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-3H-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-sulfanilamides. 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-dihydrobenzoxa-
thiazine 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 sulfur atom to be axial. Furthermore, when the nitrogen atom is in the bridgehead position of a six-membered ring, a single diastereomer with an axial sulfur atom 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 procedures.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 stereo isomeric ratios depending on the conditions.

When thionyl chloride in the presence of 2.4 equiv. of triethylamine (modified method of Wudl and Lee) 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

\[ \text{Scheme 1. Cyclization reactions of amino alcohols.} \]
Table 1. Isomer ratios (based on the \(^1\)H NMR spectra of crude products) and total yields of the synthesised compounds.

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<tbody>
<tr>
<td>3a:3b</td>
<td>3:2 (68)</td>
<td>3:2 (83)</td>
<td>3:2 (87)</td>
<td>7:3 (79)</td>
<td>0:1 (50)</td>
<td>0:1 (27)</td>
</tr>
<tr>
<td>4a:4b</td>
<td>1:1 (75)</td>
<td>3:2 (58)</td>
<td>1:1 (48)</td>
<td>1:1 (60)</td>
<td>1:0 (30)</td>
<td>1:0 (32)</td>
</tr>
<tr>
<td>5a:5b</td>
<td>3:2 (88)</td>
<td>4:1 (58)</td>
<td>3:1 (57)</td>
<td>4:1 (50)</td>
<td>2:3 (43)</td>
<td>2:3 (30)</td>
</tr>
<tr>
<td>6a:6b</td>
<td>93:7 (67)</td>
<td>—</td>
<td>94:6 (85)</td>
<td>—</td>
<td>3:1 (30)</td>
<td>3:1 (20)</td>
</tr>
</tbody>
</table>

* 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 \(N\)-sulfinylanilides and \(N,N\)-sulfinylidimidazole was attempted. With \(N\)-sulfinylanilides, 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 Sp2 mechanism). The reactions of \(N\)-sulfinylurethane (method B) and \(N\)-sulfinyl-p-toluenesulfonylamide (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 \(N,N\)-sulfinylidimidazole 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.

Conformations. The assignment of conformations is based on the \(^1\)H and \(^13\)C NMR spectral data shown in Tables 2-4.

Benzoazathiazines. In the case of benzoazathiazines, 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 \(J\)(4eq,4a) and \(J\)(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 \(J\)(4eq,4a) and \(J\)(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. Thus, in 3a the deshielded \(H\)-4 has equatorial (\(\phi = 4.2\) Hz) and the shielded \(H\)-4 has axial (\(\phi = 11.5\) 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 \(\delta\) 2.40 and 3.58 (\(\phi = -14.0\) Hz) and both exhibit a small coupling to the bridgehead proton \(H\)-4a \(J\)(4eq,4a) = 2.4 Hz and \(J\)(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. Thus, \(J\)(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 (\(\delta_{\text{TMS}} = 0\)) for compounds 3a-6a, 6b in CDCl\(_3\).

<table>
<thead>
<tr>
<th>Compound</th>
<th>H-4eq</th>
<th>H-4ax</th>
<th>H-8a</th>
<th>NCH(_3)Ph</th>
<th>H-4a,5,6,7,8 (9 H)</th>
<th>ArH (5 H)</th>
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<tbody>
<tr>
<td>3a</td>
<td>3.05 (2.67)*</td>
<td>3.04 (2.57)*</td>
<td>3.96</td>
<td>4.75,3,67</td>
<td>0.85–2.03</td>
<td>7.26–7.36</td>
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<tr>
<td>3b</td>
<td>2.50</td>
<td>3.26</td>
<td>4.57</td>
<td>4.15,3,81</td>
<td>1.02–1.92</td>
<td>7.27–7.37</td>
</tr>
<tr>
<td>4a</td>
<td>2.40</td>
<td>3.58</td>
<td>5.09</td>
<td>4.21,3,51</td>
<td>1.20–2.15</td>
<td>7.27–7.36</td>
</tr>
<tr>
<td>4b</td>
<td>2.82</td>
<td>3.36</td>
<td>4.41</td>
<td>4.18,3,94</td>
<td>1.22–2.37</td>
<td>7.26–7.37</td>
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* In \(C_6D_6\).
Table 3. Proton–proton coupling constants (Hz) for compounds 3a–b, 6a,b.

<table>
<thead>
<tr>
<th>Compound</th>
<th>2J(4eq,4ax)</th>
<th>3J(4eq,4a)</th>
<th>3J(4ax,4a)</th>
<th>3J(4a,8a)</th>
<th>3J(8a,8eq)</th>
<th>3J(8a,8ax)</th>
<th>NCH₂</th>
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<tr>
<td>3a</td>
<td>−14.5</td>
<td>4.2</td>
<td>11.5</td>
<td>10.7</td>
<td>4.2</td>
<td>10.7</td>
<td>−14.4</td>
</tr>
<tr>
<td>3b</td>
<td>−12.5</td>
<td>3.9</td>
<td>12.1</td>
<td>10.7</td>
<td>4.0</td>
<td>10.7</td>
<td>−14.1</td>
</tr>
<tr>
<td>4a</td>
<td>−12.2</td>
<td>2.4</td>
<td>3.3</td>
<td>−a</td>
<td>−a</td>
<td>−a</td>
<td>−14.0</td>
</tr>
<tr>
<td>4b</td>
<td>−13.2</td>
<td>4.6</td>
<td>7.7</td>
<td>4.0</td>
<td>4.0</td>
<td>8.0</td>
<td>−14.1</td>
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</table>

* Not observable.

Table 4. 13C NMR chemical shifts for compounds 3a,b–6a,b in CDCl₃ solution (δTMS = 0).

<table>
<thead>
<tr>
<th>Comp.</th>
<th>C-3a</th>
<th>C-4</th>
<th>C-4a</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
<th>C7a</th>
<th>C-8</th>
<th>C-8a</th>
<th>C-1'</th>
<th>C-2',6'</th>
<th>C-3',5'</th>
<th>C-4'</th>
<th>NCH₂</th>
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<tr>
<td>3a</td>
<td>50.17</td>
<td>34.73</td>
<td>28.00</td>
<td>25.17</td>
<td>24.46</td>
<td>32.22</td>
<td>81.04</td>
<td>136.72</td>
<td>128.66</td>
<td>128.79</td>
<td>127.59</td>
<td>43.77</td>
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<td>3b</td>
<td>43.98</td>
<td>39.00</td>
<td>28.82</td>
<td>25.15*</td>
<td>25.04*</td>
<td>31.24</td>
<td>71.51</td>
<td>136.15</td>
<td>128.59</td>
<td>128.69</td>
<td>127.91</td>
<td>53.27</td>
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<tr>
<td>4a</td>
<td>44.51</td>
<td>35.38</td>
<td>24.61</td>
<td>25.18</td>
<td>19.78</td>
<td>30.64</td>
<td>65.34</td>
<td>136.13</td>
<td>128.61</td>
<td>128.56</td>
<td>127.82</td>
<td>53.85</td>
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<tr>
<td>4b</td>
<td>43.50</td>
<td>34.07</td>
<td>27.78</td>
<td>22.95b</td>
<td>22.77b</td>
<td>31.06</td>
<td>77.99</td>
<td>136.26</td>
<td>128.53</td>
<td>128.53</td>
<td>127.66</td>
<td>51.85</td>
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<td>5a</td>
<td>67.78</td>
<td>29.17c</td>
<td>23.85d</td>
<td>23.52d</td>
<td>29.32c</td>
<td>84.33</td>
<td>136.94</td>
<td>128.47</td>
<td>128.71</td>
<td>127.89</td>
<td>50.32</td>
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<tr>
<td>5b</td>
<td>61.56</td>
<td>28.71</td>
<td>24.03*</td>
<td>23.94*</td>
<td>30.65</td>
<td>89.61</td>
<td>136.60</td>
<td>128.62</td>
<td>128.95</td>
<td>127.89</td>
<td>47.90</td>
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<tr>
<td>6a</td>
<td>56.82</td>
<td>28.25</td>
<td>20.66f</td>
<td>20.97f</td>
<td>26.40</td>
<td>81.50</td>
<td>137.09</td>
<td>128.68</td>
<td>128.74</td>
<td>127.89</td>
<td>47.47</td>
<td></td>
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<tr>
<td>6b</td>
<td>56.99</td>
<td>28.74</td>
<td>22.30</td>
<td>20.32</td>
<td>28.89</td>
<td>84.16</td>
<td>136.20</td>
<td>128.29</td>
<td>128.58</td>
<td>127.74</td>
<td>46.32</td>
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* a, b, c, d e f Alternative assignment is also possible.

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

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. This difference is 9.5 ppm for C-8a and 6.2 ppm for C-4 in 3a and 3b. In 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. 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. 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. 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. The difference between the chemical shifts of the NCH₃Ph carbons in 3a (43.81 ppm) and 3b (53.23 ppm) confirms that the benzyl group is axial in 3a since there are two δ Cuomo 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 NCH₃Ph 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 (δH₂₃a 2.60 and δH₂₃b 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 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 ¹³C NMR spectra were recorded in CDCl₃ 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 F₂₅₄ 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 (Na₂SO₄). 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 (Na₂SO₄). 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 (Na₂SO₄) 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-toluenesulfonylamide 11 (4.6 mmol, 2 equiv.)
in dichloromethane (21 ml) was added at r.t. The reac-
tion mixture was stirred for 3 h, after which 40 ml of 5% aqueous
potassium carbonate solution were added. After ex-
traction with dichloromethane, drying and evapora-
tion, 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 chro-
matography (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 chro-
matographed (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-3H-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 chro-
matographed (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-3H-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 chro-
matographed (ethyl acetate–petroleum ether 1:4). The com-
ponent 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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