PREPARATION OF SOME THIO DERIVATIVES OF PYRIDINECARBOTHIOAMIDES

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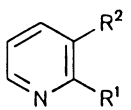
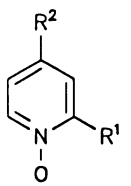
Within the framework of antituberculous research of pyridine derivatives[1] we were also interested in the preparation of alkyl thio derivatives. Condensation of 2-chloro-3-pyridinecarbonitrile (*I*) with propane-1-thiol and butane-1-thiol produced the 2-alkylthio derivatives *II* and *III*, respectively. In a similar way the reaction of 4-chloro- 2-cyanopyridine-1-oxide (*VI*) with butane-1-thiol afforded the 4-alkylthio derivative *VII*. The compounds *II*, *III*, and *VII* were further transformed by addition of hydrogen sulfide in pyridine solution into corresponding pyridinecarbothioamides *IV*, *V*, and *VIII*, respectively. The structures of all new compounds were confirmed by IR and ^{1}H NMR spectra and elemental analysis.





	R^1	R^2
I	Cl	CN
II	$S(CH_2)_2CH_3$	CN
III	$S(CH_2)_3CH_3$	CN
IV	$S(CH_2)_2CH_3$	$CSNH_2$
V	$S(CH_2)_3CH_3$	$CSNH_2$

	R^1	R^2
VI	CN	Cl
VII	CN	$S(CH_2)_3CH_3$
VIII	$CSNH_2$	$S(CH_2)_3CH_3$

The prepared compounds *IV*, *V*, *VII*, and *VIII* were investigated in the form of dimethyl sulfoxide solution for their activity against *Mycobacterium tuberculosis* $H_{37}Rv$, *M. kansasii* PKG 8, *M. avium* 80/72 and *M. fortuitum* 1021 on liquid Šula's medium by means of the dilution method in comparison with antituberculous agents isoniazide and ethionamide. The compounds *IV*, *V*, and *VIII* have shown a small, particular efficacy against *M. tuberculosis* $H_{37}Rv$.

EXPERIMENTAL

Melting points were determined on a Kofler block apparatus and are uncorrected. Samples for elemental analysis were dried in vacuo of about 100 Pa over phosphorus pentoxide at room temperature. Infrared spectra were recorded on a Perkin–Elmer model 577 spectrometer; wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on a spectrometer BS 497 (Tesla Brno) at 100 MHz using tetramethylsilane as internal standard; chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz.

2-Propylthio-3-pyridinecarbonitrile (*II*)

A solution of propane-1-thiol (2 ml, 22 mol) in N,N-dimethylformamide (25 ml) was stirred at room temperature under nitrogen, sodium methoxide (1.1 g, 20 mmol) was added and then 2-chloro-3-pyridinecarbonitrile[2] (*I*; 2.8 g, 20 mmol). After stirring at room temperature for 3 h, the solvent was distilled off in vacuo. The residue was diluted with water (30 ml) and then extracted three times with ether. The combined ether extracts were dried ($MgSO_4$), filtered and evaporated. The crude product was distilled in vacuo yielding 3.1 g (87%) of the title compound, b.p. 57 – 58 °C/13 Pa. IR spectrum ($CHCl_3$): 3 020 (Ar-H); 2 948, 2 920, 2 860 (C–H); 2 224 (CN); 1 555, 1 535 (Ar); 1 449 (CH_2); 1 380 (CH_3). ^1H NMR spectrum (CD_3SOCD_3): 1.60 t, 3 H (CH_3, J = 7.3); 1.49 – 1.9 m, 2 H (CH_2CH_3); 3.25 t, 2 H (SCH_2, J = 7.0); 7.31 dd, 1 H (H-5, J(4,5) = 7.9; J(5,6) = 4.9); 8.19 dd, 1 H (H-4, J(4,5) = 7.9; J(4,6) = 1.9); 8.70 dd, 1 H (H-6, J(4,6) = 1.9; J(5,6) = 4.9). For $C_9H_{10}N_2S$ (178.3) calculated: 60.64% C, 5.65% H, 15.72% N, 17.99% S; found: 60.58% C, 5.58% H, 15.60% N, 17.82% S.

2-Butylthio-3-pyridinecarbonitrile (*III*)

Using the same procedure as for *II*, only instead of propane-1-thiol, butane-1-thiol (2.4 ml, 22 mmol) was added and the mixture was stirred for 4 h. Yield 3.3 g (84%), b.p. 69 – 71 °C/13 Pa. IR spectrum ($CHCl_3$): 3 020 (Ar–H); 2 944, 2 920, 2 858 (C–H); 2 230 (CN); 1 562, 1 540 (Ar); 1 455 (CH_2); 1 378 (CH_3). ^1H NMR spectrum (CD_3SOCD_3): 0.92 t, 3 H (CH_3, J = 6.4); 1.2 – 1.8 m, 4 H ($CH_2CH_2CH_3$); 3.27 t, 2 H (SCH_2, J = 7.0); 7.31 dd, 1 H (H-5, J(4,5) = 7.8; J(5,6) = 4.9); 8.19 dd, 1 H (H-4, J(4,5) = 7.8; J(4,6) = 1.8); 8.71 dd, 1 H (H-6, J(4,6) = 1.8; J(5,6) = 4.9. For $C_{10}H_{12}N_2S$ (192.3) calculated: 62.47% C, 6.29% H, 14.57% N, 16.68% S; found: 62.11% C, 6.73% H, 14.43% N, 16.49% S.

4-Butylthio-2-cyanopyridine-1-oxide (*VII*)

Butane-1-thiol (1.2 g, 13 mmol) was added to the solution of sodium (0.3 g, 13 mmol) in ethanol (6 ml). Then a solution 4-chloro-2-cyanopyridine-1-oxide[3] (*VI*; 2.0 g, 13 mmol) in ethanol (6 ml) was added and the mixture was refluxed for 4 h. After cooling, the mixture was filtered and the filtrate was evaporated to dryness. The crude product was recrystallized from methanol–water. Yield 1.6 g (75%), m.p. 99 – 101 °C. IR spectrum (KBr): 3 055, , 3 030 (Ar–H); 2 960, 2 938, 2 880 (C–H); 1 595, 1 490 (Ar); 1 462 (CH_2); 1 380 (CH_3); 1 278 (N–O). ^1H NMR spectrum ($CDCl_3$): 0.96 t, 3 H (CH_3, J = 6.5); 1.12 – 1.92 m, 4 H ($CH_2CH_2CH_3$); 3.1 t, 2 H (SCH_2, J = 7.2); 7.20 dd, 1 H (H-5, J(3,5) = 3.0; J(5,6) = 7.0); 8.08 d, 1 H

(H-6, J(5,6) = 7.0); 8.65 d, 1 H (H-3, J(3,5) = 3.0). For $C_{10}H_{12}N_2OS$ (208.3) calculated: 57.67% C, 5.81% H, 13.45% N, 15.39% S; found: 57.10% C, 5.51% H, 13.01% N, 15.01% S.

General Procedure for Preparation of Carbothioamides *IV*, *V*, and *VIII*

An appropriate pyridine carbonitrile (about 5 mmol) was dissolved in pyridine (10 ml), then added triethylamine (1 ml) and into the mixture dry hydrogen sulfide was passed at 50 °C for 2 – 4 h. After cooling, the mixture was diluted with water (50 ml). The precipitated solid was filtered off, washed with cold water and crystallized from ethanol–water.

2-Propylthio-3-pyridinecarbothioamide (IV). Nitrile *II* (0.9 g) afforded 0.8 g (74%) of compound *IV*, m.p. 114.5 – 116 °C. IR spectrum (KBr): 3 300, 3 240 (N–H); 3 020 (Ar–H); 2 950, 2 918, 2 858 (C–H); 1 620 (NH_2); 1 560, 1 540 (Ar); 1 445 (CH_2); 1 378 (CH_3). ^{1}H NMR spectrum (CD_3SOCD_3): 0.97 t, 3 H (CH_3, J = 7.0); 1.63 m, 2 H (CH_2CH_3); 3.10 t, 2 H (SCH_2, J = 7.5); 7.13 dd, 1 H (H-5, J(4,5) = 7.8; J(5,6) = 4.9); 7.50 dd, 1 H (H-4, J(4,5) = 7.8; J(4,6) = 1.7); 8.41 dd, 1 H (H-6, J(4,6) = 1.7; J(5,6) = 4.9). For $C_9H_{12}N_2S_2$ (212.3) calculated: 50.91% C, 5.70% H, 13.19% N, 30.20% S; found: 50.69% C, 6.09% H, 12.98% N, 30.05% S.

2-Butylthio-3-pyridinecarbothioamide (V). Nitrile *III* (0.9 g) afforded 0.9 g (84%) of compound *V*, m.p. 86 – 87.5 °C. IR spectrum (KBr): 3 300, 3 240 (N–H); 3 030 (Ar); 2 940, 2 920, 2 850 (C–H); 1 608 (NH_2); 1 560, 1 540 (Ar); 1 455 (CH_2); 1 376 (CH_3). ^{1}H NMR spectrum (CD_3SOCD_3): 0.89 t, 3 H (CH_3, J = 7.0); 1.2 – 1.7 m, 4 H ($CH_2CH_2CH_3$); 3.12 t, 2 H (SCH_2, J = 7.0); 7.13 dd, 1 H (H-5, J(4,5) = 7.8; J(5,6) = 4.9); 7.50 dd, 1 H (H-4, J(4,5) = 7.8; J(4,6) = 1.7); 8.42 dd, 1 H (H-6, J(4,6) = 1.7; J(5,6) = 4.9). For $C_{10}H_{14}N_2S_2$ (226.4) calculated: 53.06% C, 6.23% H, 12.38% N, 28.33% S; found: 53.13% C, 6.12% H, 12.41% N, 28.38% S.

4-Butylthio-2-thiocarbamoylpyridine-1-oxide (VIII). Nitrile *VII* (1.0 g) afforded (reaction was carried out at room temperature) after crystallization from ethanol 1.1 g (95%) of compound *VIII*, m.p. 116 – 118 °C (decomp.). IR spectrum (KBr): 3 270 (N–H); 3 100, 3 030 (Ar–H); 2 960, 2 930, 2 870 (C–H); 1 618 (NH_2); 1 530, 1 500 (Ar); 1 450 (CH_2); 1 375 (CH_3); 1 268 (N–O). ^{1}H NMR spectrum ($CDCl_3$): 0.98 t, 3 H (CH_3, J = 6.5); 1.32 – 1.92 m, 4 H ($CH_2CH_2CH_3$); 3.06 t, 2 H (SCH_2, J = 7.4); 7.16 dd, 1 H (H-5, J(3,5) = 3.0; J(5,6) = 7.0); 8.03 d, 1 H (H-6, J(5,6) = 7.0); 8.90 d, 1 H (H-3, J(3,5) = 3.0). For $C_{10}H_{14}N_2OS_2$ (242.2) calculated: 49.56% C, 5.82% H, 11.56% N, 26.46% S; found: 49.82% C, 5.82% H, 11.57% N, 26.45% S.

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