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An NMR Conformational Study of Ring- and *N*-Inversion, and Prototropic Tautomerism in Stereoisomeric 2-[Arylamino(imino)]-4a,5,6,7,8,8a-hexahydro-(4*H*)-1,3,4-benzoxadiazines

Ari Rosling,[a] Karel D. Klika,[c] Ferenc Fülöp,[b] Reijo Sillanpää[c] and Jorma Mattinen[a,*]

[a]Department of Organic Chemistry, Åbo Akademi University, FIN-20500 Turku, Finland, [b]Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, Szeged, Hungary and [c]Department of Chemistry, University of Turku, FIN-20014 Turku, Finland

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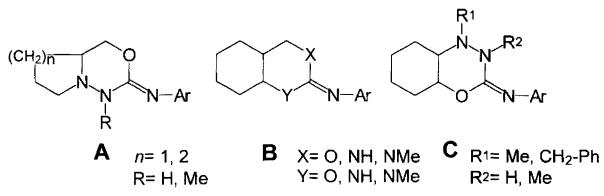
The tautomeric *cis* and *trans* 2-arylamino-4a,5,6,7,8,8a-hexahydro-(4*H*)-1,3,4-benzoxadiazines **12a,b**–**15a,b** and the *cis* and *trans* 3*N*,4*N*-dimethyl-2-phenyl imino analogues **10** and **11** were synthesized. Based on the ^{15}N and ^{13}C NMR chemical shifts, the amino form was unambiguously found to be predominant in each tautomeric compound **12a,b**–**15a,b**. X-Ray crystallographic analysis also proved the predominance of the amino structure in the solid state. Estimations of the vicinal H–H coupling constants at room temperature indicated that the *O-in* conformer was slightly predominant in *cis* amino compounds **14a,b**–**15a,b**, except the 3*N*,4*N*-dimethyl imino compound **11**, which was found to adopt an anancomeric *O-in* conformation. NOE experiments and low temperature ^{13}C NMR measurements together with X-ray crystallographic analysis were used to elucidate the *N*-inversion and conformational preference of the *N*-methyl substituents in *cis* and *trans* 3*N*,4*N*-dimethyl-2-phenyliminoperhydro-1,3,4-benzoxadiazines **10** and **11**. In the solid state the X-ray crystallographic structure of **10** indicated that the *N*4-methyl is orientated axially and that the *N*3-methyl is coplanar with the O–C2–N3–N4 segment of the hetero ring. The same conformational preference was also found in solution for both **10** and **11**.

Many 2-imino-substituted 1,3-heterocycles have been extensively studied. Besides their synthesis[1] and potential amino/imino tautomerism,[2] this class of compounds has attracted attention for their application in chemotherapy.[3] In particular the determination of the predominant tautomer has been a subject of controversy for a number of years.[2] In earlier work the tautomerism of 2-imino-substituted 1,3,4-heterocyclic ring systems containing a bridgehead nitrogen (**A**) was studied (Fig. 1).[4] In contrast with the results on related mono-[3,5] and bi-cyclic 1,3-heterocycles (**B**),[1] compounds of structure (**A**) were found to exist predominantly in the amino form. In this paper the prototropic tautomerism studies were extended to include another type of potentially tautomeric 1,3,4-heterocyclic system (**C**; R^2=H). In addition to the prototropic tautomerism, there are two further dynamic processes, ring and nitrogen inversion, involved in the conformational behaviour of the stereoisomeric 4a,8a-tetramethylene-1,3,4-oxadiazines of structure (**C**). The preferred conformations and tautomers were estimated from different NMR experiments, ^1H NMR simulation using PERCHit[6] and X-ray diffraction analysis.



A *n*= 1, 2; R= H, Me **B** X= O, NH, NMe; Y= O, NH, NMe **C** R^1= Me, CH_2-Ph; R^2= H, Me

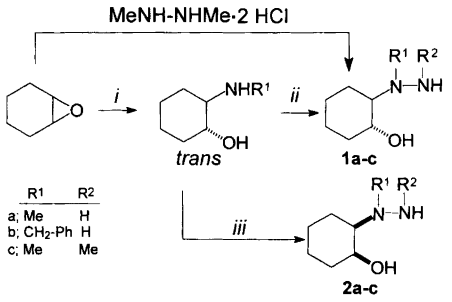
Fig. 1. Structures of the earlier studied (**A, B**) and the currently studied compounds (**C**).

* To whom correspondence should be addressed.

Results and discussion

Synthesis. The syntheses of *cis* and *trans* hydrazino alcohols **1a,b** and **2a,b** have been reported in previous work.[7] The ring opening of cyclohexene oxide with 1,2-dimethylhydrazine dihydrochloride in the presence of

sodium hydroxide in MeOH afforded solely the *trans* *N,N'*-dimethyl-substituted hydrazino alcohol **1c** (Scheme 1). The corresponding *N,N'*-dimethyl-substituted *cis* isomer **2c** was prepared by esterification of the *cis* monomethyl-substituted hydrazino alcohol **2a** with ethyl chloroformate.[8] Subsequent reduction of the *N*-ethoxy carbonyl derivative required surprisingly hard reaction conditions (60 h refluxing with 4 equivalents of lithium aluminium hydride in THF) to obtain a 43% yield of **2c**.[8]



Scheme 1. i, RNH_2–MeOH; ii, $NaNO_2$–H^+, LAH–THF; iii; Ac_2O, $SOCl_2$–$CHCl_3$, 20% HCl, $NaNO_2$–H^+, LAH–THF.

The known reaction using MeI–MeOH followed by alkali treatment[9] was used to ring close the isothiourea derivatives **3a,b**–**6a,b**, **7** and **8** to the corresponding tetramethylene-1,3,4-benzoxadiazines (Scheme 2). The *cis*-3*N*,4*N*-dimethyl thiourea derivative **8** failed to undergo cyclization under the given conditions yielding only the isothiuronium derivative **9**. The isothiuronium derivative **9** was transformed into the ring closed compound **11** in 80–90% yield using NaH/THF.

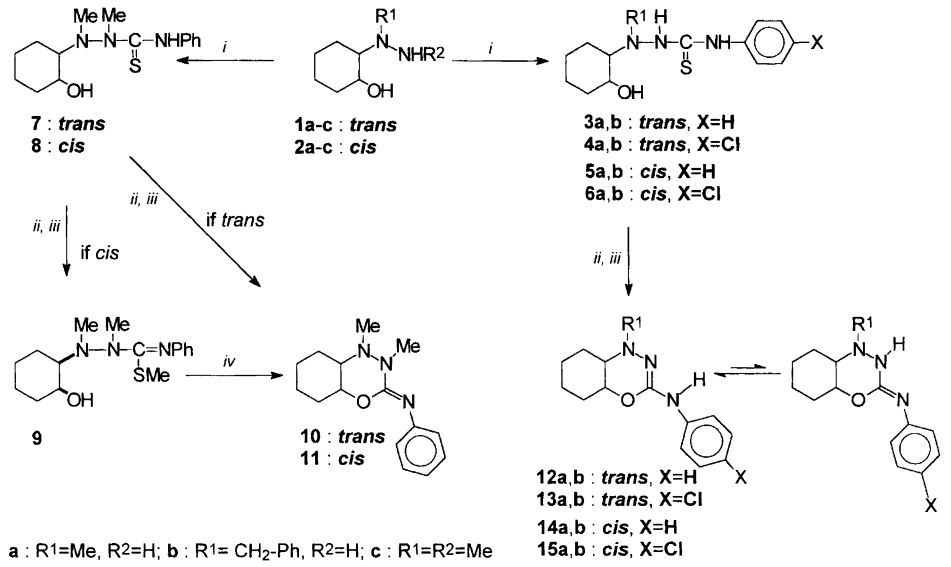
Prototropic tautomerism and conformational analysis. The structures of **10**, **11** and **12a,b**–**15a,b** were established by means of ^1H,^{13}C and ^{15}N NMR studies together with X-ray diffraction analysis. The unequivocal assignment of the spectra was achieved through the concerted use of different 1D and 2D NMR experiments. The principle of determining the conformation in related 1,3-oxazines has been previously reported in detail.[10]

Prototropic tautomerism. Since the 1950s many studies using spectroscopic methods (IR, UV, MS, NMR) have sought to determine the predominant tautomeric structure in cyclic amidines. Sohár *et al.*[11a,b] and Jackman *et al.*[12] reported, on the basis of extensive ^1H and ^{13}C NMR studies, a general method to distinguish unambiguously between the amino and imino tautomers by the significant differences in their electron distributions in the aromatic region. The interpretations concerning the identity of the tautomers and the general validity of the method were confirmed by Tóth *et al.* in subsequent work using ^{15}N NMR measurements.[5]

Results from previous work concerning the prototropic tautomerism in perhydropyrrolo- and perhydropyrido-1,3,4-(*O,N,N*)-oxadiazines[4] were inconsistent with the methodology presented in the works of Sohár *et al.* and Jackman *et al.*[12] This prompted us to extend our investigations of prototropic tautomerism into a new, different 1,3,4-(*O,N,N*) heterocyclic system, **12a,b**–**15a,b** (Scheme 2) and the analogous fixed imino derivatives **10** and **11**. The ^1H and ^{13}C NMR data (Tables 1 and 2,

Table 1. ^1H chemical shifts (δ) of the aromatic region in **10**, **11**, **12a,b** and **14a,b**.

	cis/trans	*o*-H	*m*-H	*p*-H
10	*trans*	6.91	7.12	6.81
11	*cis O-in*	7.00	7.21	6.91
12a	*trans*	7.26	7.22	6.89
12b	*trans*	7.21	7.15	6.86
14a	*cis*	7.28	7.22	6.88
14b	*cis*	7.26	7.19	6.87



Scheme 2. i, ArNCS–Et_2O; ii, MeI–MeOH; iii, KOH–MeOH; iiii, NaH–THF.

Table 2. ^{13}C chemical shifts (δ) of the aromatic region in **10**, **11**, **12a,b** and **14a,b**.

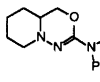
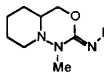
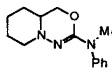
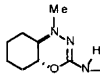
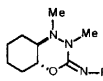
	cis/trans	C-2	*s*	*o*	*m*	*p*
10	*trans*	149.5	149.4	124.4	128.5	121.4
11	*cis O-in*	148.2	148.2	123.8	128.3	121.1
12a	*trans*	142.8	140.2	117.4	128.8	120.9
12b	*trans*	142.2	140.2	117.3	128.6	120.7
14a	*cis*	142.2	140.2	117.2	128.8	120.8
14b	*cis*	142.1	140.3	117.2	128.2	120.7

respectively) of the aromatic ring for **10**, **11** and **12a,b**–**15a,b** displayed the same characteristic features as those compounds previously investigated, implying a clear predominance of the amino structure in **12a,b**–**15a,b**.

The ^{13}C chemical shift of the *ipso* and *ortho* carbons in **12a,b**–**15a,b** were substantially shielded (ca. −7 ppm and −9 ppm, respectively) compared with those in **10** and **11**, whereas no significant differences were observed in the chemical shift of the *para* carbons. This evidently shows that there is no conjugation of the π-bond system from the hetero ring into the aromatic ring. Hence, the effect on the chemical shift of the *ipso* and *ortho* carbons can be explained by an inductive effect from the isolated double bond present in the predominant amino form. However, no satisfactory explanation can be forwarded as to why **12a,b**–**15a,b** preferentially adopt the amino structure with an isolated double bond rather than the imino form, which, at least in principle, would be expected to be energetically more favoured as the double bond would be in conjugation with the aromatic system.

The ^{15}N NMR chemical shifts of **10** and **12a** and **16**–**18** (Table 3) provided the most reliable method for determing the position of the tautomeric equilibrium in the present compounds. The ^{15}N chemical shifts of the potentially tautomeric structure **16** and the fixed amino form **17** and imino form **18**, provided a means to calculate the tautomeric composition, using either the *endo* or the *exo* nitrogen chemical shifts. Taking into account a methyl substituent correction of +2 ppm,[5] a 0.90±0.2 preference for the amino structure in **16** was calculated, using either the *endo* or the *exo* nitrogen chemical shifts. Comparing the ^{15}N chemical shifts of **10** and **12a** with those of **16** and **17**, one can estimate the tautomeric equilibrium in **12a** to be essentially the same as observed for **16**, i.e. strongly biased (9:1) towards the amino form. Additionally, X-ray analysis showed an amino structure in the solid state for both **16**[4] and **12a** (Fig. 2). Selected bonding parameters for **12a** are shown in Table 7. The water molecule seen in the X-ray structure of **12a** originates from water-contaminated recrystallization solvent. Favourable packing effects are probably responsible for the incorporation of water molecules into the crystal structure of **12a** whenever traces of water are present [contacts between O(2)–H(2)···N(4) and N(9)–H(1)···O(2), 2.810(2) and 2.903 Å, respectively].

Table 3. Selected ^{13}C and ^{15}N chemical shifts for 2-aminothiazines **19**, **20**,[2] perhydropyrido-1,3,4-oxadiazines **16**–**18**[4] and **10** and **12a**.

		C-2	*s*	*o*	*m*	*p*	N(3)	N(4)	*exo* N
	**19**	152.3	150.0	122.8	128.5	122.5	−328.4[a]	—	−173.7[a]
	**20**	150.6	145.1	128.8	128.3	126.5	−191.3[a]	—	−316.4[a]
	**16**	143.2	140.1	117.6	128.9	121.1	−190.2[b]	−305.0[b]	−321.8[b]
	**17**	148.1	148.0	123.6	128.5	121.6	−298.0[b]	−316.8[b]	−231.6[b]
	**18**	146.9	145.5	123.0	128.5	123.3	−182.4[b]	−303.3[b]	−337.3[b]
	**12a**	142.8	140.2	117.4	128.8	120.7	−187.1[b]	−313.8[b]	−321.7[b]
	**10**	149.5	149.4	124.4	128.5	121.4	−296.6[b]	−321.0[b]	−231.0[b]

[a]The ^{15}N chemical shifts are converted and referred to external formamide −298.0 ppm (90% solution in DMSO) by adding −29.8 ppm to those values given in Ref. 3. [b]The ^{15}N chemical shifts are referred to external formamide −298.0 ppm (90% solution in DMSO).

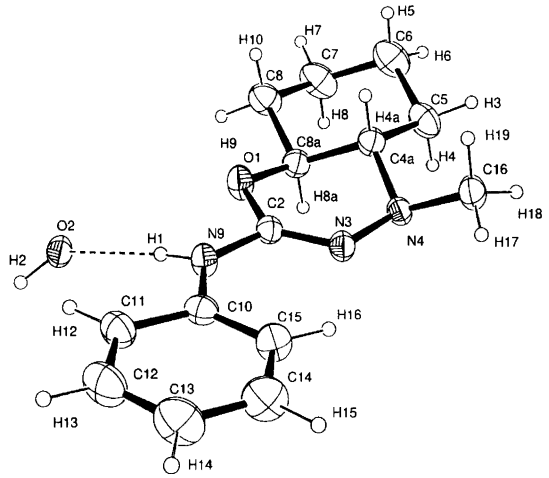


Fig. 2. Molecular structure and labelling of **12a**. Bonding parameters are shown in Table 7.

However, this does not invalidate the interpretations of a predominant amino structure for **12a**.

Ring inversion. It is well kown that totally saturated *trans*-fused hexahydro-4a,8a-benzoxadiazines can only adopt one anancomeric chair–chair ring conformation. However, as a result of the partially unsaturated hetero ring in **12a,b** and **13a,b**, the conformation of the hetero ring should really be described as a half-chair or sofa rather than as a chair and this can be clearly seen in the X-ray structure of **10** and **12a** (Figs. 2 and 3, respectively). Selected bonding parameters for **10** and **12a** are shown in Tables 7 and 8, respectively. The most striking feature in the NMR data of the *trans*-fused monomethyl-

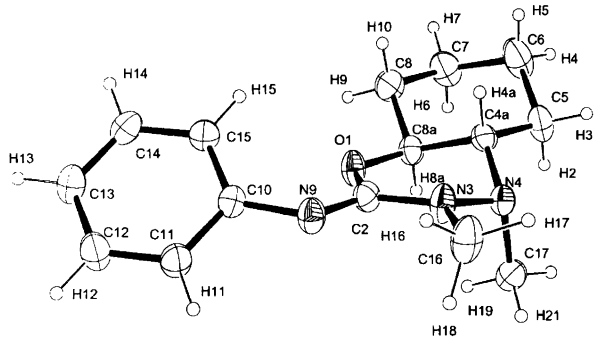


Fig. 3. Molecular structure and labelling of **10**. Bonding parameters are shown in Table 8.

and dimethyl-substituted **12a,b**, **13a,b** and **10** is the small ^3J axial–axial couplings between the bridgehead protons (8.2–8.3 and 10.3 Hz, respectively) (Table 4) compared with the typical values of approximately 11.5 Hz in bicyclic 1,3-oxazines.[1,13] The small $^3J_{H4a,H8a}$ values, also observed in previous work on related 1,3,4-benzoxadiazines,[7] are probably due to electronegative effects caused by the additional nitrogen at position 4. Consistent with this assertion is the difference ($\approx$2 Hz) in the $^3J_{H4a,H8a}$ values between the monomethyl-substituted **12a,b**, **13a,b** and the dimethyl-substituted **10**, caused by the *endo* position of the double bond in the former compounds enabling a better conjugation in the hetero ring and consequent change in electron density in the N4 vicinity.

Two stable chair–chair conformations, *O-in* and *O-out* (oxygen orientated axially or equatorially towards the cyclohexane ring, respectively), are possible for the *cis* isomers, the equilibrium position of which is dependent on the steric requirements of the N4 substituent. Importantly, the impact of the anomeric effect on the preferred ring conformation should not be underestimated; it might explain the failure of attempts to predict the preferred conformation of related ring systems using molecular modelling programs, which have not taken the anomeric effect into account.[14] At room temperature the vicinal coupling constants showed that the monomethyl-substituted *cis* isomer **14a** (Table 4) exists in an equilibrium between the the *O-in* and *O-out* conformers in proportions of 53% and 47% (within an accuracy of $\pm$2%), respectively (calculated on ^3J axial–axial). The corresponding ratio in the *N*-benzyl derivative **14b** was calculated to be 76% and 24%, respectively (within an accuracy of $\pm$5%). These results are similar to the results from previous work.[7] The 3*N*,4*N*-dimethyl derivative **11** adopts a pure *O-in* conformation as concluded from its vicinal coupling constant values.

N-*Inversion.* The low barrier to nitrogen inversion (6.4–8.5 kcal mol^{-1} in unhindered cyclic secondary and tertiary amines)[15a,b] readily accounts for the difficulty in detecting the interconversion between the conformers of **12a**–**15a** in which the N4-methyl is orientated equatorially or axially (Scheme 3). The N4–Me_{eq} conformation was found, tentatively, to be preferred in the *trans* isomers **12a** and **13a** as concluded from their NMR spectral data (Table 5). There is a marked shielding effect

Table 4. Selected coupling constants *J*H,H/Hz for **10**, **11**, **12a,b** and **14a,b**.

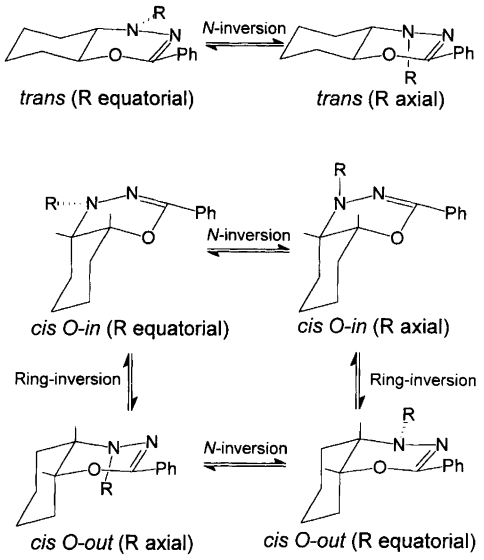
Compd.	*cis/trans*	4a,8a	4a,5ax	4a,5eq	5ax,5eq	5ax,6ax	5eq,6eq	6ax,7ax	6eq,7eq	7ax,8ax	7eq,8eq	8ax,8a	8eq,8a
10	*trans*	10.3	11.6	3.7	—12.6	13.4	3.0	13.0	2.5	13.5	3.1	11.4	4.4
11	*cis O-in*	3.3	12.3	4.9	—13.4	13.6	2.9	13.2	3.7	13.6	2.7	2.4	3.7
12a	*trans*	8.2	11.4	4.1	—12.8	13.2	2.9	13.1	2.8	13.1	3.0	11.6	4.4
14a	*cis*[a]	2.7	8.1	3.8	—14.0	8.7	8.0	8.4	7.5	8.7	7.5	3.3	7.1
12b	*trans*	8.3	11.2	3.9	—13.1	12.6	2.9	13.3	3.1	14.2	2.9	11.4	4.7
14b	*cis*[a]	2.5	10.0	4.0	—13.5	10.6	6.4	11.0	5.2	11.2	5.2	3.3	5.2

[a] Mixture of the *O-in* and *O-out* conformations.

Table 5. Selected ^{1}H and ^{13}C chemical shifts for **10**, **11**, **12a** and **14a**, and related tetramethylenedihydro-1,3,4-oxadiazines[7] **19** and **20**.

Compd.	*cis/trans*	C8*a*	C4*a*	N3C$\underline{H}_3$	N4C$\underline{H}_3$	H8a	H4a	N3CH_3	N4CH_3
10	*trans*	75.0	64.6	37.80	36.9	4.16	2.89	3.08	2.54
12a	*trans*	78.8	62.9	—	43.6	4.07	2.13	—	2.65
19	*trans*	78.1	62.0	—	42.7	4.09	2.27	—	2.78
11	*cis O-in*	68.8	57.9	39.16	42.1	4.79	2.76	3.20	2.70
14a	*cis*[a]	75.3	56.4	—	43.2	4.42	2.79	—	2.68
20	*cis*[b]	73.6	55.5	—	42.3	4.48	2.95	—	2.80

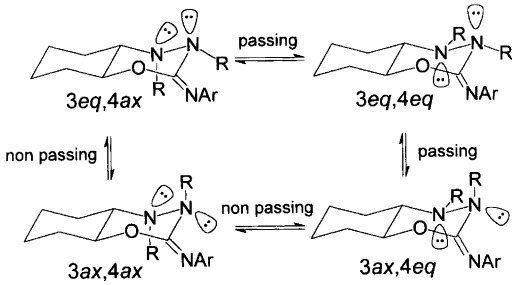
[a]Mixture of the *O-in* and *O-out* conformations (53:47). [b]Mixture of the *O-in* and *O-out* conformations (55:45).



Scheme 3. Conformational route map for *cis* and *trans* hexahydro-1,3,4-benzoxadiazines **3a,b**, **5a,b**, **12a,b** and **14a,b**.

and, hence, an upfield shift for H-4a as reported for an axial proton adjacent to an equatorial *N*-methyl, compared with an axial proton adjacent to an axial *N*-methyl (2.13 ppm in **12a** compared to 2.89 ppm in **10**).[14,16a,b] There is no discernible effect from an axial *N*-methyl causing a 1,3-syn-*axial* compression shift on the C-8a signal and the chemical shift of 78.8 ppm for C-8a in **12a** is consistent with the *N*4-methyl equatorially orientated.[17] One might expect an axial methyl to shift the C-8a signal upfield at least by 3–6 ppm.[18] This is consistent with the observed upfield shift of C-8a (75.0 ppm) in **10**. In addition, in the solid state, the *N*4-methyl for **12a** is orientated equatorially as determined by X-ray crystallographic analysis (Fig. 2). However, we cannot yet give any reliable estimation of the extent of the bias towards the 4N–Me_{eq} form. The *N*-methyl orientation in the corresponding *cis* isomer **12b** was not predictable from the room temperature spectra, where the conformational analysis is overly complicated as a consequence of both ring and nitrogen inversions (Scheme 3). It is impossible to separate the effects on chemical shift due to ring inversion (*O-in*↔*O-out*) or *N*-inversion (equatorial↔axial methyl) for both processes are rapid at room temperature.

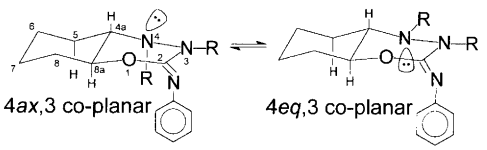
The *N*-inversion process involving two adjacent methyl-substituted nitrogens in hexahydropyridazines[15a,19] and its 1,3,4-oxa-[20] and thia-[21] analogues have been extensively studied. However, less attention has been paid to the corresponding diazadecalin structures,[17] indeed, for *cis*-fused compounds, no data on such *N*-inversion are available in the literature. Low-temperature ^{13}C NMR spectra of the *trans*-fused 3*N*,4*N*-dimethyl-2-phenyliminoperhydro-1,3,4-benzoxadiazine **10** showed clear dynamic processes in the temperature range +25 to −95 °C. The first changes were observed between +25 and −40 °C within which range the resonances of C-4a, *N*4-methyl and C-2 broadened and coalesced. However, only one set of signals was detected after coalescence, indicating a highly biased system. Broadening was next observed for the C-8a, C-5 and *N*3-methyl signals in the temperature range of −30 to −80 °C. The rest of the signals broadened in the temperature range of −65 to −95 °C, but did not pass through coalescence. All these changes are in accordance with the freezing out of 'slow' passing inversion, 3eq,4ax↔3eq,4eq (Scheme 4), of which the latter population is present in an undetectable concentration after coalescence. No subsequent broadening of any signal corresponding to the slowing of the low-energy, non-passing inversion (3eq,4ax↔3ax,4ax↔3ax,4eq) could be observed in the temperature range +25 down to −95 °C. This could result from the non-passing inversion not yet slowing down, or that the concentrations of the two latter conformations (3ax,4ax, 3ax,4eq) are present in



Scheme 4. Conformational route map for *trans*-3*N*,4*N*-dimethylhexahydro-1,3,4-benzoxadiazine **10**.

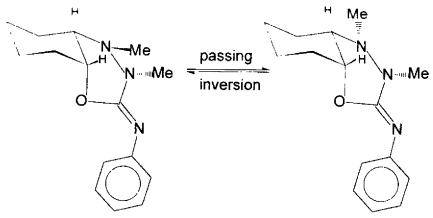
amounts too small to affect the lineshape. The conformational preference of the 4ax,3eq was also concluded from ^{1}H, ^{13}C and NOE difference experiments. The molecular structure of **10** (Fig. 3) obtained by X-ray crystallographic analysis also indicated the orientation of the *N*4-methyl as axial, whereas the *N*3-methyl was, surprisingly, coplanar with the O–C2–N3–N4 segment in the hetero ring. The bond angles (122.4°, 121.2 and 114.2) around N3 (Table 8) show that the hybridisation of N3 is intermediate between sp^3 and sp^2 character. The strong sp^2 character at N3 causes a quasi-rigid structure in the O–C2–N3–Me segment, consequently reducing the four component equilibrium shown in Scheme 4, to the two component equilibrium shown in Scheme 5. The unexpectedly strong broadening effect observed on C-2 must, in this case, be the consequence of a large $\Delta\delta_{C\text{-}2}$ between the interconverting conformers originating from stereoelectronic effects, as no steric compression effects (γ-effects) are present. A reasonable explanation would be hyperconjugation possibly existing in the N4–N3–C2–(N–Ph) segment of the 4eq,3-coplanar conformer. The disruption of such hyperconjugation as the 4eq,3-coplanar conformer converts into the 4ax,3-coplanar form would most likely result in a large $\Delta\delta_{C\text{-}2}$. The strong conformational preference of the 4ax,3-coplanar conformer, is explained by the 1,3 *syn*-diaxial interaction between the axial *N*4–Me and H-5ax, H-8a, being exceeded by the even larger steric interactions between the equatorial *N*4-methyl and the co-planar *N*3-methyl. Additionally, there is a favourable positive anomeric effect present in the 4ax,3-coplanar conformer [the free electron pair on N4 is antiperiplanar to the N3–C(2) bond]. Riddell and Katritzky[17] found, by contrast, that the corresponding totally saturated 4a,8a-tetramethylene-1,3,4-oxadiazine preferentially adopts the 4eq,3ax conformer.

The conformational route map for the corresponding *cis* isomer **11** consists of eight different conformers interconverting through ring- and nitrogen-inversions. However, the situation is reduced to a four-component equilibrium as **11** exists in a pure *O-in* conformation. ^{13}C and NOE difference measurements implied a 4ax,3eq conformational preference for **11**. In particular, the upfield resonance of the C-8a signal (68.8 ppm) is in good agreement with a γ-effect present on C-8a from an axial *N*4-methyl [compare with **14a** and values given in Refs. 10(b), 13 and 14]. Furthermore, a strong NOE difference was obtained between the *N*4-methyl and the H-8a signals.



Scheme 5. The changes observed in the low-temperature ^{13}C spectra of **10** correspond to the 'slowing' of the passing *N*-inversion (4ax, 3coplanar↔4eq, 3-coplanar).

The low-temperature ^{13}C NMR results for **11** were initially confusing, due to rather small changes in the appearance of the spectra. The maximum broadening of the *N*4-methyl signal occurred at +35 °C and at lower temperatures the signal resharpened without splitting. At +35 °C, the C-2 signal started to broaden and then resharpened below 0 °C. After this, no change was observed until −50 °C when all the other aliphatic signals started to broaden. The aromatic signals showed indications of broadening only at −90 °C. None of the ^{13}C signals, except for N4–Me and C-2, appeared to go through coalescence. Bearing in mind the results from the corresponding *trans*-fused **10**, it is tempting to postulate that the N3–Me signal is also in a quasi-rigid coplanar orientation, thus reducing the conformational equilibrium to a two component system; namely 4ax,3-coplanar↔4eq,3-coplanar (Scheme 6), where the former is the major and only observed population. The same arguments presented for the predominance of the 4ax,3-coplanar conformation for compound **10** are also valid for **11**.



Scheme 6. The changes observed in the low-temperature ^{13}C spectra of **11** correspond to the 'slowing' of the passing *N*-inversion (4ax, 3coplanar↔4eq, 3-coplanar).

There is also the possibility of *syn* and *anti* geometrical isomerisation in **10** and **11**, but the minor effects observed on the aromatic ^{13}C signals at low temperature indicate the absence of such an interconversion. The expected effect from *syn/anti* isomerisation on the ^{13}C signals of the carbocycle are much less than the observed effects.[12] Additionally, application of the Anet equations[22] on several ^{13}C signals in **10** and **11** gave the value of the free energy of activation ($\Delta G^{\ddagger}$) in acceptable agreement with reported $\Delta G^{\ddagger}_{\text{minor}\rightarrow\text{ts}}$ values of 11–13 kcal mol^{-1} for 'passing' *N*-inversion.[20–22] For accurate and reliable values for the $\Delta G^{\ddagger}_{\text{minor}\rightarrow\text{ts}}$ for **10** and **11**, a complete lineshape analysis on the ^{13}C signals is required.

Conclusions

Our conformational study on stereoisomeric 2-[arylamino-(imino)] - 4a,5,6,7,8,8a - hexahydro - (4*H*) - 1,3,4 - benzoxadiazines had some unexpected results. The modification of earlier studied carbocycle-fused 1,3-oxazines, by substitution of a nitrogen atom for a methylene group (1,3,4-*O*,*N*,*N*), reversed the predominance of the prototropic amino/imino tautomerism. Earlier, the imino form had been found to be predominant and even reported as

the only existing tautomer in analogous compounds.[3,5] However, by contrast, a strongly dominant amino form was observed for **12a,b**–**15a,b**. This originates from the fact that the introduced nitrogen causes the π-bond to remain in the hetero ring rather than conjugate to the aromatic ring. The reported general method[12] of determining the predominant tautomeric form using the significantly different electron distribution observed in the aromatic region between the imino and amino forms, was not applicable to these compounds. The only reliable method to estimate the tautomeric equilibrium was based on ^{15}N chemical shifts in comparison to values measured from model compounds where no tautomerism was possible (fixed amino and imino forms).

The unexpected conformational preference of the 4ax,3-coplanar conformation in **10** and **11** originates from N3 adopting substantial sp^2 character enabling π-bond conjugation in the O–C2–N3–N4 segment, consequently forcing the N3 substituent into a planar orientation. The planar orientation of the N3–Me in **10** was revealed by X-ray crystallographic analysis, consistent with the results of the NMR work. Comparing the low-temperature NMR results obtained on the corresponding *cis* isomer **11** with those of **10**, we propose similar *N*-inversion behaviour for **11**, with a predominant 4ax,3-coplanar conformation.

Experimental

Melting points were determined on a Stuart Scientific SMP 1 melting point apparatus and are uncorrected. The silica gel used in column chromatography was obtained from Merck (Kieselgel 60, 230–400 Mesh ASTM) and the petroleum ether used had a boiling range of 40–60 °C. High-resolution mass spectra were obtained on a VG-7070E spectrometer.

NMR spectra were acquired using a JEOL JNM-A-500 spectrometer operating at 500.16 MHz for ^1H, 125.78 MHz for ^{13}C, and 50.688 MHz for ^{15}N or a JEOL JNM-L-400 spectrometer operating at 399.78 MHz for ^1H and 100.54 MHz for ^{13}C. Spectra were normally recorded at 25 °C for samples in $CDCl_3$; low temperature measurements were recorded for samples in [$^2H_6$] acetone. Proton and carbon spectra were referenced internally to trimethylsilane and nitrogen spectra were referenced externally to 90% formamide in [$^2H_6$] DMSO, assigned as −298 ppm. The H,H coupling constants and ^1H chemical shifts given for **10**, **11**, **12a,b** and **15a,b** were obtained with the PERCHit program.[6]

1D proton spectra were acquired with normal single-pulse excitation, 45° flip angle, and with spectral widths of 8 kHz consisting of 65K data points, zero-filled to 128K prior to Fourier transformation. NOE and ROE difference spectra were acquired on deoxygenated samples using irradiation times of 6–8 s, with mixing times of 30 ms for the ROE difference spectra, and 8K data points, zero-filled to 32K and with 1 Hz exponential weighting applied prior to Fourier transformation. 2D homonuclear correlation experiments included both absolute-value COSY and phase-sensitive TOCSY. 1D carbon spectra were acquired with normal single-pulse excitation, broad-band proton decoupling, 45° flip angle, and with spectral widths of 34 kHz consisting of 64K data points, zero-filled to 128K and with 1 Hz exponential weighting applied prior to Fourier transformation. DEPT spectra (90° and 135°) were acquired and processed using similar conditions.

2D heteronuclear correlation experiments for the assignment of the alicyclic and phenyl rings and the relative assignments of the methyls relied primarily on conventional carbon-detected CH shift correlation with partial homonuclear decoupling in the *f*1 dimension. When the concerted use of COSY and CH-shift experiments was insufficient for the unequivocal assignment of the carbons of the alicyclic portion, HSQC_TOCSY with BIRD filter readily provided an unambiguous result. The phase-sensitive spectra were acquired with mixing times of 15 and 28 ms. For the assignment of C-2, *ipso*-C and the methyl carbons, long-range correlation experiments included both 2D absolute-value mode HMBC with BIRD filter (60 ms evolution delay) and 1D selective INEPT. INEPT_SEL experiments typically utilised conditions and processing as for DEPT, but with a soft, rectangular proton-selective pulse of 9 ms and delays set for long-range couplings.

1D nitrogen spectra were acquired by a combination of polarisation transfer experiments [INEPT (refocused), DEPT, and INEPT_SEL] acquired with broad-band proton decoupling, pulse recycle time of 4.3 s and with spectral widths of 25 kHz consisting of 32K data points, zero-filled to 128K and with 0.25 Hz exponential weighting applied prior to Fourier transformation. For the tautomeric compounds, INEPT $1/(4J)$ spectra utilising delays calculated from a one-bond J constant of 90 Hz, uniquely defined the detected nitrogen at that chemical shift as the proton bearing one. For the detection of other nitrogens, long-range coupling was utilised; the approach taken was to search for the resonances by the acquisition of INEPT or DEPT spectra of appropriate J constant values (2–12 Hz), together with variation of such parameters as the 3rd and 4th delays in the case of INEPT or the final proton irradiation pulse in the case of DEPT. Assignment of the nitrogens was made using INEPT_SEL by selectively irradiating appropriate protons with a soft, rectangular pulse of 9 ms, with delays set for long-range couplings.

2-Hydrazino-1-cyclohexanols **1a,b** and **2a,b** were prepared according to earlier reported methods.[7]

trans-2-(N,N'-Dimethylhydrazino)-1-cyclohexanol (**1c**). Hydrazino alcohol **1c** was prepared by adding 15 ml of methanol containing NaOH (0.88 g, 0.022 mol) to a stirred solution of cyclohexene oxide (2.00 g, 0.02 mol) and 1,2-dimethylhydrazine hydrochloride (2.93 g, 0.022 mol). The mixture was left overnight at r.t. The solvent was then evaporated off and the residue flash

chromatographed (silica gel; toluene–methanol 85 : 15) to afford 1.84 g (58%) of *trans*-2-(*N,N'*-dimethylhydrazino)-1-cyclohexanol **1c**. ^{1}H NMR ($CDCl_3$): δ 3.35 (m, 1 H), 2.64 (br s, $-CH_3$), 2.57 (br s, $-CH_3$), 2.10–1.90 (m, 2 H), 1.86–1.66 (m, 3 H), 1.44–1.00 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 79.8, 76.6, 42.4, 38.5, 30.6, 27.8, 25.1 and 24.5.

cis-*2-(*N,N'*-Dimethylhydrazino)-1-cyclohexanol* (**2c**). Ethyl chloroformate (2.63 ml, 2.98 g, 0.028 mol) was added dropwise to a stirred solution of **2a** (3.65 g, 0.025 mol) in diethyl ether (40 ml) and $KHCO_3$ (2.80 g, 0.028 mol) in 10 ml of water and the mixture was left overnight at r.t. The organic phase was separated and the aqueous phase was further extracted with ethyl acetate (3 × 25 ml). The organic phases were combined, dried (Na_2SO_4) and the solvent removed. The crude carbamate was used without further purification. The crude carbamate was reduced to *cis*-2-(*N,N'*-dimethylhydrazino)-1-cyclohexanol **2c** by prolonged reflux (60 h) in a suspension of at least 4 equiv. lithium aluminium hydride in THF. The crude product obtained was purified by flash chromatography (silica gel: toluene–methanol 85 :15) to afford **2c** (1.71 g, 43% overall). ^{1}H NMR ($CDCl_3$): δ 4.09 (m, 1 H), 2.56 (br s, $-CH_3$), 2.50 (br s, $-CH_3$) 2.39 (m, 1 H), 1.92–1.55 (m, 4 H), 1.47–1.15 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 71.2, 65.4, 40.7, 35.7, 32.2, 30.0, 24.1 and 20.5.

General procedure for the preparation of isothiourea derivatives (**3a,b–6a,b** and **7**, **8**). Hydrazino alcohol (**1a–c**, **2a–c**) (10 mmol) was dissolved in 20 ml of dry diethyl ether, and phenyl isothiocyanate or 4-chlorophenyl isothiocyanate (11 mmol) was added. A crystalline product soon precipitated from the solution and was collected by filtration. All the products were used without further purification, with the exception of **8** which failed to crystallise and was purified by flash chromatography to afford an oily product. The spectral data for the 4-chlorophenyl derivatives **4a,b** and **6a,b** are not presented as they are essentially the same as the corresponding phenyl derivatives.

3a: 68%, m.p. 144–146 °C. ^{1}H NMR ($CDCl_3$): δ 9.81 (br s, 1 H, NH), 7.70 (m, 2 H, *ortho*-H), 7.38 (br s, 1 H, NH), 7.34 (m, 2 H, *meta*-H), 7.16 (m, 1 H, *para*-H), 4.08 (m, H-1), 2.68 (br s, 3 H, $-CH_3$), 2.55 (m, H-2), 2.32 (br s, OH), 2.03 (m, 1 H), 1.92 (m, 1 H), 1.79 (m, 1 H), 1.69 (m, 1 H), 1.38–1.14 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ: δ 179.2 (C=S), 138.4 (*ipso*-C), 128.5 (*meta*-C), 125.1 (*para*-C), 123.1 (*ortho*-C), 70.8 (C-8a), 69.7 (C-4a), 41.0 (CH_3), 35.5 (C-8), 24.6, 24.4 and 24.0.

5a: 75%, m.p. 133–136 °C. ^{1}H NMR ($CDCl_3$): δ 9.35 (br s, 1 H, NH), 7.98 (br s, 1 H, NH), 7.63 (m, 2 H, *ortho*-H), 7.34 (m, 2 H, *meta*-H), 7.17 (m, 1 H, *para*-H), 4.49 (m, H-1), 2.70 (m, 4 H, CH_3 and OH), 2.59 (m, H-2), 1.90–1.75 (m, 3 H), 1.65–1.55 (m, 2 H), 1.50–1.35 (m, 2 H), 1.28 (m, 1 H), 1.40–1.16 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 179.0 (C=S), 138.2 (*ipso*-C), 128.5 (*meta*-C), 125.3 (*para*-C), 123.6 (*ortho*-C), 66.0 (C-8a), 66.0 (C-4a), 42.0 (CH_3), 32.8 (C-8), 25.0, 24.3 and 18.9.

3b: 79%, m.p. 168–170 °C. ^{1}H NMR ($CDCl_3$): δ 9.50 (br s, 1 H, NH), 7.50 (br s, 1 H, NH), 7.40–7.20 (m, 9 H, Ar), 7.10 (m, *para*-H), 3.97 (d, 1 H, J = 12.8, CH_2–Ph), 3.93 (d, 1 H, J = 12.8 CH_2–Ph), 3.59 (m, H-1), 2.69 (m, H-2), 2.12–1.98 (m, 3 H), 1.85–1.65 (m, 2 H), 1.45–1.17 (m, 4 H). ^{13}C NMR ($CDCl_3$): δ 179.0 (C=S), 138.2, 136.3, 129.5, 128.6, 128.4, 127.9, 125.3, 123.5, 72.0 (C-8a), 68.3 (C-4a), 58.5 (CH_2–Ph), 35.6 (C-8), 24.6, 24.6 and 24.0.

5b: 71%, m.p. 171–173 °C. ^{1}H NMR ($CDCl_3$): δ 8.75 (br s, 1 H, NH), 8.59 (br s, 1 H, NH), 7.40–7.20 (m, 5 H, CH_2-Ph), 7.25 (m, 2 H, *meta*-H), 7.17 (m, 2 H, *ortho*-H), 7.11 (m, 1 H, *para*-H), 4.70 (m, H-1), 4.08 (m, 2 H, CH_2–Ph), 3.63 (br s, 1 H, OH), 2.86 (m, H-2), 2.03 (m, 1 H), 1.93 (m, 1 H), 1.82 (m, 1 H), 1.75–1.60 (m, 2 H), 1.50–1.40 (m, 2 H), 1.29 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 179.7 (C=S), 137.9, 136.5, 129.8, 128.7, 128.3, 127.9, 125.4, 124.0, 68.3 (C-8a), 64.6 (C-4a), 59.0 (CH_2–Ph), 33.2 (C-8), 25.2, 24.6 and 19.1.

7: 55%, m.p. 148–150 °C. ^{1}H NMR ($CDCl_3$): δ 10.81 (br s, 1 H, NH), 7.66 (m, 2 H, *ortho*-H), 7.31 (m, 2 H, *meta*-H), 7.11 (m, 1 H, *para*-H), 3.51 (br s, 3 H, $-CH_3$), 3.45 (m, 1 H), 2.59 (m, 1 H), 2.55 (br s, 3 H, $-CH_3$), 2.06–1.15 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 179.8, 139.9, 128.3, 124.5, 123.8, 71.0, 69.2, 35.4 ($-CH_3$), 32.8 ($-CH_3$), 32.8, 26.6, 24.4 and 24.0.

8: 54%, oil, (silica gel; toluene–methanol 4 : 1; R_f = 0.5). ^{1}H NMR ($CDCl_3$): δ 10.19 (br s, 1 H, NH), 7.60 (m, 2 H, *ortho*-H), 7.36–7.30 (m, 3 H, *meta*-H and NH), 7.14 (m, 1 H, *para*-H), 4.13 (br s, 1 H), 3.66 (m, 1 H), 3.33 (br s, 3 H, $-CH_3$), 2.64 (br s, 3 H, $-CH_3$), 2.54 (m, 1 H), 2.00–1.15 (m, 8 H). ^{13}C NMR ($CDCl_3$): δ 180.7, 139.4, 128.5, 124.9, 124.0, 65.6, 65.1, 37.9 ($-CH_3$), 32.1, 29.6 ($-CH_3$) 24.4, 22.8 and 19.0.

General procedure for the cyclization of thioureas **3a,b–6a,b** *and* **7**, **8** *by treatment with MeI and alkali.* The thiourea derivative (2 mmol) was dissolved in 10 ml of dry methanol followed by the addition of methyl iodide (2.5 ml, 40 mmol). The mixture was stirred for 5–6 h at r.t., after which the methanol and excess methyl iodide were evaporated off. The residue was dissolved in 25 ml of 15% methanolic potassium hydroxide and stirred at r.t. overnight. The solvent was removed and the residue dissolved in ice-cold water (25 ml), which was then extracted with chloroform (3 × 40 ml). The combined organic phases were dried (Na_2SO_4) and evaporated to dryness. Recrystallization of the solid residues furnished pure ring-closed products in fairly good yields. However, no ring-closed product was isolated from the reaction of **8**, which instead yielded the crystalline isothiouronium derivative **9**.

Stirring **9** with NaH in THF for 5 h at r.t. afforded the corresponding ring-closed adduct **11** in quantitative yield as an oil which was purified by flash chromatography (silica gel; petroleum ether–ethyl acetate, 7 : 3,

R_f=0.4). The spectral data for the 4-chlorophenyl derivatives **13a,b** and **15a,b** are not presented as they are essentially the same as those for the corresponding phenyl derivatives.

9: Yield 78%, m.p. 98–100 °C. ^{1}H NMR ($CDCl_3$): δ 7.21 (m, 2 H, *meta*-H), 6.91 (m, 1 H, *para*-H), 6.87 (m, 2 H, *meta*-H), 4.00 (br s, 1 H), 2.82 (br s, 3 H), 2.62–2.57 (m, 4 H), 2.01 (m, 1 H), 1.92 (br s, 3 H), 1.81 (m, 1 H), 1.70–1.30 (m, 5 H), 1.23 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ 149.0, 148.9, 128.7, 121.2, 121.2, 65.7, 65.1, 38.1 (–CH_3), 30.4, 30.1 (–CH_3), 24.6, 23.4 and 15.9 (–CH_3).

trans-*4-Methyl-2-phenylamino-4a,5,6,7,8,8a-hexahydro-(4H)-1,3,4-benzoxadiazine* (**12a**). Yield 58%, m.p. 96–98 °C (petroleum ether). ^{1}H NMR ($CDCl_3$): δ 7.28 (m, 2 H, *ortho*-H), 7.22 (m, 2 H, *meta*-H), 6.89 (m, 1 H, *para*-H), 5.55 (br s, 1 H, NH), 4.08 (m, J=4.4, 8.2 and 11.6, H-8a), 2.65 (br s, 3 H, –CH_3), 2.13 (m, J=4.1, 8.2 and 11.4, H-4a), 2.10 (m, J=1.8, 2.9, 3.5, 4.1 and 12.8, H-5eq), 2.06 (m, J=1.8, 3.0, 3.5, 4.4 and 12.5, H-8eq), 1.82 (m, J=2.8, 3.0, 4.0, 4.1 and 14.2 H-7eq), 1.82 (m, J=1.8, 2.8, 2.9, 4.2, 4.3 and 14.2, H-6eq), 1.43 (m, J=4.0, 11.6, 12.4 and 13.1, H-8ax), 1.39 (m, J=3.5, 4.1, 13.1, 13.2 and 14.2, H-6ax), 1.38 (m, J=3.5, 4.2, 13.1, 13.1 and 14.2, H-7ax) and 1.20 (m, J=4.3, 11.4, 12.8 and 13.2, H-5ax). ^{13}C NMR ($CDCl_3$): δ 142.8 (C-2), 140.2 (*ipso*-C), 128.8 (*meta*-C), 120.9 (*para*-C), 117.4 (*ortho*-C), 78.8 (C-8a), 62.9 (C-4a), 43.6 (CH_3), 30.5 (C-8), 27.9 (C-5), 24.4 (C-6) and 23.7 (C-7). HRMS: calcd. for $C_{14}H_{18}N_3O$, 245.1528; found 245.1543.

trans-*4-Benzyl-2-phenylamino-4a,5,6,7,8,8a-hexahydro-(4H)-1,3,4-benzoxadiazine* (**12b**). Yield 57%, m.p. 153–155 °C (diisopropyl ether). ^{1}H NMR ($CDCl_3$): δ 7.43–7.26 (m, 5 H, CH_2–$C_6\underline{H}_5$), 7.21 (m, 2 H, *ortho*-H), 7.15 (m, 2 H, *meta*-H), 6.86 (m, 1 H, *para*-H), 5.55 (br s, 1 H, NH), 4.28 (d, 1 H, J=13.3, $C\underline{H}_2$–Ph), 4.10 (m, J=4.7, 8.3 and 11.4, H-8a), 3.78 (br s, 1 H, J=13.3, $C\underline{H}_2$–Ph), 2.33 (m, J 3.9, 8.3 and 11.2, H-4a), 2.24 (m, J=1.7, 2.9, 3.4, 3.9 and 13.1, H-5eq), 2.02 (m, J=1.5, 2.9, 4.7, 4.7 and 13.6, H-8eq), 1.80 (m, J=1.7, 2.7, 2.9, 3.1, 3.5 and 13.5, H-6eq), 1.80 (m, J=1.7, 2.7, 2.9, 3.1, 3.5 and 13.5, H-7eq), 1.38 (m, J=3.5, 11.4, 13.6 and 13.3, H-8ax), 1.38 (m, J=4.0, 4.7, 13.3, 13.7 and 14.2, H-7ax), 1.34 (m, J=2.7, 3.4, 12.6, 13.1 and 13.3, H-6ax) and 1.27 (m, J=3.9, 11.2, 12.6 and 13.1, H-5ax). ^{13}C NMR ($CDCl_3$): δ 142.2 (C-2), 140.2 (C-10) 138.0 (C-17), 129.7 (C-19, C-21), 128.6 (C-12,C-14), 128.0 (C-18, C-22), 126.9 (C-20), 120.7 (C-13), 117.3 (C-11,C-15), 78.5 (C-8a), 59.9 (C-4a), 58.2 (–$C\underline{H}_2$–Ph), 30.5 (C-8), 28.0 (C-5), 24.3 (C-6) and 23.7 (C-7). HRMS: calcd. for $C_{20}H_{23}N_3O$, 321.1841; found 321.1849.

trans-*3,4-Dimethyl-2-phenyliminoperhydro-1,3,4-benzoxadiazine* (**10**). Yield 65%, m.p. 101–103 °C (diisopropyl ether). ^{1}H NMR [$(CD_3C)O_2$]: δ 7.12 (m, 2 H, *meta*-H), 6.91 (m, 2 H, *ortho*-H), 6.81 (m, 1 H, *para*-H), 4.16 (m, J=4.4, 10.3 and 11.4, H-8a), 3.08 [br s, N(3)–CH_3], 2.89 (m, J=3.7, 10.3 and 11.8, H-4a), 2.54 [br s, N(4)–CH_3], 2.10 (m, J=1.7, 3.0, 3.8, 4.4 and 12.3, H-8eq), 1.90 (m, J=1.8, 3.0, 3.7, 3.9 and 12.6, H-5eq), 1.79 (m, J=1.7, 2.5, 3.0, 3.7, 4.3 and 13.3, H-6eq), 1.78 (m, J=1.8, 2.5, 3.1, 3.7, 4.0 and 14.1, H-7eq), 1.40 (m, J=4.0, 11.4, 12.3 and 13.5, H-8ax), 1.32 (m, J=3.7, 3.9, 13.0, 13.3 and 13.4, H-6ax), 1.28 (m, J=3.7, 11.8, 12.6 and 13.4, H-5ax) and 1.23 (m, J=3.8, 4.3, 13.0, 13.5 and 14.1, H-7ax). ^{13}C NMR [$(CD_3C)O_2$]: δ 149.6 (C-2), 149.5 (*ipso*-C), 128.8 (*meta*-C), 124.4 (*ortho*-C), 121.5 (*para*-C), 75.0 (C-8a), 64.6 (C-4a), 37.8 [N(3)–$C\underline{H}_3$], 36.9 [N(4)–$C\underline{H}_3$], 31.8 (C-8), 29.4 (C-5), 25.4 (C-6) and 24.3 (C-7). HRMS: calcd. for $C_{15}H_{21}N_3O$, 259.1685; found 259.1699.

cis-*4-Methyl-2-phenylamino-4a,5,6,7,8,8a-hexahydro-(4H)-1,3,4-benzoxadiazine* (**14a**). Yield 53%, m.p. 119–121 °C (diisopropyl ether). ^{1}H NMR ($CDCl_3$): δ 7.28 (m, 2 H, *ortho*-H), 7.22 (m, 2 H, *meta*-H), 6.88 (m, 1 H, *para*-H), 5.60 (br s, NH), 4.42 (m, J=0.9, 2.7, 3.3 and 7.1, H-8a), 2.79 (m, J=2.7, 3.8 and 8.1, H-4a), 2.68 (br s, 3 H, –CH_3), 2.02 (m, J=4.0, 7.1, 7.5 and 13.6, H-8eq), 1.75 (m, J=3.3, 8.1, 8.7 and 14.0, H-5ax), 1.71 (m, J=0.9, 3.3, 3.5, 7.5, 8.0 and 13.5, H-6eq), 1.70 (m, J=3.3, 4.1, 8.7 and 13.6, H-8ax), 1.64 (m, J=3.5, 4.0, 8.4, 8.7 and 13.6, H-7ax), 1.62 (m, J=0.2, 3.7, 3.8, 8.0 and 14.0, H-5eq), 1.42 (m, J=0.2, 3.8, 4.1, 7.5, 7.5 and 13.6, H-7eq) and 1.30 (m, J=3.7, 3.8, 8.4, 8.7 and 13.5, H-6ax). ^{13}C NMR ($CDCl_3$): δ 142.2 (C-2), 140.2 (*ipso*-C), 128.8 (*meta*-C), 120.8 (*para*-C), 117.2 (*ortho*-C), 75.3 (C-8a), 56.4 (C-4a), 43.2 ($C\underline{H}_3$), 29.6 (C-8), 22.5 (C-5), 21.7 (C-7) and 21.6 (C-6). HRMS: calcd. for $C_{14}H_{18}N_3O$, 245.1528; found 245.1538.

cis-*4-Benzyl-2-phenylamino-4a,5,6,7,8,8a-hexahydro-(4H)-1,3,4-benzoxadiazine* (**14b**). Yield 51%, m.p. 114–116 °C (diisopropyl ether). ^{1}H NMR ($CDCl_3$): δ 7.43–7.26 (m, 5 H, CH_2–$C_6\underline{H}_5$), 7.25 (m, 2 H, *ortho*-H), 7.19 (m, 2 H, *meta*-H), 6.87 (m, 1 H, *para*-H), 5.60 (br s, 1 H, NH), 4.46 (m, J=2.5, 3.3 and 5.2, H-8a), 4.16 (d, 1 H, J=13.2, $C\underline{H}_2$–Ph), 3.91 (br s, 1 H, J=13.2, $C\underline{H}_2$–Ph), 2.87 (m, J=2.5, 4.0 and 10.0, H-4a), 2.03 (m, J=1.6, 4.0, 5.2, 5.2 and 14.3, H-8eq), 1.76 (m, J=1.6, 4.0, 4.0, 5.2, 6.4 and 14.7, H-6eq), 1.70 (m, J=4.0, 10.0, 10.2 and 13.5, H-5ax), 1.68 (m, J=0.9, 2.9, 4.0, 6.4 and 13.5, H-5eq), 1.56 (m, J=4.0, 4.0, 11.0, 11.2 and 13.5, H-7ax), 1.56 (m, J=3.3, 4.2, 11.2 and 14.3, H-8ax), 1.43 (m, J=3.2, 4.2, 5.2, 5.2 and 13.5, H-7eq) and 1.21 (m, J=2.9, 3.2, 10.6, 11.0 and 14.7, H-6ax). ^{13}C NMR ($CDCl_3$): δ 142.1 (C-2), 140.3 (C-10) 138.2 (C-17), 129.3 (C-19, C-21), 128.8 (C-12,C-14), 128.2 (C-18, C-22), 127.1 (C-20), 120.7 (C-13), 117.2 (C-11,C-15), 74.7 (C-8a), 58.8 (–$C\underline{H}_2$–Ph), 53.2 (C-4a), 29.9 (C-8), 22.7 (C-6), 20.8 (C-5) and 20.7 (C-7). HRMS: calcd. for $C_{20}H_{23}N_3O$, 321.1841; found 321.1849.

cis-*3,4-Dimethyl-2-phenyliminoperhydro-1,3,4-benzoxadiazine* (**11**). Yield 97% (from **9**), m.p. 83–86 °C (petro-

Table 6. Experimental X-ray details on **10** and **12a**.

Formula	$C_{15}H_{21}N_3O$	$C_{14}H_{19}N_3O$
Formula weight	259.35	245.32
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$ (No. 14)	$C2/c$ (No. 15)
a/Å	8.572(5)	17.553(3)
b/Å	18.811(3)	6.814(2)
c/Å	9.730(3)	24.23(1)
β/°	113.82(3)	96.55(2)
Z	4	8
V/Å^3	1435(1)	2879(1)
F(000)	560.0	992.00
μ/mm^{-1}	0.77	0.70
D_c/g cm^{-3}	1.200	1.067
Crystal dimensions/mm	0.22 × 0.24 × 0.32	0.30 × 0.32 × 0.36
Data collection		
$2\theta_{max}$/°	50	50
Scan mode	ω–2θ	ω–2θ
Scan speed (deg/min)	4.0	8.0
Scan width (deg)	1.15 + 0.30 tan θ	1.34 + 0.30 tan θ
Reflections collected	2802	2315
Unique reflections	2623	2213
R_{int}	0.022	0.015
Observed reflections	1339 [$I > 2.00\sigma(I)$]	1339 [$I > 2.00\sigma(I)$]
Number of variables	182	174
R	0.051	0.043
R_w	0.043	0.040
Goodness-of-fit on F	1.81	1.78
$(\Delta\rho)_{max}/(\Delta\rho)_{min}$	0.21/−0.18	0.17/−0.14

Table 7. Selected bond lengths, bond angles and torsion angles for **12a**.

Bond lengths (Å)		Dihedral angles (deg)		Torsion angles (deg)	
O(1)–C(2)	1.366(2)	C(2)–O(1)–C(8a)	113.9(2)	O(1)–C(2)–N(3)–N(4)	−1.1(3)
O(1)–C(8a)	1.448(3)	N(4)–N(3)–C(2)	118.0(2)	O(1)–C(2)–N(9)–C(10)	−173.1(2)
N(3)–N(4)	1.443(2)	N(3)–N(4)–C(4a)	114.2(2)	O(1)–C(8a)–C(4a)–N(4)	59.9(2)
N(3)–C(2)	1.272(3)	N(3)–N(4)–C(16)	106.0(1)	O(1)–C(8a)–C(4a)–C(5)	−178.5(2)
N(4)–C(4a)	1.466(3)	C(4a)–N(4)–C(16)	112.3(2)	N(3)–N(4)–C(4a)–C(5)	−169.7(2)
N(4)–C(16)	1.478(3)	O(1)–C(2)–N(3)	128.3(2)	N(3)–N(4)–C(4a)–C(8a)	−49.7(2)
N(9)–C(2)	1.378(3)	O(1)–C(2)–N(9)	107.9(2)	N(3)–C(2)–O(1)–C(8a)	12.8(2)
N(9)–C(10)	1.403(3)	N(3)–C(2)–N(9)	123.9(2)	N(3)–C(2)–N(9)–C(10)	6.0(3)
C(4a)–C(8a)	1.516(3)	N(4)–C(4a)–C(5)	111.8(2)	N(4)–N(3)–C(2)–N(9)	180.0(2)
		N(4)–C(4a)–C(8a)	117.5(2)	N(4)–C(4a)–C(8a)–C(8)	179.9(2)
		C(5)–C(4a)–C(8a)	119.4(2)	N(9)–C(2)–O(1)–C(8a)	−168.1(1)
		O(1)–C(8a)–C(4a)	109.4(2)	N(9)–C(10)–C(11)–C(12)	179.2(2)
		O(1)–C(8a)–C(8)	108.1(2)	C(2)–O(1)–C(8a)–C(4a)	−42.0(2)
		C(4a)–C(8a)–C(8)	112.3(2)	C(2)–N(3)–N(4)–C(4a)	21.4(2)
				C(2)–N(9)–C(10)–C(15)	−4.6(3)

leum ether–diethyl ether). ^{1}H NMR [$(CD_3C)O_2$]: δ 7.21 (m, 2 H, *meta*-H), 7.00 (m, 2 H, *ortho*-H), 6.91 (m, 1 H, *para*-H), 4.79 (m, J=0.6, 1.0, 2.4, 3.3 and 3.7, H-8a), 3.20 [br s, N(3)–CH_3], 2.76 (m, J=3.3, 4.9 and 12.3, H-4a), 2.70 (br s, N(4)–CH_3), 2.05 (m, J=2.1, 2.7, 3.7, 3.7 and 14.7, H-8eq), 1.84 (m, J=2.9, 3.5, 3.7, 4.0 and 13.4, H-6eq), 1.77 (m, J=1.6, 2.9, 4.0, 4.9 and 13.4, H-5eq), 1.54 (m, J=4.0, 12.3, 13.4 and 13.6, H-5ax), 1.48 (m, J=2.7, 3.2, 3.7, 4.5 and 13.7, H-7eq), 1.43 (m, J=3.5, 3.7, 13.2, 13.6 and 13.7, H-7ax), 1.36 (m, J=2.4, 4.5, 13.6 and 14.7, H-8ax) and 1.28 (m, J=3.2, 4.0, 13.2, 13.4 and 13.6, H-6ax). ^{13}C NMR [$(CD_3C)O_2$]: δ 148.24 (C-2), 148.17 (*ipso*-C), 128.3 (*meta*-C), 123.8 (*ortho*-C), 121.1 (*para*-C), 68.8 (C-8a), 57.9 (C-4a), 42.1 [N(4)–CH_3], 39.2 [N(3)–CH_3], 29.8 (C-8), 25.7 (C-5), 24.3 (C-6) and 19.7 (C-7). HRMS: calcd. for $C_{15}H_{21}N_3O$, 259.1685; found 259.1696.

X-Ray crystallography. Experimental details of the structure determination of **10** and **12a** are presented in Table 6. Crystals of **10** were obtained from diisopropyl ether as colourless needles and **12a** from a slowly evaporating chloroform solution as colourless bars. Data collection was performed on a Rigaku AFC5S X-ray diffractometer with graphite monochromated Mo Kα (radiation λ= 0.710 69 Å). Data were corrected for Lorentz and polarisation effects. The crystals showed no decomposition during data collection.

Table 8. Selected bond lengths, bond angles and torsion angles for **10**.

Bond lengths (Å)		Dihedral angles (deg)		Torsion angles (deg)	
O(1)–C(2)	1.353(3)	C(2)–O(1)–C(8a)	122.5(2)	O(1)–C(2)–N(3)–N(4)	−16.1(3)
O(1)–C(8a)	1.452(3)	N(4)–N(3)–C(2)	122.4(2)	O(1)–C(2)–N(3)–C(16)	−177.8(2)
N(3)–N(4)	1.425(3)	N(4)–N(3)–C(16)	114.2(2)	O(1)–C(2)–N(9)–C(10)	−4.9(4)
N(3)–C(2)	1.372(3)	C(2)–N(3)–C(16)	121.2(2)	O(1)–C(8a)–C(4a)–N(4)	49.4(2)
N(3)–C(16)	1.454(4)	N(3)–N(4)–C(4a)	106.9(1)	N(3)–N(4)–C(4a)–C(8a)	−59.2(2)
N(4)–C(4a)	1.463(3)	N(3)–N(4)–C(17)	110.5(2)	N(3)–C(2)–O(1)–C(8a)	3.5(3)
N(4)–C(17)	1.468(3)	C(4a)–N(4)–C(17)	115.1(2)	N(4)–N(3)–C(2)–N(9)	166.2(2)
N(9)–C(2)	1.276(3)	C(2)–N(9)–C(10)	122.5(2)	N(4)–C(4a)–C(8a)–C(8)	171.4(2)
N(9)–C(10)	1.416(3)	O(1)–C(2)–N(3)	118.0(2)	N(9)–C(2)–O(1)–C(8a)	−178.9(2)
C(4a)–C(5)	1.515(3)	O(1)–C(2)–N(9)	122.7(2)	N(9)–C(2)–N(3)–C(16)	4.4(4)
C(4a)–C(8a)	1.505(4)	N(3)–C(2)–N(9)	119.3(2)	C(2)–O(1)–C(8a)–C(4a)	−20.7(2)
C(8a)–C(8)	1.504(3)	N(4)–C(4a)–C(5)	114.7(2)	C(2)–N(3)–N(4)–C(4a)	44.0(3)
C(10)–C(11)	1.402(4)	N(4)–C(4a)–C(8a)	111.0(2)	C(2)–N(3)–N(4)–C(17)	−82.0(3)
C(10)–C(15)	1.392(3)	C(5)–C(4a)–C(8a)	110.4(2)	C(2)–N(9)–C(10)–C(15)	−39.6(4)
C(11)–C(12)	1.388(4)	O(1)–C(8a)–C(4a)	110.9(2)	C(5)–C(4a)–C(8a)–C(8)	−60.3(2)
C(12)–C(13)	1.374(3)	O(1)–C(8a)–C(8)	109.2(2)	C(16)–N(3)–N(4)–C(17)	81.0(3)
C(13)–C(14)	1.377(4)	C(4a)–C(8a)–C(8)	111.6(2)		
C(14)–C(15)	1.389(4)				

The structures were solved by direct methods (SIR92),[23] expanded using Fourier techniques[24] and refined by full-matrix least-squares analysis $[\Sigma w(|F_o| - |F_c|)^2]$. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at calculated positions with isotropic displacement factors ($1.2 \times$ that of the host atom). All the calculations were carried out using the teXsan crystallographic software package from Moleculare Structure Corporation.[25]

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