Characterization of products synthesised in the interaction of 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol with piperidine or morpholine

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Synthesis and characterization of piperidine or morpholine 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol were explored influences of the ratio of reactants on the course of the reaction were determined.

Key words: 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol; quaternary salts; *Mycobacterium tuberculosis*

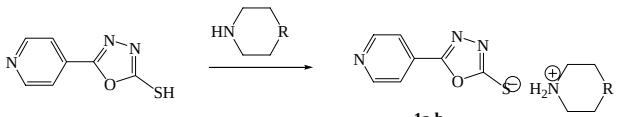
INTRODUCTION

1,3-benzoxazole-2-thiol is known to form 2-amino-substituted oxazoles upon heating with a surplus of morpholine or piperidine [1]. 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol heated with an equivalent amount of morpholine or piperidine in dimethylformamide as a solvent undergoes a cleavage of oxazole ring and the corresponding *N*'-(1-carbothioyl)isonicotinohydrazide is formed [2]. Also, it has been established that in the presence of double surplus of morpholine *N*'-(4-morpholinylcarbothioyl)isonicotinohydrazide and (in the presence of double surplus of piperidine) piperidinium 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiolate are formed.

RESULTS AND DISCUSSION

In the current study, the interaction of 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol with secondary amines (piperidine and morpholine) was explored. Independently of the ratio of the reaction agents the same products were obtained; the identity of those was confirmed by elemental analysis and melting point data measurement.

Analysis of the IR and the NMR ^{1}H data revealed the formation of the corresponding 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiolate salts **1a** and **1b**. Thus, the possibility of the formation of the corresponding thiosemicarbazide is excluded by the absence of the absorption bonds at 1680–1670 cm^{-1} (ascribed to C = O group) as well as at 1520 and 1320 cm^{-1} (ascribed to C = S group) in the IR spectra and thera are no signals of C(S)NH (at 7.8–8.8 ppm) and C(O)NHNH (at 9.2–10.4 ppm) groups in the data of NMR ^{1}H spectra of compounds **1a** and **1b**. Finally, the quaternary salt structures of **1a** and **1b** were confirmed by the mass-spectra data.



1a R = CH_2 ; **1b** R = O

1a,b

The primary screening showed compounds **1a, b** exhibited an effective tuberculosis antimicrobical acquisition and the concentration of 6.25 mg/ml, exerted a >90% inhibition of the Mycobacterium tuberculosis strain H_{37}RV (ATCC 27294). The investigation were performed within the programme "Tuberculosis Antimicrobical Acquisition Coordination Faculty (TAACE)" through a research and development contract with the US National Institute of Allergy and Infectious Diseases.

EXPERIMENTAL

NMR ^{1}H spectra were recorded on a Tesla BS-567A NMR spectrometer at 80 MHz with TMS as the internal standard. IR spectra were recorded on a UR-10 in KBr spectrometer. Mass-spectra were mea-

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sured on an AMD 604 (AMD Interco GmbH) using electron ionisation (E1, 70 eV).

Synthesis of piperidinium 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiolate (1a). 5.38 g (30 mmol) of 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol [3], 2.55 g (30 mmol) of piperidine were added to 20 cm^3 of anhydrous dimethyl sulfoxide (DMSO) and the reaction mixture was heated for 10 h at 60 °C. Then DMSO was partially evaporated (till the first crystals appeared), diluted with benzene and the formed crystals were filtered off and washed with 2-propanol. Obtained: 4.1 g (51%) of **1**, mp 74–75 °C, δ_H (p pm) in $(CD_3)_2SO$: 1.68 (6H, m, $3CH_2$), 3.08 (4H, m, CH_2NCH_2), 7.76 (2H, d, J = 6.0, 3–H, 5–H), 8.77 (2H, d, J = 6.0, 2–H, 6–H). MS, m/z (% rel. int.) : 264 (0.2) M^+; 181 (5); 179 (100) [oxazol 1]$^+$; 119 (9); 92 (20); $[C_5H_{11}N]^+$; 84 (37) $[C_5H_{11}N\text{-}1]^+$; 78 (6) $[C_6H_5N\text{-}1]^+$; 57 (13); 43 (8); 41 (15). Found: C, 54.52; H, 6.05; N, 21.25. $C_{12}H_{16}N_4OS$ requires: C, 54.52; H, 6.09; N, 21.20%).

Synthesis of morpholine-4-ium 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiolate (1b). The preparation of **2b** was carried out as described for **1a.** From 2.69 g (15 mmol) of 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol 1.3 g (15 mol) of morpholine to 10 cm^3 of anhydrous DMSO was obtained: 2.1 g (55%) of **2**, mp 166–167 °C, δ_H (p pm) in $(CD_3)_2SO$: 3.15 (4H, m, CH_2NCH_2), 3.79 (4H, m, CH_2OCH_2), 7.76 (2H, d, J = 6.0, 3–H, 5–H), 8.65 (2H, d, J = 6.0, 2–H, 6–H). MS, m/z (% rel. int.) : 267 (4) [M+1]; 266 (2) $[M^+]$; 239 (5); 225 (5); 211 (6); 183 (7); 179 (10), [oxazol]$^+$; 141 (10); 113 (15); 87 (36) $[C_4H_9NO]^+$; 86 (20) $[C_4H_9NO\text{-}1]^+$; 57 (100); 43 (40); 41 (16). Found: C, 49.70; H, 5.26; N, 21.11. $C_{11}H_{14}N_4O_2S$ requires: C, 49.61; H, 6.09; N, 21.04%.

CONCLUSIONS

1. Piperidine or morpholine with 5-(4-pyridinyl)-1,3,4-oxadiazole-2-thiol when heated at 60 °C in DMSO formed quaternary salts.

2. The quaternary salts showed a >90% inhibition in primary screening against the *Mycobacterium tuberculosis* strain $H_{37}RV$.

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JUNGINIŲ, GAUTŲ SĄVEIKAUJANT 5-(4-PIRIDINIL)-1,3,4-OKSADIAZOL-2-TIOLIUI SU PIPERIDINU ARBA MORFOLINU, IDENTIFIKACIJA

S a n t r a u k a

Nustatyta, kad sąveikaujant 5-(4-piridinil)-1,3,4-oksadiazol-2-tioliui su piperidinu arba morfolinu oksadiazolo žiedas neskyla, o susidaro atitinkamos ketvirtinės amonio druskos. Pirminiai gautų junginių farmakologinio aktyvumo nustatymo tyrimai parodė didelį prieštuberkuliozinį aktyvumą (94–96%) *Mycobacterium tuberculosis* $H_{37}RV$ atžvilgiu (ATCCC27294).