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Synthesis of Pyrrolo[3,2-*d*][1,3]thiazoles

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Abstract—By oxidation of monothiooxamides with $K_3[Fe(CN)_6]$ pyrrolo[3,2-*d*][1,3]thiazoledicarboxylic acid was obtained used further in the synthesis of 2,4,5-trimethyl-4H-pyrrolo[3,2-*d*][1,3]thiazole.

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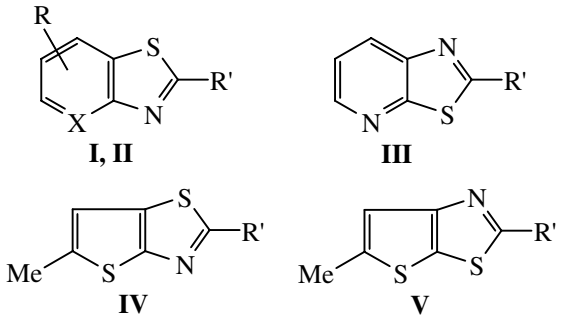
We showed formerly that oxidation in alkaline solutions with $K_3[Fe(CN)_6]$ of monothiooxamides containing phenyl or heteroaromatic rings resulted in formation of fused thiazoles **I–V** in good yield [1–5].

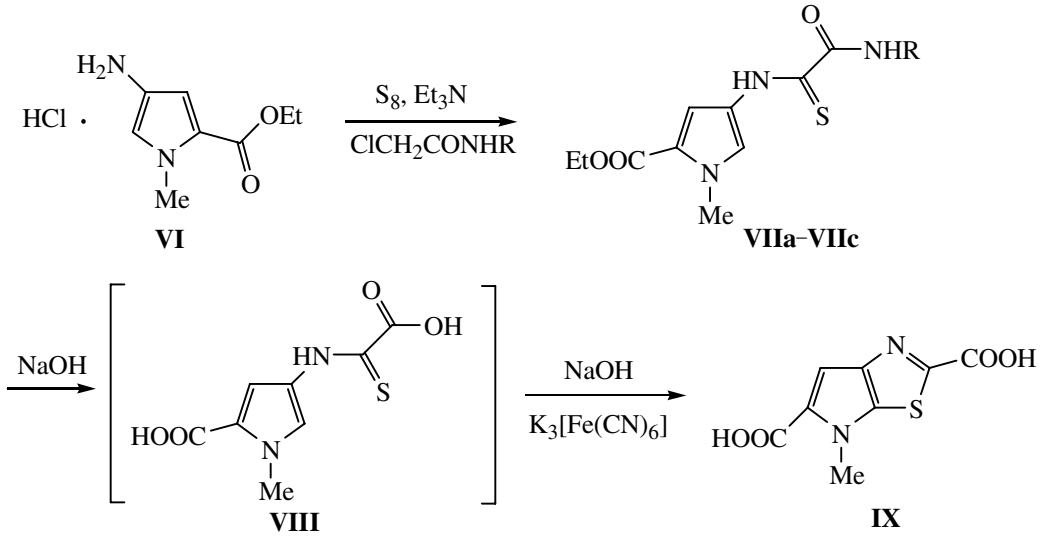


I, II **III** **IV** **V**

X = CH (**I**), N (**II**); R' = $CONH_2$, CONHAlk, CONHAr.

We report here on the synthesis of monothiooxamides based on pyrrole and on their cyclization into a pyrrolothiazole substances whose derivatives are used as anti-phlogistic pharmaceuticals and immunomodulators [6], inhibitors and anticoagulants for prevention and treatment of thrombosis and embolism [7, 8], and also as components of photomaterials [9].

Ethyl 4-amino-1-methyl-1*H*-pyrrole-2-carboxylate hydrochloride (**VI**) [10, 11] was applied as initial compound. Its treatment with chloroacetamides and sulfur in the presence of triethylamine by the procedure we have previously developed [1–5] gives thiooxamides **VIIa–VIIc** in 55–66% yield. The oxidative cyclization of the latter with the thiazole system formation occurred at the treatment with $K_3[Fe(CN)_6]$ in 20% solution of NaOH at 20°C. Therewith in all cases a single product was

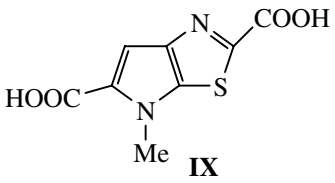


VI **VIIa–VIIc** **VIII** **IX**

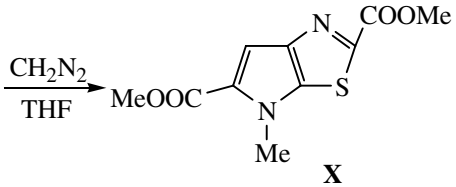
R = Ph (**a**), 4-ClC_6H_4 (**b**), H (**c**).

obtained, 4-methyl-4*H*-pyrrole[3,2-*d*][1,3]thiazole-2,5-dicarboxylic acid (**IX**), evidently through intermediate formation of diacid **VIII** resulting from the hydrolysis.

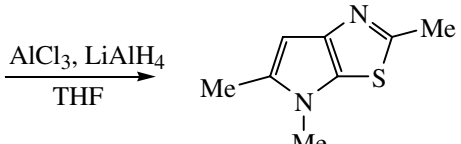
Special experiments demonstrated that diacid **VIII** readily formed at treating compounds **VIIa–VIIc** with 20% solution of NaOH already at room temperature, and under the conditions of the oxidative cyclization it turned into diacid **IX** in good yield.



IX



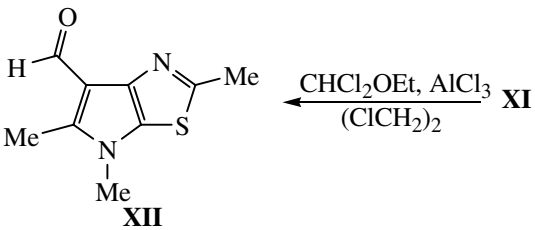
X



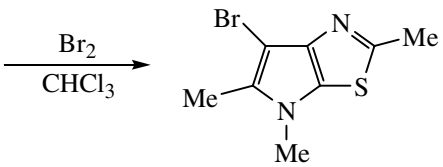
XI

Under the treatment with diazo methane diacid **IX** was converted into ester **X** that then was reduced with $LiAlH_4$ in the presence of $AlCl_3$ in anhydrous THF yielding 2,4,5-trimethyl-4*H*-pyrrole[3,2-*d*]-[1,3]thiazole (**XI**).

The latter was readily involved into electrophilic substitutions that provided in good yields 2,4,5-trimethyl-4*H*-pyrrole[3,2-*d*][1,3]thiazole-6-carbaldehyde (**XII**) and 6-bromo-2,4,5-trimethyl-4*H*-pyrrole[3,2-*d*][1,3]-thiazole (**XIII**) respectively.

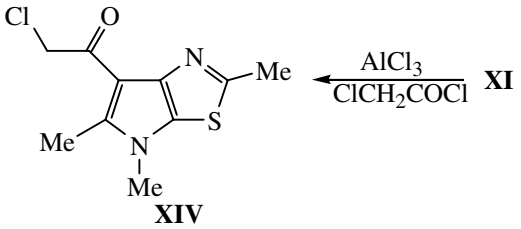


XII

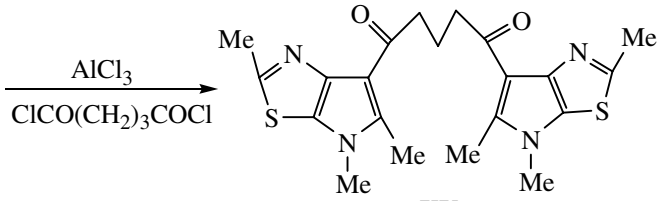


XIII

Reactions of thiazole **XI** with chloroacetyl chloride and glutaryl dichloride in the presence of aluminum chloride led to the formation of acyl derivatives **XIV** and **XV**.

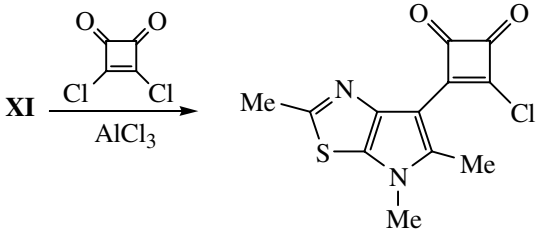


XIV

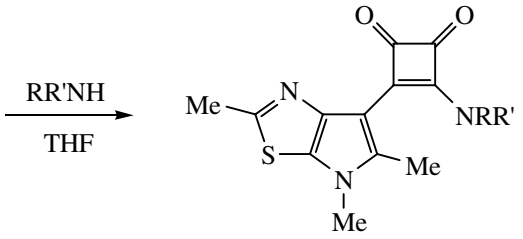


XV

In reaction of compound **XI** with 3,4-dichlorocyclobut-3-ene-1,2-dione only one chlorine atom was replaced. Reaction product 4-(2,4,5-trimethyl-4*H*-pyrrole[3,2-*d*][1,]thiazol-6-yl)-3-chlorocyclobut-3-ene-1,2-dione (**XVI**) cleanly reacted with aniline and morpholine in THF giving the corresponding amino derivatives **XVIIa** and **XVIIb**.



XVI



XVIIa, XVIIb

R = H, R' = Ph (**a**), R, R' = $(CH_2)_2O(CH_2)_2$ (**b**).

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker AC-300 (300 MHz) from solutions in $CDCl_3$ and DMSO-d_6. Mass spectra were taken on Kratos instru-

ment with a direct sample admission into the ion source, ionizing electrons energy 70 eV, control voltage 1.75 kV. Melting points were measured on a Boëtius heating block and are given uncorrected. We used in the study commercial reagents of Acros.

Monothiooxamides VIIa–VIIc. To a preliminary prepared mixture of 0.96 g (5.7 mmol) of salt **VI**, 1.0 g of sulfur, and 1 ml of Et_3N in 5 ml of DMF was added 5.3 mmol of an appropriate chloroacetamide. The mixture was stirred for 8 h at 20°C, then it was diluted with water, extracted with ethyl acetate, the extract was washed with water, dried with magnesium sulfate, evaporated, and the residue was subjected to chromatography on silica gel (eluent ethyl acetate–petroleum ether, 1:2). Yields are reported with respect to initial chloroacetamide.

Ethyl 4-[(2-anilino-2-oxoethanethioyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylate (VIIa). Yield 55%, mp 121–123°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, CH_3, *J* 7.12 Hz), 3.90 s (3H, CH_3), 4.28 m (2H, CH_2), 7.20 m (1H$_{arom}$), 7.40 m (2H$_{arom}$), 7.54 C (1H, pyrrole), 7.80 d (2H$_{arom}$, *J* 7.78 Hz), 8.27 s (1H, pyrrole), 10.43 s (1H, NH), 12.59 s (1H, NH). Mass spectrum, *m*/*z*: 331 [*M*]$^+$. Found, %: C 58.29; H 5.33; N 12.51; S 9.49. $C_{16}H_{17}N_3O_3S$. Calculated, %: C 57.99; H 5.17; N 12.68; S 9.68. *M* 331.39.

Ethyl 4-({2-[(4-chlorophenyl)amino]-2-oxoethanethioyl}amino)-1-methyl-1*H*-pyrrole-2-carboxylate (VIIb). Yield 60%, mp 144–145°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, CH_3, *J* 7.14 Hz), 3.90 s (3H, CH_3), 4.25 m (2H, CH_2), 7.43 d (2H$_{arom}$, *J* 8.59 Hz), 7.50 s (1H, Ht), 7.82 d (2H$_{arom}$, *J* 8.50 Hz), 8.21 s (1H, Ht), 10.55 s (1H, NH), 12.53 s (1H, NH). Mass spectrum, *m*/*z*: 365 [*M*]$^+$. Found, %: C 52.30; H 4.22; Cl 9.80; N 11.64; S 8.90. $C_{16}H_{16}ClN_3O_3S$. Calculated, %: C 52.53; H 4.41; Cl 9.69; N 11.49; S 8.77. *M* 365.83.

Ethyl 4-[(2-amino-2-oxoethanethioyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylate (VIIc). Yield 66%, mp 176–178°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30 t (3H, CH_3, *J* 6.98 Hz), 3.90 s (3H, CH_3), 4.25 m (2H, CH_2), 7.50 s (1H, Ht), 7.92 s (1H, NH_2), 8.05 s (1H, NH_2), 8.20 s (1H, Ht), 12.29 s (1H, NH). Mass spectrum, *m*/*z*: 255 [*M*]$^+$. Found, %: C 47.25; H 5.04; N 16.60; S 12.40. $C_{10}H_{13}N_3O_3S$. Calculated, %: C 47.05; H 5.13; N 16.46; S 12.56. *M* 255.29.

4-[(Carboxycarbothioyl)amino]-1-methyl-1*H*-pyrrole-2-carboxylic acid (VIII). In 8.4 mmol of 20% NaOH was dissolved 0.2 mmol of monothiooxamide **VIIa–VIIc**. The mixture was stirred for 24 h, then it was acidified and extracted with ethyl acetate, the extract was dried and evaporated. Yield 98%, mp 178–180°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.89 s (3H, CH_3), 7.30 s (1H, Ht), 8.19 s (1H, Ht), 12.39 s (1H, NH). Mass spectrum, *m*/*z*: 228 [*M*]$^+$. Found, %: C 42.22; H 3.70; N 12.46; S 13.80. $C_8H_8N_2O_4S$. Calculated, %: C 42.10; H 3.53; N 12.27; S 14.05. *M* 228.22.

4-Methyl-4*H*-pyrrolo[3,2-*d*][1,3]thiazole-2,5-dicarboxylic acid (IX). In 8.4 mmol of 20% NaOH was dissolved 0.2 mmol of monothiooxamide **VIIa–VIIc**. The solution was filtered, and to the filtrate was added dropwise at stirring 0.44 mmol of $K_3[Fe(CN)_6]$ in 0.44 ml of water. The mixture was stirred for 24 h, then it was acidified and extracted with ethyl acetate, the extract was dried and evaporated. Yield 90%, mp 218–220°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.09 s (3H, CH_3), 7.36 s (1H, Ht). Mass spectrum, *m*/*z*: 226 [*M*]$^+$. Found, %: C 42.60; H 2.47; N 12.20; S 14.04. $C_8H_6N_2O_4S$. Calculated, %: C 42.48; H 2.67; N 12.38; S 14.18.

Dimethyl 4-methyl-4*H*-pyrrolo[3,2-*d*][1,3]-thiazole-2,5-dicarboxylate (X). In anhydrous THF was dissolved 0.01 mol of acid **IX**, and at 1°C 0.024 mol of diazomethane ether solution was added. The reaction mixture was left overnight, then the solvent was distilled off. Yield 96%, mp 138–140°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.85 s (3H, OCH_3), 3.95 s (3H, OCH_3), 4.10 s (3H, CH_3), 7.42 s (1H, Ht). Mass spectrum, *m*/*z*: 254 [*M*]$^+$. Found, %: C 47.05; H 3.73; N 11.15; S 12.40. $C_{10}H_{10}N_2O_4S$. Calculated, %: C 47.14; H 3.96; N 11.02; S 12.61. *M* 254.26.

2,4,5-Trimethyl-4*H*-pyrrolo[3,2-*d*][1,3]thiazole (XI). To 3.5 mmol of $AlCl_3$ in 20 ml of anhydrous THF was added 0.4 mmol of dicarboxylate **X**, then 6 mmol of $LiAlH_4$ was added to the solution in one portion. The reaction mixture was stirred for 2 h, then 20 ml of benzene was added, and the mixture was carefully diluted with 10 ml of water. The organic layer was separated, washed with water, dried with magnesium sulfate, and evaporated. Yield 87%, oily substance. ^{1}H NMR spec-trum (DMSO-d_6), δ, ppm: 2.30 s (3H, CH_3), 2.63 s (3H, CH_3), 3.60 s (3H, CH_3), 6.15 s (1H, Ht). Mass spectrum, *m*/*z*: 166 [*M*]$^+$. Found, %: C 57.93; H 5.83; N 16.99; S 19.04. $C_8H_{10}N_2S$. Calculated, %: C 57.80; H 6.06; N 16.85; S 19.29. *M* 166.24.

2,4,5-Trimethyl-4*H*-pyrrolo[3,2-*d*][1,3]thiazole-6-carbaldehyde (XII). In anhydrous dichloroethane was dissolved 0.5 mmol of azole **XI**, 1.05 mmol of $AlCl_3$ was added at stirring, then to the mixture was added dropwise 0.6 mmol of $CHCl_2OEt$. The stirring was continued till

disappearance of the initial substrate from the reaction mixture, then the mixture was poured into water, extracted with dichloromethane, the extract was washed with water, dried, and evaporated. Yield 94%, mp 133–135°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.62 s (3H, CH_3), 2.73 s (3H, CH_3), 3.72 s (3H, CH_3), 10.00 s (1H, CHO). Mass spectrum, *m*/*z*: 194 [*M*]$^+$. Found, %: C 55.79; H 5.36; N 14.27; S 16.31. $C_9H_{10}N_2OS$. Calculated, %: C 55.65; H 5.19; N 14.42; S 16.51. *M* 194.25.

6-Bromo-2,4,5-trimethyl-4*H*-pyrrolo[3,2-*d*][1,3]-thiazole (XIII). To a solution of 0.6 mmol of azole **XI** in chloroform was added 0.6 mmol of Br_2, and the mixture was stirred for 30 min till disappearance of the initial thiazole. The solution was evaporated in a vacuum, and the residue was subjected to chromatography on silica gel (eluent ethyl acetate–petroleum ether, 1:2). Yield 97%, mp 97–99°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 s (3H, CH_3), 2.69 s (3H, CH_3), 3.68 s (3H, CH_3). Mass spectrum, *m*/*z*: 245 [*M*]$^+$. Found, %: C 39.33; H 3.57; Br 32.47; N 11.47; S 13.07. $C_8H_9BrN_2S$. Calculated, %: C 39.20; H 3.70; Br 32.60; N 11.33; S 12.88. *M* 245.14.

2-Chloro-1-(2,4,5-trimethyl-4*H*-pyrrolo[3,2-*d*]-[1,3]thiazol-6-yl)ethanone (XIV). In anhydrous dichloroethane was dissolved 0.5 mmol of azole **XI**, 1.05 mmol of $AlCl_3$ was added at stirring, then to the mixture was added dropwise 0.6 mmol of $ClCH_2COCl$ till disappearance of the initial thiazole. The reaction mixture was poured into water, extracted with dichloromethane, the extract was washed with water, dried, and evaporated. Yield 99%, mp 159–161°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.65 s (3H, CH_3), 2.77 s (3H, CH_3), 3.72 s (3H, CH_3), 5.03 s (2H, CH_2). Mass spectrum, *m*/*z*: 242 [*M*]$^+$. Found, %: C 49.67; H 4.32; Cl 14.46; N 11.72; S 13.07. $C_{10}H_{11}ClN_2OS$. Calculated, %: C 49.48; H 4.57; Cl 14.61; N 11.54; S 13.21. *M* 242.72.

1,5-Bis(2,4,5-trimethyl-4*H*-pyrrolo[3,2-*d*][1,3]-thiazol-6-yl)pentane-1,5-dione (XV). To a mixture of 0.6 mmol of azole **XI** and 0.3 mmol of glutaryl dichloride in 20 ml of dichloromethane was added at cooling 0.8 g of $AlCl_3$, and the stirring at cooling was continued for 40 min and then for 5 h at room temperature (TLC monitoring). The mixture was poured on ice, extracted with dichloromethane (3×50 ml), the organic layer was washed with 2% water solution of $NaHCO_3$, with saturated NaCl solution, and dried with $MgSO_4$. The solvent was evaporated, and the residue was subjected to chromatography on silica gel (eluent ethyl acetate–petroleum ether, 2:1). Yield 68%, mp 178–180°C (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.60 s (6H, CH_3), 2.71 s (6H, CH_3), 3.35 s (2H, CH_2), 3.65 br.s (10H, CH_3 + CH_2). Mass spectrum, *m*/*z*: 428 [*M*]$^+$. Found, %: C 58.98; H 5.13; N 13.22; S 14.78. $C_{21}H_{24}N_4O_2S_2$. Calculated, %: C 58.85; H 5.04; N 13.07; S 14.96. *M* 428.57.

3-Chloro-4-(2,4,5-trimethyl-4*H*-pyrrolo[3,2-*d*]-[1,3]thiazol-6-yl)cyclobut-3-ene-1,2-dione (XVI). To a mixture of 2.56 mmol of azole **XI**, 10.27 mmol of $AlCl_3$ in 80 ml of dichloroethane and 25 ml of heptane was added in an argon flow 0.387 g (2.56 mmol) of 3,4-dichloro-3-cyclobutene-1,2-dione in 20 ml of dichloroethanethe reactin mixture was stirred for 5 h (TLC monitoring). The mixture was poured on ice, extracted with dichloromethane (3×50 ml), the organic layer was washed with 2% water solution of $NaHCO_3$, with saturated NaCl solution, and dried with $MgSO_4$. The solvent was evaporated, and the residue was subjected to chromatography on silica gel (eluent ethyl acetate–petroleum ether, 1:1). Yield 65%, mp 189–190°C (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.79 s (3H, CH_3), 2.85 s (3H, CH_3), 3.75 s (3H, CH_3). Mass spectrum, *m*/*z*: 280 [*M*]$^+$. Found, %: C 51.52; H 3.40; Cl 12.48; N 9.70; S 11.60. $C_{12}H_9ClN_2O_2S_2$. Calculated, %: C 51.34; H 3.23; Cl 12.63; N 9.98; S 11.42. *M* 280.73.

Aminotrimethylpyrrolothiazolecyclobutenediones XVIIa and XVIIb. General procedure. To a stirred solution of 1 mmol of reagent **XVI** in THF at room temperature was added a solution of 1 mmol of amine in THF. The separated precipitate was filtered off, washed with THF, and dried.

3-Anilino-4-(2,4,5-trimethyl-4*H*-pyrrolo-[3,2-*d*][1,3]thiazol-6-yl)cyclobut-3-ene-1,2-dione (XVIIa). Yield 95%, mp 307–309°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.78 s (3H, CH_3), 2.98 s (3H, CH_3), 3.68 s (3H, CH_3), 7.10 m (1H$_{arom}$), 7.40 m (2H$_{arom}$), 7.62 d (2H$_{arom}$, *J* 7.92 Hz), 11.90 s (1H, NH). Mass spectrum, *m*/*z*: 337 [*M*]$^+$. Found, %: C 64.30; H 4.26; N 12.10; S 9.76. $C_{18}H_{15}N_3O_2S$. Calculated, %: C 64.08; H 4.48; N 12.45; S 9.50. *M* 337.40.

3-Morpholino-4-(2,4,5-trimethyl-4*H*-pyrrolo-[3,2-*d*][1,3]thiazol-6-yl)cyclobut-3-ene-1,2-dione (XVIIb). Yield 90%, mp >350°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.78 s (3H, CH_3), 2.98 s (3H, CH_3), 3.68 s (3H, CH_3), 3.80 m (2H, CH_2), 3.85 m (2H, CH_2), 4.02 m (2H, CH_2), 4.28 m, (2H, CH_2). Mass spectrum, *m*/*z*: 331 [*M*]$^+$. Found, %: C 57.73; H 5.30; N 12.55; S 9.84. $C_{16}H_{17}N_3O_3S$. Calculated, %: C 57.99; H 5.17; N 12.68; S 9.68. *M* 331.39.

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