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The Conformational Behaviour of 4,4a,5,6,7,8-Hexahydropyrido[1,2-*d*][1,3,4]oxadiazine Derivatives Studied by NMR Spectroscopy and Molecular Mechanics

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The diastereomers (1′*R**,2*R**)- and (1′*S**,2*R**)-1-amino-2-(1′-hydroxypiperidinebenzyl) and 1-amino-2-(1-hydroxy-1,1-diphenylmethyl)piperidine have been synthesized and transformed into the corresponding 4,4a,5,6,7,8-hexahydropyrido[1,2-*d*][1,3,4]oxadiazines. Similarly to the unsubstituted parent compound 2-phenylhexahydropyrido[1,2-*d*][1,3,4]oxadiazine, both the (4*R**,4a*R**)- and the (4*S**,4a*R**)-2,4-diphenylhexahydropyrido[1,2-*d*][1,3,4]oxadiazines were found to be predominantly in the *trans*-annellated conformation. This was concluded from low temperature NMR measurements, the chemical shift differences of the methylene protons adjacent to the bridged nitrogen, or the ΔH° values derived from *ab initio* calculations. In 2,4,4-triphenylhexahydropyrido[1,2-*d*][1,3,4]oxadiazine the conformational preference was switched to a slight predominance of the *cis* N-in conformation (53%). The conformational preference in the solid state for the (4*R**,4a*R**)- and the (4*S**,4a*R**)-2,4-diphenylhexahydropyrido[1,2-*d*][1,3,4]oxadiazines was the same as in solution. The ^{15}N chemical shifts of the bridgehead nitrogens were found to correlate to some extent with the conformational preference, while no correlation was observed between the geminal coupling constant of the methylene protons adjacent to the bridgehead and the adopted ring annellation.

Much attention has been paid to the stereochemical preferences of a conformationally mobile bridgehead nitrogen in bicyclic and polycyclic systems containing a 1,3-arrangement of heteroatoms, as this moiety is common in numerous alkaloids possessing interesting biological activities.[1,2] The conformational preferences and energetics of *N*-inversion in such systems have been explored and estimated by methods such as dipole moment measurements, infrared and photoelectron spectroscopy, electrochemical methods etc.,[2] but by far the most frequent, and perhaps the most reliable method, is NMR spectroscopy, which includes variable temperature measurements (^1H, ^{13}C) and determination of specific vicinal and geminal H,H coupling constants. The conformational preferences in quinolizidine-related compounds containing an N–C–O moiety have also been studied by force field molecular mechanics (MM285),[3a,b] although the energetic stabilities calculated with the MM285 program were, to some extent, inconsistent with the experimental results.[3a]

We now report a conformational analysis of some 2-phenylhexahydropyrido[1,2-*d*][1,3,4]oxadiazine derivatives: the C-4 monophenyl-substituted diastereomers **6** (4*R**,4a*R**) and **7** (4*S**,4a*R**) and the C-4 diphenyl-substituted derivative **8**. Their conformational preferences were elucidated by means of NMR spectroscopy, ^1H NMR simulation (PERCHit)[4] and X-ray diffraction. Comparison were also made with semiempirical and *ab initio* calculations for prediction of the conformational preference and estimation of the free and activation energies of nitrogen inversion for quinolizidine-related structures containing an N–N–C–O segment.

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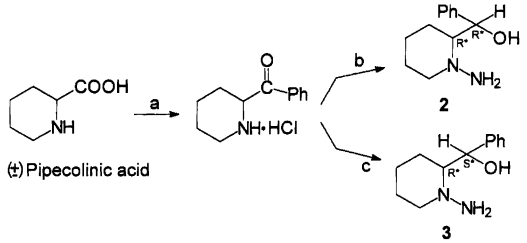
Results and discussion

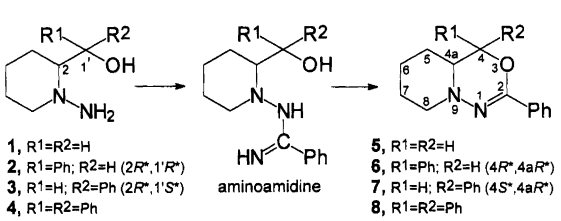
Synthesis. The synthesis of **1** has been reported earlier.[5] The diastereomeric 1-amino-2-(1′-hydroxybenzyl)piperidines **2** and **3** (Scheme 1) were prepared via the corresponding 2-(1′-hydroxybenzyl)piperidines, obtained by slight modification of the methodology reported by Ookawa and Soai.[6] Amination of the 2-(1′-hydroxybenzyl)piperidines was performed as earlier described by Rosling *et al.*[5] The pharmacologically[7a–c] and chemically[8] interesting 2-(1-hydroxy-1,1-diphenylmethyl)piperidine, **4**, prepared according to literature procedures,[9] was aminated similarly and afforded the corresponding diphenyl-substituted hydrazino alcohol **4**.

The one-pot, acid-catalysed ring closures of **1**,[5] **2** and **3** with benzimidate[10] proceeded smoothly, affording **5**–**7** in 55–81% yields (Scheme 2). However, the ring closure of hydrazino alcohol **4** gave mainly the aminoamidine intermediate (70% yield) and only minor amounts of **8** (20% yield), evidently as a result of the increased steric hindrance at C-1′.

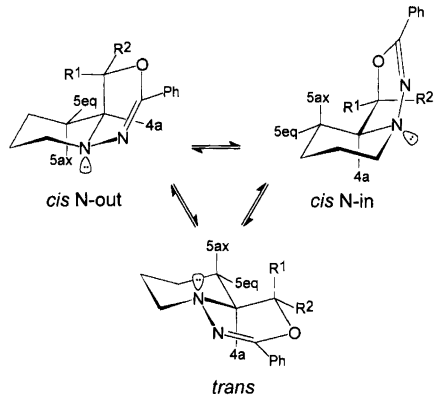
Conformational analysis. Hexahydropyrido[1,2-*d*][1,3,4]-oxadiazines can potentially exist in a three-component equilibrium (Scheme 3). Conformational analysis of related unsubstituted perhydropyrido[1,2-*c*][1,3,]oxazines[11–13] and -thiazines[13,14] revealed that these compounds exist in a two-component equilibrium involving a predominant *trans* and a *cis* C(1)-out conformation (Scheme 4). Consequently, one might expect **5** to exist in a similar equilibrium, though now involving the *trans* and the *cis* N-in conformation. The proportion of the *cis* N-in conformation for **5** might be expected to be higher than that of the *cis* C(1)-out conformation in the perhydropyrido[1,2-*c*][1,3]oxazine, as the two H–H



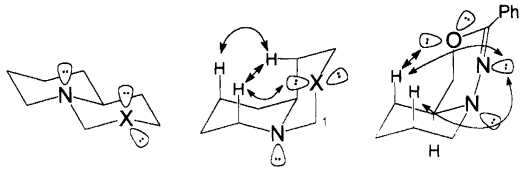
Scheme 1. a, $POCl_5$; $AlCl_3$–benzene; b, $ClCOOCH_2Ph$–base; K-Selectride–THF, 78 °C; KOH–MeOH; $NaNO_2$–H^+; LAH/THF; c, $NaBH_4$–MeOH; $NaNO_2$–H^+; LAH–THF.



Scheme 2. The one-pot, acid catalysed ring closure of **1**–**4** with benzimidate proceeds via the appropriate aminoamidine intermediate.



Scheme 3. The potential three-component equilibrium for hexahydropyrido[1,2-*d*][1,3,4]oxadiazines **5**–**8**, arising from ring and nitrogen inversion.



Scheme 4. The interactions indicated for the *cis* C(1)-out conformer of perhydropyrido[1,2-*c*][1,3]oxazine are believed to be reduced in the *cis* N-in conformer of hexahydropyrido[1,2-*d*][1,3,4]oxadiazine **5**, resulting in an increased proportion of the *cis* N-in conformer.

gauche butane interactions present in the *cis* C(1)-out conformation (Scheme 4) are replaced by two, somewhat weaker, H–lone pair interactions in the *cis* N-in conformation of **5**.[13,15] Additionally, the *gauche* butane interactions between the N-1 lone pair and the axial C-5 and C-7 protons are reduced by the sp^2 hybridization of N-1 and the planar geometry of the N(9)–N(1)–C(2)–O(3) segment, which leads to the proton and lone pair being farther apart. The spatial divergence caused by this structural arrangement is expected to exceed the convergence resulting from the shorter N–N bond.

In earlier work[5] it was concluded from the NMR data (Tables 1–3) that hexahydropyrido[1,2-*d*][1,3,4]oxadiazine **5** exists in a pure *trans* conformation. The large difference in the chemical shifts of the C-8 methylene protons ($\Delta\delta$ 8eq,8ax = 0.92 ppm) was especially indicative of **5** adopting a *trans* conformation.[12] The PERCHit calculated ^3J(H,H) values (Table 2) were those expected for a rigid *trans* chair–(half-chair) conformation. Additionally, *trans*-fusion was confirmed[5] in the solid state by X-ray analysis (molecular structure is shown in Fig. 1). Selected bond lengths and angles are shown in Fig. 2 and selected torsion angles in Table 4. *Ab initio* calculations (Table 5) suggest that **5** should exist in an equilibrium between the *trans* and *cis* N-in conformations, in proportions of 98.5% and 1.5%, respectively.

Table 1. Selected ^{1}H and ^{15}N chemical shifts of **5–8**, measured at room temperature.

Compd.	Relative config.	*trans*:*cis*	δ (H) H-4ax	H-4eq	H-4a	H-8eq	H-8ax	Δ8eq,8ax	δ (N) N9
5		**98:2**[a]	4.16	4.29	2.58	3.53	2.61	0.92	−296.8
6	4*R**,4a*R**	100:0[b]	5.06	—	2.41	3.62	2.64	0.98	−295.1
7	4*S**,4a*R**	85:15[c]	—	5.36	3.02	3.66	2.80	0.86	−302.5
8		47:53[d]	—	—	3.97	3.66	3.09	0.57	−304.9

[a]Estimated on the basis of ΔG° obtained from *ab initio* calculations. [b]Predicted to adopt a pure *trans* conformation (see the text). [c]Extrapolation based on the separate signal integrals of the two conformers from low-temperature experiments. [d]The estimate of the equilibrium was based on the calculated Δ5eq,5ax value (0.23 ppm) for a 100% *cis* conformer, using the results for **6** and **7**.

Table 2. Selected H,H coupling constants of **5–8** calculated with PERCHit.

Compd.	*trans*:*cis*	4ax,4a	4eq,4a	4a,5ax	4a,5eq	5ax,6ax	6ax,7ax	7ax,8ax	8eq,8ax
5	98:2	9.0	3.0	11.3	3.7	13.6	13.0	13.1	−11.4
6	100:0	8.0	—	11.4	2.7	13.3	13.5	12.6	−11.6
7	85:15	—	3.5	12.0	2.8	13.3	13.1	12.2	−13.4
8	47:53	—	—	11.7	2.8	12.0	12.7	12.8	−13.4

Table 3. Selected ^{13}C chemical shifts of **5–8**, measured at room temperature.

Compd.	*trans*:*cis*	C4	C4a	C8	C5	C7	C6
5	98:2	69.6	54.6	56.1	27.2	25.6	23.5
6	100:0	81.6	60.6	56.3	26.9	25.5	23.6
7	85:15	79.1	57.3	56.3	24.5	24.1	23.5
8	47:53	82.5	57.8	55.9	21.2	22.7	24.5

Similarly to **5**, the equilibrium for (4a*R**,4*R**)-2,4-diphenylperhydropyrido[1,2-*d*][1,3,4]oxadiazine **6** is also expected to be strongly biased towards the *trans* conformation. The introduction of an equatorial phenyl substituent at C-4 in **5** is not expected to have any marked affect on the conformational equilibrium, because the C-4 phenyl substituent would be axially orientated if the *cis* N-in conformation were adopted, in contrast with the energetically more favoured equatorial orientation in the *trans* conformation. No contribution of the other possible *cis* conformation, i.e. *cis* N-out (Scheme 3), is expected in the equilibrium, for, although in this conformation the phenyl substituent at C-4 is equatorially orientated, because of the severe *gauche* butane interactions present between C-4 and C-6 and C-4 and C-8, this conformer is precluded. This expectation was realised as the NMR data (Tables 1–3) of **6** were essentially the same as those of **5**. In particular, the large Δδ 8eq,8ax = 0.98 ppm and the similar ^{13}C resonances (i.e. there are no apparent compression shift effects present[16]) are strong indications that **6** adopts *trans*-fusion. The *trans* conformer was also evident in the solid state by X-ray analysis (Fig. 1). The calculated $^{3}J(H,H)$ values proved the absence of any significant amount of the *cis* N-out conformation in the equilibrium.

The ^{1}H and ^{13}C NMR spectra of the corresponding C-4 diastereomer **7** at 25 °C, indicated that **7** exists in a conformational equilibrium with a small proportion of the *cis* N-in conformation. The signal resonances of C-5 and C-7 in **7** are shifted upfield by 2.4 and 1.4 ppm, respectively, compared with the corresponding carbon resonances in **6**. This shielding of C-5 and C-7 originates from the non-bonded interactions between C-4 and C-5 and C-4 and C-7 which is possible only in the *cis* N-in conformation (Scheme 3).[16] Furthermore, also consistent with a shift in the position of the equilibrium, Δδ 8eq,8ax is slightly decreased[13] (0.86 ppm) and the H-4a signal is shifted downfield[13] (δ 3.02 ppm) compared with the corresponding values in **5** and **6** (δ 2.58 and 2.41 ppm, respectively). In the ^{13}C NMR spectrum at −100 °C, only the signal for C-5 passed through coalescence (T_c = −85 ± 5 °C), with the remaining signals approaching coalescence. Unfortunately, the separate signals of C-5, major and minor appearing at 27.8 and 18.5 ppm, respectively, are not totally resharpened at −100 °C and therefore an accurate equilibrium ratio can not be presented based on the signal integrals, though 85:15 (with an accuracy of ±5) can be given with reasonable reliability [ΔG°_{188} 0.6 kcal mol^{-1}, $\Delta G^{\ddagger}_{188}$ (minor → ts) 8.1 kcal mol^{-1}].

This increase in the *cis* N-in population results from the unfavourable axial orientation of the C-4 phenyl in the *trans* conformation of **7**, which is avoided in the *cis* N-in conformation. However, the perpendicular orientation between the C-4 phenyl group and the oxadiazine ring to which it is attached (molecular structure of **7** shown in Fig. 1), minimizes the interactions between the *ortho* and the 5ax hydrogens,[17] thereby resulting in only a rather small influence of the axial C-4 phenyl on the *trans*, *cis* N-in equilibirum. As a result of the partial planar geometry of the oxadiazine ring and the bridgehead nitrogen, there are no additional, substantial γ-effects. The molecular structure of **7** (Fig. 1) and the selected bond angles in Fig. 2 also indicate that the

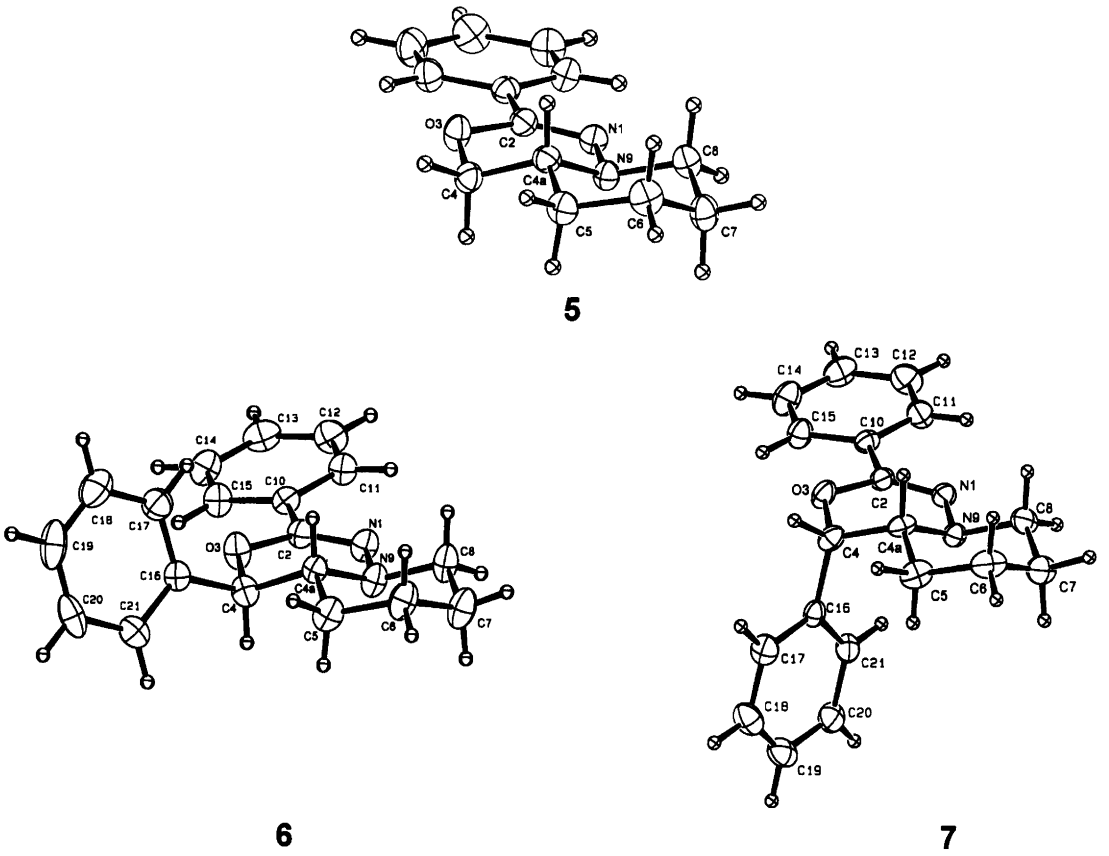


Fig. 1. Numbering and molecular structures in **5–7**.

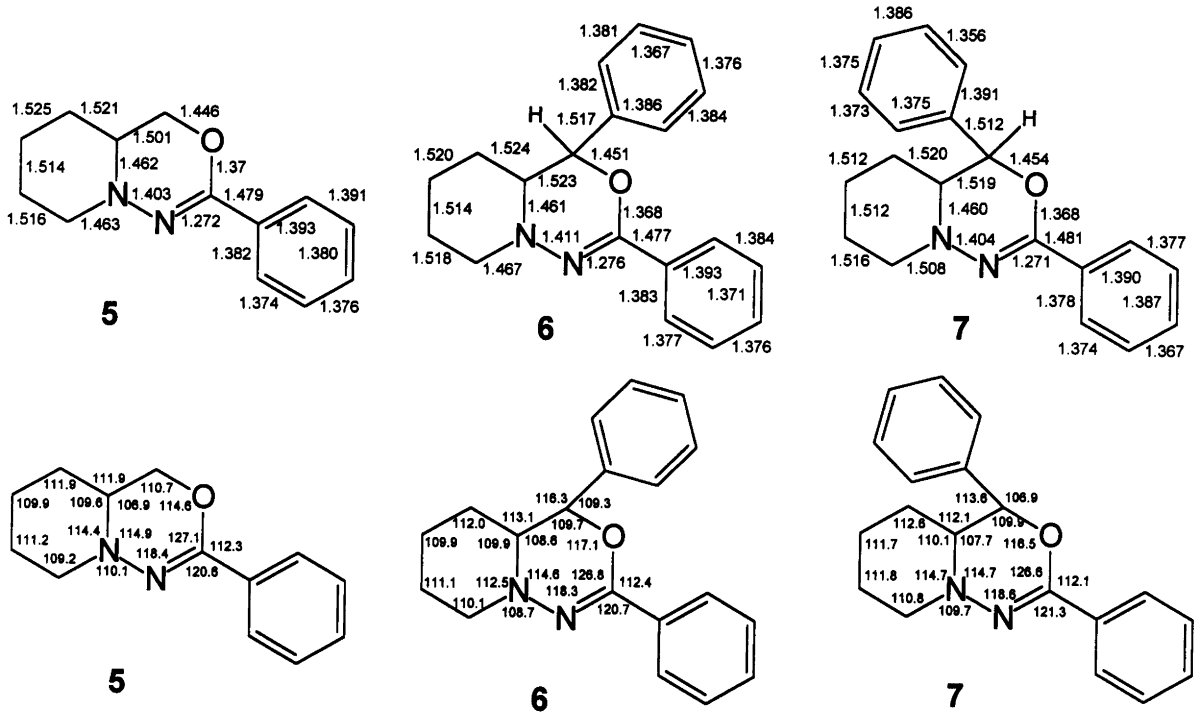


Fig. 2. Selected bond lengths and angles in **5–7**.

Table 4. Selected torsion angles in **5–7**.

Angle	5	6	7
O(3)–C(2)–N(1)–N(9)	2.1(3)	0.9(4)	2.6(4)
O(3)–C(2)–C(10)–C(11)	179.8(2)	169.3(4)	−8.8(3)
O(3)–C(2)–C(10)–C(15)	−1.3(3)	−11.1(6)	171.6(2)
O(3)–C(4)–C(4a)–N(9)	−57.1(2)	−54.4(4)	−53.6(3)
N(1)–N(9)–C(4a)–C(5)	173.3(2)	175.5(4)	176.6(2)
N(1)–N(9)–C(4a)–C(4)	52.2(2)	53.0(5)	52.4(3)
N(1)–C(2)–O(3)–C(4)	−8.6(3)	−4.7(6)	−5.8(4)
N(9)–C(8)–C(7)–C(6)	−56.7(2)	−53.6(6)	−56.8(3)
N(9)–C(4a)–C(5)–C(6)	53.8(2)	51.5(5)	55.2(3)
C(2)–O(3)–C(4)–C(4a)	36.8(2)	32.2(5)	31.3(3)
C(2)–N(1)–N(9)–C(8)	−156.8(2)	−157.9(4)	−154.2(2)
C(2)–N(1)–N(9)–C(4a)	−25.9(2)	−27.1(6)	−27.7(3)
C(2)–C(10)–C(11)–C(12)	177.7(2)	−179.4(4)	−179.8(3)
C(8)–N(9)–C(4a)–C(5)	−57.5(2)	−56.1(5)	−58.6(3)
C(8)–N(9)–C(4a)–C(4)	−179.0(2)	−178.6(4)	177.2(2)
C(8)–C(7)–C(6)–C(5)	55.0(3)	50.9(6)	53.8(3)
C(4a)–N(9)–C(8)–C(7)	59.1(2)	57.6(5)	59.8(3)
C(4a)–C(5)–C(6)–C(7)	−53.6(3)	−502(6)	−53.2(3)

Table 5. The calculated energies relative to the minimum-energy conformer for each molecule. Energies are in kcal mol^{-1} and dipole moments are in debye units (1 D = 3.336×10^{-30} C m). The calculated heats of formation are given in parentheses.

	Ab initio		AM1		PM3	
Compd.	ΔE	μ	ΔE	μ	ΔE	μ
5 *trans*	0[a]	2.1	11	1.9	5	1.8
5 *cis* N-in	10.4	2.0	0 (85)	1.9	0 (58)	1.9
5 *cis* N-out	28.5	2.5	19	2.2	18	2.3
6 *trans*	—	—	7.5	2.0	9	2.0
6 *cis* N-in	—	—	0 (224)	1.7	0 (183)	1.8
6 *cis* N-out	—	—	16.5	2.3	20	2.6
7 *trans*	0[b]	1.9	19	1.7	11	1.7
7 *cis* N-in	1.5	2.0	0 (233)	1.9	0 (189)	2.1
7 *cis* N-out	—	—	30	2.6	33	2.6
8 *trans*	—	—	0 (402)	1.9	11	1.9
8 *cis* N-in	—	—	26	1.7	0 (333)	1.8
8 *cis* N-out	—	—	19	2.4	30	2.6

[a]The total energy of this conformer is −685.340164 Hartree.
[b]The total energy of this conformer is −914.884348 Hartree.

phenyl group is not strictly axial in the *trans* conformation and thus the steric interactions are also less severe than otherwise anticipated.

The ^1H and ^{13}C NMR spectra of **8** revealed significant differences in comparison to **5**, **6**, and **7**. Δδ 8eq,8ax (0.57 ppm) and the low-field shift of H-4a (δ 3.97 ppm) indicate a non-biased *trans/cis* N-in equilibrium. Previous results,[18] together with the present, allow an estimate for the value of Δδ 8eq,8ax for a 100% *cis* conformation of 0.23 ppm. Calculations using this value suggest a 47% *trans* and 53% *cis* N-in equilibrium for **8**.

The marked increase in the *cis* N-in population is obviously due to fewer steric interactions between the two geminal phenyl groups and the rest of the molecule in the *cis* N-in conformation compared with the *trans* conformer. Evidently, it is the relative orientation of the two phenyl substituents at C-4 that is the deciding factor on the equilibrium position of **8**. As shown in the molecular structures of **6** and **7** (Fig. 1), a single phenyl group at C-4 can orientate perpendicularly to the oxadiazine ring, but[17] in the case of **8**, the severe interactions between the *ortho* protons exclude the possibility of both phenyl rings adopting such a perpendicular orientation and it is more probable that the C-4 phenyl rings are perpendicular to each other. Unfortunately, no X-ray structure was obtainable for **8**.

The ^{15}N chemical shift has been used to determine the conformational preferences in quinolizidine-related compounds. The 13–23 ppm deshielding observed for the resonances of the bridgehead nitrogens in *trans* structures compared with the corresponding *cis* conformations[19,20] is explained by hyperconjugation between the antiperiplanar nitrogen lone pair and the antibonding bridge C–H orbitals. However, it is well known that the ^{15}N chemical shift is very sensitive to changes in the surrounding geometry and the consequences of γ and different stereoelectronic effects can easily exceed the resonance differences stemming from ring-fusion geometry.[19] The ^{15}N chemical shifts of the bridgehead nitrogens in **5–8** (Table 1) demonstrated the correct relative order in consideration of the equilibrium: thus the N-9 signals of the biased *trans*-fused **5** and **6** (−296.8 and −295.1 ppm, respectively) are downfield in comparison with those of **7** and **8** (−302.5 and −304.9 ppm, respectively). However, the chemical shift of N-9 (−302.5 ppm) in **7** is not consistent with the determined *cis*, *trans* equilibrium (15:85) (Table 1), possessing rather an unexpected upfield resonance that originates from the additional shielding by the axial C-4 phenyl group. The N-9 chemical shifts of the predominant *trans*-fused structures **5–7** are not fully consistent with resonances earlier observed for related *trans* compounds.[21]

The H,H vicinal coupling constants could not be used to estimate the equilibria in **5–8** as the piperidine ring adopts an identical conformation in both of the expected conformers, i.e. the *trans* and *cis* N-in conformations. Estimation of the equilibrium based on the ^{13}C chemical shifts was also not possible, as reliable model values were not available.

The H,H geminal coupling constants for the $N–CH_2–O$ protons (Scheme 4) can be used to assign the predominant conformation (*cis* or *trans*) in compounds containing a bridgehead nitrogen,[2] where a more positive value of $^2J_{gem}$ implies *trans* fusion. Crabb and Jupp[22] reported application of this parameter for the adjacent methylene protons at C-9 in 1-methylperhydrooxazolopyridines, but we were not able to observe any correlation between the corresponding $^2J_{gem}$ values of the C-8 protons (Table 2) and the predominant conformations in **5–8**. This inconsistency may derive from the proximity of the sp^2 hybridized nitrogen and the N9–N1=C2(Ph)–O segment enabling hyperconjugation of the bridgehead nitrogen lone pair and consequently

resulting in variations in the electron density in the vicinity of C-8.[23]

Molecular mechanics

Computational details. The molecules studied in this work are rather large for quantum chemical *ab initio* calculations. However, **5** and **7** have been studied at the Hartree–Fock level of approximation by using the GAMESS program[24] and the 6–31G* basis set.[25] The *ab initio* calculations give a basis-set-dependent total energy for the molecules. The total energies can be compared directly for different conformers of a molecule or, more generally, for isomers. In order to compare different molecules one can calculate the enthalpy of formation at 0 K by subtracting the energies of free atoms.

The semiempirical calculations involve the use of the AM1[26] and PM3[27] Hamiltonians as incorporated in the MOPAC 5.0[28] program. The MOPAC program is parametrized to predict the experimental heats of formation. A historical overview of the development of the semiempirical methods can be found in Ref. 29. The performance and various pitfalls of the semiempirical models have been thoroughly analysed in the literature.[30] One feature of the models is that the geometry of molecules containing several aromatic rings sometimes proves to be incorrect.

Discussion. The calculated energies relative to the minimum energy conformation are reported in Table 5. The most striking feature of the theoretical calculations is that the *ab initio* method and the semiempirical models predict different minimum energy conformations. Part of the explanation may be that the *ab initio* results refer to a single molecule (i.e. gas phase) at 0 K, while the semiempirical methods have been parametrized by use of experimental thermodynamic data at ambient temperature. The geometries of each conformer of **5** calculated with the three methods are almost identical, though the *ab initio* method predicts that the whole N(9)–N(1)–C(2)–O(3)–C(9) moiety is almost planar (Table 6). This planarity is in agreement with the molecular structure of **5** (Fig. 1) adopting a *trans*-annellated conformation. Selected torsion angles in **5** are presented in Table 4. Neither of the semiemperical methods, of which AM1 was slightly better, can accurately reproduce the planar geometry evidently present in the oxadiazine ring of *trans*-fused **6** and **7** (Fig. 1), respectively. The geometry and torsion angles calculated by *ab initio* on **7** (torsion angles in Table 6) were essentially identical with those obtained by X-ray diffraction (Table 4). The calculated structures are most distorted in the *cis* N-out conformers, where the steric strain is expected to be large. The semiempirical models reproduce this structural feature fairly accurately in **5**, but not in **6** and **7**. It may be speculated that the capability of the semiempirical models to extend the π system to this moiety and thereby increase the delocalisation-energy contribution may play a role in determining the order of the conformers.

The calculated dipole moments (Table 5) are fairly small for all the systems studied. This indicates that polar solvents do not alter the preference order of the conformations of the molecules.[31]

The charges in Table 7 were calculated by the Löwdin method[32] in the *ab initio* calculations and by using the Mulliken population analysis[33] in the semiempirical models. The PM3 Hamiltonian predicts different charges for the sp^3 hybridized nitrogen atom, while the AM1 charges are comparable to those calculated by the *ab initio* method in all cases. The effect of the phenyl groups on C-9 is evident. The phenyl groups strongly withdraw electrons from the carbon atom to which they are attached, but otherwise the charge distribution remains unchanged.

Conclusions

The usefulness and general applicability of earlier reported NMR parameters for estimation of the conformational equilibria in hexahydropyrido[1,2-*d*]-[1,3,4]oxadiazines have been studied and recognized to be rather limited. The measured parameters are sensitive to changes in geometry around the mobile tertiary nitrogen in the bridgehead position, but these differences are easily overwhelmed or distorted by changes in the ring structures (e.g. flattening or puckering of the rings and variations in size of the fused rings), additional heteroatoms, and the effects of substituents in either of the rings. The difference in the chemical shifts of the C-8 methylene protons (ca. 1.0 ppm in the *trans* and ca. 0.2 ppm in the *cis* conformers) appears to be the parameter of choice, reflecting the conformational preference with certain reliability, albeit limited in accuracy, in quinolizidine-related compounds. An accurate estimate is impossible as $\Delta\delta$ 8eq,8ax for stereohomogeneous *cis* and *trans* conformers differ slightly from one derivative to another.

Of the molecular modelling calculations, only the *ab initio* results (energetic stabilities and geometries) were in good agreement with the experimental methods, thereby providing a meaningful tool for estimation of the conformational preferences and the positions of the equilibria for the compounds studied. However, the size of the studied molecules tended to be a limiting factor for the *ab initio* calculations.

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 light petroleum used had a boiling range of 40–60 °C. NMR spectra were obtained on JEOL JNM-L-400 and JNM-A-500 instruments and the experi-

Table 6. Selected torsion angles in degrees for **5–8**, calculated by means of different molecular mechanistic methods.

	Ab initio				AM1				PM3			
Compd.	Ph–CN	Ph–CO	OC–NN	CO–CN	Ph–CN	Ph–CO	OC–NN	CO–CN	Ph–CN	Ph–CO	OC–NN	CO–CN
5 *trans*	0	0	−1	6	6	5	−6	15	−7	−5	−6	12
5 *cis* N-in	0	0	3	−9	2	0	9	−15	4	1	7	−11
5 *cis* N-out	8	9	4	11	9	11	9	6	10	12	7	11
6 *trans*	—	—	—	—	10	11	−6	18	37	41	−8	21
6 *cis* N-in	—	—	—	—	−22	−24	8	−18	−25	−29	8	−16
6 *cis* N-out	—	—	—	—	−41	−38	2	7	−43	−43	4	4
7 *trans*	4	4	−1	3	22	23	−7	20	37	41	−8	17
7 *cis* N-in	−4	−5	3	−10	2	0	9	−16	−40	−43	8	−13
7 *cis* N-out	—	—	—	—	24	26	6	22	33	35	3	30
8 *trans*	—	—	—	—	17	19	−7	19	30	35	−9	20
8 *cis* N-in	—	—	—	—	2	0	7	−20	4	0	8	−17
8 *cis* N-out	—	—	—	—	−42	−38	3	24	−44	−42	4	23

Table 7. Calculated net atomic charges. Löwdin charges are reported for the *ab initio* method and Mulliken charges for the semiempirical models.

	Ab initio					AM1					PM3				
Compd.	N4	N3	C2	O3	C9	N4	N3	C2	O3	C9	N4	N3	C2	O3	C9
5 *trans*	−0.16	−0.18	0.16	−0.27	−0.10	−0.22	−0.15	0.12	−0.28	−0.12	−0.01	−0.21	0.14	−0.22	−0.09
5 *cis* N-in	−0.15	−0.18	0.16	−0.27	−0.09	−0.21	−0.16	0.12	−0.28	−0.11	−0.01	−0.20	0.14	−0.21	−0.09
5 *cis* N-out	−0.16	−0.19	0.17	−0.27	−0.11	−0.19	−0.15	0.12	−0.27	−0.15	0	−0.20	0.14	−0.21	−0.12
6 *trans*	—	—	—	—	—	−0.23	−0.15	0.11	−0.28	0.02	−0.02	−0.19	0.12	−0.21	0.05
6 *cis* N-in	—	—	—	—	—	−0.20	−0.15	0.12	−0.27	0.03	0	−0.19	0.13	−0.21	0.06
6 *cis* N-out	—	—	—	—	—	−0.15	−0.12	0.07	−0.23	0.04	0	−0.18	0.12	−0.20	0.09
7 *trans*	−0.15	−0.19	0.16	−0.26	0.04	−0.22	−0.15	0.12	−0.27	0.03	−0.01	−0.20	0.14	−0.21	0.06
7 *cis* N-in	−0.15	−0.18	0.16	−0.26	0.04	−0.21	−0.19	0.13	−0.21	0.05	−0.02	−0.19	0.13	−0.21	0.05
7 *cis* N-out	—	—	—	—	—	−0.25	−0.13	0.09	−0.26	0	−0.04	−0.17	0.08	−0.20	0.03
8 *trans*	—	—	—	—	—	−0.17	−0.13	0.08	−0.24	0.17	0	−0.18	0.11	−0.21	0.21
8 *cis* N-in	—	—	—	—	—	−0.21	−0.15	0.12	−0.28	0.18	−0.01	−0.19	0.13	−0.21	0.22
8 *cis* N-out	—	—	—	—	—	−0.18	−0.11	0.06	−0.23	0.14	0.01	−0.17	0.09	−0.21	0.18

mental conditions were essentially the same as those reported in Ref. 21. The chemical shifts (δ), given in ppm, are referred to internal tetramethylsilane. The coupling constants given for **5–8** were calculated with the PERCHit program.[4] The elemental analyses were performed on a Perkin Elmer Analysator 2400 for C, H, N, S/O.

1-Amino-2-hydroxymethylpiperidine **1** and 2-phenyl-4,4a,5,6,7,8-hexahydropyrido[1,2-*d*][1,3,4]oxadiazine **5** were prepared according to methods reported earlier.[5]

The ring-closed compounds **5–8** were purified by column chromatography (silica gel; light petroleum–diethyl ether 75:25 as the eluent). For X-ray analysis, the compounds were further recrystallised.

*(2*R**,1′*R**)-1-Amino-2-(1′-hydroxybenzyl)piperidine* (**2**). Crude **2** was obtained in 28% overall yield from a seven-step reaction. ^{1}H NMR: δ 4.64 (1 H, d, J=7.9 Hz, H-1′), 3.10 (1 H, m), 2.31–2.25 (2 H, m), 1.65–1.50 (3 H, m), 1.10–0.95 (3 H, m). ^{13}C NMR: δ 142.0, 128.2, 127.6, 127.6, 81.0 (C-1′), 69.3 (C-2), 63.6 (C-6), 28.7, 25.4, 23.4.

*(2*R**,1′*S**)-1-Amino-2-(1′-hydroxybenzyl)piperidine* (**3**). Crude **3** was obtained in 47% overall yield from a six-step reaction. ^{1}H NMR: δ 5.16 (1 H, d, J=2.6 Hz, H-1′), 3.14 (1 H, m), 2.38–2.27 (2 H, m), 1.65–1.42 (3 H, m), 1.30–1.20 (2 H, m), 1.10 (m, 1 H). ^{13}C NMR: δ 141.8, 127.8, 126.7, 126.7, 74.5 (C-1′), 70.0 (C-2), 62.8 (C-6), 24.9, 24.8, 23.6.

1-Amino-2-(1-hydroxy-1,1-diphenylmethyl)piperidine (**4**), was obtained in a 25% overall yield from a six-step reaction, m.p. 210–212 °C (recrystallised from diethyl ether–methanol). ^{1}H NMR: δ 3.46 (1 H, m), 2.95 (1 H, m), 1.85–1.65 (3 H, m), 1.45–1.30 (2 H, m), 1.18 (1 H, m). ^{13}C NMR: δ 148.3, 156.3, 127.8, 127.6, 126.6, 126.2, 126.0, 126.0, 80.5 (C-1′), 67.2 (C-2), 58.9 (C-6), 24.8, 20.1, 18.4.

*(4*R**,4a*R**) - 2,4 - Diphenyl - 4,4a,5,6,7,8 - hexahydropyrido[1,2-*d*][1,3,4]oxadiazine* (**6**). Yield 61%, m.p. 134–136 °C. ^{1}H NMR: δ 7.85–7.80 (2 H, m, Ar), 7.42–7.28 (8 H, m, Ar), 5.06 (1 H, d, J=8.0 Hz, H-4$_{ax}$), 3.62 (1 H, m, J=−1.8, 2.7, 3.7 and −11.6 Hz, H-8$_{eq}$), 2.64 (1 H, m, J=2.7, −11.6 and 12.6 Hz, H-8$_{ax}$), 2.41 (1 H, m, J=2.7, 8.0 and 11.4 Hz, H-4a), 1.76 (1 H, m, J=1.9, 2.7, 2.7, 3.9, 4.4 and −13.2 Hz, H-7$_{eq}$), 1.74 (1 H, m, J=−1.8, 3.0, 3.0, 3.9, 4.1 and −13.7 Hz, H-6$_{eq}$), 1.72 (1 H, m, J=3.0, 3.7, 12.6, −13.1 and 13.5 Hz, H-7$_{ax}$), 1.40 (1 H, m, J=1.9, 2.7, 3.0 and

−13.1 Hz, H-5_{eq}), 1.28 (1 H, m, J=4.1, 11.4, −13.1 and 13.3 Hz, H-5_{ax}), 1.20 (1 H, m, J=3.8, 4.4, 13.3, 13.5 and −13.7 Hz, H-6_{ax}). ^{13}C NMR: δ 146.4 (C-2), 137.3 (C-16) 132.6 (C-10), 129.0, 128.8, 128.5, 128.0, 127.5, 125.4, 81.6 (C-4), 60.6 (C-4a), 56.3 (C-8), 26.9 (C-5), 25.5 (C-7), 23.6 (C-6). Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.11; H, 6.90; N, 9.59. Found: C, 77.93; H, 7.02; N, 9.43.

(4S,4aR*) - 2,4 - Diphenyl - 4,4a,5,6,7,8 - hexahydropyrido[1,2-*d*][1,3,4]oxadiazine* (**7**). Yield 55%, m.p. 105–108 °C ^{1}H NMR: δ 7.90–7.85 (2 H, m, Ar), 7.38–7.28 (8 H, m, Ar), 5.36 (1 H, d, J=3.5 Hz, H-4_{eq}), 3.66 (1 H, m, J=1.6, 2.6, 3.9 and −12.1 Hz, H-8_{eq}), 3.02 (1 H, m, J=2.8, 3.5 and 12.0 Hz, H-4a), 2.80 (1 H, m, J=3.5, −12.1 and 12.2 Hz, H-8_{ax}), 1.70 (1 H, m, J= 1.6, 2.1, 2.8, 4.0, 4.3, and −13.4 Hz, H-6_{eq}), 1.57 (1 H, m, J=1.7, 2.1, 2.6, 3.5, 3.7 and −13.9 Hz, H-7_{eq}), 1.56 (1 H, m, J=3.9, 4.3, 12.1, 13.1 and −13.9 Hz, H-7_{ax}), 1.35 (1 H, m, J=2.8, 2.8, 3.7 and −13.4 Hz, H-5_{eq}), 1.33 (1 H, m, J=3.7, 3.7, 13.1, 13.3 and −13.4 Hz, H-6_{ax}), 0.97 (1 H, m, J=4.0, 12.0, 13.3 and −13.4 Hz, H-5_{ax}). ^{13}C NMR: δ 144.4 (C-2), 138.4, 132.7, 129.5, 128.1, 128.0, 128.0, 127.2, 125.4, 79.1 (C-4), 57.3 (C-4a), 56.3 (C-8), 24.5 (C-5), 24.1 (C-7), 23.5 (C-6). Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.11; H, 6.90; N, 9.59. Found: C, 78.05; H, 6.93; N, 9.60.

2,4,4 - Triphenyl - 4,4a,5,6,7,8 - hexahydropyrido[1,2 - d*]-[1,3,4]oxadiazine* (**8**). Yield 20%, m.p. 151–153 °C. ^{1}H NMR: δ 8.05–7.97 (2 H, m, Ar), 7.53–7.47 (4 H, m, Ar), 7.43–7.15 (9 H, m, Ar), 3.97 (1 H, m, J=2.8 and 11.7 Hz, H-4a), 3.66 (1 H, dm, J=1.7, 2.1, 4.1 and −13.4 Hz, H-8_{eq}), 3.09 (1 H, m, J=2.8, 12.8 and −13.4 Hz, H-8_{ax}), 1.77 (1 H, m, J=2.1, 2.7, 3.1, 3.8, 3.8, and −13.3 Hz, H-6_{eq}), 1.67 (1 H, m, J=3.8, 4.1, 12.7, 12.8 and −13.5 Hz, H-7_{ax}), 1.47 (1 H, m, J=3.8, 11.7, 12.0 and −13.3 Hz, H-5_{ax}), 1.46 (1 H, m, J=3.5, 4.0, 12.0, 12.7 and −13.3 Hz, H-6_{ax}), 1.43 (1 H, m, J=1.2, 1.7, 2.7, 2.8, 3.5 and −13.5 Hz, H-7_{eq}), 1.09 (1 H, m, J=2.8, 3.1, 3.9 and −13.3 Hz, H-5_{eq}). ^{13}C NMR: δ 144.2, 143.2, 142.4, 133.0, 128.6, 128.4, 128.2, 128.1, 127.3, 127.1, 126.1, 125.5, 125.0, 82.5 (C-4), 57.8 (C-4a), 55.9 (C-8), 24.5 (C-6), 22.7 (C-7) 21.2 (C-5). Anal. Calcd. for $C_{25}H_{24}N_2O$: C, 81.55; H, 6.57; N, 7.61. Found: C, 81.46; H, 6.72; N, 7.54.

X-Ray crystallography. Experimental details on the structure determination of **6** and **7** are presented in Table 8. Crystals of **6** and **7** were obtained from diisopropyl ether–diethyl ether as colourless plates and bright prisms, respectively. 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 did not decompose during data collection.

The structures were solved by a direct methods (SIR92),[34] expanded using Fourier techniques[35] and refined by full-matrix least squares analysis

Table 8. Experimental X-ray details.

	6	**7**
Formula	$C_{19}H_{20}N_3O$	$C_{19}H_{20}N_2O$
Formula weight	292.38	292.38
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$ (No. 14)	$P\bar{1}$ (No. 2)
a/Å	9.992(4)	9.621(4)
b/Å	17.027(8)	11.641(6)
c/Å	9.991(4)	7.681(3)
α/°		108.01(4)
β/°	109.44(2)	95.03(4)
γ/°		76.95(4)
Z	4	2
V/Å^3	1603(1)	796.8(7)
F(000)	552.0	312
μ/cm^{-1}	0.76	0.76
D_c/g cm^{-3}	1.212	1.219
Crystal dimensions	0.20 × 0.36 × 0.40	0.30 × 0.30 × 0.30
Data collection		
$2\theta_{max}$/°	50	50
Scan mode	ω–2θ	ω–2θ
Scan speed	4.0	8.0
Scan width (deg)	1.37 + 0.30 tan θ	1.63 + 0.30 tan θ
Reflections	2521	2987
Unique reflections	2347	2804
R_{int}	0.040	0.019
Observed reflect.	1151 [I > 2.00σ(I)]	1487 [I > 3.00σ(I)]
No. of variables	199	230
R	0.053	0.030
R_w	0.046	0.036
Goodness-of-fit on	1.55	1.62
$(\Delta\rho)_{max}/(\Delta\rho)_{min}$	0.21/−0.20	0.12/−0.13

$[\Sigma w(|F_o|-|F_c|)^2]$. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included at calculated positions with a fixed isotropic displacement factor (1.2× that of the host atom). All calculations were carried out using the teXsan crystallographic software package from Molecular Structure Corporation.[36]

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