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Synthesis and characterization of *n*-hydroxyalkyl and oxazolinyl ethionamide derivatives

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Multidrug-resistant tuberculosis (MDR-TB) is a serious problem worldwide, especially in people living with human immunodeficiency virus. In considering the MDR-TB problem, ethionamide (ETH) is a structural analog of isoniazid that is typically used when the patient exhibits resistance to the front-line drugs, being one of the most frequently used drugs, for the treatment of drug-resistant tuberculosis. Due to the importance of ETH in TB treatment, the aim of our work was the synthesis and characterization of oxazolinyl (**1**,**2**) and *N*-hydroxyalkyl (**3**–**5**) ETH derivatives.

Keywords: tuberculosis; ethionamide; oxazolinyl nucleus

1. Introduction

Multidrug resistance is commonly defined as the ability of an organism to demonstrate resistance to two or more drugs, making the treatment less effective. Multidrug-resistant tuberculosis (MDR-TB) is currently a serious problem worldwide, especially in people harboring the human immunodeficiency virus. MDR-TB can be defined as strains that are resistant to at least rifampicin and isoniazid (Figure 1), important first-line drugs used in TB treatment (*1, 2*). With respect to MDR-TB, ethionamide (ETH, Figure 1) is a structural analog of isoniazid that is typically used in case of loss of activity of the front-line drugs and is one of the most frequently used drugs for the treatment of drug-resistant tuberculosis (*3*). As with isoniazid, ETH is a prodrug that requires activation to inhibit the synthesis of mycolic acids, leading to bactericidal activity (*4, 5*). Mycolic acids are an important class of compounds, mainly found in the cell walls of a group of bacteria in the *Mycolata* taxon. They are important for the survival of *Mycobacterium tuberculosis*; for example, they allow these bacteria to be more effective in the host's immune system by growing inside macrophages (*4, 5*). Due to the importance of ETH in TB treatment, the aim of our work

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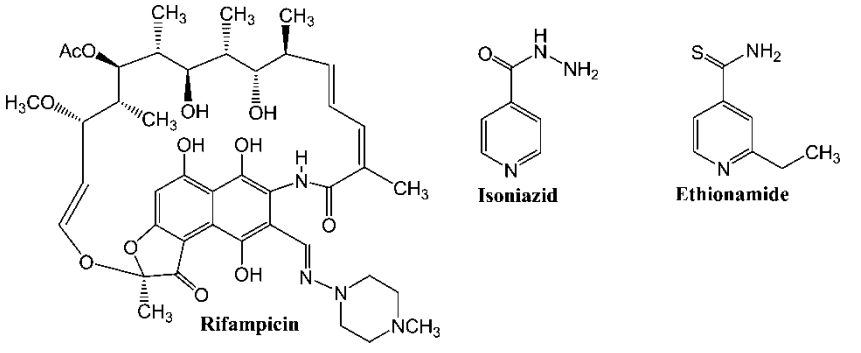


Figure 1. Important drugs used in TB treatment.

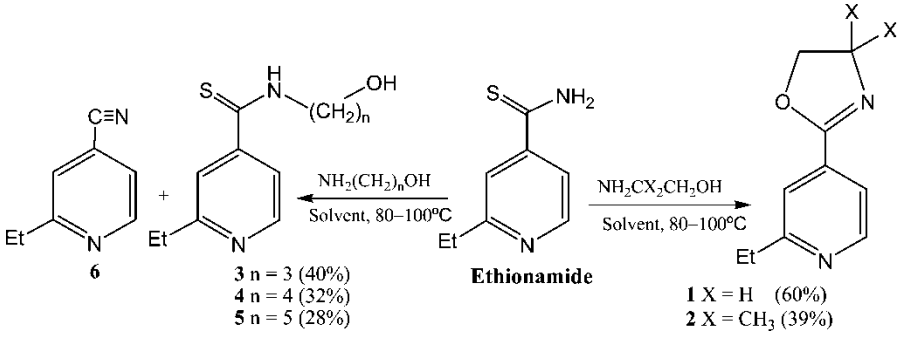
was the synthesis and characterization of *N*-hydroxyalkyl and oxazolinyl ETH derivatives. The reason for the introduction of amino alcohols and oxazolinyl groups into ETH structure is the fact that compounds bearing these groups possess anti-TB activity.

2. Results and discussion

Compounds **1–5** were prepared by reacting ETH with an excess of amino alcohols (5 equiv.) in different solvents at 80–100 °C during 24 h (Scheme 1). For example, using DMF in these conditions, compounds **3–5** were observed as the major products together with nitrile **6** as a byproduct.

Reaction of ETH with ethanolamine in DMF afforded oxazoline **1** as the major product (60% yield). An explanation for this result is the reaction of amino alcohol with the intermediate nitrile **6** followed by cyclization (*6–8*). The intermediary of **6** was confirmed by treating this compound with ethanolamine in DMF at 100 °C leading to the formation of compound **1**.

During the preparation of thioamides **3–5**, we also observed the formation of the corresponding amides as a byproduct. An attempt to improve the yield of **3** by reaction of ETH with 3-bromo-1-propanol in the presence of sodium hydride in DMF at room temperature also furnished nitrile **6**. Treatment of **6** with 3-amino-1-propanol in DMF at 100 °C for four days gave the corresponding amide of compound **3**, identified by NMR, suggesting that nitrile **6** could also be an intermediate for the formation of the amide derivatives from the corresponding thioamides. The reaction between ETH and the more hindered 2-amino-2-methyl-1-propanol in DMF as solvent at 100 °C furnished



Scheme 1. Preparation of ethionamide derivatives.

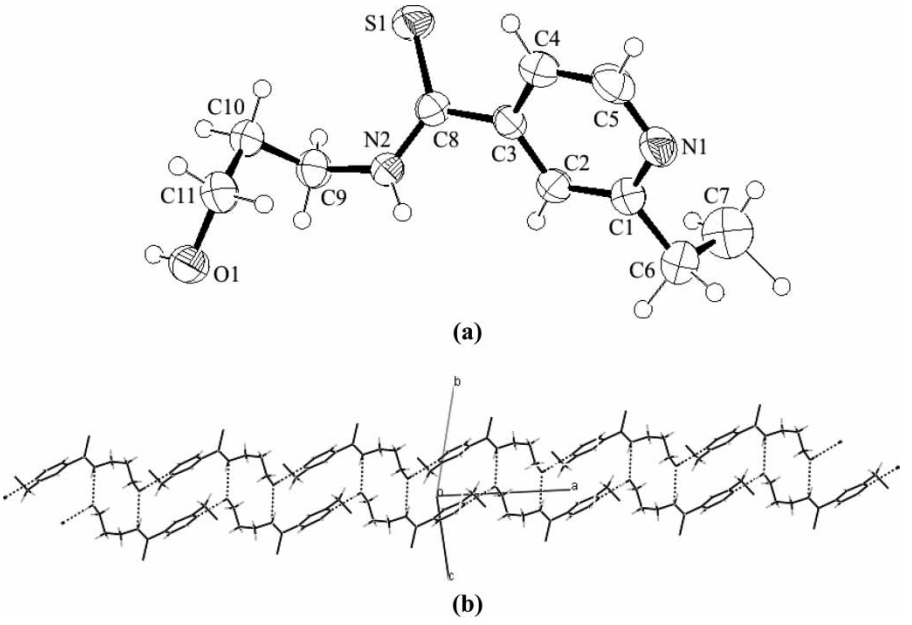


Figure 2. (a) Crystal structure and (b) the hydrogen bond arrangement of compound **3**.

the nitrile **6** as the major product (50% yield) and the desired compound **2** in only 20% yield. To improve the yields, the use of other solvents such as DMSO and ethanol were studied. The first furnished similar yields under the same conditions, while the use of ethanol as a solvent furnished the desired compound **2** in 39% yield. The moderate yield obtained in all cases for the formation of this compound can be explained by the presence of the gem-dimethyl group in the amino alcohol, inhibiting the formation of the cyclized product.

All compounds were characterized by elemental analysis, infrared, ^{1}H NMR and ^{13}C NMR spectroscopy. The structure of compound **3** was confirmed by X-ray crystallography (Figure 2). In this crystal structure is observed a disorder in terminal methyl, where C7 is located at two different sites. The occupational distribution is not equivalent; one site presents an occupational factor around 0.55. The hydroxyl group is involved in medium hydrogen bonds (HB) with adjacent molecules, and is a HB acceptor for the NH group (O−N distance of 2.814(3) Å) and a donor for the nitrogen atom of the aromatic ring (O−N distance of 2.843(3) Å). These interactions form a one-dimensional arrangement parallel to the ***a*** crystallographic axis, as can be seen in Figure 2b.

3. Experimental

3.1. *X-ray diffraction data*

The crystal was mounted on a four-circle P4 Siemens diffractometer and analysed with graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) at 298 K. The XSCANS program (*9*) was used to refine the unit-cell parameters and to manage the data collection. The structure **3** was solved and refined using SHELXL-97 (*10*). Crystal data of **3**: $C_{11}H_{16}N_2OS$, $M_r = 224.33\ g\ mol^{-1}$, monoclinic $P2_1/n$. Unit-cell, $a = 10.649(2)$ Å, $b = 9.717(2)$ Å, $c = 12.219(2)$ Å, $\beta = 103.31(3)^\circ$, $V = 1230.4(4)$ Å^3, $Z = 4$, $F(000) = 480$, $d_x = 1.211\ g\ cm^{-3}$. The number of measured reflections was 2419, $0 \le h \le 12$, $0 \le k \le 11$, $-14 \le l \le 14$, $2\theta_{max} = 51.00^\circ$ and $R_{int} = 0.0316$ for

2291 unique reflections. The isotropic extinction correction (x) was performed, according to the method described by Larson (*11*), for non-hydrogen atoms, and the anisotropic thermal parameters were refined. All hydrogen atoms were found from Fourier maps and they were fixed at geometric idealized calculated positions. The final refinement presented $R(F) = 0.052$, $wR(F^2) = 0.108$ and $S = 1.029$ for 1458 observed reflections [$F \geq 4\sigma(F)$]. The ORTEP3-for Windows (*12*) and Mercury (*13*) programs were used to make Figures 2a and 2b, respectively. The CCDC 654134 contains the supplementary crystallographic data for this compound. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) 1 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

3.2. *General procedure for the preparation of derivatives 1–5*

To a solution of the amino alcohol (5 mmol) in DMF (10 mL) at 80–100 °C was slowly added ETH (1 mmol). The reaction mixture was stirred at this temperature for 24 h and extracted with dichloromethane/water. The organic phase was dried over sodium sulphate, filtered and evaporated under reduced pressure. The residue was chromatographed on silica gel 60 G (70–230-mesh; Merck) using as eluent, a mixture of dichoromethane and methanol, to furnish compounds **1–5**.

3.2.1. *2-Ethyl-4-(4,5-diidro-oxazolyl-2)-pyridine (**1**)*

Yield 60%, (oil); IR (CsI) 3404, 2970, 2877, 1652, 1602 and 1555 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.28 (t, 3H, CH_3, $J = 7.7$), 2.77–2.84 (q, 2H, CH_2 ethyl, $J = 7.7$), 3.98–4.04 (t, 2H, CH_2N, $J = 9.6$), 4.35–4.41 (t, 2H, CH_2O, $J = 9.6$), 7.50–7.52 (d, 1H, H_5, $J = 5.0$), 7.60 (s, 1H, H_3), 8.52–8.54 (d, 1H, H_6, $J = 5.0$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (CH_3), 31.3 (CH_2 ethyl), 55.0 (CH_2N), 67.9 (CH_2O), 119.2 (C-3), 120.3 (C-5), 135.4 (C-4), 149.6 (C-6), 163.3 (C-2), 164.2 (O−C=N). Anal. Calc. for $C_{10}H_{13}N_2O.H_2O$: C, 61.84; H, 7.27; N, 14.42. Found C, 62.13; H, 6.97; N, 13.98.

3.2.2. *2-Ethyl-4-(4,5-diidro-4,4-dimethyl-oxazolyl-2)-pyridine (**2**)*

Yield 39%, (oil); IR (CsI) 3438, 2969, 2895, 1652, 1602, 1556 and 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.24–1.31 (t, 3H, CH_3 ethyl, $J = 7.7$), 1.34 (s, 6H, CH_3), 2.82–2.89 (q, 2H, CH_2 ethyl, $J = 7.7$), 4.12 (s, 2H, CH_2O), 7.55–7.56 (d, 1H, H_5, $J = 5.0$), 7.66 (s, 1H, H_3), 8.58–8.59 (d, 1H, H_6, $J = 5.0$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3 ethyl), 27.4 (CH_3), 31.5 (CH_2 ethyl), 68.1 (CH_2N), 79.3 (CH_2O), 119.4 (C-3), 120.5 (C-5), 135.9 (C-4), 149.8 (C-6), 160.9 (C-2), 164.4 (O−C=N). Anal. Calc. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found C, 70.13; H, 7.97; N, 13.56.

3.2.3. *2-Ethyl-**N**-(3-hydroxypropyl)-pyridine-4-carbothioamide (**3**)*

Yield 40%, m.p. (104–105 °C); IR (CsI) 3194, 2925, 2872, 1604, 1553 and 817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.23–1.28 (t, 3H, CH_3, $J = 7.7$), 1.94–2.02 (m, 2H, CH_2), 2.76–2.84 (q, 2H, CH_2 ethyl, $J = 7.7$), 3.88–3.98 (m, 4H, CH_2N and CH_2O), 7.35–7.37 (d, 1H, H_5, $J = 5.0$), 7.51 (s, 1H, H_3), 8.41–8.43 (d, 1H, H_6, $J = 5.0$), 9.30 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 29.7 (CH_2 alkyl), 31.3 (CH_2 ethyl), 46.5 (CH_2N), 61.9 (CH_2O), 117.8 (C-3), 119.8 (C-5), 148.3 (C-4, C-6), 164.3 (C-2), 196.1 (C=S). Anal. Calc. for $C_{11}H_{16}N_2OS$ C, 58.90; H, 7.19; N, 12.49. Found C, 59.13; H, 6.87; N, 12.08.

3.2.4. *2-Ethyl-**N**-(4-hydroxybutyl)-pyridine-4-carbothioamide (**4**)*

Yield 32%, (oil); IR (CsI) 3206, 2922, 2852, 1602, 1544 and 816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.25 (t, 3H, CH_3, $J = 7.7$), 1.74–1.82 (m, 2H, CH_2), 1.90–1.94 (m, 2H, CH_2), 2.64–2.72 (q, 2H, CH_2 ethyl, $J = 7$), 3.74–3.79 (m, 4H, CH_2N and CH_2O), 7.27–7.28 (d, 1H, H_5, $J = 5.0$), 7.50 (s, 1H, H_3), 8.08–8.10 (d, 1H, H_6, $J = 5.0$), 10.08 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 25.1–29.9 (CH_2 alkyl), 31.3 (CH_2 ethyl), 47.3 (CH_2N), 61.7 (CH_2O), 118.2 (C-3), 120.3 (C-5), 148.6–150.1 (C-4, C-6), 163.7 (C-2), 195.8 (C=S). Anal. Calc. for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.75. Found C, 60.13; H, 7.87; N, 11.98.

3.2.5. *2-Ethyl-**N**-(5-hydroxypentyl)-pyridine-4-carbothioamide (**5**)*

Yield 28%, (oil); IR (CsI) 3225, 2930, 2852, 1601, 1551 and 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25–1.30 (t, 3H, CH_3, $J = 7.7$), 1.43–1.61 (m, 4H, CH_2 alkyl), 1.77–1.82 (m, 2H, CH_2 alkyl), 2.76–2.83 (q, 2H, CH_2 ethyl, $J = 7.7$), 3.64–3.67 (t, 2H, CH_2N, $J = 6.0$), 3.77–3.83 (q, 2H, CH_2O, $J = 6.9$), 7.28–7.30 (d, 1H, H_5, $J = 5.0$), 7.53 (s, 1H, H_3), 8.40–8.42 (d, 1H, H_6, $J = 5.0$), 8.60 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.3 (CH_3), 26.3–31.8 (CH_2 alkyl), 46.9 (CH_2N), 62.4 (CH_2O), 118.0 (C-3), 119.7 (C-5), 149.3–149.5 (C-4, C-6), 163.3 (C-2), 197.0 (C=S); Anal. Calc. for $C_{13}H_{20}N_2OS$: C, 61.87; H, 7.99; N, 11.10. Found C, 61.57; H, 7.97; N, 11.18.

3.2.6. *2-Ethyl-4-ciano-pyridine (**6**)*

(oil); IR (CsI) 3057, 2937, 2878, 2236, 1594, 1550 and 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.31–1.36 (t, 3H, CH_3, $J = 7.7$), 2.86–2.94 (q, 2H, CH_2 ethyl, $J = 7.7$), 7.35–7.37 (*d*, 1H, H_5, $J = 5.0$), 7.53 (s, 1H, H_3), 8.70–8.72 (d, 1H, H_6, $J = 5.0$); ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.4 (CH_3), 31.2 (CH_2 alkyl), 116.8 (CN), 122.3–122.4 (C-3, C-5), 150.1 (C-4, C-6), 165.1 (C-2).

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