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Exceptional isolation of both imine and enamine desmotropes of 4,1-benzothiazepines

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Dedicated to the memory of Professor Gábor Bernáth PhD, DSc, University of Szeged, who died on 1 October 2009

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ABSTRACT

The desmotropy of differently substituted (*R**)-3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines and 3-ethoxycarbonyl-2-aryl-1,5-dihydro-4,1-benzothiazepines was investigated. The target 4,1-benzothiazepines were obtained via the ring transformation of (2*R**,2a*S**)-2-chloro-2a-aryl-2,2a-dihydro-2*H*,4*H*-azeto[1,2-*a*][3,1]benzothiazin-1-ones with sodium ethoxide in ethanol. The β-amino ester intermediate of the ring-enlargement reaction was isolated. Surprisingly, the desmotropes obtained could be separated by column chromatography and proved to be unexpectedly stable in solution. Further comparative studies revealed the existence of only the enamine forms of regioisomeric 2-ethoxycarbonyl-3-aryl-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine derivatives; in this case, no desmotropy occurred. The structures were proved by means of NMR and IR spectroscopy.

1. Introduction

Tautomerism frequently occurs among heterocyclic systems. It is of great importance, e.g., for the correct interpretation of the detailed mechanisms of reactions or the biological activities of potentially tautomeric compounds.[1] In particular cases, when the interconversion of tautomers is slow, they can be separated by means of various instrumental chromatographic methods, but equilibration usually proceeds relatively rapidly.[2] There are examples of the isolation of tautomers with complex-forming molecules.[3] In rare cases, when the energy barrier between the two tautomers is sufficiently high, there is a possibility of the existence of both (all) of the individual tautomers as separate compounds. This latter phenomenon is called desmotropy.

The term was introduced by Jacobson to describe certain substances, which may occur in either of two structurally different forms.[4] Later, the present meaning of desmotropy was defined by Hantzsch and Herrmann: if a substance can be isolated in two stable forms it should be called desmotropic, while if it cannot be isolated it should be termed tautomeric.[5] This was followed by the modern definition of desmotropy as 'tautomerism in which both tautomers have been isolated.'[6] They can be separated either by crystallization from different solvents[7] or in exceptional cases by column chromatography.[8] It is noteworthy that there have been reports of the separation of tautomers where the authors did not use the term desmotropy.[9]

In fact, only a few examples of desmotropy are known in the literature.[7,10–14] The pioneering IR-spectroscopic studies,[10a,b] later confirmed by X-ray measurements, were performed on substituted hydantoins, thiohydantoins, imidazolidinones and imidazolidinthiones.[10c,d] Desmotropic pairs were subsequently found amongst pyrazole,[7,11] tetrazole[12] and pyridoxal[13] derivatives. The known examples have been investigated mainly with the aid of IR and solid-state NMR spectroscopy and/or X-ray crystallography, because of the instability of the desmotropes in solution.

We earlier investigated the ring-transformation reactions of different monochloro-β-lactam-fused benzothiazines in the presence of

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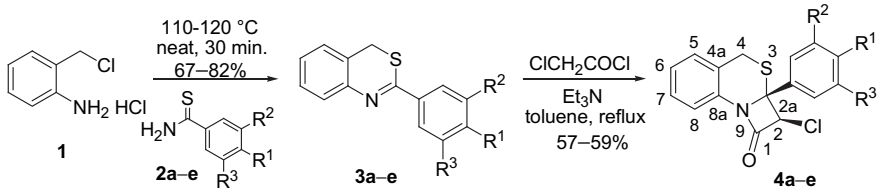
base.[8,15] These enlargement reactions led to benzene-fused 1,4- and 4,1-benzothiazepine derivatives, preparation of which otherwise involves difficulties. During our studies of the ring transformation of (2*R**,2a*S**)-2-chloro-2a-phenyl-2,2a-dihydro-2*H*,4*H*-azeto[1,2-*a*][3,1]benzothiazin-1-one (1) with sodium ethoxide in ethanol, a desmotropic (imine and enamine) 4,1-benzothiazepine pair was obtained.[8]

In view of the fact that there are currently so few examples, desmotropy seems to be a comparatively unexplored, but rather exciting field of organic chemistry. Consequently, as a continuation of our earlier work, we set out to study the possible desmotropy of 1,4- and 4,1-benzothiazepines.

2. Results and discussion

The treatment of 2-aminobenzyl alcohol with thionyl chloride resulted in 2-aminobenzyl chloride hydrochloride (**1**),[16] fusion of which with thiobenzamides **2a**–**e** provided the key intermediate 4*H*-3,1-benzothiazine derivatives **3a**–**e** in good yields (Scheme 1).[16,17]



a: $R^1 = R^2 = R^3 = H$; **b**: $R^1 = Cl$, $R^2 = R^3 = H$; **c**: $R^1 = Me$, $R^2 = R^3 = H$;
d: $R^1 = OMe$, $R^2 = R^3 = H$; **e**: $R^1 = H$, $R^2 = R^3 = OMe$

Scheme 1.

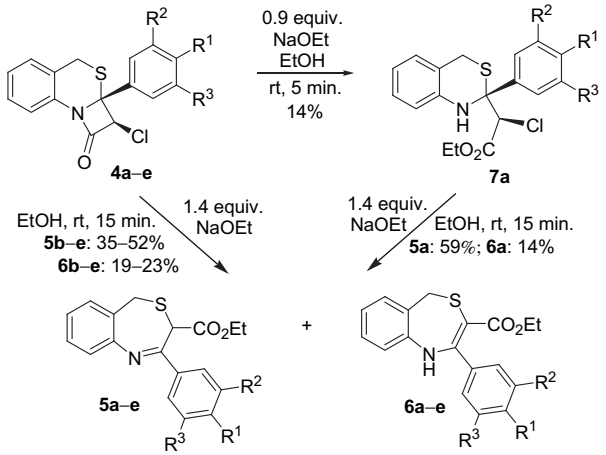
For the preparation of our target monochloro-β-lactam derivatives (**4a**–**e**), we made use of the Staudinger reaction. The reactions of **3a**–**e** with chloroacetyl chloride in refluxing toluene in the presence of triethylamine gave azeto[2,1-*a*][3,1]benzothiazin-1-one derivative **4a**–**e** in relatively good yields (Scheme 1).

To investigate the possible desmotropism for different substituents and to compare substituent effects, the monochloro-β-lactam derivatives **4a**–**e** were treated with sodium ethoxide in dry ethanol at room temperature. The reactions proceeded rapidly: in 10 min the starting materials had disappeared. In each case, two products, **5b**–**e** and **6b**–**e** were obtained (Scheme 2). After column chromatography and evaporation of the eluent, trituration with *n*-hexane furnished the separate desmotropes **5b**–**e** and **6b**–**e** as crystalline compounds in relatively good yields. The pure desmotropes were stable for different periods of time and it was possible to perform NMR spectroscopic investigations in solution. However, it must be noted that under some circumstances (either basic or acidic treatment) the isolated pure products again formed equilibrium mixtures. As might be expected, therefore, the compounds are able to equilibrate.

We earlier proposed a reaction mechanism for the ring transformation of lactams, in which the first step is ethanolysis of the β-lactam ring, furnishing the α-chloro-ester **7**, which gives the products, most probably through the episulfonium salt after the elimination of HCl. Treatment of **4a** with 0.9 equiv of sodium ethoxide in ethanol led to the first isolation of a compound, structural analysis of which indicated **7a**, one of the possible intermediates. Upon treatment of **7a** with an excess of sodium ethoxide, **5a** and **6a** were obtained (Scheme 2).

In the next step, it appeared to be worthwhile to investigate the ring transformations of the regioisomeric monochloro-β-lactam-condensed 1,3-thiazines **8a**–**d**. The reactions of **8a**–**d** with sodium ethoxide gave only one product in each case, the enamine 1,4-benzothiazepines **9a**–**d** being obtained in good yields. Not even traces of the imines **10a**–**d** were detected (Scheme 3). Most probably in **10a**–**d** continuous conjugation is not possible and thus the enamine form is obviously preferred (see in Structure part).

For further investigation of the desmotropes, X-ray and differential scanning calorimetry (DSC) investigations are in progress. To obtain the energetics of the studied compounds theoretical calculations are also planned.



a: $R^1 = R^2 = R^3 = H$; **b**: $R^1 = Cl$, $R^2 = R^3 = H$; **c**: $R^1 = Me$, $R^2 = R^3 = H$;
d: $R^1 = OMe$, $R^2 = R^3 = H$; **e**: $R^1 = H$, $R^2 = R^3 = OMe$

Scheme 2.

3. Structure

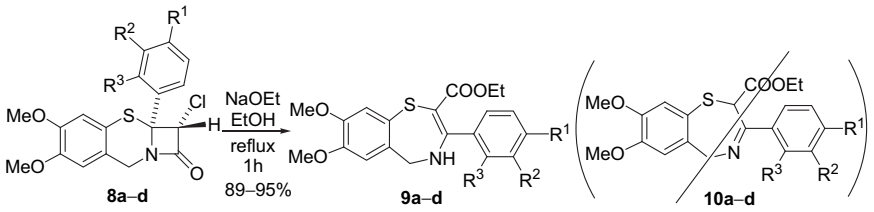
The IR, ^1H and ^{13}C NMR data proving the presumed structures of the new compounds are given in Tables 1 and 2. Only the following additional remarks are necessary:

The presence of the aryl-iminothiohydrin moiety in **3d**,**e** is unambiguously demonstrated by the ^{13}C NMR carbon signals at 160.8 and 161.1 ppm, respectively, of the N=C(Ar)–S group, and by the ^1H and ^{13}C NMR signals of the arylsubstituent.

The azetidinone structure of **4d**,**e** follows straightforwardly from the ν(C=O) IR band in the expected region[18] (at 1769 and 1763 cm^{-1}), the carbonyl and $NC_{quat.}S$ ^{13}C NMR signals (at 160.0 and 70.8 ppm for **4d** and at 159.6 and 70.9 ppm, respectively, for **4e**) and the ^1H NMR singlet of the CHCl group (5.27 and 5.25 ppm).

As concerns the desmotropy of the pairs **5**–**6**, in case of *p*-chloro (**b**) and *p*-methoxy (**d**) derivatives, the tautomers proved to be stable in DMSO-d_6 solution: equilibration was not observed during the solvation and measurements, and the samples investigated remained homogeneous.

The imine tautomeric forms **5b** and **5d** are unambiguously indicated by the ^1H and ^{13}C NMR signals of the methine (SCH) group



a: $R^1 = R^2 = R^3 = H$; **b**: $R^1 = Cl$, $R^2 = R^3 = H$; **c**: $R^1 = R^2 = OMe$, $R^3 = H$; **d**: $R^1 = R^2 = H$, $R^3 = Cl$

Scheme 3.

(at 5.07 and 45.7 ppm for **5b** and at 5.10 and 45.5 ppm for **5d**, respectively). In accordance, **6b** and **6d** reveal the characteristic IR, ^1H and ^{13}C NMR spectral data of the enamino (NH–C=C) moiety: νNH: 3312 cm^{-1} (**6d**), δNH: 8.59 (**6b**) and 8.56 ppm (**6d**), and $\delta NC(sp^2)$ and $\delta SC(sp^2)$: 151.8 and 100.8 ppm (**6b**) and 153.1 and 100.4 ppm (**6d**).

The imine tautomeric forms of **5c** (in $CDCl_3$) and **5e** (in DMSO-d_6) are similarly stable. These solutions did not change during the solvation, during the measurement or subsequently. However, when **5c** was dissolved in DMSO-d_6: a mixture of tautomers was formed.

Compounds **6c** and **6e**, existing immediately after solvation in DMSO-d_6 as the pure enamines, slowly tautomerized to the imine form. In the case of **6c**, after 2 weeks the enamine:imine ratio was ~3:1. The 3,5-dimethoxyphenyl derivative **6e** proved to be a ~6.5:1 mixture of the enamine and imine forms immediately after solvation in DMSO-d_6, the ratio changing to ~4:1 in 17 h.

The thiazepines **9a–d** are homogeneous enamine tautomers in DMSO-d_6 solution and equilibrization was not observed. This is obvious from the appearance of the νNH IR band (3323±9 cm^{-1}) and the two $C(sp^2)$ lines (at 88.0±0.8 and 156.8±1.8 ppm) in the ^{13}C NMR spectra.

In summary, desmotropy was observed in $CDCl_3$ solution: the pure tautomers remained unchanged for days. In DMSO-d_6 solution, the originally preferred enamine form transformed slowly to the imine tautomer. The equilibrium, however, remained in favour of the enamine form.

The mesomerism [–NH–C=C–COOEt ↔ $-N^+H$=C–C=C(OEt)O^-] of the β-enaminoester[19] moiety stabilizes the enamine form, but the continuous conjugation via the C=N bond of the condensed aromatic ring and the Ar group can partly compensate the energetically favoured structure in the imine form. The result is the existence of a tautomeric equilibrium. In **9a–d**, continuous conjugation is not possible and thus the enamine form is obviously preferred.

The structure of **7a** (of importance from the aspect of the presumed reaction mechanism) follows from the spectral data given below:

- A νNH band appears at ~3400 cm^{-1} in the IR.
- Two saturated C atoms, one tertiary and one quaternary, are present in the molecule, as confirmed by the ^{13}C NMR lines at 70.9 ($C_{quat.}$) and 62.2 ppm (CH).
- The ^1H NMR singlet of the CH group is also observed (at 4.93 ppm).

In consequence of the molecular symmetry, the methylene Hs of **3d**,**e** are chemically equivalent (they give a singlet in the ^1H NMR spectra), while in the asymmetric azetidinones **4d**,**e** the corresponding Hs are non-equivalent (they give an AB-type spectrum: two doublets). In the ^1H NMR spectrum (recorded in $CDCl_3$ solution) of **4e**, however, the methylene group signal is a singlet because of accidental isochrony.[20] This was confirmed by repeated measurement in DMSO-d_6 solution, when not a singlet, but two doublets were observed (cf. Table 1, FN 'k').

In the ^1H NMR spectra of **6b–e** and **9a–c**, the methylene group signal is likewise a singlet due to the fast inversion of the seven-membered heteroring. Because of the steric hindrance between the ester and the *ortho*-chloro-substituted phenyl groups, the conformational motion in **9d** is slow and hence the methylene Hs become non-equivalent. They therefore display double doublets (the neighbouring NH causes a further double split).

4. Experimental

4.1. General

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 in the Institute of Pharmaceutical Chemistry. Merck Kieselgel $60F_{254}$ plates were used for TLC, and Merck Silica gel 60 (0.063–0.100) for column chromatography. Benzothiazines **3a–c**,[16,17] azeto-1,3-thiazines **4a–c**[16,17] and azeto-1,3-thiazines **8a–d**[21] were prepared by literature methods.

IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrometer. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution in 5-mm tubes at room temperature, on a Bruker DRX 500 spectrometer at 500 (^1H) or 125 (^{13}C) MHz, with TMS (δ_{TMS}=0 ppm) as internal reference, and the deuterium signal of the solvent as the lock. Assignments were supported by DEPT, HMQC and HMBC measurements. DEPT spectra were run in a standard manner, using only the Θ=135° pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs.

4.2. General procedure for the preparation of 4*H*-3,1-benzothiazine derivatives 3a–e from 2-aminobenzyl alcohol

To a stirred and cooled (10–15 °C) mixture of thionyl chloride (6.5 mL, 89 mmol) and chloroform (30 mL), 2-aminobenzyl alcohol (5 g, 41 mmol) dissolved in chloroform (100 mL) was added dropwise during 1 h. After the addition, the reaction mixture was stirred for a further 1 h at room temperature and then evaporated (50 °C). The crystalline residue was taken up in diethyl ether (40 mL), filtered and washed with diethyl ether (2×40 mL). Compound **1** was used without further purification.

For the transformation of compounds **3**, the method of El-Desoky[17] was used with slight modifications, as follows. 2-Aminobenzyl chloride hydrochloride (**1**) (2.7 g, 15 mmol) was thoroughly mixed with the appropriate thioamide (**2d**,**e**) (15 mmol) and the mixture was maintained at 110–120 °C for 30 min. To the cooled melt, chloroform (30 mL) was added and the solid formed was suspended. To the suspension, water was added (10 mL) and the aqueous phase was made just alkaline with 10% NaOH solution under intensive shaking. The organic layer was separated, extracted with water (30 mL), dried (Na_2SO_4), filtered and evaporated. The residues thus obtained were purified by column chromatography with *n*-hexane:ethyl acetate 9:1 as eluent to give **3a–e**. **3a–c** Are

Table 1
Characteristic IR frequencies[a] and ^{1}H NMR data[b] for **3d**,**e**, **4d**,**e**, **5b**–**e**, **6b**–**e**, **7a** and **9a**–**d**[c]

Compound	NNH band	νC=O band	νC–O band (ester)	$\gamma C_{Ar}H$ band[d]	CH_3 (3H)[e]	XCH_2 m (2H)[f]	H-5∼d[d,g]	H-6∼t[d,g]	H-7∼t[d,g]	H-8∼d[d,g]	OCH_2 qa (2H)	ArH-2′,6′∼d (2H)	ArH-3′,5′∼d/t (2H)	ArH-4′∼t (1H)	NH s (1H)
3d	—	—	—	833	—	4.00	7.18	7.39	7.26	7.45	—	8.14	7.00	—	—
3e	—	—	—	827	—	4.01	7.18	7.39	7.28	7.48	—	7.35	—	6.64	—
4d	—	1769	—	829	—	3.64, 3.72	7.16[h]	7.16[h]	∼7.38[i]	7.89	—	∼7.38[i]	6.89	—	—
4e	—	1763	—	846	—	3.70[k]	7.17[h]	7.16[h]	7.38	7.87	—	∼6.59[l]	—	6.44	—
5b	—	1725	1279, 1086	826	0.88	3.36, 3.60	7.25[h]	7.05	7.26[h]	6.85	3.64	8.00	7.56	—	—
5c	—	1725	1214, 1023	836	1.01	3.45, 3.70	7.26	7.12	7.32	7.02	3.85	7.89	7.29	—	—
5d	—	1742	1205, 1180, 1025	844	0.93	3.36, 3.63	7.26[h]	7.05[i]	7.28[h]	6.86	3.67	8.01	7.06[i]	—	—
5e	—	1732[m]	1195, 1152	844	0.94	3.38, 3.64	7.28	7.08	7.29	6.89	3.69	7.18	—	6.70	—
6b	—	1650	1269, 1058	848	0.74	3.97	7.02	6.79	7.06	7.18	3.66	7.33	7.43	—	8.59
6c	3290	1667	1212, 1057	834	0.76	3.99	7.07	6.83	7.10	7.28	3.69	7.24[h]	7.24[h]	—	8.56
6d	3312	1658	1226, 1057, 1028	848	0.77	3.86	7.28	6.81	7.09	7.05	3.70	7.27	6.96	—	8.56
6e	3310	1667	1220, 1129	809	0.80	3.99	7.06	6.81	7.09	7.27	3.71	6.51	—	6.56	8.56
7a	∼3400	1736	1181, 1166	801	0.85	3.27, 3.57	6.89[h]	6.67	7.12	6.89[h]	3.88	7.55	7.25[h]	7.25[h]	—
9a	3321	1638	1275, 1260, 1054	866	0.62	4.78	7.04	—	—	6.95	3.58	7.10	7.30	7.34	7.00[m]
9b	3315	1635	1278, 1260, 1051	808	0.72	4.78	7.04	—	—	6.96	3.64	7.34	7.11	—	7.08[m]
9c	3332	1670[n]	1231, 1055	866	0.70	4.76	7.03	—	—	6.96[h]	3.62	6.66	6.88[o]	—	6.95[h]
9d	3318	1636	1290, 1070,[n] 1027	849	0.72	4.61, 4.94	7.05[h]	—	—	6.96	3.63	7.37[p]	7.06,[h] 7.30	7.24	7.09[h]

[a] In KBr discs (cm^{-1}). Further IR bands, $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ bands (*mono*- or *para*-disubstituted benzene ring): 765 (**3d**, **5d**, **6e**), 757 (**3e**, **5c**,**e**, **6c**,**d**, **9b**–**d**), 742 (**4d**,**e**), 742, 698 (**7a**), 758, 701 (**9a**).
[b] In DMSO-d_6 or $CDCl_3$ (**3d**,**e**, **4d**,**e**, **5c**, **7a**) solution at 500 MHz. Chemical shifts in ppm (δ_{TMS}=0 ppm), coupling constants in hertz. Further signals: $ArCH_3$, s (3H): 2.43 (**5c**), 2.37 (**6c**); OCH_3, s (3H): 3.89 (**3d**,**e**), 3.81 (**4d**), 3.77 (**4e**, **9a**–**d**, for **9c** two overlapping signals), 3.84 (**5d**), 3.79 (**6d**, **9d**), 3.78 (**9a**,**b**), 3.70, 3.74 (**9c**); SCH, s (1H): 5.07 (**5b**), 4.54 (**5c**), 5.10 (**5d**,**e**); CHCl (**7a**), s (1H): 4.93.
[c] Assignments were supported by DEPT (except for **5b** and **6b**), HMQC (except for **3d** and **9d**), HMBC (except for **3d**).
[d] Condensed benzene ring.
[e] Ethyl group, *J*: 7.1 or 7.4 (**6e**, **9b**).
[f] X=S, s (**3d**,**e**, **4e**, **6b**–**e**), 2×d, *J*: 16.3 (**4d**), 12.6 (**5b**–**e**), 15.5 (**9a**), X=NH, d, *J*: 5.0 (**9a**–**c**) or 2×dd, *J*: 14.0 and 5.5 or 14.0 and 4.8 (**11d**).
[g] The atom numbering of benzothiazines was also used for benzothiazepines.
[h] Overlapping signals.
[i] Overlapping signals.
[k] In DMSO-d_6: 3.44 and 4.04 2×d, *J*: 16.5.
[l] Broad.
[m] t.
[n] Split band-pair with the second maximum at 1714 (**5e**), 1650 (**9c**), 1054 (**9d**).
[p] ∼d, H-6.
[o] d, *J*: 8.8.

Table 2
^{13}C NMR chemical shifts[a] for **3d**,**e**, **4d**,**e**, **5b**–**e**, **6b**–**e**, **7a** and **9a**–**d**[b]

Compound	CH_3 Et	C=O	$C_{quat.}$ (N)	SCH_2[c]	C-4a	C-5	C-6	C-7	C-8	C-8a	OCH_2 Et	C-1′	C-2′,6′	C-3′,5′	C-4′
			Benzothiazine or benzothiazepine ring[d]									Aryl group			
3d	—	—	160.8	29.1	120.2	127.2	128.8	127.6[e]	127.3[e]	145.1	—	131.1	130.4	114.2	162.9
3e	—	—	161.1	29.1	120.1	127.3	128.9	128.1	127.5	144.7	—	140.5	106.5	161.2	104.5
4d	—	160.0	70.8	29.8	121.3	128.98[e]	125.1	129.01[e]	121.0	133.6	68.1	128.5	129.3	114.1	160.4
4e	—	159.6	70.9	29.8	121.2	128.97[e]	125.1	129.03[e]	120.9	133.6	67.7	139.1	106.5[f]	161.0	100.8
5b	14.5	168.9	163.9	29.9	126.9	129.2	126.2	129.6	123.4	149.5	62.4	136.7	130.2	129.6	136.8
5c	14.2	168.9	164.6	30.8	126.7	129.3	125.9	129.0	123.1	149.5	62.6	135.4	127.9	129.8	141.6
5d	14.6	169.3	164.0	30.0	127.1	129.7	125.7	129.0	123.4	149.9	62.2	130.1[e]	130.2[e]	114.9	162.6
5e	14.6	169.1	164.6	29.9	127.0	129.8	126.0	129.1	123.4	149.6	62.3	140.0	106.5	161.5	103.9
6b	14.4	166.9	151.8	41.3	133.3	129.5	122.0	128.1	122.4	142.3	60.5	140.0	131.4	128.8	134.2
6c	14.4	167.5	153.1	41.9	132.8	129.6	121.6	128.0	122.4	142.4	60.4	138.3[e]	129.3[g]	129.5[g]	139.1[e]
6d	14.5	167.6	153.1	42.1	132.5	129.7	121.6	128.0	122.3	142.5	60.4	133.3	131.0	114.2	160.8
6e	14.4	167.3	152.1	41.6		129.6	121.7	128.0	122.4	142.4	60.5	142.9	107.7	160.9	101.7
7a	13.9	167.9	70.9	29.3	118.4	118.3	128.5[e]	128.87[e]	117.3	142.3	62.6	141.3	128.93	128.1	128.92[e]
9a	14.3	167.9	158.6	87.7	130.0	115.9	149.1	149.6	113.4	136.3	59.7	141.8	128.5	128.6	129.2
9b	14.4	167.5	157.4	88.1	129.6	116.0	149.2	149.6	113.4	136.3	59.8	133.8	130.4	1289.6	140.5
9c	14.6	168.2	158.5	87.2	130.2	115.9	149.1[e]	149.5	113.6	136.2	59.7	134.2	112.5	149.0[e]	150.3
9d	14.5	166.6	155.0	88.8	129.4	116.0	149.1	149.5	113.1	136.5	59.7	132.0	140.5	130.3	127.5

[a] In ppm (δ_{TMS}=0 ppm) at 125.7 MHz. Solvent: DMSO-d_6, for **3d**,**e**, **4d**,**e**, **5c** and **7a** $CDCl_3$. Further signals, $ArCH_3$: 21.9 (**5c**), 21.7 (**6c**); NCH_2 (thiazepine): 48.5 (**9b**,**c**), 48.4 (**9a**), 48.2 (**9d**); SCH or S(=C), thiazepine: 45.7 (**5b**), 46.9 (**5c**), 45.5 (**5d**), 46.0 (**5e**), 100.8 (**6b**), 100.5 (**6c**,**e**), 100.4 (**6d**); OCH_3: 55.9 (**3d**), 56.0 (**3e**), 55.7 (**4d**), 55.8 (**4e**), 56.3 (**5d**), 56.4 (**5e**), 56.2 (**6d**,**e**), 56.63 (**9a**), 56.6 (**9b**), 56.4, 56.5, 56.6 (**9c**), 56.59, 56.63 (**9d**); CHCl: 62.2 (**7a**).
[b] Assignments were supported by DEPT (except for **5b** and **6b**), HMQC (except for **3d** and **9b**) and HMBC (except for **3d**) measurements.
[c] NCH_2 (**9a**–**d**).
[d] The numbering of the carbons in the condensed ring of benzothiazine was also used for the benzothiazepine derivatives.
[e] Reversed assignment is also possible.
[f] Due to steric hindrance, a broadened signal.
[g] Overlapping lines.

known compounds, the spectroscopical and analytical data were identical to those reported.[16,17]

*4.2.1. 2-Phenyl-4H-3,1-benzothiazine (**3a**).* Pale-yellow crystalline powder, mp 54–56 °C (from diisopropyl ether), lit.[17] mp 55–58 °C; 2.3 g, 67%; R_f (42%, *n*-hexane:ethyl acetate 9:1).

*4.2.2. 2-(4-Chlorophenyl)-4H-3,1-benzothiazine (**3b**).* Pale-yellow crystalline powder, mp 121–123 °C (from diisopropyl ether), lit.[17] mp 122–125 °C; 2.7 g, 70%; R_f (40%, *n*-hexane:ethyl acetate 9:1).

*4.2.3. 2-(4-Methylphenyl)-4H-3,1-benzothiazine (**3c**).* Pale-yellow crystalline powder, mp 104–106 °C (from diisopropyl ether), lit.[16] mp 104–106 °C; 2.9 g, 81%; R_f (45%, *n*-hexane:ethyl acetate 9:1).

*4.2.4. 2-(4-Methoxyphenyl)-4H-3,1-benzothiazine (**3d**).* A pale-yellow crystalline powder, mp 122–123 °C (from diisopropyl ether); 3.1 g, 82%; R_f (43%, *n*-hexane:ethyl acetate 9:1). Anal. Calcd for $C_{15}H_{13}NOS$ (255.34): C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.82; H, 4.91; N, 5.73; S, 12.77.

*4.2.5. 2-(3,5-Dimethoxyphenyl)-4H-3,1-benzothiazine (**3e**).* A pale-yellow crystalline powder, mp 57–58 °C (from diisopropyl ether); 3.2 g 76%; R_f (40%, *n*-hexane:ethyl acetate 9:1). Anal. Calcd for $C_{16}H_{15}NO_2S$ (285.36): C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.62; H, 5.15; N, 5.02; S, 11.43.

4.3. General procedure for azetobenzothiazines (4d,e)

To a stirred solution of the corresponding 4*H*-3,1-benzothiazine derivatives **3d**,**e** (2.0 mmol) in anhydrous toluene, chloroacetyl chloride (0.24 mL, 3.0 mmol) was added. The solution was treated to reflux and triethylamine (0.40 mL, 3.0 mmol) in anhydrous toluene or benzene (20 mL) was added dropwise during 4 h at reflux. The addition of acid chloride (3.0 mmol) and triethylamine (0.40 mL, 3.0 mmol) was repeated twice under the same conditions as above. The reaction mixture was then cooled and extracted with brine (20 mL), and the organic layer was dried with Na_2SO_4. After evaporation, the residue was taken up in benzene (5 mL) and passed through a short column of silica, the solvent was evaporated off, and the oily residue crystallized on trituration with ethanol.

4.3.1. (2R,2aS*)-2-Chloro-2a-(4-methoxyphenyl)-2,2a-dihydro-2H,4H-azeto[1,2-a][3,1]benzothiazin-1-one (**4d**).* A white crystalline powder, mp 178–179 °C (from methanol); 0.39 g, 59%; R_f (75%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{17}H_{14}ClNO_2S$ (331.82): C, 61.53; H, 4.25; N, 4.22; S, 9.66. Found: C, 61.82; H, 4.11; N, 4.34; S, 9.87.

4.3.2. (2R,2aS*)-2-Chloro-2a-(3,5-dimethoxyphenyl)-2,2a-dihydro-2H,4H-azeto[1,2-a][3,1]benzothiazin-1-one (**4e**).* A white crystalline powder, mp 160–163 °C (from methanol); 0.41 g, 57%; R_f (70%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{18}H_{16}ClNO_3S$ (361.84): C, 59.75; H, 4.46; N, 3.87; S, 8.86. Found: C, 59.57; H, 4.31; N, 4.04; S, 9.10.

4.4. General procedure for the preparation of (*R**)-3-ethoxycarbonyl-2-aryl-3,5-dihydro-4,1-benzothiazepines (5b–e) and 3-ethoxycarbonyl-2-phenyl-1,5-dihydro-4,1-benzothiazepines (6b–e)

Azeto-3,1-thiazine **4b**–**e** (1 mmol) was dissolved in dichloromethane (1 mL). To this stirred solution, sodium ethoxide (100 mg, 1.41 mmol), dissolved in dry ethanol (10 mL) was added. The reaction mixture was allowed to stand at room temperature for 15 min. After evaporation, the residue was subjected to column chromatography [Merck Silica gel 60 (0.063–0.100)], using *n*-hexane:ethyl acetate 9:1, followed by *n*-hexane:ethyl acetate 4:1 as eluent (for the separation of **5b** and **6b**, *n*-hexane:ethyl acetate:acetonitrile:dichloromethane 85:5:6:4 was used as eluent). After evaporation of the corresponding

fractions, the oily residues (**5** or **6**) crystallized on trituration with *n*-hexane (3 mL).

4.4.1. (R)-3-Ethoxycarbonyl-2-(4-chlorophenyl)-3,5-dihydro-4,1-benzothiazepine (**5b**).* A white crystalline powder, mp 167–170 °C; 150 mg, 45%; R_f (58%, *n*-hexane:ethyl acetate:acetonitrile: dichloromethane 85:5:6:4). Anal. Calcd for $C_{18}H_{16}NO_2ClS$ (345.84): C, 62.51; H, 4.66; N, 4.05; S, 9.27. Found: C, 62.80; H, 4.72; N, 4.17; S, 9.15.

*4.4.2. 3-Ethoxycarbonyl-2-(4-chlorophenyl)-1,5-dihydro-4,1-benzothiazepine (**6b**).* A white crystalline powder, mp 149–152 °C; 76 mg, 22%; R_f (52%, *n*-hexane:ethyl acetate:acetonitrile:dichloromethane 85:5:6:4). Anal. Calcd for $C_{18}H_{16}NO_2ClS$ (345.84): C, 62.51; H, 4.66; N, 4.05; S, 9.27. Found: C, 62.71; H, 4.50; N, 3.88; S, 9.41.

4.4.3. (R)-3-Ethoxycarbonyl-2-(4-methylphenyl)-3,5-dihydro-4,1-benzothiazepine (**5c**).* A white crystalline powder, mp 142–144 °C; 127 mg, 39%; R_f (55%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{19}H_{19}NO_2S$ (325.43): C, 70.12; H, 5.88; N, 4.30; S, 9.85. Found: C, 69.83; H, 5.81; N, 4.12; S, 9.60.

*4.4.4. 3-Ethoxycarbonyl-2-(4-methylphenyl)-1,5-dihydro-4,1-benzothiazepine (**6c**).* A white crystalline powder, mp 136–138 °C; 68 mg, 21%; R_f (45%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{19}H_{19}NO_2S$ (325.43): C, 70.12; H, 5.88; N, 4.30; S, 9.85. Found: C, 70.24; H, 6.11; N, 4.15; S, 9.68.

4.4.5. (R)-3-Ethoxycarbonyl-2-(4-methoxyphenyl)-3,5-dihydro-4,1-benzothiazepine (**5d**).* A white crystalline powder, mp 108–110 °C; 178 mg, 52%; R_f (55%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{19}H_{19}NO_3S$ (341.43): C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found: C, 66.74; H, 5.77; N, 3.92; S, 9.57.

*4.4.6. 3-Ethoxycarbonyl-2-(4-methoxyphenyl)-1,5-dihydro-4,1-benzothiazepine (**6d**).* A white crystalline powder, mp 174–176 °C; 79 mg, 23%; R_f (45%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{19}H_{19}NO_3S$ (341.43): C, 66.84; H, 5.61; N, 4.10; S, 9.39. Found: C, 66.58; H, 5.79; N, 4.03; S, 9.55.

4.4.7. (R)-3-Ethoxycarbonyl-2-(3,5-dimethoxyphenyl)-3,5-dihydro-4,1-benzothiazepine (**5e**).* A white crystalline powder, mp 98–100 °C; 189 mg, 51%; R_f (55%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{20}H_{21}NO_4S$ (371.45): C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.83; H, 5.99; N, 3.81; S, 8.75.

*4.4.8. 3-Ethoxycarbonyl-2-(3,5-dimethoxyphenyl)-1,5-dihydro-4,1-benzothiazepine (**6e**).* A white crystalline powder, mp 95–97 °C; 71 mg, 19%; R_f (45%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{20}H_{21}NO_4S$ (371.45): C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.82; H, 5.84; N, 4.01; S, 8.76.

4.5. Preparation of intermediate 7a

Azeto-3,1-thiazine **4a** (200 mg, 0.66 mmol) was dissolved in dichloromethane (1 mL). To this stirred solution, sodium ethoxide (41 mg, 0.60 mmol) in dry ethanol (10 mL) was added. The reaction mixture was allowed to stand at room temperature for 5 min. After evaporation, the residue was subjected to column chromatography [Merck Silica gel 60 (0.063–0.100)], using *n*-hexane:ethyl acetate 9:1, followed by *n*-hexane:ethyl acetate 4:1 as eluent. After evaporation of the corresponding fractions, the oily residues crystallized on trituration with *n*-hexane (3 mL).

*4.5.1. Ethyl chloro-(2-phenyl-1,2-dihydro-4H-3,1-benzothiazin-2-yl) acetate (**7a**).* A white crystalline powder, mp 110–112 °C (from diisopropyl ether); 32 mg, 14%; R_f (74%, *n*-hexane:ethyl acetate 4:1). Anal. Calcd for $C_{18}H_{18}ClNO_2S$ (347.86): C, 62.15; H, 5.22; N, 4.03; S, 9.22. Found: C, 62.31; H, 5.47; N, 4.22; S, 9.42.

4.6. General procedure for 1,4-benzothiazepines (9a–d)

Azeto-1,3-thiazine **8a**–**d** (1.5 mmol) was dissolved in dry ethanol (20 mL). To this stirred solution, sodium ethoxide (200 mg, 3 mmol) was added. The reaction mixture was treated to reflux for 1 h, and then filtered. Upon cooling, the yellow crystals that separated out were filtered off and recrystallized.

*4.6.1. Ethyl 3-phenyl-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (**9a**).* A yellow crystalline powder, mp 166–167 °C; 0.51 g, 91%; R_f (62%, toluene:methanol 9:1). Anal. Calcd for $C_{20}H_{21}NO_4S$ (371.45): C, 64.67; H, 5.70; N, 3.77; S, 8.63. Found: C, 64.86; H, 5.57; N, 3.90; S, 8.69.

*4.6.2. Ethyl 3-(4-chlorophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (**9b**).* A yellow crystalline powder, mp 195–196 °C; 0.54 g, 89%; R_f(65%, toluene:methanol 9:1). Anal. Calcd for $C_{20}H_{20}ClNO_4S$ (405.90): C, 59.18; H, 4.97; N, 3.45; S, 7.90. Found: C, 58.92; H, 5.21; N, 3.69; S 8.10.

*4.6.3. Ethyl 3-(3,4-dimethoxyphenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (**9c**).* A yellow crystalline powder, mp 199–202 °C; 0.62 g 95%; R_f (60%, toluene:methanol 9:1). Anal. Calcd for $C_{22}H_{25}NO_6S$ (431.50): C, 61.24; H, 5.84; N, 3.25; S, 7.43. Found: C, 61.39; H, 5.94; N, 3.41; S, 7.63.

*4.6.4. Ethyl 3-(2-chlorophenyl)-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepine-2-carboxylate (**9d**).* A yellow crystalline powder, mp 196–198 °C; 0.57 g, 94%; R_f(67%, toluene:methanol 9:1). Anal. Calcd for $C_{20}H_{20}ClNO_4S$ (405.90): C, 59.18; H, 4.97; N, 3.45; S, 7.90. Found: C, 59.01; H, 4.77; N, 3.39; S, 8.12.

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References and notes

1. Elguero, J.; Katritzky, A. R.; Denisko, O. V. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: San Diego, 2000; Vol. 76, pp 2–64.
2. (a) Morijasu, M.; Kato, A.; Heshimoto, Y. *Chem. Lett.* **1984**, 1181–1184; (b) Morijasu, M.; Kato, A.; Heshimoto, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2955–2956; (c) Naidong, W.; Roets, E.; Busson, R.; Hoogmartens, J. *J. Pharm. Biomed. Anal.* **1990**, *8*, 881–889; (d) Skrdla, P. J.; Antonucci, V.; Lindemann, C. *J. Chromatogr. Sci.* **2001**, *39*, 431–440.
3. (a) Tanaka, K.; Nagahiro, R.; Ohba, S.; Eishima, M. *Tetrahedron Lett.* **2001**, *42*, 925–929; (b) Kanemitsu, H.; Uehara, K.; Fukuzumi, S.; Ogo, S. *J. Am. Chem. Soc.* **2008**, *130*, 17141–17147; (c) Yagi, M.; Hirano, S.; Toyota, S.; Kato, M.; Toda, F. *Cryst. Eng. Commun.* **2002**, *4*, 143–145.
4. (a) Jacobson, P. *Chem. Ber.* **1887**, *20*, 1732–1734; (b) Jacobson, P. *Chem. Ber.* **1888**, *21*, 2624–2631; (c) Stewart, A. W. *Recent Advances in Organic Chemistry*; Longmans Green: London, 1908; p 10.
5. Hantzsch, A.; Herrmann, W. A. *Chem. Ber.* **1887**, *20*, 2801–2811.
6. Lempert, K.; Nyitrai, J.; Zauer, K.; Kálmán, A.; Argay, G.; Duisenberg, A. J. M.; Sohár, P. *Tetrahedron* **1973**, *29*, 3565–3569.
7. Foces-Foces, C.; Llamas-Saiz, A. L.; Claramunt, R. M.; López, C.; Elguero, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1143–1145.
8. Csomós, P.; Fodor, L.; Sinkonen, J.; Pihlaja, K.; Bernáth, G. *Tetrahedron Lett.* **2006**, *47*, 5665–5667.
9. (a) Shin, C.-G.; Masaki, M.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1657–1660; (b) Namiki, Y.; Kihara, N.; Koda, S.; Hane, K.; Yasuda, T. *J. Antibiot.* **1993**, *46*, 1149–1155; (c) Vicente, J.; González-Herrero, P.; García-Sánchez, Y.; Pérez-Cadenas, M. *Tetrahedron Lett.* **2004**, *45*, 8859–8861; (d) Wang, A.; Zhang, H.; Tandel, S.; Black, A.; Nabity, T. S.; Biehl, E. R. *Arkivoc* **2001**, *i*, 154–171; (e) Sorokin, V. V.; Kriven'ko, A. P.; Ramazanov, A. K. *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 2782–2786.
10. (a) Lempert, K.; Nyitrai, J.; Sohár, P.; Zauer, K. *Tetrahedron Lett.* **1964**, *5*, 2679–2684; (b) Lempert, K.; Nyitrai, J.; Sohár, P. *Tetrahedron Lett.* **1965**, *6*,

1795–1799; (c) Nyitrai, J.; Lempert, K. *Tetrahedron* **1969**, *25*, 4265–4275; (d) Nyitrai, J.; Lempert, K. *Acta Chim. Acad. Sci. Hung.* **1972**, *73*, 43–61.
11. (a) Foces-Foces, C.; Alkorta, I.; Elguero, J. *Acta Crystallogr.* **2000**, *B56*, 1018–1028; (b) García, M. A.; López, C.; Claramunt, R. M.; Kenz, A.; Pierrot, M.; Elguero, M. *Helv. Chim. Acta* **2002**, *85*, 2763–2776.
12. (a) Böcskei, Z.; Simon, K.; Rao, R.; Caron, A.; Rodger, C. A.; Bauer, M. *Acta Crystallogr.* **1998**, *C54*, 808–810; (b) Bauer, M.; Harris, R. K.; Rao, R. C.; Apperley, D. C.; Rodger, C. A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 475–481.
13. Sala, L. F.; Martell, A. E.; Motekaitis, R. J. *Inorg. Chim. Acta* **1987**, *135*, 123–127.
14. (a) Desiraju, G. R. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1025–1030; (b) Casas, J. S.; Castellano, E. E.; Macías, A.; Playá, N.; Sánchez, A.; Sordo, J.; Varela, J. M.; Zukerman-Schpector, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 475–481; (c) Bauer, M.; Harris, R. K.; Rao, R. C.; Apperley, D. C.; Rodger, C. A. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1025–1030; (d) Aranova, E. B.; Ginak, A. I. *Russ. J. Gen. Chem.* **2001**, *71*, 1605–1607; (e) Aranova, E. B.; Ginak, A. I. *Russ. J. Appl. Chem.* **2002**, *75*, 1885–1886; (f) Aranyi, P., et al. Sanofi-Aventis, PCT WO 2005009969; *Chem. Abstr.* **2005**, *142*, 197895; (g) Finta, Z., et al. Sanofi-Aventis, PCT WO 2005100320; *Chem. Abstr.* **2005**, *143*, 410963; (h) Reviriego, F.; Alkorta, I.; Elguero, J. *J. Mol. Struct.* **2008**, *891*, 325–328; (i) Boldt, P.; Zippel, S.; Ratzkowsky, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2615–2617; (j) Holczer, W.; Claramunt, R. M.; López, C.; Alkorta, I.; Elguero, J. *Solid State Nucl. Magn. Res.* **2008**, *34*, 68–76.
15. Fodor, L.; Csomós, P.; Csámpai, A.; Sohár, P., in press.
16. Csomós, P.; Fodor, L.; Bernáth, G.; Sinkkonen, J.; Salminen, J.; Wiinamäki, K.; Pihlaja, K. *Tetrahedron* **2008**, *64*, 1002–1011.
17. El-Desoky, S. I.; Kandeel, E. M.; Abd-el-Raham, A. H. *J. Heterocycl. Chem.* **1999**, *36*, 153–160.
18. Holly, S.; Sohár, P. In *Theoretical and Technical Introduction to the Series Absorption Spectra in the Infrared Region*; Láng, L., Prichard, W. H., Eds.; Akadémiai Kiadó: Budapest, 1975; p 113.
19. Wamhoff, H.; Dürbeck, H. W.; Sohár, P. *Tetrahedron* **1971**, *27*, 5873–5891.
20. Sohár, P. *Nuclear Magnetic Resonance Spectroscopy*; CRC: Boca Raton, FL, 1983; Vol. 1, p 69.
21. Fodor, L.; Szabó, J.; Szűcs, E.; Bernáth, G.; Sohár, P.; Tamás, J. *Tetrahedron* **1984**, *40*, 4089–4095.