THE CONFORMATIONAL PREFERENCE OF SOME TETRA-HYDROPYRROLO[1,2-*d*][1,3,4]OXADIAZINE DERIVATIVES AS STUDIED BY NMR SPECTROSCOPY AND X-RAY ANALYSIS

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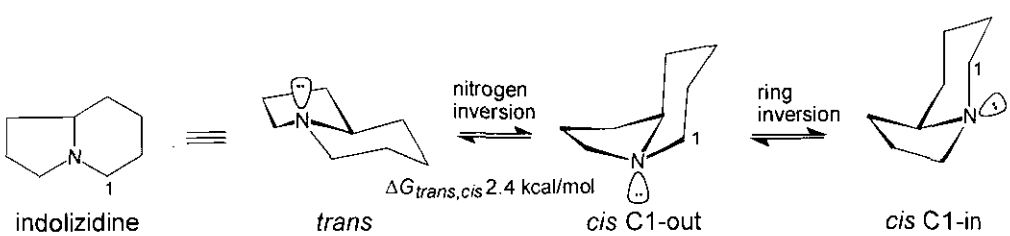
Abstract – The diastereomeric (4*S*,4a*S*)- and (4*R*,4a*S*)-2,4-diphenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazines and their 2,4,4-triphenyl-substituted analog were synthesised. Their conformational behavior, elucidated by means of NMR spectroscopy and X-Ray analysis, revealed some surprising features. The unsubstituted parent compound (4a*S*)-2-phenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine was shown by X-Ray analysis to adopt the same conformational preference in the solid state as in solution, the *cis* N-out conformation. However, both (4*S*,4a*S*)-2,4-diphenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine and its 2,4,4-triphenyl-substituted analog adopted a *trans* conformation in the solid state, in contrast to their predominant *cis* conformations adopted in solution. The determination of the conformation in solution required the examination of several parameters including homonuclear NOEs, vicinal H,H and H,C coupling constants, the $^{2}J_{H\text{-}7\alpha,H\text{-}7\beta}$ value, the $\Delta\delta$ H-7α,H-7β value, δ H4a, and the ^{15}N chemical shift of the bridgehead nitrogen.

INTRODUCTION

Determination of the conformational preference in indolizidines (Scheme 1) containing one or more additional heteroatoms is of major interest, as numerous alkaloids[1] of medicinal and biological interest include such structures. The conformational behavior of indolizidine derivatives and related compounds with additional heteroatoms[2a-c] has been studied by means

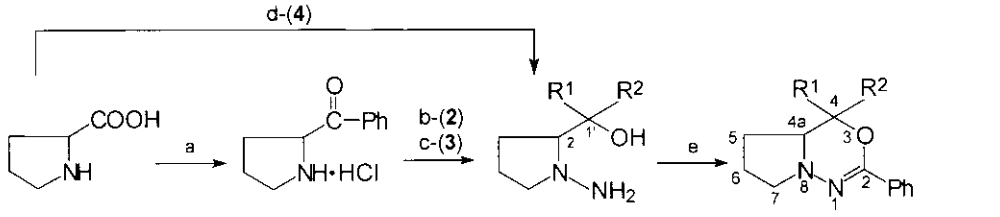


Scheme 1

of different methodologies,[3] of which NMR spectroscopic methods[3] have been most frequently applied. Several NMR parameters, *e.g.* specific $^2J_{H,H}$ and proton chemical shifts, are reported to be sensitive to the stereochemistry of the bridgehead nitrogen[3] and thus indicative for distinguishing between the *cis*- and *trans*-fused conformers. However, whether these parameters were applicable to the presently studied compounds was not apparent[4] since these parameters are also sensitive to other interactions of steric and electronic origin.[5a-c] For reliable estimates of the equilibrium and the conformational preference in novel indolizidine-related compounds, a set of comparative derivatives is required. Accordingly, new tetrahydro-pyrrolo[1,2-*d*][1,3,4]oxadiazine derivatives, *viz.* the 4-phenyl-substituted diastereomers (**6**) (4*S*,4a*S*) and (**7**) (4*R*,4a*S*) and the 4,4-diphenyl-substituted derivative (**8**), were synthesised for stereochemical studies by means of ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy and X-Ray analysis.

RESULTS AND DISCUSSION

Synthesis. The syntheses of the parent compounds (**1**) and (**5**) have been reported previously.[6] Hydrazino alcohols (**2-4**) were prepared in essentially the same way as their corresponding piperidine analogs[4] (Scheme 2). Disconcertingly, the pyrrolidinyl phenyl ketone was much less stable[7] than the corresponding piperidine analog,[4] markedly reducing the overall yield of **2**. The one-pot, acid-catalysed, ring closures of **1-4** with benzimidate to afford **5-8**, respectively, proceeded with similar reactivity and resulted in similar yields to those of their corresponding piperidine analogs.[4]



Scheme 2. a, $POCl_3$; $AlCl_3$-benzene; b, $ClCOOCH_2Ph$-$NaHCO_3$; K-Selectride-THF, -78 °C; KOH-MeOH; $NaNO_2$-CH_3COOH; LAH-THF; c, $NaBH_4$-MeOH; $NaNO_2$-H^+; LAH-THF; d, $ClCOOCH_2Ph$- $NaHCO_3$; PhMgBr; KOH-MeOH; $NaNO_2$- CH_3COOH; LAH-THF; e, PhC(NH)OEt-EtOH; H^+

Spectroscopic studies. The *trans* configuration in hydrindane (Figure 1) is favored by only 0.3 kcal/mol, in contrast with 2.7 kcal/mol for the decalin system[8] and 2.4 kcal/mol for indolizidine (Scheme 1).[9] The small ΔG^0 difference between the carbocycle-fused *cis*- and *trans*-hydrin-

danes originates from ring fusion strain which raises the free energy of *trans*-hydrindane. In indolizidine, the corresponding ring fusion strain is relieved by the flattening of the bridgehead-nitrogen geometry. Insertion of additional heteroatoms, especially in position 3 with respect to the nitrogen, results in new stereoelectronic effects (generalized anomeric effect)[10] and new non-bonding interactions (*gauche butane interactions*)[11] which influence the conformational preference. Thus, the predominant *trans* conformation in indolizidine (Scheme 1) is changed to a predominant *cis* C1-out conformation in perhydropyrrolo[1,2-*c*][1,3]oxazine (Figure 1).[2a] These results are consistent with the stability results found for the 1,3-hetero analogs of *cis* and *trans*-hydrindanes, where the *cis* derivatives were observed to be more stable.[12a-c]

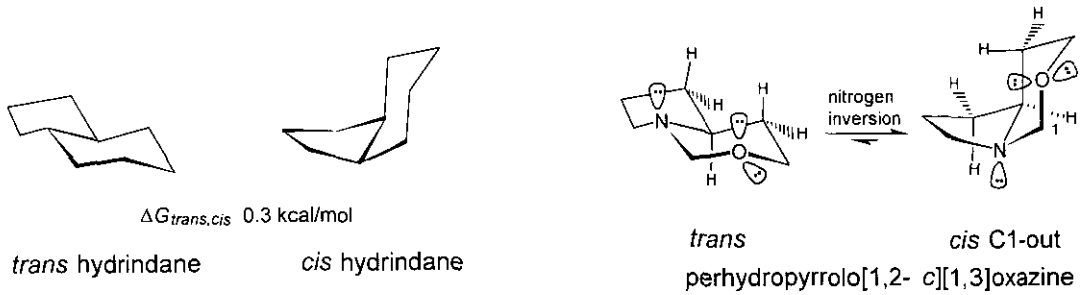
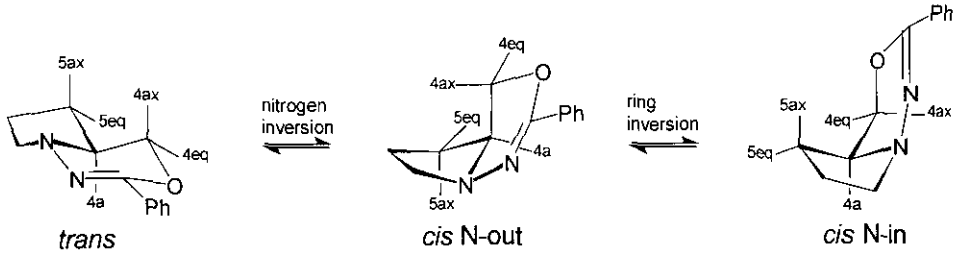


Figure 1

The conformational behavior of the 2-phenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]-oxadiazines (**5-8**) (Scheme 3) can not be predicted unequivocally on the basis of intuitive interpretations of the stereoelectronic effects and the gauche butane type interactions. The impact of the sp^2 hybridized nitrogen on the stereoelectronic effects is not well understood and relevant information was not forthcoming from the literature. Moreover, it is unclear how the adjacent sp^2 hybridized nitrogen affects the barrier to inversion of the bridgehead nitrogen. However, it is known that an adjacent heteroatom increases the activation energy for inversion of a tertiary nitrogen.[13]



Scheme 3

Presumptuously, it could be expected that either NOE measurements or vicinal H,C coupling constants would readily provide an abundance of unequivocal evidence for the adopted

conformation. However, due to the flattening of the bridgehead nitrogen, the sofa conformation of the oxadiazine ring, and the conformational mobility of the five-membered ring, models of the various conformations could each be minutely adjusted to provide a generalized fit to the NOE or $J_{H,C}$ data. Thus clear interpretation of these data was not simple and consistency of all the data together was required for interpretation of the preferred conformation.

Compound (**5**)[6] appeared to exist in a strongly biased equilibrium with a predominant *cis* N-out conformation on the basis of its NMR data (Tables 1-4) by comparison to the reported NMR data on related compounds (in particular the chemical shift of H-4a and the chemical shift difference of H-7α and H-7β, Δδ H-7α,H-7β). The preference for a *cis* N-in conformation can be readily discarded based on the large (8.9 Hz) and medium (3.8 Hz) couplings between H-4a and H-4β and H-4α, respectively. Of note was the small, but definitive, NOE observed between H-4β and H-7β, possible only in the *cis* N-out conformation. Low-temperature NMR, downto -100 °C, failed to realise any evidence for a conformational equilibrium. The same conformational preference was also determined to be present in the solid state by X-Ray analysis (Figure 2). Selected bonding parameters are given in Table 6.

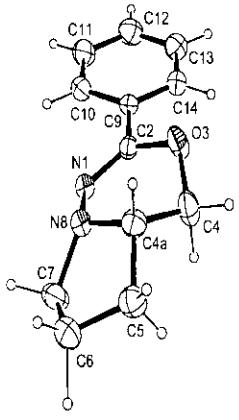


Figure 2. Molecular structure of **5**. Hydrogens and phenyl groups attached to carbons C-4 and C-5 - C-7 are denoted as β when they lie on the opposite side of an idealised bicyclic plane with respect to H-4a, and α if they are on the same side.

The NMR data for (4*S*,4a*S*)-2,4-diphenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine (**6**) (Tables 1-4) are in accord with those for **5**, *i.e.* they are consistent with **6** also adopting a predominant *cis* N-out conformation with an equatorial 4α-phenyl substituent. The downfield shifts of the C-4 and C-4a signals of **6**, at 80.0 and 61.7 ppm, respectively, are consistent with the corresponding signal shifts in **5** (68.1 and 55.1 ppm, respectively), taking into account a phenyl substituent effect. Both the small Δδ H-7α,H-7β [14a-c] (0.02 ppm) and the downfield shift

of H-4a[14a-c] (3.03 ppm) give clear indication for a predominant *cis* conformation. The conformational preference could not be determined based on the vicinal H,H coupling constants, extracted by ^{1}H NMR simulation using PERCHit,[15] of the five-membered ring as the observed differences in the $^3J_{H,H}$ values between **6** and **5** might originate from conformational changes occurring only in the flexible pyrrolidine ring and/ or from changes arising from the ring and nitrogen inversions described in Scheme 3. Since the observed large coupling between H-4a and H-4β indicates either a *trans* or a *cis* N-out conformation, this was not disconcerting. Again, but of significantly greater magnitude, a determinative NOE was again observed between H-4β and H-7β. The coupling of 4.4 Hz between H-4β and C-16/20 indicates that the C-4 phenyl group is orientated at an oblique angle to the oxadiazine ring (an orthogonal orientation would yield a coupling of 5.6 Hz[16]), and the NOEs further indicates that the rotation is in a clockwise-manner from the perspective of viewing the rotation of the phenyl group from the position of C-4.

In ^{1}H NMR low-temperature experiments, the signal resonance of H-4 revealed a clear change in the chemical shift (upfield by 0.50 ppm), while the signals of H-7α and H-7β displayed minor shifts of 0.1 and -0.1 ppm, respectively. No other changes were observed. In the corresponding ^{13}C NMR spectral experiments, a conformational equilibrium was clearly in effect in **6** as all the carbon signals were clearly approaching coalescence at -100 °C. Although the current results are insufficient for an unequivocal determination of the minor conformer, presumably it is the *trans* conformer as this would maintain the C-4α phenyl group in an equatorial orientation. In the solid state, **6** was shown to adopt a *trans* conformation (Figure 3, selected bonding parameters are given in Table 6) in contrast to the preferred *cis* N-out conformation in solution. This divergent behaviour is considered to be quite unusual.

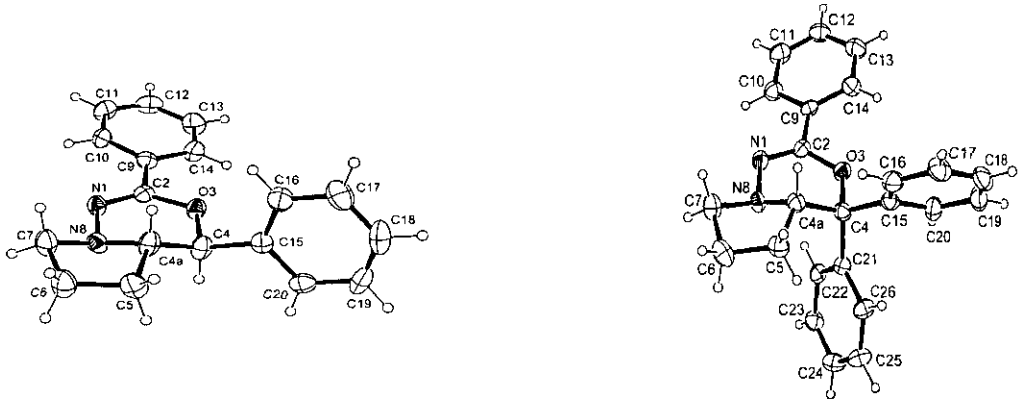


Figure 3. Molecular structures of (4a*S*,4*S*)-2-phenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine (**6**) (left) and the corresponding (4a*S*)-2,4,4-triphenyl (**8**) (right) substituted derivative.

The differences in the NMR data of (4*R*,4a*S*)-2,4-diphenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazine (**7**) (Tables 1 and 2) from those of **6** imply an altered conformational preference for **7**. Whether the preferred conformation is *cis* N-in or *trans* is not immediately evident. The downfield shift of the H-4a signal (δ = 3.28 ppm) suggests that **7** adopts a *cis* conformation. The origin of the considerable downfield shift of the H-4 signal (δ = 5.75 ppm) is difficult to rationalise, though adoption of the *cis* N-in conformation leads to an increased van der Waals repulsion between H-4a and H-4α and this could account for the observed deshielding of H-4α. The relatively large increase in $\Delta\delta$ H-7α,H-7β (0.50 ppm) suggests a non-biased equilibrium with equal proportions of the *trans*- and *cis*-fused conformers. However, the value of $\Delta\delta$ H-7α,H-7β in 1-methyl-2-phenylimino-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]-oxadiazine (**9**) (shown to adopt an anancomeric *cis* N-in conformation[17]) is 0.67 ppm and consequently a large $\Delta\delta$ H-7α,H-7β does not necessarily reflect a marked increase in the proportion of the *trans* conformer in these compounds. The most striking feature in the ^{13}C NMR spectrum is the considerable upfield shift of the C-5 signal. This upfield shift probably results from an anisotropic effect caused by the 4-phenyl substituent, which is possible only if **7** adopts the *cis* N-in conformation. The existence of the anisotropic effect is also evident from the upfield shifts of the C-5 methylene protons (1.60 and 1.33 ppm). From the foregoing observations, **7** is therefore expected to adopt a predominately *cis* N-in conformation. The coupling of 4.0 Hz between H-4β and C-16/20 indicates that the C-4 phenyl group is also orientated at an oblique angle to the oxadiazine ring. NOE experiments also indicated the rotation to be in a clockwise-manner.

In the range +25 to -100 °C, the ^{1}H spectral resonances of **7** remained essentially unchanged, though an increase in line broadening was detected. In the ^{13}C NMR spectrum at -100 °C only the signals for C-4 and C-4a had passed through coalescence, with the remaining signals approaching coalescence. Unfortunately, the minor set of signals for C-4 and C-4a after coalescence were not yet observable at -100 °C. The identity of the minor conformation is unclear and it could be either the *trans* or the *cis* N-out conformation. Unfortunately, viable crystals of **7** were not forthcoming to permit an X-Ray analysis.

Low-temperature ^{1}H and ^{13}C NMR experiments on 2,4,4-triphenyl-4*H*-4a,5,6,7- tetrahydro-pyrrolo[1,2-*d*][1,3,4]oxadiazine (**8**) revealed two relatively well-separated sets of signals at temperatures below -80 °C as the conformer interconversion became slow on the NMR time-scale. From the signal integrals of the well separated H-4 and C-7 methylene protons, the ratio of the interconverting conformers was determined as 7:3. The essential ^{1}H signals of the interconverting conformers were assigned by 2-D exchange spectroscopy. By comparison of

the NMR data to that for **5-7**, the presence of the *trans conformer* in solution might be excluded. This would, unusually, again be in contrast to the preferred *trans* conformation found in the solid state by X-Ray analysis (Figure 3, selected bonding parameters are given in Table 6). Evidence to support the major conformer as *cis* N-in is the upfield shift of the C-5 signal. By adopting this conformation, C-5 lies within the shielding space emanating from the equatorial 4β-phenyl substituent with a perpendicular orientation towards the oxadiazine ring. Moreover, it is most probable that the geminal phenyl groups are perpendicularly orientated towards each other, and consequently the axial 4α-phenyl group is orthogonal to the oxadiazine ring.[4] This orientation explains the downfield shift of H-4a (δ = 4.25 ppm) as it falls within the deshielding space of the axial 4α-phenyl group. NOE data also support the assignment of the major conformer as *cis* N-in, most notably the strong NOE between H-4a and H-47α. The minor conformer was confirmed as the *cis* N-out conformation on the basis of the markedly upfield shift of C-6 (19.8 ppm). The only plausible explanation for the upfield shift of the C-6 signal in the minor conformer is the shielding effect from the 4β-phenyl group. This type of interaction is possible only in the *cis* N-out conformation, and no other interactions present in the two other conformations are expected to cause such a strong shielding on C-6. Moreover, consistent with this assertion, H-7α in the minor conformer is also shifted upfield (2.91 ppm) in comparison with the corresponding shifts in **5-7**. Even more remarkably, one of the minor hydrogens on C-5 or C-6, and unfortunately its identity could not been confirmed but more than likely it is H-6β, was shifted to 2.4 ppm and the prevailing argument again applies.

The differences in the ^{15}N chemical shifts of the bridgehead nitrogens for **5-8** were marginal (Table 1), though expected and consonant with results of Crabb and Takeushi.[5b] Consequently, the small differences make the utilisation of ^{15}N NMR for determination of the conformational equilibrium in 5/6-fused systems less attractive.

Table 1. Selected ^{1}H and ^{15}N chemical shifts (in ppm) for tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazines (**5-9**).

				δ (H)						δ (N)
Compd.	**T/K**	**solvent**	***cis/trans***	**H-4β**	**H-4α**	**H-4a**	**H-7β**	**H-7α**	**Δ7α,7β**	**N8**
5	298	$CDCl_3$	*cis* N-out	3.81	4.51	3.16	3.29	3.27	0.02	-297.9
6	298	$CDCl_3$	*cis* N-out	4.66	-	3.03	3.37	3.40	0.03	-295.4
7	298	$CDCl_3$	*cis* N-in	-	5.75	3.28	3.60	3.05	0.55	-293.4
8	298	$CDCl_3$	7:3	-	-	3.75	3.63	3.13	0.50	-292.0
8 major	173	CD_2Cl_2	*cis* N-in	-	-	4.42	3.50	3.25	0.25	-
8 minor	173	CD_2Cl_2	*cis* N-out	-	-	3.25	3.57	2.91	0.66	-
9[a]	298	$CDCl_3$	*cis* N-in	3.91	4.10	3.78	3.38[b]	2.71[b]	0.67	-

[a]See reference 17, [b]may be interchanged.

Table 2. Selected ^{13}C chemical shifts (in ppm) for tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazines (**5-9**).

Compd.	T/K	solvent	*cis*/*trans*	C-4	C-4a	C-7	C-5	C-6
5	298	$CDCl_3$	*cis* N-out	68.1	55.1	54.1	26.3	21.4
6	298	$CDCl_3$	*cis* N-out	80.0	61.7	54.1	26.7	20.8
7	298	$CDCl_3$	*cis* N-in	78.4	59.8	54.5	22.8	21.3
8	298	CD_2Cl_2	7:3	84.5	63.1	55.3	25.0	22.1
8 major	173	CD_2Cl_2	*cis* N-in	80.4	62.8	56.7	23.5	23.0
8 minor	173	CD_2Cl_2	*cis* N-out	89.2	61.7	52.9	25.6	19.8
9	298	$CDCl_3$	*cis* N-in	68.0	57.8	52.0	28.2	22.0

Table 3. Selected H,H coupling constants (in Hz) for tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazines (**5-9**), calculated using PERCHit (^1H NMR simulation).[15]

Compd.	*cis*/*trans*	4β,4a	4α,4a	4a,5β	4a,5α	7α,7β
5	*cis* N-out	8.9	3.8	9.2	7.0	-9.3
6	*cis* N-out	8.3	-	9.2	6.8	-9.1
7	*cis* N-in	-	3.6	10.7	6.9	-10.4
8	N-in/N-out	-	-	10.2	7.3	-10.6
9	*cis* N-in	3.1	4.7	7.7[a]	6.8[a]	-8.6

[a]may be interchanged.

Table 4. Selected vicinal H,C coupling constants (in Hz) for tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazines (**5-8**) in $CDCl_3$ at 298 K.

Compd.	*cis*/*trans*	H5β,C4	H5α,C4	H4β,C5	H4α,C5	H4a, C15	H4β,C2	H4α,C2	H4, C16/20
5	*cis* N-out	6.9	1.5	2.2	0	-	1.1	5.2	-
6	*cis* N-out	5.8	0	2.0	-	2.0	0	-	4.4
7	*cis* N-in	3.8	0	-	2.5	1.5	-	3.0	4.0
8	3:1	4.6	0	-	-	a	-	-	-

a, couplings not measured, couplings indicated to be zero are approximate.

CONCLUSIONS

The flexibility of the five-membered ring in **5-8** allows conformational changes to occur in the pyrrolidine ring independently of any conformational changes in the oxadiazine ring. Thus, the vicinal coupling constants do not reliably describe the possible three-component equilibrium in **5-8** arising from ring and nitrogen inversion. The applicability of $\Delta\delta$ H7α,H7β, δ H-4a, and δ N8 as conformational indicators in related compounds is strongly dependent on the well-defined,

trans-diaxial relationship between the lone pair and the adjacent C-H antibonding orbital. Obviously, this specific spatial arrangement is not well defined in **5-8**, hence reducing the usefulness of the afore-mentioned parameters. Additionally, in certain conformations in **5-8** there is a possibility for delocalisation of the N8 lone pair into the conjugated system consisting of the N1-C(2)Ph-O1 segment. This delocalisation can apparently also affect the above-mentioned parameters and further erode their usefulness. The most frequently applied parameter for estimation of the equilibrium in bicyclic bridgehead-nitrogen-containing compounds is the $^{2}J_{H\text{-}7\alpha,H\text{-}7\beta}$ value.[2,14] However, as in previous work on quinolizidine-related structures,[4] we did not detect any correlation between the adopted stereochemistry and the geminal H,H coupling constants of the methylenes adjacent to the bridghead nitrogen in **5-8**. Similar conclusions can be drawn from the work of Cahill *et al.*[18] In the application of $\Delta\delta$ H-7α,H-7β and the $^{2}J_{H\text{-}7\alpha,H\text{-}7\beta}$ value, the similar geometries in the *trans* and *cis* N-out forms, *i.e.* the parallel arrangement of the lone pair and the adjacent C-H_{ax} bond, mean that these two conformers can not be distinguished by these parameters. Furthermore, this specific geometrical relationship can change within both conformations due to flexibility of the pyrrolidine ring.

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. NMR spectra were obtained on JEOL JNM-L-400 and JNM-A-500 instruments and the experimental conditions were essentially the same as those reported in ref. 19. The chemical shifts (δ) given in ppm are referred to internal tetramethylsilane for ^{1}H and ^{13}C (both 0 ppm) and to external dimethylformamide for ^{15}N (-298 ppm). The H,H coupling constants given for **5-8** were calculated with the PERCHit program.[15] The elemental analyses were performed on a Perkin Elmer Analysator 2400 C, H, N, S / O.

1-Amino-2-hydroxymethylpyrrolidine (**1**) and 2-phenyl-4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*]-[1,3,4]oxadiazine (**5**) were prepared according to earlier reported methods.[6] The preparation of hydrazino alcohols (**2-4**)[4,7,20] and their transformation into the corresponding 4*H*-4a,5,6,7-tetrahydropyrrolo[1,2-*d*][1,3,4]oxadiazines (**6-8**) followed previously reported methodology.[4,6]

All the ring-closed compounds (**6-8**) were purified by column chromatography using ethyl acetate:petroleum ether (15:85) as eluent. For X-Ray analysis the compounds were further recrystallised from appropriate solvents.

(2S,1'S)-*1-Amino-2-(1'-phenyl)pyrrolidinemethanol* (**2**). Yield 18%, (oil). ^{1}H NMR: 7.54-7.30 (m, 5H, Ar), 6.00 (br s, 1H), 4.72 (d, J = 8.3 Hz, H-1'), 3.60-3.05 (m, 3H), 2.10 (m, 1H), 2.00-1.75 (m, 2H), 1.50 (m, 1H). ^{13}C NMR 141.5, 128.1, 127.5, 127.0, 80.3, 70.7, 62.3, 26.1 and 20.2.

(2S,1'R)-*1-Amino-2-(1'-phenyl)pyrrolidinemethanol* (**3**). Yield 30%, (oil). ^{1}H NMR: 7.65-7.36 (m, 5H, Ar), 5.24 (d, J = 2.9 Hz, H-1'), 3.90-3.35 (m, 4H), 2.80 (m, 1H), 2.60 (m, 1H), 2.00-1.75 (m, 3H), 1.60 (m, 1H). ^{13}C NMR: 141.8, 128.1, 127.0, 126.0, 73.4, 70.8, 61.2, 22.1 and 21.0.

(2S)-*1-Amino-2-(1',1'-diphenyl)pyrrolidinemethanol* (**4**). Recrystallised from ether/methanol (35%), mp 210-212 °C . ^{1}H NMR: 7.61 (m, 2H, Ar), 7.51 (m, 2H, Ar), 7.33-7.25 (m, 4H, Ar), 7.20-7.13 (m, 2H, Ar), 4.81 (br s,1H), 3.55 (dd, 1H, J = 5.5 and 9.8 Hz), 3.28 (m, 1H), 2.60 (m, 1H), 2.42 (br s, 2H), 2.01 (m, 1H), 1.75-1.60 (m, 3H). ^{13}C NMR: 147.5, 145.7, 128.3, 128.0, 126.6, 126.5, 125.9, 125.7, 77.9, 76.4, 60.2, 28.0 and 22.0. *Anal.* Calcd for $C_{17}H_{20}N_2O$: C, 76.14; H, 7.53; N, 10.45. Found: C, 76.05; H, 7.58; N, 10.41.

(4S,4aS)-*2,4-Diphenyl-4H-4a,5,6,7-tetrahydropyrrolo[1,2-d][1,3,4]oxadiazine* (**6**). Compound (**6**) (least polar, R_f = 0.8, toluene-methanol = 4:1) was recrystallised from petroleum ether affording colourless crystals (51%), mp 127-129 °C. ^{1}H NMR: 7.88-7.83 (m, 2H, Ar), 7.44-7.31 (m, 8H, Ar), 4.66 (d, J = 8.3 Hz, H-4β), 3.40 (m, J = 0.4, 4.8, 8.1 and -9.1 Hz, H-7α), 3.37 (m, J = 7.1, 7.2 and -9.1 Hz, H-7β), 3.03 (m, J = 0.1, 6.8, 8.3 and 9.2 Hz, H-4a), 1.90 (m, J = 2.2, 4.8, 7.1, 9.2 and -12.4 Hz, H-6β), 1.83 (m, J = 0.4, 2.2, 6.8, 8.3 and -12.9 Hz, H-5α), 1.83 (m, J = 7.1, 8.1, 8.3, 9.7 and -12.4 Hz, H-6α), 1.68 (m, J = 9.2, 9.2, 9.7 and -12.9 Hz, H-5β). ^{13}C NMR: 147.4 (C-2), 137.8 (C-15), 132.5 (C-9), 129.0, 128.7, 128.6, 128.1, 126.8 (C-16,20), 125.4, 80.0 (C-4), 61.7 (C-4a), 54.1 (C-7), 26.7 (C-5), 20.8 (C-6). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.72; H, 6.54; N, 10.07. Found: C, 77.61; H, 6.57; N, 10.00.

(4R,4aS)-*2,4-Diphenyl-4H-4a,5,6,7-tetrahydropyrrolo[1,2-d][1,3,4]oxadiazine* (**7**). Compound (**7**) (least polar, R_f = 0.8, toluene-methanol = 4:1) was obtained as a solid (recrystallised from petroleum ether) (48%), mp 115-117 °C. ^{1}H NMR: 7.93-7.84 (m, 2H, Ar), 7.40-7.30 (m, 8H, Ar), 5.75 (d, J = 3.6 Hz, H-4α), 3.60 (ddd, J = 2.8, 8.5 and -10.4 Hz, H-7β), 3.28 (ddd, J = 3.6, 6.9 and 10.7 Hz, H-4a), 3.05 (dt, J = 8.8, 9.0 and -10.4 Hz, H-7α), 1.77 (m, J = 2.8, 7.4, 8.8, 13.0 and -13.0 Hz, H-6β), 1.73 (m, J = 3.0, 6.6, 8.5, 9.0 and -13.0 Hz, H-6α), 1.60 (m, J = 3.0, 6.9, 7.4 and -11.1 Hz, H-5α), 1.33 (m, J = 6.6, 10.7, 13.0 and -11.1 Hz, H-5β). ^{13}C NMR: 147.5 (C-2), 137.8 (C-15), 132.5 (C-9), 129.0, 128.7, 128.6, 128.1, 126.8 (C-16,20), 125.4, 78.4 (C-4), 59.8 (C-4a), 54.5 (C-7), 22.8 (C-5), 21.3 (C-6). *Anal.* Calcd for $C_{18}H_{18}N_2O$: C, 77.72; H, 6.54; N, 10.07. Found: C, 77.65; H, 6.64; N, 9.97.

(4aS)-*2,4,4-Triphenyl-4H-4a,5,6,7-tetrahydropyrrolo[1,2-d][1,3,4]oxadiazine* (**8**). Compound (**8**) (most nonpolar, R_f = 0.85, toluene-methanol = 4:1) was recrystallised from petroleum ether (with a few drops of diethyl ether), affording colourless crystals (26%), mp 133-135 °C. ^{1}H NMR: 7.98-7.94 (m, 2H, Ar), 7.57-7.54 (m, 2H, Ar), 7.40-7.22 (m, 11H, Ar), 3.75 (dd, J = 7.3 and 10.2 Hz, H-4a), 3.63 (ddd, J = 2.2, 8.4 and -10.6 Hz, H-7β), 3.13 (ddd, J = 8.8, 9.2 and -10.6 Hz, H-7α), 1.84 (m, J = 4.7, 7.3, 9.7 and 12.9 Hz, H-5α), 1.77 (m, J = 4.7, 8.4, 9.2, 11.6 and -13.0 Hz, H-6α), 1.76 (m, J = 2.1, 5.8, 8.8, 9.7 and -13.0 Hz, H-6β), 1.66 (m, J = 5.8, 10.2, 11.6 and -12.9 Hz, H-5β). ^{13}C NMR: 145.9, 143.9, 142.6, 132.6, 129.1, 128.3, 128.1, 127.8, 127.3, 126.6, 126.5, 125.5, 84.4 (C-4), 62.6 (C-4a), 54.8 (C-7), 24.8 (C-5), 21.6 (C-6). *Anal.* Calcd for $C_{24}H_{22}N_2O$: C, 81.38; H, 6.27; N, 7.91. *Found*: C, 81.08; H, 6.46; N, 7.65.

X-RAY CRYSTALLOGRAPHY

Experimental details of the structure determinations of **6** and **8** are presented in Table 5. Crystals of **6** and **8** were obtained from petroleum ether as colorless plates and bright prisms, respectively. Data collection was performed on a Rigaku AFC5S X-Ray diffractometer with graphite monochromated MoK$_\alpha$ (radiation λ = 0.71069 Å). Data were corrected for Lorentz and polarization effects. The crystals underwent no decomposition during data collection.

The structures were solved by direct methods (SIR92),[21] expanded using Fourier techniques[22] 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 factor (1.2 × that of the host atom). All the calculations were carried out on the teXsan crystallographic software package from Molecular Structure Corporation.[23]

Table 5. Experimental X-Ray details.

	6	**8**		**6**	**8**
Formula	$C_{18}H_{18}N_2O$	$C_{24}H_{22}N_2O$	Data collection		
Formula weight	278.35	354.45	$2\theta_{max}$ / °	50	50
Crystal system	orthorhombic	orthorhombic	Scan mode	ω-2θ	ω-2θ
Space group	$P2_12_12_1$ (#19)	$P2_12_12_1$ (#19)	Scan speed (°/min)	8.0	4.0
a / Å	10.909(2)	9.576(2)	Scan width (°)	1.42 + 0.30 tan θ	1.26 + 0.30 tan θ
b / Å	16.110(2)	21.958(3)	Reflections collected	1558	1974
c / Å	8.552(1)	9.091(2)	Observed reflections	1048 (I>2.00σ(I))	1353 (I>2.00σ(I))
Z	4	4	Number of variables	190	245
V / Å^3	1503.1(3)	1911.6(6)	R	0.048	0.040
F(000)	592.00	752.00	R_w	0.046	0.036
μ / cm^{-1}	0.77	0.76	Goodness-of-fit on F	1.58	1.29
D_c / g cm^{-3}	1.230	1.232	$(\Delta\rho)_{max}/(\Delta\rho)_{min}$	0.25 / -0.21	0.13 / -0.16
Crystal dimensions	0.22 x 0.32 x 0.34	0.22 x 0.32 x 0.36			

Table 6. Selected bond lengths, and bond and torsion angles for **5**, **6**, and **8**.

Bond lengths (Å)	**5**	**6**	**8**
O(3) - C(2)	1.360 (4)	1.358(5)	1.375(3)
O(3) - C(4)	1.448(4)	1.457(5)	1.486(4)
N(1) - N(8)	1.377(3)	1.407(4)	1.392(4)
N(1) - C(2)	1.276(3)	1.283(5)	1.283(4)
N(8) - C(7)	1.450(4)	1.456(5)	1.444(4)
N(8) - C(4a)	1.471(4)	1.458(6)	1.457(4)
C(4) - C(4a)	1.497(5)	1.492(6)	1.528(4)
C(4) - C(15)	-	1.500(6)	1.531(4)
C(4) - C(21)	-	-	1.531(4)
C(4a) - C(5)	1.511(5)	1.513(6)	1.549(4)

Bond angles (deg)	**5**	**6**	**8**
C(2) - O(3) - C(4)	112.0(2)	118.5(3)	119.6(2)
N(8) - N(1) - C(2)	119.3(2)	115.6(4)	114.4(3)
N(1) - N(8) - C(7)	115.6(2)	114.9(3)	115.9(2)
N(1) - N(8) - C(4a)	119.8(2)	115.3(3)	113.7(2)
C(7) - N(8) - C(4a)	110.2(3)	105.1(4)	107.2(2)
O(3) - C(2) - N(1)	124.7(3)	126.9(4)	126.5(3)
O(3) - C(2) - C(9)	114.3(2)	112.7(4)	112.5(3)
N(1) - C(2) - C(9)	121.0(3)	120.3(4)	121.0(3)
N(8) - C(4a) - C(5)	104.9(3)	102.1(4)	103.1(2)
N(8) - C(4a) - C(4)	108.2(3)	108.6(4)	107.3(2)
C(5) - C(4a) - C(4)	115.3(3)	121.6(4)	119.1(3)
O(3) - C(4) - C(4a)	108.3(3)	108.4(4)	105.9(2)
O(3) - C(4) - C(15)	-	108.0(4)	103.1(2)
O(3) - C(4) - C(21)	-	-	108.9(2)
C(4a) - C(4) - C(15)	-	114.3(4)	115.0(3)
C(4a) - C(4) - C(21)	-	-	110.8(2)

Torsion angles (deg)	**5**	**6**	**8**
O(3) - C(2) - N(1) - N(8)	9.2(5)	4.5(6)	0.3(4)
O(3) - C(4) - C(4a) - N(8)	54.0(4)	-55.0(5)	52.9(3)
N(1) - C(2) - O(3) - C(4)	23.6(5)	-6.2(6)	-7.8(4)
N(1) - N(8) - C(4a) - C(4)	-24.5(4)	57.9(5)	-65.9(3)
N(1) - N(8) - C(7) - C(6)	170.0(3)	170.7(4)	-172.8(2)
N(1) - N(8) - C(4a) - C(5)	-148.0(3)	-174.4(4)	167.5(2)
C(2) - N(1) - N(8) - C(4a)	-7.6(4)	-31.6(5)	37.7(3)
C(7) - N(8) - C(4a) - C(5)	-10.3(4)	-46.8(5)	38.1(3)
C(7) - N(8) - C(4a) - C(4)	113.2(3)	-174.5(4)	164.7(2)
C(5) - C(4a) - C(4) - C(15)	-	70.5(6)	-77.6(3)
C(5) - C(4a) - C(4) - C(21)	-	-	51.4(4)
C(2) - O(3) - C(4) - C(15)	-	155.2(3)	-141.7(2)
C(2) - O(3) - C(4) - C(21)	-	-	98.6(3)

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