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Short Note

Synthesis and Crystal Structure of A Pyrithione Derivative: Bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium} tetrachlorocuprate(2-)

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Abstract: The pyrithione derivative, bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium} tetrachlorocuprate(2-) (**1a**) has been obtained by the reaction of one equivalent of 2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride with one and a half equivalents of copper (II) chloride dihydrate in methanol in a very good yield. The structure of this product was confirmed by X-ray crystallography, infrared spectroscopy, and elemental analysis.

Keywords: pyrithione derivative; imidazoline derivative; tetrachlorocuprate(2-); X-ray crystallography

1. Introduction

Coordination chemistry of pyrithione (*N*-hydroxypyridine-2(1*H*)-thione (Hmpo)), its heavy metal salts, and complexes have been widely investigated. Hmpo constitutes a universal O, S-donor ligand [1–4]. The infrared spectra of Hmpo indicates that the compound exists predominantly in its tautomeric thione form [5,6]. Recent UV spectra of pyrithione have shown that tautomeric equilibrium depends on the solvent used. Thione form dominates in polar and protic solvents, whereas 2-mercaptopyridine *N*-oxide exists in non-polar solvents [7]. Strong bactericidal and fungicidal properties of pyrithione have been well demonstrated [8]. Pyrithione acts as a proton conductor and inhibits the membrane transport processes in fungi. However, it was found that fungi can detoxify this agent at low concentration [9]. A zinc complex of *N*-hydroxypyridine-2(1*H*)-thione (zinc pyrithione) is widely used in dandruff shampoos for treating dandruff and seborrhoeic dermatitis [10]. Moreover, it was demonstrated that zinc pyrithione exhibits also antibacterial properties. Zinc pyrithione is a good example of an antibiofilm agent, which improves the antibacterial activity of silver sulfadiazine ointment [11]. Copper pyrithione has been recently considered in supplanting zinc pyrithione in view of its low toxicity [12]. Pyrithione derivative, 2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide, as a free base [CAS Registry Number 90764-93-5] [13–15] and its water-soluble acid addition salts, hydrobromide [CAS Registry Number 6937-05-9] [13–16] and hydrochloride [CAS Registry Number 62377-10-0] [17], are regarded as useful chemical agents that control microbial growth. They possess both fungistatic and bacteriostatic effects and may serve as preservatives.

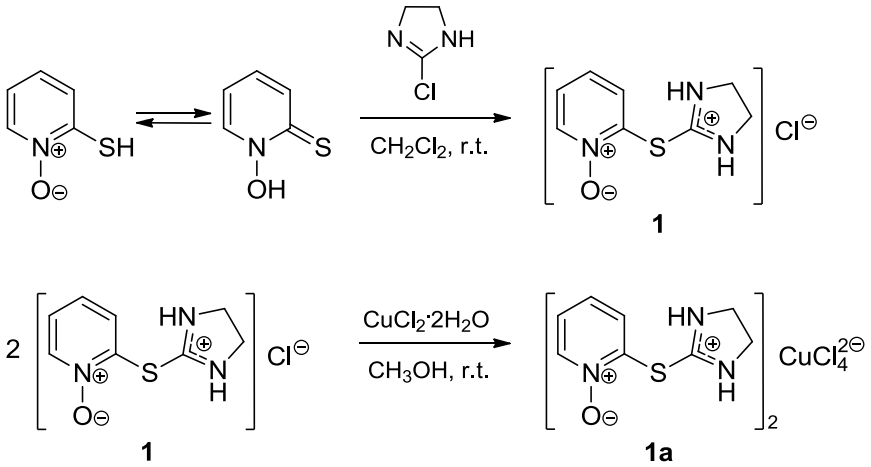
2. Results and Discussion

The title compound: bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium} tetrachlorocuprate(2-) (**1a**) was synthesized by slow evaporation of methanolic solution of the

2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride (**1**) with excess of copper (II) chloride dihydrate.

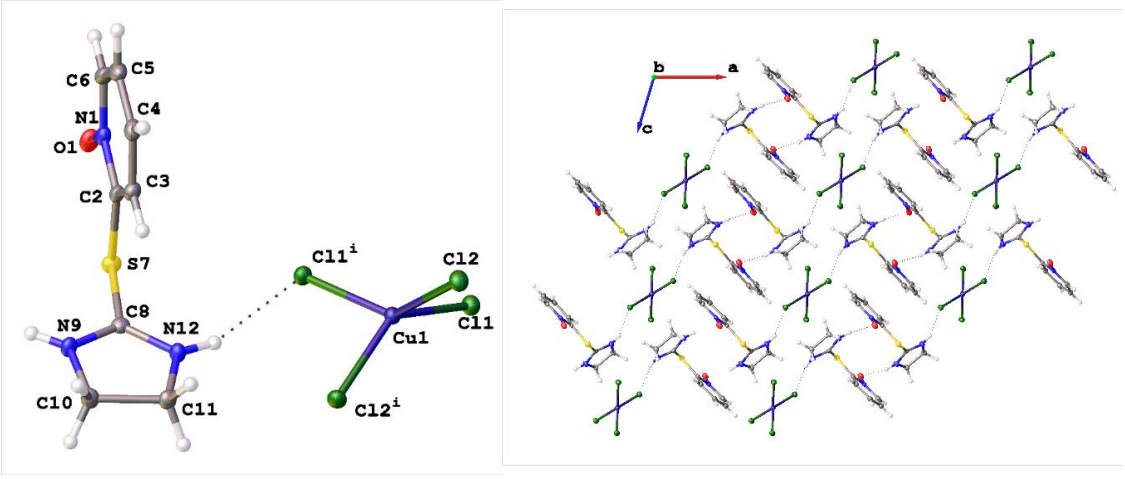
For the preparation of 2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide (as free base or acid addition salt), 2-bromopyridine 1-oxide was reacted with an imidazolidine-2-thione in a halogenated hydrocarbon solvent (chloroform) or in ethanol. According to the literature's data, the mixture required heating for 12 h to give acid addition salt (hydrobromide). The free base may be obtained in dioxane by treatment with an equivalent of dimethylaniline [13,14].

Generally, 2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride (**1**) [CAS Registry Number 62377-10-0] can be synthesized as a result of the nucleophilic attack of the sulfur atom of 2-mercaptopyridine 1-oxide on C2 carbon of 2-chloro-4,5-dihydro-1*H*-imidazole (2-chloroimidazoline). The reaction was carried out in dichloromethane at room temperature in high yield and the product 1 precipitated after mixing the reactants. This method provides a certain advantage over traditional thermal heating. The reaction completes within a significantly shorter time. In the next step, brown single crystals of the bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium} tetrachlorocuprate(2-) (**1a**) suitable for X-ray diffraction analysis were obtained by slow evaporation of methanolic solution, containing the 2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride (**1**) and copper (II) chloride dihydrate at room temperature (Scheme 1).



Scheme 1. Synthesis of the 2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride (**1**) and bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium} tetrachlorocuprate(2-) (**1a**).

The crystal structure of the bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium} tetrachlorocuprate(2-) (**1a**) is shown in Figure 1a (see also supplementary crystallographic data). The asymmetric unit of **1a** consists of the organic cation and one half of the C_2 symmetric $[CuCl_4]^{2-}$ anion. In the 2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1*H*-imidazol-3-ium cation, the two rings attached to the S atom are nearly perpendicular with the dihedral angles between the imidazoline and pyridine best planes of 87.1° and the pyridine *N*-oxide group is oriented anti-relative to the imidazolinium ring. The conformation adopted by the cation results in a large deviation from 120° of the endocyclic bond angles at the pyridine C2 atom, [N1-C2-S7 111.01(11)° and C3-C2-S7 129.23(11)°], and in short intramolecular contact H3···C8 of 2.51 Å. The most probable reason for these angular deviations is repulsive interactions between H3 and C8. The cations are connected by a pair of N-H···O hydrogen bonds [N9···O1^{i} 2.7714(16) Å, H9···O1^{i} 1.91 Å, <N9-H9···O1^{i} 166°; symmetry code i: −x+1/2, −y+3/2, −z] into centrosymmetric dimers that, in turn, interact with $[CuCl_4]^{2-}$ anions via N-H^{+}···Cl^{-} bonds [N12···Cl1^{i} 3.2622(12) Å, <N12-H12··· Cl1^{i} 156°; symmetry code i: x, y+1, z], forming chains extended along [1 0 1] (Figure 1b). In addition, there is a short contact C2-S7··· Cl2i [S2··· Cl2i 3. 3279(5) Å, < C2-S7··· Cl2i 169.60(5)° symmetry code i: −x, −y+1, −z] pointing to a weak chalcogen bonding between cations and anions from adjacent chains.



(**a**) (**b**)

Figure 1. (**a**) ORTEP [18] representation of the molecular structure of 1a. Displacement ellipsoids are shown at the 50% probability level; 'i' relates to symmetry generated atoms. (**b**) Crystal packing viewed along the b axis with hydrogen bonds shown as dashed lines. Chains of hydrogen-bonded ionic species are extended along [1 0 1].

3. Materials and Methods

3.1. General Methods and Physical Measurements

All reagents and solvents were purchased from commercial sources and used without further purification. The IR spectra were recorded on a Nicolet 380FT-IR spectrophotometer. The ^{1}H NMR spectrum of compound **1** was registered at 20–22 °C on Varian Gemini 200 (^{1}H = 200 MHz), using the signal of DMSO-d_6 as an internal standard. The values of chemical shifts are given in ppm and coupling constants (J) are expressed in hertz (Hz). Measured C, H, N elemental analyzes were within 0.40% of calculated values. The diffraction data for single crystals of **1a** were collected with an Oxford Diffraction XcaliburE diffractometer using Mo Kα radiation. The intensity data were collected and processed using CrysAlisPro Software [19]. The structure was solved by direct methods with the program SHELXS-97 [20] and refined by the full-matrix least-squares method on F^2 with SHELXL-2018 [21]. All H atoms were refined as riding on their carriers.

3.2. Synthesis of 2-[(4,5-Dihydro-1H-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride (**1**)

2-Chloro-4,5-dihydro-1*H*-imidazole sulfate [22] (5.1 g, 25 mmol) was added gradually to a 5% solution of sodium hydroxide at a temperature of 5 °C and extracted with dichloromethane (4 × 20 mL). The combined organic phases were dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated under reduced pressure to a volume of 30 mL. 2-Mercaptopyridine 1-oxide (3.18 g, 25 mmol) was added to the resulting solution of 2-chloro-4,5-dihydro-1*H*-imidazole in dichloromethane. When the exothermic reaction had subsided, the white precipitate was filtered, washed with dichloromethane, and dried. The product was obtained as a white solid and yield was 5 g (86%); mp. 172–175 °C; IR (KBr) ν (cm^{-1}): 3000, 2891, 2835, 2634, 1595, 1561, 1466, 1417, 1289, 1249, 1213, 1201, 1084, 1025, 840, 762; ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 3.93 (s, 4H, 2×CH_2); 7.42–7.60 (m, 2H, arom.); 7.93 (dd, J_1 = 1.8 Hz, J_2 = 8.0 Hz, 1H, arom.); 8.49 (d, J = 5.5 Hz, 1H, arom.); 10.87 (br.s, 2H, 2×NH^+). Anal. calculated for $C_8H_{10}ClN_3OS$ (231.70): C, 41.47; H, 4.35; N, 18.14. Found: C: 41.41; H, 4.32; N, 17.87.

3.3. Synthesis of Bis{2-[(1-oxidopyridin-2-yl)sulfanyl]-4,5-dihydro-1H-imidazol-3-ium} tetrachlorocuprate(2-) (**1a**)

Copper(II) chloride dihydrate (0.553 g, 3.24 mmol) was dissolved in 1 mL of anhydrous methanol and the solution was gradually added (dropwise) to a solution of

2-[(4,5-dihydro-1*H*-imidazol-2-yl)thio]pyridine 1-oxide hydrochloride (0.5 g, 2.16 mmol) (**1**) in anhydrous methanol (10 mL) at a temperature of 40 °C. Upon slow evaporation of the solvent over 24 h at room temperature (20–22 °C), brown crystals were formed. Precipitate was filtered off, washed with methanol (2 × 0.5 mL), and dried in a desiccator. The product was obtained as a brown crystals and yield was 0.46 g (71%); mp. 143–148 °C; IR (KBr) ν (cm^{-1}): 3175, 3068, 3033, 2869, 2596, 1591, 1553, 1471, 1421, 1278, 1211, 1154, 1093, 1019, 834, 772; ^{1}H NMR (200 MHz, DMSO-d_6) δ (ppm): 3.95 (s, 4H, 2×CH_2); 7.46–7.57 (m, 2H, arom.); 7.92 (d, J = 7.0 Hz, 1H, arom.); 8.49 (d, J = 5.7 Hz, 1H, arom.); 10.69 (br.s, 2H, 2×NH^+). Anal. calculated for $C_{16}H_{18}Cl_4CuN_6O_2S_2$ (595.84): C, 32.25; H, 3.04; N, 14.10. Found: C, 32.18; H, 2.99; N, 14.12.

Crystal data for **1a**: $2(C_8H_{10}N_3OS)\cdot CuCl_4$, monoclinic, space group C2/c, a = 20.9638(10), b = 6.8597(3), c = 15.9721(7) Å, β = 106.708(5)°, V = 2199.90(17) Å^3, Z = 4, T = 130 K, d_x = 1.805 g·cm^{-3}, μ(*Mo K*α) = 1.697 mm^{-1}, 8519 were collected up to θ_{max} = 27.0° (R_{int} = 0.0159, R_σ = 0.0164). Final R indices for 2364 reflections with $I > 2\sigma(I)$ and 141 refined parameters were: R_1 = 0.0191, wR_2 = 0.0505 (R_1 = 0.0222, wR_2 = 0.0512 for all 2629 data). Crystallographic data for compound **1a** have been deposited with the Cambridge Crystallographic Data Centre, with the deposition No. CCDC 1914490.

Supplementary Materials: Supplementary files are available online. CCDC 1914490 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Cambridge Crystallographic Data Centre http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).

Author Contributions: F.S. and L.B. conceived and designed the experiments; L.B. performed the experiments; M.G. analyzed the data; L.B. and M.G. wrote the paper.

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Conflicts of Interest: The authors declare no conflict of interest.

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