I.

Pergamon

Tetrahedron 54 (1998) 13639–13644

TETRAHEDRON

Ring–Chain Tautomerism of 2-Aryl-substituted Imidazolidines

László Lázár, Anikó Göblyös, Ferenc Evanics‡, Gábor Bernáth and Ferenc Fülöp*

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701 Szeged, POB 121, Hungary

‡Institute of Pharmaceutical Analysis, Albert Szent-Györgyi Medical University, H-6701 Szeged, POB 121, Hungary

Received 1 July 1998; revised 18 August 1998; accepted 3 September 1998

Abstract. *N*-Methyl-, *N*-ethyl-, *N*-(*n*-propyl)-, *N*-(*iso*-propyl)- and *N*-phenyl-2-arylimidazolidines proved to be ring–chain tautomeric mixtures in $CDCl_3$. The ratios of the open and ring forms in the tautomeric equilibria of these compounds is described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$, used earlier for the ring–chain equilibria of saturated 2-aryl-1,3-*O*,*N*-heterocycles. These are the first examples among 2-arylimidazolidines of ring–chain tautomeric processes characterized by a Hammett-type correlation. © 1998 Elsevier Science Ltd. All rights reserved.

Keywords: imidazolidines; diamines; tautomerism; electronic and steric effects.

The structures and reactivities of numerous five- and six-membered, saturated, *N*-unsubstituted 1,3-*X*,*N*-heterocycles (*X* = *O*, *S*, *NR*) can be characterized by the ring–chain tautomeric equilibria of the 1,3-*X*,*N*-heterocycles and the corresponding Schiff bases.[1]

The oxazolidines and tetrahydro-1,3-oxazines are groups of saturated 1,3-*X*,*N*-heterocycles whose ring–chain tautomerism has been studied most thoroughly.[1-3] For 2-aryl-substituted derivatives of these types of compounds, a clear-cut correlation was found between the log K_X values of the equilibria (K_X = [ring]/[chain]) and the Hammett–Brown constants σ^+ of the substituents on the 2-aryl group. The ring–chain tautomerism of these compounds could be described by Equation (1) in both the liquid and gas phases:[2-4]

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

In contrast, ring–chain tautomeric processes in the corresponding 1,3-*N*,*N*-heterocycles have been observed only in special cases.[1,5-9] Very little is known concerning the effect of the substituents on the tautomeric equilibria of these compounds.[10-15] Therefore, our aim was to investigate the scope and limitations of Equation (1) by studying the ring–chain tautomerism of some 2-aryl-substituted 1-alkyl- and 1-phenyl-imidazolidines.

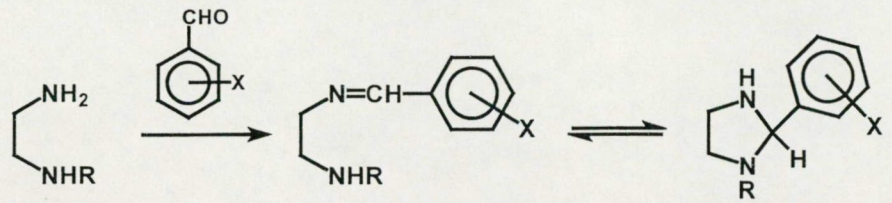
Model compounds **6-10** were prepared by the reactions of *N*-methyl- (**1**), *N*-ethyl- (**2**), *N*-(*n*-propyl)- (**3**), *N*-(*iso*-propyl)- (**4**) and *N*-phenylethylenediamine (**5**) with equivalent amounts of substituted benzaldehydes (Scheme 1). The ^{1}H NMR spectra of **6-10** revealed that all of these compounds (except **9i**, in which no ring form could be detected) participated in a ring–chain equilibrium in $CDCl_3$ solution.

The ratios of the concentrations of the ring and chain forms for the tautomeric equilibria (log K_X), determined by integration of the well-separated N-C*H*Ar-N (ring) and N=C*H* (chain) proton singlets, seemed

*e-mail: fulop@pharma.szote.u-szeged.hu

PII: S0040-4020(98)00840-0

to correlate with the electronic effects of substituents *X* (Table 1). It is noteworthy that the ratio of the open form of the *p*-nitrophenyl-substituted *N*-methylimidazolidine (**6aA**) in $CDCl_3$ is 6.6%, in contrast with the literature[13,14] data (0%).



R = Me: **1**	**6Aa-i**	**6Ba-i**
R = Et: **2**	**7Aa-i**	**7Ba-i**
R = *n*Pr: **3**	**8Aa-i**	**8Ba-i**
R = *i*Pr: **4**	**9Aa-i**	**9Ba-i**
R = Ph: **5**	**10Aa-i**	**10Ba-i**

X = NO_2(*p*): **a**, CN(*p*): **b**, Br(*m*): **c**, Br(*p*): **d**, Cl(*p*): **e**, H: **f**, Me(*p*): **g**, OMe(*p*): **h**, NMe_2(*p*): **i**

Scheme 1

Through the use of HMBC and HMQC spectroscopy, not only the characteristic N-C*H*Ar-N and N=C*H*Ar singlets could be distinguished, but also the methylene signals of the ring and open forms. This was especially useful in the case of some *p*-methoxy- and *p*-dimethylamino-substituted derivatives, where tautomeric ratios could be determined only by integrating the methylene signals, because of the overlapping or coalesced lines. Data on the aliphatic protons of 2-(*p*-bromophenyl) derivatives (**6d-10d**) was chosen to demonstrate the ^{1}H NMR spectra of the prepared 2-arylimidazolidines (see Experimental).

Table 1. The ratios (%) of the ring forms (**B**) in tautomeric equilibria for compounds **6-10**[a]

Compd.	X	σ^+	**6**[a] R = Me	**6**[b] R = Me	**7** R = Et	**8** R = *n*Pr	**9** R = *i*Pr	**10**[a] R = Ph	**10**[b] R = Ph
a	*p*NO_2	0.79	93.4	94.8	84.0	85.4	33.4	68.6	56.0
b	*m*NO_2	0.73	94.4	95.3	85.8	85.9	34.8	68.0	55.0
c	*m*Br	0.405	89.4	93.6	75.2	73.4	17.3	52.6	38.7
d	*p*Br	0.15	86.8	89.1	69.5	69.0	12.2	46.1	31.3
e	*p*Cl	0.114	86.6	90.1	68.6	67.8	10.5	42.4	29.6
f	H	0	83.5	85.6	60.3	60.1	8.1	35.7	21.0
g	*p*Me	-0.311	78.9	79.7	48.2	50.3	5.1	27.5	14.7
h	*p*OMe	-0.778	68.2	71.3	37.9	37.0	3.1	15.8	8.3
i	*p*NMe_2	-1.7	43.6	c	16.7	14.9	~0	4.6	2.2

[a]For the equilibria in $CDCl_3$. [b]For the equilibria in DMSO-d_6. [c]Due to overlapping coalesced lines, the tautomeric ratio could not be determined at 300 K.

When Equation (1) was applied to the log K_X values, good linear correlations were obtained versus the Hammett–Brown parameter σ^+ for all five sets of imidazolidines **6-10** (Fig. 1, Table 2). To the best of our knowledge, these are the first examples among 2-arylimidazolidines of ring–chain tautomeric processes

characterized by a Hammett-type correlation. The first application of Equation (1) to describe a ring–chain tautomeric process among 2-aryl-1,3-*N*,*N*-heterocycles was recently published for 2-arylhexahydropyrimidines.[15a]

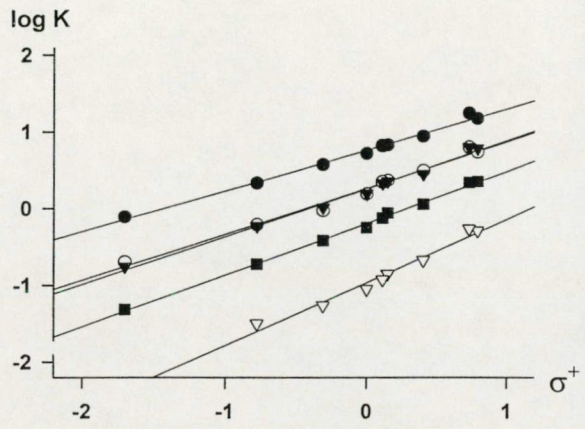


Fig. 1. Plots of log K (in $CDCl_3$) for **6** (●), **7** (○), **8** (▼), **9** (▽) and **10** (■) *vs* Hammett-Brown parameter σ^+

The interconversion of ring–chain tautomers, *i.e.* the mobility of the equilibria, is unequivocally proved by the difference in the tautomeric ratios for *N*-methyl- (**6**) and *N*-phenyl-substituted imidazolidines (**10**) in $CDCl_3$ and DMSO-d_6. For 1-phenylimidazolidines **10**, similarly to the analogous 1,3-*O*,*N*-heterocycles,[16] the cyclic forms are preferred in $CDCl_3$, while the open forms are rather preferred in DMSO-d_6, which is due to the different hydrogen-bonding abilities of these solvents. However, for 1-methylimidazolidines **6**, the proportions of the ring forms of these compounds were somewhat higher in DMSO-d_6 than in $CDCl_3$. The solvent had only small, but unequivocal effects on the slopes of the regression lines in both series of compounds.

The data in Table 2 shows that the constants ρ (in $CDCl_3$) for 1-phenyl- (0.67) and especially 1-(*iso*-propyl)imidazolidines (0.82) are greater than the usual ρ values[1] for oxazolidines (0.50-0.60), while those for 1-methyl- (0.53), 1-ethyl- (0.59) and 1-(*n*-propyl)imidazolidines (0.62) are very similar to the usual values for oxazolidines. The significant differences in ρ for compounds **6-10** suggests that for imidazolidines, in contrast to 1,3-*O*,*N*-heterocycles, the value of ρ is not characteristic of the ring system.

Table 2. Linear regression analysis data on compounds **6-10** and the parent 2-aryloxazolidines (**11**)[3]

Compd.	No. of points	Slope[a] (ρ)	Intercept[a]	Correlation coefficient	c[b]
6[c]	9	0.53(2)	0.75(4)	0.990	1.85
6[d]	8	0.61(4)	0.84(6)	0.970	–
7[c]	9	0.59(3)	0.25(6)	0.984	1.35
8[c]	9	0.62(2)	0.25(5)	0.989	1.35
9[c]	8	0.82(5)	-0.97(7)	0.973	0.13
10[c]	9	0.67(1)	-0.20(3)	0.997	0.90
10[d]	9	0.72(2)	-0.48(5)	0.993	–
11[c]	7	0.60(4)	-1.10(2)	0.989	0

[a]Standard deviations are given in parentheses. [b]For the meaning of c, see the text. [c]For the equilibria in $CDCl_3$. [d]For the equilibria in DMSO-d_6.

The equilibria of imidazolidines **6-10** in $CDCl_3$ involve a considerable amount of the ring form, despite the 5-*endo-trig* ring-closure process of the tautomeric forms (**A** → **B**) according to Baldwin's rules.[17] A comparison of the intercepts (the c value is the difference in intercepts of the given 2-arylimidazolidine and the parent unsubstituted 2-aryloxazolidine[3]) reveals that the ratios of the ring forms in the tautomeric equilibria of *N*-methyl-, *N*-ethyl-, *N*-(*n*-propyl)- and *N*-phenylimidazolidines are markedly higher than those for oxazolidines. The steric effect of the α-carbon of the *N*-substituent plays a crucial role in the addition of the NHR group to the C=N bond. An increase in the steric requirement of the *N*-substituent, *i.e.* the number of methyl groups on the carbon adjacent to the nitrogen (*N*-Me → *N*-Et → *N*-*i*Pr), decreased the ratio of the ring forms in the tautomeric equilibria. However, introduction of a methyl group onto the β-carbon of the *N*-substituent (*N*-Et → *N*-*n*Pr) did not significantly influence the intercept values.

The above results indicate that the electronic effect of the substituent on the 2-aryl group definitively determines the ratio of ring and open-chain tautomers in all series of imidazolidines **6-10**. The ring-chain ratios are influenced not only by the substituent *X* on the aromatic ring, but also by the substituent on the *N* atom of the imidazolidine ring. The proportion of the ring form increases in the following sequence of *N*-substituents: *i*Pr < Ph < *n*Pr ≈ Et < Me. Efforts to elucidate the electronic effects of the substituents on the *N*-phenyl group on the tautomeric equilibria of 2-arylimidazolidines are in progress.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AVANCE DRX 400 spectrometer at 300 K, using a "5 mm inverse Z gradient" probehead. The samples were dissolved in $CDCl_3$ or in DMSO-d_6 containing 0.03% TMS as reference. For the equilibria to be established,[18] the solutions were left to stand at ambient temperature for 1 day before the ^{1}H NMR spectra were run. The number of scans was usually 64.

Melting points were determined on a Kofler micro melting point apparatus and are not corrected. The physical data on compounds **6-10** are listed in Table 3.

General method for the synthesis of 2-arylimidazolidines

To a solution of the appropriate diamine (3 mmol) in 20 mL of absolute methanol, an equivalent amount of aromatic aldehyde was added (in the case of liquid aldehydes, a freshly distilled sample was used), and the mixture was left to stand at ambient temperature for 1 h. The solvent was evaporated off and the evaporation was repeated after the addition of 10 mL of benzene. 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 filtered off and recrystallized. All of the recrystallized new compounds (**10b,d,g-i**) gave satisfactory data on elemental analysis (C, H, N ±0.3%).

NMR spectroscopic data on the aliphatic protons of 2-(p-bromophenyl) derivatives **6d-10d** *in* $CDCl_3$

The protons of the open forms **A** are numbered according to the corresponding protons of the ring forms **B** (δ in ppm; in brackets the multiplicity, couplings in Hz and assignment, respectively; *om* = overlapping multiplets).

6Ad: 8.28 (*s*, 1H, N=C*H*), 3.72 (*t*, 2H, *J* = 6.0, 4-CH_2), 2.91 (*t*, 2H, *J* = 6.0, 5-CH_2), 2.47 (*s*, 3H, NCH_3); **6Bd**: 3.86 (*s*, 1H, 2-C*H*), 3.32 (*ddd*, 1H, *J* = -16.4, 7.7, 2.5, 5-CH_2), 3.24 (*dd*, 1H, *J* = -8.0, 7.7, 4-CH_2), 3.08 (*ddd*, 1H, *J* = -8.0, 8.0, 2.5, 4-CH_2), 2.44 (*dd*, 1H, *J* = 16.4, 8.0, 5-CH_2), 2.20 (*s*, 3H, NCH_3).

Table 3. Physical data on imidazolidines 6-10

Compd.	M.p. (°C)	Formula	M.W.	δ N=C*H*Ar chain (A)	δ N-C*H*Ar-N ring (B)
6a	37-39[a,b]	$C_{10}H_{13}N_3O_2$	207.23	8.42	4.07
6b	oil	$C_{10}H_{13}N_3O_2$	207.23	8.41	4.08
6c	oil	$C_{10}H_{13}N_2Br$	241.14	8.26	3.88
6d	oil	$C_{10}H_{13}N_2Br$	241.14	8.28	3.86
6e	oil[c]	$C_{10}H_{13}N_2Cl$	196.68	8.23	3.66
6f	oil	$C_{10}H_{14}N_2$	162.24	8.32	3.87
6g	oil[c]	$C_{11}H_{16}N_2$	176.26	8.29	3.84
6h	oil[c]	$C_{11}H_{16}N_2O$	192.26	8.25	3.89
6i	oil[c]	$C_{12}H_{19}N_3$	205.31	8.17	3.76
7a	oil	$C_{11}H_{15}N_3O_2$	221.26	8.40	4.20
7b	oil	$C_{11}H_{15}N_3O_2$	221.26	8.56	4.22
7c	oil	$C_{11}H_{15}N_2Br$	255.17	8.26	4.02
7d	oil	$C_{11}H_{15}N_2Br$	255.17	8.28	4.00
7e	oil	$C_{11}H_{15}N_2Cl$	210.71	8.28	3.76
7f	oil	$C_{11}H_{16}N_2$	176.26	8.34	4.02
7g	oil	$C_{12}H_{18}N_2$	190.29	8.29	3.96
7h	oil	$C_{12}H_{18}N_2O$	206.29	8.26	3.95
7i	oil	$C_{13}H_{21}N_3$	219.33	8.20	3.69
8a	oil	$C_{12}H_{17}N_3O_2$	235.29	8.42	4.22
8b	oil	$C_{12}H_{17}N_3O_2$	235.29	8.58	4.23
8c	oil	$C_{12}H_{17}N_2Br$	269.19	8.26	4.02
8d	oil	$C_{12}H_{17}N_2Br$	269.19	8.28	4.00
8e	oil	$C_{12}H_{17}N_2Cl$	224.74	8.29	4.01
8f	oil	$C_{12}H_{18}N_2$	190.29	8.33	4.01
8g	oil	$C_{13}H_{20}N_2$	204.32	8.29	3.97
8h	oil	$C_{13}H_{20}N_2O$	220.32	8.26	3.95
8i	oil	$C_{14}H_{23}N_3$	233.36	8.20	3.69
9a	oil	$C_{12}H_{17}N_3O_2$	235.29	8.42	4.62
9b	oil	$C_{12}H_{17}N_3O_2$	235.29	8.58	4.63
9c	oil	$C_{12}H_{17}N_2Br$	269.19	8.26	4.43
9d	oil	$C_{12}H_{17}N_2Br$	269.19	8.28	4.42
9e	oil	$C_{12}H_{17}N_2Cl$	224.74	8.28	4.42
9f	oil	$C_{12}H_{18}N_2$	190.29	8.34	4.43
9g	oil	$C_{13}H_{20}N_2$	204.32	8.30	4.38
9h	oil	$C_{13}H_{20}N_2O$	220.32	8.26	4.36
9i	oil	$C_{14}H_{23}N_3$	233.36	8.20	3.84
10a	oil	$C_{15}H_{15}N_3O_2$	269.31	8.36	5.49
10b	66-71[d]	$C_{15}H_{15}N_3O_2$	269.31	8.35	5.49
10c	oil	$C_{15}H_{15}N_2Br$	303.21	8.19	5.34
10d	64-66[a]	$C_{15}H_{15}N_2Br$	303.21	8.23	5.35
10e	oil	$C_{15}H_{15}N_2Cl$	258.75	8.27	5.41
10f	oil	$C_{15}H_{16}N_2$	224.31	8.28	5.39
10g	60-62[a]	$C_{16}H_{18}N_2$	238.34	8.25	5.37
10h	31-33[a]	$C_{16}H_{18}N_2O$	254.34	8.21	5.35
10i	88-89[a]	$C_{17}H_{21}N_3$	267.38	8.18	5.35

[a]Recrystallized from *n*-hexane. [b]Lit.[13] m.p. 39-40 °C. [c]Lit.[19] oil. [d]Recrystallized from iPr_2O–EtOAc.

7Ad: 8.28 (*s*, 1H, N=C*H*), 3.75 (*t*, 2H, *J* = 5.6, 4-CH_2), 2.96 (*t*, 2H, *J* = 5.6, 5-CH_2), 2.70 (*q*, 2H, *J* = 7.3, CH_2CH$_3$), 1.11 (*t*, 3H, *J* = 7.3, CH$_2$CH_3); **7Bd**: 4.00 (*s*, 1H, 2-C*H*), 3.40 (*dt*, 1H, *J* = -8.2, 3.2, 5-CH_2), 3.25 (*dt*, 1H, *J* = -10.7, 8.2, 4-CH_2), 3.09 (*ddd*, 1H, *J* = -10.7, 8.2, 3.2, 4-CH_2), 2.55 (*dq*, 1H, *J* = -11.8, 7.3, CH_2CH$_3$), 2.38 (*q*, 1H, *J* = 8.2, 5-CH_2), 2.18 (*dq*, 1H, *J* = -11.8, 7.3 CH_2CH$_3$), 1.05 (*t*, 3H, *J* = 7.3 CH$_2$CH_3).

8Ad: 8.28 (*s*, 1H, N=C*H*), 3.75 (*t*, 2H, *J* = 5.8, 4-CH_2), 2.95 (*t*, 2H, *J* = 5.8, 5-CH_2), 2.62 (*t*, 2H, *J* = 7.3, CH_2CH$_2$CH$_3$); 1.5 (*om*, 2H, CH$_2$CH_2CH$_3$), 0.91 (*t*, 3H, *J* = 7.5, CH$_2$CH$_2$CH_3); **8Bd**: 4.00 (*s*, 1H, 2-C*H*), 3.37 (*om*, 1H, 4-CH_2) 3.24 (*om*, 1H, 5-CH_2), 3.09 (*om*, 1H, 4-CH_2), 2.39 (*om*, 2H, CH_2CH$_2$CH$_3$), 2.13 (*om*, 1H, 5-CH_2), 1.45 (*om*, 2H, CH$_2$CH_2CH$_3$), 0.86 (*t*, 3H, *J* = 7.5, CH$_2$CH$_2$CH_3).

9Ad: 8.28 (*s*, 1H, N=C*H*), 3.72 (*t*, 2H, *J* = 6.0, 4-CH_2), 2.94 (*t*, 2H, *J* = 6.0, 5-CH_2), 2.84 (*h*, 1H, *J* = 6.3, C*H*(CH$_3$)$_2$), 1.06 (*d*, 6H, *J* = 6.3, CH(CH_3)$_2$); **9Bd**: 4.42 (*s*, 1H, 2-C*H*), 3.10 (*om*, 2H, 4-CH_2), 3.00 (*om*, 1H, C*H*(CH$_3$)$_2$), 2.75 (*om*, 2H, 5-CH_2), 0.98 (*d*, 6H, *J* = 6.2, CH(CH_3)$_2$).

10Ad: 8.23 (*s*, 1H, N=C*H*), 3.83 (*t*, 2H, *J* = 5.5, 4-CH_2), 3.47 (*t*, 2H, *J* = 5.5, 5-CH_2); **10Bd**: 5.35 (*s*, 1H, 2-C*H*), 3.24 (*om*, 2H, 4-CH_2); 3.45 (*m*, 1H, 5-CH_2), 3.63 (*om*, 1H, 5-CH_2).

Acknowledgements. The authors' thanks are due to the Hungarian Research Foundation (OTKA grants No. T 20454 and No. T 015567) for financial support. The award of a "Magyary Z." scholarship to L. L. is also gratefully acknowledged.

REFERENCES

1. Valters, R. E.; Fülöp F.; Korbonits, D. *Adv. Heterocyclic Chem.* **1996**, *66*, 1.
2. Fülöp, F.; Pihlaja, K.; Mattinen J.; Bernáth, G. *J. Org. Chem.* **1987**, *52*, 3821.
3. Fülöp, F.; Neuvonen, K.; Pihlaja, K.; Bernáth, G.; Argay G.; Kálmán, A. *J. Org. Chem.* **1993**, *58*, 1967.
4. Vainiotalo, P.; Ronkanen, S.; Fülöp F.; Pihlaja, K. *Tetrahedron* **1990**, *46*, 3689.
5. Grimmett, M. R. in *Comprehensive Heterocyclic Chemistry II* (Eds.: Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V.), Pergamon, Oxford, 1996, Vol. 3, p. 153.
6. Evans, R. F. in *The Chemistry of Heterocyclic Compounds* (Ed.: Taylor, E. C.), Vol. 52. *The Pyrimidines*, John Wiley & Sons, New York, 1994, p. 817.
7. Wang., W.; Liang, T. C.; Zheng, M.; Gao, X. *Tetrahedron Lett.* **1995**, *36*, 1181.
8. *(a)* Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Res. (S)* **1996**, 134; *(b)* Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1997**, 169.
9. Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Mendeleev Commun.* **1997**, 111.
10. Pihlaja, K.; Simeonov, M. F.; Fülöp, F. *J. Org. Chem.* **1997**, *62*, 5080.
11. Chapuis, C.; Gauvreau, A; Klaebe, A.; Lattes, A.; Perie, J. J. *Bull. Soc. Chim. Fr.* **1973**, 977.
12. *(a)* Korbonits, D.; Tóbiás-Héja, E.; Kolonits, P. *Chem. Ber.* **1991**, *124*, 1199; *(b)* Korbonits, D.; Tóbiás-Héja, E.; Simon, K.; Kolonits, P. *Chem. Ber.* **1991**, *124*, 2065.
13. Witek, S.; Bielawska, A.; Bielawski, J. *Heterocycles* **1980**, *14*, 1313.
14. Parinello, G.; Mülhaupt, R. *J. Org. Chem.* **1990**, *55*, 1772.
15. *(a)* Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 53; *(b)* Zelenin, K. N.; Ukraintsev, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 109.
16. Fülöp, F.; Pihlaja, K. *Tetrahedron* **1993**, *49*, 6701.
17. *(a)* Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734; *(b)* Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476.
18. Alva Astudillo, M. E.; Chokotho, N. C. J.; Jarvis, T. C.; Johnson, C. D.; Lewis, C. C.; McDonnell, P. D. *Tetrahedron* **1985**, *41*, 5919.
19. Robert, Y; Fernandez, J.-P.; Dubief, R.; Chapat, J.-P.; Sentenac-Roumanou, H.; Fatome. M.; Laval. J.-D.; Subra, G. *Eur. J. Med. Chem. - Chim. Ther.* **1982**, *17*, 235.

II.

SUBSTITUENT EFFECTS IN THE RING-CHAIN TAUTOMERISM OF 1,2-DIARYLIMIDAZOLIDINES

Anikó Göblyös, László Lázár, Ferenc Evanics,[‡] and Ferenc Fülöp*

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, H-6701 Szeged, POB 121, Hungary

[‡]Institute of Pharmaceutical Analysis, Albert Szent-Györgyi Medical University. H-6701 Szeged, POB 121, Hungary

Abstract – 1,2-Diaryl-substituted imidazolidines proved to be ring-chain tautomeric mixtures in $CDCl_3$ at 300 K. Both 1- and 2-aryl groups exerted significant electronic effect on the tautomeric equilibria, which could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$.

Physical and chemical properties of disubstituted organic compounds are influenced significantly by the electronic or steric effects of both substituents.[1-3] This phenomenon plays a crucial role in the ring-chain tautomerism of saturated 1,3-*N*,*N*-heterocycles.[4-6] For 1-alkyl- or 1-phenyl-substituted 2-arylimidazolidines, tautomeric equilibria were determined not only by the electronic effects of the substituents on the 2-aryl group, but also by the steric effects of the *N*-alkyl group, which could be described by Equation (1):[6]

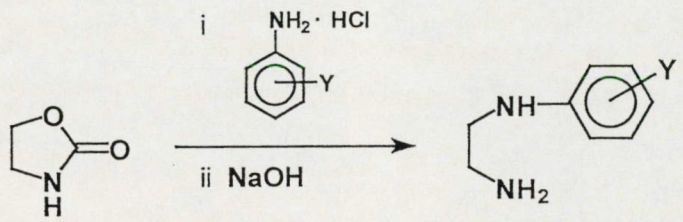
$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad \text{(Eq. 1)}$$

As a continuation of our previous studies[6] on the ring-chain tautomerism of imidazolidines, our present aim was to study the electronic effects of aryl groups in positions 1 and 2. Studies on the electronic effects of aryl groups on the tautomeric equilibria of 1,3-*X*,*N*-heterocycles (X = O, N, S) are restricted mostly to 2-aryl derivatives:[7] the effects of aryl substituents at other positions have been investigated in only a few cases. For 4-aryl-2,2-dialkyl-substituted 1,3,4-oxadiazines, electron-withdrawing groups on the phenyl ring increased the ratios of the ring-closed tautomers.[8] An aryl substituent at position 4 or 6 did not exert

*e-mail: fulop@pharma.szote.u-szeged.hu

observable electronic effects on the ring-chain tautomeric ratios of 2,4- or 2,6-diaryl-substituted tetrahydro-1,3-oxazines.[9]

N-Arylethylenediamines, the starting materials for the synthesis of 1,2-diarylimidazolidines, were prepared according to the convenient method of Poindexter *et al.* by reacting equivalent amounts of 2-oxazolidinone (**1**) with the appropriate substituted aromatic amine hydrochlorides (Scheme 1).[10] To provide large differences in electronic properties, *p*-nitro (**2**), *m*-chloro (**3**), *p*-methyl (**5**), *p*-methoxy (**6**) and *p*-dimethylamino (**7**) derivatives were chosen besides the unsubstituted *N*-phenylethylenediamine (**4**).

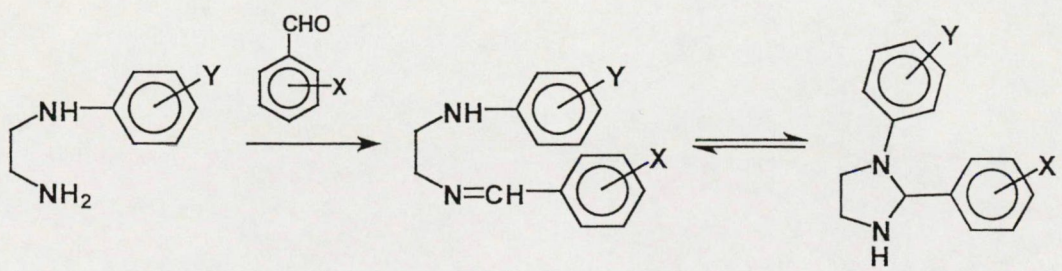


1 **2, 3, 5-7**

Y = *p*-NO_2: **2**; *m*-Cl: **3**; *p*-Me: **5**; *p*-OMe: **6**; *p*-NMe_2: 7

Scheme 1

The ring-closures of ethylenediamines (**2**, **3**, **5-7**) with equivalent amounts of substituted benzaldehydes were carried out under mild reaction conditions (ambient temperature, 1 h) to give imidazolidines (**8**, **9**, **11-13a-i**) in good yields (Scheme 2). Compounds (**10a-i**) were prepared earlier.[6]



Y = *p*-NO_2:	**2**	**8Aa-i**	**8Ba-i**
Y = *m*-Cl:	**3**	**9Aa-i**	**9Ba-i**
Y = H:	**4**	**10Aa-i**	**10Ba-i**
Y = *p*-Me:	**5**	**11Aa-i**	**11Ba-i**
Y = *p*-OMe:	**6**	**12Aa-i**	**12Ba-i**
Y = *p*-NMe_2:	**7**	**13Aa-i**	**13Ba-i**

X = *p*-NO_2: **a**; *m*-NO_2: **b**; *m*-Br: **c**; *p*-Br: **d**; *p*-Cl: **e**; H: **f**; *p*-Me: **g**; *p*-OMe: **h**; *p*-NMe_2: **i**

Scheme 2

The ^{1}H NMR spectra of imidazolidines (**8-13 a-i**) unequivocally proved that these compounds exist as ring-chain tautomeric mixtures in $CDCl_3$ at 300 K. Data on (**11a**) was chosen to demonstrate the ^{1}H NMR spectra of the prepared 1,2-diarylimidazolidines. The chemical shifts and multiplicities of the aliphatic protons in the spectra of (**11a**) correspond to the values for 2-(*p*-bromophenyl)-1-phenylimidazolidine (**10d**).[6] The ratios at equilibrium were determined by integration of the well-separated N-C*H*Ar-N (ring) and N=C*H* (chain) singlets (Table 1).

Table 1 Ring (**B**) percentages at tautomeric equilibrium for compounds (**8-13**) in $CDCl_3$ at 300K

Compd.			**8**	**9**	**10**[a]	**11**	**12**	**13**
		Y	*p*-NO_2	*m*-Cl	H	*p*-Me	*p*-OMe	*p*-NMe_2
	X	σ^+	0.79	0.4	0	-0.311	-0.778	-1.7
a	*p*-NO_2	0.79	57.4	62.2	68.6	71.9	69.4	73.3
b	*m*-NO_2	0.73	49.9	62.2	68.0	70.5	62.2	66.4
c	*m*-Br	0.405	45.6	49.5	52.6	56.2	63.9	55.8
d	*p*-Br	0.15	39.4	41.6	46.1	48.1	46.0	46.6
e	*p*-Cl	0.114	37.0	39.9	42.4	45.0	42.6	45.4
f	H	0	37.7	35.2	35.7	37.1	33.3	34.5
g	*p*-Me	-0.311	30.8	26.9	27.5	28.4	25.6	26.9
h	*p*-OMe	-0.778	18.5	16.5	15.8	18.1	16.7	16.1
i	*p*-NMe_2	-1.7	6.2	5.6	4.6	5.2	4.3	2.7

[a]Literature[6] data.

When Equation (1) was applied to the log K_X values, good linear correlations were obtained versus the Hammett-Brown parameter σ^+ of the substituent X on the 2-phenyl group for all five new sets of imidazolidines (**8, 9, 11-13**) (Figure 1, Table 2).

According to the data in Table 2, the value of ρ in Equation (1) is markedly influenced by the electronic character of substituent Y on the 1-phenyl group. A more electron-donating substituent Y produces a higher ρ value. This means that differences in the ring-chain tautomeric ratios in a set of 2-aryl-substituted imidazolidines are decreased by introducing an electron-withdrawing substituent on the nitrogen. Our efforts to find a mathematical relationship between the electronic parameters of substituent Y and the value of ρ have not resulted in an acceptable correlation. The electronic character of Y did not have any significant effect on the log $K_{X=H}$ values of Equation (1).

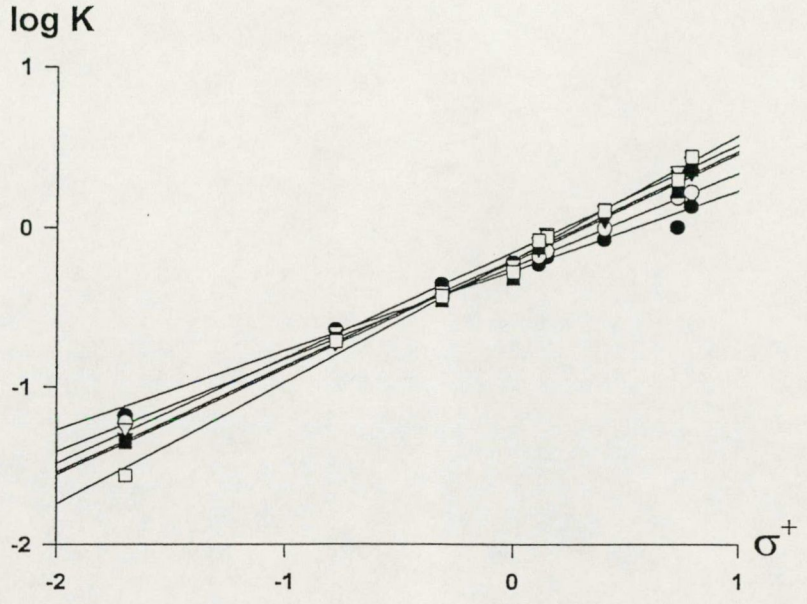


Figure 1 Plots of log K for (**8**): ●, (**9**): ○, (**10**): ▼, (**11**): ▽, (**12**): ■ and (**13**): □ *vs* Hammett-brown parameter σ^+

Table 2 Linear regression analysis data on compounds (**8-13**)

Compd	Y	No. of points	Slope (ρ)[a]	Intercept[a]	Correlation coefficient
8	*p*-NO_2	9	0.49(3)	-0.27(6)	0.991
9	*m*-Cl	9	0.58(0)	-0.25(1)	0.999
10[b]	H	9	0.67(1)	-0.20(3)	0.997
11	*p*-Me	9	0.67(2)	-0.15(4)	0.997
12	*p*-OMe	8	0.68(4)	-0.20(9)	0.989
13	*p*-NMe_2	7	0.77(3)	-0.20(6)	0.996

[a]Standard deviations are given in parentheses. [b]Literature[6] data.

The above results demonstrate that the ring-chain tautomeric equilibria of 1,2-diaryl-substituted imidazolidines are significantly influenced by the electronic characters of both the aryl group at position 2 and (to a lesser extent) the aryl group at position 1. Efforts to explain the above results on the basis of electon densities at amine (NHC_6H_4Y) and imine ($N{=}CHC_6H_4X$) moieties are in progress.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AVANCE DRX 400 spectrometer at 300 K, using a "5 mm inverse Z gradient" probehead. The samples were dissolved in $CDCl_3$ containing 0.03% TMS as a reference. For the equilibria to be established,[11] the solutions were left to stand at ambient temperature for 1 day before the ^{1}H NMR spectra were run. The number of scans was usually 64.

Melting points were determined on a Kofler micro melting point apparatus and are not corrected. The physical data on compounds (**8, 9, 11-13**) are listed in Table 3. *N*-(*m*-Chlorophenyl)- (**3**), *N*-(*p*-tolyl)- (**5**), *N*-(*p*-methoxyphenyl)- (**6**) and *N*-(*p*-dimethylaminophenyl)ethylenediamine (**7**) were prepared by known procedures.[10]

N-(*p*-Nitrophenyl)ethylenediamine (2)

Equimolar quantities (0.2 mol) of 2-oxazolidone and *p*-nitroaniline were heated neat in a 160-170 °C oil bath under nitrogen until all CO_2 evolution had ceased. The dark reaction mixture was allowed to cool to rt. It was then dissolved in 150 mL of 10% NaOH and extracted with $CHCl_3$. The combined organic extracts were washed with brine and then dried over anhydrous Na_2SO_4. The solvent was distilled off *in vacuo* and the resulting crystalline substance was purified by column chromatography on silica gel (eluent: methanol). Yield: 5.41 g (17.3%). mp 135-137 °C (lit.,[12] mp 139-141 °C). The NMR and IR spectra of compound (**2**) correspond to the literature[12] data.

General method for the synthesis of 2-arylimidazolidines (8, 9, 11-13a-i)

To a solution of the appropriate diamine (3 mmol) in 20 mL of absolute methanol, an equivalent amount of aromatic aldehyde was added (in the case of liquid aldehydes, a freshly distilled sample was used), and the mixture was left to stand at ambient temperature for 1 h. The solvent was evaporated off and the evaporation was repeated after the addition of 10 mL of toluene. 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 filtered off and recrystallized.

^{1}H NMR spectroscopic data on 2-(*p*-nitrophenyl)-1-(*p*-tolyl)imidazolidine (11a)

The protons of the open form (**A**) are numbered according to the corresponding protons of the ring form (**B**) (δ in ppm; in brackets the multiplicity, couplings in Hz and assignment, respectively).

(**11Aa**): 8.35 (*s*, 1H, N=C*H*), 8.25 (*d*, 2H, *J* = 8.8, $C_6H_5NO_2$), 7.88 (*d*, 2H, *J* = 8.8, $C_6H_5NO_2$), 6.99 (*d*, 2H, *J* = 8.5, C_6H_5Me), 6.58 (*d*, 2H, *J* = 8.5, C_6H_5Me), 3.88 (*dt*, 2H, *J* = 5.8, 1.3, 4-CH_2), 3.49 (*t*, 2H, *J* = 5.7, 5-CH_2), 2.24 (*s*, 3H, CH_3); (**11Ba**): 8.17 (*d*, 2H, *J* = 8.8, $C_6H_5NO_2$), 7.58 (*d*, 2H, *J* = 8.8, $C_6H_5NO_2$),

Table 3 Physical and analytical data on imidazolidines (8, 9, 11-13 a-i)[a]

Compd	mp (°C)	Yield (%)	Formula	Analysis Calculated/Found (%) C	H	N	δ N=C*H*Ar (*s*) chain (A)	δ N-C*H*Ar-N (*s*) ring (B)
8a	179-181[b]	72	$C_{15}H_{14}N_4O_4$	57.32 57.07	4.49 4.38	17.83 17.65	8.33	5.61
8b	oil	~100	$C_{15}H_{14}N_4O_4$	57.32 –	4.49 –	17.83 –	8.32	5.62
8c	oil	~100	$C_{15}H_{14}N_3O_2Br$	51.74 –	4.05 –	12.07 –	8.18	5.48
8d	128-133[c]	69	$C_{15}H_{14}N_3O_2Br$	51.74 51.69	4.05 4.84	12.07 11.90	8.20	5.48
8e	140-143[c]	76	$C_{15}H_{14}N_3O_2Cl$	59.31 59.18	4.65 4.72	13.83 13.77	8.21	5.49
8f	oil	~100	$C_{15}H_{15}N_3O_2$	66.90 –	5.61 –	15.60 –	8.25	5.51
8g	109-110[c]	64	$C_{16}H_{17}N_3O_2$	67.83 67.94	6.05 7.82	14.83 14.69	8.21	5.47
8h	oil	~100	$C_{16}H_{17}N_3O_3$	64.20 –	5.72 –	14.04 –	8.17	5.46
8i	oil	~100	$C_{17}H_{20}N_4O_2$	65.37 –	6.45 –	17.94 –	8.08	5.39
9a	oil	~100	$C_{15}H_{14}N_3O_2Cl$	59.31 –	4.65 –	13.83 –	8.37	5.49
9b	oil	~100	$C_{15}H_{14}N_3O_2Cl$	59.31 –	4.65 –	13.83 –	8.36	5.49
9c	oil	~100	$C_{15}H_{14}N_2BrCl$	53.36 –	4.18 –	8.30 –	8.21	5.35
9d	oil	~100	$C_{15}H_{14}N_2BrCl$	53.36 –	4.18 –	8.30 –	8.23	5.35
9e	oil	~100	$C_{15}H_{14}N_2Cl_2$	61.45 –	4.81 –	9.55 –	8.24	5.36
9f	oil	~100	$C_{15}H_{15}N_2Cl$	69.63 –	5.84 –	10.83 –	8.29	5.39
9g	oil	~100	$C_{16}H_{17}N_2Cl$	70.45 –	6.28 –	10.27 –	8.25	5.36
9h	oil	~100	$C_{16}H_{17}N_2OCl$	66.55 –	5.93 –	9.70 –	8.22	5.35
9i	oil	~100	$C_{17}H_{20}N_3Cl$	67.65 –	6.68 –	13.92 –	8.16	5.32
11a	69-71[c]	55	$C_{16}H_{17}N_3O_2$	67.83 67.59	6.05 5.81	14.83 14.66	8.35	5.44
11b	74-75[d]	49	$C_{16}H_{17}N_3O_2$	67.83 67.95	6.05 6.10	14.83 14.79	8.35	5.44
11c	oil	~100	$C_{16}H_{17}N_2Br$	60.58 –	5.40 –	8.83 –	8.19	5.30
11d	72-74[c]	64	$C_{16}H_{17}N_2Br$	60.58 60.71	5.40 5.27	8.83 8.79	8.22	5.31

Table 3 (continued)

11e	58-61[d]	52	$C_{16}H_{17}N_2Cl$	70.45 70.18	6.28 6.07	10.27 10.33	8.23	5.32
11f	oil	~100	$C_{16}H_{18}N_2$	80.63 –	7.61 –	11.75 –	8.28	5.35
11g	68-70[d]	49	$C_{17}H_{20}N_2$	80.91 81.03	7.99 8.16	11.10 10.95	8.24	5.32
11h	51-53[d]	45	$C_{17}H_{20}N_2O$	76.09 75.84	7.51 7.35	10.44 10.28	8.21	5.31
11i	52-54[d]	52	$C_{18}H_{23}N_3$	76.83 76.62	8.24 8.17	14.93 14.80	8.20	5.27
12a	oil	~100	$C_{16}H_{17}N_3O_3$	64.20 –	5.72 –	14.04 –	8.36	5.39
12b	oil	~100	$C_{16}H_{17}N_3O_3$	64.20 –	5.72 –	14.04 –	8.28	5.39
12c	oil	~100	$C_{16}H_{17}N_2OBr$	57.67 –	5.14 –	8.41 –	8.21	5.26
12d	62-64[d]	48	$C_{16}H_{17}N_2OBr$	57.67 57.40	5.14 4.93	8.41 8.26	8.23	5.26
12e	51-53[d]	51	$C_{16}H_{17}N_2OCl$	66.55 66.34	5.93 5.86	9.70 9.71	8.24	5.27
12f	oil	~100	$C_{16}H_{18}N_2O$	75.56 –	7.13 –	11.01 –	8.28	5.28
12g	81-83[d]	55	$C_{17}H_{20}N_2O$	76.09 76.18	7.51 7.43	10.44 10.38	8.25	5.26
12h	58-60[d]	58	$C_{17}H_{20}N_2O_2$	71.81 71.64	7.09 6.81	9.85 9.78	8.21	5.25
12i	80-82[c]	60	$C_{18}H_{23}N_3O$	72.70 72.56	7.80 7.67	14.13 14.14	8.15	5.21
13a	79-81[d]	47	$C_{17}H_{20}N_4O_2$	65.37 –	6.45 –	17.94 –	8.35	5.37
13b	oil	~100	$C_{17}H_{20}N_4O_2$	65.37 –	6.45 –	17.94 –	8.34	5.37
13c	oil	~100	$C_{17}H_{20}N_3Br$	58.97 –	5.82 –	12.13 –	8.19	5.24
13d	89-91[d]	49	$C_{17}H_{20}N_3Br$	58.97 58.71	5.82 5.58	12.13 12.04	8.23	5.24
13e	82-85[c]	52	$C_{17}H_{20}N_3Cl$	67.65 67.49	6.68 6.38	13.92 13.75	8.24	5.25
13f	oil	~100	$C_{17}H_{21}N_3$	76.37 –	7.92 –	15.72 –	8.22	5.28
13g	60-62[d]	52	$C_{18}H_{23}N_3$	76.83 76.70	8.24 7.99	14.93 15.08	8.25	5.25
13h	78-79[c]	48	$C_{18}H_{23}N_3O$	72.70 72.58	7.80 7.63	14.13 14.01	8.21	5.23
13i	oil	~100	$C_{19}H_{26}N_4$	73.51 –	8.44 –	18.05 –	8.14	5.19

[a]Analitical data were determined only for recrystallized new compounds. [b]Recrystallized from iPr_2O– EtOAc. [c]Recrystallized from *n*-hexane–iPr_2O. [d]Recrystallized from *n*-hexane.

6.99 (*d*, 2H, *J* = 8.5, C_6H_5Me), 6.38 (*d*, 2H, *J* = 8.5, C_6H_5Me), 5.44 (*s*, 1H, 2-C*H*), 3.68 (*ddd*, 1H, *J* = -8.5, 6.9, 3.8, 5-CH_2), 3.41 (*q*, 1H, *J* = 7.5, 5-CH_2), 3.29 (*ddd*, 1H, *J* = -11.6, 6.6, 3.5, 4-CH_2), 3.16 (*ddd*, 1H, *J* = -11.6, 7.5, 6.6, 4-CH_2), 2.23 (*s*, 3H, CH_3).

REFERENCES

1. R. Arnaud and Y. Vallée, *J. Chem. Soc., Perkin Trans. 2*, 1997, 2737.
2. H.-J. Zhu, B.-T. Zhao, W.-M. Dai, J. Zhou, and X.-J. Hao, *Tetrahedron: Asymmetry*, 1998, **9**, 2879.
3. S. Uchiyama, T. Santa, T. Fukushima, H. Homma, and K. Imai, *J. Chem. Soc., Perkin Trans. 2*, 1998, 2165.
4. C. Chapuis, A. Gauvreau, A. Klaebe, A. Lattes, and J. J. Perie, *Bull. Soc. Chim. Fr.*, 1973, 977.
5. G. Parrinello and R. Mülhaupt, *J. Org. Chem.*, 1990, **55**, 1772.
6. L. Lázár, A. Göblyös, F. Evanics, G. Bernáth, and F. Fülöp, *Tetrahedron*, 1998, **54**, 13639.
7. R. E. Valters, F. Fülöp, and D. Korbonits, *Adv. Heterocyclic Chem.*, 1996, **66**, 1.
8. B. L. Milman and A. A. Potekhin, *Khim. Get. Soedin.*, 1973, 902.
9. F. Fülöp, L. Lázár, G. Bernáth, R. Sillanpää, and K. Pihlaja, *Tetrahedron*, 1993, **49**, 2115.
10. G. S. Poindexter, D. A. Owens, P. L. Dolan, and E. Woo, *J. Org. Chem.*, 1992, **57**, 6257.
11. M. E. Alva Astudillo, N. C. J. Chokotho, T. C. Jarvis, C. D. Johnson, C. C. Lewis, and P. D. McDonnell, *Tetrahedron*, 1985, **41**, 5919.
12. T. F. Chung, Y. M. Wu, and C. H. Cheng, *J. Org. Chem.*, 1984, **49**, 1215.

ACKNOWLEDGEMENT

The authors' thanks are due to the Hungarian Research Foundation (OTKA grant No. T 20454) for financial support.

Received, 11th May, 1999

III.

A 2-arilszubsztituált imidazolidinek gyűrű-lánc tautomériája[1]

GÖBLYÖS Anikó, LÁZÁR László, BERNÁTH Gábor és FÜLÖP Ferenc

Szegedi Tudományegyetem, Gyógyszerkémiai Intézet, 6701 Szeged, POB 121

EVANICS Ferenc

Szegedi Tudományegyetem, Gyógyszeranalitikai Intézet, 6701 Szeged, POB 121

Bevezetés

Számos öt- és hattagú, telített *N*-szubsztituálatlan 1,3-*X,N*-heterociklus (*X* = *O*, *S*, *NR*) szerkezete és reaktivitása az 1,3-*X,N*-heterociklus és a megfelelő Schiff-bázis gyűrű-lánc tautomer egyensúlyával jellemezhető.[2]

A telített 1,3-*X,N*-heterociklusok közül az oxazolidinek és tetrahidro-1,3-oxazinok gyűrű-lánc tautomériáját tanulmányozták a legrészletesebben.[2-4] Az ilyen típusú vegyületek 2-arilszubsztituált származékai esetén lineáris összefüggést (I) találtak az egyensúlyok log K_X = [gyűrűs]/[nyílt] értékei és a 2-arilcsoport X-szubsztituensének Hammett-Brown σ^+ konstansa között. Megállapították, hogy a 2-aril-oxazolidinek esetén az (I) egyenlet mind folyadék, mind gázfázisban érvényes.[4, 5]

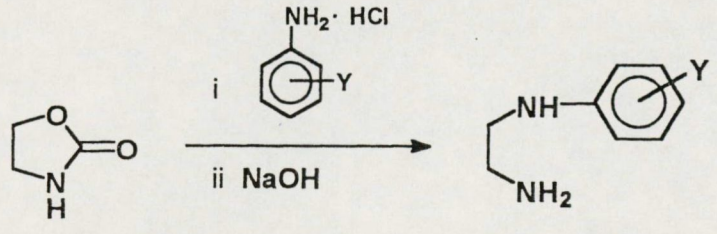
$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (I)$$

Az 1,3-*O,N*-vegyületekkel ellentétben, a megfelelő 1,3-*N,N*-heterociklusok gyűrű-lánc tautomériáját csak néhány esetben írták le.[2, 6-10] Ennek megfelelően, az 1,3-*N,N*-heterociklusok tautomer egyensúlyát befolyásoló szubsztituenshatásokról is csak kevés ismerettel rendelkezünk.[11-16]

Mindezek alapján célszerűnek láttuk, hogy megvizsgáljuk néhány 1-alkil- vagy arilszubsztituált 2-aril-imidazolidin modellvegyület gyűrű-lánc tautomer egyensúlyát. Kísérleteinkkel tanulmányozni kívántuk az (I) egyenlet érvényességi határát, valamint az 1- és 2-helyzetű szubsztituensek tautomer egyensúlyra gyakorolt sztérikus és/vagy elektronikus hatását. Jól ismert jelenség, hogy a diszubsztituált vegyületek fizikai és kémiai tulajdonságait mindkét szubsztituens sztérikus és elektronikus hatása jelentősen befolyásolhatja,[17-19] amit korábban a telített 1,3-*N,N*-heterociklusok gyűrű-lánc tautomériájában is tapasztaltak.[1a, 12, 15]

Eredmények

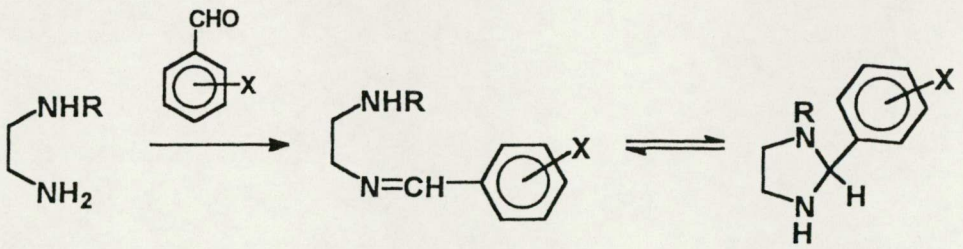
A terveinkben szereplő 2-aril-imidazolidinek szintézisét *N*-szubsztituált etilén-diaminok gyűrűzárásaival kívántuk megvalósítani. A gyűrűzárásokhoz szükséges *N*-arilszubsztituált etilén-diaminokat (**2-6**) Poindexter és munkatársai módszerével állítottuk elő: ekvivalens mennyiségű 2-oxazolidinon és a megfelelően szubsztituált anilin-hidrokloridok reakciójával (1. ábra).[20] A szubsztituált anilinek kiválasztása során célunk volt, hogy minél változatosabb σ^+-értékű Y-szubsztituenseket tartalmazó diaminokat készítsünk. Az *N*-alkil- és *N*-fenil-etilén-diaminokat (**7-11**) kereskedelmi forgalomból szereztük be.



1 **2-6**

Y = *p*NO_2: **2**; *m*Cl: **3**; *p*Me: **4**; *p*OMe: **5**; *p*NMe_2: **6**

1. ábra



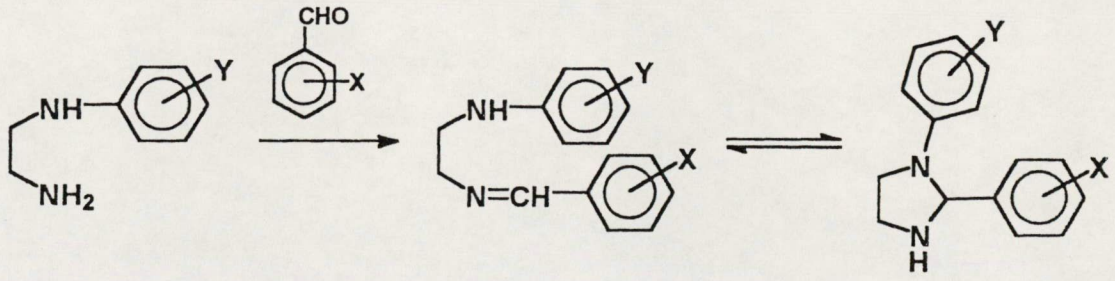
R = Me: 7	**12Aa-i**	**12Ba-i**
R = Et: 8	**13Aa-i**	**13Ba-i**
R = Pr: 9	**14Aa-i**	**14Ba-i**
R = *i*Pr: 10	**15Aa-i**	**15Ba-i**
R = Ph: 11	**16Aa-i**	**16Ba-i**

X = *p*NO_2: **a**; *m*NO_2: **b**; *m*Br: **c**; *p*Br: **d**; *p*Cl: **e**; H: **f**; *p*Me: **g**; *p*OMe: **h**; *p*NMe_2: **i**

2. ábra

Az *N*-metil- (**7**), *N*-etil- (**8**), *N*-propil- (**9**), *N*-izopropil- (**10**), *N*-fenil- (**11**) és *N*-(szubsztituált-fenil)-etilén-diaminokat (**2-6**) szobahőmérsékleten, metanolos oldatban ekvivalens mennyiségű szubsztituált benzaldehidekkel reagáltattuk, s jó termeléssel kaptuk a megfelelő 1,2-diszubsztituált imidazolidineket (**12-21**) (2. és 3. ábra).

A **12-16** ill. **17-21** vegyületek ^{1}H NMR spektrumai azt mutatták, hogy ezek a vegyületek (a **15i** kivételével, melyben gyűrűs formát nem lehetett kimutatni) $CDCl_3$ oldatban, 300 K-en gyűrűs és nyílt láncú formák elegyeként vannak jelen. A tautomer egyensúlyok komponensarányait a jól elkülönülő N-C*H*Ar-N (gyűrűs) és N=C*H*Ar (nyílt láncú) szingulett jelek integráljaiból határoztuk meg (1. és 2. táblázat).



Y = *p*NO_2: **2**	**17Aa-i**	**17Ba-i**
Y = *m*Cl: **3**	**18Aa-i**	**18Ba-i**
Y = H: **11**	**16Aa-i**	**16Ba-i**
Y = *p*Me: **4**	**19Aa-i**	**19Ba-i**
Y = *p*OMe: **5**	**20Aa-i**	**20Ba-i**
Y = *p*NMe_2: **6**	**21Aa-i**	**21Ba-i**

X = *p*NO_2: **a**; *m*NO_2: **b**; *m*Br: **c**; *p*Br: **d**; *p*Cl: **e**; H: **f**; *p*Me: **g**; *p*OMe: **h**; *p*NMe_2: **i**

3. ábra

1. táblázat

A gyűrűs (B) formák aránya a 12-16 vegyületek 300 K-en mért tautomer egyensúlyaiban

Vegyület	X	σ^+	12[a] R = Me	12[b] R = Me	13 R = Et	14 R = *n*Pr	15 R = *i*Pr	16[a] R = Ph	16[b] R = Ph
a	*p*NO_2	0,79	93,4	94,8	84,0	85,4	33,4	68,6	56,0
b	*m*NO_2	0,73	94,4	95,3	85,8	85,9	34,8	68,0	55,0
c	*m*Br	0,405	89,4	93,6	75,2	73,4	17,3	52,6	38,7
d	*p*Br	0,15	86,8	89,1	69,5	69,0	12,2	46,1	31,3
e	*p*Cl	0,114	86,6	90,1	68,6	67,8	10,5	42,4	29,6
f	H	0	83,5	85,6	60,3	60,1	8,1	35,7	21,0
g	*p*Me	-0,311	78,9	79,7	48,2	50,3	5,1	27,5	14,7
h	*p*OMe	-0,778	68,2	71,3	37,9	37,0	3,1	15,8	8,3
i	*p*NMe_2	-1,7	43,6	c	16,7	14,9	~0	4,6	2,2

[a]Egyensúly $CDCl_3$-ban. [b]Egyensúly DMSO-d_6-ban. [c]300 K-en az átfedő jelek miatt a tautomer arányokat nem tudtuk meghatározni.

2. táblázat

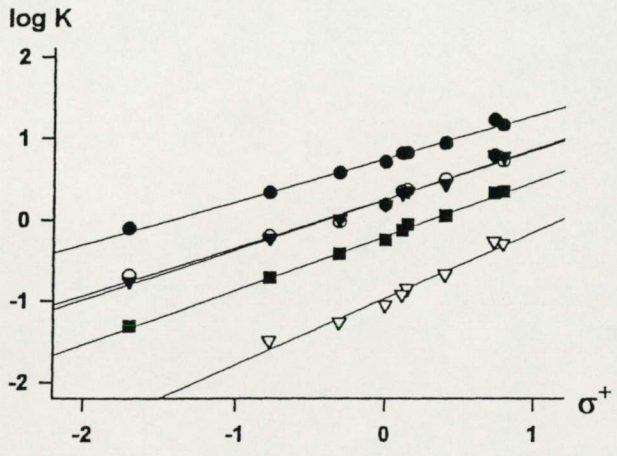
A gyűrűs (B) formák aránya a 16-21 vegyületek $CDCl_3$ oldatban, 300 K-en mért tautomer egyensúlyaiban

Vegyület			17	18	16	19	20	21
		Y	*p*NO_2	*m*Cl	H	*p*Me	*p*OMe	*p*NMe_2
	X	σ^+	0,79	0,4	0	-0,311	-0,778	-1,7
a	*p*NO_2	0,79	57,4	62,2	68,6	71,9	69,4	73,3
b	*m*NO_2	0,73	49,9	62,2	68,0	70,5	62,2	66,4
c	*m*Br	0,405	45,6	49,5	52,6	56,2	63,9	55,8
d	*p*Br	0,15	39,4	41,6	46,1	48,1	46,0	46,6
e	*p*Cl	0,114	37,0	39,9	42,4	45,0	42,6	45,4
f	H	0	37,7	35,2	35,7	37,1	33,3	34,5
g	*p*Me	-0,311	30,8	26,9	27,5	28,4	25,6	26,9
h	*p*OMe	-0,778	18,5	16,5	15,8	18,1	16,7	16,1
i	*p*NMe_2	-1,7	6,2	5,6	4,6	5,2	4,3	2,7

Figyelemreméltó, hogy az 1-metil-2-(*p*-nitro-fenil)-imidazolidin (**12a**) $CDCl_3$-ban, az irodalmi adatokkal (0 %)[14,15] ellentétben, 6,6 % nyílt láncú formát (A) tartalmaz. Heteronukleáris korrelációs (HMBC, HMQC) spektroszkópiával a jellegzetes N-C*H*Ar-N, ill. N=C*H*Ar szinguletteken kívül a gyűrűs és nyílt formák metilénjeleit is meg tudtuk különböztetni. Ez különösen hasznos volt néhány *p*OMe és *p*NMe_2-szubsztituált származék esetén, ahol az átfedő jelek miatt a tautomer arányokat csak a metilénjelek integrálásával lehetett meghatározni. Az alifás protonok NMR spektrumadatait a **12d-16d** 2-(*p*-bróm-fenil)-származékok példáin keresztül mutatjuk be (ld. kísérleti rész).

Amikor az egyensúlyi tautomer arányok logaritmusát (log K_X) a 2-arilcsoport X-szubsztituensé-

nek Hammett-Brown σ^+ paramétere függvényében ábrázoltuk, valamennyi imidazolidin-sorozat esetén igen jó korrelációval jellemezhető lineáris összefüggést találtunk (4. ábra, 3. és 4. táblázat), vagyis az (I) egyenlet alkalmasnak bizonyult e vegyületek tautomer egyensúlyainak leírására is.



4. ábra A **12** (●), **13** (○), **14** (▼), **15** (▽) and **16** (■) vegyületek log K értékei ($CDCl_3$-ban) a σ^+ Hammett-Brown paraméter függvényében

Tudomásunk szerint a 2-aril-imidazolidinek esetén ez az első példa gyűrű-lánc tautomer egyensúly Hammett-típusú egyenlettel történő jellemzésére. Az (I) egyenletet a 2-aril-1,3-*N,N*-heterociklusok gyűrű-lánc tautomériájának leírására elsőként a 2-aril-hexahidropirimidinek esetén, a közelmúltban alkalmazták.[16a]

A gyűrű-lánc tautomerek egymásba alakulását, azaz az egyensúly mobilitását az 1-metil- és 1-fenil-imidazolidinek $CDCl_3$-ban és DMSO-d_6-ban mért eltérő tautomer arányai bizonyítják (1. táblázat). A **16** 1-fenil-imidazolidinek, hasonlóan az 1,3-*O,N*-heterociklusokhoz,[21] $CDCl_3$-ban több, míg DMSO-d_6-ban kevesebb gyűrűs formát tartalmaztak, ami valószínűleg az oldószerek eltérő hidrogénkötő képességével van összefüggésben. Az 1-metil-imidazolidin-sorozat (**12**) tautomériájának oldószerfüggését vizsgálva az előzőtől eltérő hatást tapasztaltunk: a gyűrűs formák aránya valamivel nagyobb volt DMSO-d_6-ban, mint $CDCl_3$-ban. Az oldószer mindkét vegyületsorozat esetén csak kismértékben befolyásolta a regressziós egyenesek meredekségét (ρ).

A 3. táblázat adatai azt mutatják, hogy a regressziós egyenes meredeksége (ρ) az 1-fenil-($CDCl_3$-ban: 0,67) és különösen az 1-izopropil-imidazolidinek (0,82) esetén nagyobb, mint az oxazolidinekre jellemző ρ érték (0,50-0,60),[2] míg az 1-metil- (0,53), 1-etil- (0,59) és 1-propil-imidazolidinek (0,62) ρ értékei az oxazolidinekéhez hasonlóak. A **12-16** vegyületek ρ értékeiben mutatkozó jelentős különbségekből arra következtethetünk, hogy az

3. táblázat

A 12-16 vegyületek, valamint a 2-aril-oxazolidinek (22)[4] lineáris regressziós analízisének adatai

Vegyület	Pontok száma	Meredekség[a] (ρ)	Tengely-metszet[a]	Korrelációs koefficiens	c[b]
12[c]	9	0,53(2)	0,75(4)	0,990	1,85
12[d]	8	0,61(4)	0,84(6)	0,970	–
13[c]	9	0,59(3)	0,25(6)	0,984	1,35
14[c]	9	0,62(2)	0,25(5)	0,989	1,35
15[c]	8	0,82(5)	-0,97(7)	0,973	0,13
16[c]	9	0,67(1)	-0,20(3)	0,997	0,90
16[d]	9	0,72(2)	-0,48(5)	0,993	–
22[c]	7	0,60(4)	-1,10(2)	0,989	0

[a]A zárójelben a standard deviáció értéke található. [b]c érték az adott 2-aril-imidazolidinek és a szubsztituálatlan 2-aril-oxazolidin[4] tengelymetszetérték különbsége. [c]Az adatok a $CDCl_3$-ban mért egyensúlyra vonatkoznak. [d]Az adatok a DMSO-d_6-ban mért egyensúlyra vonatkoznak.

imidazolidinek esetén – ellentétben az 1,3-*O*,*N*-heterociklusokkal – a ρ értéke nem jellemző az adott gyűrűrendszerre.

A 12-16 imidazolidinek egyensúlyi elegyei, noha a nyitott formák gyűrűzárása (A → B) a Baldwin-szabályok[22] szerint nem kedvezményezett folyamat (5-*endo*-*trig*), jelentős mennyiségű gyűrűs formát tartalmaznak. A tengelymetszetek összehasonlításaiból kitűnik, hogy az *N*-metil-, *N*-etil-, *N*-propil- és *N*-fenilimidazolidinek tautomer elegyeiben a gyűrűs forma mennyisége jelentősen nagyobb, mint az oxazolidinek esetén.

4. táblázat

A 16-21 vegyületek lineáris regressziós analízisének adatai

Vegyület	Y	Pontok száma	Meredekség (ρ)[a]	Tengely-metszet[a]	Korrelációs koefficiens
17	*p*NO_2	9	0,49(3)	-0,27(6)	0,991
18	*m*Cl	9	0,58(0)	-0,25(1)	0,999
16	H	9	0,67(1)	-0,20(3)	0,997
19	*p*Me	9	0,67(2)	-0,15(4)	0,997
20	*p*OMe	8	0,68(4)	-0,20(9)	0,989
21	*p*NMe_2	7	0,77(3)	-0,20(6)	0,996

[a]A standard deviációkat zárójelben adtuk meg.

Az *N*-szubsztituens α-szénatomjának sztérikus hatása döntő szerepet játszik az NHR-csoport C=N kötésre történő addíciójában. A nitrogén mellettei szénatomon lévő metilcsoportok számának növelése (*N*-Me → *N*-Et → *N*-*i*Pr) csökkentette a tautomer egyensúlyban a gyűrűs formák arányát. Az *N*-szubsztituens β-szénatomjához kapcsolódó metilcsoportnak (*N*-Et → *N*-Pr) azonban már nem volt jelentős hatása a tengelymetszet értékére. A gyűrűs formák aránya az *N*-szubsztituensek következő sorrendjében növekszik: *i*Pr < Ph < Pr ≈ Et < Me.

Az arilcsoportok elektronikus hatásának tautomer egyensúlyra gyakorolt hatását az 1,3-*X*,*N*-heterociklusok esetén legtöbbször a 2-arilszármazékok esetén tanulmányozták,[2] más helyzetű arilszubsztituensek hatásáról csak kevés ismeretünk van. A 2,2-dialkil-4-aril-szubsztituált-1,3,4-oxadiazinok esetén a fenilgyűrűn lévő elektronszívó csoportok növelték a gyűrűs forma arányát.[23] A 4- vagy 6-helyzetben lévő arilszubsztituens elektronikus hatása viszont nem befolyásolta számottevően a 2,4- vagy 2,6-diarilszubsztituált tetrahidro-1,3-oxazinok gyűrű-lánc tautomer arányait.[24]

Az 1,2-diarilszubsztituált imidazolidinek (16-21) regressziós egyenleteit összehasonlítva azt találtuk, hogy az egyenesek meredekségét (ρ) az 1-fenilcsoport Y szubsztituensének elektronikus hatása jelentősen befolyásolja: minél erősebb elektronküldő tulajdonságú az Y szubsztituens, annál nagyobb a ρ értéke. Ez azt jelenti, hogy a gyűrű-lánc tautomer arányokban az egy adott 2-aril-imidazolidin vegyületsorozaton belül mutatkozó eltérések elektronszívó csoportot tartalmazó *N*-arilszubsztituens esetén mérséklődnek. Nem sikerült azonban elfogadható korrelációjú összefüggést találni az Y szubsztituens elektronikus paraméterei és a ρ értékek között. Az Y elektronikus tulajdonsága nem gyakorolt szignifikáns hatást az (I) egyenlet log $K_{X=H}$ értékeire.

Az 1-szubsztituált 2-aril-imidazolidinek (12-21) gyűrű-lánc tautomériáját tanulmányozva megállapítottuk, hogy e vegyületek tautomer egyensúlyát a 2-helyzetű arilcsoport X-szubsztituensének elektronikus hatása, valamint az imidazolidingyűrű nitrogénatomján lévő szubsztituens sztérikus, illetve elektronikus hatásai jelentősen befolyásolják. A fenti eredményeknek az amin (NHC_6H_4Y) és az imin ($N=CHC_6H_4X$) részek elektronsűrűségével történő értelmezésén még jelenleg is dolgozunk.

Kísérleti rész

Anyagok és módszerek

A ^{1}H NMR spektrumok 5 mm-es, inverz Z grádiensű próbafej használatával, 300 K-en Bruker AVANCE DRX 400 spektrométeren készültek. A $CDCl_3$-ban, vagy DMSO-d_6-ban oldott minták referenciaanyagként 0,03 % TMS-t tartalmaztak. Az

egyensúly beállása céljából,[25] a spektrumok felvétele előtt az oldatokat egy napig, szobahőmérsékleten állni hagytuk. Az olvadáspontokat Kofler-mikro-olvadáspont-mérő készüléken mértük, az értékek nem korrigáltak. A **12-16** vegyületek fizikai adatait az 5. táblázat, a **17-21** vegyületekét a 6. táblázat tartalmazza. Az *N*-(*m*-klór-fenil)- (**3**), *N*-(*p*-tolil)- (**4**), *N*-(*p*-metoxi-fenil)- (**5**) és az *N*-[(*p*-dimetil-amino)-fenil)]etilén-diamint (**6**) irodalmi módszer alkalmazásával állítottuk elő.[20]

Az N-(p-nitro-fenil)-etilén-diamin (**2**) *szintézise*

Ekvivalens mennyiségű (0,20 mol) 2-oxazolidinon és *p*-nitro-anilin keverékét nitrogén atmoszférában, a CO_2-fejlődés befejeződéséig 160-170 °C-os olajfürdőn tartottuk. A szobahőmérsékletre hűtött sötét reakcióelegyet 150 ml 10 %-os NaOH-oldatban oldottuk és kloroformmal extraháltuk. Az egyesített szerves fázisokat sós vízzel mostuk, Na_2SO_4-on szárítottuk, bepároltuk. A kristályos maradékot oszlopkromatográfiásan (adszorbens: szilikagél, eluens: metanol) tisztítottuk. Termelés: 5,41 g (17,3 %). Op.: 135-137 °C (irodalmi[26] op.: 139-141 °C). A **2** vegyület NMR és IR spektruma az irodalmi adatokkal azonos.[26]

Általános módszer az 1-szubsztituált-2-aril-imidazolidinek (**12-21**) *szintézisére*

A megfelelő *N*-szubsztituált etilén-diamin (3 mmol) abszolút metanolos (20 ml) oldatához ekvivalens mennyiségű aromás aldehidet adtunk (folyékony aldehidek esetén frissen desztillált mintát használtunk), majd az oldatot szobahőmérsékleten 1 órán át állni hagytuk. Az oldószert bepároltuk, majd a bepárlást 10 ml toluol hozzáadása után megismételtük. A kristályos termékeket szűrtük és átkristályosítottuk (termelés: 60-80 %). Az olajként kapott termékeket 24 órán át vákuumexszikkátorban szárítottuk. Az NMR spektrumok az olajok 95 %-nál nagyobb tisztaságát bizonyították. Valamennyi átkristályosított új vegyület elemi analízis adata a számítottnak megfelelő volt (C, H, N ± 0,3 %).

A **12d-16d** *2-(p-bróm-fenil)-származékok alifás protonjainak NMR spektroszkópiás adatai ($CDCl_3$, 300 K)*

A nyílt láncú tautomereket (**A**) is a gyűrűs formáknak (**B**) megfelelően számoztuk. A kémiai eltolódást (δ) ppm-ben, a csatolási állandót (*J*) Hz-ben adtuk meg; *om* = átfedő multiplett.

12Ad: 8,28 (*s*, 1H, N=C*H*), 3,72 (*t*, 2H, *J* = 6,0, 4-CH_2), 2,91 (*t*, 2H, *J* = 6,0, 5-CH_2), 2,47 (*s*, 3H, NCH_3); **12Bd**: 3,86 (*s*, 1H, 2-C*H*), 3,32 (*ddd*, 1H, *J* = -16,4, 7,7, 2,5, 5-CH_2), 3,24 (*dd*, 1H, *J* = -8,0, 7,7, 4-CH_2), 3,08 (*ddd*, 1H, *J* = -8,0, 8,0, 2,5, 4-CH_2), 2,44 (*dd*, 1H, *J* = 16,4, 8,0, 5-CH_2), 2,20 (*s*, 3H, NCH_3).

13Ad: 8,28 (*s*, 1H, N=C*H*), 3,75 (*t*, 2H, *J* = 5,6, 4-CH_2), 2,96 (*t*, 2H, *J* = 5,6, 5-CH_2), 2,70 (*q*, 2H, *J* = 7,3, CH_2CH$_3$), 1,11 (*t*, 3H, *J* = 7,3, CH$_2$CH_3); **13Bd**: 4,00 (*s*, 1H, 2-C*H*), 3,40 (*dt*, 1H, *J* = -8,2, 3,2, 5-CH_2), 3,25 (*dt*, 1H, *J* = -10,7, 8,2, 4-CH_2), 3,09 (*ddd*, 1H, *J* = -10,7, 8,2, 3,2, 4-CH_2), 2,55 (*dq*, 1H, *J* = -11,8, 7,3, CH_2CH$_3$), 2,38 (*q*, 1H, *J* = 8,2, 5-CH_2), 2,18 (*dq*, 1H, *J* = -11,8, 7,3 CH_2CH$_3$), 1,05 (*t*, 3H, *J* = 7,3 CH$_2$CH_3).

14Ad: 8,28 (*s*, 1H, N=C*H*), 3,75 (*t*, 2H, *J* = 5,8, 4-CH_2), 2,95 (*t*, 2H, *J* = 5,8, 5-CH_2), 2,62 (*t*, 2H, *J* = 7,3, CH_2CH$_2$CH$_3$); 1,5 (*om*, 2H, CH$_2$CH_2CH$_3$), 0,91 (*t*, 3H, *J* = 7,5, CH$_2$CH$_2$CH_3); **14Bd**: 4,00 (*s*, 1H, 2-C*H*), 3,37 (*om*, 1H, 4-CH_2) 3,24 (*om*, 1H, 5-CH_2), 3,09 (*om*, 1H, 4-CH_2), 2,39 (*om*, 2H, CH_2CH$_2$CH$_3$), 2,13 (*om*, 1H, 5-CH_2), 1,45 (*om*, 2H, CH$_2$CH_2CH$_3$), 0,86 (*t*, 3H, *J* = 7,5, CH$_2$CH$_2$CH_3).

15Ad: 8,28 (*s*, 1H, N=C*H*), 3,72 (*t*, 2H, *J* = 6,0, 4-CH_2), 2,94 (*t*, 2H, *J* = 6,0, 5-CH_2), 2,84 (*h*, 1H, *J* = 6,3, C*H*(CH$_3$)$_2$), 1,06 (*d*, 6H, *J* = 6,3, CH(CH_3)$_2$); **15Bd**: 4,42 (*s*, 1H, 2-C*H*), 3,10 (*om*, 2H, 4-CH_2), 3,00 (*om*, 1H, C*H*(CH$_3$)$_2$), 2,75 (*om*, 2H, 5-CH_2), 0,98 (*d*, 6H, *J* = 6,2, CH(CH_3)$_2$).

16Ad: 8,23 (*s*, 1H, N=C*H*), 3,83 (*t*, 2H, *J* = 5,5, 4-CH_2), 3,47 (*t*, 2H, *J* = 5,5, 5-CH_2); **16Bd**: 5,35 (*s*, 1H, 2-C*H*), 3,24 (*om*, 2H, 4-CH_2); 3,45 (*m*, 1H, 5-CH_2), 3,63 (*om*, 1H, 5-CH_2).

Köszönetnyilvánítás

A szerzők köszönetet mondanak az OTKA (témaszámok: T 20454 és T 015567) támogatásáért.

Összefoglalás

Munkánk során 1-metil-, etil-, propil-, izopropil-, fenil- és arilszubsztituált 2-aril-imidazolidineket állítottunk elő, melyek $CDCl_3$-ban, 300 K-en gyűrű-lánc tautomer elegyeknek bizonyultak. Megállapítottuk, hogy a tautomer egyensúly komponensarányai és a 2-helyzetű arilszubsztituens elektronikus hatása között a log $K_X = \rho\sigma^+ + \log K_{X-H}$ egyenlettel leírható összefüggés áll fenn. Az általunk előállított vegyületek az első olyan 2-aril-imidazolidinek, melyek gyűrű-lánc tautomériája

5. táblázat

A 12-16 imidazolidinek fizikai adatai

Vegyület	Op. (°C)	Összegképlet	Moltömeg	δ N=C*H*Ar (*s*) nyílt láncú forma (A)	δ N-C*H*Ar-N (*s*) gyűrűs forma (B)
12a	37-39[a,b]	$C_{10}H_{13}N_3O_2$	207,23	8,42	4,07
12b	olaj	$C_{10}H_{13}N_3O_2$	207,23	8,41	4,08
12c	olaj	$C_{10}H_{13}N_2Br$	241,14	8,26	3,88
12d	olaj	$C_{10}H_{13}N_2Br$	241,14	8,28	3,86
12e	olaj[c]	$C_{10}H_{13}N_2Cl$	196,68	8,23	3,66
12f	olaj	$C_{10}H_{14}N_2$	162,24	8,32	3,87
12g	olaj[c]	$C_{11}H_{16}N_2$	176,26	8,29	3,84
12h	olaj[c]	$C_{11}H_{16}N_2O$	192,26	8,25	3,89
12i	olaj[c]	$C_{12}H_{19}N_3$	205,31	8,17	3,76
13a	olaj	$C_{11}H_{15}N_3O_2$	221,26	8,40	4,20
13b	olaj	$C_{11}H_{15}N_3O_2$	221,26	8,56	4,22
13c	olaj	$C_{11}H_{15}N_2Br$	255,17	8,26	4,02
13d	olaj	$C_{11}H_{15}N_2Br$	255,17	8,28	4,00
13e	olaj	$C_{11}H_{15}N_2Cl$	210,71	8,28	3,76
13f	olaj	$C_{11}H_{16}N_2$	176,26	8,34	4,02
13g	olaj	$C_{12}H_{18}N_2$	190,29	8,29	3,96
13h	olaj	$C_{12}H_{18}N_2O$	206,29	8,26	3,95
13i	olaj	$C_{13}H_{21}N_3$	219,33	8,20	3,69
14a	olaj	$C_{12}H_{17}N_3O_2$	235,29	8,42	4,22
14b	olaj	$C_{12}H_{17}N_3O_2$	235,29	8,58	4,23
14c	olaj	$C_{12}H_{17}N_2Br$	269,19	8,26	4,02
14d	olaj	$C_{12}H_{17}N_2Br$	269,19	8,28	4,00
14e	olaj	$C_{12}H_{17}N_2Cl$	224,74	8,29	4,01
14f	olaj	$C_{12}H_{18}N_2$	190,29	8,33	4,01
14g	olaj	$C_{13}H_{20}N_2$	204,32	8,29	3,97
14h	olaj	$C_{13}H_{20}N_2O$	220,32	8,26	3,95
14i	olaj	$C_{14}H_{23}N_3$	233,36	8,20	3,69
15a	olaj	$C_{12}H_{17}N_3O_2$	235,29	8,42	4,62
15b	olaj	$C_{12}H_{17}N_3O_2$	235,29	8,58	4,63
15c	olaj	$C_{12}H_{17}N_2Br$	269,19	8,26	4,43
15d	olaj	$C_{12}H_{17}N_2Br$	269,19	8,28	4,42
15e	olaj	$C_{12}H_{17}N_2Cl$	224,74	8,28	4,42
15f	olaj	$C_{12}H_{18}N_2$	190,29	8,34	4,43
15g	olaj	$C_{13}H_{20}N_2$	204,32	8,30	4,38
15h	olaj	$C_{13}H_{20}N_2O$	220,32	8,26	4,36
15i	olaj	$C_{14}H_{23}N_3$	233,36	8,20	3,84
16a	olaj	$C_{15}H_{15}N_3O_2$	269,31	8,36	5,49
16b	66-71[d]	$C_{15}H_{15}N_3O_2$	269,31	8,35	5,49
16c	olaj	$C_{15}H_{15}N_2Br$	303,21	8,19	5,34
16d	64-66[a]	$C_{15}H_{15}N_2Br$	303,21	8,23	5,35
16e	olaj	$C_{15}H_{15}N_2Cl$	258,75	8,27	5,41
16f	olaj	$C_{15}H_{16}N_2$	224,31	8,28	5,39
16g	60-62[a]	$C_{16}H_{18}N_2$	238,34	8,25	5,37
16h	31-33[a]	$C_{16}H_{18}N_2O$	254,34	8,21	5,35
16i	88-89[a]	$C_{17}H_{21}N_3$	267,38	8,18	5,35

[a]Átkristályosítva *n*-hexánból. [b]Irodalmi[14] adat: op. 39-40 °C. [c]Irodalmi[27] adat: olaj. [d]Átkristályosítva *i*Pr_2O- EtOAc-ból.

6. táblázat

A 17-21 imidazolidinek fizikai adatai[a]

Vegyület.	Op. (°C)	Összegképlet	Moltömeg	δ N=C*H*Ar (*s*) nyílt láncú forma (A)	δ N-C*H*Ar-N (*s*) gyűrűs forma (B)
17a	179-181[a]	$C_{15}H_{14}N_4O_4$	314,30	8,33	5,61
17b	olaj	$C_{15}H_{14}N_4O_4$	314,30	8,32	5,62
17c	olaj	$C_{15}H_{14}N_3O_2Br$	348,21	8,18	5,48
17d	128-133[b]	$C_{15}H_{14}N_3O_2Br$	348,21	8,20	5,48
17e	140-143[b]	$C_{15}H_{14}N_3O_2Cl$	303,75	8,21	5,49
17f	olaj	$C_{15}H_{15}N_3O_2$	269,31	8,25	5,51
17g	109-110[b]	$C_{16}H_{17}N_3O_2$	283,33	8,21	5,47
17h	olaj	$C_{16}H_{17}N_3O_3$	299,33	8,17	5,46
17i	olaj	$C_{17}H_{20}N_4O_2$	312,38	8,08	5,39
18a	olaj	$C_{15}H_{14}N_3O_2Cl$	303,75	8,37	5,49
18b	olaj	$C_{15}H_{14}N_3O_2Cl$	303,75	8,36	5,49
18c	olaj	$C_{15}H_{14}N_2BrCl$	337,66	8,21	5,35
18d	olaj	$C_{15}H_{14}N_2BrCl$	337,66	8,23	5,35
18e	olaj	$C_{15}H_{14}N_2Cl_2$	293,20	8,24	5,36
18f	olaj	$C_{15}H_{15}N_2Cl$	258,75	8,29	5,39
18g	olaj	$C_{16}H_{17}N_2Cl$	272,78	8,25	5,36
18h	olaj	$C_{16}H_{17}N_2OCl$	288,78	8,22	5,35
18i	olaj	$C_{17}H_{20}N_3Cl$	301,82	8,16	5,32
19a	69-71[b]	$C_{16}H_{17}N_3O_2$	283,33	8,35	5,44
19b	74-75[c]	$C_{16}H_{17}N_3O_2$	283,33	8,35	5,44
19c	olaj	$C_{16}H_{17}N_2Br$	317,24	8,19	5,30
19d	72-74[b]	$C_{16}H_{17}N_2Br$	317,24	8,22	5,31
19e	58-61[c]	$C_{16}H_{17}N_2Cl$	272,78	8,23	5,32
19f	olaj	$C_{16}H_{18}N_2$	238,34	8,28	5,35
19g	68-70[c]	$C_{17}H_{20}N_2$	252,36	8,24	5,32
19h	51-53[c]	$C_{17}H_{20}N_2O$	268,36	8,21	5,31
19i	52-54[c]	$C_{18}H_{23}N_3$	281,41	8,20	5,27
20a	olaj	$C_{16}H_{17}N_3O_3$	299,33	8,36	5,39
20b	olaj	$C_{16}H_{17}N_3O_3$	299,33	8,28	5,39
20c	olaj	$C_{16}H_{17}N_2OBr$	333,24	8,21	5,26
20d	62-64[c]	$C_{16}H_{17}N_2OBr$	333,24	8,23	5,26
20e	51-53[c]	$C_{16}H_{17}N_2OCl$	288,78	8,24	5,27
20f	olaj	$C_{16}H_{18}N_2O$	254,34	8,28	5,28
20g	81-83[c]	$C_{17}H_{20}N_2O$	268,36	8,25	5,26
20h	58-60[c]	$C_{17}H_{20}N_2O_2$	284,36	8,21	5,25
20i	80-82[b]	$C_{18}H_{23}N_3O$	297,41	8,15	5,21
21a	79-81[c]	$C_{17}H_{20}N_4O_2$	312,38	8,35	5,37
21b	olaj	$C_{17}H_{20}N_4O_2$	312,38	8,34	5,37
21c	olaj	$C_{17}H_{20}N_3Br$	346,28	8,19	5,24
21d	89-91[c]	$C_{17}H_{20}N_3Br$	346,28	8,23	5,24
21e	82-85[b]	$C_{17}H_{20}N_3Cl$	301,82	8,24	5,25
21f	olaj	$C_{17}H_{21}N_3$	267,38	8,22	5,28
21g	60-62[c]	$C_{18}H_{23}N_3$	281,41	8,25	5,25
21h	78-79[b]	$C_{18}H_{23}N_3O$	297,41	8,21	5,23
21i	olaj	$C_{19}H_{26}N_4$	310,45	8,14	5,19

[a]Átkristályosítva iPr_2O– EtOAc-ból. [b]Átkristályosítva *n*-hexán–iPr_2O-ből. [c]Átkristályosítva *n*-hexánból.

Hammett-típusú egyenlettel jellemezhető. A tautomer egyensúlyt az imidazolidingyűrű nitrogénatomján lévő szubsztituens sztérikus, ill. elektronikus hatásai is jelentősen befolyásolták.

Ring-chain tautomerism of 2-aryl-substituted imidazolidines. *A. Göblyös, L. Lázár, F. Evanics, G. Bernáth* and *F. Fülöp*

1-Methyl-, ethyl-, (*n*-propyl)-, isopropyl-, phenyl- and aryl-substituted 2-arylimidazolidines proved to be ring-chain tautomeric mixtures in $CDCl_3$ at 300 K. The relation between the ratios of the tautomeric forms and the electronic effect of the 2-aryl-substituent could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$. The prepared compounds are the first examples among the 2-arylimidazolidines of ring-chain tautomeric processes characterized by a Hammett-type correlation. The steric and electronic effects of the substituents on the nitrogen of the imidazolidine ring significantly influence the tautomeric equilibrium.

IRODALOM

[1] A közlemény alapjául az angol nyelven megjelent (a) *L. Lázár, A. Göblyös, F. Evanics, G. Bernáth, F. Fülöp*: Tetrahedron, *54*. 1998. 13639. (b) *A. Göblyös, L. Lázár, F. Evanics, F. Fülöp*: Heterocycles, *51*. 1999. 2431. dolgozatok szolgáltak.

[2] *R. E. Valters, F. Fülöp, D. Korbonits*: Adv. Heterocyclic Chem., *66*. 1. 1996.

[3] *F. Fülöp, K. Pihlaja, J. Mattinen, G. Bernáth*: J. Org. Chem., *52*. 3821. 1987.

[4] *F. Fülöp, K. Neuvonen, K. Pihlaja, G. Bernáth, G. Argay, A. Kálmán*: J. Org. Chem., *58*. 1967. 1993.

[5] *P. Vainiotalo, S. Ronkanen, F. Fülöp, K. Pihlaja*: Tetrahedron, *46*. 3689. 1990.

[6] *M. R. Grimmett*: Comprehensive Heterocyclic Chemistry II (Szerk.: *A. R. Katritzky, C. W. Rees, E. F. V. Scriven*), Pergamon Press, Oxford, 1996. *3. kötet* 153.

[7] *R. F. Evans*, The Chemistry of Heterocyclic Compounds (Szerk.: *E. C. Taylor*), *52*. kötet, The Pyrimidines, John Wiley & Sons, New York, 1994. 817.

[8] *W. Wang, T. C. Liang, M. Zheng, X. Gao*: Tetrahedron Lett., *36*. 1995. 1181.

[9] (a) *R. B. Moodie, M. Z. Moustras, G. Read, J. P. B. Sandall*: J. Chem. Res. (S), 1996. 134. (b) *R. B. Moodie, M. Z. Moustras, G. Read, J. P. B. Sandall*: J. Chem. Soc., Perkin Trans. 2, 1997. 169.

[10] *K. N. Zelenin, V. V. Alekseyev, I. V. Ukraintsev, I. V. Tselinsky*: Mendeleev Commun., 1997. 111.

[11] *K. Pihlaja, M. F. Simeonov, F. Fülöp*: J. Org. Chem., *62*. 1997. 5080.

[12] *C. Chapuis, A. Gauvreau, A. Klaebe, A. Lattes, J. J. Perie*: Bull. Soc. Chim. Fr., 1973. 977.

[13] (a) *D. Korbonits, E. Tóbiás-Héja, P. Kolonits*: Chem. Ber., *124*. 1991. 1199. (b) *D. Korbonits, E. Tóbiás-Héja, K. Simon, P. Kolonits*: Chem. Ber., *124*. 1991. 2065.

[14] *S. Witek, A. Bielawska, J. Bielawski*: Heterocycles, *14*. 1980. 1313.

[15] *G. Parinello, R. Mülhaupt*: J. Org. Chem., *55*. 1990. 1772.

[16] (a) *K. N. Zelenin, V. V. Alekseyev, I. V. Ukraintsev, I. V. Tselinsky*: Org. Prep. Proc. Int., *30*. 1998. 53. (b) *K. N. Zelenin, I. V. Ukraintsev*: Org. Prep. Proc. Int., *30*. 1998. 109.

[17] *R. Arnaud, Y. Vallée*: J. Chem. Soc., Perkin Trans. 2, 1997. 2737.

[18] *H.-J. Zhu, B.-T. Zhao, W.-M. Dai, J. Zhou, X.-J. Hao*: Tetrahedron: Asymmetry, *9*. 1998. 2879.

[19] *S. Uchiyama, T. Santa, T. Fukushima, H. Homma, K. Imai*: J. Chem. Soc., Perkin Trans. 2., 1998. 2165.

[20] *G. S. Poindexter, D. A. Owens, P. L. Dolan, E. Woo*: J. Org. Chem., *57*. 1992. 6257.

[21] *F. Fülöp, K. Pihlaja*: Tetrahedron, *49*. 1993. 6701.

[22] (a) *J. E. Baldwin*: J. Chem. Soc., Chem. Commun., 1976. 734. (b) *C. D. Johnson*: Acc. Chem. Res., *26*. 1993. 476.

[23] *B. L. Milman, A. A. Potekhin*: Khim. Get. Soedin., 1973. 902.

[24] *F. Fülöp, L. Lázár, G. Bernáth, R. Sil-lanpää, K. Pihlaja*: Tetrahedron, *49*. 1993. 2115.

[25] *M. E. Alva Astudillo, N. C. J. Chokotho, T. C. Jarvis, C. D. Johnson, C. C. Lewis, P. D. McDonnell*: Tetrahedron, *41*. 1985. 5919.

[26] *T. F. Chung, Y. M. Wu, C. H. Cheng*: J. Org. Chem., *49*. 1984. 1215.

[27] *Y. Robert, J.-P. Fernandez, R. Dubief, J.-P. Chapat, H. Sentenac-Roumanou, M. Fatome, J.-D. Laval, G. Subra*: Eur. J. Med. Chem. - Chim. Ther., *17*. 1982. 235.

Szegedi Tudományegyetem, Gyógyszerkémiai Intézet
Érkezett: 2000. VI. 6.
Közlésre elfogadtuk: 2000. IX. 12.

IV.

RING-CHAIN TAUTOMERISM OF 2-ARYL-SUBSTITUTED-HEXAHYDROPYRIMIDINES AND TETRAHYDROQUINAZOLINES

Anikó Göblyös, László Lázár and Ferenc Fülöp*

Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary

*Corresponding author. Tel.: +36-62-545564; Fax: +36-62-545705; e-mail: fulop@pharma.szote.u-szeged.hu

Dedicated to Professor András Messmer on the occasion of his 80th birthday.

Abstract – 2-Aryl-substituted-1-isopropyl- and 1-phenylhexahydropyrimidines and 3-isopropyl- and 3-phenyl-1,2,3,4-tetrahydroquinazolines proved to be ring-chain tautomeric mixtures in $CDCl_3$ at 300 K, whereas only ring-closed tautomers could be detected for the 1- or 3-methyl-substituted analogues. The ratios of the ring-chain tautomeric forms at equilibrium could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$.

Keywords: diamines, tautomerism, pyrimidines, quinazolines

Introduction

The ring-chain tautomerism of five- and six-membered 1,3-*X,Y*-heterocycles (*X,Y* = *O*, *S*, *NR*) has been studied thoroughly in recent years.[1] This phenomenon allows 1,3-*O,N*-heterocycles to be exploited as intermediates in the synthesis of *N*-substituted-amino alcohols[2] or as aldehyde sources in carbon transfer reactions.[3] Depending on the nature of the substituent at position 2 selective functionalizations of *N*-monosubstituted-ethylene- or propylene-diamines can be achieved on the basis of the ring-chain tautomeric character of their 2-substituted 1,3-*N,N*-heterocyclic derivatives.[4]

For the ring-chain tautomerism of 2-(*X*-phenyl)-substituted-oxazolidines and tetrahydro-1,3-oxazines, a linear correlation was earlier found between the equilibrium ring-chain ratio (K = [ring]/[open]) and the electronic character (σ^+) of the substituent *X* on the 2-phenyl ring (Eq. 1):[1]

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

The ring-chain tautomerism of 1,3-*N,N*-heterocycles has been observed in only a few cases[1a,4,5] and, in contrast with the five- and six-membered 2-aryl-1,3-*O,N*-heterocycles, merely a limited number of examples of the application of Eq. 1[6,7] are known among the analogous 1,3-*N,N*-heterocyclic compounds.

Previous studies on 1-substituted-2-arylimidazolidines showed that these five-membered 1,3-*N,N*-heterocyclic compounds participate in ring-chain tautomerism, the equilibria of which can be described by Eq. 1.[7] Substituents at position 1 caused a significant effect on the ring-chain tautomeric ratios. However, less is known about the ring-chain tautomerism of the corresponding six-membered analogues. Of this type of compounds, only *N*-unsubstituted-2-arylhexahydropyrimidines (**1**) were investigated earlier; they proved to be the first example of 2-aryl-1,3-*N,N*-heterocycles that participate in a ring-chain tautomeric equilibrium ($CDCl_3$) characterized by Eq. 1.[6] It is noteworthy that the benzologues of **1**, 1,3-unsubstituted-2-aryltetrahydroquinazolines, were described as ring-closed tautomers in DMSO-d_6, without detectable amounts of the open forms.[8]

As a continuation of our previous studies on 1,2-disubstituted-imidazolidines,[7] our present aim was to investigate the substituent effects on the ring-chain tautomeric character of some 1-substituted-2-arylhexahydropyrimidines and 3-substituted-2-aryl-1,2,3,4-tetrahydroquinazolines for the purpose of refining the scope and limitations of application of Eq. 1 among six-membered 1,3-*N,N*-heterocycles.

Results and discussion

The condensation of *N*-monosubstituted-1,2- or 1,3-diamines with the appropriate aromatic aldehydes provides a convenient method for the synthesis of saturated 2-aryl-1-substituted-*N,N*-heterocycles.[6,7] Of the 1,3-diamines required for the synthesis of hexahydropyrimidines, *N*-methyl- (**12**) and *N*-isopropylpropylenediamine (**13**) were commercial products, while *N*-phenylpropylenediamine (**4**) was prepared by the reduction of β-alanine anilide (**3**) with $LiAlH_4$. The starting materials for the tetrahydroquinazolines, 2-(methyl-, isopropyl- or phenylaminomethyl)anilines (**9-11**), were synthesized by similar reductions of the appropriate *N*-substituted-aminocarboxamides (**6-8**), obtained by the ring-opening reactions of isatoic anhydride (**5**) with the appropriate amines (Scheme 1).[9]

- Insert Scheme 1 -

Model compounds **14-16** and **17-19** were prepared by the condensation of propylenediamines (**4**, **12**, **13**) or *o*-aminobenzylamines (**9-11**) with equivalent amounts of the appropriate substituted benzaldehydes under mild conditions (ambient temperature, 1 h) (Scheme 2).

- Insert Scheme 2 -

The ^{1}H NMR spectra of **15**, **16**, **18**, and **19** (in $CDCl_3$ solution at 300 K) revealed that these compounds participate in ring-chain tautomeric equilibria of the 1,3-*N*,*N*-heterocycles (**B**) and the corresponding Schiff bases (**A**), while in the spectra of the *N*-methyl-substituted-hexahydropyrimidines (**14a,g**) and tetrahydroquinazolines (**17a,g**) no open-chain form could be detected. Despite the electron-donating *p*-dimethylamino substituent on the 2-phenyl ring, which is favourable for the shift of the equilibrium towards the open tautomer, **14g** and **17g** proved to be exclusively ring-closed tautomers. The predominance of the ring-closed forms in the case of the *N*-methyl-substituted-hexahydropyrimidines (**14a,g**) is in accordance with the literature data on 2-phenyl and 2-(*p*-nitrophenyl) derivatives.[4a,c]

The equilibrium ratios were determined by integration of the well-separated N-C*H*-N (ring, **B**) and N=C*H* (chain, **A**) singlets (Tables 1 and 3). The selected data on **15c** and **18f** reflect the ^{1}H NMR spectra of the prepared hexahydropyrimidines and tetrahydroquinazolines exhibiting a tautomeric character (see Experimental).

- Insert Table 1 -

When Eq. 1 was applied to the log K_X values, good linear correlations were obtained *vs.* the Hammett-Brown parameter σ^+ of the substituent X on the 2-phenyl group for compounds **15**, **16**, **18** and **19** (Figure 1, Table 2).

- Insert Figure 1 and Table 2 -

The linear regression analysis data in Table 2 show that the slope ρ for 1-isopropylhexahydropyrimidines (**15**: 0.77) has approximately the same value as that for the corresponding six-membered 1,3-*O*,*N*-heterocycle[1a,10] (**20**: 0.74), while ρ for 1-phenylhexahydropyrimidines (**16**: 0.42) is considerably smaller. The 3-phenyl-substituted-tetrahydroquinazolines (**19**) have a markedly higher ρ value (0.93) than those for the 2-

isopropyl-tetrahydroquinazolines (**18**) and 2-aryl-3,1-benzoxazines (**21**). The significant differences in ρ for **1**, **15** and **16** or for **18** and **19** suggest that for the six-membered 1,3-*N,N*-heterocycles, in contrast with the 1,3-*O,N*-heterocycles[1a] and similarly to the imidazolidines,[7] the value of ρ is not characteristic of the ring system, and depends strongly on the *N*-substituent. While *N*-isopropyl-heterocycles **15** and **18** have very similar ρ values, the ρ values for *N*-phenyl derivatives **16** and **19** are very different.

The nitrogen substituent causes a marked effect not only on the value of ρ, but also on the intercept. The effects of the substituents on the stability of the ring form relative to the analogous 1,3-*O,N*-heterocycle can be expressed by a value c, which is the difference in intercept for the given 2-aryl-1,3-*N,N*-heterocycle and the corresponding unsubstituted saturated 2-aryl-1,3-*O,N*-heterocycle. A positive c value means a more stable ring form than that of the corresponding 2-aryl-1,3-*O,N*-heterocycle.[7a,10] For the six-membered 1,3-*Y,N*-heterocycles **1**, **14-16** and **20**, the value of c is minimal for the *N*-phenyl substituent, and the stability of the ring-closed form increases in the following sequence of *Y*: NPh < N*i*Pr < O < NH < NMe.

Similarly as with the analogous 1,3-*O,N*-heterocycles,[10] a condensed benzene ring increases the stability of the ring form (*cf.* **15** and **18** or **16** and **19**). For the tetrahydroquinazolines **17-19** and the related 3,1-benzoxazine **21**, the *N*-phenyl substituent again causes the strongest destabilizing effect and the stability of the ring-closed form increases in the following sequence of *Y*: NPh < O < N*i*Pr < NMe.

Conclusion

In conclusion, the ring-chain tautomerism of six-membered saturated 1-substituted-2-aryl-1,3-*N,N*-heterocycles is strongly dependent on the substituents on the nitrogen and on the presence of a condensed benzene ring. Compounds with a small *N*-substituent (Me) exist exclusively in ring-closed form. Compounds with larger substituents (*i*Pr or Ph) participate in ring-chain tautomeric equilibria that can be characterized by the Hammett-type Eq. 1.

Experimental

^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicities were recorded as *s* (singlet), *d* (doublet), *dd* (double doublet), *t* (triplet), *m* (multiplet) and *om* (overlapping multiplet). For the equilibria of tautomeric compounds to be

established,[6,7,11] the samples were dissolved in $CDCl_3$ and the solutions were left to stand at ambient temperature for 1 day before the ^1H NMR spectra were run. The number of scans was usually 64.

IR spectra were run in KBr discs on a Perkin-Elmer Paragon 1000 PC FT-IR spectrometer controlled by GRAMS Analyst for PE 1000 3.01A software. Mass spectra were recorded on a Shimadzu QP 8000 instrument using electrospray ionization. Melting points were determined on a Kofler micro melting point apparatus and are not corrected. The physical data on compounds **14-19** are listed in Table 3.

Compounds **6**[9a], **7**[9b] and **8**[9c] were prepared according to known procedures.

β-Alanine anilide (3)

To a stirred and cooled (ice-salt bath) solution of *N*-benzyloxycarbonyl-β-alanine (**2**, 22.32 g, 0.10 mol) and triethylamine (10.12 g, 0.10 mol) in dry toluene (150 mL), ethyl chloroformate (10.85 g, 0.10 mol) was added dropwise at a rate to keep the internal temperature below –10 °C. After 15 min, a solution of aniline (9.31 g, 0.10 mol) in dry $CHCl_3$ (20 mL) was dropped to the mixture, the internal temperature being kept below –10 °C. Stirring was continued for 30 min with cooling and for 30 min without and the mixture was then heated slowly to reflux and refluxed for 5 min. The mixture was allowed to cool down and washed with saturated aqueous $NaHCO_3$ solution (2 x 100 mL) and water (100 mL) after the addition of $CHCl_3$ (250 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give *N*-benzyloxycarbonyl-β-alanine anilide as a white crystalline residue, which was filtered off, washed with Et_2O and recrystallized from EtOAc. Yield 21.96 g (75%), mp 135-136 °C (lit.,[12] mp 137-138 °C); ^1H NMR ($CDCl_3$) δ: 2.59 (*m*, 2H, CH_2CO), 3.55 (*m*, 2H, CH_2N), 5.10 (*s*, 2H, OCH_2), 5.45 (*br s*, 1H, N*H*), 7.11 (*m*, 1H, NC_6H_5), 7.26-7.38 (*om*, 7H, $CH_2C_6H_5$, NC_6H_5) 7.49 (*d*, 2H, J = 7.8 Hz, NC_6H_5), 7.55 (*br s*, 1H, N*H*); IR ν_{max} 3329, 3293, 1686, 1657, 1533, 1247 cm^{-1}; MS *m/z* 299 $[M+1]^+$. Analysis: calculated for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39; found: C, 68.24; H, 5.85; N, 9.12.

N-Benzyloxycarbonyl-β-alanine anilide (21.96 g, 0.07 mol) was suspended in 33% HBr in AcOH (90 mL) and the mixture was left to stand at room temperature for an hour with occasional shaking. The crystals of **3** hydrobromide that were formed were filtered off and dissolved in ice-cold water (75 mL). The solution was made alkaline with 20% NaOH and extracted with $CHCl_3$ (5 x 100 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The crystalline residue was purified by column

chromatography on silica gel (eluent: toluene : MeOH = 1 : 1). Yield 9.10 g (74%), mp 190-192 °C, ^{1}H NMR ($CDCl_3$) δ: 2.47 (m, 2H, C*H*$_2$CO), 3.12 (m, 2H, NC*H*$_2$), 7.07 (m, 1H, C$_6$*H*$_5$), 7.31 (m, 2H, C$_6$*H*$_5$), 7.54 (d, 2H, *J* = 7.8 Hz, C$_6$*H*$_5$), 9.92 (br s, 1H, N*H*); IR ν_{max} 1659, 1599, 1556, 1498, 1445, 751 cm^{-1}; MS *m/z* 165 [M+1]$^+$. Analysis: calculated for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06; found: C, 65.71; H, 7.12; N, 16.87.

General method for the synthesis of *N*-phenylpropylenediamine (4) and 2-(methyl-, isopropyl- or phenylaminomethyl)anilines (9-11)

To a stirred suspension of $LiAlH_4$ (11.39 g, 0.30 mol) in dry THF (350 mL), a solution of β-alanine anilide (**3**) or the appropriate 2-amino-*N*-substituted-benzamide (**6-8**) (0.10 mol) in dry THF (**3**: 200 mL, **6-8**: 50 mL) was added dropwise. The mixture was stirred and refluxed for 7.5 h and then cooled and the excess of $LiAlH_4$ was decomposed by addition of a mixture of water (20 mL) and THF (50 mL). The inorganic salts were filtered off and washed with EtOAc (3 x 200 mL). The combined organic filtrates and washings were dried over Na_2SO_4 and evaporated under reduced pressure to give the crude diamines as oily (**4**, **9**, **10**) or crystalline products (**11**, mp 80-81 °C, lit.[9c] mp 81-83 °C).

Crude diamine **4** was distilled *in vacuo*. Yield 14.08 g (93%). Bp 100-105 °C/1-2 mm. The ^{1}H NMR data on the product correspond to the literature[13] data.

For purification, crude diamines **9-11** were converted to the crystalline dihydrochlorides by treatment of their ethanolic (10 mL) solutions with an excess of 22% ethanolic HCl and Et_2O. The crystalline dihydrochlorides were filtered off and recrystallized from MeOH-Et_2O.

(**9**): Yield 16.35 g (78%), mp 210-212 °C (lit.[14] mp 236-238 °C), ^{1}H NMR (D_2O) δ: 2.84 (*s*, 3H, C*H*$_3$), 4.36 (*s*, 2H, C*H*$_2$), 7.46 (*m*, 1H, C$_6$*H*$_4$), 7.50-7.61 (*om*, 3H, C$_6$*H*$_4$); IR ν_{max} 2773, 2565, 1538, 1496, 1454, 766, 754 cm^{-1}; MS *m/z* 137 [M+1]$^+$. Analysis: calculated for $C_8H_{14}Cl_2N_2$: C, 45.95; H, 6.75; N, 13.40; found: C, 45.68; H, 6.57; N, 13.26.

(**10**): Yield 18.65 g (79%), mp 193-195 °C (lit.[15] mp 191 °C), ^{1}H NMR (D_2O) δ: 1.42 (*d*, 6H, *J* = 6.6 Hz, 2 x C*H*$_3$), 3.62 (*m*, 1H, C*H*), 4.36 (*s*, 2H, C*H*$_2$), 7.46 (*m*, 1H, C$_6$*H*$_4$), 7.50-7.63 (*om*, 3H, C$_6$*H*$_4$); IR ν_{max} 2800, 1561, 1502, 1444, 1392, 1145, 763, 754 cm^{-1}; MS *m/z* 165 [M+1]$^+$. Analysis: calculated for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06; found: C, 65.71; H, 7.12; N, 16.87.

(**11**): Yield 23.79 g (88%), mp 165-167 °C, ^{1}H NMR (D_2O) δ: 4.76 (*s*, 2H, C*H*$_2$), 7.34 (*m*, 2H, C$_6$*H*$_4$, C$_6$*H*$_5$), 7.40-7.60 (*om*, 7H, C$_6$*H*$_4$, C$_6$*H*$_5$); IR ν_{max} 2727, 2583, 1497, 1478, 1430, 760,

690 cm^{-1}; MS *m/z* 199 $[M+1]^+$. Analysis: calculated for $C_{13}H_{16}Cl_2N_2$: C, 57.58; H, 5.95; N, 10.33; found: C, 57.33; H, 5.67; N, 10.21.

Pure diamine bases **9-11** were obtained from the above dihydrochlorides by alkaline treatment (20% NaOH), extraction (CH_2Cl_2) and evaporation under reduced pressure. The free bases were dried in a vacuum desiccator for 24 h before further transformations.

General method for the synthesis of 2-arylhexahydropyrimidines (14-16) and 2-aryl-1,2,3,4-tetrahydroquinazolines (17-19)

To a solution of the appropriate diamine (**4**, **9-13**, 3 mmol) in absolute MeOH (20 mL), an equivalent amount of aromatic aldehyde was added (in the case of liquid aldehydes, a freshly distilled sample was used), and the mixture was left to stand at ambient temperature for 1 h. The solvent was evaporated off and the evaporation was repeated after the addition of toluene (10 mL). 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 filtered off and recrystallized. All of the recrystallized new compounds (**17a**, **18a-g**, **19a-f**) gave satisfactory data on elemental analysis (C, H, N ±0.3%).

- Insert Table 3 -

^{1}H NMR spectroscopic data on 1-isopropyl-2-(4-bromophenyl)hexahydropyrimidine (15c) and 3-isopropyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinazoline (18f) in $CDCl_3$

The protons of the open form (**A**) are numbered according to the corresponding protons of the ring form (**B**) (δ in ppm, in brackets the multiplicity, couplings in Hz and assignment, respectively).

(**15cA**): 1.00 (*d*, 6H, *J* = 6.3 Hz, 2 x CH_3), 1.80-1.87 (*m*, 2H, 5-CH_2), 2.66 (*t*, 2H, J = 7.0 Hz, 6-CH_2), 2.68-2.80 (*m*, 1H, C*H*), 3.63 (*t*, 2H, *J* = 6.5 Hz, 4-CH_2), 7.52 (*dd*, 4H, *J* = 20.3, 8.5 Hz, C_6H_4), 8.19 (*s*, 1H, N=C*H*); (**15cB**): 0.75 (*d*, 3H, *J* = 6.5 Hz, CH_3), 0.85 (*d*, 3H, *J* = 6.8 Hz, CH_3), 1.59-1.71 (*m*, 2H, 5-CH_2), 2.39-2.45 (*m*, 1 H, 6-CH_2), 2.62-2.74 (*m*, 1 H, C*H*), 2.63-2.72 (*m*, 1 H, 4-CH_2), 3.01-3.05 (*m*, 1 H, 6-CH_2), 3.13 (*t*, 1 H, J = 6.96 Hz, 4-CH_2), 4.14 (*s*, 1H, NC*H*N), 7.29 (*d*, 2H, *J* = 8.1 Hz, C_6H_4), 7.42 (*d*, 2H, *J* = 8.1 Hz, C_6H_4).

(**18fA**): 1.06 (*d*, 6H, *J* = 6.2 Hz, 2 x CH_3), 2.77-2.80 (*m*, 1H, C*H*), 3.87 (*s*, 3H, OCH_3), 3.90 (*s*, 2H, CH_2), 6.96-7.05 (*om*, 3H, C_6H_4), 7.14-7.18 (*m*, 1H, C_6H_4), 7.26-7.28 (*m*, 1H, C_6H_4), 7.31-7.32 (*m*, 1H, C_6H_4), 7.85 (*d*, 2H, *J* = 8.7 Hz, C_6H_4), 8.38 (*s*, 1H, N=C*H*); (**18fB**): 1.01 (*d*, 3H, *J* = 6.4 Hz, CH_3), 1.17 (*d*, 3H, *J* = 6.5 Hz, CH_3), 2.89-2.80 (*m*, 1H, C*H*), 3.76 (*s*, 2H,

CH_2), 3.79 (*s*, 3H, OCH_3), 4.14 (*br s*, 1H, N*H*), 5.14 (*s*, 1H, NC*H*N), 6.54 (*d*, 1H, $J = 7.9$ Hz, C_6H_4), 6.63-6.66 (*m*, 1H, C_6H_4), 6.83-6.90 (*om*, 3H, C_6H_4), 6.96-7.04 (*m*, 1H, C_6H_4), 7.37-7.40 (*m*, 2H, C_6H_4).

Acknowledgements

We are grateful to Dr. Tamás Martinek for helpful discussions concerning the NMR assignments and to the Hungarian Research Foundation (OTKA No. T034901, T034452) for financial support.

References

1. a) Valters, R. E.; Fülöp, F.; Korbonits, D. *Adv. Heterocyclic Chem.* **1996**, *66*, 1-71. b) Martinek, T.; Lázár, L.; Fülöp, F.; Riddell, F. G. *Tetrahedron*, **1998**, *54*, 12887-12896. c) Star, A.; Fuchs, B. *J. Org. Chem.* **1999**, *64*, 1166-1172. d) Star, A.; Goldberg, I.; Fuchs, B. *Angew. Chem. Int. Ed.* **2000**, *39*, 2685-2689. e) Muntean, L.; Grosu, I.; Mager, S.; Plé, G.; Balog, M. *Tetrahedron Lett.* **2000**, *41*, 1967-1970. f) Neuvonen, K.; Fülöp, F.; Neuvonen, H.; Koch, A.; Kleinpeter, E.; Pihlaja, K. *J. Org. Chem.* **2001**, *66*, 4132-4140.
2. a) Blanchet, J.; Bonin, M.; Micouin, L.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 6423-6426. b) Brózda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry*, **2000**, *11*, 3017-3025.
3. a) Singh, K.; Singh, J.; Singh, H. *Tetrahedron*, 1998, **54**, 935-942. b) Singh, K.; Deb, P. K.; *Tetrahedron Lett.* **2000**, *41*, 4977-4980. c) Singh, K.; Deb, P. K.; Venugopalan, P.; *Tetrahedron* **2001**, *57*, 7939-7949.
4. a) Parrinello, G.; Mülhaupt, R. *J. Org. Chem.* **1990**, *55*, 1772-1779. b) Wang, W.; Liang, T. C.; Zheng, M.; Gao X. *Tetrahedron Lett.* **1995**, *36*, 1181-1184. c) Jentgens, C.; Hofmann, R.; Guggisberg, A.; Bienz, S.; Hesse, M. *Helv. Chim. Acta*, **1997**, *80*, 966-978.
5. a) Witek, S.; Bielawska, A.; Bielawski, J. *Heterocycles* **1980**, *14*, 1313-1317. b) Cimerman, Z.; Stefanac, Z. *Polyhedron* **1985**, *4*, 1755-1760. c) Korbonits, D.; Tóbiás-Héja, E.; Kolonits, P. *Chem. Ber.* **1991**, *124*, 1199-1202. d) Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Res. (S)* **1996**, 134-135. e) Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. 2* **1997**, 169-171. f) Pihlaja, K.; Simeonov, M. F.; Fülöp, F. *J. Org. Chem.* **1997**, *62*, 5080-5088. g) Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Mendeleev Commun.* **1997**, 111-112. h) Zelenin, K. N.; Ukraintsev, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 109-114.

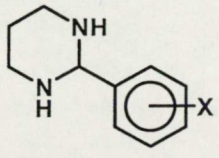
6. Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 53-61.
7. a) Lázár, L.; Göblyös, A.; Evanics, F.; Bernáth, G.; Fülöp, F. *Tetrahedron* **1998**, *54*, 13639-13644. b) Göblyös, A.; Lázár, L.; Evanics, F.; Fülöp, F. *Heterocycles* **1999**, *51*, 2431-2438.
8. a) Vanden Eynde, J. J.; Godin, J.; Mayence, A.; Maquestiau, A.; Anders, E. *Synthesis* **1993**, 867-869. b) Lessel, J. *Arch. Pharm. (Weinheim)* **1994**, *327*, 329-336.
9. a) Hayao, S.; Havera, H. J.; Strycker, W. G.; Leipzig, T. J.; Kulp, R. A.; Hartzler, H. E. *J. Med. Chem.* **1965**, *8*, 807-811. b) Kornet, M. J. *J. Heterocyclic Chem.* **1992**, *29*, 103. c) Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, *11*, 1208-1213.
10. Fülöp, F.; Pihlaja, K.; Mattinen, J.; Bernáth, G. *J. Org. Chem.* **1987**, *52*, 3821-3825.
11. Fülöp, F.; Pihlaja, K.; Neuvonen, K.; Bernáth, G.; Argay, Gy.; Kálmán, A. *J. Org. Chem.* **1993**, *58*. 1967-1969.
12. Ishibashi, N.; Kouge, K.; Shinoda, I.; Kanehisa, H.; Okai, H. *Agric. Biol. Chem.* **1988**, *52*, 819-828.
13. Orelli, L. R.; Garcia, M. B.; Niemevz, F.; Perillo, I. A. *Synth. Commun.* **1999**, *29*, 1819-1833.
14. Smith, R. F.; Briggs, P. C.; Kent, R. A.; Albright, J. A.; Walsh, E. J. *J. Heterocyclic Chem.* **1965**, *2*, 157-161.
15. Orth, R. E.; Jones, J. W. *J. Pharm. Sci.* **1961**, *50*, 866-868.

Table 1 Proportions (%) of ring forms (**A**) in tautomeric equilibria ($CDCl_3$, 300 K) for compounds **14-19**

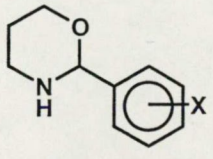
Compd.	X	σ^+	**14**	**15**	**16**	**17**	**18**	**19**
a	*p*NO_2	0.79	~100	26.2	11.2	~100	99.2	97.5
b	*m*NO_2	0.73	–	24.4	9.2	–	99.2	96.4
c	*p*Br	0.15	–	12.3	5.5	–	97.9	83.1
d	H	0	–	7.6	5.9	–	95.9	75.2
e	*p*Me	-0.311	–	4.9	3.0	–	92.1	64.1
f	*p*OMe	-0.778	–	2.2	2.3	–	87.3	46.8
g	*p*NMe_2	-1.7	~100	~0	1.1	~100	72.6	16.5

Table 2 Linear regression analysis data on compounds **15**, **16**, **18** and **19**, 2-arylhexahydropyrimidines (**1**),[6] 2-aryl-1,3-oxazines (**20**)[10] and 2-aryl-3,1-benzoxazines (**21**)[10]

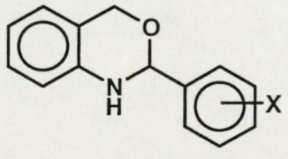
Compound	No. of points	Slope (ρ)[a]	Intercept[a]	Correlation coefficient	c[b]
15 (N*i*Pr)	6	0.77(3)	-1.04(4)	0.997	-0.89
16 (NPh)	7	0.42(3)	-1.28(6)	0.988	-1.13
1 (NH)	7	0.84(1)	0.93(1)	0.99	1.08
20 (O)	7	0.74(6)	-0.15(5)	0.984	0
18 (N*i*Pr)	7	0.72(7)	1.49(14)	0.978	0.38
19 (NPh)	7	0.93(8)	0.67(16)	0.984	-0.44
21 (O)	7	0.78(3)	1.11(2)	0.997	0



1



20



21

[a]Standard deviations are given in parentheses. [b]Relative ring stability constant, see the text.

Table 3 Physical data on compounds **14-19**

Comp.	Mp (°C)	Yield (%)	MS *m/z* $[M+1]^+$	IR ν_{max} (cm^{-1})	δ N=C*H* chain (**A**)	δ N-C*H*-N ring (**B**)
14a	88-90[a,e]	85	222	1517, 1346, 1101, 972, 838	–	3.82
14g	oil	d	220	2941, 1608, 1525, 1352, 815	–	3.58
15a	oil	d	250	2965, 1645, 1602, 1520, 1346	8.38	4.35
15b	oil	d	250	2965, 1648, 1529, 1349, 720	8.36	4.36
15c	oil	d	283/285	2965, 1645, 1486, 1011, 819	8.19	4.14
15d	oil	d	205	2964, 1645, 1451, 755, 694	8.28	4.19
15e	oil	d	219	2965, 1647, 1379, 1174, 813	8.24	4.16
15f	oil	d	235	2962, 1645, 1607, 1513, 1251	8.21	4.16
15g	oil	d	248	2962, 1608, 1526, 1361, 1179	8.14	–
16a	oil	d	284	1602, 1519, 1345, 749, 693	8.37	5.32
16b	oil	d	284	1603, 1529, 1506, 1350, 751	8.57	5.33
16c	oil	d	317/319	1602, 1504, 1486, 1010, 749	8.23	5.21
16d	oil	d	239	1645, 1603, 1505, 750, 693	8.28	5.29
16e	oil	d	253	1645, 1603, 1507, 749, 693	8.24	5.27
16f	oil	d	269	1605, 1510, 1252, 1167, 750	8.21	5.20
16g	oil	d	282	1604, 1526, 1365, 745, 694	8.15	5.24
17a	101-103[c]	67	270	3393, 1519, 1489, 1345, 749	–	4.31
17g	oil	d	268	1607, 1523, 1490, 1346, 749	–	4.63
18a	58-61[a]	83	298	1518, 1499, 1348, 1267, 743	5.41	8.58
18b	132-134[b]	72	298	3429, 1528, 1348, 1266, 747	5.42	8.57
18c	103-105[a]	75	331/333	1497, 1484, 1268, 1008, 749	5.21	8.39
18d	92-94[a]	75	253	3412, 1607, 1486, 1267, 747	5.25	8.46
18e	85-88[a]	82	267	3410, 1607, 1502, 1486, 745	5.19	8.42
18f	104-106[a]	69	283	3410, 1607, 1510, 1245, 749	5.17	8.38
18g	58-60[a]	70	296	1661, 1598, 1370, 1164, 813	5.14	8.38
19a	103-107[a]	87	332	1592, 1519, 1499, 1344, 753	6.05	8.52
19b	55-57[a]	89	332	1526, 1493, 1347, 749, 694	6.04	8.58
19c	79-82[b]	92	365/367	3397, 1596, 1500, 1010, 756	5.88	8.30
19d	94-95[a]	73	287	3413, 1596, 1494, 1445, 746	6.05	8.46
19e	80-82[a]	84	301	3401, 1494, 1264, 755, 743	6.02	8.42
19f	73-75[a]	87	317	1605, 1508, 1495, 1247, 753	5.89	8.27
19g	oil	d	330	1603, 1588, 1527, 1166, 749	4.95	8.28

[a]Recrystallized from *n*-hexane. [b]Recrystallized from *n*-hexane–iPr_2O. [c]Recrystallized from iPr_2O. [d]The conversion was quantitative according to the ^1H NMR spectra. [e]Lit.[4a] mp 90-91 °C.

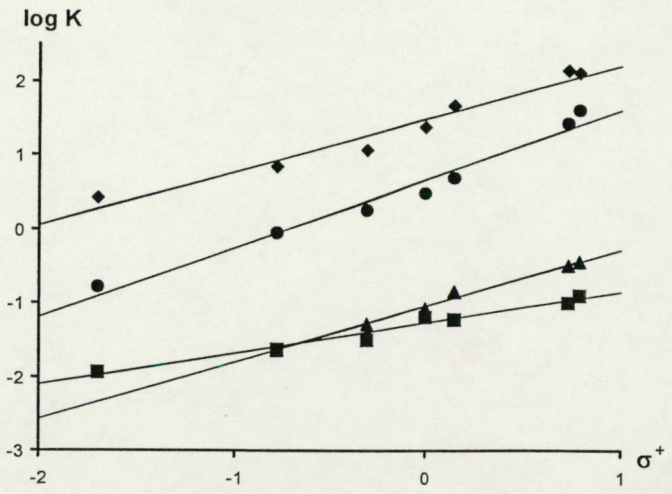
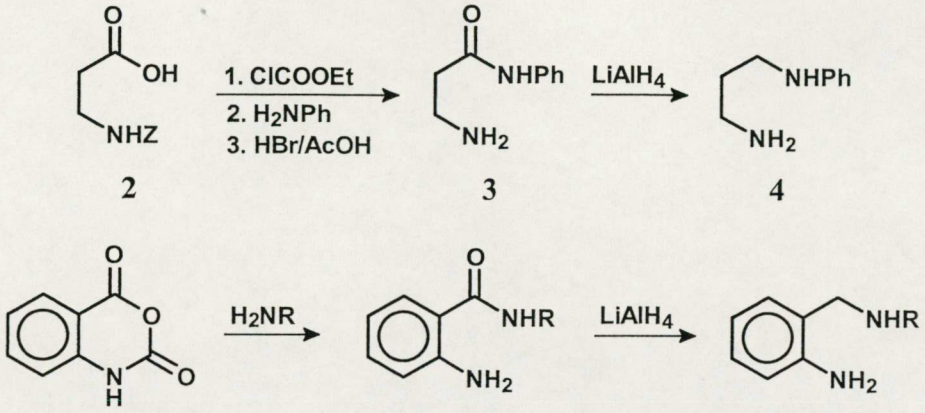
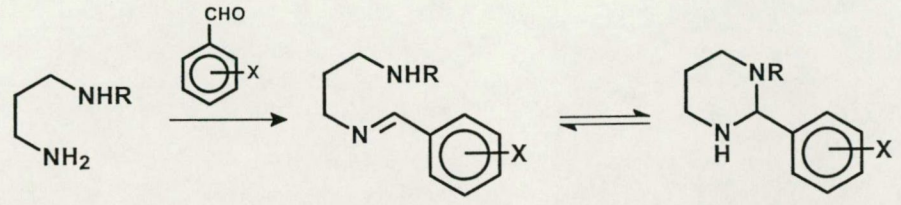


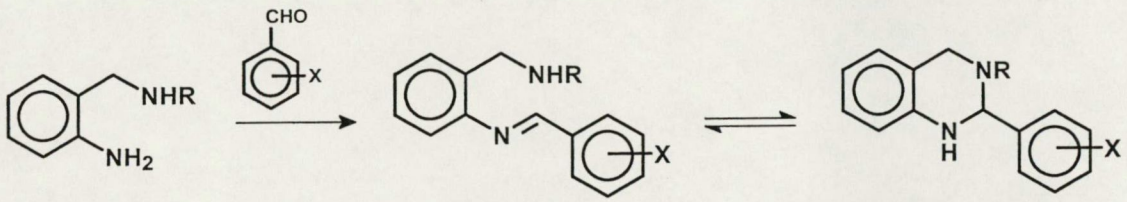
Figure 1 Plots of log K (in $CDCl_3$) for **15** (▲), **16** (■), **18** (◆), **19** (●) *vs.* Hammett-Brown parameter σ^+


O
OH
NHZ
1. ClCOOEt
2. H2NPh
3. HBr/AcOH
O
NHPh
NH2
LiAlH4
NHPh
NH2
2
3
4
O
O
N
H
O
H2NR
O
NHR
NH2
LiAlH4
NHR
NH2
5
R = Me: 6
R = iPr: 7
R = Ph: 8
R = Me: 9
R = iPr:10
R = Ph:11

Scheme 1



R = Me: **12** **14Aa,g** **14Ba,g**
R = *i*Pr: **13** **15Aa-g** **15Ba-g**
R = Ph: **4** **16Aa-g** **16Ba-g**



R = Me: **9** **17Aa,g** **17Ba,g**
R = *i*Pr: **10** **18Aa-g** **18Ba-g**
R = Ph: **11** **19Aa-g** **19Ba-g**

X = *p*NO_2: **a**; *m*NO_2: **b**; *p*Br: **c**; H: **d**; *p*Me: **e**; *p*OMe: **f**; *p*NMe_2: **g**

Scheme 2

Tetrahedron

(b)

Regional Editor:
Professor R J K Taylor

Department of Chemistry
University of York
Heslington
York
YO10 5DD
U.K.

TEL: +44 (0)1904 432606
FAX: +44 (0) 1904 434523
EMAIL tet@york.ac.uk

1 October, 2001

Professor Ferenc Fulop
Institute of Pharmaceutical Chemistry
University of Szeged
H-6720 Szeged
POB 121
Hungary

Dear Professor Fulop

Reference No: **RT-2001-40394** (Please quote in all correspondence)
Ring-chain Tautomerism of 2-aryl-substituted-hexahydropyrimidines and Tetrahydroquinazolines
Aniko Goblyos, Laszlo Lazar and Ferenc Fulop

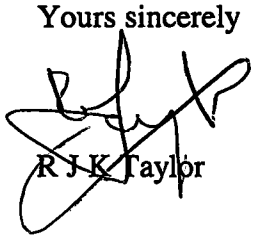
We have appreciated the opportunity to consider your paper for publication. It has been examined by an independent referee, whose report is enclosed.

We shall be pleased to accept your paper subject to modification as required by the referee **and** the editorial comments outlined in red on the enclosed copy of your original typescript. I have retained one copy of your original typescript.

Please submit the revised version in duplicate, returning the one with our marked modifications to us.

Following the Instructions to Authors announced in Tetrahedron Vol 55 No 46, the publishers no longer process camera ready manuscripts and therefore request an electronic version. I would be grateful if you could complete the enclosed "Electronic File Submission Form" and return it with your revised manuscript on disk as well as the hard copies.

Yours sincerely



R J K Taylor

V.

RING-CHAIN TAUTOMERISM OF 2-ARYL-SUBSTITUTED *cis* AND *trans* DECAHYDROQUINAZOLINES

Anikó Göblyös, Tamás Martinek, László Lázár, Ferenc Fülöp*

Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary

*Corresponding author. Tel.: +36-62-545564; Fax: +36-62-545705; e-mail: fulop@pharma.szote.u-szeged.hu

Abstract - In $CDCl_3$ at 300 K, 2-aryl-substituted *cis*- and *trans*-3-isopropyldecahydroquinazolines and *trans*-3-phenyl-decahydroquinazolines proved to be three-component (r^1-o-r^2) ring-chain tautomeric mixtures, whereas only ring-closed tautomers could be detected for the 3-methyl-substituted analogues. The proportions of the ring-chain tautomeric forms at equilibrium were strongly influenced by the *N*-substitutents and the ring anellation, and could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$. These are the first examples among 2-aryl-1,3-*N,N* heterocycles of a three-component ring-chain tautomeric equilibrium characterized by a Hammett-type equation.

Keywords: tautomerism; diamines; quinazolines; electronic effect.

Introduction

A large number of examples have emerged in recent years demonstrating that ring-chain tautomerism occurs not only among *N*-unsubstituted saturated 1,3-*O,N* heterocycles, but also among their 1,3-*N,N* analogues.[1-5] On the basis of their ring-chain tautomeric character, 1,2-disubstituted saturated 1,3-*N,N* heterocycles can be exploited as intermediates in the selective functionalization of *N*-monosubstituted ethylene- or propylenediamines; the selectivity of the reaction is strongly influenced by the nature of the substituent at position 2.[6]

For 2-aryl-substituted imidazolidines, hexahydropyrimidines and 1,2,3,4-tetrahydroquinazolines, similarly to their 1,3-*O,N* analogues,[1] a Hammett-type linear correlation was found between the ring-chain ratios for the tautomeric equilibria (K = [ring]/[open]) and the electronic character (σ^+) of the substituent on the 2-phenyl ring (Eq. 1):[3-5]

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

For *N*-substituted 2-aryl-1,3-*N,N* heterocycles, the ring-chain tautomeric process and the values of ρ and log $K_{X=H}$ in Eq. 1 depend strongly on the steric and electronic characters of the substituent on the nitrogen.[4,5] In contrast with the 1,3-*O,N* analogues, the value of ρ proved not to be characteristic of the 1,3-*N,N* ring system.[3-5]

As a continuation of our previous studies on five- and six-membered 1,3-*N,N* heterocycles,[4,5] our present aim was to investigate the effects of substituents and the geometry of the ring anellation on the ring-chain tautomeric character of some 3-substituted 2-aryldecahydroquinazolines for the purpose of refining the scope and limitations of application of Eq. 1 among six-membered 1,3-*N,N* heterocycles.

Results and discussion

Starting materials for the synthesis of decahydroquinazoline model compounds were prepared from *cis*- and *trans*-2-aminocyclohexanecarboxylic acid (**1a,b**) by a combination of standard chemical procedures (Scheme 1).[7-10] *cis*- and *trans*-2-(Methyl- or isopropyl or phenylaminomethyl)cyclohexyl amines (**9a,b**, **10a,b** and **11a,b**) were synthesized by $LiAlH_4$ reduction of the corresponding *N*-substituted amino carboxamides (**6a,b**, **7a,b** and **8a,b**), which were obtained either by the direct amidation of amino esters **2a,b** with methylamine[7-9] or via the *N*-protected amino acids **3a,b** by using the mixed anhydride method.[10]

Model compounds **12-17** were prepared by the reactions of diamines **9-11a,b** with equivalent amounts of substituted benzaldehydes (Scheme 2). The ^1H NMR spectra of **12-17** revealed that, in $CDCl_3$ solution at 300 K *cis*- and *trans*-3-isopropyl-2-aryldecahydroquinazolines (**14a-g** and **15a-g**) and *trans*-3-phenyl-substituted 2-aryldecahydroquinazolines (**17a-g**) participate in three-component (r^1-o-r^2) ring-chain tautomeric equilibria, having both electron-donating and electron-withdrawing substituents on the 2-phenyl ring. For *cis*-3-phenyl-2-aryldecahydroquinazolines (**16**), ring-chain tautomeric equilibria could be detected only for compounds bearing an electron-withdrawing substituent X (**16a-c**); for the 2-phenyl derivative (**16d**) and the compounds with an electron-donating substituent X on the 2-phenyl ring (**16e-g**), only the presence of the open-chain tautomer was observed. Similarly to other *N*-methyl-substituted six-membered 2-aryl-1,3-*N,N* heterocycles,[5] in the cases of *cis*- and *trans*-3-methyl-2-aryldecahydroquinazolines (**12a,g** and **13a,g**), no open-chain tautomeric forms (**A**) could be detected. Despite the presence of the electron-donating *p*-dimethylamino substituent on the 2-phenyl ring, which is favourable for the shift of the equilibrium towards the open tautomer,[1] the NMR spectra of **12g** and **13g** showed exclusively the presence of ring-closed tautomers.

The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria (K_X) were determined at 300 K by integration of the well-separated N-C*H*Ar-N (ring) and N=C*H* (chain) proton singlets (Table 7) in the ^{1}H NMR spectra of compounds **12, 13, 14, 15** and **16**. For compounds **15**, the ratios of the ring-closed tautomers were calculated by deconvolution because of their partly overlapping N-C*H*Ar-N singlets (Tables 1 and 2).

For compounds **17**, tautomeric ratios (K_X) could not be determined at 300 K because of the fast interconversion of the tautomeric forms; the signal of the *minor* ring form therefore appeared only at lower temperatures in the ^{1}H NMR spectrum. Values of K_X and the ratios of the ring forms at 300 K for compounds **17** (Tables 2 and 3) were calculated according to the van't Hoff equation (2) on the basis of the tautomeric ratios determined at lower temperatures (Table 4):[11]

$$\ln K_X = -\Delta H^0/RT + \Delta S^0/R \qquad (2)$$

In consequence of the very similar NMR spectroscopic characters of these 2-aryldecahydroquinazolines, with the same *N*-substituent and ring anellation, determination of the relative configuration of the *major* and *minor* ring-closed tautomers and conformational analysis were performed only for the *p*-nitrophenyl derivatives **12a-17a** (Table 5). Data on **12aB** and **16aA** were chosen to illustrate the ^{1}H NMR spectra of the prepared tautomeric compounds (see Experimental). 2-Aryl substituents did not change the sequence of the chemical shifts of the characteristic N-C*H*Ar-N and N=C*H*Ar protons.

In the EXSY spectra of **14a** and **15a**, there is a negative cross-peak between the N=C*H*Ar singlet of the open form and both N-C*H*Ar-N signals of the *major* and *minor* ring forms, while there is no negative cross-peak between the N-C*H*Ar-N signals of the cyclic tautomers. This proves the interconversion of the ring-closed tautomers (**B** and **C**) through the open-chain form (**A**). The relative configurations of the *major* ring-closed tautomers of **14a** and **15a** were deduced from the NOESY spectra, in which the cross-peak for the protons at positions 2 and 8a proves their *cis* arrangement (**B**) (Scheme 2). The same relative configuration of H-2 and H-8a for the *major* ring-closed tautomer was found for all the remaining 2-(*p*-nitrophenyl)decahydroquinazolines (**12a, 13a, 16a** and **17a**). In the ring-chain tautomeric equilibria of the corresponding 2-aryldecahydro-3,1-benzoxazines (**18, 19**), the *major* ring-closed tautomeric form also had *cis* arranged H-2 and H-8a.[12]

The configuration of the azomethine double bond was determined by observing the intensity of the NOE interaction between H-2 and H-8a in model compounds which contain the open tautomeric form in a higher proportion (**16a** and **17a**). A high-intensity NOESY cross-peak

can be detected for both compounds, which suggests the *E* configuration of the C=N double bond and shows that the H(8a)–C(8a)–N(1)–C(2) torsion angle is within the region of ±60°.

The data in Tables 1 and 2 indicate that the proportions of the diastereomeric ring-closed tautomers in the equilibria, which are proportional to the relative stabilities of these ring forms, are greatly influenced by the relative configurations of the chiral centres. In an attempt to find a relationship between the relative stability and the predominant conformation of the ring epimers, a conformational analyis of *cis*- and *trans*-3-isopropyl-2-(*p*-nitrophenyl)-decahydroquinazolines (**14a** and **15a**) was performed by using NMR and modelling means. An earlier conformational analysis on decahydroquinazoline derivatives led to the conclusion that *cis*-fused derivatives could exist in two interconvertible chair-chair conformations (*N-in* or *N-out*), the equilibrium of which was strongly dependent on the substitution of the nitrogen at position 1. For 1-unsubstituted *cis*-decahydroquinazolines, the conformational equilibrium is shifted dominantly towards the *N-in* conformer, while the 1-methyl *cis* derivative can be characterized by a dominant *N-out* conformation.[9,14,15]

The conformation for **14aB** (*major* ring form) can readily be determined by analysis of the crucial NMR spectral parameters. The coupling constants of the signals of the protons at positions 4a and 4 are similar, ^3J (H-4$_{eq}$, H-4a) = 2.27 Hz and ^3J (H-4$_{ax}$, H-4a) = 3.27 Hz, and low value, which suggests an *equatorial* orientation of H-4a relative to the heterocyclic ring. NOE interactions can be detected from H-2 to H-4$_{ax}$ and H-8a, which is evidence of a predominantly *equatorial* aryl group in accordance with its steric demand. On the basis of these results, it can be concluded that the *major* ring-closed tautomer **14aB** predominantly occupies an *N-in* conformation (Scheme 3). The low relative concentration of the *minor* ring-closed tautomer **14aC** did not facilitate the extraction of useful NMR data and therefore a standard conformational search procedure[13] was carried out to find the lowest energy conformation. The resulting structure (Scheme 3) of **14aC** shows an *N-out* conformation with the sterically demanding aryl group in the *equatorial* position. The energy difference between **14aB** and **14aC**, estimated from the average ring-ring tautomeric ratio, is approximately 6.6 kJ/mol. The steric repulsion between H-4$_{ax}$ and H-5$_{ax}$ and the repulsion between H-2 and H-7$_{ax}$ in **14C** may account for the observed stability difference.

The *major trans* ring-anellated diastereomer **15aB** exhibits a vicinal coupling constant (^3J(H-4a, H-4$_{eq}$) = 3.53 Hz and ^3J(H-4a, H-4$_{ax}$) = 9.06 Hz) and NOE interaction (H-2–H-4$_{ax}$, H-2–H-8a) pattern, which is in accordance with the expected conformation with the aryl group in an *equatorial* position (Scheme 4). The residual amount of the *minor* component in the sample made molecular modelling necessary. The conformational search for the *minor* epimer **15aC**

gave a chair-chair conformation in which the aryl group has an *axial* orientation (Scheme 4). The *axial* position of the 2-aryl group explains the lower stability (ΔG = 2.9 kJ/mol) of **15aC** as compared with **15aB**.

When Eq. 1 was applied to the log K_X values, good linear correlations were obtained *vs.* the Hammett-Brown parameter σ^+ of the substituent X on the 2-phenyl group for compounds **14**, **15** and **17** (Figure 1 and Table 6), which are the first examples among 2-aryl-1,3-*N*,*N*-heterocycles of three-component ring-chain tautomeric processes characterized by a Hammett-type correlation. The shift of the tautomeric equilibrium towards the open-chain tautomer meant that a linear correlation could not be calculated for the few plots of compounds **16**.

The linear regression analysis data in Table 6 show that the slopes for 3-substituted-2-aryldecahydroquinazolines (**14**, **15** and **17**) lie within a wider range (0.51–1.21) than those for the corresponding 2-aryldecahydro-3,1-benzoxazines (**18** and **19**: 0.55-0.64) and, similarly as for other 2-aryl-1,3-*N*,*N* heterocycles exhibiting ring-chain tautomerism, the value of ρ is not characteristic of the ring system. Ring anellation does not seem to influence the value of ρ: *cis*- and *trans*-3-isopropyl-2-aryldecahydroquinazolines have very similar values of ρ (0.51 and 0.57).The substituent on the nitrogen exerted a similar effect on the value of ρ to that found for 3-isopropyl and 3-phenyl-substituted 2-aryl-1,2,3,4-tetrahydroquinazolines:[5] the value of ρ was somewhat higher for 3-phenyl derivatives for the equilibria involving either the *major* (**15B-17B**) or the *minor* (**15C-17C**) ring forms.

Both the substituent on the nitrogen and the ring anellation caused marked effects on the value of the intercept. To characterize the effects of the anellated ring on the stability of the ring form, a substitution effect parameter (c_s) was calculated as the difference in the intercepts for the given 2-aryldecahydroquinazolines and the corresponding 2-arylhexahydropyrimidines (**20** and **21**) bearing the same substituent on the nitrogen. This kind of relative ring stability constant was introduced earlier for the saturated 2-aryl-1,3-*O*,*N* heterocycles bearing substituents at positions 4-6.[1,12] Positive values of c_s mean a more stable ring form relative to the corresponding 2-arylhexahydropyrimidine. The values of c_s for compounds **14B**, **15B**, **15C**, **17B** and **17C** indicate that the anellated ring had a considerable stabilizing effect on the ring form for each compound except **17C**. This effect was more pronounced for the *N*-isopropyl-substituted derivatives (**14** and **15**) than for the *N*-phenyl compounds (**17**). For 3-isopropyl- and 3-phenyldecahydroquinazolines, the *trans*-anellated cyclohexane ring (**15B**: c_s = 2.00) had a higher stabilizing effect than that of the *cis* ring anellation (**14B**: c_s = 0.98). The

lack of a stabilizing substituent effect in the *cis*-3-phenyldecahydroquinazolines (**16**) led to a nearly quantitative shift of the equilibria toward the open-chain tautomers (**16A**).

The effect of the substituted nitrogen atom at position 3 on the stability of the ring-closed tautomeric form can be expressed by a heteroatom effect parameter (c_h), which is calculated as the difference in intercept for the given 2-aryl-decahydroquinazoline and the corresponding 2-aryldecahydro-3,1-benzoxazine (**18B,C** and **19B,C**).[4,5] The value of c_h refers to the stability difference of the given 1,3-*O,N* and 1,3-*N,N* heterocycles. There is no clear connection between the values of c_h and the type of the substituent on the nitrogen, but the data in Table 6 demonstrate that the ring form for compounds **14B**, **15B**, **17B** and **17C** is less stable than that for the corresponding decahydrobenzoxazine. Since the ring-chain tautomeric equilibria of *cis*- and *trans*-3-methyl-substituted decahydroquinazolines (**12** and **13**) are appreciably shifted towards the ring-closed tautomer, the stability of the ring-closed form of *cis* and *trans*-2-aryldecahydroquinazolines and -3,1-benzoxazines increases in the following sequence of the heteroatom at position 3: NPh < N*i*Pr < O < NMe.

Conclusions

In conclusion, the ring-chain tautomerism of *cis*- and *trans*-3-substituted-2-aryldecahydroquinazolines is strongly dependent on the substituents on the nitrogen and on the *cis-trans* ring anellation. Compounds with a small *N*-substituent (Me) exist exclusively in the ring-closed form, independently of the type of ring anellation. Compounds with larger *N*-substituents (*i*Pr or Ph) participate in three-component ring-chain tautomeric mixtures involving diastereomeric ring-closed forms besides the open-chain tautomer. In all cases, H-2 and H-8a of the *major* ring form (**B**) are *cis*-arranged. The ratios of the ring-closed tautomers were higher for the *trans*-anellated compounds. For the *cis*- and *trans*-3-isopropyl-2-aryldecahydroquinazolines (**14** and **15**) and *trans*-3-phenyl-2-aryldecahydroquinazolines (**17**), three-component ring-chain tautomeric equilibria characterized by a Hammett-type equation have been detected for the first time among 2-aryl-1,3-*N,N* heterocyles.

Experimental

^{1}H NMR spectra were recorded on a Bruker AVANCE DRX 400 spectrometer at 300 K. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or to TSP (D_2O) as internal standards; multiplicities were recorded as *s* (singlet), *d* (doublet), *dd* (double doublet), *ddd* (double double doublet), *dt* (double triplet), *t* (triplet), *m* (multiplet) or *om* (overlapping

multiplet). For the equilibria to be established in tautomeric compounds,[3,16] the samples were dissolved in $CDCl_3$ and the solutions were left to stand at ambient temperature for 1 day before the ^1H NMR spectra were run. The number of scans was usually 64.

Melting points were determined on a Kofler micro melting point apparatus and are not corrected. The physical data on compounds **12-17** are listed in Table 7.

Compounds **3a,b**[10] and **6a,b**[8] were prepared according to known procedures.

General method for the preparation of *cis*- and *trans*-*N*-isopropyl- and *N*-phenyl-2-(benzyloxycarbonylamino)cyclohexanecarboxamides (4a,b and 5a,b)

To a stirred and cooled (ice-salt bath) suspension of *cis*- or *trans* 2-(benzyloxy-carbonylamino)-cyclohexanecarboxylic acid (**3a,b**) (2.77 g, 0.01 mol) and triethylamine (1.01 g, 0.01 mol) in dry toluene (100 mL), ethyl choroformate (1.08 g, 0.01 mol) was added dropwise at a rate low enough to keep the internal temperature below –10 °C. After 15 min, a solution of isopropylamine or freshly distilled aniline (0.01 mol) in dry CH_2Cl_2 (10 mL) was added dropwise to the mixture, the internal temperature being kept below –10 °C. Stirring was continued for 30 min with cooling and for 30 min without, and the mixture was then heated slowly to reflux and refluxed for 5 min. The mixture was allowed to cool down and washed with saturated aqueous $NaHCO_3$ solution (2 x 50 mL) and water (80 mL) after the addition of $CHCl_3$ (200 mL). The combined organic phases were dried (Na_2SO_4) and evaporated under reduced pressure to give a white crystalline residue, which was filtered off, washed with Et_2O and recrystallized from iPr$_2$O-EtOAc.

(**4a**): Yield: 2.75 g (86%); mp 129-130 °C; ^1H NMR ($CDCl_3$) δ: 1.08 (d, 3H, J = 6.6 Hz, CH_3), 1.08 (d, 3H, J = 6.6 Hz, CH_3), 1.40 (m, 2H, (CH_2)$_4$); 1.50-1.78 (om, 5H, (CH_2)$_4$), 2.01 (m, 1H, (CH_2)$_4$), 2.53 (m, 1H, COC*H*), 3.87 (m, 1H, NC*H*), 4.04 (m, 1H, NC*H*(CH$_3$)$_2$), 5.08 (s, 2H, OCH_2), 5.44 (br s, 1H, N*H*), 5.68 (br s, 1H, N*H*), 7.27-7.37 (om, 5H, C$_6H_5$). Analysis: calculated for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80; found: C, 67.72; H, 8.15; N, 8.69.

(**4b**): Yield: 1.20 g (38%); mp 201-202 °C; ^1H NMR ($CDCl_3$) δ: 1.03 (d, 3H, J = 6.6 Hz, CH_3), 1.06 (d, 3H, J = 6.6 Hz, CH_3), 1.13-1.51 (om, 4H, (CH_2)$_4$), 1.75 (m, 2H, (CH_2)$_4$), 1.98 (m, 2H, (CH_2)$_4$), 2.27 (m, 1H, COC*H*), 3.51 (m, 1H, NC*H*), 4.02 (m, 1H, NC*H*(CH$_3$)$_2$), 5.02 (d, 1H, N*H*, J = 8.6 Hz), 5.08(s, 2H, OCH_2), 5.78 (br s, 1H, N*H*), 7.33 (m, 5H, C$_6H_5$). Analysis: calculated for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80; found: C, 67.69, H, 8.08; N, 8.68.

(**5a**): Yield: 2.86 g (81%); mp 169-172 °C (lit.[10] mp 172-173 °C); ^{1}H NMR ($CDCl_3$) δ: 1.45 (m, 2H, $(CH_2)_4$), 1.57-1.70 (om, 3H, $(CH_2)_4$), 1.84 (m, 2H, $(CH_2)_4$), 2.07 (m, 1H, $(CH_2)_4$), 2.80 (m, 1H, COC*H*), 3.99 (m, 1H, NC*H*), 5.08 (s, 2H, OCH_2), 5.55 (d, 1H, J = 6.7 Hz, N*H*), 7.10 (t, 1 H, J = 7.4 Hz, C_6H_5), 7.28-7.32 (om, 7H, C_6H_5), 7.46 (d, 2H, J = 7.9 Hz, C_6H_5)), 7.55 (br s, 1H, N*H*).

(**5b**): Yield: 1.17 g (33%); mp 217-218 °C; ^{1}H NMR ($CDCl_3$) δ: 1.15-1.85 (om, 6H, $(CH_2)_4$), 1.99 (m, 1H, $(CH_2)_4$), 2.10 (m, 1H, $(CH_2)_4$), 2.52 (m, 1 H, COC*H*), 3.66 (m, 1 H, NC*H*), 4.98-5.13 (om, 3H, OCH_2, N*H*), 7.08 (t, 1H, J = 7.4 Hz, C_6H_5), 7.18-7.32 (om, 7H, 2 x C_6H_5), 7.48 (d, 2H, J = 7.7 Hz, C_6H_5). Analysis: calculated for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95; found: C, 71.34; H, 6.63; N, 7.82.

General method for the preparation of *cis*- and *trans*-*N*-isopropyl- and *N*-phenyl-2-aminocyclohexanecarboxamides (7a,b and 8a,b)

The appropriate *N*-substituted *cis*- or *trans*-2-(benzyloxycarbonylamino)cyclohexane-carboxamide (**4a,b** or **5a,b**) (0.01 mol) was suspended in 33% hydrobromic acid in acetic acid (12 mL) and the mixture was left to stand at room temperature for 1 h with occasional shaking. The crystalline hydrobromide salt of **7a,b** or **8a,b** that was formed was filtered off and dissolved in ice-cold water (75 mL). The solution was made alkaline with 10% NaOH and extracted with EtOAc (5 x 50 mL). The combined organic phases were dried over Na_2SO_4 and evaporated under reduced pressure. The crystalline residue was recrystallized from EtOH.

(**7a**): Yield: 1.44 g (78%); mp 83-86 °C; ^{1}H NMR ($CDCl_3$) δ: 1.14 (d, 6H, J = 6.5 Hz, $CH(CH_3)_2$), 1.29-1.68 (om, 7H, $(CH_2)_4$), 1.74 (br s, 2H, NH_2) 1.83 (m, 1H, $(CH_2)_4$), 2.31 (m, 1H, COC*H*), 3.28 (m, 1H, NC*H*), 4.06 (m, 1H, NC*H*$(CH_3)_2$), 7.80 (br s, 1H, CON*H*). Analysis: calculated for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20; found: C, 64.92; H, 10.73; N, 14.96.

(**7b**): Yield: 1.56 g (85%); mp 105-108 °C; ^{1}H NMR ($CDCl_3$) δ: 1.08-1.52 (om, 12H, $CH(CH_3)_2$, $(CH_2)_4$, NH_2) 1.73 (m, 3H, $(CH_2)_4$), 1.80-1.90 (om, 2H, $(CH_2)_4$, COC*H*); 2.92 (ddd, 1H, J = 7.32, 11.58, 4.03 Hz, NC*H*); 4.09 (m, 1H, NC*H*$(CH_3)_2$) 5.92 (br s, 1H, CON*H*). Analysis: calculated for $C_{10}H_{20}N_2O$: C, 65.18; H, 10.94; N, 15.20; found: C, 64.95; H, 10.72; N, 15.01.

(**8a**): Yield: 1.84 g (84%); mp 122-124 °C (lit.[10] mp 143-144 °C); ^{1}H NMR ($CDCl_3$) δ: 1.36-1.73 (om, 7H, $(CH_2)_4$), 1.84 (br s, 2H, NH_2), 1.98 (m, 1H, $(CH_2)_4$), 2.50 (m, 1H, COC*H*); 3.36

(m, 1H, NC*H*); 7.05 (t, 1H, J = 7.4 Hz, C_6H_5); 7.29 (t, 2H, J = 8.36 Hz, C_6H_5), 7.58 (d, 2H, J = 8.44 Hz, C_6H_5), 11.31 (br s, 1H, CONH).

(**8b**): Yield: 1.90 g (87%), mp 108-110 °C, ^{1}H NMR ($CDCl_3$) δ: 1.13-1.55 (om, 6H, $(CH_2)_4$, NH_2), 1.77 (m, 2H, $(CH_2)_4$), 2.15 (m, 1H, COC*H*), 2.91 (ddd, 1H, J = 10.58, 10.83, 4.28 Hz, NC*H*), 7.06 (t, 1 H, *J* = 7.40 Hz, C_6H_5), 7.29 (t, *J* = 7.9 Hz, 2H, C_6H_5), 7.55 (d, 2H, *J* = 7.9 Hz, C_6H_5), 9.55 (br s, 1H, CONH). Analysis: calculated for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83; found: C, 71.29; H, 8.08; N, 12.60.

General method for the preparation of *cis*- and *trans*-2-(methyl, isopropyl- or phenylaminomethyl)cyclohexylamines (9a,b, 10a,b and 11a,b)

To a stirred suspension of $LiAlH_4$ (2.28 g, 0.06 mol) in dry THF (50 mL), a solution of the appropriate amide (**6a,b**,**7a,b** or **8a,b**) (0.02 mol) in dry THF (20 mL) was added dropwise. The mixture was stirred and refluxed for 4 h and then cooled, and the excess of $LiAlH_4$ was decomposed by addition of a mixture of water (4.5 mL) and dry THF (30 mL). The inorganic salts were filtered off and washed with EtOAc (3 x 75 mL). The combined organic filtrate and washings were dried over Na_2SO_4 and evaporated under reduced pressure to give crude diamines as oily (**9a,b** and **10a,b**) or crystalline (**11a,b**) products.

The crude diamines were purified by distillation (**9a,b** and **10a**), by column chromatography on silica by using a mixture of $CHCl_3$ and MeOH (1 : 1) as eluent (**11a**), or as hydrochloride salts (**10b** and **11b**).

(**9a**): Yield: 1.55 g (54%); bp 82-90 °C (6 mmHg); The ^{1}H NMR data on the product correspond to the literature[9] data.

(**9b**): Yield: 2.30 g (81%); bp 80-85 °C (4 mmHg); ^{1}H NMR ($CDCl_3$) δ: 0.92-1.30 (om, 5H, $(CH_2)_4$), 1.62-1.84 (om, 4H, $(CH_2)_4$, CC*H*), 2.38-2.60 (om, 4H, NC*H*, CH_3), 2.50 (dd, 1H, *J* = 5.9, 11.6 Hz, NCH_2), 2.71 (dd, 1H, *J* = 5.6, 11.6 Hz, NCH_2). Analysis: calculated for $C_8H_{18}N_2$: C, 67.55; H, 12.76; N, 19.69; found: C, 67.36; H, 12.95; N, 19.48.

(**10a**): Yield: 2.56 g (75%); bp 85-89 °C (2-3 mmHg); ^{1}H NMR ($CDCl_3$) δ: 1.05 (d, 6H, *J* = 6.3 Hz, $CH(CH_3)_2$), 1.20-1.68 (om, 12H, $(CH_2)_4$, CC*H*C, NH_2, NH); 2.47 (dd, 1H, *J* = 6.6 Hz, 11.5 Hz, NCH_2); 2.62 (dd, 1 H, *J* = 7.4 Hz, 11.5 Hz, NCH_2); 2.75 (m, 1 H, $CH(CH_3)_2$), 3.11 (m, 1 H, NC*H*). Analysis: calculated for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45; found: C, 70.36; H, 12.75; N, 16.19.

(**11a**): Yield: 2.90 g (71%); mp 44-46 °C; ^{1}H NMR ($CDCl_3$) δ: 1.29 (m, 1H, $(CH_2)_4$), 1.37-1.71 (om, 7H, $(CH_2)_4$), 1.80 (m, 1H, CC*H*), 3.02 (dd, 1H, *J* = 6.3 Hz, 12.5 Hz, NCH_2), 3.14-

3.21 (om, 2 H, NCH_2, NC*H*), 6.61 (d, 2H, J = 7.8 Hz, C_6H_5), 6.67 (t, 1H, *J* = 7.3 Hz, C_6H_5), 7.16 (m, 2 H, C_6H_5). Analysis: calculated for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71; found: C, 76.21; H, 9.65; N, 13.59.

Crude diamines **10b** and **11b** were converted to crystalline dihydrochloride salts by treatment of their ethanolic solutions (10 mL) with an excess of 22% ethanolic HCl and Et_2O. The crystalline dihydrochlorides were filtered off and recrystallized from MeOH–Et_2O.

(**10b**.2HCl): Yield: 3.84 g (79%); mp 200-203 °C; ^{1}H NMR (D_2O) δ: 1.17-1.56 (om, 10 H, CH(CH_3)$_2$, (CH_2)$_4$), 1.80 (m, 2H, (CH_2)$_4$), 1.98 (m, 2H, (CH_2)$_4$), 2.08 (m, 1H, CC*H*), 3.03 (dd, 1H, *J* = 10.4 Hz, 12.6 Hz, NCH_2), 3.14 (ddd, 1H, *J* = 4.0, 10.3, 10.6 Hz, NC*H*), 3.29 (dd, 1 H, J = 3.3 Hz, 12.7 Hz, NCH_2), 3.47 (m, 1 H, C*H*(CH_3)$_2$). Analysis: calculated for $C_{10}H_{24}Cl_2N_2$: C, 49.38; H, 9.95; N, 11.52; found: C, 49.22; H, 9.78; N, 11.36.

(**11b**.2HCl): Yield: 4.81 g (87%); mp 193-195 °C; ^{1}H NMR (D_2O) δ: 1.14-1.44 (om, 4H, (CH_2)$_4$), 1.71 (m, 2H, (CH_2)$_4$), 1.88-2.05 (om, 3H, (CH_2)$_4$, CC*H*), 3.09 (dt, 1H, *J* = 3.9, 10.3 Hz, NC*H*), 3.39 (dd, 1H, *J* = 10.1 Hz, 12.8 Hz, NCH_2), 3.57 (dd, 1H, *J* = 3.7 Hz, 12.8 Hz, NCH_2), 7.35-7.53 (om, 5H, C_6H_5). Analysis: calculated for $C_{13}H_{22}Cl_2N_2$: C, 56.32; H, 8.00; N, 10.10; found: C, 56.06; H, 7.85; N, 9.88.

Pure diamine bases **10b** and **11b** were obtained from the above dihydrochlorides by alkaline treatment (20% NaOH), extraction (CH_2Cl_2) and evaporation under reduced pressure. The free bases were dried in a vacuum desiccator for 24 h before the further transformations.

(**10b**): ^{1}H NMR ($CDCl_3$) δ: 0.92-1.32 (om, 6 H, (CH_2)$_4$), 1.04 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.05 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.60-1.87 (om, 7H, NH_2, N*H*, (CH_2)$_4$), 2.42 (dt, 3.8, 10.2 Hz, 1H, NC*H*), 2.52 (dd, 1H, *J* = 5.8, 11.4 Hz, NCH_2), 2.69-2.78 (om, 1H, NCH_2, C*H*(CH_3)$_2$). Analysis: calculated for $C_{10}H_{22}N_2$: C, 70.53; H, 13.02; N, 16.45; found: C, 70.36; H, 12.84; N, 16.22.

(**11b**): mp 38-39 °C; ^{1}H NMR ($CDCl_3$) δ: 0.98-1.39 (om, 5H, (CH_2)$_4$), 1.69 (m, 2H, (CH_2)$_4$), 1.69 (m, 2H, (CH_2)$_4$), 1.75-1.84 (om, 2H, (CH_2)$_4$, CC*H*), 2.44 (dt, 1H, *J* = 4.0, 10.3 Hz, NC*H*), 3.04 (dd, 1H, *J* = 5.5 Hz, 12.2 Hz, NCH_2), 3.21 (dd, 1H, *J* = 6.2 Hz, 12.2 Hz, NCH_2); 6.61 (d, 2H, *J* = 7.7 Hz, C_6H_5), 6.66 (t, 1H, *J* = 7.3 Hz, C_6H_5), 7.15 (m, 2H, C_6H_5). Analysis: calculated for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87; N, 13.71; found: C, 76.27; H, 9.63; N, 13.48.

General method for the synthesis of 3-substituted 2-aryldecahydroquinazolines (12-17)

To a solution of the appropriate diamine (**9-11a,b**, 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 left to stand at ambient temperature for 1 h. The solvent was evaporated off and the evaporation was repeated after the addition of toluene (10 mL). 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%. The crystalline products were filtered off and recrystallized. All of the recrystallized new compounds (**12a,g, 13g, 14g, 15a** and **17c-g**) gave satisfactory data on elemental analysis (C, H, N ±0.3%).

^{1}H NMR spectroscopic data on (4a*r*,2*c*,8a*c*)-3-methyl-2-(4-nitrophenyl)decahydroquinazoline (12aB) and *cis*-*N*-(4-nitrobenzylidene)-2-(phenylaminomethyl)cyclohexylamine (16aA) in $CDCl_3$

The protons of the open form (**A**) are numbered according to the corresponding protons of the quinazoline ring form (**B**) (δ in ppm, in brackets the multiplicity, couplings in Hz and assignment, respectively).

(**12aB**): 1.31 (m, 1H, (C*H*$_2$)$_4$), 1.27 (m, 1H, (C*H*$_2$)$_4$), 1.49 (m, 1H, (C*H*$_2$)$_4$), 1.55 (m, 1H, (C*H*$_2$)$_4$), 1.59 (m, 1H, (C*H*$_2$)$_4$), 1.63 (m, 1H, CC*H*), 1.75 (m, 1H, (C*H*$_2$)$_4$), 1.78 (m, 1H, (C*H*$_2$)$_4$), 1.86 (s, 3H, C*H*$_3$), 2.43 (dd, 1H, J = 3.5 Hz, 11.6 Hz, NC*H*$_2$), 2.88 (dd, 1H, J = 2.0 Hz, 11.6 Hz, NC*H*$_2$), 3.05 (m, 1H, NC*H*), 3.81 (s, 1H, C*H*), 7.65 (d, 2H, J = 8.5 Hz, C$_6$*H*$_4$), 8.21 (d, 2H, J = 8.7 Hz, C$_6$*H*$_4$).

(**16aA**): 1.47 (*m*, 1H, (C*H*$_2$)$_4$), 1.51 (*m*, 1H, (C*H*$_2$)$_4$), 1.63 (*m*, 1H, (C*H*$_2$)$_4$), 1.73 (*m*, 2H, (C*H*$_2$)$_4$), 1.82 (*m*, 2H, (C*H*$_2$)$_4$), 1.85 (*m*, 1H, (C*H*$_2$)$_4$), 1.99 (*m*, 1H, CC*H*), 2.93 (*dd*, 1H, J = 5.8 Hz, 12.3 Hz, NC*H*$_2$), 3.10 (*dd*, 1H, J = 7.8 Hz, 12.3 Hz, NC*H*$_2$), 3.66 (*bs*, 1H, NC*H*), 6.52 (*d*, 2H, J = 8.1 Hz, C$_6$*H*$_5$), 6.65 (*t*, 1H, J = 6.6 Hz, C$_6$*H*$_5$), 7.11 (*t*, 2H, J = 7.6 Hz, C$_6$*H*$_5$), 7.89 (*d*, 2H, J = 8.5 Hz, C$_6$*H*$_4$), 8.26 (*d*, 2H, J = 8.5 Hz, C$_6$*H*$_4$), 8.35 (*s*, 1H, NH=C*H*).

ACKNOWLEDGEMENTS

The authors thanks are due to the Hungarian Research Foundation (OTKA No. T034901 and T034452) for financial support.

REFERENCES

1. Valters, R. E.; Fülöp, F.; Korbonits, D. *Adv. Heterocyclic Chem.* **1996**, *66*, 1-71.
2. a) Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Res. (S)* **1996**, 134-135. b) Moodie, R. B.; Moustras, M. Z.; Read, G.; Sandall, J. P. B. *J. Chem. Soc.,*

Perkin Trans. 2 **1997**, 169-171. c) Pihlaja, K.; Simeonov, M. F.; Fülöp, F. *J. Org. Chem.* **1997**, *62*, 5080-5088. d) Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Mendeleev Commun.* **1997**, 111-112. e) Zelenin, K. N.; Ukraintsev, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 109-114. f) Joutsiniemi, K.; Vainiotalo, P.; Fülöp, F.; Lázár, L. *Rapid Commun. Mass Spectrom.* **1998**, *12*, 876-882.

3. Zelenin, K. N.; Alekseyev, V. V.; Ukraintsev, I. V.; Tselinsky, I. V. *Org. Prep. Proc. Int.* **1998**, *30*, 53-61.
4. a) Lázár, L.; Göblyös, A.; Evanics, F.; Bernáth, G.; Fülöp, F. *Tetrahedron* **1998**, *54*, 13639-13644. c) Göblyös, A.; Lázár, L.; Evanics, F.; Fülöp, F. *Heterocycles* **1999**, *51*, 2431-2438.
5. Göblyös, A.; Lázár, L.; Fülöp, F. *Tetrahedron* accepted for publication.
6. a) Parrinello, G.; Mülhaupt, R. *J. Org. Chem.* **1990**, *55*, 1772-1779. b) Wang, W.; Liang, T. C.; Zheng, M.; Gao X. *Tetrahedron Lett.* **1995**, *36*, 1181-1184. c) Jentgens, C.; Hofmann, R.; Guggisberg, A.; Bienz, S.; Hesse, M. *Helv. Chim. Acta*, **1997**, *80*, 966-978.
7. Armarego, W. L. F.; Kobayashi, T. *J. Chem. Soc. (C)* **1971**, 238-245.
8. Pihlaja, K.; Fülöp, F.; Mattinen, J.; Bernáth, G. *Acta Chem. Scand.* **1987**, *B41*, 228-231.
9. Booth, H.; Khedhair, K. A.; Al-Shirayda, A. R. Y. *Tetrahedron* **1988**, *44*, 1465-1475.
10. Bernáth, G.; Gera, L.; Göndös, G.; Pánovics, I.; Ecsery, Z. *Acta Chim. Acad. Sci. Hung.* **1976**, *89*, 61-84.
11. Günter, H. *NMR-Spektroskopie*, Georg Thieme Verlag, Stuttgart, New York, **1983**, 229.
12. Fülöp, F.; Pihlaja, K.; Mattinen, J., Bernáth, G. *J. Org. Chem.* **1987**, *52*, 3821-3825.
13. Martinek, T.; Riddell, F. G.; Wilson, C. F. *J. Chem Soc., Perkin Trans. 2*, **2000**, 2192-2198.
14. Armarego, W. L. F.; Reece, P. A. *J. Chem. Soc., Perkin Trans. 1.* **1974**, 2313-2319.
15. Fülöp, F.; Bernáth, G.; Pihlaja, K. *Adv. Heterocyclic Chem.* **1998**, *69*, 349-477.
16. Fülöp, F.; Pihlaja, K.; Neuvonen, K.; Bernáth, G.; Argay, Gy.; Kálmán, A. *J. Org. Chem.* **1993**, *58*, 1967-1969.

Table 1 Proportions (%) of tautomeric forms (**A, B** and **C**) in tautomeric equilibria for *cis* compounds **12, 14** and **16** ($CDCl_3$, 300 K)

Compd.	X	σ^+	**12A**	**12 B**	**12 C**	**14A**	**14 B**	**14 C**	**16A**	**16 B**	**16 C**
a	*p*NO_2	0.79	~0	91.3	8.7	27.4	66.6	6.0	83.3	11.4	5.3
b	*m*Br	0.405				39.8	57.2	3.0	98.4	1.6	~0
c	*p*Cl	0.114				47.4	48.3	4.3	98.5	1.5	~0
d	H	0				55.9	42.8	1.3	~100	~0	~0
e	*p*Me	-0.311				62.5	37.5	~0	~100	~0	~0
f	*p*OMe	-0.778				74.3	25.7	~0	~100	~0	~0
g	*p*NMe_2	-1.7	~0	~100	~0	88.9	11.1	~0	~100	~0	~0

Table 2 Proportions (%) of tautomeric forms (**A, B** and **C**) in tautomeric equilibria for *trans* compounds **13, 15** and **17** ($CDCl_3$, 300 K)

Compd.	X	σ^+	**13A**	**13B**	**13C**	**15A**	**15B**[a]	**15C**[a]	**17A**	**17B**[b]	**17C**[b]
a	*p*NO_2	0.79	~0	~100	~0	5.9	89.5	4.6	32.0	54.0	14.0
b	*m*Br	0.405				15.5	73.7	10.8	64.1	29.3	6.6
c	*p*Cl	0.114				12.2	82.4	5.4	71.9	24.5	3.6
d	H	0				11.0	85.0	4.0	77.9	18.2	3.9
e	*p*Me	-0.311				17.4	77.7	4.9	88.4	10.3	1.3
f	*p*OMe	-0.778				33.6	63.8	2.6	94.5	5.0	0.5
g	*p*NMe_2	-1.7	~0	~100	~0	67.7	32.3	~0	98.9	1.1	~0

[a]The proportions of the ring forms were determined by deconvolution because of the overlapping lines. [b]The proportions of the tautomeric forms of **17a-f**, measured at 233 – 273 K, were extrapolated to 300 K by using the van't Hoff equation.

Table 3 Proportions (%) of ring forms (**B** and **C**) in tautomeric equilibria for compounds **17a-f** in $CDCl_3$ at 233 – 273 K

Compound	233 K	237 K	241 K	245 K	249 K	253 K	263 K	273 K
17aB	59.3	55.3	55.9	56.0	56.6	57.0	55.6	56.8
17aC	31.9	29.9	28.8	26.4	25.9	24.1	21.8	19.0
17bB	51.2	50.5	50.6	50.6	47.9	47.6	47.3	51.2
17bC	22.0	20.1	18.2	16.7	14.5	12.8	~0	~0
17cB	36.3	36.4	36.6	36.6	35.9	35.4	31.6	30.9
17cC	20.6	18.9	17.3	15.9	14.5	12.3	8.5	2.1
17dB	29.1	29.6	29.3	28.9	28.7	28.4	25.7	23.2
17dC	14.4	13.1	11.8	10.0	8.7	6.0	~0	~0
17eB	19.2	18.6	19.3	17.7	18.7	17.0	14.1	14.6
17eC	16.4	15.4	13.0	11.6	8.5	7.0	1.4	~0
17fB	9.1	9.6	9.4	9.2	8.3	8.3	6.8	6.8
17fC	4.4	4.3	4.1	3.7	3.1	2.3	1.6	~0

Table 4 Values of $-\Delta H^0/R$ and $-\Delta S^0/R$ for compounds **17a-f**

Compound[a]	$-\Delta H^0/R$ [b]	$-\Delta S^0/R$ [b]	Correlation coefficient	K (300 K)
17aB	906 (81)	2.50 (0.04)	0.961	1.693
17aC	1797 (129)	6.87 (0.04)	0.980	0.418
17bB	1525 (113)	5.87 (0.05)	0.973	0.457
17bC	2438 (310)	10.65 (0.07)	0.953	0.081
17cB	1009 (88)	4.44 (0.05)	0.957	0.342
17cC	2433 (192)	11.10 (0.08)	0.970	0.050
17dB	902 (91)	4.46 (0.05)	0.942	0.234
17dC	2855 (385)	13.53 (11)	0.970	0.050
17eB	1025 (126)	5.57 (0.07)	0.917	0.117
17eC	3069 (314)	14.44 (0.09)	0.960	0.015
17fB	855 (90)	5.79 (0.04)	0.947	0.053
17fC	2716 (271)	14.35 (0.09)	0.961	0.005

[a]For compound **17g**, the value of K for the equilibrium **17gB** ⇌ **17gA** was determined from the spectrum at 300 K, as the amount of the *minor* ring form (**17gC**) was ~0.
[a]Standard deviations are given in parentheses.

Table 5 Selected characteristic ^{1}H chemical shifts (ppm, δ_{TMS} = 0 ppm) and coupling constants (Hz) for compounds **12a-17a**

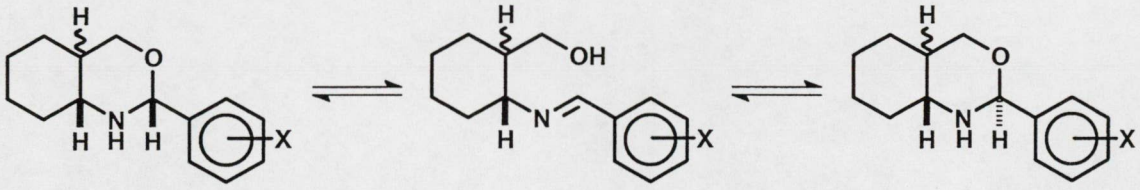
Compound	H-2	H-4_{eq}	H-4_{ax}	H-4a	H-8a	$^3J(4_{eq},4a)$	$^3J(4_{ax},4a)$
12aB	3.81	2.87	2.42	1.60	3.05	2.01	3.53
12aC	4.07	2.70	2.63	1.67	2.80	5.29	<1
13aB	3.88	2.97	2.02	1.45	2.27	3.53	11.08
14aA[a]	8.39	2.46	2.36	1.79	3.61	b	b
14aB	4.39	2.81	2.59	1.67	3.02	2.27	3.27
14aC	4.58	3.16	2.62	1.66	2.96	b	b
15aA[a]	8.39	2.40	2.54	1.33	3.10	b	b
15aB	4.44	2.97	2.18	1.39	2.28	3.53	9.06
15aC	5.04	2.85	2.54	1.32	3.08	3.02	11.58
16aA[a]	8.35	3.06	2.92	1.98	3.66	7.55	5.79
16aB	5.90	3.32	3.20	1.70	3.20	b	b
16aC	5.03	3.67	3.35	2.22	3.72	<1	5.38
17aA[a,c]	8.38	2.98	2.87	2.05	3.07	b	b
17aB[c]	5.94	3.63	2.81	1.45	2.28	3.27	11.58
17aC[c]	5.06	3.51	2.75	1.63	2.47	3.02	11.33

[a]The protons of the open form (**A**) are numbered according to the corresponding protons of the quinazoline ring forms (**B** and **C**). [b]Coupling constants were not available due to overlapping of the lines and the low proportion of the tautomeric form at equilibrium. [c]Data from the spectra run at 253 K.

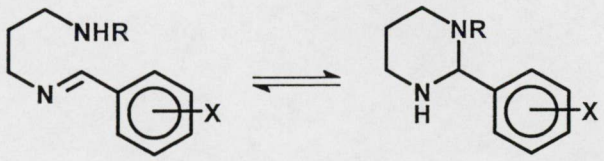
Table 6 Linear regression data on compounds **14**, **15**, **17**, *cis*- and *trans*-2-aryldecahydro-3,1-benzoxazines (**18** and **19**) and 3-substituted 2-arylhexahydropyrimidines (**20** and **21**)

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a]	Correlation coefficient	Substitution effect (c_s)[b]	Heteroatom effect (c_h)[b]
14A ⇌ **14B**	7	0.51(2)	-0.06(4)	0.994	0.98	-0.72
15A ⇌ **15B**	7	0.57(8)	0.72(16)	0.957	2.00	-0.40
15A ⇌ **15C**	6	0.71(10)	-0.43(12)	0.952	0.85	0.26
17A ⇌ **17B**	7	0.85(5)	-0.59(10)	0.985	0.69	-1.71
17A ⇌ **17C**	6	1.21(9)	-1.39(11)	0.988	-0.11	-0.70
18A ⇌ **18B**[c]	7	0.60(2)	0.66(3)	0.998	0.81	0
18A ⇌ **18C**[c]	7	0.60(6)	-0.45(12)	0.978	-0.30	0
19A ⇌ **19B**[c]	7	0.55(6)	1.12(12)	0.973	1.27	0
19A ⇌ **19C**[c]	7	0.64(3)	-0.69(6)	0.995	-0.54	0
20A ⇌ **20B**[d]	6	0.77(3)	-1.04(4)	0.997	0	-0.89
21A ⇌ **21B**[d]	7	0.42(3)	-1.28(6)	0.988	0	-1.13

[a]Standard deviations are given in parentheses. [b]Relative ring stability constant: see the text. [c]For compounds **18** and **19** (ref. 12), linear regression analysis was performed separately for the equilibria involving C-2 epimeric ring forms. [d]Data from ref. 5.



cis: **18B** **18A** **18C**
trans: **19B** **19A** **19C**



R = *i*Pr: **20A** **20B**
R = Ph: **21A** **21B**

X = *p*NO_2, *m*Br, *p*Cl, H, *p*Me, *p*OMe, *p*NMe_2

Table 7 Physical data on decahydroquinazolines **12-17**

Compd.	M. p. (°C)	Yield (%)	Formula	M. W.	δ N=C*H*Ar chain (**A**)	δ N-C*H*Ar-N ring (**B**)	ring (**C**)
12a	50-53[a]	82	$C_{15}H_{21}N_3O_2$	275.35	–	3.81	4.06
12g	55-57[a]	87	$C_{17}H_{27}N_3$	273.43	–	3.59	–
13a	oil	c	$C_{15}H_{21}N_3O_2$	275.35	–	3.88	–
13g	78-81[a]	76	$C_{17}H_{27}N_3$	273.43	–	3.67	–
14a	oil	c	$C_{17}H_{25}N_3O_2$	303.41	8.39	4.39	4.58
14b	oil	c	$C_{17}H_{25}BrN_2$	337.31	8.22	4.23	4.39
14c	oil	c	$C_{17}H_{25}ClN_2$	292.86	8.25	4.25	4.43
14d	oil	c	$C_{17}H_{26}N_2$	258.41	8.29	4.26	4.42
14e	oil	c	$C_{18}H_{28}N_2$	272.44	8.25	4.23	–
14f	oil	c	$C_{18}H_{28}N_2O$	288.44	8.22	4.22	–
14g	58-60[a]	79	$C_{19}H_{31}N_3$	301.48	8.16	4.25	–
15a	100-103[a]	85	$C_{17}H_{25}N_3O_2$	303.41	8.39	4.44	5.04
15b	oil	c	$C_{17}H_{25}BrN_2$	337.31	8.18	4.24	4.31
15c	oil	c	$C_{17}H_{25}ClN_2$	292.86	8.24	4.26	4.32
15d	oil	c	$C_{17}H_{26}N_2$	258.41	8.28	4.27	4.37
15e	oil	c	$C_{18}H_{28}N_2$	272.44	8.18	4.25	4.29
15f	oil	c	$C_{18}H_{28}N_2O$	288.44	8.20	4.23	4.27
15g	oil	c	$C_{19}H_{31}N_3$	301.48	8.13	4.19	–
16a	oil	c	$C_{20}H_{23}N_3O_2$	337.43	8.35	5.90	5.03
16b	oil	c	$C_{20}H_{23}BrN_2$	371.33	8.21	5.89	–
16c	oil	c	$C_{20}H_{23}ClN_2$	326.87	8.19	5.89	–
16d	oil	c	$C_{20}H_{24}N_2$	292.43	8.30	5.88	–
16e	62-63[a]	89	$C_{21}H_{26}N_2$	306.46	8.24	5.87	–
16f	oil	c	$C_{21}H_{26}N_2O$	322.46	8.22	5.88	–
16g	oil	c	$C_{22}H_{29}N_3$	335.50	8.16	–	–
17a	oil	c	$C_{20}H_{23}N_3O_2$	337.43	8.38[b]	5.94[b]	5.06[b]
17b	oil	c	$C_{20}H_{23}BrN_2$	371.33	8.21[b]	5.85[b]	4.88[b]
17c	83-85[a]	72	$C_{20}H_{23}ClN_2$	326.87	8.24[b]	5.86[b]	4.89[b]
17d	77-80[a]	75	$C_{20}H_{24}N_2$	292.43	8.30[b]	5.93[b]	4.90[b]
17e	68-70[a]	83	$C_{21}H_{26}N_2$	306.46	8.26[b]	5.91[b]	4.89[b]
17f	92-93[a]	74	$C_{21}H_{26}N_2O$	322.46	8.21[b]	5.89[b]	4.84[b]
17g	83-85[a]	86	$C_{22}H_{29}N_3$	335.50	8.14	5.88	–

[a]Recrystallized from *n*-hexane. [b]From the spectra run at 253 K.

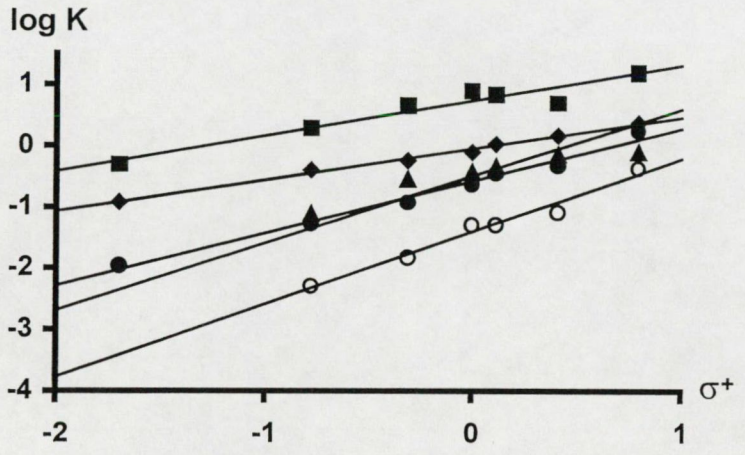
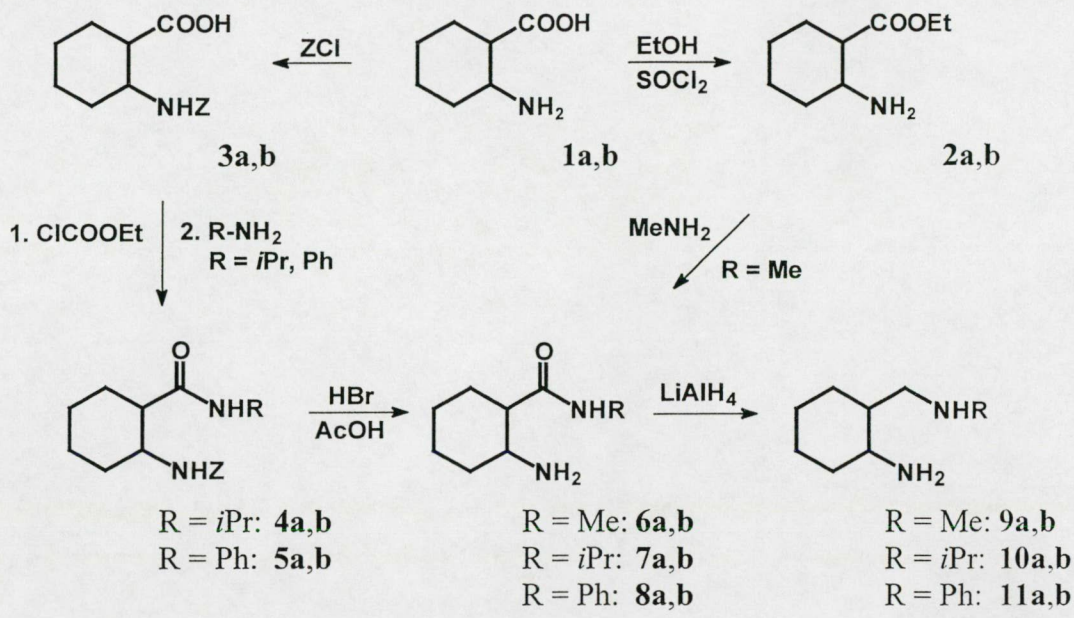
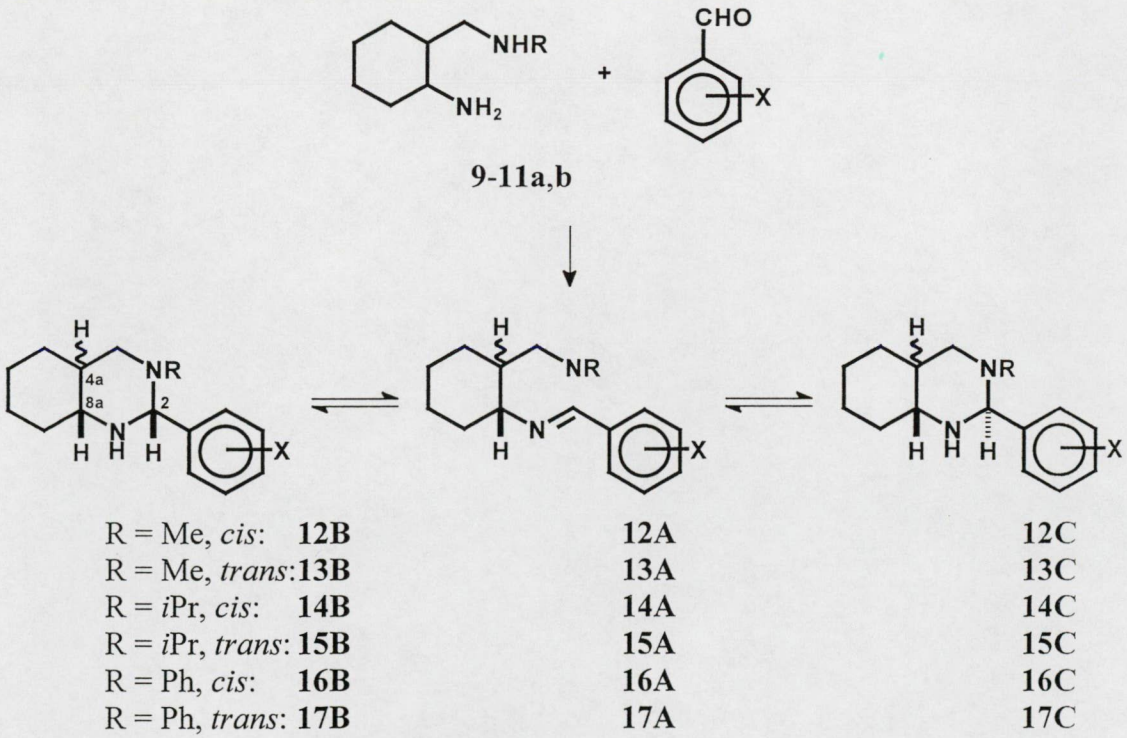


Figure 1 Plots of log K (in $CDCl_3$) for **14B** (♦), **15B** (■), **15C** (▲), **17B** (●) and **17C** (○) *vs* Hammett-Brown parameter σ^+



Z = $COOCH_2C_6H_5$; *cis*: **a**, *trans*: **b**

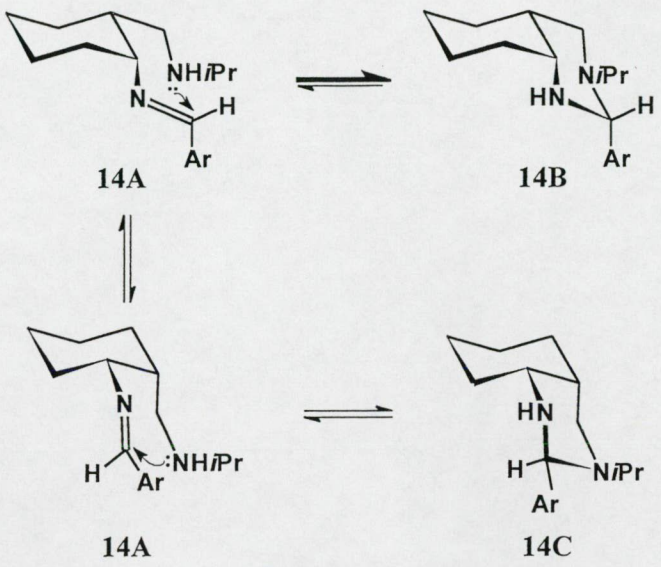
Scheme 1



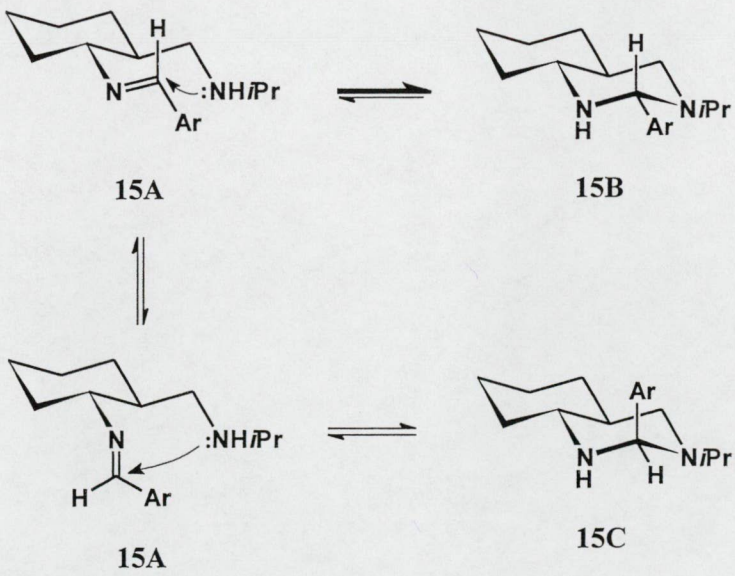
R = Me, *cis*:	**12B**	**12A**	**12C**
R = Me, *trans*:	**13B**	**13A**	**13C**
R = *i*Pr, *cis*:	**14B**	**14A**	**14C**
R = *i*Pr, *trans*:	**15B**	**15A**	**15C**
R = Ph, *cis*:	**16B**	**16A**	**16C**
R = Ph, *trans*:	**17B**	**17A**	**17C**

X = NO_2(*p*): **a**, Br(*m*): **b**, Cl(*p*): **c**, H: **d**, Me(*p*): **e**, OMe(*p*): **f**, NMe_2(*p*): **g**

Scheme 2



Scheme 3



Scheme 4