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Synthesis and Some Transformations of 6(8)-Substituted 4-Hydrazino-2-methylquinolines

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Abstract—6(8)-Substituted 4-hydrazino-2-methylquinolines were synthesized by reaction of the corresponding 4-chloro-2-methylquinolines with hydrazine hydrate. Reactions of the title compounds with ethyl acetoacetate and acetone gave 2,4-dimethyl-1*H*-pyrrolo[3,2-*c*]quinolines and 4-(5-ethoxy-3-methyl-1*H*-pyrazol-1-yl)-2-methylquinolines.

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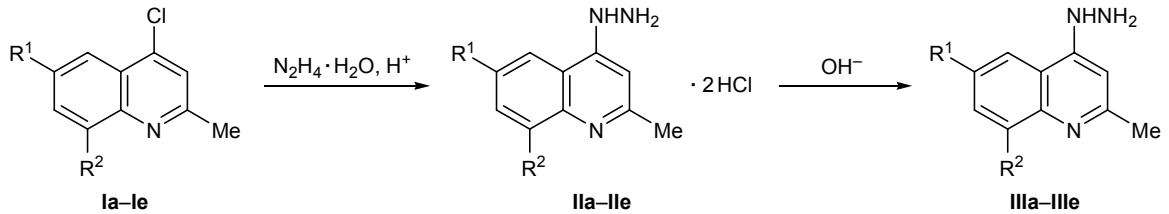
Azoquinolines constitute a class of organic compounds that exhibit high biological activity and low toxicity. Azoquinoline-containing drugs are used in the therapy of bacterial and fungal infections and tumors [1–5]. With a view to obtain quinoline derivatives with pyrrole and pyrazole rings, we examined reactions of 6(8)-substituted 4-chloro-2-methylquinolines **Ia**–**Ie** [6, 7] with hydrazine hydrate. Optimal conditions were found for that reaction. The corresponding substituted 4-hydrazino-2-methylquinolines **IIa**–**IIe** dihydrochlorides were obtained in high yields by heating the reactants at a ratio of 1 : 1.2 in ethanol in the presence of a catalytic amount of hydrochloric acid over a period of 15 h (Scheme 1). The concentration of hydrogen chloride in the products was determined by titration. Treatment of **IIa**–**IIe** with alkali gave the corresponding free bases **IIIa**–**IIIe**.

We made an attempt to synthesize fused pyrrolo- or pyrazoloquinolines via reactions of compounds **IIIa**–**IIIe** with ethyl acetoacetate under different conditions. Heating of equimolar amounts of the reactants in ethanol in the presence of sulfuric acid resulted in the formation of substituted 2,4-dimethyl-1*H*-pyrolo-[3,2-*c*]quinolines **IVa**–**IVe** (Scheme 2). Presumably, the reaction begins with formation of intermediate hydrazones which, like aromatic hydrazo compounds, undergo concerted [3,3]-sigmatropic shift. The subsequent hydrolysis of the ester group in ethyl 2,4-dimethyl-1*H*-pyrrolo[3,2-*c*]quinoline-3-carboxylates and decarboxylation yields compounds **IVa**–**IVe**.

Compounds **IVa**–**IVe** were also synthesized by condensation of hydrazinoquinolines **IIIa**–**IIIe** with acetone in ethanol in the presence of sulfuric acid. This reaction involved intermediate formation of analogous hydrazones which underwent similar rearrangement (Scheme 3). It was interesting that compounds **IIIa**–**IIIe** reacted with ethyl acetoacetate in ethanol in the absence of sulfuric acid to give the corresponding substituted 4-(5-ethoxy-3-methyl-1*H*-pyrazol-1-yl)-2-methylquinolines **Va**–**Ve** (Scheme 4).

Scheme 1.

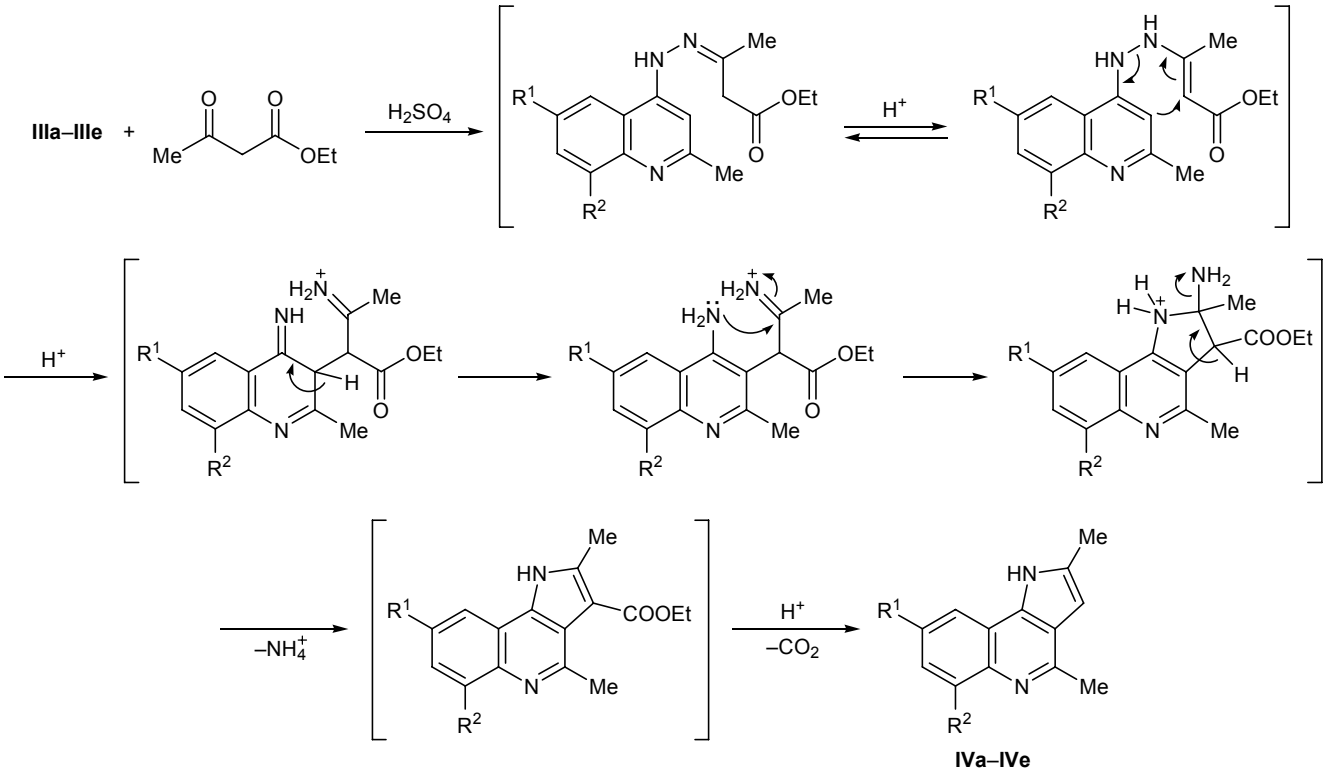


Ia–Ie **IIa–IIe** **IIIa–IIIe**

$R^1 = R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$ (**b**); $R^1 = H$, $R^2 = Me$ (**c**); $R^1 = MeO$, $R^2 = H$ (**d**); $R^1 = H$, $R^2 = MeO$ (**e**).

† Deceased.

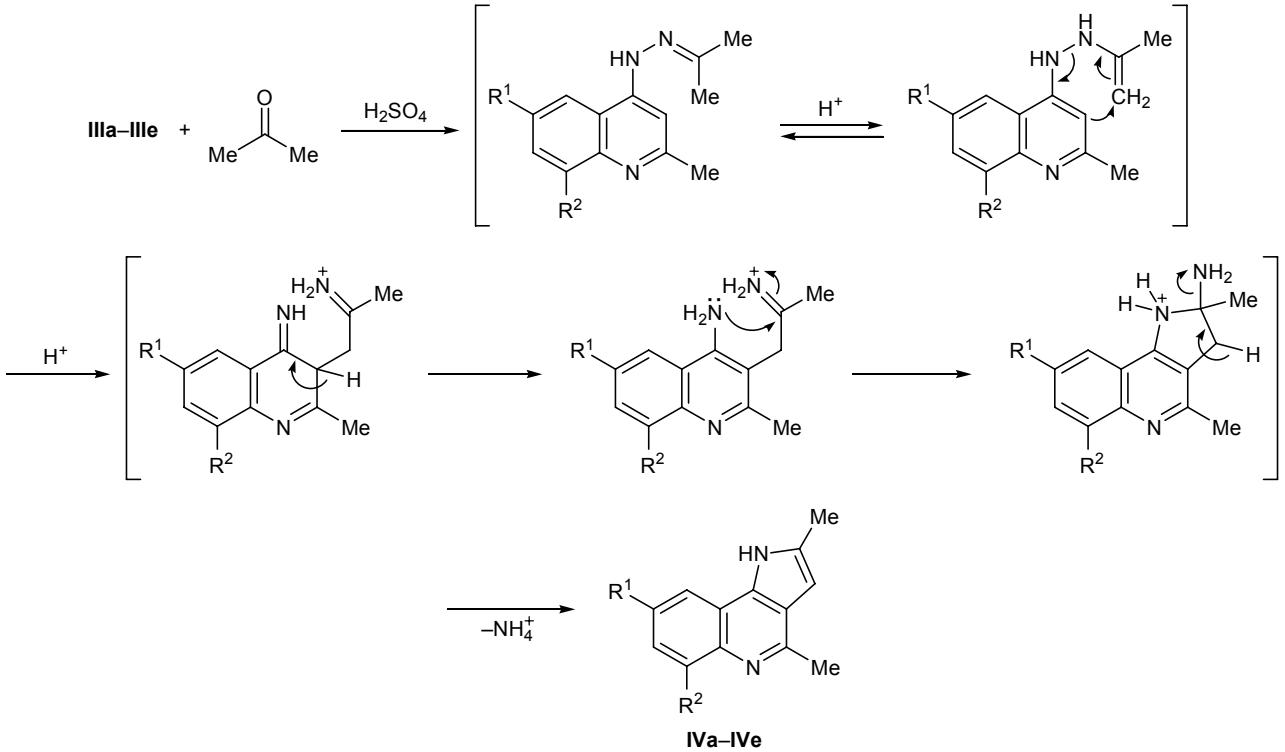
Scheme 2.



IVa–IVe

$R^1 = R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$ (**b**); $R^1 = H$, $R^2 = Me$ (**c**); $R^1 = MeO$, $R^2 = H$ (**d**); $R^1 = H$, $R^2 = MeO$ (**e**).

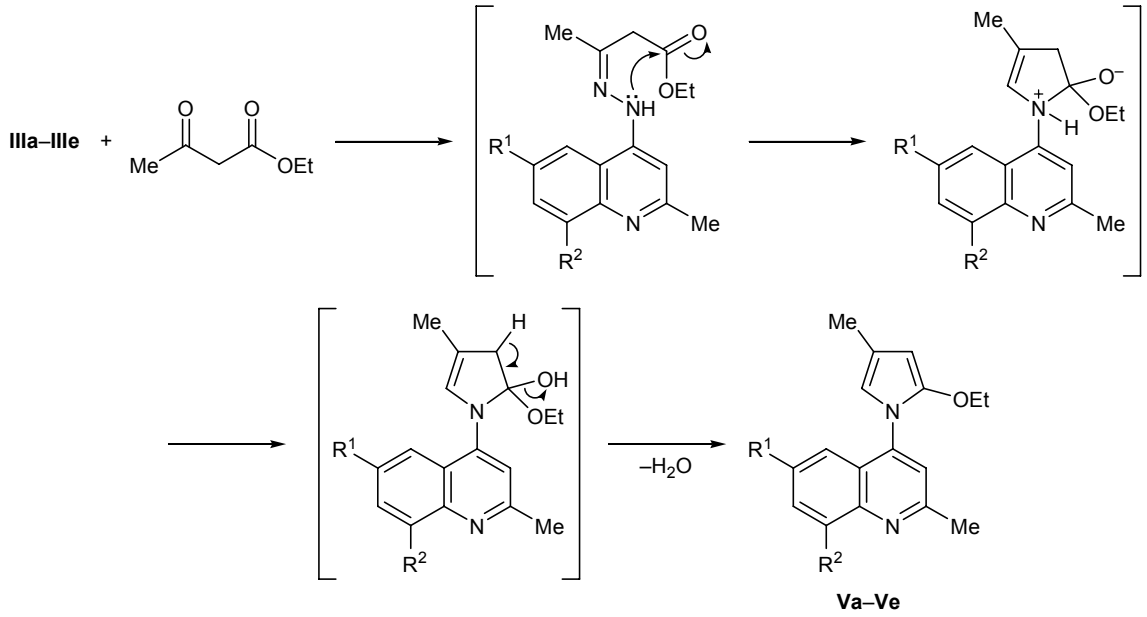
Scheme 3.



IVa–IVe

$R^1 = R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$ (**b**); $R^1 = H$, $R^2 = Me$ (**c**); $R^1 = MeO$, $R^2 = H$ (**d**); $R^1 = H$, $R^2 = MeO$ (**e**).

Scheme 4.



$R^1 = R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$ (**b**); $R^1 = H$, $R^2 = Me$ (**c**); $R^1 = MeO$, $R^2 = H$ (**d**); $R^1 = H$, $R^2 = MeO$ (**e**).

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Mercury-300 spectrometer using DMSO-d_6 as solvent. The IR spectra were obtained on a UR-20 spectrometer from samples dispersed in mineral oil. The purity of the products was checked by thin-layer chromatography on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

4-Hydrazino-2-methylquinoline dihydrochlorides IIa–IIe (*general procedure*). A mixture of 10 mmol of 4-chloro-2-methylquinoline **Ia**–**Ie** [6, 7], 0.71 ml (12 mmol) of 85% hydrazine hydrate, and 1 ml of concentrated hydrochloric acid in 15 ml of ethanol was heated for 15 h on a water bath. The mixture was cooled, and the precipitate was filtered off and washed with alcohol.

4-Hydrazino-2-methylquinoline dihydrochloride (IIa). Yield 1.80 g (87%), mp 346–347°C (decomp.), R_f 0.50 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3325, 3200 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.50 s (3H, NCH_3), 6.60 s (1H, H_{arom}), 7.20–9.00 m (7H, $4H_{arom}$, NH, NH_2). Found, %: C 48.61; H 5.40; N 17.18. $C_{10}H_{13}Cl_2N_3$. Calculated, %: C 48.78; H 5.28; N 17.07.

4-Hydrazino-2,6-dimethylquinoline dihydrochloride (IIb). Yield 2.47 g (95%), mp 334–336°C, R_f 0.49 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3235, 3185 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, 6-CH_3), 2.60 s (3H, 2-CH_3), 6.65 s (1H, H_{arom}), 7.10–8.80 m (6H, H_{arom}, NH, NH_2). Found, %: C 50.89; H 5.65; N 16.39. $C_{11}H_{15}Cl_2N_3$. Calculated, %: C 50.76; H 5.77; N 16.15.

4-Hydrazino-2,8-dimethylquinoline dihydrochloride (IIc). Yield 2.34 g (90%), mp 321–323°C, R_f 0.60 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3400, 3260 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, 8-CH_3), 2.75 s (3H, 2-CH_3), 6.40 s (1H, H_{arom}), 7.20–8.20 m (5H, H_{arom}, NH_2), 12.40–13.40 s (NH, HCl). Found, %: C 50.88; H 5.65; N 16.00. $C_{11}H_{15}Cl_2N_3$. Calculated, %: C 50.76; H 5.77; N 16.15.

4-Hydrazino-6-methoxy-2-methylquinoline dihydrochloride (IId). Yield 2.62 g (95%), mp 312–313°C, R_f 0.50 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3380, 3245 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.60 s (3H, 2-CH_3), 4.00 s (3H, OCH_3), 6.20 s (1H, H_{arom}), 7.60–8.90 m (5H, H_{arom}, NH_2), 10.62 s (NH, HCl). Found, %: C 47.71; H 5.51; N 15.31. $C_{11}H_{15}Cl_2N_3O$. Calculated, %: C 47.83; H 5.43; N 15.22.

4-Hydrazino-8-methoxy-2-methylquinoline dihydrochloride (IIe). Yield 2.54 g (92%), mp 298–299°C, R_f 0.51 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3340, 3250 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.55 s (3H, 2-CH_3), 3.93 s (3H, OCH_3), 6.40 s ($1H_{arom}$), 7.20–8.10 m (5H, H_{arom}, NH_2), 12.00 s (NH,

HCl). Found, %: C 47.64; H 5.61; N 15.31. $C_{11}H_{15}Cl_2N_3O$. Calculated, %: C 47.83; H 5.43; N 15.22.

4-Hydrazino-2-methylquinolines IIIa–IIIe (*general procedure*). 4-Hydrazino-2-methylquinoline dihydrochloride **IIa–IIe**, 1 mmol, was dissolved in water, the solution was filtered and adjusted to pH 9, and the precipitate was filtered off.

4-Hydrazino-2-methylquinoline (IIIa). Yield 1.76 g (92%), mp 275°C (decomp.), R_f 0.52 (alcohol–hexane, 3:1). IR spectrum, ν, cm^{-1}: 3400, 3260 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 6.40 s (1H, H_{arom}), 7.30–8.20 m (6H, H_{arom}, NH_2), 11.90 s (1H, NH). Found, %, C 69.24; H 6.49; N 24.35. $C_{10}H_{11}N_3$. Calculated, %: C 69.36; H 6.36; N 24.28.

4-Hydrazino-2,6-dimethylquinoline (IIIb). Yield 1.83 g (98%), mp 242°C (decomp.), R_f 0.52 (alcohol–toluene, 1:2). IR spectrum, ν, cm^{-1}: 3450, 3180 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, 6-CH_3), 2.65 s (3H, 2-CH_3), 6.40 s (1H, H_{arom}), 7.40–8.50 m (5H, H_{arom}, NH_2), 9.70–10.50 s (1H, NH). Found, %: C 70.72; H 6.79; N 22.34. $C_{11}H_{13}N_3$. Calculated, %: C 70.59; H 6.95; N 22.46.

4-Hydrazino-2,8-dimethylquinoline (IIIc). Yield 1.80 g (96%), mp 224–226°C (decomp.), R_f 0.50 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3295, 3155 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.45 s (3H, 8-CH_3), 2.75 s (3H, 2-CH_3), 6.45 s (1H, H_{arom}), 7.60–8.83 m (5H, H_{arom}, NH_2), 9.30–10.62 d (1H, NH). Found, %: C 70.71; H 6.84; N 22.59. $C_{11}H_{13}N_3$. Calculated, %: C 70.59; H 6.95; N 22.46.

4-Hydrazino-6-methoxy-2-methylquinoline (IIId). Yield 1.97 g (97%), mp 218°C (decomp.), R_f 0.60 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3325, 3220 (NH, NH_2). ^1H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 4.00 s (3H, OCH_3), 6.40 s (1H, H_{arom}), 7.30–8.90 m (6H, H_{arom}, NH, NH_2). Found, %: C 65.21; H 6.19; N 20.80. $C_{11}H_{13}N_3O$. Calculated, %: C 65.02; H 6.40; N 20.69.

4-Hydrazino-8-methoxy-2-methylquinoline (IIIe). Yield 1.89 g (93%), mp 301°C (decomp.), R_f 0.53 (alcohol–toluene, 1:1). ^1H NMR spectrum, δ, ppm: 2.53 s (3H, CH_3), 3.93 s (3H, OCH_3), 6.20 s (1H, H_{arom}), 7.40–8.90 m (6H, H_{arom}, NH, NH_2). Found, %: C 64.87; H 6.57; N 20.53. $C_{11}H_{13}N_3O$. Calculated, %: C 65.02; H 6.40; N 20.69.

2,4-Dimethyl-1*H*-pyrrolo[3,2-*c*]quinolines IVa–IVd (*general procedure*). *a*. A mixture of 2 mmol of substituted 4-hydrazino-2-methylquinoline **IIIa–IIIe**, 0.26 ml (2 mmol) of ethyl acetoacetate, 1 ml of ethanol, and 0.2 ml of concentrated sulfuric acid was heated for 10–12 h on a water bath. The solvent was distilled off, the residue was treated with water, the aqueous phase was filtered, the filtrate was adjusted to pH 9, and the precipitate was filtered off.

b. A mixture of 2 mmol of compound **IIIa–IIIe**, 0.3 ml of acetone, 1 ml of ethanol, and 0.2 ml of concentrated sulfuric acid was heated for 10–12 h on a water bath. The mixture was then treated as described above in *a*. Samples of compounds **IVa–IVe** synthesized according to the two methods showed no depression of the melting point on mixing.

2,4-Dimethyl-1*H*-pyrrolo[3,2-*c*]quinoline (IVa). Yield 0.28 g (72%, *a*, 0.34 g (88%, *b*), mp 155–156°C, R_f 0.56 (alcohol–hexane, 2:1). IR spectrum: ν 3220 cm^{-1} (NH). ^1H NMR spectrum, δ, ppm: 2.80 s (3H, 4-CH_3), 3.00 s (3H, 2CH_3), 6.70 s (1H, H_{arom}), 7.30–8.30 m (4H, H_{arom}), 8.80 s (1H, NH). Found, %: C 79.64; H 6.04; N 14.39. $C_{13}H_{12}N_2$. Calculated, %: C 79.59; H 6.12; N 14.28.

2,4,8-Trimethyl-1*H*-pyrrolo[3,2-*c*]quinoline (IVb). Yield 0.35 g (83%, *a*), 0.29 g (68%, *b*), mp 252°C, R_f 0.63 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3340, 3185 (NH). ^1H NMR spectrum, δ, ppm: 2.45 s (3H, 8-CH_3), 2.70 s (3H, 4-CH_3), 3.00 s (3H, 2-CH_3), 6.80 s (1H, H_{arom}), 7.80–8.80 m (3H, H_{arom}), 10.15 s (1H, NH). Found, %: C 80.21; H 6.59; N 13.45. $C_{14}H_{14}N_2$. Calculated, %: C 80.00; H 6.67; N 13.33.

2,4,6-Trimethyl-1*H*-pyrrolo[3,2-*c*]quinoline (IVc). Yield 0.30 g (70%, *a*), 0.21 g (50%, *b*), mp 147–149°C, R_f 0.58 (alcohol–toluene, 1:1). ^1H NMR spectrum, δ, ppm: 2.50 s (3H, 6-CH_3), 2.70 s (3H, 4-CH_3), 3.05 s (3H, 2-CH_3), 6.70 s (1H, H_{arom}), 7.35–8.40 m (3H, H_{arom}), 11.85 s and 12.45 s (1H, NH). Found, %: C 79.83; H 6.78; N 13.19. $C_{14}H_{14}N_2$. Calculated, %: C 80.00; H 6.67; N 13.33.

8-Methoxy-2,4-dimethyl-1*H*-pyrrolo[3,2-*c*]-quinoline (IVd). Yield 0.33 g (73%, *a*), 0.30 g (65%, *b*), mp 224–225°C, R_f 0.59 (alcohol–toluene, 1:1). ^1H NMR spectrum, δ, ppm: 2.55 s (3H, 4CH_3), 3.10 s (3H, 2-CH_3), 4.00 s (3H, OCH_3), 6.80 s (1H, H_{arom}), 7.30–8.40 m (3H, H_{arom}), 10.90 s and 11.85 s (1H, NH). Found, %: C 74.19; H 6.31; N 12.45. $C_{14}H_{14}N_2O$. Calculated, %: C 74.34; H 6.19; N 12.39.

6-Methoxy-2,4-dimethyl-1*H*-pyrrolo[3,2-*c*]quinoline (IVe). Yield 0.30 g (66%, *a*), 0.24 g (52%, *b*), mp 311°C, R_f 0.58 (alcohol–toluene, 1:1). IR spectrum, ν, cm^{-1}: 3340, 3185 (NH). ^1H NMR spectrum, δ,

ppm: 2.65 s (3H, 4-CH_3), 3.00 s (3H, 2-CH_3), 4.00 s (3H, OCH_3), 6.95 s (1H, H_{arom}), 7.20–8.50 m (3H, H_{arom}), 10.50 s and 12.20 s (1H, NH). Found, %: C 80.21; H 6.59; N 13.45. $C_{14}H_{14}N_2O$. Calculated, %: C 74.34; H 6.19; N 12.39.

Substituted 4-(5-ethoxy-3-methyl-1*H*-pyrazol-1-yl)-2-methylquinolines Va–Ve (*general procedure*). A mixture of 2 mmol of compound **IIIa**–**IIIe**, 0.26 ml (2 mmol) of ethyl acetoacetate, and 25 ml of ethanol was heated for 12 h on a water bath. The solvent was distilled off, the residue was treated with water, the solution was filtered, the filtrate was neutralized to pH 7, and the precipitate was filtered off.

4-(5-Ethoxy-3-methyl-1*H*-pyrazol-1-yl)-2-methylquinoline (Va). Yield 0.39 g (74%), mp 195°C, R_f 0.48 (alcohol–hexane, 3:1). ^{1}H NMR spectrum, δ, ppm: 1.55 (3H, $CH_2C\mathbf{H}_3$), 2.75 s (3H, CH_3), 2.80 s (3H, CH_3), 4.22 q (2H, OCH_2), 6.62 s (1H, H_{arom}), 7.20–8.00 m (4H, H_{arom}). Found, %: C 71.79; H 6.50; N 15.84. $C_{16}H_{17}N_3O$. Calculated, %: C 71.91; H 6.37; N 15.73.

4-(5-Ethoxy-3-methyl-1*H*-pyrazol-1-yl)-2,6-dimethylquinoline (Vb). Yield 0.32 g (55%), mp 245°C, R_f 0.61 (alcohol–toluene, 1:1). ^{1}H NMR spectrum, δ, ppm: 1.55 t (3H, $CH_2C\mathbf{H}_3$), 2.35 s (3H, CH_3), 2.60 s (3H, CH_3), 2.75 s (3H, CH_3), 4.25 q (2H, OCH_2), 6.65 s (1H, H_{arom}), 7.20–8.00 m (3H, H_{arom}). Found, %: C 72.45; H 6.87; N 15.08. $C_{17}H_{19}N_3O$. Calculated, %: C 72.59; H 6.76; N 14.95.

4-(5-Ethoxy-3-methyl-1*H*-pyrazol-1-yl)-2,8-dimethylquinoline (Vc). Yield 0.25 g (45%), mp 198–199°C, R_f 0.60 (alcohol–toluene, 1:1). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, $CH_2C\mathbf{H}_3$), 2.30 s (3H, CH_3), 2.70 s (3H, CH_3), 2.85 s (3H, CH_3), 4.20 q (2H, OCH_2), 6.60 s (1H, H_{arom}), 7.35–8.25 m (3H, H_{arom}). Found, %: C 72.41; H 6.89; N 15.07. $C_{17}H_{19}N_3O$. Calculated, %: C 72.59; H 6.76; N 14.95.

4-(5-Ethoxy-3-methyl-1*H*-pyrazol-1-yl)-6-methoxy-2-methylquinoline (Vd). Yield 0.30 g (50%), mp 188°C, R_f 0.59 (alcohol–toluene, 1:1). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, $CH_2C\mathbf{H}_3$), 2.65 s (3H, CH_3), 2.80 s (3H, CH_3), 3.95 (3H, OCH_3), 4.30 q (2H, OCH_2), 6.60 s (1H, H_{arom}), 7.30–8.10 m (3H, H_{arom}). Found, %: C 68.56; H 6.55; N 14.02. $C_{17}H_{19}N_3O_2$. Calculated, %: C 68.67; H 6.40; N 14.14.

4-(5-Ethoxy-3-methyl-1*H*-pyrazol-1-yl)-8-methoxy-2-methylquinoline (Ve). Yield 0.31 g (51%), mp 322°C, R_f 0.47 (alcohol–toluene, 1:1). ^{1}H NMR spectrum, δ, ppm: 1.25 t (3H, $CH_2C\mathbf{H}_3$), 2.60 s (3H, CH_3), 2.85 s (3H, CH_3), 4.00 s (3H, OCH_3), 4.35 q (2H, OCH_2), 6.65 s (1H, H_{arom}), 7.40–8.36 m (3H, H_{arom}). Found, %: C 68.81; H 6.27; N 14.30. $C_{17}H_{19}N_3O_2$. Calculated, %: C 68.67; H 6.40; N 14.14.

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