

Synthesis of Substituted 2-Methyl-4-quinolyl Isothiocyanates and 4-Mercaptoquinolines

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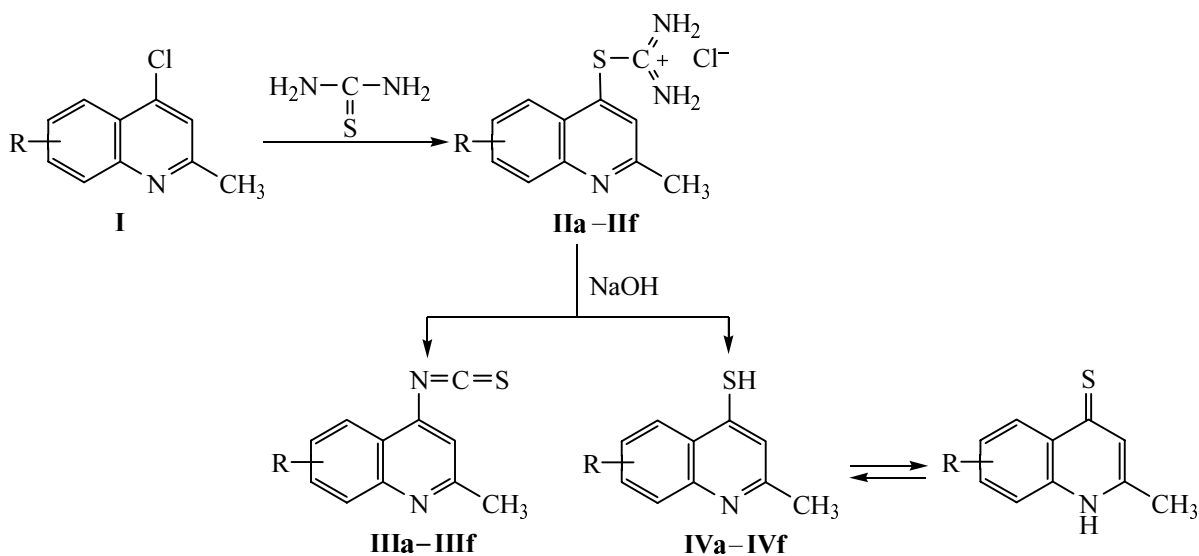
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Abstract—Synthesis was performed of substituted 2-methyl-4-quinoline thiuronium salts by reaction of 2-methyl-4-chloroquinolines with thiourea. The alkaline hydrolysis of these salts afforded the corresponding 2-methyl-4-quinolyl- isothiocyanates and 2-methyl-4-mercaptoquinolines.

We formerly reported on the new route of the alkaline hydrolysis of 2-methyl-4-quinoline thiuronium salts affording 2-methyl-4-quinolyl isothiocyanate [1]. In extension of this research we studied here the reaction with thiourea of 2-methyl-4-chloroquinolines containing in the benzene ring different (electron-donor and electron-acceptor) substituents. The reaction occurred at heating the initial components in the ratio quinoline to thiourea equal to 1:1.1 in anhydrous acetone resulting in the quinolylthiuronium salts in a nearly quantitative yield.

The alkaline hydrolysis of the salts obtained took two pathways: an intramolecular rearrangement analogous to Smiles rearrangement [2–5] affording the corresponding

quinolyl isothiocyanates, and a bimolecular cleavage of a S–C bond giving rise to substituted 2-methyl-4-mercaptoquinolines. The ratio of the final products depended on the character and the position of substituents, and from the 6-methoxy derivative the substitution product was not obtained at all. As expected, the electronic effects of substituents in positions 6 and 8 of the benzene ring were identical. The observed increase in the yield of rearrangement products in the systems under study in all likelihood is due to the existence of the molecule in a conformation most feasible for the rearrangement. This fact apparently governs the lack of compound **IVc** in the hydrolysis products of S-(2-methyl-6-methoxy-4-quinolyl)thiuronium chloride.



R = 6-CH₃ (a), 8-CH₃ (b), 6-OCH₃ (c), 8-OCH₃ (d), 6-Br (e), 8-Cl (f).

EXPERIMENTAL

^1H NMR spectra were registered on a spectrometer Mercury-300 Varian NMR in DMSO, IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates (development in iodine vapor).

S-(2-Methyl-4-quinolyl)thiuronium chlorides IIa–IIf. A mixture of 0.01 mol of an appropriate substituted 2-methyl-4-chloroquinoline [6(8)-methyl, 6(8)-methoxy, 6-bromo, 8-chloro] and 0.99 g (0.013 mol) of thiourea in 50 ml of anhydrous acetone was heated on a water bath for 8–10 h. On cooling the precipitated yellow crystals were filtered off and washed with anhydrous acetone.

S-(2,6-Dimethyl-4-quinolyl)thiuronium chloride (IIa) Yield 2.54 g (95%), mp 210–215°C. Found, %: Cl 13.31; N 15.63; S 12.05. $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{S}$. Calculated, %: Cl 13.27; N 15.70; S 11.96.

S-(2,8-Dimethyl-4-quinolyl)thiuronium chloride (IIb) Yield 2.62 g (98%), mp 150–155°C. Found, %: Cl 13.14; N 15.82; S 12.08. $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{S}$. Calculated, %: Cl 13.27; N 15.70; S 11.96.

S-(2-Methyl-6-methoxy-4-quinolyl)thiuronium chloride (IIc) Yield 2.64 g (93%), mp 205–210°C. Found, %: Cl 12.71; N 14.76; S 11.43. $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{OS}$. Calculated, %: Cl 12.52; N 14.81; S 11.29.

S-(2-Methyl-8-methoxy-4-quinolyl)thiuronium chloride (IId) Yield 2.66 g (94%), mp 180–185°C. Found, %: Cl 12.41; N 14.95; S 11.37. $\text{C}_{12}\text{H}_{14}\text{ClN}_3\text{OS}$. Calculated, %: Cl 12.52; N 14.81; S 11.29.

S-(2-Methyl-6-bromo-4-quinolyl)thiuronium chloride (IIe) Yield 3.19 g (96%), mp 175–180°C. Found, %: Cl 10.90; N 12.46; S 9.50. $\text{C}_{11}\text{H}_{11}\text{BrClN}_3\text{S}$. Calculated, %: Cl 10.68; N 12.63; S 9.62.

S-(2-Methyl-8-chloro-4-quinolyl)thiuronium chloride (IIf) Yield 2.56 g (89%), mp 215–217°C. Found, %: Cl 24.78; N 14.77; S 10.98. $\text{C}_{11}\text{H}_{11}\text{Cl}_2\text{N}_3\text{S}$. Calculated, %: Cl 24.65; N 14.58; S 11.11.

Substituted 2-methyl-4-quinolyl isothiocyanates IIIa–IIIf and 2-methyl-4-mercaptoquinolines IVa–IVf. A water solution of 0.01 mol of thiuronium salt IIa–IIf was alkalinized to pH~10 and was heated on a water bath for 1.5 h. On cooling the separated precipitate of IIIa–IIIf was filtered off, washed with water, and recrystallized from a mixture ethanol–water, 1:1. The filtrate was acidified with hydrochloric acid to pH 6, and

bright-yellow precipitates of compounds IVa–IVf with a specific odor were filtered off.

2,6-Dimethyl-4-quinolyl isothiocyanate (IIIa). Yield 0.85 g (39.7%), mp 170–175°C, R_f 0.72 (from ethanol). IR spectrum, cm^{-1} : 2250–1930 ($-\text{N}=\text{C}=\text{S}$). ^1H NMR spectrum, δ , ppm: 2.40 s (3H, CH_3), 2.80 s (3H, NCCH_3), 7.00 s (H^3 , H_{arom}), 7.5–8.2 m (3H, H_{arom}). Found, %: C 67.41; H 4.59; N 12.95; S 15.11. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{S}$. Calculated, %: C 67.29; H 4.67; N 13.08; S 14.95.

2,6-Dimethyl-4-sulfanylquinoline (IVa). Yield 0.70 g (37%), mp 215°C, R_f 0.69 (from ethanol). IR spectrum, cm^{-1} : 1215 ($>\text{C}=\text{S}$), 3220 ($>\text{NH}$). ^1H NMR spectrum, δ , ppm: 2.22 s (3H, CH_3), 2.70 s (3H, NCCH_3), 6.45 s (H^3 , H_{arom}), 7.2–7.9 m (3H, H_{arom}) 9.02 s (H, $>\text{NH}$). Found, %: C 69.97; H 5.98; N 7.29; S 17.15. $\text{C}_{11}\text{H}_{11}\text{NS}$. Calculated, %: C 69.84; H 5.82; N 7.41; S 16.93.

2,8-Dimethyl-4-quinolyl isothiocyanate (IIIb). Yield 0.94 g (44%), mp 155–157°C, R_f 0.59 (from acetone). IR spectrum, cm^{-1} : 2250–1930 ($-\text{N}=\text{C}=\text{S}$). ^1H NMR spectrum, δ , ppm: 2.22 s (3H, CH_3), 2.70 s (3H, NCCH_3), 6.80 s (H^3 , H_{arom}), 7.2–7.9 m (3H, H_{arom}). Found, %: C 67.15; H 4.78; N 13.27; S 14.84. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{S}$. Calculated, %: C 67.29; H 4.67; N 13.08; S 14.95.

2,8-Dimethyl-4-sulfanylquinoline (IVb). Yield 0.56 g (29.8%), mp 280–281°C, R_f 0.70 (from ethanol–hexane, 2:1). IR spectrum, cm^{-1} : 1240 ($>\text{C}=\text{S}$), 3330 ($>\text{NH}$). ^1H NMR spectrum, δ , ppm: 2.33 s (3H, CH_3), 2.80 s (3H, NCCH_3), 7.10 s (H^3 , H_{arom}), 7.3–8.0 m (3H, H_{arom}), 10.20 s (H, $>\text{NH}$). Found, %: C 70.03; H 6.01; N 7.60; S 16.79. $\text{C}_{11}\text{H}_{11}\text{NS}$. Calculated, %: C 69.84; H 5.82; N 7.41; S 16.93.

2-Methyl-6-methoxy-4-quinolyl isothiocyanate (IIIc). Yield 1.62 g (70.6%), mp 195–200°C, R_f 0.62 (from acetone). IR spectrum, cm^{-1} : 2240–1940 ($-\text{N}=\text{C}=\text{S}$). ^1H NMR spectrum, δ , ppm: 2.65 s (3H, NCCH_3), 4.20 s (3H, OCH_3), 7.0 s (H^3 , H_{arom}), 7.20–8.0 m (3H, H_{arom}). Found, %: C 62.79; H 4.54; N 12.25; S 13.70. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{OS}$. Calculated, %: C 62.61; H 4.35; N 12.17; S 13.91.

2-Methyl-6-methoxy-4-sulfanylquinoline (IVc). Not found.

2-Methyl-8-methoxy-4-quinolyl isothiocyanate (IIId). Yield 0.91 g (39.7%), mp 193–195°C, R_f 0.66 (from acetone). IR spectrum, cm^{-1} : 2250–1930 ($-\text{N}=\text{C}=\text{S}$). ^1H NMR spectrum, δ , ppm: 2.55 s (3H, NCCH_3), 3.90 s (3H, OCH_3), 6.90 s (H^3 , H_{arom}), 7.1–7.9 m (3H, H_{arom}). Found, %: C 62.78; H 4.47; N 12.25; S 14.08. $\text{C}_{12}\text{H}_{10}\text{N}_2\text{OS}$. Calculated, %: C 62.61; H 4.35; N 12.17; S 13.91.

2-Methyl-8-methoxy-4-sulfanylquinoline (IVd). Yield 0.69 g (33.5%), mp 170–174°C, R_f 0.67 (from ethanol–hexane, 2:1). IR spectrum, cm^{-1} : 1220 ($>\text{C}=\text{S}$), 3200 ($>\text{NH}$). ^1H NMR spectrum, δ , ppm: 2.20 s (3H, NCCH_3), 3.20 s (3H, OCH_3), 6.5 s (H^3 , H_{arom}), 6.9–7.7 m (3H, H_{arom}) 11.00 s (H, $>\text{NH}$). Found, %: C 64.52; H 5.58; N 6.70; S 15.77. $\text{C}_{11}\text{H}_{11}\text{NOS}$. Calculated, %: C 64.39; H 5.37; N 6.83; S 15.61.

2-Methyl-6-bromo-4-quinolyl isothiocyanate (IIIe). Yield 0.5 g (18%), mp 190–195°C. IR spectrum, cm^{-1} : 2250–1930 ($-\text{N}=\text{C}=\text{S}$). ^1H NMR spectrum, δ , ppm: 2.60 s (3H, NCCH_3), 6.80 s (H^3 , H_{arom}), 7.0–7.6 m (3H, H_{arom}). Found, %: C 47.50; H 2.70; N 10.21; S 11.29. $\text{C}_{11}\text{H}_7\text{BrN}_2\text{S}$. Calculated, %: C 47.31; H 2.51; N 10.04; S 11.47.

2-Methyl-6-bromo-4-sulfanylquinoline (IVe). Yield 2.29 g (50.6%), mp 225°C, R_f 0.57 (from ethanol–hexane, 1:1). IR spectrum, cm^{-1} : 1225 ($>\text{C}=\text{S}$), 3300 ($>\text{NH}$). ^1H NMR spectrum, δ , ppm: 2.70 s (3H, NCCH_3), 7.0 s (H^3 , H_{arom}), 7.3–8.1 m (3H, H_{arom}) 11.20 s (H, $>\text{NH}$). Found, %: C 47.36; H 3.32; N 5.43; S 12.77. $\text{C}_{10}\text{H}_8\text{BrNS}$. Calculated, %: C 47.24; H 3.15; N 5.51; S 12.60.

2-Methyl-8-chloro-4-quinolyl isothiocyanate (III f). Yield 0.07 g (3%), mp 300°C (decomp.). IR spectrum, cm^{-1} : 2245–1920 ($-\text{N}=\text{C}=\text{S}$). ^1H NMR

spectrum, δ , ppm: 2.40 s (3H, NCCH_3), 6.40 s (H^3 , H_{arom}), 6.8–7.5 m (3H, H_{arom}). Found, %: C 56.13; H 3.12; N 12.10; S 13.78. $\text{C}_{11}\text{H}_7\text{ClN}_2\text{S}$. Calculated, %: C 56.29; H 2.99; N 11.94; S 13.65.

2-Methyl-8-chloro-4-sulfanylquinoline (IV f). Yield 1.36 g (65%), mp 220–223°C, R_f 0.57 (from ethanol–hexane, 1:1). IR spectrum, cm^{-1} : 1215 ($>\text{C}=\text{S}$), 3250 ($>\text{NH}$). ^1H NMR spectrum, δ , ppm: 2.20 s (3H, NCCH_3), 6.45 s (H^3 , H_{arom}), 6.7–7.3 m (3H, H_{arom}) 10.0 s (H, $>\text{NH}$). Found, %: C 57.56; H 4.00; N 6.56; S 15.41. $\text{C}_{10}\text{H}_8\text{ClNS}$. Calculated, %: C 57.28; H 3.82; N 6.68; S 15.27.

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