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# Synthesis of Substituted in Benzene Ring 4-[(2-Aminophenyl)thio]-, 4-[(2-Mercaptophenyl)amino]-2-methylquinolines and (4E)-4-[(2-Mercaptophenyl)imino]-2-methyl-1,4-dihydroquinolines

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**Abstract**—By a reaction of 2-methyl-4-chloroquinolines with *o*-mercaptoaniline under various conditions syntheses were performed of substituted in the benzene ring 4-[(2-aminophenyl)thio]-2-methylquinolines and (4*E*)-4-[(2-mercaptophenyl)imino]-2-methyl-1,4-dihydroquinolines that were respectively by isomerization or rearrangement converted into 4-[(2-mercaptophenyl)amino]-2-methylquinolines.

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Among nitrogen and sulfur heterocycles a special place is reserved for derivatives of 4-amino- and 4-mercaptoquinolines possessing antitumor, analgesic, antibacterial, and other actions [1, 2].

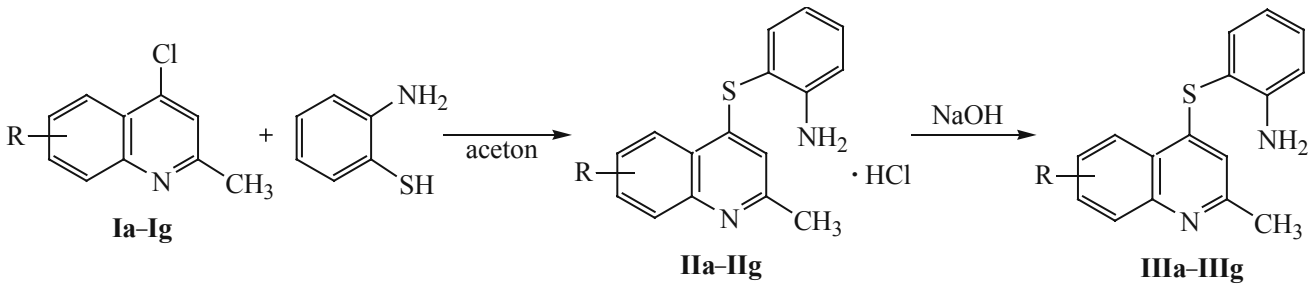
We report here on reactions of nucleophilic substitution by *o*-mercaptoaniline of 2-methyl-4-chloroquinolines **Ia–Ig** containing various substituents in the benzene ring [3]. It was shown that the reaction between equivalent quantities of the above compounds at room temperature in acetone solution was completed in two days to produce hydrochlorides of the corresponding substituted 4-[(2-aminophenyl)thio]-2-methylquinolines **IIa–IIg** that were easily converted into the corresponding bases **IIIa–IIIg** (Scheme 1).

The heating in ethanol of equivalent quantities of 2-methyl-4-chloroquinolines **Ia–Ig** and *o*-mercaptoaniline in the presence of catalytic amount of hydrochloric acid in 5–6 h resulted in the formation of hydrochlorides of the corresponding substituted (4*E*)-4-[(2-mercaptophenyl)imino]-2-methyl-1,4-dihydroquinolines **IVa–IVg** in high yields. The corresponding free bases **Va–Vg** were also obtained in the form of yellow crystals (Scheme 2).

The bases obtained at boiling in ethanol and aprotic polar solvents or at long storage at room temperature transformed into colorless substances, 4-[(2-mercaptophenyl)amino]-2-methylquinolines **VIa–VIg** evidently through isomerization (Scheme 3).

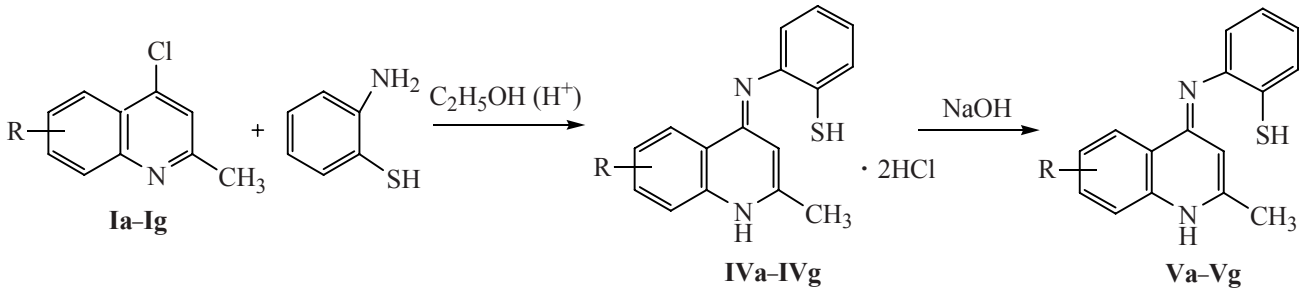
The transition from conjugated to aromatic system was confirmed by UV spectra of ethanol solutions of compounds **Va–Vg** and **VIa–VIg** of concentration $5 \times 10^{-5}$ mol l$^{-1}$ based on the intensity difference at the absorption maximum 334 nm characteristic of compounds **V** (see the figure).

**Scheme 1.**

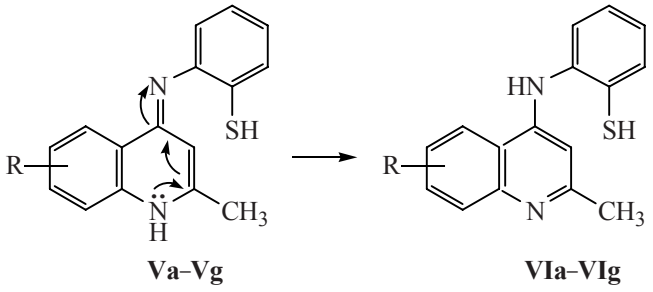



**Ia–Ig** **IIa–IIg** **IIIa–IIIg**

**Scheme 2.**



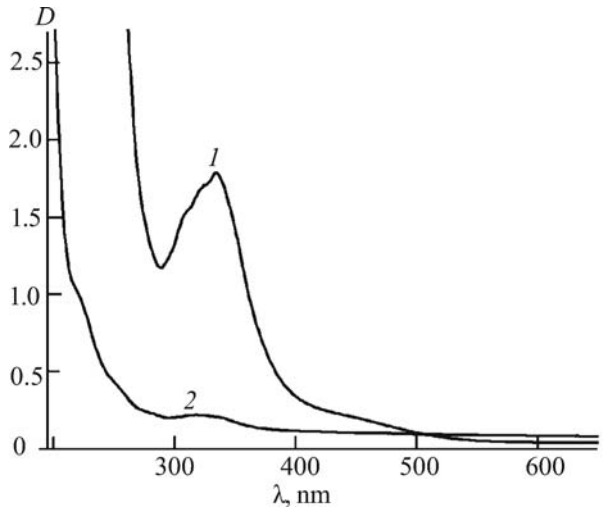

**Scheme 3.**




Compounds **VIa–VIg** were also obtained by a rearrangement of the corresponding 4-[(2-amino-phenyl)-thio]quinolines **IIIa–IIIg**. Optimum conditions of the reaction were developed; it was shown that the rearrangement occurred at heating the initial compounds either in alcoholic or aqueous solution in the presence of acid.

## EXPERIMENTAL

$^1$H NMR spectra were registered on a spectrometer Varian Mercury-300 from solutions in DMSO-$d_6$. UV spectra were recorded on a spectrophotometer Specord-50 in ethanol at room temperature from solutions of concentration $5 \times 10^{-5}$ mol l$^{-1}$. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates (development in iodine vapor).




UV spectra of compounds **Vf** (*1*) and **VIf** (*2*).

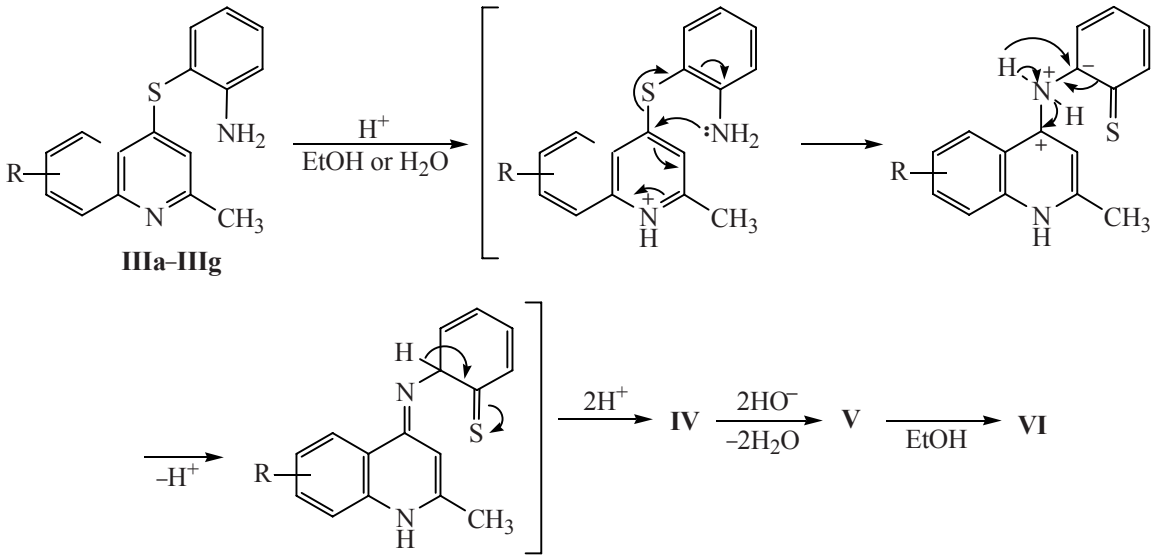
**Substituted 4-[(2-aminophenyl-)thio]--2-methylquinolines IIIa–IIIg.** A mixture of 0.01 mol of an appropriate substituted 2-methyl-4-chloroquinoline [3] and 1.7 ml (0.01 mol) of *o*-mercaptoaniline in 5 ml of anhydrous acetone was stirred at room temperature for 2 days. The obtained hydrochloride crystals were filtered off and washed with anhydrous acetone, dried, the yield and melting point were estimated. Water solution of 0.01 mol of the corresponding substituted 4-[(2-aminophenyl)-thio]-2-methylquinoline hydrochloride was filtered from any possible impurities and alkalinized with water solution of NaOH to pH 9. The separated precipitate was filtered off, washed with water, dried, and its yield with respect to hydrochloride was estimated.

**4-[(2-Aminophenyl)thio]-2-methylquinoline (IIIa).** Yield of hydrochloride **IIa** 2.66 g (88%), mp 202–205°C. Yield of compound **IIIa** 2.27 g (97%), mp 109–110°C, $R_f$ 0.65 (ethanol–toluene, 1:3). $^1$H NMR spectrum, δ, ppm: 2.70 s (3H, $CH_3$), 5.10 s (2H, $NH_2$), 6.40–7.90 m ($9H_{arom}$). Found, %: C 72.24; H 5.18; N 10.71; S 12.17. $C_{16}H_{14}N_2S$. Calculated, %: C 72.18; H 5.26; N 10.53; S 12.03.

**4-[(2-Aminophenyl)thio]-2,6-dimethylquinoline (IIIb).** Yield of hydrochloride **IIb** 2.53 g (80%), mp 174–175°C. Yield of compound **IIIb** 2.20 g (98%), mp 137–138°C, $R_f$ 0.63 (ethanol–toluene, 1:5). $^1$H NMR spectrum, δ, ppm: 2.40 s (3H, $CH_3$), 2.60 s (3H, $NCCH_3$), 5.15 s (2H, $NH_2$), 6.45–7.95 m ($8H_{arom}$). Found, %: C 72.67; H 5.84; N 10.15; S 11.66. $C_{17}H_{16}N_2S$. Calculated, %: C 72.86; H 5.71; N 10.00; S 11.43.

**4-[(2-Aminophenyl)thio]-2,8-dimethylquinoline (IIIc).** Yield of hydrochloride **IIc** 2.37 g (75%), mp 210–211°C. Yield of compound **IIIc** 2.00 g (95%), mp 87–89°C, $R_f$ 0.62 (ethanol–toluene, 1:5). $^1$H NMR spectrum,

**Scheme 4.**




δ, ppm: 2.42 s (3H, $CH_3$), 2.60 s (3H, $NCCH_3$), 5.15 s (2H, $NH_2$), 6.40–7.99 m (8$H_{arom}$). Found, %: C 72.74; H 5.86; N 9.87; S 11.61. $C_{17}H_{16}N_2S$. Calculated, %: C 72.86; H 5.71; N 10.00; S 11.43.

**4-[(2-Aminophenyl)thio]-2-methyl-6-methoxyquinoline (IIId).** Yield of hydrochloride **IId** 2.63 g (79%), mp 191–193°C. Yield of compound **IIId** 2.28 g (97%), mp 172–173°C, $R_f$ 0.50 (ethanol–toluene, 1:5). $^1$H NMR spectrum, δ, ppm: 2.60 s (3H, $NCCH_3$), 3.90 s (3H, $OCH_3$), 5.20 s (2H, $NH_2$), 6.45–7.95 m (8$H_{arom}$). Found, %: C 68.87; H 5.56; N 9.40; S 10.94. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.92; H 5.41; N 9.46; S 10.81.

**4-[(2-Aminophenyl)thio]-2-methyl-8-methoxyquinoline (IIIe).** Yield of hydrochloride **IIe** 2.69 g (81%), mp 168–171°C. Yield of compound **IIIe** 2.30 g (96%), mp 103–105°C, $R_f$ 0.47 (ethanol–toluene, 1:5). $^1$H NMR spectrum, δ, ppm: 2.65 s (3H, $NCCH_3$), 3.93 s (3H, $OCH_3$), 5.20 s (2H, $NH_2$), 6.40–7.90 m (8$H_{arom}$). Found, %: C 68.99; H 5.37; N 9.37; S 10.68. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.92; H 5.41; N 9.46; S 10.81.

**4-[(2-Aminophenyl)thio]-6-bromo-2-methylquinoline (IIIf).** Yield of hydrochloride **IIf** 2.67 g (70%), mp 168–170°C. Yield of compound **IIIf** 2.37 g (98%), mp 96–98°C, $R_f$ 0.68 (ethanol–aqueous HCl). $^1$H NMR spectrum, δ, ppm: 2.70 s (3H, $NCCH_3$), 5.15 s (2H, $NH_2$), 6.90–8.00 m (8$H_{arom}$). Found, %: C 55.72; H 3.65; N 8.03; S 9.17. $C_{16}H_{13}BrN_2S$. Calculated, %: C 55.65; H 3.77; N 8.12; S 9.28.

**4-[(2-Aminophenyl)thio]-2-methyl-8-chloroquinoline (IIIg).** Yield of hydrochloride **IIg** 2.13 g (90%), mp 218–220°C. Yield of compound **IIIg** 2.48 g (92%), mp 129–130°C, $R_f$ 0.60 (ethanol–toluene, 1:10). $^1$H NMR spectrum, δ, ppm: 2.40 s (3H, $NCCH_3$), 5.10 s (2H, $NH_2$), 6.40–7.50 m (8$H_{arom}$). Found, %: C 63.97; H 4.22; N 9.41; S 10.72. $C_{16}H_{13}ClN_2S$. Calculated, %: C 63.89; H 4.33; N 9.32; S 10.65.

**Substituted (4*E*)-4-[(2-mercaptophenyl)imino]-2-methyl-1,4-dihydroquinolines Va–Vg.** *a*. A mixture of 0.01 mol of substituted 2-methyl-4-chloro-quinoline [3], 1.25 g (1.07 ml, 0.01 mol) of *o*-mercaptoaniline, 1 ml of concn. HCl in 30 ml of ethanol was heated on a water bath for 5–6 h. The precipitated crystals were filtered off, dried, the yield and melting point were estimated.

*b*. A mixture of 0.005 mol of an appropriate substituted 4-[(2-aminophenyl)thio]-2-methyl-quinoline **IIIa–IIIg**, 10 ml of ethanol, and 0.75 ml of concn. HCl was heated on a water bath for 3–5 h. Then the reaction mixture was subjected to workup as in procedure *a*. The corresponding dihydrochlorides were isolated.

Dihydrochlorides **IVa–IVg** obtained by procedures *a* and *b* were dissolved in water, the water solution was filtered from any possible impurities and alkalinized with water solution of NaOH to pH ~7–7.5. The separated precipitates were filtered off.

Mixed samples of compounds **Va–Vg** obtained by procedures *a* and *b* do not show depression of the melting point.

**(4*E*)-4-[(2-Mercaptophenyl)imino]-2-methyl-1,4-dihydroquinoline (Va).** Yield of dihydrochloride **IVa** 3.17 g (94%) (*a*), 1.67 g (99%) (*b*), mp 249–251°C. Yield of compound **Va** 2.45 g (98%), mp 194–197°C. Found, %: C 72.36; H 5.17; N 10.45; S 12.14. $C_{16}H_{14}N_2S$. Calculated, %: C 72.18; H 5.26; N 10.53; S 12.03.

**(4*E*)-4-[(2-Mercaptophenyl)imino]-2,6-dimethyl-1,4-dihydroquinoline (Vb).** Yield -of dihydrochloride **IVb** 3.44 g (98%) (*a*), 1.70 g (97%) (*b*), mp 237–238°C. Yield of compound **Vb** 2.66 g (97%), mp 225–227°C. Found, %: C 72.76; H 5.87; N 10.12; S 11.28. $C_{17}H_{16}N_2S$. Calculated, %: C 72.86; H 5.71; N 10.00; S 11.43.

**(4*E*)-4-[(2-Mercaptophenyl)imino]-2,8-dimethyl-1,4-dihydroquinoline (Vc).** Yield of dihydrochloride **IVc** 3.47 g (99%) (*a*), 1.68 g (96%) (*b*), mp 202–203°C. Yield of compound **Vc** 2.71 g (98%), mp 182–183°C. Found, %: C 72.94; H 5.64; N 9.89; S 11.56. $C_{17}H_{16}N_2S$. Calculated, %: C 72.86; H 5.71; N 10.00; S 11.43.

**(4*E*)-4-[(2-Mercaptophenyl)imino]-2-methyl-6-methoxy-1,4-dihydroquinoline (Vd).** Yield of dihydrochloride **IVd** 3.52 g (96%) (*a*), 1.78 g (97%) (*b*), mp 197–199°C. Yield of compound **Vd** 2.73 g (96%), mp 168–170°C. Found, %: C 68.81; H 5.52; N 9.38; S 10.68. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.92; H 5.41; N 9.46; S 10.81.

**(4*E*)-4-[(2-Mercaptophenyl)imino]-2-methyl-8-methoxy-1,4-dihydroquinoline (Ve).** Yield of dihydrochloride **IVe** 3.56 g (97%) (*a*), 1.76 g (96%) (*b*), mp 182–183°C. Yield of compound **Ve** 2.79 g (97%), mp 172–174°C. Found, %: C 68.79; H 5.47; N 9.54; S 10.93. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.92; H 5.41; N 9.46; S 10.81.

**(4*E*)-6-Bromo-4-[(2-mercaptophenyl)imino]-2-methyl-8-methoxy-1,4-dihydroquinoline (Vf).** Yield of dihydrochloride **IVf** 3.33 g (80%) (*a*), 2.04 g (98%) (*b*), mp 256–257°C. Yield of compound **Vf** 2.65 g (96%), mp 207–208°C. Found, %: C 55.71; H 3.68; N 8.23; S 9.12. $C_{16}H_{13}BrN_2S$. Calculated, %: C 55.65; H 3.77; N 8.12; S 9.28.

**(4*E*)-4-[(2-Mercaptophenyl)imino]-2-methyl-8-chloro-1,4-dihydroquinoline (Vg).** Yield of dihydrochloride **IVg** 3.64 g (98%) (*a*), 1.80 g (97%) (*b*), mp 210–211°C. Yield of compound **Vg** 2.82 g (96%), mp 124–126°C. Found, %: C 63.78; H 4.41; N 9.43; S 10.48. $C_{16}H_{14}ClN_2S$. Calculated, %: C 63.89; H 4.33; N 9.32; S 10.65.

**Substituted 4-[(2-mercaptophenyl)amino]-2-methylquinolines VIa–VIg.** Compounds **Va–Vg** (0.005 mol) at boiling in ethanol or aprotic polar solvents for ~0.5 h were converted into white crystals of compounds **VIa–VIg**.

**4-[(2-Mercaptophenyl)amino]-2-methylquinoline (VIa).** Yield 1.21 g (91%), mp 214–216°C, $R_f$ 0.58 (ethanol–toluene, 2:1). $^1$H NMR spectrum, δ, ppm: 2.60 s (3H, $CH_3$), 6.00–8.20 m ($9H_{arom}$), 10.70 s (1H, NH). Found, %: C 72.36; H 5.17; N 10.45; S 12.14. $C_{16}H_{14}N_2S$. Calculated, %: C 72.18; H 5.26; N 10.53; S 12.03.

**4-[(2-Mercaptophenyl)amino]-2,6-dimethylquinoline (VIb).** Yield 1.33 g (95%), mp 247–248°C, $R_f$ 0.58 (ethanol–toluene, 1:1). $^1$H NMR spectrum, δ, ppm: 2.40 s (3H, $CH_3$), 2.60 s (3H, $NCCH_3$), 6.10–8.20 m ($8H_{arom}$), 10.65 s (1H, NH). Found, %: C 72.93; H 5.65; N 9.87; S 11.58. $C_{17}H_{16}N_2S$. Calculated, %: C 72.86; H 5.71; N 10.00; S 11.43.

**4-[(2-Mercaptophenyl)amino]-2,8-dimethylquinoline (VIc).** Yield 1.29 g (92%), mp 206–207°C, $R_f$ 0.49 (ethanol–toluene, 1:1). $^1$H NMR spectrum, δ, ppm: 2.25 s (3H, $CH_3$), 2.50 s (3H, $NCCH_3$), 6.50–8.50 m ($8H_{arom}$), 10.15 C (1H, NH). Found, %: C 72.75; H 5.86; N 10.17; S 11.27. $C_{17}H_{16}N_2S$. Calculated, %: C 72.86; H 5.71; N 10.00; S 11.43.

**4-[(2-Mercaptophenyl)amino]-2-methyl-6-methoxyquinoline (VId).** Yield 1.38 g (93%), mp 263–264°C, $R_f$0.55 (ethanol–toluene, 2:1). $^1$H NMR spectrum, δ, ppm: 2.60 s (3H, $NCCH_3$), 3.93 s (3H, $OCH_3$), 6.00–8.20 m ($8H_{arom}$), 10.05 s (1H, NH). Found, %: C 68.78; H 5.54; N 9.56; S 10.95. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.92; H 5.41; N 9.46; S 10.81.

**4-[(2-Mercaptophenyl)amino]-2-methyl-8-methoxyquinoline (VIe).** Yield 1.35 g (91%), mp 249–251°C, $R_f$0.67 (ethanol–toluene, 1:2). $^1$H NMR spectrum, δ, ppm: 2.65 s (3H, $NCCH_3$), 3.95 s (3H, $OCH_3$), 6.20–8.25 m ($8H_{arom}$), 10.10 s (1H, NH). Found, %: C 68.80; H 5.60; N 9.40; S 10.65. $C_{17}H_{16}N_2OS$. Calculated, %: C 68.92; H 5.41; N 9.46; S 10.81.

**6-Bromo-4-[(2-mercaptophenyl)amino]-2-methylquinoline (VIf).** Yield 1.60 g (93%), mp 224–225°C, $R_f$0.62 (ethanol–toluene, 1:3). $^1$H NMR spectrum, δ, ppm: 2.70 s (3H, $NCCH_3$), 6.20–8.30 m ($8H_{arom}$), 10.20 s (1H, NH). Found, %: C 55.70; H 3.65; N 8.25; S 9.12. $C_{16}H_{13}BrN_2S$. Calculated, %: C 55.65; H 3.77; N 8.12; S 9.28.

**4-[(2-Mercaptophenyl)amino]-2-methyl-8-chloroquinoline (VIg).** Yield 2.67 g (89%), mp 216–217°C, $R_f$ 0.68 (ethanol–toluene, 1:3). $^1$H NMR spectrum, δ, ppm: 2.50 s (3H, $NCCH_3$), 6.40–8.20 m ($8H_{arom}$), 5.10 s (1H, NH). Found, %: C 63.95; H 4.29; N 9.40; S 10.55. $C_{17}H_{13}ClN_2S$. Calculated, %: C 63.89; H 4.33; N 9.32; S 10.65.

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