Facile Synthesis of Novel *N*-Aryl-4,5,6,7-tetrahydro-benzosultams by Oxyfunctionalisation of Bicyclic Isothiazolium Salts*

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Dedicated to Professor Dr. W. Kantlehner on the occasion of his 60th birthday

3-Hydroxy- (**17a – j**) and 3-alkoxy-4,5,6,7-tetrahydro-benzosultams **18a – m** were prepared in good yields by oxidation of the bicyclic isothiazolium salts **10** with magnesium monoperoxyphthalate (MMPP · $6H_2O$) in acetonitrile or corresponding alcohol. A HPLC-API-MS(MS) method was used to monitor the oxidation process of **10** with MMPP. 3-Oxo-4,5,6,7-tetrahydro-benzosultams **19a – c, h, j** were also obtained.

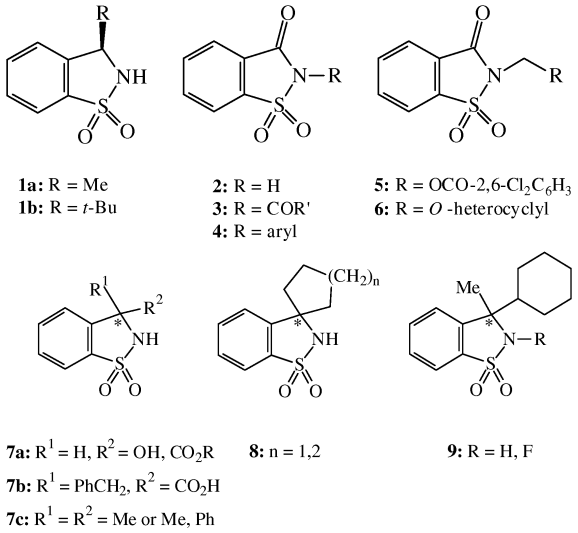
Key words: Sultams, Oxidation, Magnesium Monoperoxyphthalate (MMPP)

Introduction

Sultams such as Oppolzer's camphersultam [1] and benzosultams **1** [2] which can be synthesized from saccharine **2**, are an important class of chiral auxiliaries for π-facial discrimination in asymmetric reactions. Several *N*-substituted 1,2-benzisothiazol-3(2*H*)-ones and their 1,1-dioxides have been extensively studied as biologically active compounds [3].

The development of serine protease inhibiting 3-oxobenzosultams **3 – 6** have been recently described [4]. There are several new methods for the synthesis of 3-mono-, 3,3-di- and spiro-substituted benzosultams **7 – 9** [2, 4, 5]. *N*-Protected saccharine **2** (R=MPM) was treated with DIBALH to give 3-functionalized sultams **7a**, which were converted into sultams **7b** [5a]. Phenylcarbinolsulfonamides, which underwent TMSCl-NaI-MeCN reagent mediated cyclization, react to 3,3-disubstituted sultams **7c** and chiral spiro-2,3-dihydro-1,2-benzisothiazole 1,1-dioxides **8** in high yields [5b].

Finally, chiral *N*-fluorosultams **9** which are efficient reagents for electrophilic asymmetric fluorination of lithium enolates were developed [6]. 3-Aryl-



substituted benzosultams also received attention as potent HIV-1 inhibitors [7].

In recent years, we have studied synthetic methods of oxyfunctionalization of mono- and bicyclic isothiazolium salts to a range of *O*-functionalized derivatives in 3-position and of the sulfur [8]. This pathway to a new class of chiral sultams of the typ **16** or **17** is very convenient and controlled by the oxidants.

In the course of our study on the oxidation of the salts **10** we have investigated the influence of the sub-

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stituents (R^1) at the 2-aryl ring and the stereochemical aspects of the formation of sultims **13** [8a]. The 3-hydroperoxy sultams **16** are novel chemoselective electrophilic oxidants for sulfur, nitrogen and phosphorus heteroatoms in non-aqueous media [9]. A HPLC-API-MS(MS) method was presented for reaction monitoring of the oxidation of isothiazolium salts **10** with H_2O_2 in acetic acid [10]. Using this method, the position of the primary oxidizing attack on the C-3-atom of **10** was determined for the first time and the transient intermediate **11** was characterized as structurally explicit [10].

Here we report a new approach to 3-hydroxy- and 3-alkoxy-substituted *N*-aryl-4,5,6,7-tetrahydro-benzosultams **17** and **18** in a one-step process by oxidation of salts **10** with magnesium monoperoxyphthalate hexahydrate (MMPP · $6H_2O$) in acetonitrile or alcohol.

Results and Discussion

The synthesis of isothiazolium salts **10** (Scheme 1) has been performed by a known procedure from β-thiocyanatovinyl aldehydes and suitably substituted anilines in the presence of perchloric acid in glacial acetic acid by intramolecular cyclocondensation [8a]. Salts **10a, i, j** were prepared for the first time.

The oxidation of the salts **10h – j** with excess 30% H_2O_2 in glacial acetic acid at room temperature (1 h) gives stable hydroperoxy sultims *rac-cis*-**13h – j** and hydroperoxy sultams **16h – j** as crystalline products after 24 hours.

In the case of the oxidation of new salt **10a** with H_2O_2 in acetic acid at r.t. only a 3-hydroperoxy sultam **16a** could be obtained (70%). The 3-hydroperoxy sultams **16b, c** were stable compounds [8a], whereas the corresponding sultims **13b, c** of donor-substituted salts were never obtained. As expected, the oxidation of salts **10a, h, j** with 30% H_2O_2 in AcOH at 80 °C gave the 3-oxosultams **19a, h, j** in moderate yields (40 – 51%, method A). Compound **19i** was not isolated at all.

Furthermore, we investigated the oxidation of bicyclic salts **10a – j** with MMPP · $6H_2O$ in the ultrasound bath at 60 °C (3 h), as described for monocyclic salts [11], and we obtained from unsubstituted and acceptor-substituted salts **10d – j** 3-hydroxysultams **17d – j** as colorless crystals in very high yield (68 – 85%), see Table 1. Surprisingly, under the same reaction conditions the salts **10a – c** with donor substituents in the 2-arylring yielded 3-oxosultams **19a, b** (83,85%, method B) and a mixture of **17c**/**19c** (1:4 (80%)).

Table 1. Synthesis of 3-hydroxysultams **17** with MMPP · $6H_2O$ in CH_3CN (50 °C) and ultrasound.

Compound	R^1	Yield (%)	M. p. (°C)
17a	2-OCH_3	53[a]	140
17b	4-OCH_3	47[a]	147
17c	4-CH_3	59[a]	158
17d	H	84[b]	145
17e	4-CO_2CH_3	81	164
17f	2-Cl	76[b]	133
17g	2,6-Cl_2	85	163
17h	4-Cl	78	143
17i	2-NO_2	68	155
17j	4-NO_2	81	153

[a] Without ultrasound bath at r. t.; [b] overall yields of **17d** (28%) and **17f** (36%) from salts **10d, f** over sultams **16d, f** with Na_2SO_3 [8a].

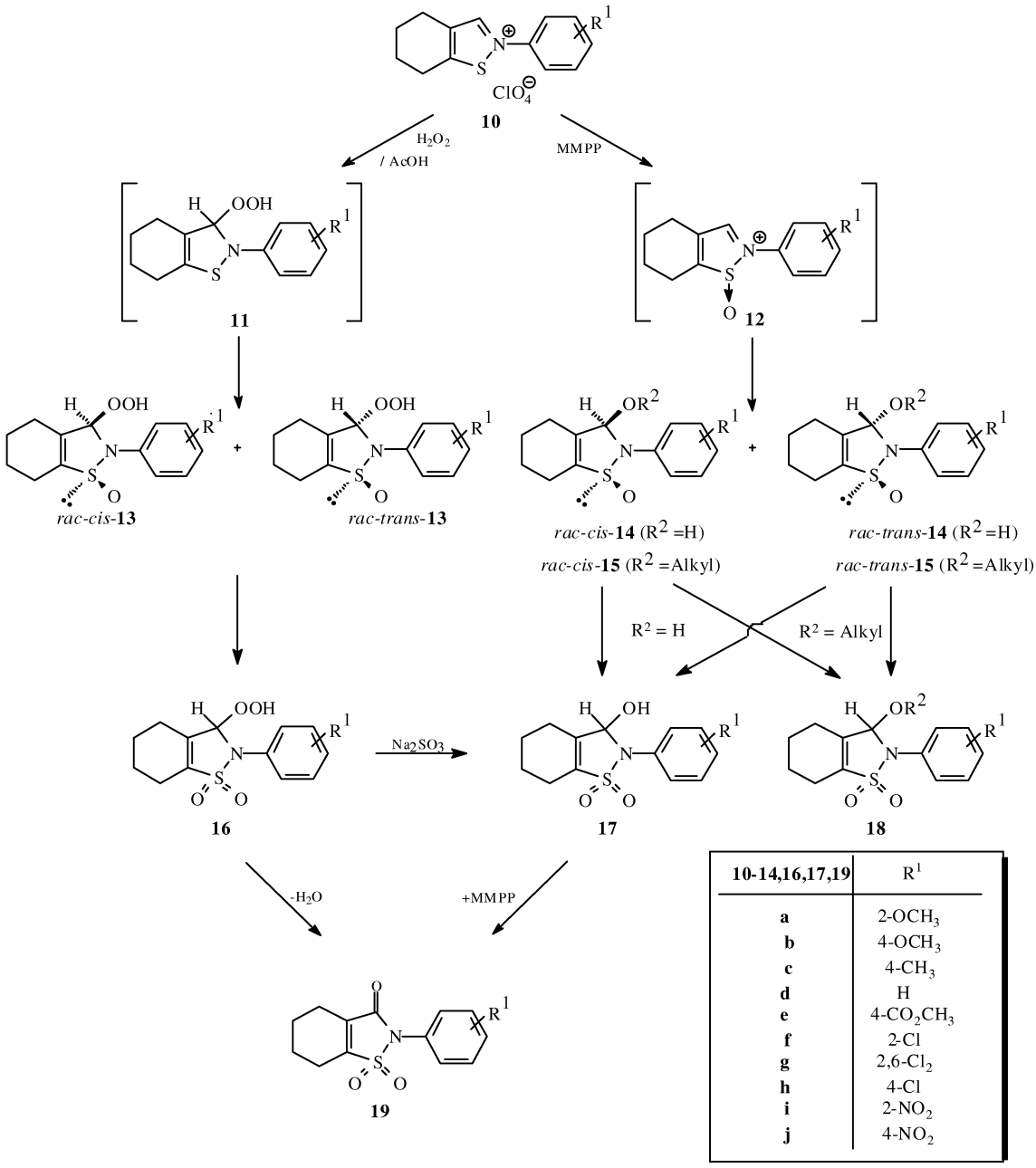
On the other hand, the oxidation of salts **10a – c** with MMPP · $6H_2O$ gave without ultrasound at r.t. (3 h) 3-hydroxysultams **17a – c** in 47 – 59% yield. This synthesis with MMPP to 3-hydroxybenzosultams **17a – j** was very convenient in contrast to the oxidation-reduction pathway of the salts **10d, f** *via* the hydroperoxides **16d, f** and reduction with Na_2SO_3 (Scheme 1, Table 1) [8a].

By HPLC-MS(MS) reaction monitoring of the oxidation of salt **10e** with MMPP · $6H_2O$ in CH_3CN the 3-hydroxysultims *rac-cis*-**14e** and *rac-trans*-**14e** could be detected as intermediates after 5 minutes in a 1:2 ratio (Scheme 1).

Interestingly, when the salts **10** with *p*-substituents in the 2-aryl ring reacted with MMPP · $6H_2O$ in alcohols without ultrasound, the 3-alkoxysultams **18** were found in good yields (51 – 87%, Table 3) after 6 hours, whereas small amounts of **17** were always generated when an ultrasound bath was used. In the case of oxidation of *o*-substituted salts **10**, 3-alkoxysultams **18i, j, l** was obtained only in a moderate yield (29 – 35%).

Spectroscopic characteristics of sultams **17** and **18** are the infrared absorption of the sulfonyl function at 1275 – 1296 cm^{-1} and 1149 – 1157 cm^{-1}. The ^1H NMR spectra of 3-hydroxysultams **17** are indicated by the 3-H proton absorption at $\delta = 5.85 - 6.22$ ppm and the ^{13}C NMR chemical shifts of C-3 at $\delta = 82.0 - - 86.0$ ppm, C-7a at 133.9 – 135.3 ppm and C-3a at 142.9 – 144.9 ppm. For the 3-alkoxysultams **18** the 3-H absorptions appear at 5.64 – 6.21 ppm and the C-3 signals at 85.3 – 91.9.

The structure of the 3-alkoxysultams **18** was proved by X-ray crystal structure analysis of **18k** (R^1 = 4-Cl, $R^2 = C_2H_5$, Scheme 1). The isothiazole ring in **18k** is approximately planar. The sultam **18k** shows intermolecular hydrogen bonds between the atoms C(1)-



10-14,16,17,19	R^1
a	2-OCH_3
b	4-OCH_3
c	4-CH_3
d	H
e	4-CO_2CH_3
f	2-Cl
g	2,6-Cl_2
h	4-Cl
i	2-NO_2
j	4-NO_2

Scheme 1.

H(1)···O(2) (3.24 Å) and forms 'head-to-tail' dimeric units about a center of symmetry.

A HPLC-MS(MS) online investigation of this oxidation process of the salt **10e** in CH_3OH has shown the formation of 3-methoxysultims *rac-cis*-**15e** and *rac-trans*-**15e** after 5 minutes. The reactive *S*-oxide **12e** could also not be found in this experiment. The very fast formation of *rac-cis/trans-S*-oxides **15e** is mediated by a nucleophilic attack of the alcohol on C-3 of the reactive primary not isolable intermediate **12e**.

We have developed a useful one-step method for the synthesis of 3-hydroxy- and 3-alkoxy-functionalized

Table 2. Analytical data of 2-aryl-2,3,4,5,6,7-hexahydro-3-hydroxy-1,2-benzisothiazole 1,1-dioxides **17**.

Comp.	^{1}H NMR ([D$_6$]acetone), δ (ppm), J (Hz)	^{13}C NMR ([D$_6$]acetone), δ (ppm)	EI-MS m/z (%)	Molecular formula – molecular weight	IR (cm^{-1})	EA calcd./found
17a	7.45 – 6.97 (m, 4 H), 5.65 (s, 1 H), 3.81 (s, 3 H), 2.48 – 2.37 (m, 4 H), 1.82 – 1.75 (m, 4 H)	157.7, 143.4, 133.9, 132.2, 129.6, 122.4, 120.6, 112.7, 82.7, 55.5, 22.7, 21.3, 21.2, 18.3	295 (M$^+$, 26), 277 (96)	$C_{14}H_{17}NO_4S$ 295.36	1281 (SO$_2$), 1153 (SO$_2$)	C 56.93/56.88 H 5.80/5.94 N 4.74/4.71 S 10.86/11.03
17b	7.36/6.97 (2 d, J = 10.2, 4 H), 5.71 (s, 1 H), 3.80 (s, 3 H), 2.50 – 2.25 (m, 4 H), 1.90 – 1.76 (m, 4 H)	160.0, 144.9, 134.9, 129.1, 128.9, 115.9, 85.0, 56.4, 23.9, 22.6, 22.5, 19.5	295 (M$^+$, 39), 277 (100)	$C_{14}H_{17}NO_4S$ 295.36	1284 (SO$_2$), 1153 (SO$_2$)	C 56.93/56.90 H 5.80/6.03 N 4.74/4.82 10.86/10.95
17c	7.33/7.20 (2 d, J = 9.2, 4 H), 5.81 (s, 1 H), 2.47 – 2.20 (m, 4 H), 2.31 (s, 3 H), 1.96 – 1.77 (m, 4 H)	143.9, 133.5, 130.5, 129.9, 122.8, 82.6, 22.6, 21.1, 21.2, 20.2, 18.2	279 (M$^+$, 12), 261 (68)	$C_{14}H_{17}NO_3S$ 279.36	1277 (SO$_2$), 1155 (SO$_2$)	C 60.19/60.11 H 6.13/6.02 N 5.01/4.89 S 11.48/11.56
17e	8.03/7.54 (2 d, J = 8.6, 4 H), 6.05 (s, 1 H), 3.87 (s, 3 H), 2.54 – 2.37 (m, 4 H), 1.86 – 1.80 (m, 4 H)	167.4, 144.8, 142.2, 134.5, 132.1, 126.0, 118.6, 82.6, 52.8, 23.9, 22.5, 22.4, 19.3	323 (M$^+$, 37), 306 (100)	$C_{15}H_{17}NO_5S$ 323.37	1714 (CO), 1279 (SO$_2$), 1149 (SO$_2$)	C 55.71/55.83 H 5.30/5.22 N 4.33/4.28 S 9.92/10.04
17g	7.64 – 7.48 (m, 3 H), 5.85 (s, 1 H), 2.56 – 2.39 (m, 4 H), 1.92 – 1.82 (m, 4 H)	142.9, 139.9, 137.5, 134.1, 131.1, 129.5, 129.3, 84.6, 22.7, 21.1, 21.0, 18.3	333 (M$^+$, 6), 161 (100)	$C_{13}H_{13}Cl_2NO_3S$ 334.22	1278 (SO$_2$), 1160 (SO$_2$)	C 46.72/46.79 H 3.92/4.07 N 4.19/4.13 S 9.60/9.74
17h	7.63 7.49 (2 d, J = 9.0, 4 H), 5.91 (s, 1 H), 2.65 – 2.50 (m, 4 H), 1.92 – 1.82 (m, 4 H)	143.8, 137.0, 135.3, 130.0, 129.6, 122.7, 82.5, 22.9, 21.5, 21.4, 18.4	299 (M$^+$, 25)	$C_{13}H_{14}ClNO_3S$ 299.78	1294 (SO$_2$), 1157 (SO$_2$)	C 52.09/52.17 H 4.71/4.82 N 4.67/4.75 S 10.70/10.63
17i	8.05 – 8.04 (m, 1 H), 8.01 – 7.68 (m, 3 H), 5.91 (s, 1 H), 2.53 – 2.29 (m, 4 H), 1.90 – 1.76 (m, 4 H)	144.2, 136.8, 135.7, 134.6, 134.1, 131.3, 127.1, 125.9, 86.0, 23.6, 21.9, 21.8, 19.1	310 (M$^+$, 34), 292 (57)	$C_{13}H_{14}N_2O_5S$ 310.33	1537 (NO$_2$), 1356 (NO$_2$), 1292 (SO$_2$), 1163 (SO$_2$)	C 50.31/50.22 H 4.55/4.73 N 9.03/8.89 S 10.33/10.49
17j	8.35/7.66 (2 d, J = 9.3, 4 H), 6.22 (s, 1 H), 2.62 – 2.45 (m, 4 H), 1.93 – 1.84 (m, 4 H)	145.0, 143.9, 134.4, 132.4, 126.6, 118.2, 82.7, 24.0, 22.4, 22.3, 19.3	310 (M$^+$, 26), 292 (48)	$C_{13}H_{14}N_2O_5S$ 310.33	1510 (NO$_2$), 1342 (NO$_2$), 1290 (SO$_2$), 1153 (SO$_2$)	C 50.31/50.51 H 4.55/4.61 N 9.03/8.87 S 10.33/10.45

Table 3. Synthesis of 3-alkoxysultams **18** with MMPP · 6H$_2$O at r. t.

Compound	R^1	R^2	Yield (%)	M.p. (°C)
18a	2-OCH$_3$	C$_2$H$_5$	87	123
18b	2-OCH$_3$	*i*-C$_3$H$_7$	72	127
18c	4-OCH$_3$	C$_2$H$_5$	78	117
18d	4-OCH$_3$	*i*-C$_3$H$_7$	78	95
18e	4-OCH$_3$	*t*-C$_4$H$_9$	65	148
18f	4-CH$_3$	CH$_3$	71	114
18g	4-CH$_3$	C$_2$H$_5$	86	104
18h	4-COOCH$_3$	C$_2$H$_5$	51	110
18i	2-Cl	CH$_3$	35	78
18j	2,6-Cl$_2$	CH$_3$	29	126
18k	4-Cl	C$_2$H$_5$	59	120
18l	2-NO$_2$	C$_2$H$_5$	33	68
18m	4-NO$_2$	C$_2$H$_5$	69	132

bicyclic sultams **17a – j** and **18a – m** by oxidation of isothiazolium salts **10a – j** with MMPP · 6H$_2$O. It most

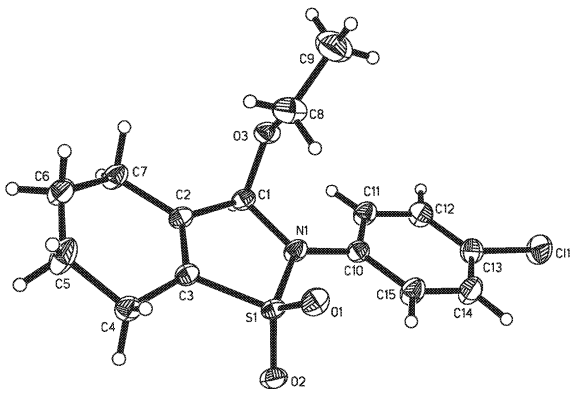


Fig. 1. Molecular structure of 2-(4-chlorophenyl)-3-ethoxy-2,3,4,5,6,7-hexahydro-1,2-benzisothiazole 1,1-dioxide **18k** [16].

probably proceeds through primary attack at MMPP at the sulfur atom of salts **10** to form the reactive not isolable intermediate **12**, which reacts with the *O*-nucleophiles water or alcohol to **17** and **18**. In the case of all donor-substituted 2-aryl salts **10a – c** the oxidation directly proceeds firstly to 3-oxosultams **19a – c**.

Experimental Section

General: Melting points: Boetius micro-melting-point apparatus; corrected. IR spectra: Genisis FTIR Unicam Analytical System (ATI Mattson); KBr pellets; values in cm^{-1}. UV/vis spectra: Beckman DU-650. ^{1}H NMR: Varian Gemini-200 and Varian Unity-400; δ in ppm rel. to TMS as internal standard, *J* in Hz. ^{13}C NMR spectra: 50 or 100 MHz, recorded on the named spectrometers. MS: Quadrupole-MS VG 12-250; 70 eV. HPLC-MS: LC 1100 (Applied Biosystems), API 2000 (Perkin Elmer). Elemental analyses: Heraeus CHNO Rapid Analyzer.

*2-Aryl-4,5,6,7-tetrahydro-1,2-benzisothiazolium perchlorates (**10**)*

The salts **10b, d, h** were prepared according to [12]; **10c, e** according to [8a]; **10f, g** to [13]. The new salts **10a, i, j** were prepared according to [14]. **10a**: 76%. yellow crystals, m.p. 166 – 167 °C. **10i**: 56%. beige crystals, m. p. 198 – 200 °C. **10j**: 86%. yellow crystals, m. p. 114 – 116 °C.

*2-Aryl-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1-oxides (rac-cis-**13**)*

General procedures: H_2O_2 (0.7 ml, 30%) was added to a stirred suspension of **10** (0.26 mmol) in AcOH (0.7 ml) at r.t. (1 h). After **10** was dissolved, a colorless precipitate of *rac-cis*-**13** was obtained which was immediately isolated; otherwise oxidation to **16** could have occurred. The isolation compounds *rac-cis*-**13** were washed with H_2O and recrystallized from *i*-PrOH. Compounds **13e, f, g** were described in [8a] and **13h** in [8b].

*2-(2-Nitrophenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1-oxide (rac-cis-**13i**)*

Yield: 59%, m. p. 112 – 114 °C. – IR (KBr): $\nu = 1063$ s (SO), 1356 s (NO_2), 1529 s (NO_2). – UV (ethanol): λ_{max} (lg ε) 206.0 (3.90). – ^{1}H NMR ([D$_6$]acetone): $\delta = 1.79$ (m, 4H, 2 CH_2), 2.41 (m, 4H, 2 CH_2), 5.76 (s, 1H, 3-H), 7.69 – 8.07 (m, 4H, arom. H), 11.00 (s, 1H, OOH). – ^{13}C NMR ([D$_6$]acetone): $\delta = 21.3$, 21.4, 22.2, 23.7 (C-4, C-5, C-6, C-7), 102.1 (C-3), 125.6, 129.6 (2 arom. CH), 133.7 (arom. C), 134.1, 135.1 (2 arom. CH), 136.4 (C-7a), 140.3 (arom. C), 144.1 (C-3a). – EI-MS: $m/z = 309$ (M^+). – $C_{13}H_{14}N_2O_5S$ (311.62): calcd. C 50.11, H 4.53, N 8.99, S 10.29; found C 50.20, H 4.64, N 8.88, S 10.45.

Table 4. Crystal data and structure refinement for **18k**.

Empirical formula	$C_{15}H_{18}ClNO_3S$
Formula weight	327.81
Temperature [K]	213(2)
Crystal system	tetragonal
Space group	$P4(1)/a$
a [Å]	12.9753(15)
b [Å]	12.9753(15)
c [Å]	37.715(4)
β[°]	90
Volume [Å^3]	6349.7(13)
Z	16
Density [Mg/m^3]	1.372
Absorption coeff. [mm^{-1}]	0.381
Crystal size [mm]	$0.30 \times 0.30 \times 0.20$
θ Range for data collect. [°]	1.66 – 27.00
Index ranges	$-16 \geq h \geq 13$
	$-14 \geq k \geq 16$
	$-38 \geq l \geq 48$
Reflections collected	19884
Independent reflections	3479
	[$R_{int} = 0.0388$]
Absorption correction	SADABS
Max. /min. transmission	0.9277 / 0.8943
Data / parameters	3479 / 266
Goodness-of-Fit on F^2	0.942
Final *R* indices [$I > 2(I)$]	$R_1 = 0.0360$, $wR_2 = 0.1034$
R Indices (all data)	$R_1 = 0.0523$, $wR_2 = 0.1092$
Lgst diff peak/hole [e Å^{-3}]	$0.356/-0.276$

*2-(4-Nitrophenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1-oxide (rac-cis-**13j**)*

Yield: 23%. In mixture with **16j**. – IR (KBr): $\nu = 1054$ s (SO). – UV (ethanol): λ_{max} (lg ε) 243.5 (4.25). – ^{1}H NMR ([D$_6$]acetone): $\delta = 1.82$ (m, 4H, 2 CH_2), 2.43 (m, 4H, 2 CH_2), 6.32 (s, 1H, 3-H), 7.49, 8.27 (4H, $J_{AB} = 9.0$ Hz, arom. H), 11.02 (s, 1H, OOH). – ^{13}C NMR ([D$_6$]acetone): $\delta = 21.2$, 23.0, 23.9, 24.6 (C-4, C-5, C-6, C-7), 101.2 (C-3), 117.4, 128.4 (4 arom. CH), 135.7 (C-7a), 143.7 (arom. C), 144.2 (C-3a), 147.8 (arom. C). – EI-MS: $m/z = 309$ (M^+). – $C_{13}H_{14}N_2O_5S$ (311.62): calcd. C 50.11, H 4.53, N 8.99, S 10.29; found C 50.25, H 4.59, N 9.13, S 10.60.

*2-Aryl-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1,1-dioxides (**16**)*

General procedure: H_2O_2 (0.7 ml, 30%) was added at r. t. to a stirred suspension of **10a, h – j** (0.26 mmol) in AcOH (0.7 ml). After 24 h, colorless crystals of **16a, h – j** were obtained, isolated, and recrystallized from EtOH. Compounds **16b, c, e – g** were described in [8a] and **16d** in [15].

*2-(2-Methoxyphenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1,1-dioxide (**16a**)*

Yield: 70%, m.p. 147 – 150 °C. – IR (KBr): $\nu = 1157$ s (SO_2), 1295 s (SO_2). – ^{1}H NMR ([D$_6$]acetone): $\delta = 1.84$

(m, 4H, 2 CH_2), 2.43 (m, 4H, 2 CH_2), 3.87 (s, 3H, OCH_3), 6.03 (s, 1H, 3-H), 6.98 – 7.78 (m, 4H, arom. H), 10.88 (s, 1H, OOH). – ^{13}C NMR ([D_6]acetone): $\delta = 18.4$, 21.0, 21.1, 22.7 (C-4, C-5, C-6, C-7), 55.6 (OCH_3), 92.1 (C-3), 112.6, 120.8 (2 arom. CH), 122.3 (arom. C), 129.9, 132.2 (2 arom. CH), 136.1 (C-7a), 140.0 (C-3a), 157.3 (arom. C). – EI-MS: $m/z = 293$ (M–H_2O). – $C_{14}H_{17}NO_5S$ (311.38): calcd. C 54.00, H 5.50, N 4.50, S 10.30; found C 54.13, H 5.54, N 4.64, S 10.17.

*2-(4-Chlorophenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1,1-dioxide (***16h***)*

Yield: 78%, m.p. 124 – 132 °C. – IR (KBr): $\nu = 1160$ s (SO_2), 1270 s (SO_2). – UV (ethanol): λ_{max} (lg ε) 236.0 (4.16). – ^{1}H NMR ([D_6]acetone): $\delta = 1.83$ (m, 4H, 2 CH_2), 2.49 (m, 4H, 2 CH_2), 5.80 (s, 1H, 3-H), 7.01, 7.22 (4H, $J_{AB} = 9.0$ Hz, arom. H), 10.85 (s, 1H, OOH). – ^{13}C NMR ([D_6]acetone): $\delta = 19.0$, 21.4, 21.5, 23.4 (C-4, C-5, C-6, C-7), 92.1 (C-3), 123.3 (arom. C), 124.2, 130.3 (4 arom. CH), 133.7 (arom. C), 137.1 (C-7a), 140.1 (C-3a). – EI-MS: $m/z = 315$ (M^+). – $C_{13}H_{14}ClNO_4S$ (315.79): calcd. C 49.44, H 4.48, N 4.44, S 10.15; found C 49.01, H 4.23, N 4.47, S 10.17.

*2-(2-Nitrophenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1,1-dioxide (***16i***)*

Yield: 83%, m. p. 113 – 116 °C. – IR (KBr): $\nu = 1157$ s (SO_2), 1278 s (SO_2), 1358 s (NO_2), 1531 s (NO_2). – UV (ethanol): λ_{max} (lg ε) 208.0 (4.01). – ^{1}H NMR ([D_6]acetone): $\delta = 1.85$ (m, 4H, 2 CH_2), 2.45 (m, 4H, 2 CH_2), 5.99 (s, 1H, 3-H), 7.78 – 8.12 (m, 4H, arom. H), 11.32 (s, 1H, OOH). – ^{13}C NMR ([D_6]acetone): $\delta = 19.9$, 22.4, 22.5, 24.4 (C-4, C-5, C-6, C-7), 95.5 (C-3), 127.2 (arom. CH), 128.0 (arom. C), 132.4 (arom. CH), 135.2, 135.4, (2 arom. CH), 137.7 (C-7a), 138.0 (arom. C), 141.5 (C-3a). – EI-MS: $m/z = 327$ (M^+). – $C_{13}H_{14}N_2O_6S$ (327.62): calcd. C 47.66, H 4.31, N 8.55, S 9.79; found C 47.51, H 4.42, N 9.61, S 9.91.

*2-(4-Nitrophenyl)-2,3,4,5,6,7-hexahydro-3-hydroperoxy-1,2-benzisothiazole 1,1-dioxide (***16j***)*

Yield: 46%, m.p. 125 – 127 °C. – IR (KBr): $\nu = 1153$ s (SO_2), 1286 s (SO_2), 1342 s (NO_2), 1508 s (NO_2). – UV (ethanol): λ_{max} (lg ε) 203.5 (4.18). – ^{1}H NMR ([D_6]acetone): $\delta = 1.85$ (m, 4H, 2 CH_2), 2.45 (m, 4H, 2 CH_2), 6.48 (s, 1H, 3-H), 7.61, 8.32 (4H, $J_{AB} = 9.0$ Hz, arom. H), 10.90 (s, 1H, OOH). – EI-MS: $m/z = 327$ (M^+). – $C_{13}H_{14}N_2O_6S$ (327.62).

*2-Aryl-2,3,4,5,6,7-hexahydro-3-hydroxy-1,2-benzisothiazole 1,1-dioxides (***17***)*

General procedure: – Method A – MMPP · $6H_2O$ (0.9 mmol) was added to a suspension of **10d – j** (0.3 mmol) in acetonitrile and the mixture was left in the ultrasound bath for 3 hours at 50 °C. The excess MMPP was decomposed by addition of thiosulfate, the generated acid was neutralized with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O (3 x). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the 3-hydroxysultams **17d- j** were purified by recrystallization from isopropyl alcohol. – Method B – MMPP · $6H_2O$ (0.9 mmol) was added to a suspension of **10a – c** (0.3 mmol) in acetonitrile and the mixture was stirred for 6 hours at r.t. The isolation and purification of **17a – c** were accomplished as described before (see Table 1, 2). Compounds **17d, f** were described in [8a].

*3-Alkoxy-2-aryl-2,3,4,5,6,7-hexahydro-1,2-benzisothiazole 1,1-dioxides (***18***)*

General procedure: MMPP · $6H_2O$ (0.9 mmol) was added to a suspension of **10a – j** (0.3 mmol) in alcohol and the mixture was stirred for 6 h at r.t. The excess MMPP was decomposed by addition of thiosulfate, the generated acid was neutralized with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O (3 x). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the 3-alkoxysultams **18a – m** were purified by recrystallization from EtOH-water (3:2) (see Table 3, 5).

*2-Aryl-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2H)-one 1,1-dioxides (***19***)*

General procedure: – Method A – H_2O_2 (0.7 ml, 30%) was added to a suspension of **10a,h – j** (0.26 mmol) in AcOH (0.7 ml). The solution was stirred for 6 h at 80 °C. After cooling, the 3-oxosultams **19a, h, j** were isolated and recrystallized from ethanol; **19i** was not isolated. – Method B – A stirred solution of isothiazolium salts **10a – c** (0.3 mmol) in acetonitrile was treated with MMPP · $6H_2O$ (0.9 mmol) and the mixture was left in the ultrasound bath for 3 h at 50 °C. The excess MMPP · $6H_2O$ is decomposed by addition of thiosulfate, the generated acid is neutralized with saturated aqueous $NaHCO_3$ and the mixture was extracted with Et_2O (3 x). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the 3-oxosultams **19a – c** were purified by recrystallization from ethanol.

Compounds **19b, d** were described in [15] and **19c, e – g** in [8a].

*2-(2-Methoxyphenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (***19a***)*

Yield: 40% (method A), 83% (method B); m.p. 138 – 141 °C. – IR (KBr): $\nu = 1140$ s (SO_2), 1325 s (SO_2), 1734 s (C=O). – ^{1}H NMR ([D_6]acetone): $\delta = 1.81 - 1.95$ (m, 4H, 2 CH_2), 2.44 – 2.63 (m, 4H, 2 CH_2), 3.80 (s, 3H, OCH_3), 7.01 – 7.57 (m, 4H, arom. H). – ^{13}C NMR ([D_6]acetone):

Table 5. Analytical data of 3-alkoxy-2-aryl-2,3,4,5,6,7-hexahydro-1,2-benzisothiazole 1,1-dioxides **18**.

Comp.	^{1}H NMR ([D$_6$]acetone), δ (ppm), J (Hz)	^{13}C NMR ([D$_6$]acetone), δ (ppm)	EI-MS m/z (%)	Molecular formula – molecular weight	IR (cm^{-1})	EA calcd./found
18a	7.51 – 7.41 (m, 2 H), 7.20-7.17 (m, 1 H), 7.09 – 7.04 (m, 1 H), 5.90 (s, 1 H), 3.89 (s, 3 H), 3.63, 3.35 (ABC$_3$, ^2J = 8.1, ^3J = 6.9, 2 H), 2.45 – 2.34 (m, 4 H), 1.93 – 1.78 (m, 4 H), 1.09 (t, J = 6.6, 3 H)	158.2, 142.0, 136.8, 132.2, 131.5, 130.6, 121.6, 113.6, 88.7, 60.0, 56.2, 23.6, 21.9, 21.8, 19.2, 15.3	323 (M$^+$, 38), 278 (74), 149 (100)	$C_{16}H_{21}NO_4S$ 323.44	1294 (SO$_2$), 1157 (SO$_2$)	C 59.42/59.49 H 6.54/6.59 N 4.33/4.21 S 9.91/10.04
18b	7.54 – 7.40 (m, 2 H), 7.20 – 7.17 (m, 1 H), 7.09 – 7.04 (m, 1 H), 5.89 (s, 1 H), 3.90 (s, 3 H), 3.70 (^3J = 6.3, 1 H), 2.45 – 2.34 (m, 4 H), 1.89 – 1.79 (m, 4 H), 1.02 (d, 6 H)	158.2, 142.8, 135.4, 132.4, 131.6, 130.5, 121.6, 113.6, 88.5, 71.4, 56.3, 23.8, 23.4, 23.0, 22.0, 21.9, 19.2	337 (M$^+$, 28), 278 (100)	$C_{17}H_{23}NO_4S$ 337.44	1296 (SO$_2$), 1153 (SO$_2$)	C 60.51/60.80 H 6.87/7.05 N 4.15/4.23 S 9.50/9.76
18c	7.38/ 7.00 (2 d, J = 9.1, 4 H), 5.78 (s, 1 H), 3.82 (s, 3 H), 3.54, 3.31 (ABC$_3$, ^2J = 9.2, ^3J = 7.0, 2 H), 2.42 – 2.31 (m, 4 H), 1.83 (m, 4 H), 1.08 (t, J = 7.0, 3 H)	159.7, 142.4, 137.0, 129.2, 127.9, 115.8, 89.6, 60.1, 56.2, 23.9, 22.3, 22.2, 19.4, 15.7	323 (M$^+$, 74), 278 (100)	$C_{16}H_{21}NO_4S$ 323.44	1292 (SO$_2$), 1152 (SO$_2$)	C 59.42/59.40 H 6.54/6.42 N 4.33/4.13 S 9.91/9.80
18d	7.39/ 7.01 (2 d, J = 9.0, 4 H), 5.78 (s, 1 H), 3.83 (s, 3 H), 3.42 (^3J = 6.1, 1 H), 2.40 – 2.37 (m, 4 H), 1.83 – 1.80 (m, 4 H), 1.03 (d, 6 H)	159.7, 142.8, 135.5, 130.9, 128.7, 115.8, 89.4, 71.4, 55.8, 23.7, 23.5, 23.1, 21.9, 21.8, 19.1	337 (M$^+$, 28), 278 (30), 122 (100)	$C_{17}H_{23}NO_4S$ 337.44	1297 (SO$_2$), 1153 (SO$_2$)	C 60.51/60.20 H 6.87/7.13 N 4.15/4.03 S 9.50/9.35
18e	7.39/ 7.03 (2 d, J = 8.7, 4 H), 5.78 (s, 1 H), 3.85 (s, 3 H), 2.53-2.33 (m, 4 H), 1.90 – 1.79 (m, 4 H), 1.02 (s, 9 H)	159.4, 144.2, 134.2, 133.1, 128.5, 115.3, 86.6, 84.4, 55.8, 29.1, 23.3, 22.0, 21.9, 18.9	351 (M$^+$, 3), 295 (16), 122 (100)	$C_{18}H_{24}NO_4S$ 350.46	1282 (SO$_2$), 1151 (SO$_2$)	C 61.69/61.78 H 6.90/7.26 N 3.40/3.29 S 9.15/8.98
18f	7.36/ 7.24 (2 d, J = 8.2, 4 H), 5.93 (s, 1 H), 3.11 (s, 3 H), 2.43 (m, 4 H), 2.32 (s, 3 H), 1.83 (m, 4 H)	142.1, 138.1, 136.5, 134.8, 131.5, 123.5, 88.7, 50.7, 24.0, 22.5, 22.4, 21.5, 19.6	293 (M$^+$, 57), 262 (100)	$C_{15}H_{19}NO_3S$ 293.41	1295 (SO$_2$), 1153 (SO$_2$)	C 61.40/61.20 H 6.53/6.46 N 4.77/4.67 S 10.93/11.40
18g	7.35/ 7.23 (2 d, J = 8.4, 4 H), 5.91 (s, 1 H), 3.47, 3.29 (ABC$_3$, ^2J = 9.3, ^3J = 7.2, 2 H), 2.41 (m, 4 H), 2.32 (s, 3 H), 1.83 (m, 4 H), 1.06 (t, J = 7.2, 3 H)	142.3, 137.0 136.2, 134.6, 131.1, 123.4, 88.3, 59.5, 23.8, 22.2, 22.1, 21.2, 19.3, 15.7	307 (M$^+$, 57), 262 (100)	$C_{16}H_{21}NO_3S$ 307.44	1287 (SO$_2$), 1154 (SO$_2$)	C 62.51/62.22 H 6.89/6.86 N 4.56/4.49 S 10.43/10.61
18h	8.04/ 7.54 (2 d, J = 9.2, 4 H), 6.12 (s, 1 H), 3.86 (s, 3 H), 3.31 (ABC$_3$, ^2J = 13.6, ^3J = 7.0, 2 H), 2.44 – 2.34 (m, 4 H), 1.90 – 1.81 (m, 4 H), 1.04 (t, J = 7.0, 3 H)	167.3, 142.6, 141.9, 137.3, 132.2, 126.4, 118.5, 86.9, 59.1, 52.9, 24.1, 22.4, 22.2, 19.4, 15.8	351 (M$^+$, 31), 306 (100)	$C_{17}H_{21}NO_5S$ 351.43	1716 (C=O), 1279 (SO$_2$), 1155 (SO$_2$)	C 58.10/58.52 H 6.02/5.78 N 3.99/4.17 S 9.13/9.42
18i	7.67 – 7.50 (m, 4 H), 5.86 (s, 1 H), 3.31 (s, 3 H), 2.51 – 2.37 (m, 4 H), 1.94-1.84 (m, 4 H)	141.3, 137.3, 135.4, 133.6, 133.2, 131.4, 131.0, 128.7, 90.4, 51.5, 23.4, 21.5, 21.4, 18.9	313 (M$^+$, 11), 282 (39)	$C_{14}H_{16}ClNO_3S$ 313.81	1306 (SO$_2$), 1161 (SO$_2$)	C 53.59/54.08 H 5.14/5.36 N 4.46/4.88 S 10.22/10.03
18j	7.83 – 7.60 (m, 3 H), 5.64 (s, 1 H), 3.33 (s, 3 H), 2.36 – 2.25 (m, 4 H), 1.72 (m, 4 H)	141.8, 136.5, 134.5, 132.3, 131.6, 130.8, 130.7, 130.2, 91.2, 52.9, 23.5, 21.3, 21.2, 19.0	347 (M$^+$, 26), 316 (43)	$C_{14}H_{15}Cl_2NO_3S$ 347.90	1292 (SO$_2$), 1165 (SO$_2$)	C 48.33/48.76 H 4.35/4.55 N 4.03/3.96 S 9.22/9.01
18k	7.51 (m, 4 H), 6.05 (s, 1 H), 3.45, 3.31 (ABC$_3$, ^2J = 8.1, ^3J = 7.0, 2 H), 2.48 – 2.39 (m, 4 H), 1.92 – 1.84 (m, 4 H), 1.11 (t, J = 7.0, 3 H)	141.4, 136.0, 135.2, 129.6, 129.5, 121.9, 86.6, 58.3, 22.9, 21.2, 21.0, 18.2, 14.6	350 (M+Na$^+$, 100), 282 (39)	$C_{15}H_{18}ClNO_3S$ 327.81	1276 (SO$_2$), 1153 (SO$_2$)	C 54.95/55.50 H 5.53/5.93 N 4.27/4.44 S 9.78/9.69
18l	8.21 – 7.62 (m, 4 H), 5.74 (s, 1 H), 3.70, 3.40 (ABC$_3$, ^2J = 8.1, ^3J = 6.8, 2 H), 2.43 – 2.26 (m, 4 H), 1.97 – 1.72 (m, 4 H), 1.15 (t, J = 7.0, 3 H)	142.4, 136.7, 135.8, 134.7, 133.8, 131.5, 126.5, 125.8, 91.9, 61.6, 23.8, 21.8, 21.7, 19.2, 15.3	338 (M$^+$, 3), 293 (100)	$C_{15}H_{18}N_2O_5S$ 338.4	1535 (NO$_2$), 1354 (NO$_2$), 1296 (SO$_2$), 1163 (SO$_2$)	C 53.20/52.84 H 5.36/5.42 N 8.28/8.75 S 9.48/10.11
18m	8.33/ 7.65 (2 d, J = 9.3, 4 H), 6.21 (s, 1 H), 3.34 (ABC$_3$, ^2J = 10.4, ^3J = 7.0, 2 H), 2.48 – 2.41 (m, 4 H), 1.88 – 1.85 (m, 4 H), 1.08 (t, J = 7.0, 3 H)	142.9, 142.1, 136.7, 126.0, 122.8, 117.8, 86.5, 58.7, 23.6, 21.8, 21.6, 18.8, 15.2	338 (M$^+$, 30), 293 (100)	$C_{15}H_{18}N_2O_5S$ 338.4	1508 (NO$_2$), 1340 (NO$_2$), 1286 (SO$_2$), 1153 (SO$_2$)	C 53.20/53.68 H 5.36/5.79 N 8.28/7.83 S 9.48/9.13

$\delta = 20.1, 21.6, 21.8, 22.1$ (C-4, C-5, C-6, C-7), 57.1 (OCH_3), 114.5 (arom. CH), 119.1 (arom. C), 122.4 (arom. CH), 132.7, 133.3 (2 arom. CH), 137.5 (C-3a), 148.3 (C-7a), 158.7 (arom. C), 160.7 (C-3). – EI-MS: $m/z = 293$ (M^+). – $C_{14}H_{15}NO_4S$ (293.33): calcd. C 57.33, H 5.15, N 4.77, S 10.93; found C 57.39, H 5.01, N 4.85, S 11.07.

*2-(4-Chlorophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (***19h***)*

Yield: 51% (method A), m. p. 111 – 113 °C. – IR (KBr): $\nu = 1170$ s (SO_2), 1330 s (SO_2), 1740 s (C=O). – UV (ethanol): λ_{max} ($\lg\varepsilon$) 265.5 (3.21). – ^{1}H NMR ([D_6]acetone): $\delta = 1.84 - 1.91$ (m, 4H, 2 CH_2), 2.49 – 2.67 (m, 4H, 2 CH_2), 7.40, 7.49 (4H, $J_{AB} = 8.2$ Hz, arom. H). – ^{13}C NMR ([D_6]acetone): $\delta = 19.6, 20.9, 21.0, 21.3$ (C-4, C-5, C-6, C-7), 128.2 (arom. C), 129.7 (2 arom. CH), 130.6 (2 arom. CH), 136.2 (arom. C), 136.8 (C-3a), 146.8 (C-7a), 160.1 (C-3). – EI-MS: $m/z = 297$ (M^+). – $C_{13}H_{12}ClNO_3S$ (297.77): calcd. C 52.43, H 4.07, Cl 11.90, N 4.70, S 10.77; found C 52.15, H 3.95, Cl 11.79, N 4.75, S 10.73.

*2-(4-Nitrophenyl)-4,5,6,7-tetrahydro-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (***19j***)*

Yield: 49% (method A), m. p. 157 – 159 °C. – IR (KBr): $\nu = 1183$ s (SO_2), 1297 s (SO_2), 1345 s (NO_2), 1519 s (NO_2), 1735 s (C=O). – UV (ethanol): λ_{max} ($\lg\varepsilon$) 271.0 (3.99). – ^{1}H NMR ([D_6]acetone): $\delta = 1.90 - 1.96$ (m, 4H, 2 CH_2), 2.54 – 2.70 (m, 4H, 2 CH_2), 7.86, 8.45 (4H, $J_{AB} = 9.0$ Hz, arom. H). – ^{13}C NMR ([D_6]acetone): $\delta = 19.2, 20.8, 20.9, 21.22$ (C-4, C-5, C-6, C-7), 125.2 (2 arom. CH), 130.6 (2 arom. CH), 135.5 (arom. C), 137.5 (C-3a), 146.9 (arom. C), 147.3 (C-7a), 156.7 (C-3). – EI-MS: $m/z = 308$ (M^+). – $C_{13}H_{12}N_2O_5S$ (308.32): calcd. C 50.64, H 3.92, N 9.09, S 10.40; found C 50.76, H 3.81, N 9.02, S 10.47.

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