Synthesis and stereochemistry of 4-arylimino-1,3-oxazino- and 1,3-thiazino[4,3,*a*]isoquinolines

Ferenc Fülöp[a]* Tamás Martinek[a] and Gábor Bernáth[a,b]

[a] *Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, POB 121, Hungary*
[b] *Research Group for Heterocyclic Chemistry, Hungarian Academy of Sciences, POB 121, Szeged, H-6701, Hungary*
E-mail: fulop@pharma.szote.u-szeged.hu

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Abstract

Thioureas **2-5** were prepared from homocalycotomine and isocyanates. When **2** and **3** were treated with methyl iodide and then with alkaline, 9,10-dimethoxy-4-arylimino-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline, **6** and **7** were formed. The corresponding 9,10-dimethoxy-4-arylimino-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-thiazino [4,3-*a*]isoquinolines **8** and **9** were synthesized from **4** and **5** treatment with hydrogen chloride. The predominant conformations and the conformational equilibria were studied by means of NMR spectroscopy and molecular modelling calculations. The 1,3-X,N heterocyclic ring attains a flattened twist conformation, due to the orbital interaction between the bridgehead nitrogen lone pair and the C=N double bond.

Keywords: Oxazine, isoquinoline, isocyanate, synthesis, stereochemistry

Introduction

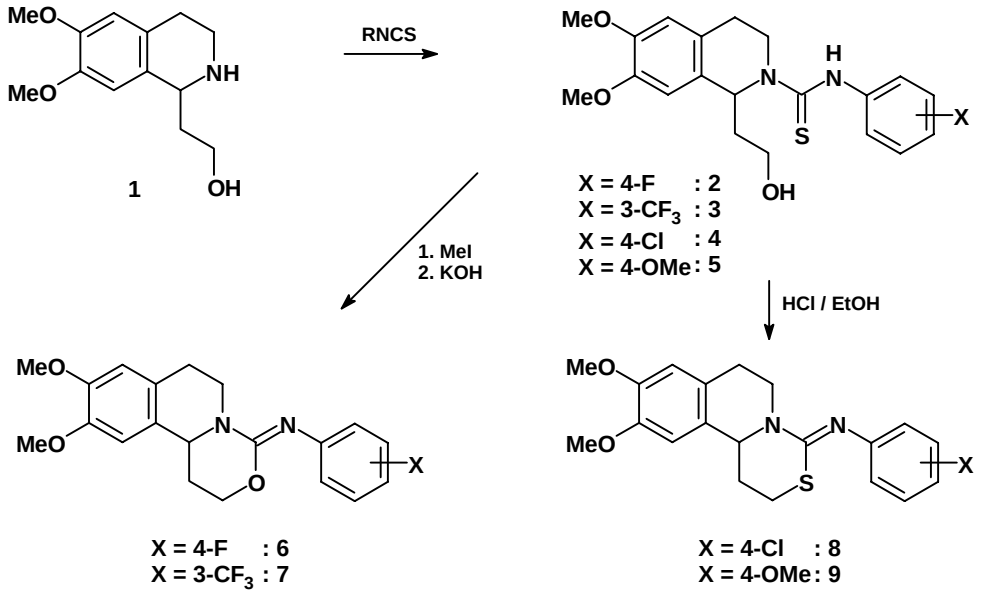
Benzo[*a*]quinolizidines and their heteroanalogues, which belong to the important family of simple tetrahydroisoquinolines, have been studied from both stereochemical and pharmacological aspects.[1-5] The hetero atoms, the substituents on the saturated rings and the configurations of the substituted carbon atoms have been demonstrated to exert pronounced effects on the conformations of these compounds.[6-8]

On the other hand, only a few papers (see e.g. refs 9-11) deal with the synthesis of the closely analogous 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinolines. As a continuation of our systematic studies[5-15] on isoquinoline-fused 1,3-heterocycles, we now report on the synthesis of 1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinolines. These compounds are interesting from both pharmacological and stereochemical points of view. In this paper, the synthesis and

determination of the stereostructure of 4-arylimino-substituted-1,3-oxazino- and 1,3-thiazino[4,3-*a*]isoquinoline derivatives will be discussed.

Results and Discussion

General procedures. Homocalycotomine **1** was prepared from the corresponding 1-ethoxycarbonylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[16] by lithium aluminium hydride reduction according to the literature.[19] The reaction of **1** with aryl isothiocyanates provided the thioureas **2-5** in good yields. The methyl iodide reactions of **2** and **3**, followed by methyl mercaptan elimination on alkali treatment, gave the 1,3-oxazino[4,3-*a*]isoquinolines **6** and **7**. When the thioureas **4** and **5** were heated under reflux with ethanolic hydrogen chloride, the 1,3-thiazino[4,3-*a*]isoquinolines **8** and **9** were formed.

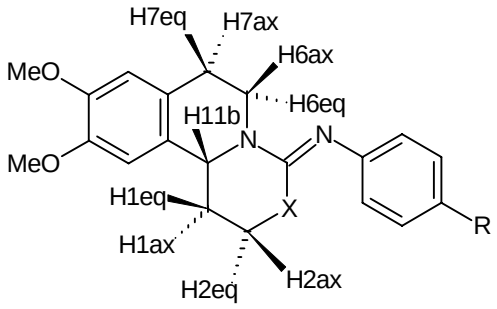


Scheme 1

Structural studies. The assignment of the NMR signals was straightforward, via the application of standard 2D methods such as ^{1}H COSY45, NOESY and HSQC. The conformations of the title compounds were deduced mainly from the ^{3}J(H,H) data, together with analysis of the NOE interaction patterns. Conformational analysis was carried out on **6** and **8**. The spectral characteristics of **7** and **9** were very similar to those of **6** and **8.**

Table 1. Selected vicinal coupling constants (Hz)

	H-11b,H-1ax	H-11b,H1eq	H-1ax,H-2ax	H-1eq,H-2ax	H-6ax,H-7ax
6	10.6	3.2	10.8	3.5	10.8
8	10.2	3.9	7.9	5.4	10.6



X = O, R = F : **6**
X = S, R = Cl :**8**

The coupling constants ^{3}J(H-11b,H-1) can readily be obtained from the COSY45 spectra of the oxazine and thiazine derivatives studied. The measured values of 10.6, 3.2 Hz and 10.2, 3.9 Hz for **6** and **8**, respectively, prove the predominant axial position of H-11b relative to the 1,3-X,N heterocyclic ring, and the clear *trans* diaxial relative orientation of H-11b and H-1ax. The vicinal coupling constants between H-6 and H-7 reveal the predominant average time scale conformation to be the staggered one, but no medium-range NOESY cross-peak was observed neither from H-6ax nor from H-7ax to H-11b. The absence of any 1,3 or 1,4 NOE interaction within the tetrahydroisoquinoline moiety suggests the pseudoequatorial orientation of H-11b; this is supported by the estimated distance of 2.5 ±0.25 Å (ISPA[20]) between H-11 and H-11b.

For **6**, a vicinal coupling constant of 10.83 Hz was measured, which serves as evidence of a rigid torsion of the H-2ax—H-1ax bond with a dihedral angle of 180°. The ^{3}J(H-2ax,H-1ax) value of 7.91 Hz for **8** points to the flexibility of the thiazine ring, resulting in depopulation of the *trans* diaxial position of the torsion H-2ax—H-1ax, due to the increased covalent radius of the sulfur atom.

In order to determine the exact conformations of rings B and C, further considerations are required as regards the coordination sphere of the bridgehead nitrogen. The π-bond in the position α to N(5) may interact with the lone pair of the nitrogen, which can lower the conformational energy of the molecule. The energy gain is at maximum when the bridgehead nitrogen attains an sp^3 trigonal coordination sphere and the substituents on N(5) and C(4) are in the same plane. Due to the 1,3 repulsive interactions, the orbital overlap takes place partially while C(6) and the C=N bond occupy a diequatorial position in ring C. There is only a small deviation of the coordination sphere from trigonal around N(5). This phenomenon may cause a strong flattening of the 1,3-X,N heterocyclic ring, as suggested by several X-ray measurements on analogous compounds and our previous results.

With incorporation of the NMR-derived dihedral restraints into the model, molecular modelling calculations were performed to obtain possible conformational states of the studied compounds consistent with the experimental data. The calculations were performed in two steps, the first step including a minimization, using the MM2 force field[21] together with the experimentally derived torsion restraints. The second step comprised a minimization using the PM3 semi-empirical quantum mechanical method[22] without restraints. The resulting structures are shown in Figure 1.

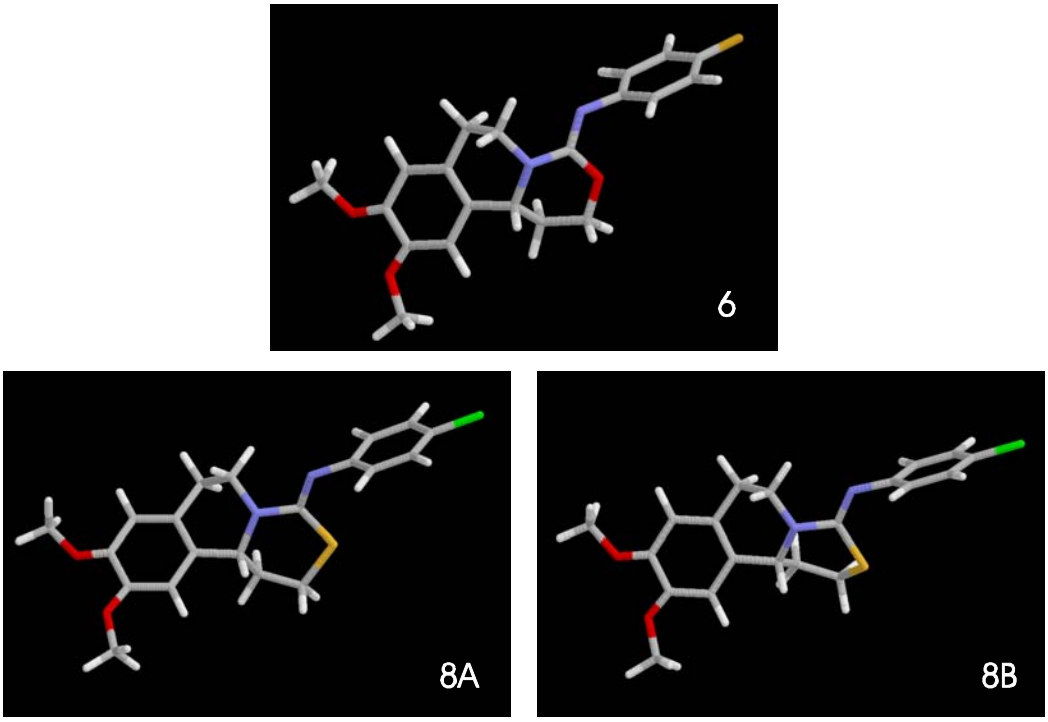


Figure 1. Perspectivic view of the structures obtained by molecular modelling using NMR derived dihedral restraints. Structure **8A** depicts the predominant conformation of **8**.

It is clearly seen in the structure of **6** that ring C is in a twist conformational state, and ring B too occupies a twist conformation, where C(6) is out of the best plane. The opposite rotamer (with C(7) out of the plane) would be less stable because of the resulting deviation of the N(5) lone pair from its orthogonal position relative to the plane defined by N(5) – C(4) – N=. The confomation of ring B in **8** is the same as that in **6**. However, the experimentally observed intermediate ^{3}J(H-2ax,H-1ax) value for **8** can only be explained by a twist – twist-boat equilibrium for the thiazine ring. The strong flattening of ring C can also be observed for the possible conformations.

Experimental Section

General Procedures. NMR spectra were recorded in $CDCl_3$ solution at 300 K on a Bruker AVANCE DRX 400 spectrometer, with the deuterium signal of the solvent as lock. During ^{1}H and ^{13}C NMR measurements, TMS was applied as internal standard. Samples were dissolved in 0.5 ml solvent and placed in 5 mm NMR tubes. Nitrogen bubbling was used to degas samples.

General procedure for thioureas (2-5)

Homocalycotomine **1** (2.21 g, 10 mmol) was suspended in toluene (50 ml), aryl isothiocyanate

(10 mmol) was added, and the mixture was heated under reflux for 1 h. After evaporation of the solvent, the desired crystalline compounds **2-5** were obtained in practically quantitative yields; they were used in crude form without further purification.

General procedure for oxazinoisoquinolines (6) and (7)

The appropriate thiourea derivative **2** or **3** (5 mmol) was stirred with methyl iodide (1.42 g, 10 mmol) in methanol (15 ml) at room temperature for 3 h. After evaporation of the solvent, the oily residue was stirred for 3 h in methanol (50 ml) containing potassium hydroxide (6 g). The mixture was then evaporated, and water (20 ml) was added. The product was separated by extraction with chloroform (3x20 ml). The oily product of **6** was purified via the HCl salt.

General procedure for thiazinoisoquinolines (8) and (9)

The appropriate thiourea derivative **4** or **5** (5 mmol) was refluxed for 30 min in ethanol (30 ml) containing 10% dry hydrogen chloride. After evaporation of the solvent, the residue was dissolved in water and neutralized with sodium hydrogencarbonate; crystalline thiazines **8** and **9** were obtained.

9,10-Dimethoxy-4-(*p*-fluorophenylimino)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline hydrochloride (6)·HCl. White crystals, mp 169-172 °C (from ethanol-diethyl ether), yield 76%. Analysis, calculated for $C_{20}H_{22}ClFN_2O_3$ (392.86): C, 61.15; H, 5.64; N, 7.13. Found: C, 61.34; H, 5.44; N, 7.19%. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.16-2.33 (1H, m, H-1ax), 2.75-2.87 (2H, m, H-1eq, H-7eq), 3.41 (1H, ddd, H-7ax, *J*=13.60, 10.83, 4.78 Hz), 3.59 (1H, ddd, H-6ax, *J*=12.09, 10.83, 4.03 Hz), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 4.54 (1H, ddd, H-2eq, *J*=10.83, 3.53, 4.28 Hz), 4.77 (1H, ddd, H-2ax, *J*=11.58, 10.83, 2.27 Hz), 4.97-5.07 (2H, m, H-6eq, H-11b), 6.61 (1H, s, H-11), 6.67 (1H, s, H-8), 6.97 (2H, dd, m-Ar, J=8.56, 9.06 Hz), 7.47 (2H, dd, m-Ar, *J*=9.06, 4.78 Hz), 12.31 (1H, bs, NH*Cl); ^{13}C NMR ($CDCl_3$) δ (ppm): 28.5, 47.5, 54.9, 56.4, 56.7, 67.4, 108.0, 112.0, 115.9, 116.2, 125.2, 127.0, 127.4, 127.5, 131.1, 148.6, 149.5, 155.78, 162.6.

9,10-Dimethoxy-4-(*m*-trifluoromethylphenylimino)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline hydrochloride (7)·HCl. White crystals, mp 116-117 °C (from ethyl acetate), yield 75%. Analysis, calculated for $C_{21}H_{22}ClF_3N_2O_3$ (442.87): C, 56.95; H, 5.01; N, 6.33. Found: C, 57.12; H, 5.21; N, 6.67%. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.00-2.14 (1H, m, H-1ax), 2.56-2.67 (2H, m, H-1eq, H-7eq), 3.10 (1H, ddd, H-6ax, *J*=12.09, 11.58, 3.27 Hz), 3.19 (1H, ddd, H-7ax, *J*=15.86, 11.58, 4.28 Hz), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 4.20-4.29 (2H, m, H-2ax, H-2eq), 4.66-4.74 (2H, m, H-6eq, H-11b), 6.61 (1H, s, H-11), 6.67 (1H, s, H-8), 7.09-7.17 (2H, m, Ar), 7.21 (1H, bs, Ar), 7.29 (1H, t, Ar, *J*=7.81 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 27.7, 30.9, 43.9, 54.0, 56.3, 56.6, 64.5, 108.3, 112.2, 118.2, 118.3, 120.9, 121.0, 127.4, 128.0, 129.0, 130.9, 131.2, 148.2, 148.5, 149.4, 150.2.

9,10-Dimethoxy-4-(*p*-chlorophenylimino)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-thiazino[4,3-*a*]isoquinoline (8). White crystals, mp 169-170 °C (from ethyl acetate), yield 79%. Analysis, calculated for $C_{20}H_{21}ClN_2O_2S$ (388.92.): C, 61.77; H, 5.44; N, 7.20. Found: C, 61.79; H, 5.60; N,

7.32%. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.01-2.13 (1H, m, H-1ax), 2.59-2.74 (2H, m, H-1eq, H-7eq), 2.88-3.04 (2H, m, H-2ax, H-2eq), 3.05-3.16 (2H, m, H-6ax, H-7ax) 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.68-4.79 (2H, m, H-6eq, H-11b), 6.63 (1H, s, H-11), 6.67 (1H, s, H-8), 6.79 (2H, d, Ar, *J*=8.56 Hz), 7.22 (2H, d, Ar, *J*=8.56 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 25.9, 28.8, 34.3, 44.4, 56.3, 56.6, 57.0, 109.3, 111.9, 124.3, 128.2, 129.0, 129.1, 148.2, 148.3, 149.2, 155.3.

9,10-Dimethoxy-4-(*p*-methoxyphenylimino)-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-thiazino[4,3-*a*]isoquinoline (9). White crystals, mp 148-150 °C (from ethyl acetate), yield 67%. Analysis, calculated for $C_{21}H_{24}N_2O_3S$ (384.50): C, 65.60; H, 6.29; N, 7.29. Found: C, 65.54; H, 6.39; N, 7.17%. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.99-2.12 (1H, m, H-1ax), 2.57-2.74 (2H, m, H-1eq, H-7eq), 2.86-3.01 (2H, m, H-2ax, H-2eq), 3.03-3.16 (2H, m, H-6ax, H-7ax), 3.77 (3H, s, Ar-OMe) 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 4.68-4.80 (2H, m, H-6eq, H-11b), 6.63 (1H, s, H-11), 6.67 (1H, s, H-8), 6.76-6.86 (4H, m, Ar); ^{13}C NMR ($CDCl_3$) δ (ppm): 25.9, 28.8, 34.5, 44.4, 55.8, 56.3, 56.6, 57.1, 109.3, 111.9, 114.4, 123.6, 128.3, 129.2, 143.8, 148.1, 148.3, 155.5, 155.9.

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