Pergamon

Tetrahedron 54 (1998) 1013–1020

TETRAHEDRON

Synthesis and Ring–Chain Tautomerism of Angularly Substituted Cycloalkane-Fused Tetrahydro-1,3-oxazines♦

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Received 31 October 1997; accepted 13 November 1997

***Abstract**: Starting from 1-methyl-1-cyclopentene and -cyclohexene, regioisomeric 1,3-amino alcohols **6a,b** and **7a,b** were prepared by regio- and stereospecific reactions. When the amino alcohols were condensed with aromatic aldehydes, well-defined products **8-11** were obtained, which exist as three-component tautomeric mixtures in $CDCl_3$ solution. When equation (1) was applied in all four sets **8-11**, good linear correlations were obtained. For regioisomeric compounds, introduction of the methyl group in the bridgehead position resulted in reverse effects on the stability.*

INTRODUCTION

Because of the theoretical and pharmacological importance of carbocycle-fused saturated heterocycles, the synthesis and conformational study of cycloalkane *cis*- or *trans*-fused saturated 1,3-heterocycles has been one of our main research topics for many years.[1] Although a great number of publications deal with carbocycle-fused 1,3-heterocycles, very little attention has been paid to derivatives substituted at the annelations.[2,3]

The well-known ring–chain tautomerism of tetrahydro-1,3-oxazines and oxazolidines sheds light on the reactivities of these compounds. Comparative studies have been carried out on the ring–chain tautomerism of a wide range of 2-aryl-substituted tetrahydro-1,3-oxazines: tetrahydro-1,3-oxazines, 1,3- and 3,1-perhydrobenzoxazines, and hexahydrocyclopent[*d*]- and cyclopent[*e*]-1,3-oxazines.[4,5-7] For all these series, the following equation is valid:

$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

where K_X = [ring]/[chain] and ρ is a constant characteristic of the ring system. In $CDCl_3$ solution at ambient temperature, ρ is 0.76(4) for tetrahydro-1,3-oxazines. It has also been demonstrated that $\log K_{X=H}$ changes with the substituents of the oxazine ring at positions 4, 5 and 6. A new constant *c* was introduced, as the difference between the intercept values for the oxazine in question and the unsubstituted 2-phenyl-1,3-tetrahydro-1,3-oxazine, where the intercept is -0.15. The constant *c* reflects the steric and electronic contributions of the substituents at positions 4, 5 and 6, and its value is characteristic of the stability of the oxazines.[5]

Our present aim was a comparative study of the ring–chain tautomerism of cycloalkane-fused 1,3-oxazines with a methyl group at the bridgehead, in order to study the steric effect of the methyl substituent.

RESULTS AND DISCUSSION

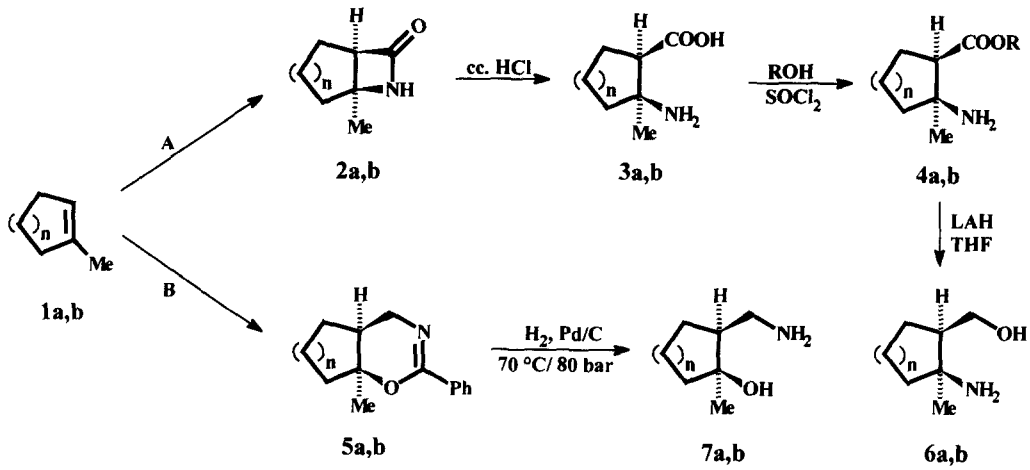
The synthetic routes to the model amino alcohols are shown in Scheme 1. The reaction of chlorosulphonyl isocyanate (CSI) with different cycloalkenes is a well-known route for the synthesis of

♦ Saturated Heterocycles, Part 260. Part 259: Huber, I., Fülöp, F., Szabó, Á., and Bernáth, G. *J. Heterocyclic Chem.*, submitted for publication

0040-4020/98/$19.00 © 1997 Published by Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(97)10355-6

cycloalkane-fused β-lactams.[8,9] There are several examples in the literature for the regio- and stereospecificity of the cycloaddition, in accordance with the Markovnikov orientation of CSI addition.[10-12] Starting from 1-methyl-1-cyclopentene or -cyclohexene (**1a,b**), cycloaddition of CSI furnished the corresponding β-lactams **2a** and **2b** in a regio- and stereospecific reactions. Treatment of the azetidinones with hydrochloric acid resulted in amino acids **3a** and **3b**, which are 2-methyl-substituted analogues of *cispentacin*, a naturally occurring antibiotic recently isolated from *Bacillus cereus* and *Streptomyces setonii*, which exerts a marked protective effect against *Candida albicans* and *Cryptococcus neoformans* in mice.[13-18]

Esterification of **3a** and **3b** (the low yield of the ethyl ester of **3b** led us to prepare the methyl ester),[19] followed by lithium aluminium hydride (LAH) reduction of the amino esters **4a** and **4b**, furnished the amino alcohols **6a** and **6b** (Scheme 1).



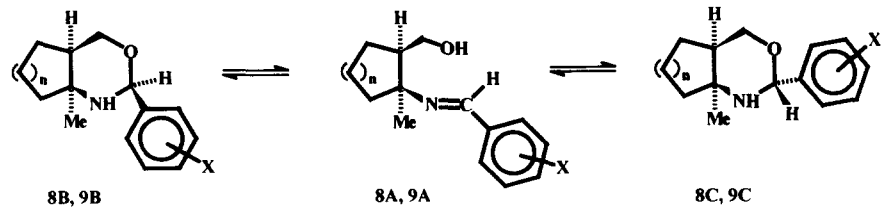
A: $ClSO_2NCO$/ether; B: *N*-hydroxymethylbenzamide/glacial acetic acid, conc. H_2SO_4; **a**: n = 1; **b**: n = 2; **4a**: R = Et; **4b**: R = Me

Scheme 1

The syntheses of the regioisomeric amino alcohols also started from 1-methyl-1-cyclopentene or -cyclohexene. Amidoalkylation of various olefins is a good preparative method for the synthesis of dihydro-1,3-oxazines, suitable precursors for the synthesis of 1,3-amino alcohols.[20,21] The reaction proceeds *via* a 1,4-polar cycloaddition, which occurs regiospecifically and stereospecifically *cis*, yielding products in accordance with Markovnikov's rule.[1] Starting from the corresponding cycloalkene, cycloaddition of *N*-hydroxy-methylbenzamide furnished 1,3-oxazines **5a** and **5b** in a regio- and stereospecific reaction. Catalytic reduction of the 1,3-oxazines in the presence of palladium-on-carbon gave the amino alcohols **7a** and **7b**, respectively (Scheme 1).

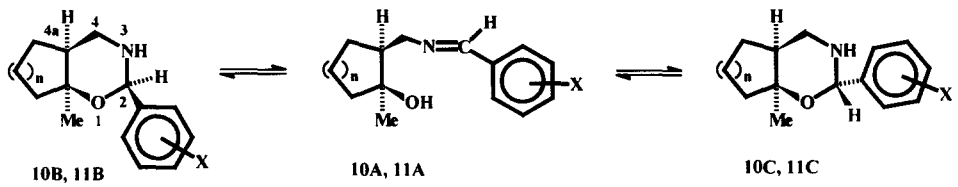
Determination of the stereochemistry of the starting substances **2** and **5** was based on the ROESY spectra. The integrals of the corresponding crosspeaks were used to estimate the distance of the hydrogen and methyl group at the ring anelation. The results showed that **2a**, **2b**, **5a** and **5b** have *cis*-fused rings. Since the further reaction steps in the synthesis do not affect the stereochemistry at these positions, the stereochemistry of the other compounds was not investigated further. The ROESY data on **2a**, **2b**, **5a** and **5b** may be found in the Experimental section.

Amino alcohols **6a,b** and **7a,b** were condensed in ethanolic solution with nine (sets **8**, **9** and **10**) or eight (set **11**) aromatic aldehydes with different electronic characters. The reactions reached completion within a few hours, even at room temperature, and, after evaporation and purification, well-defined products were obtained, which existed as three-component tautomeric mixtures in $CDCl_3$ solution (Scheme 2). For the tautomeric equilibria to be reached, the substances were left to stand for 24 hours in $CDCl_3$.



8B, 9B 8A, 9A 8C, 9C

8: n = 1; 9: n = 2; X = *p*NO_2: a, *p*CN: b, *p*Cl: c, *m*Br: d, *p*Br: e, H: f, *p*Me: g, *p*MeO: h, *p*NMe_2: i



10B, 11B 10A, 11A 10C, 11C

10: n = 1; X = *p*NO_2: a, *m*NO_2: b, *p*Br: c, *p*Cl: d, *m*MeO: e, H: f, *p*Me: g, *p*MeO: h, *p*NMe_2: i

11: n = 2; X = *p*NO_2: a, *p*Br: b, *p*Cl: c, *m*MeO: d, H: e, *p*Me: f, *p*MeO: g, *p*NMe_2: h

Scheme 2

Previous dynamic NMR measurements revealed that the *cis*-oxazadecalins attain a homogeneous double-chair conformation, where the heteroatom (O or NH) attached to the cyclohexane ring is in the *axial* position and the 2-aryl group is *equatorial*.[5,22] Analysis of the ROESY spectra of the tautomeric mixtures of **8-11** showed that the preferred rings are those in which the methyl and aryl groups are in the *trans* arrangement (**B** forms), and 2-aryl is always *equatorial* (*e.g.* the calculated distances of Me-2H in **10a** are: 2.4 Å (**10Ba**) and 3.8 Å (**10Ca**).

These results differ from those of our earlier experiments on 2-aryl-substituted cycloalkane-fused tetrahydro-1,3-oxazines, where only two-component tautomeric mixtures were observed. The determination of the tautomeric ratios was based on the integrals of the well-separated proton signals. In the 400 MHz spectra, the signals of the C-2 methylene protons of the ring forms and the corresponding methine proton of the open-chain form were used (Table 2). The characteristic data are given in Table 1.

Table 1. Selected ^{1}H-NMR Chemical Shifts (δ, ppm) and Coupling Constants (*J*, Hz) for Compounds **8a-i**, **9a-i**, **10a-h** and **11a-h**[a]

Compound	Form	Chemical shifts (ppm)					Couplings (Hz)		
		2H	$4H_{ax}$	$4H_{eq}$	4aH	Me	4*ax*4a	4*eq*4a	4*ax*4*eq*
8Bi	*N-in*	5.14	4.06	3.99	1.50	1.37	2.7	1.5	-11.8
8Ci	*N-out*	5.22	3.68	3.82	1.67	1.31	6.8	3.0	-11.3
8Ai	open	8.18	3.43	3.96	1.93	1.17	11.8	6.6	-11.8
9Bi	*N-in*	5.35	4.29	3.69	1.20	1.37	2.5	1.1	-11.6
9Ci	*N-out*	5.31	4.01	3.81	1.72	1.20	11.6	4.8	-11.6
9Ai	open	8.14	3.66	4.32	1.40	1.29	3.5	2.0	-11.1
10Ba	*O-in*	5.35	3.36	3.03	1.59	1.44	3.6	1.0	-14.3
10Ca	*O-out*	5.41	2.73	3.10	1.59	1.42	12.1	6.4	-14.2
10Aa	open	8.34	3.82	3.99	1.98	1.35	5.4	5.3	-12.4
11Ba	*O-in*	5.56	3.59	3.71	1.27	1.42	3.5	1.5	-14.1
11Ca	*O-out*	5.52	3.26	2.90	1.71	1.41	12.3	4.8	-14.2
11Aa	open	8.28	3.53	4.28	1.69	1.42	3.0	4.8	-12.8

[a] For easier comparison of the spectroscopic data the ring and chain forms, the same numbering (Scheme 2, **8B**, **9B**) has been used.

The selected NMR data in Table 1 clearly show that the different C-2 epimeric ring forms have different predominant conformations (*in* and *out*), preferably those where the 2-aryl group is *equatorial* (Scheme 3). The coupling constant data on the open forms are averaged values for the *in* and *out* forms, where the dominant conformation is the *in* (Scheme 3). The percentages of the ring forms change in parallel with the electron-donating–electron-withdrawing character of the aryl substituent.

Table 2. Ring–chain Tautomerism Data for Compounds **8-11**

Com-pound	X	σ^+	R^B (%)	R^C (%)	O (%)	log K
8a	*p*NO_2	0.790	67.3	31.0	1.7	1.76
8b	*p*CN	0.660	70.3	28.4	1.3	1.75
8c	*m*Br	0.410	65.4	31.5	3.1	1.50
8d	*p*Br	0.150	64.8	31.0	4.1	1.35
8e	*p*Cl	0.110	71.8	22.8	5.4	1.24
8f	H	0.0	63.7	30.1	6.2	1.18
8g	*p*Me	-0.310	58.7	29.8	11.5	0.89
8h	*p*OMe	-0.780	54.6	27.8	17.6	0.67
8i	*p*NMe_2	-1.700	36.3	19.8	43.9	0.11
9a	*p*NO_2	0.790	60.5	39.2	>0.5	-
9b	*p*CN	0.660	60.4	38.6	1.0	1.97
9c	*m*Br	0.410	54.8	44.0	1.2	1.91
9d	*p*Br	0.150	54.2	42.5	3.3	1.47
9e	*p*Cl	0.110	54.5	41.5	4.0	1.37
9f	H	0.0	53.8	41.3	4.9	1.29
9g	*p*Me	-0.310	51.9	39.5	8.6	1.03
9h	*p*OMe	-0.780	48.9	37.6	13.5	0.81
9i	*p*NMe_2	-1.700	29.6	23.0	47.4	0.05
10a	*p*NO_2	0.790	73.4	6.7	19.9	0.61
10b	*m*NO_2	0.674	72.1	6.5	21.4	0.56
10c	*p*Br	0.150	49.5	4.2	46.3	0.06
10d	*p*Cl	0.110	46.3	4.3	49.4	0.01
10e	*m*OMe	0.047	38.5	3.3	58.2	-0.14
10f	H	0.0	36.6	3.3	60.2	-0.18
10g	*p*Me	-0.310	25.6	2.5	71.2	-0.41
10h	*p*OMe	-0.780	18.3	2.2	79.5	-0.59
10i	*p*NMe_2	-1.700	4.4	0.4	95.2	-1.30
11a	*p*NO_2	0.790	32.1	15.8	52.1	-0.04
11b	*p*Br	0.150	13.7	6.0	80.3	-0.61
11c	*p*Cl	0.110	13.9	6.0	81.3	-0.61
11d	*m*OMe	0.047	9.5	4.2	86.3	-0.80
11e	H	0.0	9.6	3.9	86.5	-0.81
11f	*p*Me	-0.310	5.7	2.6	91.7	-1.04
11g	*p*OMe	-0.780	4.0	2.0	94.0	-1.20
11h	*p*NMe_2	-1.700	>0.5	>0.5	<99.5	-

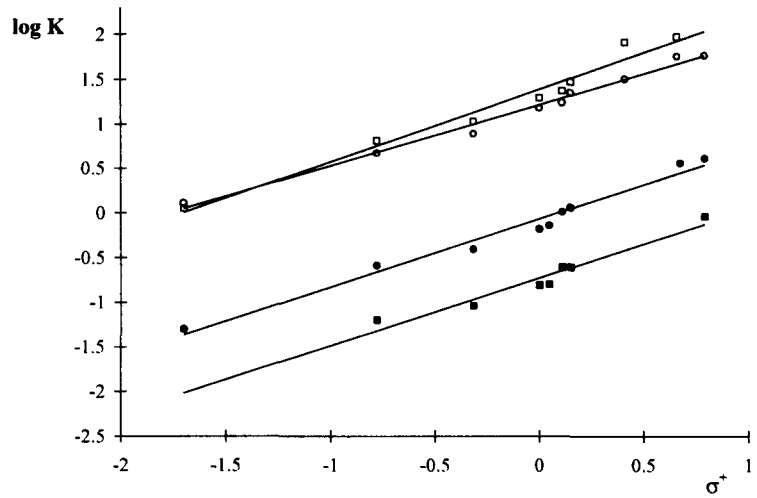
When equation (1) was applied to the log K values, good linear correlations were obtained versus the Hammett σ^+ for all four compounds **8-11** (Figure 1, Table 3). For the methyl-substituted derivatives **8** and **9**, the *c* values, the sums of the steric and electronic effects for the substituted oxazines, are high compared to those for the compounds with no methyl substituent at the bridgehead. The bridgehead methyl substituent next to the nitrogen atom stabilizes the ring forms relative to the open chain forms.

Table 3. Linear Regression Data for Compounds **8-11**

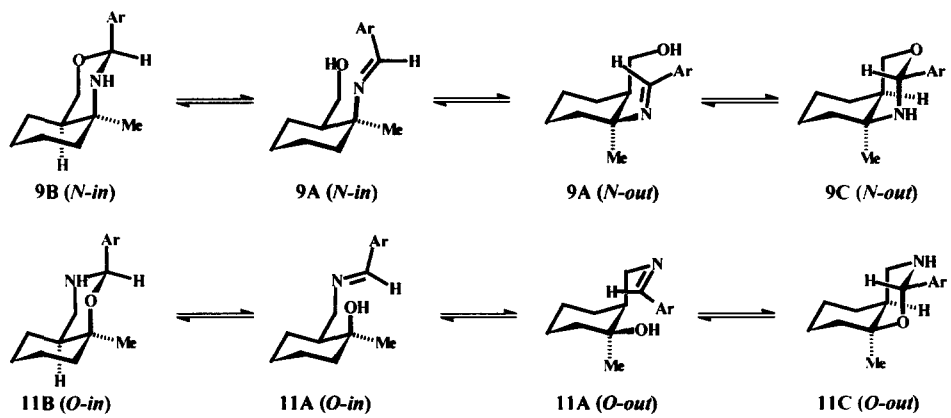
Compound	No. of points	Slope[a]	Intercept[a]	Correlation coefficient	c^a
8	9	0.69 (0.72)	1.21 (0.22)	0.994	1.36 (0.37)
9	8	0.81 (0.75)	1.39 (0.79)	0.986	1.54 (0.94)
10	9	0.76 (0.71)	-0.07 (0.46)	0.988	0.08 (0.61)
11	7	0.76 (0.72)	-0.73 (0.42)	0.971	-0.58 (0.57)

[a] The data on the corresponding cycloalkane-fused tetrahydro-1,3-oxazines, without an annellation methyl group, are given in brackets[5,6]

Figure 1. Hammett Plots (Equation 1) for Compounds **8** (○), **9** (□), **10** (●), and **11** (■)



We believe that this stabilization may occur by a relative destabilization of the imino (open-chain) form. In this molecule, the aryl is necessarily *trans* to the cycloalkyl about the C=N double bond and the hydrogen *cis* to the cycloalkyl ring suffers from steric interactions not present with H at the bridgehead. The smaller *c* values for the cyclopentane-fused compounds can be explained by the strain due to the cyclopentane ring fusion, which relatively destabilizes the ring forms (Scheme 3).



Scheme 3

The effect of the bridgehead methyl group changes dramatically in the regioisomeric compounds **10** and **11**, as can be seen by the very small *c* values (Figure 1, Table 4). In these molecules, there is no relative destabilization of the open-chain imino form as described above, but the bridgehead methyl in the *trans* methyl aryl isomers **10b, 11b** is *axial* in the 1,3-oxazine ring. This will buttress the *axial* oxygen substituent into the cycloalkyl ring, destabilizing the cyclic forms of the molecule.

We suggest, therefore, that the relative changes in stability on introduction of the bridgehead methyl arise from relative destabilization of the open-chain imine form in the series **8** and **9**, and from relative destabilization of the cyclic forms in the series **10** and **11**.

EXPERIMENTAL

The NMR spectra were recorded on a BRUKER AVANCE DRX 400 spectrometer, using a "5 mm inverse Z gradient" probehead. The samples were dissolved in $CDCl_3$ containing 0.03% of TMS as reference, except for **3a**, **4a**, **3b** and **4b**, where the hydrochloride form was used in D_2O with 0.05% of DSS as reference. The number of scans was usually 64 for ^1H and 2K for ^{13}C spectra. The parameters of 2D spectra (COSY, HMBC, HMQC and ROESY) depended on the concentrations of the samples (number of scans) and the relative dispersion of the spectrum (resolution in F1 and F2). All NMR measurements were carried out at 300 K.

Melting points were determined on a Kofler apparatus and are uncorrected. The physical and analytical data on compounds **2-7** are listed in Table 4.

Table 4. Physical and Analytical Data on Compounds **2-7**

Compound	Yield (%)	M.p./B.p. (°C)	Found (%)			Formula (M.W.)	Requires (%)		
			C	H	N		C	H	N
2a	84.7	a	67.17	8.86	11.19	$C_7H_{11}NO$ (125.17)	67.24	8.76	11.53
2b	88.9	a	69.03	9.41	10.06	$C_8H_{13}NO$ (139.20)	69.44	9.49	9.87
3a	91.6	187-89[b]	46.80	7.85	7.80	$C_7H_{14}NO_2Cl$ (179.65)	46.89	7.75	7.93
3b	94.1	221-23[b]	49.61	8.33	7.23	$C_8H_{16}NO_2Cl$ (193.67)	49.50	8.65	7.42
4a	82.4	154-57[c]	52.05	8.74	6.74	$C_9H_{18}NO_2Cl$ (207.70)	52.35	8.89	6.51
4b	78.3	181-84[c]	52.05	8.74	6.74	$C_9H_{18}NO_2Cl$ (207.70)	52.41	8.93	6.87
5a	49.6	55-58[d]	78.10	7.96	6.51	$C_{14}H_{17}NO$ (215.30)	78.05	7.78	6.72
5b	51.7	51-53[d]	78.56	8.35	6.11	$C_{15}H_{19}NO$ (229.32)	78.49	8.52	6.32
6a	79.3	125-27 (Bp_{23})	65.07	11.70	10.84	$C_7H_{15}NO$ (129.20)	65.44	11.62	10.71
6b	66.2	135-38 (Bp_{27})	67.09	11.96	9.78	$C_8H_{17}NO$ (143.23)	67.56	11.74	9.86
7a	56.8	123-26 (Bp_{23})	65.07	11.70	10.84	$C_7H_{15}NO$ (129.20)	65.23	11.54	10.92
7b	75.1	80-82 (Bp_5)	67.09	11.96	9.78	$C_8H_{17}NO$ (143.23)	66.83	11.81	10.08

[a]The oily product was used without futher purification. Solvent for recrystallization: [b]Acetone–water. [c]Ethyl acetate–isopropyl ether. [d]Hexane.

***cis*-5-Methyl-6-azabicyclo[3.2.0]heptan-7-one (2a), *cis*-6-Methyl-7-azabicyclo[4.2.0]octan-8-one (2b)**

A mixture of 156.0 mmol of cycloalkene **1a** or **1b** and 23.15 g (163.6 mmol) of chlorosulphonyl isocyanate was refluxed in 100 ml of dry ether for 8 h. 33 g of sodium sulphite in 200 ml water was then added dropwise cautiously. The pH was held at 7-8 by addition of 15% aqueous potassium hydroxide. After separation of the organic phase, the aqueous layer was extracted twice with diethyl ether. The combined organic layers were dried (Na_2SO_4) and evaporated. **2a**: ^1H-NMR ($CDCl_3$): δ 6.17 (1 H, bs, NH); 3.02 (1 H, dd, ^3J = 7.8, ^3J = 1.6); 1.98 (1 H, m); 1.89-1.77 3 H, m); 1.56 (1 H, m); 1.52 (3 H, s, Me); 1.36 (1 H, m). ^{13}C-NMR ($CDCl_3$): δ 170.1; 62.9; 60.4; 35.9; 25.9; 24.2; 23.1. ROESY data in Å: 2.3 (Me-H1), 2.5 (Me-H2), 2.1 (H1-H2). **2b**: ^1H-NMR ($CDCl_3$): δ 5.97 (1 H, bs, NH); 2.82 (1 H, m); 1.88 (1 H, m); 1.80-1.58 (5 H, m); 1.58-1.44 (2 H, m);

1.33 (3H, s, Me);^{13}C-NMR ($CDCl_3$): δ 171.3; 54.0; 53.9; 32.0; 27.4; 19.8; 18.2; 17.4. ROESY data in Å: 2.1 (Me-H1), 2.5 (H1-H2).

cis-2-Amino-2-methyl-1-cyclopentanecarboxylic acid hydrochloride (3a), _cis_-2-Amino-2-methyl-1-cyclohexanecarboxylic acid hydrochloride (3b)

To 10 mmol of azetidinone **2a** or **2b**, 25 ml of conc. aqueous hydrochloric acid was added. After stirring for 2 h at room temperature, the mixture was evaporated to dryness in vacuo. The solid residue was washed with acetone and recrystallized from ethanol–diethyl ether. **3a**: ^{1}H-NMR (D_2O): δ 2.85 (1 H, dd, ^3J = 10.2, ^3J = 9.0; 2.19 (1 H, m); 1.98-1.72 (5 H, m); 1.45 (3 H, s, Me); ^{13}C-NMR (D_2O): δ 176.5; 62.6; 51.9; 37.8; 27.8; 23.6; 23.5; 23.3; 20.8. **3b**: ^{1}H-NMR (D_2O): δ 2.55 (1 H, dd, ^2J = -11.3, ^3J = 3.9); 1.95-1.79 (2 H, m); 1.70-1.48 (4 H, m); 1.46-1.28 (3 H, m); 1.33 (3 H, s, Me); ^{13}C-NMR (D_2O): δ 177.8; 54.3; 49.0; 35.2; 25.1; 24.9; 23.2; 20.1

Ethyl _cis_-2-amino-2-methyl-1-cyclopentanecarboxylate hydrochloride (4a)

Thionyl chloride (2.22 ml, 30.5 mmol) was added dropwise with stirring to 25 ml of dry ethanol at -12 °C. 2-Amino-2-methyl-1-cyclopentanecarboxylic acid hydrochloride (**3a**) (5.0 g, 27.8 mmol) was added in one portion to the mixture, which was stirred for 30 min at 0 °C. After standing for 3 h at room temperature, the mixture was refluxed for a further 30 min and then evaporated. The residue was recrystallized from isopropyl ether–ethyl acetate. **4a**: ^{1}H-NMR (D_2O): δ 4.15 (2 H, q, ^3J = 7.0); 2.87 (1 H, dd, ^3J = 9.8, ^3J = 9); 2.17 (1 H, m); 1.98-1.72 (5 H, m); 1.44 (3 H, s, Me); 1.20 (3 H, t, ^3J = 7.0); ^{13}C-NMR (D_2O): δ 174.7; 62.9; 62.7; 52.5; 52.2; 38.1; 37.8; 28.1; 27.9; 23.7; 20.9.

Methyl _cis_-2-amino-2-methyl-1-cyclohexanecarboxylate hydrochloride (4b)

Thionyl chloride (6.6 ml, 90.6 mmol) was added dropwise with stirring to 80 ml of dry methanol at -12 °C. 2-Amino-2-methyl-1-cyclopentanecarboxylic acid hydrochloride (**3b**) (16.0 g, 82.6 mmol) was added in one portion to the mixture, which was stirred for 30 min at 0 °C. After standing for 3 h at room temperature, the mixture was refluxed for a further 30 min and then evaporated. The residue was recrystallized from isopropyl ether–ethyl acetate. **4b**: ^{1}H-NMR (D_2O): δ 3.68 (3 H, s, COOMe); 2.65 (1 H, dd, ^2J = -11.7, ^3J = 3.9); 1.93-1.80 (2 H, m); 1.70-1.49 (4 H, m); 1.47-1.28 (2 H, m); 1.31 (3 H, s, Me); ^{13}C-NMR (D_2O): δ 176.0; 54.5; 52.9; 49.0; 35.5; 25.0; 24.9; 23.2; 20.1

cis-2-Hydroxymethyl-1-methyl-1-cyclopentylamine (6a), _cis_-2-Hydroxymethyl-1-methyl-1-cyclohexylamine (6b)

To a slurry of LAH (4.66 g, 21.9 mmol) in 150 ml of dry THF, amino ester **4a** or **4b** (43.0 mmol) in 20 ml of THF was added dropwise at 0 °C. After stirring and refluxing for 2 h (the end of the reduction was detected by means of TLC), the mixture was decomposed with 10 ml of water under ice cooling. The inorganic material was filtered off and washed with THF. After drying and evaporation, the resulting yellow oils were vacuum distilled at 20 mm Hg. **6a**: ^{1}H-NMR ($CDCl_3$): δ 3.78 (1 H, dd, ^2J = -11.4, ^3J = 3.5); 3.63 (1 H, dd, ^2J = -11.4, ^3J = 6.3); 3.07-2.13 (3 H, bs, NH_2 and OH); 1.83-1.50 (7 H, m); 1.26 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$): δ 63.4; 62.6; 60.1; 48.8; 43.3; 30.1; 29.6; 26.7; 21.8. **6b**: ^{1}H-NMR ($CDCl_3$): δ 4.17 (1 H, dd, ^2J = -11.4, ^3J = 2.7); 3.49 (1 H, dd, ^2J = -11.4, ^3J = 2.7); 1.81-1.52 (4 H, m); 1.50-1.14 (5 H, m); 1.24 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$): δ 65.4; 52.2; 45.7; 42.3; 29.2; 25.9; 25.8; 22.1

cis-7a-Methyl-2-phenylcyclopent[_e_]-4,4a,5,6,7,7a-hexahydro-1,3-oxazine (5a), _cis_-8a-Methyl-2-phenyl-4a,5,6,7,8,8a-hexahydro-(4_H_)-1,3-benzoxazine (5b)

To a solution of _N_-hydroxymethylbenzamide (15.1 g, 100 mmol) and the cycloalkene **1a** or **1b** (120 mmol) in glacial acetic acid (80 ml), a mixture of conc. sulphuric acid (10.0 g) and glacial acetic acid (30 ml) was added dropwise, with stirring and cooling in ice-water at 15-18 °C. The mixture was stirred for 6 h at room temperature, then poured onto 500 g of ice, and the solution was extracted with diethyl ether (2x30 ml). The aqueous fraction was made alkaline with 30% sodium hydroxide solution under cooling in ice, and extracted with diethyl ether (3x50 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to obtain an oily residue, which was purified by vacuum distillation. **5a**: ^{1}H-NMR ($CDCl_3$): δ 7.93 (2 H, m, Ar); 7.38 (3 H, m, Ar); 3.65 (1 H, dd, ^2J = -16.6, ^3J = 5.0); 3.54 (1 H, dd, ^2J = -16.6, ^3J = 1.5); 2.09 (1 H, m); 1.98 (1 H, m); 1.92-

1.53 (5 H, m); 1.41 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$): δ 155.9; 135.2; 130.8; 128.6; 127.6; 85.0; **44.2**; 44.1; 40.3; 28.8; 24.6; 24.5. ROESY data in Å: 3.0 (Me-H4$_{ax}$), 2.4 (H4a-H4$_{eq}$), 2.9 (Me-H4a). **5b**: ^{1}H-NMR ($CDCl_3$): δ 7.97 (2 H, d, ^3J = 6.7 Ar); 7.45-7.30 (3 H, m, Ar); 3.83 (1 H, dd, ^2J = -17.2, ^3J = 5.5); 3.35 (1 H, dd, ^2J = -17.2, ^3J = 1); 2.01 (1 H, m); 1.79-1.22 (8 H, m); 1.34 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$): δ 154.4; 134.6; 130.1; 127.9; 126.9; 75.2; 47.4; 37.8; 36.2; 27.2; 26.9; 25.0; 21.8. ROESY data in Å: 2.7 (Me-H4$_{ax}$), 2.4 (Me-H4a).

***cis*-2-Aminomethyl-1-methyl-1-cyclopentanol (7a), *cis*-2-Aminomethyl-1-methyl-1-cyclohexanol (7b)**

Oxazine **5a** or **5b** (35.0 mmol) was dissolved in 200 ml of methanol and this solution was heated for 2 days in the presence of 10% palladium-on-carbon (1.73 g) at 70 °C and 80 bar. After cooling, filtration and evaporation, the resulting oil was distilled at reduced pressure. **7a**: ^{1}H-NMR ($CDCl_3$): δ 3.01 (2 H, d, ^3J = 4.0); 2.92-2.64 (3 H, NH_2 and OH); 1.83-1.70 (3 H, m); 1.70-1.52 (4 H, m); 1.32 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$): δ 81.2; 48.6; 42.4; 41.9; 28.8; 28.1; 22.4. **7b**: ^{1}H-NMR ($CDCl_3$): δ 3.21 (1 H, dd, ^2J = -12.6, ^3J = 3.5); 2.90 (1 H, dd, ^2J = -12.6, ^3J = 3.0); 1.83-1.58 (4 H, m); 1.45 (1 H, m); 1.40-1.18 (4H, m); 1.29 (3 H, s, Me); ^{13}C-NMR ($CDCl_3$): δ 72.7; 45.2; 44.1; 40.4; 30.4; 26.7; 26.5; 22.8

General procedure to react amino alcohols with aromatic aldehydes (8-11)

Freshly distilled amino alcohol **6a,b** or **7a,b** (1 mmol) was dissolved in 10 ml of dry ethanol, and 1 mmol of freshly distilled or crystallized aldehyde was added. After the mixture had stood for 3 h at room temperature, the solvent was evaporated off, and the product was crystallized. If an oily product formed, the evaporation was repeated twice after the addition of benzene. All products were dried under vacuum for 24 h.

Financial support from the National Scientific Research Foundation, Hungary (OTKA, T 20454 and T 015567) is gratefully acknowledged.

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