Syntheses and Transformations of α-Aminobenzylnaphthol Derivatives

PhD Thesis

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ANNEX

I.

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TETRAHEDRON

Substituent effects in the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines

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Abstract—Condensation of Betti base analogue amino naphthols with substituted benzaldehydes led to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**3**–**9**) which proved to be three-component (r^1–o–r^2) tautomeric mixtures in $CDCl_3$ at 300 K. The electronic effects of the 3-aryl groups on the ratios of the ring-chain tautomeric forms at equilibrium could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$. The value of the intercept was found to be strongly influenced by the steric arrangement of the 1,3-diaryl substituents. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

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 the saturated 1,3-*X*,*N* heterocycles whose ring-chain tautomerism has been studied most thoroughly.[2] The tautomeric character of 1,3-*O*,*N* heterocycles offers a great number of synthetic possibilities, e.g. they can be used as intermediates in the synthesis of *N*-substituted amino alcohols[3] or nitrogen-bridged heterocyclic systems[4] and they serve as aldehyde sources in carbon transfer reactions.[5]

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

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

In contrast with the great number of studies on the dependence of the tautomeric equilibria of tetrahydro-1,3-oxazines on the aromatic substituent at position 2, less is known on the effects of such substituents at other positions. The investigation of ring-chain tautomeric 2-aryltetrahydro-1,3-oxazines bearing a substituted phenyl group at position 4 or 6 showed that the substituent on the 4/6-phenyl group does not exert a significant influence on the parameters in Eq. (1). However, the presence of the aryl group itself stabilized the cyclic tautomer, more significantly at position 4 than at position 6.[6] The influence of the electronic character of a substituted phenyl group attached at a position other than 2 was found to be more pronounced in the ring-chain tautomeric equilibria of analogous 1,3,4-*O*,*N*,*N* or-1,3-*N*,*N* ring systems. For 4-aryl-2,2-dialkyl-substituted 1,3,4-oxadiazines, the electron-withdrawing groups on the 4-phenyl ring increased the proportions of the ring-closed tautomers.[7] In the ring-chain equilibria of 1,2-diarylimidazolidines, the 2-aryl substituent dependence of which was observed to follow Eq. (1), electron-donating substituents on the 1-phenyl ring produced higher values of ρ.[8]

Our present aim was to study the substituent effects on the ring-chain tautomerism of naphthalene-condensed 1,3-oxazine derivatives bearing aryl groups at positions 2 and 4, with the aims of a refinement of the scope and limitations of application of Eq. (1) among six-membered 1,3-*O*,*N* heterocycles, and a quantitative characterization of the effects of both aryl substituents on the ring-chain equilibria.

2. Results and discussion

Betti's classical procedure, a Mannich-type aminoalkylation reaction of 2-naphthol,[9] was applied to prepare the starting materials for the synthesis of the present target compounds. Condensation of 2-naphthol (**1**) and benzaldehyde or substituted benzaldehydes in the presence of ammonia,

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Keywords: amino alcohols; oxazines; substituent effects; tautomerism.

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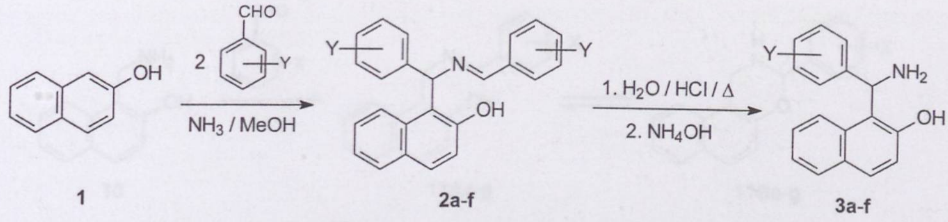


Y = NO_2(*m*): (57%) **a**, Br(*m*): (47%) **b**, Cl(*p*): (53%) **c**, H: (56%) **d**, Me(*p*): (71%) **e**, OMe(*p*): (45%) **f**

Scheme 1.

and subsequent acidic hydrolysis, gave amino naphthols **3a–f** in good yields (Scheme 1). The potential utility of the Mannich-type phenolic bases makes the aminoalkylation reaction of naphthol derivatives a subject of current chemical interest.[10] For example, the enantiomers of Betti base **3d** and its *N*-substituted derivatives were found to be potent chiral catalysts in additions of dialkylzincs to aldehydes,[11] and this contributed to the enhanced attention recently paid to the preparation of chiral *N*-substituted amino naphthol derivatives.[12]

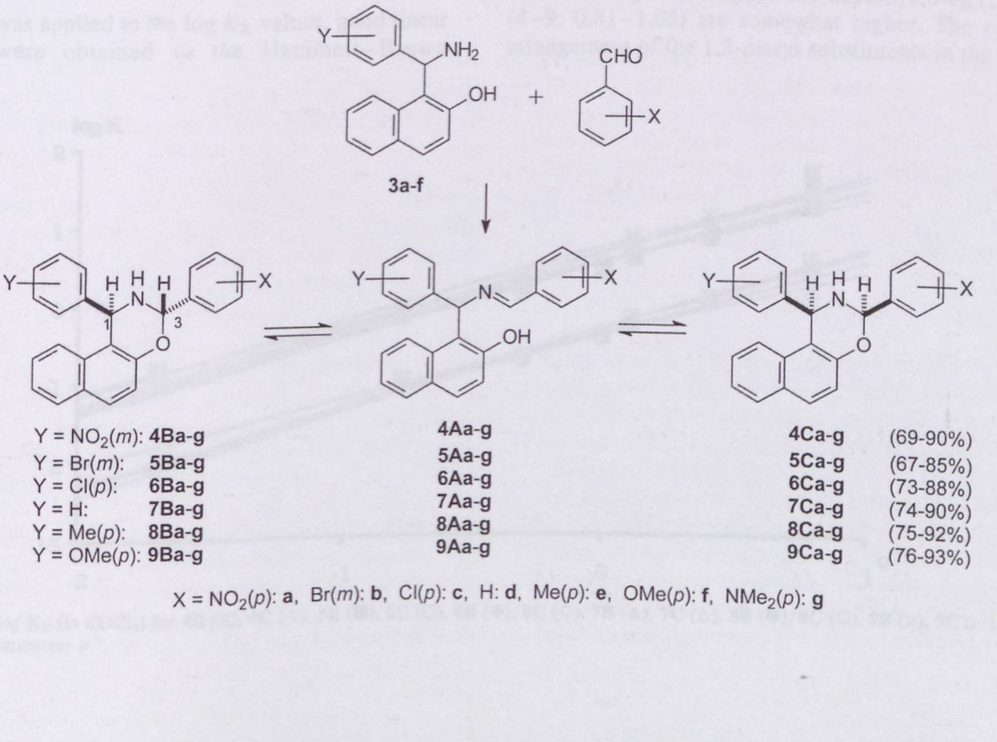
Condensations of amino naphthols **3a–f** with equivalent amounts of aromatic aldehydes resulted in naphthoxazine model compounds **4–9** as crystalline products (Scheme 2). The ^{1}H NMR spectra of **4–9** revealed that, in $CDCl_3$ solution at 300 K, the **a–f** members of each set of compounds **4–9** participated in three-component ring-chain tautomeric equilibria containing C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**). For the 3-(*p*-dimethylaminophenyl)-substituted derivatives (**4g–9g**), the tautomeric equilibria contained only one ring-closed form (**B**).

The intermediate of the Betti reaction was earlier presumed to have a ring-chain tautomeric character.[13] By condensation of the Betti base with aromatic aldehydes, Smith and Cooper prepared 1-phenyl-3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines, and studied their ring-chain tautomeric equilibria by means of 60 MHz ^{1}H NMR.[13a] They made the assumption that 1,3-diaryl groups prefer pseudoequatorial and therefore a *cis* arrangement in the *major* ring-closed tautomer. In contrast with this assumption, and the *cis* position of the diaryl groups found for the *major* ring-closed tautomers in both 2,4- and 2,6-diaryl-perhydro-1,3-oxazines,[6] the NOESY spectra of **6a** unequivocally showed that the *major* ring forms in all tautomeric equilibria (**4–9**) contain the 1,3-diaryl substituents in the *trans* position (**B**).

To characterize the effects of the aryl substituent at position 1 on the tautomeric character of this ring system, 1-unsubstituted 3-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**11**) were also prepared from the readily available[14] 1-aminomethyl-2-naphthol (**10**) and aromatic aldehydes. In $CDCl_3$ at 300 K, **11a–g** proved to participate in ring-chain tautomeric equilibria (Scheme 3).

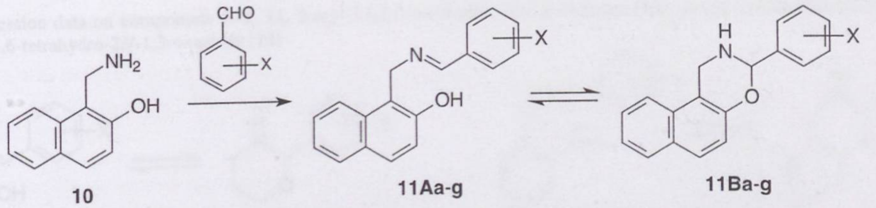
The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equilibria of **4–9** and **11** (K_X) were determined by integration of the well-separated O–C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets or doublets (Table 3) in the ^{1}H NMR spectra (Table 1).

In consequence of the very similar NMR spectroscopic



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.



10 11Aa-g 11Ba-g

X = NO_2(*p*): (72%) **a**, Br(*m*): (83%) **b**, Cl(*p*): (78%) **c**, H: (85%) **d**, Me(*p*): (75%) **e**,
OMe(*p*): (80%) **f**, NMe_2(*p*): (77%) **g**

Scheme 3.

Table 1. Proportions (%) of the ring-closed tautomeric forms (**B** and **C**) in tautomeric equilibria for compounds **4–9** and **11** ($CDCl_3$, 300 K)

Compound	X	σ^+	**4** (Y=*m*NO_2), 0.73		**5** (Y=*m*Br), 0.405		**6** (Y=*p*Cl), 0.114		**7** (Y=H), 0		**8** (Y=*p*Me), −0.311		**9** (Y=*p*OMe), −0.778		**11**, –
			B	**C**	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**	**B**	**C**	**B**
a	*p*NO_2	0.79	89.0	8.3	90.9	7.0	93.6	3.6	86.1	10.8	89.0	7.6	88.5	8.3	95.2
b	*m*Br	0.405	85.2	8.1	82.0	9.5	82.0	9.4	79.5	10.6	76.7	11.3	79.5	10.0	88.0
c	*p*Cl	0.114	80.1	7.5	77.3	8.6	76.6	8.4	72.4	9.7	71.7	9.3	72.8	9.1	79.4
d	H	0	73.6	7.9	68.0	8.4	70.1	7.8	64.4	9.3	63.6	8.7	62.2	8.2	72.3
e	*p*Me	−0.311	63.6	6.3	57.3	6.6	60.0	6.1	52.6	7.7	50.9	6.8	53.2	6.6	58.3
f	*p*OMe	−0.778	47.7	3.7	42.1	5.4	43.5	4.6	37.8	5.9	36.6	4.7	38.1	5.4	45.4
g	*p*NMe_2	−1.7	13.3	~0	9.8	~0	10.2	~0	10.4	~0	9.0	~0	8.6	~0	10.3

characteristics of 1,3-diaryl-2,3-dihydro-2*H*-naphth[1,2-*e*]-[1,3]oxazines **4–9**, determination of the relative configurations of the *major* and *minor* ring-closed tautomers was performed only for **6a**. Data on **6a**, **9g** and **11f** were chosen to illustrate the ^1H NMR spectra of the prepared tautomeric compounds (see Experimental). 1,2-Diaryl substituents did not change the sequence of the chemical shifts of the characteristic O–C*H*Ar-N and N=C*H*Ar protons. The configuration of the azomethine double bond was found to be *E*, according to the NOE interaction observed between the Nph–C*H*Ar-N and N=C*H*Ar protons.

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 3-phenyl group for **4–9** and **11** (Figure 1 and Table 2).

The linear regression analysis data in Table 2 show that, as is customary among 2-aryl-1,3-*O*,*N* heterocycles,[1,2] the value of ρ is positive in each case, i.e. electron-withdrawing substituents on the 3-phenyl ring favour the ring-closed tautomer. While the value of ρ for 1-unsubstituted 3-aryl-2,3-dihydro-2*H*-naphth[1,2-*e*][1,3]oxazines (**11**: 0.81) is the same (within experimental error) as that for the parent 2-arylperhydro-1,3-oxazines (**12**: 0.76), the values of ρ for 1,3-diaryl-2,3-dihydro-2*H*-naphth[1,2-*e*][1,3]oxazines (**4–9**: 0.81–1.05) are somewhat higher. The *cis* or *trans* arrangement of the 1,3-diaryl substituents in the ring forms

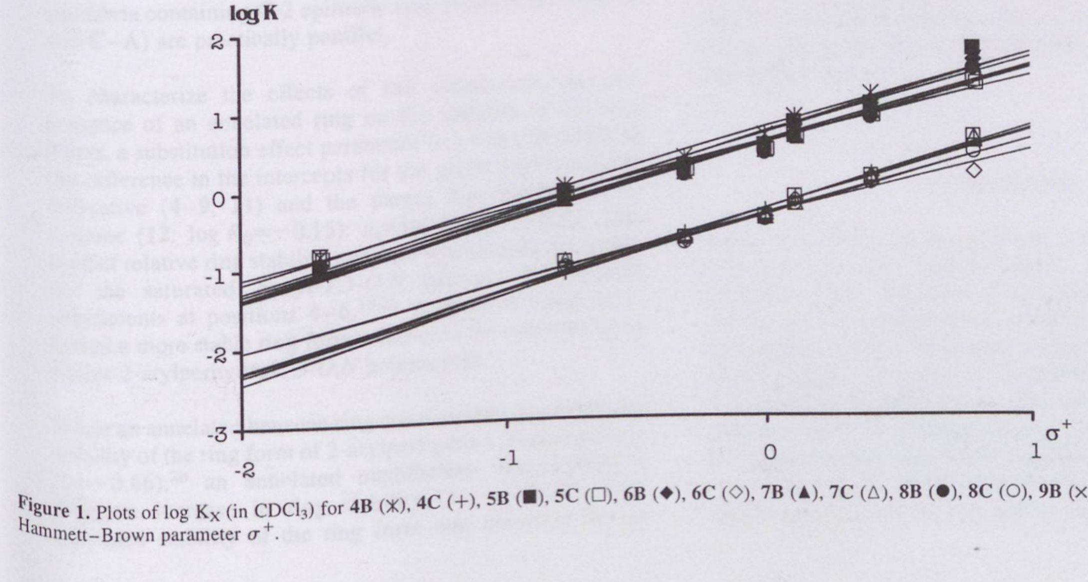
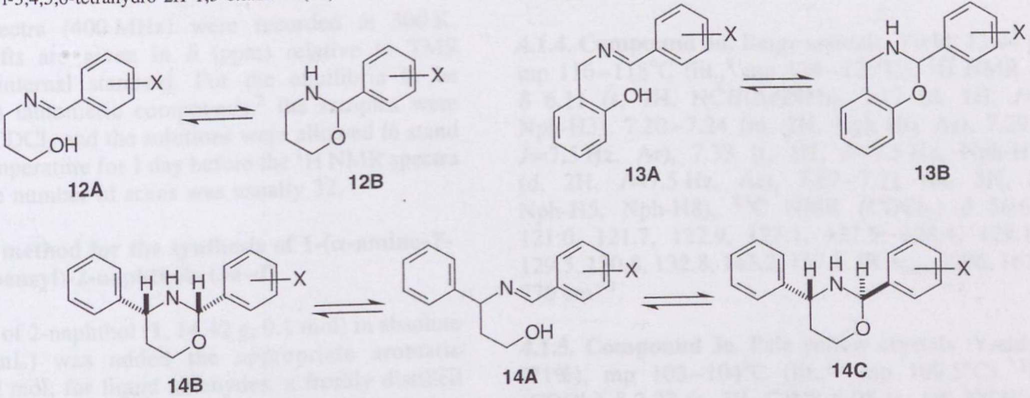


Figure 1. Plots of log K_X (in $CDCl_3$) for **4B** (⋇), **4C** (+), **5B** (■), **5C** (□), **6B** (◆), **6C** (◇), **7B** (▲), **7C** (△), **8B** (●), **8C** (○), **9B** (×), **9C** (−), **11B** (❐) vs Hammett–Brown parameter σ^+.

Table 2. Linear regression data on compounds **4–9**, **11**, 2-aryl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**12**), 2-aryl-3,4-dihydro-2*H*-1,3-benzoxazines (**13**) and 2-aryl-4-phenyl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**14**)


12A **12B** **13A** **13B** **14B** **14A** **14C**

$X = NO_2(p),\ NO_2(m),\ Cl(m),\ Cl(p),\ H,\ Me(p),\ OMe(p),\ NMe_2(p)$

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a]	Correlation coefficient	c[b]
4A⇌**4B**	7	0.93 (4)	0.70 (8)	0.995	0.85
4A⇌**4C**	6	1.04 (2)	−0.33 (2)	0.999	−0.18
5A⇌**5B**	7	1.00 (8)	0.64 (15)	0.985	0.79
5A⇌**5C**	6	1.01 (9)	−0.33 (10)	0.985	−0.18
6A⇌**6B**	7	0.96 (5)	0.62 (10)	0.993	0.77
6A⇌**6C**	6	0.81 (8)	−0.42 (10)	0.979	−0.27
7A⇌**7B**	7	0.92 (6)	0.53 (13)	0.988	0.68
7A⇌**7C**	6	0.98 (9)	−0.34 (10)	0.983	−0.19
8A⇌**8B**	7	0.95 (6)	0.49 (12)	0.989	0.64
8A⇌**8C**	6	0.95 (5)	−0.42 (6)	0.993	−0.27
9A⇌**9B**	7	0.95 (6)	0.52 (11)	0.991	0.67
9A⇌**9C**	6	0.94 (8)	−0.40 (9)	0.986	−0.25
11A⇌**11B**	7	0.81 (4)	0.52 (8)	0.994	0.67
12A⇌**12B**[c]	7	0.74 (6)	−0.15 (5)	0.984	–
13A⇌**13B**[c]	7	0.82 (4)	−0.66 (3)	0.995	−0.51
14A⇌**14B**[d]	6	0.72 (2)	0.42 (5)	0.997	0.57
14A⇌**14C**[d]	6	0.99 (4)	−1.12 (8)	0.996	−0.97

[a] Standard deviations are given in parentheses.

[b] Relative ring stability constant: see the text.

[c] Data from Ref. 2b.

[d] For compounds **14** (Ref. 6), tautomeric ratios were remeasured and the linear regression analysis was performed separately for the equilibria involving C-2 epimeric ring forms.

of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines does not seem to influence the value of ρ; the plots for the equilibria containing C-2 epimeric ring forms of **4–9** (**B–A** and **C–A**) are practically parallel.

To characterize the effects of the substituents and the presence of an annelated ring on the stability of the ring forms, a substitution effect parameter (c_s) was calculated as the difference in the intercepts for the given naphthoxazine derivative (**4–9**, **11**) and the parent 2-arylperhydro-1,3-oxazine (**12**: $\log K_0=-0.15$): $c_s=\log K_{X=H}-\log K_0$. 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.[1b,2b] A positive value of c_s means a more stable ring form relative to the corresponding parent 2-arylperhydro-1,3-*O,N* heterocycle.

While an annelated benzene ring considerably decreased the stability of the ring form of 2-arylperhydro-1,3-oxazine (**13**: $c_s=-0.66$),[2b] an annelated naphthalene ring caused a dramatic increase in ring stability (**11**: $c_s=0.67$). This increased stability of the ring form was observed for all naphthoxazines having *trans* diaryl substituents (**4–9 B**: $c_s=0.63-0.85$), while the negative c_s values for the *cis* isomers of these compounds (**4–9 C**: $c_s=-0.18-\!-0.27$) indicates that the stabilizing effect of the naphthalene ring is diminished by the unfavourable steric arrangement of the aryl substituents.

3. Conclusions

Some new Betti base analogue amino naphthols were obtained by the Mannich-type aminoalkylation of 2-naphthol. The reactions of substituted amino naphthols and substituted benzaldehydes led to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines which at 300 K proved to be three-component tautomeric mixtures in $CDCl_3$ containing C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**). The influence of aryl substituents at position 3 on the ring-chain tautomeric equilibria could be described by the Hammett equation. Study of the influence of aryl substituents at position 1 is still in progress.

4. Experimental

^{1}H NMR spectra (400 MHz) were recorded at 300 K. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) as internal standard. For the equilibria to be established in tautomeric compounds,[2] the samples were dissolved in $CDCl_3$ and the solutions were allowed to stand at ambient temperature for 1 day before the ^{1}H NMR spectra were run. The number of scans was usually 32.

4.1. General method for the synthesis of 1-(α-amino-*Y*-substituted-benzyl)-2-naphthols (3a–f)

To a solution of 2-naphthol (**1**, 14.42 g, 0.1 mol) in absolute MeOH (50 mL) was added the appropriate aromatic aldehyde (0.2 mol; for liquid aldehydes, a freshly distilled sample was used) and 25% methanolic ammonia solution (20 mL). The mixture was left to stand at ambient temperature for 2 days, during which a crystalline product (**2a–f**) separated out. The crystals were filtered off and washed with cool MeOH (2×20 mL), dried and suspended in 20% HCl (200 mL). The mixture was stirred and refluxed for 3 h, and the crystalline hydrochloride of **3a–f** that separated out was filtered off and washed with EtOAc (2×25 mL). The hydrochloride was suspended in H_2O (30 mL), and the mixture was treated with conc. NH_4OH (30 mL) and extracted with EtOAc (3×50 mL). After drying (Na_2SO_4) and evaporation, crystalline **3a–f** was obtained, which was recrystallized from *i*Pr_2O.

4.1.1. Compound 3a. Beige crystals. Yield: 16.76 g (57%), mp 111–113°C. ^{1}H NMR ($CDCl_3$) δ 6.27 (s, 1H, NC*H*(Ar)NPh), 7.16 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.27 (t, 1H, *J*=7.0 Hz, Nph-H6), 7.40 (t, 1H, *J*=7.0 Hz, Nph-H7), 7.40 (t, 1H, *J*=8.0 Hz, Ar), 7.70 (d, 1H, *J*=9.0 Hz, Nph-H8), 7.71–7.76 (m, 2H, Nph-H4, Nph-H5), 7.77 (d, 1H, *J*=8.0 Hz, Ar), 8.10 (d, 1H, *J*=8.0 Hz, Ar), 8.38 (s, 1H, Ar), ^{13}C NMR ($CDCl_3$) δ 55.2, 114.5, 121.3, 121.5, 122.9, 123.6, 123.8, 127.9, 129.0, 129.9, 131.0, 131.2, 132.1, 134.5, 144.8, 148.9, 157.2. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.51; H, 4.75; N, 9.64. IR ν_{max} 3361, 1521, 1347, 730 cm^{-1}.

4.1.2. Compound 3b. White crystals. Yield: 15.42 g (47%), mp 118–120°C. ^{1}H NMR ($CDCl_3$) δ 6.10 (s, 1H, NC*H*(Ar)NPh), 7.14–7.17 (m, 2H, Nph-H3, Ar), 7.25 (t, 1H, *J*=8.5 Hz, Nph-H6), 7.34–7.38 (m, 3H, Nph-H7, Ar), 7.62 (s, 1H, Ar), 7.66 (d, 1H, *J*=8.5 Hz, Nph-H8), 7.71 (d, 1H, *J*=8.5 Hz, Nph-H4), 7.73 (d, 1H, *J*=8.0 Hz, Nph-H5), ^{13}C NMR ($CDCl_3$) δ 55.9, 115.1, 121.1, 121.5, 123.2, 123.5, 126.7, 126.8, 127.2, 129.5, 130.6, 131.1, 131.1, 131.7, 132.5, 145.3, 157.7. Anal. Calcd for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27. Found: C, 62.39; H, 4.17; N, 4.35. IR ν_{max} 3353, 1436, 1284, 810 cm^{-1}.

4.1.3. Compound 3c. Light beige crystals. Yield: 15.03 g (53%), mp 109–111°C (lit.,[15] mp 120°C). ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1H, NC*H*(Ar)NPh), 7.15 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.23–7.28 (m, 3H, Nph-H6, Ar), 7.34 (t, 1H, *J*=8.0 Hz, Nph-H7), 7.39 (d, 2H, *J*=8.5 Hz, Ar), 7.66 (d, 1H, *J*=8.5 Hz, Nph-H8), 7.71 (d, 1H, *J*=9.0 Hz, Nph-H4), 7.73 (d, 1H, *J*=8.0 Hz, Nph-H5), ^{13}C NMR ($CDCl_3$) δ 55.8, 115.4, 121.0, 121.4, 123.0, 127.1, 129.2, 129.3, 129.3, 129.7, 130.4, 132.4, 134.4, 141.4, 157.5. IR ν_{max} 3345, 1623, 1237, 829 cm^{-1}.

4.1.4. Compound 3d. Beige crystals. Yield: 13.94 g (56%), mp 116–118°C (lit.,[9] mp 124–125°C). ^{1}H NMR ($CDCl_3$) δ 6.11 (s, 1H, NC*H*(Ar)NPh), 7.17 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.20–7.24 (m, 2H, Nph-H6, Ar), 7.29 (d, 2H, *J*=7.5 Hz, Ar), 7.33 (t, 1H, *J*=7.5 Hz, Nph-H7), 7.44 (d, 2H, *J*=7.5 Hz, Ar), 7.67–7.71 (m, 3H, Nph-H4, Nph-H5, Nph-H8), ^{13}C NMR ($CDCl_3$) δ 56.6, 115.9, 121.0, 121.7, 122.9, 127.1, 127.9, 128.4, 129.1, 129.3, 129.5, 130.8, 132.8, 143.2, 157.8. IR ν_{max} 3296, 1622, 1238, 770 cm^{-1}.

4.1.5. Compound 3e. Pale yellow crystals. Yield: 18.67 g (71%), mp 103–104°C (lit.,[16] mp 109.5°C). ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 6.08 (s, 1H, NC*H*(Ar)NPh), 7.09 (d, 2H, *J*=8.0 Hz, Ar), 7.14 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.21 (t, 1H, *J*=9.0 Hz, Nph-H6), 7.31–7.35 (m, 3H, Nph-H7, Ar), 7.69–7.73 (m, 3H, Nph-H4, Nph-H8, Nph-H5), ^{13}C NMR ($CDCl_3$) δ 21.6, 56.1, 115.9, 121.0, 121.7, 122.9, 127.0, 127.6, 129.2, 129.2, 130.0, 130.2, 132.6, 138.2, 140.0, 157.6. IR ν_{max} 3347, 1468, 1235, 814 cm^{-1}.

4.1.6. Compound 3f. Beige crystals. Yield: 12.55 g (45%), mp 117–118°C. ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, OCH_3), 6.06 (s, 1H, NC*H*(Ar)NPh), 6.80 (d, 2H, *J*=8.5 Hz, Ar), 7.15 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.22 (t, 1H, *J*=7.5 Hz, Nph-H6), 7.32 (t, 1H, *J*=7.5 Hz, Nph-H7), 7.35 (d, 2H, *J*=8.5 Hz, Ar), 7.65–7.72 (m, 3H, Nph-H4, Nph-H5, Nph-H8), ^{13}C NMR ($CDCl_3$) δ 55.6, 55.7, 114.5, 115.7, 120.8, 121.5, 122.8, 126.8, 128.8, 128.9, 129.2, 130.0, 132.3, 135.0, 157.1, 159.5. Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.13; N, 5.01. Found: C, 77.32; H, 6.23; N, 5.11. IR ν_{max} 3287, 1510, 1249, 824 cm^{-1}.

4.2. 1-Aminomethyl-2-naphthol (10)

Compound **10** was prepared from 2-naphthol (11.44 g, 0.08 mol) and hexamethylenetetramine (11.20 g, 0.08 mol) according to Ref. 14a.

4.2.1. Compound 10. Yellow crystals. Yield: 8.52 g (62%), mp 131–133°C (lit.,[17] mp 135–138°C). ^{1}H NMR (DMSO) δ 4.30 (s, 2H, NCH_2NPh), 7.07 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.24 (t, 1H, *J*=7.5 Hz, Nph-H6), 7.37 (t, 1H, *J*=7.5 Hz, Nph-H7), 7.68 (d, 1H, *J*=9.0 Hz, Nph-H4), 7.75 (d, 1H, *J*=8.5 Hz, Nph-H5), 7.87 (d, 1H, *J*=8.5 Hz, Nph-H8), ^{13}C NMR (DMSO) δ 45.0, 115.6, 119.5, 122.9, 123.0, 127.1, 129.0, 129.2, 129.5, 134.0, 156.1. IR ν_{max} 1268, 1238, 813, 741 cm^{-1}.

4.3. General method for the synthesis of 3-aryl- and 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (4–9 and 11)

To a solution of the appropriate amino naphthol (**3a–f** or **10**, 1 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 24 h. The crystalline products were filtered off, washed with Et_2O and

Table 3. Physical and analytical data on naphth[1,2-*e*][1,3]oxazines **4–9** and **11**

Compound	Mp (°C)	Yield (%)	Formula	M.W.	C% Found (calculated)	H% Found (calculated)	N% Found (calculated)
4a	207–208^{a}	78	$C_{24}H_{17}N_3O_5$	427.41	67.38 (67.44)	4.02 (4.01)	9.81 (9.83)
4b	173–175^{b}	81	$C_{24}H_{17}BrN_2O_3$	461.31	62.51 (62.49)	3.70 (3.71)	6.06 (6.07)
4c	167–168^{b}	69	$C_{24}H_{17}ClN_2O_3$	416.86	69.12 (69.15)	4.12 (4.11)	6.72 (6.72)
4d	146–147^{a}	83	$C_{24}H_{18}N_2O_3$	382.41	75.43 (75.38)	4.75 (4.74)	7.33 (7.33)
4e	161–163^{a}	75	$C_{25}H_{20}N_2O_3$	396.44	75.61 (75.74)	5.09 (5.08)	7.08 (7.07)
4f	126–128^{b}	86	$C_{25}H_{20}N_2O_4$	412.44	72.68 (72.80)	4.89 (4.89)	6.78 (6.79)
4g	201–202^{b}	90	$C_{26}H_{23}N_3O_3$	425.48	73.37 (73.40)	5.46 (5.45)	9.88 (9.88)
5a	193–195^{b}	72	$C_{24}H_{17}BrN_2O_3$	461.31	62.58 (62.49)	3.70 (3.71)	6.08 (6.07)
5b	123–125^{b}	67	$C_{24}H_{17}Br_2NO$	495.21	58.30 (58.21)	6.45 (6.46)	2.84 (2.83)
5c	163–164^{b}	80	$C_{24}H_{17}BrClNO$	450.76	63.88 (63.95)	3.81 (3.80)	3.12 (3.11)
5d	132–134^{a}	75	$C_{24}H_{18}BrNO$	416.31	69.17 (69.24)	4.37 (4.36)	3.35 (3.36)
5e	143–145^{a}	82	$C_{25}H_{20}BrNO$	430.34	69.85 (69.78)	4.67 (4.68)	3.24 (3.25)
5f	108–110^{a}	85	$C_{25}H_{20}BrNO_2$	446.34	67.17 (67.27)	4.51 (4.52)	3.13 (3.14)
5g	161–164^{a}	70	$C_{26}H_{23}BrN_2O$	459.38	67.88 (67.98)	5.06 (5.05)	3.11 (6.10)
6a	181–182^{b}	81	$C_{24}H_{17}ClN_2O_3$	416.86	69.09 (69.15)	4.11 (4.11)	6.73 (6.72)
6b	147–148^{a}	75	$C_{24}H_{17}BrClNO$	450.76	64.02 (63.95)	3.81 (3.80)	3.11 (3.11)
6c	155–156^{b,c}	78	$C_{24}H_{17}Cl_2NO$	406.31	70.93 (70.95)	4.23 (4.22)	3.46 (3.45)
6d	154–156^{a}	85	$C_{24}H_{18}ClNO$	371.86	77.48 (77.52)	4.89 (4.88)	3.78 (3.77)
6e	163–165^{a}	73	$C_{25}H_{20}ClNO$	385.89	77.78 (77.81)	5.21 (5.22)	3.64 (3.63)
6f	163–164^{b}	86	$C_{25}H_{20}ClNO_2$	401.89	74.69 (74.72)	5.01 (5.02)	3.48 (3.49)
6g	177–178^{b}	88	$C_{26}H_{23}ClN_2O$	414.93	75.31 (75.26)	5.58 (5.59)	3.76 (6.75)
7a	176–178^{a,d}	74	$C_{24}H_{18}N_2O_3$	382.41	75.42 (75.38)	4.74 (4.74)	7.34 (7.33)
7b	153–155^{a}	81	$C_{24}H_{18}BrNO$	416.31	69.33 (69.24)	4.36 (4.36)	3.35 (3.36)
7c	171–173^{b,e}	86	$C_{24}H_{18}ClNO$	371.86	77.45 (77.52)	4.87 (4.88)	3.76 (3.77)
7d	146–148^{a,f}	90	$C_{24}H_{19}NO$	337.42	85.39 (85.43)	5.67 (5.68)	4.15 (4.15)
7e	155–157^{a,g}	77	$C_{25}H_{21}NO$	351.44	85.51 (85.44)	6.03 (6.02)	3.98 (3.99)
7f	143–146^{a,h}	81	$C_{25}H_{21}NO_2$	367.44	81.84 (81.72)	5.75 (5.76)	3.82 (3.81)
7g	225–227^{a,i}	78	$C_{26}H_{24}N_2O$	380.48	82.19 (82.07)	6.37 (6.36)	7.35 (7.36)
8a	181–183^{b}	75	$C_{25}H_{20}N_2O_3$	396.44	75.69 (75.74)	5.09 (5.08)	7.07 (7.07)
8b	116–117^{b}	92	$C_{25}H_{20}BrNO$	430.34	69.71 (69.78)	5.68 (4.68)	3.26 (3.25)
8c	137–138^{b}	83	$C_{25}H_{20}ClNO$	385.89	77.92 (77.81)	5.21 (5.22)	3.64 (3.63)
8d	131–133^{b}	89	$C_{25}H_{21}NO$	351.44	85.39 (85.44)	6.02 (6.02)	3.98 (3.99)
8e	148–149^{b,j}	77	$C_{26}H_{23}NO$	365.47	85.52 (85.45)	6.33 (6.34)	3.83 (3.83)
8f	128–132^{b}	85	$C_{26}H_{23}NO_2$	381.47	82.02 (81.86)	6.07 (6.08)	3.68 (3.67)
8g	197–198^{b}	76	$C_{27}H_{26}N_2O$	394.51	82.11 (82.20)	6.65 (6.64)	7.08 (7.10)
9a	157–159^{b}	84	$C_{25}H_{20}N_2O_4$	412.44	72.75 (72.80)	4.88 (4.89)	6.78 (6.79)
9b	177–178^{b}	77	$C_{25}H_{20}BrNO_2$	446.34	67.36 (67.27)	4.52 (4.52)	3.13 (3.14)
9c	180–182^{a}	84	$C_{25}H_{20}ClNO_2$	401.89	74.89 (74.72)	5.01 (5.02)	3.50 (3.49)
9d	156–159^{a}	93	$C_{25}H_{21}NO_2$	367.44	81.68 (81.72)	5.76 (5.76)	3.82 (3.81)
9e	177–178^{a}	88	$C_{26}H_{23}NO_2$	381.47	81.71 (81.86)	6.07 (6.08)	3.66 (3.67)
9f	182–184^{a,k}	76	$C_{26}H_{23}NO_3$	397.47	78.66 (78.57)	5.84 (5.83)	3.52 (3.52)
9g	177–179^{a}	79	$C_{27}H_{26}N_2O_2$	410.51	79.11 (79.00)	6.39 (6.38)	6.83 (6.82)
11a	161–162^{b}	72	$C_{18}H_{14}N_2O_3$	306.32	70.65 (70.58)	4.62 (4.61)	9.16 (9.15)
11b	154–156^{b}	83	$C_{18}H_{14}BrNO$	340.21	63.44 (63.55)	4.15 (4.15)	4.13 (4.12)
11c	155–157^{a}	78	$C_{18}H_{14}ClNO$	295.76	72.97 (73.10)	4.76 (4.77)	4.74 (4.74)
11d	109–111^{a}	85	$C_{18}H_{15}NO$	261.32	82.81 (82.73)	5.78 (5.79)	5.36 (5.36)
11e	125–126^{a}	75	$C_{19}H_{17}NO$	275.35	82.72 (82.88)	6.23 (6.22)	5.08 (5.09)
11f	146–147^{a}	80	$C_{19}H_{17}NO_2$	291.34	78.48 (78.33)	5.88 (5.88)	4.82 (4.81)
11g	152–154^{a}	77	$C_{20}H_{20}N_2O$	304.39	78.88 (78.92)	6.63 (6.62)	9.21 (9.20)

[a] Recrystallized from *i*Pr_2O.
[b] Recrystallized from *i*Pr_2O-EtOAc.
[c] Lit.,[15] mp 150°C.
[d] Lit.,[13a] mp 174–175°C.
[e] Lit.,[13a] mp 173°C.
[f] Lit.,[13a] mp 144–145°C.
[g] Lit.,[18] mp 169°C.
[h] Lit.,[18] mp 95°C.
[i] Lit.,[13a] mp 192–193°C.
[j] Lit.,[16] mp 149°C.
[k] Lit.,[16] mp 181°C.

recrystallized. All of the recrystallized new compounds (**4a–g**, **5a–g**, **6a**, **6b**, **6d–g**, **7b**, **8a–d**, **8f**, **8g**, **9a–e**, **9g**, **11a–g**) gave satisfactory data on elemental analysis (C, H, N±0.3%). The physical and analytical data for compounds **4–9** and **11** are listed in Table 3.

With regard to the similarities in the ^{1}H NMR data, full spectra are described only for three representatives of the prepared compounds (**6a**, **9g** and **11f**). In a consequence of the very low relative concentrations and the extensive signal overlaps in the aromatic region, a full NMR characterization of the *minor* ring closed tautomers **C** was not possible. The ^{1}H NMR chemical shifts of the characteristic O–C*H*Ar-N and N=C*H*Ar protons of each tautomer and the characteristic IR wavenumbers for compounds **4–9** and **11** are given in Table 4.

Table 4. NMR and IR spectroscopical data on naphth[1,2-*e*][1,3]oxazines **4–9** and **11**

Compound	δN=*CH* (**A**)	δN–*CH*–O (**B**)	δN–*CH*–O (**C**)	$\nu_{max.}$ (cm^{-1})
4a	8.80(s)	5.75(s)	6.04(s)	3854, 1598, 1343, 1233
4b	8.61(s)	5.68(s)	5.96(d)	3332, 1527, 1352, 1238
4c	8.64(s)	5.69(s)	5.99(s)	3332, 1527, 1345, 1234
4d	8.68(s)	5.72(s)	6.03(s)	3332, 1525, 1349, 1233
4e	8.62(s)	5.70(s)	6.02(s)	1525, 1468, 1347, 1232
4f	8.55(s)	5.66(s)	5.98(s)	3338, 1526, 1348, 1232
4g	8.43(s)	5.66(s)	–	1601, 1344, 1181, 741
5a	8.32(s)	5.69(d)	5.91(d)	1518, 1339, 1232, 753
5b	8.55(s)	5.62(s)	5.87(d)	3322, 1234, 989, 774
5c	8.57(s)	5.63(s)	5.88(d)	33316, 1233, 986, 957
5d	8.61(s)	5.65(d)	5.91(d)	3317, 1467, 1233, 704
5e	8.55(s)	5.62(s)	5.90(d)	3321, 1238, 986, 931
5f	8.50(s)	5.60(s)	5.89(s)	1515, 1251, 1234, 985
5g	8.39(s)	5.60(s)	–	3308, 1365, 1233, 955
6a	8.73(s)	5.68(s)	5.91(d)	3320, 1519, 1339, 814
6b	8.56(s)	5.61(s)	5.89(d)	3307, 1233, 990, 825
6c	8.57(s)	5.60(s)	5.90(d)	3320, 1233, 984, 745
6d	8.60(s)	5.64(s)	5.92(d)	3320, 1236, 825, 747
6e	8.51(s)	5.57(s)	5.88(d)	3314, 1233, 985, 745
6f	8.50(s)	5.60(s)	5.91(s)	1515, 1231, 930, 749
6g	8.39(s)	5.59(s)	–	3850, 1597, 1367, 1182
7a	8.73(s)	5.73(s)	5.94(s)	3307, 1518, 1340, 1231
7b	8.55(s)	5.63(s)	5.91(d)	3308, 1229, 924, 750
7c	8.62(s)	5.65(s)	5.93(d)	3320, 1235, 984, 750
7d	8.63(s)	5.71(s)	5.97(s)	1236, 932, 743, 698
7e	8.56(s)	5.65(s)	5.94(d)	3320, 1237, 834, 749
7f	8.53(s)	5.66(s)	5.94(d)	3320, 1512, 1169, 983
7g	8.43(s)	5.65(d)	–	1602, 1455, 1366, 1181
8a	8.65(s)	5.72(s)	5.88(s)	3311, 1521, 1341, 1233
8b	8.55(s)	5.67(s)	5.89(d)	3317, 1232, 989, 789
8c	8.53(s)	5.64(s)	5.88(d)	3850, 1231, 987, 807
8d	8.54(s)	5.68(s)	5.89(s)	1233, 985, 808, 746
8e	8.52(s)	5.66(s)	5.90(s)	3302, 1233, 987, 746
8f	8.51(s)	5.66(s)	5.90(s)	1450, 1248, 1229, 903
8g	8.39(s)	5.63(s)	–	1604, 1365, 1182, 812
9a	8.69(s)	5.72(s)	5.87(s)	3292, 1510, 1342, 1229
9b	8.50(s)	5.63(s)	5.86(d)	3313, 1508, 1247, 1233
9c	8.54(s)	5.64(s)	5.87(d)	3316, 1511, 1247, 1233
9d	8.55(s)	5.68(s)	5.89(d)	3850, 1505, 1454, 942
9e	8.51(s)	5.65(s)	5.88(s)	3320, 1510, 1170, 747
9f	8.50(s)	5.65(s)	5.89(s)	1607, 1511, 1253, 831
9g	8.40(s)	5.62(s)	–	1605, 1509, 1251, 811
11a	8.58(s)	5.93(d)	–	3314, 1510, 1338, 1224
11b	8.43(s)	5.84(s)	–	3308, 1245, 1231, 811
11c	8.46(s)	5.85(s)	–	3253, 1225, 951, 818
11d	8.50(s)	5.89(s)	–	3248, 1227, 740, 695
11e	8.47(s)	5.87(s)	–	1225, 996, 910, 811
11f	8.39(s)	5.83(s)	–	3266, 1248, 1227, 813
11g	8.29(s)	5.81(s)	–	1601, 1368, 1181, 815

4.4. ^{1}H NMR spectroscopic data on 6a, 9g and 11f in CDCl$_3$

The protons of the open form (**A**) are numbered according to the corresponding protons of the naphth[1,2-*e*][1,3]oxazine ring form (**B**, **C**) (δ in ppm, in brackets the multiplicity, couplings in Hz and assignment, respectively).

4.4.1. Compound 6aB. ^{1}H NMR (CDCl$_3$) δ 5.63 (s, 1H, NC*H*(Ar)NPh), 5.68 (s, 1H, NC*H*(Ar)O), 7.24 (d, 1H, *J*=9.0 Hz, H5), 7.27–7.32 (m, 4H, Ar), 7.32–7.35 (m, 3H, H7, H8, H9), 7.78 (d, 2H, *J*=9.0 Hz, Ar), 7.79–7.83 (m, 2H, H6, H10), ^{13}C NMR (CDCl$_3$) δ 53.6, 81.6, 114.6, 119.4, 123.1, 123.8, 124.1, 127.3, 127.8, 129.0, 129.3, 129.5, 130.1, 131.1, 131.2, 131.4, 141.2, 146.1, 148.4, 152.5.

4.4.2. Compound 9gA. ^{1}H NMR (CDCl$_3$) δ 3.03 (s, 6H, *p*-N(CH_3)2), 3.73 (s, 3H, *p*-OCH_3), 6.31 (s, 1H, NC*H* (Ar)NPh), 6.68 (d, 2H, *J*=8.5 Hz, Ar), 6.78 (d, 2H, *J*=8.5 Hz, Ar), 7.22 (d, 1H, *J*=9.0 Hz, Nph-H3), 7.23–7.39 (m, 3H, Ar, Nph-H6), 7.37 (t, 1H, *J*=7.5 Hz, Nph-H7), 7.63 (d, 2H, *J*=8.5 Hz, Ar), 7.72 (d, 1H, *J*=9.0 Hz, Nph-H4), 7.74 (d, 1H, *J*=8.0 Hz, Nph-H5), 7.83 (d, 1H, *J*=8.5 Hz, Nph-H8), 8.40 (s, 1H, C*H*=N), ^{13}C NMR (CDCl$_3$) δ 40.6, 55.7, 74.3, 112.1, 114.6, 120.8, 117.5, 122.2, 122.8, 123.0, 127.6, 129.2, 129.3, 129.4, 129.9, 131.1, 132.5, 134.5, 153.5, 156.3, 159.6, 161.7.

4.4.3. Compound 11fA. ^{1}H NMR (CDCl$_3$) δ 3.86 (s, 3H, OCH_3), 5.36 (s, 2H, H1), 6.96 (d, 2H, *J*=7.0 Hz, Ar), 7.15 (d, 1H, *J*=8.5 Hz, Nph-H3), 7.31 (t, 1H, *J*=8.0 Hz, Nph-H6), 7.48 (t, 1H, *J*=8.0 Hz, Nph-H7), 7.68 (d, 1H, *J*=8.5 Hz, Nph-H4), 7.71 (d, 2H, *J*=7.0 Hz, Ar), 7.77 (d, 1H, *J*=8.5 Hz, Nph-H5), 7.79 (d, 1H, *J*=9.0 Hz, Nph-H8), 8.39

(s, 1H, CH=N), ^{13}C NMR (CDCl$_3$) δ 55.9, 60.3, 112.9, 114.7, 120.5, 121.4, 121.5, 123.1, 126.9, 128.0, 128.9, 129.1, 130.8, 132.2, 155.6, 162.3, 163.0.

4.4.4. Compound 11fB. ^{1}H NMR (CDCl$_3$) δ 3.82 (s, 3H, OCH_3), 4.37 (d, 1H, J=17.0 Hz, H1), 4.53 (d, 1H, J=17.0 Hz, H1), 5.83 (s, 1H, NCH(Ar)NPh), 6.94 (d, 2H, J=7.0 Hz, Ar), 7.14 (d, 1H, J=9.0 Hz, H5), 7.35 (t, 1H, J=8.0 Hz, H8), 7.47 (t, 1H, J=8.0 Hz, H9), 7.57 (d, 2H, J=8.0 Hz, Ar), 7.64 (d, 1H, J=9.0 Hz, H10), 7.67 (d, 1H, J=9.0 Hz, H6), 7.77 (d, 1H, J=8.5 Hz, H7), ^{13}C NMR (CDCl$_3$) δ 42.7, 55.7, 87.3, 114.0, 114.3, 119.9, 121.6, 121.7, 123.9, 126.9, 128.0, 129.3, 129.4, 131.6, 131.9, 152.7, 160.2.

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SUBSTITUENT EFFECTS IN THE RING-CHAIN TAUTOMERISM OF 1-ARYL-2,3-DIHYDRO-1*H*-NAPHTH[1,2-*e*][1,3]OXAZINES

II.

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SUMMARY

The condensation of Betti base analogue aminonaphthols with substituted benzaldehydes or aliphatic aldehydes led to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (16-22) and 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (23-29), which proved to be three-component (r^1⇌o⇌r^2, 16-22) or two-component (r^1⇌r^2, 23-29) tautomeric mixtures in $CDCl_3$ at 300 K. The electronic effects of the 3-aryl or 3-alkyl groups on the tautomeric ratios could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$ (16-22) and $\log K_X = 7.88V^x + 0.55$ (23-29), respectively. Study of the influence of aryl substituents at position 1 led to the conclusion that in the *trans* form a stereoelectronic effect is present; this was supported by dual substituent parameter treatment of the ^{13}C chemical shift changes induced by phenyl substituents.

Keywords: aminonaphthols, tautomerism, substituent effects, oxazines

INTRODUCTION

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.[1-12]

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SUMMARY

The condensation of Betti base analogue aminonaphthols with substituted benzaldehydes or aliphatic aldehydes led to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**16-22**) and 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**23-29**), which proved to be three-component (r^1-o-r^2, **16-22**) or two-component (r^1-r^2, **23-29**) tautomeric mixtures in $CDCl_3$ at 300 K. The electronic effects of the 3-aryl or 3-alkyl groups on the tautomeric ratios could be described by the equation $\log K_X = \rho\sigma^+ + \log K_{X=H}$ (**16-22**) and $\log K_R = 7.88V^a + 0.55$ (**23-29**) respectively. Study of the influence of aryl substituents at position 1 led to the conclusion that in the *trans* form a stereoelectronic effect is present; this was supported by dual substituent parameter treatment of the ^{13}C chemical shift changes induced by phenyl substituents.

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INTRODUCTION

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],[2]

For the tautomeric equilibria of oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2, a Hammett-type linear correlation was found in both the liquid phase and the gas phase between the log K_X (K_X = [ring]/[chain]) values for the equilibria and the electronic character (σ^+) of the substituents X on the 2-phenyl group (eq. 1). The value of ρ in eq. 1 proved to be characteristic of the ring system and dependent on temperature and the nature of the solvent:[1],[2]

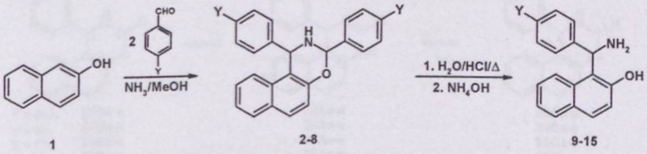
$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad (1)$$

The scope and limitations of eq. 1 have been thoroughly studied from the aspect of its applicability in the case of complex tautomeric mixtures containing several types of open and/or cyclic forms, and the influence of the steric and/or electronic effects of the substituents at positions other than 2 on the parameters in eq. 1.[2]-[6] The previous investigations did not offer a precise mathematical formula with which to characterize the effects of substituents at positions other than 2, or restricted only to the substituent-induced changes in the parameters of eq. 1.[6]

One of our present aims was to study the substituent effects on the ring-chain tautomerism of naphthalene-condensed 1,3-oxazine derivatives bearing aryl groups at position 4 and aryl/alkyl groups at position 2. A further aim was to find a generalized multivariate extension of eq. 1 describing double substituent effects in the ring-chain tautomeric equilibria of 1,3-disubstituted 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines and for a better understanding of the ring-chain tautomeric process in order to characterize the propagation of the substituent effect in the naphthoxazine model compounds by correlation analysis of the ^{13}C chemical shifts.

MATERIALS AND METHODS

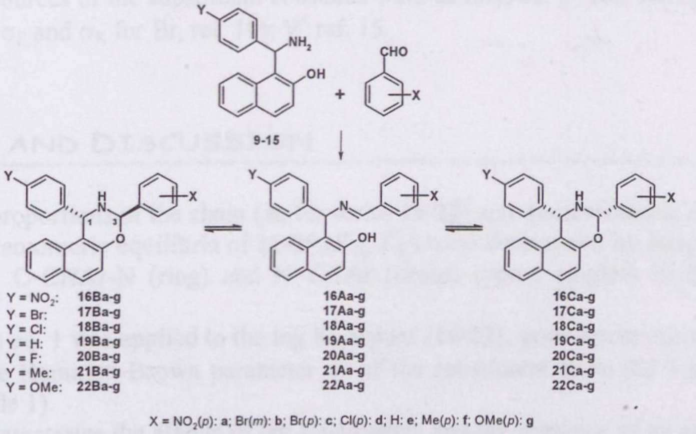
Betti's classical procedure, a Mannich-type aminoalkylation of 2-naphthol, was applied to prepare the starting materials for the synthesis of the present target compounds. The condensation of 2-naphthol (**1**) and benzaldehyde or substituted benzaldehydes in the presence of ammonia, and subsequent acidic hydrolysis, gave aminonaphthols **9-15** in good yields (Scheme 1).[7],[8]



Y = NO_2: 2,9; Br: 3,10; Cl: 4,11; H: 5,12; F: 6,13; Me: 7,14; OMe: 8,15

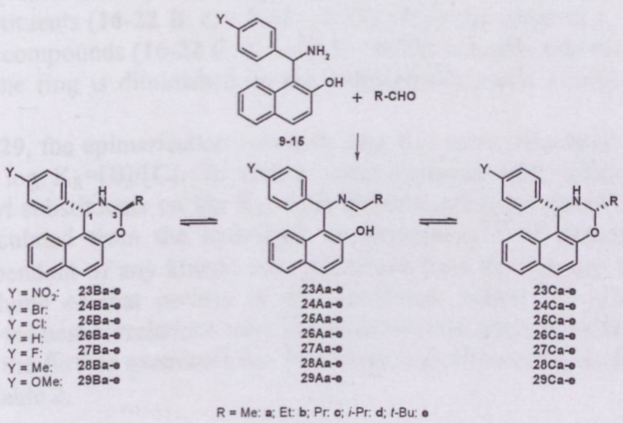
Scheme 1

Condensations of **9-15** with equivalent amounts of aromatic aldehydes resulted in naphthoxazine model compounds **16-22** as crystalline products (Scheme 2). The ^1H NMR spectra of **16-22** revealed that, in $CDCl_3$ solution at 300 K, the members **a-g** of each set of compounds **16-22** participated in three-component ring-chain tautomeric equilibria involving C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**).



Scheme 2

To find evidence for the effects of the alkyl substituents, 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **23-29** were prepared by condensation of **9-15** with equivalent amounts of aliphatic aldehydes (Scheme 3). The ^1H NMR spectra of **23-29** showed that, in $CDCl_3$ solution at 300 K, the members **a-g** of each set of compounds **23-29** participated in two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** and **C**). The chain forms (**A**) could not be detected.



Scheme 3

The relative configurations of **B** and **C** for each set of compounds (**16-29**) were proved by means of NOE measurements. Statistical calculations were carried out by using SPSS statistical software and a probability $p<0.05$ was chosen as the limit of significance.[9]

The sources of the substituent constants were as follows: σ^+ ref. 10; σ_F and σ_R, ref. 11 (except for σ_F and σ_R for Br, ref. 10); V^a ref. 15.

RESULTS AND DISCUSSION

The proportions of the chain (**A**, for series **16-22**) and diastereomeric ring forms (**B** and **C**) in the tautomeric equilibria of **16-29** (K_X, K_R) were determined by integration of the well-separated O-C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets in the ^{1}H NMR spectra.

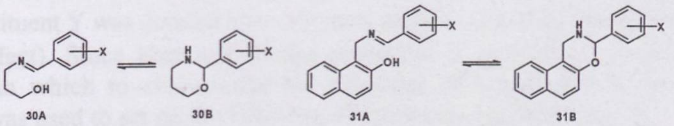
When eq. 1 was applied to the log K_X values (**16-22**), good linear correlations were obtained *vs* the Hammett-Brown parameter σ^+ of the substituent X on the 3-phenyl group for **16-22** (Table 1).

To characterize the effects of the substituents and the presence of an annelated ring on the stability of the ring forms, a substitution effect parameter (c_s) was calculated as the difference in the intercepts for the given naphthoxazine derivative (**16-22**) and the parent 2-arylperhydro-1,3-oxazine (**30**: log K_0 = -0.15): $c_s = \log K_{X=H} - \log K_0$. 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.[2],[4] A positive value of c_s means a more stable ring form relative to the corresponding parent 2-arylperhydro-1,3-*O,N* heterocycle.

An annelated naphthalene ring caused a dramatic increase in ring stability (**31**: c_s = 0.67).[8] This increased stability of the ring form was observed for all naphthoxazines having *trans* diaryl substituents (**16-22 B**: c_s = 0.62 – 0.85), while the negative c_s values for the *cis* isomers of these compounds (**16-22 C**: c_s = -0.15 – -0.28) indicates that the stabilizing effect of the naphthalene ring is diminished by the unfavourable steric arrangement of the aryl substituents.

For **22-29**, the epimerization constants (log K_R) were calculated from the ratio of the ring forms, log K_R=[**B**]/[**C**]. To find a linear equation with which to describe the influence of alkyl substituents on log K_R, three different alkyl substituent parameters were studied: E_s (calculated from the hydrolysis or aminolysis[12] of esters) and two steric parameters independent of any kinetic data: ν(derived from the van der Waals radii[13],[14]) and V^a (the volume of that portion of the substituent within 0.3 nm of the reaction centre[15]). Since the best correlations were observed with the alkyl substituent parameter V^a, this was used in the further examinations. The linear regression analysis data for series **15-21** are given in Table 2.

Table 1. Linear regression data on compounds **16-22**, 2-aryl-3,4,5,6-tetrahydro-2*H*-1,3-oxazines (**30**) and 3-aryl-2,3-dihydro-2*H*-naphth[1,2-*e*][1,3]oxazines (**31**)



X = $NO_2(p)$, NO2(*m*), Cl(*m*), Cl(*p*), H, Me(*p*), OMe(*p*), $NMe_2(p)$

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a]	Correlation coefficient	c_S[b]
16A ⇌ **16B**	7	1.04(4)	0.70(8)	0.994	0.85
16A ⇌ **16C**	7	0.97(2)	-0.30(2)	0.992	-0.15
17A ⇌ **17B**	7	1.02(8)	0.63(15)	0.987	0.78
17A ⇌ **17C**	7	1.03(9)	-0.34(10)	0.991	-0.19
18A ⇌ **18B**	7	1.03(5)	0.61(10)	0.988	0.76
18A ⇌ **18C**	7	0.82(8)	-0.41(10)	0.978	-0.26
19A ⇌ **19B**	7	1.05(6)	0.51(13)	0.988	0.66
19A ⇌ **19C**	7	0.98(9)	-0.35(10)	0.983	-0.20
20A ⇌ **20B**	7	1.10(6)	0.65(12)	0.968	0.80
20A ⇌ **20C**	7	1.00(5)	-0.35(6)	0.979	-0.20
21A ⇌ **21B**	7	1.04(6)	0.47(11)	0.982	0.62
21A ⇌ **21C**	7	0.95(8)	-0.43(9)	0.993	-0.28
22A ⇌ **22B**	7	1.03(4)	0.50(8)	0.985	0.65
22A ⇌ **22C**	7	0.94(4)	-0.40(8)	0.986	-0.25
30A ⇌ **30B**[c]	7	0.74(6)	-0.15(5)	0.984	–
31A ⇌ **31B**[d]	7	0.81(4)	0.52(8)	0.994	0.67

[a]Standard deviations are given in parentheses. [b]Relative ring stability constant: see the text. [c]Data from ref. 4. [c]Data from ref. 8.

Table 2. Linear regression data on compounds **23-29**

Equilibrium	No. of points	Slope (ρ)	Intercept	Correlation coefficient
23B ⇌ **23C**	5	8.62(7)	0.63(9)	0.922
24B ⇌ **24C**	5	9.82(10)	0.40(12)	0.963
25B ⇌ **25C**	5	7.58(8)	0.62(9)	0.957
26B ⇌ **26C**	5	6.36(8)	0.54(11)	0.966
27B ⇌ **27C**	5	8.39(9)	0.51(7)	0.987
28B ⇌ **28C**	5	7.42(11)	0.51(10)	0.904
29B ⇌ **29C**	5	7.61(6)	0.53(8)	0.898

The influence of the 3-aryl group on the tautomeric equlibria of 1,3-naphthoxazines **16-22** could be described by using eq. 1. However, the Hammett-type parameters proved inadequate to describe the influence of aryl substituents at position 1. Accordingly, the effect of substituent Y was divided into two parts with the aid of σ_F (inductive effect) and σ_R (resonance effect). Since Hammett-Brown parameter σ^+ proved a convenient substituent parameter with which to characterize the influence of substituent X on the tautomeric equilibria, it was used to set up the following Hansch-type equation (eq. 2):

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

The multiple linear regression analysis data of eq. 2 are listed in Table 3. The influence of substituent Y on the *cis*-chain equilibria (**C**–**A**) was found not to be significant. In the case of *trans*-chain equilibria (**B**–**A**) a significant dependence was found for the field effect of substituent Y. The substituent effect is related to the configuration of C-1 atom and thereby the spatiality of the model compound. This observation is in accord with the concept of the stereoelectronically mediated substituent effect.[16]

To check the presence of the stereoelectronic effect in compounds **23-29** relating to the geometry of C-1, multiple linear regression analysis of log K_R was performed according to eq. 3. The analysis results are listed in Table 3:

$$\log K_R = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho^R V^a \qquad (3)$$

Table 3. Multiple linear regression analysis of log K values for **16-29**

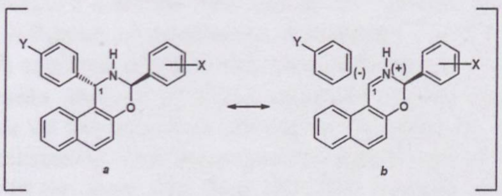
	Equilibria	k	ρ_F^Y	ρ_R^Y	ρ^X / ρ^R	r
acc. to eq. 2	**16-22A** $\rightleftharpoons$ **16-22B**	0.32	0.33	–[a]	1.46	0.979
	16-22A $\rightleftharpoons$ **16-22C**	-0.53	–[a]	–[a]	1.32	0.972
acc. to eq. 3	**23-29B** $\rightleftharpoons$ **23-29C**	0.48	0.22	–[a]	7.97	0.919

[a] Insignificant (p>0.05)

The significant dependence of log K_R with the through-space effect (σ_F) of substituent Y in **23-29**, together with the σ_F dependence of log K for **16-22**, led us to conclude that only the free energies of the *trans* forms are influenced by the through-space effect of substituent Y, which can be explained by *anomeric effect* quantitatively influenced by aryl substituents at position 1.

The Substituent influenced Changes of ^{13}C chemical Shifts (SCS) can be analysed by dual substituent parameter approaches.[17] The best correlation was obtained with the equation SCS = $\rho_F\sigma_F + \rho_R\sigma_R$. For all the studied 1,3-heterocyclic systems a negative ρ_F and therefore reverse behaviour of the electron density was observed for C-2.[17]

On the other hand, if a stereoelectronic effect is present in the *trans* form, the absolute value of ρ_F must be decreased, while the aryl substituents cause an opposite dependence in the carbon chemical shifts. This can be explained with the aid of the double bond–no bond resonance structure ***b*** (Scheme 4), because electron-withdrawing substituents increase the sp^2 character of C-1 and therefore resonance structure ***b*** is more favourable.



Scheme 4

To check the previous hypothesis, the chemical shifts of C-1 were measured in $CDCl_3$. Chemical shift changes induced by an aryl substituent (SCS) for a given compound were calculated as the difference of the ^{13}C chemical shift for the substituted one relative to the unsubstituted (X=H, Y=H) one:

$$SCS = \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad (4)$$

The multiple regression analysis data of eq. 4 for C-1 are presented in Table 4. The difference between the value of ρ_F^Y for C-1 in *trans* form (-1.12) and that obtained in *cis* form (-1.51) is 0.39, which can be interpreted as new evidence of the presence of the substituent (Y)-influenced *anomeric effect* in the *trans* form (Table 4).

Table 4. Multiple linear regression analysis of C1 chemical shifts for **16-22** according to eq. 4

	ρ_F^Y	ρ_R^Y	ρ_F^X	ρ_R^X	r
A	-1.81	–[a]	–[a]	0.45	0.967
B	-1.12	0.75	–[a]	–[a]	0.982
C	-1.51	0.60	-0.49	–[a]	0.983

[a] Insignificant (p>0.05)

CONCLUSION

Some new Betti base analogue aminonaphthols were obtained by the Mannich-type aminoalkylation of 2-naphthol. The reactions of substituted aminonaphthols and substituted benzaldehydes or aliphatic aldehydes led to 1,3-diaryl- or 3-alkyl-1-aryl-2,3-dihydro-1*H*-

naphth[1,2-*e*][1,3]oxazines which at 300 K proved to be three- or two-component tautomeric mixtures in $CDCl_3$, containing C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**). The influence of aryl substituents at position 3 on the ring-chain tautomeric equilibria could be described by the Hammett equation, and the influence of alkyl substituents at position 3 could be described by the equation $\log K_R = 7.88V^a + 0.55$

The common influence of substituents at positions 1 and 3 on the tautomeric (**16-22**) or epimeric (**23-29**) equlibria could be described with the use of Hansch-type equations. Multiple linear regression analysis of these equations proved that substituent Y has a through-space influence on the equilibria relating to the geometry of the molecule (*trans* arrangement of the substituents). This was explained with the aid of a substituent-dependent stereoelectronic effect in the *trans* ring form (**B**). This concept was supported by double substituent parameter treatment of the ^{13}C chemical shift changes of C-1 induced by phenyl substituents. A significant through-space inductive effect dependence was found for both ring forms, with negative slopes. The difference between the slopes provided further evidence for the presence of an *anomeric effect* in the *trans* ring form.

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III.

Stereoelectronic Effect in Ring-Chain Tautomerism of 1,3-Diarylnaphth[1,2-*e*][1,3]oxazines and 3-Alkyl-1-arylnaphth[1,2-*e*][1,3]oxazines

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Abstract: The disubstitution effects of X and Y in 1-(Y-substituted-phenyl)-3-(X-substituted-phenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines on the ring-chain tautomerism, the delocalization of the nitrogen lone pair (anomeric effect) and the ^{13}C NMR chemical shifts were analyzed by using multiple linear regression analysis (Eqs 2, 3, 5 and 6). Study of the three-component equilibrium $\mathbf{B} \rightleftharpoons \mathbf{A} \rightleftharpoons \mathbf{C}$ revealed that the chain$\rightleftharpoons$trans ($\mathbf{A} \rightleftharpoons \mathbf{B}$) equilibrium constants are significantly influenced by the inductive effect (σ_F) of substituent Y on the 1-phenyl ring. In contrast, no significant substituent dependence on Y was observed for the chain$\rightleftharpoons$cis ($\mathbf{A} \rightleftharpoons \mathbf{C}$) equilibrium. There was an analogous dependence for the epimerization ($\mathbf{C} \rightleftharpoons \mathbf{B}$) constants of 1-(Y-substituted-phenyl)-3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. With these model compounds, significant overlapping energies of the nitrogen lone pair was observed by NBO analysis in the trans forms **B** (to $\sigma^*_{C1\text{-}C1'}$, $\sigma^*_{C1\text{-}C10b}$ and $\sigma^*_{C3\text{-}O4}$) and in the cis forms **C** (to $\sigma^*_{C1\text{-}H}$, $\sigma^*_{C1\text{-}C10b}$ and $\sigma^*_{C3\text{-}O4}$). The effects of disubstitution revealed some characteristic differences between the cis and trans isomers. However, the results do not suggest that the anomeric effect predominates in the preponderance of the trans over the cis isomer. When the ^{13}C chemical shift changes induced by substituents X and Y (SCS) were subjected to multiple linear regression analysis, negative ρ_F^Y and ρ_F^X values were observed at C-1 and C-3 for both the cis and trans isomers. On the other hand, positive ρ_R^Y values were obtained for both isomeric series, while the ρ_R^X values were negative, indicating the appearance of direct resonance and resonance-induced polar effects, respectively. The classical double bond – no-bond resonance structures proved useful in explaining the substituent sensitivities of the donation energies and the behavior of the SCS values.

Keywords: 1,3-DIARYLNAPHTHOXAZINES, 3-ALKYL-1-ARYLNAPHTHOXAZINES, RING-CHAIN TAUTOMERISM, ANOMERIC EFFECT, *AB INITIO* NBO CALCULATION, SCS ANALYSIS

Introduction

The ring-chain tautomeric interconversion of *N*-unsubstituted 1,3-*O*,*N*-heterocycles and the corresponding hydroxyalkylimines can often be exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry.[1] From quantitative studies on such equilibria, it has been concluded that the tautomeric ratios for oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2 can be characterized by an aromatic substituent dependence:

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

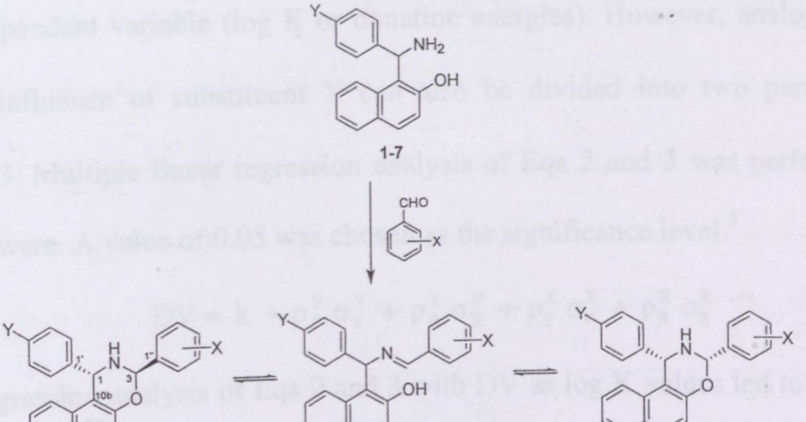
where K_X is the [ring]/[chain] ratio and σ^+ is the Hammett-Brown parameter of substituent X on the 2-phenyl group. The scope and limitations of Eq. 1 have been thoroughly studied from the aspects of the applicability of this equation in the case of complex tautomeric mixtures containing several types of open and/or cyclic forms, and the influence of the steric and/or electronic effects of the substituents at positions other than 2 on the parameters in Eq. 1.[1,2] Previous quantitative investigations on the ring-chain tautomeric equilibria of some 1,3-*Y*,*N*-heterocyclic model compounds (Y = *O*, *NR*) did not result in precise mathematical formulas with which to characterize the effects of substituents at positions other than 2, or were restricted to the recording of the substituent-induced changes in the parameters in Eq. 1.[3]

A recent study on the ring-chain tautomeric equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines demonstrated that the tautomeric ratios were strongly influenced not only by the aryl group at position 3, but also by that at position 1.[4] As a continuation of that work, our present aim was to clarify the influence of the substituents and to attempt to find a generalized multivariate extension of Eq. 1 describing double substituent effects (e.g. a double aromatic substituent dependence and the alkyl/aryl substituent effects) in the ring-chain tautomeric equilibria of 1,3-disubstituted 2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. For a better understanding of the ring-chain tautomeric process a further aim was a characterization of the propagation of the substituent effect in the naphthoxazine model compounds by quantum chemical calculations and correlation analysis of the ^{13}C chemical shifts. Special emphasis was put on the question of the potential influence of the delocalization of the nitrogen lone pair (i.e. anomeric effect) on the ring-chain equilibria or on the propagation of the effects of the phenyl substituents.

Results and discussion

1,3-Diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. ***Synthesis.*** 1,3-Diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **10**, **11**, **13** and **14** were prepared according to a known procedure,[4] involving the ring-closure reactions of the Betti base (**4**) and its Y-substituted analogs (**3**, **6** and **7**) with equivalent amounts of aromatic aldehydes. To extend the electronic characteristics and increase the diversity of the substituents Y in the model compounds, three new α-aminonaphthols (**1**, **2** and **5**) were synthetized and converted in an analogous manner to the corresponding naphthoxazine derivatives (**8**, **9** and **12**) (Scheme 1).

SCHEME 1



Y = NO_2: **1,8**; Br: **2,9**; Cl: **3,10**; H: **4,11**; F: **5,12**; Me: **6,13**; OMe: **7,14**
X = *p*NO_2: **a**; *m*Br: **b**; *p*Br: **c**; *p*Cl: **d**; H: **e**; *p*Me: **f**; *p*OMe: **g**

The ^{1}H NMR spectra of **8**, **9** and **12** revealed that, in $CDCl_3$ solution at 300 K, the members **a-g** of each set of compounds **8**, **9** and **12** participated in three-component ring-chain tautomeric equilibria involving C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**). The relative configurations of the cyclic tautomers were determined by NOE measurements.[4] The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) in the tautomeric equilibria of **8**, **9** and **12** were determined by integration of the well-separated O-C*H*Ar-N (ring) and N=C*H*Ar (chain) proton singlets or doublets (some cases in the ring forms) in the ^{1}H NMR spectra (Table S1 and S2.

Hansch analysis of equilibrium constants. The three-component equilibrium (**B**$\rightleftharpoons$**A**$\rightleftharpoons$**C**) offers an interesting system on which to study the properties of the cis (**C**) and trans isomers (**B**), because they are in thermodynamic equilibrium in solution via the chain form.

The influence of the 3-aryl group on the tautomeric equilibria of 1,3-naphthoxazines **8-14** could be described by using Eq. 1.[4] The Hammett-Brown parameter σ^+ was found to be inadequate to describe the influence of aryl substituents at position 1.[4] The effect of substituent Y was therefore divided into two parts: σ_F (inductive effect) and σ_R (resonance effect). Since the Hammett-Brown parameter σ^+ has proved to be a convenient substituent parameter with which to characterize the influence of substituent X on tautomeric equilibria,[4] it was used to set up the following Hansch quantitative structure-properties relationship (QSPR) model (Eq. 2):

$$DV = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho^X \sigma^{+X} \qquad \text{(Eq. 2)}$$

where DV is the dependent variable (log K or donation energies). However, analogously with that of substituent Y, the influence of substituent X can also be divided into two parts (σ_F and σ_R), as represented by Eq. 3. Multiple linear regression analysis of Eqs 2 and 3 was performed by using the SPSS statistical software. A value of 0.05 was chosen as the significance level.[5]

$$DV = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad \text{(Eq. 3)}$$

Multiple linear regression analysis of Eqs 2 and 3 with DV as log K values led to the results listed in Table 1. As regards substituent X, both inductive and resonance effects seem to be significant for equilibria **A**$\rightleftharpoons$**B** and **A**$\rightleftharpoons$**C**. On the other hand, substituent Y does not affect the equilibrium **A**$\rightleftharpoons$**C** at all, and only inductive effects are significant for the equilibrium **A**$\rightleftharpoons$**B.**

There is a relatively large difference in the values of the equilibrium constants for **A**$\rightleftharpoons$**B** and **A**$\rightleftharpoons$**C** (on the average, $K_B : K_C \approx 11 : 1$, Tables S1 and S2). The sensitivities of K_B and K_C to substituent X within both isomeric series are marked. The observed of values both ρ_F^X (inductive) and ρ_R^X (resonance) are positive. Positive values mean that the electron-withdrawing (EW) substituents increase the relative proportion of the ring form both inductively and by resonance. Interestingly, somewhat more positive ρ

values are observed for the equilibrium **A**$\rightleftharpoons$**B**, indicating that the sensitivity of the equilibrium in question to substituent X depends on the orientation of the phenyl ring at position 1 (a disubstitution effect). The positive values for all of the observed ρ's indicate that the EW substituents on both phenyl rings increase the relative proportion of the ring form for both equilibria studied. Extensive previous data demonstrate that for 1,3-*O*,*N*-heterocycles EW substituents on the phenyl ring situated between the two heteroatoms (i.e. substituent X) increase the relative proportion of the ring tautomers as compared with the parent compound (X = H).[1-4,6] Good correlations of log K with σ^+ show that both inductive and resonance effects are usually significant. For excellent reasons, this can be stated to be *normal behavior of the substituent dependence of the ring-chain equilibria*. The origin of this effect is now understood.[6] As regards substituents X, the present results are in harmony with the above concept. In contrast with the above behavior, in the case of a phenyl substituent on C-1, the sensitivities of the K values for the cis and trans isomers differ. For the equilibrium **A**$\rightleftharpoons$**C**, no significant dependence on substituent Y was observed. For the equilibrium **A**$\rightleftharpoons$**B**, a positive value of ρ_F^Y (0.32) was found, but there was no significant dependence on resonance parameter ρ_R. Accordingly, the present results show for the first time that aromatic ring substituents which are not attached to a phenyl ring situated between two heteroatoms can have a systematic effect on the relative proportions of the ring tautomers. The diminished inductive sensitivity, as compared with that of substituent X, reflects the fact that the substituent in question is situated farther away from the reaction center. In summary, the equilibrium **A**$\rightleftharpoons$**B** seems to be somewhat more sensitive to both substituent X and substituent Y than the equilibrium **A**$\rightleftharpoons$**C**. The origins of these substituent effects and their connections with stereoelectronic effects caused by the electron donation of the nitrogen lone pair (potential anomeric effects)[7] are discussed below with the aid of the donation energies calculated for the minimum energy conformations.

Table 1. Multiple linear regression analysis of log K values for **8-21**

		k	ρ_F^Y	ρ_R^Y	ρ^X, ρ_F^X and ρ_R^X, ρ^R		r
Acc. to Eq. 2	**8-14A⇌8-14B**	0.32(0.03)[a]	0.33(0.06)	–[b]	1.44(0.04)		0.980
	8-14A⇌8-14C	-0.53(0.03)	–[b]	–[b]	1.30(0.05)		0.971
Acc. to Eq. 3	**8-14A⇌8-14B**	0.34(0.03)	0.30(0.05)	–[b]	1.17(0.04)	1.87(0.06)	0.992
	8-14A⇌8-14C	-0.53(0.04)	–[b]	–[b]	1.08(0.06)	1.66(0.08)	0.981
Acc. to Eq. 5	**15-21C⇌15-21B**	0.48(0.04)	0.22(0.05)	–[b]	7.97(0.76)		0.919

[a] Standard deviations; [b] Insignificant (significance value > 0.05)

Hansch analysis of the donation energies for the rigid model structures. Donation energy calculations were performed with conformationally rigid models in order to clarify the potential connections between the anomeric effect and the relative stabilities of the cis and trans isomers. The conformational search protocol involved PM3 geometry minimization, followed by optimization at the *ab initio* level, using the HF/6-31G* base set for all of the compounds. The final conformations, with **8aB** and **8aC** as examples, are shown in Figures 1 and 2, respectively.. *Ab initio* calculations were performed by second-order perturbative analysis of the Fock matrix in the NBO base,[8-11] where the energy of donation (kcal/mol) of a lone pair to a given anti-bonding orbital could be calculated. We considered that, by comparison with the experimental findings, the factors governing the relative stability of the cis and trans isomers, and the substituent sensitivity of the ^{13}C NMR chemical shifts could be evaluated more reliably.

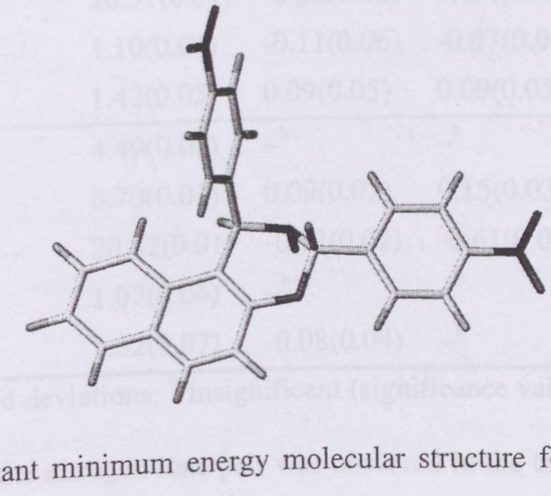


FIGURE 1. Final predominant minimum energy molecular structure for **8aB**, obtained by using *ab initio* HF/6-31G* calculations.

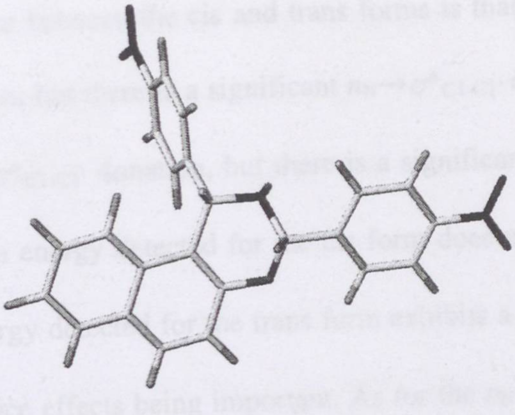


FIGURE 2. Final predominant minimum energy molecular structure for **8aC**, obtained by using *ab initio* HF/6-31G* calculations.

In the present calculated model conformations, the nitrogen lone pair can overlap with six different vicinal antibonding orbitals associated with C1 ($\sigma^*_{C1\text{-}H}$, $\sigma^*_{C1\text{-}C1'}$ and $\sigma^*_{C1\text{-}C10b}$) or with C3 ($\sigma^*_{C3\text{-}H}$, $\sigma^*_{C3\text{-}C1''}$ and $\sigma^*_{C3\text{-}O4}$). The overlapping energy values are listed in Table S3. The results of Hansch analysis of the energy values as DV according to Eq. 2 are given in Table 2.

Table 2. Multiple linear regression analysis of overlapping energy values according to Eq. 2 for **8-14**

	Overlapping	k	ρ_F^Y	ρ_R^Y	ρ^X	r
B	$n_N \rightarrow \sigma^*_{C1\text{-}C1'}$	3.13(0.01)[a]	0.34(0.01)	0.37(0.02)	-0.13(0.01)	0.983
	$n_N \rightarrow \sigma^*_{C1\text{-}C10b}$	8.94(0.01)	–[b]	–[b]	-0.25(0.02)	0.915
	$n_N \rightarrow \sigma^*_{C3\text{-}O4}$	20.31(0.01)	-0.36(0.02)	-0.24(0.03)	-0.16(0.01)	0.956
	$n_N \rightarrow \sigma^*_{C3\text{-}C1''}$	1.10(0.04)	-0.11(0.06)	-0.07(0.04)	0.12(0.05)	0.909
	$n_N \rightarrow \sigma^*_{C3\text{-}H}$	1.42(0.03)	0.09(0.05)	0.09(0.05)	-0.05(0.03)	0.865
C	$n_N \rightarrow \sigma^*_{C1\text{-}H}$	4.49(0.01)	–[b]	–[b]	-0.13(0.01)	0.799
	$n_N \rightarrow \sigma^*_{C1\text{-}C10b}$	8.70(0.01)	0.09(0.02)	0.15(0.03)	-0.25(0.01)	0.942
	$n_N \rightarrow \sigma^*_{C3\text{-}O4}$	20.82(0.01)	-0.72(0.02)	-0.61(0.03)	-0.10(0.02)	0.984
	$n_N \rightarrow \sigma^*_{C3\text{-}C1''}$	1.07(0.04)	–[b]	–[b]	-0.08(0.02)	0.819
	$n_N \rightarrow \sigma^*_{C3\text{-}H}$	1.62(0.07)	-0.08(0.04)	–[b]	–[b]	0.642

[a] Standard deviations; [b] Insignificant (significance value > 0.05)

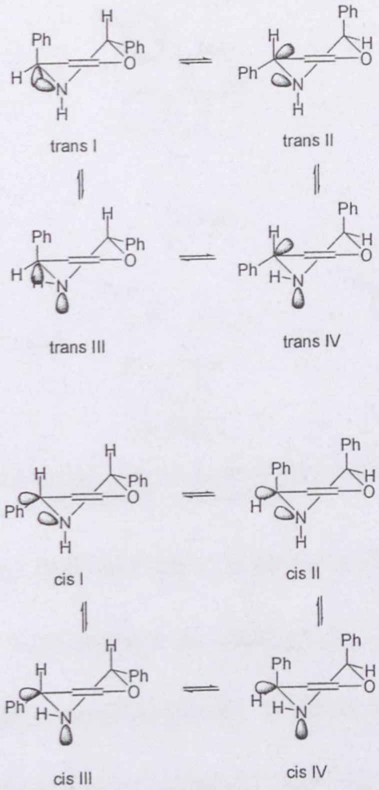
Significant overlapping of the nitrogen lone pair was observed in the trans forms **B** (to $\sigma^*_{C1\text{-}C1'}$, $\sigma^*_{C1\text{-}C10b}$ and $\sigma^*_{C3\text{-}O4}$) and in the cis forms **C** (to $\sigma^*_{C1\text{-}H}$, $\sigma^*_{C1\text{-}C10b}$ and $\sigma^*_{C3\text{-}O4}$). As concerns the donation energies, the clearest difference between the cis and trans forms is that, for the trans form, there is no significant $n_N \rightarrow \sigma^*_{C1\text{-}H}$ donation, but there is a significant $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation. On the other hand, for the cis form there is no $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation, but there is a significant $n_N \rightarrow \sigma^*_{C1\text{-}H}$ donation. Further, while the $n_N \rightarrow \sigma^*_{C1\text{-}H}$ donation energy detected for the cis form does not depend on the substituent Y, the $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation energy detected for the trans form exhibits a clear substituent dependence on Y, both inductive and resonance effects being important. As for the $n_N \rightarrow \sigma^*_{C1\text{-}C10b}$ donation, for the cis form there is a slight dependence on substituent Y, but for the trans isomer no analogous dependence was observed. However, the sum of the different significant donation energies listed above are relatively close to each other: for X=Y=H, they are 34.98 and 36.80 (in other words the sum of the k values in Table 2) for the trans and cis isomers, respectively. It should be noted that the cis isomers exhibit somewhat larger donation energy sums. This is contrary to the idea *that an anomeric effect controls* the marked stability difference between the cis and trans series.

For the trans forms (**B**), the overlapping energy for $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ was clearly dependent on substituent Y ($\rho_F^Y = 0.34$ and $\rho_R^Y = 0.37$; Table 2). On the other hand, for the cis forms (**C**), the overlapping energy for $n_N \rightarrow \sigma^*_{C1\text{-}C10b}$ was substituent-dependent, but to an essentially smaller extent ($\rho_F^Y = 0.09$ and $\rho_R^Y = 0.15$; Table 2). Thus, the extent of the effect of substituent Y on the donation energies seems to depend on the configuration. In both cases, electron donation/withdrawal by both inductive and resonance mechanisms is important, but the sensitivity to the resonance effect is slightly higher. The positive values of both ρ_F^Y and ρ_R^Y mean that EW substituents increase the value of the DV. It is generally thought that the mechanism of the anomeric effect is the overlapping between an occupied lone pair orbital and an anti-bonding orbital of an adjacent polar bond. According to this interpretation, electron density is transferred from N-2 to the C1 –C1' antibonding orbital. This can be explained as follows. In the case of $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ overlapping, the positive ρ_F^Y and ρ_R^Y values can be understood in terms of the contribution of the corresponding double bond – no-bond resonance structure ***e*** (Scheme 4). EW substituents stabilize structure ***e*** both inductively and by direct resonance. The stabilization of resonance structure ***e*** results in an increase in the donation energy in question as compared with that of the parent compound, and consequently positive ρ values are observed.

Both **B** and **C** possess a half-chair structure. Scheme 2 gives the relevant conformations due to nitrogen/ring inversions. It is generally thought that in 1,3-oxazine systems the equatorial orientation of the substituent attached to the O-*C*-N carbon is favored.[12] The 1,3-axial-pseudo-axial orientations (cis II and IV) of the cis forms are highly unfavored due to the severe steric interaction, and their presence can be neglected. Hence, the equatorial–pseudo-equatorial orientations (cis I and III) preponderate in the cis forms. As a result of the equatorial preponderance of 3-phenyl substituents (trans I and III), the trans forms exhibit 1-phenyl pseudo-axial orientations.[12] Thus, the minimum energy conformations used in the NBO analysis (trans I and cis I, cf. Figures 1 and 2) are relevant model structures. In the orientation trans I (see Scheme 2), overlap between the nitrogen lone pair and the sigma antibonding orbital of the C1-C1' bond is possible, even if it is not as favored as it could be in the orientation trans III. In cis I, the spatial orientations of the nitrogen lone pair and the C1-C1' anti-bonding orbital do not allow overlap. Accordingly, the calculations did not indicate any significant $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C1\text{-}C1'}}$ donation for the cis isomers. Interestingly, for trans I the dependence of the overlapping energy of $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C1\text{-}C1'}}$ on substituent Y is clearly significant ($\rho_{\mathrm{F}}^{\mathrm{Y}} = 0.34$ and $\rho_{\mathrm{R}}^{\mathrm{Y}} = 0.37$; Table 2) the overlapping increasing with EW substituents. As concerns the $\sigma^*_{\mathrm{C1\text{-}C10b}}$ orbital, the favorable overlapping of the nitrogen lone pair is possible in orientations I, which possess an equatorial nitrogen lone pair orientation for both the cis and the trans isomers. The calculated donation energies are about three times greater than those for $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C1\text{-}C1'}}$ donation in the case of the trans isomers. However, in contrast with the above, the dependence on substituent Y is small for the cis isomers and insignificant for the trans isomers. The differences between the calculated substituent-dependent stereoelectronic effects (anomeric effects) at C-1 can therefore be understood on a conformational basis.

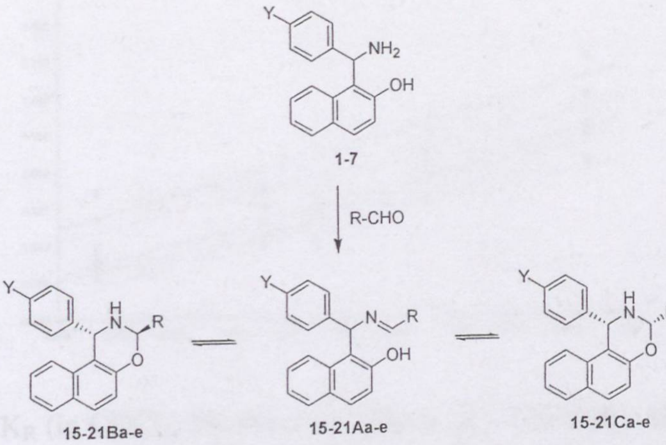
The largest values of the overlapping energies observed for our compounds are connected with the $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ transmission. However, the donation energies in question for both the cis and the trans series are very close to each other. Hence, this anomeric effect can not explain the stability differences between the isomers. For both the trans (**B**) and the cis forms (**C**), the overlapping energy for $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ was clearly dependent on substituent Y (**B**: $\rho_{\mathrm{F}}^{\mathrm{Y}} = -0.36$ and $\rho_{\mathrm{R}}^{\mathrm{Y}} = -0.24$; **C**: $\rho_{\mathrm{F}}^{\mathrm{Y}} = -0.72$ and $\rho_{\mathrm{R}}^{\mathrm{Y}} = -0.61$, Table 2). Reverse behavior (values of $\rho < 0$) means that the sensitivity of the process in question is diminished by electron-donating (ED) substituent. Since both the inductive and resonance sensitivities in question exhibit a reverse substituent dependence, the value of the donation energy is decreased on ED substitution. It can be assumed that the deviations in the half-chair structure itself between the cis and trans isomers are small. Thus, the different magnitudes of the ρ values indicate that the substituent dependence of the donation energy in question is dependent on the orientation of the substituted phenyl ring at C-1, the eq'-Ph–N–C–O pathway being able to transmit the effect of substituent Y more efficiently than the ax'-Ph–N–C–O pathway. The variation in the substituent dependence of the $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ donation energy can be explained by comparison with $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C1\text{-}C1'}}$ transfer (**B**: $\rho_{\mathrm{F}}^{\mathrm{Y}} = 0.34$ and $\rho_{\mathrm{R}}^{\mathrm{Y}} = 0.37$; **C**: $\rho_{\mathrm{F}}^{\mathrm{Y}}$ and $\rho_{\mathrm{R}}^{\mathrm{Y}}$, not significant), if we neglect the contributions of the $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}C1''}}$ and $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}H}}$ transformations for which the donation energy values are small and for which the $\rho_{\mathrm{F}}^{\mathrm{Y}}$ and $\rho_{\mathrm{R}}^{\mathrm{Y}}$ values in most cases are significant, but relatively small. The donation ability of one nitrogen lone pair is limited as regards the number and extent of different donations. The routes giving the maximal stabilization of the molecular structure prevail. For the donation $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C1\text{-}C1'}}$ observed for the trans isomer, both the $\rho_{\mathrm{F}}^{\mathrm{Y}}$ and $\rho_{\mathrm{R}}^{\mathrm{Y}}$ values are positive. This means that EW substituents increase the value of the donation energy. In contrast, for $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ both $\rho_{\mathrm{F}}^{\mathrm{Y}}$ and $\rho_{\mathrm{R}}^{\mathrm{Y}} < 0$. This means that EW substituents decrease the value of the donation energy. This decrease compensates the increase in $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C1\text{-}C1'}}$. These two effects compete. As a consequence, the absolute values of $\rho_{\mathrm{F}}^{\mathrm{Y}}$ and $\rho_{\mathrm{R}}^{\mathrm{Y}}$ for $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ donation for the trans isomer are only about half those observed for the cis isomer. The $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ transmission also seems to be sensitive to substituent X, but to an essentially smaller extent than above. It has been shown by Neuvonen *et al.* that an increase in the contribution of $n_{\mathrm{N}}\rightarrow\sigma^*_{\mathrm{C3\text{-}O4}}$ donation facilitates the ring opening in ring-chain tautomerism.[6]

SCHEME 2



3-Alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. The ring-chain tautomeric ratio is determined by the free energy difference between the tautomeric forms. Therefore, the observed systematic change in log K can not be simply related to the energetic changes either in the ring form or in the chain form. To find evidence of the substituent effect in the ring form, the tautomeric system of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **15-21** was analyzed. Condensations of aminonaphthols **1-7** with equivalent amounts of aliphatic aldehydes resulted in the naphthoxazine model compounds **15-21** (Scheme 3).

SCHEME 3



Y = NO$_2$: **1,15**; Br: **2,16**; Cl: **3,17**; H: **4,18**; F: **5,19**; Me: **6,20**; OMe: **7,21**
R = Me: **a**; Et: **b**; Pr: **c**; *i*Pr: **d**; *t*Bu: **e**

The ^{1}H NMR spectra of **15-21** showed that, in CDCl$_3$ solution at 300 K, the members **a-e** of each set of compounds **15-21** participated in two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** and **C**). The relative configurations of **B** and **C** were proved by using NOE measurements (see Experimental). In any set of compounds, chain forms (**A**) could not be detected. This is in accordance with the results of earlier studies on the condensation products of 2- or 3-aminoalkanols and aliphatic carbonyl compounds, in which branching of the chain in 2-alkyl substituents proved to stabilize the cyclic tautomers.[13] The proportions (%) of the ring forms are given in Table S4.

The epimerization constants were calculated from the ratio of the ring forms, log K_R=[**B**]/[**C**]. To find a linear equation to describe the influence of the alkyl substituents on log K_R, three different alkyl substituent parameters were studied: E_s (calculated from the hydrolysis or aminolysis[14] of esters) and two other steric parameters independent of any kinetic data: ν (derived from the van der Waals radii[15]) and V^a (the volume of the portion of the substituent that is within 0.3 nm of the reaction center[16]). Good correlations were found with all three alkyl substituent parameters. The linear regression analysis data for series **15-21** are given in Table S3. As the best correlations were observed *vs* the Meyer parameters (V^a, Eq. 4), this was used for the further examinations (Figure 3).

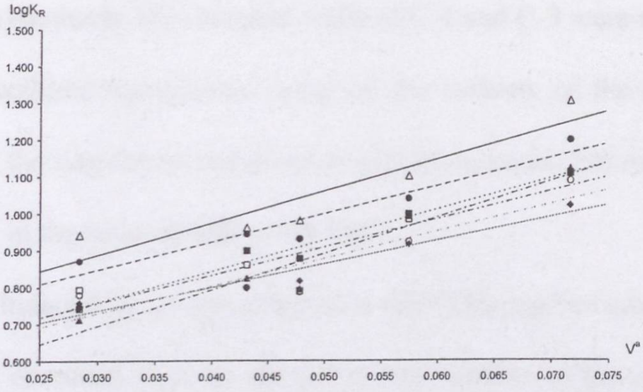


FIGURE 3. Plots of log K_R (in $CDCl_3$) for **15a-e** (Δ), **16a-e** (▲), **17a-e** (●), **18a-e** (♦), **19a-e** (■), **20a-e** (○) and **21a-e** (□) *vs* Meyer parameter V^a

$$\log K_R = 0.55 + 7.88V^a \qquad \text{(Eq. 4)}$$

To study the common influence of the aryl substituents at position 1 and the alkyl substituents at position 3, multiple linear regression analysis of log K_R as dependent variable was performed according to Eq. 5. The analysis results are listed in Table 1.

$$\log K_R = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho^R V^a \qquad \text{(Eq. 5)}$$

The significant dependence of log K_R on the inductive effect (σ_F) of substituent Y for **15-21**, together with the σ_F dependence of log K for **8-14**, led us to conclude that only the free energy of the trans forms are influenced by the inductive effect of substituent Y, which can be explained by the anomeric effect influenced quantitatively by Y. The ρ_F^Y value obtained via Eq. 5 is relatively close to that obtained according to Eq. 3 for the equilibrium trans⇌chain (**B**⇌**A**). This supports the validity of the ρ_F^Y values, indicating that these parameters reflect the pure contribution of Y.

Influences of the substituents on the ^{13}C NMR chemical shifts of compounds 8-14. The ^{13}C NMR chemical shift changes induced by phenyl substituents (SCS) on C-2 have been analyzed by several different dual substituent parameter approaches.[6,17] The best correlation was obtained with the equation SCS = $\rho_F \sigma_F + \rho_R \sigma_R$.[11] For all the studied 1,3-heterocyclic systems, negative ρ_F values were observed, indicating reverse behavior of the electron density on C-2.[6]

To check the previous hypothesis, the chemical shifts of C-1 and C-3 were measured in $CDCl_3$ and are listed in Table S6. To facilitate comparison, some of the carbons of the chain forms are indicated analogously with those of the ring forms and given in quotation marks. For example, "C-3" in the series **8-14A** corresponds to C-3 in the series **8-14B** and **8-14C**.

Chemical shift changes induced by an aryl substituent (SCS) for a given compound were calculated as the differences in the ^{13}C chemical shift for the substituted relative to the unsubstituted (X=H, Y=H) compound.

$$\mathrm{SCS} = \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho_F^X \sigma_F^X + \rho_R^X \sigma_R^X \qquad \text{(Eq. 6)}$$

The multiple regression analysis data obtained via Eq. 6 for C-1 and C-3 are presented in Table 3.

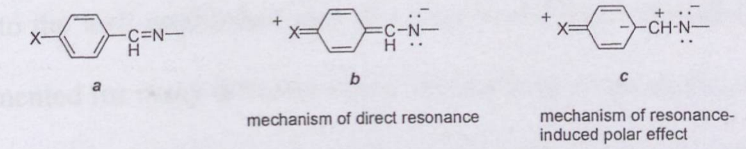
Table 3. Multiple linear regression analysis of chemical shifts for **8-14** according to Eq. 6

		ρ_F^Y	ρ_R^Y	ρ_F^X	ρ_R^X	r
For C-1	**A**	-1.81(0.11)[a]	–[b]	–[b]	0.45(0.16)	0.967
	B	-1.12(0.06)	0.75(0.09)	–[b]	–[b]	0.982
	C	-1.51(0.08)	0.60(0.13)	-0.49(0.08)	–[b]	0.983
For C-3	**A**	1.74(0.14)	2.31(0.21)	-2.96(0.14)	–[b]	0.977
	B	–[b]	0.44(0.15)	-1.56(0.09)	-0.56(0.15)	0.968
	C	-0.53(0.07)	-0.30(0.11)	-1.88(0.07)	-0.44(0.11)	0.987

[a] Standard deviations; [b] Insignificant (significance value > 0.05)

The trans isomers **B** exhibit low-field (i.e. high-frequency) C-1 ^{13}C NMR chemical shifts as compared with those of the cis isomers **C**, ΔSCS being about 3 ppm. The values of ρ_F^Y and ρ_R^Y for C-1 seem to depend on the configuration. The trans isomers exhibit somewhat less negative ρ_F^Y values but slightly more positive ρ_R^Y values. Thus, the sensitivity to the inductive effect is somewhat stronger within the cis series. It was shown above that the sensitivity to the anomeric effect was larger in the trans series.

The anomeric effect can explain the differences in sensitivity of the ^{13}C NMR chemical shifts of C-1 to substituent Y between the trans and the cis series. A significant $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ donation was observed in the trans series, but not in the cis series. The valence bond representation of the anomeric effect is the double bond – no-bond resonance structure (Scheme 4). For the trans isomers, the resonance structure ***e*** and therefore the sp^2 character of C-1 are more prominent as compared with those for the cis isomers. Typically, the sp^2 hybridized carbons exhibit lower-field ^{13}C NMR chemical shifts than those of the sp^3 hybridized carbons. Therefore, the trans series exhibits low-field C-1 shifts. If a substituent-dependent stereoelectronic effect $n_N \rightarrow \sigma^*_{C1\text{-}C1'}$ is present in the trans form, the absolute value of ρ_F^Y has to be decreased because the phenyl substituents cause an opposite dependence in the carbon chemical shifts. Since EW substituents stabilize resonance form ***e***, the sp^2 character of C-1 is increased. As a consequence, a less negative ρ_F^Y value is observed. Unexpectedly, both the trans and cis isomers exhibit positive ρ_R^Y values. Instead, they give negative ρ_R^X values, analogously observed earlier for 1,3-*O*,*N*-heterocycles. ρ_R values are measures of prevailing resonance interactions. In principle, there are two possible mechanisms for the resonance interaction of a side-chain-substituted benzene derivative (a C=N double bond as an example). Direct (normal) resonance is based on an interaction of type ***b***. A resonance-induced polar effect, which is indirect resonance, is based on an interaction of type ***c***.



In direct resonance, ED substituents increase the electron density at the probe site (C-1) resulting in up-field ^{13}C NMR chemical shifts (i.e. smaller shift values) and consequently in $\rho_R > 0$. In contrast, in resonance-induced polar effects, ED substituents decrease the electron density at the probe site (C-1), resulting in $\rho_R < 0$. The observed positive ρ_R^Y values indicate the operation of direct resonance. This can be understood by the appearance of the double bond – no-bond structure *f*, which is sensitive to resonance interaction and corresponding to $n_N \rightarrow \sigma^*_{C1\text{-}C10b'}$ donation (see above). In summary, the behavior of the ^{13}C NMR chemical shifts of C-1 can be nicely explained on the basis of the anomeric effect directed on C-1.

The values of ρ_F^X and ρ_R^X for C-3 also seem to depend on the configuration. The trans isomers exhibit a somewhat less negative ρ_F^X values but slightly more negative ρ_R^X values. Accordingly, the sensitivity to the inductive effect is again somewhat stronger for the cis series. For C-1, positive ρ_R^Y values were observed for both the trans and the cis forms (Table 3), whereas for C-3, negative ρ_R^X values were found for both series.

SCHEME 4

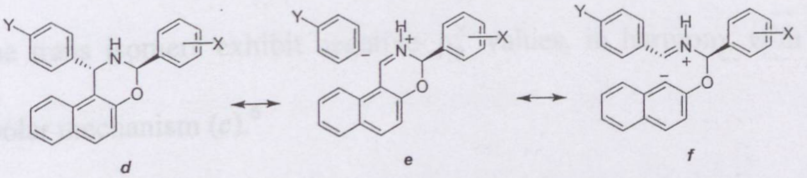
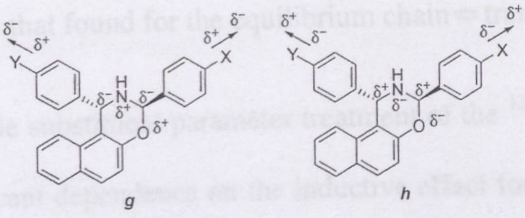


Table 3 reveals a reverse trend of the inductive substituent effects (i.e. ρ_F^Y for C-1 and ρ_F^X for C-3 < 0) for both the cis and the trans series. This behavior means that the EW substituents induce upfield ^{13}C NMR chemical shifts as compared with those of the corresponding non-substituted derivative. This behavior is contrary to the well-established idea of a generalized inductive effect, but its appearance is nowadays well documented for many different series of unsaturated side-chain derivatives of substituted benzene. The origin of the reverse trend of the substituent effect is qualitatively satisfactorily understood. On the other hand, the appearance of the analogous effect with saturated carbon centers such as those situated between the two heteroatoms in 1,3-*O*,*N*-heterocycles has been much less well studied.[6] The trans and cis series in the present work offer an interesting opportunity to study this type of reversed trend of substituent effect. The negative ρ_F values have been explained by Neuvonen *et al.* by the concept of the substituent-sensitive polarization of the N–C–O system.[6] The substituent interaction with the polar C–O and/or C–N bond results in dipolar induction, as depicted in Figure 4. In consequence, with EW substituents the electron density at the carbon joined to a heteroatom is increased, whereas with ED substituents it is decreased. The idea of substituent interaction with the polar bond (PSI = polar substituent interaction) is, like that of π-polarization, in conflict with the concept of the generalized inductive effect. Interestingly, the concept of PSI now seems to hold in connection with the polar (C-1)–N bonds in the title compounds.



g X = Y = EW

h X = Y = ED

FIGURE 4. Polar substituent interactions in the trans form

Both the cis and the trans isomers exhibit negative ρ_R^X values, in harmony with the operation of a resonance induced polar mechanism (***c***).[6]

Conclusions

The influence of aryl substituents at positions 1 and 3 on the ring-chain equilibria of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines could be described by using Hansch equations. Multiple linear regression analysis via Eqs 2, 3, 5 and 6 allowed determination of the influences of substituents Y and X situated on the 1- or 3-phenyl ring, respectively. Previous systematic quantitative investigations on the ring-chain tautomeric equilibria of 1,3-*O*,*N*-heterocyclic compounds (Y = *O*, *N*) have shown that EW substituents X on the phenyl ring attached to the carbon situated between the heteroatoms increase the relative proportion of the ring tautomer inductively and by resonance. It has now been proved for the first time that EW substituents on the 1-phenyl ring have an analogous inductive influence on trans⇌chain (**B**⇌**A**) tautomeric equilibria. By means of model structures, the overlapping of the nitrogen lone pair with six different vicinal antibonding orbitals (anomeric effect) associated with C-1 (σ^*_{C1-H}, $\sigma^*_{C1-C1'}$ and $\sigma^*_{C1-C10b}$) or with C-3 (σ^*_{C3-H}, $\sigma^*_{C3-C1''}$ and σ^*_{C3-O4}) was studied. The anomeric effects associated with C-1 turned out to be dependent on the configurations of the isomers. The stereoelectronic effect was also studied in the case of 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines. The influence of alkyl substituents on the values of the epimerization constant (K_R)

could be described in terms of their Meyer parameters V^a. The results of multiple linear regression analysis of the log K_R values reveal a significant dependence on the inductive effect of substituent Y (σ_F), which is comparable with that found for the equilibrium chain$\rightleftharpoons$trans (**A**$\rightleftharpoons$**B**).

With two substituents (double substituent parameter treatment of the ^{13}C chemical shift changes of C-1 and C-3) there was a significant dependence on the inductive effect for both ring forms with negative ρ values. On the other hand, both the cis and the trans isomers gave positive ρ_R^Y values at C-1, but negative ρ_R^X values at C-3, indicating the appearance of a resonance-induced polar effect and direct resonance, respectively. The chemical shift changes induced by substituents Y (SCS) could be explained with the aid of the double bond – no-bond resonance structures ***e*** and ***f***. Our conclusions were supported by the calculated energies of donation of the nitrogen lone pair to the C1–C1' and C1–C10b anti-bonding orbitals.

Experimental Section

1-[Amino-(4-nitrophenyl)methyl]-2-naphthol hydrochloride (1.HCl): To a solution of 2-naphthol (14.42 g, 0.10 mol) and 4-nitrobenzaldehyde (30.22 g, 0.20 mol) in absolute MeOH (100 mL), 25% methanolic ammonia solution (8 mL) was added. The mixture was left to stand at ambient temperature for 24 h and the crystalline product that separated out was filtered off, washed with MeOH (2 x 50 mL), dried and suspended in 20% HCl (200 mL). The mixture was stirred at 50-60 °C for 4 h. The solvent was then evaporated off and the oily residue crystallized on treatment with EtOAc. The pale-yellow crystals were filtered off, washed with EtOAc (2 x 30 mL) and recrystallized from MeOH–Et_2O (20 mL : 200 mL). Yield: 8.27 g (25%), mp 190-192 °C. Analysis: calculated for $C_{17}H_{15}ClN_2O_3$: C, 61.73; H, 4.57; N, 8.47; found: C, 61.77; H, 4.53; N, 8.51. ^1H NMR (DMSO) δ: 6.46 (s, 1H, C*H*NH2), 7.32-7.42 (m, 2H, H-3, H-6), 7.54 (t, 1H, J = 7.8 Hz, H-7), 7.72 (d, 2H, J = 8.6 Hz, H-2'), 7.88 (d, 1H, J = 5.6 Hz, H-5), 7.91 (d, 1H, J = 6.0 Hz, H-4), 8.14 (d, 1H, J = 8.3 Hz, H-8), 8.24 (d, 2H, J = 8.6 Hz, H-3'); ^{13}C

NMR (DMSO) δ: 50.00, 113.26, 118.79, 121.89, 123.17, 123.52, 128.08, 128.1, 128.78, 128.84, 131.15, 131.84, 145.07, 146.93, 153.95

1-[Amino-(4-bromophenyl)methyl]-2-naphthol (2) and 1-[amino-(4-fluorophenyl)methyl]-2-naphthol (5): Compounds **2** and **5** were prepared from 2-naphthol (14.42 g, 0.10 mol) and 4-bromobenzaldehyde (37.00 g, 0.20 mol) or 4-fluorobenzaldehyde (24.82 g, 0.20 mol) according to ref. 4. **2**: Yield: 5.25 g (16%), mp 115-116 °C (*i*Pr_2O). Analysis: calculated for $C_{17}H_{14}BrNO$: C, 62.21; H, 4.30; N, 4.27; found: C, 62.20; H, 4.32; N, 4.25. ^{1}H NMR (CDCl3) δ: 6.10 (s, 1H, C*H*NH2), 7.14 (d, 1H, J = 8.8 Hz, H-3), 7.25 (t, 1H, J = 8.1 Hz, H-6), 7.31-7.36 (m, 3H, H-2', H-7), 7.41 (d, 2H, J = 8.6 Hz, H-3'), 7.65 (d, 1H, J = 8.8 Hz, H-8), 7.70 (d, 1H, J = 8.8 Hz, H-4), 7.72 (d, 1H, J = 8.1 Hz, H-5); ^{13}C NMR (CDCl3) δ: 55.25, 114.78, 120.61, 121.23, 121.95, 122.46, 127.33, 128.55, 129.21, 129.42, 130.21, 131.86, 131.95, 141.45, 156.85

5: Yield: 6.15 g (23%), mp 115-117 °C (*i*Pr_2O). Analysis: calculated for $C_{17}H_{14}FNO$: C, 76.39; H, 5.28; N, 5.24; found: C, 76.42; H, 5.31; N, 5.22. ^{1}H NMR (CDCl3) δ: 6.12 (s, 1H, C*H*NH2), 6.97 (t, 2H, J = 8.6 Hz, H-3'), 7.15 (d, 1H, J = 8.8 Hz, H-3), 7.24 (t, 1H, J = 7.6 Hz, H-6), 7.33 (t, 1H, J = 7.3 Hz, H-7), 7.42 (dd, 2H, J = 5.5, 8.56 Hz, H-2'), 7.65 (d, 1H, J = 8.6 Hz, H-8), 7.70 (d, 1H, J = 8.8 Hz, H-4), 7.72 (d, 1H, J = 8.1 Hz, H-5); ^{13}C NMR (CDCl3) δ: 55.16, 115.06, 115.70, 120.86, 121.22, 122.51, 126.64, 128.61, 128.77, 129.47, 129.56, 131.89, 138.31, 156.90, d (161.16, 163.66)

General method for the synthesis of 3-aryl- or alkyl-substituted 1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (8-21): To a solution of the appropriate aminonaphthol (1 mmol) or aminonaphthol hydrochloride (**1.HCl**) in absolute MeOH (20 mL), an equivalent amount of aromatic or aliphatic aldehyde (for liquid aldehydes, a freshly distilled sample was used) and (in the case of **1.HCl**) Et_3N (0.11 g. 1.1 mmol) was added, and the mixture was left to stand at ambient temperature for 24 h. The crystalline products (**8a-g**, **9a-g**, **12a-g**, **10c**, **11c**, **13c**, **14c**, **15a**, **15d**, **15e**, **16a-e**, **17a**, **17c-e**, **18a-e**, **19a-e**, **20a-e**, **21a**, **21d** and **21e**) were filtered off and recrystallized. When no crystals separated out, the solvent was evaporated off. For **15b**, **15c**, **17b**, **21b** and **21c**, the oily residue was partitioned between

H_2O (10 mL) and $CHCl_3$ (10 mL), and the organic layer was separated, dried and evaporated. All of the oily products (**15b**, **15c**, **17b**, **21b** and **21c**) were dried in a vacuum desiccator for 24 h. The NMR spectra proved that the purities of these compounds were greater than 95%.

All of the new naphthoxazines gave satisfactory data on elemental analysis (C, H, N ±0.3%). The physical data on compounds **15-21a-e** are listed in Table S7.

In consequence of the very similar NMR spectroscopic characters of 3-alkyl-1-aryl-2,3-dihydro-2*H*-naphth[1,2-*e*][1,3]oxazines **15-21a-e**, determination of the relative configurations of the major and minor ring-closed tautomers was performed only for **20a**. Its data were chosen to illustrate the ^{1}H NMR spectra of the prepared tautomeric compounds. 3-Alkyl-1-aryl substituents did not change the sequence of the chemical shifts of the characteristic O-C*H*R-N and N=C*H*R protons. The NOESY spectra of **20a** unequivocally showed that the *major* ring forms in all tautomeric equilibria (**15-21a-e**) contain the 3-alkyl-1-aryl substituents in the *trans* position (**B**).

20a: 1:6 cis-trans mixture: 1.44 (d, 3H, J = 5.8 Hz, Me-3trans), 1.52 (d, 3H, J = 5.8 Hz, Me-3cis), 4.83 (q, 1H, J = 5.8 Hz, H-3cis), 4.90 (q, 1H, J = 5.8 Hz, H-3trans), 5.45 (s, 1H, H-1trans), 5.72 (s, 1H, H-1, cis), 7.02-7.11 (Ar), 7.12-7.18 (Ar), 7.21-7.28 (Ar), 7.29-7.35 (Ar); ^{13}C NMR (CDCl3): overlaping signals in the aromatic region

Statistical calculations. The sources of the substituent constants were as follows: σ^+: ref. 18b; σ_F, σ_R: ref. 18a (except σ_F and σ_R for Br: ref. 18b); V^a: ref. 16. Statistical calculations were performed with the aid of the SPSS statistical program, version 9.0.

Quantum chemical calculations. Hartree-Fock energies were calculated and NBO analysis was performed by using the *ab initio* GAUSSIAN 98 program package.[19] All structures were optimized without any restriction. The optimized structures obtained were analyzed and the results were visualized with the modeling program SYBYL 6.7.[20]

Acknowledgment

The authors' thanks are due to the Hungarian Research Foundation (OTKA No. T034901 and T030452) for financial support.

Supporting information available: Measured log K values. Donor-acceptor stabilization energies obtained from the second-order perturbation theory analysis of the Fock matrix in the NBO base. Linear regression analysis data for **15-21**. ^{13}C chemical shifts for oxazines **8-14**. Physical data on **8-21**. Cartesian coordinates and HF energies for **8a-g**. Coordinates of the other compounds studied are available on request. This material is available free of charge via the Internet at http://pubs.acs.org.

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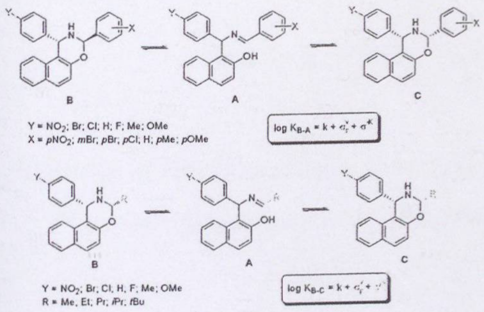

IV.

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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IV.

Abstract

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 (r^1-o-r^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 Eq. 1. Study of the effects of substituents X and Y on the tautomeric equilibria (by the aid of the multiple linear regression analysis of Eqs. 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 (Eq. 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 Eq. 1 as concerns 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* heterocyclic ring on the parameter of Eq. 1.[3-5]

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

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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Abstract

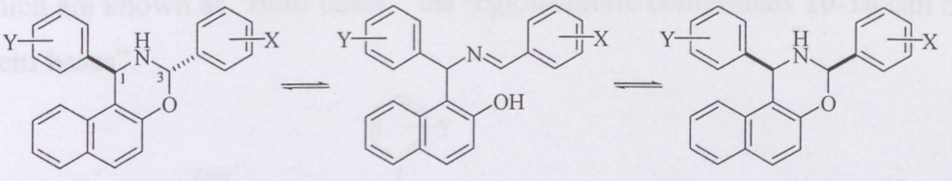
A number of 2-[α-amino-Y-substituted-benzyl)-1-naphthol hydrochlorides were prepared by a convenient Mannich-type aminoalkylation. 2,4-Diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines were prepared through the ring-closure reactions of the starting aminonaphthols with aromatic aldehydes, which proved to furnish three-component (r^1-o-r^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 Eq. 1. Study of the effects of substituents X and Y on the tautomeric equilibria (by the aid of the multiple linear regression analysis of Eqs. 2 and 3) revealed that the *trans*$\rightleftharpoons$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 (Eq. 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 Eq. 1 as concerns 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* heterocyclic ring on the parameter of Eq. 1:[3-5]

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

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 (Fig. 1).



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

X = NO_2(*p*), Br(*m*), Br(*p*), Cl(*p*), H, Me(*p*), OMe(*p*)
Y = NO_2(*p*), NO_2(*m*), Br(*m*), Br(*p*), Cl(*p*), H, F(*p*), Me(*p*), OMe(*p*)

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

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

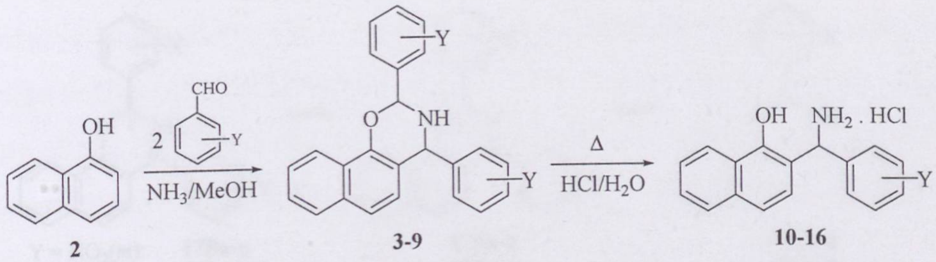
$$\log K = k + \rho_F^Y \sigma_F^Y + \rho_R^Y \sigma_R^Y + \rho^X \sigma^{+X} \qquad \text{(Eq. 2)}$$

Our present aim was to examine the applicability of Eq. 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] Via this Mannich aminoalkylation reaction, a series of secondary and tertiary 2-aminomethyl-1-naphthol derivatives were synthesized earlier,[8,9] and some recent modifications of this procedure (*e.g.* application of preformed methylene iminium salts) considerably extended the accessibility 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]

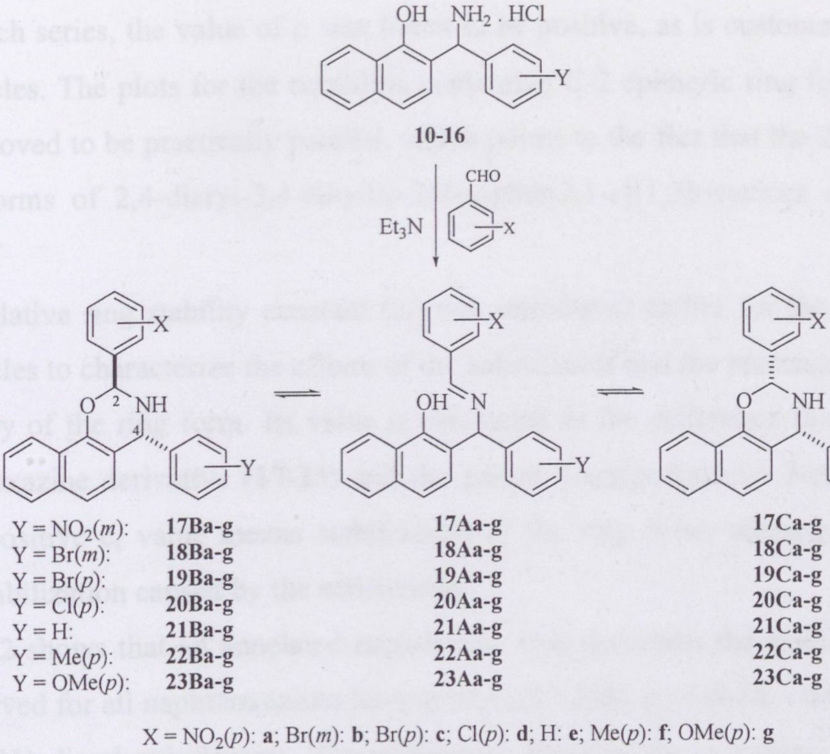
The condensation of 1-naphthol (**2**) and benzaldehyde or substituted benzaldehydes in the presence of ammonia, and subsequent acidic hydrolysis, furnished aminonaphthol hydrochlorides **10-16** in moderate yields (Scheme 1). In consequence of the close analogy to 1-(α-aminobenzyl)-2-naphthols, which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



Y = NO$_2$(*m*): **3,10**; Br(*m*): **4,11**; Br(*p*): **5,12**; Cl(*p*): **6,13**; H: **7,14**; Me(*p*): **8,15**; OMe(*p*): **9,16**

Scheme 1

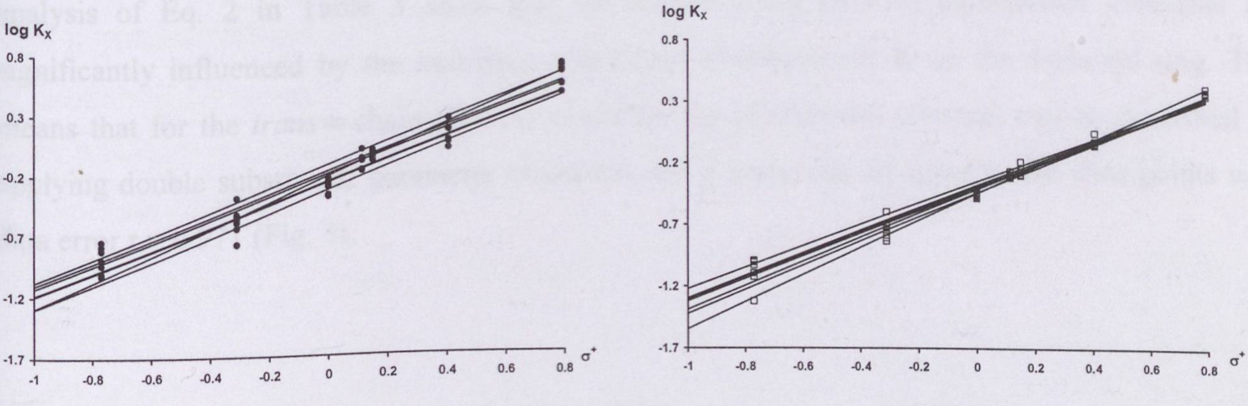
In contrast with the regioisomeric 1-(α-aminobenzyl)-2-naphthols, which are relatively stable crystalline substances,[3] the bases of **10-16** proved to be quite unstable compounds, which were therefore liberated in situ in the further transformations. The naphthoxazine model compounds **17-23** were prepared by condensations of aminonaphthol hydrochlorides **10-16** with equivalent amounts of aromatic aldehydes in the presence of Et$_3$N (Scheme 2). The ^{1}H 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**) besides 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 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-2*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*.



Scheme 2

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 experimental). When Eq. 1 was applied to the log K values (K = [ring]/[chain]), good linear correlations were obtained *vs* the Hammett-Brown parameter σ^+ of the substituent X on the 2-phenyl group for compounds **17-23** (Fig. 2, Table 2).

-Insert Table 1-



a

b

Figure 2. ***a***: Plots of log K_X for **17-23B** (●) *vs* Hammett-Brown parameter σ^+.
b: Plots of log K_X for **17-23C** (□) *vs* Hammett-Brown parameter σ^+

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**$\rightleftharpoons$**A** and **C**$\rightleftharpoons$**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**: $\log K_0 = -0.15$).[2] A positive c_s value means stabilization of the ring form, whereas a negative c_s value indicates destabilization caused by the substituents.

Table 2 shows that an annelated naphthalene ring decreases the stability of the ring form; this was observed for all naphthoxazines having *trans* (**17-23B**: $c_s = -0.18 - 0.03$) or *cis* (**17-23C**: $c_s = -0.30 - -0.21$) diaryl substituents. The differences between the c_s values for the *trans* and *cis* series are smaller than that found for regioisomeric naphthoxazines (**1B**: $c_s = 0.68$, **1C**: $c_s = -0.19$),[3] which can be explained by the less unfavourable steric arrangement of the diaryl substituents in **17-23**.

-Insert Table 2-

While the inductive effect of substituent Y (characterized by substituent parameter σ_F) was found to be significant as concerns the tautomeric equilibrium constant according to Eq. 2 for the 1,3-diaryl-substituted naphthoxazines (**1**), our aim was to study the applicability of Eq. 2 for the present model compounds **19-23**. The significance level was taken as 0.05. The linear regression analysis of Eq. 2 in Table 3 show that the *trans*$\rightleftharpoons$chain (**B**$\rightleftharpoons$**A**) equilibrium constants are significantly influenced by the inductive effect (σ_F) of substituent Y on the 4-phenyl ring. This means that for the *trans*$\rightleftharpoons$chain (**B**$\rightleftharpoons$**A**) equilibria the equilibrium constant can be described by applying double substituent parameter treatment, and a plane can be fitted to the data points with data error r = 0.971 (Fig. 3).

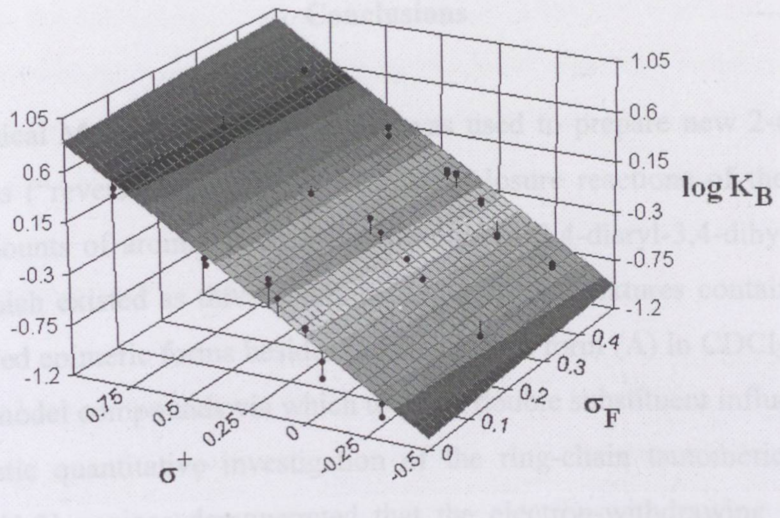


Figure 3. Plots of log K$_B$ for **19-23B** (●) *vs* Hammett parameters σ^+ and σ_F

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**$\rightleftharpoons$**A** seems to be somewhat more sensitive to both substitution X and substitution Y than is equilibrium **C**$\rightleftharpoons$**A**. These substituent effects can be explained in terms of a stereoelectronic effect related to the relative configuration of C-4.

For a better understanding of the ring-chain tautomeric process, Eq. 3 was introduced. It was observed that the correlation coefficients were significantly improved by using Eq. 3 (see 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]

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

-Insert Table 3-

Conclusions

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 resulted in 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines, which existed as three-component tautomeric mixtures containing major (**B**) and minor (**C**) ring-closed epimeric forms besides the open-chain form (**A**) in $CDCl_3$ at 300 K, and they proved to be good model compounds via which to study 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 demonstrated that the electron-withdrawing substituent X on a phenyl ring attached to a carbon 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*$\rightleftharpoons$chain ($\mathbf{B}\rightleftharpoons\mathbf{A}$) tautomeric equilibria.

Experimental Section

^{1}H NMR spectra (400 MHz) were recorded at 300 K. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) 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 day before the ^{1}H NMR spectra were run. The number of scans was usually 32.

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 analysis were performed by 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)

To a solution of 1-naphthol (**2**, 7.2 g, 0.05 mol) in absolute MeOH (40 mL), the appropriate aromatic aldehyde (0.1 mol; in the case of liquid aldehydes, a freshly distilled sample was used) and 5 mL 25% methanolic ammonia solution were added. The mixture was left to stand at ambient temperature for 2 days, during which a crystalline (**3-6**) or oily product (**7-9**) separated out. The crystalline product (**3-6**) was filtered off and washed with cold MeOH (2 x 50 mL). In the event of an oily product (**7-9**), the solvent was decanted off and this procedure was repeated three times after the addition of MeOH (20 mL), and then the excess of MeOH was evaporated off. To the crude oily or crystalline naphthoxazines **3-9**, 20% hydrochloric acid (100 mL) was added and the mixture was stirred and refluxed for 1 h. The solvent was evaporated off and the oily residue was crystallized by treatment with 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%), mp 156-157 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): $\delta = 6.31$ (s, 1H, C*H*NH_2), 7.41-7.59 [m, 3H, C(4)-H, C(6)-H, C(7)-H], 7.60-7.75 [m, 2H, C(3)-H, C(4')-H], 7.87 [dd, 1H, J = 8.8, 4.0 Hz, C(5)-H], 8.02 [d, 1H, J = 7.6 Hz, C(5')-H], 8.19 [d, 1H, J = 7.6 Hz, C(3')-H], 8.35 [dd, 1H, J = 8.8, 5.3 Hz, C(8)-H], 8.46 [s, 1H, C(2')-H], 9.44 (bs, 3H, NH_2, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): $\delta = 46.80$, 118.86, 120.36, 122.33, 122.51, 122.97, 124.69, 124.89, 125.64, 126.86, 127.79, 130.2, 134.36, 134.46, 140.49, 147.93, 150.21

2-(α-Amino-3-bromobenzyl)-1-naphthol hydrochloride (11):

Yield: 9.48 g (52%), mp 158-159 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): $\delta = 6.14$ (s, 1H, C*H*NH_2), 7.36 [t, 1H, J = 8.1 Hz, C(5')-H], 7.48-7.56 [m, 5H, C(4)-H, C(6)-H, C(7)-H, C(4')-H, C(6')-H], 7.62 [d, 1H, J = 8.6 Hz, C(3)-H], 7.78 (bs, 1H, C(2')-H], 7.84-7.88 [m, 1H, C(5)-H], 8.29-8.36 [m, 1H, C(8)-H], 9.20 (bs, 2H, NH_2), 10.16 (bs, 1H, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): $\delta = 51.70$, 118.81, 120.26, 121.70, 121.75, 122.54, 125.15, 125.51, 126.45, 126.71, 127.86, 130.10, 130.83, 130.93, 133.98, 140.75, 149.87

2-(α-Amino-4-bromobenzyl)-1-naphthol hydrochloride (12):

Yield: 8.57 g (47%), mp 117-119 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): $\delta = 6.13$ (s, 1H, C*H*NH_2), 7.46-7.55 [m, 5H, C(4)-H, C(6)-H, C(7)-H, C(2')-H], 7.57-7.65 [m, 3H, C(3)-H, C(3')-H], 7.82-7.88 [m, 1H, C(5)-H], 8.31-8.37 [m, 1H, C(8)-H], 9.24 (bs, 2H, NH_2), 10.18 (bs, 1H, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): $\delta = 51.49$, 119.12, 120.21, 121.17, 122.52, 124.84, 125.21, 125.48, 126.64, 127.81, 129.77, 130.60, 131.44, 132.30, 133.96, 137.60, 149.83

2-(α-Amino-4-chlorobenzyl)-1-naphthol hydrochloride (13):

Yield: 8.01 g (50%), mp 167-169 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): $\delta = 6.14$ (s, 1H, C*H*NH_2), 7.47 [d, 2H, J = 8.1 Hz, C(2')-H], 7.49-7.58 [m, 5H, C(4)-H, C(6)-H, C(7)-H, C(3')-H], 7.60 [d, 1H, J = 8.6 Hz, C(3)-H], 7.82-7.88 [m, 1H, C(5)-H], 8.30-8.36 [m, 1H, C(8)-H], 9.19 (bs, 2H, NH_2), 10.16 (bs, 1H, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): δ = 51.33, 119.10, 120.23, 122.55, 124.82, 125.17, 125.64, 126.67, 127.90, 128.77, 129.40, 129.41, 129.80, 132.71, 133.96, 137.15, 149.83

2-(α-Aminobenzyl)-1-naphthol hydrochloride (14):

Yield: 8.14 g (57%), mp 171-174 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): δ = 6.14 (s, 1H, C*H*NH_2), 7.34 [t, 1H, J = 7.3 Hz, C(4')-H], 7.40 [t, 2H, J = 7.3 Hz, C(3')-H], 7.47-7.58 [m, 5H, C(4)-H, C(6)-H, C(7)-H, C(2')-H], 7.60 [d, 1H, J = 8.8 Hz, C(3)-H], 7.82-7.88 [m, 1H, C(5)-H], 8.30-8.37 [m, 1H, C(5)-H], 9.13 (bs, 2H, NH_2), 10.14 (bs, 1H, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): δ = 51.57, 119.43, 120.06, 122.47, 124.68, 125.17, 125.48, 126.63, 126.96, 126.98, 128.11, 128.40, 128.60, 129.00, 133.90, 138.14, 149.77

2-(α-Amino-4-methylbenzyl)-1-naphthol hydrochloride (15):

Yield: 8.24 g (55%), mp 165-166 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): δ = 2.27 (s, 3H, Ar-C*H*$_3$), 6.12 (s, 1H, C*H*NH_2), 7.19 [d, 2H, J = 8.1 Hz, C(3')-H], 7.43 [d, 2H, J = 8.1 Hz, C(2')-H], 7.46-7.54 [m, 3H, C(4)-H, C(6)-H, C(7)-H], 7.62 [d, 1H, J = 8.6 Hz, C(3)-H], 7.81-7.87 [m, 1H, C(5)-H], 8.32-8.38 [m, 1H, C(8)-H], 9.14 (bs, 2H, NH_2), 10.12 (bs, 1H, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): δ = 20.63, 51.52, 119.76, 120.14, 122.65, 125.05, 125.28, 125.40, 126.57, 127.38, 127.86, 128.30, 129.33, 129.70, 133.88, 135.29, 137.28, 149.72

2-(α-Amino-4-methoxybenzyl)-1-naphthol-hydrochloride (16):

Yield: 9.47 g (60%), mp 168-169 °C. ^{1}H NMR (400 MHz, DMSO, 20 °C): δ = 3.73 (s, 3H, OMe), 6.31 (s, 1H, C*H*NH_2), 6.95 [d, 2H, J = 7.6 Hz, C(3')-H], 7.47 [d, 2H, J = 8.8 Hz, C(2')-H], 7.49-7.53 [m, 3H, C(4)-H, C(6)-H, C(7)-H], 7.64 [d, 1H, J = 8.6 Hz, C(3)-H], 7.81-7.88 [m, 1H, C(5)-H], 8.31-8.38 [m, 1H, C(8)-H], 9.10 (bs, 2H, NH_2), 10.09 (bs, 1H, OH); ^{13}C NMR (400 MHz, DMSO, 20 °C): δ = 51.30, 55.16, 113.93, 114.60, 119.81, 120.18, 122.57, 124.92, 125.24, 125.36, 126.49, 127.84, 128.98, 129.40, 130.13, 133.81, 149.58, 158.90

General method for the synthesis of 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines (17-23)

To a solution of the appropriate aminonaphthol hydrochloride (**10-16**, 1 mmol) in absolute MeOH (20 mL), Et_3N (0.11 g, 1.1 mmol) and an equivalent amount of aromatic aldehyde (for liquid aldehydes, a freshly distilled sample was used) were added. The mixture was left to stand at ambient temperature for 24 h. A crystalline product was then filtered off, washed with MeOH and recrystallized (Table 4). In the event of an oily product, the solvent was evaporated off and the residue was partitioned between H_2O and $CHCl_3$ (10 mL each). The separated organic layer was dried with Na_2SO_4 and the solvent was then evaporated off. An 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 of 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 ($CDCl_3$) 5.42 (bs, 1H, H-4 *trans*), 5.62 (bs, 1H, H-2 *trans*), 5.80 (bs, 1H, H-2 *cis*), 6.14 (bs, 1H, H-4 *cis*), 6.34 (s, 1H, NphC*H*ArNH *Schiff-base*), 8.66 (s, 1H, NH=C*H*Ar *Schiff-base*)

18a: Mixture of Schiff-base (12%), *cis*-ring form (31%) and *trans*-ring form (57%). Selected signals: ^{1}H NMR ($CDCl_3$) 5.29 (d, 1H, J = 6.0 Hz, H-4 *trans*), 5.65 (d, 1H, J = 10.3 Hz, H-4 *cis*), 5.86 (d, 1H, J = 12.6 Hz, H-2 *trans*), 6.33 (d, 1H, J = 10.0 Hz, H-2 *cis*), 6.37 (s, 1H, NphC*H*ArNH *Schiff-base*), 8.82 (s, 1H, NH=C*H*Ar *Schiff-base*)

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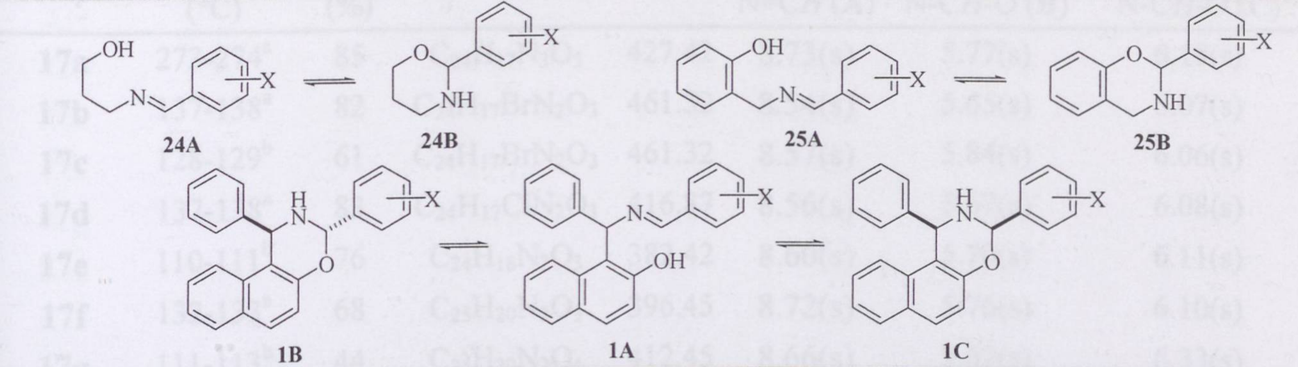
Table 1. Proportions (%) of the ring-closed tautomeric forms (**B** and **C**) in tautomeric equilibria for compounds **17-23** ($CDCl_3$, 300 K)

			17		**18**		**19**		**20**		**21**		**22**		**23**	
			(Y = *m*NO_2)		(Y = *m*Br)		(Y = *p*Br)		(Y = *p*Cl)		(Y = H)		(Y = *p*Me)		(Y = *p*OMe)	
		σ^+	0.73		0.41		0.15		0.11		0		-0.31		-0.78	
Compd.	X		**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

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



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

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

		k	ρ_F^Y	ρ_R^Y	ρ^X or ρ_F^X	ρ_R^X	r
Acc. to Eq. 2	**19-23A** $\rightleftharpoons$ **19-23B**	-0.44	0.28	–[a]	1.29		0.971
	19-23A $\rightleftharpoons$ **19-23C**	-0.58	–[a]	–[a]	1.27		0.965
Acc. to Eq. 3	**19-23A** $\rightleftharpoons$ **19-23B**	-0.46	0.25	–[a]	1.15	1.62	0.984
	19-23A $\rightleftharpoons$ **19-23C**	-0.58	–[a]	–[a]	1.05	1.66	0.976

[a] Insignificant (significance value > 0.05)

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

Compd.	Mp (°C)	Yield (%)	Formula	M.W.	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 *i*Pr$_2$O–EtOAc; [b]Recrystallized from *i*Pr$_2$O

V.

Syntheses and transformations of 1-(α-aminobenzyl)-2-naphthol derivatives

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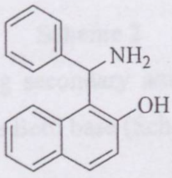
Abstract

The syntheses and transformations of 1-(α-aminobenzyl)-2-naphthol (Betti base) derivatives are reviewed. Special attention is paid to the applications of enantiopure Betti base derivatives as chiral ligands in asymmetric transformations.

Keywords:
Aminonaphthols, Betti base, Naphthoxazines, Tautomerism, Stereoselective synthesis

I. Introduction

One hundred years ago, Betti reported a straightforward synthesis of 1-(α-aminobenzyl)-2-naphthol (the Betti base) [1-5], starting from 2-naphthol, benzaldehyde and ammonia. The Betti procedure can be interpreted as an extension of the Mannich condensation, with formaldehyde replaced by aromatic aldehyde, secondary amine by ammonia and the C-H acid by an electron-rich aromatic compound such as 2-naphthol. The preparation of substituted Betti base derivatives by the modified Mannich reaction has subsequently become of considerable importance because a C-C bond is formed under mild experimental conditions. In the past decade, interest in the chemistry of the Betti base has intensified. Preparation of the enantiomers of the Betti base and its *N*-substituted derivatives is of significance since they can serve as chiral catalysts. On the other hand, Betti base derivatives provide convenient access to many useful synthetic building blocks because the amino and the phenolic hydroxy groups can be converted into a wide variety of compounds.

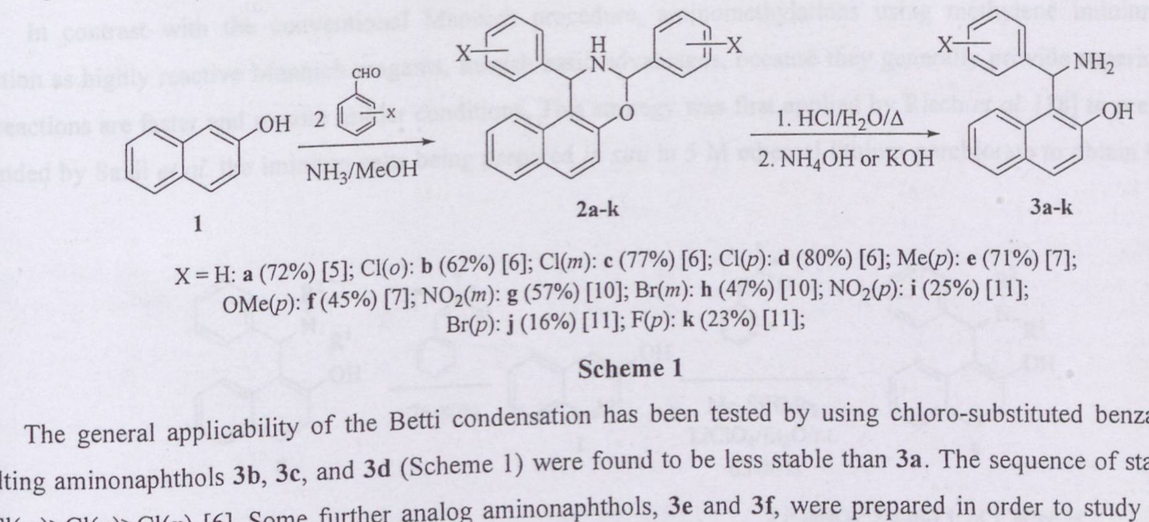


Betti base

II. Syntheses of 1-(α-aminobenzyl)-2-naphthol derivatives

A. Syntheses of racemic compounds

The chemistry of the Betti bases started at the beginning of the 20th century, when Betti reported the synthesis of 1-(α-aminobenzyl)-2-naphthol. The reaction was performed with 2-naphthol (**1**), benzaldehyde and ammonia (in a ratio of 1:2:1) to obtain 1,3-diphenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**2a**). The subsequent acidic hydrolysis and extraction with NH_4OH gave the desired aminonaphthol **3a** (Scheme 1) [1-4].



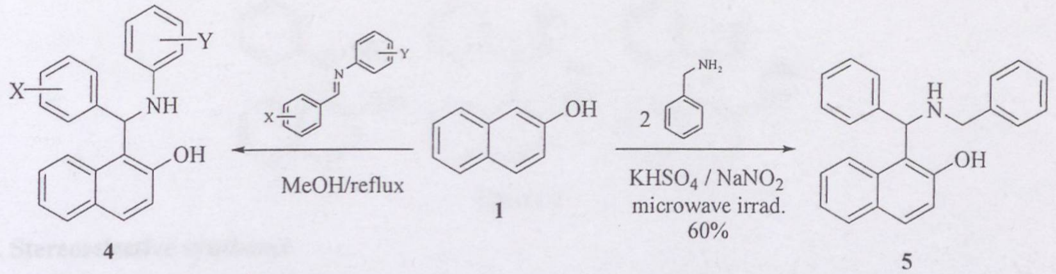
X = H: **a** (72%) [5]; Cl(*o*): **b** (62%) [6]; Cl(*m*): **c** (77%) [6]; Cl(*p*): **d** (80%) [6]; Me(*p*): **e** (71%) [7];
OMe(*p*): **f** (45%) [7]; NO_2(*m*): **g** (57%) [10]; Br(*m*): **h** (47%) [10]; NO_2(*p*): **i** (25%) [11];
Br(*p*): **j** (16%) [11]; F(*p*): **k** (23%) [11];

Scheme 1

The general applicability of the Betti condensation has been tested by using chloro-substituted benzaldehydes. The resulting aminonaphthols **3b, 3c**, and **3d** (Scheme 1) were found to be less stable than **3a**. The sequence of stability was X = H>Cl(*m*)>Cl(*o*)>Cl(*p*) [6]. Some further analog aminonaphthols, **3e** and **3f**, were prepared in order to study the stability of these compounds with respect to acidic hydrolysis [7]. In these early papers, compounds **2a-k** were described as naphthoxazines, but in later publications it was pointed out that in $CDCl_3$ **2a-k** participate in a three-component tautomeric mixture containing two epimeric naphthoxazines besides the Schiff base [8-10]. Since these aminonaphthols serve as good starting materials for study of the substituent effects in the ring-chain tautomerism of naphthalene-condensed 2,4-disubstituted oxazines, the series of aminonaphthols were extended with **3g-k** by means of the classical Betti procedure [10,11].

The reactions of 2-naphthol (**1**) with substituted benzylidene-anilines in methanol led to the formation of *N*-monosubstituted Betti bases **4** (Scheme 2) [12]. The results can be interpreted as an extension of the Betti reaction because benzylideneanilines serve as aldehyde sources in the reaction, while primary amines were used instead of ammonia.

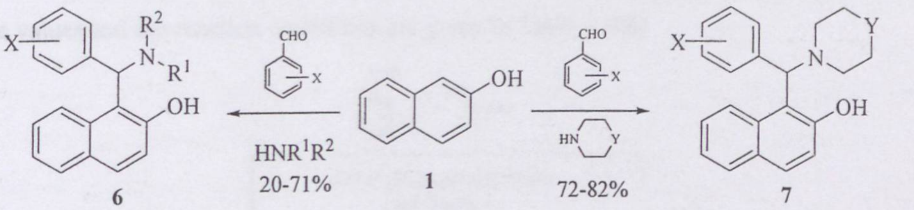
In a study of the diazotization of 2-naphthol (**1**) with amines, by induction with microwave irradiation in the absence of solvent, replacement of the aromatic amine by benzylamine led to the formation of α-(2-hydroxy-1-naphthyl)dibenzylamine (**5**) instead of the expected benzylazo-2-naphthol (Scheme 2) [13].



$X = pNO_2; mNO_2; pCl; H; pMe$
$Y = pCl; H; pMe; pOMe$

Scheme 2

The Betti condensation was extended by using secondary amines,[14,15] resulting in **6**, or cyclic amines [14-17], resulting in **7** as the *N,N*-disubstituted derivatives of the Betti base (Scheme 3).

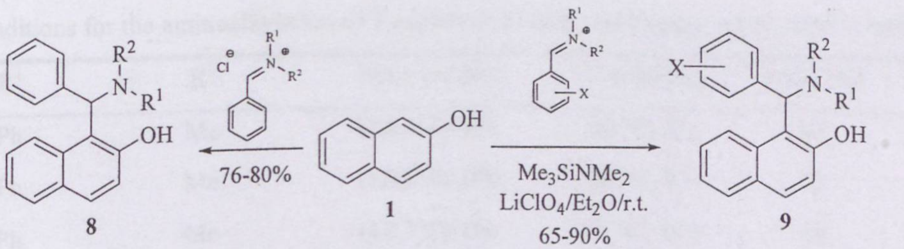


$X = H; pOMe$
$R^1 = Me; Et; nPr$
$R^2 = Me; Et; nPr$

$X = pCl; H; pOMe, Y = \text{-}CH_2\text{-}$
$X = H; 3,4\text{-}OMe; pOMe; pNMe_2, Y = O$

Scheme 3

In contrast with the conventional Mannich procedure, aminomethylations using methylene iminium salts, which function as highly reactive Mannich reagents, furnish basic advantages, because they generally provide superior yields, while the reactions are faster and require milder conditions. This strategy was first applied by Risch *et al.* [18] to prepare **8** and was extended by Saidi *et al.* the iminium salts being prepared *in situ* in 5 M ethereal lithium perchlorate to obtain **9** [19] (Scheme 4).



$R^1, R^2 = Me, Me$: **a**; $\text{-}(CH_2)_5\text{-}$: **b**

$X = mNO_2; 2,4\text{-di-}Cl; pCl; pCN; H$
$R^1, R^2 = Me, Me; \text{-}(CH_2)_4\text{-}; \text{-}(CH_2)_5\text{-}; \text{-}(CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}$

Scheme 4

B. Syntheses of enantiomeric compounds

a. Resolutions of the racemates by separation of the diastereomers

The first resolution of 1-(α-aminobenzyl)-2-naphthol was performed by diastereomeric salt formation with tartaric acid by Betti [20,21]. Naso *et al.* reported the resolution of **3a** through treatment of the racemic compound with an equivalent amount of (2*R*,3*R*)-tartaric acid in a 95% ethanol-methanol mixture (6:1). Fractional crystallization afforded the less soluble salt (+)-**3a**, and its absolute configuration was found to be (*S*) (determined by X-ray diffraction analysis of its hydrobromide salt, **3a**.HBr) [22]. The *N,N*-dimethylamino derivative of **3a** (Chart 2) was resolved in a similar manner. The diasteromeric salts obtained from the racemate and (2*R*,3*R*)-tartaric acid were separated by fractional crystallization from acetone [22]. The *N*-butyl derivative of **3a** (Chart 2) could be resolved by using an equivalent amount of (2*R*,3*R*)-tartaric acid in acetone [23].

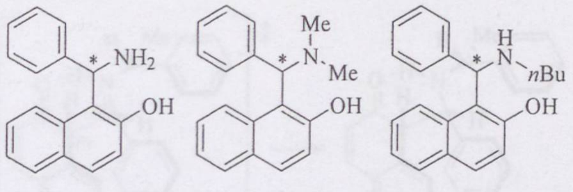
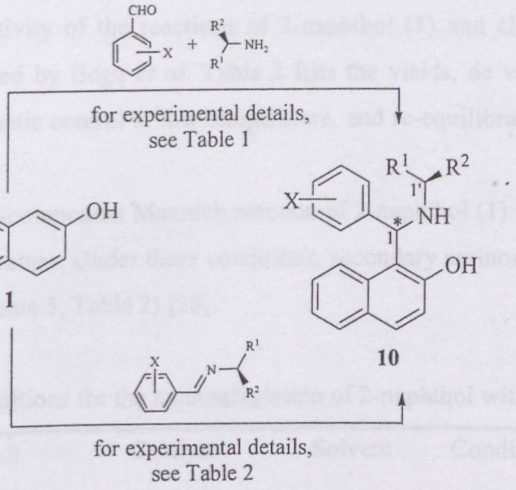


Chart 2

b. Stereoselective syntheses

Palmieri reported an enantioselective synthesis of **10a** under solvent-free conditions, starting from benzaldehyde, 2-naphthol (**1**) and (*R*)-1-phenylethylamine. Of the two possible diastereomers, the diastereomeric excess (de) of the (*R*,*R*) isomer was found to be 98% [24]. Since **10a** could be obtained in excellent yield and de, the reaction was later extended to substituted benzaldehydes (Scheme 5 and Table 1) [25].

A variety of such aminonaphthols were prepared by Palmieri *et al.*, (*R*)-1-phenylethylamine being replaced by other chiral amines. The de values and the reaction conditions are given in Table 1 [26].

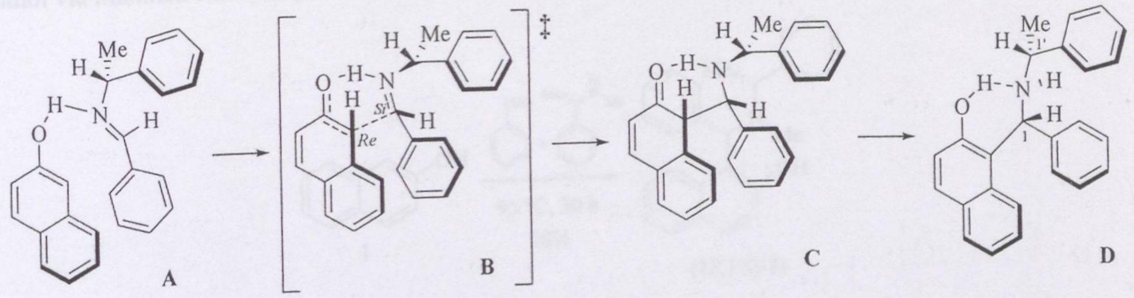


Scheme 5

Table 1. Reaction conditions for the aminoalkylation of 2-naphthol (**1**) with enantiopure amines and substituted benzaldehydes

X	R^1	R^2	Main product	Conditions	Yield (%)	de (%)	Ref.
H	Ph	Me	(1*R*,1'*R*)-**10a**	60 °C, 8 h	93	98	[24]
*p*Me	Ph	Me	(1*R*,1'*R*)-**10b**	60 °C, 8 h	72	92	[25]
*p*OMe	Ph	Me	(1*R*,1'*R*)-**10c**	60 °C, 14 h	66	61	[25]
*p*Cl	Ph	Me	(1*R*,1'*R*)-**10d**	60 °C, 7 h	72	62	[25]
mNO_2	Ph	Me	(1*R*,1'*R*)-**10e**	60 °C, 14 h	86	50	[25]
*o*OMe	Ph	Me	(1*S*,1'*R*)-**10f**	60 °C, 9 h	75	50	[26]
H	-CH_2-OH	Ph	(1*S*,1'*R*)-**10g**	60 °C, 8 h	66	56	[26]
H	1-naphthyl	Me	(1*R*,1'*R*)-**10h**	60 °C, 14 h	80	60	[26]

The diastereoselectivity of the reaction was explained by the asymmetric transformation of the second kind induced by the preferential crystallization [25]. The diastereoselectivity of the reaction was interpreted by Palmieri *et al.* as given in Scheme 6. It is assumed that an aldiminium type complex (**A**) is initially formed through protonation of the C=N nitrogen. In the first step of this Friedel-Crafts reaction, the rate-limiting stage of the whole reaction, the formation of the arenium σ-complex *ul*-(*Re*,*Si*)-(*R*,*R*)-**10a**-σ (**C**), proceeds through a six-membered transition state *ul*-(*Re*,*Si*)-(*R*,*R*)-**10a**-***TS*** (**B**), as shown in Scheme 6. The relative stability of the transition state **10a**-***TS***, calculated for all four possible combinations, at the semi-empirical PM3 level, accorded with the stereoselectivity observed for this Mannich reaction [26].



ΔEatt

80.215 kcal/mol

ul-(*Re*,*Si*)-(*R*,*R*)-**10a**-***TS*** 0.00
93.804 kcal/mol
ul-(*Si*,*Re*)-(*S*,*R*)-**10a**-***TS*** +0.61
lk-(*Si*,*Si*)-(*R*,*R*)-**10a**-***TS*** +0.91
lk-(*Re*,*Re*)-(*S*,*R*)-**10a**-***TS*** +1.04

ul-(*Re*,*Si*)-(*R*,*R*)-**10a**-σ 0.00
54.109 kcal/mol
ul-(*Si*,*Re*)-(*S*,*R*)-**10a**-σ +0.17
lk-(*Si*,*Si*)-(*R*,*R*)-**10a**-σ + 1.87
lk-(*Re*,*Re*)-(*S*,*R*)-**10a**-σ + 1.82

(*R*,*R*)-**10a** 0.00
42.031 kcal/mol
(1*S*,1'*R*)-**10a** +0.27

Scheme 6

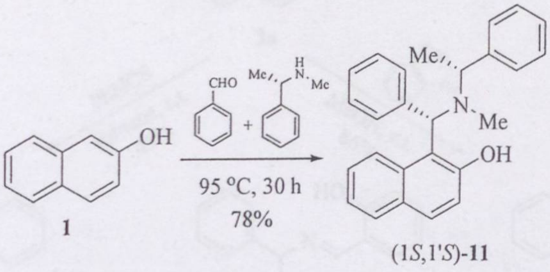
The mechanism and diastereoselectivity of the reactions of 2-naphthol (**1**) and chiral imines, which involve donor-acceptor interactions, were also investigated by Boga *et al*. Table 2 lists the yields, de values and experimental conditions. Those authors assumed the presence of kinetic control at low temperature, and re-equilibration (by thermodynamic control) at high temperature [27].

Saidi *et al.* reported a one-pot, three-component Mannich reaction of 2-naphthol (**1**) with imines prepared *in situ* in 5 M ethereal lithium perchlorate at room temperature. Under these conditions, secondary aminonaphthols could be obtained in high yields with high diastereoselectivities (Scheme 5, Table 2) [28].

Table 2. Reaction conditions for the aminoalkylation of 2-naphthol with chiral imines

X	R^1	R^2	Main product	Catalyst	Solvent	Conditions	Yield (%)	de (%)	Ref.
H	Me	Ph	(1*R*,1'*S*)-**10a**	–	CH_2Cl_2	20 °C, 1 d	75	0	[27]
H	Me	Ph	(1*S*,1'*S*)-**10a**	–	CH_2Cl_2	20 °C, 10 d	95	70	[27]
H	Me	Ph	(1*R*,1'*S*)-**10a**	Et_3N	CH_2Cl_2	20 °C, 10 d	50	0	[27]
H	Me	Ph	(1*S*,1'*S*)-**10a**	CH_3SO_3H	CH_2Cl_2	20 °C, 10 d	87	60	[27]
H	Me	Ph	(1*R*,1'*S*)-**10a**	–	CH_2Cl_2	-20 °C, 7 d	50	20	[27]
H	Me	Ph	(1*R*,1'*S*)-**10a**	–	THF	20 °C, 3 d	84	20	[27]
H	Ph	Me	(1*R*,1'*R*)-**10a**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	75	98	[28]
*p*Cl	Ph	Me	(1*R*,1'*R*)-**10d**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	78	98	[28]
mNO_2	Ph	Me	(1*R*,1'*R*)-**10e**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	70	80	[28]
2,4-di-Cl	Ph	Me	(1*R*,1'*R*)-**10i**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	70	90	[28]
*p*CN	Ph	Me	(1*R*,1'*R*)-**10j**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	72	90	[28]
*p*Br	Ph	Me	(1*R*,1'*R*)-**10k**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	60	86	[28]
*p*OMe	Ph	Me	(1*R*,1'*R*)-**10c**	$LiClO_4$/TMSCl	Et_2O	r.t., 6 h	55	50	[28]

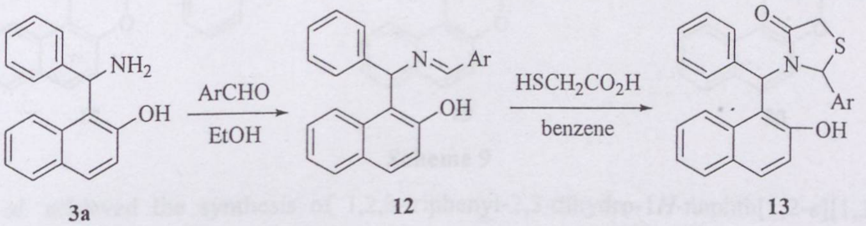
Chan *et al.* reported a new, one-step synthesis of (1*S*,1'*S*)-**11** starting from 2-naphthol (**1**), benzaldehyde and (*S*)-(–)-*N*-α-dimethylbenzylamine. This was the first example of a straightforward asymmetric synthesis of an optically active tertiary aminonaphthol via Mannich aminoalkylation of 2-naphthol (Scheme 7) [29].



Scheme 7

III. Transformations

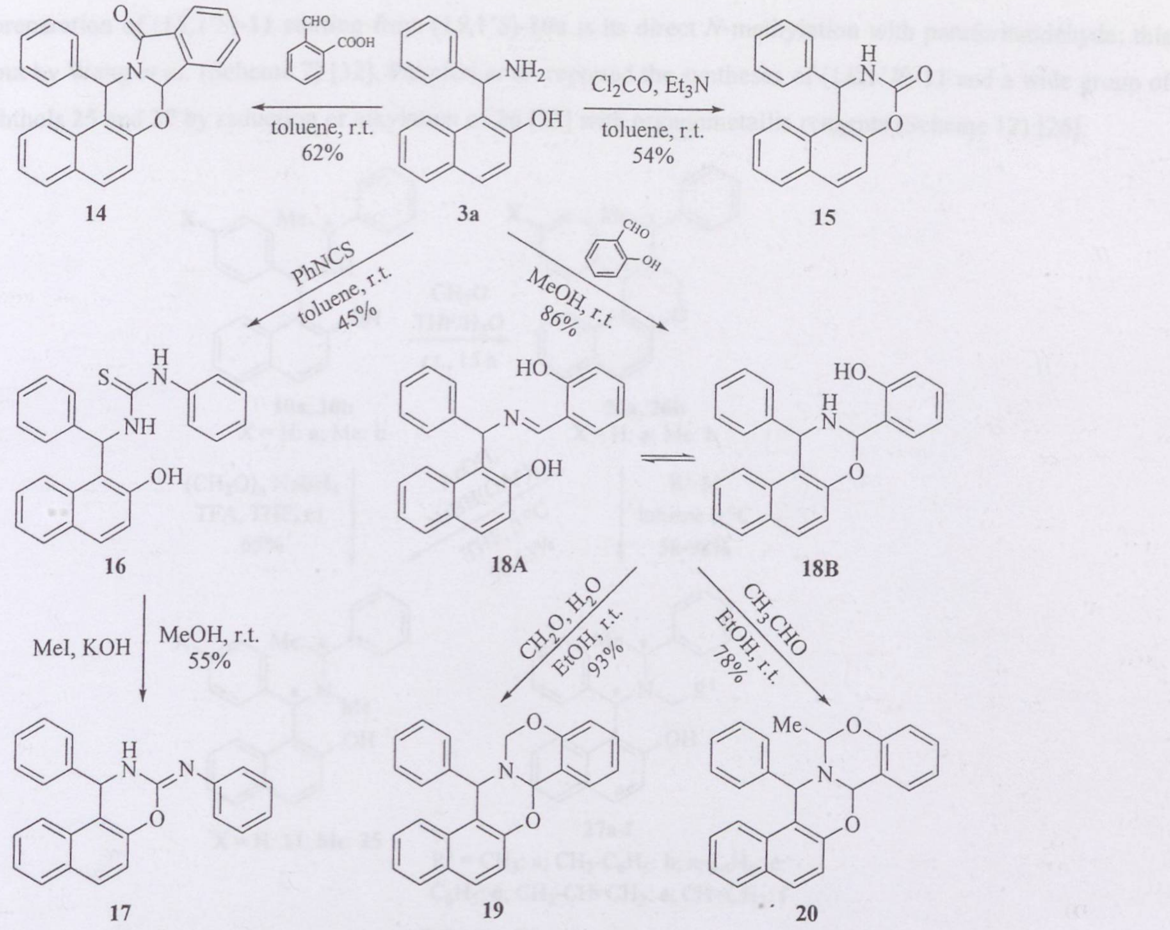
In spite of the great reaction possibility resulting from the two functional groups in the Betti base, relatively few publications have appeared on this field. Desai *et al.* used the racemic Betti base for the transformation into 4-thiazolidinones **13**. The first step was the preparation of the Schiff bases **12** with substituted benzaldehydes, but the tautomeric capability of the condensation products was not discussed at all. Compounds **12** were then treated with mercaptoacetic acid to obtain 2-aryl-3-[α-(2-hydroxy-1-naphthyl)-benzyl]-4-thiazolidinones (**13**), which exerted antibacterial activity (Scheme 8) [30].



Ar = C_6H_5: **a**; 2-OH-C_6H_4: **b**; 4-OH-C_6H_4: **c**; 4-Cl-C_6H_4: **d**; 4-OMe-C_6H_4: **e**; 5-Br,2-OH-C_6H_3: **f**; 3,5-di-Br,2-OH-C_6H_2: **g**; 3,4-CH_2O_2-C_6H_3: **h**; 4-NO_2-C_6H_4: **i**; 3-NO_2-C_6H_4: **j**; 4-Me-C_6H_4: **k**

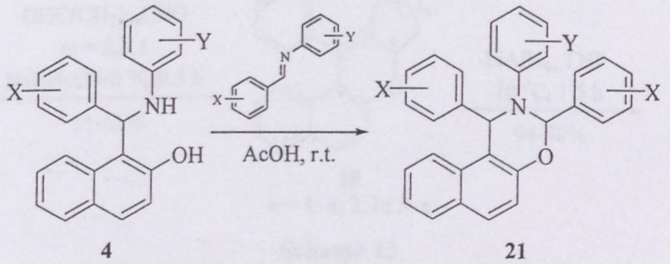
Scheme 8

The present authors utilized the high reactivity of the Betti base to study its reactions with 2-carboxybenzaldehyde, phosgene, phenyl isothiocyanate (followed by ring closure with methyl iodide) and salicylaldehyde (followed by ring closure with formaldehyde and acetaldehyde). The products and reaction conditions are shown in Scheme 9 [31].



Scheme 9

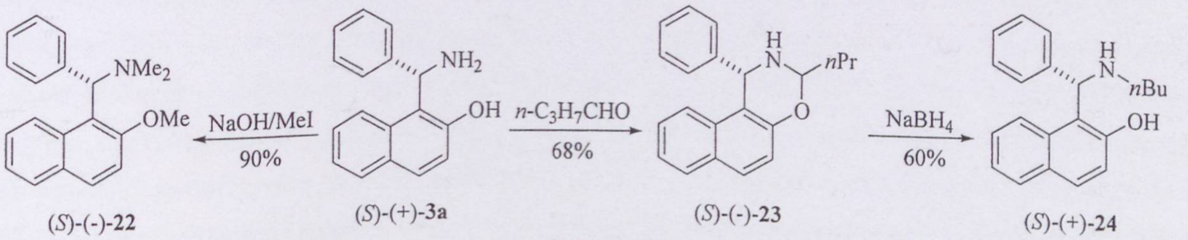
Hanumathu *et al.* achieved the synthesis of 1,2,3-triphenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**21**) by the reactions of 1-(α-phenylaminobenzyl)-2-naphthol derivatives **4** either with benzaldehyde or with substituted benzylidene-aniline in acetic acid, but the influence of the substituents on the diastereomeric ratios was not discussed (Scheme 10) [12].



X = *p*NO$_2$; *m*NO$_2$; *p*Cl; H; *p*Me,   Y = *p*Cl; H; *p*Me; *p*OMe

Scheme 10

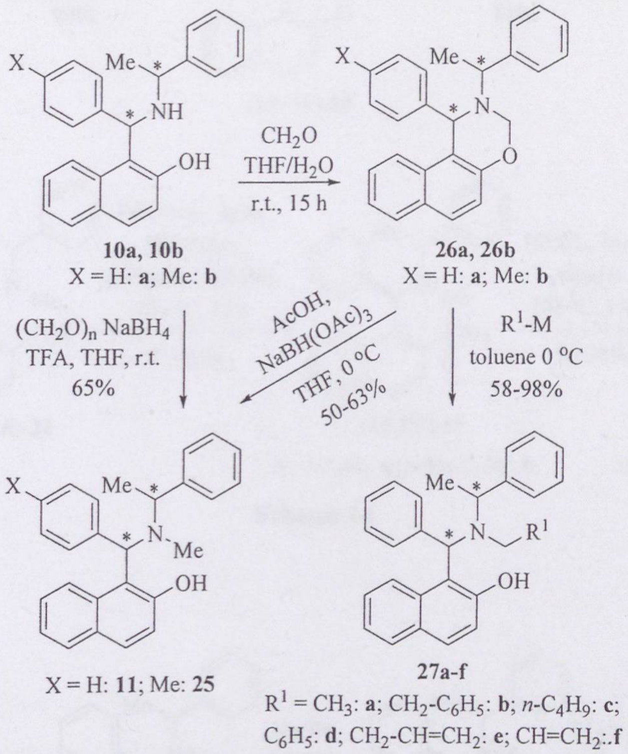
Treatment of (*S*)-(+)-**3a** with NaOH/MeI led to the trimethyl derivative (*S*)-(–)-**22** (Scheme 11) [22]. In order to prove the (*S*) configuration of the (+)-**24** produced, Palmieri *et al.* treated (*S*)-(+)-**3a** with *n*-butanal, yielding the oxazine (–)-**23**, which was reduced with NaBH$_4$ to (+)-**24** (Scheme 11) [23].



Scheme 11

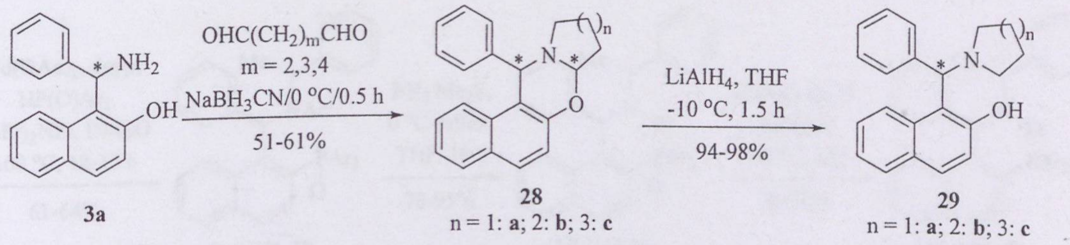
The enantiomers of the Betti base derivatives are not only good chiral ligands in asymmetric synthesis, but can also be applied as simple starting materials in the enantioselective syntheses of other chiral inductors.

A simple preparation of (1*S*,1'*S*)-**11** starting from (1*S*,1'*S*)-**10a** is its direct *N*-methylation with paraformaldehyde; this was first carried out by Wang *et al.* (Scheme 7) [32]. Palmieri *et al.* reported the syntheses of (1*R*,1'*R*)-**11** and a wide group of tertiary aminonaphthols **25** and **27** by reduction or alkylation of **26** [33] with organometallic reagents (Scheme 12) [26].



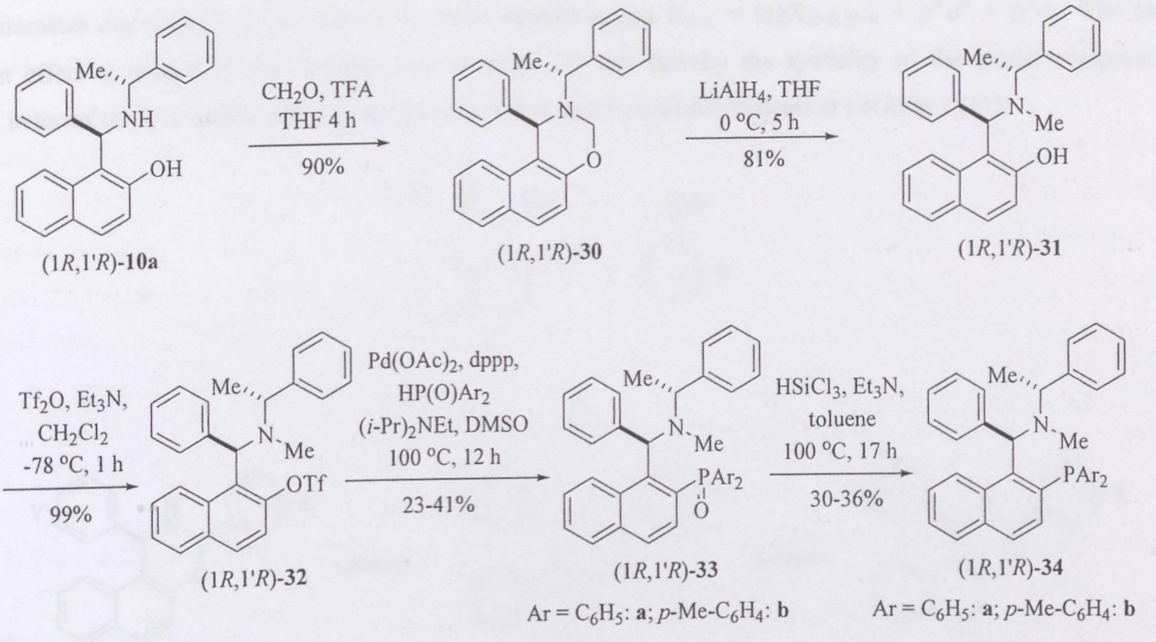
Scheme 12

The syntheses of (*R*)- and (*S*)-1-[α-(1-azacycloalkyl)benzyl]-2-naphthol **28** were attained by Hu *et al.* via selective *N*-cyclizations of (*R*)-(–) and (*S*)-(+) Betti bases with dials in the presence of $NaBH_3CN$ to give 1-azacycloalka[2,1-*b*]oxazines **29**, followed by selective cleavage of the C-O bonds with $LiAlH_4$ (Scheme 13) [34,35].

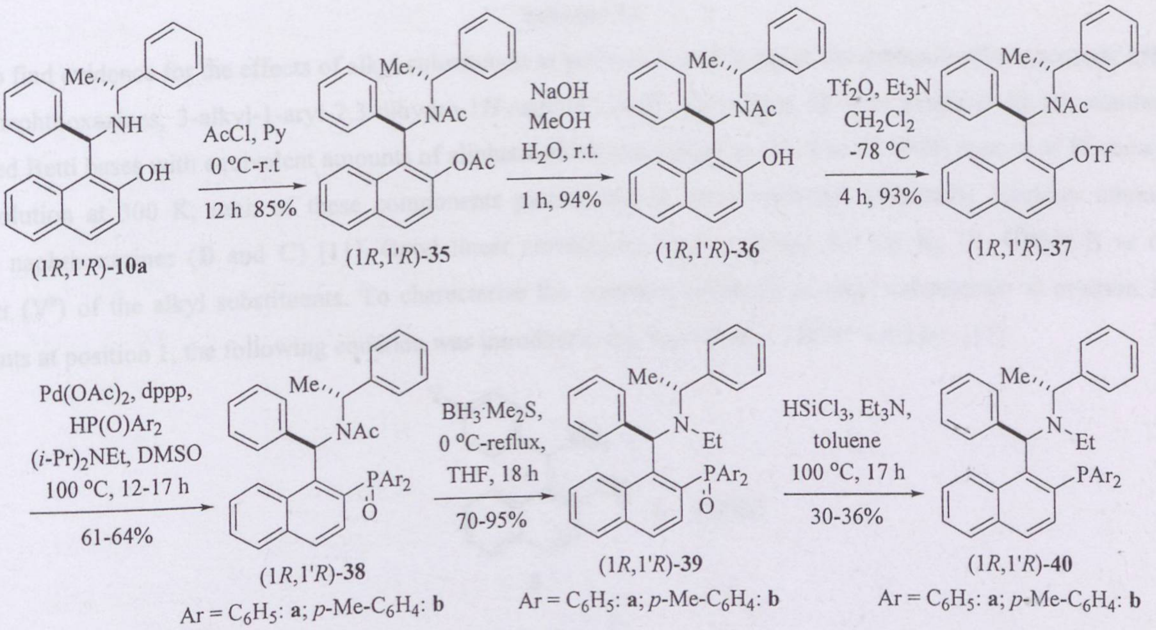


Scheme 13

Ding *et al.* described the synthesis of a new type of chiral amino phosphine ligands from (1*R*,1'*R*)-**10a** as starting material, formed by asymmetric 1-aminoalkylation of 2-naphthol (**1**) with (*R*)-1-phenylethylamine and benzaldehyde (Schemes 14 and 15) [36].

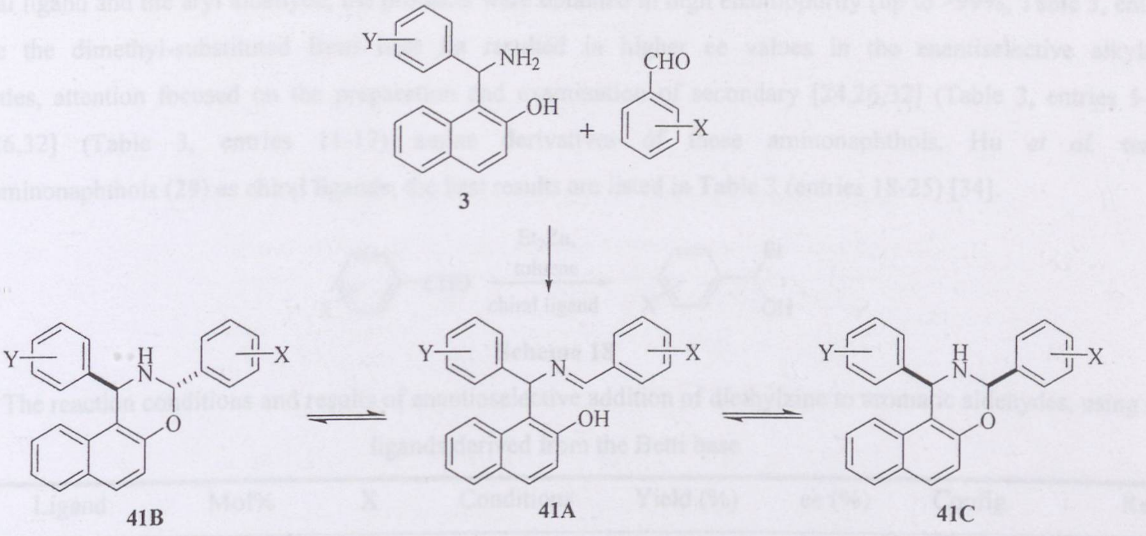


Scheme 14



Scheme 15

Although the condensation products of 1-(α-aminobenzyl)-2-naphthol and benzaldehyde or substituted benzaldehydes are known in the literature and their structures have been discussed as naphthoxazines [1-7] or Schiff bases [30]. Smith *et al.* first observed that the condensation products of **3a** with benzaldehyde or substituted benzaldehyde (Y = *p*NO_2, 3,4-di-Cl, *p*Br, *p*Cl, H, *p*-*i*Pr, *p*NMe_2, Scheme 16) in $CDCl_3$ solution formed three-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** and **C**) besides the open tautomer (**A**) [8]. The electronic effects of the 3-aryl groups on the tautomeric ratios could be described [10] by the equation $\log K_X = \log K_{X=H} + \rho\sigma^+$. Smith *et al.* made the assumption that 1,3-diaryl groups prefer a pseudoequatorial position and therefore a *cis* arrangement in the major ring-closed tautomer. In contrast with this assumption, from the NOESY spectrum of **41** (with X = *p*Cl, Y = *p*NO_2), the present authors proved that the major ring form in all tautomeric equilibria contains the 1,3-diaryl substituents in the *trans* position [10]. The common influence of aryl substituents at positions 1 and 3 (Scheme 16) was also studied. Multiple linear regression analysis of the log K values revealed that these are influenced in the *trans*-chain equilibria by a through-space inductive effect (σ_F) of substituent Y besides the Hammett-Brown parameter of substituent X. This meant that the following equation could be introduced to characterize the double parameter dependence of the *trans* ring-chain equilibria: $\log K_{B\text{-}A} = \log K_{X=H,Y=H} + \rho^{X}\sigma^{+} + \rho^{Y}\sigma_{F}$. The unexpected substituent effect is related to the configuration of atom C-1 and thereby the spatiality of the model compound. It was explained in terms of an anomeric effect quantitatively influenced by aryl substituents at position 1 [11].

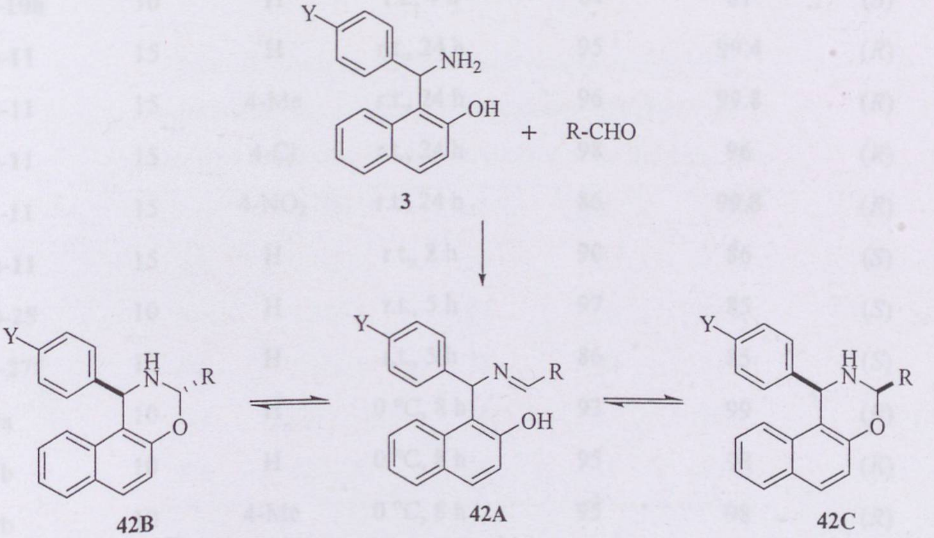


Y = *m*NO_2; *m*Br; *p*Cl; H; *p*Me; *p*OMe

X = *p*NO_2; *m*Br; *p*Br; 3,4-di-Cl; *p*Cl; H; *p*Me *p*-iPr; *p*NMe_2

Scheme 16

To find evidence for the effects of alkyl substituents at position 3, and to prove the presence of an anomeric effect in this kind of naphthoxazines, 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines **42** were prepared by the condensation of substituted Betti bases with equivalent amounts of aliphatic aldehydes (Scheme 17). The ^{1}H NMR spectra of **42** showed that, in $CDCl_3$ solution at 300 K, each of these components participated in two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**B** and **C**) [11]. Good linear correlations were obtained for log K_R (K_R=[**B**]/[**C**]) *vs* the Meyer parameter (V^a) of the alkyl substituents. To characterize the common influence of alkyl substituents at position 3 and aryl substituents at position 1, the following equation was introduced: $\log K_R = 0.48 + 7.97V^a + 0.22\sigma_F$ [11].



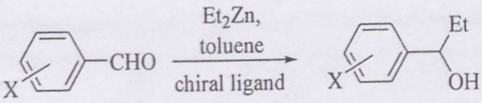
Y = NO_2; Br; Cl; H; F; Me; OMe

R = Me; Et; Pr; *i*Pr; *t*Bu

Scheme 17

IV. Applications

The first resolution of **3a** was reported by Betti. Enantiomers of **3a** were used for resolution of 2-(*p*-anisyl)-propanaldehyde [37] and glyceraldehydes [38] and to discriminate between aldohexoses and ketohexoses [39]. However, in spite of the availability and low cost of the Betti base, there has been a long silence over this optically active material. This was broken by Naso *et al.* who described a detailed protocol for resolution of the two isomers [22], with their application as chiral ligands in the enantoselective addition of diethylzinc to aryl aldehydes (Scheme 18) [23]. As indicated in Table 3, depending on the chiral ligand and the aryl aldehyde, the products were obtained in high enantiopurity (up to >99%, Table 3, entries 1-4) [23]. Since the dimethyl-substituted Betti base **8a** resulted in higher ee values in the enantiselective alkylation of benzaldehydes, attention focused on the preparation and examination of secondary [24,26,32] (Table 3, entries 5-10) and tertiary [26,32] (Table 3, entries 11-17) amine derivatives of these aminonaphthols. Hu *et al.* tested *N*-cycloalkylaminonaphthols (**29**) as chiral ligands; the best results are listed in Table 3 (entries 18-25) [34].

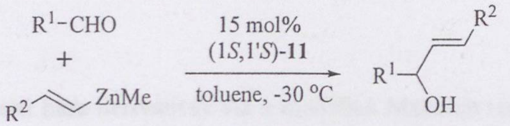


Scheme 18

Table 3. The reaction conditions and results of enantioselective addition of diethylzinc to aromatic aldehydes, using chiral ligands derived from the Betti base

Entry	Ligand	Mol%	X	Conditions	Yield (%)	ee (%)	Config.	Ref.
1	(*R*)-**3a**	13.3	H	r.t., 24 h	85	35	(*S*)	[23]
2	(*S*)-**8a**	13.3	H	r.t., 12 h	93	96	(*R*)	[23]
3	(*S*)-**8a**	13.3	2-Me	r.t., 24 h	75	>99	(*R*)	[23]
4	(*S*)-**8a**	13.3	4-Me	r.t., 24 h	94	96	(*R*)	[23]
5	(1*R*,1'*R*)-**10a**	6	H	r.t., 4 h	89	87	(*S*)	[24]
6	(1*S*,1'*S*)-**10a**	15	4-Me	r.t., 24 h	90	92	(*R*)	[32]
7	(1*S*,1'*S*)-**10a**	15	4-Cl	r.t., 24 h	88	87	(*R*)	[32]
8	(1*S*,1'*R*)-**10f**	10	H	r.t., 4 h	81	89	(*S*)	[26]
9	(1*R*,1'*R*)-**10g**	10	H	r.t., 24 h	68	15	(*S*)	[26]
10	(1*R*,1'*R*)-**10h**	10	H	r.t., 4 h	84	81	(*S*)	[26]
11	(1*S*,1'*S*)-**11**	15	H	r.t., 24 h	95	99.4	(*R*)	[32]
12	(1*S*,1'*S*)-**11**	15	4-Me	r.t., 24 h	96	99.8	(*R*)	[32]
13	(1*S*,1'*S*)-**11**	15	4-Cl	r.t., 24 h	98	96	(*R*)	[32]
14	(1*S*,1'*S*)-**11**	15	4-NO_2	r.t., 24 h	86	99.8	(*R*)	[32]
15	(1*R*,1'*R*)-**11**	15	H	r.t., 2 h	90	86	(*S*)	[26]
16	(1*R*,1'*R*)-**25**	10	H	r.t., 5 h	97	85	(*S*)	[26]
17	(1*R*,1'*R*)-**27f**	10	H	r.t., 5 h	86	85	(*S*)	[26]
18	(*S*)-**29a**	10	H	0 °C, 8 h	93	99	(*R*)	[34]
19	(*S*)-**29b**	10	H	0 °C, 8 h	95	98	(*R*)	[34]
20	(*S*)-**29b**	10	4-Me	0 °C, 8 h	95	98	(*R*)	[34]
21	(*S*)-**29b**	10	4-F	0 °C, 8 h	96	98	(*R*)	[34]
22	(*S*)-**29c**	10	H	0 °C, 8 h	93	73	(*R*)	[34]
23	(*R*)-**29a**	10	H	0 °C, 8 h	91	98	(*S*)	[34]
24	(*R*)-**29b**	10	H	0 °C, 8 h	91	98	(*S*)	[34]
25	(*R*)-**29c**	10	H	0 °C, 8 h	92	75	(*S*)	[34]

The applicability of the tertiary aminonaphthols was extended by utilizing the addition of alkenylzinc to aldehydes (Scheme 19) [29]. The best results are given in Table 4.

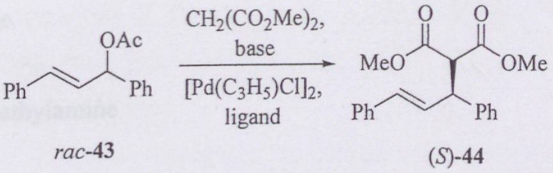


Scheme 19

Table 4. Results of the enantioselective addition of alkenylzinc to aldehydes, using chiral ligands derived from the Betti base

R^1	R^2	Yield (%)	ee (%)	Config.
$Ph(CH_2)_2$	*c*-C_6H_{11}	93	95	(*S*)
n-C_4H_9	*o*-NO_2-phenyl	77	98	(*R*)
n-C_4H_9	*o*-Cl-phenyl	90	>99	(*R*)
n-C_4H_9	*o*-Br-phenyl	87	98	(*R*)
n-C_4H_9	*m*-Br-phenyl	92	94	(*R*)

Ding *et al.* tested the asymmetric induction properties of aminophosphine ligands derived from the Betti bases **34** and **40** in the Pd(0)-catalyzed allylic substitution of 1,3-diphenylprop-2-en-1-yl acetate with dimethyl malonate (Scheme 20) [36]. The main results are listed in Table 5.



Scheme 20

Table 5. The reaction conditions and the results of the Pd(0)-catalyzed asymmetric substitution of (±)-**43**, using chiral aminophosphine ligands derived from the Betti base

Ligand	Solvent	Time (h)	Yield (%)	ee (%)
34a	CH_2Cl_2	24	99	71.2
34a	CH_2Cl_2	24	99	72.2
34b	CH_2Cl_2	24	96	61.5
40a	$ClCH_2CH_2Cl$	24	67	70.2
40b	CH_2Cl_2	24	83	59.7

V. Biological effects

Little attention has been paid to the discussed compounds as concerns their biological activity. Desai *et al.* examined the *in vitro* antituberculotic activity of **12** and **13** (Scheme 8) against the $H_{37}R_V$ strain of *Mycobacterium tuberculosis* in Lowenstein-Jensen egg medium at 0.02 mg/mL. The retardation of the growth rate was studied for up to 6 weeks at 37 °C. The antibacterial activities of **12** and **13** were tested by means of an N-agar pour-plate method in DMF, and they proved to be active against *E. coli* and *S. aureus* [30]. It was found that **16** does not possess significant antimycobacterial activity; the presence of a thiazolidine nucleus is necessary for good antituberculotic activity, and the presence of halogen atoms enhances the antibacterial activity.

VI. Conclusions and outlook

The preparation of substituted Betti base derivatives via a modified Mannich reaction is of significance because a C-C bond is formed under mild experimental conditions and these compounds provide convenient access to many useful synthetic building blocks because of the two functional groups. On the other hand, the enantiomers of the Betti base and its *N*-substituted derivatives can be successfully applied as chiral ligands in asymmetric transformations. Both in that field and in pharmacological investigations, rapid developments are to be expected.

VII. Abbreviations

AcCl	acetyl chloride
AcOH	acetic acid
Ar	aryl
d	day
de	diastereomeric excess
DMSO	dimethyl-sulfoxide
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
Et_3N	triethylamine
h	hour
(*i*-Pr)$_2$NEt	diisopropyl-ethylamine
Me	methyl
MeOH	methanol
Ph	phenyl
Py	pyridine
r.t.	room temperature
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
THF	tetrahydrofuran
TMSCl	trimethylsilylchloride

VIII. Acknowledgments

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VI.

Transformation reactions of the Betti base analog aminonaphthols

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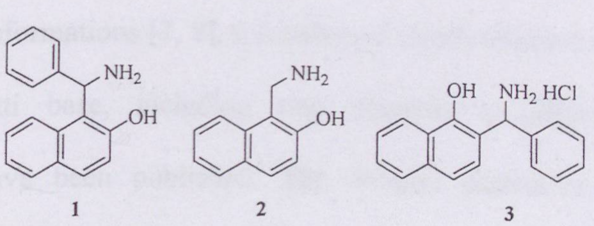
By means of simple or domino ring-closure reactions of 1-(α-aminobenzyl)-2-naphthol (Betti base: **1**), 1-aminomethyl-2-naphthol (**2**) and 2-(α-aminobenzyl)-1-naphthol (reverse Betti base: **3**) with phosgene, ethyl benzimidate, 2-carboxybenzaldehyde, levulinic acid, salicylaldehyde/formalin or salicylaldehyde/acetaldehyde, naphth[1,2-e][1,3]oxazine and naphth[2,1-e][1,3]oxazine derivatives were prepared. All of the nitrogen-bridged polycyclic derivatives of **1** and **3** containing a number of centers of asymmetry were formed with nearly complete diastereoselectivity. Considerable differences were observed in the ring-closing abilities of the unsubstituted and phenyl-substituted aminonaphthols **1** and **2** and of the regioisomeric compounds **1** and **3**.

Chart 1



1 **2** **3**

Introduction

Although Betti's classical procedure for the preparation of 1-(α-aminobenzyl)-2-naphthol (**1**: Betti base) was published more than a century ago [1], the possibilities of the application of this versatile synthon in the ring-closure reactions to give naphthalene-condensed heterocyclic derivatives have not been thoroughly investigated. The few publications that have appeared on this topic focus on the reactions of **1** with aldehydes. Condensation products of **1** and substituted benzaldehydes proved to participate in ring-chain tautomeric equilibria involving two diastereomeric naphthoxazines and an open imine form, the ratios of which were strongly influenced by the electronic effects of the substituents on the aromatic aldehyde [2-5]. The ring-chain tautomeric character of these condensation products of **1** and substituted benzaldehydes was utilized by Desai *et al.* to prepare 4-thiazolidone derivatives with antibacterial activity by the addition of mercaptoacetic acid to the imine forms [6].

Since Naso *et al.* first reported the application of the enantiomers of **1** in asymmetric transformations [7, 8], a number of transformation reactions of the enantiopure Betti base, including ring closures to afford heterocyclic intermediates have been published. The *N*-butyl derivative of (*S*)-**1** was prepared by reductive alkylation via the corresponding ring-chain tautomeric naphthoxazine intermediate [8]. Nonracemic 1-[α-(1-azacycloalkyl)benzyl]-2-naphthols were synthetized by Hu *et al.* via nitrogen-bridged tetracyclic naphthoxazine derivatives obtained by reductive cyclization of the enantiomers of **1** with dials in the presence of $NaBH_3CN$ [9, 10].

Our present aim was to extend the synthetic applicability of aminonaphthol **1** for the preparation of new heterocyclic derivatives. To investigate the effects of the phenyl substituent and the chemical behavior of the regioisomeric structures **1** and **3**, these transformations were also performed by starting from aminonaphthols **2** and **3**.

Results and Discussion

The starting aminonaphthols **1-3** were prepared by known procedures [11-13]. Phenyl-substituted regioisomeric compounds **1** and **3** were synthesized by Mannich aminoalkylation of the corresponding 1- or 2-naphthol with benzaldehyde in the presence of ammonia [11, 12]. Acidic hydrolysis of the naphthoxazine intermediates leads to aminonaphthol **1** or **3**, respectively. In consequence of the facile decomposition of the free base, compound **3** was used in the further transformations as the hydrochloride. Aminonaphthol **2** was obtained by the reaction of 2-naphthol and hexamethylenetetramine in acetic acid, followed by acidic hydrolysis of the intermediate condensation product [12].

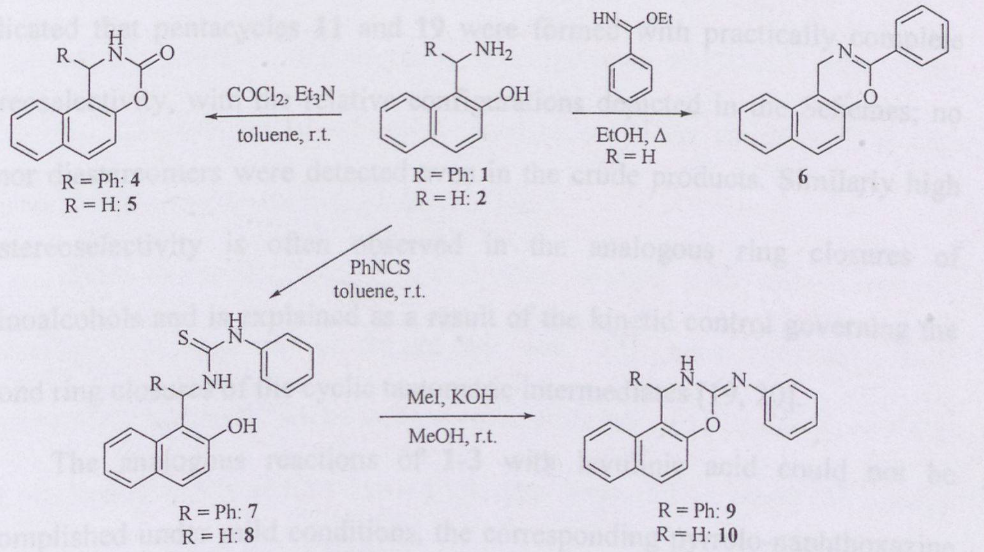
In the first stage of the transformation reactions of compounds **1-3** to yield heterocyclic derivatives, a one-carbon segment with sp^2 configuration was inserted between the hydroxy and amino groups.

When aminonaphthols **1-3** were treated with phosgene in the presence of Et_3N, the corresponding naphthalene-condensed 1,3-oxazin-2-ones (**4**, **5** and **18**) were formed in each case (Schemes 1 and 4). The similar ring closures of the analogous 2-aminomethylphenol were investigated recently [14]. The reactions of **1-3** with ethyl benzimidate in boiling EtOH gave the desired 1,3-oxazine derivative (**6**) only in the case of the unsubstituted aminophenol **2**; with the phenyl-substituted regioisomers **1** and **3**, only decomposition of the starting aminonaphthols was observed (Scheme 1). Whereas the preparation of dihydro-1,3-oxazine derivatives by the ring closure of aminoalcohols with imidates is well known in the literature [15], compound **2** was the first aminophenol for which this transformation was successfully accomplished.

For the preparation of 2-phenylimino-substituted 1,3-oxazines, aminonaphthols **1-3** were reacted with phenyl isothiocyanate. In the cases of 1-

substituted 2-naphthols **1** and **2**, the corresponding thiourea derivatives **7** and **8** were formed in good yields. Thioureas **7** and **8** were converted to the corresponding *S*-methyl isothiourea derivatives with methyl iodide, and subsequent treatment with methanolic KOH gave the corresponding 2-arylimino-substituted 1,3-oxazines **9** and **10** via methyl mercaptan elimination (Scheme 1). This type of ring closure is well known among *N*-thiocarbamoyl-substituted aminoalcohols [16], but as far as we are aware compounds **9** and **10** are the first 2-arylimino-substituted 1,3-oxazine derivatives formed from *N*-thiocarbamoyl-substituted aminophenols. Endocyclic-exocyclic tautomerism of the C=N bond was not investigated.

Scheme 1



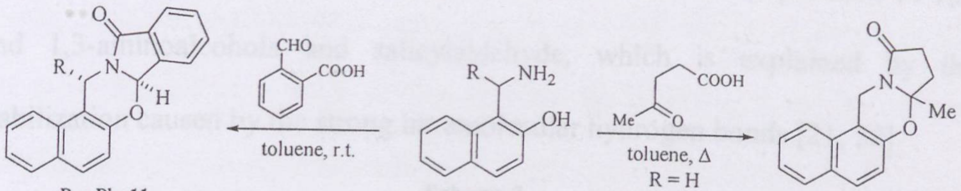
As mentioned above, the ring closures of *N*-unsubstituted aminonaphthols **1-3** with oxo compounds (*i.e.* the insertion of a one-carbon segment with *sp*^{3} configuration) result in naphthalene-condensed 1,3-oxazines with a ring-chain tautomeric character [2-5]. If the oxo compound used in this reaction contains another functional group capable of reacting with the amino group of the naphthoxazine formed, the tautomeric equilibrium can be shifted completely toward the ring-closed form by this second ring closure, resulting in nitrogen-bridged heterocycles. This principle was successfully applied earlier in the domino ring-closure reactions of *N*-unsubstituted aminoalcohols or aminophenols with γ- or δ-oxoacids [17, 18].

The reactions of aminonaphthols **1-3** with 2-carboxybenzaldehyde under mild conditions (r.t.) gave the corresponding isoindole-condensed naphthoxazines **11**, **12** and **19** (Schemes 2 and 4). NMR measurements indicated that pentacycles **11** and **19** were formed with practically complete stereoselectivity, with the relative configurations depicted in the Schemes; no minor diastereomers were detected even in the crude products. Similarly high diastereoselectivity is often observed in the analogous ring closures of aminoalcohols and is explained as a result of the kinetic control governing the second ring closures of the cyclic tautomeric intermediates [19, 20].

The analogous reactions of **1-3** with levulinic acid could not be accomplished under mild conditions, the corresponding pyrrolo-naphthoxazine (**13**) being produced only in the case of the unsubstituted aminonaphthol **2**

(Scheme 2). Elevated temperature again caused the decomposition of aminonaphthols **1** and **3** instead of cyclization.

Scheme 2



R = Ph: **11**
R = H: **12**

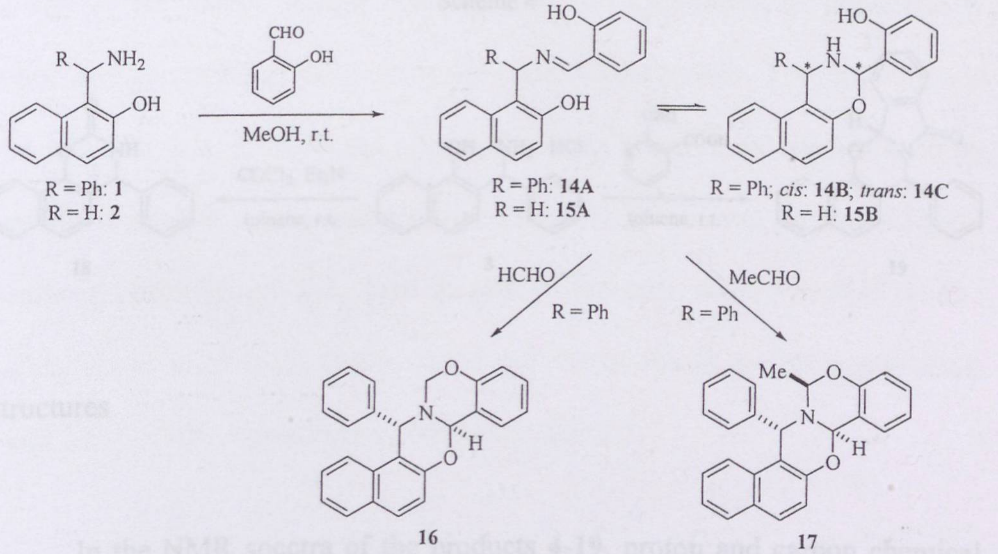
R = Ph: **1**
R = H: **2**

R = H: **13**

A complete shift of the ring-chain tautomeric equilibrium of 1,3-*O*,*N*-heterocycles can be achieved by means of another transformation. If the oxo compound contains another functional group (*e.g.* OH) capable of coupling with the amino group of the ring-closed tautomers via an appropriate agent, this reaction can be a second ring closure with another aldehyde. This type of transformation was exploited earlier in the preparation of 1,3-*O*,*N*-heterocycle-condensed 1,3-oxazines by subsequent cyclization of the aminoalcohols with salicylaldehyde and another aldehyde [21-23].

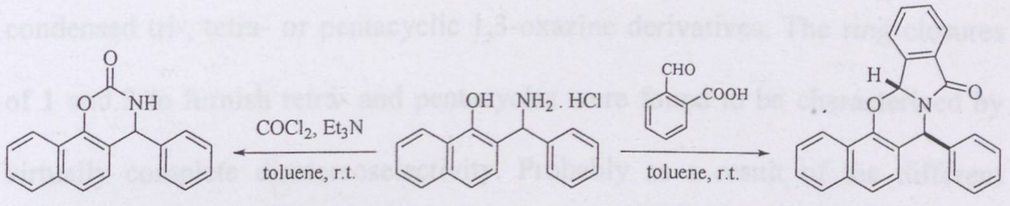
When aminonaphthols **1** and **2** were reacted with salicylaldehyde, crystalline condensation products (**14** and **15**) were formed. NMR measurements revealed that the tautomeric equilibrium of **15** in $CDCl_3$ at 300 K was practically totally shifted toward the open form (**15A**), while the phenyl-substituted compound **14** was found to participate under similar conditions in a three-component tautomeric equilibrium involving the *trans* (**14B**: 56.7%) and the *cis* (**14C**: 8.5%) cyclic diastereomers besides the Schiff base (**14A**: 34.8%). These data are in accordance with earlier observations on the predominance of the open form in the tautomeric equilibria of the condensation products of 1,2- and 1,3-aminoalcohols and salicylaldehyde, which is explained by the stabilization caused by the strong intramolecular hydrogen bonds [21, 22].

Scheme 3



Treatment of compound **14** with 40% formalin or ethanolic acetaldehyde solution resulted in the formation of phenyl-substituted naphthoxazino-benzoxazines **16** and **17** as crystalline products, whereas the similar transformations of **15** failed. The difference in cyclization behavior between **14** and **15** can be explained on the basis of the better crystallization ability of the pentacyclic products (**16** and **17**) formed from **14**, which causes a continuous shift of the tautomeric equilibrium toward the predominant cyclic tautomer (**14B**) [21, 22]. In contrast, Stankevich *et al.* related the successful formation of oxazolobenzoxazines in analogous reactions to the increased ratio of the cyclic form in the tautomeric equilibria of the 2-(*o*-hydroxyphenyl)-oxazolidine intermediates [23]. According to the NMR data, pentacycles **16** and **17** were formed with high stereoselectivity (*de* ~100%), with the relative configurations depicted in Scheme 3.

Scheme 4



Structures

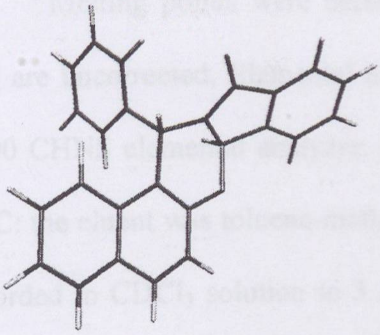
In the NMR spectra of the products **4-19**, proton and carbon chemical shifts can be assigned by using COSY, HSQC and HMBC experiments. The relative configurations of the diastereomers for **6**, **14**, **16**, **17** and **18** were deduced from the NOESY spectra, in which the cross-peak for the protons of the chiral C atoms proved their *trans* arrangement for all these compounds.

The structures were also confirmed by molecular modeling. The conformational protocol comprised a stochastic search via the Merck Molecular

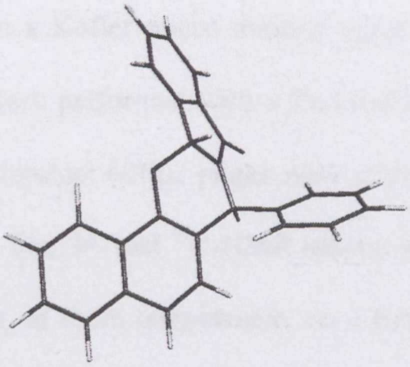
Force Field (MMFF94), and a subsequent minimization of the resulting low-energy conformations at the *ab initio* level, using the HF/3-21G* basis set for **11**, **14**, **16**, **17** and **19**. The resulting structures proved to be rigid, since no minor conformation was found within the 6 kcal/mol energy window. The final conformations for **11**, **16**, **17** and **19** are shown in Figure 1.

Our results prove that the Betti base (**1**) and its aminonaphthol analogs (**2** and **3**) are useful starting materials for the preparation of naphthalene-condensed tri-, tetra- or pentacyclic 1,3-oxazine derivatives. The ring closures of **1** and **3** to furnish tetra- and pentacycles were found to be characterized by virtually complete diastereoselectivity. Probably as a result of the different chemical stabilities of **1-3**, considerable differences were observed in the cyclization abilities of the unsubstituted and phenyl-substituted aminonaphthols **1** and **2** and of the regioisomeric compounds **1** and **3**.

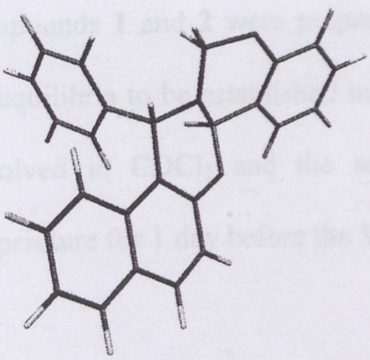
Figure 1. Final predominant minimum energy molecular structures for **11**, **16**, **17** and **19**, obtained by using *ab initio* HF/3-21G* calculations.



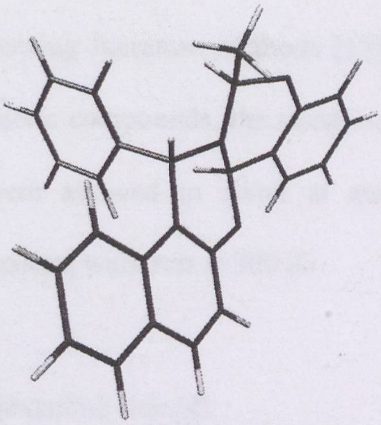
11



19



16



17

EXPERIMENTAL

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyzer. Merck Kieselgel $60F_{254}$ plates were used for TLC: the eluent was toluene-methanol 4:1. The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes, at room temperature, on a Brüker *Avance* DRX400 spectrometer at 400.13 (^{1}H) and 100.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Compounds **1** and **2** were prepared by following literature methods [18]. 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 day before the VT-NMR spectra were run at 300 K.

1-Phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**4**)

Aminonaphthol **1** (0.30 g, 1.20 mmol) was dissolved in abs. toluene (10 mL), and Et_3N (0.24 g, 2.41 mmol) and phosgene (0.63 mL; 20% in toluene, 1.20 mmol) were added. The mixture was stirred at r.t. for 3 h and then H_2O (40 mL) and EtOAc (40 mL) were added. The organic layer was separated, dried

(Na_2SO_4) and evaporated. The oily residue crystallized on treatment with Et_2O (20 mL). The crystalline product was filtered off and recrystallized from *i*Pr_2O (30 mL). Yield: 0.18 g (54%), m.p.: 210-211 °C; ^{1}H-NMR (deuteriochloroform): δ 6.08 (1H, d, J = 2.0 Hz, 1-H), 5.96 (1H, bs, NH), 7.24-7.36 (6H, m, 5H, Ph), 7.38-7.44 (2H, m, 8-H, 9-H), 7.54-7.59 (1H, m, 6-H), 7.81-7.89 (2H, m, 7-H, 10-H); ^{13}C-NMR (deuteriochloroform): δ 56.6 (1-C), 113.2 (10b-C), 117.4 (5-C), 123.0 (10-C), 125.4 (4'-C), 127.2 (2'-C, 6'-C), 127.4 (6a-C), 127.7 (8-C), 129.0 (9-C), 129.1 (6-C), 129.7 (3'-C, 5'-C), 130.9 (7-C), 131.2 (10a-C), 141.9 (1'-C), 148.4 (4a-C), 150.4 (3-C)

Anal. Calcd. for $C_{18}H_{13}NO_2$ (275.31): C, 78.53; H, 4.76; N, 5.09. Found: C, 78.75; H, 4.75; N, 5.09%

2,3-Dihydro-1*H*-naphth[1,2-*e*][1,3]oxazin-3-one (**5**)

Aminonaphthol **2** (0.30 g, 1.73 mmol) was dissolved in abs. toluene (10 mL) and Et_3N (0.35 g, 3.47 mmol) and phosgene (20% in toluene, 0.90 mL; 1.73 mmol) were added. The mixture was stirred at r.t. for 4 h and then H_2O (40 mL) and EtOAc (40 mL) were added. The organic layer was separated, dried (Na_2SO_4) and evaporated. The oily residue crystallized on treatment with *n*-hexane (20 mL). The crystalline product was filtered off and recrystallized from *n*-hexane-*i*Pr_2O (4:1, 50 mL). Yield: 0.11 g (32%), m.p.: 166-168 °C; ^{1}H-NMR (deuteriochloroform): δ 4.94 (2H, s, 2 x 1-H), 5.72 (1H, bs, NH), 7.22 (1H, d, J = 9.1 Hz, 5-H), 7.46-7.60 (3H, m, 8-H, 9-H, 10-H), 7.81 (1H, d, J = 8.8 Hz, 6-H), 7.87 (1H, d, J = 8.1 Hz, 7-H); ^{13}C-NMR (deuteriochloroform): δ 41.5 (1-C), 108.7 (10b-C), 117.3 (5-C), 121.8 (10-C), 125.6 (8-C), 127.8 (9-C), 129.1 (7-C), 129.3 (6a-C), 130.1 (6-C), 133.2 (10a-C), 147.4 (4a-C), 150.6 (3-C)

Anal. Calcd. for $C_{12}H_9NO_2$ (199.21): C, 72.35; H, 4.55; N, 7.03. Found: C, 72.19; H, 4.54; N, 7.01%

3-Phenyl-1*H*-naphth[1,2-*e*][1,3]oxazine (**6**)

A mixture of aminonaphthol **2** (0.40 g, 2.31 mmol) and ethyl benzimidate (0.31 g, 2.31 mmol) was refluxed in EtOH (20 mL) for 8 h. After evaporation, the residue crystallized on treatment with Et_2O (20 mL). The crystalline product was filtered off and recrystallized from *i*Pr_2O (30 mL). Yield: 0.22 g (37%), m.p.: 161-162 °C; ^{1}H-NMR (deuteriochloroform): δ 5.13 (2H, s, 2 x 1-H), 7.21 (1H, d, J = 8.8 Hz, 5-H), 7.39-7.51 (4H, m, 8-H, 3'-H, 4'-H, 5'-H), 7.55 (1H, t, J = 7.8 Hz, 9-H), 7.67 (1H, d, J = 8.8 Hz, 6-H), 7.75 (1H, d, J = 8.8 Hz, 7-H), 7.82 (1H, d, J = 8.1 Hz, 8-H), 8.10-8.15 (2H, m, 2'-H, 6'-H); ^{13}C-NMR (deuteriochloroform): δ 43.5 (1-C), 110.9 (10b-C), 116.7 (5-C), 122.3 (10-C), 125.1 (8-C), 127.2 (9-C), 127.5 (3'-C, 5'-C), 128.5 (2'-C, 6'-C), 128.8 (6-C), 128.9 (7-C), 130.1 (6a-C), 131.3 (4'-C), 132.3 (10a-C), 146.6 (1'-C), 152.6 (4a-C), 154.4 (3-C)

Anal. Calcd. for $C_{18}H_{13}NO$ (259.31): C, 83.38; H, 5.05; N, 5.40. Found: C, 83.61; H, 5.04; N, 5.41%

N^1-[α-(2-Hydroxy-1-naphthyl)benzyl]-N^2-phenylthiourea (**7**)

A mixture of aminonaphthol **1** (0.50 g, 2.00 mmol) and phenyl isothiocyanate (0.35 mL, 2.93 mmol) in abs. toluene (20 mL) was stirred for 1 day. The crystals that separated out were filtered off and washed with toluene (2 x 20 mL) and used in the next step without further purification. Yield: 0.35 g (45%), m.p.: 177-179 °C; ^{1}H-NMR (deuteriochloroform): δ 6.11 (1H, bs, C*H*-NH), 7.07-7.47 (10H, m, 3-H, 2'-H, 3'-H, 5'-H, 6'-H, NH-*Ph*), 7.54 (1H, t, J = 7.3 Hz, 4'-H), 7.60-7.69 (1H, m, 6-H), 7.69-7.94 (4H, m, 4-H, 5-H, 7-H, 8-H); ^{13}C-NMR (deuteriochloroform): δ 55.8 (CH-NH), 109.7 (3-C), 118.0 (8-C), 118.9 (1-C), 123.9 (4''-C), 125.3 (2''-C, 6''-C), 126.3 (3''-C, 5''-C), 126.7 (6-C), 128.0 (7-C), 128.7 (2'-C, 6'-C), 129.2 (4-C), 130.0 (4'-C), 130.3 (3'-C, 5'-C), 132.3 (4a-C), 134.7 (5-C), 135.8 (8a-C), 136.5 (1''-C), 152.0 (1'-C), 153.4 (2-C), 192.3 (NH-*C*=S-NH)

Anal. Calcd. for $C_{24}H_{20}N_2OS$ (384.50): C, 74.97; H, 5.24; N, 7.29. Found: C, 74.76; H, 5.22; N, 7.31%

N^1-(2-Hydroxy-1-naphthyl)methyl-N^2-phenylthiourea (**8**)

A mixture of aminonaphthol **2** (0.50 g, 2.89 mmol) and phenyl isothiocyanate (0.40 mL, 3.34 mmol) in abs. toluene (20 mL) was stirred for 1 day. The crystals that separated out were filtered off and washed with toluene (2 x 20 mL) and used in the next step without further purification.. Yield: 0.42 g (47%), m.p.: 152-155 °C; ^{1}H-NMR (deuteriochloroform): δ 4.80 (1H, bs, NH), 5.27 (2H, d, J = 4.3 Hz, *CH$_2$*-NH), 6.88 (1H, bs, NH), 7.12 (2H, d, J = 7.8 Hz, 2'-H, 6'-H), 7.19 (1H, d, J = 8.8 Hz, 3-H), 7.23-7.40 (4H, m, 6-H, 7-H, 3'-H, 5'-H), 7.44 (1H, t, J = 8.1 Hz, 4'-H), 7.67 (1H, d, J = 5.3 Hz, 4-H), 7.69 (1H, d, J = 6.0 Hz, 5-H), 7.75 (1H, d, J = 8.1 Hz, 8-H); ^{13}C-NMR (deuteriochloroform): δ 40.8 (*C*H$_2$-NH), 115.0 (1-C), 120.5 (3-C), 121.2 (8-C), 123.4 (6-C), 125.4 (2'-C, 6'-C), 127.3 (4'-C), 128.0 (7-C), 129.3 (5-C), 129.4 (4a-C), 130.5 (4-C), 130.6 (3'-C, 5'-C), 133.3 (8a-C), 135.6 (1'-C), 153.7 (2-C), 180.3 (NH-*C*=S-NH)

Anal. Calcd. for $C_{18}H_{16}N_2OS$ (308.41): C, 70.10; H, 5.23; N, 9.08. Found: C, 69.92; H, 5.23; N, 9.06%

1-Phenyl-3-phenylimino-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**9**)

To a solution of thiourea 7 (0.30 g, 0.78 mmol) in MeOH (10 mL), MeI (0.40 mL, 6.43 mmol) was added and the solution was stirred for 2 h. After evaporation of the solvent, the residue was stirred in 3 M methanolic KOH (20 mL) for 4 h. Following evaporation, H_2O (30 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (3 x 20 mL). After drying (Na_2SO_4) and evaporation of the solvent, the crystalline oxazine was obtained on treatment with *n*-hexane (20 mL); it was filtered off and recrystallized from *n*-hexane-*i*Pr_2O (5:1, 36 mL). Yield: 0.15 g (55%), m.p.: 156-158 °C; ^{1}H-NMR (deuteriochloroform): δ 6.27 (1H, bs, 1-H), 7.01 (1H, t, J = 7.3 Hz, 4'-H), 7.16-7.47 (12H, m, 5-H, 8-H, 9-H, 2'-H, 3'-H, 5'-H, 6'-H, N-*Ph*), 7.67-7.71 (1H, m, 6-H), 7.79-7.84 (2H, m, 7-H, 10-H); ^{13}C-NMR (deuteriochloroform): δ 56.0 (1-C), 114.7 (10b-C), 116.4 (5-C), 119.4 (5-C), 122.7 (10-C), 123.1 (8-C), 123.3 (6-C), 124.5 (7-C), 125.1 (2''-C, 6''-C), 127.4 (4''-C), 127.6 (3''-C, 5''-C), 128.8 (4'-C), 129.0 (2'-C, 6'-C), 129.2 (3'-C, 5'-C), 129.6 (6a-C), 131.3 (10a-C), 139.7 (1'-C), 143.8 (N-*C*(Ph)), 144.7 (4a-C), 147.0 (*C*=N)

Anal. Calcd. for $C_{24}H_{18}N_2O$ (350.42): C, 82.26; H, 5.18; N, 7.99. Found: C, 82.48; H, 5.17; N, 7.97%

3-Phenylimino-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**10**)

To a solution of thiourea **8** (0.40 g, 1.30 mmol) in MeOH (10 mL), MeI (0.50 mL, 8.03 mmol) was added and the solution was stirred for 2 h. After evaporation of the solvent, the residue was stirred in 3 M methanolic KOH (20 mL) for 4 h. Following evaporation, H_2O (30 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (3 x 20 mL). After drying (Na_2SO_4) and evaporation of the solvent, the crystalline oxazine was obtained on treatment with *n*-hexane (20 mL); it was filtered off and recrystallized from *n*-hexane-*i*Pr_2O (3:1, 40 mL). Yield: 0.20 g (56%), m.p.: 158-160 °C; ^{1}H-NMR (deuteriochloroform): δ 4.97 (2H, s, 2 x 1H), 5.12 (1H, bs, NH), 7.05 (1H, t, J = 7.3 Hz, 4'-H), 7.10 (1H, d, J = 9.3 Hz, 5-H), 7.33 (2H, t, J = 7.8 Hz, 2'-H, 6'-H), 7.41-7.50 (3H, m, 8-H, 3'-H, 5'-H), 7.55 (1H, t, J = 7.8 Hz, 9-H), 7.66 (1H, d, J = 8.3 Hz, 6-H), 7.73 (1H, d, 9.1 Hz, 7-H), 7.82 (1H, d, J = 8.3 Hz, 10-H); ^{13}C-NMR (deuteriochloroform): δ 42.2 (1-C), 112.3 (10b-C), 116.4 (5-C), 119.7 (10-C), 122.3 (8-C), 122.8 (9-C), 125.0 (4'-C), 127.2 (6-C), 128.8 (2'-C, 6'-C), 129.2 (3'-C, 5'-C), 130.2 (6a-C), 130.9 (10a-C), 139.0 (7-C), 145.7 (1'-C), 146.9 (4a-C), 185.2 (3-C)

Anal. Calcd. for $C_{18}H_{14}N_2O$ (274.33): C, 78.81; H, 5.14; N, 10.21. Found: C, 78.70; H, 5.14; N, 10.16%

(7a*R**,14*S**)-14-Phenyl-7a*H*,12*H*,14*H*-naphth[1',2':5,6][1,3]oxazino[2,3-*a*]isoindol-12-one (**11**)

To a solution of aminonaphthol **1** (0.50 g, 2.00 mmol) in abs. toluene (20 mL), 2-carboxybenzaldehyde (0.30 g, 2.01 mmol) was added. The mixture was stirred at r.t. for 5 days, during which a white solid separated out. The solvent was evaporated off and the residue crystallized on treatment with Et_2O (20 mL). The crystalline product was filtered off and recrystallized from $i\mathrm{Pr}_2O$ (30 mL). Yield: 0.45 g (62%), m.p.: 221-222 °C; ^{1}H-NMR (deuteriochloroform): δ 6.09 (1H, s, 14-H), 6.95 (1H, s, 7a-H), 7.19 (1H, d, J = 9.1 Hz, 6-H), 7.22-7.33 (5H, m, Ph), 7.42-7.47 (2H, m, 2-H, 3-H), 7.48-7.61 (3H, m, 8-H, 9-H, 10-H), 7.70 (1H, d, J = 7.3 Hz, 5-H), 7.73-7.79 (2H, m, 4-H, 1-H), 7.87 (1H, d, J = 7.1 Hz, 11-H); ^{13}C-NMR (deuteriochloroform): δ 50.7 (14-C), 79.2 (7a-C), 111.9 (14a-C), 118.7 (6-C), 123.8 (1-C), 124.0 (3-C), 124.3 (4'-C), 124.4 (2-C), 127.2 (10-C), 128.3 (11-C), 128.6 (5-C), 128.7 (2'-C, 6'-C), 129.1 (3'-C, 5'-C), 129.9 (4a-C), 130.2 (8-C), 130.6 (4-C), 131.5 (14b-

C), 132.5 (9-C), 132.6 (11a-C), 140.7 (7b-C), 141.9 (1'-C), 151.4 (6a-C), 165.4 (12-C)

Anal. Calcd. for $C_{25}H_{17}NO_2$ (363.42): C, 82.63; H, 4.72; N, 3.85. Found: C, 82.45; H, 4.72; N, 3.84%

7a*H*,12*H*,14*H*-Naphth[1',2':5,6][1,3]oxazino[2,3-*a*]isoindol-12-one (**12**)

To a solution of aminonaphthol **2** (0.30 g, 1.73 mmol) in abs. toluene (20 mL), 2-carboxybenzaldehyde (0.26 g, 1.73 mmol) was added. The mixture was stirred at r.t. for 1 day, during which white solid separated out. The solvent was evaporated off and the residue crystallized on treatment with Et_2O (20 mL). The crystalline product was filtered off and recrystallized twice from *i*Pr_2O-EtOAc (3:1, 40 mL). Yield: 0.18 g (36%), m.p.: 176-178 °C; ^{1}H-NMR (deuteriochloroform): δ 4.90 (1H, d, J = 16.9 Hz, 14-H), 5.52 (1H, d, J = 16.9 Hz, 14-H), 6.08 (1H, s, 7a-H), 7.17 (1H, d, J = 9.1 Hz, 6-H), 7.45 (1H, t, J = 7.3 Hz, 10-H), 7.54-7.86 (7H, m, 1-H, 2-H, 3-H, 4-H, 5-H, 8-H, 9-H), 7.94 (1H, d, J = 7.3 Hz, 11-H); ^{13}C-NMR (deuteriochloroform): δ 38.0 (14-C), 82.2 (7a-C), 111.1 (14a-C), 119.0 (6-C), 121.6 (1-C), 124.1 (3-C), 124.2 (2-C), 124.8 (10-C), 127.5 (11-C), 128.9 (5-C), 129.3 (8-C), 130.8 (4-C), 132.5 (9-C), 135.8 (4a-C), 140.7 (14b-C), 143.2 (11a-C), 149.6 (7b-C), 149.9 (6a-C), 168.6 (12-C)

Anal. Calcd. for $C_{19}H_{13}NO_2$ (287.32): C, 79.43; H, 4.56; N, 4.87. Found: C, 79.58; H, 4.55; N, 4.87%

7a-Methyl-8,9-dihydro-7a*H*,10*H*,12*H*-naphth[1,2-*e*]pyrrolo[2,1-*b*][1,3]oxazin-10-one (**13**)

To a solution of aminonaphthol **2** (0.40 g, 2.31 mmol) in abs. toluene (10 mL), levulinic acid (0.27 g, 2.31 mmol) was added. The mixture was refluxed for 3 h, and the solvent was evaporated off. The product was purified by column chromatography (silica gel, eluent: toluene-MeOH, 14:1). Yield: 0.09 g (17%), m.p.: 104-106 °C; ^{1}H-NMR (deuteriochloroform): δ 1.62 (3H, s, Me), 2.17-2.28 (1H, m, 9-H), 2.43-2.67 (3H, m, 9-H, 2 x 8-H), 4.43 (1H, d, J = 16.6 Hz, 12-H), 5.41 (1H, d, J = 16.6 Hz, 12-H), 6.99 (1H, d, J = 8.8 Hz, 6-H), 7.37 (1H, t, J = 7.3 Hz, 3-H), 7.50 (1H, t J = 7.6 Hz, 2-H), 7.65 (1H, d J = 9.1 Hz, 5-H), 7.70 (1H, d, J = 8.3 Hz, 4-H), 7.76 (1H, d, J = 8.3 Hz, 1-H); ^{13}C-NMR (deuteriochloroform): δ 22.8 (Me), 29.3 (9-C), 31.8 (8-C), 36.2 (12-C), 91.1 (7a-C), 109.9 (12a-C), 119.4 (6-C), 121.4 (1-C), 124.2 (3-C), 127.1 (2-C), 128.7 (4-C), 129.0 (5-C), 129.2 (4a-C), 131.0 (12b-C), 149.9 (6a-C), 174.8 (10-C)

Anal. Calcd. for $C_{16}H_{15}NO_2$ (253.30): C, 75.87; H, 5.97; N, 5.53. Found: C, 76.08; H, 5.96; N, 5.54%

3-(2-Hydroxyphenyl)-1-phenyl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**14**)

A solution of aminonaphthol **1** (1.50 g, 6.03 mmol) and salicylaldehyde (0.74 g, 6.03 mmol) in MeOH (40 mL) was stirred at r.t. for 1 h. The solvent was evaporated off and the residue crystallized on treatment with Et_2O (40 mL). The crystalline product was filtered off and recrystallized from *i*Pr_2O-EtOAc (3:1, 80 mL). Yield: 1.83 g (86%), m.p.: 180-181 °C; ^{1}H-NMR (deuteriochloroform): δ 5.68 and 5.78 (*trans* diastereomer, major compound), 5.88 and 5.95 (*cis* diastereomer, minor compound), 8.60 (Schiff base); ^{13}C-NMR (deuteriochloroform): δ 54.2 and 79.0 for the *trans* diastereomer, 57.0 and 83.7 for *cis* diastereomer, and 166.9 for the Schiff base

3-(2-Hydroxyphenyl)-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine (**15**)

A solution of aminonaphthol **2** (1.50 g, 8.67 mmol) and salicylaldehyde (1.06 g, 8.67 mmol) in MeOH (40 mL) was stirred at r.t. for 1 h. The solvent was evaporated off and the residue crystallized on treatment with Et_2O (40 mL).

The crystalline product was filtered off and recrystallized from *i*Pr_2O-EtOAc (6:1, 70 mL). Yield: 1.45 g (67%), m.p.: 175-177 °C; ^{1}H-NMR (deuteriochloroform): δ 5.30 (2H, s, CH_2-N=CH), 6.79 (1H, t, J = 7.6 Hz, 3'-H), 6.90 (1H, d, J = 8.1 Hz, 3-H), 7.00 (1H, t, J = 8.1 Hz, 4'-H), 7.08 (1H, d, J = 8.6 Hz, 5'-H), 7.10 (1H, d, J = 8.1 Hz, 4-H), 7.36 (1H, t, J = 7.8 Hz, 6-H), 7.52 (1H, t, J = 8.6 Hz, 7-H), 7.72 (1H, d, J = 8.8 Hz, 6'-H), 7.79 (1H, d, J = 7.8 Hz, 5-H), 7.99 (1H, d, J = 8.6 Hz, 8-H), 8.37 (1H, s, N=C*H*); ^{13}C-NMR (deuteriochloroform): δ 51.8 (*C*H_2-N=CH), 114.9 (1-C), 115.5 (1'-C), 117.5 (5'-C), 118.0 (3-C), 118.4 (3'-C), 122.9 (8-C), 123.7 (6-C), 127.5 (7-C), 128.9 (4-C), 130.2 (5-C), 131.8 (2'-C), 132.7 (4'-C), 133.2 (4a-C), 135.6 (8a-C), 151.9 (2-C), 163.0 (6'-C), 166.4 (N=*C*H)

Anal. Calcd. for $C_{18}H_{15}NO_2$ (277.33): C, 77.96; H, 5.45; N, 5.05. Found: C, 78.14; H, 5.45; N, 5.06%

(7a*R**,15*S**)-15-Phenyl-7a*H*,13*H*,15*H*-naphth[1',2':5,6][1,3]oxazino[3,2-c][1,3]benzoxazine (**16**)

To a solution of **14** (0.30 g, 0.85 mmol) in EtOH (20 mL), 40% aqueous formaldehyde (2.5 mL) was added. The mixture was stirred at r.t. for 30 min., during which white crystals separated out. The crystalline product was filtered off, and recrystallized from *i*Pr_2O-EtOAc (3:1, 40 mL). Yield: 0.29 g (93%), m.p.: 214-216 °C; ^{1}H-NMR (deuteriochloroform): δ 4.91 (1H, d, J = 6.8 Hz, 13-H), 4.96 (1H, d, J = 6.8 Hz, 13-H), 5.53 (1H, s, 15-H), 5.61 (1H, s, 7a-H), 6.92-7.01 (2H, m, 11-H, 9-H), 7.13 (1H, d, J = 9.0 Hz, 6-H), 7.22-7.36 (9H, m, 2-H, 3-H, 8-H, 10-H, Ph), 7.38-7.42 (1H, m, 5-H), 7.74-7.81 (2H, m, 1-H, 4-H); ^{13}C-NMR (deuteriochloroform): δ 57.9 (15-C), 77.9 (13-C), 78.7 (7a-C), 111.3 (15a-C), 117.2 (11-C), 119.1 (6-C), 120.3 (7b-C), 121.3 (9-C), 122.8 (1-C), 123.8 (3-C), 127.1 (2-C), 128.0 (5-C), 128.7 (2'-C, 6'-C), 128.9 (4'-C), 129.3 (10-C), 129.4 (3'-C, 5'-C), 130.0 (4-C), 130.8 (8-C), 132.0 (4a-C),.2 x 141.5 (15b-C, 1'-C), 150.7 (6a-C), 153.3 (11a-C)

Anal. Calcd. for $C_{25}H_{19}NO_2$ (365.44): C, 82.17; H, 5.24; N, 3.83. Found: C, 82.39; H, 5.25; N, 3.82%

(7a*R**,13*R**,15*S**)-13-Methyl-15-phenyl-7a*H*,13*H*,15*H*-naphth[1',2':5,6][1,3]oxazino[3,2-c][1,3]benzoxazine (**17**)

A mixture of compound **14** (0.30 g, 0.85 mmol), EtOH (20 mL) and acetaldehyde (2 mL) was stirred at r.t. until the TLC showed no more starting material (for *ca.* 10 h). The solvent was evaporated off and the residue crystallized on treatment with Et_2O (30 mL). The crystalline product was filtered off and recrystallized from *i*Pr_2O-EtOAc (4:1, 50 mL). Yield: 0.25 g (78%), m.p.: 226-228 °C; ^{1}H-NMR (deuteriochloroform): δ 1.78 (3H, d, J = 5.5 Hz, Me), 5.15 (1H, q, J = 5.5 Hz, 13-H), 5.70 (1H, s, 15-H), 5.89 (1H, s, 7a-H), 6.94-7.07 (2H, m, 9-H, 11-H),7.19 (1H, d, J = 9.1 Hz, 6-H), 7.27-7.41 (9H, m, 2-H, 3-H, 8-H, 10-H, Ph), 7.44-7.49 (1H, m, 5-H), 7.80-7.86 (2H, m, 3-H, 4-H); ^{13}C-NMR (deuteriochloroform): δ 19.8 (Me), 54.7 (15-C), 79.4 (13-C), 81.1 (7a-C), 111.0 (15a-C), 116.8 (11-C), 119.1 (6-C), 120.3 (7b-C), 121.0 (9-C), 122.3 (1-C), 123.7 (3-C), 128.6 (2-C), 128.7 (5-C), 128.9 (2'-C, 6'-C), 129.0 (4'-C), 129.4 (10-C), 129.5 (3'-C, 5'-C), 130.0 (4-C), 130.6 (8-C), 132.1 (4a-C), 2 x 141.9 (15b-C, 1'-C), 151.5 (6a-C), 153.7 (11a-C)

Anal. Calcd. for $C_{26}H_{21}NO_2$ (379.46): C, 82.30; H, 5.58; N, 3.69. Found: C, 82.49; H, 5.56; N, 3.70%

4-Phenyl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazin-2-one (**18**)

Aminonaphthol hydrochloride **3** (0.30 g, 1.05 mmol) was suspended in abs. toluene (10 mL), and Et_3N (0.34 g, 3.15 mmol) and phosgene (0.55 mL; 20% in toluene, 1.05 mmol) were added. The mixture was stirred at r.t. for 4 h and then EtOAc (40 mL) and H_2O (40 mL) were added. The organic layer was separated, dried (Na_2SO_4) and evaporated. The oily residue crystallized on treatment with *n*-hexane (20 mL). The crystalline product was filtered off and recrystallized from *n*-hexane-iPr$_2$O (40-10 mL). Yield: 0.09 g (31%), m.p.: 196-198 °C; ^{1}H-NMR (deuteriochloroform): δ 5.78 (1H, s, 4-H), 5.97 (1H, bs, NH), 6.93 (1H, d, J = 8.6 Hz, 5-H), 7.31-7.41 (5H, m, Ph), 7.49-7.62 (3H, m, 6-H, 8-H, 9-H), 7.78 (1H, d, J = 7.8 Hz, 7-H), 8.36 (1H, d, J = 8.6 Hz, 10-H); ^{13}C-NMR (deuteriochloroform): δ 58.6 (4-C), 114.8 (4a-C), 121.7 (6-C), 123.5 (10-C), 124.6 (8-C), 127.1 (9-C), 127.4 (7-C), 127.7 (4’-C), 127.8 (2’-C, 6’-C), 129.1 (5-C), 129.5 (3’-C, 5’-C), 133.9 (10a-C), 141.8 (6a-C), 142.9 (1’-C), 144.4 (10b-C), 150.3 (2-C)

Anal. Calcd. for $C_{18}H_{13}NO_2$ (275.31): C, 78.53; H, 4.76; N, 5.09. Found: C, 78.32; H, 4.75; N, 5.08%

(7S*,13bR*)-7-Phenyl-7H,9H,13bH-naphth[2’,1’:5,6][1,3]oxazino[2,3-*a*]isoindol-9-one (**19**)

To a suspension of aminonaphthol hydrochloride **3** (0.50 g, 1.75 mmol) in abs. toluene (20 mL), 2-carboxybenzaldehyde (0.27 g, 1.73 mmol) and Et_3N (0.20 g, 1.98 mmol) were added. The mixture was stirred at r.t. for 8 days and then was washed consecutively with H_2O (50 mL) and with 2 M HCl solution (50 mL) after adding of EtOAc (50 mL). The organic layer was separated, dried

(Na_2SO_4) and evaporated. The oily residue crystallized on treatment with *n*-hexane (20 mL). The crystalline product was filtered off and recrystallized from *n*-hexane-*i*Pr_2O (8:1, 45 mL). Yield: 0.27 g (42%), m.p.: 156-158 °C; ^{1}H-NMR (deuteriochloroform): δ 6.17 (1H, s, 7-H), 6.51 (1H, s, 13b-H)), 7.10 (1H, d, J = 8.6 Hz, 6-H), 7.25-7.37 (3H, m, 2'-H, 4'-H, 6'-H), 7.42-7.58 (7H, m, 2-H, 3-H, 5-H, 13-H, 3'-H, 5'-H), 7.63 (1H, t, J = 7.6 Hz, 11-H), 7.76-7.89 (3H, m, 4-H, 10-H, 12-H), 8.24-8.30 (1H, m, 1-H); ^{13}C-NMR (deuteriochloroform): δ 52.9 (7-C), 80.2 (13b-C), 114.6 (6a-C), 121.7 (5-C), 121.9 (1-C), 124.0 (2-C), 124.2 (3-C), 125.2 (14b-C), 126.0 (4'-C), 126.2 (11-C), 127.0 (10-C), 127.8 (4-C), 128.4 (6-C), 129.0 (13-C), 129.1 (2'-C, 6'-C), 130.7 (3'-C, 5'-C), 132.5 (12-C), 132.8 (4a-C), 133.9 (9a-C), 140.7 (13a-C), 142.0 (1'-C), 148.5 (14a-C), 166.1 (9-C)

Anal. Calcd. for $C_{25}H_{17}NO_2$ (363.42): C, 82.63; H, 4.72; N, 3.85. Found: C, 82.86; H, 4.73; N, 3.86%

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VII.

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TETRAHEDRON

Synthesis and stereochemical studies of 1- and 2-phenyl-substituted 1,3-oxazino[4,3-*a*]isoquinoline derivatives

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Abstract—Starting from the 1$'$- or 2$'$-phenyl-substituted 1-(2$'$-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline diastereomers **3** and **6**, 4-unsubstituted and 4-(*p*-nitrophenyl)- and 4-oxo-substituted 1-phenyl- and 2-phenyl-9,10-dimethoxy-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinolines (**7–12**) were prepared. The relative configurations and the predominant conformations of the products were determined by NMR spectroscopy, by quantum chemical calculations and, for (2R^*,4S^*,11bR^*)-9,10-dimethoxy-4-(*p*-nitrophenyl)-2-phenyl-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinoline (**11**), by X-ray diffraction. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

In consequence of their interesting biologically active properties, widespread natural occurrence and synthetic utility, considerable interest has been demonstrated towards partially saturated isoquinolines.[1–3] Their tricyclic derivatives, containing another saturated hetero-ring annelated to positions 1,2 of tetrahydroisoquinoline (azeto[2,1-*a*]isoquinolines, benzo[*e*]indolizidines, benzo[*a*]quinolizidines and their hetero analogues), have also been studied thoroughly from chemical, stereochemical and pharmacological aspects.[4–9]

Recent systematic studies on 1-, 2- and 4-substituted saturated 1,3-oxazino[4,3-*a*]-,[10–13] 1,2,3-oxathiazino[4,3-*a*]-[14] and 1,3,2-oxazaphosphorino[4,3-*a*]isoquinolines[15,16] led to the conclusion that the heteroatoms, the substituents on the saturated rings and the configurations of the substituted carbon atoms exert pronounced effects on the conformational equilibria of these compounds. Our present aims were to investigate the influence of 1- and 2-phenylsubstitution on the conformation of 1,3-oxazino[4,3-*a*]isoquinolines, and (the corresponding effects) of substituents at position 4; accordingly, the 4-unsubstituted derivatives and the 4-(*p*-nitrophenyl) and 4-oxo analogues were prepared.

2. Results and discussion

2.1. Syntheses

The phenyl-substituted amino alcohols **3** and **6** (1$'$- and 2$'$-phenylhomocalycotomine) were prepared similarly to their methyl analogues (1$'$- or 2$'$-methylhomocalycotomine).[14] Formaldehyde addition to 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**1**) followed by NaBH$_4$ reduction and crystallization resulted in the diastereomerically pure amino alcohol **3**. This reduction of the intermediate **2** occurred with high diastereoselectivity (*de* >95%), which can be rationalized in terms of the steric effect of the phenyl substituent directing the attack of the hydride ions (Scheme 1). The relative configuration (1R^*,1$'R^*$) of **3** was deduced from its ring-closed derivatives (**7–9**).

The 2$'$-phenyl-substituted amino alcohol **6** was obtained from the β-amino ketone derivative **5** by NaBH$_4$ reduction. Compound **5** was formed in good yield, analogously to its methyl derivative,[12] by addition and subsequent decarboxylation of the oxo acid, prepared in situ by hydrolysis of the corresponding ethyl benzoylacetate **4**, to 6,7-dimethoxy-3,4-dihydroisoquinoline. The reduction of the amino ketone **5** resulted in a 2:1 mixture of (1R^*,2$'R^*$, **6**) and its (1R^*,2$'S^*$) isomer, from which diastereomerically pure **6** could be obtained by fractional crystallization (Scheme 1). The diastereomeric ratio could be determined from the well-separated H-2$'$ lines in the ^{1}H NMR spectrum. The relative configuration (1R^*,2$'R^*$) of **6** stems from literature[17] data.

Keywords: oxazines; isoquinolines; stereochemistry; molecular modelling.

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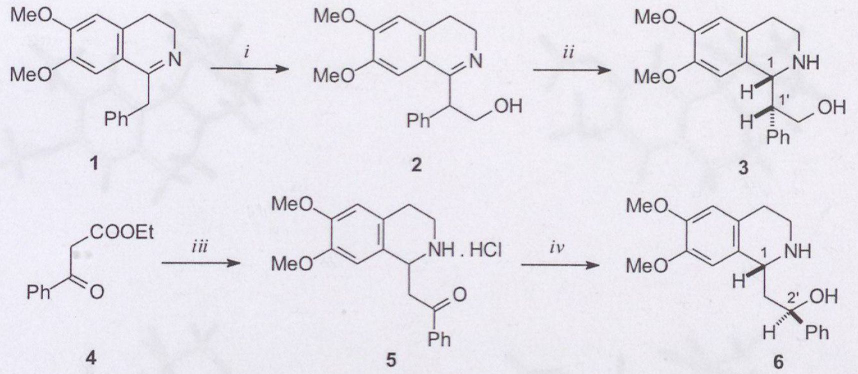


Scheme 1. *Reagents and conditions*: (i) $CH_2O/NaOEt/EtOH/rt$; (ii) $NaBH_4/MeOH/0°C\rightarrow rt$, then crystallization; 62% (i+ii); (iii) 1. $NaOH/H_2O/rt$, 2. 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride/$HCl/H_2O/MeOH/rt$, 74%; (iv) $NaBH_4/MeOH/0°C\rightarrow rt$, then crystallization; 47%.

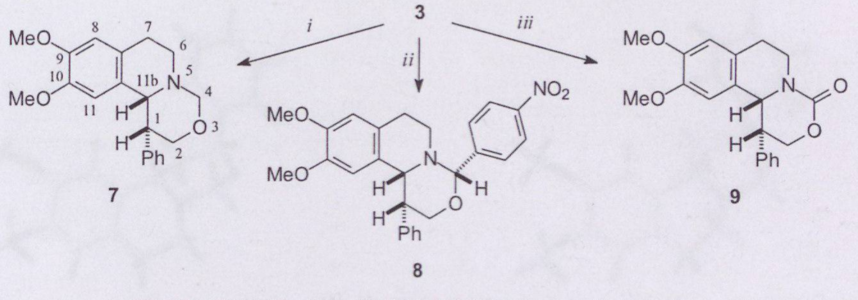
The ring-closure reaction of 1-substituted 1,2,3,4-tetrahydroisoquinoline 1,3-amino alcohols with one-carbon fragments is a common method for the synthesis of 1,3-oxazino[4,3-*a*]isoquinolines. This transformation is often applied for homocalycotomines bearing substituents in the side-chain for the purpose of determining the configuration of the substituted atoms in rigid ring-closed products.[17–20]

Treatment of amino alcohols **3** and **6** with formaldehyde gave 4-unsubstituted oxazino[4,3-*a*]isoquinolines **7** and **10** under mild conditions. The ring closures of **3** and **6** with *p*-nitrobenzaldehyde resulted in compounds **8** and **11**. In the latter reactions, the formation of C-4 epimeric pairs is possible. However, as the NMR spectra indicated, the diastereomer containing H-4 and H-11b in *cis* position was formed as the major product (*de* >99 and *de* ~95%, respectively) in both ring-closures; it could be obtained in diastereomerically pure form by crystallization.

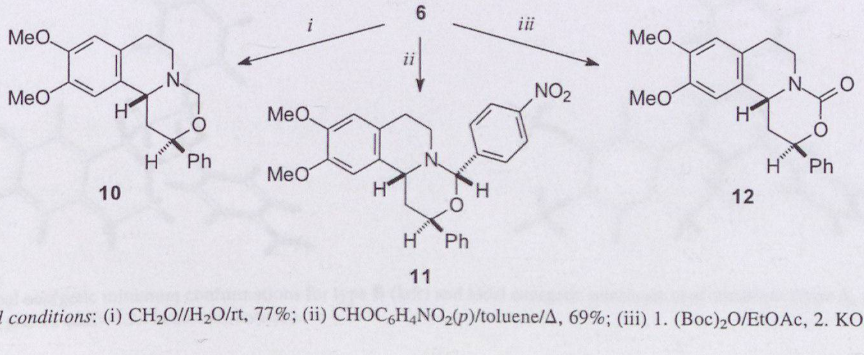
The 4-oxo derivatives **9** and **12** were synthesized in slightly different ways: the ethyl or *tert*-butyl urethanes obtained from amino alcohols **3** or **6** were treated with NaOMe or KO*t*Bu, respectively.[12,21] As the NMR data proved, the transformation **6→12** occurred without change in the configuration. Under the conditions applied in the reaction **3→9**, no cyclic product (**12**) could be obtained from **6** (Schemes 2 and 3).

2.2. NMR measurements and quantum chemical calculations

All compounds were found to have a twisted-chair conformation in the tetrahydropyridine ring and a chair (**7**, **8**, **10 and 11**) or a twisted-chair-like (**9**, **12**) conformation in the perhydrooxazine ring. The conformation of the oxazine moiety was evidenced by NOE measurements and corroborated by some $^3J(H,H)$ coupling constants. NOEs were observed between the axial protons or substituents:



Scheme 2. *Reagents and conditions*: (i) $CH_2O/MeOH/H_2O/rt$, 69%; (ii) $CHOC_6H_4NO_2(p)$/toluene/Δ, 72%; (iii) 1. $ClCOOEt/NaHCO_3$, 2. NaOMe/Δ, 51%.



Scheme 3. *Reagents and conditions*: (i) $CH_2O//H_2O/rt$, 77%; (ii) $CHOC_6H_4NO_2(p)$/toluene/Δ, 69%; (iii) 1. $(Boc)_2O/EtOAc$, 2. KO*t*Bu /THF/Δ, 66%.

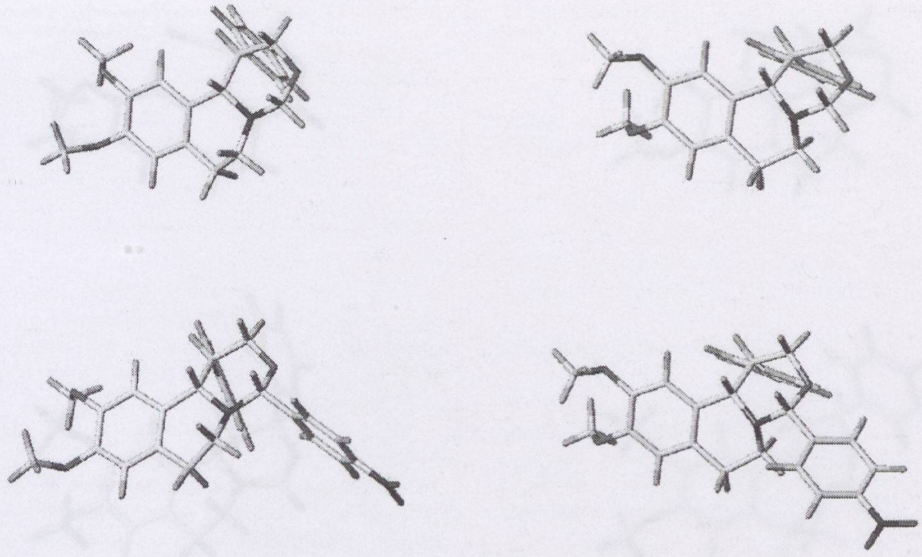


Figure 1. Calculated global energetic minimum conformations for type **A** (left) and local energetic minimum conformations (type **B**, right) for compounds **7** (ΔE=1.33 kcal/mol, top) and **8** (ΔE=0.32 kcal/mol, bottom).

H-11b$_{axial}$↔H-4$_{axial}$ (**7**, **8**, **10** and **11**); H-4$_{axial}$↔H-*o* of the 2-phenyl substituent (**10**, **11**); H-4$_{axial}$↔H-2$_{axial}$ (**8**); H-11b$_{axial}$↔H-2$_{axial}$ (**7**, **9**); H-11b$_{axial}$↔H-*o* of the 2-phenyl substituent (**10–12**). *Trans*-^3J(H,H) coupling constants were found between H-11b and H-1$_{ax}$ in **10** (10.9 Hz) and **11** (10.5 Hz). In compounds **9** and **12**, the oxazine ring is flatter because of the introduction of a carbonyl group at position 4. Therefore, the hybridization of C-4 is changed from sp^3 to sp^2 and the amide bond acquires a partial double bond character, while the sp^3 hybridization at the nitrogen atom is reduced. Both changes lead to higher planarity of the perhydrooxazine ring.

In compounds **7–12**, the tetrahydropyridine and the perhydrooxazine rings are *cis*-fused. Three types of structures (**A–C**) were predicted, which differ in the direction of the lone pair on the nitrogen; *anti* to O-3 for type **A** and *syn* to O-3 for type **B**, while in type **C**, the oxazine ring is flattened and C-11b, N-5, C-4 and O-3 are lying nearly planar. Structures **A** and **B** can be conceived to be convertible into each other by nitrogen inversion. Type **A** includes compounds **7** and **8**, type **B** compounds **10** and **11**, and type **C** **9** and **12**. These assignments could be made by using the NMR results (esp. NOE measurements) and accompanying quantum chemical calculations, which also gave the corresponding global energy minima (type **A** for **7** and **8**, type **B** for **10** and **11**, and type **C** for **9** and **12**, see Figs. 1–3).

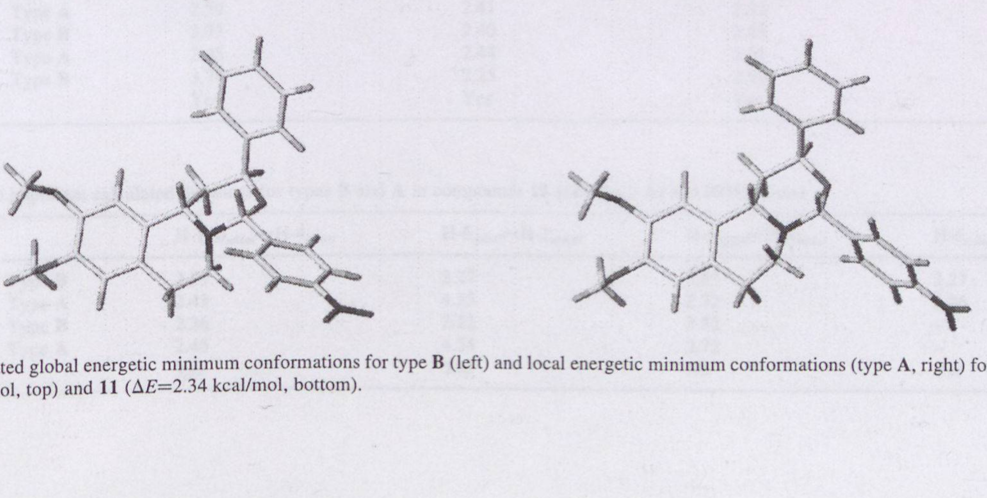


Figure 2. Calculated global energetic minimum conformations for type **B** (left) and local energetic minimum conformations (type **A**, right) for compounds **10** (ΔE=1.90 kcal/mol, top) and **11** (ΔE=2.34 kcal/mol, bottom).

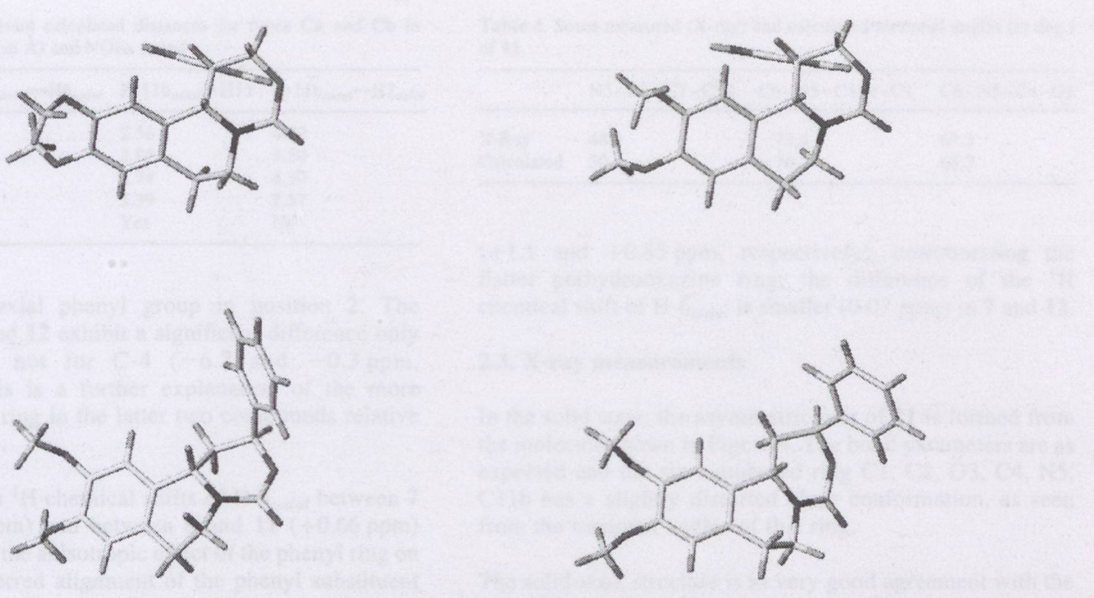


Figure 3. Calculated energetic minimum conformations for type **C** with inverted twist-chairs of the tetrahydropyridine ring (C-7 *trans* to H-11b-**Ca**, left, and C-7 *cis* to H-11b-**Cb**, right) for compounds **9** (ΔE=3.87 kcal/mol, top) and **12** (ΔE=2.13 kcal/mol, bottom).

The type **A** structure is indicated by the following NOEs (Table 1): H6$_{axial}$↔H-11b$_{axial}$ for all compounds, H-6$_{equatorial}$↔H-4$_{equatorial}$ for **7**, and H-6$_{equatorial}$↔H-2$''$ of the *p*-nitrophenyl substituent for **8**. Together with the NOE results (the chair conformation of the perhydrooxazine ring) and the equatorial position of H-1 (corresponding to its relatively small coupling constant $^3J_{\text{H-11b, H-1}}$ of 3.3 (**7**) and 2.4 (**8**) Hz, respectively), the relative configuration of the carbon atoms at positions 11b and 1 is proved to be *R**,*R**. In consequence of the synthetic pathway, this is also the relative configuration of the amino alcohol **3**.

Structural proof for type **B** is provided by the following NOEs, which are fully in line with the distances obtained from the accompanying MO calculations (Table 2): H-6$_{equatorial}$↔H-4$_{equatorial}$ and H-6$_{axial}$↔H-1$_{axial}$ in **10**, and H-6$_{equatorial}$↔H-2$''$ of the *p*-nitrophenyl substituent and H6$_{axial}$↔H-1$_{axial}$ in **11**. Additionally, reported coupling constants of a known compound of type **B** (similar to **10**), (2*R*,11b*R*)-1,6-7-11b-tetrahydro-9,10-dimethoxy-2-(4-methoxyphenyl)-2*H*-[1,3]-oxazino[4,3-*a*]-isoquinoline,[17] are very close to the measured coupling constants of **10**.

The calculations of type **C** compounds led to two different energy minima structures, **Ca** and **Cb**, which are pseudo-rotamers of the tetrahydropyridine ring (Fig. 3). The two structures differ in some proton–proton distances, and the experimentally determined structure (by NOE measurements) was found to be **Ca** (Table 3).

The phenyl substituents in position 1 (NOEs between H-2$_{equatorial}$↔H-2$'$ of the phenyl substituent in **7**–**9**) or position 2 (NOEs see above, **10**–**12**) always adopt the axial position, whereas the *p*-nitrophenyl substituent (position 4) in **8** and **11** is equatorially oriented.

Significant differences in ^{13}C chemical shifts can be seen for C-11b and C-4 in the isomeric pairs **7** and **10** (−10.8 and −7.6 ppm, respectively) and **8** and **11** (−9.7 and −10.4 ppm, respectively). This may be due to a strong

Table 1. Some important calculated distances for types **A** and **B** in compounds **8** and **7** (in Å) and NOEs found

Distance		H-11b$_{axial}$↔H6$_{axial}$	H-11b$_{axial}$↔H4$_{axial}$	H-11b$_{axial}$↔H2$_{axial}$	H-6$_{axial}$↔H4$_{axial}$
7	Type **A**	2.59	2.41	2.52	2.73
	Type **B**	3.77	2.40	2.49	3.89
8	Type **A**	2.45	2.44	2.51	2.69
	Type **B**	3.74	2.25	2.52	3.88
NOE found?		Yes	Yes	Yes	Yes

Table 2. Some important calculated distances for types **B** and **A** in compounds **10** and **11** (in Å) and NOEs found

Distance		H-11b$_{axial}$↔H-4$_{axial}$	H-6$_{axial}$↔H-1$_{axial}$	H-6$_{axial}$↔H-4$_{axial}$	H-6$_{equatorial}$↔H-4$_{equatorial}$
10	Type **B**	2.39	2.27	3.83	2.27
	Type **A**	2.43	4.55	2.72	2.26
11	Type **B**	2.26	2.22	3.82	–
	Type **A**	2.45	4.54	2.72	–
NOE found?		Yes	Yes	No	Yes

Table 3. Some important calculated distances for types **Ca** and **Cb** in compounds **9** and **12** (in Å) and NOEs found

Distance		$\text{H-11b}_{axial}\leftrightarrow\text{H6}_{axial}$	$\text{H-11b}_{axial}\leftrightarrow\text{H11}$	$\text{H-11b}_{axial}\leftrightarrow\text{H7}_{axial}$
9	Type **Ca**	3.04	2.56	4.27
	Type **Cb**	3.88	2.85	3.50
12	Type **Ca**	2.71	2.74	4.30
	Type **Cb**	3.82	3.39	2.57
NOE found?		Yes	Yes	No

γ-effect of the axial phenyl group in position 2. The isomeric pair **9** and **12** exhibit a significant difference only for C-11b, and not for C-4 (−6.7 and −0.3 ppm, respectively). This is a further explanation of the more flattened oxazine ring in the latter two compounds relative to **7**, **8**, **10** and **11**.

The differences in ^{1}H chemical shifts of H-4$_{axial}$ between **7** and **10** (+0.54 ppm) and between **8** and **11** (+0.66 ppm) may be caused by the anisotropic effect of the phenyl ring on H-4$_{axial}$ in a preferred alignment of the phenyl substituent around the C-4–C-1′ bond (torsional angle O-3–C-2–C-*i*–C-*o*=13.6°, taken from the X-ray results for **11**). Additionally, a downfield shift caused by steric compression of especially the *o*-protons of the 2-phenyl substituent to the H-4$_{axial}$ proton is possible. The preferred angle around the C-4–C-*i* bond may also explain the relatively small changes in the chemical shifts of H-11b in the pairs **7**/**10** and **8**/**11** (+0.20 and +0.11 ppm, respectively). The much bigger change for the pair **9**/**12** (−0.73 ppm) is caused by another preferred rotational angle around the C-4–C-1′ bond in these compounds.

The steric compression of the axial moieties in position 1 to H-6$_{axial}$ in **10** and **11** with respect to their corresponding isomers **7** and **8** also leads to a downfield shift of H-6$_{axial}$ (+1.1 and +0.85 ppm, respectively), corroborating the flatter perhydrooxazine ring; the difference of the ^{1}H chemical shift of H-6$_{axial}$ is smaller (0.07 ppm) in **7** and **12**.

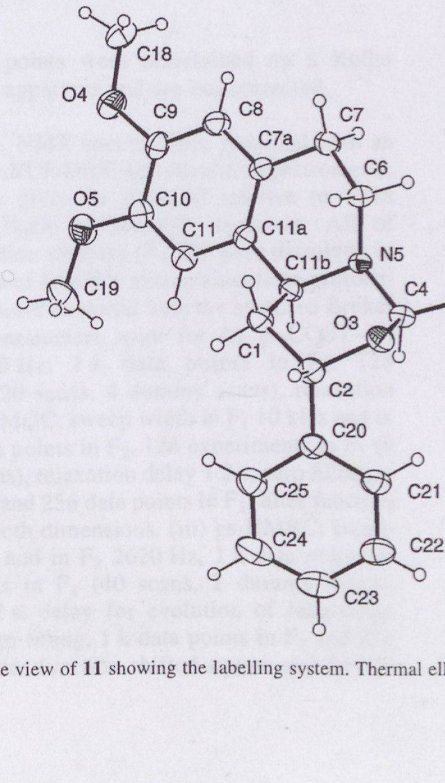


Figure 4. ORTEP perspective view of **11** showing the labelling system. Thermal ellipsoids are drawn at the 30% probability level.

Table 4. Some measured (X-ray) and calculated torsional angles (in deg.) of **11**

	N5–C6–C7–C7a	C6–N5–C11b–C1	C6–N5–C4–O3
X-Ray	48.4	−73.4	63.3
Calculated	50.1	−76.7	68.3

2.3. X-ray measurements

In the solid state, the asymmetric unit of **11** is formed from the molecule shown in Figure 4. The bond parameters are as expected and the six-membered ring C1, C2, O3, C4, N5, C11b has a slightly distorted chair conformation, as seen from the torsional angles of this ring.

The solid-state structure is in very good agreement with the calculated structure regards the pyramidality of N5 and the ring conformations obtained. Table 4 gives as some selected torsional angles, found in X-ray structure and calculated in the theoretical study in this work. It is clearly seen that **11** occurs in the **B** form both in the solid state and in solution; the same result was obtained by studying the NMR spectra of this compound and corroborated the relevant results on the other compounds studied.

The solid-state conformation of **11** is in good agreement with the NOE enhancements observed in solution. A qualitative comparison of the NOE enhancements from the NOESY spectra of **11** corroborates the stereochemistry of **11** as obtained both in the solid state and calculated in the quantum-chemical study (Table 5).

Table 5. Qualitative NOE enhancements (s=strong, m=medium, w=weak) from the NOESY spectra, and the distances, extracted from the X-ray structure and ab initio calculated (both in Å), between some selected hydrogens of **11**

H positions	NOE strength	Distance (in Å)	
		By X-ray	Calculated
6_{ax}–6_{eq}	S	1.574	1.742
1_{ax}–2	M	2.214	2.318
1_{eq}–2		2.418	2.577
1_{eq}–11b	M	2.302	2.481
4–11b	M	2.306	2.264
11–11b	M	2.499	2.576
1_{eq}–11	W	2.632	2.576
7_{eq}–8	W	2.526	2.545
7_{ax}–8		2.868	2.995

Differences between H–H distances obtained by X-ray diffraction and calculated in ab initio calculations should essentially be due to uncertainties in determining hydrogen positions in the X-ray analysis.

2.4. Conclusions

It may be concluded that phenyl substituents significantly influence the conformation of the prepared 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline diastereomers. The 1-phenyl-substituted (**7**, **8**) and 2-phenyl-substituted (**10**, **11**) compounds could be characterized by different preferred conformations (**A** and **B**), while the 4-unsubstituted and 4-(*p*-nitrophenyl) derivatives proved to have the same predominant conformations. Phenyl substituents in positions 1 and 2 were axial, whereas the 4-(*p*-nitrophenyl) group both in **8** and in **11** was equatorial. An oxo group at position 4 caused a flattening of the 1,3-oxazine ring (**C**).

3. Experimental

3.1. General

Syntheses. Melting points were determined on a Kofler micro melting point apparatus and are not corrected.

NMR measurements. NMR spectra were recorded with an ARX 300 or an AVANCE DRX 400 (Bruker) spectrometer. Chemical shifts are given in δ (ppm) relative to TMS ($CDCl_3$) or TSP (D_2O) as internal standards. All of the oxazinoisoquinoline samples (**7–12**) were dissolved in $CDCl_3$ or, in the case of NOESY measurements, in acetone-D_6. The 2D spectra were acquired with the standard Bruker software. Typical parameters were for (i) gs-COSY-45: sweep width 2620 Hz, 1 k data points in F_2, 128 experiments in F_1 (20 scans, 4 dummy scans), relaxation delay 1.2 s; (ii) gs-HMQC: sweep width in F_1 10 kHz and in F_2 2620 Hz, 1 k data points in F_2, 128 experiments in F_1 (8 scans, 2 dummy scans), relaxation delay 1.2 s, zero filling to 2 k data points in F_2 and 256 data points in F_1, filter function square sine-bell in both dimensions. (iii) gs-HMBC: sweep width in F_1 10 kHz and in F_2 2620 Hz, 1 k data points in F_2, 128 experiments in F_1 (40 scans, 2 dummy scans), relaxation delay 1.2 s, delay for evolution of long-range couplings 50 ms, zero filling, 1 k data points in F_2 and 256 data points in F_1, filter function shifted square sine-bell in both dimensions. (iv) NOESY: sweep width 2670 Hz, 1 k data points in F_2, 128 experiments in F_1 (40 scans, 4 dummy scans), relaxation delay $\sim 5\times T_1$, mixing time $\sim T_1$. The pulse widths (90°) for all experiments were 12.5 μs (^{1}H), and 11.3 μs (^{13}C), respectively.

Quantum chemical calculations. Quantum chemical calculations were carried out using the ab initio program package GAUSSIAN 98 version A.7.[22] The different conformations of the compounds were optimized without any restrictions at the HF/6-31G* level of theory. The selected minimum energy conformations were analysed and the results were visualized with the modelling program Sybil 6.7.[23]

X-Ray diffraction studies. Data were collected on a Rigaku AFC5S diffractometer with graphite monochromated Mo K_α radiation ($\lambda=0.71069$ Å) in the $\omega-2\theta$ scan mode at room temperature. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods (SIR92)[24] and refined by full matrix least-squares techniques (SHELXL-97)[25] to an $R1$ value of 0.055 ($wR2=0.101$). The final R values were based on the reflections with $I>2\sigma(I)$. The heavy atoms were refined anisotropically. The hydrogen atoms were allowed to ride on their host atoms with a fixed distance and isotropic temperature factors (1.2 or 1.5 times B_{eq} of the carrying atom). Calculations were performed with teXsan for Windows[26] crystallographic software. The figures were drawn with ORTEP-3 for Windows.[27] (The final atomic coordinates and full lists of bond lengths and angles for **11** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 198906).

3.1.1. (1*R**,1′*R**)-1-(2′-Hydroxy-1′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (3).

To a solution of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**1**, 14.1 g, 0.05 mol) in MeOH (200 mL) paraformaldehyde (3.75 g, 0.125 mol) was added. Freshly prepared ethanolic NaOEt solution was added dropwise to the stirred suspension until a homogeneous solution was obtained (about 0.5 g Na in 25 mL EtOH was needed). After stirring for 5 h at room temperature, the mixture was evaporated at <40°C in vacuo and the residue was partitioned between cold water (150 mL) and $CHCl_3$ (150 mL). The separated aqueous layer was extracted with $CHCl_3$ (2×150 mL). The combined organic phases were dried (Na_2SO_4) and evaporated at <40°C to yield crude 1-(2′-hydroxy-1′-phenylethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline as a yellowish-brown oil, which was dissolved in MeOH (250 mL). The solution was stirred and cooled in an ice bath, and $NaBH_4$ (5.67 g, 0.15 mol) was added in small portions. The mixture was stirred for 3 h with cooling and for 3 h without, then evaporated, and the residue was dissolved in 5% HCl (150 mL). The solution was made alkaline with 20% NaOH under ice cooling and extracted with $CHCl_3$ (3×150 mL). The combined organic solutions were dried (Na_2SO_4) and evaporated to give crude crystalline **3** with *de* >95%. The crystals were filtered off, washed with Et_2O and recrystallized from *i*Pr_2O–EtOAc to obtain diastereomerically pure **3**.

Overall yield 9.77 g (62%), mp 134–135°C. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 2.46–2.65 (H-4, m, 2H), 2.81 (H-3, m, 1H), 3.08 (H-3, dt, J=12.3, 4.8 Hz, 1H), 3.46 (H-1′, m, 1H), 3.72 (MeO, s, 3H), 3.83 (MeO, s, 3H), 4.12 (H-2′, H-1, m, 2H), 4.59 (H-2′, d, J=3.8 Hz, 1H), 6.51 (H-5, H-8, s, 2H), 7.16–7.28 (Ph, m, 5H). Analysis: calculated for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47; found: C, 72.59; H, 7.23; N, 4.38.

3.1.2. 1-(2′-Oxo-2′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (5). Ethyl 3-oxo-3-phenylpropanoate (21.1 g, 0.11 mol) was added to a solution of NaOH (4.40 g, 0.11 mol) in water (110 mL) and the mixture was left to stand at room temperature with occasional shaking for 24 h. A solution of 6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride (22.8 g, 0.10 mol) in 50% aqueous MeOH (100 mL), conc. HCl (2.5 mL) were then added and the mixture was again left to stand at room temperature with occasional shaking for 6 h. The mixture was made alkaline with 10% Na_2CO_3 solution and extracted with CH_2Cl_2 (3×100 mL). The dried (Na_2SO_4) extracts were evaporated and the oily residue was converted to the crystalline hydrochloride salt by treatment of its methanolic solution with an excess of 22% ethanolic HCl and Et_2O. The crystalline hydrochloride was filtered off and recrystallized from MeOH–Et_2O.

Yield 25.73 g (74%), mp 189–190°C. ^1H NMR (400 MHz, D_2O) δ 3.04–3.20 (H-4, m, 2H), 3.50 (H-3, m, 1H), 3.63 (H-3, m, 1H), 3.77 (MeO, s, 3H), 3.87 (MeO, s, 3H), 3.91 (H-1′, dd, J=19.2, 3.5 Hz, 1H), 4.03 (H-1′, dd, J=19.2, 8.4 Hz, 1H), 5.15 (H-1, m, 1H), 6.84 (H-5, s, 1H), 6.95 (H-8, s, 1H), 7.60 (*m*-Ph, t, J=7.8 Hz, 2H), 7.75 (*p*-Ph, t, J=7.7 Hz, 1H), 8.04 (*o*-Ph, d, J=7.9 Hz, 2H). Analysis: calculated for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.37; N, 4.03; found: C, 65.80; H, 6.49; N, 3.95.

3.1.3. (1*R* *,2′*R* *)-1-(2′-Hydroxy-2′-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6). Compound **5** (17.39 g, 0.05 mol) was suspended in methanol (200 mL). The suspension was stirred and cooled in an ice bath. $NaHCO_3$ (4.20 g, 0.05 mol) and then small portions of $NaBH_4$ (5.67 g, 0.15 mol) were added. Stirring was continued until the mixture had warmed up to room temperature (about 3 h). It was then stirred for a further 3 h and processed in the usual way to give a yellowish-brown oil containing an approximately 2:1 mixture of the (1*R* *,2′*R* *) and (1*R* *,2′*S* *) diasteromers. The oily product was crystallized on treatment with Et_2O. The crystals were filtered off and washed with Et_2O. Recrystallization from *i*Pr_2O–EtOAc gave diastereomerically pure **6**.

Yield 7.32 g (47%), mp 134–136°C. ^1H NMR (400 MHz, $CDCl_3$) δ 2.03 (H-1′, ddd, J=14.8, 7.7, 2.9 Hz, 1H), 2.38 (H-1′, ddd, J=14.8, 7.4, 2.8 Hz, 1H), 2.63 (H-4, dt, J=15.5, 5.0 Hz, 1H), 2.85–2.94 (H-4, m, 1H), 3.01 (H-3, ddd, J=12.2, 7.9, 4.3 Hz, 1H), 3.27 (H-3, dt, J=12.4, 5.7 Hz, 1H), 3.82 (MeO, s, 3H), 3.86 (MeO, s, 3H), 4.27 (H-1, dd, J=6.8, 2.0 Hz, 1H), 4.87 (H-2′, dd, J=7.7, 2.6 Hz, 1H), 6.46 (H-5, s, 1H), 6.59 (H-8, s, 1H), 7.21–7.27 and 7.32–7.40 (Ph, 2×m, 5H). The ^1H NMR spectrum of **6** is in accordance with literature[17] data on the (1*R*,2′*R*) isomer. Analysis: calculated for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47; found: C, 72.74; H, 7.22; N, 4.37.

3.1.4. (1*R* *,11b*R* *)-9,10-Dimethoxy-1-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (7). Amino alcohol **3** (0.94 g, 3 mmol) was added to a stirred mixture of 37% formaldehyde solution (10 mL) and H_2O (10 mL). Crystals of **10** started to separate from the solution after the slow dissolution of amino alcohol **6**. Stirring was continued for 1 h, and the crystalline product was then filtered off, washed with cold water, dried and recrystallized from *i*Pr_2O.

Yield 0.67 g (69%), mp 143–144°C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (H-6_{ax}, m, 1H), 2.59 (H-7, m, 1H), 2.97 (H-6_{eq}, H-7, m, 2H), 3.24 (H-1, br, 1H), 3.75 (MeO-9, MeO-10, s, 6H), 3.93 (H-11b, d, J=3.3 Hz, 1H), 4.10 (H-2_{ax}, dd, J=11.2, 3.3 Hz, 1H), 4.11 (H-4_{ax}, d, J=7.9 Hz, 1H), 4.28 (H-2_{eq}, d, J=11.3 Hz, 1H), 4.70 (H-4_{eq}, d, J=7.9 Hz, 1H), 6.44 (H-8, s, 2H), 6.58 (H-11, s, 1H), 7.08 (*m*-Ph, *p*-Ph, m, 3H), 7.53 (*o*-Ph, d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5 (C-7), 43.6 (C-1), 46.3 (C-6), 55.5 (MeO-10), 55.8 (MeO-9), 63.6 (C-11b), 73.6 (C-2), 87.5 (C-4), 108.6 (C-11), 111.1 (C-8), 125.8 (C-4′-Ph), 127.1 (C-11a), 127.1 (C-7a), 127.4 (C-3′-Ph), 130.1 (C-2′-Ph), 141.2 (C-1′-Ph), 146.8 (C-10), 147.0 (C-9). Analysis: calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N; 4.30; found: C, 73.69; H, 6.95; N, 4.12. IR ν_{max} 2834, 1517, 1263, 1142, 1103 cm^{-1}. EIMS *m/z* (%): M+1 326 (20), 314 (100).

3.1.5. (2*R* *,11b*R* *)-9,10-Dimethoxy-2-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (10). To a solution of amino alcohol **6** (0.94 g, 3 mmol) in MeOH (10 mL), 37% formaldehyde solution (0.5 mL) was added. The mixture was allowed to stand at room temperature for 1 h. It was then poured into H_2O (50 mL) and extracted with $CHCl_3$ (3×25 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. The oily product crystallized on treatment with Et_2O. The crystals were filtered off and recrystallized from *n*-hexane.

Yield 0.75 g (77%), mp 100–102°C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.31 (H-1_{eq}, ddd, J=14.3, 3.1, 3.1 Hz, 1H), 2.58 (H-1_{ax}, ddd, J=13.3, 11.0, 5.5 Hz, 1H), 2.81 (H-7, m, 2H), 2.87 (H-6_{ax}, m, 1H), 3.50 (H-6_{eq}, m, 1H), 3.86 (MeO-9, s, 3H), 3.89 (MeO-10, s, 3H), 4.13 (H-11b, dd, J=10.9, 3.2 Hz, 1H), 4.39 (H-4_{eq}, d, J=10.1 Hz, 1H), 4.65 (H-4_{ax}, d, J=10.1 Hz, 1H), 5.11 (H-2, br, 1H), 6.58 (H-11, s, 1H), 6.62 (H-8, s, 1H), 7.32 (*p*-Ph, t, J=7.2 Hz, 1H), 7.45 (*m*-Ph, t, J=7.3 Hz, 2H), 7.54 (*o*-Ph, d, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.3 (C-7), 30.5 (C-1), 43.8 (C-6), 52.8 (C-11b), 55.8 (MeO-9), 56.2 (MeO-10), 73.1 (C-2), 79.9 (C-4), 109.1 (C-11), 111.7 (C-8), 126.3 (C-7a), 126.7 (C-2′-Ph), 127.2 (C-4′-Ph), 128.7 (C-3′-Ph), 129.6 (C-11a), 140.2 (C-1′-Ph), 147.4 (C-9), 147.8 (C-10). Analysis: calculated for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30; found: C, 73.99; H, 7.27; N, 4.16. IR ν_{max} 2916, 2866, 1518, 1243, 1229, 1139 cm^{-1}. EIMS *m/z* (%): [M^+] 325 (2), 314 (100).

3.1.6. (1*R* *,4*S,11b*R* *)-9,10-Dimethoxy-1-phenyl-4-(*p*-nitrophenyl)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino-[4,3-*a*]isoquinoline (8) and (2*R* *,4*S**,11b*R* *)-9,10-dimethoxy-2-phenyl-4-(*p*-nitrophenyl)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (11).** Amino alcohol **3** or **6** (0.94 g, 3 mmol) was refluxed with an equimolar amount of *p*-nitrobenzaldehyde (0.45 g) in dry toluene

(30 mL). When no more starting material could be detected on TLC (6 h for **8** and 8 h for **11**), the solvent was evaporated off and the residual oil crystallized on treatment with Et$_2$O. The crystalline product was filtered off and recrystallized from *i*Pr$_2$O–EtOAc.

8: Yield 0.97 g (72%), mp 181–182°C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.22 (H-6$_{ax}$, ddd, J=11.0, 10.9, 3.8 Hz, 1H), 2.46 (H-7$_{ax}$, d, J=14.7 Hz, 1H), 2.60 (H-6$_{eq}$, m, 1H), 2.80 (H-7$_{eq}$, m, 1H), 3.45 (H-1, br, 1H), 3.74 (MeO-9, s, 3H), 3.77 (MeO-10, s, 3H), 4.24 (H-11b, br, 1H), 4.34 (H-2, m, 2H), 4.95 (H-4, s, 1H), 6.44 (H-8, s, 2H), 6.61 (H-11, s, 1H), 7.11 (*p*-Ph, t, J=7.3 Hz, 1H), 7.18 (*m*-Ph, t, J=6.9 Hz, 2H), 7.64 (*o*-Ph, d, J=7.1 Hz, 2H), 7.78 (H-2$''$-*p*-O$_2$N-C$_6$H$_4$, d, J=8.6 Hz, 2H), 8.28 (H-3$''$-*p*-O$_2$N-C$_6$H$_4$, d, J=8.8 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 28.5 (C-7), 43.5 (C-1), 45.5 (C-6), 55.6 (MeO-10), 55.9 (MeO-9), 64.4 (C-11b), 73.7 (C-2), 95.9 (C-4), 108.7 (C-11), 111.0 (C-8), 123.8 (C-3$''$-*p*-O$_2$N-C$_6$H$_4$), 126.1 (C-4$''$-Ph), 127.0 (C-11a), 127.2 (C-7a), 127.8 (C-3$'$-Ph),129.0 (C-2$''$-*p*-O$_2$N-C$_6$H$_4$), 130.1 (C-2$'$-Ph), 140.8 (C-1$'$-Ph), 146.5 (C-1$''$-*p*-O$_2$N-C$_6$H$_4$),147.0 (C-9), 147.3 (C-10), 148.3 (C-4$''$-*p*-O$_2$N-C$_6$H$_4$). Analysis: calculated for C$_{26}$H$_{26}$N$_2$O$_5$: C, 69.94; H, 5.87; N, 6.27; found: C, 69.75; H, 5.60; N, 6.18. IR ν_{max} 2915, 2841, 1523, 1346, 1100 cm^{-1}. EIMS *m*/*z* (%): 446 [M]$^+$ (3), 314 (100).

11: Yield 0.92 g (69%), mp 166–168°C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.37–2.77 (H-1, H-7, m, 4H), 2.48 (H-6$_{eq}$, ddd, J=11.7, 5.7, 3.1 Hz, 1H), 3.07 (H-6$_{ax}$, ddd, J=11.5, 10.5, 4.3 Hz, 1H), 3.86 (MeO-9, s, 3H), 3.93 (MeO-10, s, 3H), 4.35 (H-11b, d, J=10.5 Hz, 1H), 5.47 (H-2, d, J=5.8 Hz, 1H), 5.61 (H-4, s, 1H), 6.62 (H-8, H-11, s, 2H), 7.33 (*p*-Ph, t, J=7.2 Hz, 1H), 7.45 (*m*-Ph, t, J=7.7 Hz, 2H), 7.56 (*o*-Ph, d, J=7.7 Hz, 2H), 7.77 (H-2$'$-*p*-O$_2$N-C$_6$H$_4$, d, J=8.5 Hz, 2H), 8.24 (H-3$''$-*p*-O$_2$N-C$_6$H$_4$, d, J=8.6 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 28.7 (C-1), 28.8 (C-7), 37.1 (C-6), 54.7 (C-11b), 55.8 (MeO-9), 56.2 (MeO-10), 73.8 (C-2), 85.5 (C-4), 109.2 (C-11), 111.6 (C-8), 123.4 (C-3$''$-*p*-O$_2$N-C$_6$H$_4$), 126.4 (C-2$'$-Ph), 126.4 (C-7a), 127.4 (C-4$'$-Ph), 127.7 (C-2$''$-*p*-O$_2$N-C$_6$H$_4$), 128.9 (C-3$'$-Ph), 130.0 (C-11a), 139.8 (C-1$'$-Ph), 146.4 (C-1$''$-*p*-O$_2$N-C$_6$H$_4$), 147.4 (C-10), 147.5 (C-4$''$-*p*-O$_2$N-C$_6$H$_4$), 147.9 (C-9). Analysis: calculated for C$_{26}$H$_{26}$N$_2$O$_5$: C, 69.94; H, 5.87; N, 6.27; found: C, 70.16; H, 5.58; N, 6.13. IR ν_{max} 2958, 2830, 1522, 1347, 1272 cm^{-1}. EIMS *m*/*z* (%): M+1 447 (7), 314 (100).

3.2. Crystal data for 11

C$_{26}$H$_{26}$N$_2$O$_5$, M_r=446.49, orthorhombic, space group *Pbca* (No 60), lattice parameters: a=16.550(5), b=29.566(3), c=9.156(3) Å, Z=8, V=4480.5(18) Å^3, D_c=1.324 g/cm^3, μ(Mo K$_\alpha$)=0.092 mm^{-1}, F(000)=1888, T=294 K; pale-yellow prism, crystal dimensions 0.32×0.36×0.38 mm^3.

3.2.1. (1*R* *,11b*R* *)-9,10-Dimethoxy-1-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinolin-4-one (9). To a stirred mixture of amino alcohol **3** (0.94 g, 3 mmol), toluene (25 mL), NaHCO$_3$ (0.38 g, 4.5 mmol) and H$_2$O (25 mL), ethyl chloroformate (0.35 g, 3.2 mmol) was added and the mixture was stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined extracts were dried (Na$_2$SO$_4$) and evaporated to yield 1.11 g (96%) of ethyl (1*R* *,1$'$*R* *)-1-(2$'$-hydroxy-1$'$-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate as a crystalline product (mp 160–161°C), which was used in the next step without further purification.

The previous urethane derivative (1.11 g, 2.9 mmol) was thoroughly mixed with NaOMe (0.15 g, 2.8 mmol) and the mixture was kept under N$_2$ at 160–165°C for 45 min. The melt was extracted with hot EtOAc (5×30 mL), and the combined organic phases were washed with 5% HCl (2×30 mL) and H$_2$O (2×30 mL), dried (Na$_2$SO$_4$) and evaporated. The oily residue crystallized on treatment with Et$_2$O. The crystals were filtered off and recrystallized from *i*Pr$_2$O–EtOAc.

Yield 0.52 g (53%), mp 150–152°C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.18 (H-7$_{ax}$, ddd, J=16.4, 12.3, 4.6 Hz, 1H), 2.38 (H-7$_{eq}$, ddd, J=15.6, 2.5, 2.5 Hz, 1H), 2.94 (H-6$_{ax}$, ddd, J=12.5, 12.5, 3.1 Hz, 1H), 3.59 (H-1, dd, J=3.6, 3.9 Hz, 1H), 3.80 (MeO-9, s, 3H), 3.84 (MeO-10, s, 3H), 4.53 (H-6$_{eq}$, m, 1H), 4.57 (H-2$_{eq}$, d, J=11.0 Hz, 1H), 4.82 (H-2$_{ax}$, dd, J=11.1, 4.1 Hz, 1H), 5.20 (H-11b, d, J=3.9 Hz, 1H), 6.42 (H-8, s, 1H), 6.64 (H-11, s, 1H), 6.89 (*o*-Ph, d, J=7.7 Hz, 2H), 7.10 (*m*/*p*-Ph, m, 3H); ^{13}C NMR (CDCl$_3$) δ 28.0 (C-7), 41.3 (C-6), 43.9 (C-1), 55.7 (MeO-9), 56.1 (MeO-10), 57.6 (C-11b), 70.8 (C-2), 109.0 (C-11), 111.1 (C-8), 124.6 (C-7a), 127.1 (C-4$'$-Ph), 128.1 (C-2$'$-Ph), 128.5 (C-11a), 128.5 (C-3$'$-Ph), 136.8 (C-1$'$-Ph), 147.8 (C-9/C-10), 153.2 (C-4). Analysis: calculated for C$_{20}$H$_{21}$NO$_4$: C, 70.78; H, 6.24; N, 4.13; found: C, 70.91; H, 6.08; N, 4.19. IR ν_{max} 2994, 2835, 1691, 1430, 1253, 1106 cm^{-1}. EIMS *m*/*z* (%): M+1 340 (100).

3.2.2. (2*R* *,11b*R* *)-9,10-Dimethoxy-2-phenyl-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinolin-4-one (12). Di-*tert*-butyl dicarbonate (1.09 g, 5 mmol) was added in small portions to a solution of **6** (0.94 g, 3 mmol) in EtOAc (30 mL) at 0°C. The mixture was stirred at room temperature for 16 h, then washed with 1 M HCl (25 mL), saturated aqueous NaHCO$_3$ (25 mL) and H$_2$O (25 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo. Treatment of the oily residue with Et$_2$O gave crystalline *tert*-butyl (1*R* *,2$'$*R* *)-1-(2$'$-hydroxy-2$'$-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carboxylate (1.02 g, 82%, mp 119–120°C), which was used in the next step without further purification.

KO*t*Bu (0.34 g, 3 mmol) was added in one portion to a stirred solution of the previous *N*-Boc derivative (1.02 g, 2.5 mmol) in freshly distilled THF (40 mL) at 0°C. After 30 min, saturated aqueous NH$_4$Cl solution (40 mL) and EtOAc (40 mL) were added to the mixture and the organic layer was separated. The aqueous layer was extracted with EtOAc (2×40 mL). The combined organic phases were washed with H$_2$O (30 mL), dried (Na$_2$SO$_4$) and evaporated. The oily residue crystallized on treatment with Et$_2$O. The crystals were filtered off and recrystallized from *i*Pr$_2$O–EtOAc.

Yield 0.68 g (81%), mp 128–131°C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.44 (H-1$_{ax}$, ddd, J=14.0, 9.0, 4.2 Hz, 1H), 2.63 (H-7$_{eq}$, m, 1H), 2.69 (H-1$_{eq}$, ddd, J=14.0, 4.9, 4.9 Hz, 1H), 2.98 (H-7$_{ax}$, m, 1H), 3.01 (H-6$_{ax}$, m, 1H), 3.84 (MeO-10, s, 3H), 3.86 (MeO-9, s, 3H), 4.47 (H-11b, dd, J=8.8, 5.0 Hz, 1H), 4.63 (H-6_{eq}, m, 1H), 5.46 (H-2, t, J=4.2 Hz, 1H), 6.51 (H-11, s, 1H), 6.64 (H-8, s, 1H), 7.35–7.43 (Ph, m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.3 (C-7), 35.3 (C-1), 42.5 (C-6), 50.9 (C-11b), 55.8 (MeO-9), 56.2 (MeO-10), 75.2 (C-2), 107.6 (C-11), 111.9 (C-8), 125.0 (C-2$'$-Ph), 127.2 (C-7a), 127.5 (C-11a), 128.0 (C-4$'$-Ph), 128.8 (C-3$'$-Ph), 139.1 (C-1$'$-Ph), 147.8 (C-10), 148.1 (C-9), 152.9 (C-4). Analysis: calculated for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13; found: C, 70.52; H, 5.97; N, 4.06. IR ν_{max} 3854, 3752, 1686, 1509, 1267, 1245 cm^{-1}. EIMS m/z (%): M+1 340 (35), 399 (100).

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