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Synthesis of 2-Bromomethyl-4-methyl-2,3-dihydrofuro[3,2-*c*]-quinoline and Some Its Transformations

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Abstract—Electrophilic intramolecular heterocyclization of 3-(2-chloroprop-2-en-1-yl)-2-methylquinolin-4-ol by the action of bromine gave 2-bromomethyl-2-chloro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline hydrobromide which was converted into 2-hydroxymethyl-, 2-alkoxymethyl-, and 2-dialkylaminomethyl-4-methylfuro[3,2-*c*]quinolines by treatment with the corresponding nucleophiles.

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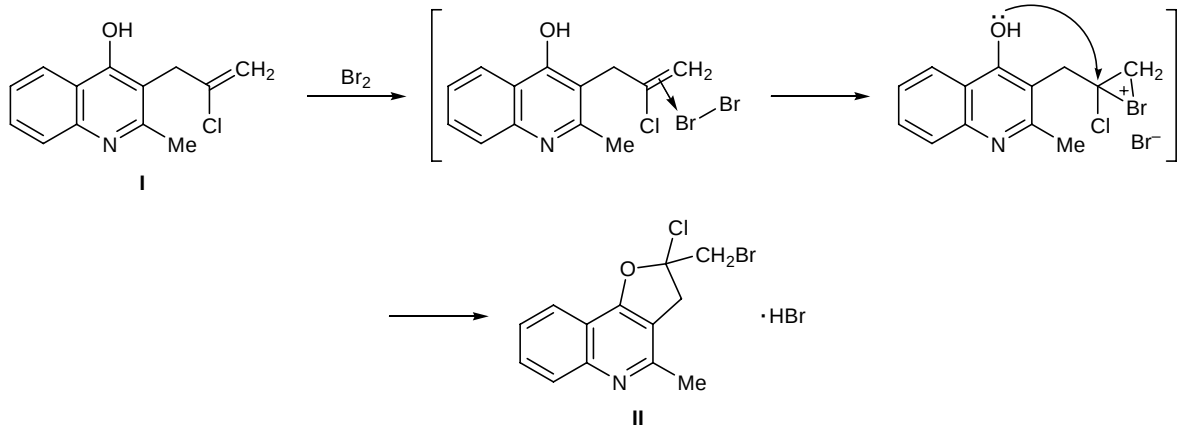
Quinoline derivatives are quite promising and accessible intermediate products for the synthesis of various polynuclear heterocyclic systems that are interesting from the viewpoint of their biological activity [1, 2]. In particular, many furo[3,2-*c*]quinoline derivatives were found to exhibit strong antiallergic, antiinflammatory, vasodilating, antiarrythmic, antispasmodic, psychotropic, bronchodilating, neurotropic, antifungal, and coronary activity [3].

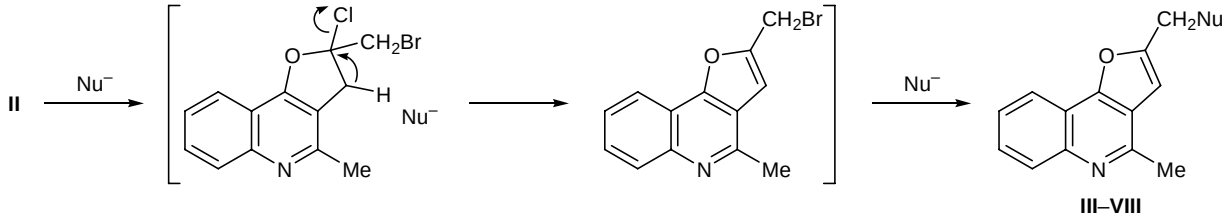
While continuing our studies on transformations of 3-(2-chloroprop-2-en-1-yl)-4-hydroxyquinolines [4], we developed a convenient procedure for the synthesis of 2-bromomethyl-2-chloro-4-methyl-2,3-dihydrofuro-[3,2-*c*]quinoline hydrobromide via electrophilic intramolecular heterocyclization of 3-(2-chloroprop-2-en-1-yl)-4-hydroxy-2-methylquinoline and examined reactions of the cyclization product with a number of nucleophiles.

Initial 3-(2-chloroprop-2-en-1-yl)-4-hydroxy-2-methylquinoline (**I**) was synthesized by the procedure described in [4]. Treatment of **I** with a solution of bromine in chloroform at room temperature for 1–2 h gave 2-bromomethyl-2-chloro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline hydrobromide (**II**) (Scheme 1). The ^{1}H NMR spectrum of **II** contained signals at δ 3.24 (s, 2H, CH_2) and 3.62 ppm (s, 2H, CH_2Br). As shown in Scheme 1, addition of bromine at the double C=C bond of the chloroallyl group gives intermediate bromonium ion which can be stabilized in two ways: via nucleophilic addition of bromide ion or by heterocyclization involving the electron-donor hydroxy group. If the hydroxy group is sufficiently nucleo-

Scheme 1.



Scheme 2.



III–VIII

III, Nu = HO; **IV**, Nu = MeO; **V**, Nu = EtO; **VI**, Nu = *i*-PrO; **VII**, Nu = Et_2N; **VIII**, Nu = morpholino.

philic, the rate of heterocyclization exceeds the rate of nucleophilic addition.

Bromomethylfuroquinoline **II** reacted with various nucleophiles (Nu = OH, OR, R_2N) to form the corresponding 2-substituted 4-methylfuro[3,2-*c*]quinolines **III**–**VIII** in high yields (Scheme 2). In the first step, nucleophile promotes elimination of hydrogen chloride from the dihydrofuran ring, and next follows nucleophilic replacement of the bromine atom in the 2-bromomethyl group. Insofar as the second step is faster than the first one, intermediate 2-bromomethyl-4-methylfuro[3,2-*c*]quinoline cannot be isolated. The structure of products **III**–**VIII** was proved by the ^{1}H NMR data. The 3-H proton in **III**–**VIII** resonated in the ^{1}H NMR spectra as a singlet at δ 6.75–6.90 ppm.

2-Hydroxymethyl-, 2-alkoxymethyl-, and 2-diethylaminomethyl-4-methylfuro[3,2-*c*]quinolines **III**–**VII** were obtained by heating initial 2-bromomethyl-2-chloro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline hydrobromide (**II**) with 3 equiv of the corresponding nucleophile (aqueous–alcoholic alkali, sodium alkoxides, and diethylamine in dimethylformamide). In the synthesis of 2-morpholinomethyl-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline (**VIII**), the reaction was carried out with equimolar amounts of the reactants in DMF in the presence of anhydrous pyridine.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75IR spectrometer. The ^{1}H NMR spectra were measured on a Varian Mercury-300 instrument (300 MHz) from solutions in DMSO-d_6. The purity of the products was checked by TLC on Silufol UV-254 plates (development with iodine vapor).

2-Bromomethyl-2-chloro-4-methyl-2,3-dihydrofuro[3,2-*c*]quinoline hydrobromide (II). 3-(2-Chloroprop-2-en-1-yl)-2-methyl-4-hydroxyquinoline (**I**) [4], 5.84 g (0.025 mol), was dissolved in 30 ml of $CHCl_3$, 50 ml of a 0.5 M solution of bromine (0.025 mol) in $CHCl_3$ was added dropwise under vigorous stirring, and the mixture was stirred for 1 h at room temperature. The precipitate was filtered off, washed with $CHCl_3$, and dried. Yield 9.1 g (92%), mp 247–249°C. ^{1}H NMR spectrum, δ, ppm: 2.75 s (3H, CH_3), 3.24 s (2H, CH_2), 3.62 s (2H, CH_2Br), 7.5–8.2 m (4H, H_{arom}). Found, %: C 39.71; H 2.93; Cl+Br 49.81; N 3.70. $C_{13}H_{12}Br_2ClNO$. Calculated, %: C 39.64; H 3.04; Cl+Br 49.68; N 3.55.

(4-Methylfuro[3,2-*c*]quinolin-2-yl)methanol (III). Compound **II**, 0.79 g (0.002 mol), was added to 0.006 mol of an aqueous–alcoholic solution of alkali. The mixture was heated for 2 h on a water bath, the alcohol was distilled off, the residue was dissolved in a dilute acid, the solution was filtered, the filtrate was made alkaline, and the precipitate was filtered off. Yield 0.49 g (87%), mp 237–240°C, R_f 0.54 (toluene–ethanol, 2:1). ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 4.6 s (2H, CH_2), 4.90 s (1H, OH), 6.8 s (1H, 3-H), 7.5–8.2 m (4H, H_{arom}). Found, %: C 73.31; H 5.10; N 6.70. $C_{13}H_{11}NO_2$. Calculated, %: C 73.23; H 5.16; N 6.57.

2-Alkoxymethyl-4-methylfuro[3,2-*c*]quinolines IV–VI (*general procedure*). Quinoline **II**, 0.002 mol, was added to a solution of sodium alkoxide prepared from 50 ml of the corresponding anhydrous alcohol and 0.14 g (0.006 mol) of metallic sodium. The mixture was heated for 2 h on a water bath, the solvent was distilled off, the residue was dissolved in a dilute acid, the solution was filtered and neutralized to pH 8, and the precipitate was filtered off.

2-Methoxymethyl-4-methylfuro[3,2-*c*]quinoline (IV). Yield 0.40 g (86%), mp 74–75°C, R_f 0.62 (toluene–ethanol, 2:1). ^{1}H NMR spectrum, δ, ppm: 2.70 s (3H, CH_3), 3.62 s (3H, OCH_3), 4.65 s (2H, CH_2), 6.90 s (1H, 3-H), 7.5–8.2 m (4H, H_{arom}). Found, %: C 74.06; H 5.61; N 6.24. $C_{14}H_{13}NO_2$. Calculated, %: C 74.00; H 5.72; N 6.16.

2-Ethoxymethyl-4-methylfuro[3,2-*c*]quinoline (V). Yield 0.44 g (91%), mp 69–71°C, R_f 0.62

(toluene–ethanol, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, $OCH_2C\mathbf{H}_3$), 2.72 s (3H, 4-CH_3), 3.40 q (2H, $OC\mathbf{H}_2CH_3$), 3.85 s (2H, CH_2), 6.80 s (1H, 3-H), 7.3–8.2 m (4H, H_{arom}). Found, %: C 74.57; H 6.31; N 5.68. $C_{15}H_{15}NO_2$. Calculated, %: C 74.68; H 6.22; N 5.80.

2-Isopropoxymethyl-4-methylfuro[3,2-*c*]quinoline (VI). Yield 0.46 g (90%), mp 66–68°C, R_f 0.69 (toluene–ethanol, 3:1). ^{1}H NMR spectrum, δ, ppm: 1.20 d (6H, CH_3), 2.90 s (3H, 4-CH_3), 3.80 m (1H, OCH), 4.65 s (2H, OCH_2), 6.90 s (1H, 3-H), 7.5–8.2 m (4H, H_{arom}). Found, %: C 75.36; H 6.52; N 5.61. $C_{16}H_{17}NO_2$. Calculated, %: C 75.29; H 6.66; N 5.49.

***N*,*N*-Diethyl(4-methylfuro[3,2-*c*]quinolin-2-yl)methanamine (VII).** Diethylamine, 0.65 ml (0.006 mol), was added to a solution of 0.79 g (0.002 mol) of compound **II** in 10 ml of DMF, and the mixture was heated for 3 h under reflux. The solvent was distilled off under reduced pressure, the residue was dissolved in a dilute acid, the solution was filtered, and the filtrate was neutralized to pH 8. An oily material separated and was extracted into benzene. Removal of the solvent from the extract left 0.51 g (95%) of compound **VII** as an oily substance, R_f 0.63 (toluene–ethanol, 1.8:1). ^{1}H NMR spectrum, δ, ppm: 1.12 m (6H, CH_3), 2.60 q (4H, CH_2), 2.82 s (3H, 4-CH_3), 4.85 s (2H, 2-CH_2), 6.8 s (1H, 3-H), 7.45–8.2 m (4H, H_{arom}). Found, %: C 76.24; H 7.37; N 10.57. $C_{17}H_{20}N_2O$. Calculated, %: C 76.12; H 7.46; N 10.44.

4-Methyl-2-morpholinomethylfuro[3,2-*c*]quinoline (VIII). Morpholine, 0.2 ml (0.002 mol), was added to a solution of 0.79 g (0.002 mol) of furoquinoline **II** in 10 ml of DMF containing 0.5 ml of anhydrous pyridine, and the mixture was heated for 3 h under reflux. The solvent was distilled off under reduced pressure, the residue was dissolved in a dilute acid, the solution was filtered, and the filtrate was neutralized to pH 8. An oily material separated and was extracted into diethyl ether. Removal of the solvent from the extract left 0.4 g (70%) of compound **VIII** as a crystalline substance, R_f 0.69 (toluene–ethanol, 2:1). ^{1}H NMR spectrum, δ, ppm: 2.52 t (4H, CH_2NCH_2), 2.80 s (3H, 4-CH_3), 3.60 t (4H, CH_2OCH_2), 3.80 s (2H, 2-CH_2), 6.83 s (1H, 3-H), 7.45–8.2 m (4H, H_{arom}). Found, %: C 72.21; H 6.43; N 10.11. $C_{17}H_{18}N_2O_2$. Calculated, %: C 72.34; H 6.38; N 9.93.

REFERENCES

1. Orekhov, A.P., *Khimiya alkaloidov* (Chemistry of Alkaloids), Moscow: Akad. Nauk SSSR, 1955, p. 208.
2. Abass, M., *Heterocycles*, 2005, vol. 65, p. 901.
3. Aleksanyan, I.L., *Cand. Sci. (Chem.) Dissertation*, Erevan, 1985.
4. Avetisyan, A.A., Aleksanyan, I.L., and Pivazyan, A.A., *Russ. J. Org. Chem*., 2006, vol. 42, p. 739.