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Synthesis and Conformational Study of Stereoisomeric 3-Benzylperhydro-1,2,3-benzoxathiazine and -benzoxathiazole 2-oxides*

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cis- and *trans*-fused 3-benzyl-3,4,4a,5,6,7,8,8a-octahydro-1,2,3-benzoxathiazine 2-oxides and 3-benzyl-3*H*-3a,4,5,6,7,7a-hexahydro-1,2,3-benzoxathiazole 2-oxides have been prepared by means of cyclization of *cis*-and *trans*-*N*-benzyl-2-aminomethyl- and -2-amino-cyclohexanols with thionyl chloride and *N*-sulfinylamides. Depending on the ring-closure reagent, different ratios of the diastereomers were found. Configurational and conformational assignments were based on the analysis of ^{1}H and ^{13}C NMR spectra.

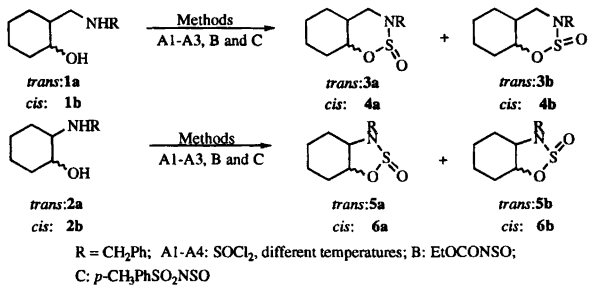
The use of chiral sulfoxides in organic synthesis is a well-known and valuable strategy.[1] Oxathiazolidine 2-oxide and 3,4-dihydrobenzoxathiazine 2-oxide derivatives have been used to prepare optically pure sulfoxides, and the isomerization of the aminosulfite group has been studied under acidic conditions.[2,3] It is necessary to obtain one of the diastereomeric oxathiazine 2-oxides stereoselectively or the equilibrium state of the isomerization must lie on one side or the other in order to benefit the synthesis of chiral sulfoxides. On the other hand it is not obvious why one of the isomeric 3,4-dihydrobenzoxathiazine 2-oxides is preferred.[4] Perhydrobenzoxathiazine 2-oxides should be conformationally more mobile, which has a further influence on the diastereomer ratios. Earlier investigations have shown that the saturated analogues of benzoxathiazines and benzoxathiazoles prefer the sulfinyl oxygen to be axial. Furthermore, when the nitrogen atom is in the bridgehead position of a six-membered ring, a single diastereomer with an axial sulfinyl oxygen is formed.[5,6] This paper describes the synthesis and conformational study of compounds **3** to **6** (Scheme 1).

Results and discussion

Synthesis. The 1,2- and 1,3-amino alcohols were prepared according to literature prodecures.[7,8] They were cyclized at three different temperatures by means of three different reagents (Scheme 1). The *cis*- and *trans*-fused saturated benzoxathiazine and benzoxathiazole 2-oxides were formed in different stereoisomeric ratios depending on the conditions.

When thionyl chloride in the presence of 2.4 equiv. of triethylamine (modified method of Wudl and Lee)[9] was applied *cis*-oxathiazines were formed as an equimolar mixture of the diastereomers **4a** and **4b**, regardless of temperature (Table 1). Under the same conditions, the diastereomeric ratio of *trans*-oxathiazines **3a** and **3b** was 2:3. The *trans*-oxathiazolidine was also a mixture of two diastereomers. Depending on the temperature the stereoisomer ratio varied from 3:2 to 4:1. In the case of the *cis*-oxathiazolidine, very high stereoselectivity was found (product ratio 95:5).

It has been reported that oxathiazolidine 2-oxides are equilibrated by triethylamine hydrochloride.[2] Method A2 was therefore repeated by keeping the reaction mixture at 0 °C for 24 h before removing the triethylamine hydrochloride formed. This did not cause any significant



R = CH_2Ph; A1-A4: $SOCl_2$, different temperatures; B: EtOCONSO;
C: *p*-CH_3PhSO_2NSO

Scheme 1. Cyclization reactions of amino alcohols.

*Dedicated to the 50th birthday of Professor Erich Kleinpefer (Germany).

Table 1. Isomer ratios (based on the ^{1}H NMR spectra of crude products) and total yields of the synthezised compounds.

	Isomer ratios (yields in parentheses)					
Compound	Method A1 ($SOCl_2$, −17 °C)	A2 ($SOCl_2$,5 °C)	A3 ($SOCl_2$,25 °C)	A2[a] ($SOCl_2$,5 °C)	B (EtOCONSO,25 °C)	C (*p*-CH_3PhSO_2NSO,25 °C)
3a:**3b**	3:2 (68)	3:2 (83)	3:2 (87)	7:3 (79)	0:1 (50)	0:1 (27)
4a:**4b**	1:1 (75)	3:2 (58)	1:1 (48)	1:1 (60)	1:0 (30)	1:0 (32)
5a:**5b**	3:2 (86)	4:1 (58)	3:1 (57)	4:1 (50)	2:3 (43)	2:3 (30)
6a:**6b**	93:7 (67)	—	94:6 (65)	—	3:1 (38)	3:1 (20)

[a] After a period of 24 h at 0 °C before work-up.

changes in the isomer ratios. To improve the stereoselectivity, the ring closure induced by *N*-sulfinylamides and *N,N'*-sulfinyldiimidazole was attempted. With *N*-sulfinyl amides, the reactive intermediate is different (the first step being an addition to the double bond) from that with thionyl chloride (the first step proceeding by an S_N2 mechanism).[10] The reactions of *N*-sulfinylurethane (method B) and *N*-sulfinyl-*p*-toluenesulfonamide[11] (method C) with **1a** and **1b** yielded a single isomer, albeit in low yields. For the oxathiazolidines, methods B and C did not improve the stereoselectivity, although the isomer ratio did change somewhat. Reaction of *N,N'*-sulfinyldiimidazole with **1a** and **2a** yielded the ring-closure product in only trace amounts (monitored by ^{1}H NMR spectroscopy). For *N*-methyl-substituted analogues, however, it proved successful.[10]

Conformations. The assignment of conformations is based on the ^{1}H and ^{13}C NMR spectral data shown in Tables 2–4.

Benzoxathiazines. In the case of benzoxathiazines, the *cis* isomers (**4a** and **4b**) can exist in two stable chair–chair conformations ('O-in' and 'O-out'). The *trans* isomers (**3a** and **3b**), of course, can attain one double chair conformation only, with equatorial and axial sulfinyl oxygens, respectively. The coupling constants ^3J(4eq,4a) and ^3J(4ax,4a) are characteristically different for the 'O-in' and 'O-out' conformers. H-4a is axial relative to the oxathiazine ring in the 'O-out' form. One of the coupling constants is therefore considerably larger than the other. In the 'O-in' conformation, H-4a is equatorial and the values of ^3J(4eq,4a) and ^3J(4ax,4a) are smaller and closer to each other. Table 3 shows that, for *trans* isomers bound to an 'O-out' conformation, one of the vicinal coupling constants is ca. 12 Hz and the other ca. 4 Hz. Both coupling constants for **4a** with the 'O-in' conformation are relatively small (2.4 Hz and 3.3 Hz). The coupling constants of 7.7 and 4.6 Hz for **4b** indicate that it exists in conformational equilibrium between 'O-in' and 'O-out' forms.

The anisotropy effect of the S=O bond in cyclic systems indicates that protons *syn* to this bond are deshielded and those *anti* to it are shielded.[9] Thus, in **3a** the deshielded H-4 has equatorial (^3J=4.2 Hz) and the shielded H-4 has axial (^3J=11.5 Hz) orientation with respect to the vicinal bridgehead proton H-4a. In **3b** the situation is reversed (Fig. 1). In the ^{1}H NMR spectrum of diastereomer **4a**, the geminal protons adjacent to the ring nitrogen resonate at δ 2.40 and 3.58 (^2J = −14.0 Hz) and both exhibit a small coupling to the bridgehead proton H-4a [^3J(4eq,4a)=2.4 Hz and ^3J(4ax,4a)=3.3 Hz, respectively] (Fig. 2). In support of these assignments the other bridgehead proton (H-8a) is deshielded in **3b** and **4a** and shielded in **3a** and **4b**.

When the lone-pair orbital of nitrogen bisects the angle between geminal protons, the geminal coupling constant becomes more negative.[12] Thus, ^2J(4ax,4eq) of −14.5 Hz for **3a** and −12.5 Hz for **3b** indicate that the benzyl group is axial in **3a** and equatorial in **3b**. The value of −13.2 Hz for **4b** supports the conclusion that it

Table 2. ^{1}H NMR chemical shifts (δ_{TMS} = 0) for compounds **3a,b**–**6a,b** in $CDCl_3$.

Compound	H-4eq	H-4ax	H-8a	NCH_2Ph	H-4a,5,6,7,8 (9 H)	Ar*H* (5 H)
3a	3.05 (2.67)[a]	3.04 (2.57)[a]	3.96	4.75,3.67	0.85–2.03	7.26–7.36
3b	2.50	3.26	4.57	4.15,3.81	1.02–1.92	7.27–7.37
4a	2.40	3.58	5.09	4.21,3.51	1.20–2.15	7.27–7.36
4b	2.82	3.36	4.41	4.18,3.94	1.22–2.37	7.26–7.37

Compound	H-3a	H-7a	NCH_2Ph	H-4,5,6,7 (8 H)	Ar*H* (5 H)
5a	2.60	4.57	4.41,4.28	1.05–2.26	7.27–7.36
5b	3.14	3.85	4.22,3.98	1.14–2.29	7.27–7.43
6a	3.55	5.00	4.20 (3.92,3.83)[a]	1.16–1.92	7.28–7.43
6b	3.23	4.54	4.39,4.16	—	—

[a] In C_6D_6.

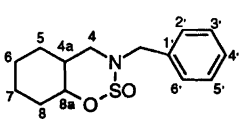
Table 3. Proton–proton coupling constants (Hz) for compounds **3a,b–6a,b.**

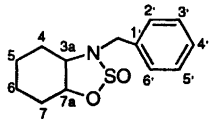
Compound	^2J(4eq,4ax)	^3J(4eq,4a)	^3J(4ax,4a)	^3J(4a,8a)	^3J(8a,8eq)	^3J(8a,8ax)	NCH_2
3a	−14.5	4.2	11.5	10.7	4.2	10.7	−14.4
3b	−12.5	3.9	12.1	10.7	4.0	10.7	−14.1
4a	−12.2	2.4	3.3	—[a]	—[a]	—[a]	−14.0
4b	−13.2	4.6	7.7	4.0	4.0	8.0	−14.1

Compound	^3J(3a,7a)	^3J(3a,4eq)	^3J(3a,4ax)	^3J(7a,7eq)	^3J(7a,7ax)	NCH_2
5a	10.0	3.6	11.5	4.1	11.7	−15.1
5b	10.2	3.4	10.6	3.8	11.8	−14.1
6a	5.1	5.1	6.7	5.7	5.7	−14.4
6b	5.5	5.5	9.6	4.4	4.4	−14.6

[a] Not observable.

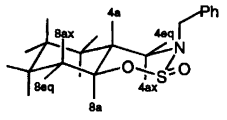
Table 4. ^{13}C NMR chemical shifts for compounds **3a,b–6a,b** in $CDCl_3$ solution ($\delta_{TMS}=0$).



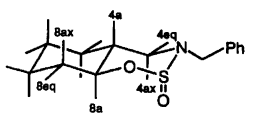


Comp.	C-3a	C-4	C-4a	C-5	C-6	C-7	C7a	C-8	C-8a	C-1′	C-2′,6′	C-3′,5′	C-4′	NCH_2
3a		50.17	34.73	28.00	25.17	24.46		32.22	81.04	136.72	128.66	128.79	127.59	43.77
3b		43.98	39.00	28.82	25.15[a]	25.04[a]		31.24	71.51	136.15	128.59	128.69	127.91	53.27
4a		44.51	35.38	24.61	25.18	19.78		30.64	65.34	136.13	128.61	128.56	127.82	53.85
4b		43.50	34.07	27.78	22.95[b]	22.77[b]		31.06	77.99	136.26	128.53	128.53	127.66	51.85
5a	67.78	29.17[c]		23.85[d]	23.52[d]	29.32[c]	84.33			136.94	128.47	128.71	127.89	50.32
5b	61.56	28.71		24.03[e]	23.94[e]	30.65	89.61			136.60	128.62	128.95	127.89	47.90
6a	56.82	28.25		20.66[f]	20.97[f]	26.40	81.50			137.09	128.68	128.74	127.89	47.47
6b	56.99	28.74		22.30	20.32	26.89	84.16			136.20	128.29	128.58	127.74	46.32

[a,b,c,d,e,f] Alternative assignment is also possible.

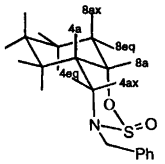


3a

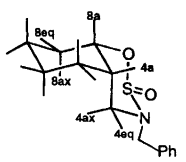


3b

Fig. 1. Conformations of *trans*-fused benzoxathiazines **3a** and **3b**.



"O-in"

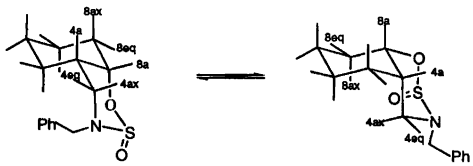


"O-out"

Fig. 2. Compound **4a** exists entirely in the 'O-in' conformation with the sulfinyl oxygen in an axial position.

is a mixture of two interconverting chair–chair conformations (Fig. 3).

A useful configurational and conformational indicator is the γ-effect, i.e., an axial S=O bond results in shielding of the carbon atom in the γ position as compared with the case where the S=O is equatorial.[13] This difference is 9.5 ppm for C-8a and 6.2 ppm for C-4 in **3a** and **3b**. In



"O-in" "O-out"

Fig. 3. Conformational equilibria of compound **4b**; the amount of both conformations is about equal.

4a, the shifts for C-8a (65.34 ppm) and C-4 (44.51 ppm) clearly show the axial orientation of the sulfinyl oxygen. In **4b**, the shift for C-8a (77.99 ppm) is more downfield than expected because there is an axial carbon (C-8), instead of hydrogen in the 'O-out' form, which results in the loss of the major part of the 'γ' shift.[13] The shift for C-4 in **4b** is upfield from what would be expected due to the γ-effect of the axial C-8 in the 'O-out' form.[14] The chemical shift of C-7 forms another nice configurational and conformational indicator since, for **4a**, it falls 4.7 ppm and 5.3 ppm downfield from that for **3a** and **3b**, respectively, as expected, since the ring oxygen is in the axial position in **4a**. The C-7 shift for **4b** (22.77 ppm) is between the value for **4a** and the mean value for **3a** and **3b**, again a good indicator of the conformational equilib-

rium of **4b**.[15] The chemical shift difference for C-5 (in **4a** ca. 4 ppm downfield from those in **3a** and **3b**) stems from the same effect.

In **4b**, the axial C-4 causes a downfield shift at C-6 in the 'O-out' form.[14] The difference between the chemical shifts of the NCH_2Ph carbons in **3a** (43.81 ppm) and **3b** (53.23 ppm) confirms that the benzyl group is axial in **3a** since there are two γ_{gauche}-effects from both oxygens in **3a**, compared with only one in **3b**. The axial benzyl group causes a downfield shift at C-4a in **3a**. It is not clear what the exact orientation of the benzyl group in **4b** is, but the NCH_2Ph chemical shift indicates some axial character, i.e., the nitrogen is inverted.

Benzoxathiazolidines. From the anisotropy effect of the S=O bond it is obvious that, of the two *trans* isomers, **5a** ($\delta_{H\text{-}3a}$ 2.60 and $\delta_{H\text{-}7a}$ 4.57) is the one with a pseudoaxial sulfinyl oxygen (Fig. 4). A comparison of the chemical shifts of C-7a and C-3a in **5a** (84.33 and 67.78 ppm) and **5b** (89.61 and 61.56 ppm) confirms this assignment. The coupling constants for the *cis*-fused isomers indicate conformational equilibria for both. These values suggest that **6a** is a ca. 1:1 mixture of the 'O-in' and 'O-out' conformers and that there is a roughly 4:1 preference for the 'O-in' conformation in **6b**.

Compared with **6b** the downfield shifts of H-7a (5.00 ppm) and H-3a (3.55 ppm) and the upfield shift of C-7a (81.50 ppm) show that **6a** is the isomer with the sulfinyl oxygen *exo* to the cyclohexane ring (Fig. 5). The shifts for C-5 and C-6 confirm that the contributions of the two conformers to **6a** are about equal. The C-5 shift (22.30 ppm) of **6b** obviously suffers the S=O, C-4 *syn*-axial interaction which may partly compensate the high field effect. The C-6 shift (20.32 ppm) is in agreement

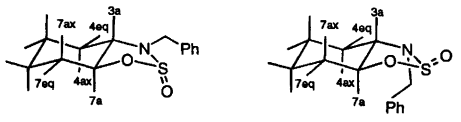


Fig. 4. Conformations of *trans*-fused benzoxathiazolidines **5a** and **5b**.

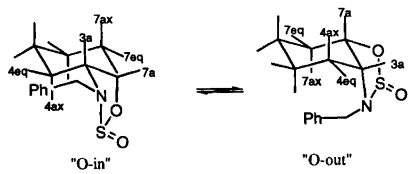


Fig. 5. Conformations of **6a**; the amount of both forms is about equal.

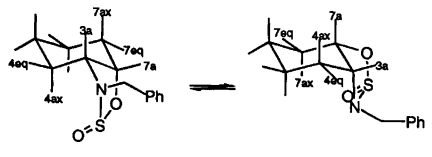


Fig. 6. Conformations of **6b**; the 'O-in' form is favoured.

with the ca. 80 % preference of the 'O-in' conformation (Fig. 6) and the presence of the C–O axial interaction.

In both isomers, the benzyl group probably adopts the orientation in which there is no eclipsed interaction between itself and the sulfinyl oxygen.

Experimental

General procedures. Melting points were recorded on an electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 400 and 500 MHz with Jeol JNM-LA400 and Jeol JNM-A500 FT-spectrometers at 27 °C, with TMS as an internal standard. For column chromatography Merck silica gel 60 Art. 9385 was used. Preparative thin-layer chromatography was performed with Merck silica gel 60 $F_{254}S$ Art. 13792.

General methods for ring-closure reactions. Method A1. To a solution of the amino alcohol **1a**, **1b**, **2a** or **2b** (0.50 g) and triethylamine (2.4 equiv.) in anhydrous diethyl ether (100 ml) at −17 °C a solution of thionyl chloride (1.1 equiv.) in anhydrous diethyl ether (5 ml) was added. The mixture was allowed to warm to r.t. and stirred for an additional 5 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5%, 50 ml), and then with water (4 × 50 ml), and dried (Na_2SO_4). The solvent was removed to give the crude product, which was subjected to preliminary purification by column chromatography to give a mixture of two isomers in each case.

Method A2. To a solution of the amino alcohol **1a**, **1b** or **2a** (0.50 g) and triethylamine (2.4 equiv.) in anhydrous benzene (50 ml) at 5 °C, a solution of thionyl chloride (1.1 equiv.) in anhydrous benzene (10 ml) was added. The solution was allowed to warm to r.t. and stirred for an additional 5 h. The reaction mixture was washed with aqueous sodium hydrogen carbonate solution (5%, 50 ml), and then with water (4 × 50 ml), and dried (Na_2SO_4). The solvent was removed to give the crude product, which was subjected to preliminary purification by column chromatography to give a mixture of two isomers in each case.

Method A3. As method A2, but thionyl chloride was added at r.t.

Method B. To a solution of urethane (0.41 g, 4.6 mmol) and pyridine (0.74 ml, 9.2 mmol) in 15 ml of anhydrous diethyl ether, a solution of thionyl chloride (0.33 ml, 4.6 mmol) in anhydrous diethyl ether (5 ml) was added dropwise at −7 °C. The suspension was stirred for 30 min with cooling, and then for 2 h at room temperature. The precipitate was filtered off and washed with anhydrous diethyl ether. The filtrate was added dropwise to a solution of the amino alcohol **1a**, **1b**, **2a** or **2b** (2.3 mmol) in 20 ml of anhydrous diethyl ether, at r.t. After 4 h the mixture was extracted with water, then dried (Na_2SO_4) and the solvent was evaporated off. The crude product

was chromatographed on silica gel to yield either a single isomer or a mixture of two isomers.

Method C. To a solution of amino alcohol **1a**, **1b**, **2a** or **2b** (2.3 mmol) in 20 ml of dichloromethane, a solution of *N*-sulfinyl-*p*-toluenesulfonamide[11] (4.6 mmol, 2 equiv.) in dichloromethane (21 ml) was added at r.t. The reaction mixture was stirred for 3 h, after which 40 ml of 5% aqueous potassium carbonate solution were added. After extraction with dichloromethane, drying and evaporation, the residue was chromatographed on silica gel to yield either a single isomer or a mixture of two isomers.

Separation and purification of isomers. trans-Fused 3-benzyl-3,4,4a,5,6,7,8,8a-octahydro-1,2,3-benzoxathiazine 2-oxides **3a** and **3b**: From a mixture of the two isomers fractional crystallization from ethanol yielded isomer **3a** in pure form (10%, m.p. 105–106 °C). 200 mg of crude product (from method B) were subjected to preparative thin-layer chromatography (ethyl acetate–petroleum ether 1:3). The compound with $R_f = 0.42$ was identified as pure isomer **3b** (100 mg, 50%, colourless oil).

cis-Fused 3-benzyl-3,4,4a,5,6,7,8,8a-octahydro-1,2,3-benzoxathiazine 2-oxides **4a** and **4b**: The crude product (from method C) was purified by column chromatography (ethyl acetate–petroleum ether 1:3) to yield isomer **4a** (R_f in TLC 0.51, 180 mg, 32%) which was crystallized from diethyl ether (m.p. 67–72 °C). 126 mg of crude product (from method A3) was column chromatographed (ethyl acetate–petroleum ether 1:3) to yield isomer **4b** (R_f in TLC 0.65, 28 mg, 22 %, colourless oil, no satisfactory elemental analysis obtained).

trans-Fused 3-benzyl-3*H*-3a,4,5,6,7,7a-hexahydro-1,2,3-benzoxathiazole 2-oxides **5a** and **5b**: 370 mg of crude product (from method A3) were column chromatographed (ethyl acetate–petroleum ether 1:4). The less mobile component (R_f in TLC 0.45, 120 mg, 32%) was crystallized from diethyl ether–petroleum ether to yield isomer **5a** (m.p. 61–63 °C). The more mobile component (R_f in TLC 0.50, 40 mg, 11%) was crystallized from ether to yield isomer **5b** (m.p. 49–51 °C).

cis-Fused 3-benzyl-3*H*-3a,4,5,6,7,7a-hexahydro-1,2,3-benzoxathiazole 2-oxides **6a** and **6b**: 350 mg of crude product (from method A3) were column chromatographed (ethyl acetate–petroleum ether 1:4). The component with $R_f = 0.42$ was identified as pure isomer **6a** (220 mg, 63%, m.p. 57–59 °C). Isomer **6b** was not obtained in pure form; the spectral data on **6b** are taken from an 84:16 mixture of **6a** and **6b**.

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