Sultam and Sultim Structures, Part 5 [1]. Weak Hydrogen Bonds in Molecular Networks of 2-Hetaryl-3-oxosultams in Comparison with 2-Aryl-3-oxosultams

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Dedicated to Professor Gerhard Maas on the occasion of his 60th birthday

Stable 3-oxosultams were synthesized by oxidation of the 2-hetaryl-substituted isothiazolium salts. X-Ray crystal structure analyses of the sultams reveal the existence of strong and weak hydrogen bonds, which lead to different interaction combinations and solid state structures. While the bond lengths and angles in the isothiazol rings of the sultams are similar, the dihedral angles between the isothiazol rings and the hetaryl substituents are influenced by the position of the nitrogen atom in the pyridine ring and its substituents. The sultams form chain structures, dimeric head-to-tail structures or two-dimensional networks.

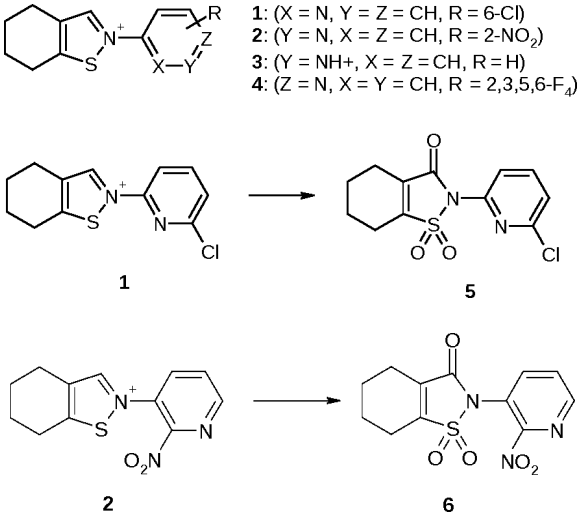
Key words: Sultams, Intermolecular Hydrogen Bonds

Introduction

Isothiazol-3-(2*H*)-ones and their 1,1-dioxides are known to exhibit a broad range of biological activities [2 – 5], especially the class of *N*-substituted 1,2-benzisothiazole-3-(2*H*)-one 1,1-dioxides are pharmaceutically active compounds [4]. Monocyclic 2,4,5-triaryl-substituted isothiazol-3-(2*H*)-one 1,1-dioxides, which are synthesized by oxidation of the corresponding isothiazolium salts [6], cause inhibition of the human leukocyte elastase (HLE) [7, 8]. Recently we reported the crystal structures of 3-hydroxy-, 3-hydroperoxy- and 3-oxo-sultims and -sultams [9, 10]. We discovered strong and weak hydrogen bonds in intermolecular networks, leading to "head-to-tail" cyclodimers, tetrameric units or polymers. Predominantly strong intermolecular S–O···HO hydrogen bonds, weak C–H···O=C and aromatic C–H···O–SO interactions are characteristic for these compounds.

Herein we report about the oxidation of 2-hetaryl-isothiazolium salts **1** – **4** to 3-oxosultams **5** – **9**, and the X-ray crystal structure analyses of the products.

These compounds bear sulfonyl, carbonyl and hetaryl groups, which are interesting hydrogen bond acceptors in three-dimensional structures with only weak hydrogen bonds.

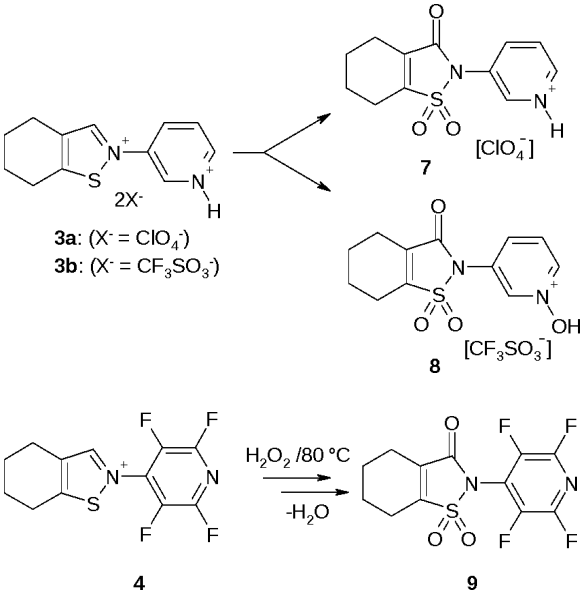


Results and Discussion

The novel 2-hetaryl-3-oxosultams **6**, **7** and **8** are synthesized by oxidation of their corresponding isothi-

Table 1. Crystal data and structure refinement for 3-oxosultams **5** – **9**.

	5	**6**	**7**	**8**	**9**
Empirical formula	$C_{12}H_{11}ClN_2O_3S$	$C_{12}H_{11}N_3O_5S$	$C_{12}H_{13}ClN_2O_7S$	$C_{13}H_{13}F_3N_2O_7S_2$	$C_{12}H_8F_4N_2O_3S$
Formula weight	298.74	309.3	364.75	430.37	336.27
Temperature, K	213	213	213	213	213
Crystal system	monoclinic	monoclinic	monoclinic	triclinic	triclinic
Space group	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P\bar{1}$	$P\bar{1}$
a, Å	8.754(2)	15.400(1)	8.246 (1)	7.659(1)	7.923(1)
b, Å	12.994 (2)	8.1687(4)	12.802(2)	8.492(1)	8.954(1)
c, Å	11.793(3)	10.920(1)	14.277(3)	14.104(1)	10.377(1)
α, deg	90	90	90	72.87(1)	107.61(1)
β, deg	99.95(3)	105.62(1)	96.60(1)	79.25(1)	109.68(1)
γ, deg	90	90	90	76.31(1)	95.75(1)
V, Å^3	1321.2(5)	1323.0(1)	1496.9(3)	845.0(2)	643.7(1)
Z	4	4	4	2	2
D_{calcd}, g cm^{-3}	1.502	1.553	1.618	1.691	1.735
Absorption coeff.	0.452	0.272	0.434	0.389	0.316
Cryst. size, mm^3	$0.20 \times 0.20 \times 0.20$	$0.25 \times 0.25 \times 0.2$	$0.25 \times 0.25 \times 0.20$	$0.3 \times 0.1 \times 0.1$	$0.3 \times 0.3 \times 0.2$
θ range for data collect, deg	3.0 – 28.0	3.6 – 28.0	3.4 – 33.4	3.4 – 28.0	3.6 – 28.0
Index ranges	$-11 \le h \le 11$	$-20 \le h \le 19$	$-12 \le h \le 12$	$-9 \le h \le 10$	$-10 \le h \le 9$
	$-15 \le k \le 15$	$0 \le k \le 10$	$-19 \le k \le 19$	$-10 \le k \le 11$	$-11 \le k \le 11$
	$-15 \le l \le 15$	$0 \le l \le 14$	$-22 \le l \le 21$	$0 \le l \le 18$	$0 \le l \le 13$
Reflections collected	11361	3175	18514	4070	3086
Independent reflections	2990	3175	5784	4070	3086
Absorption correction	DIFABS	XRED	DIFABS	XRED	XRED
Parameters	216	234	245	298	231
Final R_1/wR_2 [$I \ge 2\sigma(I)$]	0.031/0.067	0.031/0.090	0.075/0.156	0.035/0.085	0.029/0.073
Final R_1/wR_2 (all data)	0.056/0.072	0.038/0.092	0.095/0.165	0.045/0.090	0.038/0.076
Goodness-of-fit on F^2	0.805	1.059	1.096	0.826	0.989
Lgs. diff peak/hole, e Å^{-3}	0.233/−0.240	0.508/−0.367	0.586/−0.596	0.483/−0.688	0.419/−0.373



azolium salts **2**, **3a** and **3b** with hydrogen peroxide in glacial acetic acid (80 °C, 10 h).

The oxidation of the bis-salts **3a** and **3b** leads to salts **7** and **8**, which were investigated by IR and NMR spectroscopy. The results are described in the Experimental Section.

The solid state structures of **5** – **9** were determined by single crystal X-ray diffraction analysis. The crystallographic data are given in Table 1, selected bond lengths and angles in Table 2. In the following we compare the structures of these 2-hetaryl compounds with those of the 2-aryl-3-oxosultams.

The bond lengths and the bond angles in the five compounds are very similar. Therefore, we can conclude that there is no influence of the different substituents at the N1 atom on the bond parameters in the sultam ring. The mean C1–C2 bond length of 1.486(2) Å is a typical value for a C(sp^2)–C(sp^2) single bond [11], the C2–C3 bond lengths (mean value 1.331(2) Å) are typical for a C(sp^2)–C(sp^2) double bond. The C1–N1 bond (1.405(2) Å) corresponds to a C(sp^2)–N(sp^2) single bond.

The C3–S1 and N1–S1 bond lengths also have typical values. The sultam rings are nearly planar. The mean deviations from the least square planes are below 0.01 Å. In contrast to the bond lengths and angles, the dihedral angles between the sultam ring and its six-membered ring substituent at atom N1 differ

Table 2. Bond lengths (Å) and angles (deg) of the sultam ring for 3-oxosultams **5** – **9**.

Bonds	**5**	**6**	**7**	**8**	**9**	Mean value
S1–O1	1.425(1)	1.427(1)	1.421(2)	1.432(1)	1.432(1)	1.428
S1–O2	1.424(1)	1.430(1)	1.431(2)	1.436(1)	1.431(1)	1.430
N1–C1	1.404(2)	1.401(2)	1.399(3)	1.411(2)	1408(2)	1.405
C1–C2	1.483(2)	1.486(2)	1.487(3)	1.489(2)	1.487(2)	1.486
C2–C3	1.328(2)	1.330(2)	1.330(3)	1.333(2)	1.334(2)	1.331
C3–S1	1.752(2)	1.749(1)	1.746(2)	1.746(2)	1.754(1)	1.749
S1–N1	1.704(1)	1.687(1)	1.694(2)	1.686(1)	1.695(1)	1.693
C1–O3	1.213(2)	1.205(2)	1.212(3)	1.203(2)	1.204(2)	1.207
N1–C1–C2	109.7(2)	108.9(1)	109.5(2)	109.0(2)	108.9(1)	109.2
C1–C2–C3	113.9(2)	114.0(1)	114.0(2)	114.0(2)	114.0(1)	114.0
C2–C3–S1	111.5(1)	111.3(1)	110.9(2)	111.2(1)	111.2(1)	112.2
C3–S1–N1	92.5(1)	92.59(6)	92.2(2)	93.13(8)	92.37(6)	93.2
S1–N1–C1	112.3(2)	113.2(1)	112.3(2)	112.7(1)	112.70(9)	112.7

considerably. The dihedral angles of the five 3-oxosultams **5** – **9** have the following values: 3.4° (**5**), 61.9° (**6**) 35.1° (**7**), 42.7° (**8**), and 82.8° (**9**). The dihedral angles in **7** and **8** are expected to be similar to the angle observed in **5**, because in all these compounds the hetaryl ring features no substituents in *ortho* position. The larger dihedral angles in **7** and **8** are induced by strong hydrogen bonding (see Figs. 3 and 4).

Intermolecular interactions

The combination of strong and weak hydrogen bonds leads to three different kinds of inter-molecular arrangements. For the compounds **5** and **8** a chain structure results.

In compound **5** (Fig. 1) a weak intermolecular hydrogen bond between the atoms S1–O1···H–C10A is formed (C10–H10 0.95(3) Å, H(10)···O1 2.41(3) Å, C10–O1 3.22 (3) Å, C10–H10···O1 143(2)°).

Due to the 2_1 screw axis in the monoclinic space group $P2_1/n$, a helical chain structure (Fig. 2) is formed. In compound **8** (Fig. 1) a strong intermolecular hydrogen bond between the atoms O4–H4···O7 exists: O4–H4 0.92(3) Å, H4···O 1.59(3) Å, O4–H4···O 178(3)°.

The result of additional weak hydrogen bonds between the atoms C11–H11···O and C11–H11···F are linear chains by translation along the crystallographic *a* axis (Fig. 3).

The compounds **7** and **9** form head-to-tail dimers by combination of strong and weak hydrogen bonds around a center of symmetry (Fig. 4).

In compound **7** (Fig. 5) bifurcated hydrogen bonds are formed between the oxygen atoms O5 and O7 of the perchlorate anion and the N2 atom. The bond parameters are N2–H2 0.90(3) Å, H2···O 2.213(3) Å, N2···O 2.920(3) Å, N2–H2···O5 135.1(3)°, H2···O 2.554(3) Å, N2···O 3.213(3) Å, N2–H2···O 130.6(3)°.

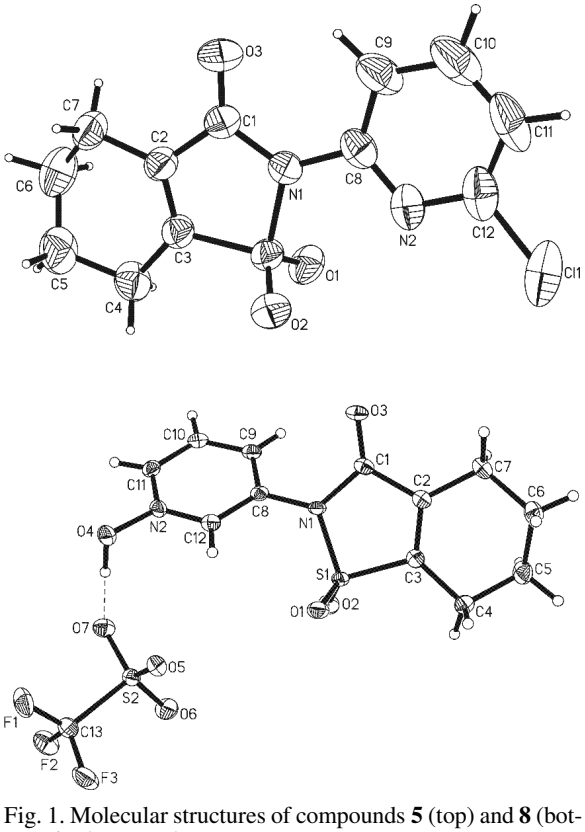


Fig. 1. Molecular structures of compounds **5** (top) and **8** (bottom) in the crystal.

In compound **9** (Fig. 6) a weak hydrogen bond exists between the atoms C4–H4···F with the following parameters: C4–H4a 0.96(3) Å,

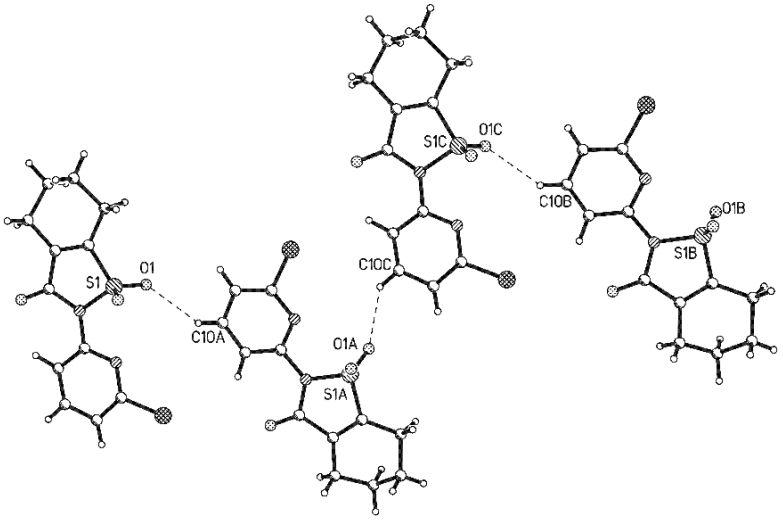


Fig. 2. Helical chain along the 2_1 screw axis with weak intermolecular hydrogen bonds in the crystals of compound **5**.

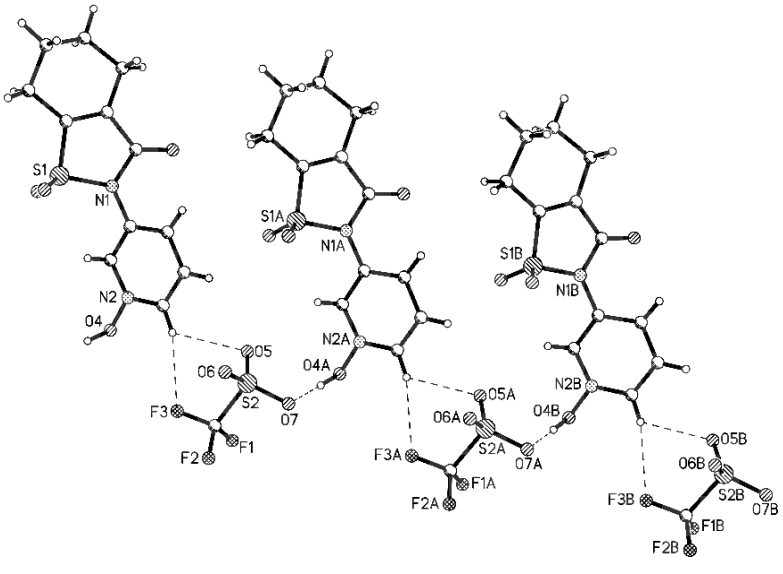


Fig. 3. Chain formed by weak and strong hydrogen bonds in compound **8**.

H4···F 2.553(3), C4···F 3.270(3) Å, C4–H4···F 131.3(3)°.

Compound **6** (Fig. 7) forms a two-dimensional network in the crystallographic *ac* plane, where the molecules are connected by weak intermolecular hydrogen bonds C6–H6···O, C9–H9···O, and C10–H10···N (Fig. 8).

Experimental Section

General

Melting points: Boetius micro-melting point apparatus; corrected. UV/Vis spectra: Beckman DU 650; λ_{max} in nm ($\log \varepsilon$). IR spectra: Genesis FTIR Unicam Analytical System (ATI Mattson), KBr pellets, cm^{-1}. ^1H NMR (200 or 300 MHz), ^{13}C NMR (50 or 75 MHz), ^{19}F NMR (188 MHz) spectra: Varian Gemini-200 or Varian Gemini-300 spectrometers; δ in ppm relative to Me_4Si and $CFCl_3$ as internal standards. MS: Quadrupole-MS VG 12-250; 70 eV. Elemental analysis: Heraeus CHNO Rapid Analyzer.

The salts **1** and **4** were prepared according to [12], the new salt **2** and the bis-salts **3a**, **3b** according to the literature procedure [7]. **2**: yield 25 %, m. p. 134 – 136 °C; **3a**: yield 100 %, m. p. 232 – 233 °C; **3b**: yield 90 %, m. p. 171 – 173 °C. The 3-oxosultams **5** and **9** were synthesized according to the literature [12].

The 2-(pyridin-3-yl)-2,3,4,5,6,7-hexa-hydro-1,2-benzisothiazol-3-one 1,1-dioxides **6**, **7** and **8** were prepared by oxi-

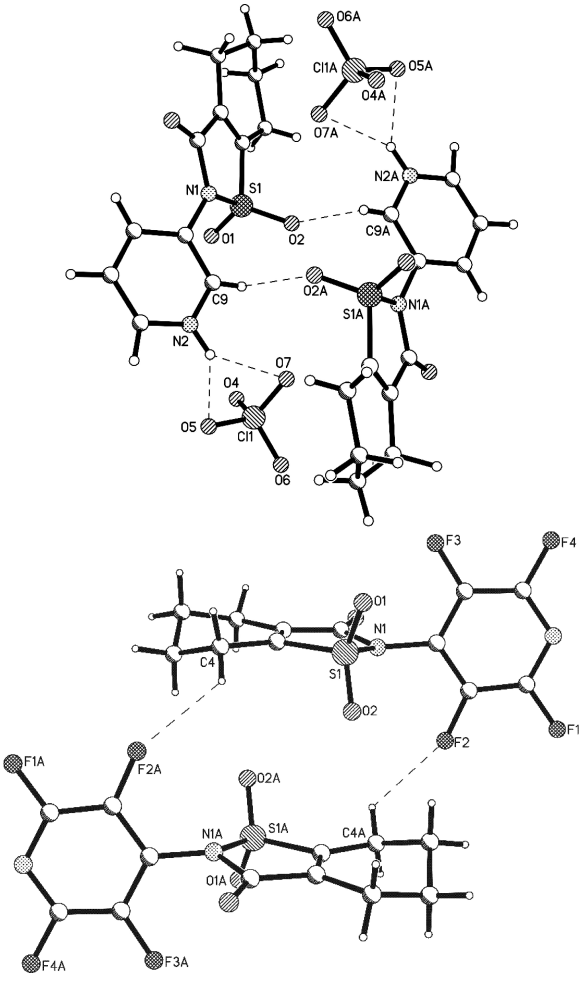


Fig. 4. Head-to-tail dimers in compounds **7** (top) and **9** (bottom). Symmetry code: A: $-x$, $-y$, $-z$.

dation of the corresponding salts **2**, **3a** and **3b** with hydrogen peroxide and glacial acetic acid at 80 °C [12].

*2-(2-Nitro-pyridin-3-yl)-2,3,4,5,6,7-hexahydro-1,2-benzisothiazol-3-one 1,1-dioxide (**6**)*

Yield: 8 %. M. p. 161 – 163 °C. – IR (KBr): ν = 1185 (SO_2), 1316 (SO_2), 1340 (NO_2), 1551 (NO_2), 1736 cm^{-1} (C=O). – UV (ethanol): λ_{max} (lg ε) = 218 nm (3.99). – ^{1}H NMR ([D$_6$]aceton): δ = 1.88 (m, 2H, CH_2), 1.97 (m, 2H, CH_2), 2.53 (m, 2H, CH_2), 2.70 (m, 2H, $CH_{2'}$), 8.18, (dd, J = 4.8 Hz, 1H, arom. H), 8.56 (d, J = 7.7 Hz, 1H, arom. H), 8.92 (d, J = 3.8 Hz, 1H, arom. H). – ^{13}C NMR ([D$_6$]aceton): δ (ppm) = 20.3, 21.7, 22.1, 25.8, 120.6, 131.6, 138.0, 143.8, 149.2, 151.6, 155.9, 174.5. – HRMS: ((+)-ESI): *m/z* = 310.04922 (calcd. 310.04977 for $C_{12}H_{12}O_5SN_3$, $[M+H]^+$).

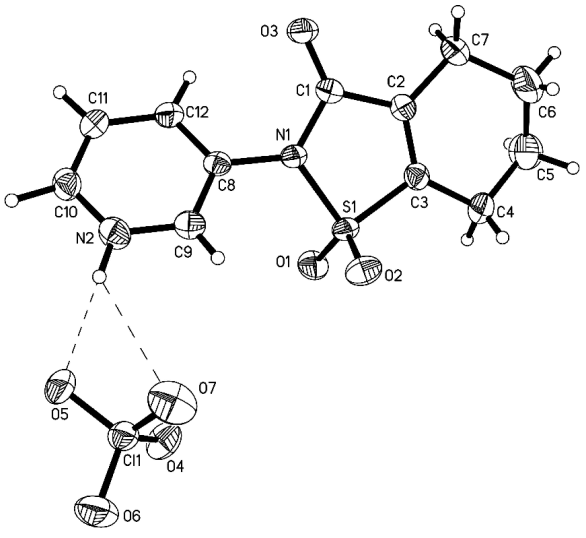


Fig. 5. Molecular structure of compound **7** in the crystal.

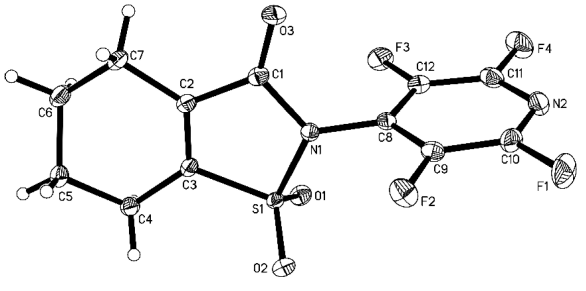


Fig. 6. Molecular structure of compound **9** in the crystal.

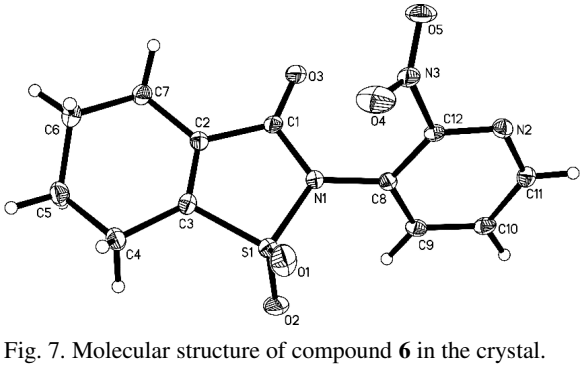


Fig. 7. Molecular structure of compound **6** in the crystal.

*2-(Pyridin-3-yl)-2,3,4,5,6,7-hexahydro-1,2-benzisothiazol-3-one 1,1-dioxide perchlorate (**7**)*

Yield: 34 %. M. p. 203 – 205 °C. – IR (KBr): ν = 1081s (ClO_4), 1187s (SO_2), 1349s (SO_2), 1734s cm^{-1} (CO). – UV (ethanol): λ_{max} (lg ε) = 206 nm (3.79). – ^{1}H NMR ([D$_6$]DMSO): δ = 1.93 (m, 2H, CH_2), 2.01 (m, 2H, CH_2), 2.61 (m, 2H, CH_2), 2.76 (m, 2H, CH_2), 8.55 (m, 1H, arom.

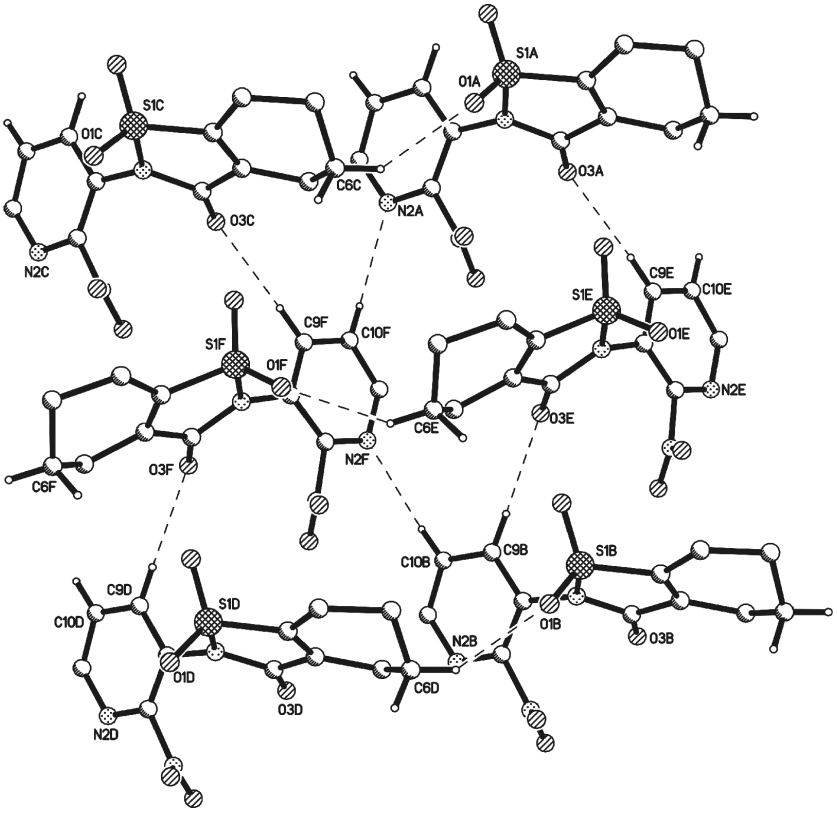


Fig. 8. Two-dimensional network by weak intermolecular hydrogen bonds in crystals of compound **6** (symmetry code: A: x, y, $1-z$; B: x, y, z; C: x, $1+y$, $1-z$; D: x, $1+y$, z; E: x, $0.5-y$, $z-0.5$; F: x, $1.5-y$, $z-0.5$).

H), 8.80 (m, 1H, arom. H), 9.33 (m, 1H, arom. H), 9.47 (m, 1H, arom. H). – ^{13}C NMR ([D$_6$]DMSO): δ = 20.2, 21.6, 21.8, 22.0, 130.9, 131.4, 138.4 (C 3a), 141.4, 143.7, 145.4, 148.1 (C 7a), 160.3 (C=O). – MS (EI, 70 eV): *m/z* (%) = 264 (100) $[M–HClO_4]^{+\cdot}$. – $C_{12}H_{13}O_7SN_2Cl$ (309.30): calcd. C 39.51, H 3.59, N 17.68, S 8.79; found C 39.43, H 3.51, N 17.66, S 8.95.

*2-(N-Hydroxy-pyridin-3-yl)-2,3,4,5,6,7-hexahydro-1,2-benzisothiazol-3-one 1,1-dioxide trifluoromethylsulfonate (**8**)*

Yield: 5 %. M. p. 131 – 133 °C. – IR (KBr): ν = 1170 (SO_2), 1327 (SO_2), 1743 cm^{-1} (CO). – UV (ethanol): λ_{max} (lg ε) = 224 nm (5.34). – ^{1}H NMR ([D$_6$]DMSO): δ = 1.73 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 2.42 (m, 2H, CH_2), 2.59 (m, 2H, CH_2), 7.55 (d, J = 8.8 Hz, 1H, arom. H), 7.65 (t, J = 6.8 Hz, J = 8.8 Hz, 1H, arom. H), 8.40 (d, J = 6.8 Hz, 1H, arom. H), 8.45 (s, 1H, arom. H). – ^{13}C NMR ([D$_6$]DMSO): δ = 18.7, 20.2, 20.3, 20.5, 125.7, 127.6, 129.4, 137.2, 138.1, 140.1, 145.6, 159.2. – ^{19}F NMR ([D$_6$]DMSO): δ = −78.2. – MS: ((+)-ESI): *m/z* = 281 $[M–CF_3SO_3]^+$. – $C_{13}H_{13}O_7S_2N_2F_3$ (430.30): calcd. C 40.88, H 3.43, N 6.81, S 7.80; found C 40.80, H 3.42, N 6.87, S 7.79.

Crystal structure analyses

Single crystals of **5**, **6** and **9** were obtained from acetone, those of **7** and **8** from glacial acetic acid. The reflection intensities of the crystals of compounds **6**, **8** and **9** were measured on a Stoe IPDS1 diffractometer, those of the compounds **5** and **7** on a Siemens SMART CCD diffractometer. The relevant crystallographic data are listed in Table 1. The structures were solved by Direct Methods using SHELXS-97 [13]. The refinement was done with SHELXL-97 [14].

CCDC 700936 (**5**), 700937 (**6**), 700938 (**7**), 700939 (**8**), and 700940 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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