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2-METHYL-4-CHLORO(MERCAPTO)-6(8)-METHOXYQUINOLINE INTERACTION WITH SULFUR NUCLEOPHILES AND BENZYL CHLORIDES

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Interaction of 2-methyl-4-chloro-6(8)-methoxyquinolines with various S-nucleofiles, as well as 2-methyl-4-mercapto-8-methoxyquinoline with benzyl chlorides were synthesized substituted bis[4-(quinolin-4-yl)phenyl]sulfides, 4,4′-bis(quinolin-4-ylsulfanylmethyl)biphenyls, 4,4′-[oxybis(benzene-4,1-diylsulfanediyl)]bis(2-methylquinolines), 1,4-bis(quinolin-4-ylsulfanyl)benzenes and 4-(1,3-benzothiazol-2-ylsulfanyl)quinolines.

***Keywords*:** quinoline, reaction of nucleophilic substitution, thiol.

Introduction. Quinoline derivatives are of great importance in chemistry, biology and medicine [1]. They exhibit a wide range of biological activities [2, 3], and are used for preparation of new materials and substances. They also exhibit good antiproliferative properties [4]. Sulfur containing compounds comprising more than one heterocyclic fragment attract increased interest as fluorophores [5–7] and play an important role in studying various biological systems [8]. Quinoline derivatives are also promising as fluorophores [9], antioxidants and radioprotectors [10].

Materials and Methods. Previously we studied the reactions of benz-substituted 2(4)-chloro-4(2)methylquinolines with various nukleophiles [11–14]. With a view to synthesize new quinoline derivatives in the present work we examined reactions of 4-chloro-2-methylquinolines (Ia, Ib) with 4,4′-sulfanediyldibenzenethiol, 1,3-benzothiazole-2-thiol, biphenyl-4,4′-diyldimethanethiol, (oxydibenzene-4,1-diyl)dimethanethiol and benzene-1,4-diyldimethanethiol. Optimal reaction conditions were found. Bis-quinoline derivatives were mainly formed at different reactant ratios. The reactions ensured high yields when mixtures of 4-chloroquinolines Ia, Ib [15, 16] with the corresponding binucleophiles at a ratio of 2 : 1 (1:1 in the reaction with 1,3-benzothiazole-2 thiol) were heated in boiling ethanol over a period of 3–5 *h*. As a result, we isolated substituted, bis[4-(quinolin--4-yl)phenyl]sulfides (IIa, IIb), 4,4′-bis(quinolin-4--ylsulfanylmethyl)biphenyls (IIIa, IIIb), 4,4′-[oxybis(benzene-4,1-diylsulfanediyl)]-bis(2-methylquinolines) (IVa, IVb), 1,4-bis(quinolin-4-ylsulfanyl)benzenes (Va, Vb) and 4-(1,3-benzothiazol-2-ylsulfanyl)quinolines (VIa, VIb) (Scheme 1).

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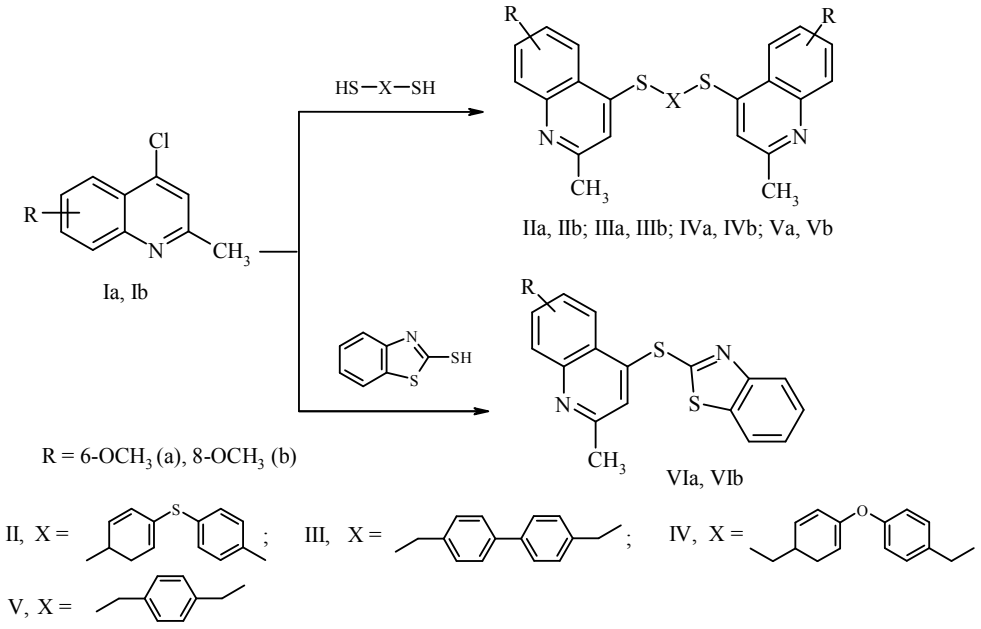
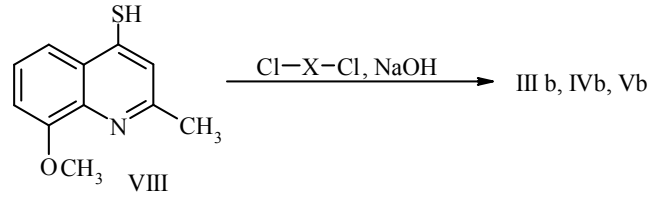


Scheme 1.

Compounds IIIb, IVb and Vb were also synthesized independently by reaction of 2-methyl-4-tiol-8-methoxyquinolines (VII) [17] with 4,4′-bis(chloromethyl) biphenyl, 4,4′-oxybis(chloromethylbenzene) and 1,4-bis(chloromethyl)benzene at a ratio of 2 : 1 in aqueous sodium hydroxide on stirring for 2 *h* at room temperature (Scheme 2).



Scheme 2.

Experimental Part. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury-300 from solution in DMSO-d_6. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates (development in iodine vapor).

***Compounds IIa, IIb* (*General Procedure*).** A mixture of 0.02 *mol* of 4-chloroquinoline Ia, Ib [15, 16] and 0.01 *mol* 4,4′-sulfanediyldibenzenethiole in 50 *mL* of ethanol was heated for 3–5 *h* under reflux with stirring. After cooling, the precipitate was filtered off, washed with ethanol and dried.

4,4′-[Sulfanediylbis(benzene-4,1-diylsulfanediyl)]bis(2-methyl-6-methoxyquinoline) (IIa). Yield 5.74 *g* (97%), mp 103–104°*C*, R_f 0.59 (ethanol–toluene, 1: 8). ^{1}H NMR spectrum, δ, *ppm*: 2.46 s (6H, CH_3); 3.75 s (6H, OCH_3); 6.98 s (2H, 3H-arom.); 7.35 dd (4H, H-arom., J = 17.85, 7.54 *Hz*); 7.52–7.71 m (8H, H-arom.);

7.82 td (2H, H-arom., *J* = 7.54, 1.59 *Hz*). Found, %: C 69.03; H 4.63; N 4.91; S 16.42. $C_{34}H_{28}N_2O_2S_3$. Calculated, %: C 68.89; H 4.76; N 4.73; S 16.23.

4,4'-[Sulfanediylbis(benzene-4,1-diylsulfanediyl)]bis(2-methyl-8-methoxyquinoline) (IIb). Yield 5.80 *g* (91%), mp 135–136°*C*, R_f 0.56 (ethanol–toluene, 1 : 8). Found, %: C 69.06; H 4.92; N 4.94; S 16.39. $C_{34}H_{28}N_2O_2S_3$. Calculated, %: C 68.89; H 4.76; N 4.73; S 16.23.

***Compounds IIIa, IIIb; IVa, IVb and Va, Vb* (*General Procedure*).**

A. The reactions were carried out as described above for IIa, IIb.

B. A mixture of 0.4 *g* (10 *mmol*) of sodium hydroxide and 10 *mmol* of quinoline VII [17] in 10 *mL* of water was stirred for 15 *min* at room temperature. The corresponding bis(chloromethyl) derivative (5 *mmol*) was then added, the mixture was stirred for 2 *h*, and the precipitate was filtered off, washed with water and dried. The products showed no depression of the melting point on mixing with samples prepared as described in A.

4,4'-[Biphenyl-4,4'-diylbis(methylenesulfanediyl)]bis(2-methyl-6-methoxyquinoline) (IIIa). Yield 4.99 *g* (85%) (A), mp 242–243°*C*, R_f 0.60 (ethanol–toluene, 1 : 50). 1H NMR spectrum, *δ*, *ppm*: 2.63 s (6H,CH_3); 3.12 s (6H, OCH_3); 4.53 s (4H, CH_2); 6.98 s (2H, 3H-arom.); 7.41–7.67 m (8H, H-arom.); 7.7–7.8 td (2H, H-arom., *J* = 7.54, 1.59 *Hz*); 7.96 dd (4H, H-arom., *J* = 17.85, 7.54 *Hz*). Found, %: C 73.61; H 5.26; N 4.89; S 11.03. $C_{36}H_{32}N_2O_2S_2$. Calculated, %: C 73.44; H 5.48; N 4.76; S 10.89.

4,4'-[Biphenyl-4,4'-diylbis(methylenesulfanediyl)]bis(2-methyl-8-methoxyquinoline) (IIIb). Yield 4.47 *g* (93%) (A), 2.79 *g* (95%) (B); mp 246–247°*C*, R_f 0.62 (ethanol–toluene, 1 : 50). Found, %: C 73.58; H 5.63; N 4.91; S 10.71. $C_{36}H_{32}N_2O_2S_2$. Calculated, %: C 73.44; H 5.48; N 4.76; S 10.89.

4,4'-[Oxybis(benzene-4,1-diylmethylenesulfanediyl)]bis(2-methyl-6-methoxyquinoline) (IVa). Yield 5.62 *g* (93%) (A), mp 219–220°*C*, R_f 0.50 (ethanol–toluene, 1 : 25). Found, %: C 71.26; H 5.49; N 4.46; S 10.79. $C_{36}H_{32}N_2O_3S_2$. Calculated, %: C 71.49; H 5.33; N 4.63; S 10.60.

4,4'-[Oxybis(benzene-4,1-diylmethylenesulfanediyl)]bis(2-methyl-8-methoxyquinoline) (IVb). Yield 5.62 *g* (93%) (A), 2.78 *g* (92%) (B); mp 123–124°*C*, R_f 0.52 (ethanol–toluene, 1 : 25). ^{1}H NMR spectrum, *δ*, *ppm*: 2.53 s (6H, CH_3); 3.68 s (6H, OCH_3); 4.59 s (4H, CH_2); 7.07 s (2H, 3H-arom.); 7.55 dd (2H, H-arom., *J* = 7.94, 1.59 *Hz*); 7.67–7.77 m (6H, H-arom.); 7.80 s (2H, H-arom.) 7.90 d (4H, H-arom., *J* = 7.94 *Hz*). Found, %: C 71.26; H 5.49; N 4.46; S 10.79. $C_{36}H_{32}N_2O_3S_2$. Calculated, %: C 71.49; H 5.33; N 4.63; S 10.60.

4,4'-[Benzene-1,4-diylbis(methylenesulfanediyl)]bis(2-methyl-6-methoxyquinoline) (Va). Yield 4.81 *g* (94%) (A), mp 252–253°*C*, R_f 0.63 (ethanol–toluene, 1 :10). ^{1}H NMR spectrum, *δ*, *ppm*: 2.53 s (6H, CH_3); 3.95 s (6H, OCH_3); 4.45 s (4H, CH_2); 7.14–7.16 m (8H, H-arom.); 7.45 dd (4H, H-arom., *J* = 7.94, 1.59 *Hz*). Found, %: C 70.35; H 5.26; N 5.63; S 12.69. $C_{30}H_{28}N_2O_2S_2$. Calculated, %: C 70.28; H 5.50; N 5.46; S 12.51.

4,4'-[Benzene-1,4-diylbis(methylenesulfanediyl)]bis(2-methyl-8-methoxyquinoline) (Vb). Yield 4.40 *g* (86%) (A), 2.30 g (90%) (B); mp 223–224°*C*, R_f 0.63 (ethanol–toluene, 1 : 10). Found, %: C 70.35; H 5.26; N 5.63; S 12.69. $C_{30}H_{28}N_2O_2S_2$. Calculated, %: C 70.28; H 5.50; N 5.46; S 12.51.

Compounds VIa, VIb were synthesized as described above for IIa, IIb from 1,3-benzothiazole-2-thiol; the products were recrystallized from aqueous ethanol.

4-(1,3-Benzothiazol-2-ylsulfanyl)-2-methyl-6-methoxyquinoline (VIa). Yield 2.35 *g* (89%), mp 130–131°*C*, R_f 0.56 (ethanol–toluene, 1 : 30). Found, %: C 63.99; H 4.02; N 7.95; S 18.75. $C_{18}H_{14}N_2OS_2$. Calculated, %: C 63.88; H 4.17; N 8.28; S 18.95.

4-(1,3-Benzothiazol-2-ylsulfanyl)-2-methyl-8-methoxyquinoline (VIb). Yield 2.38 *g* (90%), mp 100–101°*C*, R_f 0.53 (ethanol–toluene, 1 : 20). $C_{18}H_{14}N_2OS_2$. Calculated, %: C 63.88; H 4.17; N 8.28; S 18.95. ^{1}H NMR spectrum, δ, *ppm*: 2.64 s (3H, CH_3); 3.26 s (3H, OCH_3); 7.12–7.63 m (4H, H-arom.); 7.75 d (1H, H-arom., J = 6.35 *Hz*); 7.92 d (1H, H-arom., J = 7.94 *Hz*); 7.97 dd (2H, H-arom., J = 17.46, 7.94 *Hz*). Found, %: C 67.19; H 4.21; N 9.42; S 19.75. $C_{17}H_{14}N_2S_2$. Calculated, %: C 67.05; H 4.38; N 8.69; S 19.89.

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