Synthesis, Stereochemistry and Ring-Chain Tautomerism of Some New Bis(1,3-perhydrooxazin-2-yl)benzene Derivatives

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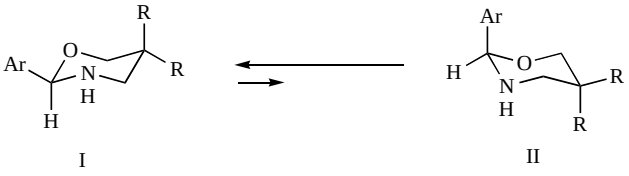
Abstract: The synthesis of some new compounds exhibiting two 1,3-perhydrooxazine units connected to the same aromatic ring and of their ditosylated derivatives was carried out in good yields by the direct condensation reaction of the corresponding aminoalcohols with aromatic dicarbonyl compounds. The stereochemistry and the ring-chain tautomerism of these compounds were investigated by NMR and EI-MS.

Keywords: 1,3-perhydrooxazine, ring-chain tautomerism, conformational analysis, *like-unlike* isomers, NMR, mass-spectrometry.

INTRODUCTION

The investigations on the stereochemistry of 1,3-perhydrooxazines [1-21] were focused on three important directions: a) the conformational analysis of the compounds bearing different substituents located at the heterocycle; b) the determination of the barriers for the flipping of the ring and for the inversion of configuration at the nitrogen atom and c) the determination of the kinetic and thermodynamic parameters for the ring-chain tautomerism. The ring – chain tautomerism of six membered ring is a process which was observed for a large number of heterocycles including sugars, [22] 1,3-oxathiane, [23-25] 1,3-diazine [26-29] and 1,3-perhydrooxazine derivatives [1]

The conformational analysis of substituted-1,3-perhydrooxazines [2] revealed high similarity with the stereochemistry of the corresponding 1,3-dioxane [30, 31] or 1,3-diazine derivatives. [21, 32-34] 2-Aryl-1,3-perhydro-oxazines (Scheme **1**) exhibit anancomeric structures and the conformational equilibrium (I ⇆ II) of the flipping of the heterocycle is shifted towards the conformer exhibiting the aromatic substituent in the equatorial orientation (I).



I II

Scheme 1.

The investigations on the ring-chain tautomerism of 2-aryl-1,3-perhydrooxazines (III⇆IV; Scheme **2**) showed the linear correlation between the stability of the cyclic form and the Hammets-Brown parameters of substituents located at the aryl ring [1]. The shifting of the equilibrium towards the acyclic tautomer is influenced by the electronic effects of the substituents of the aromatic unit and by the steric hindrance of the large substituents located at the 1,3-perdydrooxazine ring [1]. The ratios between the chain and ring forms were measured from ^{1}H NMR spectra and the ring–chain tautomerism was monitored by the *cis-trans* isomerization reaction (*e.g.* 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazines and 2,4-diaryl-3,4-dihydro-2*H*-naphth[2,1-*e*][1,3]oxazines) [16, 17].

In previous works [23-25] we successfully investigated the ring chain tautomerism of some 1,3-oxathiane compounds including derivatives with two heterocyclic units. In our experiments we used compounds in which the ring-chain tautomerism determines the equilibrium between different diastereoisomers. We investigated spiro-1,3-oxathiane derivatives exhibiting *cis* and *trans* isomers [23, 24] and *bis*(1,3-oxathian-2-yl)benzene derivatives with two chiral centers showing *like* and *unlike* isomers [25] and we established, using NMR experiments, the kinetic parameters of the tautomerization processes.

We considered of interest to continue the investigations of the ring-chain tautomerism in heterocyclic compounds series using *bis*(1,3-perhydrooxazin-2-yl)benzene derivatives (which exhibit *like* and *unlike* isomers) and to monitor the tautomerization processes by NMR and by mass-spectrometry.

RESULTS AND DISCUSSION

New 1,3-perhydrooxazine derivatives (**1**-**4**) were obtained in fair to good yields by the condensation reaction of 3-amino-1-propanol and of its N-tosylated derivative with

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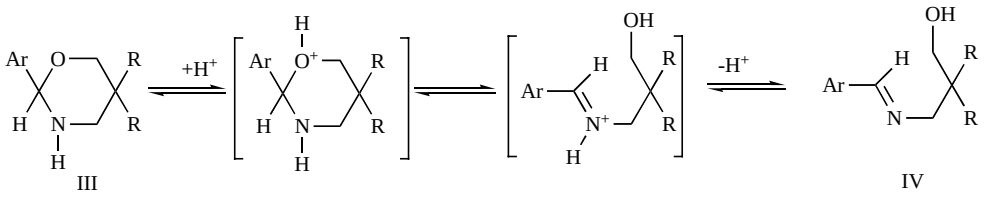
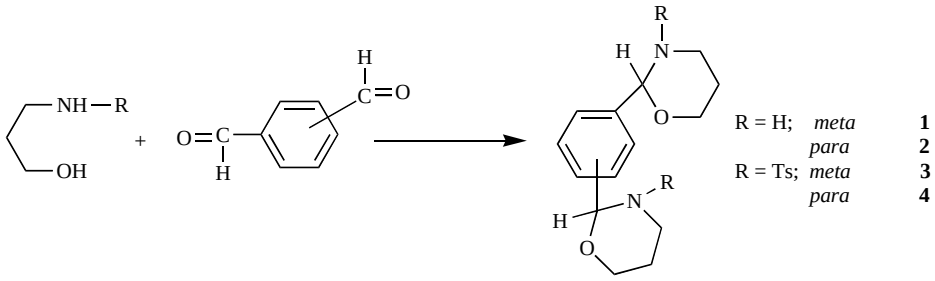


Scheme 2.



Scheme 3.

Table 1. Results of the Synthesis of 1-4

Compound	1	2	3	4
Yields (%)	59	67	52	58

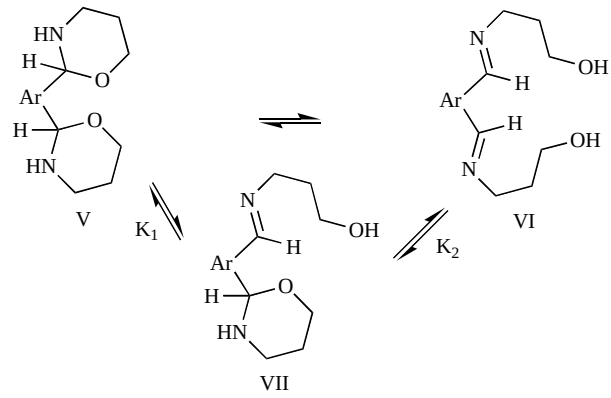
iso-phthaldialdehyde and *tere*-phthaldialdehyde (Scheme **3**, Table **1**).

Compounds **1**-**4** were investigated by NMR experiments and mass-spectrometry (EI). The stereochemistry investigations of these derivatives reveal the anancomeric structure of the compounds and the shifting of the conformational equilibria towards the conformer exhibiting the aromatic group in equatorial orientation. The anancomeric structures are suggested by the NMR spectra which exhibit different signals for the protons located in axial and equatorial positions. The tosyl groups in **3** and **4** display axial orientations (as expected from literature data) [35], and they are obtained as single *cis*-*cis* isomers (the aromatic group at position 2 is taken as reference).

The investigations revealed important differences between the stereochemistry of compounds **1**, **2** and **3**, **4**. Perhydrooxazines **1** and **2** exhibit the ring-chain tautomerism, while the tosylated compounds **3** and **4** due to the substitution at the nitrogen atom, are not involved in tautomeric equilibria. The tautomeric equilibria for **1** and **2** takes place in solution (e.g. $CDCl_3$ during the NMR experiments) and they are running between three structures (bisperhydrooxazine V, double Schiff base VI, and mono-perhydrooxazine, mono-Schiff base VII; Scheme **4**).

The tautomeric equilibria are not completely shifted towards one of the isomers, the rate of the process is not very high, and thus all three structures can be easily detected by NMR and by mass spectrometry. However, the equilibria are fast enough to incapacitate the chemical or chromatographic separation of the three tautomers. The two 1,3-oxazine units are far one of the other and they act independently making possible the identification of the structure VII.

The NMR spectra of **1** and **2** display three sets of signals which correspond to the bisperhydrooxazine (cycle-cycle form, V), the mono-perhydrooxazine, mono-Schiff base (cycle-chain form, VII) and to the double Schiff base (chain-chain form, VI). Some of the specific signals in the ^{1}H NMR spectra, belonging to these very different structures, are very well separated and the ratio between these three forms could be measured and the equilibrium constants could be estimated (Tables **2** and **3**). For instance the protons located at position 2 of the 1,3-perhydrooxazine ring (in the cyclic form) exhibit a singlet at about 5 ppm, while the same protons in the Schiff base form (iminic protons) give a more deshielded signal at about 8-9 ppm. ^{1}H NMR spectrum of **2** (Fig. **1**) exhibits two close singlets (δ_V = 5.18 and δ_{VII} = 5.21 ppm) for the protons located at positions 2, 2' in V and 2 in VII and two other singlets for the imine protons of isomers VI and VII (δ_{VI} = 8.31 and δ_{VII} = 8.28 ppm). The signals belonging to the chain - ring form VII show the same



Scheme 4.

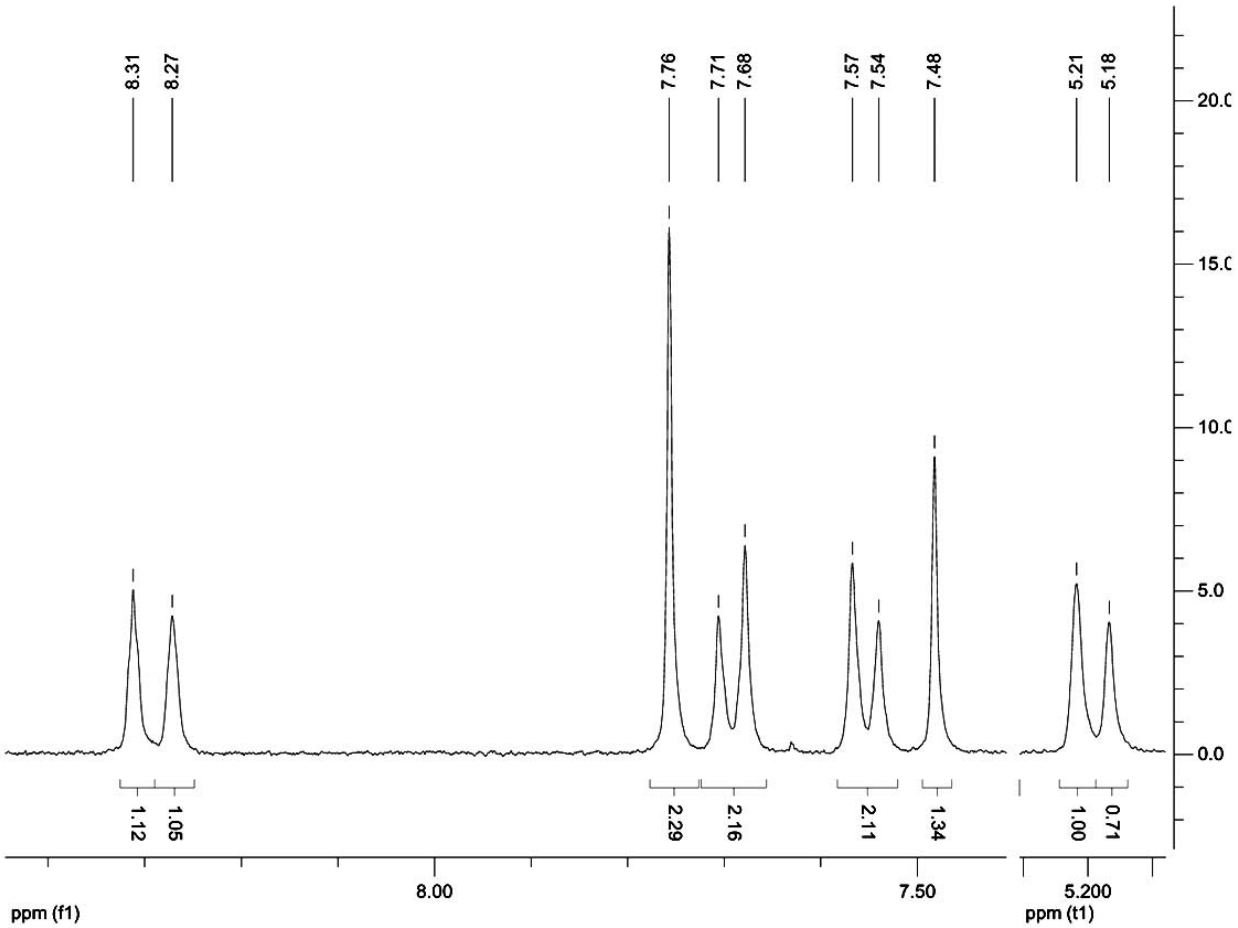


Fig. (1). ^{1}H NMR spectrum ($CDCl_3$, 300 MHz, relevant fragments).

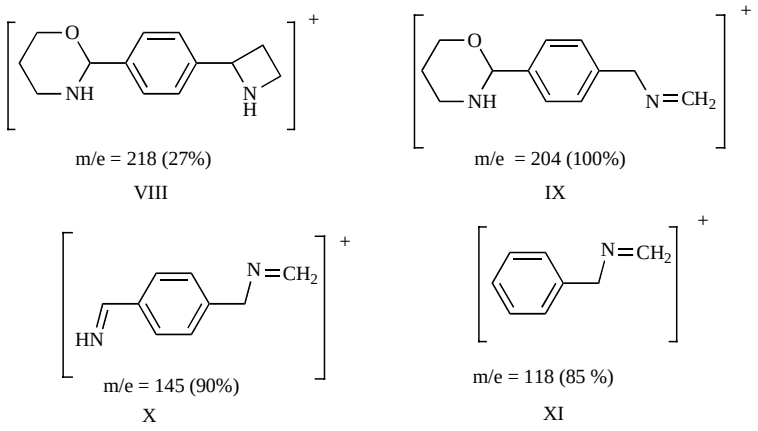
Table 2. ^{1}H NMR Data (Selected) for Compounds 1 and 2

Compd.	Tautomer	2-H	-CH=N-
1	V	5.16	-
	VI	-	8.30
	VII	5.18	8.26
2	V	5.18	-
	VI	-	8.31
	VII	5.21	8.27

Table 3. Thermodynamic Data for the Ring-Chain Tautomerism (Scheme 4) of Compounds 1 and 2

Compd	Ratios (%) of the tautomers with chain and ring forms			K_1	K_2
	ring-ring (V)	ring-chain (VII)	chain-chain (VI)		
1	20	47	33	2.35	0.70
2	17	54	29	3.17	0.53

intensities and facilitate their assignment. Similar differences can be observed in the ^{13}C NMR spectrum, too. It is worthy to mention the modification of the positions of the signals belonging to the carbon atoms at position 2, 2'. As an example, in the case of **2** the ^{13}C NMR spectrum exhibits two signals (δ_V = 88.28 and δ_{VII} = 88.45ppm) for the aminoacetalic carbon atoms (V and VII) and other two signals for the imine carbon atoms of VI and VII (δ_{VI} = 160.9 and δ_{VII} = 161.22 ppm). The three tautomeric forms of **2** can be easily observed investigating the signals belonging



Scheme 5.

to the 1,4-phenylene moiety, too. The ^{1}H NMR spectrum (Fig. **1**) shows only one singlet for the aromatic protons of V (δ_V = 7.48 ppm) and of VI (δ_{VI} = 7.76 ppm), while for VII the 1,4-phenylene protons exhibit an AB system (δ_{VII} = 7.56, δ_{VII}' = 7.70 ppm).

The EI-MS investigations (using as sample a $CHCl_3$ solution of the compounds and the direct introduction procedure) revealed the molecular ions $[M]^+$ (m/e = 248) and characteristic fragment ions for the cyclic and iminic tautomers (Scheme **5**). Some of the peaks observed in the mass spectra of **1** and **2** could be assigned to the double cycle, cycle-chain or chain-chain forms. In agreement with the literature data [36] in the EI-MS spectrum of **2** the ion $[M\text{-}CH_2O]^+$ (VIII, m/e = 218; 27%) was considered characteristic for the cycle-cycle form, the peak $[M\text{-}CH_2\text{-}CH_2O]^+$ (IX, m/e = 204; 87%) was associated with the cycle-imine structure, while the ions $[C_9H_9N_2]^+$ (X, m/e = 145, 100%) and $[C_8H_8N]^+$ (XI, m/e = 118; 71%) were assigned to the double imine isomer. In the EI-MS spectrum of **1** the similar peaks could be observed at comparable relative intensities: m/e (%) = 218 (29); 204 (81); 145 (100); 118 (69).

EXPERIMENTAL SECTION

General

^{1}H and ^{13}C-NMR spectra were recorded at room temperature using $CDCl_3$ as solvent in 5 mm tubes on a Varian Gemini spectrometer equipped with a multinuclear head operating at 300 MHz for protons and 75 MHz for carbon atoms. The mass spectra have been recorded with a Varian MAT 311 spectrometer. Melting points were measured with a Kleinfeld melting point apparatus and they are uncorrected. Elemental analyses (C, H, N) were conducted at "Babes-Bolyai" University using a Perkin Elmer Analyzer; their results were found to be in good agreement (±0.3%) with the calculated values.

General Procedure for the Synthesis of Compounds 1 and 2

Stoichiometric amounts of 3-amino-1-propanol, and carbonyl compounds (11 mmol) were refluxed in benzene and the water formed during the reaction was removed using a *Dean-Stark* trap. After the water was separated the solvent was removed and the bis(1,3-perhydrooxazines) were purified by crystallization.

1,3-bis(1,3-perhydrooxazin-2-yl)benzene (1)

Yellow crystals, m.p. = 187-188 °C, yields 59%. Anal. Calcd for $C_{14}H_{20}N_2O_2$ (248.32): C, 67.71; H, 8.12; N, 11.28; found: C, 67.88; H, 8.26; N, 11.41. ^{1}H-NMR ($CDCl_3$)(V-VII): δ (ppm) 1.48-1.95 [4H, overlapped peaks, 5,5'-H (V-VII)], 3.12-4.24 [8H, overlapped peaks, 4,4'-H, 6,6'-H (V-VII)], 5.16 [1H, s, 2-H (VII structure), 5.19 [2H, s, 2,2'-H (V structure)], 7.32-7.72 [4H, overlapped peaks, aromatic protons (V-VII)], 8.24 [1H, s, 2'-H (VII structure)], 8.28 [2H, s, 2,2'-H (VI structure)]. ^{13}C-NMR ($CDCl_3$)(V-VII): δ (ppm) 26.30, 29.04, 31.28, 43.79, 58.55, 60.50, 60.71, 67.27 [V-VII], 87.78 [$C^{2,2'}$, V structure], 87.98 [C^2, VII structure], 125.12, 125.59, 127.42, 127.73, 134.83, 137.32, 139.72, 142.49 [V-VII], 160.40 [$C^{2,2'}$, VI structure], 160.73 [$C^{2'}$, VII structure]. EI-MS m/z (%): 248 (42), 218 (29), 204 (81), 145 (100), 130 (32), 118 (69), 117 (27), 91 (22), 79 (15), 77 (17).

1,4-bis(1,3-perhydrooxazin-2-yl)benzene (2)

Yellow crystals, m.p. = 216-217 °C, yields 67%. Anal. Calcd for $C_{14}H_{20}N_2O_2$ (248.32): C, 67.71; H, 8.12; N, 11.28; found: C, 67.54; H, 7.93; N, 11.49. ^{1}H-NMR ($CDCl_3$) (structures V-VII): δ (ppm) 1.24-2.03 [4H, overlapped peaks, 5,5'-H (V-VII)], 3.11-4.28 [8H, overlapped peaks, 4,4'-H, 6,6'-H (V-VII)], 5.14 [1H, s, 2-H (VII structure), 5.17 [2H, s, 2,2'-H (V structure)], 7.45 [4H, s, aromatic protons (V structure)], 7.52 [2H, d, *J* = 8.1 Hz, aromatic protons (VII structure)], 7.66 [2H, d, *J* = 8.1 Hz, aromatic protons (VII structure)], 7.72 [4H, s, aromatic protons (VI structure)], 8.23 [1H, s, 2'-H (VII structure)], 8.27 [2H, s, 2,2'-H (VI structure)]. ^{13}C-NMR ($CDCl_3$)(structures V-VII): δ (ppm) 26.80, 29.54, 33.21, 44.29, 59.05, 60.99, 61.20, 67.77 (V-VII), 88.28 [$C^{2,2'}$, V structure], 88.45 [C^2, VII structure], 125.61, 126.09, 127.91, 128.23, 135.32, 137.61, 140.21, 142.98 [V-VII], 160.90 [$C^{2,2'}$, VI structure], 161.22 [$C^{2'}$, VII structure]. EI-MS m/z (%): 248 (48), 218 (27), 204 (87), 145 (100), 130 (37), 118 (71), 117 (24), 91 (29), 79 (19), 77 (14).

Synthesis of N-tosyl-3-amino-1-propanol

To a solution of (10 mmol) 3-amino-1-propanol and (11 mmol) of triethylamine solved in dichloromethane at the -

5^0C, tosylchloride (10 mmol) was slowly added during 24 h at the same temperature. When the reaction was completed, 20 ml of dichloromethane was added and the reaction mixture was washed twice with 10 cm^3 of sulfuric acid 2N solution. After drying on Na_2SO_4 the solvent was removed and N-tosyl-3-amino-1-propanol was purified by crystallization from ethanol.

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.7 [2H , m, -CH_2-], 2.43 [3H, s, -CH_3], 2.47 [2H, m, -CH_2N-], 3.73 [2H, m, -CH_2O-], 5.1 [1H, -NH-], 7.75-7.32 [4H, aromatic protons].

General Procedure for the Synthesis of Compounds 3 **and** 4

Stoichiometric amounts of N-tosyl-3-amino-1-propanol and carbonyl compounds (11 mmol) and catalytic amounts (0.05 g) of *p*-toluenesulfonic acid were refluxed in benzene and the water formed during the reaction was removed using a *Dean-Stark* trap. After the water was separated and the reaction mixture was cooled to room temperature, the catalyst was neutralized under stirring with excess of 0.1 M KOH solution. The organic layer was washed twice with 20 cm^3 of water. After drying on Na_2SO_4 the solvent was removed and the N-substituted bis(perhidro-1,3-oxazines) were purified by crystallization from ethanol and/or flash-chromatography.

1,3-bis(3-tosyl-1,3-perhydrooxazin-2-yl)benzene (3)

White solid, m.p. = 204-205 °C, Yield 46%. Anal. Calcd for $C_{28}H_{32}N_2O_6S_2$ (556.69): C, 60.41; H, 5.79; N, 5.03; S, 11.52 found: C, 60.57; H, 5.92; N, 5.22 S, 11.74. ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.40 [2H, m, 5,5'-H_{eq}]; 2.47 [6H, s, CH_3-C_6H_4-], 3.30 [2H, m, 5,5'-H_{ax}], 3.68 [4H, m, 4(4'),6(6')-H_{ax}], 3.87 [4H, m, 4(4'),6(6')-H_{eq}], 6.69 [2H, s, 2,2'-H], 7.36 [2H, d, *J* = 8 Hz, -C_6H_4-SO_2-], 7.55 [1H, s, m-C_6H_4-], 7.61 [3H, overlapped peaks, m-C_6H_4-], 7.91 [2H, d, *J* = 8 Hz, -C_6H_4-SO_2-]. ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.78 [$C^{5,5'}$], 36.34 [CH_3-C_6H_4-], 39.98 [$C^{4,4'}$], 66.03 [$C^{6,6'}$], 88.19 [$C^{2,2'}$], 121.96, 126.02, 128.31, 128.37, 129.13, 131.96, 135.67, 136.45, 137.98, 144.31 [aromatic carbon atoms]. EI-MS m/z (%): 401[M-Ts]$^+$ (11), 400 (44), 240 (100), 155 (39), 91 (85).

1,4-bis(3-tosyl-1,3-perhydrooxazin-2-yl)benzene (4)

White solid, m.p. = 233 - 234 °C, yields 58%. Anal. Calcd for $C_{28}H_{32}N_2O_6S_2$ (556.69): C, 60.41; H, 5.79; N, 5.03; S, 11.52 found: C, 60.60; H, 5.67; N, 4.88 S, 11.29 ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.45 [2H, m, 5,5'-H_{eq}]; 2.46 [6H, s, CH_3-C_6H_4-], 3.29 [2H, m, 5,5'-H_{ax}], 3.63 [4H, m, 4(4'),6(6')-H_{ax}] 3.82 [4H, m, 4(4'),6(6')-H_{eq}], 6.68 [2H, s, 2,2'-H], 7.35 [2H, d, *J* = 8 Hz, -C_6H_4-SO_2-], 7.5 [4H, s, -C_6H_4-], 7.67 [2H, d, *J* = 8 Hz, -C_6H_4-SO_2-], ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.57 [$C^{5,5'}$], 32.13 [$\underline{C}H_3$-C_6H_4-], 45.78 [$C^{4,4'}$], 60.83 [$C^{6,6'}$], 84.57 [$C^{2,2'}$], 126.78, 128.31, 128.62, 129.67, 137.06, 137.45, 137.98, 144.31 [aromatic carbon atoms]. EI-MS m/z (%): 401[M-Ts]$^+$ (19), 400 (57), 240 (100), 155 (45), 91 (99).

CONCLUSIONS

The NMR and EI-MS investigations of compounds **1** and **2** with two 1,3-perhydrooxazine rings connected to the same aromatic unit revealed the running ring-chain tautomerism. This process is slow enough for being possible the recording in NMR and in MS of different signals for the three different isomers, but it is too fast for being possible the separation of the cycle-cycle, cycle-imine or double imine tautomers. The corresponding N,N-ditosylated derivatives were obtained as double perhydrooxazine derivatives and they don't exhibit tautomers. All investigated cyclic compounds are anancomeric and the aromatic unit prefers the equatorial orientation.

ACKNOWLEDGEMENTS

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