Tetrahedron Vol 46, No 5, pp 1625-1652, 1990
Printed in Great Britain

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EXPERIMENTAL STUDIES OF THE ANOMERIC EFFECT. PART III.[1]
ROTAMERIC PREFERENCES ABOUT THE EXO-CYCLIC C_2-X BOND IN EQUATORIAL AND AXIAL 2-METHOXY- AND 2-METHYLAMINO-TETRAHYDROPYRANS.

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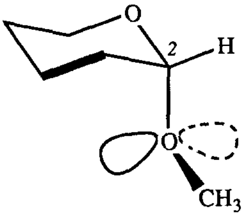
(*Received in UK* 10 *October* 1989)

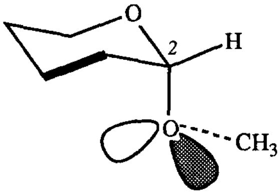
Abstract - Values of $^3J(CC)$, $^3J(CH)$, $^4J(CH)$ and $^3J(HH)$, supported by n.O.enhancements, in nmr spectra of 2-methoxy- and 2-methylamino-tetrahydropyrans, point to a very strong preference for rotamers in which an exo-cyclic heteroatom lone pair is antiperiplanar to the endo-cyclic C_2-O bond ("exo-anomeric effect")

In 2-methoxytetrahydropyrans, the axial ($1a_1 \rightleftharpoons 1a_2 \rightleftharpoons 1a_3$) and equatorial ($2e_1 \rightleftharpoons 2e_2 \rightleftharpoons 2e_3$) conformations can each assume 3 staggered rotamers with respect to rotation about the exo-cyclic C_2O bond. On steric grounds, ($1a_1$) and especially ($1a_3$) are disfavoured relative to ($1a_2$). For the same reasons, ($2e_1$), and ($2e_3$) are disfavoured relative to ($2e_2$). On the other hand ($1a_2$) and ($1a_3$) are stabilised relative to ($1a_1$), by n-σ* overlap involving lone pair of the exo-cyclic oxygen,[2] as first suggested by Altona.[3] Similarly, rotamers ($2e_2$) and ($2e_3$) are stabilised by n-σ* overlap, relative to ($2e_1$). Thus the most abundant conformations are expected to be ($1a_2$) and ($2e_2$), in agreement with the exo-anomeric effect as originally defined [4,5]

Although strong evidence for the dominance of ($1a_2$) and ($2e_2$) in the solid state has been provided by X-ray and neutron diffraction data,[6-11] the situation for molecules in solution is not clear. Early investigations utilised calculated and experimental dipole moments,[12] and 3-bond coupling constants (methoxy carbon to anomeric hydrogen) in methyl glycopyranosides.[5,6,13,14] The latter were interpreted in terms of a dominance of ($1a_2$) and ($2e_2$) The relatively larger values of $^3J_{CH}$ in β-glycopyranosides (equatorial OMe) may arise from a significant proportion of rotamer ($2e_3$), (cf. ref.13) but an alternative explanation involves a relatively smaller dihedral angle for the CH_3-O-C-H pathway in the β-glycosides The present investigation has involved measurements of 3-bond coupling constants, supplemented by some n.O.e. experiments, in order to identify the dominant



(1a$_1$)



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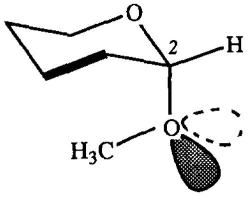

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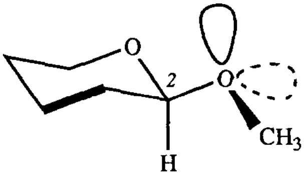

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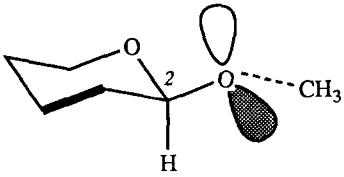

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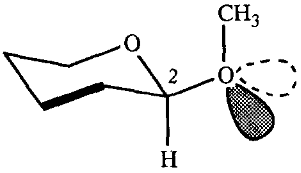


(2e$_3$)

rotamers in solutions of 2-methoxy-4-methyltetrahydropyrans and 2-methylamino-4-methyltetrahydropyrans. Three bond coupling constants were measured for analogous cyclohexane compounds so that the effect on J values of a ring oxygen could be evaluated

The required molecules (3), (4), (5 ⇌ 6), (7), (8), (9 ⇌ 10), (11), (12), (13 ⇌ 14), (17), (18), (19), (20), (21) and (22 ⇌ 23) were synthesised by standard procedures (see EXPERIMENTAL). ^{13}C Chemical shifts (including, in some cases, isotope shifts) have already been noted,[2] or are now reported in

Table 1. Carbon-13 chemical shifts (δ/ppm from Me_4Si) for *cis*- and *trans*-[methoxy-^{13}C]-4-t-butyl-1-methoxy-cyclohexane and *cis*- and *trans*-[methoxy-^{13}C]-1-methoxy-2-methylcyclohexane in CD_2Cl_2.

T/K	294	294	294	162	162	294
carbon	(3)	(4)	$(5 \rightleftharpoons 6)$	(5)	(6)	(7)
1	75.04[a]	80.15[c]	80.81[e]	79.36	80.96	85.66[g]
2	30.56[b]	32 84[d]	35.26[f]	36.43	32.24	38.70[h]
3	21.81	26.04	30.21	28.96	30.80	24.30
4	48.56	48.09	24.55	26.17	19.25	26.08
5	21.81	26 04	21 98	20.40	25.25	25.37
6	30 56[b]	32.84[d]	28.20[f]	27.63	29.78	30.91[h]
$\underline{C}Me_3$	32.80	32 54	-	-	-	-
MeO	55.58	55.56	56.28	56.13	55.22	56.26
Me	27.67	27.80	16.33	19.60	10.70	18.87

[a] isotope shift $^2\Delta = \delta(^{13}\underline{C}\text{-O-}^{13}C) - \delta(^{13}\underline{C}\text{-O-}^{12}C) = -2.65$ ppb

[b] isotope shift $^3\Delta = \delta(^{13}\underline{C}\text{-O-C-}^{13}C) - \delta(^{13}\underline{C}\text{-O-C-}^{12}C) = -6.50$ ppb

[c] $^2\Delta = -4.55$ ppb

[d] $^3\Delta = -1.90$ ppb

[e] $^2\Delta = -3.55$ ppb

[f] $^3\Delta = 0$ ppb

[g] $^2\Delta = -2.90$ ppb

[h] $^3\Delta = -0.10$ ppb

Tables 1, 2 and 5. Assignments relied on substituent shift parameters,[15,16,17] DEPT experiments and 2D ^{13}C-^{1}H shift correlation experiments. ^{1}H chemical shifts, if not already published,[2] are noted in Tables 6, 7 and 8, or in the Experimental section Coupling constants involving carbons of methoxy and methylamino groups were identified without ambiguity from fully coupled and fully decoupled spectra of molecules specifically enriched in ^{13}C at carbons of MeO and MeN (see Tables 3, 4 and 9). The measurement of J values at low temperature ($\sim$ 162K) was obligatory for molecules containing significant proportions of two conformations. However, J values are inherently temperature sensitive,[18] and it was therefore necessary also to measure J values at low temperature for conformationally homogeneous molecules, so as to allow valid comparisons to be made.

Table 2. Carbon-13 chemical shifts (δ/ppm from Me_4Si) for <u>cis</u>- and <u>trans</u>-[methoxy-^{13}C]-2-methoxy-3-methyltetrahydropyran and <u>cis</u>- and <u>trans</u>-methoxy-^{13}C]-2-methoxy-4-methyltetrahydropyran in CD_2Cl_2.

T/K	294	294	162	162	294	294
carbon	(8)	(9 $\rightleftharpoons$ 10)	(9)	(10)	(11)	(12)
2	102.08[a]	107.17[c]	108.12	e	98.68[f]	103.36[h]
3	35.35[b]	35.25[d]	36.31	e	39.07[g]	40.32[i]
4	26.74	29.74	32.21	e	24.65	29.74
5	26.01	24.77	25.87	e	34.67	34.32
6	59.59	64.75	66.54	e	59.79	65.37
MeO	54.90	55.72	56.66	e	54.51	55.94
Me	16.80	16.75	17.21	e	22.44	22.00

[a] isotope shift $^2\Delta = \delta(^{13}\underline{C}\text{-O-}^{13}C) - \delta(^{13}\underline{C}\text{-O-}^{12}C) = -0.8$ ppb

[b] isotope shift $^3\Delta = \delta(^{13}\underline{C}\text{-O-C-}^{13}C) - \delta(^{13}\underline{C}\text{-O-C-}^{12}C) = -2.3$ ppb

[c] $^2\Delta = -0.50$ ppb

[d] $^3\Delta = -2.30$ ppb

[e] not seen

[f] $^2\Delta = -0.20$ ppb

[g] $^3\Delta = -0.60$ ppb

[h] $^2\Delta = -3.30$ ppb

[i] $^3\Delta = -0.70$ ppb

Detailed investigations of $^3J_{CH}$ values[19-22] indicate a dependence on the dihedral angle similar to the well-known Karplus relationships for $^3J_{HH}$ values In alicyclic ring systems, $^3J_{CH}$ values occur in the ranges 1.5-4.5 Hz for a dihedral angle ϕ of $\sim 60°$, and 6.0-8.5 Hz for $\phi \sim 180°$. However, as with the comparable $^3J_{HH}$ situation $^3J_{CH}$ values are expected to be sensitive to the nature and orientation of substituents on, or close to, the coupling pathway.[23-28] The situation for $^3J_{CC}$ values is much less certain,[19] partly because $^3J_{CC}$ values are relatively small and experimental values are therefore subject to large percentage errors. Nevertheless, a Karplus-like correlation has often been assumed. $^3J_{CC}$ values are in the ranges 0-1.0 Hz ($\phi \sim 60°C$) and 3-4.5 Hz ($\Phi \sim 180°$).[20,29,30,31,32,33,34]

Table 3. Observed coupling constants (Hz, error due to digitisation ± 0.3 Hz) to methoxy carbon in cyclohexanes and tetrahydropyrans possessing axial methoxy groups (solvent CD_2Cl_2).

Compound	Conformation	T/K	$^1J_{CH}$	$^3J_{CH}$	$^2J_{CC}$	$^3J_{CC}$	$^3J_{CC}$
(3)	(3)	294	139.80	3.61[a]	2.11	2.41[b]	2.41[c]
(3)	(3)	162	140.21	3.13	1.44	1.53[b]	1.53[c]
(5 ⇌ 6)	(5)	162	140.22	3.55[d]	1.73	3.10[b]	0.60[c,e]
(8)	(8)	294	141.47	3.78	2.26	3.36[f]	-
(8)	(8)	162	141.81	3.25	1.82	2.98[e,f]	-
(11)	($11a_2$)	294	141.43	3.53	2.32	3.36[f]	-
(11)	($11a_2$)	162	141.77	3.09	1.58	2.86[f]	-

[a] lit.,[21] 3.9 Hz

[b] coupling to 2-C

[c] coupling to 6-C

[d] lit.,[21] 4.3 Hz at room temp.

[e] $w_{\frac{1}{2}}$, less $w_{\frac{1}{2}}$ for corresponding 3-C signal

[f] coupling to 3-C

Table 4 Observed coupling constants (Hz, error due to digitisation ± 0.3 Hz) to methoxy carbon in cyclohexanes and tetrahydropyrans possessing equatorial methoxy groups (solvent CD_2Cl_2).

Compound	Conformation	T/K	$^1J_{CH}$	$^3J_{CH}$	$^2J_{CC}$	$^3J_{CC}$	$^3J_{CC}$
(4)	(4)	294	140.06	3.77[a]	1.89	2.22[b]	2.22[c]
(4)	(4)	162	140.52	3.28	1.38	1.49[b]	1.49
(5 ⇌ 6)	(6)	162	140.40	3.18[d]	1.25	1.10[b,f]	1.10[c]
(7)	($7e_2$)	294	140.00	4.65[e]	2.14	3.04[b]	1.04[c]
(7)	($7e_2$)	162	140.40	4.09	1.87	3.25[b]	0.45[c,f]
(9 ⇌ 10)	(9)	162	142.39	3.68	1.7[g]	2.9[g,h]	-
(12)	($12e_2$; $12e_3$)	294	142.01	4.27	2.40	3.64[h]	-
(12)	($12e_2$; $12e_3$)	162	142.41	4.03	2.10	3.15[h]	-

[a] lit.,[21] 3.7 Hz

[b] coupling to 2-C

[c] coupling to 6-C

[d] lit.[21] 4.3 Hz for (5 ⇌ 6) at room temp.

[e] lit[21] 4.9 Hz for (7) at room temp.

[f] $w_{\frac{1}{2}}$, less $w_{\frac{1}{2}}$ for corresponding 3-C signal.

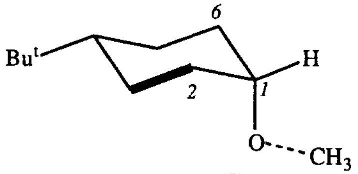
[g] $w_{\frac{1}{2}}$, less $w_{\frac{1}{2}}$ for corresponding MeO signal.

[h] coupling to 3-C

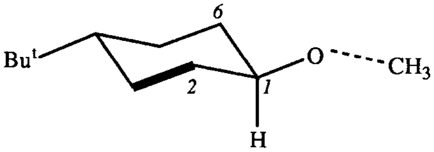
2-*Methoxytetrahydropyrans*

(a) *Conformations with axial OMe*

In this part of the study, the specific aim was to determine rotameric preferences about the *exo*-cyclic C-O bond in *trans*-2-methoxy-4-methyltetrahydropyran, a molecule known to be confined to ring conformation (11), with methyl equatorial and methoxy axial.[2]



(3)



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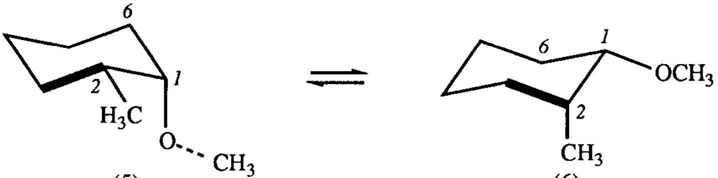
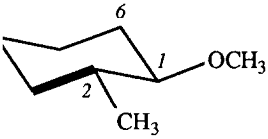


(5) (6)



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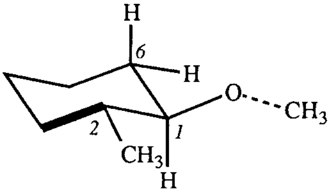
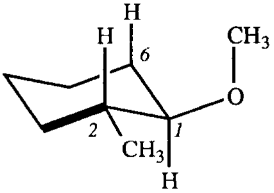
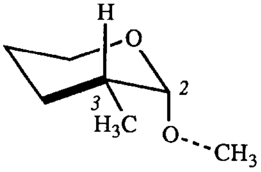


(7e$_2$)

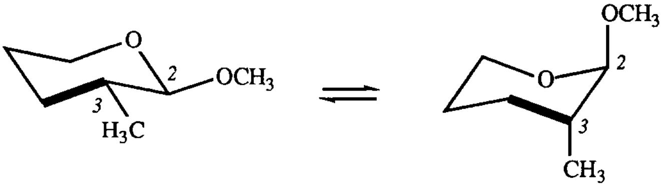


(7e$_3$)

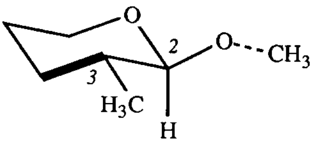
The low temperature ^{13}C n.m.r spectrum of *cis*-1-methoxy-2-methylcyclohexane (5$\rightleftharpoons$6) revealed signals for both major (5) and minor (6) conformations (Table 1). In conformation (5), the intense van der Waals repulsion experienced by the rotamer in which the OMe is *syn* to the equatorial methyl should ensure that only the illustrated rotamer (OMe *syn* to C-6) will be populated to a significant extent. Conformation (5) is thus a model for dihedral angles of ~60° (CH_3-O-C_1-H), ~60° (CH_3-O-C_1-C_6) and ~180° (CH_3-O-C_1-C_2) in *cyclohexanes* possessing an *axial* CH_3O substituent.



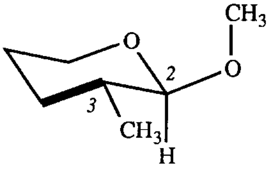
(8)



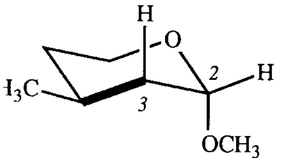
(9) (10)



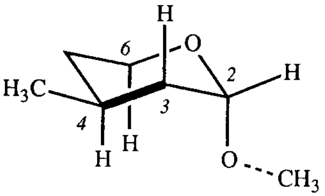
(9e$_2$)



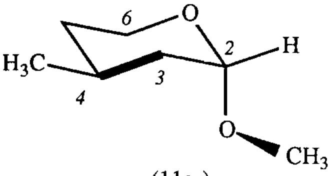
(9e$_3$)



(11)



(11a$_2$)



(11a$_1$)

cis-1-Methoxy-4-t-butylcyclohexane (3) must involve two equally populated rotamers according as to whether OMe is *syn* to C-2 or, as illustrated, *syn* to C-6. The measured $^3J_{CC}$ to methoxy carbon is thus an *average* of couplings for dihedral angles of ∿60° (CH_3-O-C_1-C_6) and ∿180° (CH_3-O-C_1-C_2).

cis-2-Methoxy-3-methyltetrahydropyran is largely confined to ring conformation (8), in which the 3-methyl group is equatorial and the anomeric 2-methoxy is axial. Further, the strongly favoured rotamer is expected to have the OMe *anti* to the equatorial Me, as illustrated. It follows that *cis*-2-methoxy-3-methyltetrahydropyran (8) is a model for dihedral angles of ∿60° (CH_3-O-C_2-H) and ∿180° (CH_3-O-C_2-C_3) in *tetrahydropyrans* possessing an *axial* CH_3O substituent at C-2.

The following interpretation of the observed ^3J values in trans-2-methoxy-4-methyltetrahydropyran (11) is a little crude, as it relies on 3 assumptions:-

(a) the reasonable assumption that rotamers with an 'inside' CH_3O group [cf. $(1a_3)$] are insignificantly populated;

(b) the assumption that a methyl substituent close to the coupling pathway has an insignificant substituent effect on $^3J_{CC}$. Thus the $^3J_{CC}$ couplings between methoxy carbon and C-6 in (5), and between methoxy carbon and C-3 in (11), are assumed to be insensitive to the replacement of ring hydrogen by methyl. Likewise the $^3J_{CH}$ between methoxy carbon and ring hydrogen in (5) and (8) are assumed to be unaffected by the replacement of ring hydrogen by methyl;

(c) the assumption that a change in geometry between cyclohexanes and tetrahydropyrans has little effect on the ^3J values under consideration.

Interpretation of $^3J_{CH}$ $(CH_3\text{-}O\text{-}C_2\text{-}H)$ in (11).

$^3J_{CH}$ (60°, cyclohexanes) = $^3J(CH_3\text{-}O\text{-}C_1\text{-}H)$ in (5)
= 3.55 Hz.
$^3J_{CH}$ (60°, tetrahydropyrans) = $^3J(CH_3\text{-}O\text{-}C_2\text{-}H)$ in (8)
= 3.25 Hz.
Hence 'substituent effect' of ring O is -0.30 Hz.
Observed $^3J_{CH}$ $(CH_3\text{-}O\text{-}C\text{-}H)$ in (3) is 3.13 Hz.
Therefore $^3J_{CH}$ $(CH_3\text{-}O\text{-}C\text{-}H)$ (calc) in $(11a_2)$ is 3.13-0.30 = 2.83 Hz.
But $^3J_{CH}$ $(CH_3\text{-}O\text{-}C\text{-}H)$ (observed) in (11a) is 3.09 Hz.
This is consistent with the dominant rotamer being $(11a_2)$
Clearly, however, a distinction cannot be made between $(11a_2)$ and $(11a_1)$.

Interpretation of $^3J_{CC}$ $(CH_3\text{-}O\text{-}C_2\text{-}C_3)$ in (11).

$^3J_{CC}$ (60°, cyclohexanes = $^3J(CH_3\text{-}O\text{-}C_1\text{-}C_6)$ in (5)
= 0 60 Hz
^3J $(CH_3\text{-}O\text{-}C\text{-}C)$ in (3) = $0.5[^3J_{CC}\ (180°) + {}^3J_{CC}\ (60°)]$
= 1.53 Hz
Therefore $^3J_{CC}$ (180°, cyclohexanes) = 2.46 Hz.
In (5), $^3J_{CC}$ (180°) = $^3J(CH_3\text{-}O\text{-}C_1\text{-}C_2)$ = 3.10 Hz.
Therefore 'substituent effect' of a terminal equatorial Me on $^3J_{CC}$ (180°, cyclohexanes) is + 0.64 Hz.

If this parameter is transferred to tetrahydropyrans, the calculated value of $^3J_{CC}$ (180°) in $(1a_2)$ and $(11a_2)$ is given by:
observed $^3J_{CC}(CH_3\text{-}O\text{-}C_2\text{-}C_3)$ in (8), less 0.64, = 2.98-0.64 = 2.34 Hz.
The observed $^3J_{CC}(CH_3\text{-}O\text{-}C_2\text{-}C_3)$ in (11) is 2.86 Hz.

It is concluded that (11) exists largely as rotamer ($11a_2$). Moreover, since any appreciable proportion of ($11a_1$) should lower an average of ($11a_1$) and ($11a_2$), the observation of a value which is higher than anticipated implies that ($11a_1$) is not significantly populated

Interpretation of $^4J_{CH}$ ($\underline{C}H_3$-O-C-$\underline{H}$) values

The fully coupled ^{13}C n.m.r. spectrum of trans-[methoxy-^{13}C]2-methoxy-4-methyltetrahydropyran (11, with 92.5% enrichment of OCH_3) revealed the methoxy carbon as a quartet of doublets of doublets; the corresponding cis-isomer (12) gave a spectrum in which the methoxy carbon was a quartet (due to $^1J_{CH}$) of doublets (due to $^3J_{CH}$). The additional coupling of 0.98 Hz in the trans-isomer (11) was identified by selective ^1H irradiation as a stereospecific 4-bond coupling between the methoxy carbon and the axial hydrogen at 3-C. Similar experiments identified a 4-bond coupling of 0.63 Hz between methoxy carbon and the axial hydrogen at 3-C in cis-[methoxy^{13}C]2-methoxy-3-methyltetrahydropyran (8) The values of 4-bond proton-proton coupling constants ($^4J_{HH}$) in saturated cyclic molecules show a Karplus-like correlation with the two dihedral angles involved, the maximum values occurring for a 'W' geometry in which both dihedral angles are about 180°.[35] A similar situation probably applies to $^4J_{CH}$ coupling; most of the $^4J_{CH}$ reported[36,37] to be in the range 1 to 1.5 Hz correspond to a 'W' geometry. Measurements on cyclohexane-d_{11} at 169 K, where ring inversion is very slow, have disclosed $^4J_{CH}$ values of 0.31 Hz (axial C-H, both dihedral angles 60°) and 0.5 Hz (equatorial C-H, dihedral angles of 60° and 180°).[22] The observation of appreciable $^4J_{CH}$ values from methoxy carbon to 3-H_{ax} in both (8) and (11) reinforces the evidence which favours the dominance of rotamers (8) and ($11a_2$), in which the CH_3-O-C-C-H pathway has the favourable 'W' geometry.

Nuclear Overhauser enhancement experiments

N.O.e difference experiments were not consistently satisfactory In cases where an n.O.enhancement was clearly observed, the percentage enhancement was not always reproducible to within ± 10% of the enhancement Very small (< 2%) enhancements were not always observed at all in a repeat experiment. Further, and possibly due to intermittent spectrometer instability, only about 1 in 3 spectra proved to be 'clean', a 'clean' spectrum being one in which signals not expected to show any enhancement gave little or no response of any kind In spite of these drawbacks, the results described below support the more definite conclusions drawn from the values of coupling constants.

Several n.O.e. difference experiments were carried out on pure trans-2-methoxy-4-methyltetrahydropyran (11) and on a mixture of (11) with its cis-isomer (12). Irradiation of the methoxy protons of the trans-molecule (11) in $CFCl_3$:$CDCl_3$ (85:15 v/v) caused appreciable positive enhancements only for 2-H (4-6%) and 6-H_a (4-7%), and a small but definite enhancement of 4-H_a (∿ 1%). A second experiment involving irradiation of the C-methyl protons of (11) gave the expected positive enhancements for 3-H_e (5%), 5-H_e (5%) and [3-H_a + 5-H_a] (8%), and an INDOR-like response for 4-H_a. Similar results were obtained when the two experiments were repeated using CD_2Cl_2 as solvent.

In summary, the experimental investigations of trans-2-methoxy-4-methyltetrahydropyran (11) and model compounds, have provided strong evidence for the dominance of rotamer ($11a_2$), in agreement with theoretical considerations; the presence of rotamer ($11a_1$), has been established by an n.O.e. difference experiment, but its relative abundance cannot be calculated.

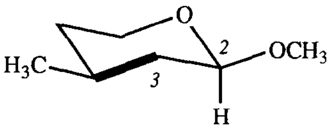
(b) Conformations with equatorial OMe.

In this part of the work, the specific aim was to determine rotameric preferences about the exo-cyclic C-O bond in cis-2-methoxy-4-methyltetrahydropyran, which is very largely confined to the single ring conformation (12) with both substituents equatorial (cf.[2]).

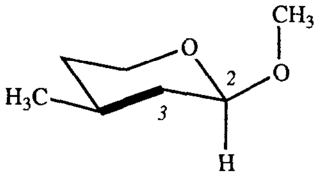
The model compound trans-1-methoxy-2-methylcyclohexane is also expected to occur predominantly in the diequatorial conformation (7). The intense repulsive interactions which are expected to occur when the $O-CH_3$ bond is syn- to the $C-CH_3$ bond should ensure that only rotamers ($7e_2$) and ($7e_3$) need be considered. Rotamer ($7e_3$) is disfavoured, relative to ($7e_2$), by an additional repulsive interaction between the methoxy carbon and an axial ring hydrogen. Moreover, an n.O e difference experiment in which the methoxy protons were irradiated gave positive enhancements for 6-H_e (1% at 270 K, 3% at 235 K) and 1-H (4% at 270 K, 8% at 235 K) but no enhancements for other protons, including 6-H_a, at either 270 K or 235 K. Evidently trans-1-methoxy-2-methylcyclohexane (7) exists largely as ($7e_2$) and is therefore a "model" for dihedral angles of ~ 60° (CH_3-O-C_1-H) and 180° ($CH_3-O-C_1-C_2$) in cyclohexanes substituted by an equatorial methoxy group.

The corresponding tetrahydropyran "model" is conformation ($9e_2$) of trans-2-methoxy-3-methyltetrahydropyran (9). However, a complication in this case is the probability that the diaxial conformation (10) will accompany the diequatorial conformation (9) owing to the relative stabilisation, by the anomeric effect, of an axial 2-methoxy group in a tetrahydropyran. Indeed, Descotes et al.,[38] used the observed value of

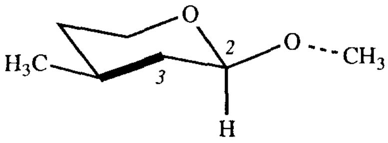
${}^3J_{H_2H_3}$, in conjunction with values from model commpounds, to calculate the proportions of (9) (52%) and (10) (48%) at room temperature in $CDCl_3$. In the present work, the ^{13}C n m.r. spectrum of ($9 \rightleftharpoons 10$) showed the expected broadening of lines as the temperature was lowered. Remarkably, however, only the 7 signals for conformation (9) were detected at 162 K. This observation is perfectly intelligible if the separate thermodynamic parameters for the 3-methyl and 2-methoxy groups, in monsubstituted tetrahydropyran, are considered. The $\Delta G^{o}_{a\rightarrow e}$ value of a 3-Me group in 3-methyltetrahydropyran[39] is -1.44 kcal mol^{-1} and should be independent of temperature since ΔS^{o}(Me) is expected to be ~ 0. Therefore a lowering of temperature should lead to a gradually increasing preference for the equatorial orientation. On the other hand, the proportion of 2-methoxytetrahydropyran with axial methoxy is largely independent of temperature.[2] It follows that (9) is increasingly favoured over (10) as the temperature is lowered. Therefore the coupling constants measured for ($9 \rightleftharpoons 10$) at 162 K apply largely to conformation (9). However, by analogy with (12), for which n.O.e. difference experiments (see below) suggest that the preferred rotamer ($12e_2$) is accompanied by rotamer ($12e_3$), the favoured rotamer ($9e_2$) is almost certainly accompanied by a small proportion of ($9e_3$).



(12)



(12e3)



(12e2)

<u>Interpretation of</u> $^3J_{CH}(CH_3\text{-}O\text{-}C_2\text{-}H)$ <u>in (12)</u>

$^3J_{CH}$ (60°, cyclohexanes) = $^3J_{CH}(CH_3\text{-}O\text{-}C_1\text{-}H)$ in (7)
= 4.09 Hz
$^3J_{CH}$ (60°, tetrahydropyrans) = $^3J_{CH}(CH_3\text{-}O\text{-}C_2\text{-}H)$ in (9)
= 3.68 Hz

Hence 'substituent effect' of ring O is -0.41 Hz.
Now observed $^3J_{CH}(CH_3\text{-}O\text{-}C\text{-}H)$ in (4) is 3.28 Hz.
Therefore $^3J_{CH}(CH_3\text{-}O\text{-}C\text{-}H)$ (<u>Calc</u>.) in ($12e_2$) is 3.28-0.41 = 2.87 Hz.
But $^3J_{CH}(CH_3\text{-}O\text{-}C\text{-}H)$ (<u>Obs.</u>) in ($12e_2$) is 4.03 Hz.
The discrepancy between calculation and observation is appreciable, and may be due to a population of ($12e_3$) which is higher than expected. However, other factors include the assumptions involved in the calculation (see earlier) and the knowledge that the frequency of a single line position is only accurate to ± 0.15 Hz (digitisation error).

<u>Interpretation of</u> $^3J_{CC}(CH_3\text{-}O\text{-}C_2\text{-}C_3)$ <u>in (12)</u>

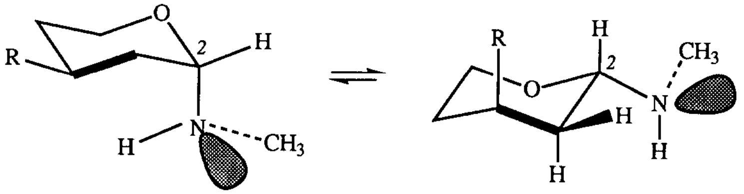
$^3J_{CC}$ (60°, cyclohexanes) = $^3J(CH_3\text{-}O\text{-}C_1\text{-}C_6)$ in (7)
= 0 45 Hz
$^3J(CH_3\text{-}O\text{-}C\text{-}C)$ in (4) = $0.5[^3J_{CC}(180°) + {}^3J_{CC}(60°)]$
= 1.49 Hz

Therefore $^3J_{CC}$ (180°, cyclohexanes) = 2.53 Hz
In (7), $^3J_{CC}$ (180°) = $^3J(CH_3\text{-}O\text{-}C_1\text{-}C_2)$ = 3.25 Hz.
Therefore 'substituent effect' of a terminal equatorial Me on $^3J_{CC}$ (180°, cyclohexanes) is + 0.72 Hz.
If this parameter is transferred to tetrahydropyrans, the <u>calculated</u> value of $^3J_{CC}$ (180°) in ($2e_2$) and ($12e_2$) is given by.
observed $^3J_{CC}(CH_3\text{-}O\text{-}C_2\text{-}C_3)$ in (9), <u>less</u> 0.72 Hz = 3.15-0.72 = 2.43 Hz.
The <u>observed</u> $^3J_{CC}(CH_3\text{-}O\text{-}C_2\text{-}C_3)$ in (12) is 3 15 Hz.
The appreciable discrepancy between calculated and observed figures may be due to some of the factors already mentioned for the $^3J_{CH}$ coupling constants (see above). However, the observation of a $^3J_{CC}$ value in (12) which is higher than the predicted value cannot be explained by an unusually high population of rotamer ($12e_3$), which would cause a reduction in the expected value of $^3J_{CC}$.

Thus, whilst the observed coupling constants $^3J_{CH}$ and $^3J_{CC}$ indicate ($12e_2$) as the major rotamer for (12), the proportion of the accompanying minor rotamer ($12e_3$) cannot be stated.

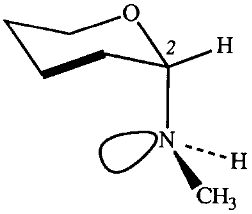
<u>Nuclear Overhauser enhancement experiments</u>

Several n.O e difference experiments were carried out on pure <u>cis</u>-2-methoxy-4-methyltetrahydropyran (12) and on a mixture of (12) with the <u>trans</u>-isomer (11). Irradiation of the methoxy protons of (12) in $CFCl_3$: $CDCl_3$ (85:15) produced enhancements only for 2-H (5-7%) and 3-H$_a$ (1%). INDOR-like responses were observed for 5-H$_e$, 6-H$_e$ and 5-H$_a$ due to the simultaneous and inevitable irradiation of 6-H$_a$, which has a chemical shift close to that of the methoxy protons. Although, owing to differing relaxation possibilities, enhancements provide no direct guide to the relative population of rotamers, the enhancement of 3-H$_a$ upon irradiation of OCH_3 does provide evidence for the participation of rotamer (12e$_3$). In a second experiment involving irradiation of the C-Me protons, the expected enhancements were observed for 3-H$_e$ (3-5%), 5-H$_e$ (1-3%), 3-H$_a$ (2%) and 5-H$_a$ (2-4%). Similar results to the above were obtained when the solvent was CD_2Cl_2 except that the closeness in chemical shift of signals for 3-H$_a$ and C-Me prevented clear observation of effects on 3-H$_a$ when the OCH_3 signal was irradiated

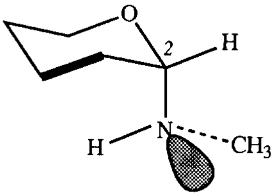


(13, R = H)
(22, R = CH_3)

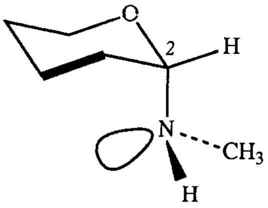
(14, R = H)
(23, R = CH_3)



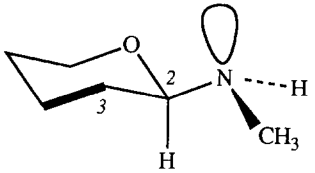
(15a$_1$)



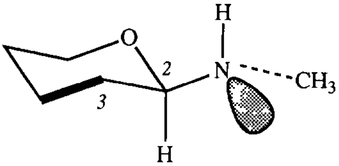
(15a$_2$)



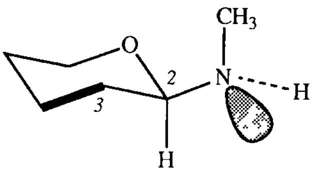
(15a$_3$)



(16e$_1$)



(16e$_2$)

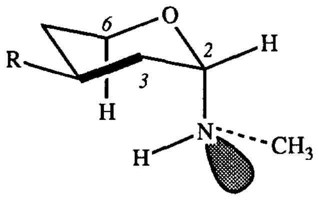


(16e$_3$)

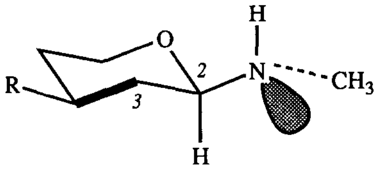
In summary, the investigations of cis-2-methoxy-4-methyltetrahydropyran (12) and model compounds have demonstrated the dominance of rotamer ($12e_2$). The presence of rotamer ($12e_3$) has been demonstrated by an n.O.e. difference experiment, but its relative abundance cannot be determined.

2-Methylaminotetrahydropyrans.

In 2-methylaminotetrahydropyran ($13 \rightleftharpoons 14$), the staggered rotamers most deserving of consideration include ($15a_1$), ($15a_2$) and ($15a_3$) for axial substitution, and ($16e_1$), ($16e_2$) and ($16e_3$) for equatorial substitution. The dominant rotamers were identified by measurements of the 3-bond coupling constants $^3J_{CH}(\underline{C}H_3\text{-N-}C_2\text{-}\underline{H})$, $^3J_{CC}(CH_3\text{-N-}C_2\text{-}C_3)$ and $^3J_{HH}(H\text{-N-}C_2\text{-H})$, all listed in Table 9. As in the case of the 2-methoxytetrahydropyrans discussed earlier, couplings to carbon were measured from spectra of amines highly enriched with ^{13}C, in this case at the N-methyl carbon. The molecules examined included (17-21), for which the ring inversion equilibria are heavily biased in favour of the conformations illustrated; this follows from the $-\Delta G^o_{a \rightarrow e}$ values of 4.9 and 2.9 kcal.mol^{-1} determined indirectly for ring inversion in t-butylcyclohexane[40] and phenylcyclohexane,[41] respectively. Also studied was trans-2-methylamino-4-methylaminotetrahydropyran, which contains appreciable proportions of both (22) and (23).[2,42]



(18, R = Ph)
(20, R = t-Bu)



(17, R = CH3)
(19, R = Ph)
(21, R = t-Bu)

In addition to the 3-bond coupling constants already mentioned, Table 9 includes the 1-bond coupling constants ($^1J_{CH}$) to N-methyl carbon and the 2-bond coupling constants ($^2J_{CC}$) to N-methyl carbon from C_2 The values of J_{CH} measured in ^{13}C n.m.r. spectra were confirmed (to within 0.15 Hz) by analysis of the corresponding ^1H nmr spectra of the ^{13}C-enriched molecules. Clearly, the J values reported in Table 9 for ($22 \rightleftharpoons 23$) at 280 K are weighted averages of those in the individual conformations The coupling constants ^3J(H-N-C-H) were measured from the well-resolved signals for 2-H and N-CH_3 in the ^1H nmr spectra obtained under conditions of slow intermolecular exchange of protons on nitrogen. In practice, the necessary conditions were achieved either at room temperature after intensive drying of the amine over solid KOH, or at reduced temperature. The value of ^3J(H-N-C_2-H) in (22) was measured at 163 K, where both N-H exchange and the ring inversion ($22 \rightleftharpoons 23$) are relatively slow.

Table 5. Carbon-13 chemical shifts (δ/ppm from Me_4Si) for cis- and trans-[methylamino-^{13}C]-2-methylamino-4-phenyltetrahydropyran and cis- and trans-[methylamino-^{13}C]-4-t-butyl-2-methylaminotetrahydropyran ($CDCl_3$, 297 K).

carbon	(18)	(19)	(20)	(21)
2	84.83	89.46	85.00	89.97
3	37.20	39.70	29.70	33.90
4	35.62	41.58	39.60	45.90
5	32.92	33.17	27.00	26.95
6	58.45	66.16	58.50	66.50
MeN	31.71	31.86	31.00	32.00
1'	a	145.06	-	-
2',6'	a	128.41	-	-
3',5'	a	126.57	-	-
4'	a	126.25	-	-
Me	-	-	26.90	27.08
$\underline{C}Me_3$	-	-	32.00	32.00

a not measured.

Table 6 ^1H nmr data (400 MHz, 297 K) for trans-2-methylamino-4-phenyltetrahydropyran (18) ($CDCl_3$.

Chemical Shifts (δ/ppm)

2-H	4.52	5-H_a	1.70
3-H_e	1.83	6-H_e	3.70
3-H_a	2.00	6-H_a	3.81
4-H_a	2.95	MeN	2.47
5-H_e	1.83	HN	1.6 (broad)[a]

Coupling Constants (Hz)

$^3J_{2e3e}$	2.14	$^3J_{2e3a}$	4.57

a tentative

Table 7 ^1H nmr data for <u>cis</u>-2-methylamino-4-phenyltetrahydropyran (19) ($CDCl_3$, 295 K, 400 MHz).

	Chemical Shifts (δ/ppm)		
2-H	3.98	$5\text{-}H_a$	1.70
$3\text{-}H_e$	2.00	$6\text{-}H_e$	4.08
$3\text{-}H_a$	1.43	$6\text{-}H_a$	3.55
$4\text{-}H_a$	2.80	MeN	2.55
$5\text{-}H_e$	1.70	HN	1.6 (broad)
	Coupling Constants (Hz)		
$^3J_{3e3a}$	12.9	$^3J_{2a3e}$	1.9
$^2J_{6e6a}$	11.7	$^3J_{5e6e}$	1.8
$^3J_{2a3a}$	10.2	$^3J_{5a6e}$	4.2

Values of $^3J_{CH}(\underline{C}H_3\text{-}N\text{-}C_2\text{-}\underline{H})$ and $^3J_{CC}(CH_3\text{-}N\text{-}C_2\text{-}C_3)$ in Table 9 correspond well with dihedral angles of ~60° and ~180°, respectively, whilst values of $^3J_{HH}(H\text{-}N\text{-}C_2\text{-}H)$ correspond well with a dihedral angle of ~180°.[1,43] It follows that molecules with an <u>equatorial</u> NHMe have a strong preference for rotamer ($16e_2$), which combines minimum steric repulsions with maximum $n\text{-}\sigma^*$ overlap (N-lone pair antiperiplanar to the endocyclic C_2-O bond), in agreement with predictions based on the <u>exo</u>-anomeric effect. The 3-bond coupling constants for molecules with an <u>axial</u> NHMe show that rotamer ($15a_2$) is strongly preferred. Whilst in ($15a_2$) the stabilising $n\text{-}\sigma^*$ overlap is at a maximum, destabilising steric effects are expected to be greater than in rotamer ($15a_3$), as the crucial 'inside' substituent on nitrogen is a hydrogen atom, rather than a less bulky lone pair. Evidently this is another example (cf.[1]) in which a stabilising anomeric effect outweighs a destabilising steric effect.

N.O.e. difference experiments on ($13 \rightleftharpoons 14$) and (18) were consistent with the rotameric preferences deduced from coupling constants. 2-Methylaminotetrahydropyran ($13 \rightleftharpoons 14$) is known to exist at room temperature very largely (~93%) in ring conformation (14), with NHMe equatorial. Irradiation of the N-Me signal in the ^1H spectrum caused enhancements for N-H (3%) and 2-H (3%), but no enhancements for either $3\text{-}H_e$ or $3\text{-}H_a$, thus confirming the strong preference for rotamer ($16e_2$) [$\equiv$(14)]. In the case of <u>trans</u>-2-methylamino-4-phenyltetrahydropyran, which is confined to ring conformation (18), irradiation of the N-methyl signal caused enhancements only for $2\text{-}H_a$ (4%) and $6\text{-}H_a$ (3%), confirming the dominance of the rotamer illustrated [$\equiv$($15a_2$)].

Table 8 ^{1}H nmr data (400 MHz, 297 K) for <u>cis</u>-4-t-butyl-2-methylamino-tetrahydropyran (21) ($CDCl_3$).

Chemical Shifts (δ/ppm)

2-H	4.52[a]	6-H_e	4.04
2-H	3.82	6-H_a	3.39
3-H_e	1.82	MeN	2.42[a]
3-H_a	0.98	MeN	2.52
4-H	1.2-1.35	t-Bu	0.84[a]
5-H_e	1.52	t-Bu	0.85
5-H_a	1.2-1.35		

Coupling constants (Hz)

$^{2}J_{3e3a}$	12.7	$^{3}J_{2a3a}$	10.1
$^{2}J_{5e5a}$	11.9	$^{3}J_{2e3a}$	5.0[a]
$^{2}J_{6e6a}$	11.5	$^{3}J_{5e6e}$	1.6
$^{3}J_{2a3e}$	2.0	$^{3}J_{5e6a}$	2.2
$^{3}J_{2e3e}$	1.4[a]	$^{3}J_{5a6e}$	4.3

a <u>trans</u>-isomer (20)

Table 9 Observed coupling constants (Hz, error due to digitisation ± 0.3 Hz) to N-methyl carbon and to N-attached proton in tetrahydropyrans possessing 2-methylamino groups (solvent $CDCl_3$ unless stated otherwise).

				Couplings to N-$\underline{C}H_3$				Couplings to to N-$\underline{H}$	
Compound	Geometry	Conformation	T/K	$^{1}J_{CC}$	$^{3}J_{CH}$	$^{2}J_{CC}$	$^{3}J_{CC}$[a]	$^{3}J_{HH}$[b]	$^{3}J_{HH}$[c]
($13\rightleftharpoons14$)	-	(14)	297	d	d	d	d	11.3	5.9
(17)	cis	(17)	280	134.0	3.30	1.94	3.67	12.3[e]	5.4[e]
($22\rightleftharpoons23$)	trans	($22\rightleftharpoons23$)	280	133.8	2.94	1.53	3.59	d	d
($22\rightleftharpoons23$)	trans	(22)	163[f]	d	d	d	d	11.3	d
(18)	trans	(18)	295	134.2	2.95	d	3.52	9.1	5.6
(19)	cis	(19)	295	134.4	3.29	d	3 57	12.1	5.5
(20)	trans	(20)	295	134.1	2.68	1.32	g	12.0[h]	5.2[h]
(21)	cis	(21)	295	134.2	3.27	1.29	3.69	11.9[h]	5.2[h]

a CH_3-N-C_2-C_3

b H-N-C_2-H

c H-N-CH_3

d not measured

e 170 K in $CFCl_3/CDCl_3$ (85/15)

f CD_2Cl_2

g not seen clearly

h 190 K in $CFCl_3/CDCl_3$ (2/1)

EXPERIMENTAL

General. - The general comments of Part 1[2] are applicable. For measurement of carbon-carbon and carbon-hydrogen coupling constants from ^{13}C spectra, accumulations employed 64K data points over 10,000 Hz (at 62.9 MHz), or 128K data points over 25,000 Hz (at 100.6 MHz). Proton-proton coupling constants were measured from ^{1}H spectra accumulated using 16K data points over 2500 Hz (at 250 MHz) or 32K data points over 4000 Hz (at 400 MHz). F.I.D.s were generally processed without exponential multiplication and without resolution enhancement. Exceptionally, both ^{13}C and ^{1}H spectra of (18) and (19) were subjected to resolution enhancement by Gaussian multiplication. Band widths are quoted as widths at half height ($W_{\frac{1}{2}}$) and are adjusted by substraction of $W_{\frac{1}{2}}$ for a carbon not subjected to coupling. The generous error limits quoted for J values are those due to the maximum possible digitisation limits $\pm 2\Delta/N$, where Δ is the spectral width for N data points. In n.O.e. difference experiments[44,45] at 400 MHz, the following parameters were used: D1 (relaxation) 3s, D2 (irradiation) 4s, and S3 (decoupler power) 50 L.

cis- and trans-4-t-Butyl-1-methoxycyclohexane. - To a stirred slurry of sodium hydride (0.50 g. of a 50% dispersion in mineral oil, equivalent to 10.4 mmol.) in tetrahydrofuran (10 cm^3) at 45-50° was added iodomethane (1.14 g., 5.8 mmol). A mixture of cis- and trans-4-t-butylcyclohexanol (0.9 g., 5.8 mmol) in dry tetrahydrofuran (5 cm^3) was added dropwise to the foregoing mixture during 20 min. The reaction mixture was stirred for a further 40 min., cooled and treated cautiously with water (5 cm^3). The solution was extracted with ether (3 x 10 cm^3) and the combined ether extracts were shaken with saturated aqueous sodium chloride (20 cm^3), dried (Na_2SO_4) and evaporated giving crude cis- and trans-4-t-butyl-1-methoxycyclohexane (0.77 g., 79%). Purification by glc used a 10' x $\frac{1}{4}$" aluminium column packed with 20% Carbowax 20M on Chromosorb W. The column temperature was 103° and the isomers had retention volumes of 300 cm^3 (cis) and 480 cm^3 (trans). The isomers were collected as a single fraction (Found: C, 78.3; H, 13.3. Calc. for $C_{11}H_{22}O$: C, 77.6; H, 13.0%). The ^{1}H nmr spectrum (250 MHz; $CFCl_3/CDCl_3$ = 80/20 v/v) included signals for the cis-isomer at δ 3.36 (m; 1-H), 3.25 (s; OCH_3), 1.73-2.10 (m; 2-H_e, 3-H_e, 5-H_e and 6-H_e), 0.9-1.5 (m; 2-H_a, 3-H_a, 4-H_a, 5-H_a and 6-H_a) and 0.86 (s; t-Bu). The trans-isomer showed signals at δ 3.30 (s; OCH_3), 2.99 (tt; $^{3}J_{aa}$ 10.4 Hz, $^{3}J_{ae}$ 4.1 Hz; 1-H), 1.73-2.10 (m; 2-H_e, 3-H_e, 5-H_e, 6-H_e); 0.9-1.5 (m; 2-H_a, 3-H_a, 4-H_a, 5-H_a, and 6-H_a), and 0.86 (s; t-Bu).

The ^{13}C nmr spectrum (62.90 MHz) in the same solvent showed signals for the cis-isomer at δ 74.74 (1-C), 55.44 (CH_3O), 48.4 (4-C), 32.0 [$(CH_3)_3\underline{C}$], 30.3 (2,6-C), 27.6 [$(\underline{C}H_3)_3C$] and 21.5 (3,5-C). The trans-isomer gave signals at δ 80.0 (1-C), 55.44 (CH_3O), 47.80 (4-C), 37.80 [$(CH_3)_3\underline{C}$], 32.50 (2,6-C), 27.70 [$(\underline{C}H_3)_3C$] and 25.80 (3,5-C).

cis- and trans-[Methoxy-^{13}C]-4-t-butyl-1-methoxycyclohexane. - The preceding preparation was repeated using *cis*- and *trans*-4-t-butylcyclohexanol (0.7 g) and [^{13}C]iodomethane (1 g., 90.5 ^{13}C atom %). Distillation of the crude product gave *cis*- and *trans*-[methoxy-^{13}C]-4-t-butyl-1-methoxycyclohexane (0.71 g, 88%), estimated purity 95% (glc). The sample gave M^+ 171.1703 (^{13}C $^{12}C_{10}H_{22}O$ requires M 171.1705). The ^1H nmr spectrum (250 MHz, CD_2Cl_2) included signals for the *cis*-isomer at δ 3.24 (s; $O^{12}CH_3$) and δ 3.24 (d, $^1J_{CH}$ 139.9 Hz; $O^{13}CH_3$) and for the *trans*-isomer at δ 3.28 (s; $O^{12}CH_3$) and δ 3.28 (d, $^1J_{CH}$ 140.1 Hz; $O^{13}CH_3$). ^{13}C nmr data are given in Tables 1,3 and 4.

cis- and trans-1-Methoxy-2-methylcyclohexane. - The general method described above was used to convert a mixture (0.65 g., 5.7 mmol) of *cis*- and *trans*-2-methylcyclohexanol, and iodomethane (1.14 g., 8.0 mmol) into crude *cis*- and *trans*-1-methoxy-2-methylcyclohexane (0.53 g., 73%). Purification by glc employed the same column as for 4-t-butyl-1-methoxycyclohexane, at a temperature of 70°. The component with retention volume of 210 cm^3 was collected and found to be *cis*- and *trans*-1-methoxy-2-methylcyclohexane (Found: C, 74.8; H, 12.9. Calc. for $C_8H_{16}O$: C, 74.9; H, 12.6%). The ^1H nmr spectrum (250 MHz, $CFCl_3/CDCl_3$ 80/20 v/v) showed signals for the *cis*-isomer at δ 3.28 (s; OCH_3), 3.16 (m; 1-H), 1.0-2.1 (m; 2,3,4,5,6-H) and 0.91 (d; $^3J_{HH}$ 6.9 Hz; 2-Me). The *trans*-isomer showed signals at δ 3.31 (s; OCH_3), 2.60 (td; $^3J_{1a6e}$ 3.9 Hz, $^3J_{1a2a} + {}^3J_{1a6a} = 19.4$ Hz; 1-H), 1.0-2.1 (m; 2,3,4,5,6-H) and 0 96 (d; $^3J_{HH}$ 6.4 Hz; 2-Me). The ^{13}C nmr spectrum (62.90 MHz) in the same solvent showed signals for the *cis*-isomer at δ 80.5 (1-C), 56.2 (CH_3O), 35.4 (2-C), 29.8 (3-C), 28.0 (6-C), 24.7 (4-C), 21.5 (5-C) and 16.8 (2-CH_3). The *trans*-isomer gave signals at δ 85.6 (1-C), 56.2 (CH_3O), 38.7 (2-C), 34.2 (3-C), 30.6 (6-C), 25.9 (4-C), 25.2 (5-C) and 19.0 (2-CH_3). ^{13}C nmr shifts in CD_2Cl_2 are listed in Table 1.

cis- and trans-[Methoxy-^{13}C]-1-methoxy-2-methylcyclohexane. - The preceding preparation was repeated using *cis*- and *trans*-2-methylcyclohexanol (0.55 g) and [^{13}C]iodomethane (1 g., 90.5 ^{13}C atom %) Distillation of the crude product gave *cis*- and *trans*-[methoxy- ^{13}C]-1-methoxy-2-methylcyclohexane (0.26 g., 41.8%), estimated to be > 99% pure (glc). (Found: M^+ 129.1230. ^{13}C $^{12}C_7H_{16}O$ requires M^+ 129.1705). The ^1H nmr spectrum (250 MHz; CD_2Cl_2) included signals for the *cis*-isomer at δ 3.30 (s; $O^{12}CH_3$) and 3.29 (d, $^1J_{CH}$ 140.0 Hz; $O^{13}CH_3$), and for the *trans*-isomer at δ 3.26 (s; $O^{12}CH_3$) and 3.26 (d, $^1J_{CH}$ 139.9 Hz; $O^{13}CH_3$). ^{13}C nmr data are given in Tables 1, 3 and 4.

cis- *and* trans-2-*Ethoxy*-3-*methyltetrahydropyran*. - Following the literature,[46] freshly distilled acrolein (8.96 g.) and ethyl propenyl ether (19.38 g) gave a mixture (13.34 g., 58.7%) of *cis*- and *trans*-2-ethoxy-3-methoxy-3,4-dihydro-2H-pyran, b.p. 52-56°/14 mm Hg. (lit.,[46,47] 149-152°/760 mm Hg and 52°/11 mm Hg, respectively) (Found: M^+ 142.0995; Calc. for $C_8H_{14}O_2$: M 142.0994). Hydrogenation of the above compound (14.59) (cf. ref.48) gave *cis*- and *trans*-2-ethoxy-3-methyltetrahydropyran (8.63 g., 58.3%), b.p. 62-68°/23 mm Hg (lit., [46,48] 152-3°/760 mm Hg and 58°/22 mm, respectively) (Found: M^+ 144.1143. Calc. for $C_8H_{16}O_2$: M 144.1151).

cis- *and* trans-2-*Methoxy*-3-*methyltetrahydropyran*. - Using the published method,[48] 2-ethoxy-3-methyltetrahydropyran (9.14 g) was converted into 5-methyl-3,4-dihydro-2H-pyran (3.55 g. 57%), b.p. 110-112°/760 mm Hg (lit.,[46] 111-113°/760 mm Hg). The dihydropyran (2.32 g) was reacted with methanol (0.79 g) by the method of Woods and Kramer,[49] giving a mixture (2.18 g, 71%) of *cis*- and *trans*-2-methoxy-3-methyltetrahydropyran, b.p. 137-139°/760 mm Hg (Found: M^+ 130.0992. Calc. for $C_7H_{14}O_2$: M 130.0993). The ^1H nmr spectrum (400 MHz; CD_2Cl_2) showed signals for the *cis*-isomer at δ 4.38 (d, $^3J_{2e3a}$ 3.08 Hz, 2-H), 3.65 (td; $6\text{-}H_a$), 3.46 (dm, $^2J_{6e6a}$ 11.0 Hz; $6\text{-}H_e$), 3.31 (s; OCH_3), 1.75 (m; 3-H), 1.65 (m; one of 5-H), 1.50 (m; one of 5-H), 1.48 (m, both 4-H) and 0.85 (d, ^3J 6.9 Hz; 3-Me). The *trans*-isomer gave signals at δ 3.94 (d, $^3J_{2,3}$ 6.5 Hz; 2-H), 3.88 (ddt; one of 6-H), 3.43 (m; one of 6-H), 3.38 (s; OCH_3), 1.81 (m; one of 5-H), 1.51 (m; both of 4-H), 1.51 (m; 3-H), 1.23-1.19 (m; one of 5-H) and 0.94 (d, ^3J 6.8 Hz; 3-Me). Assignments were confirmed by both 'normal' and 'long-range' $^1H/^1H$ COSY experiments.

^{13}C nmr chemical shifts are listed in Table 2 and were confirmed by $^{13}C/^1H$ heteronuclear shift correlation experiments at 400 MHz (^1H) utilising couplings over one bond, and couplings over two and three bonds. In the $^1J_{CH}$ correlation, 3-C (*cis*) and 3-C (*trans*) were distinguished by making cross sectional plots along the F_1 (^1H) direction at a series of ^{13}C shift positions in the F_2 dimension. In this way the low field ^1H signal (δ 1.75, *cis*) was correlated with the low field ^{13}C signal (δ 35.35). This experiment required 8K data over 12,195 Hz in the F_2 (^{13}C) dimension.

cis- *and* trans-[Methoxy-^{13}C]-2-*methoxy*-3-*methyltetrahydropyran*. -5-Methyl-3,4-dihydro-2H-pyran (1.61 g) was treated with [^{13}C]methanol (0.55 g, 92.5 ^{13}C atom %) as in the preceding preparation involving methanol. The product was a mixture of *cis*- and *trans*-[methoxy-^{13}C]-2-methoxy-3-methyltetrahydropyran (1.18 g, 55%), b.p. 136-140°/760 mm Hg (Found. M^+ 131.1017. $^{13}C^{12}C_6H_{14}O_2$ requires M 131.1027). The ^1H nmr spectrum (200 MHz; CD_2Cl_2) included signals for the *cis*-isomer at δ 3.31 (s, $O^{12}CH_3$) and δ 3 31 (d, $^1J_{CH}$ 141.5 Hz,

$O^{13}CH_3$), and for the *trans*-isomer at δ 3.38 (s; $O^{12}CH_3$) and δ 3.37 (d, $^1J_{CH}$ 141.9 Hz; $O^{13}CH_3$). ^{13}C nmr data are listed in Tables 2, 3 and 4.

cis- and trans-[Methoxy-^{13}C]-2-methoxy-4-methyltetrahydropyran. - Using the published procedure,[2] 4-methyl-3,4-dihydro-2H-pyran (1.50 g) and [^{13}C]methanol (0.50 g, 92.5 ^{13}C atom %) gave a mixture of *cis*- and *trans*-[methoxy-^{13}C]-2-methoxy-4-methyltetrahydropyran (0.50 g, 25.2%), b.p. 148-156°/760 mm Hg (Found: M^+ 131.1023. $^{13}C^{12}C_6H_{14}O_2$ requires M^+ 131.1027). The ^{1}H nmr spectrum (250 MHz; CD_2Cl_2) included signals for the *cis*-isomer at δ 3.40 (s; $O^{12}CH_3$) and δ 3.40 (d, $^1J_{CH}$ 142.0 Hz; $O^{13}CH_3$), and signals for the *trans*- isomer at δ 3.30 (s; $O^{12}CH_3$) and δ 3.29 (d, $^1J_{CH}$ 141 4 Hz, $O^{13}CH_3$). The ^{13}C nmr data are listed in Tables 2, 3 and 4.

cis- and trans-[Methylamino-^{13}C]-2-methylamino-4-methyltetrahydropyran. - To an ice-cold solution of sodium hydroxide (0.291 g) in water (7.4 cm^3) was added [^{13}C]methylamine hydrochloride (0.50 g, 93.5 ^{13}C atom %). An ice-cold mixture of *cis*- and *trans*-2-hydroxy-4-methyltetrahydropyran[2] (0.85 g) was then added, after which the solution was saturated with anhydrous potassium carbonate. The organic layer was separated, dried (K_2CO_3), filtered and dried (K_2CO_3) a second time. Filtration and bulb-tube distillation gave a mixture of *cis*- and *trans*- [methylamino-^{13}C]-2-methylamino-4-methyltetrahydropyran (0.11 g, 12%), b.p.80-90/19 mm Hg (Found: M^+ 130.1177. $^{13}C^{12}C_6H_{15}NO$ requires M 130.1187). The ^{1}H nmr spectrum (250 MHz; $CFCl_3/CDCl_3$ 85/15 v/v) included signals for the *cis*-isomer at δ 2.42 (s; $N^{12}CH_3$) and δ 2 42 (d; $^1J_{CH}$ 133.8 Hz; $N^{13}CH_3$), and signals for the *trans*-isomer at δ 2.37 (s; $N^{12}CH_3$) and δ 2 36 (d; $^1J_{CH}$ 133.7 Hz; $N^{13}CH_3$). The ^{13}C nmr data are listed in ref.2 and Table 9.

cis- and trans-2-n-Butoxy-4-phenyl-3,4-dihydro-2H-pyran. - A mixture of cinnamaldehyde (92.5 g) and n-butyl vinyl ether (70.1 g) was heated in a bomb at 200° for 18 hr , with stirring (cf.[50]). The reaction mixture was cooled and fractionally distilled, giving a mixture of *cis*- and *trans*-2-n-butoxy-4-phenyl-3,4-dihydro-2H-pyran (76.93 g, 47.3%), b.p. 152-154°/10 mm Hg (lit.[51] 114-115°/5 mm Hg)

The ^{1}H nmr spectrum (250 MHz, $CDCl_3$) included signals for the *cis*-isomer at δ 5.66 (dd, $^3J_{5,6}$ 6.15 Hz, $^4J_{4,6}$ 2.40 Hz; 6-H), 5.02 (dd, $^3J_{2a3a}$ 9.3 Hz, $^3J_{2a3e}$ 2.0 Hz; 2-H_a), 4 75 (ddd, $^3J_{5,6}$ 6.15 Hz, $^3J_{4,5}$ 2.15 Hz, $^4J_{3e,5}$ 1.70 Hz, 5-H), 3 77-3.95 (dt, ^2J 9.6 Hz, ^3J 6.7 Hz, H_A of $-OCH_AH_B-$), 3 47-3.58 (dt, ^2J 9 6 Hz, ^3J 6 7 Hz; H_B of $-OCH_AH_B-$), 3.55-3.67 (m; 4-H), 2.25 (ddt, $^2J_{3e3a}$ 13.2 Hz, $^3J_{3e4a}$ 6.35 Hz, $^3J_{2a3e}$ + $^4J_{3e,5}$ = 3.75 Hz; 3-H_e), 1 88 (ddd, $^2J_{3e3a}$ 13.4 Hz, $^3J_{3a4a}$ 10.8 Hz, $^3J_{2a3a}$ 9.2 Hz; 3-H_a), 1.52-1.68 (m, $-CH_2-CH_2-$ of Bu), 0.916 (t, J 7.3 Hz; Me). The *trans*-isomer showed signals at δ 6.39 (dd, $^3J_{5,6}$ 6.3 Hz, $^4J_{4,6}$ 2.4 Hz; 6-H), 5.01 (t, $^3J_{2e3e}$ + $^3J_{2e3a}$

5.8 Hz; 2-H_e), 4.86 (ddd, $^3J_{5,6}$ 6.30 Hz, $^3J_{4,5}$ 2.35 Hz, $^4J_{3e,5}$ 1.55 Hz; 5-H), 3.77-3.95 (dt, ^2J 9.6 Hz, ^3J 6.7 Hz; H_A of -CH_AH_B-), 3.47-3.58 (dt, ^2J 9.6 Hz, ^3J 6.7 Hz; H_B of -OCH_AH_B-), 3.55-3.67 (m; 4-H), 2.13 (dddd, $^2J_{3e3a}$ 13.8 Hz, $^3J_{3e4a}$ 6.35 Hz, $^3J_{2e3e}$ 3.5 Hz, $^4J_{3e5}$ 1.65 Hz; 3-H_e), 1.82, (ddd, $^2J_{3e3a}$ 13.6 Hz, $^3J_{3a4a}$ 10.8 Hz, $^3J_{2e3a}$ 2.35 Hz; 3-H_a), 1.29-1.47 (m; -CH_2-CH_2- of Bu), 0.933 (t, J 7.25 Hz; Me).

cis- and trans-2-n-Butoxy-4-phenyltetrahydropyran. - The foregoing product (10.0 g), dissolved in ethanol (150 cm^3) containing Raney nickel (4 g), was hydrogenated at 290 K and 760 mm Hg. The uptake was 1042 cm^3 (theory 963 cm^3). The catalyst was removed by filtration through a pad of Kieselguhr with moderate suction, and washed with ethanol. The combined filtrates were evaporated to remove ethanol, after which the residue was distilled, giving a mixture of cis- and trans-2-n-butoxy-4-phenyltetrahydropyran as a colourless oil (9.11 g, 90.4%), b.p. 162°/10 mm Hg, which gave M^+ 234.1610 ($C_{15}H_{22}O_2$ requires M 234.1620). Elemental microanalysis gave C, 76.86; H, 9.54. $C_{15}H_{22}O_2$ requires C, 76.88; H, 9.46%). The ^1H nmr spectrum (250 MHz, $CDCl_3$) included signals for the *cis*-isomer at δ 4.48 (dd, $^3J_{2a3a}$ 9.40 Hz, $^3J_{2a3e}$ 2.09 Hz; 2-H), 4.13 (dt, $^2J_{6e6a}$ 11.7 Hz, $^3J_{6e5a}$ + $^3J_{6e5e}$ 6.2 Hz; 6-H_e), 3.35-3.80 (m; 6-H_a and OCH_2 of OBu), 2.74-2.84 (m; 4-H), 1.3-2.1 (m; 3-H_e, 3-H_a and CH_2CH_2 of Bu), and 0.925 (t, ^3J 7.3 Hz; Me of Bu). The *trans*-isomer included signals at 3.87-4.00 (m; 6-H_a and 6-H_e), 3.35-3.80 (m; OCH_2 of OBu), 3.10-3.22 (m; 4-H), 1.3-2.1 (m, 3-H_e, 3-H_a and CH_2CH_2 of Bu) and 0.959 (t, ^3J 7.4 Hz; Me of Bu).

4-Phenyl-3,4-dihydro-2H-pyran. - The foregoing product (42.53 g), containing a trace of phosphorus pentoxide, was heated under reflux for 2 hr (cf.[50]). Butan-1-ol, b.p.117-120°, was largely removed by distillation at atmospheric pressure. Distillation of the residue gave a fraction (30.1 g), b.p. 104-106°/9 mm Hg. The product, dissolved in ether (50 cm^3), was treated with small strips of sodium (2 g) and stirred until evolution of hydrogen ceased. The precipitated sodium butoxide was removed by filtration and washed with dry ether. The filtrate was dried ($MgSO_4$), filtered and distilled, giving 4-phenyl-3,4-dihydro-2H-pyran (23.83 g, 82%), b.p. 103°/8 mm Hg. (Found: M^+ 160.0883. $C_{11}H_{12}O$ requires M 160.0888). Microanalysis was unsatisfactory (e.g. Found: C, 81.2; H, 7.7. $C_{11}H_{12}O$ requires C, 82.5; H, 7.6%). The ^1H nmr spectrum (250 MHz, $CDCl_3$) included signals at δ 6.56 (dd, $^3J_{5,6}$ 6.25 Hz, $^4J_{4,6}$ 1.95 Hz; 6-H), 4.75 (m; 5-H), 3.92-3.99 (m; 2-H), 3.41-3.51 (m; 4-H), 2.10-2.22 (m; one of 3-H), and 1.76-1.89 (m; one of 3-H).

cis- and trans-2-Hydroxy-4-phenyltetrahydropyran. - 4-Phenyl-3-4,dihydro-2H-pyran (10.22 g) dissolved in tetrahydrofuran (50 cm^3), was treated with water (2 cm^3) and concentrated hydrochloric acid (2 cm^3), and the mixture was stirred at room temp. for 12 hr. The mixture was basified (anhydrous Na_2CO_3) and evaporated at 15 mm Hg pressure to remove tetrahydrofuran. The residue was shaken with ether (3 x 20 cm^3) and the combined extracts were dried ($MgSO_4$), filtered and evaporated to dryness. The crystalline residue (11.02 g) was distilled, yielding white crystals (8.0 g, 70%) of a mixture of *cis*- and *trans*-2-hydroxy-4-phenyltetrahydropyran, b.p. 150°/3 mm Hg, m.p. 72° (Found: C, 74.5; H, 7.9. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%).

The ^{1}H nmr spectrum (400 MHz; $CDCl_3$) included signals for the *cis*-isomer at δ 4.84 (d; $^{3}J_{2a3a}$ 9.1 Hz; 2-H), 4.14 (td; $^{2}J_{6e6a}$ 11.5 Hz, $^{3}J_{6e5e}$ + $^{3}J_{6e5a}$ 6.1 Hz; 6-H$_e$), 3.67 (m; 6-H$_a$), 2.85 (m; 4-H), 2.15 (dm; $^{2}J_{3e3a}$ 12.8 Hz; 3-H$_e$), 1.75 (m; 5-H$_e$ and 5-H$_a$), and 1.60 (dt; $^{3}J_{2a3a}$ 9.4 Hz, $^{2}J_{3e3a}$ + $^{3}J_{3a4a}$ 25.4 Hz; 3-H$_a$). The *trans*-isomer showed signals at δ 5.43 (s; 2-H), 4.17 (td; $^{3}J_{6a5e}$ 3.1 Hz; $^{2}J_{6e6a}$ + $^{3}J_{6a5a}$ 26.0 Hz; 6-H$_a$), 3.76 (ddd; $^{2}J_{6e6a}$ 11.3 Hz, $^{3}J_{6e5a}$ 4.5 Hz, $^{3}J_{6e5e}$ 1.8 Hz; 6-H$_e$), 3.25 (tt; $^{3}J_{4a3a}$ + $^{3}J_{4a5a}$ 24.5 Hz, $^{3}J_{4a3e}$ + $^{3}J_{4a5e}$ 8.2 Hz; 4-H), 2.0 (dm; $^{2}J_{3e3a}$ 13.3 Hz; 3-H$_e$) and 1.85 (m; 3-H$_e$, 5-H$_e$ and 5-H$_a$). ^{1}H nmr assignments were confirmed by ^{1}H/^{1}H COSY experiments.

The ^{13}C nmr spectrum (100.6 MHz; $CDCl_3$) included signals for the *cis*-isomer at δ 96.39 (2-C), 65.74 (6-C), 40.57 (4-C), 40.22 (3-C) and 32.77 (5-C), and signals for the *trans*-isomer at δ 91.48 (2-C), 59.70 (6-C), 37.68 (3-C), 34.50 (4-C) and 33.00 (5-C).

cis- *and* trans-2-*Methylamino*-4-*phenyltetrahydropyran*. - Methylamine, prepared by warming methylamine hydrochloride (0.26 g) in a solution of sodium hydroxide (0.37 g) in water (2 cm^3), was passed into ice-cold water (0.7 cm^3). The resulting solution was added to a solution of *cis*- and *trans*-2-hydroxy-4-phenyltetrahydropyran (0.44 g) in tetrahydrofuran (50 cm^3). The mixture was stirred for 24 hr. at room temperature and then evaporated at 40°/10 mm Hg to remove tetrahydrofuran. The residue was taken up into ether (30 cm^3) and the resulting solution was dried ($MgSO_4$), filtered and evaporated to leave a crude sample of *cis*- and *trans*-2-methylamino-4-phenyltetrahydropyran (approximate ratio *cis*/*trans* = 12) (0.44 g, 93% crude), which suffered appreciable decomposition on attempted distillation. (Found on undistilled sample: M$^+$ 191. 1290. $C_{12}H_{17}NO$ requires M 191.1310). Experiments in which the 2-hydroxy-4-phenyltetrahydropyran in tetrahydrofuran was treated with a solution of methylamine hydrochloride in aqueous NaOH gave poor yields. ^{1}H nmr details are listed in Tables 6, 7 and 9 whilst ^{13}C nmr details are given in Table 5 and 9. ^{1}H nmr assignments were confirmed by ^{1}H/^{1}H COSY experiments.

cis- and trans-[Methylamino-^{13}C]-2-methylamino-4-phenyltetrahydropyran - The foregoing preparation was repeated using [^{13}C]methylamine hydrochloride (0.26 g, 93.5 ^{13}C atom %), sodium hydroxide (0.29 g), water (4 cm^3), cis- and trans-2-hydroxy-4-phenyltetrahydropyran (0.25 g) and tetrahydrofuran (50 cm^3). The crude product (0.27 g) had M$^+$ 192.13387 ($^{13}C^{12}C_{11}H_{17}NO$ required M 192.13437). The ^{1}H nmr spectrum (400 MHz, $CDCl_3$) included signals for the cis-isomer at δ 2.506 (s; $N^{12}CH_3$) and δ 2.505 (d; $^1J_{CH}$ 134.47 Hz; $N^{13}CH_3$) and signals for the trans-isomer at δ 2.423 (s; $N^{12}CH_3$) and δ 2.422 (d; $^1J_{CH}$ 134.23 Hz; $N^{13}CH_3$). The ^{3}C nmr data are listed in Tables 5 and 9.

4-t-Butyl-3,4-dihydro-2H-pyran (cf.[52]). - 2-Ethoxy-5,6-dihydro-2H-pyran (11.06 g),[53] dissolved in dry tetrahydrofuran (60 cm^3) was stirred for 20 min. with copper(I) bromide (0.60 g). To this mixture at -15° was gradually added, with stirring, a solution in tetrahydrofuran (50 cm^3) of t-butylmagnesium chloride [from t-butyl chloride (16 1 g, 2 equivalents)].
The dark blue mixture was allowed to come to room temp., after which stirring was continued for 12 hr. A saturated aqueous solution of ammonium chloride (30 cm^3) was added, and the mixture was then extracted with n-pentane (3 x 30 cm^3). The combined extracts were washed with saturated sodium chloride and dried ($MgSO_4$). The solution was filtered, heated to remove solvent and purified by flash chromatography on silica, using hexane-ether (2:3) as eluant. The product, obtained as an undistilled colourless oil, was 4-t-butyl-3,4-dihydro-2H-pyran (3.71 g, 68%). Mass spectroscopy gave M$^+$ 140.1203 ($C_9H_{16}O$ requires M 140.1201). The ^{1}H nmr spectrum (250 MHz, $CDCl_3$) included signals at δ 6.38 (dd; $^3H_{5,6}$ 6.5 Hz, $^4J_{4,6}$ 2.4 Hz; 6-H), 4.63 (dt; $^3J_{5,6}$ 6.5 Hz, $^3J_{4,5}$ + $^4J_{3,5}$ 3.8 Hz; 5-H), 4.12 (dt; $^2J_{2e2a}$ 10.7 Hz, $^3J_{2e3e}$ + $^3J_{2e3a}$ 7.2 Hz; 2-H_e), 3.87 (td; $^2J_{2e2a}$ + $^3J_{2a3a}$ 21 Hz, $^3J_{2a3e}$ 3 Hz; 2-H_a), 2.00 (m; 4-H), 1.75 (m; 3-H_a), 1.25 (m; 3-H_e) and 0.88 (s; t-Bu).

cis- and trans-4-t-Butyl-2-hydroxytetrahydropyran. - To tetrahydrofuran (50 cm^3) was added 4-t-butyl-3,4-dihydro-2H-pyran (2.28 g) and water (5 cm^3), followed by concentrated hydrochloric acid (1 cm^3). The mixture was stirred for 16 hr at room temperature, treated with solid sodium carbonate until effervescence ceased and evaporated to remove tetrahydrofuran. The residue was extracted with ether (3 x 15 cm^3) and the combined extracts were dried ($MgSO_4$), filtered and evaporated to leave a white crystalline solid. Distillation gave white crystals of cis- and trans- 4-t-butyl-2-hydroxytetrahydropyran (1.51 g, 59%), b p. 165°/3 mm Hg, m.p. 50-54° (Found: C, 68.2; H, 11.7. $C_9H_{18}O_2$ requires C, 68.3; H, 11.5%) The ^{1}H nmr spectrum (400 MHz, $CDCl_3$) included signals for the cis-isomer at δ 4.66 (ddd; $^3J_{2a3a}$ 8.6 Hz, $^3J_{2a3e}$ 2.0 Hz, $^3J_{2aOH}$ 5.8 Hz; 2H_a), 4.07 (ddd; $^2J_{6e6a}$ 11 6 Hz, $^3J_{6e5a}$ 4.3 Hz, $^3J_{6e5e}$ 1.7 Hz; 6-H_e), 3.46 (dt; $^2J_{6e6a}$ + $^3J_{6a5a}$ 23.4 Hz,

$^3J_{6a5e}$ 2.3 Hz; 6-H$_a$), 3.16 (d; $^3J_{2aOH}$ 6.1 Hz; OH), 1.94 (dq; $^2J_{3e3a}$ 12.4 Hz, $^3J_{3e4a}$ 4.9 Hz, $^3H_{3e2a}$ 2.2 Hz; 3-H$_e$), 1.51 (dm; $^2J_{5e5a}$ 9.3 Hz; 5-H$_e$), 1.3 (m; 4-H and 5-H$_a$), 1.10 (td; $^2J_{3a3e}$ + $^3J_{4a3a}$ 24.5 Hz, $^3J_{2a3a}$ 9.4 Hz; 3-H$_a$), and 0.87 (s; t-Bu). The *trans*-isomer showed signals at δ5.37 (t, partly resolved, $w_{\frac{1}{2}}$ 6 Hz; 2-H$_e$), 3.99 (ddd; $^2J_{6e6a}$ + $^3J_{6a5a}$ 24 Hz, $^3J_{6a5e}$ 2.4 Hz; 6-H$_a$), 3.69 (ddd, $^2J_{6e6a}$ 11.1 Hz, $^3J_{6e5a}$ 4.7 Hz; $^3J_{6e5e}$ 1.8 Hz; 6-H$_e$), 2 58 (bs; OH), 1.78 (dm; $^2J_{3e3a}$ 13 1 Hz; 3-H$_e$), 1.69 (tt; $^3J_{4a5a}$ + $^3J_{4a3a}$ 15.0 Hz; $^3J_{4a5e}$ + $^3J_{4e3e}$ 6.8 Hz; 4-H$_a$), 1.59 (dm, $^2J_{5e5a}$ 13.5 Hz; 5-H$_e$), 1.37 (dq; $^2J_{5a5e}$ + $^3J_{5a4a}$ + $^3J_{5a6a}$ 37.8 Hz, $^3J_{5a6e}$ 4.8 Hz; 5-H$_a$), 1.40 (dt; $^2J_{3e3a}$ + $^3J_{3a4a}$ 26 Hz; $^3J_{3a2e}$ 3.5 Hz; 3-H$_a$), and 0.85 (s; t-Bu). These assignments were confirmed by $^1H/^1H$ COSY experiments

The ^{1}H nmr spectrum (250 MHz, CDCl$_3$) of a thoroughly dried sample revealed the hydroxyl signals of *cis*- and *trans*-isomers as a doublet ($^3J_{2aOH}$ 6.2 Hz, *cis*) and a triplet ($^3J_{2eOH}$ + $^4J_{3aOH}$ 4.8 Hz, *trans*).

cis- and trans-4-t-Butyl-2-methylaminotetrahydropyran. - To an ice-cold solution of sodium hydroxide (0.30 g) in water (2 cm^3) was added methylamine hydrochloride (0.26 g) The mixture was warmed and the liberated methylamine was bubbled into ice-cold water (2.4 cm^3). The aqueous methylamine was added to an ice-cold solution of *cis*- and *trans*-4-t-butyl-2-hydroxytetrahydropyran (0.41 g) in tetrahydrofuran (7cm^3). The mixture was heated in a sealed tube at 50° for 18 hr, after which tetrahydrofuran was removed by evaporation at 40°/10 mm Hg. The residue was dissolved in ether (50 cm^3) and the solution was dried (MgSO$_4$), filtered and evaporated, leaving a mixture of *cis*- and *trans*-4-t-butyl-2-methylaminotetrahydropyran (0.32 g, 73% crude). The product, a yellow oil, decomposed on attempted distillation *in vacuo*. The mass spectrum gave M$^+$ 171.16176 ($C_{10}H_{21}NO$ requires M, 171.16236). Details of the ^{1}H nmr spectrum are given in Tables 8 and 9; ^{13}C nmr spectral details are shown in Tables 5 and 9

cis- and trans-4-t-Butyl-[methylamino-^{13}C]-2-methylaminotetrahydropyran - The preceding preparation was repeated using the following quantities: sodium hydroxide (0.30 g), water (2 cm^3), [^{13}C]methylamine hydrochloride (0.22 g, 93 5 ^{13}C atom %), ice-cold water (1 8 cm^3), *cis*- and *trans*-4-t-butyl-2-hydroxytetrahydropyran (0 44 g) and tetrahydrofuran (0.7 cm^3). The product, a pale yellow oil, was a mixture of *cis*- and *trans*-4-t-butyl-[methylamino-^{13}C]-2-methylaminotetrahydropyran, and gave M$^+$ 172.1658 ($^{13}C^{12}C_9H_{20}NO$ requires M, 172.16567). The ^{1}H nmr spectrum (250 MHz, CDCl$_3$) included signals for the *cis*-isomer at δ 2.51 (s; $N^{12}CH_3$) and 2.52 (d; $^1J_{CH}$ 134.2 Hz; $N^{13}CH_3$) and a signal for the *trans*-isomer at δ 2.42 (d; $^1J_{CH}$ 134.0 Hz; $N^{13}CH_3$). The ^{13}C nmr spectral details are listed in Tables 5 and 9 The ratio of *cis*- to *trans*-isomers was approximately 20.

Acknowledgements: We thank the S.E.R.C. for the award of studentships to J.M.D. and S.A.R., and the University of Salah Al-deen for the award of a scholarship to K.A.K. We thank R.A. Fleming and M. Barnes for recording some of the nmr spectra.

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