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Synthesis of 6,8-Substituted 4-(Hydroxyphenylamino)- and 4-(Aminophenylamino)-2-methylquinolines

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Abstract—A procedure has been developed for the synthesis of 4-(hydroxyphenylamino)- and 4-(aminophenylamino)-2-methylquinolines having a substituent in the 6(8)-position of the quinoline ring from the corresponding 4-chloro-2-methylquinolines and *o*-, *m*-, and *p*-aminophenols and *o*-, *m*-, and *p*-phenylenediamines.

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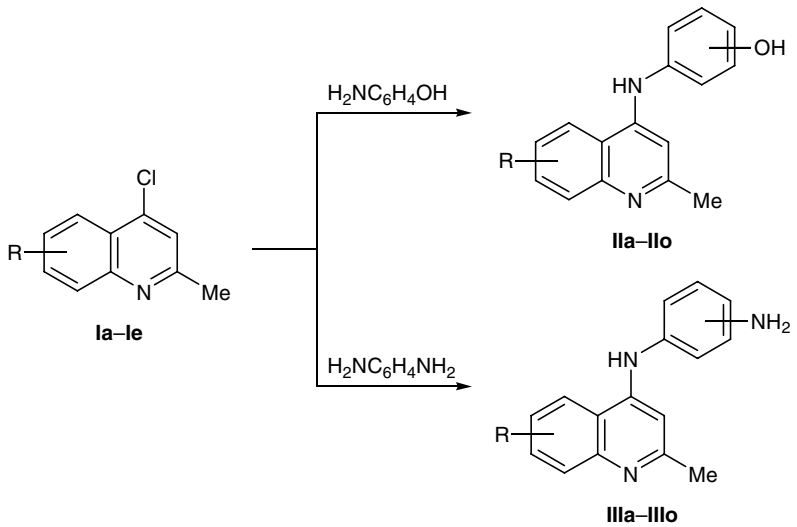
Functionally substituted 4-aminoquinoline derivatives are used as effective medical agents; examples are such drugs as Haloquin, Quingamin, Aminoacrichin, Hydroxychloroquin, etc. [1]. Substituted 4-aminoquinolines inhibit protein kinase enzymes responsible for some cellular activity. High biological activity of these compounds may lead to a number of diseases, including cancer [2–4].

With a view to synthesize new substituted 4-aminoquinoline derivatives, in the present work we examined nucleophilic substitution of the chlorine atom in 6,8-substituted 4-chloro-2-methylquinolines **Ia**–**Ie** by the action of *o*-, *m*-, and *p*-aminophenols and *o*-, *m*-, and *p*-phenylenediamines. Optimal conditions for the reaction were found. The corresponding substituted 4-(2-hydroxyphenylamino)-, 4-(3-hydroxyphenylamino)-, and 4-(4-hydroxyphenylamino)-2-methylquinolines **IIa**–**IIn** and 4-(2-aminophenylamino)-2-methylquinolines **IIIa**, **IIId**, **IIIg**, **IIIj**, and **IIIm** were obtained in high yield by heating equimolar amounts of 4-chloro-2-methylquinolines **Ia**–**Ie** with *o*-, *m*-, and *p*-aminophenols or *o*-phenylenediamine in ethanol in the presence of hydrochloric acid for 6–10 h (Scheme 1). *m*-Phenylenediamine dihydrochloride and *p*-phenylenediamine sulfate reacted with quinolines only at elevated temperature to give, respectively,

Scheme 1.



I, R = H (**a**), 6-Me (**b**), 8-Me (**c**), 6-MeO (**d**), 8-MeO (**e**); **II**, **III**, R = H (**a**–**c**), 6-Me (**d**–**f**), 8-Me (**g**–**i**), 6-MeO (**j**–**l**), 8-MeO (**m**–**o**); **II**, 2-HO (**a**, **d**, **g**, **j**, **m**), 3-HO (**b**, **e**, **h**, **k**, **n**), 4-HO (**c**, **f**, **i**, **l**, **o**); **III**, 2-H_2N (**a**, **d**, **g**, **j**, **m**), 3-H_2N (**b**, **e**, **h**, **k**, **n**), 4-H_2N (**c**, **f**, **i**, **l**, **o**).

4-(3-aminophenylamino)- and 4-(4-aminophenylamino)-2-methylquinolines **IIIb**, **IIIc**, **IIIe**, **IIIf**, **IIIh**–**IIIl**, **IIIn**, and **IIIo** in high yields. The structure of the isolated compounds was confirmed by the ^{1}H NMR data. Preliminary tests showed that some derivatives, in particular 4-(hydroxyphenylamino)-2-methylquinolines, are promising as radioprotective agents; 4-(aminophenylamino)-2-methylquinolines exhibited a medium-strength antibacterial activity.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer using DMSO-d_6 as solvent. The purity of the products was checked by TLC on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

Substituted 4-chloro-2-methylquinolines Ia–Ie were synthesized according to the procedures described in [5, 6] by reaction of phosphoryl chloride with the corresponding 2-methylquinolin-4-ols.

4-Chloro-2-methylquinoline (Ia). mp 43°C [5].

4-Chloro-2,6-dimethylquinoline (Ib). Yield 18.20 g (95%), mp 61–63°C (from aq. EtOH, 1:1). Found, %: C 68.85; H 5.37; Cl 18.41; N 7.40. $C_{11}H_{10}ClN$. Calculated, %: C 68.93; H 5.22; Cl 18.54; N 7.31.

4-Chloro-2,8-dimethylquinoline (Ic). Yield 17.81 g (93%), mp 66–68°C (from aq. EtOH, 1:1). Found, %: C 69.05; H 5.12; Cl 18.62; N 7.27. $C_{11}H_{10}ClN$. Calculated, %: C 68.93; H 5.22; Cl 18.54; N 7.31.

4-Chloro-6-methoxy-2-methylquinoline (Id). mp 98–99°C; published data [6]: mp 100°C.

4-Chloro-8-methoxy-2-methylquinoline (Ie). Yield 19.71 g (95%), mp 70–72°C (from aq. EtOH, 1:1). Found, %: C 63.54; H 4.98; Cl 17.25; N 6.87. $C_{11}H_{10}ClNO$. Calculated, %: C 63.61; H 4.82; Cl 17.11; N 6.75.

Substituted 4-(hydroxyphenylamino)-2-methylquinoline dihydrochlorides IIa–IIn (*general procedure***).** A mixture of 0.01 mol of substituted 4-chloro-2-methylquinoline **Ia**–**Ie**, 1.08 g (0.01 mol) of *o*-, *m*-, or *p*-aminophenol (*p*-aminophenol was used as hydrochloride), and 1 ml of concentrated hydrochloric acid in 50 ml of alcohol was heated for 8–10 h on a water bath. The alcohol was distilled off, the residue was treated with water, the mixture was made alkaline, the resulting solution was filtered, the filtrate was acidified to pH 2–3, and the precipitate was filtered off.

2-(2-Methylquinolin-4-ylamino)phenol dihydrochloride (IIa). Yield 2.71 g (84%), mp 250°C (decomp.), R_f 0.58 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.70 s (3H, CH_3), 6.15 s (1H, H_{arom}), 7.20–8.20 m (8H, H_{arom}), 9.90 s (1H, OH), 10.30 s (1H, NH). Found, %: C 59.51; H 4.87; N 8.81. $C_{16}H_{16}Cl_2N_2O$. Calculated, %: C 59.44; H 4.95; N 8.67.

3-(2-Methylquinolin-4-ylamino)phenol dihydrochloride (IIb). Yield 3.10 g (96%), mp 300°C (decomp.), R_f 0.56 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 6.60 s (1H, H_{arom}), 7.20–8.10 m (8H, H_{arom}), 9.70 s (1H, OH). 10.80 s (1H, NH). Found, %: C 59.32; H 5.10; N 8.53. $C_{16}H_{16}Cl_2N_2O$. Calculated, %: C 59.44; H 4.95; N 8.67.

4-(2-Methylquinolin-4-ylamino)phenol dihydrochloride (IIc). Yield 2.65 g (82%), mp 360°C (decomp.), R_f 0.62 (acidic alcohol). Found, %: C 59.53; H 4.89; N 8.56. $C_{16}H_{16}Cl_2N_2O$. Calculated, %: C 59.44; H 4.95; N 8.67.

2-(2,6-Dimethylquinolin-4-ylamino)phenol dihydrochloride (IId). Yield 2.73 g (81%), mp 190–192°C (decomp.), R_f 0.56 (acidic alcohol). Found, %: C 60.48; H 5.50; N 8.47. $C_{17}H_{18}Cl_2N_2O$. Calculated, %: C 60.53; H 5.34; N 8.31.

3-(2,6-Dimethylquinolin-4-ylamino)phenol dihydrochloride (IIe). Yield 2.97 g (88%), mp 263–270°C (decomp.), R_f 0.49 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.20 s (3H, CH_3), 2.70 s (3H, CH_3), 6.45 s (1H, H_{arom}), 6.90–7.80 m (7H, H_{arom}), 9.70 s (1H, OH), 10.80 s (1H, NH). Found, %: C 60.46; H 5.44; N 8.26. $C_{17}H_{18}Cl_2N_2O$. Calculated, %: C 60.53; H 5.34; N 8.31.

4-(2,6-Dimethylquinolin-4-ylamino)phenol dihydrochloride (IIf). Yield 2.83 g (84%), mp 300°C (decomp.), R_f 0.57 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.75 s (3H, CH_3), 6.50 s (1H, H_{arom}), 7.00–8.10 m (7H, H_{arom}), 9.70 s (1H, OH), 10.80 s (1H, NH). Found, %: C 60.57; H 5.41; N 8.24. $C_{17}H_{18}Cl_2N_2O$. Calculated, %: C 60.53; H 5.34; N 8.31.

2-(2,8-Dimethylquinolin-4-ylamino)phenol dihydrochloride (IIg). Yield 3.07 g (91%), mp 134–138°C (decomp.), R_f 0.56 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.75 s (6H, CH_3), 6.20 s (1H, H_{arom}), 6.95–8.20 m (7H, H_{arom}), 9.90 s (1H, OH), 10.30 s (1H, NH). Found, %: C 60.61; H 5.24; N 8.39. $C_{17}H_{18}Cl_2N_2O$. Calculated, %: C 60.53; H 5.34; N 8.31.

3-(2,8-Dimethylquinolin-4-ylamino)phenol dihydrochloride (IIh). Yield 3.13 g (93%), mp 186–189°C (decomp.), R_f 0.54 (acidic alcohol). Found, %: C 60.63; H 5.28; N 8.40. $C_{17}H_{18}Cl_2N_2O$. Calculated, %: C 60.53; H 5.34; N 8.31.

4-(2,8-Dimethylquinolin-4-ylamino)phenol dihydrochloride (IIi). Yield 3.13 g (93%), mp 197–200°C

(decomp.), R_f 0.59 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.80 s (6H, CH_3), 6.40 s (1H, H_{arom}), 6.95–8.60 m (7H, H_{arom}), 9.70 s (1H, OH), 11.85 s (1H, NH). Found, %: C 60.69; H 5.29; N 8.42. $C_{17}H_{18}Cl_2N_2O$. Calculated, %: C 60.53; H 5.34; N 8.31.

2-(6-Methoxy-2-methylquinolin-4-ylamino)-phenol dihydrochloride (IIj). Yield 3.14 g (89%), mp 192–195°C (decomp.), R_f 0.40 (alcohol). Found, %: C 57.84; H 5.03; N 7.85. $C_{17}H_{18}Cl_2N_2O_2$. Calculated, %: C 57.79; H 5.10; N 7.93.

3-(6-Methoxy-2-methylquinolin-4-ylamino)-phenol dihydrochloride (IIk). Yield 2.86 g (81%), mp 196–198°C (decomp.), R_f 0.42 (alcohol–hexane, 2:1). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 4.00 s (3H, OCH_3), 6.20 s (1H, H_{arom}), 6.90–8.20 m (7H, H_{arom}), 9.90 s (1H, OH), 10.30 s (1H, NH). Found, %: C 57.67; H 5.20; N 8.01. $C_{17}H_{18}Cl_2N_2O_2$. Calculated, %: C 57.79; H 5.10; N 7.93.

4-(6-Methoxy-2-methylquinolin-4-ylamino)-phenol dihydrochloride (IIl). Yield 2.93 g (83%), mp 335–337°C (decomp.), R_f 0.59 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 4.00 s (3H, OCH_3), 6.40 s (1H, H_{arom}), 6.95–8.20 m (7H, H_{arom}), 9.50 s (1H, OH), 10.40 s (1H, NH). Found, %: C 57.81; H 4.98; N 7.87. $C_{17}H_{18}Cl_2N_2O_2$. Calculated, %: C 57.79; H 5.10; N 7.93.

2-(8-Methoxy-2-methylquinolin-4-ylamino)-phenol dihydrochloride (IIm). Yield 2.97 g (84%), mp 164–165°C (decomp.), R_f 0.60 (alcohol). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 4.00 s (3H, OCH_3), 6.60–8.00 m (7H, H_{arom}), 9.20 s (1H, OH), 10.00 s (1H, NH). Found, %: C 57.68; H 5.21; N 7.98. $C_{17}H_{18}Cl_2N_2O_2$. Calculated, %: C 57.79; H 5.10; N 7.93.

3-(8-Methoxy-2-methylquinolin-4-ylamino)-phenol dihydrochloride (IIn). Yield 3.25 g (92%), mp 173–174°C (decomp.), R_f 0.60 (alcohol–hexane, 2:1). Found, %: C 57.72; H 5.17; N 7.88. $C_{17}H_{18}Cl_2N_2O_2$. Calculated, %: C 57.79; H 5.10; N 7.93.

4-(8-Methoxy-2-methylquinolin-4-ylamino)-phenol dihydrochloride (IIo). Yield 3.04 g (86%), mp 193–200°C (decomp.), R_f 0.58 (acidic alcohol). Found, %: C 57.84; H 5.03; N 7.85. $C_{17}H_{18}Cl_2N_2O_2$. Calculated, %: C 57.79; H 5.10; N 7.93.

Substituted *N*-(2-aminophenyl)-2-methylquinolin-4-amines IIIa, IIId, IIIg, IIIj, and IIIm (*general procedure*). A mixture of 0.01 mol of substituted 4-chloro-2-methylquinoline **Ia**–**Ie**, 1.2 g (0.01 mol) of *o*-phenylenediamine, and 1 ml of concentrated hydrochloric acid in 50 ml of alcohol was heated for 6–8 h on a water bath. The alcohol was distilled off, the residue was treated with water and acidified to pH 3, the solution was filtered, the filtrate was made alkaline (pH 9), and the precipitate was filtered off.

***N*-(2-Aminophenyl)-2-methylquinolin-4-amine (IIIa).** Yield 2.09 g (84%), mp 117–120°C, R_f 0.51 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 5.10 s (2H, NH_2), 6.20 s (1H, H_{arom}), 7.20–8.10 m (8H, H_{arom}), 10.20 s (1H, NH). Found, %: C 77.20; H 5.98; N 16.94. $C_{16}H_{15}N_3$. Calculated, %: C 77.11; H 6.02; N 16.87.

***N*-(2-Aminophenyl)-2,6-dimethylquinolin-4-amine (IIId).** Yield 2.10 g (80%), mp 120–121°C, R_f 0.68 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 2.70 s (3H, CH_3), 5.20 s (2H, NH_2), 6.40 s (H_{arom}), 7.00–8.10 m (7H, H_{arom}), 8.90 s (1H, NH). Found, %: C 77.67; H 6.38; N 16.03. $C_{17}H_{17}N_3$. Calculated, %: C 77.57; H 6.46; N 15.97.

***N*-(2-Aminophenyl)-2,8-dimethylquinolin-4-amine (IIIg).** Yield 2.21 g (84%), mp 74–76°C, R_f 0.56 (acidic alcohol). Found, %: C 77.49; H 6.55; N 15.88. $C_{17}H_{17}N_3$. Calculated, %: C 77.57; H 6.46; N 15.97.

***N*-(2-Aminophenyl)-6-methoxy-2-methylquinolin-4-amine (IIIj).** Yield 2.29 g (82%), mp 122–125°C, R_f 0.62 (acidic alcohol). Found, %: C 73.03; H 6.15; N 15.13. $C_{17}H_{17}N_3O$. Calculated, %: C 73.12; H 6.09; N 15.05.

***N*-(2-Aminophenyl)-8-methoxy-2-methylquinolin-4-amine (IIIm).** Yield 2.48 g (89%), mp 152–154°C, R_f 0.48 (acidic alcohol). Found, %: C 73.20; H 6.03; N 15.13. $C_{17}H_{17}N_3O$. Calculated, %: C 73.12; H 6.09; N 15.05.

Substituted *N*-(3-aminophenyl)-2-methylquinolin-4-amines IIIb, IIIe, IIIh, IIIk, and IIIn (*general procedure*). A mixture of 0.01 mol of substituted 4-chloro-2-methylquinoline **Ia**–**Ie** and 1.81 g (0.01 mol) of *m*-phenylenediamine dihydrochloride in 50 ml of alcohol was heated for 8–10 h on a water bath. The alcohol was distilled off, the residue was treated with water and acidified to pH 3, the solution was filtered, the filtrate was made alkaline (pH 9), and the precipitate was filtered off.

***N*-(3-Aminophenyl)-2-methylquinolin-4-amine (IIIb).** Yield 2.12 g (85%), mp 151–152°C, R_f 0.51 (acidic alcohol). Found, %: C 77.05; H 6.10; N 16.78. $C_{16}H_{15}N_3$. Calculated, %: C 77.11; H 6.02; N 16.87.

***N*-(3-Aminophenyl)-2,6-dimethylquinolin-4-amine (IIIe).** Yield 2.55 g (97%), mp 176–178°C, R_f 0.53 (acidic alcohol). Found, %: C 77.65; H 6.40; N 15.89. $C_{17}H_{17}N_3$. Calculated, %: C 77.57; H 6.46; N 15.97.

***N*-(3-Aminophenyl)-2,8-dimethylquinolin-4-amine (IIIh).** Yield 2.31 g (88%), mp 195–198°C, R_f 0.46 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.75 s (6H, CH_3), 5.20 s (2H, NH_2), 6.10 s (1H, H_{arom}), 6.90–7.80 m (7H, H_{arom}), 8.30 s (1H, NH). Found, %: C 77.51; H 6.53; N 16.07. $C_{17}H_{17}N_3$. Calculated, %: C 77.57; H 6.46; N 15.97.

***N*-(3-Aminophenyl)-6-methoxy-2-methylquinolin-4-amine (IIIj).** Yield 2.37 g (85%), mp 223–225°C, R_f 0.69 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 3.90 s (3H, OCH_3), 5.30 s (2H, NH_2), 6.90 s (1H, H_{arom}), 7.20–8.00 m (7H, H_{arom}), 8.40 s (1H, NH). Found, %: C 73.01; H 6.17; N 14.97. $C_{17}H_{17}N_3O$. Calculated, %: C 73.12; H 6.09; N 15.05.

***N*-(3-Aminophenyl)-8-methoxy-2-methylquinolin-4-amine (IIIm).** Yield 2.62 g (94%), mp 194–196°C, R_f 0.67 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.75 s (3H, CH_3), 4.00 s (3H, OCH_3), 5.40 s (2H, NH_2), 6.95 s (1H, H_{arom}), 7.20–8.00 m (7H, H_{arom}), 8.50 s (1H, NH). Found, %: C 73.04; H 6.17; N 14.89. $C_{17}H_{17}N_3O$. Calculated, %: C 73.12; H 6.09; N 15.05.

Substituted *N*-(4-aminophenyl)-2-methylquinolin-4-amines IIIc, IIIf, IIIi, IIIl, and IIIo (*general procedure*). A mixture of 0.01 mol of substituted 4-chloro-2-methylquinoline **Ia**–**Ie** and 2.06 g (0.01 mol) of *p*-phenylenediamine sulfate in 50 ml of alcohol was heated for 8–10 h on a water bath. The alcohol was distilled off, the residue was treated with water and acidified to pH 3, the solution was filtered, the filtrate was made alkaline (pH 9), and the precipitate was filtered off.

***N*-(4-Aminophenyl)-2-methylquinolin-4-amine (IIIc).** Yield 2.27 g (91%), mp 298-299°C, R_f 0.48 (acidic alcohol). Found, %: C 77.19; H 5.95; N 16.95. $C_{16}H_{15}N_3$. Calculated, %: C 77.11; H 6.02; N 16.87.

***N*-(4-Aminophenyl)-2,6-dimethylquinolin-4-amine (IIIf).** Yield 2.58 g (98%), mp 262–263°C, R_f 0.46 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.75 s (3H, CH_3), 5.15 s (2H, NH_2), 6.45 s (1H, H_{arom}), 7.10–8.15 m (7H, H_{arom}), 9.00 s (1H, NH). Found, %: C 77.48; H 6.52; N 15.90. $C_{17}H_{17}N_3$. Calculated, %: C 77.57; H 6.46; N 15.97.

***N*-(4-Aminophenyl)-2,8-dimethylquinolin-4-amine (IIIi).** Yield 2.16 g (82%), mp 226–227°C, R_f 0.56 (acidic alcohol). ^{1}H NMR spectrum, δ, ppm: 2.80 s (6H, CH_3), 5.00 s (2H, NH_2), 6.20 s (1H, H_{arom}), 7.00–8.00 m (7H, H_{arom}), 8.40 s (1H, NH). Found, %: C 77.64; H 6.37; N 16.04. $C_{17}H_{17}N_3$. Calculated, %: C 77.57; H 6.46; N 15.97.

***N*-(4-Aminophenyl)-6-methoxy-2-methylquinolin-4-amine (IIIk).** Yield 2.71 g (97%), mp 150–153°C, R_f 0.60 (acidic alcohol). Found, %: C 73.21; H 6.02; N 15.16. $C_{17}H_{17}N_3O$. Calculated, %: C 73.12; H 6.09; N 15.05.

***N*-(4-Aminophenyl)-8-methoxy-2-methylquinolin-4-amine (IIIo).** Yield 2.62 g (94%), mp 212–213°C, R_f 0.40 (acidic alcohol). Found, %: C 73.19; H 6.01 N 15.14. $C_{17}H_{17}N_3O$. Calculated, %: C 73.12; H 6.09; N 15.05.

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