Synthesis of 2,4-Diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines and Study of the Effects of the Substituents on Their Ring-Chain Tautomerism

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Dedicated to Professor Károly Lempert on the occasion of his 80th birthday

Keywords: Amino alcohols / Mannich bases / Heterocycles / Tautomerism / Substituent effects

A number of 2-(α-amino-Y-substituted-benzyl)-1-naphthol hydrochlorides were prepared by a convenient Mannich-type aminoalkylation. 2,4-Diaryl-3,4-dihydro-2*H*-naphth-[2,1-*e*][1,3]oxazines were prepared through the ring-closure reactions of the starting aminonaphthols with aromatic aldehydes, which proved to furnish three-component (ring^1–open–ring^2) tautomeric mixtures in $CDCl_3$ at 300 K. The electronic effects of the 2-aryl groups on the ratios of the ring-chain tautomeric forms at equilibrium could be described by Equation (1). Study of the effects of substituents X and Y on the tautomeric equilibria [by the aid of the multiple linear regression analysis of Equations (2) and (3)] revealed that the *trans*-chain equilibrium constants are significantly influenced by the inductive effect (σ_F) of substituent Y on the 4-phenyl ring.

Introduction

The ring-chain tautomeric equilibrium of *N*-unsubstituted 1,3-O,N-heterocycles has been thoroughly studied in recent decades. For 2-(X-phenyl)-substituted derivatives, a clear aromatic substituent dependence [Equation (1)] has been found between the log K_X values of the equilibria (K_X = [ring]/[chain]) and the Hammett−Brown electronic parameter (σ^+) of substituent X on the 2-phenyl group.[1,2] An enormous effort has been made in recent years to refine the scope and limitations of Equation (1) as it relates to multicomponent equilibria containing different types of cyclic and/or open tautomers and to describe the quantitative effects of substituents at various positions on the 1,3-O,N-heterocycle on the parameter of Equation (1).[3−5]

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

During our systematic studies on the ring-chain tautomerism of 1,3-X,N-heterocyclic systems (X = O, NR, S), 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**1**) were prepared (Figure 1).

The common influence of aryl substituents at positions 1 and 3 on the tautomeric equilibria of **1** (Figure 1) in $CDCl_3$ at 300 K, can be described by a Hansch-type equation [Equation (2)]. Multiple linear regression analysis of these equations proved that substituent Y has an inductive effect on the *trans*-chain (**B** $\rightleftarrows$ **A**) tautomeric equilibria. This can be explained in terms of a substituent-dependent stereoelectronic effect in the *trans*-ring form **B**.[6]

$$\log K = k + \rho_F^Y\sigma_F^Y + \rho_R^Y\sigma_R^Y + \rho^X\sigma^{+x} \quad (2)$$

Our present aim was to examine the applicability of Equation (2) in a new model system; the 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines, which are regioisomers of the previously studied model compounds **1**.

Results and Discussion

2-(α-Aminobenzyl)-1-naphthols, the starting materials for the synthesis of the target naphth[2,1-*e*][1,3]oxazine model compounds, were prepared in a manner similar to that for their regioisomeric 1-(α-aminobenzyl)-2-naphthol derivatives, by Betti's classical aminoalkylation of 1-naphthol.[3,7] This Mannich aminoalkylation reaction had earlier been used to synthesize a series of secondary and tertiary 2-aminomethyl-1-naphthol derivatives,[8,9] and some recent modifications of this procedure (e.g. application of pre-

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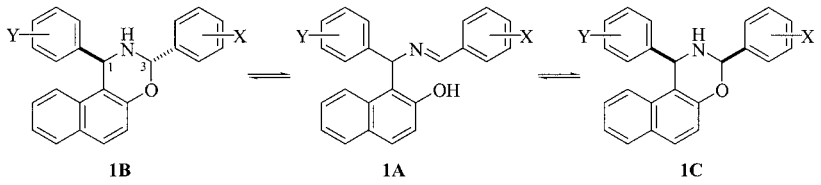
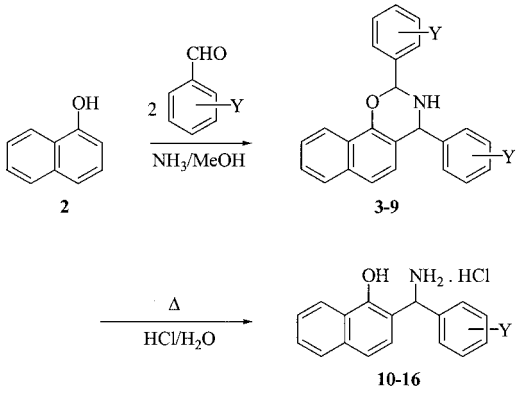


Figure 1. Ring-chain tautomeric equilibria of the 1,3-diarylnaphth[1,2-*e*][1,3]oxazines

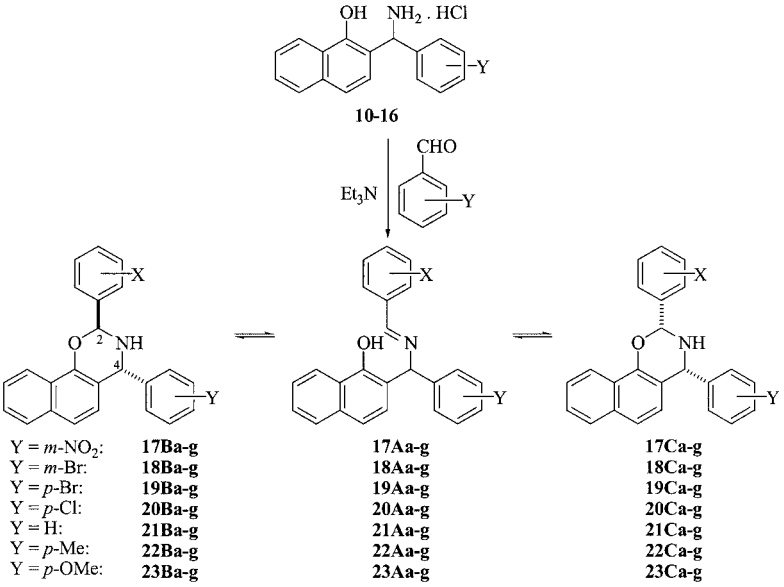
formed methyleneiminium salts) considerably extended the availability of these compounds.[10] The solvent-free asymmetric aminoalkylation of 1-naphthol with benzaldehyde and (*R*)-1-phenylethylamine has also been studied recently, but, because of the relatively low reactivity of 1-naphthol, the reaction gave only a moderate yield and displayed moderate diastereoselectivity.[11]



Scheme 1

The condensation of 1-naphthol (**2**) and benzaldehyde or substituted benzaldehydes in the presence of ammonia, and subsequent acidic hydrolysis, furnished aminonaphthol hydrochlorides **10**−**16** in moderate yields (Scheme 1). In consequence of the close analogy to 1-(α-aminobenzyl)-2-naphthols, which are known as "Betti bases", the regioisomeric compounds **10**−**16** can be referred as to "reverse Betti bases".

In contrast to the regioisomeric 1-(α-aminobenzyl)-2-naphthols, which are relatively stable crystalline substances,[3] the bases of **10**−**16** proved to be quite unstable compounds, which were therefore liberated in situ in the further transformations. The naphthoxazine model compounds **17**−**23** were prepared by condensations of aminonaphthol hydrochlorides **10**−**16** with equivalent amounts of aromatic aldehydes in the presence of Et_3N (Scheme 2). The ^1H NMR spectra of **17**−**23** proved that, in $CDCl_3$ solution at 300 K, the members **a**−**g** of each set of compounds **17**−**23** formed three-component tautomeric mixtures, containing C-2 epimeric oxazines **B** and **C** together with the open-chain tautomer **A**. Because of the very similar NMR spectroscopic characters of 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines **17**−**23**, the relative configurations of the major (**B**) and minor (**C**) ring-closed tautomers



Scheme 2

Table 1. Proportions (%) of the ring-closed tautomeric forms (**B** and **C**) in tautomeric equilibria for compounds **17**−**23** ($CDCl_3$, 300 K)

Compound	X	σ^+	**17** (Y = *m*-NO_2) 0.73		**18** (Y = *m*-Br) 0.41		**19** (Y = *p*-Br) 0.15		**20** (Y = *p*-Cl) 0.11		**21** (Y = H) 0		**22** (Y = *p*-Me) −0.31		**23** (Y = *p*-OMe) −0.78	
			B	**C**	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**
a	*p*-NO_2	0.79	60.6	27.3	57.2	30.9	57.3	29.8	56.1	30.9	50.0	35.0	45.5	38.6	50.4	34.7
b	*m*-Br	0.41	48.5	24.2	43.2	26.5	48.0	24.9	40.6	31.3	37.0	29.2	34.5	31.0	36.1	29.3
c	*p*-Br	0.15	38.5	21.1	36.8	22.8	34.7	21.9	36.6	21.6	32.4	19.0	31.3	21.6	34.1	26.0
d	*p*-Cl	0.11	40.2	19.4	36.1	20.9	35.9	20.7	35.2	21.1	30.9	23.1	30.8	23.1	30.1	24.4
e	H	0	30.5	17.1	28.9	17.9	28.0	17.6	26.8	18.8	22.5	22.4	23.2	20.9	23.0	17.8
f	*p*-Me	−0.31	26.3	9.3	19.6	12.1	18.5	11.9	17.7	13.3	16.3	13.0	13.3	10.6	19.1	16.2
g	*p*-OMe	−0.78	14.6	5.1	8.3	4.2	14.2	7.7	13.1	7.8	10.6	7.6	9.0	7.2	9.6	8.4

were determined and conformational analysis was performed only for compounds **18a** and **17g**. The NOESY spectra of compound **18a** proved that, similarly to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines,[3] the major ring-closed tautomer contains the 2,4-diaryl substituents in the *trans* position (**B**); 2D spectroscopic analysis of **17g** revealed that the configuration of the azomethine double bond is (*E*).

The proportions of the chain **A** and diastereomeric ring forms **B** and **C** in the tautomeric equilibria of **17**−**23** (Table 1) were determined by integration of the well-separated O−C*H*Ar−N (ring) and N=C*H*Ar (chain) proton singlets from the ^{1}H NMR spectra (see Exp. Sect.). When Equation (1) was applied to the log *K* values (*K* = [ring]/[chain]), good linear correlations were obtained with the Hammett−Brown parameter σ^+ of the substituent X on the 2-phenyl group for compounds **17**−**23** (Figure 2, Table 2).

For each series, the value of ρ was found to be positive, as is customary among 2-aryl-1,3-O,N-heterocycles. The plots for the equilibria containing C-2 epimeric ring forms of **17**−**23** (**B** ⇌ **A** and **C** ⇌ **A**) proved to be practically parallel, which points to the fact that the 2,4-diaryl substituents in the ring forms of 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines do not influence the value of ρ.

The relative ring stability constant (c_s) was introduced earlier for the saturated 2-aryl-1,3-O,N-heterocycles to characterize the effects of the substituents and the presence of an annelated ring on the stability of the ring form. Its value is calculated as the difference in the intercepts for the given naphthoxazine derivative **17**−**23** and the parent 2-arylperhydro-1,3-oxazine (**24**: log $K_0 = -0.15$).[2a] A positive c_s value indicates stabilization of the ring form, whereas a negative c_s value indicates destabilization caused by the substituents.

The data in Table 2 show that both the position of the annelated naphthalene ring and the steric arrangement of the diaryl substituents exert a substantial influence on the ring stabilities of naphthalene-condensed 1,3-oxazines. While naphth[1,2-*e*][1,3]oxazines bearing *trans*-1,3-diaryl substituents (**1B**) could be characterized by a high value of c_s (0.68),[3] the relative ring stability parameters for the corresponding *trans*-2,4-diarylnaphth[2,1-*e*][1,3]oxazines had negative values (**17B**−**23B**: $c_s = -0.18$ to $+0.03$),

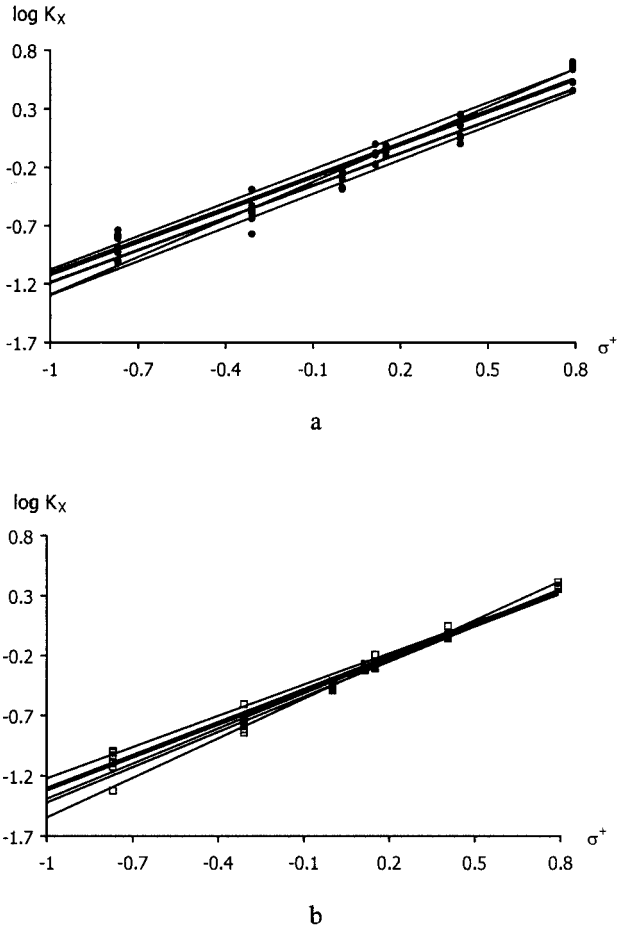
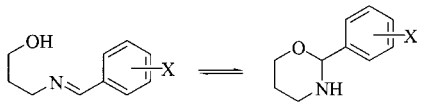


Figure 2. a: Plots of log K_X for **17**−**23B** (filled circles) vs. Hammett-Brown parameter σ^+; b: plots of log K_X for **17**−**23C** (open squares) vs. Hammett-Brown parameter σ^+

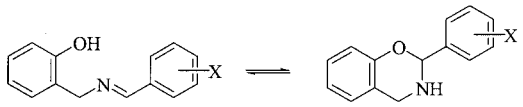
which means considerably less stable cyclic forms for the latter compounds. Such a great difference in the values of c_s was not observed for the *cis* regioisomers (**1C**: $c_s = -0.19$; **17C**−**23C**: $c_s = -0.30$ to -0.21). The smaller differences between the values of c_s for the *trans* and *cis* series of **17**−**23** than that found for the regioisomeric **1** indicate that the ring stabilities of 2,4-diarylnaphth[2,1-*e*][1,3]oxazines are less sensitive to the steric arrangement of the substituents.

While the inductive effect of substituent Y (characterized by substituent parameter σ_F) has been found to be signifi-

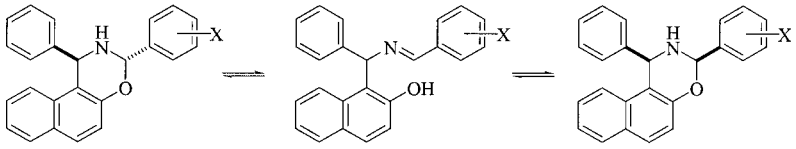
Table 2. Linear regression data on compounds **17**−**23** and the parent oxazines **1**, **24** and **25**



24A **24B**



25A **25B**



1B **1A** **1C**

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a]	Correlation coeff.	c_s[b]
17A ⇌ **17B**	7	0.95(5)	−0.12(7)	0.992	0.03
17A ⇌ **17C**	7	0.97(4)	−0.45(6)	0.994	−0.30
18A ⇌ **18B**	7	1.07(4)	−0.22(4)	0.997	−0.07
18A ⇌ **18C**	7	1.09(3)	−0.45(4)	0.998	−0.30
19A ⇌ **19B**	7	0.93(9)	−0.18(11)	0.977	−0.03
19A ⇌ **19C**	7	0.91(6)	−0.41(7)	0.988	−0.26
20A ⇌ **20B**	7	0.93(8)	−0.20(10)	0.981	−0.05
20A ⇌ **20C**	7	0.91(5)	−0.39(6)	0.991	−0.24
21A ⇌ **21B**	7	0.92(8)	−0.27(9)	0.981	−0.12
21A ⇌ **21C**	7	0.90(4)	−0.40(5)	0.994	−0.25
22A ⇌ **22B**	7	0.97(8)	−0.33(9)	0.984	−0.18
22A ⇌ **22C**	7	0.97(9)	−0.42(11)	0.994	−0.27
23A ⇌ **23B**	7	0.92(6)	−0.26(7)	0.991	−0.11
23A ⇌ **23C**	7	0.86(4)	−0.36(5)	0.994	−0.21
24A ⇌ **24B**[c]	7	0.74(6)	−0.15(5)	0.984	0
25A ⇌ **25B**[c]	7	0.82(4)	−0.66(3)	0.995	−0.51
1A ⇌ **1B**[d]	7	0.92(6)	0.53(13)	0.988	0.68
1A ⇌ **1C**[d]	6	0.98(9)	−0.34(10)	0.983	−0.19

[a] Standard deviations are given in parentheses. [b] Relative ring stability constant: see the text. [c] Data from ref.[2a] [d] Data from ref.[3]

cant for the tautomeric equilibrium constant according to Equation (2) for the 1,3-diaryl-substituted naphthoxazines (**1**), our aim was to study the applicability of Equations (2) and (3) to the present model compounds **19**−**23**. The significance level was taken as 0.05. The linear regression analysis of Equations (2) and (3) in Table 3 show that the *trans*-chain (**B** ⇌ **A**) equilibrium constants are significantly influenced by the inductive effect (σ_F) of substituent Y on the 4-phenyl ring.

$$\log K = k + \rho_F^Y\sigma_F^Y + \rho_R^Y\sigma_R^Y + \rho_F^X\sigma_F^X + \rho_R^X\sigma_R^X \quad (3)$$

Table 3. Multiple linear regression analysis of log *K* values for **19**−**23**

		k	ρ_F^Y	ρ_R^Y	ρ^X	ρ_F^X	ρ_R^X	r
Acc. to Equation (2)	**19**−**23A** ⇌ **19**−**23B**	−0.44	0.28	−[a]	1.29			0.971
	19−**23A** ⇌ **19**−**23C**	−0.58	−[a]	−[a]	1.27			0.965
Acc. to Equation (3)	**19**−**23A** ⇌ **19**−**23B**	−0.46	0.25	−[a]		1.15	1.62	0.984
	19−**23A** ⇌ **19**−**23C**	−0.58	−[a]	−[a]		1.05	1.66	0.976

[a] Insignificant (significance value > 0.05).

The validity of the parameters of Equations (2) and (3) was checked by means of regression analysis of the log $K_{calcd.}$ values [calculated by applying the parameters of Equation (2) or (3)] against log K determined from the ^{1}H NMR spectra (Figure 3).

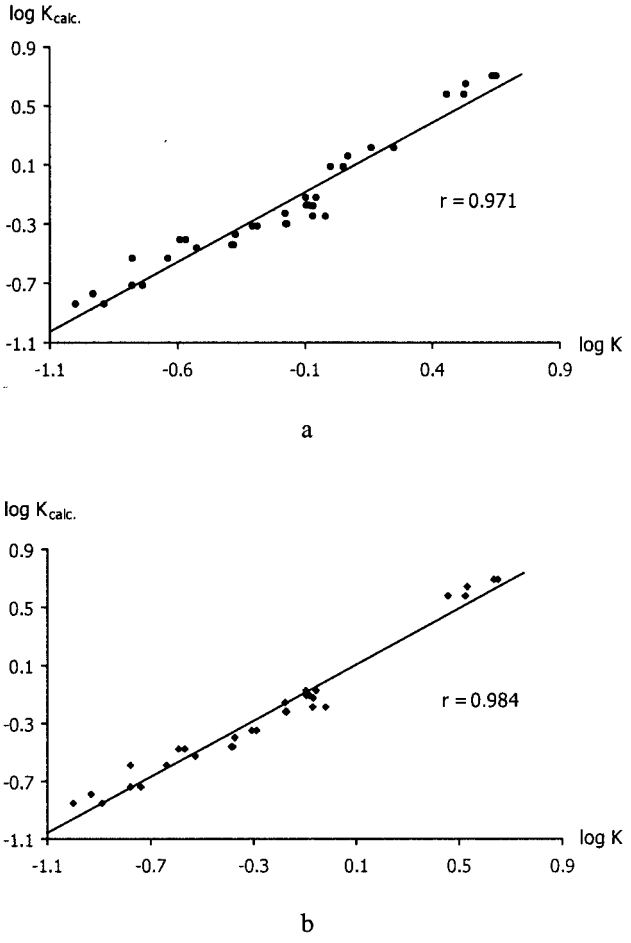


Figure 3. a: Plots of log $K_{calcd.}$ [calculated by applying Equation (2)] vs. log K (experimental) for **19**−**23B**, b: plots of log $K_{calcd.}$ [calculated by applying Equation (3)] vs. log K (experimental) for **19**−**23B**

The double substituent dependence of log K for the *trans*-chain equilibria is related to the relative configurations of C-2 and C-4 and thereby the spatiality of the model compound. This observation is in accordance with the concept of the stereoelectronically mediated substituent effect.[6] The present results are in harmony with those found for the ring-chain tautomerism of 1,3-diarylnaphth[1,2-*e*][1,3]oxazines (**1**).[6b] The positive value of ρ_F^Y (0.27) shows that aromatic ring substituents not attached to a phenyl ring situated between two heteroatoms can also have a systematic effect on the proportions of the ring tautomers. It can be concluded that equilibrium **B** ⇌ **A** seems to be somewhat more sensitive to both substitution X and substitution Y than is equilibrium **C** ⇌ **A**. These substituent effects can be explained in terms of a stereoelectronic effect related to the relative configuration of C-4.

As revealed by the results of the multiple linear regression analysis of Equation (3) (Table 3), both ρ_F^X (inductive) and ρ_R^X (resonance) are positive, i.e. both the inductive and resonance effects of electron-withdrawing substituents increase the proportion of the ring form. The origin of this effect is nowadays understood and is known as *the normal behaviour of the substituent dependence of ring-chain equilibria*.[12]

Conclusion

Betti's classical Mannich aminoalkylation was used to prepare new 2-(α-aminobenzyl)-1-naphthol derivatives ("reverse Betti bases"). The ring-closure reactions of these aminonaphthols with equivalent amounts of aromatic aldehydes yielded 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*]-[1,3]oxazines, which exist as three-component tautomeric mixtures containing major (**B**) and minor (**C**) ring-closed epimeric forms as well as the open-chain form (**A**) in $CDCl_3$ at 300 K, and they proved to be good model compounds for the study of double substituent influences on tautomeric equilibria. Systematic quantitative investigation of the ring-chain tautomeric equilibria of 2,4-diarylnaphth[2,1-*e*][1,3]oxazines indicated that the electron-withdrawing substituent X on a phenyl ring attached to a carbon atom situated between the heteroatoms increases the proportion of the ring tautomer inductively and by resonance. On the other hand, electron-withdrawing substituents on the 4-phenyl ring have an analogous inductive influence on the *trans*-chain (**B** ⇌ **A**) tautomeric equilibria.

Experimental Section

General Remarks: ^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.03 MHz) spectra were recorded at 300 K. Chemical shifts are given in δ (ppm) relative to TMS as internal standard. For the equilibria to be established in the tautomeric compounds, the samples were dissolved in $CDCl_3$ and the solutions were allowed to stand at ambient temperature for 1 d before the ^{1}H NMR spectra were run. The number of scans was usually 32. Standard 2D NMR measurements (COSY, NOESY, HSQC and HMBC) were used for assignments.

Statistical Calculations: The sources of the substituent constants were as follows: σ^+, ref.[13b]; σ_F and σ_R, ref.[13a] (except for σ_F and σ_R for Br, ref.[13b]). Linear regression analyses were performed using the SPSS 9.0 statistical program package.[14]

General Method for the Synthesis of 2-[Amino-(X-substituted-phenyl)methyl]-1-naphthol Hydrochlorides (10−16): The appropriate aromatic aldehyde (0.1 mol; freshly distilled if liquid) and 25% methanolic ammonia solution (5 mL) were added to a solution of 1-naphthol (**2**, 7.2 g, 0.05 mol) in absolute MeOH (40 mL). The mixture was left to stand at ambient temperature for 2 d, during which a crystalline (**3**−**6**) or oily product (**7**−**9**) separated. The crystalline product (**3**−**6**) was filtered off and washed with cold MeOH (2 × 50 mL). In the event of an oily product (**7**−**9**), the solvent was decanted, successive portions of MeOH (3 × 20 mL) were added and decanted and the excess of MeOH was evaporated. To the crude oily or crystalline naphthoxazines **3**−**9**, 20% hydro-

Table 4. Physical data of naphth[2,1-*e*][1,3]oxazines **17**−**23**

Compound	M.p. [°C]	Yield [%]	Empirical formula	Formula mass	δ[N=C*H* (**A**)]	δ[N−C*H*−O (**B**)]	δ[N−C*H*−O (**C**)]
17a	273−274[a]	85	$C_{24}H_{17}N_3O_5$	427.42	8.73(s)	5.77(s)	6.18(s)
17b	137−138[a]	82	$C_{24}H_{17}BrN_2O_3$	461.32	8.54(s)	5.65(s)	6.07(s)
17c	128−129[b]	61	$C_{24}H_{17}BrN_2O_3$	461.32	8.57(s)	5.84(s)	6.06(s)
17d	137−138[a]	83	$C_{24}H_{17}ClN_2O_3$	416.87	8.56(s)	5.67(s)	6.08(s)
17e	110−111[b]	76	$C_{24}H_{18}N_2O_3$	382.42	8.60(s)	5.70(s)	6.11(s)
17f	132−133[a]	68	$C_{25}H_{20}N_2O_3$	396.45	8.72(s)	5.76(s)	6.10(s)
17g	111−113[b]	44	$C_{25}H_{20}N_2O_4$	412.45	8.66(s)	5.62(s)	6.33(s)
18a	161−162[a]	81	$C_{24}H_{17}BrN_2O_3$	461.32	8.82(s)	5.86(s)	6.33(s)
18b	113−114[a]	78	$C_{24}H_{17}Br_2NO$	495.22	8.45(s)	5.72(s)	6.02(s)
18c	96−97[b]	66	$C_{24}H_{17}Br_2NO$	495.22	8.46(s)	5.71(s)	6.02(s)
18d	111−112[b]	80	$C_{24}H_{17}BrClNO$	450.77	8.45(s)	5.72(s)	6.02(s)
18e	61−62[b]	74	$C_{24}H_{18}BrNO$	416.32	8.50(s)	5.77(s)	6.06(s)
18f	123−125[b]	78	$C_{25}H_{20}BrNO$	430.35	8.44(s)	5.73(s)	6.03(s)
18g	66−67[b]	58	$C_{25}H_{20}BrNO_2$	446.35	8.41(s)	5.72(s)	6.02(s)
19a	173−174[a]	68	$C_{24}H_{17}BrN_2O_3$	461.32	8.63(s)	5.80(s)	6.14(s)
19b	167−169[a]	72	$C_{24}H_{17}Br_2NO$	495.22	8.47(s)	5.73(s)	6.04(s)
19c	131−133[b]	70	$C_{24}H_{17}Br_2NO$	495.22	8.44(s)	5.68(s)	6.00(s)
19d	153−154[b]	65	$C_{24}H_{17}BrClNO$	450.77	8.47(s)	5.72(s)	6.04(s)
19e	117−119[b]	69	$C_{24}H_{18}BrNO$	416.32	8.50(s)	5.73(s)	6.07(s)
19f	135−136[b]	64	$C_{25}H_{20}BrNO$	430.35	8.44(s)	5.72(s)	6.03(s)
19g	oil	78	$C_{25}H_{20}BrNO_2$	446.35	8.42(s)	5.70(s)	6.02(s)
20a	153−155[a]	73	$C_{24}H_{17}ClN_2O_3$	416.86	8.64(s)	5.82(s)	6.15(s)
20b	121−123[a]	71	$C_{24}H_{17}BrClNO$	450.76	8.45(s)	5.73(s)	6.04(s)
20c	127−129[b]	68	$C_{24}H_{17}BrClNO$	450.76	8.44(s)	5.71(s)	6.01(s)
20d	139−141[b]	76	$C_{24}H_{17}Cl_2NO$	406.31	8.44(s)	5.71(s)	6.07(s)
20e	126−127[b]	73	$C_{24}H_{18}ClNO$	371.86	8.49(s)	5.73(s)	6.06(s)
20f	118−119[b]	74	$C_{25}H_{20}ClNO$	385.89	8.44(s)	5.71(s)	6.04(s)
20g	oil	80	$C_{25}H_{20}ClNO_2$	401.89	8.41(s)	5.73(s)	6.07(s)
21a	145−146[a]	65	$C_{24}H_{18}N_2O_3$	382.41	8.65(s)	5.90(s)	6.17(s)
21b	121−122[b]	86	$C_{24}H_{18}BrNO$	416.31	8.48(s)	5.78(s)	6.04(s)
21c	oil	92	$C_{24}H_{18}BrNO$	416.31	8.48(s)	5.71(s)	6.02(s)
21d	105−106[b]	65	$C_{24}H_{18}ClNO$	371.86	8.46(s)	5.79(s)	6.05(s)
21e	oil	85	$C_{24}H_{19}NO$	337.42	8.52(s)	5.83(s)	6.10(s)
21f	139−141[b]	54	$C_{25}H_{21}NO$	351.44	8.45(s)	5.80(s)	6.06(s)
21g	133−134[b]	46	$C_{25}H_{21}NO_2$	367.44	8.39(s)	5.78(s)	6.04(s)
22a	169−170[a]	79	$C_{25}H_{20}N_2O_3$	396.44	8.59(s)	5.88(s)	6.13(s)
22b	140−141[a]	66	$C_{25}H_{20}BrNO$	430.34	8.32(s)	5.78(s)	6.05(s)
22c	97−99[b]	60	$C_{25}H_{20}BrNO$	430.34	8.47(s)	5.72(s)	6.08(s)
22d	oil	89	$C_{25}H_{20}ClNO$	385.89	8.44(s)	5.80(s)	6.04(s)
22e	oil	93	$C_{25}H_{21}NO$	351.44	8.48(s)	5.78(s)	6.08(s)
22f	oil	91	$C_{26}H_{23}NO$	365.47	8.36(s)	5.73(s)	5.97(s)
22g	oil	86	$C_{26}H_{23}NO_2$	381.47	8.30(s)	5.75(s)	5.98(s)
23a	106−108[b]	65	$C_{25}H_{20}N_2O_4$	412.44	8.61(s)	5.88(s)	6.14(s)
23b	80−81[b]	70	$C_{25}H_{20}BrNO_2$	446.34	8.42(s)	5.76(s)	6.03(s)
23c	116−118[b]	55	$C_{25}H_{20}BrNO_2$	446.34	8.46(s)	5.78(s)	6.04(s)
23d	110−111[b]	62	$C_{25}H_{20}ClNO_2$	401.89	8.46(s)	5.80(s)	6.05(s)
23e	oil	83	$C_{25}H_{21}NO_2$	367.44	8.50(s)	5.76(s)	6.02(s)
23f	oil	88	$C_{26}H_{23}NO_2$	381.47	8.45(s)	5.73(s)	6.10(s)
23g	oil	87	$C_{26}H_{23}NO_3$	397.47	8.41(s)	5.79(s)	6.05(s)

[a] Recrystallized from iPr_2O/EtOAc. [b] Recrystallized from iPr_2O.

chloric acid (100 mL) was added and the mixture was stirred and refluxed for 1 h. The solvent was evaporated and the oily residue was crystallized from EtOAc (100 mL). The crystalline product was filtered off, washed with EtOAc and recrystallized from a mixture of MeOH (10 mL) and Et_2O (100 mL).

2-(α-Amino-3-nitrobenzyl)-1-naphthol Hydrochloride (10): Yield 9.59 g (58%), m.p. 156−157 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 6.31 (s, 1 H, C*H*NH$_2$), 7.41−7.59 (m, 3 H, 4-H, 6-H, 7-H), 7.60−7.75 (m, 2 H, 3-H, 4′-H), 7.87 (dd, $^3J_{H,H}$ = 8.8, 4.0 Hz, 1 H, 5-H), 8.02 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 5′-H), 8.19 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, 3′-H), 8.35 (dd, $^3J_{H,H}$ = 8.8, 5.3 Hz, 1 H, 8-H), 8.46 (s, 1 H, 2′-H), 9.44 (br. s, 3 H, NH$_2$, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K): δ = 46.80 (*C*HNH$_2$), 118.86 (C-2), 120.36 (C-4), 122.33 (C-2′), 122.51 (C-8), 122.97 (C-4′), 124.69 (C-8a), 124.89 (C-3), 125.64 (C-7), 126.86 (C-6), 127.79 (C-5), 130.20 (C-5′), 134.36 (C-4a), 134.46 (C-6′), 140.49 (C-1′), 147.93 (C-3′), 150.21 (C-1) ppm.

2-(α-Amino-3-bromobenzyl)-1-naphthol Hydrochloride (11): Yield 9.48 g (52%), m.p. 158−159 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 6.14 (s, 1 H, C*H*NH$_2$), 7.36 (t, $^3J_{H,H}$ = 8.1 Hz, 1 H, 5′-H), 7.48−7.56 (m, 5 H, 4-H, 6-H, 7-H, 4′-H, 6′-H), 7.62 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 3-H), 7.78 (br. s, 1 H, 2′-H), 7.84−7.88 (m, 1 H, 5-H), 8.29−8.36 (m, 1 H, 8-H), 9.20 (br. s, 2 H, NH$_2$), 10.16 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K):

δ = 51.70 (*C*HNH$_2$), 118.81 (C-2), 120.26 (C-4), 121.70 (C-3′), 121.75 (C-3), 122.54 (C-8), 125.15 (C-8a), 125.51 (C-7), 126.45 (C-6), 126.71 (C-6′), 127.86 (C-5), 130.10 (C-2′), 130.83 (C-5′), 130.93 (C-4′), 133.98 (C-4a), 140.75 (C-1′), 149.87 (C-1) ppm.

2-(α-Amino-4-bromobenzyl)-1-naphthol Hydrochloride (12): Yield 8.57 g (47%), m.p. 117−119 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 6.13 (s, 1 H, C*H*NH$_2$), 7.46−7.55 (m, 5 H, 4-H, 6-H, 7-H, 2′-H), 7.57−7.65 (m, 3 H, 3-H, 3′-H), 7.82−7.88 (m, 1 H, 5-H), 8.31−8.37 (m, 1 H, 8-H), 9.24 (br. s, 2 H, NH$_2$), 10.18 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K): δ = 51.49 (*C*HNH$_2$), 119.12 (C-2), 120.21 (C-4), 121.17 (C-4′), 122.52 (C-8), 124.84 (C-3), 125.21 (C-8a), 125.48 (C-6), 126.64 (C-7), 127.81 (C-5), 129.77 (C-2′), 130.60 (C-6′), 131.44 (C-3′), 132.30 (C-5′), 133.96 (C-4a), 137.60 (C-1′), 149.83 (C-1) ppm.

2-(α-Amino-4-chlorobenzyl)-1-naphthol Hydrochloride (13): Yield 8.01 g (50%), m.p. 167−169 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 6.14 (s, 1 H, C*H*NH$_2$), 7.47 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2′-H), 7.49−7.58 (m, 5 H, 4-H, 6-H, 7-H, 3′-H), 7.60 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 3-H), 7.82−7.88 (m, 1 H, 5-H), 8.30−8.36 (m, 1 H, 8-H), 9.19 (br. s, 2 H, NH$_2$), 10.16 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K): δ = 51.33 (*C*HNH$_2$), 119.10 (C-2), 120.23 (C-4), 122.55 (C-8), 124.82 (C-3), 125.17 (C-8a), 125.64 (C-7), 126.67 (C-6), 127.90 (C-5), 128.77 (C-2′), 129.40 (C-5′), 129.41 (C-3′), 129.80 (C-6′), 132.71 (C-4a), 133.96 (C-4′), 137.15 (C-1′), 149.83 (C-1) ppm.

2-(α-Aminobenzyl)-1-naphthol Hydrochloride (14): Yield 8.14 g (57%), m.p. 171−174 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 6.14 (s, 1 H, C*H*NH$_2$), 7.34 (t, $^3J_{H,H}$ = 7.3 Hz, 1 H, 4′-H), 7.40 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, 3′-H), 7.47−7.58 (m, 5 H, 4-H, 6-H, 7-H, 2′-H), 7.60 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, 3-H), 7.82−7.88 (m, 1 H, 5-H), 8.30−8.37 (m, 1 H, 5-H), 9.13 (br. s, 2 H, NH$_2$), 10.14 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K): δ = 51.57 (*C*HNH$_2$), 119.43 (C-2), 120.06 (C-4), 122.47 (C-8), 124.68 (C-3), 125.17 (C-8a), 125.48 (C-6), 126.63 (C-7), 126.96 (C-5), 126.98 (C-2′), 128.11 (C-4′), 128.40 (C-6′), 128.60 (C-3′), 129.00 (C-5′), 133.90 (C-4a), 138.14 (C-1′), 149.77 (C-1) ppm.

2-(α-Amino-4-methylbenzyl)-1-naphthol Hydrochloride (15): Yield 8.24 g (55%), m.p. 165−166 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 2.27 (s, 3 H, Ar-C*H*$_3$), 6.12 (s, 1 H, C*H*NH$_2$), 7.19 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 3′-H), 7.43 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, 2′-H), 7.46−7.54 (m, 3 H, 4-H, 6-H, 7-H), 7.62 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 3-H), 7.81−7.87 (m, 1 H, 5-H), 8.32−8.38 (m, 1 H, 8-H), 9.14 (br. s, 2 H, NH$_2$), 10.12 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K): δ = 20.63 (Ar-*C*H$_3$), 51.52 (*C*HNH$_2$), 119.76 (C-2), 120.14 (C-4), 122.65 (C-8), 125.05 (C-3), 125.28 (C-8a), 125.40 (C-6), 126.57 (C-7), 127.38 (C-2′), 127.86 (C-5), 128.30 (C-6′), 129.33 (C-3′), 129.70 (C-5′), 133.88 (C-4a), 135.29 (C-4′), 137.28 (C-1′), 149.72 (C-1) ppm.

2-(α-Amino-4-methoxybenzyl)-1-naphthol Hydrochloride (16): Yield 9.47 g (60%), m.p. 168−169 °C. ^{1}H NMR (400.13 MHz, DMSO, 300 K): δ = 3.73 (s, 3 H, OC*H*$_3$), 6.31 (s, 1 H, C*H*NH$_2$), 6.95 (d, $^3J_{H,H}$ = 7.6 Hz, 2 H, 3′-H), 7.47 (d, $^3J_{H,H}$ = 8.8 Hz, 2 H, 2′-H), 7.49−7.53 (m, 3 H, 4-H, 6-H, 7-H), 7.64 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H, 3-H), 7.81−7.88 (m, 1 H, 5-H), 8.31−8.38 (m, 1 H, 8-H), 9.10 (br. s, 2 H, NH$_2$), 10.09 (br. s, 1 H, OH) ppm. ^{13}C NMR (100.03 MHz, DMSO, 300 K): δ = 51.30 (*C*HNH$_2$), 55.16 (O*C*H$_3$), 113.93 (C-3′), 114.60 (C-5′), 119.81 (C-2), 120.18 (C-4), 122.57 (C-8), 124.92 (C-3), 125.24 (C-8a), 125.36 (C-6), 126.49 (C-7), 127.84 (C-5), 128.98 (C-2′), 129.40 (C-6′), 130.13 (C-4a), 133.81 (C-1′), 149.58 (C-1), 158.90 (C-4′) ppm.

General Method for the Synthesis of 2,4-Diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines 17−23: Et$_3$N (0.11 g, 1.1 mmol) and an equivalent amount of aromatic aldehyde (freshly distilled if liquid) were added to a solution of the appropriate aminonaphthol hydrochloride (**10**−**16**, 1 mmol) in absolute MeOH (20 mL). The mixture was left to stand at ambient temperature for 24 h. Any crystalline product was then filtered off, washed with MeOH and recrystallized (Table 4). In the event of an oily product, the solvent was evaporated and the residue was partitioned between H$_2$O and CHCl$_3$ (10 mL each). The separated organic layer was dried with Na$_2$SO$_4$ and the solvent was then evaporated. The oily product was dried in a vacuum desiccator for 24 h. The NMR spectra proved that the purities of these compounds were greater than 95%. All the new compounds gave satisfactory data on elemental analysis (C, H, N ±0.3%). The physical data on compounds **17**−**23** are listed in Table 4.

17g: Mixture of Schiff base (80%), *cis*-ring form (5%) and *trans*-ring form (15%). Selected signals: ^{1}H NMR (CDCl$_3$, 300 K): δ = 5.42 (br. s, 1 H, 4-H, *trans*), 5.62 (br. s, 1 H, 2-H, *trans*), 5.80 (br. s, 1 H, 2-H, *cis*), 6.14 (br. s, 1 H, 4-H, *cis*), 6.34 (s, 1 H, NphC*H*ArNH, Schiff base), 8.66 (s, 1 H, NH=C*H*Ar, Schiff base) ppm. ^{13}C NMR (CDCl$_3$, 300 K): δ = 54.30 (C-4, *trans*), 84.00 (C-2, *trans*), 71.70 (Nph*C*HArNH, Schiff base), 162.70 (NH=*C*HAr, Schiff base) ppm. Assignments of the carbon atoms in the *cis*-ring form could not be made owing to the low concentration.

18a: Mixture of Schiff base (12%), *cis*-ring form (31%) and *trans*-ring form (57%). Selected signals: ^{1}H NMR (CDCl$_3$, 300 K): δ = 5.29 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, 4-H, *trans*), 5.65 (d, $^3J_{H,H}$ = 10.3 Hz, 1 H, 4-H, *cis*), 5.86 (d, $^3J_{H,H}$ = 12.6 Hz, 1 H, 2-H, *trans*), 6.33 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, 2-H, *cis*), 6.37 (s, 1 H, NphC*H*ArNH, Schiff base), 8.82 (s, 1 H, NH=C*H*Ar, Schiff base) ppm. ^{13}C NMR (CDCl$_3$, 300 K) 54.20 (C-4, *trans*), 82.90 (C-2, *trans*), 58.60 (C-4, *cis*), 86.80 (C-2, *cis*), 70.80 (Nph*C*HArNH, Schiff base), 161.00 (NH=*C*HAr, Schiff base) ppm.

Acknowledgments

The authors thank the Hungarian Research Foundation (OTKA no. TS04888) for financial support.

[1] R. E. Valters, F. Fülöp, D. Korbonits, *Adv. Heterocycl. Chem.* **1996**, *66*, 1−71.
[2] [2a] F. Fülöp, K. Pihlaja, J. Mattinen, G. Bernáth, *J. Org. Chem.* **1987**, *52*, 3821−3825. [2b] L. Lázár, F. Fülöp, *Eur. J. Org. Chem.* **2003**, 3025−3042.
[3] I. Szatmári, T. A. Martinek, L. Lázár, F. Fülöp, *Tetrahedron* **2003**, *59*, 2877−2884.
[4] B. L. Milman, A. A. Potekhin, *Khim. Get. Soedin.* **1973**, 902−907.
[5] A. Göblyös, L. Lázár, F. Evanics, F. Fülöp, *Heterocycles* **1999**, *51*, 2431−2438.
[6] [6a] A. Hetényi, T. A. Martinek, L. Lázár, Z. Zalán, F. Fülöp, *J. Org. Chem.* **2003**, *68*, 5705−5712. [6b] I. Szatmári, T. A. Martinek, L. Lázár, A. Koch, E. Kleinpeter, K. Neuvonen, F. Fülöp, *J. Org. Chem.*, in press
[7] M. Betti, *Org. Synth. Coll. Vol.* **1941**, *1*, 381−383.
[8] [8a] A. Hassner, N. H. Cromwell, S. J. Davis, *J. Am. Chem. Soc.* **1957**, *79*, 230−234. [8b] P. Hanumanthu, C. V. Ratman, *Indian J. Chem.* **1977**, *15B*, 1019−1021. [8c] H. Möhrle, K. Tröster, *Arch. Pharm.* **1982**, *315*, 222−227. [8d] A. R. Katritzky, X. Lan, J. N. Lam, *Chem. Ber.* **1991**, *124*, 1809−1817.
[9] [9a] S. M. Ansari, W. Robien, M. Schlederer, P. Wolscham, *Monatsh. Chem.* **1989**, *120*, 1003−1014. [9b] S. Talukdar, A. Banerji, *J. Org. Chem.* **1998**, *63*, 3468−3470. [9c] Y-J. Chen, C-S. Ge,

D. Wang, *Synlett* **2000**, *10*, 1429−1432. [9d] T. Huang, C-J. Li, *Tetrahedron Lett.* **2000**, *41*, 6715−6719.
[10] [10a] H-J. Grumbach, M. Arend, N. Risch, *Synthesis* **1996**, 883−887. [10b] M. R. Saidi, N. Azizi, M. R. Naimi-Jamal, *Tetrahedron Lett.* **2001**, *42*, 8111−8113.
[11] C. Cimarelli, A. Mazzanti, G. Palmieri, E. Volpini, *J. Org. Chem.* **2001**, *66*, 4759−4765.
[12] K. Neuvonen, F. Fülöp, H. Neuvonen, A. Koch, E. Kleinpeter, K. Pihlaja, *J. Org. Chem.* **2001**, *66*, 4132−4140.
[13] [13a] R. W. Taft, R. D. Topsom, *Prog. Phys. Org. Chem.* **1987**, *16*, 1−83. [13b] C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* **1991**, *91*, 165−195.
[14] SPSS Advanced Models 9.0, SPSS Inc.
Received November 29, 2003

