Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1173–1179

TETRAHEDRON

Studies of some hydrogenated thiazolo[2,3-*a*]isoquinoline *S*-oxides

M. D. Rozwadowska* and A. Sulima

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

Received 22 August 2002; revised 5 December 2002; accepted 2 January 2003

Abstract—Several hydrogenated thiazolo[2,3-*a*]isoquinolinone *S*-oxides have been prepared and their stereochemistry established on the basis of spectral data analysis combined with X-ray crystallography. A reversible *syn*/*anti* isomerization of diastereomeric sulfoxides has been postulated to occur via a 10b proton abstraction.

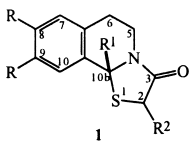
1. Introduction

In the course of our study of the hydrogenated thiazolo[2,3-*a*]isoquinoline ring system[1] we have synthesized several representative compounds of this class, including chiral non-racemic derivatives,[2] and investigated their spectral properties and steric structure.[1]

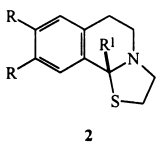
Since relatively little work concerning this heterocyclic system had been reported we have decided to continue our study to gain more information on this sulfur–nitrogen heterocycle, in particular on their reactivity.

Having two series of thiazolo[2,3-*a*]isoquinolines available: the amide-type derivatives **1**, and the tetrahydro-analogs **2**, we planned to perform some standard reactions, such as N/C-alkylation, reduction and oxidation.

Until now the chemistry of only tetrahydro-derivatives **2** had been studied in respect to the salt formation, hydride reduction and action of carbon nucleophiles.[3] Under the action of mineral acids the corresponding salts were formed, from which free bases could be liberated upon neutralization. $LiAlH_4$ reduction caused ring rupture with the formation of a *N*-(β-mercaptoethyl)tetrahydroisoquinoline derivatives. A corresponding derivative was obtained when we treated amide **1b** with sodium borohydride. The tetrahydro-compounds **2** were described[3] to be resistant toward the attack of carbon nucleophiles such as the Grignard reagents and cyanide anion.



1



2

1	R	R^1	R^2	**2**	R	R^1
a	H	H	H	**a**	H	H
b	CH_3O	H	H	**b**	CH_3O	H
c	CH_3O	CH_3	H	**c**	H	CH_3
d	H	H	CH_3	**d**	CH_3O	CH_3
e	CH_3O	H	CH_3			
f	CH_3O	CH_3	CH_3			

Several attempts at *N*-alkylation of **2** or aldol reaction with the heterocycles, **1** and **2**, led only to extensive decomposition and no expected products were isolated. Similarly, complex mixtures of polar products were formed when oxidation of tetrahydro-derivatives **2** was attempted. On the other hand, amides of type **1**, were oxidized in satisfactory yields to give diastereomeric sulfoxides, which appeared to be relatively stable compounds.

These sulfoxides, which are the subject of this study, have attracted our attention because they were needed as intermediates in a planned asymmetric synthesis of isoquinoline alkaloids[4] and also because of their unknown stereochemistry. We also wanted to examine the observed reversible *syn*/*anti* isomerization of diastereomeric sulfoxides.

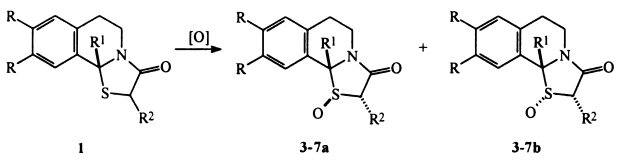
2. Result and discussion

Just as the parent thiazolo[2,3-*a*]isoquinolines, **1** and **2**, the

Keywords: thiazolo[2,3-*a*]isoquinoline *S*-oxides; chiral non-racemic derivative; spectra.

* Corresponding author. Tel.: +48-61-829-1322; fax: +48-61-8658-008; e-mail: mdroz@amu.edu.pl

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00023-1



Scheme 1.

Table 1. Oxidation of thiazolo[2,3-*a*]isoquinolin-3-one **1**

Entry	Sulfide				Oxidant[a]	Reaction time	Sulfoxide		
	No	R	R^1	R^2			Y (%)[b]	Dominating	*syn*/*anti*[c]
1	**1b**	CH_3O	H	H	A	0.5 h	91	**3b**	–
2					B	6 h	71	**3a**	–
3					C	2–2.5 h	75	**3b**	–
4					D	3 h	71	**3a**	–
5	**1c**	CH_3O	CH_3	H	A	0.5 h	94	**4b**	1/1.3
6					B	3 days	96	**4b**	1/1.4
7					D	1.5 h	97	**4a**	1.8/1
8	**1d**[d]	H	H	CH_3	A	12 h	Dec.	–	–
9					B	3 days	Dec.	–	–
10					C	3.5 h	54	**5b**	0/100
11	**1e**[d]	CH_3O	H	CH_3	A	0.5 h	90	**6b**	–
12					B	3.5 h	75	**6b**	–
13					C	2 h	71	**6b**	0/100
14	**1f**[d]	CH_3O	CH_3	CH_3	A	0.5 h	Dec.	–	–
15					B	3 days	58	**7b**	–

[a] A: *m*CPBA, 1.1 mmol/1 mmol **1**, CH_2Cl_2, 0°C; B: 30% H_2O_2, 0.7 ml/1 mmol **1**, $CHCl_3/CH_3OH$ (2:1), RT; C: 30% H_2O_2, 0.7 ml/1 mmol **1**, $CHCl_3/CH_3OH$ (2:1), reflux; D: oxone, 1.1 mmol/1 mmol **1**, $CHCl_3/CH_3OH$ (2:1), 0°C.
[b] Yield of crude product.
[c] In many cases d.e. could not be determine due to isomerization of diastereomers.
[d] ca. 1:1 mixture of diastereomers was used.

corresponding *S*-oxides have not been investigated too often; only two such compounds, including sulfoxide **4**, have been prepared by oxidation of the parent sulfides with hot 30% hydrogen peroxide.[5] No information concerning their diastereomeric purity or steric structure has been given.

In our experiments, for the oxidation of the thiazoloisoquinolines **1b–f** we used four peroxy reagents: *m*CPBA at 0°C (oxidizing system A), 30% hydrogen peroxide at RT (B), 30% hydrogen peroxide at reflux (C) and oxone at 0°C (D). As a result mixtures of two diastereomeric sulfoxides (**3–7**) were produced, with diastereoselectivity depending on the oxidation system used (Scheme 1, Table 1).

Table 1 contains the results of oxidation of several thiazoloisoquinolines **1**, along with some of the reaction conditions, yields and d.e. determined only in a few cases. Oxidation of compounds **1b**, **c**, **e** with methoxy substituents at the aromatic ring and/or with only one methyl substituent at 2C or 10bC proceeded smoothly and in satisfactory yields (Table 1, entries 1–7, 11–13). Substrates without the substituents or with two methyl groups (at 2C and 10bC) tended either to decompose totally, e.g. **1a**, or gave poor yields, e.g. **1d**, **1f** (Table 1, entries 8–10, 14, 15), or required more drastic reaction conditions, **1d**, **1f** (Table 1, entries 10, 13).

The diastereomeric distribution in the reaction products was difficult to determine precisely because of the isomerization of the diastereomers occurring in solution, and during the work-up extraction procedure. Following the progress of the oxidation by TLC, we noticed that at first the less polar diastereomer (type **a**) was always produced, but with the progress of the reaction, the second, more polar one (type **b**) started to appear, to dominate finally in the products mixture. The latter one was the only isomer isolated from the reactions carried out at reflux (Table 1, entries 10, 13).

Several of the diastereomeric sulfoxides were isolated as pure compounds and are listed in Table 2. Pure **3a** (less polar isomer) was separated simply by extraction with carbon tetrachloride of the crude product resulting from reaction with 30% hydrogen peroxide at RT (B) or oxone (D), in which it was dominant (Table 1, entry 2, 4). Isomer **3b**, the main component formed in oxidation with A and C reagent systems (Table 1, entries 1, 3), was purified by crystallization of the mixture of products from chloroform/methanol (2:1). Sulfoxides **4a** and **4b**, which showed no tendency to isomerize, were separated by fractional crystallization from 96% ethanol of crude products enriched in one of them, e.g. **4b** from oxidation with A and B systems, **4a**, from the reaction with oxone (D) (Table 1, entries 5–7, respectively). In oxidation of thiazoloisoquinolines **1d–f**, ca. 1:1 mixtures of diastereomers were used. These compounds required more drastic conditions or longer reaction times. In milder conditions (A, B) formation of two diastereomers could be observed by TLC with the more polar isomers always prevailing, yet the yields were very low. At reflux (C) yields were improved, but only the more

Table 2. Relative configuration of diastereomeric sulfoxides **3–7**

Sulfoxide	Mp (°C)	Configuration
3a	164–167	$1R^*$,10bR^* (*syn*)
3b	212–214	$1S^*$,10bR^* (*anti*)
4a	167–169	$1R^*$,10bR^* (*syn*)
4b	198–199	$1S^*$,10bR^* (*anti*)
5b	181–183	$1S^*$,$2S^*$,10bR^* (*anti*)
6b	207–209	$1S^*$,$2S^*$,10bR^* (1/10b: 2/10b *anti*, *anti*)
7b	Oil (unstable)	$1S^*$,$2S^*$,10bR^* (1/10b: 2/10b *anti*, *anti*)

Table 3. ^{1}H NMR Spectral data of sulfoxides **3**–**7** ($CDCl_3$); δ (ppm); J (Hz)

Sulfoxide	2Hβ/2[CH_3]β	2Hα/2[CH_3]α	5H$_a$	5H$_e$	6Hψ$_a$	6Hψ$_e$	10bH/10b[CH_3]
3a[a]	3.98[b] (d, J=14.5)	4.15 (d, J=14.5)	2.97[b,c] J=12.3 J=12.3 J=3.9	4.26[d] J=12.3 J=4.6 J=2.1	2.68–2.72 (m)		5.61[b]
3b[e]	3.77[b] (d, J=16.6)	3.69 (d, J=16.6)	3.09[b,c] J=12.4 J=12.4 J=3.2	4.55[d] J=12.4 J=4.7 J=1.6	2.96[c] J=15.0 J=12.4 J=4.7	2.67–2.74 (m)	5.65[b]
4a	3.64 (d, J=15.6)	3.95 (d, J=15.6)	3.07[c] J=12.9 J=12.9 J=4.4	4.55[d] J=12.9 J=5.8 J=1.6	2.87[c] J=16.7 J=12.9 J=5.8	2.69–2.75 (m)	[1.88]
4b[e]	3.90[b] (d, J=16.9)	3.57 (d, J=16.9)	3.13[b,c] J=12.4 J=12.4 J=3.2	4.52[d] J=12.4 J=4.9 J=1.5	3.00[c] J=15.3 J=12.4 J=4.9	2.72[d] J=15.3 J=3.2 J=1.5	[1.73]
5b	3.63[b] (q, J=7.4)	[1.62] (d, J=7.4)	3.11[b,c] J=12.3 J=12.3 J=2.7	4.54[d] J=12.3 J=4.9 J=2.7	2.98[d] J=15.6 J=12.3 J=4.9	2.78[c] J=15.6 J=2.7 J=2.7	5.65[b]
6b	3.62[b] (q, J=7.3)	[1.62] (d, J=7.3)	3.08[b,c] J=12.6 J=12.6 J=2.6	4.52[d] J=12.6 J=5.1 J=1.4	2.94[c] J=15.6 J=12.6 J=5.1	2.67–2.75 (m)	5.59[b]
7b	3.73[b] (q, J=7.4)	[1.59] (d, J=7.4)	3.15[b,c] J=12.5 J=12.5 J=2.7	4.50[d] J=12.5 J=5.2 J=1.4	2.91–3.08 (m)	2.66–2.72 (m)	[1.76]

[a] Measured in DMSO-d_6, in which no isomerization was taking place.
[b] Determined by NOE difference spectroscopy.
[c] dt.
[d] ddd.
[e] Determined by X-ray crystallography.[6]

polar diastereomers (**5b**, **6b**, **7b**) were present in the product mixtures (Table 1, entries 10, 13). They were purified by column chromatography (**5b**, **7b**) or by crystallization from methanol (**6b**).

It was interesting to find that in the course of the oxidation, during which the third stereogenic center was created, only two diastereomeric sulfoxides were produced, and only the more polar ones could be isolated, implying that isomerization at the C-2 carbon atom must have accompanied the oxidation process.

The steric structure of sulfoxides **3**–**7**, obtained as homogenous compounds, was established with the aid of spectral data analysis, by comparing them with those of the parent unoxidized precursors **1**[1] and with X-ray crystallographic measurements. The ^{1}H, ^{13}C NMR and MS spectral data are listed in Tables 3–6, respectively.

The relative configuration of the diastereomeric sulfoxides with two stereogenic centers was established by an X-ray study of the two more polar sulfoxides, **3b** and **4b**.[6] For both compounds the X-ray analysis proved that the sulfinyl oxygen, occupying the α-position, and the 10b substituent, in ψ-axial β orientation, were located *anti* to each other. In terms of relative configuration, **3b** and **4b** sulfoxides are the 1S^*,10bR^* (*anti* or *u*) isomers. Therefore, the 1R^*, 10bR^* (*syn* or *l*) relative configuration could be ascribed to the **3a** and **4a** partners, supported also by an observed reversible *syn*/*anti* isomerization of the diastereomers.

Table 4. ^{1}H NMR Chemical shift differences in spectra of sulfoxides **5b**, **6b**, **7b** and the parent unoxidized derivatives **1d**–**f**

Sulfide/sulfoxide	2Hβ	2CH_3α	10bH/[10bCH_3]
5b	3.63	[1.62]	5.65
1d[a]	4.04	[1.52]	5.98
Δ	*−0.41*	*+0.10*	*−0.33*
6b	3.62	[1.62]	5.59
1e[a]	4.03	[1.53]	5.93
Δ	*−0.41*	*+0.09*	*−0.35*
7b	3.73	[1.59]	[1.76]
1f[a]	4.06	[1.51]	[1.94]
Δ	*−0.33*	*+0.08*	*−0.18*

[a] Referred to spectral data of the dominating (*anti*) diastereomers of **1** in isomers mixture.[1]

Table 5. ^{13}C NMR Chemical shift differences in spectra of sulfoxides **3a**, **b** and **4a**, **b** and unoxidized derivatives **1b**, **c**

Sulfoxide/sulfide	2C	3C	10bC
3a	55.20	164.29	79.30
1b	33.96	169.75	59.23
Δ	*+21.24*	*−5.46*	*+20.07*
3b	56.00	167.10	76.80
1b	33.96	169.75	59.23
Δ	*+22.04*	*−2.65*	*+17.57*
4a	52.72	162.60	81.69
1c	33.88	169.29	68.03
Δ	*+18.84*	*−6.69*	*+13.66*
4b	53.97	166.29	76.59
1c	33.88	169.29	68.03
Δ	*+20.04*	*−3.00*	*+8.56*

Table 6. EIMS data of sulfoxides **3**–**7**; *m/z* (%)

Sulfoxide	R	R^1	R^2	M^+	M–(SO)	M–(SO)–(CHR^2CO)	M–(SO)–(C_2H_4)
3	CH_3O	H	H	281 (45)	233 (22)	191 (100)	–
4	CH_3O	CH_3	H	295 (77)	247 (38)	205 (100)	–
5	H	H	CH_3	235 (57)	187 (85)	131 (39)	159 (100)
6	CH_3O	H	CH_3	295 (31)	247 (36)	191 (100)	219 (13)
7	CH_3O	CH_3	CH_3	309 (33)	261 (42)	205 (100)	233 (3)

The above results of the X-ray analysis were correlated with spectral data and we have used these correlations to examine the configuration of the other sulfoxides studied, **5**–**7**.

The ^{1}H NMR spectra (Table 3) recorded in standard conditions showed the first order pattern and assignments could be made on the basis of splitting pattern and coupling constant values, including the long-range coupling. In a few cases the NOE difference experiments and 2D correlation techniques were applied. The spectra were very similar to those of the parent sulfides **1**,[1] only small changes in chemical shift (0.02–0.57 ppm) were observed for protons at carbon atoms directly attached to the sulfinyl function. From the data of Table 3 it is evident that the spectra of all the sulfoxides investigated resemble each other in respect to the chemical shift and the splitting pattern.

By assuming that in the structures of all the sulfoxides investigated, 10b substituent occupies the ψ-axial β orientation (10b*R* *) it was possible, by applying the NOE difference experiments, to prove in all instances, that the 2Hβ and $5H_a$ axial proton are also on the same (β) face of the molecule (Fig. 1).

The benzylic 10bH proton in the spectra of all sulfoxides absorbs as a singlet in a narrow region 5.43–5.65 ppm; while the $10bCH_3$ substituent between 1.73 and 1.88 ppm. A shielding effect of the 10b substituent could be seen when comparing the spectra with those of the precursor sulfides **1**.[1] The methylene group protons of the five-membered lactam ring in **3a**, **b** and **4a**, **b** are non-equivalent and give rise to two geminally coupled doublets (^2J=ca. 16 Hz), from which the 2Hβ proton in *anti* isomers, **3b**, **4b**, absorbs at a lower field, while in *syn*, **3a**, **4a**, at higher field.

According to the NOE experiments, the 2H proton in diastereomers **5b**, **6b** and **7b** occupies the β position (2*S* *) and appears as a quartet (^3J=ca. 7 Hz) at 3.62–3.73 ppm, showing a long-range coupling with the $5H_a$ proton (^5J=ca. 1 Hz). Thus, the *anti* relationship between the 10b substituent and the $2CH_3\alpha$ methyl group in **5b**, **6b**, **7b** could be accepted.

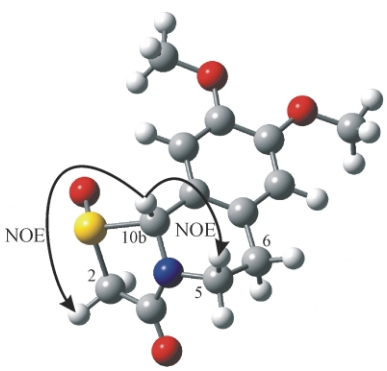


Figure 1.

To determine the configuration around the third stereogenic center, that is the chiral sulfur in sulfoxides **5b**, **6b**, **7b**, the magnetic anisotropy effect of the sulfinyl function was analyzed. This effect has been reported,[7,8] to be analogous to that of the acetylenic (C≡C) triple bond, according to which a proximate proton situated *syn*–*axial* to the S–O bond in a cyclic system should be deshielded, while that in *anti* position—shielded, when compared with the absorption of these protons in spectra of the unoxidized compounds. Since, in spectra of the three sulfoxides, **5b**, **6b** and **7b** the absorption of the 2Hβ proton and the 10b substituent (10bH in **5b** and **6b**; $10bCH_3$ in **7b**) suffered the upfield shift, while that of the $2CH_3\alpha$ group the downfield shift (Table 4) we proposed the 1*S* * (α) stereochemistry of the stereogenic sulfur, that is the 1,10b-*anti*/2,10b-*anti* (1*S* *, 2*S* *, 10b*R* *) configuration of these sulfoxides.

To complete the spectral characteristics of the sulfoxides studied, it should be added that the four ethylene bridge protons of the isoquinoline part of the molecules form a clear-cut ABMX system, in which the equatorial $5H_e$ proton is shifted by more than 1.5 ppm downfield from the others, due to the deshielding effect of the amide carbonyl. By examining the values of its three coupling constants: the geminal, the equatorial–axial and the equatorial–equatorial it was possible to assign absorption to each of the other three ethylene protons, confirmed also by 2D NMR techniques.

Some of the ^{13}C NMR spectral data of selected sulfoxides are listed in Table 5. The assignments were made by analogy to those reported for thiazolinone derivatives[9] and on the knowledge that oxidation of sulfur in this heterocyclic system causes a deshielding effect of carbon atoms at the α position to the sulfinyl function by ca. 20–25 ppm, and shielding of those at the β position, by ca. 4–9 ppm. Indeed, a downfield shift of the absorption in going from sulfides **1** to sulfoxides **3**–**7** (Table 5) can be observed for the 2C and 10bC carbon atoms, while the 3C atom suffers a small shielding effect.

It is also evident (Table 5) that the shielding effect seen by 2C is stronger in *anti* isomers (**3b**, **4b**), while the shielding of 10bC and deshielding of 3C are stronger in *syn* isomers (**3a**, **4a**). Absorption of the tetrahydroisoquinoline moiety was found in the region characteristic of this heterocyclic system.[10,11]

Electron impact mass spectral data of sulfoxides **3**–**7** (Table 6) reveal the presence of stable molecular ions (M^+) of high abundance, from which the molecular formula was

established by HRMS. The main fragmentation pathway was associated with initial elimination of the SO fragment from the molecular ion to give the $[M-SO]^+$ ions, which on losing ketene molecule, lead to [M−(SO+RCH═CO)] ions of dihydroisoquinolinium structure, being the base peaks. In the spectra of sulfoxides bearing a methyl substituent at 2C, a parallel fragmentation with the lost of ethylene molecule resulted in the formation of $[M-(SO+CH_2{=}CH_2)]$ ions of low intensity, except for compound **5**, where this ion was the base peak. The mass spectra of the diastereomeric sulfoxides did not reveal significant differences.

The absorption of the amide carbonyl in the IR spectra of sulfoxides **3**–**7** was found at higher wavenumbers (1681–1712 cm^{-1}) than those of the parent sulfides **1** (1670–1683).[1] We noticed that of the two pairs of available diastereomers, **3a**, **b** and **4a**, **b**, the **a**-type (*syn*) isomers absorb in a higher region (1711 and 1681 cm^{-1}) than the **b** (*anti*) ones (1688 and 1674 cm^{-1}).

Having established the relative configuration of the diastereomeric sulfoxides, and the fact that the *anti*-isomers (**b**-type) were the main components present in the oxidation products, we considered them at first to be the thermodynamic products. This also seemed to follow from the course of oxidation, monitored by TLC, during which the *syn*-diastereomers (**a**-type) were initially formed, due to the attack of the oxidizing agent from the less hindered β-face of the molecule (steric approach control). With the progress of the reaction the *syn* isomers were disappearing at the expense of the *anti* ones (**b**-type), to finally reach an equilibrium which in the case of sulfoxides **3a**, **b** stopped at ca 1:3.3 *syn*/*anti* ratio. The same equilibrium was formed when pure *syn*-**3a** was dissolved in chloroform, acetonitrile or methanol. Dissolution of the *anti*-**3b** in the same solvents resulted in the same 1:3.3 *syn*/*anti* position of equilibrium.

Similar reversible isomerization of diastereomeric sulfoxides has been observed in other cyclic systems as well, e.g. in 2-methylthiolane *S*-oxides[12] and some penicilline-derived sulfoxides.[13] Several mechanistic pathways for interconversion of stereoisomeric sulfoxides occurring under acid catalysis, often accompanied by racemization of optically active derivatives, have been postulated, suggesting isomerization at sulfur, in most cases.[12,14] To gain insight into the process observed during our experiments with thiazoloisoquinoline *S*-oxides, we were interested to learn about the thermodynamic stability of both diastereomers. It turned out, according to some theoretical calculations performed with the use of AM-1 (Mopac 6.0) and DFT programs (B3Lyp/6-31G*), that the *syn*-**3a** iosomer energy was lower by ca 3.1 kcal/mol (AM-1) or ca 4.7 kcal/mol (DFT) than that of the corresponding *anti*-**3b** diastereomer. Therefore, the position of the equilibrium, strongly favoring the *anti* isomers had to be considered. We have come to a conclusion, that a mechanism involving isomerization at the 10bC carbon atom rather then at the sulfinic sulfur was operating in this heterocyclic system. So, assuming a deprotonation–protonation process with 10bH proton abstraction-return, the dominance of the *anti*-diastereomers could be rationalized as resulting from a preferential proton approach from the less hindered α-side of the sulfonium ylide, e.g. opposite to that shielded by the

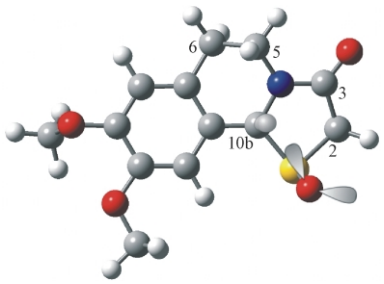


Figure 2.

sulfinyl oxygen (Fig. 2). This hypothesis could be supported by some observations made in this work. First of all, sulfoxides **4a**, **b** with methyl substituent at the 10bC carbon atom did not tend to isomerize. A deutertion experiment with D_2O performed in the NMR tube on a mixture of **3a**, **b** (1:3.3) dissolved in $CDCl_3$, resulted in a decreased 10bH proton absorption (at 5.65 and 5.48 ppm, respectively) by ca. 33%, after 4 days. It was noticed that in all cases of isomerization, found to take place also in the solid state, no side-products were formed.

3. Conclusion

A series of dihydrothiazolo[2,3-*a*]isoquinolinone sulfoxides (**3**–**7**), a class of compounds that has not been fully characterized until now, has been synthesized and their steric structure established with the help of combined X-ray crystallographic and spectral data analysis.

Oxidation with peroxy reagents of sulfur to sulfinyl function in the parent thiazoloisoquinolines **1** was found to be a diastereoselective process in which the *syn*-diastereomers (**a**-type) were the kinetically favored products, also shown by theoretical calculations to be the thermodynamically more stable compounds. They easily underwent isomerization to reach an equilibrium in which the *anti*-isomers (**b**-type) were dominant, due to steric rather then thermodynamic reasons.

Although no unambiguous criteria helpful in discriminating between diastereomeric sulfoxides could be established on the basis of the spectral data, some other suggestive observations have been made. Thus, the 1,10b-*syn* isomers were always the first ones to be formed during the oxidation with peroxy-reagents, they were the less polar (TLC) and of lower mp's.

4. Experimental

4.1. General

Melting points were determined on a Kofler block and were not corrected. IR spectra were recorded on Perkin–Elmer 180, in KBr pellets. NMR spectra were taken in $CDCl_3$ and DMSO-d_6 on Varian Gemini 300 (^1H, 300.07 MHz; ^{13}C, 75.45 MHz), with TMS as internal standard. Mass spectra (EI) and FAB techniques were obtained by using Joel D-100, 75 eV. For FAB-mass spectra, 3-nitrobenzyl alcohol was used as a matrix. Merck Silica gel 60 (70–230 mesh)

was used for column chromatography and Merck DC-Alufolien Silica gel 60_{254} for TLC.

4.2. Oxidation of thiazoloisoquinolinones 1. General procedures

4.2.1. *A*-oxidizing system. *m*CPBA (1.1 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a solution of thiazoloisoquinolinone **1** (1.0 mmol) in CH_2Cl_2 (8 ml) at 0°C. The mixture was stirred at 0°C until no more starting material was present (TLC); e.g. for a time specified in Table 1. The precipitated *m*-chlorobenzoic acid was filtered off, the filtrate was washed with 10% K_2CO_3, water and dried. The solvent was evaporated and the crude product was purified by crystallization.

4.2.2. *B*/*C*-oxidizing systems. To a solution of thiazoloisoquinolinone **1** (2 mmol) in chloroform/methanol 2:1 (15 ml) 30% hydrogen peroxide (1.5 ml) was added during 2–5 min. at 0°C. The mixture was allowed to warm to RT and stirred at this temperature (*B*-system) or at reflux (*C*-system) for the time given in Table 1. After that time water (15 ml) was added and the mixture was extracted with chloroform. The organic phase was dried, the solvent evaporated and the crude product was purified by crystallization or column chromatography on silica gel (CH_2Cl_2/methanol 100:1).

4.2.3. *D*-oxidizing system. A mixture of oxone (1.1 mmol) in water (3 ml) and thiazoloisoquinolinone **1** (1.0 mmol) in chloroform/methanol 2:1 (10 ml) was stirred at 0°C for the time given in Table 1. Then water (10 ml) was added and extracted with chloroform. The organic phase was washed with water, dried and the solvent was evaporated to give crude product, which was crystallized from ethanol.

4.2.4. *syn*-8,9-Dimethoxy-6,10b-dihydro-1-oxo-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (3a). Less polar isomer; yield 31–35% (D); colourless solid from CCl_4, mp 164–167°C; IR (cm^{-1}): 1711; ^1H NMR (DMSO-d_6) δ 2.68–2.72 (2H, m, CH_2CH_2N), 2.97 (1H, dt, J=12.3, 3.9 Hz, CH_2-C*H*HN), 3.75 and 3.76 (6H, 2s, OCH_3), 3.98 (1H, d, J=14.5 Hz, SC*H*HCO), 4.15 (1H, d, J=14.5 Hz, SCH*H*CO), 4.26 (1H, ddd, J=12.3, 4.6, 2.1 Hz, CH_2-CH*H*N), 5.61 (1H, s, SC*H*N), 6.87 and 6.95 (2H, s, ArH); ^{13}C NMR δ 28.03, 38.1, 55.2, 56.02, 56.21, 79.3, 108.18, 111.87, 119.6, 126.43, 131, 149.55, 164.29; HRMS calcd for $C_{13}H_{15}NO_4S$ (M^+): 281.0731, found: 281.0722.

4.2.5. *anti*-8,9-Dimethoxy-6,10b-dihydro-1-oxo-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (3b). More polar isomer; yield 75% (B); colourless crystals, mp 212–214°C (chloroform/methanol 2:1); IR (cm^{-1}): 1688; ^1H NMR δ 2.67–2.74 (1H, m, C*H*HCH$_2$N), 2.96 (1H, dt, J=15.0, 12.4, 4.7 Hz, CH*H*CH$_2$N), 3.09 (1H, dt, J=12.4, 3.2 Hz, CH_2-C*H*HN), 3.69 (1H, d, J=16.6 Hz, SC*H*HCO), 3.77 (1H, d, J=16.6 Hz, SCH*H*CO), 3.89 and 3.91 (6H, 2s, OCH_3), 4.55 (1H, ddd, J=12.4, 4.7, 1.6 Hz, CH_2CH*H*N), 5.65 (1H, s, SC*H*N), 6.7 and 6.79 (2H, s, ArH); ^{13}C NMR δ 28.34, 39.54, 55.7, 56, 56.14, 76.8, 108.65, 112.32, 116.44, 123.38, 130.34, 148.81, 167.1; HRMS calcd for $C_{13}H_{15}NO_4S$ (M^+): 281.0731, found: 281.0726.

4.2.6. *syn*-8,9-Dimethoxy-10b-methyl-1-oxo-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (4a). Less polar isomer; yield 45% (D); yellow crystals, mp 167–169°C (96% ethanol); IR (cm^{-1}): 1681; ^1H NMR δ 1.88 (3H, s, SC(CH_3)N), 2.69–2.75 (1H, m, C*H*HCH$_2$N), 2.87 (1H, dt, J=16.7, 12.9, 5.8 Hz, CH*H*CH$_2$N), 3.07 (1H, dt, J=12.9, 4.4 Hz, CH_2C*H*HN), 3.64 (1H, d, J=15.6 Hz, SC*H*HCO), 3.88 and 3.89 (6H, 2s, OCH_3), 3.95 (1H, d, J=15.6 Hz, SCH*H*CO), 4.55 (1H, ddd, J=12.9, 5.8, 1.6 Hz, CH_2CH*H*N), 6.61 and 6.84 (2H, s, ArH); ^{13}C NMR δ 20.15, 27.93, 36.65, 52.72, 55.84, 56.15, 81.69, 107.43, 111.39, 125.39, 127.16, 148.38, 148.53, 162.6; HRMS calcd for $C_{14}H_{17}NO_4S$ (M^+): 295.0878, found: 295.0896.

4.2.7. *anti*-8,9-Dimethoxy-10b-methyl-1-oxo-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (4b). More polar isomer; yield 43% (B); colourless crystals, mp 198–199°C (96% ethanol); IR (cm^{-1}): 1674; ^1H NMR δ 1.73 (3H, s, SC(CH_3)N), 2.72 (1H, ddd, J=15.3, 3.2, 1.5 Hz, C*H*HCH$_2$N), 3.00 (1H, dt, J=15.3, 12.4, 4.9 Hz, CH*H*CH$_2$-N), 3.13 (1H, dt, J=12.4, 3.2 Hz, CH_2C*H*HN), 3.57 (1H, d, J=16.9 Hz, SC*H*HCO), 3.87 and 3.92 (6H, 2s, OCH_3), 3.9 (1H, d, J=16.9 Hz, SCH*H*CO), 4.52 (1H, ddd, J=12.4, 4.9, 1.5 Hz, CH_2CH*H*N), 6.66 and 6.72 (2H, s, ArH); ^{13}C NMR δ 23.74, 28.46, 37.6, 53.97, 55.84, 56.09, 76.59, 108.65, 111.95, 122.2, 129.39, 148.39, 149.16, 166.29; HRMS calcd for $C_{14}H_{17}NO_4S$ (M^+): 295.0878, found: 295.0901.

4.2.8. 1,10b-*anti*/2,10b-*anti*-2-Methyl-1-oxo-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (5b). More polar isomer; yield 54% (C); colourless solid, mp 181–183°C; IR (cm^{-1}): 1685; ^1H NMR δ 1.62 (3H, d, J=7.4 Hz, SCH(CH_3)CO), 2.78 (1H, dt, J=15.6, 2.7 Hz, C*H*HCH$_2$N), 2.98 (1H, ddd, J=15.6, 12.3, 4.9 Hz, CH*H*CH$_2$N), 3.11 (1H, dt, J=12.3, 2.7 Hz, CH_2C*H*HN), 3.63 (1H, q, J=7.4 Hz, SC*H*(CH$_3$)CO), 4.54 (1H, ddd, J=12.3, 4.9, 2.7 Hz, CH_2-CH*H*N), 5.65 (1H, s, SC*H*N), 7.2–7.45 (4H, m, ArH); HRMS calcd for $C_{12}H_{13}NO_2S$ (M^+): 235.0667, found: 235.067.

4.2.9. 1,10b-*anti*/2,10b-*anti*-8,9-Dimethoxy-2-methyl-1-oxo-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (6b). More polar isomer; yield 52% (C); colourless crystals, mp 207–209°C (methanol); IR (cm^{-1}): 1712; ^1H NMR δ 1.62 (3H, d, J=7.3 Hz, SCH(CH_3)CO), 2.67–2.75 (1H, m, C*H*HCH$_2$N), 2.94 (1H, dt, J=15.6, 12.6, 5.1 Hz, CH*H*CH$_2$-N), 3.08 (1H, dt, J=12.6, 2.6 Hz, CH_2C*H*HN), 3.62 (1H, q, J=7.3 Hz, SC*H*(CH$_3$)CO), 3.88 and 3.91 (6H, 2s, OCH_3), 4.52 (1H, ddd, J=12.6, 5.1, 1.4 Hz, CH_2CH*H*N), 5.59 (1H, s, SC*H*N), 6.68 and 6.82 (2H, s, ArH); ^1C NMR δ 7.32, 28.28, 39.6, 55.94, 55.97, 58.95, 74.08, 108.69, 112.18, 116.46, 130.21, 148.69, 149.39, 170.39; HRMS calcd for $C_{14}H_{17}NO_4S$: 295.0878, found: 295.0867.

4.2.10. 1,10b-*anti*/2,10b-*anti*-8,9-Dimethoxy-2,10b-dimethyl-1-oxo-6,10b-dihydro-5*H*-thiazolo[2,3-*a*]isoquinolin-3-one (7b). More polar isomer; yield 34% (B); colourless oil; IR (cm^{-1}): 1682; ^1H NMR δ 1.59 (3H, d, J=7.4 Hz, SCH(CH_3)CO), 1.76 (1H, s, SC(CH_3)N), 2.66–2.72 (1H, m, C*H*HCH$_2$N), 2.91–3.08 (1H, m, CH*H*CH$_2$N), 3.15 (1H, dt, J=12.5, 2.7 Hz, CH_2C*H*HN), 3.73 (1H, q, J=7.4 Hz, SC*H*(CH$_3$)CO), 3.86 and 3.88 (6H, 2s, OCH_3), 4.5 (1H, ddd, J=12.5, 5.2, 1.4 Hz, CH_2CH*H*N), 6.64 and

6.69 (2H, s, ArH); HRMS calcd for $C_{15}H_{19}NO_4S$: 309.1035, found: 309.1013.

Acknowledgements

This work was financially supported by KBN grant no. 3 T09A 026 17 and 3 T09A 027 17. The authors wish to thank Dr Piotr Fiedorow for having performed necessary quantum chemical calculations.

References

1. Rozwadowska, M. D.; Sulima, A. *Tetrahedron* **2001**, *57*, 3499–3506.
2. Rozwadowska, M. D.; Sulima, A.; Gzella, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2329–2333.
3. Schneider, W.; Kammerer, E. *Arch. Pharm.* **1966**, *299*, 847–857.
4. Rozwadowska, M. D.; Sulima, A. *Polish J. Chem.* **2001**, *75*, 1847–1852.
5. Nair, M. D.; Malik, P. A.; Mehta, S. R. *Indian J. Chem.* **1967**, *5*, 221–223.
6. Gzella, A.; Rozwadowska, M. D.; Sulima, A. *Acta Crystallogr. Sect. C* **2001**, *57*, 1454–1456.
7. Sollman, P. B.; Nagarajan, R.; Dodson, R. M. *Chem. Commun.* **1967**, 552–554.
8. Kondo, K.; Negishi, A. *Tetrahedron* **1971**, *27*, 4821–4830.
9. Woolston, C. R. J.; Lee, J. B.; Swinbourn, F. J. *Magn. Reson. Chem.* **1993**, *31*, 348–351.
10. Hughes, D. W.; Holland, H. L.; MacLean, D. B. *Can. J. Chem.* **1976**, *54*, 2252–2259.
11. Menachery, M. D.; Lavanier, G. L.; Wetherby, M. L. J. *Nat. Prod.* **1986**, *49*, 745–778.
12. Rigan, J. J.; Bacon, C. C.; Johnson, C. R. *J. Org. Chem.* **1970**, *35*, 3655–3657.
13. Harrison, C. R.; Hodge, P. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1772–1775.
14. Tillet, J. G. *Chem. Rev.* **1976**, *76*, 750–757.