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Synthesis of Vinylsulfonyl(halo)pyridines and Their Reactions with Binucleophilic Reagents

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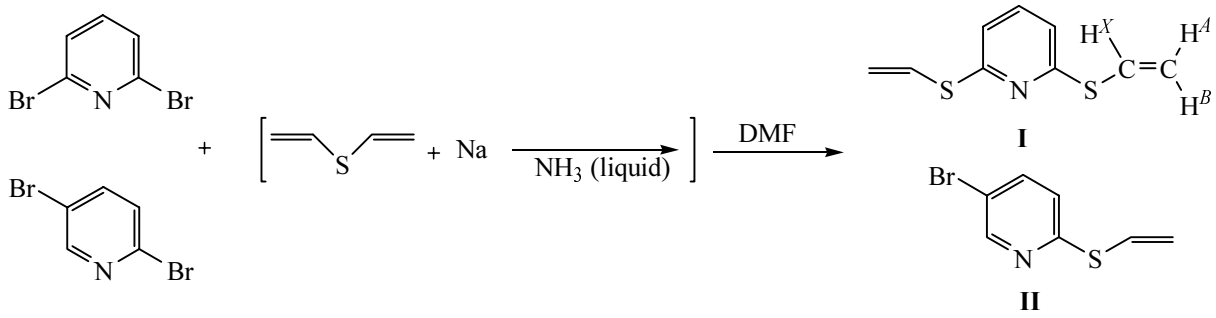
Abstract—Oxidation of vinylthio(halo)pyridines with 30–33% hydrogen peroxide solution in acetic anhydride at 20–25°C furnished vinylsulfonyl(halo)pyridines. Nucleophilic addition reactions of 2-amino-1-ethanethio hydrochloride and thiosemicarbazide to the multiple bonds of vinylsulfonyl(halo)pyridines were performed.

Preparation procedures for unsaturated sulfur-containing pyridines underlain by the use of divinyl sulfide for introduction of vinylthio- and 3-butenylthio groups [1] provided an opportunity to obtain a series of vinylthio-(halo)- and 3-butenylthio(halo)pyridines possessing a significant synthetic potential.

This study is an extension of our research in the field of the synthesis of new vinylthio(halo)pyridines and preparing thereof vinylsulfonyl(halo)pyridines aiming at evaluation of their reactivity toward binucleophilic reagents.

Preparation conditions were developed for 2,6-di-(vinylthio)pyridine (**I**) affording a 55% yield by reaction of 2,6-dibromopyridine with an ethenethiolate anion generated by divinyl sulfide cleavage with sodium in liquid ammonia. The reaction occurred in DMF at 20–25°C. Under similar conditions the 2,5-dibromopyridine gave rise to 5-bromo-2-(vinylthio)pyridine (**II**) in 62% yield.

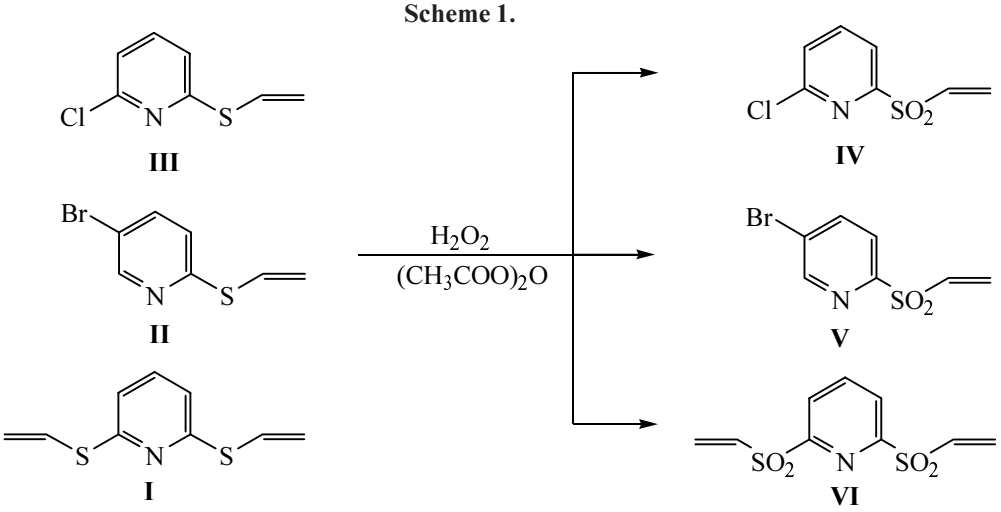


Inasmuch as the synthesis of the pyridine vinylthio derivatives by procedure [1] alongside the vinylthio-(halo)pyridines furnished also 3-butenylthio(halo)pyridines (in a ratio from 3:1 to 5:1), and we failed to separate the latter, the oxidation was performed with the mixture of compounds at the minimum content of 3-butenylthio derivatives. Therewith we failed to isolate the oxidation products of 3-butenyl-thio(halo)pyridines.

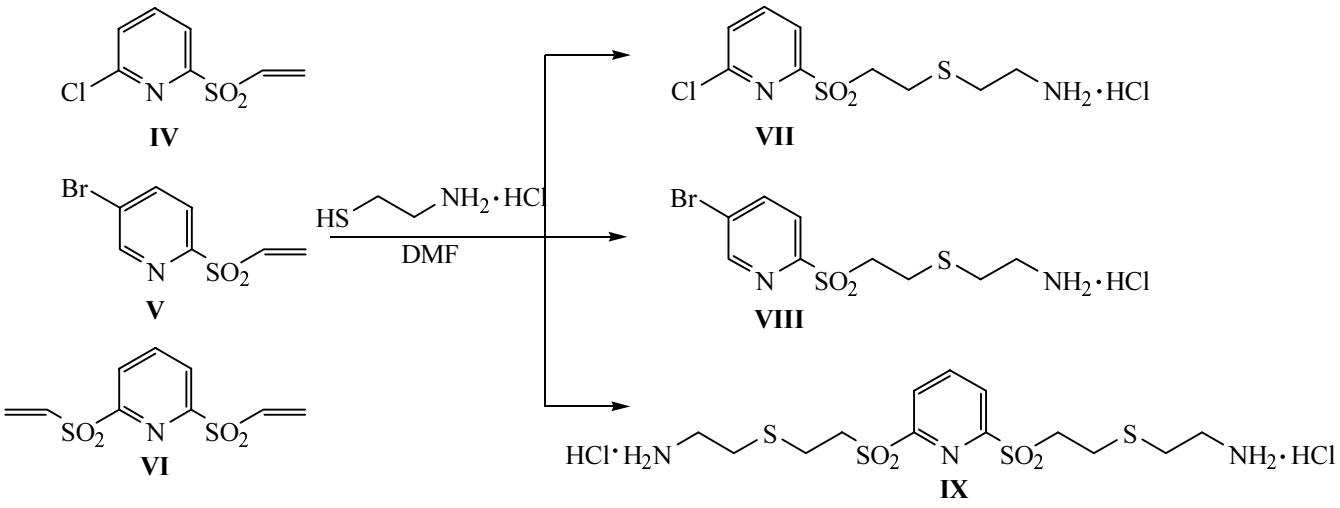
The oxidation of 2-(vinylthio)-6-chloro- (**III**), 5-bromo-2-(vinylthio)- (**II**), and 2,6-di(vinyl-thio)pyridines (**I**) by excess 30–33% hydrogen peroxide solution in acetic anhydride at 20–25°C within 48 h afforded 2-(vinyl-sulfonyl)-6-chloro- (**IV**), 5-bromo-2-(vinylsulfonyl)- (**V**), and 2,6-di(vinylsulfonyl)pyridines (**VI**) in 52, 50, and 32% yields respectively (Scheme 1).

The nucleophilic addition to vinylsulfonyl(halo)pyridines **IV–VI** of 2-amino-1-ethanethiol hydrochloride occurring in the presence of Triton B catalyst at the expense of the free SH (DMF, 20°C) provided water-soluble adducts, hydrochlorides of 2-(5-amino-3-sulfapentylsulfonyl)-6-chloro- (**VII**), 2-(5-amino-3-sulfapentyl-sulfonyl)-5-bromo- (**VIII**), and 2,6-bis(5-amino-3-sulfa-

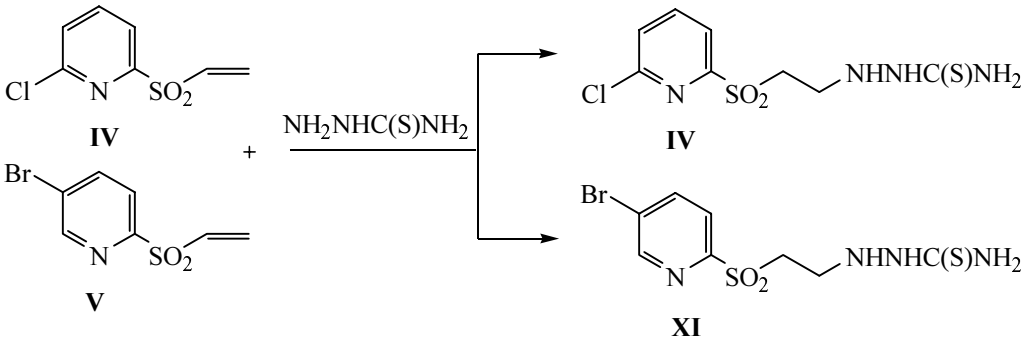
Scheme 1.



Scheme 2.



Scheme 3.



pentylsulfonyl)pyridines (**IX**) in 64, 42, and 72% yields respectively (Scheme 2).

The 2-amino-1-ethanethiol hydrochloride has been selected as nucleophilic reagent for there are many biologically active substances among compounds containing $SCH_2CH_2NH_2$ moiety.

By an example of thiosemicarbazide nucleophilic addition to vinylsulfonyl(halo)pyridines **IV** and **V** we

demonstrated the possibility to obtain pyridine derivatives containing a 2-thiosemicarbazidoethylsulfonyl fragment. 2-(2- Thiosemicarbazidoethylsulfonyl)-6-chloro- (**X**) and 5-bromo-2-(2- thiosemicarbazidoethylsulfonyl)pyridines (**XI**) were obtained in 23% yield in ethanol (70–75°C) or DMF (25°C) (Scheme 3).

The presence in the pyridine ring of a thiosemicarbazide or thiosemicarbazone moiety is known to endow these compounds with biological activity. Among these substances some possess high tuberculocidal activity [2, 3], also in this series herbicides and plant growth stimulators have been found [4]. Therefore the vinylsulfonyl(halo)pyridines we obtained are promising synthons for preparation of potentially biologically active compounds via nucleophilic addition reactions.

The structure of compounds **I–XIII** was confirmed by IR, ^{1}H and ^{13}C spectroscopy [5].

EXPERIMENTAL

IR spectra were recorded on spectrophotometer Bruker IFS-25 from samples prepared as thin films or KBr pellets. ^{1}H and ^{13}C NMR spectra were registered on spectrometer Bruker DPX-400, internal reference HMDS. GC-MS measurements were carried out on HP 5971 A instrument at the energy of ionizing electrons 70 eV.

2,6-Di(vinylthio)pyridine (I). To a solution of 9.3 g of divinyl sulfide in 200 ml of liquid ammonia was added at stirring by small portions 5.5 g of sodium metal. After evaporation of ammonia 140 ml of DMF was added. To the solution obtained was added dropwise at 20–25°C 7.1 g of 2,6-dibromopyridine in 30 ml of DMF, the mixture was stirred for 48 h at 20–25°C. The reaction mixture was treated with water, the reaction products were extracted into ethyl ether, the extract was washed with water and dried on $MgSO_4$. On removing the ether we obtained 4.6 g of viscous liquid of amber color containing according to NMR and GC-MS data 2,6-di(vinylthio)-pyridine (**I**) and 2-(3-butenylthio)-6-bromo-pyridine (**XII**) in 5:1 ratio. Compound **I**, ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.50 d (1H, H^A), 5.56 d (1H, H^B), 7.18 d.d [1H, H^X, ^3J (H^AH^X) 9.9, ^3J (H^BH^X) 16.6 Hz], 6.91 d (2H, H^3 and H^5 of pyridine), 7.36 t (1H, H^4 of pyridine); ^{13}C NMR spectrum, δ, ppm: 116.33 (Cβ), 127.41 (Cα), 117.86 (C^3 and C^5 of pyridine), 136.51 (C^4 of pyridine), 157.22 (C^2 and C^6 of pyridine), ^1J ($C^\beta H^A$) 162.2, ^1J ($C^\beta H^B$) 159.5, ^1J ($C^\alpha H^X$) 179.0 Hz. ^{1}H NMR spectrum of compound **XII** ($CDCl_3$), δ, ppm: 2.44 m (2H, CH_2=CH$\underline{CH_2}CH_2S$), 3.18 t (2H, SCH_2), 5.04 d.q (1H, H^A), 5.10 d.q (1H, H^B), 5.84 m (1H, H^X), ^2J (H^AH^B) 1.6, ^3J (H^AH^X) 10.2, ^3J (H^BH^X) 17.1, ^4J (CH_2H^X) 1.6 Hz; 6.88 d (1H, H^3 of pyridine), 7.07 d (1H, H^5 of pyridine), 7.26 t (1H, H^4 of pyridine). Mass spectrum, *m/z*: $[M]^+$ 195 (compound **I**), $[M]^{+\cdot}$ 245 (compound **XII**).

Likewise a mixture of **5-bromo-2-(vinylthio)-pyridine (II)** and **5-bromo-2-(3-butenylthio)pyridine (XIII)** was obtained in 3:1 ratio according to NMR and GC-MS data.

Compound **II**, ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.53 d (1H, H^A), 5.58 d (1H, H^B), 7.04 d.d (1H, H^X), ^3J (H^AH^X) 9.9, ^3J ($H^B H^X$) 17.1 Hz; 7.08 d (1H, H^3 of pyridine), 7.63 d (1H, H^4 of pyridine), 8.50 s (1H, H^6 of pyridine). ^{13}C NMR spectrum, δ, ppm: 117.19 (Cβ), 127.32 (Cα), 116.71 (C^5 of pyridine), 122.85 (C^3 of pyridine), 138.72 (C^4 of pyridine), 150.34 (C^6 of pyridine), 156.12 (C^2 of pyridine), ^1J($C^\beta H^A$) 162.0, ^1J ($C^\beta H^B$) 159.9, ^1J ($C^\alpha H^X$) 179.2 Hz.

Compound **XIII**, ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 m (2H, CH_2=CH$\underline{CH_2}CH_2S$), 3.15 t (2H, SCH_2); 4.45 d.q (1H, H^A), 5.12 d.q (1H, H^B), 5.85 μ (1H, H^X), ^2J (H^AH^B) 1.6, ^3J (H^AH^X) 10.2, ^3J (H^BH^X) 17.1, ^4J (CH_2, H^X) 1.6 Hz; 7.15 d (1H, H^3 of pyridine), 7.55 d (1H, H^4 of pyridine), 8.43 s (1H, H^6 of pyridine). Mass spectrum, *m/z:* $[M]^{+\cdot}$ 216 (compound II), $[M]^+$ 244 (compound **XIII**).

2-(Vinylsulfonyl)-6-chloropyridine (IV). To a solution of 2.8 g of 2-(vinylthio)-6-chloropyridine and 2-(3-butenylthio)-6-chloropyridine (in a 5:1 ratio) prepared by method [1] in 20 ml of acetic anhydride was added dropwise at 10°C 20 ml of 32% hydrogen peroxide. The reaction mixture was left standing at room temperature for 48 h. The reaction products were extracted into chloroform, the extract was washed with water and dried with $MgSO_4$. On removing chloroform at reduced pressure we obtained 2.3 g of crystalline compound **IV**. Yield 52%, mp 76–77°C (ethanol). IR spectrum, ν, cm^{-1}: 1155 and 1311 (SO_2), 1571, 1551 and 1420 (pyridine ring), 1610 (C=C), 3028, 3058, 3111 (=CH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.27 d (1H, H^A), 6.61 d (1H, H^B), 6.93 d.d (1H, H^X), ^3J (H^AH^X) 9.8, ^3J (H^BH^X) 16.6 Hz; 7.56 d (1H, H^3 of pyridine), 7.97 d (1H, H^5 of pyridine), 8.00 t (1H, H^4 of pyridine). ^{13}C NMR spectrum, δ, ppm: 120.60 (C^5 of pyridine), 128.67 (C^3 of pyridine), 140.80 (C^4 of pyridine); 131.71 (Cβ), 135.3 (Cα). Mass spectrum, *m/z*: $[M]^{+\cdot}$ 203. Found, %: C 41.08; H 2.94; Cl 17.21; N 6.56; S 15.94. $C_7H_6ClNO_2S$. Calculated, %: C 41.29; H 2.97; Cl 17.41; N 6.88; S 15.74.

5-Bromo-2-(vinylsulfonyl)pyridine (V) was prepared by oxidation of a mixture of compounds **II** and

XIII, 3:1, under similar conditions. Yield 50%, mp 88°C (ethanol). IR spectrum, ν, cm^{-1}: 1158 and 1309 (SO_2), 1562, 1547 and 1443 (pyridine ring), 1606 (C=C), 3052, 3090 and 3114 (=CH). ^{1}H NMR spectrum, δ, ppm: 6.50 d (1H, H^A), 6.60 d (1H, H^B), 6.79 d.d (1H, H^X), ^3J (H^AH^X) 9.9, ^3J (H^BH^X) 16.8 Hz; 7.89 d (H^3 of pyridine), 8.19 d (H^4 of pyridine), 8.84 C (H^6 of pyridine). Mass spectrum, *m/z*: [*M*]$^{+\cdot}$ 248. Found, %: C 33.98; H 2.70; Br 32.65; N 5.34; S 12.70. $C_7H_6BrNO_2S$. Calculated, %: C 33.89; H 2.44; Br 32.21; N 5.65; S 12.92.

2,6-Di(vinylsulfonyl)pyridine (VI) was prepared under similar conditions in a 36% yield, mp 92–93°C (ethanol). IR spectrum, ν, cm^{-1}: 1149 and 1321 (SO_2), 1568, 1550 and 1419 (pyridineOβOε ring), 1625 (C=C), 3020, 3057, 3104 (=CH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 6.32 d (1H, H^A), 6.60 d (1H, H^B), 6.96 d.d (1H, H^X), ^3J (H^AH^X) 9.9, ^3J (H^BH^X) 16.6 Hz; 8.29 m (3H, H^3, H^4, H^5 of pyridine). ^{13}C NMR spectrum, δ, ppm: 132.14 (Cβ), 134.80 (Cα), 124.83 (C^3 and C^5 of pyridine), 141.17 (C^4 of pyridine). Mass spectrum, *m/z*: [*M*]$^{+\cdot}$ 259. Found, %: C 41.88; H 3.65; N 5.65; S 24.58. $C_9H_9NO_4S_2$. Calculated, %: C 41.69; H 3.50; N 5.40; S 24.73.

2-(5-Amino-3-sulfapentylsulfonyl)-5-bromopyridine hydrochloride (VIII). To a solution of 0.32 g of 2-amino-1-ethanethiol hydrochloride in 5 ml of DMF was added two drops of Triton B, then dropwise while stirring at 20–25°C was added a solution of 0.7 g of 5-bromo-2-(vinylsulfonyl)pyridine in 10 ml of DMF. The reaction proceeded for 12 h. DMF was removed at reduced pressure, the residue was washed with acetone and dried in a vacuum to obtain 0.5 g (42%) of compound **VIII**, mp 125°C (decomp.). IR spectrum, ν, cm^{-1}: 1159 and 1323 (SO_2), 3000 br.s (NH_3^+). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 2.98 t (2H, S$\underline{CH_2}CH_2NH_2$·HCl), 3.04 t (2H, S$\underline{CH_2}CH_2SO_2$), 3.18 t (2H, CH_2SO_2), 3.86 t (2H, $\underline{CH_2}NH_2$), 8.08 d (1H, H^3 of pyridine), 8.49 d (1H, H^4 of pyridine), 9.00 s (1H, H^6 of pyridine). Found, %: C 29.53; H 4.48; Br 22.57; Cl 10.10; N 7.40; S 18.04. $C_9H_{14}BrClN_2O_2S_2$. Calculated, %: C 29.88; H 3.90; Br 22.11; Cl 9.80; N 7.74; S 17.72.

2-(5-Amino-3-sulfapentylsulfonyl)-6-chloropyridine hydrochloride (VII) was prepared in the same way in a 64% yield, mp 112–114°C (decomp.). IR spectrum, ν, cm^{-1}: 1156 and 1322 (SO_2), 2962 br.s (NH_3^+). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 2.96 t (2H, S$\underline{CH_2}CH_2NH_2$·HCl), 3.06 t (2H, S$\underline{CH_2}CH_2SO_2$), 3.15 t (2H, CH_2SO_2), 3.88 t (2H, $\underline{CH_2}NH_2$), 7.98 d (1H, H^3 of pyridine), 8.16 d (1H, H^5 of pyridine), 8.37 t (1H, H^4 of pyridine). Found, %: C 33.88; H 4.20 ; Cl 22.48; N 8.71; S 19.92. $C_9H_{14}Cl_2N_2O_2S_2$. Calculated, %: C 34.07; H 4.45; Cl 22.35; N 8.83; S 20.21.

2,6-Bis(5-amino-3-sulfapentylsulfonyl)pyridine dihydrochloride (IX) was prepared in the same manner in a 72% yield, mp 145°C (decomp.). IR spectrum, ν, cm^{-1}: 1147 and 1322 (SO_2), 2960 br.s (NH_3^+). ^{1}H NMR spectrum (DMF-d_7), δ, ppm: 3.21 t (2H, S$\underline{CH_2}CH_2NH_2$ · HCl), 3.37 t (2H, S$\underline{CH_2}CH_2SO_2$), 3.75 t (2H, CH_2SO_2), 4.00 t (2H, $\underline{H_2}NH_2$·HCl), 8.47 d (1H, H^3 and 1H, H^5 of pyridine), 8.67 s (1H, H^4 of pyridine). Found, %: C 32.20; H 5.32; Cl 14.30; N 8.48; S 26.22. $C_{13}H_{25}Cl_2N_3O_4S_4$. Calculated, %: C 32.09; H 5.18; Cl 14.57; N 8.64; S 26.36.

2-(2-Thiosemicarbazidoethylsulfonyl)-6-chloropyridine (X). To a solution of 1.8 g of 2-(vinylsulfonyl)-6-chloropyridine in 20 ml of ethanol was added at stirring a solution of 0.8 g of thiosemicarbazide in 10 ml of ethanol. The reaction proceeded for 12 h at 75°C. The reaction mixture was evacuated to get 1.1 g of thick resinous product that on recrystallization from ethanol afforded 0.6 g (23%) of compound **X**, mp 154–155°C. IR spectrum, ν, cm^{-1}: 1153 and 1314 (SO_2), 3166, 3259, 3369 (NH), 3407 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.06 br.q (2H, CH_2NH), 3.59 br.t (2H, CH_2SO_2), 7.31 br.s (2H, NH_2C=S), 7.73 s (1H, CH_2NH), 7.91 d and 8.07 d (1H, H^3 and 1H, H^5 of pyridine), 8.24 t (1H, H^4 of pyridine), 8.83 s (1H, NHC=S). ^{13}C NMR spectrum, δ, ppm: 43.94 (CH_2N), 50.32 (CH_2SO_2), 121.34 (C^3 of pyridine), 129.29 (C^5 of pyridine), 142.58 (C^4 of pyridine), 150.88 and 156.53 (C^i and C^i of pyridine), 181.34 [NH–C(S)NH_2]. Found, %: C 32.40; H 3.80; Cl 11.90; N 19.40; S 21.60. $C_8H_{11}ClN_4O_2S_2$. Calculated, %: C 32.60; H 3.76; Cl 12.03; N 19.01; S 21.75.

5-Bromo-2-(2-thiosemicarbazidoethylsulfonyl)-pyridine (XI) was prepared in the same way in a 23% yield, mp 165°C (decomp.). IR spectrum, ν, cm^{-1}: 1146 and 1317 (SO_2), 3173–3430 (NH, NH_2). ^{1}H NMR spectrum (DMCO-d_6), δ, ppm: 3.15 br.q (2H, CH_2NH), 3.68 br.t (2H, SO_2), 7.52 br.s (2H, NH_2C=S), 8.40 s (1H, CH_2NH), 7.98 d (1H, H^3 of pyridine), 8.54 d (1H, H^4 of pyridine), 8.83 C (1H, H^6 of pyridine). Found, %: C 27.98; H 3.05; Br 23.70; N 16.65; S 19.02. $C_8H_{11}BrN_4O_2S_2$. Calculated, %: C 28.32; H 3.27; Br 23.55; N 16.51; S 18.90.

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