Synthesis of optically active 3,4,5,6-tetrahydro-2*H*-1,4-thiazin-3-ones and their benzo analogues by ring transformation of glycidic esters

Karsten Woydowski,[a] Jörg Fleischhauer,[b] Jan Schiffer[b] and Jürgen Liebscher*[a]

[a] *Institut für Chemie, Humboldt-Universität Berlin, Hessische Str. 1–2, D-10115 Berlin, Germany*
[b] *Institut für Organische Chemie, RWTH-Aachen, Prof.-Pirlet-Str. 1, D-52074 Aachen, Germany*

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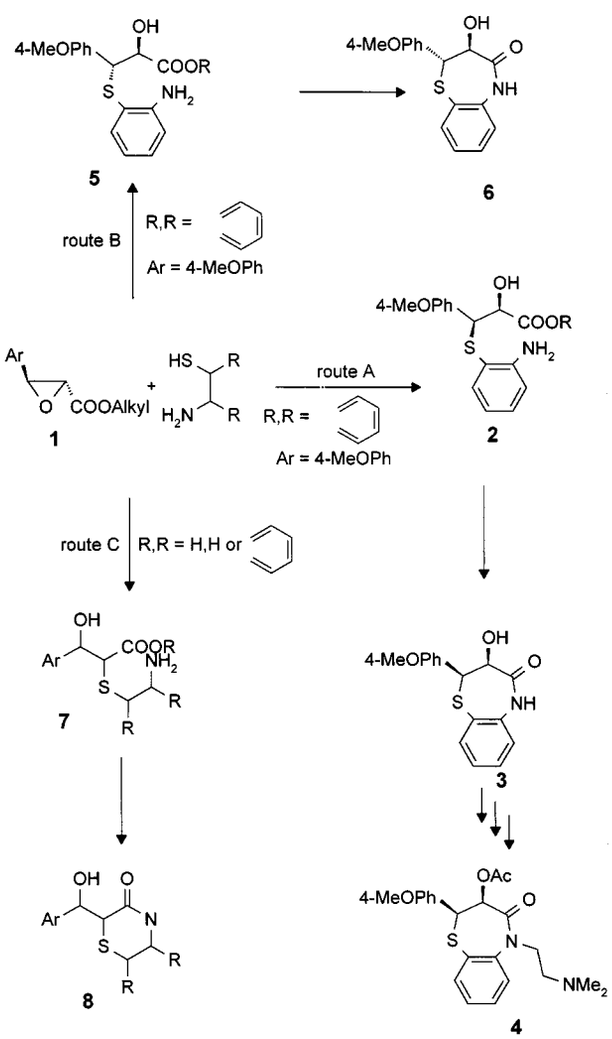
Chiral *cis* and *trans* glycidic esters **9** substituted by alkyl or ethoxycarbonyl react with cysteamine or *o*-aminothiophenol **10** by stereoselective ring transformation to non-aromatic optically active 2-(α-hydroxyalkyl)-1,4-thiazin-3-ones **12**. The attack of the mercapto function at the α-position of the glycidate occurs predominantly by inversion of configuration. As compared with known reactions of aryl-substituted glycidates with *o*-aminothiophenol or cysteamine preferentially giving thiazepinones, a remarkable effect of the substituent in the glycidate on the regiochemistry was found.

Ring transformations of arylglycidic esters **1** (3-aryl-2,3-epoxypropionic esters) with *o*-aminothiophenol have gained practical interest because of their application in the synthesis of pharmacologically active 1,5-benzothiazepin-4(5*H*)-ones such as the well-known calcium channel blocker Diltiazem® **4**.[1] Under thermal or acidic conditions, primary attack of the S-atom at the β-position of the *trans*-glycidic ester **1** opens the oxirane ring preferentially by retention of configuration (formation of a benzyl cation by protonation of the oxirane O-atom) giving α-hydroxy-β-arylthio esters **2** that finally cyclise to the *cis*-substituted 1,5-benzothiazepin-4(5*H*)-one **3** (route A).[1–7] Under basic conditions inversion of configuration was observed in the ring opening reaction of the oxirane (route B, formation of **5**) thus affording *trans*-substituted 1,5-benzothiazepin-4(5*H*)-ones **6** after cyclisation.[1,5] Inversion of configuration was also found if $MgCl_2$ or $CaCl_2$ was added[1] or microwave conditions were applied in acetic acid solution.[8] The regio- and stereoselectivity of the reactions of *o*-aminothiophenol with *cis*-glycidic esters were found to be similar to those of *trans*-glycidic esters.[9,10]

In reactions of the *trans*-glycidate **1** (Ar = 4-MeOPh) with *o*-aminothiophenol in dipolar aprotic solvents, another regioisomeric ring opening product sometimes occured, *i.e.* a β-hydroxy-α-arylthio ester was predominantly formed, which was derived from the attack of the mercapto function at the α-position.[3] If stronger basic conditions (KOH–EtOH) were applied, the primary attack of the *o*-aminothiophenolate S-atom again occurs at the α-position of the glycidic ester **1** (Ar = Ph) followed by attack of the amino group at the ester moiety thus leading to a 6-membered 3,4-dihydro-2*H*-benzo-1,4-thiazin-3-one **8** after intramolecular amide formation (route C). However the constitution of the product was doubted and the absolute and relative configuration is unknown.[11] In the reaction with cysteamine the *trans*-glycidic ester **1** (Ar = 4-MeOPh) gave a mixture of a thiazepinone (according to route B) and a 1,4-thiazin-3-one **8** (R = H) (according to route C) with inversion of configuration.[12] With a few exceptions[5,6,13] all reported syntheses shown in Scheme 1 afford racemates that were resolved in a number of cases.



Scheme 1

Reactions of aliphatic glycidic esters with *o*-aminothiophenol or cysteamine are scarce in the literature. An epoxidized 5-alkylbutenolide was reported to give ring transformation products with cysteine methyl ester, similar to route C but the stereochemistry of the resulting dihydro-1,4-thiazinone was not reported.[14]

We report now the reaction of enantiomerically pure *cis* and

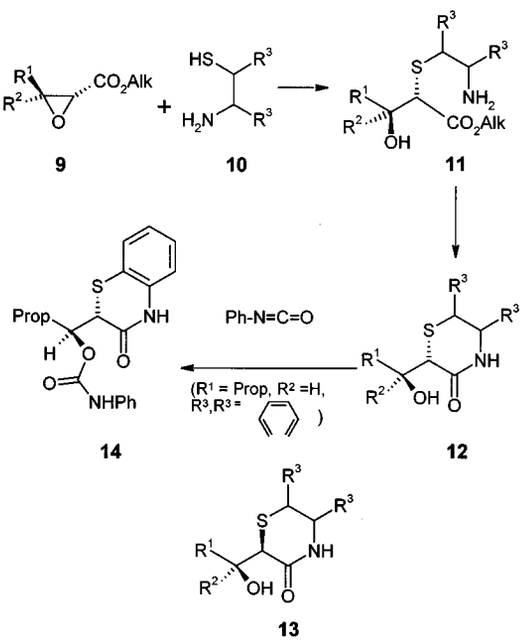
Table 1 1,4-Thiazin-3-ones **12** and **13**

R^1	R^2	Alk	R^3	R^3	**12**[a] (yield %)	**13**[a] (yield %)	Dr (**12**:**13**)
n-Pr	H	Me	H	H	**a** (65)	**a** (21)	[b]
n-Pr	H	Me	benzo		**b** (76)		>95:5
CO_2Et	H	Et	H	H	**c** (94)[c]		84:16
CO_2Et	H	Et	benzo		**d** (91)		95:5
H	Me	Me	H	H	**e** (54)	**e** (25)	[b]
H	Me	Me	benzo		**f** (52)		>95:5

[a] Dr >95:5 after column chromatography. [b] Could not be determined from the crude product. [c] Not separable by column chromatography.

trans alkylglycidic esters **9** ($R^1 = CO_2Et$, $R^2 = H$) with *o*-aminothiophenol and cysteamine in order to synthesize new optically active S,N-heterocycles. Since these starting materials lack aryl substituents at the oxirane ring a different regio- and stereoselectivity can be expected as compared with the known reactions of aryl-substituted glycidic esters **1**. Considerable difference between aryl- and alkyl-substituted glycidic esters in the mode of ring transformations with *o*-phenylenediamine has been observed before.[15,16]

The enantiomerically pure starting materials **9** were readily available by intramolecular S_N reaction starting from (*R*,*R*)-diethyl tartrate ($R^1 = COOEt$, $R^2 = H$)[17] or L-threonine ($R^1 = H$, $R^2 = Me$)[18] or by Sharpless epoxidation of *trans*-hex-2-en-1-ol followed by oxidation (R^1 or R^2 = alkyl and R^2 or $R^1 = H$, respectively).[19] Surprisingly, no thiazepinones similar to route A or B (Scheme 1) were found in reactions of the non-aryl substituted glycidates **9** with *o*-aminothiophenol or cysteamine; 2-(α-hydroxyalkyl)-2*H*-1,4-thiazin-3-ones **12** were obtained in all cases (Scheme 2). The reactions were performed in ethanolic



Scheme 2

solution and were completed by reflux in the presence of TsOH with the exception of compound **12c** which was formed at room temperature without an acid catalyst. Generally, high stereoselectivity could be achieved with *o*-aminothiophenol (see Table 1). In the case of cysteamine-derived products (**12a**, **12c** and **12e**) the epimer **13** could be detected in higher quantities and isolated with the exception of **13c**. The structures of thiazinones **12** and **13** were unambiguously elucidated. Thus X-ray crystal analysis of **12e** (see Fig. 1) and similarities in the NMR spectra of **12a**, **12c** and **12e** proved the regio- and stereochemical outcome of the reaction with cysteamine ($R^3 = H$). Since no suitable crystals were formed in the benzo-condensed series **12** (R^3R^3 = =CH–CH=CH–CH=) derived from *o*-aminothiophenol a crystalline urethane **14** was synthesized by reaction of **12b** with phenylisocyanate. X-Ray crystal analysis of **14** confirmed the constitution as well as the configuration of **12b** to be analogous to **12e**. However, the X-ray data of **14** could not be refined to satisfactory *R*-values because of disorders in the crystal.

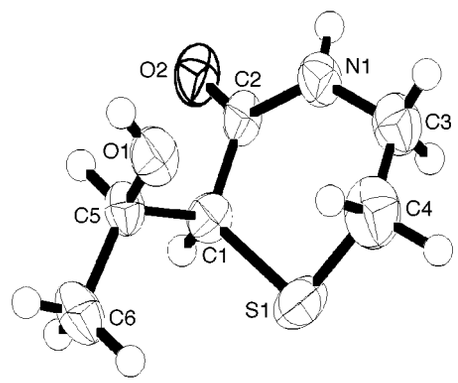


Fig. 1 X-Ray crystal structure of **12e**.

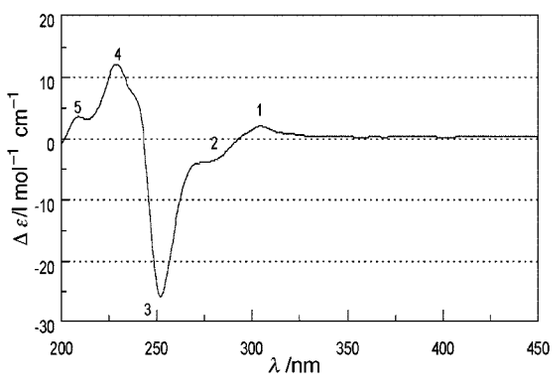


Fig. 2 CD spectrum of **12b**.

In order to get further evidence for the absolute configuration of the benzo-condensed thiazinones **12** the CD spectrum of **12b** was measured (Fig. 2) and compared with a simulation obtained by quantum chemical methods (Fig. 3). To reduce the flexibility of the molecule we substituted the *n*-propyl group (R^1) in **12b** by a methyl group. This substitution should not have any significant influence on the signs of the Cotton effects. Starting from standard structural parameters[20] we searched for low energy conformers by variation of the dihedral angle *v* (stepsize 10°) defined in Fig. 4 using the MM3 forcefield.[21–23] We obtained the potential curve shown in Fig. 5. Starting from the geometries of the three minima of Fig. 5 ($v_1 = 60°$, $v_2 = 180°$, $v_3 = 300°$) optimization of the energy resulted in the three local minima described in Table 2. In the minimum 2 with the lowest energy (Boltzmann factor 0.95) the hydrogen atom at carbon b (see Fig. 4) is above the plane of the thiazine ring.

To calculate the CD spectra for the three minima we used the programs DZDO and MCD3SP written by John Downing and Josef Michl, University of Colorado at Boulder. These programs contain the CNDO/2S method which has been developed for the calculation of transition energies and transi-

Table 2 Structural parameters (v_i), energies (E_i) and Boltzmann factors (w_i) (T = 298 K) found with MM3 for the three local minima (i = 1, 2, 3)

Minimum	v_i (°)	E_i/kcal mol^{-1}	W_i (298 K)
1	58.9	8.09	0.04
2	176.7	6.29	0.95
3	296.2	9.36	0.01

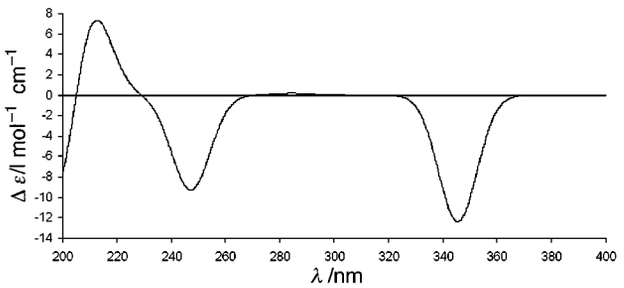


Fig. 3 Total calculated CD spectrum for the model compound.

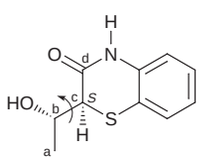


Fig. 4 Definition of the dihedral angle v = a–b–c–d in the model structure for **12b**. Above a dihedral angle of 180° is shown.

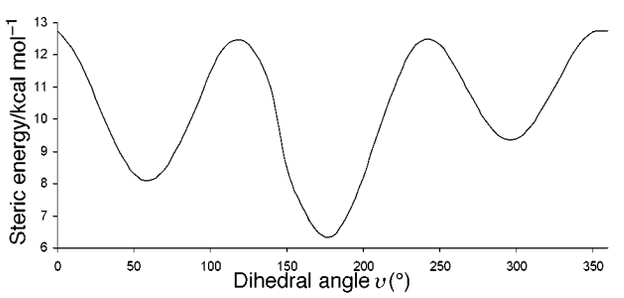


Fig. 5 Potential curve for the rotation of the 1-hydroxyethyl-ring bond by variation of v.

tion moments.[24] Configuration interaction (CI) included 196 single excited configurations formed from the 14 highest filled orbitals and 14 lowest empty orbitals. No d-orbitals for the sulfur atom were included. The CD-spectra of the three minima are quite similar to each other. To obtain the total CD spectrum in Fig. 3 these local minima CD spectra were multiplied by their Boltzmann factors (Table 2) and then superimposed.

In the experimental CD spectrum (Fig. 2) five Cotton effects (CE) are present. Starting at the long wavelength side the first is at 304 nm (positive, rather small intensity), the second at 280 nm (negative), than the third at 252 nm (negative, rather intense) and two positive CEs at 229 nm and 209 nm (four and five).

In the calculated spectrum a very small positive CE appears at 285 nm, which we correlate with the experimental first CE at 304 nm. From the analysis of the wavefunctions it follows that this transition can be classified as a π–π*-transition which is mainly located in the thiophenyl ring.

The negative third CE at 252 nm should be related to the calculated negative CE at 245 nm. From the inspection of the wavefunctions it follows that this should also be a π–π*-transition mainly located in the thiophenyl ring.

In the region of the positive fourth and fifth CE two transitions are found with positive rotational strengths which are responsible for the calculated fourth CE. Both can be classified as π–π*-transitions where the π is located in the thiophenyl group and the π* also partly in the carbonyl group.

The experimental negative CE at 280 nm should be an n–π* transition mainly localized in the carbonyl group. With the CNDO/2S method we calculate a rather strong negative CE of n–π* nature at 345 nm. We are therefore tempted to relate this calculated transition to the experimental one at 280 nm. This is supported by Kramer[25] who found that CNDO/2S but also INDO/S,[26,27] ZINDO/S[28] and CNDUV[29] give much too small n–π*-transition energies.

If one accepts these arguments one sees that the semi-empirical calculations for the molecule of *S*,*S*-configuration give at least a hint that the absolute configuration at carbon c (Fig. 4) in **12b** is also *S*.

That this can not be more than a hint follows also from the fact that the rotational strength of a transition is a scalar product of the corresponding electric and magnetic transition moments and so its sign depends strongly on the angle between the two vectors. If this angle is very different from 90 degrees one is on the safe side. In our case however for all the transitions mentioned above this angle is not very far from 90 degrees.

These results revealed a uniform configuration in both the cysteine-derived and the benzo-condensed series **12** R^3 = H or R^3R^3 = CH=CH–CH=CH, respectively. The structure of the minor stereoisomers **13** was confirmed by NMR spectroscopy showing that alternative 7-membered hydroxythiazepinone isomers analogous to **3** or **6** can be ruled out.

Thus the ring transformation of non-aryl substituted glycidic esters **9** with cysteamine or *o*-aminothiophenol occurs exclusively by attack of the mercapto function at the α-position of the glycidate and predominantly by inversion of configuration rather than at the β-position and by retention of configuration as found in the aryl-substituted series (*vide supra*). Hence a marked effect of the substituent at the oxirane moiety of glycidates exists in ring transformations with β-amino-α-mercapto binucleophiles. This difference is presumably caused by the preferential formation of intermediate benzyl cations in the β-position of aryl glycidates.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively on a Bruker AC-300 in $CDCl_3$ with TMS as internal standard. Mass spectra (HP 5995 A) were measured at 70 eV. Optical rotations were determined with a Perkin-Elmer polarimeter 241 (c 1, $CHCl_3$, d = 2 mm). Circular dichroism in terms of ellipticity θ (in deg) was measured on a JASCO J710 spectrometer (minimum wavelength 190 nm). θ and $\Delta\varepsilon$ are interrelated by the equation $\theta/33 = \Delta\varepsilon cl$. The spectral band width was 0.5 nm, the time constant 0.5 s and the temperature 24 °C. For preparative column chromatography silica (0.04–0.063 mm, Merck) was used. Starting materials **9** were obtained according to literature procedures.[17–19]

2-(α-Hydroxyalkyl)-1,4-thiazin-3-ones 12 and 13

A solution of the glycidate **9** (1.5 mmol) in 2 cm^3 dry ethanol was treated with cysteamine (127 mg, 1.65 mmol) or *o*-aminothiophenol **10** (176 mg, 1.65 mmol). The mixture was stirred under argon at room temperature for 1 h (for compounds **12a**, **12d**, **13a**) or refluxed under argon for 1–1.5 h (for compounds **12b**, **12e**, **12f**, **13e**). After cooling to room temperature TsOH (28 mg, 0.15 mmol, but 142 mg, 0.75 mmol for compound **12a**) was added and refluxing was continued for an additional 1–3 h. For compounds **12e**, **12f**, **13e** TsOH (47 mg, 0.25 mmol) was added before refluxing. Compound **12c** was obtained without TsOH by stirring at room temperature under argon for 15 h. After cooling to room temperature ethanol was evaporated and the residue was purified by column chromatography (silica gel; dichloromethane–acetone 95 : 5). In the case of compound **12a**

the residue obtained after evaporating ethanol was diluted with *ca*. 10 cm^3 dichloromethane and washed with *ca*. 10 ml diluted aqueous $NaHCO_3$ before submitting to chromatography.

(2*S*,1′*S*)-3,4,5,6-Tetrahydro-2-(1-hydroxybutyl)-2*H*-1,4-thiazin-3-one 12a. Colourless oil, $[\alpha]_D^{20} = -65.5$ (Found: C, 50.62; H, 7.98; N, 7.22; S, 16.58. $C_8H_{15}NO_2S$ requires C, 50.75; H, 8.00; N, 7.40; S, 16.94%); δ_H 0.87 (t, $J = 6.95$, CH_3), 1.31–1.62 (m, 2 CH_2), 2.74–2.88 (m, CH_2–S), 3.35 (d, $J = 8.36$, CH–S), 3.39–3.61 (m, CH_2–N), 3.90 (m, CH–O), 4.62 (s, OH), 7.66 (s, NH); δ_C 14.3 (CH_3), 18.5 (CH_2–CH_3), 27.0 (CH_2–S), 36.4 (CH_2–CH), 43.0 (CH_2–N), 45.6 (CH–S), 71.6 (CH–O), 173.2 (C=O).

(2*R*,1′*S*)-3,4,5,6-Tetrahydro-2-(1-hydroxybutyl)-2*H*-1,4-thiazin-3-one 13a. Colourless oil, $[\alpha]_D^{20} = +73.0$ (Found: C, 50.24; H, 7.81; N, 7.26; S, 16.58. $C_8H_{15}NO_2S$ requires C, 50.75; H, 8.00; N, 7.40; S, 16.94%); δ_H 0.87 (t, $J = 7.09$, CH_3), 1.38–1.60 (m, 2 CH_2), 2.81–2.96 (CH_2–S), 3.50 (d, $J = 2.13$, CH–S), 3.40–3.68 (m, CH_2–N), 4.15 (m, CH–O), 7.40 (NH); δ_C 14.3 (CH_3), 19.6 (CH_2–CH_3), 25.8 (CH_2–S), 36.4 (CH_2–CH), 44.2 (CH_2–N), 47.6 (CH–S), 71.7 (CH–O), 171.4 (C=O).

(2*S*,1′*S*)-3,4-Dihydro-2-(1-hydroxybutyl)-2*H*-1,4-benzothiazin-3-one 12b. Colourless crystals, mp 142 °C (AcOEt), $[\alpha]_D^{20} = +71.4$ (Found: C, 60.88; H, 6.52; N, 6.00; S, 13.50. $C_{12}H_{15}NO_2S$ requires C, 60.72; H, 6.38; N, 5.90; S, 13.51%); δ_H 0.93 (t, $J = 7.15$, CH_3), 1.37–1.85 (m, 2 CH_2), 3.44 (d, $J = 8.63$, CH–S), 3.91–3.97 (m, CH–O, OH), 6.94–7.32 (m, 4 CH_{Ar}), 9.67 (s, NH); δ_C 14.3 (CH_3), 18.7, 36.7 (CH_2), 47.0, 70.0 (CH), 117.8, 124.6, 127.7, 128.1 (CH_{Ar}), 119.4, 135.9 (C_{Ar}), 168.8 (C=O).

Ethyl (2*S*,2′*R*)-2-hydroxy-2-(3,4,5,6-tetrahydro-3-oxo-2*H*-1,4-thiazin-2-yl)acetate 12c. Colourless oil (Found: C, 43.86; H, 5.98; N, 6.50; S, 14.84. $C_8H_{13}NO_4$ requires C, 43.81; H, 5.99; N, 6.39; S, 14.62%); δ_H 1.20 (t, $J = 7.15$, CH_3), 2.51–2.58 and 3.10–3.19 (m, CH_2–S), 3.52–3.67 (m, CH_2–N), 3.80 (d, $J = 2.50$, CH–S), 4.14–4.23 (m, CH_2–O), 4.31 (s, br, OH), 4.98 (d, $J = 2.50$, CH–O), 7.75 (s, NH); δ_C 14.5 (CH_3), 24.8 (CH_2–S), 44.6 (CH–S), 45.5 (CH_2–N), 62.4 (CH_2–O), 74.1 (CH–O), 168.2, 172.7 (C=O).

Ethyl (2*S*,2′*R*)-2-hydroxy-2-(3-oxo-3,4-dihydro-2*H*-1,4-benzothiazin-2-yl)acetate 12d. Colourless oil, $[\alpha]_D^{20} = -36.1$ (Found: C, 53.97; H, 4.97; N, 5.30; S, 12.41. $C_{12}H_{13}NO_4S$ requires C, 53.91; H, 4.91; N, 5.24; S, 12.00%); δ_H 1.12 (t, $J = 7.15$, CH_3), 3.86–4.11 (m, CH_2, OH), 4.01 (d, $J = 4.74$, CH–S), 4.40 (d, $J = 4.47$, CH–O), 6.80–7.19 (m, 4 CH_{Ar}), 9.97 (s, NH); δ_C 14.4 (CH_3), 46.1 (CH–S), 62.6 (CH_2), 70.7 (CH–O), 117.0, 123.7, 126.7, 127.3 (CH_{Ar}), 118.1, 135.3 (C_{Ar}), 165.9, 171.0 (C=O).

(2*S*,1′*R*)-3,4,5,6-Tetrahydro-2-(1-hydroxyethyl)-2*H*-1,4-thiazin-3-one 12e. Colourless crystals, mp 99–100 °C (AcOEt–hexane), $[\alpha]_D^{20} = -110$ (Found: C, 44.78; H, 6.82; N, 6.68. $C_6H_{11}NO_2S$ requires C, 44.69; H, 6.89; N, 8.69%); δ_H 1.25 (d, $J = 6.45$, CH_3), 2.71–2.92 (m, CH_2–S), 3.49 (d, $J = 3.27$, CH–S), 3.44–3.62 (m, CH_2–N), 3.79 (m, CH–O), 4.27 (s, OH), 7.42 (s, NH); δ_C 20.4 (CH_3), 25.7 (CH_2–S), 44.2 (CH_2–N), 48.3 (CH–S), 68.4 (CH–O), 171.2 (C=O).

(2*R*,1′*R*)-3,4,5,6-Tetrahydro-2-(1-hydroxyethyl)-2*H*-1,4-thiazin-3-one 13e. Colourless oil, $[\alpha]_D^{20} = +57.2$ (Found: C, 44.70; H, 6.88; N, 8.46; S, 19.52. $C_6H_{11}NO_2S$ requires C, 44.70; H, 6.88; N, 8.69; S, 19.89%); δ_H 1.23 (d, $J = 6.27$, CH_3), 2.11–2.89 (m, CH_2–S), 3.32 (d, $J = 8.45$, CH–S), 3.39–3.62 (m, CH_2–N), 4.06 (m, CH–O), 4.78 (s, OH), 7.60 (s, NH); δ_C 20.7 (CH_3), 26.9 (CH_2–S), 43.2 (CH_2–N), 46.9 (CH–S), 68.4 (CH–O), 173.0 (C=O).

(2*S*,1′*R*)-3,4-Dihydro-2-(1-hydroxyethyl)-2*H*-1,4-benzothiazin-3-one 12f. Colourless crystals, mp 61–62 °C (AcOEt–hexane), $[\alpha]_D^{20} = -105.9$ (Found: C, 56.94; H, 5.32; N, 6.54. $C_{10}H_{11}NO_2S$ requires C, 57.38; H, 5.31; N, 6.69%); δ_H 1.28 (d, $J = 6.35$, CH_3), 3.20 (d, $J = 2.72$, OH), 3.37 (d, $J = 6.14$, CH–S), 4.04 (m, CH–O), 6.84–7.24 (m, 4 CH_{Ar}), 9.85 (s, NH); δ_C 20.3 (CH_3), 50.6 (CH–S), 65.3 (CH–O), 117.7, 124.6, 127.7, 128.4 (CH_{Ar}), 118.6, 136.2 (C_{Ar}), 167.7 (C=O); MS: (M = 208.04) (*m*/*z*) 208 (4), 164 (68), 136 (66), 44 (100).

Crystal structure determination for the compound 12e [30]

Crystals were obtained by crystallisation from hot ethyl acetate–hexane. A colourless crystal of **12e** with the dimensions $0.70 \times 0.38 \times 0.16$ mm was measured on a STOE Stadi4 diffractometer using MoKα radiation ($\lambda = 0.71073$ Å). Crystal data: $C_6H_{11}NO_2S$, $M = 161.22$, orthorhombic space group $P212121$, $a = 5.452(12)$ Å, $b = 7.353(6)$ Å, $c = 19.264(19)$ Å, $V = 772.3(19)$ Å^3, $Z = 4$, $D_c = 1.387$ g cm^{-3}, $F(000) = 344$, $\mu(\text{MoK}\alpha) = 0.359$ mm^{-1}. At 293(2) K in the range of $2.11° < \theta < 20.01°$ 3191 reflections were measured ($R_{(sig)} = 0.0233$) of which 723 were unique ($R_{(int)} = 0.0366$) and 673, flagged as observed, had intensities larger than $2\sigma(I)$. The structure was solved by direct methods and refined by least squares procedure within the SHELX program system. The final residuals were $wR_{2(all)} = 0.1317$, $R_{1(all)} = 0.0474$ and $R_{1(obs)} = 0.0464$. The maximum and minimum peaks in the final difmap were 0.430 and −0.186 e Å^{-3}, respectively.†

Acknowledgements

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† Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC web page (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/284. See http://www.rsc.org/suppdata/perkin1/1999/149/ for crystallographic files in .cif format.

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30 Full details have been deposited at the Fachinformationszentrum Karlsruhe, Gesellschaft für Wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, Germany. Any request for this material should quote a full literature citation and the reference number CSD 408920.

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