ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 12, pp. 1851–1853. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © I.L. Aleksanyan, L.P. Hambardzumyan, 2013, published in Zhurnal Organicheskoi Khimii, 2013, Vol. 49, No. 12, pp. 1866–1868.

SHORT COMMUNICATIONS

Synthesis and Transformations of 2-(4-Ethoxycarbonylphenylamino)- and 2-(2-Carboxyphenylamino)-4-methylquinolines

I. L. Aleksanyan and L. P. Hambardzumyan

Yerevan State University, ul. Aleka Manukyana 1, Yerevan, 0025 Armenia
e-mail: ialeksanyan@ysu.am

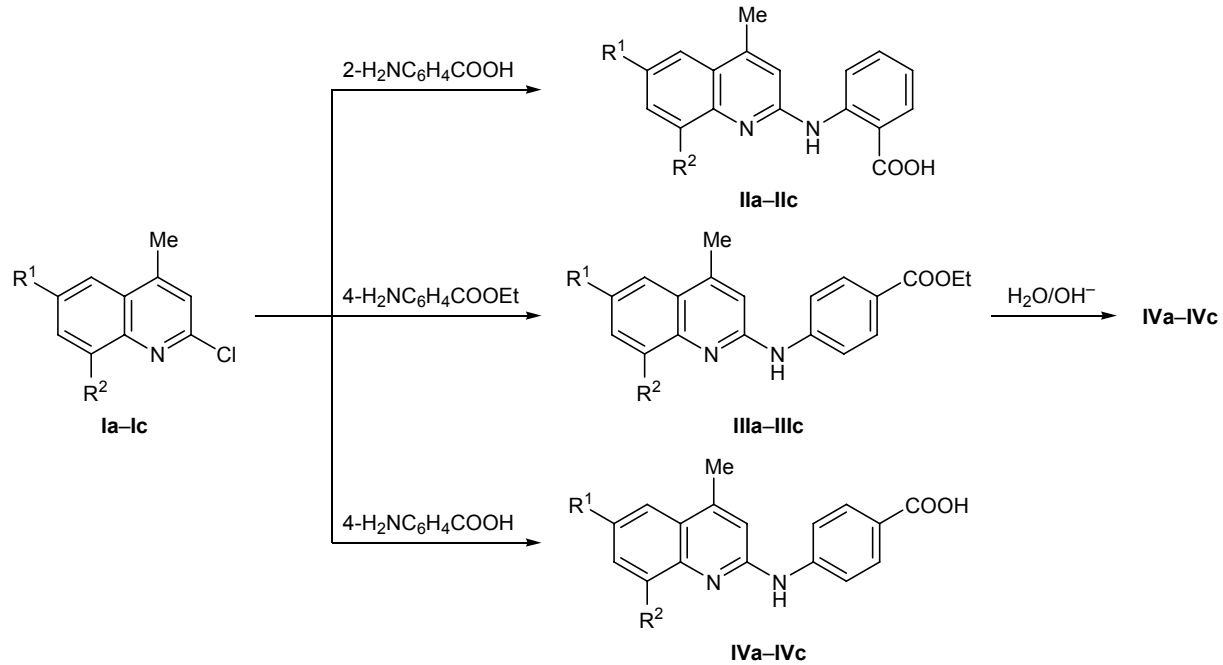
Received November 19, 2012

DOI: 10.1134/S1070428013120270

Many quinoline derivatives are known as efficient fluorophores [1] and are widely used in biochemistry and medicine for studying various biological systems. Nowadays, much attention is given to DNA fluorophores based on fused aromatic systems containing two and more rings (preferably five- or six-membered) and at least one heteroatom. Nevertheless, search for new more sensitive and selective compounds remains important [2]. Quinoline derivatives, in particular aminoquinolines, are also promising as potential antioxidants and radioprotectors [3].

In view of the above stated, in the present work we studied reactions of 2-chloro-4-methylquinolines with 2- and 4-aminobenzoic acids and ethyl 4-aminobenzoate to obtain new quinoline derivatives. By heating 2-chloro-4-methylquinolines **Ia**–**Ic** with 2-aminobenzoic acid or ethyl 4-aminobenzoate at a ratio of 1:1.1 in ethanol in the presence of HCl for 9–15 h we synthesized the corresponding 2-(2-carboxyphenylamino)- and 2-(4-ethoxycarbonylphenylamino)-4-methylquinolines **IIa**–**IIc** and **IIIa**–**IIIc**, respectively, in high yields (Scheme 1). Alkaline hydrolysis of esters **IIIa**–**IIIc**

Scheme 1.

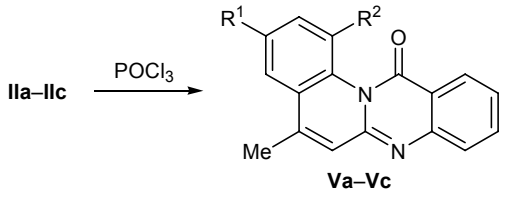


$R^1 = R^2 = H$ (**a**), $R^1 = Me$, $R^2 = H$ (**b**), $R^1 = H$, $R^2 = Me$ (**c**).

quantitatively afforded 2-(4-carboxyphenylamino)-4-methylquinolines **IVa**–**IVc**. Compounds **IVa**–**IVc** were also synthesized directly from chloroquinolines **Ia**–**Ic** and 4-aminobenzoic acid.

2-(2-Carboxyphenylamino)-4-methylquinolines **IIa**–**IIc** readily underwent intramolecular cyclization by the action of phosphoryl chloride on heating on a water bath for 3 h. The products were fused heteropolycyclic compounds, 5-methyl-12*H*-quinolino[2,1-*b*]-quinazolin-12-ones **Va**–**Vc** (Scheme 2).

Scheme 2.



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

2-(4-Methylquinolin-2-ylamino)benzoic acids IIa–IIc (*general procedure***).** A mixture of 0.01 mol of 2-chloro-4-methylquinoline **Ia**–**Ic** [4], 1.507 g (0.011 mol) of 2-aminobenzoic acid, and 1 mL of concentrated aqueous HCl in 50 mL of ethanol was heated for 14–15 h on a water bath. The solvent was distilled off, the residue was treated with water, the precipitate was filtered off and dissolved in dilute aqueous alkali, the solution was filtered, the filtrate was acidified to pH 5–6, and the precipitate was filtered off and dried.

2-(4-Methylquinolin-2-ylamino)benzoic acid (IIa). Yield 2.53 g (91%), mp 212–213°C (decomp.), R_f 0.56 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 2.77 s (3H, CH_3), 7.18 s (1H, H_{arom}), 7.38 t (1H, H_{arom}, J = 8.1 Hz), 7.45 t (1H, H_{arom}, J = 7.8 Hz), 7.62 t (1H, H_{arom}, J = 8.2 Hz), 7.79 t (1H, H_{arom}, J = 8.1 Hz), 7.92–8.14 m (4H, H_{arom}), 11.1 br.s (1H, NH). Found, %: C 73.51; H 4.91; N 10.18. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.38; H 5.04; N 10.07.

2-(4,6-Dimethylquinolin-2-ylamino)benzoic acid (IIb). Yield 2.69 g (92%), mp 164–166°C (decomp.), R_f 0.50 (ethanol–toluene, 1:4). Found, %: C 73.63; H 4.97; N 10.21. $C_{18}H_{16}N_2O_2$. Calculated, %: C 73.97; H 5.48; N 9.59.

2-(4,8-Dimethylquinolin-2-ylamino)benzoic acid (IIc). Yield 2.62 g (90%), mp 205–206°C (decomp.), R_f 0.49 (ethanol–toluene, 1:4). Found, %: C 73.71; H 5.08; N 10.09. $C_{18}H_{16}N_2O_2$. Calculated, %: C 73.97; H 5.48; N 9.59.

Ethyl 4-(4-methylquinolin-2-ylamino)benzoates IIIa–IIIc. A mixture of 0.01 mol of compound **Ia**–**Ic** [4], 1.82 g (0.011 mol) of ethyl 4-aminobenzoate, and 1 mL of concentrated aqueous HCl in 50 mL of ethanol was heated for 9–10 h on a water bath. The solvent was distilled off, the residue was treated with water, the mixture was adjusted to pH 8, and the precipitate was filtered off and recrystallized from ethanol–water (1:4).

Ethyl 4-(4-methylquinolin-2-ylamino)benzoate (IIIa). Yield 2.78 g (91%), mp 181–182°C, R_f 0.57 (ethanol–toluene, 1:3). Found, %: C 74.68; H 5.74; N 9.36. $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.45; H 5.88; N 9.15.

Ethyl 4-(4,6-dimethylquinolin-2-ylamino)benzoate (IIIb). Yield 2.85 g (89%), mp 211–212°C, R_f 0.63 (ethanol–toluene, 1:3). Found, %: C 74.92; H 6.02; N 9.06. $C_{20}H_{20}N_2O_2$. Calculated, %: C 75.00; H 6.25; N 8.75.

Ethyl 4-(4,8-dimethylquinolin-2-ylamino)benzoate (IIIc). Yield 2.91 g (91%), mp 201–202°C, R_f 0.62 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 1.39 t (3H, CH_3, J = 7.1 Hz), 2.63 d (3H, CH_3, J = 0.8 Hz), 2.72 s (3H, CH_3), 4.29 q (2H, OCH_2, J = 7.1 Hz), 6.93 q (1H, H_{arom}, J = 0.8 Hz), 7.17 d.d (1H, H_{arom}, J = 8.2, 7.0 Hz), 7.41 d (1H, H_{arom}, J = 7.0 Hz), 7.65 d (1H, H_{arom}, J = 8.2 Hz), 7.91 m and 8.11 m (2H, H_{arom}), 9.43 br.s (1H, NH). Found, %: C 75.32; H 5.96; N 8.31. $C_{20}H_{20}N_2O_2$. Calculated, %: C 75.00; H 6.25; N 8.75.

4-(4-Methylquinolin-2-ylamino)benzoic acids IVa–IVc (*general procedure***).** *a*. A solution of 0.60 g (15 mmol) of sodium hydroxide in 20 mL of water was added to a solution of 5 mmol of ester **IIIa**–**IIIc** in 40 mL of ethanol. and the mixture was heated for 4 h on a water bath. Ethanol was distilled off from the mixture, 50 mL of water was added, the mixture was filtered, the filtrate was acidified with aqueous HCl to pH 5–6, and the precipitate was filtered off.

b. A mixture of 0.01 mol of 2-chloro-4-methylquinoline **Ia**–**Ic** [4], 1.51 g (0.011 mmol) of 4-aminobenzoic acid, and 1 mL of concentrated aqueous HCl in 50 mL of ethanol was heated for 10–12 h on a water bath. The solvent was distilled off, the residue was treated with water, the precipitate was filtered off and dissolved in dilute alkali, the solution was filtered, the filtrate was acidified to pH 5–6, and the precipitate was filtered off. Samples of **IVa**–**IVc** prepared as described in *a* and *b* showed no depression of the melting point on mixing.

4-(4-Methylquinolin-2-ylamino)benzoic acid (IVa). Yield 1.31 g (94%) (*a*), 2.56 g (92%) (*b*), mp 271–273°C (decomp.), R_f 0.58 (ethanol–toluene, 1:3). Found, %: C 73.51; H 4.91; N 10.18. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.38; H 5.04; N 10.07.

4-(4,6-Dimethylquinolin-2-ylamino)benzoic acid (IVb). Yield 1.40 g (96%) (*a*), 2.66 g (91%) (*b*), mp 272–275°C (decomp.), R_f 0.57 (ethanol–toluene, 1:3). ^{1}H NMR spectrum, δ, ppm: 2.54 t (3H, CH_3), 2.70 d (3H, CH_3, J = 0.8 Hz), 7.35 q (1H, H_{arom}, J = 0.8 Hz), 7.25 d (1H, H_{arom}, J = 2.0 Hz), 7.59 d.d (1H, H_{arom}, J = 8.4, 2.0 Hz), 7.59 m and 8.06 m (2H each, H_{arom}), 7.84 d (1H, H_{arom}, J = 8.4 Hz), 11.54 br.s (1H, NH). Found, %: C 74.19; H 5.03; N 9.21. $C_{18}H_{16}N_2O_2$. Calculated, %: C 73.97; H 5.48; N 9.59.

4-(4,8-Dimethylquinolin-2-ylamino)benzoic acid (IVc). Yield 1.43 g (98%) (*a*), 2.72 g (93%) (*b*), mp 278–280°C (decomp.), R_f 0.55 (ethanol–toluene, 1:3). Found, %: C 73.71; H 5.08; N 10.09. $C_{18}H_{16}N_2O_2$. Calculated, %: C 73.97; H 5.48; N 9.59.

5-Methyl-12*H*-quinolino[2,1-*b*]quinazolin-12-ones Va–Vc (*general procedure*). A mixture of 5 mmol of compound **IIa**–**IIc** and 10 mL of phosphoryl chloride was heated for 3 h under reflux. Excess $POCl_3$ was distilled off under reduced pressure, the residue was poured onto 25 g of crushed ice and neutralized, and the precipitate was filtered off and recrystallized from ethanol–water (1:3).

5-Methyl-12*H*-quinolino[2,1-*b*]quinazolin-12-one (Va). Yield 1.25 g (96%), mp 217–218°C, R_f 0.51 (ethanol–toluene, 1:5). ^{1}H NMR spectrum, δ, ppm: 2.59 d (3H, CH_3, J = 1.2 Hz), 7.10 q (1H, H_{arom}, J = 1.2 Hz), 7.46 d.d.d (1H, H_{arom}, J = 8.0, 7.0, 1.2 Hz), 7.52 d.d.d (1H, H_{arom}, J = 7.7, 7.3, 1.2 Hz), 7.61 d.d.d (1H, H_{arom}, J = 8.3, 7.2, 1.8 Hz), 7.64 d (1H, H_{arom}, J = 8.0, 1.2 Hz), 7.78 d.d.d (1H, H_{arom}, J = 8.2, 7.0, 1.6 Hz), 7.83 d.d (1H, H_{arom}, J = 7.7, 1.8 Hz), 8.33 d (1H, H_{arom}, J = 8.1, 1.6 Hz), 9.55 d.d (1H, H_{arom}, J = 8.7, 1.2 Hz). Found, %: C 78.71; H 4.21; N 10.34. $C_{17}H_{12}N_2O$. Calculated, %: C 78.46; H 4.62; N 10.77.

3,5-Dimethyl-12*H*-quinolino[2,1-*b*]quinazolin-12-one (Vb). Yield 1.30 g (95%), mp 259–260°C (decomp.), R_f 0.53 (ethanol–toluene, 1:6). ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 2.77 d (3H, CH_3, J = 0.8 Hz), 7.59 d.d (1H, H_{arom}, J = 9.0, 2.4 Hz), 7.60 m (1H, H_{arom}), 7.84 q (1H, H_{arom}, J = 0.8 Hz), 7.85 d (1H, H_{arom}, J = 2.4 Hz), 7.95 m (1H, H_{arom}), 8.07 br.d (1H, H_{arom}, J = 8.1 Hz), 8.34 d.d (1H, H_{arom}, J = 8.1, 1.1 Hz), 9.39 d (1H, H_{arom}, J = 9.0 Hz). Found, %: C 79.11; H 4.87; N 10.48. $C_{18}H_{14}N_2O$. Calculated, %: C 78.83; H 5.11; N 10.22.

1,5-Dimethyl-12*H*-quinolino[2,1-*b*]quinazolin-12-one (Vc). Yield 1.36 g (99%), mp 217–218°C (decomp.), R_f 0.49 (ethanol–toluene, 1:5). Found, %: C 78.62; H 5.36; N 10.09. $C_{18}H_{14}N_2O$. Calculated, %: C 78.83; H 5.11; N 10.22.

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

REFERENCES

1. Solntsev, K.M., Sullivan, E.N., Tolbert, L.M., Ashkenazi, S., Leiderman, P., and Huppert, D., *J. Am. Chem. Soc*., 2004, 126, p. 12701; Strohmeier, G.A., Fabian, W.M.F., and Uray, G., *Helv. Chim. Acta*, 2004, vol. 87, p. 215; Badgujar, N.S., Pazicky, M., Traar, P., Terek, A., Uray, G., and Stadlbauer, W., *Eur. J. Org. Chem*., 2006, no. 12, p. 2715; Avetisyan, A.A., Aleksanyan, I.L., and Ambartsumyan, L.P., *Russ. J. Org. Chem*., 2007, vol. 43, p. 1052.
2. Sibirtsev, V.S., Tolmachev, A.Yu., Suslov, V.V., Garabadzhiu, A.V., and Traven', V.F., *Russ. J. Org. Chem*., 2003, vol. 39, p. 881.
3. Malakyan, M.G., Badzhinyan, S.A., Vardevanyan, L.A., Grigoryan, D.S., Egiazaryan, D.E., Avetisyan, A.A., Aleksanyan, I.L., Ambartsumyan, L.P., and Sargsyan, K.S., *Khim.-Farm. Zh*., 2009, no. 1, p. 8.
4. *Beilsteins Handbuch der organischen Chemie*, vol. H20, p. 392.