**PhD thesis**

# Syntheses and Transformations of α-Aminobenzyl Naphthol Derivatives

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## A. Introduction and aims

The structures and reactivities of numerous five- and six-membered, saturated, *N*-unsubstituted 1,3-*O*,*N* heterocycles can be characterized by the ring-chain tautomeric equlibria of the ring form and the corresponding Schiff bases.

The oxazolidines and tetrahydro-1,3-oxazines are the saturated 1,3-*X*,*N* heterocycles whose ring-chain tautomerism has been studied most thoroughly. Studies on the ring-chain tautomeric equilibria of 2-aryl-substituted oxazine derivatives led to the conclusion that the proportion of the ring-closed forms strongly depends on the electronic character of the substituent on the aromatic ring. For these compounds, a linear correlation was found between the log $K_X$ values of the equilibria ($K_X$ = [ring]/[chain]) and the Hammett-Brown parameters $\sigma^+$ of the substituents X on the 2-aryl group. (Eq. 1).

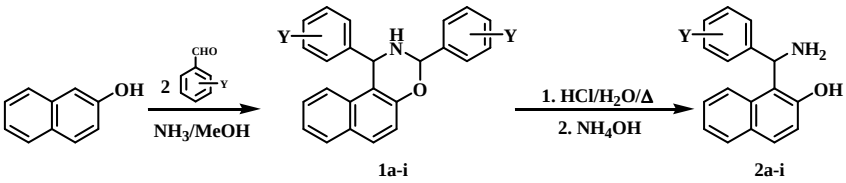
$$\log K_X = \log K_{X=H} + \rho\sigma^+ \qquad \text{Eq. 1}$$

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.

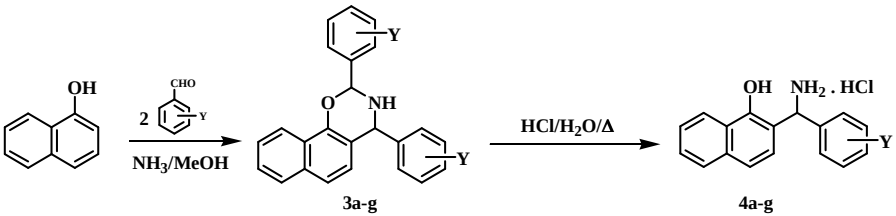
My PhD work focused on the syntheses of α-aminobenzylnaphthol derivatives and, by transformation to different substituted 1,3-diaryl-, 3-alkyl,1-aryl- and 2,4-diarylnaphthoxazines, study of the double substituent effects on the ring-chain tautomeric equilibria. A further aim was to study the synthetic applicability of α-aminobenzylnaphthol derivatives in some other ring-closure reactions.

## B. Results

**1.** By using Betti's classical procedure (starting from 2-naphthol), 1-[α-amino(Y-substituted-benzyl)]-2-naphthols (**2a-i**) were prepared (Scheme 1). The analogous transformation of 1-naphthol led to 2-[α-amino(Y-substituted-benzyl)]-1-naphthols (**4a-g**), which were isolated as hydrochloride salts (Scheme 1).



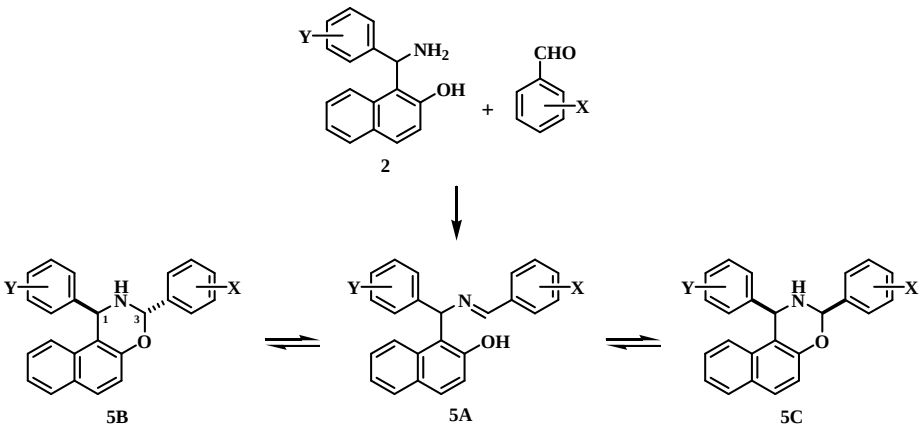

**Y = $NO_2$(*m*): a; $NO_2$(*p*): b; Br(*m*): c; Br(*p*): d; Cl(*p*): e; H: f; F(*p*): g; Me(*p*): h; OMe(*p*): i**




**Y = $NO_2$(*m*): a; Br(*m*): b; Br(*p*): c; Cl(*p*): d; H: e; Me(*p*): f; OMe(*p*): g**

**Scheme 1**

**2.** The reactions of 1-[α-amino(Y-substituted-benzyl)]-2-naphthols (**2a-i**) and substituted benzaldehydes led to 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines (**5**, Scheme 2) which at 300 K in $CDCl_3$ proved to be three-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**5B** > **5C**) besides the open tautomer (**5A**). The influence of aryl substituents at position 3 on the ring-chain tautomeric equilibria could be described by the Hammett equation (Eq. 1).




**Y = *m*$NO_2$; *p*$NO_2$; *m*Br; *p*Br; *p*Cl; H; *p*F; *p*Me; *p*OMe**
**X = *p*$NO_2$; *m*Br; *p*Br; *p*Cl; H; *p*Me *p*-OMe;**

**Scheme 2**

**3.** In order to examine 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 (**5**), multiple linear regression analysis of Eqs 2 and 3 was performed. The significant dependence of log K *vs* the inductive parameter $\sigma_F^Y$ of substituent Y for the *trans* $\rightleftharpoons$ chain (**5B** $\rightleftharpoons$ **5A**) tautomeric equilibria was explained with the aid of the anomeric effect in the *trans* ring form.

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

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

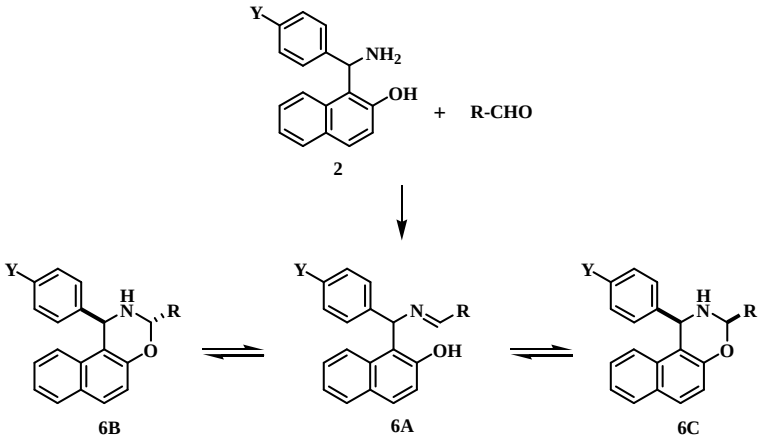
The multiple linear regression analysis of the chemical shifts of C-1 and C-3 for the *cis* and *trans* diastereomers revealed a significant dependence on $\sigma_F^Y$. The differences between the intercepts could be explained nicely in terms of the anomeric effect in the *trans* ring form. For a deeper examination of this phenomenon, the donation energies of the nitrogen lone pairs to vicinal antibonding orbitals were calculated by using NBO semi-empirical molecular modelling calculations. The calculations showed that the donation energy values are strongly influenced by the relative configuration of C-1 and C-3.

**4.** 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 **6** was analysed. Condensations of aminonaphthols **2a-i** with equivalent amounts of aliphatic aldehydes resulted in the naphthoxazine model compounds **6** (Scheme 3), which at 300 K in $CDCl_3$ proved to be two-component tautomeric mixtures containing C-3 epimeric naphthoxazines (**6B** > **6C**). The epimerization constant was calculated from the ratio of the diastereomers ($K_R$ = [**6B**]/[**6C**]). The influence of alkyl substituents on log $K_R$ could be described in terms of their Meyer parameters $V^a$ (Eq. 4).

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

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

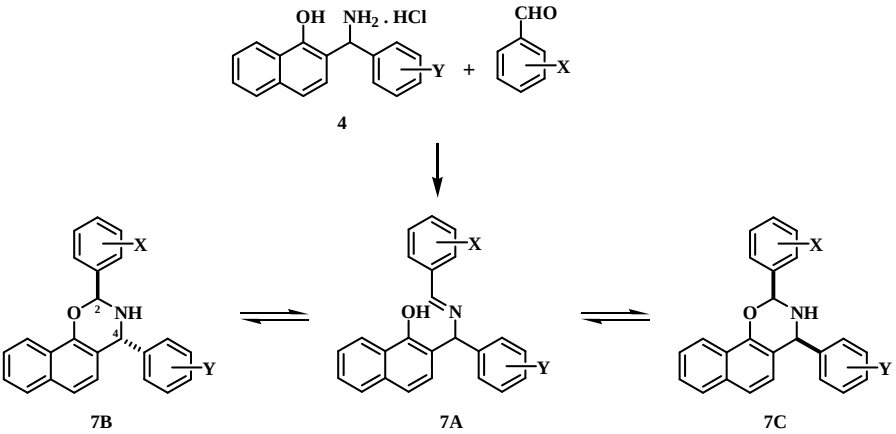
The results of multiple linear regression analysis of the log $K_R$ values (Eq. 5) reveal a significant dependence on the inductive effect of substituent Y ($\sigma_F$), which is a further proof of the anomeric effect in the *trans* ring form.




**Scheme 3**

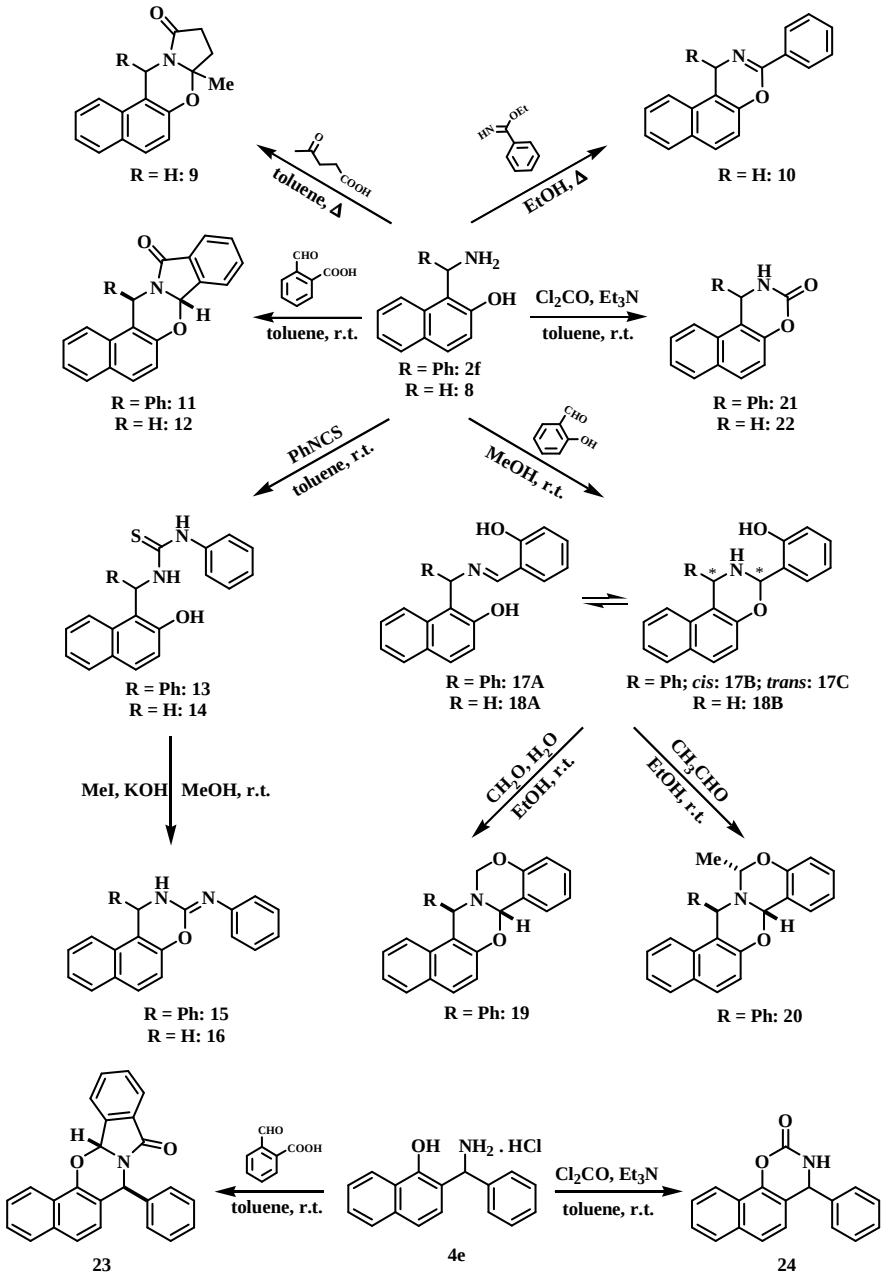
**5.** The ring-closure reactions of aminonaphthols **4a-g** with equivalent amounts of aromatic aldehydes resulted in 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines (**7**,

Scheme 4), which in $CDCl_3$ at 300 K formed three-component tautomeric mixtures containing major (**B**) and minor (**C**) ring-closured epimeric forms beside the open chain form (**A**), and they proved to be good model compounds for study of the double substituent influence on the tautomeric eqilibria. Systematic quantitative investigations on the ring-chain tautomeric equilibria of 2,4-diarylnaphth[2,1-*e*][1,3]oxazines demonstrated an analogous inductive influence on the *trans* ⇌ chain (**7B** ⇌ **7A**) tautomeric equilibria.




**Scheme 4**

**6.** By simple or domino ring-closure reactions of 1-(α-aminobenzyl)-2-naphthol (**2f**), 1-aminomethyl-2-naphthol (**8**) and 2-(α-aminobenzyl)-1-naphthol (**4e**) 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 (Scheme 5). All of the nitrogen-bridged polycyclic derivatives of **2f** and **4e** with several centres of asymmetry were formed with nearly total diastereoselectivity. Considerable differences were found in the ring-closing abilities of the unsubstituted and phenyl-substituted aminonaphthols **2f** and **8** and the regioisomeric compounds **2f** and **4e**.


R = H: 9
toluene, Δ
EtOH, Δ
R = H: 10
R = Ph: 2f
R = H: 8
toluene, r.t.
Cl2CO, Et3N
toluene, r.t.
R = Ph: 11
R = H: 12
R = Ph: 21
R = H: 22
PhNCS
toluene, r.t.
MeOH, r.t.
R = Ph: 13
R = H: 14
R = Ph: 17A
R = H: 18A
R = Ph; cis: 17B; trans: 17C
R = H: 18B
MeI, KOH
MeOH, r.t.
CH2O, H2O
EtOH, r.t.
CH3CHO
EtOH, r.t.
R = Ph: 15
R = H: 16
R = Ph: 19
R = Ph: 20
toluene, r.t.
Cl2CO, Et3N
toluene, r.t.
23
4e
24

**Scheme 5**

## C. Publications

I. **István Szatmári**, Tamás A. Martinek, László Lázár, Ferenc Fülöp
Substituent effects in the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines
*Tetrahedron* **2003**, *59*, 2877-2884. i.f.: 2.276

II. **István Szatmári**, Tamás A. Martinek, László Lázár, Andreas Koch, Erich Kleinpeter, Ferenc Fülöp
Substituent effects in the ring-chain tautomerism of 1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines
*Annals of West University of Timisoara* **2003**, *3*, 175-182. -

III. **István Szatmári**, Tamás A. Martinek, László Lázár, Andreas Koch, Erich Kleinpeter, Kari Neuvonen, Ferenc Fülöp
Stereoelectronic effect in the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines and 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines
*J. Org. Chem.* közlésre elfogadva 3.280

IV. **István Szatmári**, Tamás A. Martinek, László Lázár, Ferenc Fülöp
Substituent effects in the ring-chain tautomerism of 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines
*Eur. J. Org. Chem.* közlésre elfogadva 2.193

V. **István Szatmári**, Ferenc Fülöp
Syntheses and transformations of 1-(α-aminobenzyl)-2-naphthol derivatives
*Curr. Org. Synth.* **2004**, *1*, 111-121. -

VI. **István Szatmári**, Anasztázia Hetényi, László Lázár, Ferenc Fülöp
Transformation reactions of Betti base analogue aminonaphthols
*J. Heterocyclic Chem.* közlésre beküldve

VII. Matthias Heydenreich, Andreas Koch, László Lázár, **István Szatmári**, Reijo Sillanpää, Erich Kleinpeter, Ferenc Fülöp
Synthesis and stereochemical studies of 1- and 2-phenylsubstituted 1,3-oxazino[4,3-*a*]isoquinoline derivatives
*Tetrahedron* **2003**, *59*, 1951-1959. 2.276

## D. Conference lectures

VIII. László Lázár, **István Szatmári**, Tamás A. Martinek, Ferenc Fülöp
Substituent effects on the ring-chain tautomerism of naphthalene-condensed 2-aryl-1,3-oxazines
*XIXth European Colloquium on Heterocyclic Chemistry*
Aveiro, Portugal, 19-22 July, 2000, Abstr.: 124.

IX. **Szatmári István**
Szubsztituenshatások tanulmányozása naftalinnal kondenzált 2-aril-1,3-oxazinok gyűrű-lánc tautoméria jában.
*V. Clauder Ottó Emlékverseny*
Budapest, 2000. szeptember 21-23., Abstr.: 11.

X. **Szatmári István**, Martinek Tamás, Lázár László, Fülöp Ferenc
Szubsztituenshatások tanulmányozása naftalinnal kondenzált 2-aril-1,3-oxazinok gyűrű-lánc tautoméria jában.
*MKE Vegyészkonferencia*
Hajdúszoboszló, 2001. június 27-29., Abstr.: 115.

XI. **Szatmári István**, Lázár László, Martinek Tamás, Andreas Koch, Erich Kleinpeter, Fülöp Ferenc
A Betti-bázis alkalmazásai heterociklusok szintézisére
*MTA Heterociklusos Kémiai Munkabizottság Előadóülése*
Balatonszemes, 2002. május 23-24.

XII. **István Szatmári**, László Lázár, Tamás Martinek, Andreas Koch, Erich Kleinpeter, Ferenc Fülöp
Substituent effects on ring-chain tautomerism of naphthalene-condensed 1,3-oxazines.
*9$^{th}$ Blue Danube Symposium on Heterocyclic Chemistry*
Tatranská Lomnica, Slovak Republic, June 16-20, 2002, Abstr.: PO 134.

XIII. Ferenc Fülöp, **István Szatmári**, László Lázár, Tamás Martinek, Andreas Koch, Erich Keinpeter
Ring-chain tautomerism of regioisomeric naphthalene-condensed 1,3-oxazines
*XXth European Colloquium on Heterocyclic Chemistry*
Stockholm, Sweden, August 18-21, 2002, Abstr.: 94.

XIV. **Szatmári István**
Szubsztituenshatások tanulmányozása naftalinnal kondenzált diaril-szubsztituált 1,3-oxazinok gyűrű-lánc tautoméria jában.
*XXV. Kémiai Előadói Napok*
Szeged, 2002. október 28-30., Abstr.: 163.

XV. **Szatmári István**
Szubsztituenshatások tanulmányozása naftalinnal kondenzált diaril-szubsztituált 1,3-oxazinok gyűrű-lánc tautomériájában.
*„A szegedi ifjú szerves kémikusok támogatásáért" alapítvány előadóülése*
Szeged, 2003. január 16.

XVI. **Szatmári István**, Martinek Tamás, Lázár László, Fülöp Ferenc
Szubsztituenshatások tanulmányozása naftalinnal kondenzált 2,4-diaril-szubsztituált1,3-oxazinok gyűrű-lánc tautomériájában.
*MKE Vegyészkonferencia*
Hajdúszoboszló, 2003. június 26-28., Abstr.: 152.

XVII. **István Szatmári**, Tamás A. Martinek, László Lázár, Andreas Koch, Erich Kleinpeter, Ferenc Fülöp
Substituent effects in the ring-chain tautomerism of 1,3-diaryl-2,3-dihydro1*H*-naphth[1,2-*e*][1,3]oxazines and 3-alkyl-1-aryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines
*11$^{th}$ Physical Chemistry Conference (ROMPHYSCHEM)*
Timisoara, Romania, September 2-5, 2003, Abstr.: 43.