Substituent Effects in the Ring-Chain Tautomerism of 4-Alkyl-2-aryl substituted Oxazolidines and Tetrahydro-1,3-oxazines

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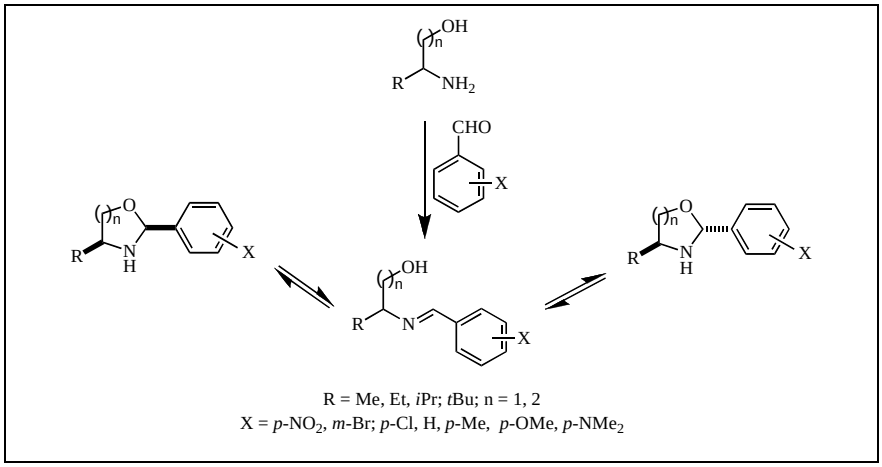

R = Me, Et, *i*Pr; *t*Bu; n = 1, 2
X = *p*-NO_2, *m*-Br; *p*-Cl, H, *p*-Me, *p*-OMe, *p*-NMe_2

The condensation products of 2-aminoethanol or 3-aminopropanol (bearing an alkyl substituent on the carbon adjacent to the nitrogen) with substituted benzaldehydes proved to exist in $CDCl_3$ at 300 K as three-component tautomeric mixtures of the diastereomeric five- or six-membered 1,3-*O*,*N*-heterocyclic ring forms and the corresponding imines. For each equilibrium, the electronic effects of the 2-aryl substituents were characterized by the Hammett equation. The steric effects of the alkyl groups could be described by Hansch-type equations for the equilibria involving oxazolidine ring forms. While the alkyl substituents did not cause any significant effect on the ring *cis*-chain and the ring *trans*-chain equilibria for tetrahydro-1,3-oxazines, increasing bulk of the 4-alkyl group increased the stability of the cyclic tautomers for the analogous oxazolidines.

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INTRODUCTION

The reversible intramolecular addition of a hydroxy group to a C=N double bond to form a cyclic structure is a well-known phenomenon among *N*-unsubstituted 1,3-*O*,*N*-heterocycles. This ring-chain tautomeric process influences the reactivity and therefore the synthetic applicability of these compounds [1]. The reduction of ring-chain tautomeric 1,3-*O*,*N*-heterocycles is a method that has often been applied for the preparation of *N*-substituted 1,2- and 1,3-amino alcohols [2]. Reformatsky and Mannich reactions with the participation of the C=N bond of the open tautomeric form of chiral, non-racemic oxazolidines provided a stereoselective procedure for the synthesis of β-amino esters [3]. Because of their ring-chain tautomeric character, oxazolidines and tetrahydro-1,3-oxazines have been applied as aldehyde sources or aldehyde protecting groups in various inter- or intra-molecular carbon-transfer reactions [4,5]. The differences in the reactivities of the ring-chain tautomeric forms of 1,3-*O*,*N*-heterocycles have been utilized in the diastereoselective transformations of chiral, non-racemic amino alcohols towards bicyclic lactams or 1,2,4-trisubstituted oxazolidines [6,7].

Because of the practical importance of this phenomenon, the substituent effects influencing the ring-chain tautomeric processes of 1,3-*O*,*N*-heterocycles have been studied thoroughly in the past 20 years. Such studies have been extended from simple, two-component equilibria to multicomponent, complicated mixtures and from the liquid to the gas and the solid phases [1,8]. It was recently demonstrated that 2-aryldihydro-3,1-benzoxazines exhibit ring-chain tautomerism under unusual conditions, inside a self-assembled capsule [9].

For the tautomeric equilibria of oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2, in both the liquid and the gas phase, a linear Hammett-type correlation was found between the log K (K = [ring]/[chain]) values of the equilibria and the electronic character (σ^+) of the substituents X on the 2-phenyl group (Eq. 1) [1]:

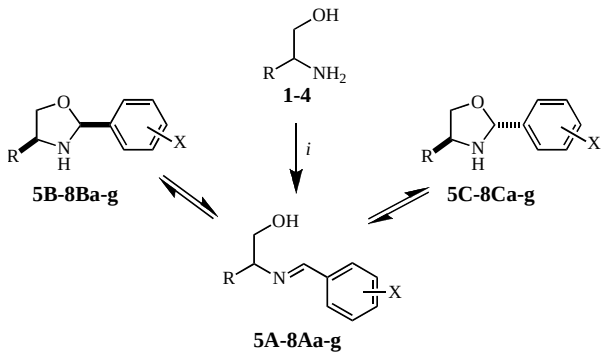
$$\log K = \rho\sigma^+ + \log K_{X=H} \qquad \text{(Eq. 1)}$$

In contrast with the great number of studies on the aromatic substituent dependence of the tautomeric equilibria caused by a substituted phenyl group at position 2 of 1,3-*O*,*N*-heterocycles, only a few examples are known of the

steric and/or electronic effects of other substituents in 2-aryl-1,3-*O*,*N*-heterocyclic systems [10-12]. Anomeric effects of the aryl and alkyl substituents proved to exert a significant influence on the tautomeric ratios of 1,3-diarylnaphth[1,2-*e*]oxazines, 2,4-diarylnaphth[2,1-*e*]oxazines and 1-alkyl-3-arylnaphth[1,2-e]oxazines, the equilibria of which could be characterized by Hansch-type equations [11,12].

As a continuation of our previous quantitative studies on the double substituent effects in the ring-chain tautomerism of five- and six-membered 1,3-*O*,*N*-heterocycles [10-12], our present aim was to investigate the tautomeric character of 4-alkyl-2-aryl-substituted oxazolidines and the corresponding 3,4,5,6-tetrahydro-2*H*-1,3-oxazines. We set out to study the scope and limitations of the application of Hansch-type equations for the tautomeric equilibria of 1,3-*O*,*N*-heterocycles.

Scheme I



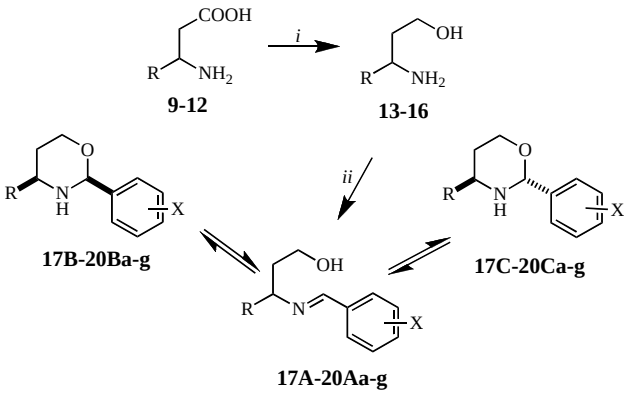
1, **5**: R = Me; **2**, **6**: R = Et; **3**, **7**: R = *i*Pr; **4**, **8**: R = *t*Bu
a: X = *p*-NO_2; **b**: *m*-Br; **c**: *p*-Cl; **d**: H; **e**: *p*-Me; **f**: *p*-OMe; **g**, *p*-NMe_2
Reagents and conditions: (*i*) XC_6H_4CHO, MeOH, r.t., 1 h, 65-100%

RESULTS AND DISCUSSION

The condensations of 2-aminoethanols bearing homologous alkyl substituents with increasing bulk (Me, Et, *i*Pr or *t*Bu) at position 2 (**1**–**4**) with equivalent amounts of aromatic aldehydes resulted in model oxazolidine compounds **5**–**8** (Scheme I). The similar reactions of 3-aminopropanols analogously substituted at position 3 (**13**–**16**), obtained by $LiAlH_4$ reduction of the corresponding β-substituted β-amino acids **9**–**12** [13], led to the tetrahydro-1,3-oxazines **17**–**20** (Scheme II). The ^{1}H nmr spectra of **5**–**8** and **17**–**20** revealed that, in $CDCl_3$ solution at 300 K, each compound participated in three-component ring-chain tautomeric equilibria involving C-2 epimeric cyclic forms (**B** and **C**) besides the open tautomer (**A**).

The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria of **5**–**8** and **17**–**20** were determined by integration of the well-separated O–C*H*Ar–N (ring) and N=C*H*Ar (chain) proton singlets in the ^{1}H nmr spectra (Tables 1 and 2). In consequence of the very similar nmr spectroscopic characteristics of the 2,4-disubstituted oxazolidines **5**–**8** and tetrahydro-1,3-oxazines **17**–**20**, determination of the relative configurations of the *major* and *minor* ring-closed tautomers was performed only for the 2-(*p*-nitrophenyl)-substituted derivatives (**5a**–**8a**; **17a**–**20a**), the NOESY spectra of which unequivocally showed that the *major* ring forms in the tautomeric equilibria of **5**–**8** and **17**–**20** contain H-2 and H-4 in the *cis* position (**B**). 4-Alkyl and 2-aryl substituents did not change the sequence of the chemical shifts of the characteristic O–C*H*Ar–N and N=C*H*Ar protons (see Experimental).

Scheme II



9, **13**, **17**: R = Me; **10**, **14**, **18**: R = Et; **11**, **15**, **19**: R = *i*Pr; **12**, **16**, **20**: R = *t*Bu
a: X = *p*-NO_2; **b**: *m*-Br; **c**: *p*-Cl; **d**: H; **e**: *p*-Me; **f**: *p*-OMe; **g**, *p*-NMe_2
Reagents and conditions: (*i*) $LiAlH_4$, THF, reflux, 8 h, 68-81%;
(*ii*) XC_6H_4CHO, MeOH, r.t., 1 h, 61-100%

Table 1
Proportions (%) of the ring-closed tautomeric forms (**B** and **C**) in tautomeric equilibria for compounds **5**–**8** ($CDCl_3$, 300 K).

Compd.		R(V^a)	**5** Me (2.84)		**6** Et (4.31)		**7** *i*Pr (5.74)		**8** *t*Bu (7.16)	
	X	σ^+	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**
a	*p*-NO_2	0.79	19.9	18.5	21.7	20.4	32.9	26.8	39.5	35.7
b	*m*-Br	0.405	15.1	11.1	16.9	12.5	31.0	19.7	39.1	26.4
c	*p*-Cl	0.114	11.7	7.9	13.4	9.3	26.8	15.2	36.1	23.0
d	H	0	10.3	6.1	12.1	8.1	25.6	14.8	33.5	22.6
e	*p*-Me	-0.311	8.2	4.7	9.2	5.4	10.4	20.6	29.1	17.6
f	*p*-OMe	-0.778	4.7	2.8	5.3	3.2	14.1	7.4	22.6	13.5
g	*p*-NMe_2	-1.7	2.3	0.8	2.3	1.3	7.5	2.1	10.0	5.1

When Eq. 1 was applied to the log K_B and log K_C values (K_B = [**B**]/[**A**], K_C = [**C**]/[**A**]) of **5**–**8** and **17**–**20**, good linear correlations were obtained *vs* the Hammett-Brown parameter σ^+ of the substituent X on the 2-phenyl group, for both the **B** ⇌ **A** and the **C** ⇌ **A** equilibria (Figure 1 and Table 3). As usual for 2-aryl-1,3-*O*,*N*-heterocycles, the aryloxazolidine [15] (**21**: log K_0 = –1.10) or 2-arylte-trahydro-1,3-oxazine [16] (**22**: log K_0 = –0.15): c_s = log $K_{X=H}$ – log K_0. A positive value of c_s means a more stable ring form relative to the corresponding parent 2-arylperhydro-1,3-*O*,*N* heterocycle. The different trends observed in the influences of the 4-alkyl substituents in the ring-chain

Table 2

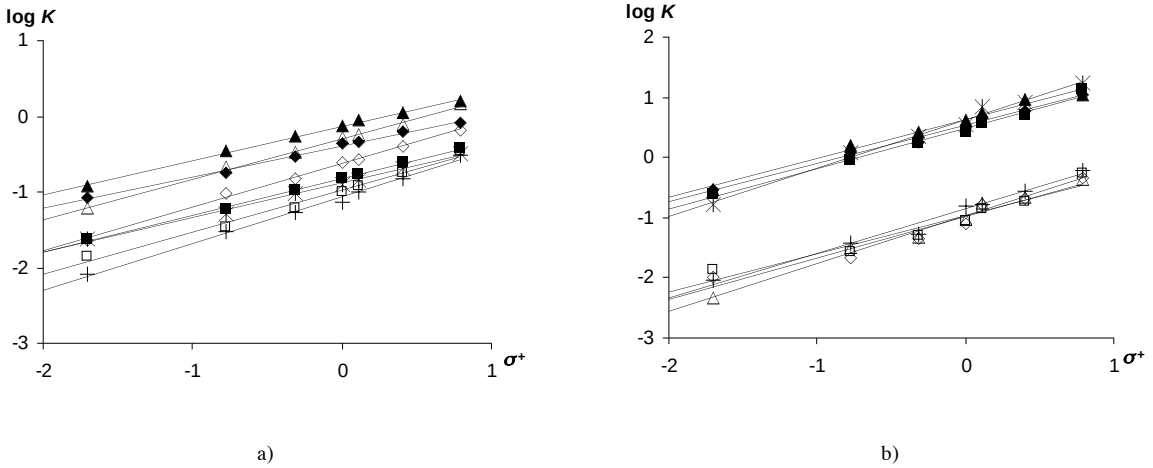
Proportions (%) of the ring-closed tautomeric forms (**B** and **C**) in tautomeric equilibria for compounds **17**–**20** ($CDCl_3$, 300 K)

Compd.		R(V^a)	**17** Me (2.84)		**18** Et (4.31)		**19** *i*Pr (5.74)		**20** *t*Bu (7.16)	
	X	σ^+	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**
a	*p*-NO_2	0.79	91.5	3.2	89.9	3.6	88.4	3.6	88.4	3.5
b	*m*-Br	0.405	86.7	2.9	81.0	2.9	83.0	2.9	88.4	2.1
c	*p*-Cl	0.114	85.4	2.1	76.9	2.9	79.9	2.9	82.1	2.6
d	H	0	75.0	3.4	71.1	2.3	74.6	1.8	79.4	1.8
e	*p*-Me	-0.311	67.9	1.3	61.4	1.8	63.3	1.5	71.7	1.3
f	*p*-OMe	-0.778	57.1	1.7	47.1	1.4	53.5	1.0	60.7	1.2
g	*p*-NMe_2	-1.7	14.0	0.7	19.4	1.1	22.6	0.8	22.9	0.4

value of ρ was positive in each case, *i.e.* the electron-withdrawing property of substituent X on the 2-phenyl ring favours the ring-closed tautomer. This behavior stems from the dipolar trend in the electron density induced at the C=N moiety by the electronic character of substituent X [14].

In contrast with the corresponding 1,3-oxazines **17**–**20**, increasing bulk of the 4-alkyl group proved to enhance the stability of the cyclic tautomers for oxazolidines **5**–**8**, which can be followed by the substitution effect parameter (c_s) introduced earlier to characterize the effects of the substituents at positions 4–6 on the stability of the ring form. Parameter c_s is calculated as the difference in the intercepts for the given compound (**5**–**8** or **17**–**20**) and the parent 2-equilibria of the homologous 1,3-*O*,*N*-heterocycles can be explained by the different conformations of the oxazolidine and oxazine rings, which allows different energetic plots of these cyclic tautomeric forms and influences the stereo-electronic effects of alkyl and aryl substituents on the equilibria of oxazolidines **5**–**8** [12]. Further examinations of the effect of this alkyl substituent are in progress.

The stability differences between the *cis* (**B**) and *trans* (**C**) isomers of the 2,4-disubstituted cyclic forms can be characterized by the differences in their substitution effect parameters (c_s), which are considerably smaller (Δc_s: 0.15–0.24) for the epimeric oxazolidines (**B**, **C**) than for the homologous epimeric oxazines (Δc_s: 1.45–1.60).



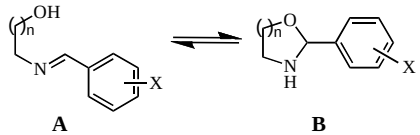
a) b)

Figure 1. (a) Plots of log K_B or log K_C ($CDCl_3$, 300 K) for **5B** (ᚷ), **5C** (+), **6B** (■), **6C** (□), **7B** (♦), **7C** (◊), **8B** (▲), **8C** (Δ) *vs* Hammett-Brown parameter σ^+. (b) Plots of log K_B or log K_C ($CDCl_3$, 300 K) for **17B** (ᚷ), **17C** (+), **18B** (■), **18C** (□), **19B** (♦), **19C** (◊), **20B** (▲), **20C** (Δ) *vs* Hammett-Brown parameter σ^+.

Table 3

Linear regression analysis data on 4-alkyl-2-aryl-substituted oxazolidines (**5**–**8**) and tetrahydro-1,3-oxazines (**17**–**20**) and the parent 4-unsubstituted 2-aryloxazolidines (**21**) and 2-aryltetrahydro-1,3-oxazines (**22**).

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a] (log $K_{X=H}$)	Correlation coefficient	c_s[b]
5A ⇌ **5B**	7	0.46 (±0.02)	–0.88 (±0.01)	0.993	0.22
5A ⇌ **5C**	7	0.62 (±0.02)	–1.07 (±0.02)	0.994	0.03
6A ⇌ **6B**	7	0.49 (±0.01)	–0.82 (±0.01)	0.999	0.28
6A ⇌ **6C**	7	0.56 (±0.03)	–0.97 (±0.02)	0.993	0.13
7A ⇌ **7B**	7	0.41 (±0.01)	–0.39 (±0.01)	0.996	0.71
7A ⇌ **7C**	7	0.58 (±0.02)	–0.63 (±0.01)	0.996	0.47
8A ⇌ **8B**	7	0.46 (±0.01)	–0.13 (±0.01)	0.996	0.97
8A ⇌ **8C**	7	0.54 (±0.01)	–0.30 (±0.01)	0.996	0.80
21A ⇌ **21B**[c]	7	0.60 (±0.04)	–1.10 (±0.02)	0.989	0
17A ⇌ **17B**	7	0.80 (±0.04)	0.62 (±0.03)	0.994	0.77
17A ⇌ **17C**	7	0.73 (±0.05)	–0.86 (±0.04)	0.990	–0.71
18A ⇌ **18B**	7	0.68 (±0.04)	0.49 (±0.03)	0.993	0.64
18A ⇌ **18C**	7	0.63 (±0.07)	–0.96 (±0.06)	0.968	–0.81
19A ⇌ **19B**	7	0.63 (±0.02)	0.53 (±0.02)	0.996	0.68
19A ⇌ **19C**	7	0.68 (±0.08)	–0.99 (±0.06)	0.971	–0.84
20A ⇌ **20B**	7	0.65 (±0.04)	0.63 (±0.03)	0.992	0.78
20A ⇌ **20C**	7	0.80 (±0.04)	–0.97 (±0.03)	0.994	–0.82
22A ⇌ **22B**[d]	7	0.74 (±0.06)	–0.15 (±0.05)	0.984	0



A **B**

n = 1: **21**, n = 2: **22**

[a] Standard error in parentheses. [b] For the meaning of substitution effect parameter (c_s), see the text. [c] Data from ref. [15]. [d] Data from ref. [16].

To study the double substituent dependence of log K_B and log K_C, multiple regression analysis was performed for equilibria **5**–**8** and **17**–**20** according to the Hansch-type equation (Eq. 2), introduced earlier to characterize the ring-chain equilibria of 1-alkyl-3-arylnaphth[1,2-*e*]-oxazines [12], where P^R is an alkyl substituent parameter and σ^{+X} is the Hammett-Brown parameter of substituent X on the 2-phenyl ring. In order to find the accurate dependence of log K_B and log K_C, four different alkyl substituent parameters were investigated: E_S (calculated from the hydrolysis and aminolysis of esters) [17], ν (derived from the van der Waals radii [18], V^a (the volume of the portion of the substituent that is within 0.3 nm of the reaction centre) [17] and G (which characterizes the shape by the ratio of the surface area of the substituent to its volume) [17]. The last three steric parameters are independent of any kinetic data.

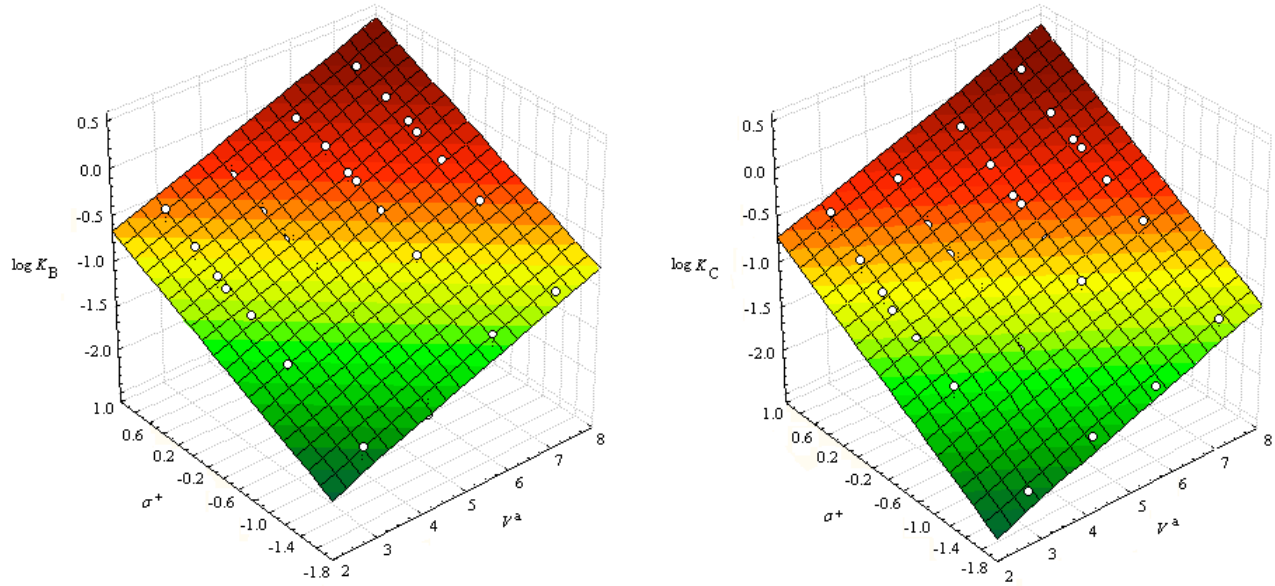
$$\log K = k + \rho^R P^R + \rho^X \sigma^{+X} \qquad \text{(Eq. 2)}$$

Multiple linear regression analysis was performed with the SPSS statistical software, and a value of 0.05 was chosen as the level of significance [19]. For the equilibria of oxazolidines (**5**–**8**), the best correlations were observed for the Meyer parameter (V^a), while for the equilibria of 1,3-oxazines (**17**–**20**), none of the four alkyl substituent parameters resulted in a significant value of ρ^R (Table 4). It is interesting to note that, in contrast with the corresponding tautomeric equilibria of 1-alkyl-3-arylnaphth[1,2-*e*][1,3]oxazines [12], the slopes of the alkyl substituent parameters (ρ^R) for the

equilibria **5–8B** ⇌ **5-8A** and **5–8C** ⇌ **5–8A** are practically the same positive values, which means that the increasing proportion of the cyclic forms **B** and **C** correlates with the increasing bulk of the alkyl substituents to nearly the same extent ($\Delta\rho^R$: <0.02) for both equilibria. The similar behaviour of the tautomeric equilibria **5–8** can probably be rationalized in terms of the similar hyperconjugative (anomeric) effects occurring in the C-2 epimeric cyclic forms [12b,20].

To refine further the effects of the substituents on the equilibria involving oxazolidines (**5–8B** ⇌ **5–8A**, **5–8C** ⇌ **5–8A**) and tetrahydro-1,3-oxazines (**17–20B** ⇌ **17–20A**, **17–20C** ⇌ **17–20A**), another Hansch-type equation (Eq. 3) was applied, including the inductive (σ_F^X) and resonance effects (σ_R^X) of the aromatic substituents besides the Meyer parameter (V^a):

$$\log K = k + \rho^R V^a + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad \text{(Eq. 3)}$$



a) b)

Figure 2. (a) Plots of log K_B for **5–8B** *vs* Meyer (V^a) and Hammett-Brown parameters (σ^+). (b) Plots of log K_C for **5–8C** *vs* Meyer (V^a) and Hammett-Brown parameters (σ^+).

Table 4

Multiple linear regression analysis of log K_B and log K_C values for **5–8** and **17–20** according to Eq. 2.

		k	ρ^R	ρ^X	r
$P^R = V^a$	**5–8B** ⇌ **5–8A**	–1.500	0.189	0.453	0.982
	5–8C ⇌ **5–8A**	–1.681	0.188	0.573	0.989
$P^R = \nu$	**5–8B** ⇌ **5–8A**	–1.352	1.035	0.453	0.972
	5–8C ⇌ **5–8A**	–1.548	1.048	0.573	0.987
$P^R = E_s$	**5–8B** ⇌ **5–8A**	–1.393	–0.476	0.453	0.968
	5–8C ⇌ **5–8A**	–1.592	–0.484	0.573	0.985
$P^R = G$	**5–8B** ⇌ **5–8A**	3.145	–0.252	0.453	0.951
	5–8C ⇌ **5–8A**	2.942	–0.251	0.573	0.966
$P^R = V^a$	**17–20B** ⇌ **17–20A**	0.510	[a]	0.689	0.984
	17–20C ⇌ **17–20A**	–0.801	[a]	0.712	0.978
$P^R = \nu$	**17–20B** ⇌ **17–20A**	0.469	[a]	0.689	0.986
	17–20C ⇌ **17–20A**	–0.851	[a]	0.712	0.977
$P^R = E_s$	**17–20B** ⇌ **17–20A**	0.460	[a]	0.689	0.986
	17–20C ⇌ **17–20A**	–0.847	[a]	0.712	0.977
$P^R = G$	**17–20B** ⇌ **17–20A**	0.655	[a]	0.689	0.983
	17–20C ⇌ **17–20A**	–1.587	[a]	0.712	0.979

[a] Insignificant (level of significance 0.05)

The data resulting from the multiple linear regression analysis according to Eq. 3 (Table 5) show that the equilibria of tetrahydro-1,3-oxazines are influenced by both the inductive and resonance effects of the aromatic substituents to a higher extent than for the analogous equilibria of oxazolidines. While the equilibria involving diastereomeric oxazolidine ring forms exhibited considerable differences in the values of both ρ_F^X and ρ_R^X, the values of ρ_R^X were found to be less sensitive to the relative configuration of the cyclic tautomer for the equilibria involving tetrahydro-1,3-oxazines.

Table 5

Multiple linear regression analysis[a] of log K_B and log K_C values for **5**–**8** and **17**–**20** according to Eq. 3.

	k	ρ^R	ρ_F^X	ρ_R^X	r
5–8B ⇌ **5–8A**	–1.532	0.189	0.386	1.114	0.974
5–8C ⇌ **5–8A**	–1.748	0.190	0.567	1.384	0.983
17–20B ⇌ **17–20A**	0.422	[a]	0.735	1.607	0.966
17–20C ⇌ **17–20A**	–0.938	[a]	0.930	1.590	0.976

[a] Insignificant (level of significance 0.05). [b] 2-(*m*-Bromophenyl) derivatives (**b**) were omitted from the calculations

CONCLUSIONS

Through the condensations of 2-alkyl-2-aminoethanols or 3-alkyl-3-aminopropanols with substituted benzaldehydes, 4-alkyl-2-aryl-substituted oxazolidines and tetrahydro-1,3-oxazines were prepared, which proved to exist in $CDCl_3$ at 300 K as three-component tautomeric mixtures of the diastereomeric five- or six-membered 1,3-*O*,*N*-heterocyclic ring forms and the corresponding imines. Electron-withdrawing substituents on the 2-phenyl ring preferred the ring-closed tautomers. Each equilibrium could be characterized by the Hammett equation, the parameters of which indicated that the stability differences between the *cis* and the *trans* cyclic forms are higher for the C-2 epimeric tetrahydro-1,3-oxazines than for the C-2 epimeric oxazolidines. Multiple linear regression analysis of the log *K* values led to the conclusion that not only the electronic effect of the 2-aryl substituent, but also the steric effect of the 4-alkyl substituent, influenced the tautomeric equilibria of the oxazolidines, which could be described by Hansch-type equations. Increasing bulk of the 4-alkyl group proved to enhance the proportion of the cyclic tautomers in the equilibria involving oxazolidines. The inductive and resonance effects of the aryl group influenced the equilibria involving tetrahydro-1,3-oxazines more markedly than those for the oxazolidines.

EXPERIMENTAL

Melting points were recorded on a Kofler hot-plate microscope apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyzer. Merck Kieselgel $60F_{254}$ plates were used for TLC. The ^{1}H nmr spectra were recorded in $CDCl_3$ solutions at 300 K on a Bruker AVANCE DRX 400 spectrometer at 400.13 MHz. Chemical shifts are given in δ (ppm) relative to TMS as internal standard; multiplicites were recorded as *s* (singlet), *bs* (broad singlet), *d* (doublet), *dd* (double doublet), *ddd* (double double doublet), *dt* (double triplet), *t* (triplet), *q* (quartet) and *m* (multiplet). In the cases of **5**–**8** and **17**–**20**, the solutions were left to stand at ambient temperature for 1 day for the equilibria to be established before the ^{1}H nmr spectra were run.

The (±)-2-amino-1-propanol (**1**), (±)-2-amino-1-butanol (**2**), (±)-2-amino-3-methyl-1-butanol (**3**), (2*S*)-2-amino-3,3-dimethyl-1-butanol (**4**) and (±)-3-aminobutanoic acid (**9**) were purchased from Aldrich. (±)-3-Aminopentanoic acid (**10**), (±)-3-amino-4-methylpentanoic acid (**11**) and (±)-3-amino-4,4-dimethylpentanoic acid (**12**) were prepared according to known procedures [13].

General Procedure for the Preparation of 3-Substituted 3-amino-1-propanols (13–16). To a stirred and cooled suspension of $LiAlH_4$ (4.74 g, 125 mmol) in dry THF (100 mL), the corresponding β-substituted amino acid (**9**–**12**, 50 mmol) was added in small portions. The mixture was stirred and refluxed for 8 h and then cooled, and the excess of $LiAlH_4$ was decomposed by the addition of a mixture of water (9.5 mL) and THF (50 mL). The inorganic salts were filtered off and washed with EtOAc (3 × 100 mL). The combined organic filtrate and washings were dried (Na_2SO_4) and evaporated under reduced pressure to give an oily product, which was distilled *in vacuo* to yield **13**–**16** as colourless oils.

13: yield: 3.04 g (68%); bp 95-97 ºC (21 torr). The ^{1}H nmr data on the product correspond to the literature [21] data.

14: yield: 3.60 g (70%); bp 75-76 ºC (4 torr). ^{1}H nmr: δ 0.92 (t, 3H, C*H*$_3$ J = 7.4 Hz), 1.28-1.55 (m, 3H, CHC*H*$_2$), 1.62-1.70 (m, 1H, CHC*H*$_2$), 2.66 (bs, 3H, N*H*$_2$, O*H*), 2.77-2.86 (m, 1H, NC*H*), 3.75-3.86 ppm (m, 2H, OC*H*$_2$). *Anal*. Calcd. for $C_5H_{13}NO$ (103.16): C, 58.21; H, 12.70; N, 13.58. Found: C, 57.95; H, 12.44; N, 13.38.

15: yield: 4.77 g (81%); bp 80-81 ºC (3 torr). ^{1}H nmr: δ 0.88 (d, 3H, C*H*$_3$, J = 6.0 Hz), 0.89 (d, 3H, C*H*$_3$, J = 6.0 Hz), 1.42-1.68 (m, 3H, CC*H*$_2$, CC*H*), 2.50-2.90 (m, 4H, NC*H*, N*H*$_2$, O*H*), 3.75-3.87 ppm (m, 2H, OC*H*$_2$). *Anal*. Calcd. for $C_6H_{15}NO$ (117.19): C, 61.49; H, 12.90; N, 11.95. Found: C, 61.20; H, 12.68; N, 12.03.

16: yield: 4.71 g (72%); bp 81-83 ºC (4 torr). ^{1}H nmr: δ 0.87 (s, 9H C(C*H*$_3$)$_3$), 1.32-1.44 (m, 1H, CC*H*$_2$), 1.65-1.73 (m, 1H, CC*H*$_2$), 2.52 (dd, 1H, NC*H*, J = 2.1, 11.2 Hz), 2.81 (bs, 3H, N*H*$_2$, O*H*), 3.75-3.87 ppm (m, 2H, OC*H*$_2$). *Anal*. Calcd. for $C_7H_{17}NO$ (131.22): C, 64.07; H, 13.06; N, 10.67. Found: C, 64.39; H, 12.76; N, 10.47.

Table 6

Physical and nmr spectroscopic data on 4-alkyl-2-aryloxazolidines (**5**–**8**).

Compd.	Mp (°C)	Yield (%)	Formula	M.W.	δ (ppm) N=C*H* (s) (**A**)	N–C*H*–O (s) (**B**)	N–C*H*–O (s) (**C**)
5a	89-91[a]	65	$C_{10}H_{12}N_2O_3$	208.22	8.44	5.54	5.72
5b	oil	~100	$C_{10}H_{12}BrNO$	242.12	8.29	5.42	5.58
5c	81-84[b]	72	$C_{10}H_{12}ClNO$	197.67	8.31	5.42	5.57
5d	62-63[a]	80	$C_{10}H_{13}NO$	163.22	8.35	5.46	5.58
5e	85-86[a]	78	$C_{11}H_{15}NO$	177.25	8.32	5.43	5.54
5f	73.5-74[a]	73	$C_{11}H_{15}NO_2$	193.25	8.29	5.41	5.52
5g	106-108[a]	77	$C_{12}H_{18}N_2O$	206.29	8.16	5.19	5.39
6a	82-83[a]	70	$C_{11}H_{14}N_2O_3$	222.25	8.40	5.53	5.67
6b	oil	~100	$C_{11}H_{14}BrNO$	256.14	8.25	5.41	5.52
6c	oil	~100	$C_{11}H_{14}ClNO$	211.69	8.26	5.41	5.50
6d	oil	~100	$C_{11}H_{15}NO$	177.25	8.30	5.44	5.50
6e	oil	~100	$C_{12}H_{17}NO$	191.28	8.27	5.41	5.46
6f	oil	~100	$C_{12}H_{17}NO_2$	207.27	8.22	5.39	5.44
6g	65-67[a]	71	$C_{13}H_{20}N_2O$	220.32	8.19	5.37	5.40
7a	oil	98	$C_{12}H_{16}N_2O_3$	236.27	8.36	5.53	5.65
7b	oil	83	$C_{12}H_{16}BrNO$	270.17	8.22	5.41	5.49
7c	oil	99	$C_{12}H_{16}ClNO$	225.72	8.23	5.41	5.48
7d	oil	75	$C_{12}H_{17}NO$	191.28	8.29	5.45	5.48
7e	oil	91	$C_{13}H_{19}NO$	205.30	8.23	5.41	5.43
7f	oil	76	$C_{13}H_{19}NO_2$	221.30	8.21	5.39	5.41
7g	71-73[b]	65	$C_{14}H_{22}N_2O$	234.34	8.14	5.38	5.37
8a	oil	~100	$C_{13}H_{18}N_2O_3$	250.30	8.34	5.49	5.59
8b	oil	~100	$C_{13}H_{18}BrNO$	284.20	8.20	5.37	5.40
8c	68-71[a]	88	$C_{13}H_{18}ClNO$	239.75	8.23	5.37	5.40
8d	oil	82	$C_{13}H_{19}NO$	205.30	8.28	5.40	5.38
8e	75-77[b]	61	$C_{14}H_{21}NO$	219.33	8.24	5.37	5.34
8f	oil	~100	$C_{14}H_{21}NO_2$	235.33	8.21	5.36	5.32
8g	54-56[a]	79	$C_{15}H_{24}N_2O$	248.37	8.13	5.33	5.27

[a]Recrystallized from diisopropyl ether. [b]Recrystallized from *n*-hexane.

General Procedure for the Preparation of 4-Alkyl-2-aryl-substituted oxazolidines (5–8) and tetrahydro-1,3-oxazines (17–20). To a solution of the corresponding amino alcohol (**1**–**4** or **13**–**16**) (3 mmol) in absolute MeOH (20 mL), an equivalent amount of aromatic aldehyde was added (for liquid aldehydes, a freshly distilled sample was used), and the mixture was allowed to stand at ambient temperature for 1 h. The solvent was then evaporated off. The oily products were dried in a vacuum desiccator for 24 h. The nmr spectra proved that the purities of these compounds were greater than 95%. Crystalline products were collected by filtration and recrystallized. All of the recrystallized new compounds (**5a**–**8g**, **17a**–**20g**) gave satisfactory data on elemental analysis (C, H, N ±0.3%).

The physical data and the chemical shifts of the characteristic N–C*H*–O and N=C*H*Ar protons for compounds **5**–**8** and **17**–**20** are listed in Tables 6 and 7.

With regard to the similarities in the ^{1}H nmr data for the members **a**–**g** of each set of oxazolidines (**5**–**8**) and tetrahydro-1,3-oxazines (**17**–**20**), the full spectra of the *major* tautomers are described only for eight representatives of these sets of compounds (**5a**, **6a**, **7a**, **8a**, **17a**, **18a**, **19a**, **20a**). The protons of the open form (**A**) are numbered according to the corresponding protons of the cyclic oxazolidine or tetrahydro-1,3-oxazine forms (**B** or **C**). In consequence of the small relative concentrations, only the characteristic O–C*H*Ar–N and N=C*H*Ar protons are listed for the detectable *minor* tautomeric forms (see Tables 6 and 7).

5aA: ^{1}H nmr: δ 1.26 (d, 3H, CH_3, J = 6.6 Hz), 1.80 (bs, 1 H, O*H*), 3.50-3.66 (m, 1H, NC*H*), 3.73 (d, 2H, OCH_2, J = 2.5 Hz), 7.92 (d, 2H, C$_6H_4$, J = 8.6 Hz), 8.27 (d, 2H, C$_6H_4$, J = 8.6 Hz) 8.44 ppm (s, 1H, N=C*H*Ar). ^{13}C nmr: δ 18.4 (CH$_3$), 67.6 (C-5), 68.0 (C-4), 124.3, 129.3, 141.9, 149.5 (C$_6$H$_4$), 159.3 ppm (C-2).

6aA: ^{1}H nmr: δ 0.88 (t, 3H, CH_3, J = 7.6 Hz), 1.46-1.75 (m, 2H, CH_2CH$_3$), 1.78 (bs, 1H, O*H*), 3.36-3.46 (m, 1H, NC*H*), 3.78 (d, 2H, OCH_2, J = 5.5 Hz), 7.92 (d, 2H, C$_6H_4$, J = 8.8 Hz), 8.27 (d, 2H, C$_6H_4$, J = 8.8 Hz), 8.40 ppm (s, 1H, N=C*H*Ar). ^{13}C nmr: δ 11.0 (CH$_3$), 25.3 (*C*H$_2$CH$_3$), 66.31 (C-5), 75.0 (C-4), 124.3, 129.3, 141.7, 149.4 (C$_6$H$_4$), 159.7 ppm (C-2).

7aA: ^{1}H nmr: δ 0.93 (d, 3H, CH_3, J = 4.5 Hz), 0.96 (d, J = 4.5 Hz, 3H, CH_3), 1.92-2.04 (m, 1H, C*H*(CH$_3$)$_2$), 2.08 (bs, 1H, O*H*), 3.07 (q, 1H, NC*H*, J = 5.5 Hz), 3.84 (d, 2H, OCH_2, J = 5.5 Hz), 7.92 (d, 2H, C$_6H_4$, J = 8.7 Hz), 8.24 (d, 2H, C$_6H_4$, J = 8.7 Hz), 8.36 ppm (s, 1H, N=C*H*Ar). ^{13}C nmr: δ 19.5, (CH$_3$), 20.8 (CH$_3$), 30.4 (*C*H(CH$_3$)$_2$), 64.7 (C-5), 79.5 (C-4), 124.2, 129.3, 141.9, 149.4 (C$_6$H$_4$), 159.7 ppm (C-2).

8aB: ^{1}H nmr: δ 0.97 (s, 9H, C(CH_3)$_3$), 1.58 (bs, 1 H, N*H*), 3.65 (t, J = 7.6 Hz, 1H, NC*H*), 3.90-3.97 (m, 2H, OCH_2), 5.49 (s,

Table 7

Physical and nmr spectroscopic data on and 4-alkyl-2-aryl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**17**–**20**).

Compd.	Mp (°C)	Yield (%)	Formula	M.W.	δ (ppm) N=C*H* (s) (**A**)	N–C*H*–O (s) (**B**)	N–C*H*–O (s) (**C**)
17a	oil	~100	$C_{11}H_{14}N_2O_3$	222.25	8.38	5.21	5.58
17b	oil	~100	$C_{11}H_{14}BrNO$	256.14	8.02	5.11	5.49
17c	oil	~100	$C_{11}H_{14}ClNO$	211.69	8.24	5.12	5.50
17d	oil	~100	$C_{11}H_{15}NO$	177.25	8.28	5.15	5.54
17e	oil	~100	$C_{12}H_{17}NO$	191.28	8.23	5.12	5.51
17f	oil	~100	$C_{12}H_{17}NO_2$	207.27	8.28	5.11	5.49
17g	oil	~100	$C_{13}H_{20}N_2O$	220.32	8.20	5.08	5.49
18a	oil	~100	$C_{12}H_{16}N_2O_3$	236.27	8.33	5.20	5.58
18b	oil	~100	$C_{12}H_{16}BrNO$	270.17	8.17	5.10	5.49
18c	oil	~100	$C_{12}H_{16}ClNO$	225.72	8.19	5.11	5.50
18d	oil	~100	$C_{12}H_{17}NO$	191.28	8.23	5.15	5.53
18e	oil	~100	$C_{13}H_{19}NO$	205.30	8.18	5.11	5.50
18f	oil	~100	$C_{13}H_{19}NO_2$	221.30	8.15	5.10	5.49
18g	78-79[b]	75	$C_{14}H_{22}N_2O$	234.34	8.04	5.07	5.49
19a	63-65[a]	72	$C_{13}H_{18}N_2O_3$	250.30	8.30	5.19	5.64
19b	oil	~100	$C_{13}H_{18}BrNO$	284.20	8.14	5.09	5.56
19c	oil	~100	$C_{13}H_{18}ClNO$	239.75	8.17	5.10	5.57
19d	oil	~100	$C_{13}H_{19}NO$	205.30	8.21	5.14	5.61
19e	oil	~100	$C_{14}H_{21}NO$	219.33	8.16	5.10	5.58
19f	oil	~100	$C_{14}H_{21}NO_2$	235.33	8.12	5.09	5.57
19g	60-61[b]	61	$C_{15}H_{24}N_2O$	248.37	8.04	5.06	5.58
20a	75-76.5[a]	77	$C_{14}H_{20}N_2O_3$	264.33	8.29	5.19	5.74
20b	oil	~100	$C_{14}H_{20}BrNO$	298.23	8.14	5.09	5.67
20c	oil	~100	$C_{14}H_{20}ClNO$	253.77	8.17	5.09	5.68
20d	oil	~100	$C_{14}H_{21}NO$	219.33	8.21	5.13	5.73
20e	oil	~100	$C_{15}H_{23}NO$	233.36	8.16	5.10	5.71
20f	oil	~100	$C_{15}H_{23}NO_2$	249.36	8.13	5.08	5.70
20g	83-84.5[b]	73	$C_{16}H_{26}N_2O$	262.40	8.08	5.06	5.70

[a]Recrystallized from diisopropyl ether. [b]Recrystallized from *n*-hexane.

1H, NC*H*O), 7.69 (d, 2H, C_6H_4, J = 8.7 Hz), 8.23 ppm (d, 2H, C_6H_4, J = 8.8 Hz). ^{13}C nmr: δ 26.8 (C(CH_3)$_3$), 34.0 (C(CH_3)$_3$), 67.7 (C-5), 69.1 (C-4), 92.1 (C-2), 123.8, 127.6, 148.1, 148.3 ppm (C_6H_4).

17aB: ^{1}H nmr: δ 1.17 (d, 3H, CH_3, J = 6.6 Hz), 1.61 (ddd, J = 3.0, 4.45, 14.1 Hz, 1H, H-5$_{eq}$), 1.44 (ddd, 1H, H-5$_{ax}$, J = 4.5, 12.1, 23.7 Hz), 1.32 (bs, 1H, N*H*), 3.91 (dt, 1H, H-6$_{ax}$, J = 2.5, 12.1 Hz), 3.07-3.17 (m, 1H, NC*H*), 4.29 (ddd, 1H, H-6$_{eq}$, J = 1.0, 4.5, 11.6 Hz), 5.21 (s, 1H, NC*H*O), 7.70 (d, 2H, C_6H_4, J = 8.7 Hz), 8.19 (d, 2H, C_6H_4, J = 8.8 Hz), ppm. ^{13}C nmr: δ 22.6 (CH_3), 35.4 (C-5), 51.2 (C-4), 68.3 (C-6), 88.2 (C-2), 124.1, 128.1, 132.9, 148.3 ppm (C_6H_4).

18aB: ^{1}H nmr: δ 0.99 (t, 3H, CH_2CH_3, J = 7.6 Hz), 1.28 (bs, 1H, N*H*), 1.35-1.47 (m, 2H, CH_2CH_3), 1.35-1.58 (m, 1H, H-5$_{ax}$), 1.62 (ddd, 1H, H-5$_{eq}$, J = 2.5, 4.0, 13.1 Hz), 2.86–2.95 (m, 1H, NC*H*), 3.91 (dt, 1H, H-6$_{ax}$, J = 2.0, 12.1 Hz), 4.31 (ddd, 1H, H-6$_{eq}$, J = 1.5, 4.5, 11.6 Hz), 5.20 (s, 1H, NC*H*O), 7.70 (d, 2H, C_6H_4, J = 8.7 Hz), 8.18 ppm (d, 2H, C_6H_4, J = 8.9 Hz) ppm. ^{13}C nmr: δ 10.4 (CH_3), 30.1 (CH_2CH_3), 32.9 (C-5), 56.7 (C-4), 68.0 (C-6), 87.9 (C-2), 123.7, 127.5, 141.0, 148.1 ppm (C_6H_4).

9aB: ^{1}H nmr: δ 0.95 (d, 3H, CH_3, J = 6.8 Hz), 1.01 (d, 3H, CH_3, J = 6.8 Hz), 1.22 (bs, 1H, N*H*), 1.47 (ddd, 1H, H-5$_{ax}$, J = 4.8, 11.8, 24.2 Hz), 1.59 (ddd, 1H, H-5$_{eq}$, J = 2.3, 4.3, 13.6 Hz), 1.89-2.01 (m, 1H, C*H*(CH_3)$_2$, 2.73 (ddd, 1H, NC*H*, J = 3.0, 6.3, 10.8 Hz), 3.90 (dt, 1H, H-6$_{ax}$, J = 2.3, 11.8 Hz), 4.34 (ddd, H-6$_{eq}$, J = 1.5, 4.8, 11.3 Hz), 5.19 (s, 1H, NC*H*O), 7.71 (d, 2H, C_6H_4, J = 8.7 Hz), 8.19 ppm (d, 2H, C_6H_4, J = 8.9 Hz). ^{13}C nmr: δ 18.9 (CH_3), 19.3 (CH_3), 30.1 (C-5), 33.7 (CH(CH_3)$_2$), 60.9 (C-4), 68.1 (C-6), 88.0 (C-2), 123.7, 127.5, 141.3, 148.2 ppm (C_6H_4).

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