SYNTHESIS AND CONFORMATIONAL BEHAVIOUR OF 2-PHENYLPERHYDROPYRROLO[1,2-*d*][1,3,4]OXADIAZINE AND 2-PHENYLPERHYDROPYRIDO[1,2-*d*][1,3,4]OXADIAZINE; NEW HETEROCYCLIC RING SYSTEMS

Ari Rosling[a], 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 [c]Department of Chemistry, University of Turku, FIN-20500, Turku, Finland

Abstract - Hydrazino alcohols, 1-amino-2-hydroxymethylpyrrolidine (**1**) and 1-amino-2-hydroxymethylpiperidine (**2**), were synthesized and subsequently ring closured with ethyl benzimidate to the title compounds (**7**) and (**8**), which have new ring systems. Variable-temperature ^{1}H nmr measurements, supported by X-ray analysis, indicated that pyrrolo-[1,2-*d*][1,3,4]oxadiazine (**7**) exists exclusively in a *cis*-fused conformation (in $CDCl_3$ at room temperature), whereas pyrido[1,2-*d*][1,3,4]oxadiazine (**8**) adopts a *trans*-fused conformation.

INTRODUCTION

The extensive studies on 1,3-amino alcohols are explained by their importance in synthetic and structural chemistry and in drug research.[1a-c] We report the synthesis of the alicyclic hydrazino alcohols, formally 1,3-amino alcohols, 1-amino-2-hydroxymethylpyrrolidine **1** and 1-amino-2-hydroxymethylpiperidine **2** and their transformation into two new bicyclic 1,3,4-*(O,N,N)*-heterocycles. The major difference in the heterocyclic systems formed from **1** and **2** as compared with carbocycle-fused ring systems studied earlier is their bridgehead nitrogen.

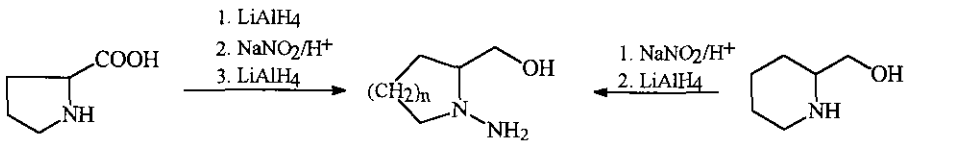
Several conformational studies on saturated bicyclic compounds with a bridgehead nitrogen and a 1,3-ar-

rangement of heteroatoms have been published by Crabb *et al.*[2] Most of the studied compounds were reported to exist as equilibrium mixtures of *trans*- and *cis*-fused conformers interconvertible by nitrogen inversion

RESULTS AND DISCUSSION

Synthesis

Hydrazino alcohols (**1**) and (**2**) were prepared from L-proline and (±)-2-hydroxymethylpiperidine, respectively (Scheme 1). The synthesis of **1** is mentioned in the literature but without any spectral data.[3,4] L-Proline was treated with $LiAlH_4$, followed by nitrosation ($NaNO_2$/AcOH) and a second reduction. (±)-2-Hydroxymethylpiperidine was treated similarly. The overall yields were satisfactory (50-80%).



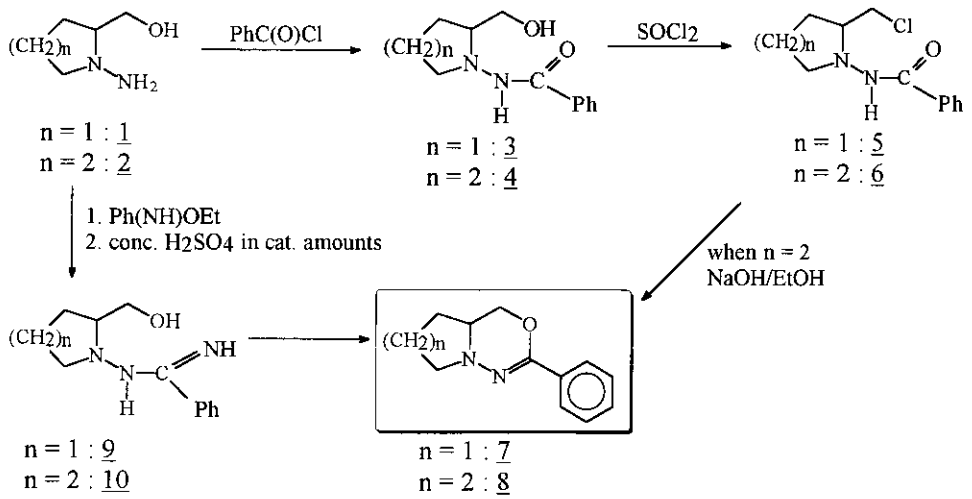
L-proline

n = 1 : 1
n = 2 : 2

2-Hydroxymethylpiperidine

Scheme 1

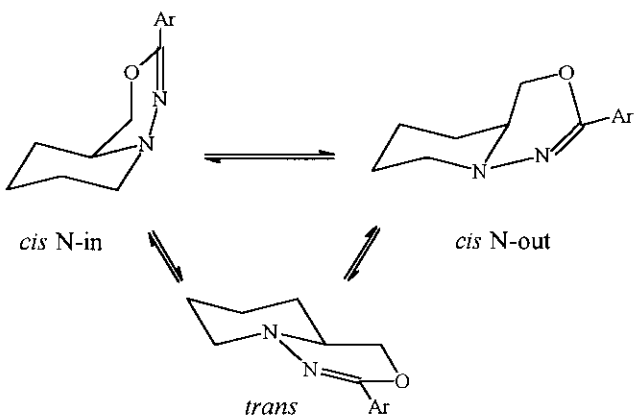
The *N*-benzoyl derivatives (**3**) and (**4**) were prepared from hydrazino alcohols (**1**) and (**2**), in good yields by the Schotten-Baumann procedure under slightly basic conditions (Scheme 2). However, if strong basic conditions were used, mainly a diacylated product was formed. The ring closure of acylamino cyclanols with thionyl chloride is a well-known reaction, reported to give excellent yields.[5a-c] However, in our case this cyclization reaction did not yield the desired products. At ambient temperature, only the 2-chloromethyl derivatives (**5**) and (**6**) were formed. On lowering of the reaction temperature, chlorination should have been avoided,[6] but in our case this led only to recovery of the starting material. There was no difference in the outcome of the reaction regardless if it was performed with or without solvent. The ring closure of **1** and **2** with ethyl benzimidate, using conc. H_2SO_4 in catalytic amounts (Scheme 2) was a convenient one-pot reaction giving the oxadiazines (**7**) and (**8**) in moderate yields.[7] The ring-closed products were formed *via* the amidine intermediates (**9**) and (**10**), which also were isolated. The chloro derivative (**6**) was cyclized by treatment with hot ethanolic sodium hydroxide solution.[8] We were not able to cyclize the corresponding chloro analogue (**5**).



Scheme 2

Conformational analysis

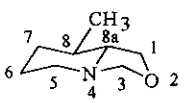
The bicyclic nitrogen bridgehead ring systems (**7**) and (**8**) have, in principle, the possibility to exist in a *cis*-fused and/or a *trans*-fused conformation due to the conformationally mobile nitrogen in the bridge (Scheme 3). Furthermore, the *cis* isomer has, through ring inversion, two possible ring conformers, *N*-in and *N*-out. The position of the conformational equilibrium in related systems[9,10] (**11, 12** and **13**), has mainly been estimated on the basis of some specific ^{1}H and ^{13}C nmr parameters and by further comparing these values with those obtained from similar, stereochemically locked model compounds. The $\Delta\delta$ ae value for the C-5 methylene protons is near 1 ppm for *trans*-fused systems, while it is reported to be close to zero in the *cis*-fused derivatives. The δH-8a is shifted by 1-1.5 ppm, depending on whether the proton is oriented *trans* or *cis* with respect to the lone pair of the bridged nitrogen.[11] Most of the compounds studied by Crabb *et al.* were found to exist as equilibrium mixtures of the *cis* and *trans* conformers in solution at room temperature. The *trans*-fused conformer predominated in most compounds, independent of type of the ring fusion (ie. 5/6 or 6/6) . The



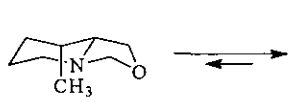
Scheme 3

nmr spectra of 7 and **8** strongly indicate that the former 5/6 fused compound (Table 1) solely exists in a *cis*-fused conformation, whereas the latter 6/6 fused analoque (Table 2) adopts a pure *trans* conformation. The X-ray crystallographic structures of 7 (Figure 1) and **8** (Figure 2) confirmed our interpretations concerning the character of the ring fusions. Selected bond distances and angles for 7 and **8** are presented in Table 3 and 4 respectively. The ^{1}H nmr data are in accordance with the obtained molecular structures.

Table 1. Selected ^{1}H nmr chemical shifts of 2-phenylpyrrolo[1,2-*d*][1,3,4]oxadiazine (7)[a] and *cis*-(8H, 8aH)- (**11**) and *trans*-(8H,8aH)-8-methylperhydrooxazolo[3,4-*a*]pyridine (**12**).



trans- **11** (100%)



trans- **12** (15%) *cis*- **12** (85%)

compd	T (K)	solvent	H-$8_{eq.}$	H-$8_{ax.}$	H-8a or H-7a	H-$5_{eq.}$	H-$5_{ax.}$	J(5eq,5ax)	$\Delta 5_{eq.}$, $5_{ax.}$
7	300	CD_2Cl_2	4.52	3.82	3.15	3.25	3.25	-9.5	0
	188	CD_2Cl_2	4.45	3.55	3.22	3.30	3.01		0.29
11[b]	293	CCl_4			1.89	2.98	2.02	-10.8	0.96
12[b]	293	CCl_4			3.22	2.66	2.56	-11.0	0.1

a, For numbering system, see crystal structure

b, Ref. 9

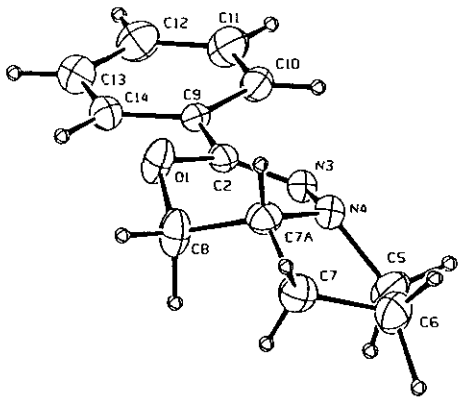
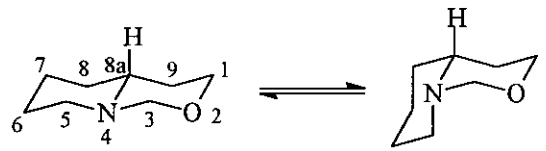


Figure 1. ORTEP plot and labeling scheme for 7. Thermal ellipsoids are shown at 30% probability levels, except for those of the H atoms, which are drawn with an isotropic displacement factor of 1.0.

Table 2. Selected ^{1}H nmr chemical shifts of 2-phenylpyrido[1,2-*d*][1,3,4]oxadiazine (**8**)[a] and perhydropyrido[1, 2-*c*][1,3]oxazine (**13**)



trans-**13** (98%) *cis*-**13** (2%)

compd.	T (K)	solvent	H-9$_{eq.}$	H-9$_{ax.}$	H-8a	H-5$_{eq.}$	H-5$_{ax.}$	J(5eq.,ax.)	$\Delta\delta_{eq.,ax.}$
8	293	CD_2Cl_2	4.28	4.11	2.53	3.44	2.55	-11.4	0.89
	188	CD_2Cl_2	4.25	4.07	2.48	3.35	2.48		0.87
13[b]	293	CCl_4			2.07	2.72	1.96	-10.6	0.78

a, For numbering system, see crystal structure

b, Ref. 10

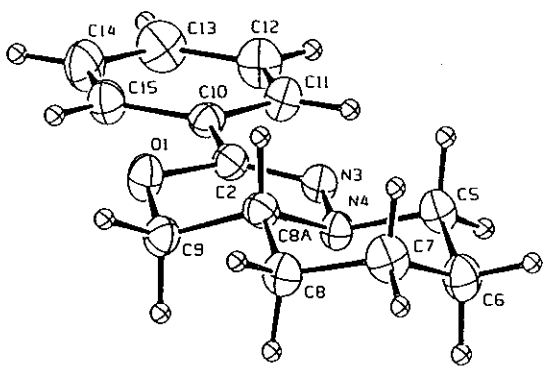


Figure 2. ORTEP plot and labeling scheme for **8**. Thermal ellipsoids are shown at 20% probability levels, except for those of the H atoms, which are drawn with an isotropic displacement factor of 1.0.

When variable-temperature nmr measurements were performed from 60 °C to -95 °C on the *trans*-fused oxadiazine (**8**), no changes were observed in the spectra. Stereochemically similar compounds show clear signs of coalescence already at -50 °C.[12] This fact does indeed, support our hypothesis that **8** exists exclusively in a *trans*-fused conformation. With the *cis*-fused oxadiazine (7), we observed some minor ^{1}H chemical shift variations as a function of temperature. The C-5-H$_{ax.}$ and the C-8-H$_{ax.}$ signals were shifted 0.24 ppm and 0.27 ppm upfield at -95 °C. These shift variations originate from the *N*-in, *N*-out ring inversion, though we can not yet completely exclude the existence of a *cis-trans* conformational equilibrium via inversion at the bridge nitrogen.

It is interesting that the Gibbs standard free energy difference favours the *trans* isomer by 1.3 kJ mol^{-1} in the hydrindanes and by about 10.3 kJ mol^{-1} in the decalins.[13] This is in contrast with the stability results found for the 1,3-hetero analogues of *cis* and *trans*-hydrindane, where the *cis* derivatives are more stable.[14,15] Our results are in good agreement with those obtained for the 1,3-hetero analogues[14,15] of hydrindane without a bridgehead nitrogen.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Nmr spectra were obtained on JEOL JNM-L-400 and JNM-A-500 instruments. The chemical shifts (δ) given in ppm are referred to tetramethylsilane. $CDCl_3$ was used as solvent unless otherwise stated. The coupling constants given for **7** and **8** are calculated by the iterative Perch program.[16] The elemental analyses were performed on a Perkin Elmer Analysator 2400 C, H, N, S / O and the high resolution mass spectra were obtained on a VG-7070E spectrometer. The specific rotations were measured on a Jasco DIP-360 digital polarimeter.

1-Amino-2-hydroxymethylpyrrolidine (1). L-Proline, 17.3 g (0.15 mol), was added in small portions to a suspension of 8.5 g (0.22 mol, 1.75 eqv.) of $LiAlH_4$ in 400 ml of dry THF and the mixture was refluxed for 6 h. The excess $LiAlH_4$ was decomposed by slowly adding 30 ml of H_2O to the ice-cold reaction mixture, which was then refluxed for 30 min. The precipitate was filtered off with suction, dissolved in 100 ml of hot THF and filtered again. The filtrates were combined, dried over Na_2SO_4 and evaporated. The oily residue was distilled in vacuo to yield a colourless oil, 2-hydroxymethylpyrrolidine, 10.02 g (66%), bp_7 83-85 °C.

2-Hydroxymethylpyrrolidine, 10.02 g (0.099 mol), was stirred in 25 ml of H_2O. 13.6 g (0.2 mol, 2 eqv.) of $NaNO_2$ dissolved in 40 ml of H_2O was added. The solution was placed in an icebath and 8.6 ml (0.15 mol, 1.5 eqv.) of glacial acetic acid was slowly added through a dropping funnel. After 30 min the icebath was removed and the solution was stirred at ambient temperature for 5 h. The solution was basified with Na_2CO_3(s) and extracted with ethyl acetate (3 x 50 ml). The organic phase was dried over Na_2SO_4 and evaporated to give 11.9 g (91%) of *N*-nitroso-2-hydroxymethylpyrrolidine as a yellowish oil. Without further purification the nitroso adduct was treated with $LiAlH_4$ in the same manner as described above (the refluxing time was reduced to 3 h) to yield 1-amino-2-hydroxymethylpyrrolidine (**1**), as a colourless oil 7.9 g, bp_3 92-96 °C, (46% overall). $[\alpha]^{25}_D$ = -55° (c 5.0, MeOH). ^{1}H Nmr: 3.78 (dd, J = 2.8 and 10.8 Hz, H′-6), 3.63 (dd, J = 7.2 and 10.8 Hz, H′′-6), 3.28 (m, 1H, H-2), 2.53 (m, 1H, H′-5), 2.31 (m, 1H, H′′-5), 1.86-1.74 (m, 3H), 1.45 (m, 1H). ^{13}C Nmr: 68.1, 67.1, 61.9, 24.8, 21.1. *Anal.* Calcd for $C_5H_{12}N_2O$: C,

51.70; H, 10.41; N, 24.12. Found: C, 51.38; H, 10.58; N, 23.10. HRms *m/z* calcd for $C_5H_{12}N_2O$: 116.0950; found: 116.0949.

1-Amino-2-hydroxymethylpiperidine (2). 1-Amino-2-hydroxymethylpiperidine (**2**) was prepared similarly as above, from 2-hydroxymethylpiperidine, without the first reduction in 75% overall yield, bp_4 105-108 °C. ^{1}H Nmr: 5.50 (br s, 2H, NH_2), 3.68 (dd, J = 8.1 and 11.4 Hz, H′-7), 3.51 (dd, J = 1.7 and 11.4 Hz, H′′-7), 3.04 (dm, J = 10.4 Hz, H′-6), 2.24-2.16 (m, 2H, H-2 and H′′-6), 1.71-1.48 (m, 4H), 1.21 (ddddd, 1H, J = 3.8, 3.8, 12.9, 12.9 and 12.9 Hz), 1.12 (m, 1H). ^{13}C Nmr: 69.5 (C-7), 64.2 (C-2), 63.5 (C-6), 28.5 (C-3), 25.6 (C-5), 23.4 (C-4). *Anal.* Calcd for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found: C, 55.24; H, 10.98; N, 20.74. HRms *m/z* calcd for $C_6H_{14}N_2O$: 130.1106; found: 130.1110.

1-Benzoylamino-2-hydroxymethylpyrrolidine (3). Hydrazino alcohol (**1**) (1.6 g, 14 mmol) was dissolved in 20 ml of benzene and stirred with benzoyl chloride (1.92 ml, 15.4 mmol) under Schotten-Baumann acylation conditions, using 10 ml (24.5 mmol) of 20% $NaHCO_3$. After 1.5 h, the precipitate was filtered and recrystallized from EtOAc to yield **3**, 2.3 g (73%), mp 185-187 °C. $[\alpha]^{25}_D$ = -26° (c 1.9, MeOH). ^{1}H Nmr: 7.76 (m, 2H, *o*-H), 7.53 (m, J = 1.3, 1.3, 6.6 and 6.6 Hz, *p*-H), 7.44 (m, 2H, *m*-H), 7.10 (br s, 1H, NH), 4.10 (br s, 1H, OH), 3.65 (dd, J = 3.0 and 12.1 Hz, H′-6), 3.53-3.43 (m, 2H, H′′-6 and H-2), 2.90-2.76 (m, 2H), 1.98-1.84 (m, 4H). ^{13}C Nmr: 167.6 (C=O), 133.0 (C′-1), 132,1 (C′-4), 128.8 (C′-3 and C′-5), 127.2 (C′-2 and C′-6), 68.3 (C-6), 61.6 (C-2), 56.3 (C-5), 25.1 (C-3), 21.6 (C-4).

1-Benzoylamino-2-hydroxymethylpiperidine (4). Hydrazino alcohol (**2**) (1.8 g, 16 mmol) was treated as above with benzoyl chloride (2.0 ml, 17 mmol) to yield 3.0 g (82%) of **4**, mp 153-156 °C. ^{1}H Nmr: 7.76 (m, 2H, *o*-H), 7.53 (m, J = 1.2, 1.2, 6.6 and 6.6 Hz, *p*-H), 7.43 (m, 2H, *m*-H), 7.08 (br s, 1H, NH), 4.10 (br s, 1H, OH), 3.76 (dd, J = 2.4 and 12.2 Hz, H′-7), 3.34-3.22 (m, 2H, H′′-7 and H-$6_{eq.}$), 2.65 (ddd, J = 3.4, 11.1 and 11.1 Hz, H-$6_{ax.}$), 2.32 (dm, J = 11.3 Hz, H-2), 2.00 (m, 1H, H′-3), 1.86-1.60 (m, 4H, H′′-3, H-$4_{eq.}$ and 5-CH_2), 1.32 (m, 1H, H-$4_{ax.}$). ^{13}C Nmr: 167.2, 132.9, 132.0, 128.7, 127.2, 66.5, 62.9, 57.2, 27.6, 25.2, 23.5.

1-Benzoylamino-2-chloromethylpyrrolidine (5). Attempts to cyclize the benzoylated product (**3**) (0.8 g, 3.6 mmol) with thionyl chloride (3.2 ml, 44 mmol) by methods described in references 5a-c gave only the chloro-substituted compound (**5**), (74%) mp 144-146 °C. ^{1}H Nmr: 7.74 (m, 2H, *o*-H), 7.52 (m, 1H, *p*-H), 7.43 (m, 2H, *m*-H), 7.23 (br s, 1H, NH), 3.66 (dd, J = 4.4 and 10.6 Hz, H′-6), 3.55 (dd, J = 6.9 and 10.6 Hz, 1H, H′′-6), 3.49 (m, 1H, H-2), 3.41 (m, 1H, H′-5), 3.15 (ddd, J = 8.6, 8.6 and 8.6 Hz, H′′-5), 2.22

(m, 1H, H′-3), 1.97-1.89 (m, 2H), 1.77 (m, 1H). ^{13}C Nmr: 166.7, 133.5, 131.7, 128.6, 126.9, 65.4, 55.2, 47.0, 27.9, 21.6.

1-Benzoylamino-2-chloromethylpiperidine (6). Compound (**4**) (0.35 g, 1.5 mmol) was treated as described above to yield a crystalline product (**6**), (60%), mp 158-160 °C. ^{1}H Nmr: 7.75 (m, 2H, *o*-H), 7.53 (m, 1H, *p*-H), 7.44 (m, 2H, *m*-H), 7.12 (br s, 1H, NH), 3.69 (dd, J = 3.1 and 11.4 Hz, H′-7), 3.59 (dd, J = 5.8 and 11.4 Hz, H′′-7), 3.26 (dm, J = 9.4 Hz, H-6eq.), 3.15 (m, 1H, H-2), 3.02 (m, 1H, H-$6_{ax.}$), 1.97 (dm, J = 13.1 Hz, H-$3_{eq.}$), 1.84-1.68 (m, 3H), 1.59 (m, 1H), 1.34 (m, 1H). ^{13}C Nmr: 166.7 (C=O), 133.6 (C′-1), 131.9 (C′-4), 128.8 (C′-3 and C′-5), 122.1 (C′-2 and C′-6), 64.2 (C-2), 55.6 (C-6), 46.8 (C-7), 29.7 (C-3), 25.5 (C-4), 23.5 (C-5).

A solution of **6** (0.17 g, 0.67 mmol) in EtOH (10 ml) was treated with NaOH (40 mg, 1 mmol) in 1 ml of EtOH as described by Leffler.[8] The refluxing time was increased to 15 min. Recrystallization from light petroleum ether (boiling range 40-60 °C) gave colourless crystals, 0.07 g (48%), mp 73-75 °C. The nmr data obtained were identical with those for **8**.

2-Phenylperhydropyrrolo[1,2-*d*][1,3,4]oxadiazine (7). Compound (7) was prepared from hydrazino alcohol (**1**) (0.5 g, 4.3 mmol) and ethyl benzimidate (0.75 g, 4.7 mmol) by using conc. H_2SO_4 in catalytic amounts as described by Bernáth *et al.*[7] The refluxing time was increased from 24 h to 50-60 h. The product (most nonpolar, R_f = 0.7, toluene-methanol = 4:1) was isolated by column chromatography (Merck Kieselgel 60, 230-400 mesh ASTM), using ethyl acetate:petroleum ether (15:85) as eluent. The product was recrystallized from n-hexane to give colourless crystals, 0.35 g (41%), mp 80-82 °C. From the same reaction mixture, the amidine intermediate (**9**) (most polar) was isolated as an oil, 0.3 g (32%) and identified by nmr.

Compound (**7**) . $[\alpha]^{25}_D$ = -340° (c 1.1, MeOH). ^{1}H Nmr: 7.89 (m, 2H, *m*-H), 7.34 (m, 3H, *p*-H and *o*-H), 4.53 (dd, J = 3.9 and 9.9 Hz, H-$8_{eq.}$), 3.82 (dd, J = 8.9 and 9.9 Hz, H-$8_{ax.}$), 3.29 (m, J = 5.1, 8.2 and 9.2 Hz, H′-5), 3.27 (m, J = 5.4, 7.9 and 9.2 Hz, H′′-5), 3.18 (m, J = 3.9, 7.2, 8.9 and 9.7 Hz, H-7a), 2.08 (m, J = 2.4, 7.2, 9.1 and 12.4 Hz, H′-7), 1.81 (m, J = 2.4, 5.1, 7.9, 9.0 and 12.9 Hz, H′-6), 1.77 (m, J = 5.4, 8.2, 8.7, 9.1 and 12.9 Hz, H′′-6), 1.55 (m, J = 8.7, 9.0, 9.7 and 12.4 Hz, H′′-7). ^{13}C Nmr: 146.6 (C-2), 132.7 (C′-1), 129.0 (C′-4), 128.2 (C′-3 and C′-5), 125.5 (C′-2 and C′-6), 68.1 (C-8), 55.1 (C-7a), 54.1 (C-5), 26.3 (C-7), 21.4 (C-6). *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.25; H, 6.95; N, 13.75.

Compound (**9**). $[\alpha]^{25}_D$ = +70° (c 4.8, MeOH). ^{1}H Nmr: 7.61 (m, 2H, *o*-H), 7.34-7.29 (m, 3H, *p*-H and *m*-H), 3.61 (dd, J = 3.3 and 11.0 Hz, H′-6), 3.49 (dd, J = 5.7 and 11.0 Hz, H′′-6), 3.16-3.10 (m, 2H, H-2 and

H′-5), 2.50 (ddd, J = 8.8, 8.8 and 8.8 Hz, H′′-5), 1.89-1.69 (m, 3H, H′-3 and 4-CH_2), 1.55 (m, 1H, H′′-3). ^{13}C Nmr: 158.4 (C=NH), 134.1 (C′-1), 130.1 (C′-4), 128.5 (C′-2 and C′-6), 126.1 (C′-3 and C′-5), 67.1 (C-6), 64.6 (C-2), 52.9 (C-5), 24.7 (C-3), 21.8 (C-4).

2-Phenylperhydropyrido[1,2-*d*][1,3,4]oxadiazine (8). 0.75 g (5.8 mmol) of hydrazino alcohol (**2**) was reacted with ethyl benzimidate (1.29 g, 8.7 mmol) and worked up in the same manner as described for **7**, to yield colourless crystals of **8**, 1.0 g (81%), mp 73-75 °C. As in the corresponding reaction with the hydrazino alcohol (**1**), we were able to isolate the amidine intermediate (**10**), which was relatively unstable and on standing at room temperature cyclized to **8**.

Compound (**8**). ^{1}H Nmr: 7.78 (m, 2H, *o*-H), 7.35-7.30 (m, 3H, *p*-H and *m*-H), 4.29 (dd, J = 3.1 and 10.3 Hz, H-$9_{eq.}$), 4.16 (dd, J = 9.0 and 10.3 Hz, H-$9_{ax.}$), 3.53 (dm, J = 1.5, 2.7, 3.9 and 11.3 Hz, H-$5_{eq.}$), 2.61 (m, J = 2.7, 11.3 and 13.0 Hz, H-$5_{ax.}$), 2.58 (m, J = 3.1, 3.2, 9.0 and 11.3 Hz, H-8a), 1.84 (m, J = 1.8, 2.7, 3.8, 4.5 and 13.4 Hz, H-$7_{eq.}$), 1.78 (m, J = 1.8, 1.9, 2.7, 2.7, 3.8 and 13.4 Hz, H-$6_{eq.}$), 1.73 (m, J = 3.9, 4.5, 13.0, 13.4 and 14.1 Hz, H-$6_{ax.}$), 1.68 (m, J = 1.9, 2.7, 3.2, 3.9 and 13.6 Hz, H-$8_{eq.}$), 1.38 (m, J = 3.8, 3.9, 12.3, 13.4 and 14.1 Hz, H-$7_{ax.}$), 1.27 (m, J = 3.8, 11.3, 12.3 and 13.6 Hz, H-$8_{ax.}$). ^{13}C Nmr: 145.6 (C-2), 132.9 (C′-1), 129.0 (C′-4), 128.0 (C′-3 and C′-5), 125.5 (C′-2 and C′-6), 69.6 (C-9), 56.1 (C-5), 54.6 (C-8a), 27.2 (C-8), 25.6 (C-6), 23.5(C-7). *Anal.*Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.20; H, 7.54; N, 12.77.

Compound (**10**). ^{1}H Nmr: 7.68 (m, 2H, *o*-H), 7.46-7.38 (m, 3H, *p*-H and *m*-H), 5.75-5.20 (br s, 2H, NH-C(NH)Ph), 3.80 (br s, 1H, OH), 3.57-3.48 (m, 2H, CH_2-OH), 2.95 (m, 1H, H-6eq.), 2.80 (br s, 1H, H-2), 2.40 (m, 1H, H-6ax.), 1.80-1.56 (m, 4H), 1.45-1.34 (m, 2H). ^{13}C Nmr: 158.6, 133.5, 130.4, 128.6, 126.2, 67.9, 66.4, 53.6, 28.2, 25.6, 23.8.

X-RAY CRYSTAL STRUCTURE DETERMINATION

Crystal data on **7**. $C_{12}H_{14}N_2O$, M_r = 202.26, orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.961(3), b = 21.067(2), c = 6.491(2) Å, V = 1088.5(8) Å^3 [by least-squares refinement on setting angles (20.4 < 2θ < 35.5) for 25 carefully centred reflections], Z = 4, D_c = 1.234 g cm^{-3}, F(000) = 432. Colourless bars, dimensions 0.20 X 0.35 X 0.40 mm, μ(Mo-K_α) = 0.75 cm^{-1}.

Crystal data on **8**. $C_{13}H_{16}N_2O$, M_r = 216.28, triclinic, space group **P**-1 (no. 2), a = 8.255(2), b = 12.181(4), c = 6.475(2) Å, α= 100.10(2), ß = 112.99(2) °, γ = 80.32(2) V = 586.5(3) Å^3 [by least-squares refinement on setting angles (40.5 < 2q < 43.9) for 25 carefully centred reflections], Z = 2, D_c = 1.224 g cm^{-3}, F(000) = 232. Colourless prisms, dimensions 0.30 x 0.35 x 0.40 mm, μ(Mo-K_α) = 0.74 cm^{-1}.

Data collection, analysis and refinement.

All data were collected at room temperature on a Rigaku AFC5S diffractometer with graphite monochromatized MoK_α (λ = 0.71069 Å) radiation, in the ω-2θ-scan mode, with an ω scan rate of 4° min^{-1} and a scan width of (1.37 + 0.30 tanθ) for **7** and a scan width of (1.68 + 0.30 tanθ) for **8**. The weak reflections [F < 10s(F)] were rescanned up to two times. The data obtained were corrected for Lorentz and polarization effects and the data on (**7**) for absorption (ψ scan, transmission factors 0.90-1.00) and for secondary extinction, coefficient = 0.5753E-05. A total of 1288 unique reflections were measured for **7** (θ_{max} = 52°) and a total of 2284 unique reflections for **8** (θ_{max} = 52° and R_{int} = 0.020). The intensities of three representative check reflections of both compounds showed only statistical fluctuations.

Both structures were solved by direct methods[17] and difference Fourier syntheses.[18] Structural parameters were refined by a full-matrix least-squares refinement, non-hydrogen atoms anisotropic, hydrogen atoms with fixed isotropic temperature parameters (1.2 times B_{eq} of the carrying atom). The aromatic hydrogens were kept in the calculated positions.

In the final cycles the 879 data on **7** with I > 2σ(I) yielded an R value of 0.037 [R_w=0.041, $w = 1/\sigma^2(F_o)$] for 164 parameters; maximum/minimum residual electron density = 0.12/-0.13 e/Å^3. Similarly in the final cycles, the 1531 data on **8** with I > 2σ(I) yielded an R value of 0.047 (R_w=0.052, $w = 1/\sigma^2(F_o)$) for 178 parameters; maximum/minimum residual electron density = 0.15/-0.22 e/Å^3.

All calculations were performed with the TEXSAN[19] crystallographic software. Neutral atom scattering and dispersion factors were those included in the program. The Figures were drawn with the ORTEP[20] program.

Table 3. Selected bond distances and angles for **7**.

O(1) - C(2)	1.360(4)	C(2) - O(1) - C(8)	112.0(2)	C(8) - O(1) - C(2) - N(3)	23.6(5)
O(1) - C(8)	1.448(4)	N(4) - N(3) - C(2)	119.3(2)	O(1) - C(2) - N(3) - N(4)	9.2(5)
N(3) - N(4)	1.377(3)	N(3) - N(4) - C(5)	115.6(2)	C(2) - N(3) - N(4) - C(7A)	-7.6(4)
N(3) - C(2)	1.276(3)	N(3) - N(4) - C(7A)	119.8(2)	N(3) - N(4) - C(7A) - C(8)	-24.5(4)
N(4) - C(5)	1.450(4)	C(5) - N(4) - C(7A)	110.2(3)	N(4) - C(7A) - C(8) - O(1)	54.0(4)
N(4) - C(7A)	1.471(4)	O(1) - C(2) - N(3)	124.7(3)	C(7A) - C(8) - O(1) - C(2)	-55.1(4)
C(2) - C(9)	1.462(4)	O(1) - C(2) - C(9)	114.3(2)		
C(7) - C(7A)	1.511(5)	N(3) - C(2) - C(9)	121.0(3)		
C(7A) - C(8)	1.497(5)	N(4) - C(7A) - C(7)	104.9(3)		
		N(4) - C(7A) - C(8)	108.2(3)		
		C(7) - C(7A) - C(8)	115.3(3)		
		O(1) - C(8) - C(7A)	108.8(3)		

Table 4. Selected bond distances and angles for **8**.

O(1) - C(2)	1.370(2)	C(2) - O(1) - C(9)	114.6(1)	C(9) - O(1) - C(2) - N(3)	- 8.6(3)
O(1) - C(9)	1.446(2)	N(4) - N(3) - C(2)	118.4(2)	O(1) - C(2) - N(3) - N(4)	2.1(3)
N(3) - N(4)	1.403(2)	N(3) - N(4) - C(5)	110.1(1)	C(2) - N(3) - N(4) - C(8A)	-25.9(2)
N(3) - C(2)	1.272(2)	N(3) - N(4) - C(8A)	114.9(1)	N(3) - N(4) - C(8A) - C(9)	52.2(2)
N(4) - C(5)	1.463(2)	C(5) - N(4) - C(8A)	114.4(2)	N(4) - C(8A) - C(9) - O(1)	-57.1(2)
N(4) - C(8A)	1.462(2)	O(1) - C(2) - N(3)	127.1(2)	C(8A) - C(9) - O(1) - C(2)	36.8(2)
C(2) - C(10)	1.479(3)	O(1) - C(2) - C(10)	112.3(2)		
C(8) - C(8A)	1.521(3)	N(3) - C(2) - C(10)	120.6(2)		
C(8A) - C(9)	1.501(3)	N(4) - C(8A) - C(8)	109.6(2)		
		N(4) - C(8A) - C(9)	106.9(2)		
		C(8) - C(8A) - C(9)	111.9(2)		
		O(1) - C(9) - C(8A)	110.7(2)		

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