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An unexpected isomerization of 1,3-benzothiazine and isoquinoline-condensed β-lactams

Lajos Fodor [a,b,*], Péter Csomós [a,b], Ferenc Fülöp [b], Antal Csámpai [c,**], Pál Sohár [c,d,***]

[a] Central Laboratory, County Hospital, H-5701 Gyula, POB 46, Hungary
[b] Institute of Pharmaceutical Chemistry, University of Szeged and Research Group of Stereochemistry of the Hungarian Academy of Sciences, H-6720, Szeged, Eötvös u. 6., Hungary
[c] Institute of Chemistry, Eötvös Loránd University, H-1518 Budapest, POB 32, Hungary
[d] Protein Modelling Research Group, Hungarian Academy of Sciences and Eötvös Loránd University, H-1518 Budapest, POB 32, Hungary

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ABSTRACT

A series of novel aryl-substituted β-lactams condensed with 1,3-benzothiazines, isoquinolines or 1,4-benzothiazepine were obtained by means of the Staudinger reaction and isomerized in the presence of sodium methoxide to the thermodynamically more stable form. The structures of the new molecules were determined by NMR spectroscopy. Theoretical calculations corroborate the experimentally observed structure–reactivity relationships.

1. Introduction

Since the discovery of penicillin, β-lactams (including penicillins, cephalosporins, monobactams, and carbapenems) have become a major class of antibacterial agents. Because of their widespread use, bacterial resistance has developed into a major health problem worldwide during the past few decades [1]. This has motivated growing interest in the preparation and biological evaluation of new types of β-lactams [2]. Moreover, some derivatives possess various other useful pharmacological effects. They include, for example, inhibitors of human leucocyte elastase [3a,b], cholesterol acyl transferase [3c] and thrombin [3d]. From a synthetic aspect, azetidin-2-one derivatives are versatile intermediates in the construction of complex heterocycles [4], non-proteogenic amino acid derivatives, peptides and peptide turn mimetics [5]. They can be utilized in the synthesis of different natural compounds, such as apiosporamide or taxol derivatives [6]. In the former compounds, which contain a relatively strained β-lactam structural unit, the reactions with nucleophilic reagents usually take place at the N1–C2 bond. Further, some β-lactam derivatives (*e.g.* α-halo-β-lactams) are versatile synthons that furnish a wide variety of functionalized lactams [7].

The reaction most widely used for the construction of azetidinone rings is the [2 + 2] ketene-imine cycloaddition known as the Staudinger reaction [2]. Several variants of this reaction have been described, in which the ketene is formed *in situ* from precursors [2,8]. The reactions of monosubstituted ketene with imines furnish two new stereogenic centres, and thus *cis*-, *trans*- or a mixture of *cis*- and *trans*-azetidinones can be obtained as products. The selectivity is therefore one of the critical issues in the Staudinger reaction [9]. For acyclic imines, a mixture of *cis*- and *trans*-azetidinones can be formed, via isomerization of the zwitterionic intermediate, whereas in the case of cyclic imines, most often only one product (*cis* or *trans*) can be isolated selectively, depending on the imine [9].

From a pharmacological aspect, there are examples where the Staudinger product is the biologically active isomer [3a]. In contrast, however, there are many examples where the Staudinger product is not the effective isomer. When penicillins or cephalosporins are prepared by the cycloaddition of protected glycines to thiazoline or thiazine rings, the newly created stereochemistry of the lactam H atoms is *trans* rather than *cis*, as in the natural substances. The *trans* isomers are biologically inactive. Isomers with antibacterial activity can be prepared only by different methods or in rare cases by epimerization [10].

* Corresponding author at: Central Laboratory, County Hospital, H-5701 Gyula, POB 46, Hungary. Tel.: +36 66 463763; fax: +36 66 526539.
** Corresponding author. Tel.: +36 1 3722911; fax: +36 1 3722592.
*** Corresponding author at: Institute of Chemistry, Eötvös Loránd University, H-1518 Budapest, POB 32, Hungary. Tel.: +36 1 3722911; fax: +36 1 3722592.
E-mail addresses: fodor@pandy.hu (L. Fodor), csampai@chem.elte.hu (A. Csámpai), sohar@chem.elte.hu (P. Sohár).

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In an earlier paper [11], we reported on the mechanisms of the reactions between differently substituted 4-thia analogues of isoquinolines, 4*H*- and 2*H*-1,3-benzothiazine derivatives and substituted acetyl chlorides. The selectivities of the reactions and the stereochemistry of the linearly or angularly condensed β-lactams formed were also extensively studied [12]. In our model systems, the substituents in the newly formed stereocentres were found in the *cis* position to each other in all cases.

In contrast with the growing interest in investigations of β-lactam transformations [2], only few examples are known of the *cis–trans* isomerization of the Staudinger products [13]. As a continuation of our investigations on *S*- and *N*-containing condensed-skeleton heterocycles [14] and azetobenzothiazines [12], it seemed worthwhile to study the Staudinger reactions of various 2*H*-1,3-benzothiazines and to devise an isomerization procedure for the β-lactams obtained. A further aim was to extend our investigations to model compounds such as azetoisoquinolines and azeto-1,4-benzothiazepines.

2. Experimental

2.1. Materials and methods

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F_{254} plates were used for TLC, and Merck Silica gel 60 (0.063–0.100) for column chromatography. Azeto-1,3-benzothiazines (**2a** and **3a**) [11,12b], and azetoisoquinoline (**5a**) [15] were prepared by literature methods.

The structures of the simplified models optimized by the B3LYP/6-31 G(d) method collected on (Fig. 1) are available from the authors on request. All calculations were carried out with the Gaussian 03 suite of programs [16].

IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500.13 (^{1}H) and 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT.AU was used to generate NOE. DEPT spectra were run in a standard manner, using only the $\Theta = 135^\circ$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs.

2.2. Synthesis

The cycloadditions of 4-phenyl-1,3-benzothiazine **1** with substituted phenylacetyl chlorides in refluxing toluene in the presence of triethylamine stereoselectively provided lactams **2a–d**, in which the 9b-phenyl is *cis* to the 1-phenyl group (Scheme 1) [17]. Interestingly, the treatment of **2a–d** with an equivalent amount of sodium methoxide in refluxing methanol furnished **3a–d**; in the latter compounds, the 9b-phenyl proved to be *trans* to the 1-phenyl group. The isomerization proceeded almost quantitatively.

In most reports on the azetoisoquinolines, the Staudinger reaction yields only one isomer; the stereochemistry or transformations of these azetidinone derivatives have been investigated in only a few cases [18]. In our case, when the reaction was carried out in refluxing toluene, azeto[2,1-*a*]isoquinolin-2-one derivatives (**5a–d**) were obtained in good yields (Scheme 2).

Similarly to azetobenzothiazines, the treatment of **5a–d** with catalytic amount of sodium methoxide (0.25 equiv.) in refluxing methanol led to partial isomerization. The latter isomerization is one of the rare transformations of β-lactams. Thus, **6a–d** could be prepared after separation from the starting **5a–d** by colomn chromatography in 28–45% yields (Scheme 2). When equivalent amounts of sodium methoxide were used in the latter isomerization reactions, mainly **4** could be isolated as decomposition product.

In the case of azeto[2,1-*d*][1,4]benzothiazin-2-one **8**, obtained from thiazepine **7**, no isomerization was observed under different basic conditions. After several days reflux only the starting **8** β-lactam could be isolated from the reaction mixture (Scheme 3).

2.2.1. General procedure for the preparation of cis-azetobenzothiazines (**2b–d**) and cis-azetobenzothiazepine (**8**)

To a stirred solution of 6,7-dimethoxy-4-phenyl-1,3(2*H*)-benzothiazine **1** (2.85 g, 10 mmol) or 6,7-dimethoxy-4-phenyl-1,4-benzothiazepine **7** (2.99 g, 10 mmol) in anhydrous toluene (30 mL), the appropriate acid chloride derivative (10 mmol) was added. The solution was refluxed and triethylamine (1.4 mL, 10 mmol) in anhydrous toluene (50 mL) was added dropwise during 1 h under reflux. The reaction mixture was then cooled and extracted in turn with 5% Na_2CO_3 solution (20 mL), 5% HCl (20 mL) and brine (20 mL), and the organic layer was dried with Na_2SO_4. After evaporation, the residue was taken up in ethanol, and the crystalline product was filtered off and recrystallized.

2.2.1.1. (1R,9bS*)-7,8-dimethoxy-1-(4-chlorophenyl)-9b-phenyl-1,9b-dihydro-2H,4H-azeto[2,1-a][1,3]benzothiazin-2-one (**2b**).* A white crystalline powder; mp 198–201 °C (from ethanol); 4.10 g, 94%; R_f (80%, toluene:ethanol 9:1). Anal. Calcd. for $C_{24}H_{20}ClNO_3S$ (437.94): C, 65.82; H, 4.60; N, 3.20; S, 7.32. Found: C, 65.67; H, 4.48; N, 3.12; S, 7.11%.

2.2.1.2. (1R,9bS*)-7,8-dimethoxy-1-(4-fluorophenyl)-9b-phenyl-1,9b-dihydro-2H,4H-azeto[2,1-a][1,3]benzothiazin-2-one (**2c**).* A white crystalline powder; mp 174–176 °C (from ethanol); 4.05 g, 96%; R_f (82%, toluene:ethanol 9:1). Anal. Calcd. for $C_{24}H_{20}FNO_3S$ (421.48): C, 68.39; H, 4.78; N, 3.32; S, 7.61. Found: C, 68.24; H, 4.71; N, 3.51; S, 7.83%.

2.2.1.3. (1R,9bS*)-7,8-dimethoxy-1-(4-methoxyphenyl)-9b-phenyl-1,9b-dihydro-2H,4H-azeto[2,1-a][1,3]benzothiazin-2-one (**2d**).* A white crystalline powder; mp 167–169 °C (from ethanol); 3.90 g, 90%; R_f (75%, toluene:ethanol 9:1). Anal. Calcd. for $C_{25}H_{23}NO_4S$ (433.52): C, 69.26; H, 5.35; N, 3.23; S, 7.40. Found: C, 69.47; H, 5.55; N, 12; S, 7.55%.

2.2.1.4. (1R,9bS*)-8,9-dimethoxy-1,10b-diphenyl-1,4,5,10b-tetrahydro-2H-azeto[2,1-d][1,4]benzothiazepin-2-one (**8**).* A white crystalline powder; mp 206–207 °C (from ethanol; Lit. [12d] mp 205–206 °C); 3.60 g, 87%; R_f (85%, toluene:ethanol 9:1). Anal. Calcd. for $C_{25}H_{23}NO_3S$ (417.52): C, 71.92; H, 5.55; N, 3.35; S, 7.68. Found: C, 72.14; H, 5.42; N, 3.51; S, 7.54%.

2.2.2. General procedure for the preparation of trans-azetobenzothiazines (**3b–d**)

To a stirred solution of *cis*-azetobenzothiazines **(2a–d)** (5 mmol) in anhydrous methanol (30 mL), NaOMe (0.27 g, 5 mmol) was added. The reaction mixture was refluxed for 3 h. After evaporation of the solvent to 5 ml, the product crystallized out.

2.2.2.1. (1S,9bS*)-7,8-dimethoxy-1-(4-chlorophenyl)-9b-phenyl-1,9b-dihydro-2H,4H-azeto[2,1-a][1,3]benzothiazin-2-one (**3b**).* A white crystalline powder; mp 145–147 °C (from ethanol); 1.84 g, 84%; R_f (85%, toluene:ethanol 9:1). Anal. Calcd. for $C_{24}H_{20}ClNO_3S$ (437.94): C, 65.82; H, 4.60; N, 3.20; S, 7.32. Found: C, 65.67; H, 4.65; N, 3.08; S, 7.11%.

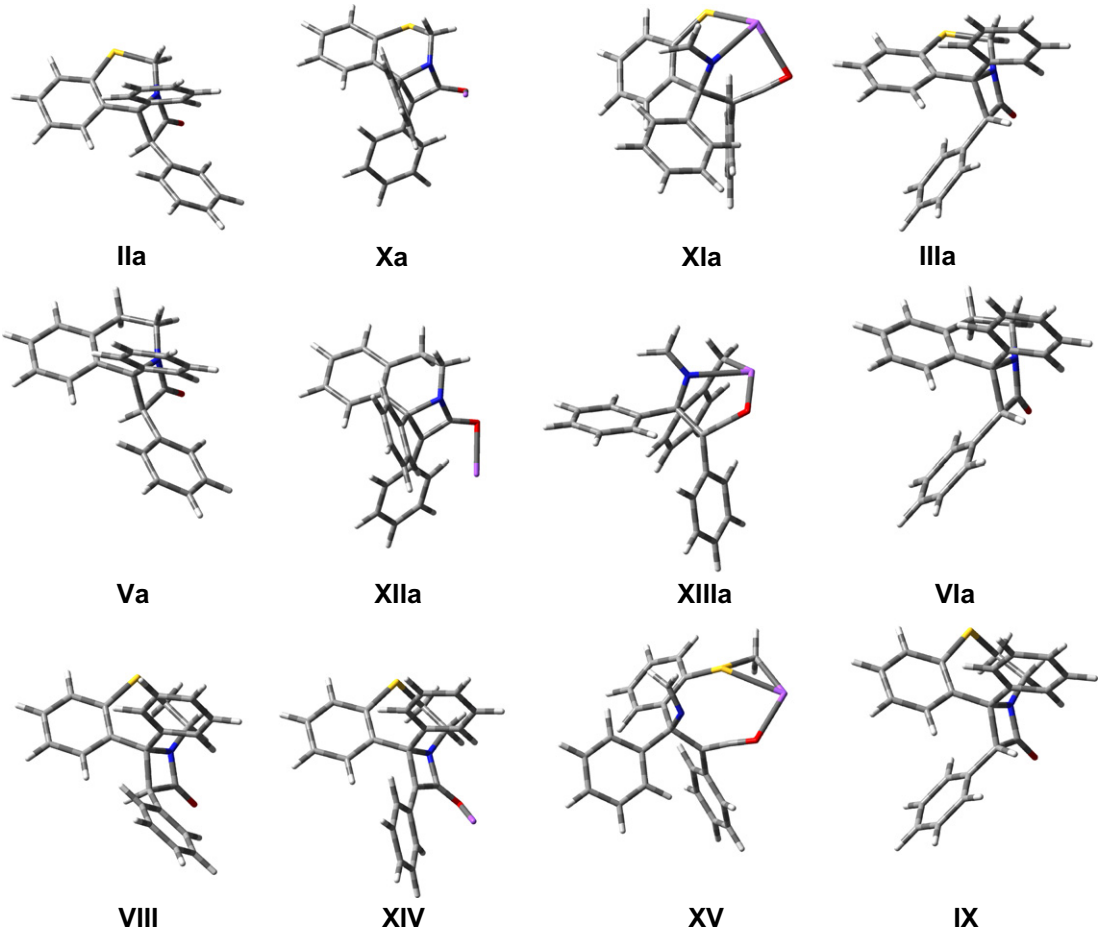
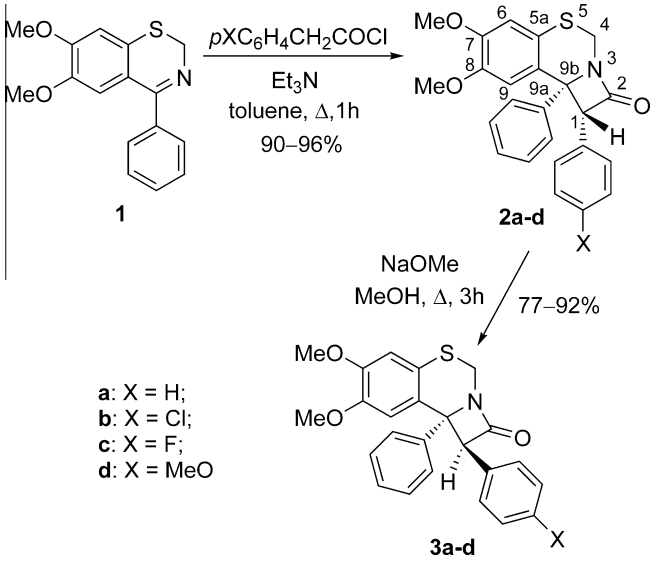
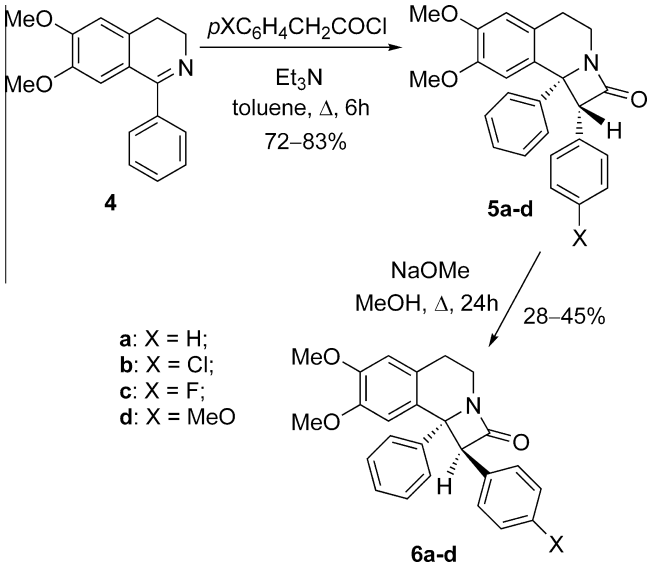


Fig. 1. Optimized structures [B3LYP/6-31 G(d)] of the simplified models of *cis* and *trans* diphenyl-substituted β-lactams and the possible intermediates involved in the epimerizations.

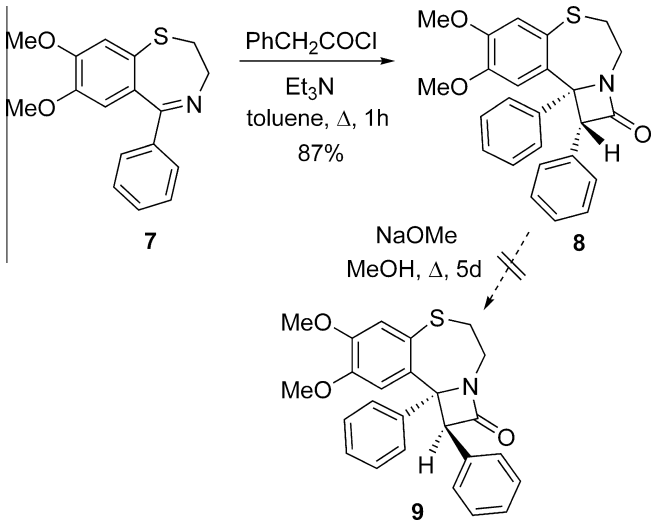


Scheme 1. Preparation and isomerization of azeto[1,2-*c*][1,3]benzothiazin-2-one derivatives **3a–d**.



Scheme 2. Preparation and isomerization of azeto[2,1-*a*]isoquinolin-2-one derivatives **5a–d**.

2.2.2.2. (1S,9bS*)-7,8-dimethoxy-1-(4-fluorophenyl)-9b-phenyl-1,9b-dihydro-2H,4H-azeto[2,1-a][1,3]benzothiazin-2-one (**3c**).* A white crystalline powder; mp 168–171 °C (from ethanol); 1.94 g, 92%; R_f (87%, toluene:ethanol 9:1). Anal. Calcd. for $C_{24}H_{20}FNO_3S$ (421.48): C, 68.39; H, 4.78; N, 3.32; S, 7.61. Found: C, 68.21; H, 4.61; N, 3.53; S, 7.45%.

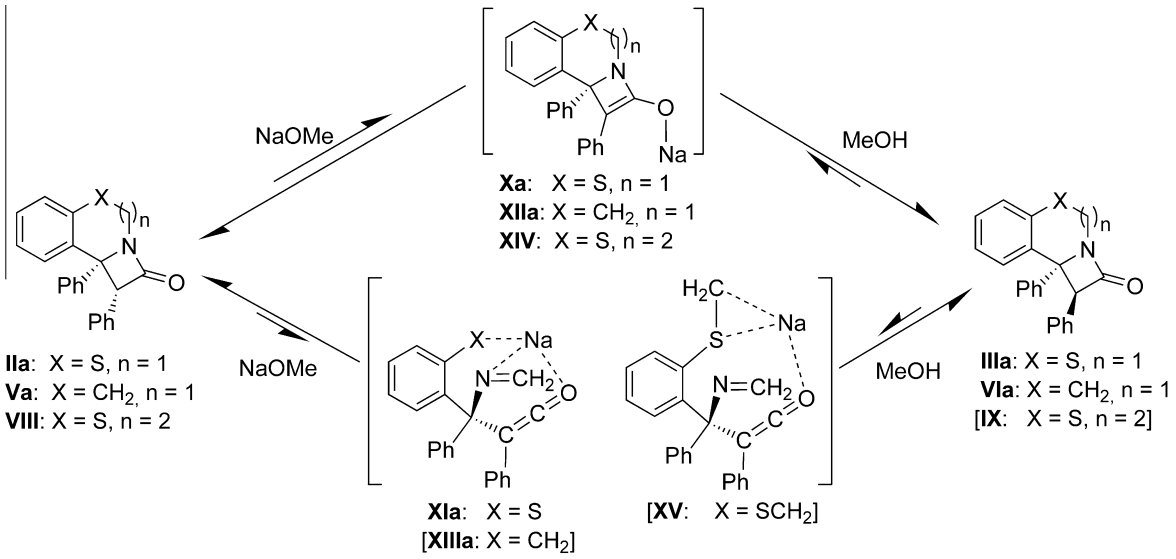


Scheme 3. Preparation of azeto[1,2-*d*][1,4]benzothiazepine derivative **8**.

2.2.2.3. (1S,9bS*)-7,8-dimethoxy-1-(4-methoxyphenyl)-9b-phenyl-1,9b-dihydro-2H,4H-azeto[2,1-a][1,3]benzothiazin-2-one (**3d**).* A white crystalline powder; mp 172–173 °C (from ethanol); 1.67 g, 77%; R_f (80%, toluene:ethanol 9:1). Anal. Calcd. for $C_{25}H_{23}NO_4S$ (433.52): C, 69.26; H, 5.35; N, 3.23; S, 7.40. Found: C, 69.47; H, 5.18; N, 3.39; S, 7.61%.

*2.2.3. General procedure for the preparation of cis-azetoisoquinolines (**5b–d**)*

To a stirred solution of 1-phenyl-6,7-dimethoxy-3,4-dihydroisoquinoline **4** (1.0 mmol) in anhydrous toluene (30 mL), triethylamine (0.14 mL, 1.0 mmol) was added. The solution was refluxed and the appropriate acid chloride derivative (1.0 mmol) in anhydrous toluene (50 mL) was added dropwise during 3 h under reflux. The addition of the appropriate acid chloride derivative (1.0 mmol) and triethylamine (0.14 mL, 1.0 mmol) was repeated once under the same conditions as above. The reaction mixture was then cooled and extracted in turn with 5% Na_2CO_3 solution (20 mL), 5% HCl (20 mL) and brine (20 mL), and the organic layer was dried with Na_2SO_4. After evaporation, the residue was taken up in diisopropyl ether, and the crystalline product was filtered off and recrystallized.



Scheme 4. Possible pathways of the base-catalysed isomerization of *cis* β-lactams **IIa**, **Va** and **VIII**.

Table 1
Energetic data on the model *cis* and *trans* β-lactams (**IIa, IIIa, Va, VIa, VIII, IX**) and the possible intermediates (**Xa, XIa, XIIa, XIIIa, XIV, XV**) calculated on the optimized structures by the B3LYP-6-31 G(d) method.

Model compound	Total energy [au] *in vacuo*	Δ*E*(*cis*–*trans*) [kJ/mol]	Total energy in MeOH [au][a]	Δ*E*(*cis*–*trans*) in MeOH [kJ/mol][a]
IIa (*cis*)	−1376.731408	2.81	−1376.749351	5.13
IIIa (*trans*)	−1376.732492		−1376.751329	
Va (*cis*)	−1017.862317	3.33	−1017.879344	4.20
VIa (*trans*)	−1017.863600		−1017.880963	
VIII (*cis*)	−1416.045720	−7.99	−1416.063936	−3.09
IX (*trans*)	−1416.042638		−1416.062743	
Possible intermediate	Total energy [au] *in vacuo*	Δ*E*(lactam–ketene) [kJ/mol]	Total energy in MeOH [au][a]	Δ*E*(lactam–ketene) in MeOH [kJ/mol][a]
Xa (lactam)	−1538.443885	−81.61	−1538.498663	−100.17
XIa (ketene)	−1538.412427		−1538.460053	
XIIa (lactam)	−1179.574782	−273.92	−1179.626656	−324.21
XIIIa (ketene)	−1179.469196		−1179.501688	
XIV (lactam)	−1577.755379	−271.08	−1577.804674	−296.58
XV (ketene)	−1577.652130		−1577.691714	

[a] Obtained with the IEFPCM solvent model, using the dielectric constant $\varepsilon = 32.63$.

Table 2
Calculated lengths of the potential coordination bonds in models **XIa**, **XIIIa** and **XV** and the atomic charges (Mulliken) on the donor atoms obtained with the B2LYP/6-31 G(d) method.

Compound	d(S–Na) [Å]	ρ(S)	d(C–Na) [Å]	ρ(C)	d(O–Na) [Å]	ρ(O)	d(N–Na) [Å]	ρ(N)
XIa	2.576	−0.371	–	–	2.443	−0.455	2.421	−0.364
XIIIa	–	–	2.361	−0.599	2.581	−0.445	2.531	−0.355
XV	2.752	+0.084	2.392	−0.664	2.392	−0.473	4.459	−0.323

2.2.3.1. (1R,9bR*)-7,8-dimethoxy-1-(4-chlorophenyl)-9b-phenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**5b**).* A white crystalline powder; mp 208–211 °C (from diisopropyl ether–ethyl acetate); 0.30 g, 72%; R_f (48%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{25}H_{22}ClNO_3$ (419.90): C, 71.51; H, 5.28; N, 3.34. Found: C, 71.38; H, 5.21; N, 3.19%.

2.2.3.2. (1R,9bR*)-7,8-dimethoxy-1-(4-fluorophenyl)-9b-phenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**5c**).* A white crystalline powder; mp 210–212 °C (from diisopropyl ether–ethyl acetate); 0.31 g, 78%; R_f (55%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{25}H_{22}FNO_3$ (403.45): C, 74.43; H, 5.50; N, 3.47. Found: C, 74.33; H, 5.39; N, 3.62%.

2.2.3.3. (1R,9bR*)-7,8-dimethoxy-1-(4-methoxyphenyl)-9b-phenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**5d**).* A white crystalline powder; mp 205–207 °C (from diisopropyl ether–ethyl acetate); 0.35 g, 83%; R_f (50%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{26}H_{25}NO_4$ (415.48): C, 75.16; H, 6.06; N, 3.37. Found: C, 74.97; H, 6.27; N, 3.52%.

*2.2.4. General procedure for the preparation of trans-azetoisoquinolines (**6a–d**)*

To a stirred solution of *cis*-azetoisoquinoline **(5a–d)** (0.60 mmol) in anhydrous methanol (30 mL), NaOMe (8 mg, 0.15 mmol; for compound **5d**, 12 mg, 0.22 mmol) was added. The reaction mixture was refluxed for 24 h, after which the solvent was evaporated off and the residue was purified by column chromatography with *n*-hexane:ethyl acetate 3:2, followed by *n*-hexane:ethyl acetate 1:1 as eluent.

2.2.4.1. (1S,9bR*)-7,8-dimethoxy-1,9b-diphenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**6a**).* A white crystalline powder; mp 219–221 °C; 78 mg, 34%; R_f (52%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{25}H_{23}NO_3$ (385.46): C, 77.90; H, 6.01; N, 3.63. Found: C, 77.79; H, 5.95; N, 3.77%.

2.2.4.2. (1S,9bR*)-7,8-dimethoxy-1-(4-chlorophenyl)-9b-phenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**6b**).* A white crystalline powder; mp 188–190 °C; 113 mg, 45%; R_f (53%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{25}H_{22}ClNO_3$ (419.90): C, 71.51; H, 5.28; N, 3.34. Found: C, 71.46; H,5.22; N, 3.52%.

2.2.4.3. (1S,9bR*)-7,8-Dimethoxy-1-(4-fluorophenyl)-9b-phenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**6c**).* A white crystalline powder; mp 216–217 °C; 77 mg, 32%; R_f (60%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{25}H_{22}FNO_3$ (403.45): C, 74.43; H, 5.50; N, 3.47. Found: C, 74.23; H, 5.42; N, 3.61%.

2.2.4.4. (1S,9bR*)-7,8-Dimethoxy-1-(4-methoxyphenyl)-9b-phenyl-1,4,5,9b-tetrahydro-2H-azeto[2,1-a]isoquinolin-2-one (**6d**).* A white crystalline powder; mp 152–154 °C; 70 mg, 28%; R_f (55%, *n*-hexane:ethyl acetate 1:1). Anal. Calcd. for $C_{26}H_{25}NO_4$ (415.48): C, 75.16; H, 6.06; N, 3.37. Found: C, 75.22; H, 6.30; N, 3.46%.

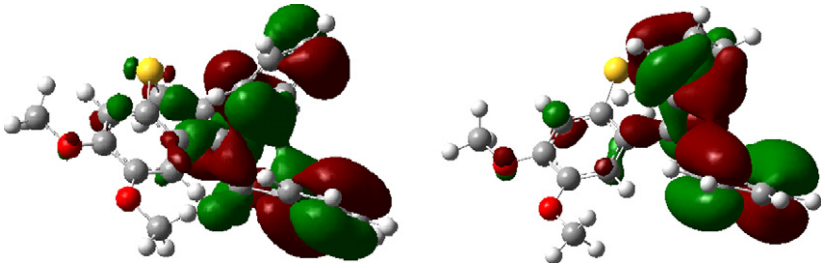
Table 3
Energetic data on the experimentally studied *cis* and *trans* β-lactams (**2a**, **3a**, **5a**, **6a**, **8**, **9**) calculated on the structures optimized by B3LYP-6-31 G(d) method with IEFPCM solvent model ($CHCl_3$, ε = 4.90).

Studied β-lactam	Total energy in $CHCl_3$ [au]	ΔE(*cis*–*trans*) [kJ/mol]
2a (*cis*)	−1605.783978	3.10
3a (*trans*)	−1605.785174	
5a (*cis*)	−1246.914963	1.98
6a (*trans*)	−1246.915725	
8 (*cis*)	−1645.099582	−17.97
9 (*trans*)	−1645.092659	

Table 4
Measured (upper rows) and calculated [GIAO/B3LYP/6-311+G(2d,p) (*lower rows in italics*)] values of ^{1}H NMR chemical shifts which are most relevant for conformation.

	OCH_3 Pos. 7	OCH_3 Pos. 8	SCH_2[a]	NCH_2[b]	H-6	H-9
2a (meas.)	4.04	3.90	4.46, 5.05	–	6.84	7.29
2a (*calc.*)	*3.86*	*3.94*	*4.22, 5.06*	–	*6.60*	*7.25*
3a (meas.)	3.83	3.20	4.37, 5.07	–	6.63	5.81
3a (*calc.*)	*3.74*	*3.11*	*4.80, 5.00*	–	*6.59*	*5.67*
6a (meas.)	3.83	3.25	2.68, 3.04	3.42, 4.08	6.63	5.84
6a (*calc.*)	*3.77*	*3.12*	*2.65, 3.54*	*3.44, 4.26*	*6.60*	*5.63*
8 (meas.)	3.95	4.02	2.77, 2.79	3.48, 4.60	7.15	7.25
8 (*calc.*)	*3.88*	*3.93*	2.51, 2.98	3.32, 4.59	7.26	7.30

[a] For **6a** C(Ar)–CH_2.
[b] For **2a** and **3a** NCH_2 is equivalent to SCH_2.



8 (HOMO-3) **8** (HOMO-4)

Fig. 2. Contour plots of HOMO-3 and HOMO-4 disclosing some π electron delocalisation between the two *cis*-oriented phenyl substituents calculated [B3LYP/6-31 G(d)] for **8** of pronounced stability.

Table 5
Characteristic IR frequencies[a] and ^{1}H NMR data[b] on compounds **2a–d**, **3a–d**, **5b–d, 6a–d**, and **8**.[c]

Compound	νC=O band	νC–O band	$\gamma C_{Ar}H$ band[d]	$\gamma C_{Ar}H$ band[e]	$\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$[f]	OCH_3 Pos. 7	OCH_3 Pos. 8	SCH_2[g] $2 \times d$	NCH_2[h] $2 \times m$	CH *s*	H–6 *s*	H–9 *s*	H–2′,6′ Ar (α to C=O)	H–3′,5′ Ar (α to N)	H–2′,6′	H–3′,5′	H–4′
2a[*]	1748	1262, 1216	854	–	746, 698	4.04	3.90	4.46, 5.05	–	4.99	6.84	7.29	~7.1 *m* (10H)[i]				
2b	1757	1212	852	819	721, 699	4.03	3.90	4.45, 5.03	–	4.93	6.84	7.23	7.03	7.12	7.11 ~ *s* (5H)		
2c	1745	1161	853	819	759, 699	4.04	3.90	4.46, 5.04	–	4.94	6.84[i]	7.24	7.07	6.84[i]	7.11 ~ *s* (5H)		
2d	1746	1219, 1026	852	810	758, 701	4.03	3.89	4.46, 5.05	–	4.93	6.83	7.26	7.01	6.68	~7.1 *m* (5H)		
3a[*]	1752	1246, 1209	862	–	741, 697	3.83	3.20	4.37, 5.07	–	5.11	6.63	5.81	6.93	7.17[i]	7.50	7.42	7.37
3b	1756	1247, 1038	843	814	744, 698	3.85	3.27	4.36, 5.06	–	5.08	6.64	5.82	6.88	7.16	7.49	7.43	7.38
3c	1752	1247, 1038	854	814	726, 698	3.84	3.27	4.35, 5.05	–	5.10	6.64	5.82	6.89	6.91	7.48	7.42	7.38
3d	1743	1246, 1027	849	834	740, 701	3.83	3.26	4.36, 5.06	–	5.05	6.64	5.85	6.84	6.70	7.48	7.41	7.37
5b	1738	1221, 1023	856	818	761, 700	3.90	4.04	2.65, 2.79	3.71, 3.83	4.87	6.72	7.17	7.02	7.09	7.14	7.09[i]	7.09[i]
5c	1739	1220, 1023	858	817	760, 700	3.90	4.05	2.66, 2.80	3.73, 3.84	4.88	6.72	7.18	7.05[i]	6.82	7.16	7.10	7.05[i]
5d	1740	1222, 1023	877	836	752, 699	3.89	4.04	2.67, 2.79	3.73, 3.84	4.86	6.71	7.19	7.00	6.65	7.16	7.09	7.04
6a	1732	1234, 1026	869	826	769, 699	3.83	3.25	2.68, 3.04	3.42, 4.08	4.89	6.63	5.84	6.93	~7.2[i]	7.48	7.38	7.31
6b	1740	1231, 1028	865	826	757, 703	3.85	3.32	2.68, 3.05	3.39, 4.07	4.85	6.64	5.82	6.86	7.18	7.46	7.38	7.32
6c	1739	1231, 1027	869	829	757, 704	3.84	3.32	2.68, 3.06	3.38, 4.08	4.89	6.65	5.84	~6.9	7.47	7.38	7.32	
6d	1740	1237, 1026	866	830	755, 701	3.84	3.31	2.68, 3.02	3.42, 4.06	4.83	6.64	5.82	6.84	6.74	7.47	7.38	7.31
8[l]	1746	1213, 1045	863	–	745,[k] 699	3.95	4.02	2.77, 2.90	3.48, 4.60	5.36	7.15	7.25	7.20	7.08[i]	6.75	~7.08 *m* (6H)[i]	

[a] In KBr discs (cm^{-1}).
[b] In $CDCl_3$ solution at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz. Further signals: OCH_3: 3.71 (**2d**): 3.72 (**3d**), 3.70 (**5d**), 3.74 (**6d**); H-4′ Ar (α to C=O): ~7.1[i] (**2a**), 7.16[i] (**3a**), ~7.2[i] (**6a**), 7.08 *m* (6H)[i] (**8**).
[c] Assignments were supported by HMQC and HMBC (except for **3a**, **c**), for compound **8** also by DIFFNOE measurements.
[d] Condensed benzene ring.
[e] *p*-Disubstituted ring.
[f] Monosubstituted ring.
[G] *J*: 10.9 (**2a**), 10.7 (**2b–d**), 12.3 (**3a**, **b**, **d**), 12.7 (**3c**). [C(sp^2)]CH_2 group, $2 \times m$ (2×1H) for **5b–d**, **6a–d** and **8**.
[h] 2 *m* (2×1H).
[i] Overlapping signals.
[k] Split band with the other maximum at 769 cm^{-1}.
[l] The numbering of the other compounds was used also for **8**.
[*] Previously published compounds, c.f. Ref. [11] (**2a**) and Ref. [12b] (**3a**).

3. Results and discussion

3.1. Theoretical calculations

To explain the significant substrate dependence observed experimentally in the course of the base-catalysed isomerization of *cis* β-lactams **2a**, **5a** and **8**, we considered two pathways, involving a simple deprotonation-protonation sequence and a base-mediated simultaneous fission of the condensed rings with the formation of a ketene intermediate, respectively, as illustrated in the simplified models **IIa**, **Va** and **VIII** (Scheme 4). To obtain the energetics of the studied epimerizations and the assumed elementary steps, DFT analysis [19] was carried out at the B3LYP level of theory [20], using the 6-31G(d) basis set [21] on the *cis*–*trans* counterparts **IIa**–**IIIa**, **Va**–**VIa** and **VIII**–**IX**, and the possible intermediate Na salts **Xa**–**XIIIa**, **XIV** and **XV** (Scheme 4). Total energy values obtained *in vacuo* were recalculated with the IEFPCM solvent model [22] (ε_{MeOH} = 32.63) representing the experimental conditions (Scheme 4, Table 1). The computed differences in the total energy values of the *cis* and *trans* β-lactams were in agreement with the data from the preparative experiments, showing that, in contrast with the *cis* β-lactams **IIa** and **Va** (representing **2a** and **5a**), **VIII** (representing **8**) is more stable than its *trans* counterpart **IX** (representing **9**) both *in vacuo* and in solution [ΔE (**VIII**–**IX**) = −7.99 kJ/mol and −3.09 kJ/mol, respectively]. It is also noteworthy that, despite similar energetics for the overall processes **IIa** → **IIIa** and **Va** → **VIIa**, the experiments showed that the isomerization of *cis*-azetobenzothiazine **2a** is much faster than that of *cis*-azetoisoquinoline **5a**. The enhanced tendency of **2a** to undergo isomerization may be interpreted in terms of the relatively significant contribution of the pathway involving a thiophenolate intermediate analogous to **XIa**, which contains a tricoordinated Na ion, as disclosed by geometry optimisation (Fig. 1, Table 2). On the other hand, the lower stability of **XIa** relative to that of the amidate salt **Xa** indicates a major contribution of the alternative pathway with the simple base-catalysed epimerization of the *cis*-azetobenzothiazine ring system. The slower isomerization of *cis*-azetoisoquinoline **5a** may be due to a negligible contribution of the pathway proceeding via a ketene intermediate analogous to **XIIIa**, with the sodium-coordinated benzylate moiety being much less stable than amidate salt **XIIa** (Table 1) involved in the alternative epimerization pathway. It should be noted here that, in spite of the thermodynamically unfavoured isomerization of **8**, the equilibrium formation of an amidate salt analogous to **XIV** can not be ruled out. The calculated

Table 6
^{13}C NMR chemical shifts[a] of compounds **2a–d**, **3a–d**, **5b–d**, **6a–d**, and **8**.[b]

Compound	OCH_3 Pos. 7, 8	CH	C=O	Benzothiazine or isoquinoline moiety[c]								Aryl groups attached to the lactam ring			
				C-5a	C-6	C-7	C-8	C-9	C-9a	C-9b	SCH_2 [d]	$C_{subst.}$ (1′)	C_{ortho}	C_{meta}	C_{para}
2a*	56.6, 57.0	69.0	168.5	123.0	112.9	149.6	148.3	112.1	132.7	67.7	40.6	132.8, 137.5	127.81,[e] 127.83, 128.1, 128.8, 129.2, 128.8, 129.2		
2b	56.6, 57.1	68.1	168.0	123.1	113.0	148.8	148.4	112.1	132.5	67.6	40.6	131.5, 137.2	127.7, 128.4, 129.0, 130.5, 129.2	128.1, 133.8	
2c	56.6, 57.1	68.1	168.3	123.1	113.0	149.7	148.4	112.1	132.6	67.7	40.7	128.8[f] 137.4	130.8,[f]127.7[g]	115.7,[f] 128.3[g]	128.0, 162.4[f]
2d	56.6, 57.0	68.5	168.9	123.9	112.9	149.6	148.3	112.1	132.8	67.7	40.6	124.9, 137.6	127.79, 130.4	114.2, 128.2	127.81, 159.2
3a*	56.3, 56.0	69.3	169.2	123.9	109.9	148.9	146.2	114.8	122.1	64.8	37.2	133.3, 142.2	127.6, 130.3	129.3, 128.84	128.75, 128.4
3b	56.3, 56.1	68.5	168.7	124.1	110.0	149.1	146.3	114.9	121.7	64.8	37.2	132.3, 141.9	127.6, 131.6	129.0, 129.3	128.9, 134.5
3c	56.3, 56.1	68.3	169.1	124.1	110.0	149.1	146.3	114.9	121.7	64.8	37.2	129.7,[f] 142.0	127.6, 131.9[f]	115.8,[f] 129.3	128.9, 162.8[f]
3d	55.9, 55.7	68.5	169.3	123.5	109.5	148.5	145.8	114.6	121.9	64.4	36.8	125.4, 141.9	127.1, 131.0	113.9, 128.8	128.3, 159.4
5b	56.5, 57.1	67.4	169.7	127.9	112.5	149.3	148.4	110.6	133.1	66.5	26.9	132.1, 138.7	127.3, 130.7	128.4, 128.8	127.7, 133.5
5c	56.5, 57.1	67.4	170.0	127.9	112.5	149.2	148.4	110.6	133.2	66.6	26.9	129.4,[f] 138.8	127.3, 131.0[f]	115.6,[f] 128.3	127.6, 162.3[f]
5d	56.5, 57.0	67.8	170.7	127.9	112.4	149.1	148.4	110.6	133.5	66.7	26.9	125.6, 139.1	127.35, 130.5	114.1, 128.2	127.42, 159.1
6a	56.2, 55.9	69.7	171.4	127.2	111.8	148.4	146.8	112.6	127.9	64.3	27.2	133.8, 143.5	126.7, 130.2	128.9, 129.1	128.12, 128.17
6b	56.2, 55.9	68.9	170.8	128.0	111.9	148.6	146.9	112.7	128.3[e]	64.3	27.2	132.4, 143.0	126.7, 131.5	129.0, 129.2	128.3,[e] 134.3
6c	56.2, 55.9	68.8	171.2	128.0	111.9	148.6	146.9	112.7	128.2[e]	64.3	27.3	129.8,[f] 143.2	126.7,[f] 126.8	115.8,[f] 129.1	128.2,[e] 162.8[f]
6d	56.2, 55.9	69.2	171.8	127.9	111.7	148.4	146.8	112.8	127.4	64.3	27.2	125.8, 143.5	126.6, 131.3	114.3, 129.1	128.0, 159.7
8	56.6, 56.8	67.0	167.9	127.7	118.6	148.4	148.7	115.0	138.6	74.9	33.4	133.2, 137.8	128.3, 128.6	128.2, 128.5	127.3, 127.8

[a] In ppm (δ_{TMS} = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$. Further signals, OCH_3 (Pos. 4, disubstituted benzene): 55.6 (**2d**, **5d** and **6d**), 55.3 (**3d**); NCH_2: 39.6 (**5b–d**), 37.6 (**6a**, **d**), 37.4 (**6b**, **c**).
[b] Assignments were supported by DEPT (except for **3b**), HMQC and HMBC (except for **3a**, **c**) measurements.
[c] This numbering was also used for compound **8**.
[d] $ArCH_2$ for **5b–d**, **6a–d**.
[e] Two overlapping lines.
[f] Due to C, F-coupling *d* [Hz], ^1J: 246.7 (**2c**), 248.2 (**3c**), 246.4 (**5c**), 247.9 (**6c**), ^2J: 21.4 (**2c**), 21.6 (**3c**, **5c** and **6c**), ^3J: 8.2 (**2c**, **3c** and **5c**), ^4J: 3.5 (**2c** and **3c**), <1 (**5c**), 3.0 (**6c**).
[g] Reversed assignments are also possible.
* Previously published compounds, c.f. Ref. [11] (**2a**) and Ref. [12b] (**3a**).

relative energy values of the simplified models **XIV** and **XV** representing the two isomerization pathways are similar to those of model pairs **XIIa**/**XIIIa** (Table 1) and associated with the weakly stabilized carbanion present in ketene **XV**. In this complex, the sodium ion is also tricoordinated by the carbanionic centre, the ketene O and the S atom, but is not coordinated by the distant imine-N atom. The view concerning the different coordination patterns in **XIa**, **XIIIa** and **XV** discussed above is supported by the distances between the sodium ion and the potential coordinating sites (Table 2) calculated for these models. The relative strength of the N → Na coordination may also be estimated from the Mulliken charge on the N atom, which seems to correlate with the atomic distance. Its shortening increases the electron-density on the N centre approaching the Na ion (Table 2). A similar tendency can be observed for the ketene O atom, but, besides coordination, the charges on the S and C atoms are also influenced by their different positions in the anionic ligands.

Finally, it must be pointed out that, although relatively small energy differences emerged for the overall isomerization processes and quite large energy differences were obtained for the possible intermediate pairs in the alternative pathways, the tendencies in the calculated values corroborate the experimentally observed structure–reactivity relationships sufficiently to support the proposed mechanisms.

In order to obtain more sophisticated energetics for the actually studied molecules we performed the geometry optimisation and subsequent energy calculation on *cis–trans* counterparts **2a–3a**, **5a–6a** and **8–9** placed in chloroform by means of B3LYP-6-31 G(d) method using IEFPCM solvent model which represents the conditions of NMR measurements (Table 3) giving information on conformation.

The calculated energetics and the relative stability of *cis–trans* counterparts obtained by modelling more realistic conditions are again in keeping with the experimental observations. Although diastereomer pairs **2a–3a** and **5a–6a** are very similar in relative stability, *cis*-azetothiazepine **8** with complete resistance to epimerisation proved to be significantly more stable than *trans* isomer **9**. The pronounced stability of **8** can at least partly be attributed to π-stacking interaction as evidenced by the calculated contour plots of HOMO-3 and HOMO-4 (Fig. 2) showing some delocalisation between the two *cis*-oriented phenyl groups.

The reality of conformations resulted by geometry optimisation in chloroform gains support from the comparison of the chemical shifts of skeletal protons measured and calculated by GIAO method [23] at B3LYP/6-311+G(2d,p) level [24] of DFT, respectively (Table 4). As it will be discussed in the next session, the most spectacular characteristics reflected from both the measured and calculated values is the significant anisotropic shield exerted by the phenyl group [25a] attached to C-1 atom on H-9 and on the methoxy

protons in Pos. 8 in *trans* isomers **3a** and **6a**. Such shielding effect causing upfield shifts on the aforementioned signals was not detected in *cis* isomers **2a**, **5a** and **8**.

3.2. NMR spectroscopy

The IR, ^{1}H and ^{13}C NMR data on the new compounds presented in this paper are given in Tables 5 and 6. They provide unambiguous proof of the presumed structures. The following additional remarks are necessary.

The presence of the azetidinone ring follows from the high IR νC=O frequencies (1732–1757 cm^{-1}) characteristic of strained β-lactams [26] and also from the appearance of the ^{13}C NMR carbonyl lines (167.9–171.8 ppm) in the expected chemical shift interval [25b].

As concerns the *cis*–*trans* isomerism, the most uncommon phenomenon is the striking difference in the chemical shifts of the methoxy H atoms in Pos. 8, which lie between 3.89 and 4.05 ppm for the *cis* compounds **2a**–**d**, **5b**–**d** and **8**, and in the interval 3.20–3.32 ppm for the *trans* isomers.

Similarly, the H-9 singlet is significantly upfield-shifted for the *trans* isomers (5.83 ± 0.02 ppm for **3a**–**d** and **6a**–**d**) as compared with their *cis* counterparts: 6.84 ± 0.01 ppm (**2a**–**d**), 7.18 ± 0.01 ppm (**5b**–**d**) and 7.25 ppm (**8**).

These observations can be explained by the anisotropic shielding of the benzene ring [25a] in Pos. 1, which lies near H-9 and the methyl H atoms in the 8-methoxy group in the preferred conformation, containing the thiazine ring in a boat-like form with out-of-plane S and C-9b. The other conformation (half-boat-like form with out-of-plane C-4) is unfavourable because of steric hindrance between the 9b-phenyl ring and one of the non-bonded electron pair on the S atom.

A further fact in support of the configuration is the ^{13}C NMR chemical shift of C-9b. This line is upfield-shifted for the more crowded *trans* isomers **3a**–**d** and **6a**–**d** (at 64.3–64.8 ppm) due to the field effect [25c], while it appears in the interval 66.5–67.7 ppm for the *cis* compounds **2a**–**d** and **5b**–**d**.

The *cis* position of the two phenyl substituents in **8** was proved by DIFFNOE measurements. On saturation of the *ortho* H atoms of one of the benzene rings, the analogous *ortho* H-signal of the other ring underwent an intensity enhancement. These results confirm the near (*cis*) position of these groups relative to the azetidinone ring.

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