2-nitrophenol with chloropropanone, as indicated in the method of R. Stoermer and H. Brockerhof[71]. Catalytic hydrogenation of 2-nitrophenoxypropanone at room temperature and pressure was then found to produce the desired aromatic system directly. Distillation of the crude hydrogenation product gave 2H-3,4-dihydro-3-methyl-1,4--benzoxazine as a viscous oil and left a dark coloured polymeric residue.

Catalytic hydrogenation of 2H-3,4-dihydro-3-methyl-1,4-benzoxazine, using a palladium catalyst at high pressure and temperature, produced a mixture of the four possible isomers of octahydro-3-methyl--1,4-benzoxazine, the isomeric ratio depending on the reaction conditions and the choice of solvent. The variation in the isomeric

ratio was later shown to be due to equilibration, since application of high temperature and pressure hydrogenation conditions to a sample composed of equal quantities of Components A and C was observed to cause equilibration giving a sample containing 82% of Component C and 6% each of Components A, B and D. Fortunately, as with the 2-methyl analogue previously discussed, the use of water as the solvent rather than cyclohexane allowed less vigorous hydrogenation conditions to be applied and consistently gave samples with an isomeric ratio of 42:46:7:5 for Components A, B, C and D. respectively.

It is interesting to note that the catalytic hydrogenation of the hydrochloride derivative of 2H-3,4-dihydro-3-methyl-1,4-benzoxazine in water gave a sample with an isomeric ratio of 62:26:6:6 for Components A, B, C and D respectively, similar to that observed for the 2-methyl analogue. The isomers are now discussed in order of their elution from the chromatography column.

A. Stereochemical Aspects

(i) Component A (cis-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl--1,4-benzoxazine)

This component gave ^{1}H and ^{13}C n.m.r. spectra (Table 44 and 45) that were observed to be temperature independent within the temperature range considered (25 °C to -70 °C). Thus, at -60 °C the 400 MHz ^{1}H n.m.r. spectrum did not differ significantly from that observed at room temperature. An examination of the chemical shifts of the lower field resonances, those associated with the protons near to the heteroatoms, showed similarities to those previously observed for the Type B conformation of cis-octahydro-1,4-benzoxazine and its

6-methyl and 7-methyl analogues (Fig. 7). Furthermore, the multiplicities of the resonances assigned to H9 and H10 clearly indicated that Component A was a cis-fused isomer in the Type B conformational arrangement.

The lack of any temperature dependence associated with ring inversion indicated that the position of the conformational equilibrium in Component A was extreme. Therefore the better resolved room temperature 400 MHz ^{1}H n.m.r. spectrum (Plate 19, Table 44) could be taken as being representative of the major conformation. Further analysis of the lower field resonances in the 400 MHz ^{1}H n.m.r. spectrum indicated the absence of couplings from an H3e proton, this being consistent with the presence of an equatorial methyl substituent on C2. Component A could therefore be assigned as cis-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1,4--benzoxazine. It is interesting to note that although in general the lower field resonances compared favourably with those in analogous systems (Fig. 7) the H2a resonance was 0.54 p.p.m. upfield of its position in the unsubstituted parent system. A similar effect was also observed on the axial resonance adjacent to the methyl substituent in the corresponding 2-methyl analogue where the H3a resonance was moved upfield by 0.49 p.p.m. relative to its shift in cis-octahydro-1,4-benzoxazine (Table 14).

The higher field resonances also compared favourably with the analogous systems (Fig. 7). This comparison together with the aid of a "decoupling" experiment enabled these higher field resonances to be assigned. Thus, irradiation of the multiplet resonating at 1.23 p.p.m. caused the loss of a large coupling to the H8a signal, previously identified as the characteristic quartet of doublets at

Plate 19

The 400 MHz ^{1}H N.M.R. Spectrum of cis-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine

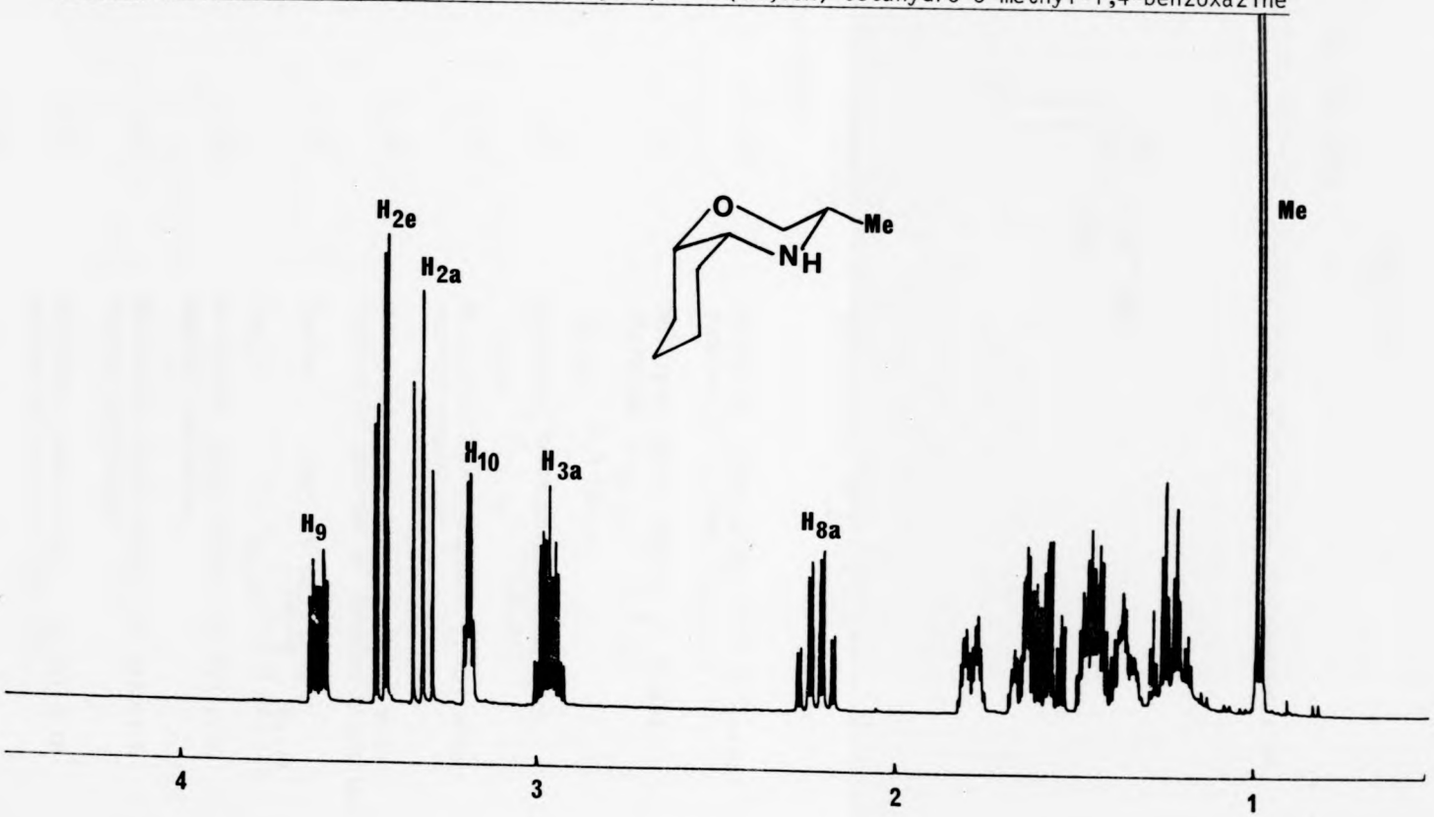
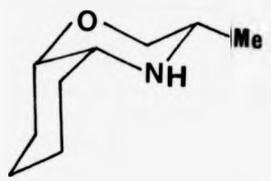


Table 44

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
9	3.61	Multiplet (band width ∿ 23 Hz) with doublet of triplet character.
2e	3.43	Multiplet with doublet of doublet character ($J_{2e,2a}$ = 11.1 Hz; $J_{2e,3a}$ = 3.6 Hz).
2a	3.36	Multiplet with triplet character ($J_{2a,2e} + J_{2a,3a}$ = 21.8 Hz).
10	3.19	Multiplet (band width ∿ 15 Hz) with quartet character.
3a	2.96	Multiplet (band width ∿ 34 Hz) with doublet of quartet of doublet character.
8a	2.22	Quartet of doublets ($J_{8a,8e} \sim J_{8a,7a} \sim J_{8a,9}$ ∿ 12.3 Hz; $J_{8a,7e}$ = 3.8 Hz).
7e	1.78	Multiplet (band width ∿ 30 Hz) with doublet character.
5e	1.65	Multiplet (band width ∿ 28 Hz) with doublet character.
5a	1.57	Multiplet (band width ∿ 35 Hz) with triplet of triplet character.
6a	1.43	Multiplet (band width ∿ 48 Hz) with quartet of triplet character.

/Table continued . . .

Table 44 continued

Proton	Shift(δ)	Description of Resonance
N-H		Obscured due to overlap with other resonances.
8e	$\sim$ 1.43	Obscured due to overlap with H6a.
6e	1.34	Poorly resolved multiplet (band width $\sim$ 28 Hz).
7a	1.23	Multiplet (band width $\sim$ 48 Hz) with quartet of triplet character.
Me	0.98	Doublet ($J_{Me,3a}$ = 6.4 Hz).

* $CDCl_3$ Solvent at 25 °C.

2.22 p.p.m.. The irradiated multiplet was therefore assigned as the H7a signal. Irradiation of H7a also caused a multiplet with doublet character at 1.78 p.p.m. to lose its only large coupling and this was therefore assigned as the H7e resonance. The signals at 1.57 and 1.65 p.p.m. with triplet of triplet and doublet character respectively were unaffected by the irradiation of the H7a resonance which indicated these to be the H5a and H5e resonances respectively. The irradiation experiment also affected the multiplet having quartet of triplet character at 1.43 p.p.m. by removing a large coupling indicating this to be the H6a resonance. The remaining resonances, those at 1.43 and 1.34 p.p.m. were assigned to H8e and H6e respectively. These two assignments were based on the observation that the signal at 1.34 p.p.m. was substantially distorted towards the adjacent H6a resonance indicating the presence of a mutual coupling. In comparison, the signal at 1.43 p.p.m. showed little distortion towards the H6a signal even though it was partially overlapping it. It was therefore assigned to the H8e resonance. The highest field resonance, a doublet at 0.98 p.p.m., was readily identified as the methyl signal.

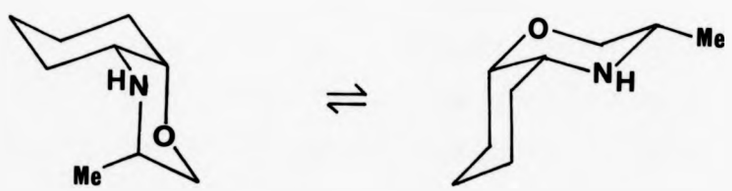
The analysis (see page 164) of the vicinal coupling constant $^{3}J_{2e,3a}$ (3.6 Hz ± 0.2 Hz) indicates that the dihedral angle along C2-C3 is 59.4° ± 0.9° for cis-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine. This is close to that observed in the unsubstituted parent system and is consistent with the observations from the octahydro-2-methyl-1,4-benzoxazine system that the presence of an equatorially disposed methyl group has little effect on the distortion in the oxazine portion of the molecule.

Since the ^{13}C n.m.r. spectra were also observed to be temperature independent down to a temperature of -62 °C, the room

temperature ^{13}C n.m.r. spectral data was therefore taken as being representative of the major conformation. The calculated ^{13}C n.m.r. spectral data for cis-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1,4--benzoxazine (Table 45) compared well with the experimentally observed values providing further support for the assignment of Component A.

As Component A has the potential to adopt both Type A and Type B conformations it is of interest to consider why the position of the conformational equilibrium is so extreme in this case, particularly since the ring system is adopting the usually less preferred Type B arrangement (86).

(85) (86)



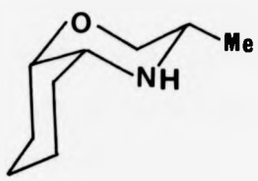
Conformation Type A Conformation Type B

From our study of the parent system, cis-octahydro-1,4-benzoxazine, we observed that the Type B conformation was about 4.0 kJ mol^{-1} less favourable than the Type A conformation. On the other hand, if this 3-methyl derivative is likened to 3-methyltetrahydropyran[16], the methyl group should favour an equatorial disposition to the extent of about 5.3 kJ mol^{-1}. In addition, however, it is important to note that the Type A conformation has a severe steric interaction between

Table 45

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	66.9	T	65.97	T
3	51.5	D	51.54	D
5	31.5	T	31.44	T
6	21.6	T	19.82	T
7	22.0	T	23.00	T
8	23.2	T	24.84	T
9	73.9	D	72.80	D
10	54.0	D	53.86	D
Me	-	Q	17.85	Q

* Calculations based on the experimental values, where possible, or calculated values for the Type B conformation of cis-octahydro-1,4-benzoaxazine (Table 16) with modifications for the effect of the methyl substituent (Table 18).

† Experimental values from sample in $CDCl_3$ + $CFCl_3$ (50:50) at -62 °C

the methyl substituent and the H5a proton which is absent in the Type B arrangement (86). Such an interaction would considerably increase the extent to which the Type B conformation is favoured. It is interesting to note that the position of the conformational equilibrium in this case is so extreme that not even line broadening was observed in the variable temperature ^{13}C n.m.r. spectra. This clearly shows the considerable impact of the steric interaction between the H5a proton and the methyl group in (85) on the preferred conformation of Component A.

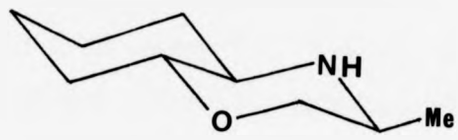
(ii) Component B (trans-(9H,10H)-cis-(3H,10H)-Octahydro-3--methyl-1,4-benzoxazine)

The lower field resonances in the 400 MHz ^{1}H n.m.r. spectrum (Table 46) of Component B were easily identified, unlike the higher field region which was more complex due to some overlapping of the resonances. The shifts of the lower field signals, those resonating between 2.44 and 3.79 p.p.m., compared favourably with those observed for trans-octahydro-1,4-benzoxazine (Fig. 8), the exceptions being the H2a resonance which resonated at higher field and the H3e resonance which was absent in Component B. The absence of the 3e proton was further confirmed by an appropriate simplification in the H2a and H2e resonances. This therefore implied the H3e position was occupied by the methyl substituent. Since this information implied a trans--fused system with an equatorial methyl group at C3, Component B was therefore assigned as trans-(9H,10H)-cis-(3H.10H)-octahydro-3-methyl--1,4-benzoxazine. It is interesting to note that the H2a resonance has moved upfield by 0.47 p.p.m., relative to trans-octahydro-1,4--benzoxazine, an effect similar to that observed in trans-(9H,10H)--cis-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine where the equatorial

Table 46

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.79	Doublet of doublets ($J_{2e,2a}$ = 11.0 Hz; $J_{2e,3a}$ = 3.1 Hz).
2a	3.17	Multiplet with triplet character ($J_{2a,2e} + J_{2a,3a}$ = 21.3 Hz).
3a	3.01	Multiplet (band width ∿ 32 Hz) with doublet of quartet of doublet character.
9	2.95	Poorly resolved multiplet (band width ∿ 26 Hz).
10	2.44	Multiplet (band width ∿ 27 Hz) with doublet of doublet of doublet character.
8e	1.86	Poorly resolved multiplet (band width ∿ 24 Hz).
6e	1.76	Poorly resolved multiplet (band width ∿ 23 Hz).
7e, 5e	1.65-1.72	Complex envelope of overlapping resonances.
N-H	1.56	Broad singlet.
5a,6a,7a,8a	1.17-1.35	Complex envelope of overlapping resonances.
Me	0.97	Doublet ($J_{Me,3a}$ = 6.4 Hz).

* $CDCl_3$ Solvent at 25 °C

methyl substituent was also observed to cause an upfield shift (0.42 p.p.m.) in the adjacent axial proton resonance.

Unfortunately, as previously mentioned, the higher field resonances, those associated with the cyclohexane portion of the molecule, were difficult to analyse and mostly appeared as a complex envelope of overlapping resonances. However, two multiplets, resonating at 1.86 and 1.76 p.p.m., associated with equatorially orientated protons could be assigned to the H8e and H6e protons respectively by comparison with similar systems (see Fig. 8). Similarly, the two overlapping resonances between 1.65 and 1.72 p.p.m. were assigned to the H7e and H5e protons. However, apart from the characteristic doublet of the methyl group at 0.97 p.p.m. the remaining signals, those due to the axially orientated protons (H5a, H6a, H7a amd H8a), could only be assigned to the complex envelope of signals between 1.17 and 1.35 p.p.m.

Comparison of the experimentally observed ^{13}C n.m.r. spectral data (Table 47) with the calculated values for trans-(9H,10H)-cis--(3H,10H)-octahydro-3-methyl-1,4-benzoxazine gave an excellent match and provided further evidence for the assignment of Component B.

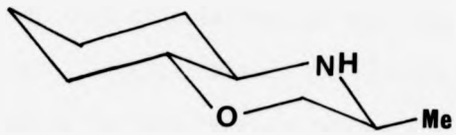
Analysis (see page 164) of the proton vicinal coupling, $J_{2e,3a}$ = 3.1 Hz ± 0.2 Hz, enabled the dihedral angle along C2-C3 to be calculated as 61.6° ± 0.9°. This value is slightly higher than might be anticipated since we would expect this system to be relatively undistorted and to have a dihedral angle close to the value of 58.5° observed for trans-octahydro-1,4-benzoxazine.

However, if the value of about 60.7° is accepted then this would imply that the equatorial methyl group at C3 is causing some

Table 47

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	74.7	T	73.76	T
3	51.1	D	50.81	D
5	30.9	T	30.64	T
6	24.6	T	24.59	T
7	24.6	T	24.59	T
8	31.5	T	31.46	T
9	81.2	D	80.44	D
10	60.3	D	60.18	D
Me	-	Q	17.62	Q

* Calculations based on the experimental values observed for trans-octahydro-1,4-benzoxazine (Table 9) with modifications for the effect of the methyl substituent (Table 18).

† $CDCl_3$ Solvent at 25 °C

puckering of the oxazine portion of the ring system. This would be unusual since most evidence suggests that an equatorial methyl group would have relatively little effect[72]. The unexpectedly high value for this system should therefore be regarded with suspicion and thus emphasises that calculations of this type should always be treated with caution. Nevertheless, the R-value method and the approach described by Forrest have, in many cases, provided a useful way of obtaining qualitative information about the extent of distortion produced by the introduction of methyl substituents into systems of this type.

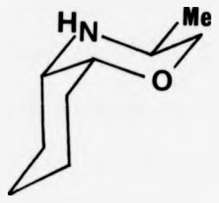
(iii) Component C (cis-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl--1,4-benzoxazine)

The stereochemical assignment of Component C was readily deduced by analysis of its 400 MHz ^{1}H n.m.r. spectrum. The 400 MHz ^{1}H n.m.r. spectrum of Component C (Table 48) displayed several well defined signals between 2.73 and 3.83 p.p.m.. These lower field resonances, those associated with the protons near to the heteroatoms, were assigned on the basis of their chemical shifts and multiplicities, and by comparison with the spectra of the other octahydro-1,4-benzoxines previously discussed. As many of these resonances compared favourably with those produced by cis-fused systems having a Type A conformation, such an arrangement was inferred for Component C. The simplification in the H2e and H2a resonances could be interpreted as being due to the absence of couplings from an H3e proton and therefore indicated that the methyl substituent at C3 was occupying an equatorial position. Consequently, Component C was identified as cis-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine in its

Table 48

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2e	3.83	Doublet of doublets ($J_{2e,2a}$ = 10.9 Hz; $J_{2e,3a}$ = 3.0 Hz).
9	3.66	Broad singlet (half-band width = 6 Hz) showing further small couplings.
3a	3.22	Multiplet (band width ∿ 33 Hz) with doublet of quartet of doublet character.
2a	3.14	Multiplet with triplet character ($J_{2a,2e}$ + $J_{2a,3a}$ = 21.1 Hz).
10	2.73	Multiplet (band width ∿ 23 Hz) with doublet character.
5a	2.11	Quartet of doublets ($J_{5a,5e}$ ∿ $J_{5a,6a}$ ∿ $J_{5a,10}$ ∿ 12.6 Hz; $J_{5a,6e}$ = 3.8 Hz).
N-H	2.01	Broad singlet.
8e	1.89	Multiplet (band width ∿ 29 Hz) with doublet character.
6e	1.77	Multiplet (band width ∿ 30 Hz) with doublet character.
7e,5e 8a,7a,6a	1.17-1.51	Complex envelope of overlapping resonances.
Me	0.91	Doublet ($J_{Me,3a}$ = 6.0 Hz).

* $CDCl_3$ Solvent at 25 °C

Type A conformational arrangement. It is interesting to note that the equatorial methyl group at C3 caused a significant upfield shift (0.55 p.p.m.) in the H2a resonance, relative to that observed in the Type A conformation of cis-octahydro-1,4-benzoxazine. This effect is similar to that observed in Component A where an upfield shift of 0.54 p.p.m. was noted for the H2a proton.

The methyl doublet at 0.91 p.p.m. was one of the few higher field resonances that could be readily assigned in the spectrum of Component C. However two resonances, associated with equatorially disposed protons, at 1.89 and 1.77 p.p.m. were assigned to the H8e and H6e signals by comparison with other analogues (Fig. 10) and the characteristic quartet of doublets at 2.11 p.p.m. was assigned to the H5a resonance. The remaining resonances appeared as a complex envelope of overlapping signals and could not be identified further. Since the ^{1}H n.m.r. spectrum was not observed to be temperature dependent the room temperature data was regarded as representing the Type A conformation of Component C. The lack of temperature dependence in the ^{1}H n.m.r. spectrum of Component C was also observed in the ^{13}C n.m.r. spectrum, confirming that the position of the conformational equilibrium in Component C was extreme.

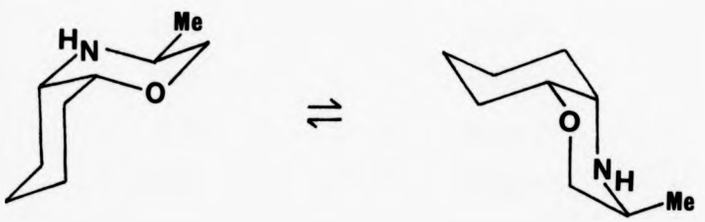
Analysis of the proton vicinal coupling constant, $J_{2e,3a}$ = 3.3 Hz ± 0.2 Hz, using equations (6), (7) and (8) indicates that the dihedral angle C2-C3 in Component C is about 60.7° ± 0.9°. However, since this system has an equatorially disposed methyl group we would not expect this group to significantly distort the oxazine portion of the molecule. The value of 60.7° ± 0.9° is thus higher than expected. Since this situation was also observed for Component B then this tends to suggest that Forrest's approach[69] is less satisfactory in the case

of the octahydro-3-methyl-1,4-benzoxazine system than in the case of the corresponding 2-methyl system.

Once again the ^{13}C n.m.r. spectral data provided further evidence for the assignment of Component C, with the experimentally observed data comparing well with the calculated values (Table 49) for cis-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine.

In view of the extreme position of the conformational equilibrium observed for Component C it is worth considering the interactions involved in this system in order to appreciate why the Type A conformation (87) is preferred.

(87) (88)



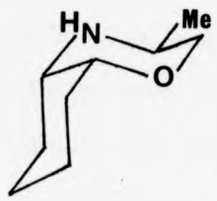
Conformation Type A Conformation Type B

We have observed, from our studies on cis-octahydro-1,4-benzoxazine, that the Type B conformation is less favourable than the Type A arrangement by about 4.0 kJ mol^{-1}. Furthermore, the Type B conformation of Component C (88) has an axially disposed methyl group at C3 which, if likened to 3-methyltetrahydropyran[16], would be less favoured than the equatorial arrangement found in (87) by 5.3 kJ mol^{-1}. Hence, assuming a simple additivity relationship for these two factors, we would predict the Type A conformation (87) to be more favoured than

Table 49

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values+	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	75.4	T	74.62	T
3	43.7	D	43.01	D
5	25.0	T	26.34	T
6	24.8	T	25.13	T
7	19.8	T	19.94	T
8	31.4	T	31.24	T
9	74.8	D	74.30	D
10	52.7	D	53.69	D
Me	-	Q	17.88	Q

* Calculations based on the experimental values observed for the Type A conformation of cis-octahydro-1,4-benzoxazine (Table 15) with modifications for the effect of the methyl substituent (Table 18).

+ $CDCl_3$ Solvent at 25 °C

the Type B conformation (88) by about 9.3 kJ mol^{-1}. This difference between the conformational free energies of (87) and (88) would be even larger if the nitrogen heteroatom in (88) enhances the steric interaction between the axial methyl group and the H10 proton. In such circumstances a value in excess of 9.4 kJ mol^{-1} would be predicted. The extreme position observed for the conformational equilibrium in favour of (87) suggests that 3-methyltetrahydropyran is not the most suitable model for obtaining the $-\Delta G^{o}$ value for the methyl group and that the effects due to the nitrogen heteroatom cannot be ignored.

(iv) Component D (trans-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl--1,4-benzoxazine)

Component D, observed to be one of the minor isomers produced during the catalytic hydrogenation reaction, was the last isomer to be eluted from the medium pressure chromatography column. This component could not be obtained in an isomerically pure form and the best fraction obtained, that used for ^{1}H n.m.r. spectroscopy, contained about 20% of the isomeric Component C.

Analysis of the 400 MHz ^{1}H n.m.r. spectrum (Table 50) of Component D allowed its stereochemistry to be deduced. The lower field region of the spectrum, those signals resonating between 2.81 and 3.91 p.p.m., were readily assigned from their characteristic multiplicities and by comparison with those systems previously discussed. In particular, the H9 and H10 resonances, although poorly resolved, were consistent only with a trans-fused ring junction. In addition, the simplification observed in the H2e and H2a resonances indicated the absence of a coupling to an H3a proton, implying that this position was occupied by a methyl substituent. Component D was therefore identified as trans-(9H,10H)-trans-(3H,10H)-octahydro-

Table 50

^{1}H n.m.r. Spectral Data

trans-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine

Proton	Shift(δ)	Description of Resonance
(400 MHz Spectrum)*		
2a	3.91	Doublet of doublets ($J_{2a,2e}$ = 11.6 Hz; $J_{2a,3e}$ = 3.0 Hz).
2e	3.67	Doublet of doublets ($J_{2e,2a}$ = 11.5 Hz; $J_{2e,3e}$ = 0.8 Hz).
3e	3.21	Poorly resolved multiplet (band width ∿ 28 Hz) with quartet of doublet character.
9	3.12	Poorly resolved multiplet (band width ∿ 29 Hz) with triplet of doublet character.
10	2.81	Poorly resolved multiplet (band width ∿ 28 Hz) with triplet of doublet character.
N-H	2.44	Broad singlet.
8e	1.89	Poorly resolved multiplet (band width ∿ 30 Hz).
6e,5e,7e	1.69-1.82	Complex envelope of overlapping resonances.
Me	1.41	Doublet ($J_{Me,3e}$ = 6.9 Hz).
8a,7a,6a,5a	1.17-1.39	Complex envelope of overlapping resonances.

* $CDCl_3$ Solvent at 25 °C

-3-methyl-1,4-benzoxazine.

It is interesting to note that the axial methyl group at C3 resulted in a shift of 0.42 p.p.m. to lower field for the H10 resonance, relative to that observed in trans-octahydro-1,4-benzoxazine. Interestingly, a shift of 0.30 p.p.m. to lower field was also observed for the comparable H9 resonances of the 2-methyl analogue trans-(9H,10H)-trans-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine, relative to that in trans-octahydro-1,4-benzoxazine. For Component D the relative positions of the H2e and H2a signals have also been reversed, in comparison with the unsubstituted parent system. However, the change in chemical shifts of the H2e (0.19 p.p.m.) and H2a (0.27 p.p.m.) signals is consistent with the change in shifts observed for the comparable signals (H3e and H3a) in the 2-methyl analogue.

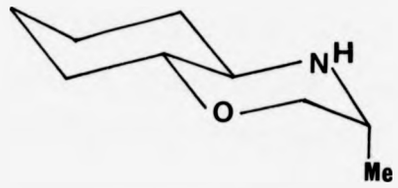
Of the remaining signals, those at higher field, the multiplet at 1.89 p.p.m. was assigned as the H8e resonance by comparison with similar analogues (Fig. 9) and the doublet at 1.41 p.p.m. was assigned to the methyl group. However, the remaining signals could only be assigned to one or other of the two separate complex envelopes of overlapping resonances. The H6e, H5e and H7e resonances were assigned to the complex envelope between 1.69 and 1.82 p.p.m. while the H5a, H6a, H7a and H8a signals were assigned to the complex envelope of resonances between 1.17 and 1.39 p.p.m.

The assignment of Component D was supported by the ^{13}C n.m.r. spectral data which showed a good correlation between the experimentally observed shifts and those predicted for trans-(9H,10H)-trans-(3H,10H)--octahydro-3-methyl-1,4-benzoxazine (Table 51). Both the ^{1}H and ^{13}C n.m.r. spectral data therefore indicated that Component D was trans-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine.

Table 51

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl-1,4-benzoxazine



Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	71.4	T	71.79	T
3	48.2	D	48.21	D
5	30.9	T	30.79	T
6	24.6	T	24.69	T
7	24.6	T	24.69	T
8	31.5	T	31.84	T
9	81.2	D	82.11	D
10	54.3	D	53.21	D
Me	-	Q	17.79	Q

* Calculations based on the experimental values observed for trans-octahydro-1,4-benzoxazine (Table 9) with modifications for the effect of the methyl substituent (Table 18).

† $CDCl_3$ Solvent at 25 °C

If one analyses the vicinal coupling constants, $J_{2a,3e}$ = 3.0 Hz ± 0.2 Hz and $J_{2e,3e}$ = 0.8 Hz ± 0.2 Hz, from the 400 MHz ^1H n.m.r. spectrum of Component D by applying equations (6), (7) and (8) then these are found to correspond to dihedral angles along the C2-C3 bond of 51.8° ± 1.4° and 53.8° ± 2.3°. These values imply that the axial methyl group at C3 is causing some flattening of the oxazine portion of the molecule as one might predict. Interestingly, the value of the dihedral angle for Component D is similar to that observed in the comparable 2-methyl system, trans-(9H,10H)-trans-(2H,9H)-octahydro-2-methyl-1,4-benzoxazine.

Although the calculated value for the dihedral angle along C2-C3 in trans-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine is clearly different from those values calculated for the other three isomers of octahydro-3-methyl-1,4-benzoxazine it would be unwise to place too much emphasis on the actual value for the dihedral angle, particularly in view of the rather high values observed for the dihedral angles in Components B and C. Nevertheless, the general conclusion which can be drawn from such an analysis is that there is a significant distortion of the oxazine portion of the molecule when a methyl substituent is placed in an axial position at C3.

Table 52

Selected ^{1}H N.M.R. Coupling Parameters of some Octahydro-1,4-benzoxazines/Hz

*Compound	$J_{2e,2a}$	$J_{2e,3a}$	$J_{2e,3e}$	$J_{2a,3a}$	$J_{3a,3e}$	$J_{3e,2a}$
T	11.3	3.4	1.2/3	11.7	12.2	2.7/8
C_A	11.3	3.2/4	N/A	12.0	12.5/8	2.6
2a T	-	4.3	0.8	-	12.1	-
2e T	-	-	-	10.2	12.1/2	2.5
2e C_A	-	-	-	10.5	12.5/6	2.8
2e C_B	-	-	-	10.0	12.0/1	2.7
3a T	11.5/6	-	0.8	-	-	3.0
3e T	11.0	3.1	-	10.3	-	-
3e C_A	10.9	3.3	-	10.2	-	-
3e C_B	11.1	3.6	-	10.7	-	-

/ over

Table 52 - continued

*Compound	$J_{2e,2a}$	$J_{2e,3a}$	$J_{2e,3e}$	$J_{2a,3a}$	$J_{3a,3e}$	$J_{3e,2a}$
6a T	∿11.4	∿3.4	N/A	∿11.7	∿12.4	∿2.7
6e T	11.3	3.4	1.3	11.7	12.1/2	2.6
6e C_A	11.3	3.6	1.1	12.0	12.6	2.8
6e C_B	11.6	3.0/2	N/A	11.9	11.9	2.8
7a T	N/A	N/A	N/A	N/A	N/A	N/A
7e T	11.3	3.4/5	1.1/3	11.7	12.1	2.6
7e C_A	11.6	3.8	N/A	12.3	12.6/7	2.8
7e C_B	11.5	3.4	N/A	11.9	11.9	2.6

*T indicates a trans-fused octahydro-1,4-benzoxazine structure.
C_A indicates a cis-fused octahydro-1,4-benzoxazine in a Type A conformational arrangement.
C_B indicates a cis-fused octahydro-1,4-benzoxazine in a Type B conformational arrangement.
Symbols 'e' and 'a' indicate the equatorial or axial orientation of the methyl substituent, while the position of this group is indicated by the preceding number.

Fig. 7

Comparison of ^{1}H N.M.R. Chemical Shifts for cis-Octahydro-1,4--benzoxazines in the Type B Conformation

Fig. 7 - continued

Comparison of ^{1}H N.M.R. Chemical Shifts for cis-Octahydro-1,4-benzoxazines in the Type B Conformation

Fig. 8

Comparison of ^{1}H N.M.R. Chemical Shifts for trans-Octahydro-1,4--benzoxazines with an Equatorial Methyl Group.

Fig. 8 - continued

Comparison of ^{1}H N.M.R. Chemical Shifts for trans-Octahydro-1,4--benzoxazines with an Equatorial Methyl Group

Fig. 9

Comparison of ^{1}H N.M.R. Chemical Shifts for trans-Octahydro-1,4--benzoxazines with an Axial Methyl Group

Fig. 10

Comparison of ^1H N.M.R. Chemical Shifts for cis-Octahydro-1,4-benzoxazines in the Type A Conformation

Fig. 10 - continued

Comparison of ^{1}H N.M.R. Chemical Shifts for cis-Octahydro-1,4--benzoxazines in the Type A Conformation

7. Investigations into the Synthesis of Methyl Analoques of Octahydro-1-benzopyran

Having investigated the effects of introducing methyl substituents into the octahydro-1,4-benzoxazine ring system it was of interest to extend these studies to the octahydro-1-benzopyran system. Our earlier work on the parent octahydro-1-benzopyran system (Chapter 1) had shown this to pose a much greater synthetic problem than that of the octahydro-1,4-benzoxazine system. This was largely because no way could be found to separate the cis and trans isomers of octahydro-1-benzopyran from the isomeric mixture produced by the hydrogenation of 2H-3,4-dihydro-1-benzopyran. It had, therefore, been necessary to devise a route which could be used to synthesize both the cis and trans isomers of octahydro-1-benzopyran independently. One of the reasons for developing the "lactone route" (Chapter 1, Fig. 5) was that it would, in theory, also be suitable for the synthesis of the isomers of the methyl substituted octahydro-1--benzopyrans. However, since the "lactone route" involved considerably more work than a simple hydrogenation of the appropriate aromatic precursor, it was decided to confirm first that the latter route would be unsuitable for the production of isomerically pure samples of methyl substituted octahydro-1-benzopyrans.

A. Investigation of the Synthesis of Methyl Substituted Octahydro--1-benzopyrans by the Catalytic Hydrogenation of an Unsaturated Precursor

The mono-methyl substituted octahydro-1-benzopyrans which were of particular interest for our studies were those having a methyl

group at C2,3,6 and 7 since these could be compared directly with the octahydro-1,4-benzoxazines we had already studied. Of these, octahydro-6-methyl-1-benzopyran and octahydro-7-methyl-1-benzopyran have previously been reported[37] as resulting from the catalytic hydrogenation of the appropriate methyl derivatives of 2H-3,4-dihydro--1-benzopyran. Unfortunately, however, no details about the stereochemistry of the products were given. Nevertheless, since octahydro-6-methyl-1-benzopyran could be readily prepared from the commercially available 2H-3,4-dihydro-6-methyl-1-benzopyran-2-one (see Experimental Section), this work was repeated to see if this route could provide a more convenient route for the production of the octahydro-6-methyl-1-benzopyran isomers than the "lactone route".

(i) The synthesis of octahydro-6-methyl-1-benzopyran by catalytic hydrogenation of 2H-3,4-dihydro-6-methyl-1-benzopyran.

The catalytic hydrogenation of 2H-3,4-dihydro-6-methyl-1--benzopyran, as expected, gave octahydro-6-methyl-1-benzopyran. Furthermore, examination of the hydrogenated material by ^{13}C n.m.r. spectroscopy revealed that no products, other than the fully saturated system, were formed. However, investigation by ^{1}H and ^{13}C n.m.r. spectroscopy revealed that the octahydro-6-methyl-1-benzopyran produced in this way consisted of only two of the four possible isomers. These were later identified as the two least strained isomers, cis-(9H,10H)-cis-(6H,10H)-octahydro-6-methyl-1-benzopyran (Plate 20, Tables 53 and 54) and trans-(9H,10H)-cis-(6H,10H)-octahydro-6-methyl--1-benzopyran (Table 55). It is interesting to note that the ratio of the cis-fused to trans-fused isomers in this product (91:9 respectively) is the same as that observed for octahydro-1-benzopyran, when prepared by the catalytic hydrogenation of 2H-3,4-dihydro-1-benzopyran.

Plate 20

The 100 MHz ^{1}H N.M.R. Spectrum of cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1-benzopyran

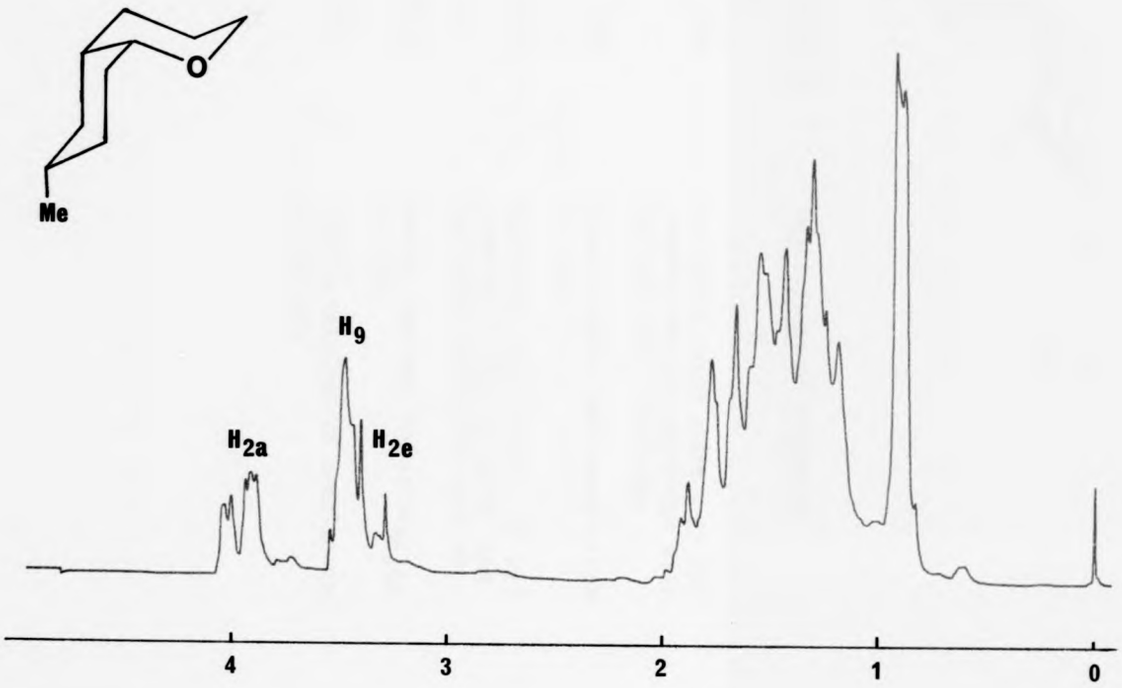
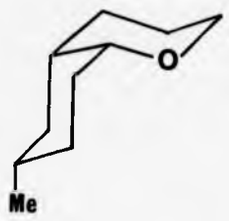


Table 53

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1-benzopyran



Proton	Shift(δ)	Description of Resonance
(100 MHz Spectrum)*		
2e	3.99	Multiplet (band width ∿ 23 Hz) showing doublet character with further small couplings.
9	3.49	Broad singlet (half-band width ∿ 7 Hz).
2a	∿ 3.42	Multiplet (band width ∿ 28 Hz) showing triplet character and partially overlapped with H9.
Me	0.92	Poorly resolved doublet ($J_{Me,6a}$ = 6.0 Hz).
Remaining Protons	∿ 1.0-1.9	Complex envelope of overlapping resonances.

* $CDCl_3$ Solvent at 25 °C.

Table 54

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1-benzopyran

Carbon No.	Calculated Values*		Experimental Values+	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.9	T	69.01	T
3	20.9	T	21.26	T
4	28.8	T	29.03	T
5	33.9	T	34.20	T
6	31.4	D	32.45	D
7	29.1	T	29.28	T
8	31.8	T	32.11	T
9	74.9	D	74.90	D
10	34.7	D	35.28	D
Me	-	Q	22.72	Q

*Calculations based on the experimental values for the Type A conformation of cis-octahydro-1-benzopyran with modifications for the effect of the methyl substituent (see Tables 5 and 18).

+$CDCl_3$ Solvent at 25 °C.

Table 55

^{13}C n.m.r. Spectral Data

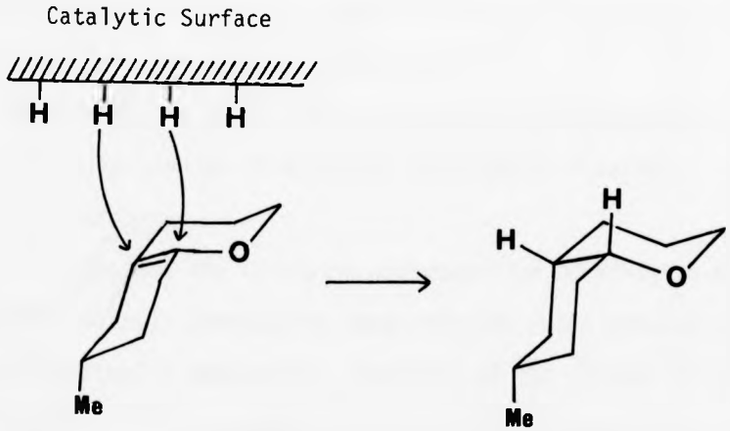
trans-(9H,10H)-cis-(6H,10H)-Octahydro-6-methyl-1-benzopyran

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	68.3	T	68.44	T
3	25.8	T	26.81	-
4	31.6	T	30.76	-
5	39.6	T	40.60	T
6	32.5	D	32.27	-
7	34.0	T	33.65	-
8	32.6	T	32.41	-
9	81.7	D	82.01	D
10	42.1	D	41.61	D
Me	-	Q	22.21	-

*Calculated values based on the experimental values from trans-octahydro-1-benzopyran (Table 2) with modifications for the effect of methyl substitution (Table 18).

†$CDCl_3$ Solvent at 25 °C.

The formation of a cis-fused isomer as the major product was not unexpected in view of our earlier discovery that the catalytic hydrogenation of 2H-3,4-dihydro-1-benzopyran proceeded via a bridgehead double-bond intermediate (38), resulting in the preferential formation of the cis-fused octahydro-1-benzopyran isomer. The formation of only one cis-fused isomer was, however, a little unexpected. A consideration of the structure of the expected hydrogenation intermediate, 2H-3,4,5,6,7,8-hexahydro-6-methyl-1-benzopyran, suggested a possible explanation for this observation. If the methyl group at C6 has a significant effect in directing the way in which the molecule can approach the catalytic surface then it will favour that in which the methyl group is directed away from the catalytic surface (89). This in turn will favour the formation of cis-(9H,10H)-cis-(6H,10H)--octahydro-6-methyl-1-benzopyran (90) and discourage the formation of cis-(9H,10H)-trans-(6H,10H)-octahydro-6-methyl-1-benzopyran.



(89) (90)

Such an effect would clearly impose a serious restriction in the use of high pressure catalytic hydrogenation as a route for the formation of methyl isomers of octahydro-1-benzopyran. On the other hand, such an effect could be used to advantage in those systems, such as the 3-methyl substituted system, which would be encouraged to undergo reduction to give the more highly strained cis-fused isomer. To investigate whether or not the methyl group on the 2H-3,4,5,6,7,8-hexahydro-1-benzopyran intermediate had a signficant effect on the way in which reduction occurred the catalytic hydrogenation of 2H-3,4,5,6,7,8-hexahydro-3-methyl-1-benzopyran was investigated.

The synthesis of 2H-3,4,5,6,7,8-hexahydro-3-methyl-1-benzopyran involved the reduction of 2-(2-carbomethoxypropyl)cyclohexanone to 2-(3-hydroxy-2-methylpropyl)cyclohexanone which was then cyclised to give the desired "hexahydro" material. This route was convenient since the 2-(2-carbomethyoxypropyl)cyclohexanone could also be used in the "lactone route" (Fig. 11 and 12) from the production of the isomers of octahydro-3-methyl-1-benzopyran.

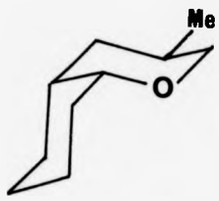
(ii) The synthesis of octahydro-3-methyl-1-benzopyran by catalytic hydrogenation of 2H-3,4,5,6,7,8-hexahydro-3-methyl--1-benzopyran.

As expected, the catalytic hydrogenation of 2H-3,4,5,6,7,8--hexahydro-3-methyl-1-benzopyran gave only the fully reduced system, octahydro-3-methyl-1-benzopyran. Analysis of the ^{1}H and ^{13}C n.m.r. spectral data of this material indicated that it consisted of one cis-fused and one trans-fused isomer in the ratio of 81:19 respectively. The predominant cis-fused isomer was shown by ^{1}H n.m.r. (Table 56) and ^{13}C n.m.r. spectroscopy (Table 57) to be

Table 56

^{1}H n.m.r. Spectral Data

cis-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl-1-benzopyran



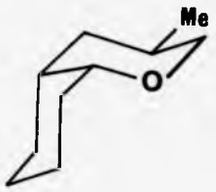
Proton	Shift(δ)	Description of Resonance
(100 MHz Spectrum)*		
2e	3.90	Multiplet (band width ∿ 21 Hz) showing doublet character ($J_{2e,2a}$ = 11.1 Hz) with further small couplings.
9	3.46	Broad singlet (half-band width = 7.0 Hz).
2a	2.98	Multiplet showing triplet character ($J_{2a,2e}$ = 11.0 Hz).
Me	0.73	Doublet ($J_{Me,3a}$ = 6.5 Hz).
Remaining Protons	∿ 0.9-2.0	Complex envelope of overlapping resonances.

* $CDCl_3$ Solvent at 25 °C.

Table 57

^{13}C n.m.r. Spectral Data

cis-(9H,10H)-trans-(3H,10H)-Octahydro-3-methyl-1-benzopyran



Carbon No.	Calculated Values*		Experimental Values+	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	77.8	T	75.43	-
3	26.6	D	26.33	-
4	38.0	T	38.80	T
5	24.7	T	25.64	-
6	25.7	T	26.24	-
7	20.2	T	20.51	T
8	31.8	T	31.92	T
9	74.9	D	75.19	-
10	34.7	D	35.81	-
Me	-	Q	17.39	Q

*Calculations based on the experimental values for the Type A conformation of cis-octahydro-1-benzopyran with modifications for the effect of the methyl substituent (see Tables 5 and 18).

+$CDCl_3$ Solvent at 25 °C.

Table 58

^{13}C n.m.r. Spectral Data

trans-(9H,10H)-cis-(3H,10H)-Octahydro-3-methyl-1-benzopyran

Carbon No.	Calculated Values*		Experimental Values†	
	Shift(δ)	Mult.	Shift(δ)	Mult.
2	77.2	T	74.67	-
3	31.4	D	31.70	-
4	40.8	T	39.80	-
5	30.4	T	-	-
6	26.8	T	25.81	-
7	25.1	T	25.18	-
8	32.6	T	32.43	-
9	81.7	D	81.67	-
10	42.1	D	41.98	-
Me	-	Q	-	-

*Calculated values based on the experimental values from trans-octahydro-1-benzopyran (Table 2) with modifications for the effect of methyl substitution (Table 18).

†$CDCl_3$ Solvent at 25 °C.

cis-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1-benzopyran, the least strained of the two possible cis-fused isomers. The minor trans-fused component had ^{13}C n.m.r. spectral data (Table 58) consistent with that predicted for the least strained of the two possible trans-fused isomers, trans-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1-benzopyran. Once again, no chromatographic separation of these two isomers could be achieved.

These observations, together with those from the hydrogenation of 2H-3,4-dihydro-6-methyl-1-benzopyran thus indicated that the catalytic hydrogenation of 2H-3,4-dihydro-1-benzopyran type systems would produce only the less strained isomers and hence that the position of the methyl substituent appeared to have no significant effect on the way in which the system approached the catalytic surface in the hydrogenation reaction.

In conclusion therefore, the catalytic hydrogenation route appeared to be unsuitable for the synthesis of methyl derivatives of octahydro-1-benzopyran. In view of these results the "lactone route" (Fig. 5) was investigated with the aim of applying it to the production of methyl derivatives of octahydro-1-benzopyran. It was convenient to investigate the feasibility of producing the four isomers of octahydro-3-methyl-1-benzopyran as the starting materials for this synthesis were readily available.

B. Investigation of the Synthesis of Methyl Substituted Octahydro-1-benzopyrans by the "Lactone Route".

The advantages of using the "lactone route" (see Fig. 5) for the preparation of isomerically pure samples of cis- and trans-octahydro-1-benzopyran have been described previously

(see Chapter 1). The analogous route for the formation of the octahydro-3-methyl-1-benzopyran isomers thus involved the preparation of the epimeric diastereoisomers of 2-(2'-carbomethoxypropyl)cyclohexanone (91, Fig. 11 and 96, Fig. 12). It was hoped that these two diastereoisomers could be reduced to the corresponding cyclohexanols (92 and 93, Fig. 11; 97 and 98 Fig. 12) which in turn could be cyclised to the corresponding octahydro-3-methyl-1-benzopyran--2-ones (94 and 95 Fig. 11; 99 and 100 Fig. 12). Finally, it was hoped that it would be possible to reduce these lactones to the corresponding octahydro-3-methyl-1-benzopyrans using the borane--dimethyl sulphide reduction method we developed and used successfully for the reduction of octahydro-1-benzopyran-2-one to octahydro-1--benzopyran.

(i) Preparation of 2-(2'-carbomethoxypropyl)cyclohexanone.

2-(2'-Carbomethoxypropyl)cyclohexanone was readily prepared using the method of Stork et al.[50]. Examination of this product by ^{13}C n.m.r. spectroscopy revealed that it consisted of equal quantities of the two epimeric diastereoisomers. Since each diastereoisomer could potentially give rise to two different isomers of octahydro--3-methyl-1-benzopyran it was advantageous to separate the diastereoisomers at this point.

Application of preparative thin layer chromatography resulted in only a partial separation of the diastereoisomers. However, repeated applications of medium pressure chromatography enabled sufficient quantities of the two isomerically pure epimers to be obtained.

Fig. 11

Proposed Route for the Synthesis of cis-(9H,10H)-trans--(3H,10H)- and trans-(9H,10H)-trans-(3H,10H)-Octahydro--3-methyl-1-benzopyran-2-one

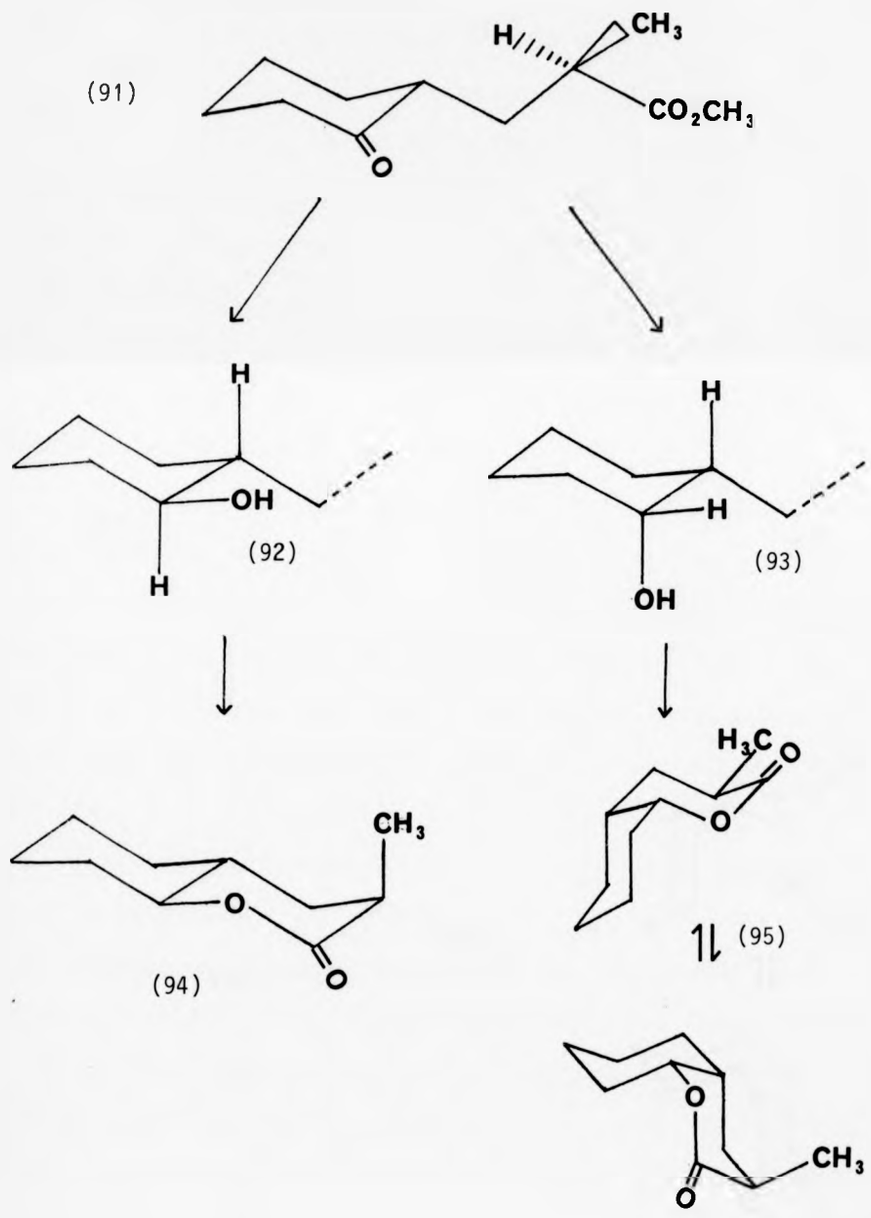
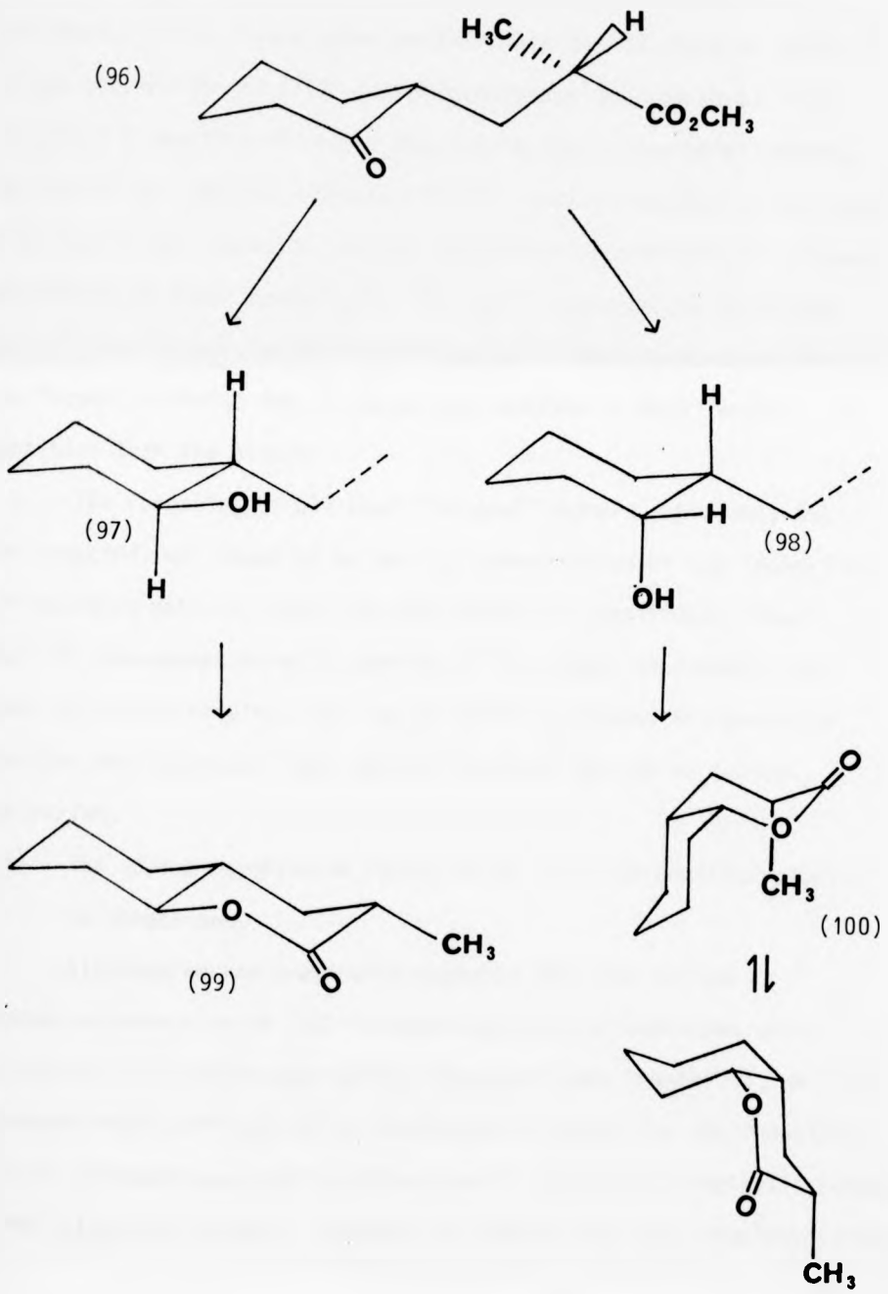


Fig. 12

Proposed Route for the Synthesis of cis-(9H,10H)-cis--(3H,10H)- and trans-(9H,10H)-cis-(3H,10H)-Octahydro--3-methyl-1-benzopyran-2-one



(ii) The catalytic hydrogenation of 2-(2'-carbomethoxypropyl)-cyclohexanone.

As we had already successfully hydrogenated 2-(2'-carbethoxyethyl)cyclohexanone to 2-(2'-carbethoxyethyl)cyclohexanol (see Chapter 1) we investigated whether this method could be used for the preparation of 2-(2'-carbomethoxypropyl)cyclohexanol. On subjecting a quantity of one of the pure epimeric diastereoisomers, that having the smaller retention time on medium pressure chromatography, to catalytic hydrogenation several hydrogenation products were formed. Examination of these products by ^{13}C n.m.r. spectroscopy indicated that all four isomers of octahydro-3-methyl-1-benzopyran-2-one had been formed, although two of these were present in much larger quantities than the others.

The formation of all four "lactone" isomers, when only two were expected, was shown to be due to epimerization of the isomerically pure starting material under the hydrogenation conditions. Thus catalytic hydrogenation of a quantity of the other diastereoisomer produced similar results. In view of this an alternative method of reduction was examined. This method involved the use of sodium borohydride.

(iii) The sodium borohydride reduction of 2-(2'-carbomethoxypropyl)-cyclohexanone.

Although we had previously observed that the sodium borohydride reduction of 2-(2'-carbethoxyethyl)cyclohexanone gave the 1,5-diol,2-(3'-hydroxypropyl)cyclohexanol (see Chapter 1), we had experienced difficulties in developing a method for the reduction of 2-(2'-carbomethoxypropyl)cyclohexanone to octahydro-3-methyl-1-benzopyran--2-one using this reagent. However, by adding precisely regulated amounts

of sodium borohydride ($^1/_4$ molar equivalents) to an isomerically pure epimer of 2-(2'-carbomethoxypropyl)cyclohexanone in a methanol-chloroform solvent mixture (see Experimental Section) the required lactones were produced. ^{13}C n.m.r. spectroscopy indicated the reaction between 2-(2'-carbomethoxypropyl)-cyclohexanone and sodium borohydride was complete within a few minutes. The reaction mixture was then further treated (see later discussion) to complete the cyclisation of any remaining 2-(2'-carbomethoxypropyl)cyclohexanol to octahydro-3-methyl--1-benzopyran-2-one.

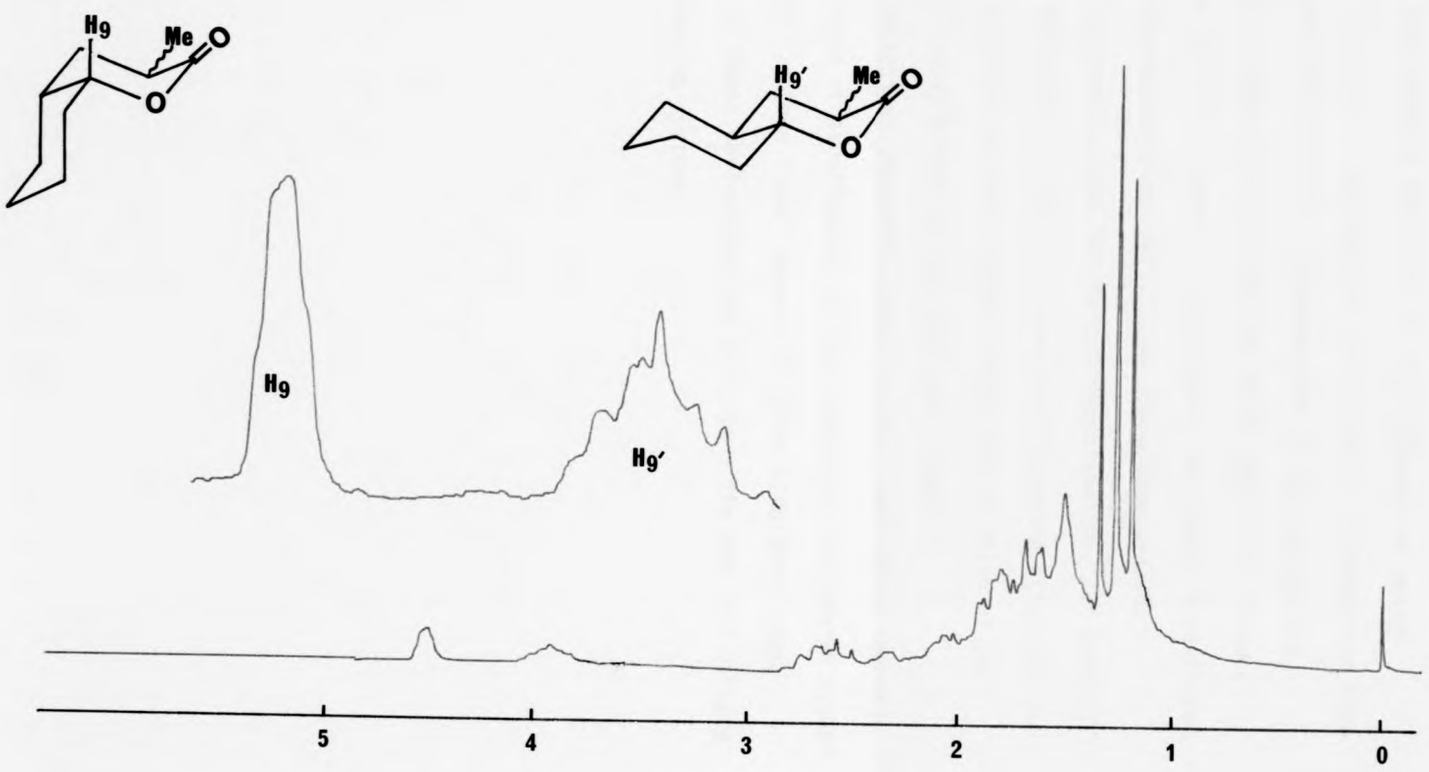
Sodium borohydride reduction of the diastereoisomer of 2-(2'-carbomethoxypropyl)cyclohexanone having the smaller retention time on medium pressure chromatography led to the formation of four compounds. The identification of these compounds by ^1H and ^{13}C n.m.r. spectroscopy was consistent with a reduction route that involved the initial formation of one cis and one trans isomer of 2-(2'-carbomethoxy-propyl)cyclohexanol. These isomers had then undergone partial cyclization to produce the corresponding octahydro-3-methyl-1--benzopyran-2-one. The remaining uncyclised material could be readily cyclised to the lactones by the addition of dilute hydrochloric acid. It is interesting to note that the small amount of unreacted started material present in the product was in an isomerically pure form i.e. epimerization had not occurred. The 100 MHz ^1H n.m.r. spectrum of the lactone isomers gave, among other signals, a broad singlet at 4.50 p.p.m. (half-band width = 8.4 Hz) and a poorly resolved multiplet at 3.71 - 4.06 p.p.m. corresponding to the H9 resonances from a cis-fused and a trans-fused isomer of octahydro-3-methyl--1-benzopyran-2-one respectively.

Reduction and cyclisation of the second isomerically pure diastereoisomer of 2-(2'-carbomethoxypropyl)cyclohexanone (that having the larger retention time upon medium pressure chromatography) produced the other two isomers of octahydro-3-methyl-1-benzopyran--2-one. It is interesting to note that in the initial reaction of this second diastereoisomer with sodium borohydride the ^{1}H and ^{13}C n.m.r. spectral data indicated the formation of only two products, a cis isomer of 2-(2'-carbomethoxypropyl)cyclohexanol and a trans-fused isomer of octahydro-3-methyl-1-benzopyran-2-one. Furthermore, addition of dilute hydrochloric acid did not cause the cyclisation of the cis-cyclohexanol product. However, heating the mixture from the reduction under reflux for two hours in benzene with a trace of p-toluenesulphonic acid caused the cis-cyclohexanol to cyclise to a cis-fused isomer of octahydro-3-methyl-1-benzopyran--2-one. The 100 MHz ^{1}H n.m.r. spectrum of the resulting lactone mixture was very similar to that observed for the lactone mixture produced from the first diastereoisomer. It showed, among other signals, a broad singlet at 4.52 p.p.m. (half-band width = 7.1 Hz) and a poorly resolved multiplet at 3.75 - 4.12 p.p.m. confirming the presence of both a cis-fused and a trans-fused isomer of octahydro-3-methyl-1-benzopyran-2-one (Plate 21).

Unfortunately, there was not sufficient time to isolate any of the individual isomers of octahydro-3-methyl-1-benzopyran-2-one and reduce them to the corresponding isomers of octahydro-3-methyl--1-benzopyran. However, there appears to be no reason why this should not be possible since the borane-dimethyl sulphide complex should be suitable for reducing octahydro-3-methyl-1-benzopyran-2-one to octahydro-3-methyl-1-benzopyran. The use of this "lactone route"

Plate 21

The 100 MHz ^{1}H N.M.R. Spectrum of a cis-fused and a trans-fused Isomer of Octahydro-3-methyl-1-benzopyran-2-one



thus offers considerable potential in the synthesis of methyl substituted octahydro-1-benzopyrans, particularly in comparison with the route involving catalytic hydrogenation of the appropriate 2H-3,4-dihydro-1-benzopyran derivatives which appears to produce only the less strained isomers. Furthermore, the methyl substituted octahydro-1-benzopyran-2-one derivatives themselves provide a potentially interesting area for further investigation. In particular it would be interesting to find out how the flattening effect of the C2 carbonyl group on the ring system affects the position of the conformational equilibrium for the cis-fused isomers.

In conclusion, therefore, there is still much to be learned about the effects of substituents on the octahydro-1-benzopyran system. The use of our "lactone route" appears to offer a suitable route for a number of these derivatives and thus opens the way to a variety of very interesting systems.

EXPERIMENTAL

Equipment

Hydrogenation apparatus

'Cook' heated type low pressure catalyst hydrogenation plant.

'Baskerville' vertical high pressure autoclave.

'Berghof' 150 ml polytetrafluoroethylene (PTFE) lined high pressure autoclave.

Distillation apparatus

Nester-Faust annular teflon spinning band distillation column

Analytical gas liquid chromatography

Pye Series 104 (fitted with a flame ionisation detector).

Preparative gas liquid chromatography

Pye Series 105 (fitted with a flame ionisation detector).

N.M.R. spectrometers

Bruker WH400 F.t. n.m.r. spectrometer.

Jeol JNM-FX100 F.t. n.m.r. spectrometer.

Hitachi Perkin-Elmer R-24 and R.24B n.m.r. spectrometers.

Infrared spectrometer

Pye Unicam SP1100.

Mass spectrometer

AEI MS12, upgraded with solid state electronics and fast pumping.

Melting point/boiling point apparatus

Buchi SMP-20.

The Octahydro-1-benzopyran System

1. Reactions Involved with the Synthesis of Octahydro-1-benzopyran

(a) 3-(2'-Hydroxyphenyl)propanol

A solution of 2H-3,4-dihydro-1-benzopyran-2-one (105g) in dry diethyl ether (100 ml) was slowly added over 1.5h to a mechanically stirred suspension of lithium aluminium hydride (15g) in dry diethyl ether (100 ml). After heating under reflux for a further 15 minutes ethyl acetate (100 ml) was cautiously added with thorough stirring. Dilute hydrochloric acid was then added cautiously until in excess. The ether layer was decanted off and the remaining aqueous layer extracted with ether. The combined extracts were then dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure on a rotary evaporator gave the required product (100.5g, 93%) as a colourless viscous liquid, identified by comparison with a sample produced by the catalytic hydrogenation of 2H-1-benzopyran--2-one (coumarin) by a previously reported procedure[36]. This material was sufficiently pure to be used without the need for further purification.

δ ^{1}H N.M.R. (60 MHz), $CDCl_3$; 1.6-2.1 (m, 2H), 2.6-2.9 (m, 2H), 3.5-3.7 (m, 2H), 5.2 (broad s, 2H), 6.6-7.2 (m, 4H).

(b) 2H-3,4-Dihydro-1-benzopyran

Phosphorus tribromide (132g) was added slowly over a period of 1h to a stirred solution of 3-(2'hydroxyphenyl)propanol (98g) in dry benzene (200 ml). The mixture was then heated for a further 3h after which time the evolution of hydrogen bromide gas had ceased. Dilute sodium hydroxide was then added until the solution became alkaline and the resulting mixture was then stirred overnight.

The benzene layer, was combined with several further benzene extractions of the aqueous layer and this was then dried over anhydrous magnesium sulphate. The benzene was then removed on a rotary evaporator under reduced pressure to give the crude product. Distillation of this material gave the required product (74g, 86%) as a colourless liquid b.p. 216 °C at 747 mm Hg (literature[73] b.p. 214 °C at 742 mm Hg).

δ^1H N.M.R. (60 MHz), $CDCl_3$; 1.7-2.15 (m, 2H), 2.6-2.9 (m, 2H), 4.0-4.2 (m, 2H), 6.55-7.15 (m, 4H).

(c) 2H-3,4,5,6,7,8-Hexahydro-1-benzopyran

This material was prepared by the method outlined by I.J. Borowitz, et al.[44].

Into the centre of a "drikold" condenser filled with methylated spirits was placed the cooling probe of a Cryocool C-100 (this arrangement enabled the condenser to be left unattended at 188 °K for long periods of time). To a flask fitted with such a condenser arrangement was then added ethylamine (75 ml), dimethylamine (75 ml) and lithium shot (4.8g). The mixture was then magnetically stirred for 1h. 2H-3,4-dihydro-1-benzopyran (9.8g) was then added over a 10 minute period and the reaction mixture allowed to stir for 22h. After removing any unreacted pieces of lithium, solid ammonium chloride was carefully added until the solution became saturated. Any volatile components were then removed under water-pump vacuum by gentle heating. Water was then added and the mixture extracted with several portions of ether. The combined ether extracts were dried over anhydrous magnesium sulphate and the ether then removed under reduced pressure to give the crude product (6g). On vacuum distillation this gave the required product

(5.5g, 55%) as a colourless liquid b.p. 40-42 °C at 0.3 mm Hg (literature[74] b.p. 80-83 °C at 15 mm Hg). Microanalysis gave C, 78.0; H, 10.35. Calc. for $C_9H_{14}O$: C, 78.2; H, 10.2%.
δ^1H N.M.R. (60 MHz), $CDCl_3$; 1.4-2.1 (m, 12H), 3.7-4.0 (m, 2H).
δ^{13}C N.M.R. $CDCl_3$; 146.72s, 104.45s, 65.59t, 28.97t, 27.34t, 25.24t, 23.32t, 23.20t, 23.03t.

A further component was obtained from the vacuum distillation ~ 0.5g, b.p. 64 °C at 0.3 mm Hg. This was shown to be 1-(3'-hydroxypropyl)cyclohexene (literature[75] b.p. 118 °C at 21 mm Hg). Mass spectrometry gave M^+ = 140 requires M^+ = 140.2.
δ^1H N.M.R. (60 MHz), $CDCl_3$; 1.2-2.4 (m, 13H), 3.4-3.75 (m, 2H), 5.4 (broad s, 1H).
δ^{13}C N.M.R. $CDCl_3$; 137.05s, 120.95d, 62.64t, 34.29t, 30.54t, 28.26t, 25.24t, 23.00t, 22.57t.

(d) Octahydro-1-benzopyran

(i) By reduction of 2H-3,4,5,6,7,8-Hexahydro-1-benzopyran

2H-3,4,5,6,7,8-Hexahydro-1-benzopyran (6g) in cyclohexane (125 ml) was hydrogenated in a 1ℓ steel autoclave (Cook) initially charged to a pressure of 6.3 atm using T1 Raney nickel[78] (3g) as catalyst. The autoclave was heated to 148 °C for 21h and then allowed to cool overnight. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the cyclohexane removed on a rotary evaporator under reduced pressure to give a colourless liquid (6g). This was found to contain equal quantities of octahydro-1-benzopyran and starting material. A sample of the octahydro-1-benzopyran was obtained by preparative gas liquid chromatography using a 12 ft x 1/4" column containing 30% SE 30 on Silocell C22 at 122 °C and N_2(g) = 152 ml min^{-1}. Although g.l.c.

gave only one peak this sample was later shown by ^{13}C n.m.r. spectroscopy to be a mixture of trans-octahydro-1-benzopyran (9%) and cis-octahydro-1-benzopyran (91%). Attempts to separate these cis and trans isomers by a range of techniques proved unsuccessful.

(ii) By hydrogenation of 2H-3,4-Dihydro-1-benzopyran

2H-3,4-Dihydro-1-benzopyran (24.5g) in cyclohexane (100 ml) was hydrogenated in a 1ℓ steel autoclave (Baskerville) initially charged to a pressure of 67 atm using T1 Raney nickel[78] (4g) as catalyst. The autoclave was heated to 120 °C for 5h and then allowed to cool overnight. The resulting reaction mixture was worked up as previously described to give the crude product as a colourless liquid (24.6g). Distillation on a spinning band column under reduced pressure was used to separate the reduction product (9.2g, 36%) from the starting material. The reduction product was identified as a mixture of the cis (91%) and trans (9%) isomers of octahydro-1-benzopyran b.p. 95 °C at 14 mm Hg (literature[36] b.p. 186-187 °C at 760 mm Hg). Microanalysis gave C, 77.25; H, 11.75. $C_9H_{16}O$ requires C, 77.1; H, 11.5%.

(iii) By hydrogenation of 3-(2'-Hydroxyphenyl)propanol

3-(2'-Hydroxyphenyl)propanol (14g) in cyclohexane (50 ml) and ethanol (75 ml) was hydrogenated in a 1ℓ steel autoclave (Baskerville) initially charged to a pressure of 65 atm using 10% palladium on charcoal (0.5g) as catalyst. The autoclave was heated to 98 °C for 6h and then allowed to cool overnight. The resulting reaction mixture was worked up in the usual way to give a colourless liquid (14g). Vacuum distillation of the crude product gave octahydro-1-benzopyran (1.4g) as a colourless liquid b.p. 32 °C at 0.1 mm Hg which was later shown to be an isomeric mixture (cis 66%, trans 34%).

A further component (7.6g) obtained from the distillation as a colourless viscous liquid b.p. 114 °C at 0.1 mm Hg was shown to be 2-(3'-hydroxypropyl)cyclohexanol (literature[36] b.p. 185-186 °C at 35 mm Hg). This product consisted of equal proportions of the cis and trans isomers. The residue from the distillation was found to contain only unreduced starting material.

trans-2(3'-Hydroxypropyl)cyclohexanol

$\delta^{13}C$ N.M.R. $CDCl_3$; 74.08, 62.13, 44.26, 35.47, 30.40, 28.99, 28.11, 25.63, 25.02.

cis-2(3'-Hydroxypropyl)cyclohexanol

$\delta^{13}C$ N.M.R. $CDCl_3$; 68.83, 62.52, 41.15, 32.70, 29.87, 27.63, 27.02, 24.93, 20.86.

Under more vigorous hydrogenation conditions a different proportion of cis and trans isomers of octahydro-1-benzopyran was obtained. Thus, for example, when 3-(2'-hydroxyphenyl)propanol was hydrogenated using the same solvent and catalyst at a pressure of 63 atm for 4h at 160 °C the octahydro-1-benzopyran product was found to contain 75% of the cis isomer and 25% of the trans isomer. An amount of 2H-3,4-dihydro-1-benzopyran was also found to be present in the reaction products.

(iv) Attempted preparation by treatment of 2-(3'-hydroxypropyl)-cyclohexanol with phosphoric acid.

2-(3'-Hydroxypropyl)cyclohexanol (10g) (previously prepared by the reduction of 3-(2'-hydroxyphenyl)propanol and consisting of equal proportions of the cis and trans isomers) was added to phosphoric acid (20g, 88%) in a distillation apparatus. The pressure in the apparatus was reduced to about 15 mm Hg using a water-pump and then the reaction mixture was stirred and heated. At about 100 °C a colourless liquid

(4.8g) distilled out of the reaction flasks. This material was then re-distilled to give a product (3g) b.p. 182 °C at 752 mm Hg later identified as 1-oxaspiro[4,5]decane (literature[76] b.p. 182 °C at 742 mm Hg). Microanalysis gave C, 77.05; H, 11.45. Calc. for $C_9H_{16}O$: C, 77.10; H, 11.5%.

δ^1H N.M.R. ($CDCl_3$); 1.0-2.1 (m, 14H), 3.65-4.1 (m, 2H).

δ^{13}C N.M.R. $CDCl_3$; 82.08s, 66.31t, 37.16t(x2), 36.05t, 25.69t(x2), 23.87t(x2).

(v) By cyclisation of trans-2-(3'hydroxypropyl)cyclohexanol

A sample of trans-2-(2'-carbethoxyethyl)cyclohexanol (1.0g, see page 243) in dry diethyl ether (10 ml) was firstly reduced by cautiously adding this to a quantity of lithium aluminium hydride (0.3g), also in dry diethyl ether (20 ml). After workup and extraction in the usual way a quantity of crude trans-2-(3'-hydroxypropyl)cyclohexanol (0.9g) was obtained. This material was identified by comparison with a known sample of 2-(3'-hydroxypropyl)cyclohexanol (see page 240).

The crude product, trans-2-(3'-hydroxypropyl)cyclohexanol (0.9g), was then subjected to high pressure catalytic hydrogenation conditions by heating the material to 154 °C in an autoclave (Berghof), charged to 32 atm using cyclohexane as solvent (10 ml) and T1 Raney nickel[78] as catalyst (3.0g) for about 17h. After working up in the usual way the reaction product (0.8g) was examined by ^{1}H and ^{13}C n.m.r. spectroscopy. This indicated that only octahydro-1-benzopyran had been produced with 67% in the trans-fused form and 33% as the cis-fused form. No starting material was observed.

(e) 2-(2'-Carbethoxyethyl)cyclohexanone

This material was prepared by the method of G. Stork, et al.[50].

The pyrrolidine enamine of cyclohexanone was first prepared in the usual way[50]. To this enamine (67g) in dry dioxan (100 ml) was added ethyl acrylate (45g) and the mixture heated under reflux for 3.5h. Water (20 ml) was then cautiously added and the mixture heated under reflux for a further 1h. The dioxan was then removed under reduced pressure on a rotary evaporator and the remaining aqueous solution extracted with ether. These extracts were washed with dilute hydrochloric acid and then with dilute sodium bicarbonate before being dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave the crude product (66g) which after vacuum distillation gave the required product (55.8g, 64%) as a colourless liquid b.p. 94-98 °C at 0.1 mm Hg (literature[77] b.p. 115-120 °C at 1.5 mm Hg).

δ^1H N.M.R. (60 MHz) $CDCl_3$; 1,1-1.35 (t, 3H), 1.3-2.6 (m, 15H), 3.95-4.35 (q, 2H).

(f)(i) 2-(2'-Carbethoxyethyl)cyclohexanol

2-(2'-Carbethoxyethyl)cyclohexanone (20.4g) in ethanol (20g) was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 44 atm using a platinum black catalyst (250 mg). The autoclave was heated to 75 °C for 17h and then allowed to cool. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the ethanol removed under reduced pressure on a rotary evaporator to give a colourless liquid (20.1g). This contained some starting material (< 10%) but the major product was a mixture of equal proportions of the cis and trans isomers of

the required product. The reaction was repeated with a further portion of the cyclohexanone (16.8g) and the isomeric products from the combined reactions separated by medium pressure chromatography before cyclization of the cyclohexanol isomers had occurred.

(ii) Separation of the 2-(2'carbethoxyethyl)cyclohexanol isomers

A medium pressure chromatography column (Whatman, 100 cm x 25 mm) freshly packed with silica (300g, Kieselgel 60) in a 20% ethyl acetate: 80% petrol (40/60) solvent mixture was loaded with the cyclohexanol isomeric mixture (14g). This was then eluted with a 20% ethyl acetate: 80% petrol (40/60) solvent mixture at a rate of 60 ml h^{-1}. After a total of 100 fractions had been collected, at a rate of 3 fractions h^{-1}, a sample from each was spotted onto a silica TLC plate which was then exposed to iodine vapour. This enabled any fraction containing eluted material to be quickly identified. The 2-(2'-carbethoxyethyl)cyclohexanone present was eluted first (retention time $\sim$ 9.7h), clearly separated from the desired cyclohexanol isomers. The cis-2-(2'-carbethoxyethyl)cyclohexanol was eluted next (retention time $\sim$ 12.3-23h) but tailed into the trans isomer (retention time $\sim$ 21-30h). ^{1}H n.m.r. and ^{13}C n.m.r. spectroscopy were therefore used to find the boundary between these isomers. The pure fractions for each isomer were then combined. Two further portions of the isomeric mixture (14g and 10g) were separated in the same manner. This enabled a substantial amount of both the cis- (9g) and trans-2-(2'-carbethoxyethyl)cyclohexanol (7g) to be obtained.

cis -2-(2'-carbethoxyethyl)cyclohexanol

$\delta^{1}H$ N.M.R. (60 MHz) $CDCl_3$; 1.15-1.4 (t, 3H), 1.1-2.5 (m, 14H), 3.8-4.0 (broad s, 1H), 4.0-4.45 (q, 2H).

$\delta^{13}C$ N.M.R. $CDCl_3$; 174.38, 68.32, 50.38, 41.15, 32.89, 32.00, 26.73, 26.66, 25.12, 20.42, 14.23.

trans-2-(2'-carbethoxyethyl)cyclohexanol

$\delta^{1}H$ N.M.R. (60 MHz) $CDCl_3$; 1.15-1.4 (t, 3H), 1.1-2.8 (m, 14H), 3.0-3.55 (m, 1H), 4.0-4.45 (q, 2H).

$\delta^{13}C$ N.M.R. $CDCl_3$; 173.57, 74.07, 60.35, 44.61, 35.67, 31.53, 30.19, 27.41, 25.53, 24.88, 14.23.

(g) trans-Octahydro-1-benzopyran-2-one

trans-2-(2'-Carbethoxyethyl)cyclohexanol (7g) was heated under reflux in benzene (50 ml) with p-toluenesulphonic acid (20mg) for about 1h in a Dean and Stark apparatus. Removal of the benzene under reduced pressure on a rotary evaporator gave the crude product. Vacuum distillation gave trans-octahydro-1-benzopyran-2-one (5.1g, 94%) as a colourless liquid b.p. 86 °C at 0.1 mm Hg (literature[51] b.p. 93-94.5 at 0.3 mm, unspecified stereochemistry). Microanalysis gave C, 69.85; H, 9.3. Calc. for $C_9H_{14}O_2$: C, 70.1; H, 9.15%.

$\delta^{1}H$ N.M.R. (60 MHz) $CDCl_3$; 1.0-2.4 (m, 11H), 2.4-2.8 (m, 2H), 3.7-4.2 (m, 1H).

$\delta^{13}C$ N.M.R. $CDCl_3$; 171.19s, 83.21d, 38.71d, 32.24t, 31.00t, 29.79t, 26.43t, 25.12t, 24.05t.

(h) cis-Octahydro-1-benzopyran-2-one

cis-2-(2'-Carbethoxyethyl)cyclohexanol (9g) was treated in the manner previously described for the trans isomer, but needed to be heated under reflux for an additional 1h to ensure complete cyclisation. Vacuum distillation gave cis-octahydro-1-benzopyran-2-one (6.5g, 94%) as a colourless liquid b.p. 88 °C at 0.1 mm Hg (literature[51] b.p. 93-94.5 °C at 0.3 mm, unspecified stereochemistry). Microanalysis

gave C, 70.0; H, 9.2. Calc. for $C_9H_{14}O_2$: C, 70.1; H, 9.15%.

δ^1H N.M.R. (60 MHz) $CDCl_3$; 1.3-2.3 (m, 11H), 2.3-2.8 (m, 2H), 4.5-4.75 (broad s, 1H).

δ^{13}C N.M.R. $CDCl_3$; 172.01s, 78.03d, 32.58d, 30.18t, 26.82t, 26.58t, 24.22t(x2), 20.11t.

(i) trans-Octahydro-1-benzopyran

A dry 3-necked flask was fitted with a magnetic stirrer, condenser and syringe injection point. A steady stream of dry nitrogen gas was passed through the apparatus and then into a sodium hypochlorite trap.

A solution of trans-octahydro-1-benzopyran-2-one (0.4g, 0.0025M) in dry diethyl ether (20 ml) was added to the flask and the apparatus flushed with dry nitrogen gas for 30 minutes. A 1:1 borane-dimethyl sulphide complex (0.3 ml, 0.0032M), from a recently opened bottle, was then injected into the stirred solution in the apparatus. Within a few minutes the precipitation of a white solid was observed but this had redissolved after 5h. Methanol (10 ml) was then injected cautiously into the stirred reaction mixture and this was followed by the addition of water (10 ml). The dimethylsulphide was then removed under vacuum and the resulting solution extracted with ether. The ether extract was dried over anhydrous magnesium sulphate and the ether then removed under reduced pressure on a rotary evaporator. This gave trans-octahydro-1-benzopyran (0.35g, 96%) as a colourless liquid. No other products were observed. Mass spectrometry gave M^+ = 140 calc. M^+ = 140.2.

^{1}H N.M.R. Spectral Data	Table 1	Plate 1
^{13}C N.M.R. Spectral Data	Table 2	Plate 2

(j) trans-Octahydro-1-benzopyran-2-ol

Following the method previously described, trans-octahydro--1-benzopyran-2-one (4.5g, 0.029 mol) was again reacted with the 1:1 borane-dimethyl sulphide complex (3 ml, 0.032M). [On this occasion however a freshly opened sample of this reagent was not available.] No white solid precipitation was observed at the beginning of the reaction and on extracting the product in the manner previously described a colourless viscous liquid remained (4g, 90%). After vacuum distillation of this viscous liquid b.p. 80 °C at 0.1 mm Hg the material solidified to give a white solid m.p. 64-67 °C. This material was found to be a mixture of the two isomeric trans-octahydro-1-benzopyran-2-ols. (Literature[79] b.p. 98-100 °C at 0.2 mm Hg, m.p. 50-63 °C, unspecified stereochemistry.) Microanalysis gave C, 69.25; H, 10.5. Calc. for $C_9H_{16}O_2$: C, 69.2; H, 10.3%. No other products were observed.

$\delta^{13}C$ N.M.R. $CDCl_3$; 96.20d, 91.36d, 79.63d, 72.71d, 41.75, 40.78, 33.29, 32.15, 32.02, 31.64, 31.03, 30.54, 29.42, 25.73, 25.56, 25.07, 24.68, 24.51.

(k) cis-Octahydro-1-benzopyran

The apparatus was arranged as previously described for the corresponding trans isomer. Boron trifluoride etherate (1.5 ml, 0.012M) in dry diethyl ether (15 ml) was added to the flask and the system flushed for 30 minutes with dry nitrogen gas. A 1:1 borane--dimethyl sulphide complex (1.8 ml, 0.019M) was then injected into the reaction vessel.

cis-Octahydro-1-benzopyran-2-one (1g, 0.006M) in dry diethyl ether (4 ml) was then slowly injected (over a 3 minute period) into the flask, whose contents were continuously stirred. Within a few

minutes a white solid precipitated, however, upon examination after a further 5h this had redissolved. At this point the resulting reaction mixture was worked up in the manner previously described for the trans isomer. This gave a colourless liquid together with some viscous material. Addition of chloroform caused the more viscous component to solidify. Filtration and removal of the chloroform under reduced pressure gave a colourless liquid (0.5g, 55%) which was shown shown to be cis-octahydro-1-benzopyran. Mass spectrometry gave M^+ = 140 requires M^+ = 140.2.

^1H N.M.R. Spectral Data	Table 6	Plate 4
^{13}C N.M.R. Spectral Data	Table 5	Plate 3

2. Reactions Involved with the Synthesis of cis-2,2-Dideutero-octahydro-1-benzopyran

(a) 1,1-Dideutero-3-(2'-hydroxyphenyl)propanol

2H-3,4-Dihydro-1-benzopyran-2-one (11g) in dry diethyl ether (10 ml) was slowly added over a 45 minute period to a stirred slurry of lithium aluminium deuteride (1g) in dry diethyl ether (50 ml). After heating under reflux for a further 15 minutes the reaction mixture was then worked up and ether extracted as previously described for the undeuterated material, 3-(2'-hydroxyphenyl)propanol. Removal of the ether under reduced pressure gave the required product as a colourless viscous liquid (11g, 96%). This material was identified by comparison with the non-deuterated material and was sufficiently pure to be used without further purification.

(b) 2H-2,2-Dideutero-3,4-dihydro-1-benzopyran

To a stirred solution of 1,1-dideutero-3-(2'-hydroxyphenyl)-propanol (10g) in dry benzene (30 ml) was slowly added phosphorus tribromide, over a 45 minute period. The mixture was heated until hydrogen bromide gas ceased to be evolved and then worked up and extracted in the manner previously described for 2H-3,4-dihydro-1--benzopyran. Removal of the benzene under reduced pressure followed by vacuum distillation gave the required product (4.6g, 52%) as a colourless liquid b.p. 161 °C at 15 mm Hg. This material was identified by comparison with the non-deuterated material.
δ ^{1}H N.M.R. (60 MHz) $CDCl_3$; 1.8-2.0 (m, 2H), 2.6-2.85 (m, 2H), 6.55-7.2 (m, 4H).

(c) cis-Octahydro-2,2-dideutero-1-benzopyran

2H-2,2-Dideutero-3,4-dihydro-1-benzopyran (1.5g) in cyclohexane (15 ml) was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 35 atm using 10% palladium on charcoal as catalyst (300 mg). The autoclave was heated to 130 °C for 38h and then allowed to cool. The resulting reaction mixture was then worked up in the manner indicated for the hydrogenation of 2H-3,4-dihydro-1-benzopyran. Vacuum distillation of the crude material (1.4g) gave octahydro-2,2-dideutero-1-benzopyran (1.2g, 77%) as a colourless liquid b.p. 32 °C at 0.1 mm Hg as a mixture of the cis (91%) and trans (9%) isomers. Mass spectrometry gave M^+ = 142 requires M^+ = 142.2.

^{1}H N.M.R. Spectral Data Plate 5

3. Reactions Involved with the Synthesis of Octahydro-2,2--dimethyl-1-benzopyran

(a) 4-(2'-Hydroxyphenyl)-2-methylbutan-2-ol

To a stirred mixture of dry magnesium turnings (35g) in dry diethyl ether (100 ml) was added a crystal of iodine together with a little methyl iodide (5g). When the reaction had initiated, methyl iodide (200g) in dry diethyl ether (150 ml) was added dropwise over about 1.5h. After a further 15 minutes 2H-3,4-dihydro-1-benzopyran-2-one (102g) in dry diethyl ether (100 ml) was slowly added. Once the addition had been completed an excess of dilute sulphuric acid was slowly added. The ether layer was then removed and the remaining aqueous layer extracted with several portions of ether. The combined extracts were then dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave the crude solid. Recrystallisation from chloroform gave the required product (110g, 89%) as a white crystalline solid m.p. 113 °C (literature[80] m.p. 112-112.5 °C). Microanalysis gave C, 73.05; H, 8.75. Calc. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95%.

(b) 2H-3,4-Dihydro-2,2-dimethyl-1-benzopyran

This material was prepared by the method outlined by L.I. Smith and P.M. Ruoff[46].

4-(2'-Hydroxyphenyl)-2-methylbutan-2-ol (40g) was heated under reflux for 15 minutes with 10% acetic acid (200 ml) and 50% sulphuric acid (300 ml). After this time the original white solid had been converted to a yellow immiscible liquid. The mixture was extracted with several portions of ether which were then combined, washed with sodium bicarbonate solution and dried over anhydrous magnesium sulphate.

Removal of the ether under reduced pressure and vacuum distillation of the resulting oil gave the required product (30g, 83%) as a colourless liquid b.p. 63 °C at 0.1 mm Hg (literature[80] b.p. 98-98.5 °C at 11.5 mm Hg).

δ^1H N.M.R. (60 MHz) $CDCl_3$; 1.3 (s, 6H), 1.6-1.9 (m, 2H), 2.55-2.85 (m, 2H)m 6.55-7.2 (m, 4H).

(c) Hydrogenation of 2H-3,4-Dihydro-2,2-dimethyl-1-benzopyran

2H-3,4-Dihydro-2,2-dimethyl-1-benzopyran (26g) in cyclohexane (150 ml) was hydrogenated in a 1ℓ steel autoclave (Baskerville) initially charged to a pressure of 78 atm using 10% palladium on charcoal as catalyst (1.5g). The autoclave was heated at 121 °C for 2h and then allowed to cool slowly overnight. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the cyclohexane removed under reduced pressure to give a colourless liquid (27g). Analytical gas liquid chromatography using a 5ft x 1/8" column containing 3% OV101 on Chromosorb W at 120 °C and N_2(g) ∿ 30 ml min^{-1} indicated that all the starting material had been reduced to give three components (in approximately equal amounts). These components were then separated by distillation under reduced pressure on a spinning band distillation column.

Component A (g.l.c. retention time = 2.9 min), isolated as a colourless liquid b.p. 95 °C at 10.5 mm Hg was identified as a mixture of cis-(84%) and trans-octahydro-2,2-dimethyl-1-benzopyran (16%). Micro-analysis gave C, 78.5; H, 12.3. $C_{11}H_{20}O$ requires C, 78.5; H, 12.0%.

cis-Octahydro-2,2-dimethyl-1-benzopyran.

δ^1H N.M.R. (100 MHz) $CDCl_3$; 1.21 (m, 6H), 1.04-2.02 (m, 13H), 3.78 (broad s, 1H).

$\delta^{13}C$ N.M.R. $CDCl_3$; 71.54s, 67.36d, 34.54d, 32.34t, 31.95q, 30.95t, 26.21t, 26.04t, 24.83t, 22.09q, 2036t.

trans-Octahydro-2,2-dimethyl-1-benzopyran

$\delta^{13}C$ N.M.R. $CDCl_3$; 74.60d, 42.19D, 37.01t, 33.12, 31.83, 31.68, 27.42, 25.91, 25.24. Some signals probably obscured by overlap with those of major isomer.

Component B (g.l.c. retention time = 3.0 min), obtained as a colourless liquid b.p. 96 °C at 10.5 mm Hg, was identified as 2H-3,4,5,6,7,8-hexahydro-2,2-dimethyl-1-benzopyran. This fraction was contaminated with a small amount of Component A.

$\delta^{1}H$ N.M.R. (60 MHz) $CDCl_3$; 1.25 (s, 6H), 1.45-2.1 (m, 12H).

$\delta^{13}C$ N.M.R. $CDCl_3$; 144.51s, 102.19s, 72.46s, 33.53, 28.68, 27.87, 26.46(x2), 23.61, 23.32, 23.12.

Component C (g.l.c. retention time = 5.7 min), isolated as a colourless liquid b.p. 63 °C at 0.2 mm Hg, was identified as an isomeric mixture of cis- (32%) and trans-2-(3'methylbutyl)cyclohexanol (68%).

$\delta^{1}H$ N.M.R. (60 MHz) $CDCl_3$; 0.8-1.0 (d, 6H), 0.9-2.0 (m, 15H), 3.0-3.45 (m, 1H of trans isomer), 3.75-3.95 (broad s, 1H of cis isomer).

cis-2-(3'-methylbutyl)cyclohexanol

$\delta^{13}C$ N.M.R. $CDCl_3$; 74.32d, 45.24d, 35.88t, 35.65t, 30.16t, 29.90t, 28.44d, 25.62t, 24.96t, 22.95q, 22.41q.

trans-2-(3'-methylbutyl)cyclohexanol

$\delta^{13}C$ N.M.R. $CDCl_3$; 69.25d, 41,68dm 36.49t, 33.05t, 29.48, 28.24, 26.68t, 25.20, 22.71q, 22.60q, 20.68t.

(d) 2H-3,4,5,6,7,8-Hexahydro-2,2-dimethyl-1-benzopyran

This material was prepared using the method previously described for 2H-3,4,5,6,7,8-hexahydro-1-benzopyran.

Lithium shot (4g) was stirred for 1h in ethylamine (75 ml) and dimethylamine (75 ml) in the apparatus previously described. 2H-3,4-Dihydro-2,2-dimethyl-1-benzopyran (9.6g) was then added over a 10 minute period and the solution stirred for 17h after which time the unreacted lithium was removed. The reaction mixture was then worked up and ether extracted as previously described. The crude product (7.6g) was distilled under vacuum to give the required product (7g, 71%) as a colourless liquid b.p. 48 °C at 0.08 mm Hg (literature[81] b.p. 83-84 °C at 12 mm Hg). Microanalysis gave C, 79.6; H, 10.85. Calc. for $C_{11}H_{18}O$: C, 79.45; H, 10.9%.

4. Reactions Involved with the Synthesis of Octahydro-6-methyl--1-benzopyran

(a) 2H-3,4-Dihydro-6-methyl-1-benzopyran-2-one

2H-6-Methyl-1-benzopyran-2-one (57g) in ethanol (100 ml) was hydrogenated at room temperature and pressure using a 10% palladium on charcoal catalyst (2g). After about 2 days the resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the ethanol removed under reduced pressure to give the required product (53g, 94%) as a colourless viscous liquid. This material was sufficiently pure to be used without the need for further purification.

(d) 2H-3,4,5,6,7,8-Hexahydro-2,2-dimethyl-1-benzopyran

This material was prepared using the method previously described for 2H-3,4,5,6,7,8-hexahydro-1-benzopyran.

Lithium shot (4g) was stirred for 1h in ethylamine (75 ml) and dimethylamine (75 ml) in the apparatus previously described. 2H-3,4-Dihydro-2,2-dimethyl-1-benzopyran (9.6g) was then added over a 10 minute period and the solution stirred for 17h after which time the unreacted lithium was removed. The reaction mixture was then worked up and ether extracted as previously described. The crude product (7.6g) was distilled under vacuum to give the required product (7g, 71%) as a colourless liquid b.p. 48 °C at 0.08 mm Hg (literature[81] b.p. 83-84 °C at 12 mm Hg). Microanalysis gave C, 79.6; H, 10.85. Calc. for $C_{11}H_{18}O$: C, 79.45; H, 10.9%.

4. Reactions Involved with the Synthesis of Octahydro-6-methyl--1-benzopyran

(a) 2H-3,4-Dihydro-6-methyl-1-benzopyran-2-one

2H-6-Methyl-1-benzopyran-2-one (57g) in ethanol (100 ml) was hydrogenated at room temperature and pressure using a 10% palladium on charcoal catalyst (2g). After about 2 days the resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the ethanol removed under reduced pressure to give the required product (53g, 94%) as a colourless viscous liquid. This material was sufficiently pure to be used without the need for further purification.

(b) 3-(2'-Hydroxy-5'methylphenyl)propanol

A solution of 2H-3,4-dihydro-6-methyl-1-benzopyran-2-one (41g) in dry diethyl ethyl (70 ml) was added over a 1h period to a stirred slurry of lithium aluminium hydride (7g) in dry diethyl ether (200 ml). After heating under reflux for 15 minutes ethyl acetate (50 ml) was cautiously added with thorough stirring. Dilute hydrochloric acid was then added until in excess. The ether layer was decanted off and the aqueous layer extracted with several further portions of ether. After drying the combined ether extracts over anhydrous magnesium sulphate the ether was removed under reduced pressure on a rotary evaporator to give the required product (29g, 69%) as a colourless viscous liquid. This material was then used without further purification.

δ^1H N.M.R. (60 MHz) $CDCl_3$; 1.55-2.0 (m, 2H), 2.15 (s, 3H), 2.5-2.8 (t, 2H), 3.4-3.65 (t, 2H), 5.2 (broad s, 2H), 6.6-7.0 (m, 3H).

(c) 2H-3,4-Dihydro-6-methyl-1-benzopyran

To a stirred solution of 3-(2'-hydroxy-5'-methylphenyl)propanol (27g) in dry benzene (100 ml), was slowly added phosphorus tribromide (33g), over a 45 minute period. The mixture was then heated under reflux until the evolution of hydrogen bromide gas ceased. Dilute sodium hydroxide was added until the solution became alkaline and the benzene layer then removed. This was combined with several benzene extractions of the aqueous layer and then dried over anhydrous magnesium sulphate. Removal of the benzene under reduced pressure followed by vacuum distillation of the resulting oil gave the required product (21g, 87%) as a colourless liquid b.p. 105 °C at 11 mm Hg (literature[37] b.p. 111-112 °C at 18 mm Hg).

δ ^{1}H N.M.R. (60 MHz) $CDCl_3$; 1.7-2.1 (m, 2H), 1.15 (s, 3H), 2.5-3.8 (t, 2H), 3.9-4.15 (t, 2H), 6.55-6.95 (m, 3H).

(d) Octahydro-6-methyl-1-benzopyran

2H-3,4-Dihydro-6-methyl-1-benzopyran (17g) in cyclohexane (150 ml) was hydrogenated in a 1ℓ steel autoclave (Baskerville) initially charged to a pressure of 80 atm using a 10% palladium on charcoal catalyst (2g). The autoclave was heated to 160 °C for 15h and then allowed to cool slowly overnight. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the cyclohexane then removed under reduced pressure on a rotary evaporator to give a colourless liquid (17g). Analytical gas liquid chromatography using a 5ft x 1/8" column containing 3% OV101 on Chromosorb W at 117 °C and N_2(g) = 35 ml min^{-1} indicated both the presence of starting material ($\sim$ 35%, retention time = 5.9 min) and the required product ($\sim$ 65%, retention time = 3.1 min). Distillation of this material using a spinning band column under reduced pressure gave the required product as a colourless liquid b.p. 98-100 °C at 14 mm Hg (literature[37] b.p. 100-101 °C at 25 mm Hg, unspecified stereochemistry). This product was later shown by ^{13}C n.m.r. spectroscopy to consist of a mixture of cis-(9H,10H)-cis--(6H,10H)-octahydro-6-methyl-1-benzopyran (91%) and trans-(9H,10H)--cis-(6H,10H)-octahydro-6-methyl-1-benzopyran (9%). Microanalysis gave C, 77.95; H, 11.65. $C_{10}H_{18}O$ requires C, 77.85; H, 11.75%.

^{1}H N.M.R. Spectral Data Table 53 Plate 20

^{13}C N.M.R. Spectral Data Tables 54 and 55

5. Reactions Involved with the Synthesis of Octahydro-3-methyl--1-benzopyran

(a) 2-(2'-Carbomethoxypropyl)cyclohexanone

This material was prepared by the method of G. Stork, et al.[50].

1-Pyrrolidino-1-cyclohexene (47.5g), prepared in the usual way[50], was added to a solution of methyl methacrylate (54g) in dry dimethyl formamide (300 ml). After the reaction mixture had been heated under reflux for about 46h water (30 ml) was added and the mixture refluxed for a further 1h. The whole solution was then poured into water (500 ml) and extracted with several portions of diethyl ether. These extracts were washed with dilute hydrochloric acid followed by dilute sodium bicarbonate and then dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure gave the crude product (44g). Vacuum distillation of this material gave the required product (32g, 51%) as a colourless liquid b.p. 80 °C at 0.1 mm Hg (literature[50] b.p. = 148-150 °C at 18 mm Hg). ^{13}C n.m.r. spectroscopy of the product indicated the presence of equal amounts of both epimeric diastereoisomers.

δ^1H N.M.R. (60 MHz) $CDCl_3$; 1.5 (d, 3H), 1.2-2.8 (m, 12H), 3.7 (s, 3H).

(b) 2-(3'-Hydroxy-2'-methylpropyl)cyclohexanone

2-(2'-Carbomethoxypropyl)cyclohexanone (2g) in dry benzene (20 ml) together with ethane-1,2-diol (0.7g) and p-toluene sulphonic acid (10mg) was heated under reflux for 3h. Removal of the benzene under reduced pressure gave the crude ketal (2.4g). This material in dry diethyl ether (15 ml) was then slowly added to a stirred mixture of lithium aluminium hydride (0.4g) in dry diethyl ether (15 ml). The resulting mixture was then left stirring overnight. Ethyl acetate (8 ml) was

then cautiously added. This was followed by the addition of dilute hydrochloric acid. The ether layer was decanted off and the remaining aqueous solution extracted with ether. The combined extracts were then dried over anhydrous magnesium sulphate. Removal of the ether on a rotary evaporator under reduced pressure gave the desired product (1.6g) which was used without further purification.

(c) 2H-3,4,5,6,7,8-Hexahydro-3-methyl-1-benzopyran

2-(3'-Hydroxy-2'-methylpropyl)cyclohexanone (1.6) in dry benzene (30 ml) was heated under reflux with p-toluene sulphonic acid (10 mg) for 1h with azeotropic removal of water. The benzene was then removed under reduced pressure to give the crude product. Vacuum distillation of this material gave the required product (0.8g, 56%) as a colourless liquid b.p. 36-38 °C at 0.1 mm Hg (literature[82] b.p. 82-83 °C at 9 mm Hg).

δ^1H N.M.R. (60 MHz) $CDCl_3$, 0.8-1.05 (d, 3H), 1.2-2.25 (m, 11H), 3.2-3.7 (m, 1H), 3.8-4.1 (m, 1H).

δ^{13}C N.M.R. $CDCl_3$; 146.1s, 103.6s, 71.1t, 34.0, 28.9, 27.8, 27.1, 23.2, 23.0, 17.3q.

(d) Octahydro-3-methyl-1-benzopyran

2H-3,4,5,6,7,8-Hexahydro-3-methyl-1-benzopyran (0.8g) in cyclohexane (15 ml) was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 37 atm using 10% palladium on charcoal (250mg) as the catalyst. The autoclave was heated to 104 °C for 9h and then allowed to cool slowly. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the cyclohexane removed under reduced pressure on a rotary evaporator to give the crude product (0.8g). Analytical gas liquid chromatography

of this material using a 5ft x 1/8" column containing 3% OV101 on Chromosorb W at 118 °C with a nitrogen flow rate of 43 ml min^{-1} indicated the presence of a small amount of starting material (~ 7%, retention time = 3.2 min) together with the required product (~ 93%, retention time = 2.7 min). Microdistillation under reduced pressure gave the required product as a colourless liquid b.p. 94-95 °C at 14 mm Hg. This material was later shown by n.m.r. spectroscopy to be a mixture of trans-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1-benzopyran (19%) and cis-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1-benzopyran (81%). Microanalysis gave C, 77.9; H, 11.75. $C_{10}H_{18}O$ requires C, 77.85; H, 11.75%. Mass spectrometry gave M^+ = 154 requires M^+ = 154.2.

^1H N.M.R. Spectral Data Table 56

^{13}C N.M.R. Spectral Data Tables 57 and 58

(e) Separation of the 2-(2'-Carbomethoxypropyl)cyclohexanone diastereoisomers

A medium pressure chromatography column (Whatman, 100cm x 25mm) freshly packed with silica (300g, Kieselgel 60) was eluted with a solvent mixture of 90% petrol (60-80) and 10% ethyl acetate (dried over molecular sieve) at a rate of 15 ml h^{-1}. The diastereoisomer mixture (10.5g) was then injected onto the column and fractions collected at a rate of $1h^{-1}$ thereafter for about 150h. Each fraction was then spotted onto a silica TLC plate which in turn was exposed to iodine vapour to find those fractions containing the diastereoisomers. Since the diastereoisomers were eluted without a visible separation ^{13}C n.m.r. spectroscopy was used to find the boundary between the pure fractions. The pure fractions were then combined to give samples

of each of the diastereoisomers (A and B).

Diastereoisomer A (3.88g, retention time ∿ 61-95h)

δ^{13}C N.M.R. $CDCl_3$; 212.04s, 176.77s, 51.37q, 48.60d, 42.19t, 37.44d, 34.80t, 33.75t, 28.15t, 25.14t, 17.81q.

Diastereoisomer B (1.56g, retention time ∿ 69-120h)

δ^{13}C N.M.R. $CDCl_3$; 211.87s, 176.39s, 51.41q, 48.22d, 41.92t, 36.74d, 34.04t, 33.31t, 28.01t, 24.99t, 17.64q.

(f) Catalytic hydrogenation of 2-(2'-carbomethoxypropyl)cyclohexanone

A quantity of the epimer of 2-(2'-carbomethoxypropyl)cyclohexanone (2.3g), having the shorter retention time on medium pressure chromatography, was placed in an autoclave (Berghof), together with cyclohexane (14 ml) and a 10% palladium on charcoal catalyst (0.6g). The autoclave was charged to 40 atm with hydrogen and then heated to 123 °C for about 16.5h. The hydrogenated reaction mixture was then filtered through a pad of "Hyflo Supercel" filter aid and the cyclohexane removed on a rotary evaporator. A colourless liquid (2.0g) was obtained.

Analysis of this material by ^{1}H and ^{13}C n.m.r. spectroscopy suggested that all four isomers of octahydro-3-methyl-1-benzopyran--2-one had been formed and that some unreduced material was also present (∿ 20%). The ^{13}C n.m.r. spectrum of the unreduced material suggested that the starting material had undergone partial epimerization such that only about two thirds of that remaining was in its original isomeric form.

δ^1H N.M.R. (60 MHz), $CDCl_3$; ∿ 0.75-2.95 (complex envelope of overlapping resonances), 3.7 (s, $-CO_2\underline{CH}_3$ of starting material), 3.6-4.2 (poorly resolved m, H9 of trans-fused isomers), 4.45-4.65 (broad s, H9 of cis-fused isomers).

$\delta^{13}C$ N.M.R. $CDCl_3$; 15.8-212.0 (complex spectrum due to the number of isomers present, over 52 signals were observed). Four signals, those at 75.64, 79.16, 80.59 and 84.40 p.p.m., were readily identified as arising from the C9 carbons in the "lactone" isomers.

(g) Reduction and cyclisation of 2-(2'-carbomethoxypropyl)cyclohexanone to octahydro-3-methyl-1-benzopyran-2-one

(i) A quantity of one of the isomerically pure diastereoisomers of 2-(2'-carbomethoxypropyl)cyclohexanone (492.8mg), that having the shorter retention time upon medium pressure chromatography, was placed in a ^{13}C n.m.r. tube together with deuterochloroform (5.25 ml) and a small amount of tetramethylsilane as reference. Sodium borohydride (23.5mg, 1/4 molar equivalent) was then added. This was followed by the addition of methanol (1.75 ml) which caused a reaction to occur. After a few minutes the ^{13}C n.m.r. spectrum of the reaction mixture was consistent with the formation of the cis and trans isomers of 2-(2'-carbomethoxypropyl)cyclohexanol as the major products although some of this material had undergone cyclisation to give a cis and a trans isomer of octahydro-3-methyl-1-benzopyran-2-one. A small amount ($\sim$ 5%) of unreduced starting material was also present.

To complete the cyclisation, the contents of the n.m.r. tube were poured into dilute hydrochloric acid (1.0M, 25 ml) and then extracted with diethyl ether. Removal of the diethyl ether on a rotary evaporator left a colourless liquid ($\sim$ 400mg) which, upon examination by ^{1}H and ^{13}C n.m.r. spectroscopy, was shown to contain equal quantities of a cis- and a trans-fused isomer of octahydro-3-methyl-1-benzopyran-2-one.

Before hydrochloric acid treatment.

$\delta^{13}C$ N.M.R., $CDCl_3$:MeOH(3:1); Complex spectrum consistent with the presence of two major and two minor components. Some signals could be assigned as follows; 81.38 (C9 of the trans-fused lactone), 80.01 (C9 of the cis-fused lactone), 74.65 (C-OH of the trans-cyclohexanol isomer), 68.67 (C-OH of the cis-cyclohexanol isomer).

After hydrochloric acid treatment.

$\delta^{13}C$ N.M.R., $CDCl_3$; 175.74s, 174.75s, 80.65d (C9 of the trans-fused lactone), 79.19d (C9 of the cis-fused lactone), 37.68d, 34.31, 33.65, 33.33, 33.11, 31.87, 31.64, 31.52, 30.73, 25.22, 25.01, 24.58, 23.94, 19.66t, 1805q, 16.76q.

$\delta^{1}H$ N.M.R. (100 MHz), $CDCl_3$; 0.76-2.73 (Complex envelope of overlapping resonances), 3.71-4.06 (poorly resolved m, H9 of a trans-fused lactone), 4.50 (broad s, H9 of a cis-fused lactone).

(ii) A quantity of one of the isomerically pure diastereoisomers of 2-(2'-carbomethoxypropyl)cyclohexanone (250mg), that having the longer retention time upon medium pressure chromatography, was placed in a ^{13}C n.m.r. tube together with deuterochloroform (5.25 ml) and a small amount of tetramethylsilane as reference. Sodium borohydride (12.5mg, 1/4 molar equivalent) was then added. This was followed by the addition of methanol (1.75 ml) which caused a reaction to occur. After a few minutes the ^{13}C n.m.r. spectrum was consistent with the formation of a trans-fused isomer of octahydro-3-methyl-1-benzopyran-2-one and a cis-fused isomer of 2-(2'-carbomethoxypropyl)cyclohexanol.

The contents of the n.m.r. tube were treated with dilute hydrochloric acid and then ether extracted, as described in (i). The colourless liquid obtained ($\sim$ 210 mg) gave ^{1}H and ^{13}C n.m.r. data that

indicated no change had occurred in the reduction products as a result of this treatment.

The reduction products were therefore heated under reflux in benzene (25 ml) with a trace of p-toluenesulphonic acid (∿ 5mg) for about 2h in a Dean and Stark apparatus. Removal of the benzene on a rotary evaporator gave the crude products as a colourless liquid (∿ 190mg). Examination of this material by ^{1}H and ^{13}C n.m.r. spectroscopy gave data consistent with the formation of one cis- and one trans-fused isomer of octahydro-3-methyl-1-benzopyran-2-one.

Before heating under reflux in benzene.

$\delta^{13}C$ N.M.R., $CDCl_3$:MeOH (3:1); 178.56, 175.66, 85.16d (C9 of a trans-fused lactone), 69.13d (C-OH of a cis-cyclohexanol isomer), 51.75q, 40.01, 39.58, 37.28. 36/96, 36.28, 36.08, 32.97, 32.55, 30.85, 26.77, 25.27, 25.16, 24.36, 20.75t, 18.08q, 17.64q.

After heating under reflux in benzene.

$\delta^{13}C$ N.M.R., $CDCl_3$; 176.10, 174.02, 84.40d (C9 of a trans-fused lactone), 75.67d (C9 of a cis-fused lactone), 39.75, 36.65, 36.21, 33.43, 33,19, 32.43, 32.28, 30.64, 29.59(x2), 25.05, 24.52, 24.11, 20.24, 17.61, 15.82.

$\delta^{1}H$ N.M.R. (100 MHz), $CDCl_3$; 0.80-2.88 (Complex envelope of overlapping resonances), 3.75-4.12 (poorly resolved m, H9 of a trans-fused lactone), 4.52 (broad s, H9 of a cis-fused lactone).

The Octahydro-1,4-benzoxazine System

1. Octahydro-1,4-benzoxazine

(a) 2-Nitrophenoxyacetic acid

This material was prepared by the method outlined by T.H. Minton and H. Stephen[83].

To a solution of sodium 2-nitrophenoxide (50g, 0.31 mol) in water (300 ml) was added a solution of sodium bromoacetate (72g, 0.45 mol) in water (300 ml). The mixture was stirred and heated under reflux for 2.5h and then allowed to cool causing much of the unreacted 2-nitrophenol to solidify in the reaction flask. The remaining aqueous solution was decanted off and portions of dilute hydrochloric acid added to gradually lower the pH. After each addition of acid any precipitated material was filtered off and examined. Initial fractions contained largely 2-nitrophenol but below about pH4 it was the 2-nitrophenoxyacetic acid which precipitated out. At this point the solution was made strongly acidic by the addition of hydrochloric acid and cooled to precipitate the desired product. Recrystallisation from water gave the 2-nitrophenoxyacetic acid (27g, 44%) as a brown crystalline solid m.p. 157-158 °C (literature[83] m.p. 156.5 °C). Microanalysis gave C, 48.8; H, 3.45; N, 7.15. Calc. for $C_8H_7NO_5$: C, 48.75, H, 3.6; N, 7.1%.

When this reaction was carried out using the sodium salt of chloroacetic acid instead of sodium bromoacetate a lower yield of 2-nitrophenoxyacetic acid (~ 31%) was obtained.

(b) 2H-1,4-Benzoxazin-3(4H)-one

2-Nitrophenoxyacetic acid (8.4g) in absolute ethanol (50 ml) was hydrogenated at atmospheric pressure using a 10% palladium on charcoal catalyst (400mg) until the appropriate amount of hydrogen had been taken up (3h). The resulting mixture was then heated to boiling and filtered while still hot through a pad of "Hyflo Supercel" filter aid. On cooling, crystals of the desired product precipitated from solution and were filtered off. The resulting filtrate was then reduced in volume to give a further crop of crystals. These two fractions were combined and recrystallised from ethanol to give 2H-1,4-benzoxazin-3(4H)-one (5.7g, 90%) as a white crystalline solid m.p. 174-174.5 °C (literature[84] m.p. 171.5 °C). Microanalysis gave C, 64.2; H, 4.6; N, 9.2. Calc. for $C_8H_7NO_2$: C, 64.4; H, 4.75; N, 9.4%.

(c) 2H-3,4-Dihydro-1,4-benzoxazine

To a stirred suspension of lithium aluminium hydride (1g) in dry diethyl ether (75 ml) was slowly added a suspension of 2H-1,4--benzoxazin-3(4H)-one (6.2g) in diethyl ether (50 ml). Following the addition, the reaction mixture was heated under reflux for 0.5h and then ethyl acetate (25 ml) was cautiously added with thorough stirring. A saturated aqueous solution of potassium sodium tartrate (50 ml) was then added and after the solution had been made alkaline with dilute sodium hydroxide the mixture was extracted with several portions of ether. These extracts were combined and then dried over anhydrous magnesium sulphate. Removal of the ether under reduced pressure followed by vacuum distillation gave the required product (4g, 71%) as a colourless liquid, b.p. 92-94 °C at 0.1 mm Hg (literature[84] b.p. 86.8 °C at 0.5 mm Hg).

(d) Octahydro-1,4-benzoxazine (isomeric mixture)

2H-3,4-Dihydro-1,4-benzoxazine (9.3g) in cyclohexane (240 ml) was hydrogenated in a 1ℓ steel autoclave (Baskerville) initially charged to a pressure of 88 atm using a 10% palladium on charcoal catalyst (1.7g). The autoclave was heated to 108 °C for 4.5h and then allowed to cool slowly overnight. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid and the cyclohexane then removed under reduced pressure on a rotary evaporator to give the crude product. Analytical gas liquid chromatography using a 5ft x 1/8" column containing 3% OV101 on Chromosorb W at 116 °C and N_2(g) = 40 ml min^{-1} indicated the presence of starting material (< 10%, g.l.c. retention time = 7.7 min) together with equal quantities of the cis isomer (g.l.c. retention time = 3.8 min) and trans isomer (g.l.c. retention time = 3.5 min) of octahydro-1,4--benzoxazine. Vacuum distillation gave the required product (mixture of isomers) as a colourless liquid b.p. 40 °C at 0.2 mm Hg.

The derived picrate was crystallised from absolute ethanol as a yellow crystalline solid m.p. 158-162 °C. Microanalysis gave C, 45.6; H, 4.8; N, 15.2. $C_{14}H_{18}N_4O_8$ requires C, 45.4; H, 4.9; N, 15.15%.

(e) Separation of cis- and trans-Octahydro-1,4-benzoxazine

An isomeric mixture of cis- and trans-octahydro-1,4-benzoxazine (1.75g) was separated on a medium pressure chromatography column (Whatman, 100cm x 15mm) freshly packed with silica (200g, Kieselgel 60) and eluted at a rate of 36 ml h^{-1} with methanol (previously dried over molecular sieve). Samples of the fractions, which were collected at a rate of 4 fractions h^{-1}, were spotted onto a silica TLC plate.

This was then exposed to iodine vapour to find those fractions containing the reduced benzoxazines. Unfortunately, the required isomers were only partially separated by the column and therefore it was necessary to examine a number of the fractions by analytical gas liquid chromatography to locate those tubes containing the pure isomers. These fractions were then combined to give Components A and B. Both isomers were completely eluted within 25h.

Component A (retention time ∿ 6.25-9.25h), isolated as a colourless liquid shown to be trans-octahydro-1,4-benzoxazine. Mass spectrometry gave M^+ = 141, requires M^+ = 141.2.

^1H N.M.R. Spectral Data	Tables 7 and 8
	Plates 6 and 7
^{13}C N.M.R. Spectral Data	Table 9

Component B (retention time ∿ 8.25-16.0h), isolated as a colourless liquid was shown to be cis-octahydro-1,4-benzoxazine. Mass spectrometry gave M^+ = 141, requires M^+ = 141.2.

^1H N.M.R. Spectral Data	Tables 12, 13 and 14
^{13}C N.M.R. Spectral Data	Tables 15 and 16
	Plate 10

2. Octahydro-6-methyl-1,4-benzoxazine

(a) 4-Methyl-2-nitrophenoxyacetic acid

To a solution of sodium 4-methyl-2-nitrophenoxide (233g, 1.33 mol) in water (600 ml) was added a solution of sodium bromoacetate (322g, 2.00 mol) in water (600 ml). The mixture was heated under reflux for 8h with continuous stirring and then allowed to cool. Much of the unreacted 2-nitrophenol solidified in the bottom of the reaction flasks and the remaining material, a thick yellow mass, was decanted off. Dilute hydrochloric acid was added to give a solution of pH1 and, after cooling in ice, the mixture was filtered to give the crude product. This was recrystallised from water to give the desired product (135g, 48%) as a pale yellow crystalline solid m.p. 141-142 °C (literature[83] m.p. 141.5 °C). Microanalysis gave C, 51.4; H, 4.15; N, 6.75. Calc. for $C_9H_9NO_5$: C, 51.2; H, 4.3; N, 6.65%.

(b) 2H-6-Methyl-1,4-benzoxazin-3(4H)-one

4-Methyl-2-nitrophenoxyacetic acid (9.2g) in absolute ethanol (150 ml) was hydrogenated for 18h at atmospheric pressure using 10% palladium on charcoal (0.7g) as catalyst. The reaction mixture was then worked up in the usual way. The crude product was recrystallised from ethanol to give 2H-6-methyl-1,4-benzoxazin-3(4H)-one (4.5g, 63%) as a white crystalline solid m.p. 209-210 °C (literature[85] m.p. 203-204 °C). Microanalysis gave C, 66.25; H, 5.5; N, 8.6. Calc. for $C_9H_9NO_2$: C, 66.25; H, 5.55; N, 8.6%.

(c) 2H-3,4-Dihydro-6-methyl-1,4-benzoxazine

2H-6-Methyl-1,4-benzoxazin-3(4H)-one (22.2g) as a suspension in dry diethyl ether (100 ml) was slowly added to a stirred slurry of lithium aluminium hydride (6.7g) in dry diethyl ether (100 ml). Following the addition the reaction mixture was stirred overnight and then worked up in the usual manner. Vacuum distillation of the crude product gave 2H-3,4-dihydro-6-methyl-1,4-benzoxazine (11.2g, 55%) as a colourless oil b.p. 83 °C at 0.1 mm Hg (literature[85] b.p. 102-104 °C at 0.1 mm Hg).

The derived picrate was recrystallised from ethanol as a yellow crystalline solid m.p. 143 °C. Microanalysis gave C, 47.8; H, 3.65; N, 15.05. Calc. for $C_{15}H_{14}N_4O_8$: C, 47.65; H, 3.75; N, 14.8%.

(d) Octahydro-6-methyl-1,4-benzoxazine (isomeric mixture)

2H-3,4-Dihydro-6-methyl-1,4-benzoxazine (3.4g) in water was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 54 atm using a 10% palladium on charcoal catalyst (280mg). The autoclave was heated to 152 °C for 12h and then allowed to cool. The resulting reaction mixture was then worked up in the usual way. The ^{13}C n.m.r. spectrum of the crude product indicated some starting material was still present ($\sim$ 15%) together with the desired "octahydro" isomers. These were present in the ratio of 40:40:8:12 for Components A, B, C and D respectively. Vacuum distillation of the crude product gave the octahydro-6-methyl-1,4--benzoxazine (3.5g) as a colourless liquid b.p. 42 °C at 0.1 mm Hg.

The derived picrate was crystallised from absolute ethanol as a yellow crystalline solid m.p. 161-185 °C. Microanalysis gave

C, 46.75; H, 5.25; N, 14.5. $C_{15}H_{20}N_4O_8$ requires C, 46.9; H, 5.25; N, 14.6%.

(e) Separation of the Octahydro-6-methyl-1,4-benzoxazine isomers

The octahydro-6-methyl-1,4-benzoxazine isomers (1.8g) were separated using the medium pressure chromatography column previously described for the octahydro-1,4-benzoxazine system. The column was eluted with a 90% ethyl acetate, 10% methanol solvent mixture (previously dried over molecular sieve) at a flow rate of 50 ml h^{-1}. Individual fractions were collected at a rate of 2 fractions h^{-1} and examined in the usual manner. The unreduced starting material was eluted well before the required products. However, the required isomers were eluted without a clear separation and therefore a number of samples were examined by ^1H n.m.r. and ^{13}C n.m.r. spectroscopy to find those fractions containing the pure isomers. In this way pure samples of 3 of the 4 isomers were obtained, they are described below in order of elution from the column (the isomers were not completely eluted until after about 30h).

Component A (retention time ~ 4.5-8.0h), isolated as a colourless liquid was shown to be cis-(9H,10H)-trans-(6H,10H)-octahydro-6-methyl--1,4-benzoxazine. Mass spectrometry gave $M^+ = 155$ requires $M^+ = 155.2$.

^1H N.M.R. Spectral Data	Table 17	Plate 11
^{13}C N.M.R. Spectral Data	Tables 19, 20	Plate 12

Component B (retention time ~ 6.0-14.0h), isolated as a colourless liquid was shown to be trans-(9H,10H)-cis-(6H,10H)-octahydro-6-methyl--1,4-benzoxazine. Mass spectrometry gave $M^+ = 155$ requires $M^+ = 155.2$.

^1H N.M.R. Spectral Data	Table 21	Plate 13
^{13}C N.M.R. Spectral Data	Table 22	

Component C (retention time ~ 11.5-13.0h), could not be isolated without contamination from Component B. To obtain a more isomerically pure sample of Component C it was necessary to re-chromatograph the enriched material from several such separations using the conditions employed in the original separation. In this way Component C was obtained with an isomeric purity of about 62%. This component was shown to be trans-(9H,10H)-trans-(6H,10H)-octahydro-6-methyl-1,4--benzoxazine.

^{1}H N.M.R. Spectral Data Table 23

^{13}C N.M.R. Spectral Data Table 24

Component D (retention time = 13-20h), isolated as a colourless liquid, was shown to be cis-(9H,10H)-cis-(6H,10H)-octahydro-6-methyl-1,4-benzoxazine. Mass spectrometry gave M^{+} = 155 requires M^{+} = 155.2.

^{1}H N.M.R. Spectral Data Table 25 Plate 14

^{13}C N.M.R. Spectral Data Table 26

3. Octahydro-7-methyl-1,4-benzoxazine

(a) 5-Methyl-2-nitrophenoxyacetic acid

A solution of sodium bromoacetate (77g, 0.48 ml) in water (300 ml) was added to a solution of sodium 5-methyl-2-nitrophenoxide (57g, 0.33 mol) in water (300 ml). The mixture was stirred and heated under reflux for 6.5h and then allowed to cool. Unreacted nitrophenol solidified in the bottom of the reaction flask and the remaining aqueous solution was decanted off and treated in the usual way. The crude product was recrystallised from water to give the 5-methyl-2-nitrophenoxyacetic acid (28g, 40%) as a pale yellow crystalline solid m.p. 160.5-161 °C (literature[83] m.p. 157-158 °C).

Microanalysis gave C, 50.95; H, 4.25; N, 6.8. Calc. for $C_9H_9NO_5$: C, 51.2; H, 4.3; N, 6.65%.

(b) 2H-7-Methyl-1,4-benzoxazin-3(4H)-one

5-Methyl-2-nitrophenoxyacetic acid (25g) in absolute ethanol (250 ml) was hydrogenated for 17h at atmospheric pressure using 10% palladium on charcoal (1.2g) as catalyst. The resulting mixture was then worked up in the usual way. The crude product was recrystallised from ethanol to give 2H-7-methyl-1,4-benzoxazin-3(4H)-one (12g, 62%) as a white crystalline solid m.p. 198 °C (literature[86] m.p. 194-196 °C). Microanalysis gave C, 66.3; H, 5.7; N, 8.6. Calc. for $C_9H_9NO_2$: C, 66.25; H, 5.55; N, 8.6%.

(c) 2H-3,4-Dihydro-7-methyl-1,4-benzoxazine

To a stirred suspension of lithium aluminium hydride (4.8g) in diethyl ether (100 ml) was slowly added a suspension of 2H-7-methyl--1,4-benzoxazin-3(4H)-one (15.8g) in diethyl ether (100 ml) so as to maintain a steady reflux. Following the addition the reaction mixture was stirred overnight and then worked up in the usual way. Vacuum distillation of the crude product gave 2H-3,4-dihydro-7-methyl--1,4-benzoxazine as a colourless oil b.p. 80-82 °C at 0.15 mm Hg. Microanalysis gave C, 72.5; H, 7.6; N, 9.65. $C_9H_{11}NO$: requires C, 72.45; H, 7.45; N, 9.4%.

(d) Octahydro-7-methyl-1,4-benzoxazine (isomeric mixture)

2H-3,4-Dihydro-7-methyl-1,4-benzoxazine (3.5g) in water (9.2 ml) was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 56 atm with 10% palladium on charcoal (300mg) as catalyst. The autoclave was heated to 153 °C for 17h and then allowed to cool slowly. The resulting reaction mixture was worked

up in the usual way. The ^{13}C n.m.r. spectrum of the crude material indicated the presence of starting material (∿ 30%) together with the desired isomers in the ratio of 42:6:42:10 for Components A, B, C and D respectively. Vacuum distillation of the crude product gave the octahydro-7-methyl-1,4-benzoxazine as a colourless liquid b.p. 57 °C at 0.5 mm Hg.

The derived picrate was crystallised from absolute ethanol as a yellow crystalline solid m.p. 156-165 °C. $C_{15}H_{20}N_4O_8$ requires C, 46.9; H, 5.25; N, 14.6%.

(e) Separation of the Octahydro-7-methyl-1,4-benzoxazine isomers

The octahydro-7-methyl-1,4-benzoxazine isomers (2.7g) were separated using the medium pressure chromatography column previously described for the octahydro-1,4-benzoxazine system. The column was eluted with a 90% ethyl acetate, 10% methanol solvent mixture (previously dried over molecular sieve) at a flow rate of about 7 ml h^{-1}. Individual fractions were collected every 1.5h and examined in the usual manner. Despite the long retention times the required isomers were eluted without clear separation. A number of samples were therefore examined by ^1H n.m.r. and ^{13}C n.m.r. spectroscopy to find those fractions containing the pure isomers. Isomerically pure samples of three of the four isomers were obtained, they are described below in order of elution from the column.

Component A (retention time ∿ 237.0-309.0h), isolated as a colourless liquid, was shown to be cis-(9H,10H)-cis-(7H,9H)-octahydro-7-methyl--1,4-benzoxazine. Mass spectrometry gave $M^+ = 155$ requires $M^+ = 155.2$.

^1H N.M.R. Spectral Data Table 27 Plate 15

^{13}C N.M.R. Spectral Data Table 28

Component B (retention time ∿ 291.0-297.0h), could not be isolated without contamination from the isomeric Components A (∿ 20%) and B (∿ 40%). However, the enriched samples of Component B enabled this component to be identified as trans-(9H,10H)-trans-(7H,9H)-octahydro--7-methyl-1,4-benzoxazine.

^{1}H N.M.R. Spectral Data Table 29

^{13}C N.M.R. Spectral Data Table 30

Component C (retention time ∿ 291.0-360.0h), isolated as a crystalline solid m.p. 73-74 °C (sublimes 45 °C at 0.5 mm Hg), was shown to be trans-(9H,10H)-cis-(7H,9H)-octahydro-7-methyl-1,4-benzoxazine. Mass spectrometry gave M^{+} = 155 requires M^{+} = 155.2.

^{1}H N.M.R. Spectral Data Table 31 Plate 16

^{13}C N.M.R. Spectral Data Table 32

Component D (retention time ∿ 351.0-420.0h), isolated as a colourless liquid, was shown to be cis-(9H,10H)-trans-(7H,9H)-octahydro-7-methyl--1,4-benzoxazine. Mass spectrometry gave M^{+} = 155 required M^{+} = 155.2.

^{1}H N.M.R. Spectral Data Table 33

^{13}C N.M.R. Spectral Data Table 34

4. Octahydro-2-methyl-1,4-benzoxazine

(a) 2-(2'-Nitrophenoxy)propionic acid

This material was prepared by the method previously described for 2-nitrophenoxyacetic acid.

To a solution of sodium 2-nitrophenoxide (193g, 1.20 ml) in water (600 ml) was added a solution of sodium 2-bromopropionate (327g, 1.87 mol) in water (600 ml). The resulting mixture was then heated under reflux with continuous stirring for 20h. This was then

allowed to cool and the reaction worked up as previously described. The product, 2-(2'-nitrophenoxy)propionic acid, was recrystallised from water to give a quantity (77g, 30%) of light brown crystals m.p. 156-158 °C (literature[87] m.p. 157-159 °C). Microanalysis gave C, 51.5; H, 4.25; N, 6.6. Calc. for $C_9H_9NO_5$: C, 51.2; H, 4.3; N, 6.65%.

When this reaction was carried out using sodium 2-chloropropionate instead of sodium 2-bromopropionate a yield of only about 3.5% was obtained.

(b) 2H-2-Methyl-1,4-benzoxazin-3(4H)-one

2-(2'-Nitrophenoxy)propionic acid (28g) in absolute ethanol (250 ml) was hydrogenated at atmospheric pressure using a 10% palladium on charcoal catalyst (1.5g) for 18h. After this time the reaction was worked up in the manner previously described for 2H-1,4-benzoxazin--3(4H)-one. Recrystallisation of the crude product from ethanol gave 2H-2-methyl-1,4-benzoxazin-3(4H)-one (12g, 56%) as a white crystalline solid m.p. 145.5-146 °C (literature[88] m.p. 142-143 °C). Microanalysis gave C, 66.25; H, 5.4; N, 8.5. Calc. for $C_9H_9NO_2$: C, 66.25; H, 5.55; N, 8.6%.

(c) 2H-3,4-Dihydro-2-methyl-1,4-benzoxazine

A suspension of 2H-2-methyl-1,4-benzoxazin-3(4H)-one (30.1g) in dry diethyl ether (300 ml) was added to a stirred slurry of lithium aluminium hydride (9.2g) in dry diethyl ether (140 ml) at a rate which maintained a steady reflux. When the addition had been completed the mixture was stirred for 15h and the reaction mixture worked up in the manner previously described for 2H-3,4-dihydro-1,4-benzoxazine. Vacuum distillation of the crude product gave 2H-3,4-dihydro-2-methyl--1,4-benzoxazine (19. 2g, 67%) as a colourless liquid b.p. 73 °C at 0.1 mm Hg.

The derived picrate was recrystallised from ethanol as a yellow crystalline solid m.p. 164-165 °C (Decomp.). Microanalysis gave C, 47.7; H, 3.65; N, 14.6. $C_{15}H_{14}N_4O_8$: requires C, 47.65; H, 3.75; N, 14.8%.

(d) Octahydro-2-methyl-1,4-benzoxazine (isomeric mixture)

2H-3,4-Dihydro-2-methyl-1,4-benzoxazine (3.6g) in water (9.4 ml) was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 56 atm using a 10% palladium on charcoal catalyst (270mg). The autoclave was heated to 152 °C for 8.5h and then allowed to cool slowly. The resulting reaction mixture was filtered through a pad of "Hyflo Supercel" filter aid, made alkaline with dilute sodium hydroxide and then extracted with ether. After drying the ether extracts over anhydrous magnesium sulphate the solvent was removed under reduced pressure on a rotary evaporator to give the crude octahydro-2-methyl-1,4-benzoxazine. Vacuum distillation of this material gave the required product as a colourless liquid b.p. 46 °C at 0.1 mm Hg. ^{13}C n.m.r. spectroscopy indicated the presence of all the octahydro-6-methyl-1,4-benzoxazine isomers in the ratio of 44:6:44:6 for Components A, B, C and D respectively.

The derived picrate was crystallised from absolute ethanol as a yellow crystalline solid m.p. 153-169 °C. Microanalysis gave C, 46.65; H, 5.1; N, 14.6. $C_{15}H_{20}N_4O_8$ requires C, 46.9; H, 5.25; N, 14.6%.

(e) Separation of the Octahydro-2-methyl-1,4-benzoxazine isomers

The octahydro-2-methyl-1,4-benzoxazine isomers (2.4g) were separated using a medium pressure chromatography column (Whatman, 100cm x 15mm) freshly packed with silica (200g, Kieselgel 60) and eluted with an 80% ethyl acetate, 20% methanol solvent mixture

(previously dried over molecular sieve) at a rate of 26 ml h^{-1}. Fractions were collected twice every hour and samples from these were then spotted onto a silica TLC plate. The plate was then exposed to iodine vapour in order to locate those fractions containing the "octahydro" isomers. Unreduced starting material was eluted first and was well separated from the required isomers which were eluted with only a partial separation To find fractions of the pure isomers it was therefore necessary to examine a number of fractions by ^{1}H and ^{13}C n.m.r. spectroscopy. In this way isomerically pure samples of Components A, C and D were obtained. Unfortunately, fractions containing Component B were heavily contaminated with Components A and C. To obtain a sufficiently pure sample of Component B for our n.m.r. studies those fractions containing Component B were combined and re-chromatographed.

The components are described below in the order in which they were eluted from the chromatography column.

Component A (retention time ∿ 10.5-25.0h), isolated as a colourless liquid, was shown to be cis-(9H,10H)-trans-(2H,9H)-octahydro-2-methyl--1,4-benzoxazine. Mass spectrometry gave M^{+} = 155 requires M^{+} = 155.2.

^{1}H N.M.R. Spectral Data Table 35 Plate 17

^{13}C N.M.R. Spectral Data Table 36

Component B (retention time ∿ 19.0-23.0h), was isolated in only 50% isomeric purity due to contamination from Components A and C. Nevertheless, this sample was sufficiently pure to enable its structure to be identified as that of trans-(9H,10H)-trans-(2H,9H)-octahydro-2--methyl-1,4-benzoxazine.

^{1}H N.M.R. Spectral Data Table 38

^{13}C N.M.R. Spectral Data Table 39

Component C (retention time ∿ 20.0-42.0h), isolated as a white crystalline solid m.p. 64-65 °C (sublimes 45 °C at 0.2 mm Hg), was shown to be trans-(9H,10H)-cis-(2H,9H)-octahydro-2-methyl--1,4-benzoxazine. Mass spectrometry gave M^+ = 155 requires 155.2.

^1H N.M.R. Spectral Data Table 40 Plate 18

^{13}C N.M.R. Spectral Data Table 41

Component D (retention time ∿ 40.0-75.0h), isolated as a colourless liquid was shown to be cis-(9H,10H)-cis-(2H,9H)-octahydro-2-methyl--1,4-benzoxazine. Mass spectrometry gave M^+ = 155 requires M^+ = 155.2.

^1H N.M.R. Spectral Data Table 42

^{13}C N.M.R. Spectral Data Table 43

(f) Hydrogenation of 2H-3,4-Dihydro-2-methyl-1,4-benzoxazine hydorchloride

2H-3,4-Dihydro-2-methyl-1,4-benzoxazine (0.5g) together with hydrochloric acid (6 ml, 1M) was heated under vacuum until only the white solid hydrochloride remained. The hydrochloride in water (6 ml) was then hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 42 atm using a 10% palladium on charcoal catalyst (110mg). The autoclave was heated to 152 °C for 5h and then allowed to cool slowly. The reaction mixture was then worked up in the usual way to give the desired product as a colourless liquid (0.5g). Analysis by ^{13}C n.m.r. spectroscopy indicated all octahydro-2-methyl-1,4-benzoxazine isomers were present, in the ratio of 67:3:23:7 for Components A, B, C and D respectively.

5. Octahydro-3-methyl-1,4-benzoxazine

(a) 2-Nitrophenoxypropanone

This material was prepared by the method outlined by R. Stoermer and H. Brockerhof[71].

To dry powdered sodium 2-nitrophenoxide (56g) was added freshly distilled chloroacetone (300 ml). The mixture was well stirred and heated at 90 °C for 25h and then at 120 °C for 2.5h. After allowing the mixture to cool the excess chloroacetone (b.p. 60 °C at 17 mm Hg) was removed by distillation under reduced pressure and the resulting product steam distilled. To the residue was then added methylated spirits (40 ml). The resulting solution was cooled in ice and then filtered to give a solid brown residue which on recrystallisation from methylated spirits gave the required product (25g, 37%) as a white crystalline solid m.p. 69.5 °C (literature[71] m.p. 69 °C). Microanalysis gave C, 55.4; H, 4.5; N, 7.15. Calc. for $C_9H_9NO_4$: C, 55.4; H, 4.65; N, 7.2%.

(b) 2H-3,4-Dihydro-3-methyl-1,4-benzoxazine

2-Nitrophenoxypropanone (10.7g) in absolute ethanol (150 ml) was hydrogenated at atmospheric pressure using a 10% palladium on charcoal catalyst (0.9g) for 15h. The resulting mixture was filtered through a pad of "Hyflo Supercel" filter aid and the ethanol removed under reduced pressure on a rotary evaporator to give the crude product (8g). Vacuum distillation gave the required product (4.9g, 60%) as a pale yellow oil b.p. 80 °C at 0.1 mm Hg (literature[71] b.p. 150-152 °C at 24 mm Hg).

The derived picrate was recrystallised from ethanol as a yellow crystalline solid m.p. 147-148 °C (literature[71] m.p. 141 °C).

Microanalysis gave C, 47.5; H, 3.75; N, 14.9. Calc. for $C_{15}H_{14}N_4O_8$: C, 47.65; H, 3.75; N, 14.8%.

(c) Octahydro-3-methyl-1,4-benzoxazine (isomeric mixture)

2H-3,4-Dihydro-3-methyl-1,4-benzoxazine (3.4g) in water (9.2 ml) was hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 54 atm using a 10% palladium on charcoal catalyst (290mg). The autoclave was heated to 152 °C for 6h and then allowed to cool slowly. The resulting reaction mixture was then worked up in the usual manner. Vacuum distillation of the crude product gave the octahydro-3-methyl-1,4-benzoxazine as a colourless liquid b.p. 40 °C at 0.1 mm Hg. ^{13}C n.m.r. spectroscopy indicated the presence of all four possible isomers in the ratio of 42:46:7:5 for Components A, B, C and D respectively.

The derived picrate was crystallised from absolute ethanol as a yellow crystalline solid m.p. 157-166 °C. Microanalysis gave C, 46.65; H, 5.3; N, 14.6. $C_{15}H_{20}N_4O_8$ requires C, 46.9; H, 5.25; N, 14.6%.

(d) Separation of the Octahydro-3-methyl-1,4-benzoxazine isomers

The octahydro-3-methyl-1,4-benzoxazine isomers (2.0g) were separated using the medium pressure chromatography column previously described for the 2-methyl system. The column was eluted with an 80% ethyl acetate, 20% methanol solvent mixture (previously dried over molecular sieve) at a flow rate of 28 ml h^{-1}. Individual fractions were collected at a rate of 1 fraction h^{-1} and examined in the usual way. The required isomers were once again eluted without clear separation but examination of a number of fractions by ^{1}H and ^{13}C n.m.r. spectroscopy enabled isomerically pure fractions of three of

the four isomers to be obtained. They are described below in order of elution from the column (the isomers were not completely eluted until after about 50h).

Component A (retention time ∿ 14.0-20.0h), isolated as a colourless liquid, was shown to be cis-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl-1,4-benzoxazine. Mass spectrometry gave M^+ = 155 requires 155.2.

^1H N.M.R. Spectral Data Table 44 Plate 19

^{13}C N.M.R. Spectral Data Table 45

Component B (retention time ∿ 18.0-24.0h), isolated as a colourless liquid, was shown to be trans-(9H,10H)-cis-(3H,10H)-octahydro-3-methyl--1,4-benzoxazine. Mass spectrometry gave M^+ = 155 requires 155.2.

^1H N.M.R. Spectral Data Table 46

^{13}C N.M.R. Spectral Data Table 47

Component C (retention time ∿ 23.0-47.0h), isolated as a colourless liquid, was shown to be cis-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl--1,4-benzoxazine. Mass spectrometry gave M^+ = 155 requires M^+ = 155.2.

^1H N.M.R. Spectral Data Table 48

^{13}C N.M.R. Spectral Data Table 49

Component D (retention time ∿ 29.0-47.0h), could not be isolated without contamination from Component C. To obtain a purer sample of this component it was necessary to re-chromatograph the enriched material from several such separations using the conditions employed in the original separation. In this way a sample of Component D having an isomeric purity of ∿ 80% was obtained. This component was shown to be trans-(9H,10H)-trans-(3H,10H)-octahydro-3-methyl-1,4--benzoxazine. Mass spectrometry gave M^+ = 155 requires M^+ = 155.2.

^1H N.M.R. Spectral Data Table 50

^{13}C N.M.R. Spectral Data Table 51

(e) Hydrogenation of 2H-3,4-Dihydro-3-methyl-1,4-benzoxazine hydrochloride

2H-3,4-Dihydro-3-methyl-1,4-benzoxazine (0.5g) was made into its hydrochloride in the manner indicated for the 2-methyl system. The hydrochloride in water (6 ml) was then hydrogenated in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 38 atm using a 10% palladium on charcoal catalyst (100 mg). The autoclave was heated to 162 °C for 5.5h and then allowed to cool slowly. The resulting reaction mixture was then worked up in the usual manner to give a colourless liquid (0.5g). Analysis by ^{13}C n.m.r. spectroscopy indicated complete reduction to the "octahydro" isomers. They were present in the ratio of 62:26:6:6 for Components A, B, C and D respectively.

(f) Equilibration of the Octahydro-3-methyl-1,4-benzoxazine isomers

A sample of octahydro-3-methyl-1,4-benzoxazine consisting of equal amounts of Components A and B (400mg) in cyclohexane (9 ml) was subjected to hydrogenation conditions in a 150 ml PTFE-lined autoclave (Berghof) initially charged to a pressure of 40 atm using a 10% palladium on charcoal catalyst (400mg). The autoclave was heated to 200 °C for 20h and then allowed to cool. The resulting reaction mixture was then worked up in the usual way to give a colourless liquid (300mg). Analysis by ^{13}C n.m.r. spectroscopy indicated the presence of all four possible isomers in the ratio of 6:82:6:6 for Components A, B, C and D respectively.

Appendix

Although there were no reports of the cis-octahydro-1--benzopyran system when our study of this system was carried out its synthesis has since been reported by Turecek[89].

Turecek prepared both the cis- and trans-fused isomers of octahydro-1-benzopyran as part of a study of the stereo-electronic effect on the decomposition of organic ions in the gas phase. However, he noted briefly that cis-octahydro-1--benzopyran "prefers the conformation with an axial position of the C-O bond on the carbocyclic six-membered ring". This is in agreement with our own observations.

References

1. J.H. van't Hoff, Bull. Soc. chim. France, 1875, 23, 295.
2. J.A. Le Bel, Bull. Soc. chim. France, 1874, 22, 337.
3. H. Sachse, Ber., 1890, 23, 1363.
4. F.G. Riddell, 'The Conformational Analysis of Heterocyclic Compounds', Academic Press, London, 1980.
5. W.G. Dauben and K.S. Pitzer, in 'Steric Effects in Organic Chemistry', ed. M.S. Newman, Chapman and Hall Ltd., London, 1956.
6. J.B. Hendrickson, J. Amer. Chem. Soc., 1961, 83, 4537.
7. M.S. Newman, J. Chem. Educ., 1955, 32, 344.
8. D.H.R. Barton, Experientia, 1950, 6, 316.
9. F.A.L. Anet and R. Anet, in 'Determination of Organic Structures by Physical Methods', ed. F.C. Nachod and J.J. Zuckerman, Academic Press, London, 1971, Vol. 3, p.344.
10. M.N. Hughes, A.M. James and N.R. Silvester, 'S.I. Units and Conversion Tables', The Machinery Publishing Co. Ltd., Brighton, Second Edition.
11. A.H. Lewin and S. Winstein, J. Amer. Chem. Soc., 1962, 84, 2464.
12. C. Romers, C. Altona, H.R. Buys and E. Havinga, in 'Topics in Stereochemistry', ed. Eliel and Allinger, Wiley Interscience, London, 1969, Vol. 4.
13. F.A.L. Anet, C.N. Bradley and G.W. Buchanan, J. Amer. Chem. Soc., 1971, 93, 258.
14. H. Booth and J.R. Everett, J. Chem. Soc., Chem. Comm., 1976, 278.
15. M. Davis and O. Hassel, Acta Chem. Scand., 1963, 17, 1181.
16. C.B. Anderson and D.T. Sepp, J. Org. Chem., 1968, 33, 3272.
17. P.J. Buckley, C.C. Costain and J.E. Perkin, Chem. Comm., 1968, 668.

18. F.A.L. Anet and I. Yavari, J. Amer. Chem. Soc., 1977, 99, 2794.

19. F.W. Vierhapper and E.L. Eliel, J. Org. Chem., 1979, 44, 1081.

20. M.J.T. Robinson, J. Chem. Soc., Chem. Comm., 1975, 844.

21. T.A. Crabb and C.H. Turner, J. Chem. Soc., Perkin Trans II, 1980, 1778.

22. N.S. Zefirov and S.V. Rogozina, Tetrahedron, 1974, 30, 2345.

23. E. Mohr, J. prakt. Chem., 1918, 98, 315.

24. W. Hückel, Annalen, 1925, 441, 1.

25. P.K. Claus, F.W. Vierhapper and R.L. Willer, J. Org. Chem., 1977, 42, 4016.

26. F.W. Vierhapper and R.L. Willer, J. Org. Chem., 1977, 42, 4024.

27. H. Booth and A.H. Bostock, Chem. Comm., 1967, 177.

28. D.V. Griffiths, Ph.D. Thesis, University of Nottingham, 1973.

29. M. Karplus, J. Chem. Phys., 1959, 30, 11.

30. M. Karplus, J. Amer. Chem. Soc., 1963, 85, 2870.

31. J.B. Lambert, H.F. Shurvell, L. Verbit, R.G. Cooks and G.H. Stout, 'Organic Structural Analysis', Collier Macmillan Publishers, London, 1976.

32. J.B. Lambert, J. Amer. Chem. Soc., 1967, 89, 1836.

33. J.B. Lambert, Acc. Chem. Res., 1971, 4, 87.

34. H. Booth and D.V. Griffiths, J. Chem. Soc., Perkin Trans. II, 1973, 842.

35. R.P. Rooney and S.A. Evans, Jr., J. Org. Chem., 1980, 45, 180.

36. P.L. de Benneville and R. Connor, J. Amer. Chem. Soc., 1940, 62, 283.

37. P.L. de Benneville and R. Connor, J. Amer. Chem. Soc., 1940, 62, 3067.

38. J.A. Hirsch and G. Schwartzkopf, J. Org. Chem., 1973, 38, 3534.

39. J.A. Hirsch and G. Schwartzkopf, J. Org. Chem., 1974, 39, 2040.

40. E. Guy and F. Winternitz, Ann. Chim., 1969, 4, 57.

41. V. Spéziale, M. Amat and A. Lattes, J. Heterocycl. Chem., 1976, 13, 349.

42. M.C. Benhamou, G. Etemad-Moghamdam, V. Spéziale and A. Lattes, Synthesis, 1979, 891.

43. S. Sethna and R. Phadke, in 'Organic Reactions', ed. R. Adams, A.H. Blatt, A.C. Cope, F.C. McGrew, C. Niemann and H.R. Snyder, Chapman and Hall Limited, London, 1953, Vol. VII, p.1.

44. I.J. Borowitz, G. Gonis, R. Kelsey, R. Rapp and G.J. Williams, J. Org. Chem., 1966, 31, 3032.

45. J. Colonge, J. Dreux and M. Thiers, Bull. Soc. chim. France, 1959, 1459.

46. L.I. Smith and P.M. Ruoff, J. Amer. Chem. Soc., 1940, 62, 145.

47. W. Carruthers, 'Some modern methods of organic synthesis', Cambridge University Press, Cambridge, Second Edition.

48. M.I. Foreman, in 'Nuclear Magnetic Resonance', Specialist Periodical Reports, The Chemical Society, London, 1975, Vol. 4.

49. C. Normant-Chefnay and P. Maitte, Bull. Soc. chim. France, 1974, 1090.

50. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz and R. Terrell, J. Amer. Chem. Soc., 1963, 85, 207.

51. H.O. House, H. Babad, R.B. Toothill and A.W. Noltes, J. Org. Chem., 1962, 27, 4141.

52. J.T. Edward and J.M. Ferland, Chem. and Ind., 1964, 975.

53. G.R. Pettit, B. Green, T.R. Kasturi and U.R. Ghatak, Tetrahedron, 1962, 18, 953.

54. A. Pelter, Chem. and Ind., 1976, 888.

55. R.U. Lemieux, R.K. Kullnig, H.J. Bernstein and W.G. Schneider, J. Amer. Chem. Soc., 1958, 80, 6098.

56. M. Barefield, A.M. Dean, C.J. Fallick, R.J. Spear, S. Sternhell, and P.W. Westerman, J. Amer. Chem. Soc., 1975, 97, 1482.

57. J.B. Stothers, 'Carbon-13 NMR Spectroscopy', Academic Press, London, 1972, Vol. 24, p.49.

58. V.M. Rao and R. Kewley, Canad. J. Chem., 1969, 47, 1289.

59. J.J. Perie, A. Lattes and A. Dobrev, Tetrahedron Letters, 1972, 4013.

60. G. Bettoni, C. Franchini, R. Perrone and V. Tortorella, Tetrahedron, 1980, 36, 409.

61. G. Barker, G.P. Ellis and D.A. Wilson, J. Chem. Soc. C., 1971, 2079.

62. H. Sliwa, Bull. Soc. chim. France, 1970, 631.

63. H. Shirai et al., Chem. Abstr., 1970, 73, 25378.

64. W.B. Smith and B.A. Shoulders, J. Phys. Chem., 1965, 69, 579.

65. H. Booth, Tetrahedron, 1966, 22, 615.

66. D.K. Dalling and D.M. Grant, J. Amer. Chem. Soc., 1967, 89, 6612.

67. A.J. Jones, C.P. Beeman and M.U. Hasan, Canad. J. Chem., 1976, 54, 126.

68. H. Booth, D.V. Griffiths and M.L. Jozefowicz, J. Chem. Soc., Perkin Trans. II, 1976, 751.

69. T.P. Forrest, J. Amer. Chem. Soc., 1975, 97, 2628.

70. M.L. Huggins, J. Amer. Chem. Soc., 1953, 75, 4123.

71. R. Stoermer and H. Brockernof, Ber., 1897, 30, 1631.

72. C. Altona and M. Sundaralingam, Tetrahedron, 1970, 26, 925.

73. R.E. Rindfusz, J. Amer. Chem. Soc., 1919, 41, 665.

74. I.J. Borowitz and G. Gonis, Tetrahedron Letters, 1964, 1151.

75. J. Colonge, R. Falcotet and R. Gaumont, Bull. Soc. chim. France, 1958, 211.

76. W.B. Renfrow, D. Oakes, C. Lauer and T.A. Walter, J. Org. Chem., 1961, 26, 935.

77. D.K. Banerjee, S. Chatterjee and S.P. Bhattacharya, J. Amer. Chem. Soc., 1955, 77, 408.

78. X.A. Dominguez, I.C. Lopez and R. Franco, J. Org. Chem., 1961, 26, 1625.

79. P. Dufey, Bull. Soc. chim. France, 1968, 4653.

80. L. Claisen, Ber., 1921, 54, 200.

81. N.P. Shusherina, T. Kh. Gladysheva, G.D. Mur and R. Ya.Levina, Chem. Abstr., 1964, 61, 14625.

82. I.J. Borowitz, G.J. Williams, L. Gross and R. Rapp, J. Org. Chem., 1968, 33, 2013.

83. T.H. Minton and H. Stephen, J. Chem. Soc., 1922, 121, 1591.

84. J. Cymerman-Craig, W.P. Rogers and M.E. Tate, Austral. J. Chem., 1956, 9, 397.

85. J.R. Geigy A.-G., Chem. Abstr., 1964, 60, 10693.

86. K.L. Kirk and L.A. Cohen, J. Amer. Chem. Soc., 1972, 94, 8142.

87. C.A. Bischoff, Ber., 1900, 33, 924.

88. K.W. Wheeler, J. Med. Pharm. Chem., 1962, 5, 1378.

89. F. Turecek, Coll. Czech. Chem. Comm., 1982, 47, 858.