Studies on the Benzoxazine Series. Part 1. Preparation and ^1H and ^{13}C Nuclear Magnetic Resonance Structural Study of Some Substituted 3,4-Dihydro-2*H*-1,3-benzoxazines

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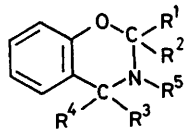
In addition to the parent compounds nine methyl-substituted 3,4-dihydro-2*H*-1,3-benzoxazines with and without *N*-methyl substitution were prepared. The former contain usually but minor amounts of the open-chain tautomer, too. The conformations and configurations of the oxazine rings were solved on the basis of ^1H and ^{13}C n.m.r. data which were best explained by assuming the *N*-methyl group predominantly axial in 3,4-dihydro-3-methyl-2*H*-1,3-benzoxazines. The oxazine ring prefers a half-chair form where the 4ax'-and 4eq'-methyl groups are practically equally stable. Hence, 3,4-dihydro-4-methyl-2*H*-benzoxazine is a 54:46 and the corresponding 3-methyl derivative an 8:92 mixture of the 4eq' and 4ax' forms. The 2,2,3,4-tetramethyl derivative is not conformationally homogeneous either. Substituent effects on ^{13}C n.m.r. chemical shifts were found to be especially useful in configurational and conformational analysis and gave an excellent fit between observed and calculated shift values.

A method for the preparation of *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines by a Mannich-type condensation of phenols with primary amines and two equivalents of formaldehyde was developed by Burke *et al.*[1] Since then the biological activities of these compounds have been a major subject of research. Different antimicrobial properties, for example bactericidal,[2] bacteriostatic,[3] and fungicidal,[4] have been revealed. They also show many pharmacological features like antitumour,[5] antituberculosis,[6] and anthelmintic[7] activity. They are also potential tranquilizing and sedating agents.[8] In addition, *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines are potential intermediates in the preparation of phenol–formaldehyde resins.[9]

On the other hand, few studies have been performed on *N*-unsubstituted 3,4-dihydro-2*H*-1,3-benzoxazines. McDonagh and Smith studied the ring–chain tautomerism of the condensation products of *o*-hydroxybenzylamine and carbonyl compounds, where the ring forms exhibit the 3,4-dihydro-2*H*-1,3-benzoxazine structure.[10]

There are a few spectroscopic and structural studies on *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines. Burke and Weatherbee presented some i.r. spectroscopic results.[11] Chylinska and Urbanski have given some dipole moment data and discussed the possibility of different ring conformations (half-chair or half-boat).[12] Brownstein *et al.* studied hindered rotation about the substituent carbon–nitrogen bond in some *N*-*o*-alkylphenyl derivatives.[13] Äyräs correlated the $^2J(HCH)$ and $^2J(CH_3CH)$ values determined for a number of cyclic compounds and included in the correlation corresponding coupling constants for some 3,4-dihydro-3-methyl-2*H*-1,3-benzoxazines.[14] Proponet *et al.* studied the effects of substitution at the aromatic ring of 3,4-dihydro-3-methyl-2*H*-1,3-benzoxazine on their i.r. and ^1H and ^{13}C n.m.r. spectra.[15] The mass spectra of these derivatives have been studied and a retro-Diels–Alder fragmentation pathway proposed.[16]



		R^1	R^2	R^3	R^4	R^5
(1),	(1m)	H	H	H	H	H, Me
(2),	(2m)	Me	H	H	H	H, Me
(3),	(3m)	H	H	Me	H	H, Me
(4),	(4m)	Me	Me	H	H	H, Me
(5),	(5m)	H	H	Me	Me	H, Me
(6),	(6m)	Me	H	Me	H	H, Me
(7),	(7m)	Me	Me	Me	H	H, Me
(8),	(8m)	Me	H	Me	Me	H, Me
(9),	(9m)	*p*-$NO_2C_6H_4$	H	H	H	H, Me
(10),	(10m)	*p*-$NO_2C_6H_4$	H	Me	H	H, Me

Results

The ^{13}C chemical shifts of the 3,4-dihydro-2*H*-1,3-benzoxazines (**1**)—(**10**) (R^5 = H; the ring forms) and (**1m**)—(**10m**) (R^5 = CH_3) are given in Table 1, and some selected ^1H n.m.r. parameters in Table 2. The values of the substituent effects on the ^{13}C chemical shifts at C-2 and C-4 were obtained from equation (1)[17] where $\delta C(x)$ is the chemical shift of a given carbon

$$\delta C(x) = \delta_p C(x) + \Sigma n_x^y SE(x) \quad (1)$$

atom in a substituted derivative, $\delta_p C(x)$ is that of the same carbon atom in the parent compound [here either (**1**) or (**1m**)] and n_x^y are the numbers of parameters $SE(x)$ caused by substitution y and acting at carbon x. Only after entering two sets of independent parameters for compounds (**3**), (**3m**), and (**7m**), each weighted by a suitable mole fraction of the conformer in question (*cf.* ref. 17), the combinations of the substituent effects given in Tables 3 and 4 gave excellent fits between the calculated and observed ^{13}C chemical shifts at C-2 and C-4, for both sets of compounds.

No derivative with an axial monomethyl substitution at C-2 exists excluding the possibility to derive a value for the pure 2ax effect. Compounds (**7**), (**8**), and (**8m**) (Figure) are practically anancomeric to avoid a strong 1,3-*syn*-diaxial interaction in the other possible half-chair conformation with the 2ax,4ax'-dimethyl substitution. According to the ^{13}C chemical shift correlation compound (**7m**) is a 88:12 (within ±3%) mixture of the 2ax,2eq,3ax,4eq' and 2eq,2ax,3ax,4ax' half-chair forms where, in addition to the 4eq' and 4ax' effects discussed later, a *gauche*-ax,eq'-CH_3,CH_3 interaction in the former conformation

Table 1. ^{13}C N.m.r. shifts for the prepared 3,4-dihydro-2*H*-1,3-benzoxazines in $CDCl_3$ solution (p.p.m. from Me_4Si)

Compound	Substitution	C-2	C-4	Me^1	Me^2	Me^3	Me^4	*N*-Me
(1)		78.07	44.01					
(2)	2eq	83.90	44.18	21.45				
(3)[a]	4eq′ ⇌ 4ax′	75.64	47.75			21.87		
(4)	2eq,2ax	86.86	40.63		26.10			
(5)	4eq′,4ax′	73.88	49.98			30.55		
cis-**(6)**	2eq,4eq′	83.39	48.98	21.65		20.76		
trans-**(6)**	2eq,4ax′	78.67	47.24	21.39			23.85	
(7)	2eq,2ax,4eq′	86.64	44.77	29.65	23.36	20.94		
(8)	2eq,4eq,4ax′	79.41	50.82	21.76		30.63	31.31	
(9)	2eq	85.82	43.67					
cis-**(10)**	2eq,4eq′	85.69	49.62			20.72		
trans-**(10)**	2eq,4ax′	81.85	46.70				23.08	
(1m)		83.65	52.02					39.59
(2m)	2eq	87.62	52.62	18.98				35.62
(3m)[b]	4ax′ ⇌ 4eq′	79.31	54.82				23.07	39.59
(4m)	2eq,2ax	89.87	50.39		25.29			37.57
(5m)	4eq,4ax′	80.77	54.53			29.62		36.28
cis-**(6m)**	2eq,4eq′	88.85	56.08	19.17		17.70		27.04
trans-**(6m)**	4eq,4ax′	81.87	57.30	18.80			23.84	34.35
(7m)[c]	2eq,2ax,4ea′ ⇌ 2eq,2ax,4ax′	90.22	50.90	27.81	22.75	19.15		31.46
(8m)	2eq,4eq′,4ax′	82.98	56.56	19.52		27.50	32.53	28.35
(9m)	2eq	90.14	51.03					37.26
cis-**(10m)**	2eq,4eq′	91.11	56.08			17.67		28.28
trans-**(10m)**	2eq,4ax′	85.02	56.39				23.53	34.89

[a] 54% 4eq′. [b] 92% 4ax′. [c] 88% 2eq,2ax,4eq′.

Table 2. ^1H N.m.r. chemical shifts (p.p.m. from Me_4Si) for 3,4-dihydro-2*H*-1,3-benzoxazines in $CDCl_3$ solution

Compound	Substitution	M.p./°C or or b.p./°C (mmHg)	H-2eq	H-2ax	H-4eq′	H-4ax′	Me^1	Me^2	Me^3	Me^4	*N*-Me
(2)	2eq	45—50 (0.01)		4.83 (q)[a]	3.80[b,c]	4.07[b,c]	1.43 (d)				
(3)[d]	4eq′⇌4ax′		4.81 (s)		4.09 (q)					1.42 (d)[e]	
(4)	2eq,2ax	65 (0.01)			3.90 (s)		1.45 (s)				
cis-**(6)**[f]	2eq,4eq′			4.81 (q)[a]		4.16 (q)	1.42 (d)		1.42 (d)[e]		
trans-**(6)**[f]	2eq,4ax′			4.81 (q)[a]	3.91 (q)		1.42 (d)			1.41 (d)[g]	
(9)	2eq	126—127		5.89 (s)	3.98[b,c]	4.26[b,c]					
cis-**(10)**[i]	2eq,4eq′			5.86 (s)		4.43 (q)			1.50 (d)[e]		
trans-**(10)**[i]	2eq,4ax′	64—65[h]		5.83 (s)	4.04 (q)					1.52_5(d)[g]	
(1m)		45—50 (1.0)	4.76 (s)		3.92 (s)						2.58 (s)
(2m)	2eq	80—85 (1.2)		4.91 (q)[j]	3.79[b,k]	4.11[b,k]	1.43 (d)				2.41(s)
(3m)[l,m]	4ax′,4eq′	40—43 (0.10)	4.69 (d)	4.91 (d)	3.72 (q)[n]					1.44 (d)[g]	2.52 (s)
(4m)	2eq,2ax	86 (0.07)			3.88 (s)		1.46 (d)				2.37 (s)
cis-**(6m)**	2eq,4eq′			5.07 (q)[j]		4.36 (q)	1.46_5 (d)		1.44 (d)[g]		2.21 (s)
trans-**(6m)**	2eq,4ax′	61—62[h] (0.07)		5.0q (q)[j]	3.70 (q)		1.46_5 (d)			1.44 (d)[g]	2.36 (s)
(9m)	2eq	113.5—114		5.87 (s)	3.80[b,k]	4.10[b,k]					2.40 (s)
cis-**(10m)**	2eq,4eq′	103[h]		6.01 (s)		4.60 (q)			1.51 (d)[g]		2.02 (s)
trans-**(10m)**	2eq,4ax′			5.92 (s)	3.85 (q)					1.59 (d)[g]	2.16 (s)

[a] $J_{H\text{-}2,CH_3}$ 5.8 Hz. [b] dd. [c] $^2J_{4,4}$ −17.4 Hz. [d] 54% of 4eq′. [e] $J_{H\text{-}4,CH_3}$ 6.7 Hz. [f] A 61:39 mixture of the *cis* and *trans* isomers in $CDCl_3$. [g] $J_{H\text{-}4,CH_3}$ 7.1 Hz. [h] For the isomer mixtures. [i] A 55:45 mixture of the *cis* and *trans* isomers in $CDCl_3$. [j] $J_{H\text{-}2,CH_3}$ 6.1 Hz. [k] $^3J_{4,4}$ −16.7 Hz. [l] 92% of 4ax′. [m] $^2J_{2,2}$ −10.0 Hz. [n] $J_{H\text{-}2eq,H\text{-}4eq'}$ 1.1 Hz.

counterbalances the effect of the *syn*-ax,ax′-CH_3,CH_3 interaction in the latter. Compounds (**2**) and (**2m**) seem to attain exclusively half-chair forms with equatorial 2-methyl groups as discussed below.

In addition to the methyl substituent effects at the alicyclic ring carbons the *C*-methyl substituent effects at the *N*-methyl carbon (set **m**) are also given (Table 5).

The empirical character of these substituent effects should not be forgotten when trying to correlate them with the structure and electronic effects. However, the independence of the $\gamma_{ax'}$-2

Table 3. Substituent effects (SE) on the ^{13}C n.m.r. chemical shifts of C-2 and C-4 of 3,4-dihydro-2*H*-1,3-benzoxazine (**1**)

Source of SE	SE at C-2 (p.p.m.)[a]	SE at C-4 (p.p.m.)[a]
2eq	5.80 ± 0.07 (6)	0.16 ± 0.03 (6)
2ax + 2,2	2.99 + 0.10 (2)	−3.54 ± 0.04 (2)
4eq′	−0.45 ± 0.09 (5)	4.82 ± 0.04 (5)
4ax′	−4.86 ± 0.11 (4)	2.42 ± 0.05 (4)
4,4	1.15 ± 0.11 (2)	−1.26 ± 0.05 (2)
2eq,4ax′	−0.32 ± 0.13 (2)	0.66 ± 0.06 (2)
2ax,4eq′	0.23 ± 0.14 (1)	−0.68 ± 0.06 (1)
R.m.s.	0.0760	0.0326
Av. diff.	±0.02	±0.01
Range	12.98	10.19

[a] Number of occurrences in parentheses.

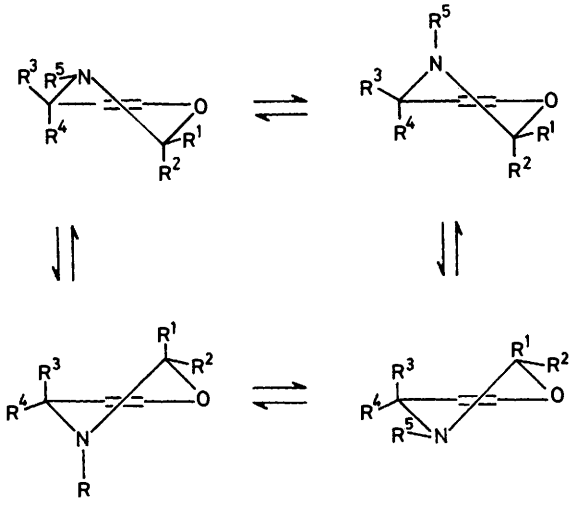


Figure. Possible conformations of substituted dihydrobenzoxazines

and the α_{ax}-4 effects on *N*-substitution can also be useful in the identification of 4eq′ *versus* 4ax′ substitution in more complex products with different *N*-substitution.

In principle, the NH derivatives can appear as mixtures of ring- and chain-tautomers in solution (and also in the liquid state) although their *C*-methyl derivatives strongly favour the ring forms. With the aid of ^{13}C n.m.r. spectroscopy the presence of the chain tautomer could be detected for compounds (**2**) (2%) and (**4**) (10%). For the former the result is parallel to the i.r. spectroscopic observations of McDonagh and Smith.[10] In $CDCl_3$ the condensation products of *p*-nitrobenzaldehyde are clearly tautomeric mixtures [the amount of the ring form is 48% for compound (**9**) and 62% for compound (**10**)]. The former case is again in good agreement with the result of McDonagh and Smith (51%).

Discussion

General.—Conformational analysis of simple six-membered-ring compounds and their hetero-analogues is well established, and their behaviour can often be predicted with the aid of conformational effects, *e.g.* by the equatorial-over-axial preferences of the substituents and the anomeric effect.[18] On the other hand, the more complex ring systems, as, for example, those containing multiple bonds or fused benzene rings, have not been studied so effectively.

Table 4. Substituent effects (SE) on the ^{13}C n.m.r. chemical shifts of C-2 and C-4 of 3,4-dihydro-3-methyl-2*H*-1,3-benzoxazine (**1m**)

Source of SE	SE at C-2 (p.p.m.)[a]	SE at C-4 (p.p.m.)[a,b]
2eq + 2eq,3ax	3.98 ± 0.02 (6)	0.60 (6)
2ax + 2,2 + 2,2,3ax	2.23 ± 0.02 (2)	−2.23 (2)
4eq′ + 4eq′,3ax	2.12 ± 0.05 (5)	4.02 (5)
4ax′	−4.90 ± 0.03 (5)	2.69 (5)
4,4 + 4,4,3ax	−0.10 ± 0.04 (2)	−4.20 (2)
2eq,3ax,4eq′	−0.91 ± 0.05 (3)	−0.56 (3)
2eq,3ax,4ax′	−0.86 ± 0.04 (3)	1.99 (3)
2ax,3ax,4eq′		−3.52 (1)
R.m.s.	0.0218	
Av. diff.	±0.01	
Range	10.91	6.91

[a] Number of occurrences in parentheses. [b] Eight parameters and 8 equations.

Table 5. The *C*-methyl substituent effects (SE) on the ^{13}C n.m.r. chemical shifts of the *N*-methyl carbon of 3,4-dihydro-3-methyl-2*H*-1,3-benzoxazine[a]

Substitution	SE (p.p.m.)
2eq,3ax	−3.97
3ax,4eq′	−6.45
3ax,4ax′	0.56
3ax,4eq′,4ax′	−1.08
2eq,3ax,4eq′	−2.13
2eq,3ax,4ax′	−1.83
2ax,3ax,4eq′	2.47
2ax,3ax + 2eq,2ax,3ax	1.95

[a] The proportion of the 2eq,2ax,3ax,4ax′ half-chair form of (**7m**) (12%) could not be taken into account.

As for conformational analysis, 3,4-dihydro-2*H*-1,3-benzoxazines (Figure) offer some intriguing structural features if compared with tetrahydro-1,3-oxazines: (i) the inherent half-chair structure with pseudoequatorial (eq′) and pseudoaxial (ax′) substitutions, (ii) a diminished number of *syn*-axial CH_3,H-interactions, and (iii) the interactions of the π-system of the aromatic moiety with the oxygen and/or nitrogen lone pairs. For example, there is only one *syn*-axial CH_3,H-interaction due to the 2ax-methyl group in compounds (**2**) and (**2m**) instead of two in 2-methyltetrahydro-1,3-oxazine. In the alicyclic part of the 3,4-dihydro-2*H*-1,3-benzoxazines there are no vicinal ^1H–^1H couplings, which emphasizes the importance of chemical shifts.

Structural analysis of the *N*-substituted tetrahydro-1,3-oxazines is complicated by the nitrogen inversion (*cf.* Figure). Therefore, the chemical shifts and the coupling constants of these compounds reflect not only the effects of substitutions at C-2 and/or C-4 but also the relative changes in the orientation of the *N*-substituents. This complicates the conformational analysis of *N*-substituted tetrahydro-1,3-oxazines.[19–26] Owing to the anomeric effect, however, the *N*-substituents seem to prefer axial orientations; equatorial preferences being observed only for bulky groups.[23–25] The magnitude of the anomeric effect has been evaluated for tetrahydro-1,3-oxazines (5.4 kJ mol^{-1}) with the aid of the conformational equilibria of 2-methyl- or 2-*p*-nitrobenzyl-substituted 3,4,4-trimethyltetrahydro-1,3-oxazines.[27]

By comparison with the axial 3-methyltetrahydro-1,3-oxazine, compound (**1m**) lacks one *syn*-axial CH_3,H-interaction (3.6 kJ mol^{-1}); the stabilization should be large enough to ensure that compound (**1m**) exists predominantly in the *N*-methyl axial

form. A repulsive interaction (n–π interaction) between the π-electron system and the axial nitrogen lone pair should yet increase this effect. Therefore, it is reasonable to assume that the *N*-methyl groups have strictly axial orientations in 3,4-dihydro-2*H*-1,3-benzoxazines. The magnitude of the geminal coupling constant (−10.0 Hz) for compound (**3m**) is in a good agreement with that for a model compound with an axial *N*-alkyl group.[20]

The calculations of the methyl substituent effect confirm the strong preference for axial *N*-methyl in 3,4-dihydro-2*H*-1,3-benzoxazines, in other words for the equatorial nitrogen lone pair. On the other hand, results for methyl-substituted tetrahydro-1,3-oxazines point out that the treatment of the ^{13}C n.m.r. data does not necessitate any assumptions as to the NH orientation.[26]

Both parent compounds (**1**) and (**1m**) undergo rapid ring inversions at room temperature (the H-2 and H-4 signals appear as singlets), analogously to the corresponding tetrahydro-1,3-oxazines.[24,25] Furthermore, 2-alkyltetrahydro-1,3-oxazines greatly favour conformations with an equatorial 2-alkyl group.[24] In principle, the situation is somewhat different in 3,4-dihydro-2*H*-1,3-benzoxazines. Instead of two *syn*-axial interactions as in tetrahydro-1,3-oxazines, the axial 2-methyl group experiences only one such interaction, which should make this orientation more favourable. Nevertheless, compounds (**2**) and (**2m**) exist exclusively in conformations with equatorial 2-methyl groups. Probably, some kind of (steric) interaction between the axial 2-methyl group and the adjacent aromatic ring destabilizes the axial orientation. Besides the 2eq-methyl group can relieve its interactions by bending towards the adjacent oxygen atom.

For the 4-methyl derivatives the situation becomes more complicated. According to Katritzky *et al.* in 3-methyltetrahydro-1,3-oxazines a 2-methyl group has a greater equatorial preference than the 4-methyl group.[25] The dihedral angles between the 4eq′- or 4ax′-methyl groups and the average plane of the 3,4-dihydro-2*H*-1,3-benzoxazine molecule are nearer to each other than those for tetrahydro-1,3-oxazines. However, one can expect that the 4eq′-methyl group has a somewhat stronger interaction with the adjacent aromatic C–H region than the 4ax′-methyl group. Also, there is some evidence that the vicinal ax′,eq or eq′,ax interactions in cyclohexene are stronger than the vicinal ax,eq interactions in cyclohexane.[28] This fact should favour the pseudoaxial orientation at least for the derivatives with (axial) *N*-methyl resulting in ax′,ax disubstitution.

Conformational Energies.—According to the ^{13}C chemical-shift correlations compound (**3**) is a 54:46 mixture of the 4eq′ and 4ax′ half-chair forms [$\Delta G°$(4ax′-CH_3) 0.4 kJ mol^{-1}]. So, the *gauche*-butane-type interaction of the 4ax′-methyl group and its interaction with the aromatic C–H region are counterbalanced by the greater interaction of the 4eq′-methyl group with the latter. For the corresponding *N*-methyl derivative (**3m**) the contributions of the 3ax,4eq′ and 3ax,4ax′ half-chair forms are 8 and 92% (K 11.5), respectively. This indicates a marked shift towards the 4ax′ form because of the 4eq′,3ax interaction in the 4eq′ form. Thereupon, if $\Delta G°$(4ax′,3ax) is neglected, $\Delta G°$-(4eq′,3ax) = $\Delta G°$(4ax′-CH_3) + 2.48 ln 11.5 kJ mol^{-1} = 6.45 kJ mol^{-1}.

Isomeric 2,4-dimethyl-substituted compounds (**6**) *cis* and *trans* are equilibrated *via* a ring–chain tautomeric process, and hence they form an equilibrium mixture. The diequatorial *cis* isomer (2eq,4eq′) is 1.1 kJ mol^{-1} more stable than the *trans* isomer (2eq,4ax′), which indicates a 0.7 kJ mol^{-1} buttressing effect in the latter in agreement with similar observations in *e.g.* 1,3-dioxanes.[29]

The proportions of *cis* and *trans* isomers of (**10**) (55 and 45%, respectively) are very close to those of the 4eq′ and 4ax′ half-chair conformations in the case of compound (**3**). So, the 2-(*p*-nitrophenyl) derivatives exhibit no buttressing effects and hence the isomer equilibrium is governed solely by the relative stabilities of 4-methyl substitution. This behaviour strongly supports the assumption that the 4-methyl carbon shifts of *cis*- and *trans*-(**10**) are free from any 2,4-disubstitution effects and therefore good model values for the 4eq′- and 4ax′-methyl carbon shifts, respectively.

^{13}C *Methyl Chemical Shifts.*—Conformational analysis of 3,4-dihydro-2*H*-1,3-benzoxazines is facilitated by the bias towards nitrogen inversion (the lone pair equatorially orientated) in compounds (**1m**)—(**10m**) but also by the anancomeric model compounds (**7**), (**8**), and (**8m**) with 4eq′- or 2eq-methyl groups, respectively.

N-*Unsubstituted compounds.* The ^{13}C chemical shifts of the 4-methyl group in compounds *cis*-(**6**) (δ 20.76 p.p.m.) and *cis*-(**10**) (δ 20.72 p.p.m.) are close to that of the 4eq′-methyl group (δ 20.94 p.p.m.) in compound (**7**). This suggests that compounds *cis*-(**6**) and *cis*-(**10**) exist in 2eq,4eq′ half-chair forms and indicates that the effect of the 2ax,4eq′-dimethyl substitution on the 4eq′-methyl carbon chemical shift in compound (**7**) is rather small. The 4-methyl shifts of compounds *trans*-(**6**) (δ 23.85 p.p.m.) and *trans*-(**10**) (δ 23.08 p.p.m.) can be considered as model values for the 4ax′-methyl group. They let us also conclude that the 2eq,4ax′-dimethyl interaction has a non-zero value in the former.

The conformationl equilibrium of compound (**3**) (54% 4eq′ + 46% 4ax′) derived from the ^{13}C chemical shifts of C-2 and C-4 allows us to test the validity of the above model values. The 4-methyl chemical shifts of the 2-(*p*-nitrophenyl) derivatives *cis*- and *trans*-(**10**) result in the best fit between the calculated and observed 4-methyl shifts of (**3**): δ (0.54 × 20.72 + 0.46 × 23.08) p.p.m. = 21.81 p.p.m. (Found: 21.87 p.p.m.).

Accordingly, *cis*- and *trans*-(**10**) seem to have no specific shift effects on the 4eq′-methyl carbon comparable to those exhibited by the corresponding dimethyl derivatives:

Compounds compared	4-Methyl shift difference (p.p.m.)	Source of effect
trans-(**6**)–*trans*-(**10**)	0.77	δ_{2eq}–4ax′
cis-(**6**)–*cis*-(**10**)	0.04	δ_{2eq}–4eq′
(**7**)–*cis*-(**10**)	0.22	δ_{2eq}–4eq′ + δ_{2ax}–4eq′

Thus the δ_{2eq}–4eq′ effect is clearly insignificant. The sum of δ_{2eq}–4ax′ and δ_{2eq}–4eq′ can also be obtained by comparing the 4-methyl chemical shifts of (**5**) and (**8**) with each other: (δ 30.63 + 31.31) − 2 × 30.55 = δ_{2eq}–4ax′ + δ_{2eq}–4eq′ = 0.84 p.p.m. (*cf.* 0.77 + 0.04 = 0.81 p.p.m. above).

The 2-methyl chemical shifts of compounds (**2**), *cis*- and *trans*-(**6**) are all close to that of compound (**8**) (δ 21.76 p.p.m.) with 2eq-methyl substitution. This supports the purely equatorial nature of their 2-methyl groups, too. The 2-methyl chemical shift (δ 21.45 p.p.m.) of compound (**2**), which is free from any further effects, is naturally the best model value for the 2eq-methyl group. The magnitude of the disubstitution effects at the 2eq-methyl carbon can then be estimated as follows:

Compounds compared	2-Methyl shift difference (p.p.m.)	Source of effect
cis-(**6**)–(**2**)	0.20	$\delta_{4eq'}$–2eq
trans-(**6**)–(**2**)	−0.06	$\delta_{4ax'}$–2eq
(**8**)–(**2**)	0.31	$\delta_{4eq'}$–2eq + $\delta_{4ax'}$–2eq

The sum of $\delta_{4eq'}$–2eq and $\delta_{4eq'}$–2ax can be obtained by comparing the 2-methyl chemical shifts of (**4**) and (**7**) with each other: δ (29.65 + 23.36) − 2 × 26.10 = $\delta_{4eq'}$–2eq + $\delta_{4eq'}$–2ax = 0.81 p.p.m. From this we obtain $\delta_{4eq'}$–2ax = 0.61 p.p.m. The above sum is equal to the corresponding result (0.81 p.p.m.; see above) for the 4-methyl group.

In conclusion, the ^{13}C chemical shifts of the 4eq′- and 2eq-methyl groups of the *N*-unsubstituted 3,4-dihydro-2*H*-1,3-benzoxazines are relatively close to each other; on the average the former resonates at 0.75 p.p.m. higher field than the latter.

N-*Substituted compounds.* In the *N*-substituted series the situation is more complicated. The 4-methyl chemical shifts of *cis*-(**6m**) and (**7m**) differ quite clearly from each other (δ 17.70 and 19.15 p.p.m., respectively), which is a further indication of the conformational inhomogeneity of and for a special polysubstitution effect in the latter. The chemical shift for *cis*-(**6m**) [*cf.* also *cis*-(**10m**)] can best be regarded as a model value for the 4eq′-methyl carbon shift in these compounds. Obviously compound *trans*-(**6m**) has a pseudoaxial 4-methyl group which resonates at δ 23.84 p.p.m. However, this value includes the δ_{2eq}–4ax′ effect.

The conformational equilibrium of compound (**3m**) (4eq′:4ax′ 8:92) makes it possible to test the above conclusions using the 4-methyl chemical shifts of *cis*- and *trans*-(**10m**) as models: δ (0.08 × 17.67 + 0.92 × 23.53) p.p.m. = 23.06 (observed 23.07) p.p.m. Thus the 4-methyl chemical shifts of the 2-(*p*-nitrophenyl) derivatives are also now free from any specific perturbation.

Analogously to the *N*-unsubstituted derivatives the following effects can be derived for the *N*-substituted derivatives:

Compounds compared	4-Methyl shift difference (p.p.m.)	Source of effect
trans-(**6m**)–*trans*-(**10m**)	0.31	δ_{2eq}–4ax′
cis-(**6m**)–*cis*-(**10m**)	0.03	δ_{2eq}–4eq′
(**7m**)–*cis*-(**10m**)	1.48	δ_{2eq}–4eq′ + δ_{2ax}–4eq′ + polysubstitution effects

The δ_{2eq}–4eq′ effect is again insignificant. The sum of δ_{2eq}–4eq′ and δ_{2eq}–4ax′ can also be obtained by comparing the 4-methyl shifts of (**5m**) and (**8m**): δ (27.50 + 32.53) − 2 × 29.62 = δ_{2eq}–4eq′ + δ_{2eq}–4ax′ = 0.79 p.p.m. [*cf.* δ (0.31 + 0.03) = 0.34 p.p.m. above]. The agreement is not so good as in the case of the *N*-unsubstituted derivatives, indicating the operation of some polysubstitution effects.

The effect of 1.48 p.p.m. (*cf.* 0.22 p.p.m. for the corresponding *N*-unsubstituted compounds) is in harmony with the conformational inhomogeneity of compound (**7m**) as discussed above, since the possible polysubstitution effects alone cannot explain its relatively high value.

The 2eq-methyl shifts for compounds (**2m**), *cis*-, *trans*-(**6m**), and (**8m**) are fairly close to each other: the shift range is, however, slightly wider than in the case of the corresponding *N*-unsubstituted derivatives (0.72 *versus* 0.31 p.p.m.) indicating a small polysubstitution effect in compound (**8m**).

The magnitude of the disubstitution effects at the 2eq–methyl carbon can be, analogously to the *N*-unsubstituted compounds, estimated as follows:

Compounds compared	2-Methyl shift difference (p.p.m.)	Source of effect
cis-(**6m**)–(**2m**)	0.19	$\delta_{4eq'}$-2eq
trans-(**6m**)–(**2m**)	−0.18	$\delta_{4ax'}$-2eq
(**8m**)–(**2m**)	0.54	$\delta_{4eq'}$–2eq + $\delta_{4ax'}$–2eq + polysubstitution effects

The sum of $\delta_{4eq'}$–2eq + $\delta_{4eq'}$–2ax, obtained by comparing the 2-methyl carbon chemical shifts of (**4m**) and (**7m**), is [δ(27.81 + 22.75) − 2 × 25.29] p.p.m. = −0.02 p.p.m., a value which differs essentially, contrary to the behaviour of the *N*-unsubstituted derivatives, from the corresponding sum (0.79 p.p.m.) obtained in respect ot the 4-methyl group. This fact attests further to the conformational inhomogeneity of compound (**7m**). Apparently, a value of −0.21 p.p.m. is obtained for $\delta_{4eq'}$–2ax from the above estimates. The 2-methyl carbon-shift difference between compounds (**8m**) and (**2m**) (0.54 p.p.m., *cf.* 0.31 p.p.m. for the *N*-unsubstituted derivatives) suggests a small polysubstitution effect but not conformational inhomogeneity for compound (**8m**).

^{13}C N-*Methyl Chemical Shifts.*—The spatial orientation of an *N*-substituent is of crucial interest in the structural study of 3,4-dihydro-2*H*-1,3-benzoxazines. Therefore, the *C*-methyl substituent effects at *N*-methyl carbon were studied in some detail (Table 5). The shift range for the axial *N*-methyl carbons in (**1m**)—(**10m**) is δ 39.59—27.04 p.p.m. The 3ax,4eq′ effect (−6.45 p.p.m.) is essentially larger than the 2eq,3ax effect (−3.97 p.p.m.), indicating a stronger ax,eq′ than ax,eq interaction as mentioned already. On the other hand, the 3ax,4ax′ effect is small (−0.56 p.p.m.). So, in this respect the ax,ax′ interation does not differ essentially from the ax,ax interaction. The values of the polysubstitution effects are large if compared, for example, with those in 1,3-dioxanes, but one must emphasize that in the latter system they occur in the C–C–C fragment whereas here they are effective in the C–N–C moiety.

^{1}H *Chemical Shifts.*—^{1}H Chemical shifts (Table 1) are of limited use, especially in the case of *N*-unsubstituted derivatives. For the diastereoisomers *cis*- and *trans*-(**6**) there is, however, a characteristic difference (δ 0.25) between the 4eq′- and 4ax′-H shifts. Configurational assignment on this basis is, however, difficult because of the conformational inhomogeneity of the possible model compound (**3**). The ^{1}H chemical shifts also seem to be inadequate for the evaluation of the conformational equilibrium of compound (**3**).

On the other hand, an exact configurational assignment of the diastereoisomers *cis*- and *trans*-(**6m**) is possible with the aid of the 4-H chemical shifts. According to the magnitude of the ^{4}J H–C–N–C–H long-range coupling constant (1.1 Hz) compound (**3m**) strongly favours the 4ax′-methyl orientation.[30] The 4-H chemical shifts of compounds (**3m**) and *trans*-(**6m**) are very close to each other suggesting an analogous spatial arrangement at their C-4 centre. If the assumption concerning the strong preference of the 2eq-methyl substitution is valid, the above observation allows the configurational assignment of the diastereoisomers *cis*- and *trans*-(**6m**).

It is interesting to note that $\Delta\delta_{ax,eq}$ is essentially greater for compounds *cis*- and *trans*-(**6m**) (0.66) than for compounds *cis*- and *trans*-(**6**) (0.25), *i.e.* the 4ax′-H resonance of compound *cis*-(**6m**) is 0.20 p.p.m. to lower field than that of compound *cis*-(**6**)

and the 4eq'-H resonance of compound *trans*-(**6m**) is 0.21 p.p.m. to higher field than that of compound *trans*-(**6**).

Experimental

o-Hydroxybenzylamine was prepared by the method of Zaugg and Schaefer.[31] The crude product was purified by sublimation (130—140 °C at 12 mmHg), with a loss in yield. *o*-(1-Aminoethyl)phenol was prepared by the Leuckart reaction of *o*-hydroxyacetophenone.[32] *o*-(1-Amino-1-methylethyl)phenol was prepared by the Grignard reaction from *o*-hydroxybenzonitrile and methylmagnesium iodide.[32] *o*-(*N*-Methylaminomethyl)phenol and *o*-[1-(*N*-methylamino)ethyl]phenol were prepared by reduction of *o*-(*N*-methyliminomethyl)phenol or *o*-[1-(*N*-methylimino)ethyl]phenol, respectively, with sodium borohydride in ethanol with the usual reaction conditions.

For the preparation of *o*-[1-(*N*-methylamino)-1-methylethyl]-phenol a method based on the reduction of an imine cannot be used. However, it can be synthesized by an indirect methylation of *o*-(1-amino-1-methylethyl)phenol with formaldehyde (as formalin).[32] The condensation of the former with the latter results in the formation of 3,4-dihydro-4,4-dimethyl-2*H*-1,3-benzoxazine (**5**) which in turn is easily reduced with sodium borohydride in ethanol in the normal reaction conditions to *o*-[1-(*N*-methylamino)-1-methylethyl]phenol.

3,4-Dihydro-2*H*-1,3-benzoxazines (both *N*-unsubstituted and *N*-substituted) were prepared by condensing a carbonyl compound with an *o*-aminomethylphenol. As to *o*-(*N*-methylaminomethyl)phenols (secondary amines) all condensation products of formaldehyde ($R^1 = R^2 = H$) could be smoothly prepared using formalin as the reagent (1.1-fold excess of formaldehyde) and 1,4-dioxane (at reflux) as the solvent. For compound (**1m**) the above procedure is an alternative to that described by Burke *et al.*[1]

In the case of *o*-aminomethylphenols (primary amines) the reaction results in a concomitant formation of 3,3'-methylene-bis-[3,4-dihydro-2*H*-1,3-benzoxazines]. However, the α-methyl substitutions seem to increase the proportion of the 'monomeric' 3,4-dihydro-2*H*-1,3-benzoxazines. At any rate careful control of the reaction conditions is necessary. The use of a slight excess of *o*-aminomethylphenol, a short reaction time (< 15 min at room temperature), and immediate evaporation of solvent increased the relative amount of 3,4-dihydro-2*H*-1,3-benzoxazine in the product. The following proportions of 'monomers' were obtained: (**1**) 10%, (**3**) 60%, and (**5**) 66%.

For (**1**) the result is not satisfactory. It should be noted, however, that earlier attempts did not produce 3,4-dihydro-2*H*-1,3-benzoxazine at all.[33] Our product analysis is based mainly on the use of ^{13}C n.m.r. chemical shifts which are known to be relatively insensitive to the presence of species other than the one wanted. In the present case this was proved by adding various amounts of different *N*-substituted 3,4-dihydro-2*H*-1,3-benzoxazines to the product mixture without essentially altering the ^{13}C chemical shifts assigned to (**1**).

All condensations of acetaldehyde or *p*-nitrobenzaldehyde ($R^1 = CH_3$ or *p*-$NO_2C_6H_4$, $R^2 = H$) could be performed by removing the water of condensation with benzene or toluene azeotropically. In general the above condensations proceed to completion. In the case of compound (**8m**) a stepwise process was needed. When no more water was separated in the water-entrainment unit, the reaction was interrupted and the solvent was removed under reduced pressure. A new quantity of acetaldehyde and solvent was added and removal of water was continued. Four or five cycles were necessary. An acid catalyst (preferably acetic acid) was not necessary and could result in a less pure product. Obviously, the phenolic hydroxy group of the starting material itself functions as an acid catalyst.

The condensations with acetone are slower than those with aldehydes, as usual. The use of a water-entrainment unit and an excess of acetone (*e.g.* three-fold) is preferred to make sure that the reactions proceed close to completion. A stepwise procedure, as described above, may also be helpful. The condensation of acetone with *o*-[2-(*N*-methylamino)ethyl]-phenol to (**7m**) is exceptionally slow. Only prolonged reflux in acetone (here also as solvent) together with the stepwise process described above (no water-entrainment unit was used) gave a satisfactory result. Attempts based on the use of the corresponding acetal, 2,2-dimethoxypropane, were not successful.

For the purification of the 3,4-dihydro-2*H*-1,3-benzoxazines, 2-*p*-nitrophenyl derivatives could be recrystallized from 95% (v/v) ethanol. Some methyl derivatives [especially the *N*-methyl derivatives, including *cis*- and *trans*-(**6m**)] could be purified by vacuum distillation. The mixture of *cis*- and *trans*-(**6**), (**7**), (**7m**), (**8**), and (**8m**) were used as received to avoid their potential decomposition.

The 2,3,4-trisubstituted derivatives (**6m**) and (**10m**) were mixtures of *cis*- and *trans*-isomers (19 and 81% and 15 and 85%, respectively) but the isomers were not separated. The *cis* and *trans* forms of (**6**) and (**10**) are always in equilibrium with each other *via* the open-chain tautomers.

Noise-decoupled ^{13}C n.m.r. spectra were taken for 1.0M solutions in $CDCl_3$ (used as a field/frequency lock signal) at room temperature on a JEOL FX-60 Fourier transform spectrometer operating at 15.03 MHz. The ^{13}C chemical shifts are reported in p.p.m. downfield from Me_4Si (as internal standard) and are considered to be accurate within 0.1 p.p.m. (Table 1). For structure determinations, if need be, single-frequency off-resonance decoupled spectra were also run. Mostly, an off-resonance of 1 200 Hz granted satisfactory results throughout the spectra.

^1H N.m.r. spectra were run on the same spectrometer, operating at 60 MHz or on a JEOL GX-400 spectrometer operating at 400 MHz. The ^1H chemical shifts are reported as above and are considered to be accurate within 0.02 p.p.m. (Table 2).

The methyl substituent effects on the ^{13}C chemical shifts at C-2 and C-4 were solved with an OPTLIN multilinear regression program on a DEC-20 computer.[17b] The *C*-methyl substituent effects at the *N*-methyl carbon were calculated manually.

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