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Synthesis of Substituted 2,4-Dimethylthieno[3,2-*c*]quinolines

A. A. Avetisyan, I. L. Aleksanyan, and K. S. Sargsyan

Erevan State University, ul. A. Manukyana 1, Erevan, 375025 Armenia
e-mail: organkim@sun.ysu.am

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Abstract—A procedure was developed for the synthesis of substituted 2,4-dimethylthieno[3,2-*c*]quinolines via intramolecular cyclization and subsequent aromatization of 3-(2-chloroprop-2-en-1-yl)- and 3-(2-oxopropyl)-2-methylquinoline-4-thiols. The latter were obtained by alkaline hydrolysis of the corresponding thiuronium salts which were prepared in turn by reactions of 4-chloro-3-(2-chloroprop-2-en-1-yl)- and 4-chloro-3-(2-oxopropyl)-2-methylquinolines with thiourea.

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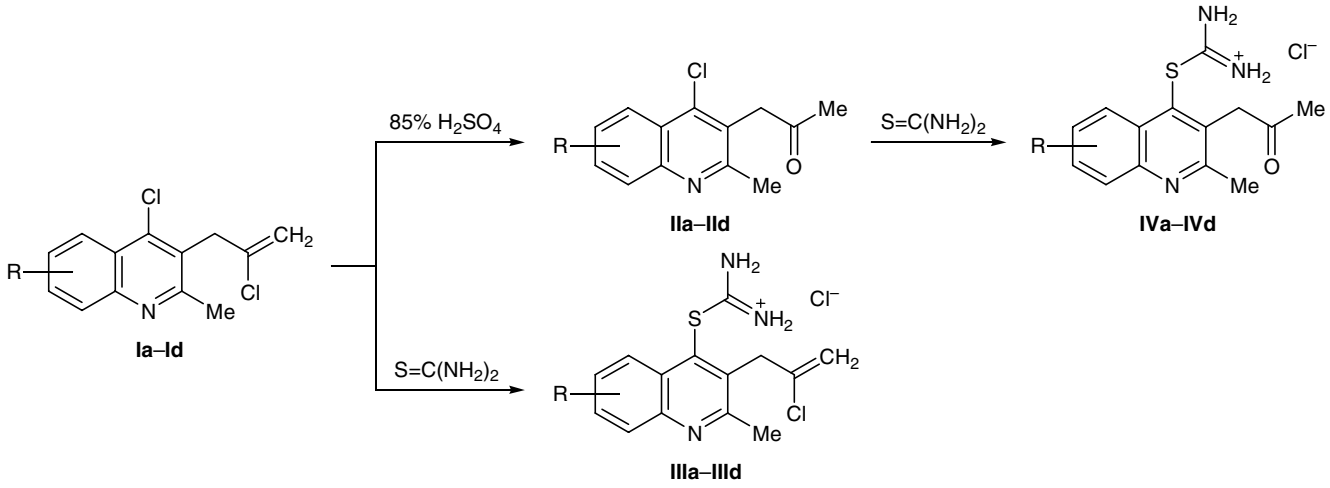
Interest in thienoquinoline derivatives originates from the fact that many compounds of this series exhibit pharmacological activity [1–3]. There are numerous publications concerning methods of synthesis of various thienoquinolines [4–7].

In the present communication we report on a new procedure for the synthesis of substituted 2,4-dimethylthieno[3,2-*c*]quinolines. As starting compounds we used 4-chloro-3-(2-chloroprop-2-en-1-yl)- and 4-chloro-3-(2-oxopropyl)-2-methylquinolines **Ia**–**Id** and **IIa**–**IId** substituted in the benzene ring [8, 9]. By heating compounds **Ia**–**Id** and **IIa**–**IId** with thiourea (molar reactant ratio 1:1.2) in anhydrous acetone we obtained the corresponding *S*-quinolylthiuronium chlorides **IIIa**–**IIId** and **IVa**–**IVd** in almost quantitative yield (Scheme 1). Thiuronium salts **IIIa**–**IIId** and **IVa**–**IVd** were subjected to hydrolysis under both acidic and alkaline conditions. Alkaline hydrolysis led to the formation of 3-(2-chloroprop-2-en-1-yl)- and 3-(2-oxopropyl)-2-methylquinoline-4(1*H*)-thiones **Va**–**Vd** and **VIa**–**VId**, respectively (Scheme 2). Their structure was proved by the IR and ^{1}H NMR data.

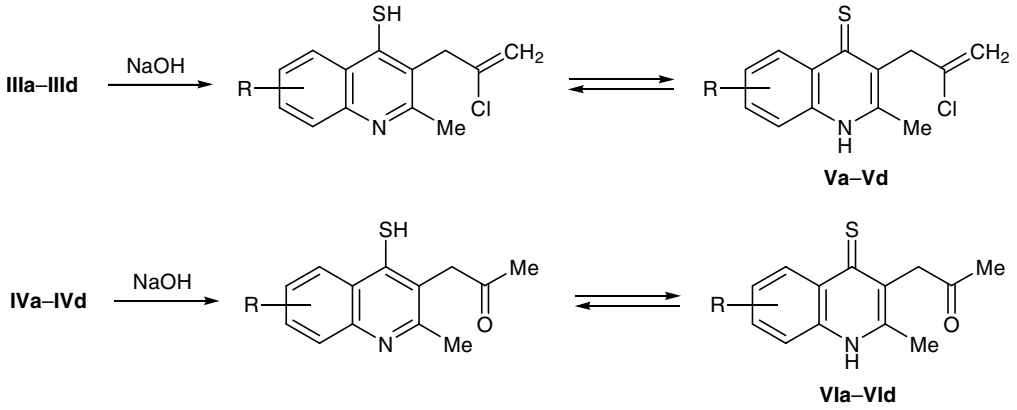
Our further studies showed that substituted dihydroquinoline-4-thiones **Va**–**Vd** and **VIa**–**VId** in 96% sulfuric acid at room temperature undergo intramolecular cyclization, yielding the corresponding thieno[3,2-*c*]quinolines **VIIa**–**VIId** (Scheme 3). Presumably, protonation of the chlorovinyl fragment in **Va**–**Vd** or

Scheme 1.



R = H (**a**), 8-Me (**b**), 6-Me (**c**), 8-MeO (**d**).

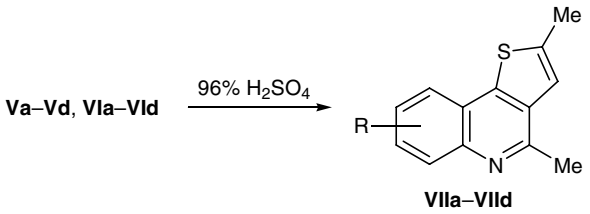
Scheme 2.



R = H (**a**), 8-Me (**b**), 6-Me (**c**), 8-MeO (**d**).

of the carbonyl group in **VIa**–**VId** favors nucleophilic attack by the sulfur atom of the 4-sulfanyl group on the electron-deficient carbon atom in the 3-substituent; the intramolecular cyclization is accompanied by dehydration and aromatization with formation of substituted 2,4-dimethylthieno[3,2-*c*]quinolines. Samples of compounds **VIIa**–**VIId** obtained by cyclization of **Va**–**Vd** and **VIa**–**VId** were fully identical.

Scheme 3.



R = H (**a**), 8-Me (**b**), 6-Me (**c**), 8-MeO (**d**).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury spectrometer using DMSO-d_6 as solvent. The IR spectra were measured on a UR-20 spectrometer from samples dispersed in mineral oil. The purity of the products was checked by TLC on Silufol UV-254 plates (development with iodine vapor).

4-Chloro-3-(2-chloroprop-2-en-1-yl)-2-methylquinolines **Ia**, **Ib**, and **Id** were synthesized by reaction of the corresponding 3-(2-chloroprop-2-en-1-yl)-2-methylquinolin-4-ols with phosphoryl chloride [8, 9].

4-Chloro-3-(2-chloroprop-2-en-1-yl)-2,6-dimethylquinoline (Ic) was synthesized as described in [8] for **Ia**, **Ib**, and **Id** from 2.5 g (0.01 mol) of 3-(2-chloroprop-2-en-1-yl)-2,6-dimethylquinolin-4-ol and 10 ml of phosphoryl chloride. The product was recrystallized from aqueous alcohol (1:1). Yield 2.53 g (95%), mp 49–51°C, R_f 0.53 (toluene–ethanol, 2.5:1). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, 6-CH_3), 2.75 s (3H, 2-CH_3), 4.05 s (2H, CH_2), 4.84 s and 5.25 s (2H, =CH_2), 7.60–8.20 m (3H, H_{arom}). Found, %: Cl 25.17; N 4.96. $C_{14}H_{13}Cl_2N$. Calculated, %: Cl 25.69; N 5.26.

1-(4-Chloro-2-methylquinolin-3-yl)propan-2-ones **IIa**, **IIb**, and **IId** were synthesized by acid hydrolysis of compounds **Ia**, **Ib**, and **Id**, respectively [8].

1-(4-Chloro-2,6-dimethylquinolin-3-yl)propan-2-one (IIc) was synthesized as described in [8] for **IIa**, **IIb**, and **IId** from 2.7 g (0.01 mol) of compound **Ic** and 10 ml of 85% sulfuric acid. Yield 2.4 g (97%), mp 148–150°C, R_f 0.62 (ethyl acetate–toluene, 4:1). IR spectrum: ν 1720 cm^{-1} (C=O). Found, %: C 67.76; H 5.84; Cl 14.46; N 5.52. $C_{14}H_{14}ClNO$. Calculated, %: C 67.87; H 5.65; Cl 14.34; N 5.65. Compound **IIc** showed a positive test with iodoform, which is typical of methyl ketones.

***S*-[3-(2-Chloroprop-2-en-1-yl)-2-methylquinolin-4-yl]isothiuronium chlorides IIIa–IIId (*general procedure*).** A mixture of 0.01 mol of compound **Ia**–**Id** and 0.91 g (12 mmol) of thiourea in 50 ml of anhydrous acetone was heated for 8–10 h on a water bath. The mixture was cooled, and the yellow crystals were filtered off and washed with acetone.

***S*-[3-(2-Chloroprop-2-en-1-yl)-2-methylquinolin-4-yl]isothiuronium chloride (IIIa).** Yield 3.1 g (95%), mp 195–200°C. Found, %: Cl 22.28; N 12.68; S 9.84. $C_{14}H_{15}Cl_2N_3S$. Calculated, %: Cl 21.64; N 12.80; S 9.75.

***S*-[3-(2-Chloroprop-2-en-1-yl)-2,8-dimethylquinolin-4-yl]isothiuronium chloride (IIIb).** Yield 2.7 g

(80%), mp 157–160°C. Found, %: Cl 20.52; N 12.41; S 9.22. $C_{15}H_{17}Cl_2N_3S$. Calculated, %: Cl 20.76; N 12.28; S 9.35.

***S*-[3-(2-Chloroprop-2-en-1-yl)-2,6-dimethylquinolin-4-yl]isothiuronium chloride (IIIc).** Yield 2.9 g (85%), mp 225°C. Found, %: Cl 20.88; N 12.13; S 9.49. $C_{15}H_{17}Cl_2N_3S$. Calculated, %: Cl 20.76; N 12.28; S 9.35.

***S*-[3-(2-Chloroprop-2-en-1-yl)-8-methoxy-2-methylquinolin-4-yl]isothiuronium chloride (IIId).** Yield 3.4 g (90%), mp 210–215°C. Found, %: Cl 19.69; N 11.94; S 8.77. $C_{15}H_{17}Cl_2N_3OS$. Calculated, %: Cl 19.83; N 11.73; S 8.93.

S-[2-Methyl-3-(2-oxopropyl)quinolin-4-yl]isothiuronium chlorides IVa–IVd were synthesized as described above for compounds **IIIa**–**IIId** from 10 mmol of the corresponding 1-(4-chloro-2-methylquinolin-3-yl)propan-2-one **IIa**–**IId** and 0.91 g (12 mmol) of thiourea.

***S*-[2-Methyl-3-(2-oxopropyl)quinolin-4-yl]isothiuronium chloride (IVa).** Yield 2.7 g (87%), mp 210–215°C. Found, %: Cl 11.58; N 13.64; S 10.18. $C_{14}H_{16}ClN_3OS$. Calculated, %: Cl 11.47; N 13.57; S 10.33.

***S*-[2,8-Dimethyl-3-(2-oxopropyl)quinolin-4-yl]-isothiuronium chloride (IVb).** Yield 2.4 g (75%), mp 220–223°C. Found, %: Cl 11.09; N 13.11; S 9.74. $C_{15}H_{18}ClN_3OS$. Calculated, %: Cl 10.97; N 12.98; S 9.89.

***S*-[2,6-Dimethyl-3-(2-oxopropyl)quinolin-4-yl]-isothiuronium chloride (IVc).** Yield 2.8 g (86%), mp 222–225°C. Found, %: Cl 11.58; N 13.64; S 10.18. $C_{15}H_{18}ClN_3OS$. Calculated, %: Cl 10.97; N 12.98; S 9.89.

***S*-[8-Methoxy-2-methyl-3-(2-oxopropyl)quinolin-4-yl]isothiuronium chloride (IVd).** Yield 3.1 g (91%), mp 235–240°C. Found, %: Cl 10.59; N 12.45; S 9.57. $C_{15}H_{18}ClN_3O_2S$. Calculated, %: Cl 10.45; N 12.37; S 9.42.

3-(2-Chloroprop-2-en-1-yl)- and 3-(2-oxopropyl)-2-methylquinoline-4(1*H*)-thiones Va–Vd and VIa–VId (*general procedure*). A solution of 0.01 mol of isothiuronium salt **IIIa**–**IIId** or **IVa**–**IVd** in water was made alkaline (pH ~10), and the mixture was heated for 1.5 h on a water bath. The mixture was cooled and acidified to pH ~6 with hydrochloric acid, and the bright yellow precipitate was filtered off and recrystallized from aqueous alcohol (1:1).

3-(2-Chloroprop-2-en-1-yl)-2-methylquinoline-4(1*H*)-thione (Va). Yield 3.1 g (71%), mp 137°C, R_f 0.53 (alcohol–hexane, 1:1.5). IR spectrum, ν, cm^{-1}: 1240 (C=S), 1655 (C=CCl), 3330 (NH). ^1H NMR spectrum, δ, ppm: 2.75 s (3H, 2-CH_3), 4.0 s (2H, CH_2), 4.85 s and 5.30 s (2H, =CH_2), 7.60–8.20 m (4H, H_{arom}), 10.20 s (1H, NH). Found, %: C 62.41; H 4.68; N 5.71; S 12.70. $C_{13}H_{12}ClNS$. Calculated, %: C 62.52; H 4.8; N 5.61; S 12.82.

3-(2-Chloroprop-2-en-1-yl)-2,8-dimethylquinoline-4(1*H*)-thione (Vb). Yield 2.1 g (80%), mp 122–124°C, R_f 0.73 (alcohol–hexane, 1:1.5). IR spectrum, ν, cm^{-1}: 1245 (C=S), 1655 (C=CCl), 3280 (NH). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, 8-CH_3), 2.70 s (3H, 2-CH_3), 4.10 s (2H, CH_2), 4.80 s and 5.20 s (2H, =CH_2), 7.20–8.10 m (3H, H_{arom}), 11 s (1H, NH). Found, %: C 63.64; H 5.41; N 5.20; S 12.21. $C_{14}H_{14}ClNS$. Calculated, %: C 63.75; H 5.31; N 5.31; S 12.14.

3-(2-Chloroprop-2-en-1-yl)-2,6-dimethylquinoline-4(1*H*)-thione (Vc). Yield 2 g (76%), mp 205–207°C, R_f 0.66 (toluene–acetone, 1.5:1). IR spectrum, ν, cm^{-1}: 1270 (C=S), 1645 (C=CCl), 3300 (NH). ^1H NMR spectrum, δ, ppm: 2.22 s (3H, 6-CH_3), 2.70 s (3H, 2-CH_3), 4.20 s (2H, CH_2), 4.90 s and 5.25 s (2H, =CH_2), 7.30–8.20 m (3H, H_{arom}), 11.20 s (1H, NH). Found, %: C 63.84; H 5.21; N 5.44; S 12.00. $C_{14}H_{14}ClNS$. Calculated, %: C 63.75; H 5.31; N 5.31; S 12.14.

3-(2-Chloroprop-2-en-1-yl)-8-methoxy-2-methylquinoline-4(1*H*)-thione (Vd). Yield 2.8 g (78%), mp 179–180°C, R_f 0.68 (alcohol–hexane, 1:1.5). IR spectrum, ν, cm^{-1}: 1270 (C=S), 1640 (C=CCl), 3320 (NH). ^1H NMR spectrum, δ, ppm: 2.55 s (3H, 2-CH_3), 3.90 s (3H, OCH_3), 4.00 s (2H, CH_2), 4.70 s and 5.00 s (2H, =CH_2), 7.20–8.0 m (3H, H_{arom}), 11.20 s (1H, NH). Found, %: C 60.26; H 4.81; N 5.17; S 11.32. $C_{14}H_{14}ClNOS$. Calculated, %: C 60.10; H 5.00; N 5.00; S 11.44.

1-(2-Methyl-4-thioxo-1,4-dihydroquinolin-3-yl)-propan-2-one (VIa). Yield 2.2 g (93%), mp 185–187°C, R_f 0.7 (alcohol–hexane, 1:1). IR spectrum, ν, cm^{-1}: 1280 (C=S), 1702 (C=O), 3400 (NH). ^1H NMR spectrum, δ, ppm: 2.43 s (3H, $COCH_3$), 2.72 s (3H, 2-CH_3), 3.91 s (2H, CH_2), 7.2–8.1 m (4H, H_{arom}), 10.2 s (1H, NH). Found, %: C 67.41; H 5.74; N 6.12; S 13.69. $C_{13}H_{13}NOS$. Calculated, %: C 67.53; H 5.63; N 6.06; S 13.85.

1-(2,8-Dimethyl-4-thioxo-1,4-dihydroquinolin-3-yl)propan-2-one (VIb). Yield 2.1 g (85%), mp 147–148°C, R_f 0.63 (toluene–ethanol, 1.5:1). IR spectrum,

ν, cm^{-1}: 1265 (C=S), 1700 (C=O), 3412 (NH). ^1H NMR spectrum, δ, ppm: 2.28 s (3H, 8-CH_3), 2.40 s (3H, $COCH_3$), 2.75 s (3H, 2-CH_3), 4.0 s (2H, CH_2), 7.6–8.4 m (3H, H_{arom}), 10.2 s (1H, NH). Found, %: C 68.71; H 6.04; N 5.91; S 13.21. $C_{14}H_{15}NOS$. Calculated, %: C 68.57; H 6.12; N 5.71; S 13.06.

1-(2,6-Dimethyl-4-thioxo-1,4-dihydroquinolin-3-yl)propan-2-one (VIc). Yield 2.0 g (83%), mp 185–187°C, R_f 0.43 (toluene–ethyl acetate, 1:6). IR spectrum, ν, cm^{-1}: 1276 (C=S), 1702 (C=O), 3250 (NH). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, 6-CH_3), 2.45 s (3H, $COCH_3$), 2.80 s (3H, 2-CH_3), 4.5 s (2H, CH_2), 7.2–8.1 m (3H, H_{arom}), 11.5 s (1H, NH). Found, %: C 68.41; H 6.28; N 5.88; S 13.22. $C_{14}H_{15}NOS$. Calculated, %: C 68.57; H 6.12; N 5.71; S 13.06.

1-(8-Methoxy-2-methyl-4-thioxo-1,4-dihydroquinolin-3-yl)propan-2-one (VId). Yield 2.3 g (87%), mp 100–102°C, R_f 0.58 (toluene–acetone, 1:1). IR spectrum, ν, cm^{-1}: 1230 (C=S), 1700 (C=O), 3350 (NH). ^1H NMR spectrum, δ, ppm: 2.43 s (3H, $COCH_3$), 2.70 s (3H, 2-CH_3), 3.69 s (3H, OCH_3), 4.50 s (2H, CH_2), 7.1–8.0 m (3H, H_{arom}), 10.5 s (1H, NH). Found, %: C 59.82; H 5.11; N 4.89; S 11.60. $C_{14}H_{15}NO_2S$. Calculated, %: C 60.10; H 5.00; N 5.00; S 11.44.

2,4-Dimethylthieno[3,2-*c*]quinolines VIIa–VIId (*general procedure*). A mixture of 0.01 mol of compound **Va–Vd** or **VIa–VId** and 10 ml of 96% sulfuric acid was left to stand at room temperature until hydrogen chloride no longer evolved (4–6 h). The mixture was then poured onto 50 g of crushed ice, the resulting aqueous solution was filtered and neutralized to pH ~8, and the precipitate was filtered off.

2,4-Dimethylthieno[3,2-*c*]quinoline (VIIa). Yield 2.1 g (99%), mp 45–47°C, R_f 0.6 (chloroform–alcohol, 10:1). ^1H NMR spectrum, δ, ppm: 2.70 s (3H, 4-CH_3), 2.85 s (3H, 2-CH_3), 7.20 s (1H, 3-H), 7.45–8.0 m (4H, H_{arom}). Found, %: C 73.08; H 5.24; N 6.71; S 15.21. $C_{13}H_{11}NS$. Calculated, %: C 73.23; H 5.16; N 6.57; S 15.00.

2,4,6-Trimethylthieno[3,2-*c*]quinoline (VIIb). Yield 2.0 g (90%), mp 49–50°C, R_f 0.57 (chloroform–alcohol, 20:1). ^1H NMR spectrum, δ, ppm: 2.30 s (3H, 6-CH_3), 2.75 s (3H, 2-CH_3), 2.90 s (3H, 4-CH_3), 7.20 s (1H, 3-H), 7.5–8.1 m (3H, H_{arom}). Found, %: C 74.11; H 5.61; N 6.04; S 14.21. $C_{14}H_{13}NS$. Calculated, %: C 74.00; H 5.72; N 6.16; S 14.09.

2,4,8-Trimethylthieno[3,2-*c*]quinoline (VIIc). Yield 1.9 g (85%), mp 88–89°C, R_f 0.58 (toluene–alcohol, 3:1). ^1H NMR spectrum, δ, ppm: 2.33 s (3H, 8-CH_3), 2.70 s (3H, 2-CH_3), 3.00 s (3H, 4-CH_3), 6.9 s (1H, 3-H), 7.45–8.2 m (3H, H_{arom}). Found, %: C 69.80; H 5.60; N 6.20; S 14.25. $C_{14}H_{13}NS$. Calculated, %: C 74.00; H 5.72; N 6.16; S 14.09.

6-Methoxy-2,4-dimethylthieno[3,2-*c*]quinoline (VIId). Yield 2.3 g (93%), mp 138–139°C, R_f 0.68 (toluene–alcohol, 5:3). ^1H NMR spectrum, δ, ppm: 2.70 s (3H, 2-CH_3), 3.00 s (3H, 4-CH_3), 4.00 s (3H, OCH_3), 6.9 s (1H, 3-H), 7.40–8.15 m (3H, H_{arom}). Found, %: C 69.00; H 5.29; N 5.90; S 13.28. $C_{14}H_{13}NOS$. Calculated, %: C 69.13; H 5.34; N 5.76; S 13.16.

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