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Studies on the Benzoxazine Series. Part 3*—Preparation and ^{13}C NMR Structural Study of γ Effects of Some *N*-Substituted 3,4-Dihydro-2*H*-1,3-benzoxazines

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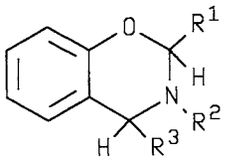
Seventeen *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines [*N*-substituent = Et, Pr^i, Bu^t, $CH_2C_6H_5$ or $CH(CH_3)C_6H_5$] were prepared and their structures studied in the light of ^{13}C chemical shifts. The γ effects caused by C(α)-methyl or C(α)-phenyl substitution at the heterocyclic ring carbons were found to be valuable structural parameters. By using *N-tert*-butyl derivatives as models, and by dividing γ_{tot} effects into their components, the rotamer populations due to the rotation around the N—C(α) bond could be evaluated. The method also allows the configurational assignment of diastereomeric *N*-α-methylbenzyl derivatives. The effect of the half-chair structure on the ^{13}C NMR parameters is discussed.

KEY WORDS 3,4-Dihydro-2*H*-1, 3-benzoxazines ^{13}C NMR spectroscopy Substituent effects Stereochemistry

INTRODUCTION

γ Effects, especially γ_{gauche}, γ_{anti} and γ_{axial}, are useful tools in ^{13}C NMR structural studies, despite the controversy concerning their exact mechanism.[1] However, relatively little attention has been paid to potential γ_{syn} effects caused by substituents larger than the methyl group at the ring carbons. In this study, the structures of some *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines (R ⩾ Me) are discussed in the light of the different γ effects, with special emphasis on the γ effects caused by α-methyl and α-phenyl substitutions.



(1) R^2 = Et
(2) R^2 = Pr^i
(3) R^2 = Bu^t
(4) R^2 = CH_2Ph
(5) R^2 = CHMePh

(a) R^1 = R^3 = H
(b) R^1 = Me, R^3 = H
(c) R^1 = H, R^3 = Me

EXPERIMENTAL

All compounds were prepared by condensation between the appropriate *N*-substituted *o*-aminomethylphenol and formaldehyde or acetaldehyde using reaction conditions described earlier.[2] All condensations proceeded smoothly to completion except those between acetaldehyde and *o*-(*N-tert*-butylaminomethyl)phenol or *o*-(*N*-α-methylbenzylaminomethyl)phenol. In these cases a fourfold excess of acetaldehyde was used and the reaction mixture (solvent, toluene or benzene) was allowed to stand (after initial mixing) for 2 weeks at room temperature.

The lower alkyl derivatives (R^2 = Et or Pr^i) were purified by distillation in vacuum. The other products (oils) were used without distillation to avoid their partial decomposition.

The compounds were characterized by their ^1H NMR spectra and by their elemental analyses (C, H, N: ±0.4%) and/or high-resolution mass spectra recorded on a VG Analytical MM 7070E mass spectrometer.

Noise-decoupled ^{13}C NMR spectra were recorded for 1.0 M solutions in $CDCl_3$ (used as a field/frequency lock signal) at room temperature, normally on a Jeol FX-60 spectrometer operating at 15.03 MHz.[3] The ^4J(HCNCH) long-range coupling constants were extracted from the spectra recorded on a JEOL GX-400 spectrometer at 400 MHz, which was also used to record the ^{13}C spectra in some cases.

RESULTS

Some of the ^{13}C chemical shifts of the *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines prepared are given in Table 1. The substituent effects at ring carbons C-2 and C-4 are given in Tables 2 and 3. 3,4-Dihydro-4-methyl-2*H*-1,3-benzoxazine is a 92 : 8 mixture of the 4eq′ and 4ax′ half-chair forms.[2] The shifts for the 4ax′ half-chair form (C-2, 78.75; C-4, 54.71; and *N*-CH_3, 40.15 ppm) were calculated by using the shift effects published

* For Part 2, see Ref. 3. This paper is also Part 1 in the series Studies on the γ Effect.

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Table 1. ^{13}C NMR chemical shifts for the prepared 3,4-dihydro-2*H*-1,3-benzoxazines in $CDCl_3$ solution (in ppm from internal Me_4Si)

Compound	R^2	C-2	C-4	*N*-C(α)	2-Me	4-Me	α-Me
		Parent compounds ($R^1 = R^3 = H$) (**1a–5a**)					
	H	78.07	44.01				
	Me	83.65	52.02	39.59			
1a	Et	81.80	49.93	45.40			13.31
2a	Pr^i	80.48	47.36	50.20			21.31
3a	Bu^t	79.04	45.28	54.18			28.25
4a	$CH_2C_6H_5$	82.14	49.61	55.50			
5a	$CH(CH_3)C_6H_5$	80.01	48.68	57.56			21.50
		2-Methyl substituted derivatives (R^1 = Me, R^3 = H) (**1b–5b**)					
	H	83.90	44.18		21.45		
	Me	87.62	52.62	35.62	18.98		
1b	Et	87.32	47.42	42.72	18.92		13.72
2b	Pr^i	85.89	42.25	50.05	19.15		21.21
3b	Bu^t	82.64	39.23	55.13	20.19		28.68
4b	$CH_2C_6H_5$	87.42	47.66	52.34	19.04		
5b(A)	$CH(CH_3)C_6H_5$	83.67	43.52	58.33	18.98		20.91
5b(B)	$CH(CH_3)C_6H_5$	85.17	41.04	58.72	18.98		21.04
		4-Methyl-substituted derivatives (R^1 = H, R^3 = Me) (**1c–5c**)					
	H	75.64	47.75			21.87	
	Me	79.31	54.82	39.59		23.07	
1c	Et	76.87	53.02	46.19		24.07	23.07
2c	Pr^i	75.97	49.79	52.16		24.69	21.55
							21.90
3c	Bu^t	74.50	47.66	54.77		25.06	28.70
4c	$CH_2C_6H_5$	77.54	52.53	56.30		24.04	
5c(A)	$CH(CH_3)C_6H_5$	74.10	52.03	58.91		24.10	22.21
5c(B)	$CH(CH_3)C_6H_5$	76.17	48.88	58.71		24.71	20.70

Table 2. ^{13}C NMR chemical shift differences between the different *N*-substituted derivatives and the corresponding *N*-methyl derivatives (in ppm) together with the rotamer populations (in %) for the *N*-substituents

	Differences at[a]			Rotamer populations[b]		
Compound	C-2	C-4	N-C(α)	*a*	*b*	*c*
1a	−1.85	−2.09	5.81	29	41	30
1b	−0.30	−5.20	7.10			
1c	−1.88	−1.69	6.04	32	46	22
4a	−1.51	−2.41	15.91	32	32	36
4b	−0.20	−4.96	16.72			
4c	−1.21	−2.18	16.15	41	28	31
				ab	*bc*	*ac*
2a	−3.17	−4.66	10.61	31	38	31
2b	−1.73	−10.37	14.43			
2c	−2.78	−4.92	12.01	30	35	35
3a	−4.61	−6.74	14.59			
3b	−4.98	−13.39[c]	19.51			
3c	−4.25	−7.05	14.62			
				ab + *ba*	*bc* + *cb*	*ac* + *ca*
5a	−3.64	−3.34	17.97	53	28	18
5b(A)	−3.95	−9.10	22.71			
5b(B)	−2.45	−11.58	23.10			
5c(A)	−4.65	−2.68	18.76	69	47	−16
5c(B)	−2.58	−5.83	18.56	15	43	41

[a] These differences represent γ_{tot} effects.
[b] In the case of series **b**, the presence of 2eq ⇌ 2ax equilibria prevents the evaluation.
[c] γ^2_{ax}-4 effect (cf. Table 3) can be subtracted, giving −13.39 − (−6.05) = −7.34 ppm.

Table 3. *C*-Methyl substituent effects (SE) as a function of *N*-substitution

Source of SE	SE at C-2 (ppm) 2eq⇌2ax	SE at C-2 (ppm) 4ax'	SE at C-4 (ppm) 2eq⇌2ax	SE at C-4 (ppm) 4ax'
N-Substitution				
H[a]	5.80	−4.86	0.16	2.42
Me[a]	3.98	−4.90	0.60[b]	2.69
Et	5.52	−4.93	−2.51	3.09
Pr^i	5.41	−4.51	−5.11	2.43
Bu^t	3.60	−4.54	−6.05[c]	2.38
$CH_2C_6H_5$	5.28	−4.60	−1.95	2.92
$CH(CH_3)C_6H_5$	3.66[d]	−5.91[e]	−5.16[d]	3.35[e]
$CH(CH_3)C_6H_5$	5.16[f]	−3.84[g]	−7.64[f]	0.20[g]

[a] See Ref. 2. These compounds exhibit pure 2eq substitutions.
[b] A model for the γ^2_{eq}-4 effect.
[c] A model for the γ^2_{ax}-4 effect.
[d] Diastereomer **5b**(A).
[e] Diastereomer **5c**(A).
[f] Diastereomer **5b**(B).
[g] Diastereomer **5c**(B).

earlier[2] and used for calculating the effects given in Table 2.

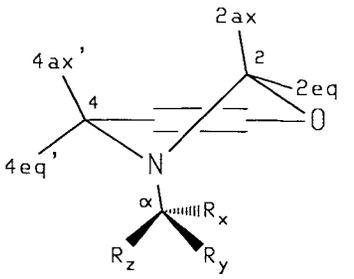
Interaction between the equatorial (C-2)—H or pseudoequatorial (C-4)—H bond and the α-substituent causes γ effects, which are best depicted as γ_{gauche}, γ_{syn} and γ_{anti} effects (see Fig. 1). For instance, in **1a** (see Table 2) the following combinations of effects are operative:

$$\text{at C-2: } \gamma_{tot} = -1.85 \text{ ppm} = a\gamma_{gauche} + b\gamma_{syn} + c\gamma_{anti}$$

$$\text{at C-4: } \gamma_{tot} = -2.09 \text{ ppm} = a\gamma_{gauche} + b\gamma_{anti} + c\gamma_{syn}$$

$$a + b + c = 1$$

The different γ effects in the *N*-tert-butyl derivatives can be utilized to solve the rotamer populations from this



R_x	R_y	R_z	Rotamer
Me	H	H	a
H	Me	H	b
H	H	Me	c
Ph	H	H	a
H	Ph	H	b
H	H	Ph	c
Me	Me	H	ab
H	Me	Me	bc
Me	H	Me	ac
Me	Ph	H	ab^1
Ph	Me	H	ba^1
H	Me	Ph	bc^2
H	Ph	Me	cb^2
Me	H	Ph	ac^3
Ph	H	Me	ca^3

Figure 1. Nomenclature for the *N*-C(α) rotamers (superscripts 1, 2 and 3 refer to the diastereomer pairs).

set of equations since for **3a**:

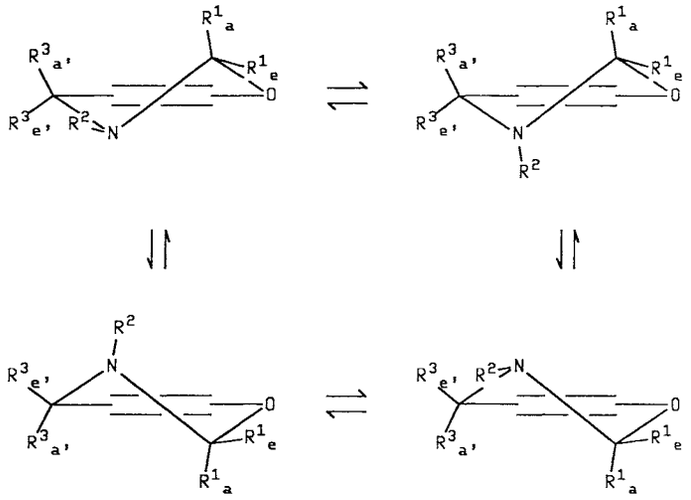
$$\text{at C-2: } \gamma_{tot} = -4.61 \text{ ppm} = \gamma_{gauche} + \gamma_{syn} + \gamma_{anti}$$

$$\text{at C-4: } \gamma_{tot} = -6.74 \text{ ppm} = \gamma_{gauche} + \gamma_{anti} + \gamma_{syn}$$

because now

$$a = b = c = 1$$

The following assumptions can be made: (i) γ_{gauche} can be neglected and (ii) $\gamma_{anti}/\gamma_{syn}$ can be taken as equal to 0.086. The first assumption is supported by the shift



Scheme 1. Conformations of 3,4-dihydro-2*H*-1,3-benzoxazines.

parameters for the methyl carbons in methyl-substituted 1,3-dioxanes (for example the effects of the 4eq- or 4ax-methyl groups at the 5eq-methyl are 0.14 and −0.06 ppm, respectively).[4] The latter is based on a study of the γ_{eq} *vs.* γ_{ax} effects in tetrahydro-1,3-oxazine and 3,4-dihydro-2*H*-1,3-benzoxazines, which are reasonable models: $\gamma^4_{eq} - 2/\gamma^4_{ax} - 2 = 0.080$ for the former[5] and $\gamma^4_{eq'} - 2/\gamma^4_{ax'} - 2 = 0.093$ for the latter.[2] Accordingly, γ_{syn} at C-2 = −4.25 ppm and γ_{anti} at C-2 = −0.37 ppm. Compounds **3b** and **3c** can be treated analogously:

	γ_{syn} effect (ppm)		γ_{anti} effect (ppm)	
Compound	At C-2	At C-4	At C-2	At C-4
3a	−4.25	−6.21	−0.37	−0.53
3b	−4.59	−6.76	−0.39	−0.58
3c	−3.91	−6.49	−0.34	−0.56

Using the above values, the molar fractions of the different rotamers can be solved for the compounds in the **a** and **c** series (Table 2). In the **b** series the conformational heterogeneity of the 2-methyl substitution prevents the solution. The following examples illustrate the calculation of the rotamer populations listed in Table 2:
Compound **1a** (Fig. 1):

$$-4.25b - 0.37c = -1.85 \text{ ppm}$$

$$-0.53b - 6.21c = -2.09 \text{ ppm}$$

$$a + b + c = 1$$

which gives $a = 0.29$, $b = 0.41$ and $c = 0.30$.
Compound **2a** (Fig. 1):

$$\text{at C-2: } \gamma_{tot} = -3.17 \text{ ppm} = ab(\gamma_{gauche} + \gamma_{syn}) + bc(\gamma_{syn} + \gamma_{anti}) + ac(\gamma_{gauche} + \gamma_{anti})$$

$$\text{at C-4: } \gamma_{tot} = -4.66 \text{ ppm} = ab(\gamma_{gauche} + \gamma_{anti}) + bc(\gamma_{anti} + \gamma_{syn}) + ac(\gamma_{gauche} + \gamma_{syn})$$

$$ab + bc + ac = 1$$

With the aid of the effects listed above and by neglecting the γ_{gauche} effect, we obtain

$$-4.25ab + (-4.25 - 0.37)bc - 0.37ac = -3.17 \text{ ppm}$$

$$-0.53ab + (-6.21 - 0.53)bc - 6.21ac = -4.66 \text{ ppm}$$

$$ab + bc + ac = 1$$

which leads to $ab = ac = 0.31$ and $bc = 0.38$.

In the case of **5a**, *ab*, *bc* and *ac* are replaced by *ab* + *ba*, *bc* + *cb*, and *ac* + *ca*, respectively (cf. Fig. 1). Because of the conformational homogeneity of the 4ax'-methyl-substitution compounds **1c**–**5c** can be treated analogously to **1a**–**5a**. For **1b**–**5b** the conformational heterogeneity of the 2-methyl substitution prevents analogous calculations (see below), even if the prevailing 2ax-methyl substitution in **3b** allows the calculations of γ_{syn} and γ_{anti} effects as above.

DISCUSSION

The C-2 or C-4 chemical shifts of an *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazine can be compared either with those of the corresponding *N*-methyl derivative or with those of the *N*-unsubstituted parent compound. The C-2/C-4 carbon chemical shifts are susceptible to the γ effects caused by (methyl) substitutions both at the C-4/C-2 (ring) carbons and at the α-carbon of the *N*-substituent. In other words:

$$\gamma_{tot} = \gamma_{eq} + \gamma_{ax} + [\gamma(N) = \gamma_{anti} + \gamma_{syn} + \gamma_{gauche}] \quad (1)$$

where

γ_{tot} = total γ effect at C-2/C-4;
γ_{eq} = γ effect at C-2/C-4 caused by the 4eq'-/2eq-methyl substitutions;
γ_{ax} = γ effect at C-2/C-4 caused by the 4ax'-/2ax-methyl substitutions;
γ_{anti} = γ effect at C-2/C-4 caused by the *anti* α-substitution;
γ_{syn} = γ effect at C-2/C-4 caused by the *syn* α-substitution;
γ_{gauche} = γ effect at C-2/C-4 caused by the *gauche* α-substitution (neglected in the calculation of the rotamer populations).

Methyl-substituted alicyclic compounds and their heteroanalogues exhibit small γ_{eq} effects (negative or positive) but large γ_{ax} effects. In principle, both effects are sensitive to the ring deformation caused by the substitution. However, condensed ring structures such as 3,4-dihydro-2*H*-1,3-benzoxazines are generally less readily deformed than monocyclic systems. In accordance with previous results,[2,6] we have postulated the present compounds to favour (although deformed) half-chair rather than half-boat or sofa forms. This postulation is not invalidated by inspection of Dreiding models and is also capable of explaining the trends discussed below.*

The rotamers with an α-methyl or an α-phenyl substituent *syn*, *anti* or *gauche* to (C-2)—H/(C-4)—H show γ_{syn}, γ_{anti} or γ_{gauche} effects, respectively (in comparison with the corresponding *N*-methyl derivatives). In other words, γ_{tot} is sensitive to the rotation about the N—C(α) bond. If the two compounds (with the same *N*-substitution) compared exhibit equal rotamer distributions, evaluation of the γ_{eq} or γ_{ax} effect is possible.

γ(*N*) Effects

Table 2 lists the $\gamma(N)$ effects of the *N*-substituted derivatives with respect to the *N*-methyl derivatives. The $\gamma(N)$ effects of the *N*-*tert*-butyl derivatives **3a**, **3b** and **3c** at C-2 are −4.61, −4.98 and −4.25 ppm, respectively,

* One of the referees has indicated that our results could be consistent with a sofa form. In the same context he mentioned that no crystal structure determination for the compounds in question is available. Independently of the fact that the solution conformations are not necessarily equivalent to those in the solid state, we hope to resolve this interesting question using x-ray diffraction in the near future.

and those at C-4 are −6.74, −7.34 (a calculated value, see Table 2) and −7.05 ppm, respectively, and these are almost constant. The difference between the γ(*N*) effects at C-2 and C-4 is inherent in the half-chair structure. On average, the γ(*N*) effect at C-4 is 1.5 ± 0.1 times more shielding than that at C-2. 1,3-Dioxane exhibits γ_{ax} effects whose values are very close to those given above: γ^6_{ax}-4 −4.74 ppm, γ^4_{ax}-2 −7.12 ppm and γ^2_{ax}-4 −7.79 ppm.[4] This suggests similar distances between the respective carbon atoms. *N-tert*-Butyl derivatives allow the evaluation of the γ_{syn} and γ_{anti} effects and the proportions (Table 2) of the different orientations (Fig. 1) for the other *N*-substituted derivatives.

For derivatives **1a**, **2a** and **4a** without methyl substitution at C-2 or C-4, the γ_{tot} terms are due to the γ(*N*) contributions only. The deviations from the statistical rotamer distributions (33.3% each) are relatively small (cf. Table 2), and because of the neglect of the γ_{gauche} effect they are not necessarily significant. However, the preponderance of orientation *b* in compound **1a** is in harmony with the steric requirements of the half-chair structure, which favours the *anti* arrangement of the *N*-substituent and the C-4 centre. For the *N*-isopropyl derivative **2a** the potential α,α-disubstitution effect complicates the situation.

For the *N*-α-methylbenzyl derivative **5a** the rotation about the N—C(α) bond together with the ring and/or nitrogen inversion processes can lead to six different orientations of the N—C(α) substituents, namely rotamers *ab*, *bc* and *ca* as well as *ba*, *cb* and *ac* (Fig. 1). In addition, restricted rotation of the α-phenyl group and disubstitution effects complicate the interpretation. Formally, the orientations with the C(α)—H bond *syn* to the (C-4)—H bond (*ab* + *ba*) are stabilized with respect to the orientation with the C(α)—H bond *syn* to the (C-2)—H bond (*ac* + *ca*).

The ratio of the upfield effects at C-4 and C-2 for **2a** (1.47) is almost equal to the above estimate (1.5). For **5a** this ratio is 0.92, the the rotamer populations reported do not correspond to the real situation. The α-phenyl group cannot rotate freely in these rotamers (*ba* and *ca*) where it is located above the heterocyclic moiety, but it minimizes the steric and repulsive electronic interactions. Hence, for example, in rotamer *ca* the *ortho*-CH fragment of the α-phenyl group is closer to the C-2 centre than to the C-4 centre, which results in an enhanced γ-effect at C-2 and a diminished effect at C-4. The validity of this assumption is tested in the configurational assignment of the diastereomeric α-methylbenzyl derivatives.

Effect of 4-methyl substitution

According to their 4-methyl chemical shifts (Table 1), *N*-substituted 4-methyl-3,4-dihydro-2*H*-1,3-benzoxazines (with the exception of the *N*-methyl derivative[2]) strongly prefer the 4ax′-methyl orientations. Therefore, their γ(*N*) effects should not differ essentially from those of the parent compounds, since the complications due to the 4eq′-methyl substitution are avoided. The results in Table 2 support this assumption. However, the *N*-ethyl derivative **1c**, when compared with the parent compound **1a**, favours to some extent orientation *b* with the α-methyl group *syn* to the C-2—H bond at the expense of orientation *c* with the α-methyl group *syn* to the C-4—H bond. This behaviour may be due to a 'buttressing' effect. The interaction between the α-methyl group and the 4eq′-hydrogen cannot, as in the parent compound **1a**, be relieved by bending because of the 4ax′-methyl substitution.

On the other hand, for the *N*-benzyl derivative **4c** orientation *b* is destabilized and orientation *a* stabilized. In the latter orientation the nitrogen lone pair and the benzylic C(α)—C(phenyl) bond are antiperiplanar. The behaviour of the *N*-isopropyl derivative **2c** does not differ essentially from that of the parent compound **2a**.

Effect of 2-methyl substitution

The study of the γ(*N*) effects in **1b**–**5b** is complicated by the 2eq ⇌ 2ax equilibria of the 2-methyl substitution (cf. Table 3), caused by the conformational restraint of the α-substitution. Six different rotamers depicted as 2eq(*a*), 2eq(*b*) and 2eq(*c*) or 2ax(*a*), 2ax(*b*) and 2ax(*c*) (see Fig. 1) can be considered for **1b**. The contribution of the 2ax-methyl substitution increases the γ_{tot} effect at C-4 and, on the other hand, the conformers with the 2eq-methyl substitution cannot experience γ(*N*) effects at C-2. Since γ_{tot} at C-2 is only slightly negative (−0.30 ppm), **1b** does not favour rotamers with 2ax-methyl substitution:

$$2ax(a)\gamma_{gauche} + 2ax(b)\gamma_{syn} + 2ax(c)\gamma_{anti} = -0.30 \text{ ppm}$$

Assuming that 2ax(*a*) : 2ax(*b*) : 2ax(*c*) = *a* : *b* : *c* for **1a**, and with the appropriate model values for the γ effects in question, the following molar fractions were obtained for **1b**: 2ax(*a*) = 0.04, 2ax(*b*) = 0.06 and 2ax(*c*) = 0.05.

Conformer 2eq(*b*) exhibits a *syn*-CH_3,CH_3 interaction, comparable to a 1,3-*syn*-diaxial CH_3,CH_3 interaction, and therefore its contribution can be neglected. Rotamers 2eq(*c*), 2ax(*a*), 2ax(*b*) and 2ax(*c*) are all able to cause γ^2_{ax}-4 and/or γ(*N*) effects at C-4:

$$\begin{aligned} 2ax(a)\gamma_{gauche} &+ 2ax(b)\gamma_{anti} + 2ax(c)\gamma_{syn} \\ &+ [2ax(a) + 2ax(b) + 2ax(c)]\gamma^2_{ax} - 4 \\ &+ 2eq(a)\gamma_{gauche} + 2eq(c)\gamma_{syn} \\ &+ [2eq(a) + 2eq(c)]\gamma^2_{eq} - 4 \\ &= -5.20 \text{ ppm and } 2ax(a) + 2ax(b) \\ &+ 2ax(c) + 2eq(a) + 2eq(c) \\ &= 1 \end{aligned}$$

With the model values for $\gamma^2_{ax} - 4$ and $\gamma^2_{eq} - 4$ given in Table 3, the following molar fractions could be solved: 2eq(*a*) = 0.19 and 2eq(*c*) = 0.66. The behaviour of the *N*-benzyl derivative **4b** does not differ essentially from that of the *N*-ethyl derivative **1b**.

For the *N*-isopropyl derivative **2b** the magnitudes of the γ_{tot} effect at C-2 (−1.73 ppm) and especially at C-4 (−10.37 ppm) indicate the presence of 2ax-methyl conformations. Since the model value for the γ_{syn} effect is only −6.76 ppm, the γ^2_{ax}-4 effect must contribute to the γ_{tot} effect at C-4. However, the lack of a ^4J(HCNCH) long-range coupling, contrary to the situation in **3b** and **5b**, does not suggest a preponderance of the 2ax-ring conformation.

The ratio of the proportions of rotamers 2ax(*ab*), 2ax(*bc*) and 2ax(*ac*) for **2b** were assumed to be equal to the ratios of *a*, *b* and *c* for the parent compound **2a**, because the (steric) interaction between the 2ax-methyl and an α-methyl substituent should not be severe. Further, the presence of conformers 2eq(*ab*) and 2eq(*bc*) was neglected because of the *syn*-α-CH_3, 2eq-CH_3 interactions. Hence, at C-2:

$$2ax(ab)(\gamma_{gauche} + \gamma_{syn}) + 2ax(bc)(\gamma_{syn} + \gamma_{anti}) + 2ax(ac)(\gamma_{gauche} + \gamma_{anti}) = -1.73 \text{ ppm}$$

$2ax(ab) : 2ax(bc) : 2ax(ac) = ab : bc : ac$ in **2a**, giving $2ax(ab) = 2ax(ac) = 0.16$, and $2ax(bc) = 0.19$. Thereafter, $2eq(ac) = 1 - \Sigma 2ax = 0.49$.

The observed γ_{tot} effect at C-4 (−10.37 ppm) can be used for testing this solution:

$$\begin{aligned} &2ax(ab)(\gamma_{gauche} + \gamma_{anti}) \\ &+ 2ax(bc)(\gamma_{syn} + \gamma_{anti}) \\ &+ 2ax(ac)(\gamma_{syn} + \gamma_{gauche}) \\ &+ [2ax(ab) + 2ax(bc) + 2ax(ac)]\gamma^2_{ax}\text{-}4 \\ &+ 2eq(ab)(\gamma_{gauche} + \gamma_{anti}) \\ &+ 2eq(bc)(\gamma_{syn} + \gamma_{anti}) \\ &+ 2eq(ac)(\gamma_{syn} + \gamma_{gauche}) \\ &+ [2eq(ab) + 2eq(bc) + 2eq(ac)]\gamma^2_{eq}\text{-}4 \\ &= -8.67 \text{ ppm (obs. } -10.37 \text{ ppm)} \end{aligned}$$

In fact, the agreement is not very good even if one takes into account the neglect of conformers 2eq(*ab*) and 2eq(*bc*) and polysubstitution effects.

γ_{ax} Effects ($\gamma^4_{ax'}$-2 effects)

The values of the γ_{ax} effects at C-2 are listed in Table 3. They are almost invariant (a correction due to the 4eq′ ⇌ 4ax′ equilibria for the *N*-unsubstituted and *N*-methyl derivatives has been performed[2]). Only the diastereomeric α-methylbenzyl derivatives **5c** exhibit deviating values.

As discussed above, the γ_{ax} effects given in Table 3 are pure effects only if the terms γ_{eq} and $\gamma(N)$ can be neglected in Eqn (1). According to the 4-methyl carbon shifts (Table 1), all derivatives (with the exception of the *N*-H and *N*-methyl derivatives) are conformationally homogeneous (pseudoaxial 4-methyl substitutions), and the contributions of the γ_{eq} effects at C-2 can be excluded.

The constancy of the γ_{ax} effects suggests that the magnitude of the γ_{syn} effects does not depend on the substitution at C-4 (Me or no substituent). The *N*-*tert*-butyl derivative **3c** can be used as a model. If only the staggered rotamers in respect of the N—C(α) bond are taken into account (cf. Fig. 1) and the potential ring deformation effects caused by the 4ax′-methyl substitution are neglected, **3c** and **3a** implicitly exhibit similar $\gamma(N)$ effects at their C-2 and C-4 carbons, and the γ_{tot} effect (−4.54 ppm) represents a pure $\gamma^4_{ax'}$-2 effect. For other *N*-substitutions the postulated γ_{ax} effects are close to this model value, with the exception of the diastereomeric *N*-α-methylbenzyl derivatives **5c**(A) and **5c**(B). This observation suggests that they are pure γ_{ax} effects. Hence, the rotamer populations in respect of the N—C(α) bond for the 4-methyl derivatives and their parent compounds show only minor alterations.

The γ_{tot} effects for the diastereomeric *N*-α-methylbenzyl derivatives **5c**(A) and **5c**(B) differ from each other and also from those of the other derivatives. The difference between their γ_{tot} effects (2.07 ppm) is attributed to the divergent rotamer populations. If the contributions of the $\gamma^4_{ax'}$-2 effects (−4.54 ppm) are taken into account, diastereomer **5c**(A) exhibits a larger (−1.37 ppm) and diastereomer **5c**(B) a smaller $\gamma(N)$ effect (0.70 ppm) than **5a**. Obviously, diastereomer **5c**(A) favours orientations where an α-substituent (either methyl or phenyl) is able to cause γ_{syn} effects at C-2 [and **5c**(B) those being able to cause $\gamma(N)$ effects at C-4]. The configurational assignment is discussed later.

γ_{eq} Effects (γ^2_{eq}-4 effects)

As discussed above, the γ_{tot} effects at C-2 of 4-methyl derivatives **1c**–**5c** could be divided into their components. The 2-methyl derivatives **1b**–**5b** are more complex, however, because the magnitudes of their γ^2-4 effects at C-4 (Table 3) vary greatly. There is some evidence that 2-alkyl-substituted tetrahydro-1,3-oxazines and their *N*-methyl derivatives strongly prefer the 2eq orientations.[7] This is also true for 2-methyl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines and their *N*-methyl derivatives.[2] However, the steric requirements for these two series are not the same. The 2-ax-methyl substitution experiences two 1,3-*syn*-diaxial-CH_3,H interactions in tetrahydro-1,3-oxazines, but only one 1,3-*syn*-(pseudoaxial–axial)-CH_3,H interaction in 3,4-dihydro-2*H*-1,3-benzoxazines. Consequently, adoption of the 2ax-methyl orientation should be easier in the latter system, and the steric requirements due to the *N*-substitution can lead to the appearance of 2ax conformations. The lack of the suitable model, namely 2ax,3-dimethyl-3,4-dihydro-2*H*-1,3-benzoxazine, complicates the interpretation of the γ_{tot} effects at C-2.

The small positive γ^2-4 effects for 2-methyl-3,4-dihydro-2*H*-1,3-benzoxazine and its *N*-methyl derivative, 0.16 and 0.60 ppm, respectively, are pure γ^2_{eq}-4 effects. The *N*-*tert*-butyl derivative **3b** allows the evaluation of the γ^2_{ax}-4 effect. The large long-range coupling constant [^4J(HCNCH) = 1.45 Hz] can best be explained as a coupling between the H-2eq and H-4eq′ hydrogens (the strong preponderance of the 2ax-methyl orientation). In the case of *N*-*tert*-butyl substitution the γ_{syn} and γ_{anti} terms can be neglected, as discussed above, and the γ_{tot} value, −6.05 ppm, is a good model for the γ^2_{ax}-4 effect.

The intermediate values of the γ_{tot} effects for the *N*-ethyl and *N*-benzyl derivatives **1b** and **4b**, −2.51 and −1.95 ppm, respectively, suggest contributions from the γ_{syn} and γ_{anti} effects. The small values of the γ_{tot} effects obtained by comparison with the corresponding *N*-methyl derivatives (Table 2, −0.30 ppm for **1b** and −0.20 ppm for **4b**) suggest the proportions of the 2ax-methyl orientations to be minor. In other words, the value −2.51 ppm for **1b** is mainly attributable to differ-

ences in the rotamer populations about the N—C(α) bond; this also applies to **1a**. Accordingly, **1b** favours the orientation with the α-methyl group *syn* to the C-4—H bond (because of *syn*-CH_3, CH_3 interaction in rotamer *b*).

The magnitude of the γ_{tot} effect for the *N*-isopropyl derivative **2b** (−5.11 ppm) suggests a marked contribution of the γ^2_{ax}-4 effect. The contributions of the different conformations for **1b**, **2b** and **4b** were discussed in connection with the γ(*N*) effects.

Stereochemical assignment of diastereomeric *N*-α-methylbenzyl derivatives

Both **5b** and **5c** appear as a pair of diastereomers. In both cases diastereomer A is the isomer with the more negative γ_{tot} effect at C-2 but with the less negative γ_{tot} effect at C-4:

	γ_{tot} at C-2 (ppm)	γ_{tot} at C-4 (ppm)
5b(A)	−3.95	−9.10 (−3.05)[a]
5b(B)	−2.45	−11.58 (−5.53)[a]
	Diff. 1.50	−2.48
	γ_{tot} at C-2 (ppm)	γ_{tot} at C-4 (ppm)
5c(A)	−4.65	−2.68
5c(B)	−2.58	−5.83
	Diff. 2.07	−3.15

[a] Corrected in respect of the γ^2_{ax}-4 effect (−6.05 ppm).

The assignment of diastereomers **5c**(A) and **5c**(B) is facilitated by their conformational homogeneity; the contributions of the 4eq′ forms can be neglected on the basis of the 4-methyl carbon shifts and the magnitude of the ^4J(HCNCH) couplings between H-2eq and H-4eq′ [**5c**(A) 1.64 Hz and **5c**(B) 1.68 Hz]. In addition, the values of the geminal coupling constants between the H-2 hydrogens [**5c**(A) −11.0 Hz and **5c**(B) −10.7 Hz] support a strong preponderance of the *N*-axial orientations, in harmony with the results for the corresponding *N*-methyl derivatives.[2]

In addition, the diastereomeric 2-methyl derivatives **5b**(A) and **5b**(B) seem to prefer certain conformations. In contrast to the behaviour of the *N*-isopropyl derivative **2b**, the ^4J(HCNCH) couplings between H-2eq and H-4eq′ (1.00 and 1.30 Hz, respectively) are clearly visible. The *N*-*tert*-butyl derivative **3b** gives a good model value for the H-2eq,H-4eq′ coupling constant (1.45 Hz). If the H-2ax,H-4eq′ and H-2eq,H-4ax′ couplings are taken to be zero, diastereomer **5b**(A) clearly favours (67%) and diastereomer **5b**(B) strongly (87%) the 2ax-methyl orientations.

Diastereomers **5c**(A) and **5c**(B) gave anomalous rotamer populations [Table 2, **5c**(A) −16% for *ac* or *ca*, **5c**(B) 15% for *ab* or *ba*, depending on the assignment]. As discussed for **5a**, the rotamers with the phenyl substituent above the heterocyclic moiety modify the γ effects at C-2 and C-4. In the case of diastereomer **5c**(A) this must be rotamer *ca*, of the (α*RS*, 4*RS*) form. The alternative assignment (*ac*) does not explain the anomalous destabilization. Analogously, rotamer *ba* explains the above rotamer population (15%) in the case of diastereomer **5c**(B), corresponding to the (α*RS*, 4*SR*) form.

If the anomalous destabilization of the *ca*. orientations in **5c**(A) and *ba* in **5c**(B) could have been prepostulated, the relative configurations of this pair of diastereomers were deducible directly from the upfield shifts at C-2 or C-4 [**5c**(A), a strong *syn*-α-Ph,H-2 interaction; **5c**(B), a strong *syn*-α-Ph,H-4 interaction].

The α-methyl carbon shifts [22.21 ppm for **5c**(A) and 20.70 ppm for **5c**(B)] support the above assignment. Because rotamer *ca*. is destabilized, the former compound does not exhibit a strong *syn*-α-CH_3,H-4 interaction and a downfield shift occurs. The lack of a potential *syn*-α-CH_3,H-2 interaction in **5c**(B) results in a less enhanced downfield shift (half-chair structure).

The above shift comparison (see above) indicates that the benzylic moieties of diastereomers **5b**(A) and **5c**(A) and also **5b**(B) and **5c**(B) have the same relative configurations. This also discloses the absolute configurations of the racemates **5b**(A) and **5b**(B) (α*RS*,2*RS* and α*RS*,2*SR*, respectively).

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