Novel Synthesis of 2-Aryl-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-ones and Their *S*-Oxides

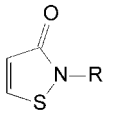
by **Anja Siegemund**, **Christine Hartung**, **Sven Baumann**, and **Bärbel Schulze***

Fakultät für Chemie und Mineralogie, Universität Leipzig, Johannisallee 29, D-04103 Leipzig
(phone: +49(0)341-9736540; fax: +49(0)341-9736599; e-mail: bschulze@organik.chemie.uni-leipzig.de)

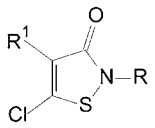
Dedicated to Professor Dr. *Manfred Mühlstädt* on the occasion of his 75th birthday

2-Aryl-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-ones **1a**–**e** were synthesized by cyclocondensation of 2-(thiocyanato)cyclohexene-1-carboxanilides **9** as a convenient new method. Their *S*-oxides **10** were prepared by two routes, either by oxidation of **1** or dehydration of *rac-cis*-3-hydroperoxysultims **11**. Furthermore, compounds **1** have been identified by HPLC–API-MS-MS as intermediates in the oxidation process of the salts **6**. The hydroperoxides **12b** and *rac-trans*-**11b** have been unambiguously detected by HPLC–MS investigations and in the reaction of *rac-cis*-**13b** with H_2O_2 to the hydroperoxides *rac-trans*-**11b** and *rac-cis*-**11b**.

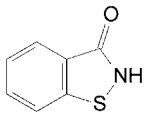
Introduction. – Isothiazol-3(2*H*)-ones **A**–**D** [1], 1,2-benzisothiazol-3(2*H*)-ones **E**, and their heterocyclic bioisosteric derivatives are potent industrial microbiocides with antifungal and antibacterial activities [2]. As reported previously, 2-alkyl-4,5,6,7-tetrahydro-1,2-benzisothiazolones are prepared by cyclization of 2-oxocyclohexane-1-carboxamides with H_2S [3a–c], or 2-(benzylsulfinyl)cyclohexene-1-carboxamides and thionylchloride [4a–c]. These bicyclic 2-alkylisothiazolones are also antibacterial agents.



A R = Me
B R = Me$(CH_2)_7$



C R = Me, R^1 = H
D R = Me$(CH_2)_7$, R^1 = Cl

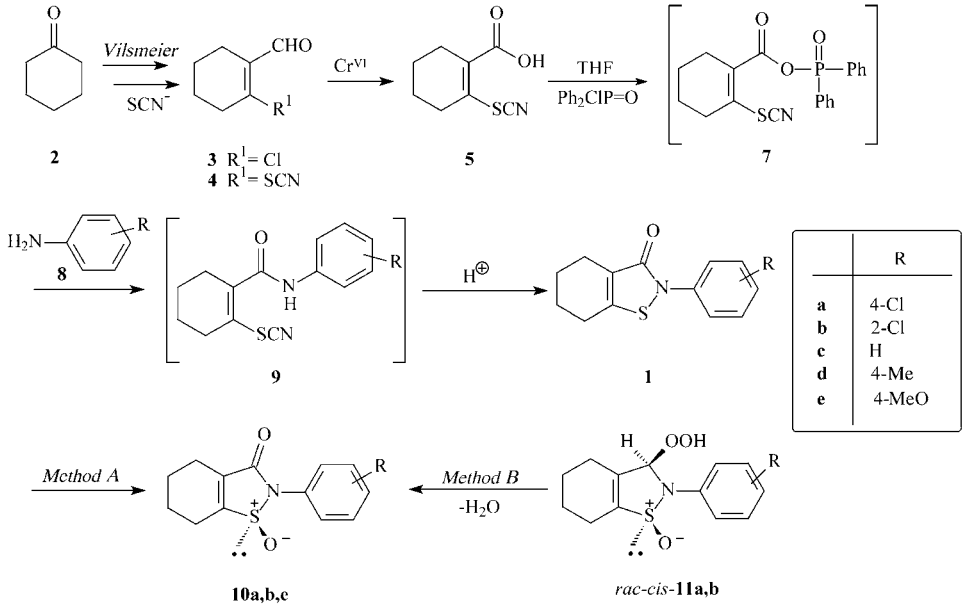


E

Here, we report a new synthesis of 2-aryl-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-ones **1** in a four step process from cyclohexanone (**2**) *via* 2-chlorocyclohexene-1-carbaldehyd (**3**) and the thiocyanate **4** (*Scheme 1*). Our strategy to synthesize bicyclic 2-arylisothiazolones of type **1** is based on the preparation of 2-(thiocyanato)cyclohexene-1-carboxylic acid (**5**), which could be easily obtained by oxidation of **4** [5], as the precursor. It was also possible to identify compounds of type **1** as intermediates in the oxidation of 2-arylisothiazolium salts **6** (*Scheme 2*) [6][7].

Results and Discussion. – According to *Scheme 1*, *Vilsmeier* reaction of cyclohexanone (**2**), vinylic SCN-substitution of **3**, and oxidation of thiocyanate **4** gave 2-(thiocyanato)cyclohexene-1-carboxylic acid (**5**) [5]. The *N*-aryl group was introduced

Scheme 1



by treatment of activated **7** with substituted anilines **8** to give the carboxanilides **9** [8]. H^+-promoted cyclization then smoothly afforded the bicyclic isothiazolones **1a**–**e**, with characteristic chemical shifts of C(3) in the ^{13}C-NMR spectra (167.2–168.3 ppm) and C=O absorption bands at 1647–1653 cm^{-1} in the IR spectra.

As expected, the oxidation of **1a**,**b**,**e** (*m*-chloroperbenzoic acid, CH_2Cl_2, 5°) led to the formation of the *S*-oxides **10a**,**b**,**e**. These compounds were also synthesized by elimination of H_2O from the isolated 3-hydroperoxy-sultims **11a**,**b**.

The structures of the new isothiazol-3(2*H*)-one 1-oxides **10** were established by IR and NMR spectroscopy. Typical signals of these compounds are found in the ^{13}C-NMR spectra at 166.0–167.0 ppm (C=O), and in the IR spectra at 1095–1108 cm^{-1} (SO). The structure of **10a** was confirmed by X-ray crystal-structure analysis (*Figure*). The isothiazole ring of **10a** is nearly planar, N(1) protruding by 0.0202 Å from the plane between C(1), C(2), C(3), and S(1). The torsion angle between the isothiazole ring and the 2-aryl substituent was 51°. The crystal packing of **10a** is stabilized by short nonclassical intermolecular C(7)–H···O(1) (2.428 Å) and Cl···H–C(4) (2.767 Å) H-bonds.

Recently, we have detected the isothiazolones **1** during the oxidation cascade of the isothiazolium perchlorates **6** with H_2O_2/AcOH by monitoring the reaction with HPLC–API-MS-MS [7]. With this method, the position of primary attack in **6** (*Scheme 2*) was determined to be C(3), and both the transient intermediates **12** and their dehydration products **1** were unambiguously identified. Their structures and fragmentation behaviors were corroborated by MS analysis of the synthesized isothiazolones **1b**,**c** under similar conditions.

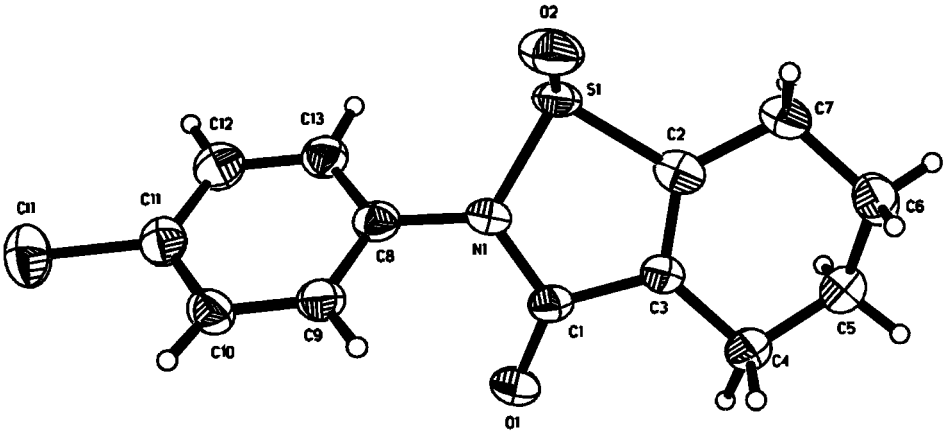
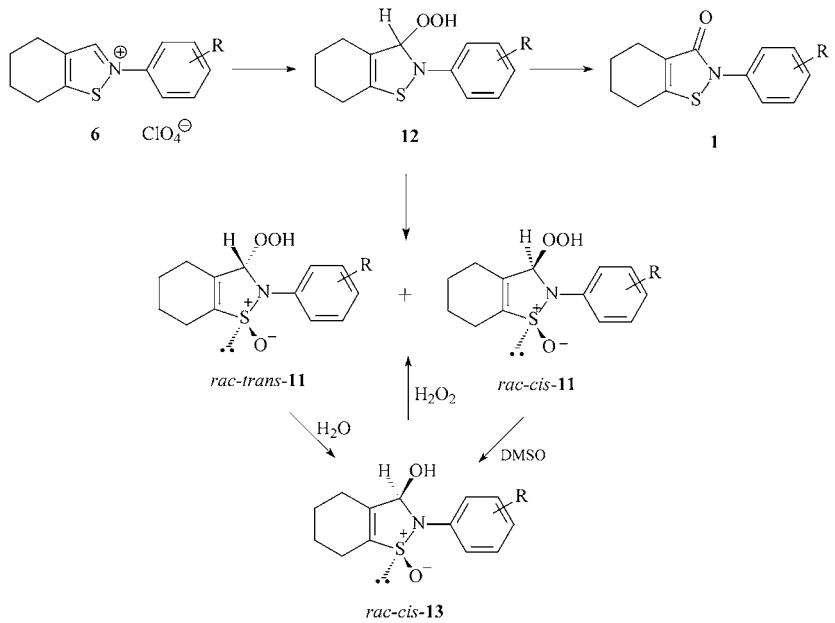


Figure. *Crystal structure of 2-(4-chlorophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-one 1-oxide* (**10a**)

Scheme 2



An unambiguous characterization of **12** [7] showed that the compound we had previously reported as 3-hydroperoxyisothiazole **12b** is in fact the so far elusive *rac-trans*-**11b** [6], which was easily converted to *rac-cis*-**13b**, as shown by HPLC–^{1}H-NMR-coupled technique. Now, we synthesized the bicyclic *rac-cis*-3-hydroxyisothiazole *S*-oxide **13b**, a stable crystalline compound, by reduction of *rac-cis*-**11b** in DMSO. In the ^{1}H-NMR spectrum, a *s* for H–C(3) appears at 5.57 ppm, and the ^{13}C-NMR signals were found at 89.8, 145.7, and 144.0 ppm, corresponding to C(3), C(3a), and C(7a),

respectively. In the IR spectrum of *rac-cis*-**13b**, the typical sulfoxide absorption is found at 1036 cm^{-1}. The reaction of *rac-cis*-**13b** with H_2O_2 led to the hydroperoxides *rac-trans*-**11b** and *rac-cis*-**11b** in a 1:1 ratio (*Scheme 2*), as corroborated by HPLC–MS investigations. This reaction from 3-hydroxy to 3-hydroperoxy sultims with H_2O_2 has been known so far only for sultams [6].

Conclusions. – The cyclocondensation of 2-(thiocyanato)cyclohexene-1-carboxanilides **9** is an efficient new method for the synthesis of 2-arylisothiazolones of type **1**. Their *S*-oxides **1** could be synthesized in fair-to-good yields either by oxidation of **1** or dehydration of the *rac-cis*-3-hydroperoxysultims **11**. Furthermore, 2-arylisothiazolones **1** and the hydroperoxides **12** were unambiguously identified in the oxidation cascade of the salts **6** by monitoring the reaction with HPLC–API-MS-MS technique.

Financial support of this work by the *Deutsche Forschungsgemeinschaft*, the *Fonds der Chemischen Industrie*, and the *UFZ Leipzig-Halle* (for HPLC–MS-analysis) is gratefully acknowledged.

Experimental Part

General. Solvents were purified by standard procedures. TLC: *Merck* aluminum plates, silica gel *60* F_{254}. Column chromatography (CC): *Merck* silica gel *60* (0.063–0.200 mm, 480–540 mesh). M.p.: *Boetius* micro-melting-point apparatus; corrected. UV/VIS Spectra: *Beckmann DU-650*; λ_{max} in nm ($\log \varepsilon$). IR spectra: *Genesis FTIR Unicam Analytical System* (*ATI Mattson*); KBr pellets; in cm^{-1}. ^{1}H-NMR. *Varian Gemini-200* and *Varian Unity-400*; δ in ppm rel. to $SiMe_4$ as internal standard, *J* in Hz. ^{13}C-NMR Spectra: 50 or 100 MHz, recorded on the above spectrometers. MS: *Quadrupole-MS VG 12-250*; 70 eV. HPLC–MS: *LC 1100* (*Applied Biosystems*), *API 2000* (*Perkin-Elmer*).

General Procedure for the Preparation of **1a–e**. To a stirred suspension of **3** (0.41 mmol) in anh. THF (3 ml) was added diphenylphosphinic chloride (0.45 mmol) under Ar gas at $-10°$, and the mixture was kept at this temp. for 30 min. Then, the corresponding aniline **8** (0.41 mmol) was added. The mixture was allowed to warm to r.t. and stirred until TLC analysis showed complete consumption of the aniline. The mixture was diluted with an equal volume of Et_2O, washed with 2M aq. NaOH soln., 1M aq. HCl soln., and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude products were purified by CC on SiO_2 with AcOEt/hexane 1:1 (*v*/*v*) as eluent.

*2-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-one* (**1a**). Yield: 26%. Colorless crystals. M.p. 112–113°. UV (EtOH): 256.0 (4.04). IR: 1651*s* (C=O). ^{1}H-NMR ($CDCl_3$): 1.86 (*m*, 2 CH_2); 2.33 (*m*, CH_2); 2.75 (*m*, CH_2); 7.72, 7.60 (*AA′BB′*, *J* = 9.0, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 22.9, 23.7, 24.0, 25.5 (C(4–7)); 116.2 (2 arom. CH); 121.1 (arom. C); 126.2 (2 arom. CH); 130.7 (arom. C); 138.6 (C(3a)); 150.8 (C(7a)); 167.9 (C(3)). EI-MS: 265 ($M^{+\cdot}$). Anal. calc. for $C_{13}H_{12}ClNOS$ (265.77): C 58.75, H 4.55, N 5.27, S 13.57; found: C 58.54, H 4.49, N 5.35, S 13.41.

*2-(2-Chlorophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-one* (**1b**). Yield: 34%. Colorless crystals. M.p. 121–123°. UV (EtOH): 277.0 (3.92). IR: 1653*s* (C=O). ^{1}H-NMR ($CDCl_3$): 1.88 (*m*, 2 CH_2); 2.44 (*m*, CH_2); 2.68 (*m*, CH_2); 7.32–7.41 (*m*, 3 arom. H); 7.48–7.54 (*m*, arom. H). ^{13}C-NMR ($CDCl_3$): 21.9, 22.7, 23.0, 24.8 (C(4–7)); 121.1 (arom. C); 128.2, 130.8, 131.1, 131.6 (4 arom. CH); 134.4 (C(3a)); 151.1 (C(7a)); 168.3 (C(3)). EI-MS: 265 ($M^{+\cdot}$). Anal. calc. for $C_{13}H_{12}ClNOS$ (265.77): C 58.75, H 4.55, N 5.27, S 13.57; found: C 58.61, H 4.61, N 5.15, S 13.31.

*4,5,6,7-Tetrahydro-2-phenyl-1,2-benzisothiazol-3(2*H*)-one* (**1c**). Yield: 51%. Colorless crystals. M.p. 114–115° (lit. 109° [3a]). UV (EtOH): 246.0 (3.85), 280.0 (3.92). IR: 1651*s* (C=O). ^{1}H-NMR ((D_6)acetone): 1.86 (*m*, 2 CH_2); 2.33 (*m*, CH_2); 2.72 (*m*, CH_2); 7.23–7.32 (*m*, arom. H); 7.40–7.50 (*m*, 2 arom. H); 7.64–7.70 (*m*, 2 arom. H). ^{13}C-NMR ((D_6)acetone): 22.8, 23.7, 24.0, 25.4 (C(4–7)); 123.2 (arom. C); 124.9, 127.7, 130.8 (5 arom. CH); 139.8 (C(3a)); 150.5 (C(7a)); 167.9 (C(3)). EI-MS: 231 ($M^{+\cdot}$). Anal. calc. for $C_{13}H_{13}NOS$ (231.33): C 67.49, H 5.66, N 6.06, S 13.86; found: C 67.55, H 5.58, N 6.01, S 13.61.

*4,5,6,7-Tetrahydro-2-(4-methylphenyl)-1,2-benzisothiazol-3(2*H*)-one* (**1d**). Yield: 48%. Colorless crystals. M.p. 90–92°. UV (EtOH): 276.5 (3.90). IR: 1653*s* (C=O). ^{1}H-NMR ((D_6)acetone): 1.85 (*m*, 2 CH_2); 2.08–2.34 (*m*, Me); 2.72 (*m*, 2 CH_2); 7.25, 7.52 (*AA′BB′*, *J* = 8.5, 4 arom. H). ^{13}C-NMR ((D_6)acetone): 20.9 (Me); 22.3,

23.1, 23.4, 24.7 (C(4–7)); 122.4, 124.3 (4 arom. CH); 130.4 (arom. C); 136.4 (C(4′)); 136.9 (C(3a)); 149.5 (C(7a)); 167.2 (C(3)). EI-MS: 245 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{15}NOS$ (245.33): C 68.54, H 6.13, N 5.71, S 13.07; found: C 68.41, H 6.01, N 5.85, S 13.23.

*4,5,6,7-Tetrahydro-2-(4-methoxyphenyl)-1,2-benzisothiazol-3(2*H*)-one* (**1e**). Yield: 53%. Colorless crystals. M.p. 96–98°. UV (EtOH): 272.0 (3.93). IR: 1647*s* (C=O). ^{1}H-NMR ((D$_6$)acetone): 1.86 (*m*, 2 CH$_2$); 2.32 (*m*, CH$_2$); 2.69 (*m*, CH$_2$); 3.83 (*s*, MeO); 7.00, 7.49 (*AA′BB′*, *J* = 9.1, arom. H). ^{13}C-NMR ((D$_6$)acetone): 22.3, 23.1, 23.4, 24.7 (C(4–7)); 55.9 (MeO); 117.9, 122.7 (4 arom. CH); 126.6 (arom. C); 131.5 (C(3a)); 149.4 (C(7a)); 159.2 (C(4′)); 167.2 (C(3)). EI-MS: 261 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{15}NO_2S$ (261.33): C 64.34, H 5.78, N 5.36, S 12.27; found: C 64.21, H 5.65, N 5.48, S 12.11.

General Procedure for the Preparation of **10a**,**b**,**e**. *Method A:* To a stirred soln. of **1** (0.1 mmol) in CH_2Cl_2 (2 ml) was slowly added *m*-chloroperbenzoic acid (MCPBA; 0.1 mmol) at 5°, and the mixture was kept for several hours at this temp. The mixture was quenched by the addition of aq. $NaHSO_3$ soln., washed with sat. aq. $NaHCO_3$ soln. and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The crude products were purified either by recrystallization or CC on SiO_2, eluting with AcOEt/hexane.

Method B: rac-cis-3-Hydroperoxysultim **11** [6] (0.1 mmol) was shortly heated in EtOH (1 ml) and conc. HCl (0.1 ml). The product precipitated upon cooling (5 h) and was collected by filtration.

*2-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-one 1-Oxide* (**10a**). Yield: 68% (*Method A*), 18% (*Method B*). Colorless crystals. M.p. 111–112°. IR: 1108*s* (S=O); 1706*s* (C=O). ^{1}H-NMR ((D$_6$)acetone): 1.88 (*m*, 2 CH$_2$); 2.43 (*m*, CH$_2$); 2.63 (*m*, CH$_2$); 7.52–7.55 (*m*, 4 arom. H). ^{13}C-NMR ((D$_6$)acetone): 21.0, 21.9, 22.0, 22.1 (C(4–7)); 128.4, 129.9 (4 arom. CH); 133.4, 134.2 (2 arom. C); 135.7 (C(3a)); 157.1 (C(7a)); 166.0 (C(3)). EI-MS: 281 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{12}ClNO_2S$ (281.79): C 55.41, H 4.29, N 4.97, S 11.38; found: C 55.27, H 4.15, N 4.77, S 11.25.

*2-(2-Chlorophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2*H*)-one 1-Oxide* (**10b**). Yield: 81% (*Method A*), 35% (*Method B*). Colorless crystals. M.p. 94–96°. IR: 1095*s* (S=O); 1710*s* (C=O). ^{1}H-NMR ((D$_6$)acetone): 1.93 (*m*, 2 CH$_2$); 2.53 (*m*, CH$_2$); 2.64 (*m*, CH$_2$); 7.44–7.59 (*m*, 4 arom. H). ^{13}C-NMR ((D$_6$)acetone): 21.5, 22.4, 22.9, 23.9 (C(4–7)); 129.4, 129.8 (2 arom. CH); 130.7 (arom. C); 131.0, 131.3 (2 arom. CH); 134.8 (arom. C); 135.7 (C(3a)); 150.8 (C(7a)); 159.4 (C(3)). EI-MS: 281 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{12}ClNO_2S$ (281.79): C 55.41, H 4.29, N 4.97, S 11.38; found: C 55.57, H 4.36, N 4.81, S 11.46.

*4,5,6,7-Tetrahydro-2-(4-methoxyphenyl)-1,2-benzisothiazol-3(2*H*)-one 1-Oxide* (**10e**). Yield: 63%. (*Method A*). Colorless crystals. M.p. 96–98°. IR: 1106*s* (S=O); 1697*s* (C=O). ^{1}H-NMR ((D$_6$)acetone): 1.86 (*m*, 2 CH$_2$); 2.40 (*m*, CH$_2$); 2.61 (*m*, CH$_2$); 3.84 (*s*, MeO); 7.04, 7.34 (*AA′BB′*, *J* = 9.0, arom. H). ^{13}C-NMR ((D$_6$)acetone): 21.6, 22.2, 22.5, 23.4 (C(4–7)); 55.8 (MeO); 115.4 (2 arom. CH); 126.6 (arom. C); 129.6 (2 arom. CH); 131.4 (C(3a)); 149.4 (C(7a)); 160.5 (C(3)); 167.0 (C(4′)). EI-MS: 277 ($M^{+\bullet}$). Anal. calc. for $C_{14}H_{15}NO_3S$ (277.32): C 60.63, H 5.45, N 5.05, S 11.56; found: C 60.41, H 5.33, N 5.15, S 11.67.

Synthesis of rac-cis-*2-Aryl-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1-Oxides* (**11**). The data of *rac-cis*-**11b** are given in [6]; *rac-cis*-**11a** was prepared according to [6].

rac-cis-*2-(4-Chlorophenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1-Oxide* (**11a**). Yield: 36%. Colorless crystals. M.p. 116–119°. UV (EtOH): 241.0 (4.19). IR: 1050*s* (S=O). ^{1}H-NMR ((D$_6$)acetone): 1.80 (*m*, 2 CH$_2$); 2.41 (*m*, 2 CH$_2$); 6.16 (*s*, H–C(3)); 7.35–7.40 (*m*, 4 arom. H); 11.04 (*s*, OOH). ^{13}C-NMR ((D$_6$)acetone): 22.0, 22.2, 23.1, 24.5 (C(4–7)); 98.3 (C(3)); 120.1 (2 arom. CH); 128.4 (arom. C); 130.3 (2 arom. CH); 141.8 (arom. C); 142.4 (C(7a)); 143.3 (C(3a)). EI-MS: 299 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{14}ClNO_3S$ (299.79): C 52.08, H 4.72, N 4.67, S 10.69; found: C 51.93, H 4.65, N 4.41, S 10.48.

rac-cis-*2-(2-Chlorophenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-1,2-benzisothiazole 1-Oxide* (**13b**). A soln. of *rac-cis*-**11b** (0.2 mmol) [6] in DMSO (0.5 ml) was stirred for 2 h. The solvent was removed by lyophilization, and the crude product was purified by recrystallization from EtOH. Yield: 49%. Colorless crystals. M.p. 132–135°. UV (EtOH): 208.5 (4.13). IR: 1036*s* (S=O). ^{1}H-NMR ((D$_6$)acetone): 1.81 (*m*, 2 CH$_2$); 2.41 (*m*, 2 CH$_2$); 5.57 (*s*, H–C(3)); 7.38–7.55 (*m*, 4 arom. H). ^{13}C-NMR ((D$_6$)acetone): 21.2, 22.2, 22.8, 23.0 (C(4–7)); 89.8 (C(3)); 107.2, 109.6, 115.5, 128.4 (4 arom. CH); 131.1, 139.1 (2 arom. C); 144.0 (C(7a)); 145.7 (C(3a)). EI-MS: 284 ($M^{+\bullet}$). Anal. calc. for $C_{13}H_{14}ClNO_2S$ (283.79): C 55.02, H 4.97, N 4.94, S 11.29; found: C 54.95, H 4.85, N 4.90, S 11.02.

Reaction of **13b** *with* H_2O_2. Isolated *rac-cis*-**13b** was dissolved in AcOH, and H_2O_2 was added. The products formed, *rac-cis*-**11b** and *rac-trans*-**11b** were separated by reversed-phase CC (*aqua 125A RP-18*; 30 × 2 mm; d_p 5 μm) and were identified by mass spectrometry.

X-Ray Crystal-Structure Analysis of **10a**. Crystals were obtained from EtOH. The intensities were measured on a *Siemens SMART CCD* diffractometer. Data collection and cell refinement are listed in the *Table*. The structure was solved by direct methods, and refinement was performed with SHELX-97 [9]. Crystallo-

graphic data have been deposited with the *Cambridge Crystallographic Data Centre*, CCDC No. 217476. Copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: +44-1233-336033; e-mail: deposit@ccdc.cam.ac.uk; internet: http://www.ccdc.cam.ac.uk).

Table 1. *Crystallographic Data of* **10a**

Empirical formula	$C_{13}H_{12}ClNO_2S$
Formula weight [g mol^{-1}]	281.75
Crystal color, habit	Colorless, plates
Temp. [K]	213(2)
Radiation, wavelength [Å]	MoK_α, 0.71073
Crystal dimensions [mm]	$0.30 \times 0.10 \times 0.10$
Crystal system	Monoclinic
Space group	$P2(1)/n$
2θ Range for cell determination [°]	4 – 56
Unit-cell parameters a [Å]; α [°]	9.6690(4); 90
b [Å]; β [°]	6.6324(3); 105.069(1)
c [Å]; γ [°]	10.1149(4); 90
V [Å^3]	626.35(5)
D [Mg/m^3]	1.494
Absorption coefficient μ [mm^{-1}]	0.464
Scan type	ω
2θ (max) [°]	56.0
Total reflections measured	5570
Symmetry-independent reflections	2563
Reflections observed ($I > 2\sigma(I)$)	2409
Variables	211
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0565$, $wR_2 = 0.1465$
R indices (all data)	$R_1 = 0.0734$, $wR_2 = 0.1567$
$\Delta\rho$ (max, min) [e Å^{-3}]	0.461, −0.493
Goodness-of-fit (s)	1.113

REFERENCES

[1] K. Taubert, S. Kraus, B. Schulze, *Sulfur Rep.* **2002**, *23*, 79.
[2] A. Siegemund, K. Taubert, B. Schulze, *Sulfur Rep.* **2002**, *23*, 279.
[3] a) B. Shroot, J. Maignan, Fr. Pat. 2492376 (*Chem. Abstr.* **1982**, *97*, 72355); b) B. Shroot, J. Maignan, U.S. Pat. 4,708,959 (*Chem. Abstr.* **1988**, *109*, 128996); c) B. Shroot, G. Lang, J. Maignan, M. Colin, Eur. Pat. 179697 (*Chem. Abstr.* **1986**, *105*, 209240).
[4] J. Maignan, S. Restle, L. Colin, German Pat. DE 3618711 (*Chem. Abstr.* **1987**, *106*, 138433); J. Maignan, S. Restle, L. Colin, U.S. Pat. 4,851,541 (B. Shroot, J. Maignan, R. Schmidt (Centr. Intern. Recher. Dermatol.), Eur. Pat. 342105 (*Chem. Abstr.* **1990**, *112*, 178954).
[5] G. Simchen, G. Entenmann, *Liebigs Ann. Chem.* **1977**, *8*, 1249.
[6] C. Hartung, K. Illgen, J. Sieler, B. Schneider, B. Schulze, *Helv. Chim. Acta* **1999**, *82*, 685.
[7] S. Baumann, M. Möder, R. Herzschuh, B. Schulze, *Chromatographia* **2003**, *57*, 147.
[8] N. R. A. Beeley, L. M. Harwood, P. C. Hedger, *J. Chem. Soc., Perkin Trans. 1* **1994**, 2245.
[9] G. M. Sheldrick, SHELX-97: a Program System for Solution and Refinement of X-Ray Crystal Structures, University of Göttingen, 1997.

Received August 29, 2003