Asymmetric Reductive Amination of Cycloalkanones, XIII[1]:

Enantioselective Amidoamination: A New Regiospecific Strategy for the Synthesis of Chiral Cyclohexane-1,2-diamino-Derivatives

Wolfgang H. Schlichter and August W. Frahm[+]*

Institut für Pharmazeutische Chemie der Universität Freiburg, H. Herderstr. 9, D-7800 Freiburg

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Asymmetric synthesis of *trans*- and *cis*-2-Benzamido- or 2-Phenyl-acetamido-cyclohexane-amines **7** and **8** by means of reductive amination and hydrogenolysis is described. Condensation of the amido-ketones **3** with chiral auxiliary (*R*)-(+) and (*S*)-(-)-1-phenylethylamine, respectively, leads to the amido-imines **4**, which are hydrogenated over *Raney*-Ni to yield simultaneously enantiomerically pure secondary *trans*- and *cis*-2-amido-cyclohexane-amines **5** and **6**.

Asymmetrische, reduktive Aminierung von Cycloalkanonen, 13. Mitt.[1]:
Enantioselektive Amidoaminierung: Eine neue regiospezifische Strategie zur Synthese von chiralen Cyclohexan-1,2-diamino-Derivaten

Die asymmetrische Synthese von *trans*- und *cis*-2-Benzamido- oder -2-Phenylacetamido-cyclohexanaminen **7** und **8** mittels reduktiver Aminierung und Hydrogenolyse wird beschrieben. Die Kondensation der Amidoketone **3** mit den chiralen Hilfsaminen (*R*)-(+)- oder (*S*)-(-)-1-Phenylethylamin führt zu den Amido-iminen **4**, die sich mit *Raney*-Nickel zu den enantiomerenreinen sekundären *trans*- und *cis*-2-Amido-cyclohexanaminen **5** und **6** hydrieren lassen.

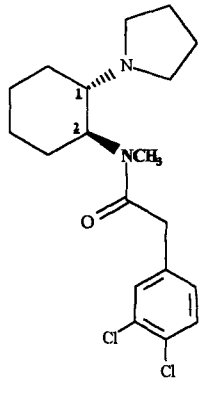
In preceding communications[2-8] we have demonstrated that reductive amination of 2-benzamido-cyclohexanone proceeds with high substantial and optical yields, giving access to both eutomers of cyclohexane-1,2-diamine-type κ-(*trans*) and σ-(*cis*)-agonists[9-16] in a single batch. The advantage of producing simultaneously *cis*- and *trans*-enantiomers of the diamine derivatives together with the regiospecifity of this diamine-synthesis[17,18] (each nitrogen can be modified independently from the other) enhances the attractiveness of this facile approach.

We have managed to transfer this reaction sequence to the phenylacetamido-ketone in even better yields, so that the active enantiomers of the phenylacetamide-type κ- (like U50, 488, Scheme 1) and σ-agonists are directly accessible now *via* this route. So far this is the only asymmetric synthesis and the only simultaneous process which leads to both of these novel classes of opioid-agonists reported in lit.[9-16].

1. *Racemic Amido-ketone Precursors* **3**

As outlined in Scheme 2 the racemic starting ketones **3** were synthesized according to lit. procedures[18,19] which could be optimized for each step to 95% yields by the following improvements:

- Two-phase-aminolysis of the epoxide **1** proceeds at low temp. in quantitative yield to the aminoalcohol without ketone formation observed as 30% side reaction at more drastic conditions (5 bar/90-100°C) commonly applied[19].



Scheme 1

- By utilizing two-phase benzoylation conditions the yield lowering ester formation could be completely suppressed when working with a necessary excess of the acid chloride.

- *Jones* Oxidation could be optimized using an Al_2O_3-absorbed pyridine-complex of CrO_3 (*vide infra*).

An attempt was made to apply this sequence to tertiary amidoketones starting with the epoxide and methylamine instead of ammonia. The three steps proceeded with similar high yields as in the secondary amide series.

2. *The Amido-imines* **4**

Condensation of the amidoketones **3** with an excess of (*R*)-(+)- or (*S*)-(-)-1-Phenylethylamine under azeotropic removal of water with benzene produces the fairly stable two diastereomeric *E*-amido-imines **4** in excellent yield.

[+] Dedicated to Professor *Felix Zymalkowski* on the occasion of his 80th birthday

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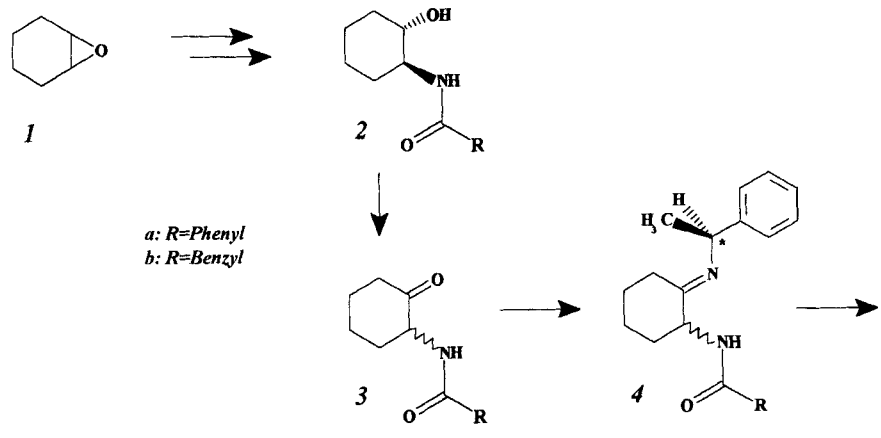
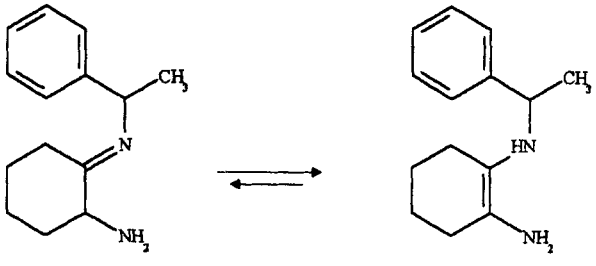


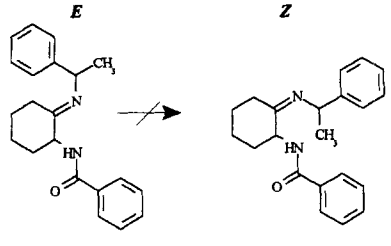
Scheme 2



Scheme 3

The main reason for their stability compared to 2-amino-imines is the engagement of the lone pair of the second N-atom in the amide moiety, hampering the stabilization of the enamine as is the case with the 2-amino-cyclohexan imines (Scheme 3).

The epimeric *E*-amido-imines **4** are obtained in high purity as shown by ^{1}H- and ^{13}C-NMR spectra, with no extra signals so indicating the absence of the *Z*-isomers (Scheme 4). Only traces of the enamine are formed.



Scheme 4

Due to steric hindrance the tertiary amido-ketones **3** could not be condensed to the imines under our mild conditions. Other tertiary amido-ketones (*e.g.* 2-phthalimido) reacted only in moderate yields to amido-imines, which could not be hydrogenated even with excessive amounts of *Raney*-Nickel. Experiments with more active Pd-catalysts are underway and should allow direct access to the tertiary amido-amines, if other chiral amines than (*R*)-(+)- or (*S*)-(-)-1-phenyl-ethylamine are used to prevent cleavage of the benzyl moiety *prior* to the crucial asymmetric imine hydrogenation.

3. *Secondary Amido-amines* **5** *and* **6**

Without further purification the amido-imines **4** were hydrogenated in a Parr-apparatus over *Raney*-Nickel, taking 6-10 days to get complete hydrogenation depending on the amount of catalyst. It can be as little as 3 g per 100 mmol and up to 12 g without loss of the enantioselectivity, and without any noticeable influence on the *cis:trans* ratio (2:1, de:33%).

Any unreacted amido-ketone is reduced to both *cis*- and *trans*-amido-alcohols, complicating the final diastereomer separation. This side reaction could be suppressed by an excess of the amine in the imine condensation.

Stereochemistry of the Imine Hydrogenation

With few exceptions[7] asymmetric cycloalkane-imine hydrogenations have always displayed a double stereoselectivity (ee > 99%, de > 99%) with alkyl-, alkoxy-, phenyl-, or phenoxy-substituents in the α-position of the imine. It must be the planarity of the amide substituent - which reduces the discrimination of the two sides of the imine double bond - that is responsible for the reduced diastereoselectivity (de = 33%). That one of the diastereomeric

amido-imine set **4**, which normally is not hydrogenated but epimerizes completely, is in this case hydrogenated in a simultaneous and competitive reaction yielding additionally *trans* configurated amido-amine **5** besides the major *cis* product **6**. Nevertheless the enantioselectivity was clearly maintained: In the ^{13}C-NMR spectra of the crude hydrogenation products two complete sets of signals appear, corresponding to *trans*- and *cis*-diastereomers **5** and **6**. From the four possible diastereomers only two are produced. So in one batch using (*S*)-(-)-1-phenyl-ethylamine two secondary amido-amines both with negative optical rotation were obtained:

5a/b *trans*-(-)-1'*S*, 1*S*[+], 2*S*

6a/b: *cis*-(-)-1'*S*, 1*S*[+], 2*R*

Since the absolute configuration of all κ-agonist-eutomers is 1*S*,2*S* whilst all 1σ-agonist-eutomers are 1*S*,2*R* configurated, the simultaneous creation of the "right" enantiomers in one batch is more than welcomed, especially since we have found an elegant new method, readily separating the isomers.

Chromatographic Separation of the Diasteromeric Secondary Amido-amines **5** *and* **6**

The separation of the *trans*/*cis*-diastereomers **5** and **6**, displaying only a slight difference in their R_f-values (*cis*:0.45/*trans*:0.38) in an optimized TLC-system, was greatly facilitated by the stereoselective liberation of the free base from the hydrochloride salt of only the *cis*-amido-amine **6** when chromatographed on silica-gel 60 (0.063-0.2) with ethyl acetate/petroleum ether mixtures. This selective deprotonation, unprecedent in lit. and due to the amphoteric character of the absorbent, was discovered during a chromatographic screening by applying the flash-technique. In numerous repetitions an absorbent to compound ratio below 150:1 seemed to be crucial: With higher ratios the initial mixture of the hydrochlorides was completely deprotonized passing through the chromatography column.

Thus, the main *cis* product **6** can be eluted completely as lipophilic free base with the polar *trans*-hydrochloride **5** · **HCl** remaining in the chromatography column. Finally **5** is eluted as its hydrochloride by ethyl acetate/dichloromethane/ethanol.

The 2-phenylacetamido-amines **5b** and **6b**, obtained in excellent 82% crude total yield (*vs* 79% crude 2-benzamido-amines **5a** and **6a**) behave exactly like the benzamido-amines, except for the higher polarity of the eluents necessary for the abovementioned separation.

For optical rotations of the secondary and primary amido-amines see Table 1.

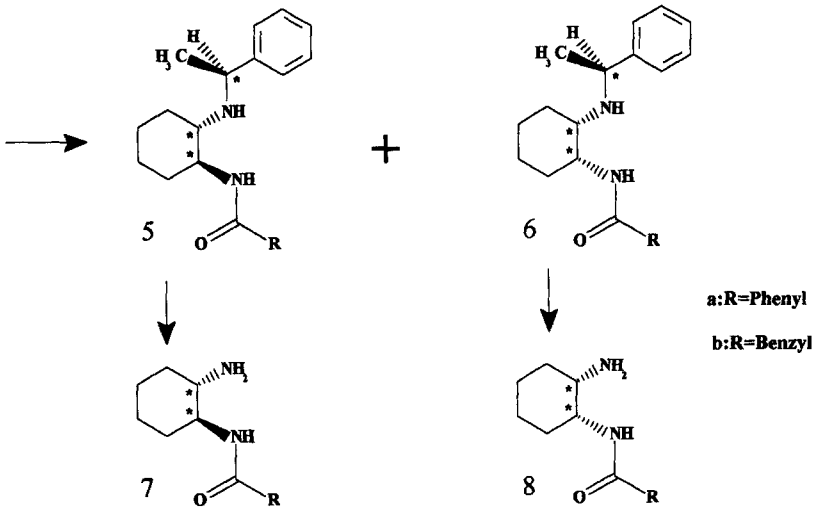
Tab. 1: Optical rotations $[\alpha]_D^{20}$ (EtOH) of the free amine-bases **5** and **6**.

Benzamido-	trans	cis	Δ
Secondary amines	*5a*: - 21.2	*6a*: -71.1	+49.9
Primary amines	*7a*: +55.2	*8a*: +20.0	+35.2
Δ	-76.4	-91.1	

Phenyl-acetamido-	trans	cis	Δ
Secondary amines	*5b*: -42.1	*6b*: -64.3	+22.2
Primary amines	*7b*: +30.8	*8b* +9.0	+21.8
Δ	-72.9	-73.3	

4. *Primary Amido-amines* **7** *and* **8**

Upon catalytic splitting off the chiral auxiliary group (10% Pd/C; ammonium formate) the pure enantiomers of *trans*- and *cis* primary amido-amines **7** and **8** were obtained



Scheme 5

[+] Without exception[2-8] reductive amination with homochiral 1-phenyl-ethylamine has proven to proceed under "like" induction, so that the newly created stereogenic center adjacent to the N-atom has the same absol. configuration as the auxiliary amine. This assumption gained further support by comparison of the observed optical rotations with those of known compounds. Final proof by means of x-ray-crystal structures and CD-spectra is underway and will be reported in full detail.

showing the opposite sign of rotation in comparison with the secondary amido-amines **5** and **6** and the auxiliary amine:

7a/b: *trans*-(+)-1*S*,2*S*

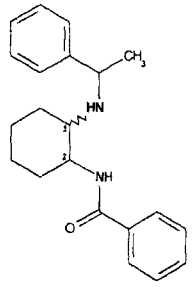
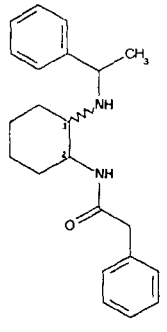
8a/b: *cis*-(+)-1*S*,2*R*

Optical activity at this stage of the synthesis indicates that chiral induction has occured. Since all these chiral compounds are new, we determined the enantiomeric excess (ee) *via* HPLC-analysis of the *Mosher*-derivatives[1-4]. It was found > 99%.

^{13}C-NMR-Data of the Amido-amines **5** and **6**

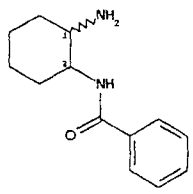
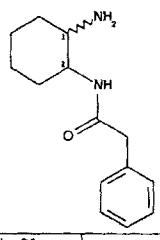
As expected, the data (Tab. 2 and 3) of the phenylacetamido-amines are completely paralleled by those of the benzamido-amines, both showing the dramatic shift-differences of up to 6 ppm between *trans* and *cis* diastereomers. In contrast to the ^{1}H-NMR-data where 2-H (amide-adjacent) is always located downfield from 1-H (amine-adjacent) the secondary amide-bonded C-2 is upfield from the secondary amine-bonded C-1, indicating

Tab. 2: ^{1}H-NMR and ^{13}C-NMR-data of secondary amido-amines **5** and **6**.

^{1}H-NMR and ^{13}H-NMR Data (TMS) in ppm ($CDCl_3$)				
	cis-*6a*		trans-*5a*	
	eq.	ax.	eq.	ax.
1-H	2.80 m*	-	-	2.42 dt
2-H	-	4.15 m *	-	3.70 ddt
3-H	1.3-1.7 m		2.22 m	1.20 dt
4-H	1.3-1.7 m		1.60 m	1.30 m
5-H	1.3-1.7 m		1.60 m	1.30 m
6-H	1.3-1.7 m		1.96 m	1.10 dt
α-H	3.82 q		3.92 q	
α-CH_3	1.34 d		1.28 d	
NH (Amin)	1.40 s		1.40 s	
NH (Amid)	7.30 br		6.60 d	
CH_2	-		-	
Arom.	7.82 (H2",H6")		7.80 (H2",H6")	
	7.20-7.50 m(8H)		7.10-7.50 m(8H)	
C-1	53.2 d		59.4 d	
C-2	48.4 d		54.5 d	
C-3	27.9 t		32.2 t	
C-4	22.5 t		24.7 t	
C-5	21.3 t		24.5 t	
C-6	28.5 t		33.2 t	
C-α	54.7 d		56.3 d	
C-ß	23.9 q		24.3 q	
C-1'	145.6 s		146.4 s	
C-2'	126.4 d		125.5 d	
C-3'	128.1 d		128.3 d	
C-4'	126.1 d		126.1 d	
C=O	166.7 s		166.8 s	
C-1"	134.9 s		134.8 s	
C-2"	126.6 d		126.9 d	
C-3"	128.3 d		128.3 d	
C-4"	131.1 d		131.2 d	
CH_2	--		--	

	cis-*6b*		trans-*5b*	
	eq.	ax.	eq.	ax.
1-H	2.64 m*	-	-	2.16 dt
2-H	-	4.02 m *	-	3.48 ddt
3-H	1.2-1.5 m		2.16 m	1.20
4-H	1.2-1.5 m		1.53m	0.9-1.3
5-H	1.2-1.5 m		1.53m	0.9-1.3
6-H	1.2-1.5 m		1.80 m	0.9-1.3
α-H	3.72 q		3.68 q	
α-CH_3	1.16 d		1.05 d	
NH (Amin)	1.40 s		1.00 s	
NH (Amid)	7.00 d		6.60 d	
CH_2	3.66 s		3.56 s	
Arom.	-		-	
	7.20-7.40 m(10H)		7.20-7.40 m(10H)	
C-1	53.0 d		58.8 d	
C-2	47.3 d		54.4 d	
C-3	27.5 t		33.2 t	
C-4	26.7 t		24.7 t	
C-5	22.0 t		24.4 t	
C-6	28.0 t		33.0 t	
C-α	54.7 d		56.0 d	
C-ß	22.8 q		24.0 q	
C-1'	144.1 s		146.6 s	
C-2'	126.4 d		126.3 d	
C-3'	128.3 d		128.1 d	
C-4'	127.1 d		127.1 d	
C=O	170.7 s		170.9 s	
C-1"	135.3 s		135.1 s	
C-2"	128.6 d		128.8 d	
C-3"	129.2 d		129.2 d	
C-4"	126.9 d		126.6 d	
CH_2	43.7 t		44.1 t	

Tab. 3: ^{1}H-NMR and ^{13}C-NMR-data of primary amido-amines **7** and **8**.

^{1}H-NMR and ^{13}C-NMR Data (TMS) in ppm ($CDCl_3$)				
	cis-*8a*		trans-*7a*	
	eq.	ax.	eq.	ax.
1-H	3.10 m			2.52 dt
2-H		4.05 m		3.70 ddt
3-H	1.75 m	1.50 m	2.12 m	1.20 dt
4-H	1.60 m	1.50 m	1.76 m	1.5-1.6 m
5-H	1.50 m	1.50 m	1.76 m	1.5-1.6 m
6-H	1.60 m	1.60 m	2.00 m	1.20 dt
NH_2	1.45 s		1.60 s	
NH (Amid)	7.00 d (7.9 Hz)		6.40 d (7.9 Hz)	
CH_2	-----		---	
2-H",6-H"	7.78 (2H)		7.78 (2H)	
3-H",4-H" 5-H"	7.40 m (3H)		7.40-7.60 m (3H)	
C-1	49.3 d		55.5 d	
C-2	50.5 d		56.5 d	
C-3	27.2 t		32.4 t	
C-4	23.4 t		25.0 t	
C-5	19.9 t		25.1 t	
C-6	32.7 t		35.5 t	
C=O	166.6 s		167.8 s	
C-1"	134.9 s		134.7 s	
C-2"	126.8 d		126.9 d	
C-3"	128.3 d		128.4 d	
C-4"	131.1 d		131.3 d	
CH_2	--		--	

	cis-*8b*		trans-*7b*	
	eq.	ax.	eq.	ax.
1-H	2.84 m			2.20 dt
2-H		3.80 m		3.40 ddt
3-H	1.50 m	1.30 m	1.80 m	0.80-1.30
4-H	1.30 m		1.60 m	0.80-1.30
5-H	1.30 m		1.60 m	0.80-1.30
6-H	1.50 m	1.30 m	1.80 m	0.80-1.30
NH_2	1.50 s		1.40 s	
NH (Amid)	6.20 d (7.3 Hz)		5.80 d (7.9 Hz)	
CH_2	3.44 s		3.50 s	
2-H",6-H"	----		-----	
3-H",4-H" 5-H"	7.20 m (5H)		7.20-7.30 m (5H)	
C-1	49.3 d		55.0 d	
C-2	50.1 d		56.1 d	
C-3	27.2 t		32.1 t	
C-4	22.8 t		24.8 t	
C-5	20.3 t		24.8 t	
C-6	31.9 t		35.0 t	
C=O	170.4 s		171.1 s	
C-1"	135.2 s		135.1 s	
C-2"	129.0 d		129.0 d	
C-3"	128.6 d		128.7 d	
C-4"	126.9 d		127.0 d	
CH_2	43.7 t		43.7 t	

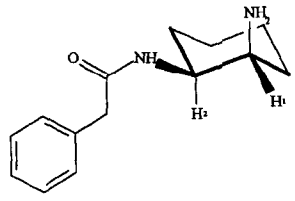
that the amide-N has the lower electronegativity compared to the free amino-N. This α-effect is associated with a β-effect on the positions C-3 and C-6, especially pronounced at C-6 of the primary amines.

Also when going from primary *via* secondary to tertiary[1] amines the alkylation of the basic N-atom has a shielding β-effect on C-2 (but not on C-6) and as expected a deshielding effect on C-1.

6. ^{1}H-NMR-Data and Conformational Analysis of the Amido-amines **5-8**

In the conformationally restricted cyclohexane-derivatives the equatorially positioned H can be easily discerned from the axial H by the size of the coupling constants. Almost complete assignment of all protons was possible, utilizing additionally 2D-COSY-NMR and HETCOR-NMR-experiments. The well known shielding effect of the axial position compared to the equatorial position can be clearly seen in most cases, reaching maximum differences up to 0.8 ppm. In the almost regiosymmetric amido-amines (two similar C-H connected to nitrogen) a decision had first to be made concerning the amide-adjacent methin proton (2-H) *vs.* the amine-adjacent methin proton (1-H) ^{1}H-NMR-signals. This question can be unequivocally answered by the couplings of 2-H with the amide-NH in the 2D-COSY-^{1}H-NMR-experiment (also after H/D-exchange by the 2-H-signal showing a reduced splitting pattern). Without exception the amide-adjacent methin proton 2-H shows resonance at least

1 ppm downfield from the amine-adjacent 1-H, which can be furtheron rationalized by the negative anisotropic effect of the mesomeric π-system of the amide-moiety (Scheme 7).



Scheme 6

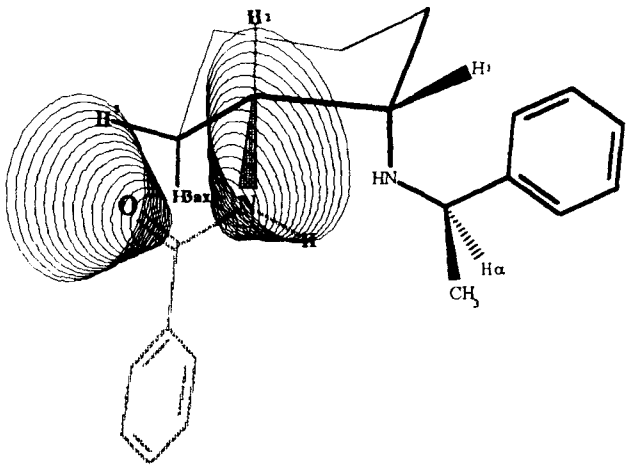
For the *trans*-compounds **5a,b** and **7a,b** (Tab. 2 and 3) where both the N-substituents are clearly anchored in an equatorial position, a coupling constant of 10.1 Hz is observed for the diaxial coupling between 1-H and 2-H ($J_{2\text{-Hax }3\text{-Hax}}$ = 11.2 Hz) and of 4.1 Hz each for the ae-coupling between 1-H/6-H and 2-H/3-H, respectively. The shielded axial position of 1-H causes a significant upfield shift to δ values between 2.16 and 2.52 ppm, while the abovementioned anisotropic effect places 2-H downfield shifted to δ values between 3.48 and 3.80 ppm. The coupling constant $J_{2\text{-H NH}}$ figures to 7-8 Hz. The exchangeable amide NH is located between 5.8 and 6.4 ppm.

From the group of *cis* diastereomers **6a,b** and **8a,b**, where generally two similar substituents are competing for the equatorial position, only the primary amido-amines **8a** and **8b** are anchored in one of the two possible chair conformations, due to the smaller NH_2-group compared to the amido-group.

In the 2D-COSY-NMR of **8a** and **8b** the 2-H is identified by its coupling with the exchangeable amide NH-proton in addition with that with 1-H and 3-H. It is located at δ 4.05 ppm (**8a**) and δ 3.80 ppm (**8b**). The 1-H pseudo-quartett (3 x J = 4.1 Hz) is highfield shifted to δ 3.10 ppm (**8a**) and δ 2.84 ppm (**8b**), respectively. The observed ae-coupling-constant of 4.1 Hz for J_{1H2H} confirms *cis* configuration of **8a** and **8b** (Scheme 6).

In contrast the *trans* compounds **7a** and **7b** exhibit 1-H signals highfield shifted to δ 2.52 ppm (**7a**) and δ 2.20 ppm (**7b**) as compared with 1-H of **8a** and **8b**, confirming the shielding effect in the axial position.

The spectra of the secondary *cis*-amido-amines **6a** and **6b** differ from those of all other compounds in that the two methin proton-resonances 1-H and 2-H of both compounds

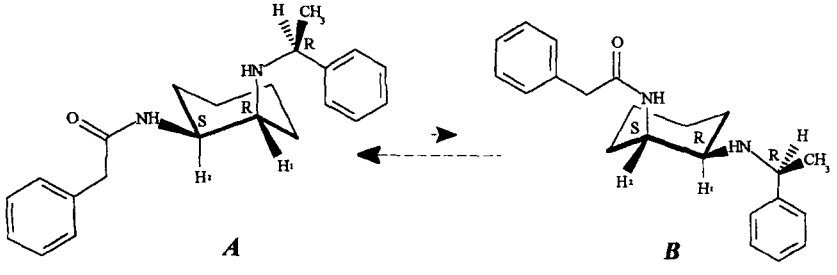


Scheme 7

do not display a clear splitting pattern, so hampering deduction of discrete coupling constants. In both compounds the 2-H signal shows line broadening with a half-band-width of 16 Hz (after H/D-exchange the coupling to the amide NH disappeared) *vs.* 14 Hz for 1-H, indicating that at ambient temp. these molecules exist in a thermodynamic equilibrium (see above), oscillating between the two possible chair-conformations A and B (Scheme 8) fast enough to cause averaging of the resonances in the time-frame of the NMR-experiment.

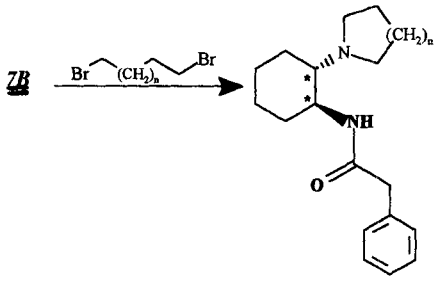
From the expected band-width (after H/D-exchange) of about 18 Hz (10 + 4 + 4) for the axial positioned 2-H and of about 12 Hz (3 x 4) for the equatorial oriented 1-H it can be calculated that the chair-conformation **A** is populated by 2/3, with one third of all molecules in the inverted conformation **B**.

We were anxious to see, if at elevated temp. this conformer distribution is significantly altered. Since the two conformers **A** and **B** should have a comparable optical rotation with opposite sign[22], (an equal distribution would result in a reduction of the optical rotation towards zero) we realised this parameter being sensitive towards changes of the **A/B** ratio. In agreement with our conformational assumptions we found a remarkable temp. dependency of the optical rotations only for the secondary amido-amines **6a** and **6b**: The $[\alpha]_D$ value was reduced from -71.1° to -46.0° for **6a** and from -64.3° to -48.0° degrees for **6b** by only raising the temp. from 20 to 65°C.



Scheme 8

From the primary phenylacetamido-amines **7b** or **8b** a one step cyclisation, well worked out in the racemic syntheses[9-16] leads to pharmacologically active pyrrolidino-compounds (Scheme 9). By variation of the aromatic substitution-pattern of the initial acid chloride a wide variety of agonists is accessible by this route, which is under further investigation.



Scheme 9

We gratefully acknowledge funds and substantial support received from the Degussa, Frankfurt a. Main, the BASF, Ludwigshafen and the Fonds der Chemischen Industrie. We also wish to thank Mr. *V. Brecht* for carefully performing detailed NMR-spectral measurements of all reported compounds.

Experimental Part

Melting points: uncorrected.- Raney-Ni type B 113 W and 10% Pd/C type E10/ND (Degussa).- Column chromatography: silica-gel 60 0.063-0.2 (Merck).- TLC: Silica-gel 60 coated aluminium; ethyl acetate/NH_3/-toluene/n-BuOH: 6:2:12:1.- Absol. ethanol distilled from CaO.- NMR-data: Varian Unity 300; 300 MHz for ^{1}H-NMR/75 MHz for ^{13}C-NMR.

trans-2-Aminocyclohexanols, general reaction

10 mmol of cyclohexenoxide (**1**) are added at 5°C to 50 ml of a magnetically stirred 35-40% aqueous solution of ammonia, or a primary or secondary amine. The oily suspension is stirred overnight with a gradual rise of temp. to 25°C to complete the reaction. Then it is evaporated to dryness, yielding ~ 95% of *trans*-2-aminocyclohexanols (e.g. 1.1 g (96%) of *trans*-2-amino-cyclohexanol[20]).

2-Acylaminoalcohols **2**, *general reaction*

10 mmol (1.15 g) *trans*-2-amino-cyclohexanol are suspended in 10 ml 2N NaOH and 13 mmol of benzoyl chloride or phenacetyl chloride in 20 ml toluene are added under vigorous magnetical stirring. After 6 h 2.5 ml NaOH (40%) are added to decompose any *O*-benzoylated by products and excessive benzoylchloride. A white, gummy solid is formed, which is washed 3 times with 50 ml of hot water to remove benzoic acid. The water phase is decanted and the solid recrystallized from acetonitril.

Elemental analysis and physical data: Tab. 4, NMR-data: Tab. 5.

2-Benzamido-cyclohexanone (**3a**)

2-Phenylacetamido-cyclohexanone (**3b**)

During 1 h 10 mmol of 2-amido-cyclohexanols **2a** or **2b** dissolved in 20 ml dichloromethane are added in portions to a stirred suspension of 85 g CrO_3-pyridine-complex on aluminiumoxid[23] in 400 ml n-hexane. After 4 h TLC indicated the end of the reaction (if some of the alcohol is still left, another 20 g of the oxidizing reagent is added and stirring is continued for 2 h).- The dark-brown suspension is filtered with Celite and the filter cake extracted two times with 400 ml n-hexane, containing 15% of dichloromethane. The combined extracts are evaporated to leave an off-white amorphous solid, recrystallized from ethyl acetate/ligroin 1:4.- Elemental analysis and physical data: Tab. 4; NMR-data: Tab. 5.

Tab. 4: Elemental analysis and physical data of the 2-amido-cyclohexanols **2** and 2-amido-cyclohexanones **3**.

trans-2-Benzamido-cyclohexanol (2a)

$C_{13}H_{17}NO_2$	Yield	mp		% C	% H	% N
MW: 219.28	2.12 g (97.1 %)	(° C)	Calcd.	71.2	7.81	6.4
	White needles	167-69	Found	70.9	7.49	6.3

trans-2-Phenylacetamido-cyclohexanol (2b)

$C_{14}H_{19}NO_2$	Yield	mp		% C	% H	% N
MW: 233.30	2.28 g (97.9 %)	(° C)	Calcd.	72.1	8.21	6.0
	White needles	149-150	Found	71.9	8.09	6.0

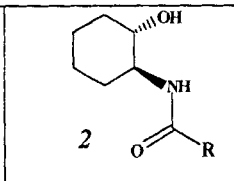
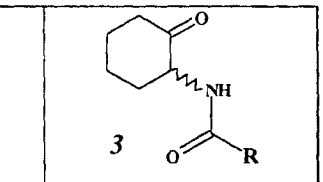
(R,S)-2-Benzamido-cyclohexanone (3a)

$C_{13}H_{15}NO_2$	Yield	mp		% C	% H	% N
MW: 217.26	2.06 g (94.9 %)	(° C)	Calcd.	71.9	6.96	6.5
	White needles	137-139	Found	71.8	7.08	6.3

(R,S)-2-Phenylacetamido-cyclohexanone (3b)

$C_{14}H_{17}NO_2$	Yield	mp		% C	% H	% N
MW: 231.29	2.29 g (98.8 %)	(° C)	Calcd.	72.7	7.41	6.1
	White solid	136-137	Found	72.4	7.52	5.8

Tab. 5: ^{1}H-NMR and ^{13}C-NMR-data of 2-amido-cyclohexanols **2** and 2-amido-cyclohexanones **3**.

^{1}H-NMR and ^{13}C-NMR Data (TMS) in ppm ($CDCl_3$)				
	Benzamido-*2a*	Phenylacetamido-*2b*	Benzamido-*3a*	Phenylacetamido-*3b*
	eq. ax.	eq. ax.	eq. ax.	eq. ax.
OH	4.57 br -	4.21 br -	- -	- -
1-H	- 3.53 m	- 3.45 m	- -	- -
2-H	- 3.65 m	- 3.55 m	- 4.67ddd	- 4.46ddd
3-H	1.90 m	1.97 m	2.78 m 2.16 m	2.60 m 2.10 m
4-H	1.12 m	1.40 m	1.90 m 1.66 m	1.82 m 1.56 m
5-H	1.12 m	1.10 m	1.80 m 1.45 m	1.80 m 1.26 m
6-H	1.64 m	1.63 m	2.56 m 2.45 m	2.48 m 2.36 m
$J_{2\text{-}H}$ (in Hz)	--	--	12.0 6.0 6.0	12.0 6.0 6.0
NH (Amide)	8.04 d (7.0 Hz)	6.85 d (6.0 Hz)	7.25 d (6.0 Hz)	6.56 d(b) (6.0 Hz)
CH_2	---	3.53 s	-----	3.56 s
2-H", 6-H"	7.82 (2H)	--	7.82 (2H)	--
3-H", 4-H",5-H"	7.40-7.50 (3H)	7.20-7.40 (5H)	7.40-7.50 (3H)	7.20-7.40 (5H)
C-1	74.6 d	74.3 d	207.7s	207.3 s
C-2	56.2 d	55.7 d	58.2 d	57.9 d
C-3	31.5 t	31.2 t	35.3 t	35.0 t
C-4	24.1 t	24.0 t	23.9 t	23.8 t
C-5	24.4 t	24.3 t	27.9 t	27.7 t
C-6	34.4 t	34.2 t	41.0 t	40.9 t
Amide				
C=O	168.9 s	171.2 s	166.6 s	170.4 s
C-1"	134.1 s	135.4 s	133.9 s	135.1 s
C-2"	127.1 d	127.2 d	126.9 d	127.0 d
C-3"	128.4 d	128.6 d	128.3 d	128.6 d
C-4"	131.5 d	129.3 d	131.4 d	129.1 d
CH_2	--	41.8 t	--	43.4 t

2-Benzamido-cyclohexanone-N-(1-phenylethyl)-imine (**4a**)

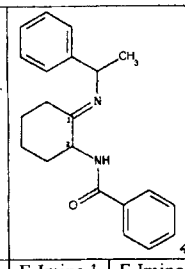
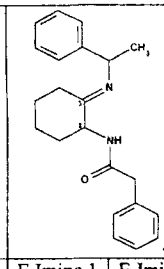
10 mmol of 2-benzamido-cyclohexanone (**3a**), 20 mg of *p*-toluenesulfonic acid and 7 mmol of (*R*)-(+)- or (*S*)-(-)-1-phenylethylamine are dissolved in 50 ml benzene, magnetically stirred and refluxed in a reaction vessel with a Dean-Stark-condenser. After 90 min 5 mmol and after further 60 min 4 mmol of (*R*)-(+)- or (*S*)-(-)-1-phenylethylamine are added. Reflux is continued for 3 h with less than 8% of the ketone left according to ^{1}H-NMR. The pale yellow reaction mixture is freed of the solvent and some of the excess amine (bath temp. 50° to 70°C, final vacuum: 4 Torr). The crude imine's purity is sufficient for the subsequent hydrogenation step. For spectroscopic purposes **4a** is purified by flash chromatography through 40 g silica-gel.

The imine solution in 50 ml dry ether is passed through quickly by means of water-suction and rinsed with 150 ml of dry ether. The solvent is stripped off completely, the remaining pale yellow oil is dried at 45°C/0.5 Torr. Attempts of distillation were unsuccessful, since even below pressures of 1 x 10^{-3} Torr the imine had to be heated up to 180°C in a Kugelrohr-apparatus. Decomposition and polymerisation prevented the collection of reasonable amounts.

2-Phenylacetamido-cyclohexanone-N-(1-phenylethyl)-imine (**4b**)

10 mmol 2-phenylacetamido-cyclohexanone were reacted as described for **4a**.- The condensation is complete after 3 h, with less than 3% of the ketone left (^{1}H-NMR).- ^{1}H-NMR and ^{13}C-NMR-data of **4a**,**4b**: Tab. 6.

Tab. 6: ^{1}H-NMR and ^{13}C-NMR-data of 2-Amido-cyclohexanone-N-(1-phenylethyl)-imines **4**.

^{1}H-NMR and ^{13}C-NMR Data (TMS) in ppm ($CDCl_3$)	 *4a*		 *4b*	
	E-Imine 1	E-Imine 2	E-Imine 1	E-Imine 2
2-H	4.35 m	4.31 m	4.11 m	4.09 m
3-H	1.25/2.83 m	1.25/2.83 m	1.12/2.65 m	1.12/2.65 m
4-H	1.7-1.9 m	1.7-1.9 m	1.7-1.9 m	1.7-1.9 m
5-H	1.4/2.00 m	1.1/1.85 m	1.4/1.94 m	1.1/1.80 m
6-H	1.72/3.03 m	1.72/3.03 m	1.70/2.90 m	1.70/2.90 m
α-H	4.82 q	4.79 q	4.65 q	4.62 q
α-CH_3	1.47 d	1.44 d	1.24 d	1.21 d
NH	8.52 br	8.52 br	7.60 br	7.60 br
aromatic	7.2-7.5 m (8H)	7.2-7.5 m (8H)	7.4-7.5 m (8H)	7.4-7.5 m (8H)
2-H",6-H"	7.88 m (2H)	7.87 m (2H)	7.04 m (2H)	7.03 m (2H)
C-1	167.6 s	167.4 s	166.8 s	166.8 s
C-2	54.73 d	54.72 d	54.64 d	54.67 d
C-3	35.1 t	34.9 t	35.0 t	34.9 t
C-4	24.0 t	23.9 t	24.0 t	24.0 t
C-5	27.6 t	26.9 t	27.6 t	26.9 t
C-6	28.9 t	28.8 t	28.8 t	28.7 t
C-α	57.4 d	57.4 d	57.5 d	57.5 d
C-ß	25.5 q	25.2 q	25.4 q	25.3 q
C-1`	145.8 s	145.5 s	145.8 s	145.5 s
C-2`	126.2 d	126.2 d	126.2 d	126.2 d
C-3`	126.6 d	126.6 d	126.6 d	126.6 d
C-4`	125.6 d	125.6 d	125.6 d	125.6 d
C=O	166.0 s	166.0 s	170.2 s	170.1 s
C-1"	134.7 s	134.7 s	135.1 s	135.1 s
C-2"	128.2 d	128.2 d	128.2 d	128.2 d
C-3"	126.9 d	126.9 d	128.7 d	128.4 d
C-4"	131.0 d	131.0 d	127.0 d	127.0 d
CH_2	-	-	44.1 t	44.1 t

trans- and cis-2-Benzamido-N-(1-phenylethyl)-cyclohexanamine (**5a · HCl** *and* **6a · HCl**)

10 mmol of benzamido-imine **4a**, dissolved in 50 ml absol. ethanol, are hydrogenated in a Parr-apparatus with 1.0 g *Raney*-Nickel at 5 bar and ambient temp. After 10 days the catalyst is filtered off, rinsed with ethanol and the filtrate is evaporated to dryness. The remaining viscous oil is dissolved in 12 ml dichloromethane and 60 ml diethylether and extracted with 8 ml 2N HCl (removing the excess of (*R*)-(+)- or (*S*)-(-)-1-phenylethylamine). The org. phase is evaporated to dryness.- The residue of diastereomeric amido-amine-hydrochlorides is taken up in 150 ml hot water. The aqueous solution is washed 2 times with 10 ml diethyl ether/petroleum ether (60°C) 1:1, then saturated with solid NaCl, and extracted with 3 portions of 25 ml dichloromethane each. The org. layer is dried ($MgSO_4$) and evaporated *i.vac.* to yield 2.83 g (79%) of a solidifying white foam. The mixture dissolved in a minimal volume of ethyl acetate is chromatographed in a column of 420 g silica-gel (the ratio of 150:1 is crucial for the selective liberation of *cis*-**6a** free base). The free base 2-benzamido-*N*-(1-phenylethyl)-cyclohexanamin (**6a**) is eluted with ethyl acetate/petroleum ether (60°C) 2:1 completely. **5a · HCl** is eluted with 200 ml of a mixture of ethyl acetate/dichloromethane/ethanol 6:2:2. The *cis*-amine **6a** is transformed into its hydrochloride by dry HCl in diethyl ether and crystallized from dichloromethane/diethyl ether to yield 1.66 g (46%) of colorless crystalline material. The eluted **5a · HCl** is recrystallized from methanol/diethyl ether as white needles: 0.81 g (23%).

trans- and cis-2-Phenylacetamido-N-(1-phenyl-ethyl)-cyclohexanamin (**5b · HCl** *and* **6b · HCl**)

10 mmol phenylacetamido-imine **4b** yield 3.07 g (82%) **5b · HCl** and **6b · HCl** as a solidifying white foam. Their chromatographic separation is executed with eluents of higher polarity:

cis-base **6b**: ethyl acetate/petroleum ether (60°) 6:1, yield: 1.8 g (48%).- **6b · HCl** from dichloromethane/diethylether 1:5.

trans **5b · HCl**: ethyl acetate/dichloromethane/ethanol 6:2:4, yield: 0.9 g (24%).- **5b · HCl** from methanol/diethylether 1:4.

Elemental analysis and physical data of **5a · HCl**, **5b · HCl**, **6a · HCl**, and **6b · HCl** are summarized in Tab. 7, NMR-data in Tab. 2.

Tab. 7: Elemental analysis and physical data of the secondary 2-amido-cyclohexanamines **5** and **6**.

trans-2-Benzamido-N-(1-phenylethyl)-cyclohexanamin-hydrochloride (5a·HCl)

$C_{21}H_{27}ClN_2O$	$[\alpha]_D^{21}$ (in EtOH)	mp		% C	% H	%N
MW.: 358.90		(° C)	Calcd.	70.3	7.58	7.8
1R,2R,1'R	+5.8 (c=1.67 g/100ml)	192-194	Found	70.0	7.69	7.8
1S,2S,1'S	- 6.6 (c=1,59 g/100ml)	190-193	Found	70.1	7.69	8.0

cis-2-Benzamido-N-(1-phenylethyl)-cyclohexanamin-hydrochloride (6a·HCl)

$C_{21}H_{27}ClN_2O$	$[\alpha]_D^{22}$ (in EtOH)	mp		% C	% H	% N
MW.: 358.90		(° C)	Calcd.	70.3	7.58	7.8
1R,2S,1'R	+71.4 (c=0.62 g/100ml)	187-189	Found	70.0	7.71	7.7
1S,2R,1'S	- 70.9 (c=0.58 g/100ml)	188-191	Found	70.1	7.94	7.9

trans-2-Phenylacetamido-N-(1-phenylethyl)-cyclohexanamin-hydrochloride(5b·HCl)

$C_{22}H_{29}ClN_2O$	$[\alpha]_D^{25}$ (in EtOH)	mp		% C	% H	%N
MW.: 372.92		(° C)	Calcd.	70.8	7.84	7.5
1R,2R,1'R	+68.7 (c=0.75 g/100ml)	198-200	Found	70.9	7.73	7.7
1S,2S,1'S	-67.9 (c=0.63 g/100ml)	200-202	Found	71.1	8.00	7.3

cis-2-Phenylacetamido-N-(1-phenylethyl)-cyclohexanamin-hydrochloride (6b·HCl)

$C_{22}H_{29}ClN_2O$	$[\alpha]_D^{26}$ (in EtOH)	mp		% C	% H	%N
MW.: 372.92		(° C)	Calcd.	70.9	7.84	7.5
1R,2S,1'R	+52.6 (c=0.97g/100ml)	189-191	Found	70.6	7.75	7.8
1S,2R,1'S	- 51.8 (c=0.82 g/100ml)	190-192	Found	71.1	7.72	7.3

*trans- and cis-2-Benzamido-cyclohexanamin-hydrochloride (***7a** *and* **8a**)

*trans- and cis-2-Phenylacetamido-cyclohexanamin-hydrochloride (***7b** *and* **8b**)

1 mmol of secondary amido-amine-hydrochloride **5a,5b,6a,6b**, dissolved in 4 ml dry methanol, are refluxed under N_2 with 300 mg anhydrous ammonium formate and 200 mg 10% Pd/C for 30 min (TLC: ethyl acetate/2N ethanolic NH_3/cyclohexane 3:2:5), then filtered over celite and rinsed with ethanol. Evaporation *i.vac.* yields a solid which is dissolved in 5 ml water. The aqueous phase is washed twice with 2 ml diethyl ether and made alkaline with conc. ammonia, saturated with NaCl and extracted three times with 10 ml dichloromethane each. The org. layer is dried over $MgSO_4$, filtered and evaporated *i.vac.* The primary amido-amine **7a,7b,8a,8b** is obtained in 86% yield as white needles from dichloromethane/ligroin or as hydrochloride by neutralizing a solution of the free base with dry HCl in diethyl ether.- Elemental analysis and physical data of the hydrochlorides: Tab. 8, NMR-data of the free bases: Tab. 3.

Tab. 8: Elemental analysis and physical data of the primary amido-amines **7** and **8**.

trans-2-Benzamido-cyclohexanamin-hydrochloride (7a·HCl)

$C_{13}H_{19}N_2OCl$	$[\alpha]_D^{25}$ (in EtOH)	mp		% C	% H	%N
MW.: 254.75		(° C)	Calcd.	61.3	7.52	11.0
1R,2R	- 26.1 (c=1.16 g/100ml)	254-256	Found	61.1	7.33	11.2
1S,2S	+25.8 (c=1.08 g/100ml)	252-255	Found	61.5	7.62	10.7

cis-2-Benzamido-cyclohexanamin-hydrochloride (8a·HCl)

$C_{13}H_{19}N_2OCl$	$[\alpha]_D^{25}$ (in EtOH)	mp		% C	% H	%N
MW.: 254.75		(° C)	Calcd.	61.3	7.52	11.0
1R,2S	-14.9 (c=1.16 g/100ml	194-196	Found	61.3	7.57	11.0
1S,2R	+15.2 (c=1.08 g/100ml)	194-197	Found	61.2	7.51	10.8

trans-2-Phenylacetamido-cyclohexanamin-hydrochloride (7b·HCl)

$C_{14}H_{20}N_2O$·HCl	$[\alpha]_D^{25}$ (in EtOH)	mp		% C	% H	%N
MW.: 268.78		(° C)	Calcd.	62.6	7.88	10.4
1R,2R	- 5.7 (c=1.67 g/100ml)	272-74 (dec)	Found	62.8	7.58	10.7
1S,2S	+4.9 (c=1.49 g/100ml)	272-75 (dec)	Found	62.5	7.97	10.4

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