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

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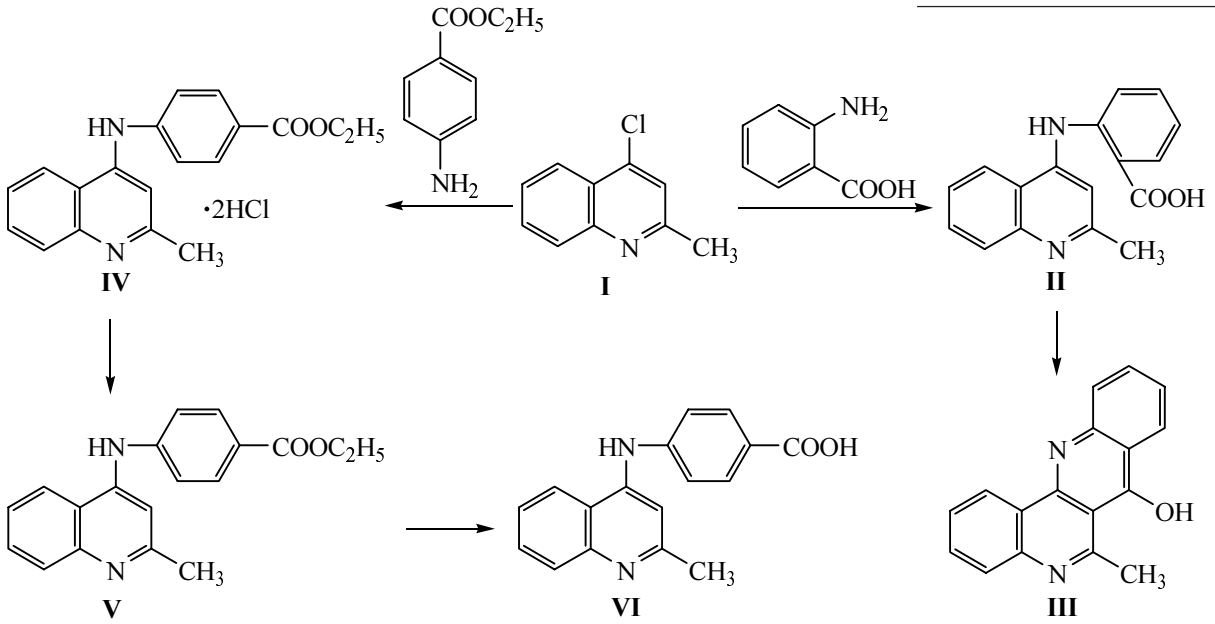
Abstract—Synthesis was performed of 4-(4-ethoxycarbonylphenylamino)- and 4-(2-carboxyphenylamino)-2-methylquinolines by reaction of 2-methyl-4-chloroquinoline with anesthesin and anthranilic acid. In concentrated sulfuric acid 4-(2-carboxyphenylamino)-2-methylquinoline underwent cyclization into 6-hydroxy-7-methylquinolino[3,2-*c*]quinoline, and the alkaline hydrolysis of 4-(4-ethoxycarbonylphenyl-amino)quinoline afforded 2-methyl-4-(4-carboxyphenylamino)quinoline.

Quinoline amino derivatives open up great synthetic opportunities for preparation of biologically active compounds of this series. Some among them exhibit antimalarial (Quinocide, Primaquine, Chloroquine, Hydroxychloroquine, Chinacrine, Melfoquine) [1, 2], antimicrobial activity [3, 4], and inhibitor properties [5, 9].

We report here on a synthesis of new derivatives of 4-phenylaminoquinoline. To this end we carried out a reaction of 2-methyl-4-chloroquinoline (**I**) with anesthesin and anthranilic acid [10]. It was established that heating of the initial compounds in ethanol at the ratio 1:1.1 in the presence of hydrochloric acid afforded within 14–15 h in high yields 4-(2-carboxyphenylamino)- (**II**) and 4-(4-ethoxycarbonylphenylamino)- (**IV**) -2-methylqiuinolines.

It was established that at heating compound **II** in sulfuric acid the substance underwent an intramolecular cyclization involving the free position *3* of the quinoline ring to furnish in a high yield 6-hydroxy-7-methylquinolino[3,2-C]quinoline (**III**).

We elaborated optimum conditions of the process. It was shown that applying polyphosphoric acid as cyclizing agent did not result in formation of the target product **III** presumably because the sulfuric acid protonated the oxy-



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gen of the carbonyl group stronger than the polyphosphoric acid. We also carried out the alkaline hydrolysis of 2-methyl-4-(4-ethoxycarbonylphenylamino)quinoline (**V**) to obtain in a quantitative yield 2-methyl-4-(4-carboxyphenylamino)quinoline (**VI**), a convenient initial compound for purposeful synthesis of more complicated systems.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. ^{1}H NMR spectra were registered on a Mercury-300 Varian NMR spectrometer in DMSO-d_6. The purity of compounds obtained was checked by TLC on Silufol UV-254 plates (development in iodine vapor).

2-Methyl-4-(2-carboxyphenylamino)quinoline (II). A mixture of 1.775 g (0.01 mol) of 2-methyl-4-chloroquinoline [10], 1.507 g (0.0011 mol) of anthranilic acid, and 1 ml of concn. HCl in 50 ml of ethanol was heated on a water bath for 14–15 h. It ethanol was distilled off, water was added to the residue, and the precipitate formed was filtered off. Then it was dissolved in diluted alkali, filtered, and the filtrate was acidified. The precipitate obtained was filtered off and recrystallized from a mixture ethanol–water, 1:1. Yield 2.82 g (82%), mp 200°C. IR spectrum, ν, cm^{-1}: 1730 (>C=O acid), 2700–3000 (OH acid). ^{1}H NMR spectrum, δ, ppm: 2.7 s (3H, CH_3), 6.7–8.8 m (9H, H_{arom}), 10.0 s (H, OH), 10.3 s (H, NH). Found, %: C 73.21; H 4.97; N 10.14. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.38; H 5.04; N 10.07.

6-Hydroxy-7-methylquinolino[3,2-*c*]quinoline (III). A mixture of 1.33 g (0.005 mol) of compound **II** and 10 ml of concn. HCl was heated on a water bath for 2 h. Then the reaction mixture was poured on 50 g of crushed ice, and the precipitate obtained was filtered off. The precipitate was dissolved in diluted alkali, filtered, and the filtrate was neutralized. The precipitate obtained was filtered off and recrystallized from ethanol. Yield 1.26 g (97%), mp 290°C, R_f 0.53 (chloroform–heptane, 2:1). ^{1}H NMR spectrum, δ, ppm: 3.10 s (3H, CH_3), 7.3–8.8 m (8H, H_{arom}), 11.6 s (H, OH). Found, %: C 78.37; H 4.52; N 10.68. $C_{17}H_{12}N_2O$. Calculated, %: C 78.46; H 4.61; N 10.77.

2-Methyl-4-(4-ethoxycarbonylphenylamino)quinoline dihydrochloride (IV). A mixture of 1.775 g (0.01 mol) of compound **I**, 1.65 g (0.01 mol) of anesthesin, and 1 ml of concn. HC1 in 50 ml of ethanol was heated on a water bath for 14–15 h. Then the ethanol was distilled off, water was added to the residue, and the obtained 2-methyl-4-(4-ethoxycarbonylphenylamino)quinoline hydrochloride was filtered off. Yield 3.3 g (96%), mp 245°C. Found, %: C 60.01; H 5.10; N 7.32. $C_{19}H_{20}C1_2N_2O_2$. Calculated, %: C 60.16; H 5.28; N 7.39.

2-Methyl-4-(4-ethoxycarbonylphenylamino)-quinoline (V). 2-methyl-4-(4-ethoxycarbonylphenylamino)quinoline hydrochloride was dissolved in water. The water solution was filtered and alkalified till pH 8. The separated precipitate was filtered off. Yield 2.9 g (95%), mp 75°C (from ethanol–water, 1:1), R_f 6.8 (chloroform–hexane, 1:6). IR spectrum, ν, cm^{-1}: 1730 (>C=O acid), 2700–3000 (OH acid). ^{1}H NMR spectrum, δ, ppm: 1.14 t (3H, CH_2CH_3), 2.7 s (3H, CH_3), 3.93 q (2H, CH_2CH_3) 6.4–8.2 m (9H, H_{arom}), 10.7 s (H, NH). Found, %: C 74.59; H 5.96; N 9.23. $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.51; H 5.88; N 9.15.

2-Methyl-4-(4-carboxyphenylamino)quinoline (VI). To a solution of 1.53 g (0.005 mol) of compound **IV** in 40 ml of ethanol was added 0.6 g (0.015 mol) of NaOH dissolved in 20 ml of water, and the mixture was heated on a water bath for 4 h. Then the ethanol was distilled off, the residue was diluted with 50 ml of water, filtered, and acidified with HCl till pH 6. The precipitate formed was filtered off. Yield 1.3 g (94%), mp 360°C (decomp.). The precipitate obtained was purified by dissolving in alkali and precipitating with acid. IR spectrum, ν, cm^{-1}: 1730 (>C=O acid), 2700–3000 (OH acid). ^{1}H NMR spectrum, δ, ppm: 2.5 s (3H, CH_3), 6.6–8.8 m (9H, H_{arom}), 10.0 s (H, OH). Found, %: C 73.44; H 5.10; N 10.13. $C_{17}H_{14}N_2O_2$. Calculated, %: C 73.38; H 5.04; N 10.07.

REFERENCES

1. Mashkovskii, P.P.M., *Drugs,* Moscow: Novaya Volna, 2002, vol. 2, p. 336.
2. Fitch, C.D., *Life Sciences,* 2004, vol. 74, p. 1957.
3. Wainwright, M. and Kristasen, J.E., *Intern. J. Antimicrob. Agents*, 2003, vol. 22, p. 479.
4. Taramelli, D., Tognazioli, C., Ravagnani, F., Leopardi, O., Giannuis, G., and Boelaert, J.R., *Antimicrob. Agents, Chemother*., 2001, vol. 45, p. 1450.
5. Boshelli, D.H., Fei, Ye, Wang, Y.D., Dutia, M., Johnson, S.L., Bigi, Wu, Miller, K., Powell, D.W., Yaczko, D., , Young, M., Tischer, M., Arndt, K., Diseafani, C., Etienne, C., Crod, J., Lucas, J., Weber, J.M., Boschelli, F., and Gibbons, J., *J. Med. Chem.,* 2001, vol. 44, p. 3965.
6. Berger, D., Dutia, M., Poweli, D., Wissner, A., DeMorin, F., Raifeld, Y., Weber, J., and Boschelli, F., *Bioorg. &, Med. Chem. Lett.,* 2002, vol. 12, p. 2989.
7. Berger, D., Dutia, M., Powell, D., Bigi, Wu, Wissner, A., DeMorin F., Weber, J., and Boschelli, F., *Bioorg. & Med. Chem. Lett.,* 2002, vol. 12, p. 2761.
8. Liach, C.A. and Brown, T.N., Europe Patent 330485, 1990; *Chem. Abstr.,* 1990, vol. 112, 158073s.
9. Geiss, K.H., Rucbsamen, K., and Traut, M., Europe Patent 387821, 1990; *Chem. Abstr*., 1991, vol. 114, 112074v.
10. *Beilst. H.*, vol. 20, p. 392.