Journal of Chemical Crystallography, Vol. 29, No. 1, 1999

X-ray diffraction and self condensation reaction of thionicotinamide S-oxide

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Received May 5, 1997

Thiobenzamide and thionicotnamide S-oxide were prepared as intermediates in the dimerization of corresponding thioamides to 1,2,4-thiadiazoles and the X-ray crystal structure of thionicotinamide S-oxide water solvate was determined. Crystals belong to orthorhombic *Pbca* space group with $a = 14.129(3)$, $b = 7.299(2)$, $c = 15.277(3)$Å, and $Z = 8$. The geometry of the molecule accords well with that found in similar compounds; an intramolecular N–H · · · O hydrogen bond is present, while the packing is mainly determined by the hydrogen bond system involving the water molecule and the side-chain of the organic molecule. The contacts between pyridine moieties, stacked along the [010] axis, complete the packing.

KEY WORDS: Aminosulphines; thionicotinamide S-oxide; thiobenzamid; X-ray structure.

Introduction

Aminosulphines[1,2] (thioamides S-oxide) $RS(O)NR'_2$ are interesting compounds because of their reactivity in forming heterocyclic systems with two or more heteroatoms (mainly sulfur and nitrogen containing, such as thiazoles, dithiazines, thiadiazoles). Biological interest on thioamides as biomodulators rises from their administration as biocides. There are some indications that the biotransformation of thioamides,[3] in particular of thionicotinamide, as well as some problems of hepatotoxicity[4] are connected with sulfur oxidation.[3] Thioamide S-oxides are excreted after administration of thioamides.[2]

Our interest is in the reaction of thioamides to form 1,2,4-thiadiazoles[5] with a particular reagent mixture: the dimethylsulfoxide/acid mixture in the presence of halide ions. The formation of 3,5-diphenyl-1,2,4-thiadiazoles[6] was reported by us to occur in dimethylsulfoxide and in the presence of hydrogen chloride or bromide, or in the presence of other acids (methanesulfonic, sulfuric acids) and halide salts, as shown in Scheme 1. A reasonable reaction pathway of dimerization of the thioamides to 1,2,4-thiadiazoles is the formation of the thioamide S-oxide as intermediate. In order to collect some information on the importance of the thioamides S-oxide in the reaction of Scheme 1, we report the preparation of thiobenzamide and thionicotinamide S-oxide and X-ray diffraction of thionicotinamide S-oxide, together with some indication on the reaction of formation of 1,2,4-thiadiazoles.

Experimental

Oxidation of thioamides was carried out in methanol with H_2O_2.[2,7] The thioamide S-oxides were obtained from the reaction mixtures by evaporating the solvent at 15–20°C in vacuum (10 mm/Hg). Thiobenzamide S-oxide: m.p. 125–127°C.[2] ^{1}H NMR in DMSO-d6, internal reference TMS: $\delta = 9.35$ (1 Hsb), 8.38 (1 Hsb) (NH_2); 7.4–7.6 (5 Hm, C_6H_5). λ_{max} 355nm

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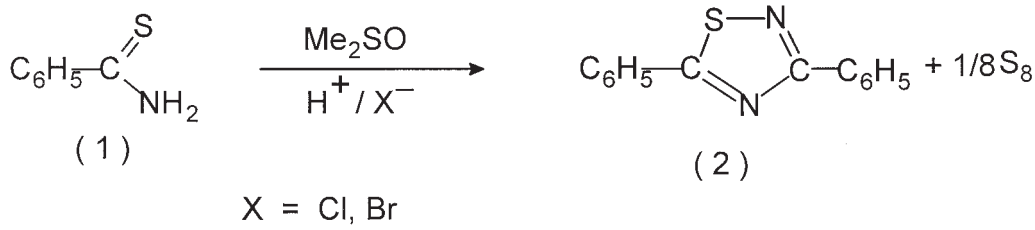


(1) (2)

Scheme 1

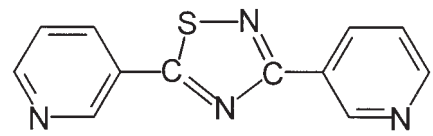
(ε = 6,500) (in DMSO with 5% of H_2O by vol.). Mass spectrum (*m/z*) (relative intensities): M^+ = 153(5), 137(40), 135(100), 121(5) 105(7), 77(79). The spectrum shows the presence of M^+ (238) of 3,5-diphenyl-(1,2,4)-thiadiazole.

Thionicotinamide S-oxide: m.p. 128–129°C (MeOH).[1]H NMR in DMSO-d6 δ = 9.35 (1 Hsb), 8.38 (1 Hsb) (NH_2); 8.8 (2 Hm), 7.5 (1 Hm, C_5H_4N). λ_{max} 360 nm (ε = 4,500) (in DMSO with 5% of H_2O by vol.). Mass spectrum (*m/z*) (relative intensities): M^+ = 154(24), 138(11), 122(7), 105(100), 78(10). The spectrum shows the presence of M^+ (240) of 3,5-dipyridyl-(1,2,4)-thiadiazole.

Data collection, structure determination and refinement are given in Table 1.

Results and discussion

When H_2O_2 is added dropwise to a solution of thionicotinamide in methanol and the solvent is eliminated *in vacuum* without heating, a crystalline solid (the thionicotinamide S-oxide, **5** of Scheme 2) is obtained. When the hydrogen peroxide is added to thiobenzamide and to thionicotinamide (in methanol) in the presence of appropriate amounts (~0.3 M) of HCl, or the reaction mixtures are gently warmed; the only recovered compounds from the reaction mixtures are 3,5-diphenyl-1,2,4-thiadiazole **2** and the 3,5-di-(3-pyridyl)-1,2,4-thiadiazole **6** respectively (together with elemental sulfur).



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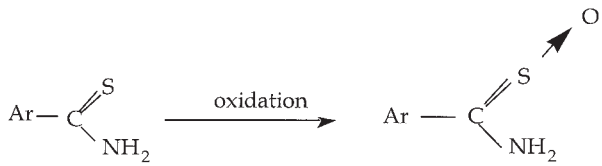
Both thiobenzamide S-oxide and thionicotinamide S-oxide show in the[1]H NMR spectrum (in DMSO-d6) with two different N-H signals (see Experimental). The sulfur oxidation does not change the geometry and, consequently, the hybridization of the nitrogen atom of the thioamide group [C(S)-NH_2]. As observed in thioamides,[8] the hindered rotation around the C-N double bond (in DMSO-d6) is also observed for the respective sulfinimides.

From preliminary kinetic measurements, it is observed that, under the same experimental conditions and in the presence of HCl or other acids, the reactivity of thiobenzamide S-oxide is lower than that of thiobenzamide. The presence of halide ions strongly enhanced the reactivity of both **1** and **4**.

Addition of small amounts (from 0.1 to 0.5



Ar = Phenyl **1** **3**

Ar = 3-pyridyl **4** **5**

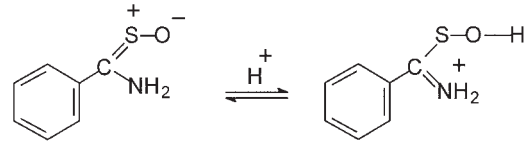
Scheme 2

Table 1. Experimental Data for the Crystallographic Analysis[a]

Formula	$C_6H_8N_2O_2S$
CCDC deposit no.	CCDC-1003/5481
Temperature (K)	294
Crystallographic system	Orthorhombic
Space group	*Pbca*
a (Å)	14.129(3)
b (Å)	7.299(2)
c (Å)	15.277(3)
V (Å^3)	1575.5(6)
Z	8
D_c (g cm^{-3})	1.45
Reflections for lattice parameters	
Number	30
θ range (°)	21.1–38.4
F(000)	720
Diffractometer	Siemens AED
Crystal size (mm)	0.31 × 0.14 × 0.47
μ (cm^{-1})	32.8
Radiation, λ (Å)	Cu$K\alpha$ 1.54178
Scan speed (°min^{-1})	3.0–12.0
Scan width (°)	1.2 + 0.35 tan θ
θ range (°)	3–70
h, *k*, *l* range	0–17, 0–8, 0–18
Scan mode	ω–2θ
No. of reflections measured	1708
No. of reflections used in the refinement [$I > 2\ \sigma(I)$]	1278
No. of refined parameters	132
$R = \Sigma\|\Delta F\|/\Sigma\|F_0\|$	0.048
$Rw = [\Sigma w(\Delta F^2)/\Sigma wF_0^2]^{1/2}$	0.050
k, *g* in $w = k[\sigma^2(F_0) + gF_0^2]^{-1}$	2.403, 1.11 × 10^{-3}
GOF	2.59
Max., min. height in final ΔF map (eÅ)$^{-3}$)	0.63, −0.38

[a] The structure was solved by direct methods using SHELXS86[10] and refined by SHELX76[11] with cycles of full-matrix anisotropic least-squares. All hydrogen atoms were located in the difference-Fourier map and refined isotropically. The study of the molecular geometry was carried out by the PARST93[12] program on an ENCORE E91 computer.

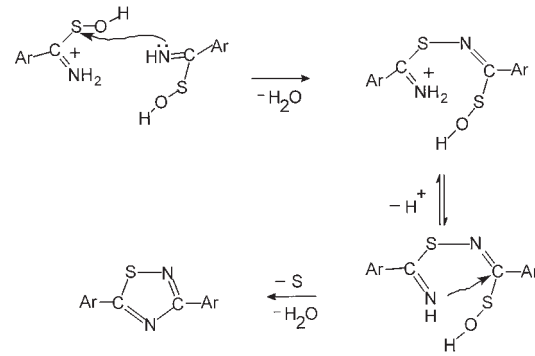
equivalent with respect to thiobenzamide) of HCl to the solution of thiobenzamide S-oxide in DMSO-d6 does not change the phenyl chemical signals in its ^{1}H NMR spectrum, but changes the two N-H signals to a single signal at δ about 8.4. In the UV/VIS spectrum, the addition of HCl to a solution of thiobenzamide S-oxide in DMSO produces the immediate disappearance of the absorption band at 360 nm related to the S-oxide compound, without the appearance of the absorption band of the 3,5-diphenyl-1,2,4-thiadiazole. Also, several hours after mixing the reagents, the neutralization of HCl with $NaHCO_3$ produces the return of the thiobenzamide S-oxide spectrum. Thiobenzamide S-oxide is probably protonated by the strong acid to form a poorly reactive species (at room temperature), Scheme 3.



Scheme 3

On the other hand, the thionicotinamide S-oxide shows the direct formation of thiadiazole spectrum. Under our experimental conditions, no evidence for protonating equilibrium of the thionicotinamide S-oxide are obtained. The spontaneous cyclization pathway of thioamide S-oxide is depicted in Scheme 4.

All attempts to crystallize the S-oxide from warmed alcohols, afforded mixtures of thiadiazole **2** or **6** and sulfur. Crystals of **2** were obtained by slow evaporation of solvent (methanol) at room temperature. Attempts to obtain crystals suitable for X-ray diffraction of **3** failed. Injection of S-oxide into a gaschromatographic apparatus with a mass detector, showed the signals related to thiadiazole **2** and **6** and sulfur; the mass ion signal may be obtained by introducing the sample with moderate heat. Clearly, the thioamides S-oxides dimerize to 1,2,4-thiadiazole quickly and spontaneously when heated or slowly by acid catalysis. It is of interest to note that in our reaction mixtures the presence of dithiadiazines (which are obtained in different experimental conditions)[9] was not observed. If the equilibrium of scheme 3 is wholly shifted toward the protonated species, this cannot be transformed in the thiadiazole derivative by the pathway of Scheme 4, which involves a tautomer of the unprotonated thioamide S-oxide.



Scheme 4

Table 2. Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($Å^2 \times 10^4$) for non-H-atoms with esd's in parentheses

	x	*y*	*z*	U_{eq} [a]
S(1)	8734(0)	1684(1)	3721(0)	487(2)
O(1)	9589(1)	2462(3)	3217(1)	574(6)
N(1)	9817(1)	2598(3)	5026(1)	421(5)
N(4)	6611(1)	1285(3)	5812(1)	433(6)
C(1)	8993(1)	1971(3)	4787(1)	351(6)
C(2)	8260(1)	1481(3)	5437(1)	332(6)
C(3)	7304(1)	1688(3)	5250(1)	377(6)
C(5)	6866(2)	660(3)	6599(1)	438(7)
C(6)	7792(2)	405(3)	6849(1)	423(7)
C(7)	8506(1)	801(3)	6262(1)	389(7)
O(2w)	9541(1)	6296(3)	3308(1)	556(6)

[a] $U_{eq} = 1/3\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* (\mathbf{a}_i \cdot \mathbf{a}_j)$.

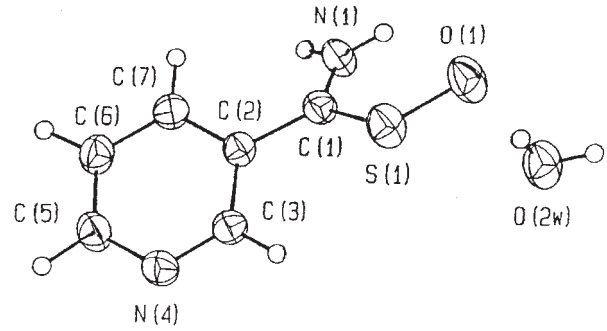


Fig. 1. Perspective view of thionicotinamide S-oxide water solvate.

Molecular geometry

The final atomic coordinates and equivalent isotropic thermal parameters are quoted in Table 2, while bond distances and angles are reported in Table 3. Figure 1 shows the perspective view of the molecule with labeling scheme.

Bond distances and angles are regular and agree with those found in similar compounds. In particular, the pyridine ring dimensions are not different with respect to the thioamidopyridine derivatives and free the pyridine molecule.[13,14] In the side chain, the C(1)-C(2) distance, 1.479(2) Å, is significantly longer than 1.466 Å, corresponding to a Csp^2-Csp^2 bond, but is comparable with that found in previous work (1.488(5) Å) and interpreted in terms of conjugation between the side chain and the pyridine molecule. Also, the reduction of the C(1)-S(1) and C(1)-N(1) bonds compared with the corresponding values in thioacetamide[15] agrees with conjugation in the pyridine-side chain, which induces a withdrawal of electron density from C(1)-C(2) into the side chain. In

Table 3. Bond Distances (Å) and Angles (deg), Selected Torsion Angles (deg), and Hydrogen Bonds with esd's in Parentheses

S(1)−O(1)	1.541(2)	C(1)−C(2)	1.479(2)
S(1)−C(1)	1.682(2)	C(2)−C(3)	1.389(2)
N(1)−C(1)	1.303(2)	C(2)−C(7)	1.398(2)
N(4)−C(3)	1.335(2)	C(5)−C(6)	1.376(4)
N(4)−C(5)	1.336(2)	C(6)−C(7)	1.380(3)
O(1)−S(1)−C(1)	105.5(1)	C(1)−C(2)−C(3)	121.1(1)
C(3)−N(4)−C(5)	117.2(2)	C(3)−C(2)−C(7)	117.8(1)
S(1)−C(1)−N(1)	120.6(1)	N(4)−C(3)−C(2)	123.9(1)
N(1)−C(1)−C(2)	121.5(1)	N(4)−C(5)−C(6)	123.6(2)
S(1)−C(1)−C(2)	117.9(1)	C(5)−C(6)−C(7)	119.1(2)
C(1)−C(2)−C(7)	121.1(1)	C(2)−C(7)−C(6)	118.6(1)
C(1)−S(1)−C(1)−N(1)	−5.2(2)	N(1)−C(1)−C(2)−C(7)	−31.8(3)
N(1)···O(1) 2.784(2)	N(1)−H(12) 0.84(3)	H(12)···O(1) 2.42(3)	
N(1)−H(12)···O(1) 107(3)			
O(2w)···O(1) 2.803(3)	O(2w)−H(1w) 0.89(5)	H(1w)···O(1) 1.91(5)	
O(2w)−H(1w)···O(1) 175(4)			
O(2w)···O(1)^{i} 2.768(2)[a]	O(2w)−H(2w) 0.88(4)	H(2w)···O(1)^{i} 1.89(4)	
O(2w)−H(2w)···O(1)^{i} 175(3)			
N(1)···O(2w)^{ii} 2.820(2)	N(1)−H(11) 0.94(3)	H(11)···O(2w)^{ii} 1.89(3)	
N(1)−H(11)···O(2w)^{ii} 168(3)			
N(1)···N(4)^{iii} 2.954(2)	N(1)−H(12) 0.84(3)	H(12)···N(4)^{iii} 2.16(3)	
N(1)−H(12)···N(4)^{iii} 159(3)			

[a] i = 2 − *x*, 1/2 + *y*, 1/2 − *z*; ii = 2 − *x*, 1 − *y*, 1 − *z*; iii = 1/2 + *x*, 1/2 − *y*, 1 − *z*.

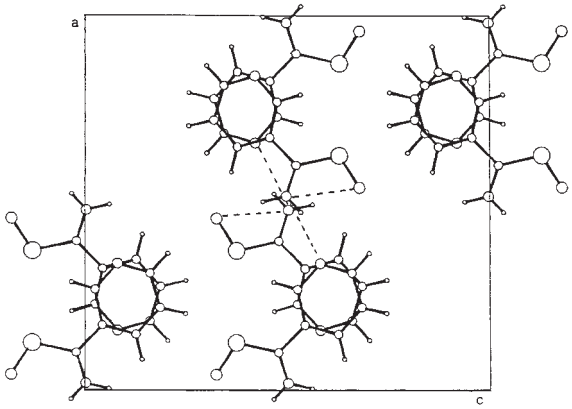


Fig. 2. Packing of thionicotinamide S-oxide along [010], water molecules are omitted for clarity.

addition the C(1)-S(1) 1.682(2), S(1)-O(1) 1.541(2), and C(1)-N(1) 1.303(2) Å distances agree well with those found in thioacetamide S-oxide:[15] 1.659(5), 1.528(4), and 1.308(7)Å, respectively, and in thioacetanilide S-oxide.[16] The pyridine ring is planar and forms an angle of 32.86(7)° with the main plane of the thioamide S-oxide group, which results in significant deviations from the planarity, as shown by the torsion angle O(1)-S(1)-C(1)-N(1)-5.2(2)°.

The hydrogen bonding network quoted in Table 3 plays an important role in the structure. An intramolecular hydrogen bond N-H · · · O, typical of thioamide S-oxide, is present and all the structure is built by intermolecular hydrogen bonds involving water molecules and oxygen and nitrogen atoms of organic molecules. This intermolecular packing arrangement can be considered to be responsible for the deviation from the planarity of the side chain. In fact, in the previously cited thioacetamide S-oxide, in the absence of the water molecule, a smaller deviation from the planarity is present, in accordance with the value (2.1(5)°) of the torsion angle O-S-C-N. As depicted in the projection along the [010] axis reported in Fig. 2, the pyridine rings are stacked in the *y* direction at a distance of *b*/2 between them.

Acknowledgments

The authors thank the Ministero dell'Università e della Ricerca Scientifica e Tecnologica and the University of Bologna (Progetto d'Ateneo: Biomodulatori Organici: sintesi, proprietà ed applicazioni).

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