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Synthesis and Some Transformations of Benzo-Substituted 2-Bromomethyl-4-methyl-2-chloro-2,3-dihydrofuro[3.2-*c*]-quinolines

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Abstract—A convenient synthetic procedure for substituted 2-bromomethyl-4-methyl-2-chloro-2,3-dihydrofuro[3.2-*c*]quinolines hydrobromides was developed, synthons for preparation of new substituted furoquinolines. Reactions with various nucleophiles were performed, and 2-(R'-methyl)-4-methyl-furo[3.2-*c*]quinolines substituted in the benzene ring were obtained.

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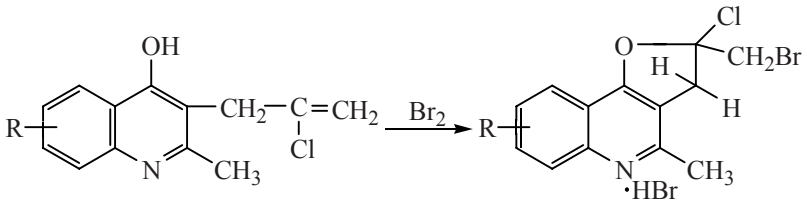
Quinolines and their derivatives are endowed with a wide range of biological activity, in particular, malaricidal, antibacterial, fungicidal, protozoicidal, tuberculocidal, antiarrhythmic, antiradiation, spasmolythic, psychotropic, and other action [1, 2] and are extensively used in the fine organic synthesis.

In continuation of our studies on the synthesis and chemical behavior of 4-hydroxy-3-(2-chloroprop-2-en-1-yl)quinolines substituted in the benzene ring [3] we developed a procedure for preparation of substituted 2-bromomethyl-4-methyl-2-chloro-2,3-dihydrofuro[3.2-*c*]-quinolines hydrobromides by electrophilic intramolecular heterocyclization and investigated the reactions of the compounds obtained with a series of nucleophiles. It was shown that in the reaction of substituted 4-hydroxy-2-methyl-3-(2-chloroprop-2-en-1-yl)quinolines **Ia–Ic** with bromine formed 2-bromomethyl-4-methyl-2-chloro-2,3-dihydro-furo[3.2-*c*]quinolines hydrobromides **IIa–IIc**.

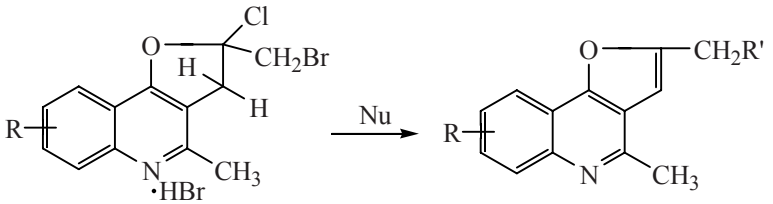


Ia– Ic **IIa– IIc**

R = 6-CH_3 (**a**), 8-CH_3 (**b**), 8-OCH_3 (**c**).

The optimum conditions of the process were found providing high yields (>70%) of the target dihydrofuro[3.2-*c*]quinolines. The bromination of compounds **Ia–Ic** was performed using an equimolar quantity of bromine in chloroform at room temperature for 1–2 h.

Aiming at the preparation of new furoquinoline derivatives we subjected the obtained 2-bromomethyl-4-methyl-2-chloro-2,3-dihydrofuro[3.2-*c*]quinolines hydrobromides **IIa–IIc** to reactions with a series of nucleophiles [Nu = HO^-, CH_3O^-, $C_2H_5O^-$, $(CH_3)_2CHO^-$, $HN(C_2H_5)_2$, morpholine] that led to the formation of 2-(R'-methyl)-4-methylfuro[3.2-*c*]quinolines 2-substituted at the methyl group **IIIa–IIIc–VIIIa–VIIIc**. The good yields (>60%) were made possible by carrying out the



IIa–IIc **IIIa–IIIc –VIIIa–VIIIc**

R = 8-CH_3 (**a**), 6-CH_3 (**b**), 8-OCH_3 (**c**); R' = OH (**III**), OCH_3 (**IV**), OC_2H_5 (**V**), $OCH(CH_3)_2$ (**VI**), $N(C_2H_5)_2$ (**VII**),

reaction at the molar ratio hydrobromide–nucleophile 1:3 (water-alcohol alkali solution, alcoholates of the corresponding alcohols, or diethylamine in DMF). In the reaction with morpholine the reagents were taken in the ratio 1:1 in DMF solution in the presence of anhydrous pyridine.

Under the action of the nucleophile which simultaneously was a base a hydrogen chloride molecule is eliminated, and the dihydrofuran ring underwent aromatization, and also occurred the nucleophilic substitution of the second halogen atom.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Varian Mercury-300 at operating frequency 300 MHz in DMSO-d_6. The homogeneity and purity of compounds obtained were checked by TLC on Silufol UV-254 plates, eluents tolyene–ethanol, 3:1 (A), 4:1 (B), 5:1 (C), development in iodine vapor.

Substituted 2-bromomethyl-4-methyl-2-chloro-2,3-dihydrofuro[3.2-*c*]quinolines hydrobromides IIa–IIc. To a solution of 25 mmol of an appropriate substituted 4-hydroxy-2-methyl-3-(2-chloroprop-2-en-1-yl)quinoline **Ia–Ic** [3, 4] in 50 ml of chloroform was added dropwise at vigorous stirring 50 ml (0.025 mol) of 0.5 M bromine solution in chloroform. The reaction mixture was stirred at room temperature for 1 h. The separated precipitate was filtered off, washed with chloroform, and dried.

2-Bromomethyl-4,8-dimethyl-2-chloro-2,3-dihydrofuro[3.2-*c*]quinoline hydrobromide (IIa). Yield 9.2 g (90%), mp 209–211°C. ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 2.70 s (3H, $NCCH_3$), 3.20 s (2H, CH_2), 3.65 s (2H, CH_2Br), 7.1–7.9 m ($3H_{arom}$). Found, %: C 41.12; H 3.61; Cl+Br 48.10; N 3.56. $C_{14}H_{14}Br_2ClNO$. Calculated, %: C 41.23; H 3.44; Cl+Br 47.96; N 3.44.

2-Bromomethyl-4,6-dimethyl-2-chloro-2,3-dihydrofuro[3.2-*c*]quinoline hydrobromide (IIb). Yield 8.66 g (85%), mp 185–187°C. ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.75 s (3H, $NCCH_3$), 3.24 s (2H, CH_2), 3.62 s (2H, CH_2Br), 7.3–8.1 m ($3H_{arom}$). Found, %: C 41.32; H 3.29; Cl+Br 48.80; N 3.56. $C_{14}H_{14}Br_2ClNO$. Calculated, %: C 41.23; H 3.44; Cl+Br 47.96; N 3.44.

2-Bromomethyl-4-methyl-6-methoxy-2-chloro-2,3-dihydrofuro[3.2-*c*]quinoline hydrobromide (IIc). Yield 8.6 g (81%), mp 197–200°C. ^{1}H NMR spectrum, δ, ppm: 2.70 s (3H, $NCCH_3$), 3.26 s (3H, CH_2), 3.70 s (2H, CH_2Br), 3.93 s (3H, OCH_3), 7.20–8.00 m ($3H_{arom}$). Found, %: C 39.53; H 3.47; Cl+Br 46.31; N 3.22. $C_{14}H_{14}Br_2ClNO_2$. Calculated, %: C 39,67; H 3.31; Cl+Br 46.16; N 3.31.

Substituted 2-hydroxymethyl-4-methylfuro-[3.2-*c*]quinolines IIIa–IIIc. To 6 mmol of aqueous-alcoholic alkali solution was added 2 mmol of quinoline **IIa–IIc**. The mixture was heated on a water bath for 2 h, then the alcohol was distilled off, the residue was dissolved in dilute hydrochloric acid, filtered, and the filtrate was alkalinized. The precipitate obtained was filtered off.

2-Hydroxymethyl-4,8-dimethylfuro[3.2-*c*]quinoline (IIIa). Yield 0.30 g (67%), mp 45–47°C, R_f 0.66 (B). ^{1}O NMR spectrum, δ, ppm: 2.22 s (3H, CH_3), 2.70 s (3H, $NCCH_3$), 4.60 s (2H, CH_2), 4.95 s (1H, OH), 6.60 s (1H, CH), 7.5–8.1 m ($3H_{arom}$). Found, %: C 74.11; H 5.65; N 6.29. $C_{14}H_{13}NO_2$. Calculated, %: C 74.00; H 5.73; N 6.17.

2-Hydroxymethyl-4,6-dimethylfuro[3.2-*c*]quinoline (IIIb). Yield 0.29 g (63%), mp 109–110°C, R_f 0.56 (A). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.75 s (3H, $NCCH_3$), 4.70 s (2H, CH_2), 5.00 s (1H, OH), 6.65 s (1H, CH), 7.5–8.0 m ($3H_{arom}$). Found, %: C 73.88; H 5.76; N 6.08. $C_{14}H_{13}NO_2$. Calculated, %: C 74.00; H 5.73; N 6.17.

2-Hydroxymethyl-4-methyl-6-methoxyfuro-[3.2-*c*]quinoline (IIIc). Yield 0.34 g (70%), mp 115–117°C, R_f 0.52 (A). ^{1}H NMR spectrum, δ, ppm: 2.70 s (3H, $NCCH_3$), 3.93 s (3H, OCH_3), 4.61 s (2H, CH_2), 4.95 s (1H, OH), 6.60 s (1H, CH), 7.2–7.9 m ($3H_{arom}$).

Found, %: C 69.24; H 5.31; N 5.84. $C_{14}H_{13}NO_3$. Calculated, %: C 69.12; H 5.39; N 5.76.

Substituted 2-alkoxymethyl-4-methylfuro-[3.2-*c*]quinolines IVa–IVc–VIa–VIc. To the sodium alcoholate solution prepared from 50 ml of an appropriate anhydrous alcohol and 0.14 g (6 g-at) of sodium metal was added 2 mmol of quinoline **IIa–IIc**. The mixture was heated on a water bath for 2 h, then the alcohol was distilled off, the residue was dissolved in dilute hydrochloric acid, filtered, and the filtrate was alkalinized to pH 8. The precipitate obtained was filtered off.

4,8-Dimethyl-2-(methoxymethyl)furo[3.2-*c*]-quinoline (IVa). Yield 0.31 g (65%), mp 100–102°C, R_f 0.66 (C). ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, CH_3), 2.65 s (3H, $NCCH_3$), 3.62 s (3H, OCH_3), 4.62 s (2H, CH_2), 6.90 s (1H, CH), 7.5–8.1 m ($3H_{arom}$). Found, %: C 74.81; H 6.14; N 5.70. $C_{15}H_{15}NO_2$. Calculated, %: C 74.69; H 6.22; N 5.81.

4,6-Dimethyl-2-(methoxymethyl)furo[3.2-*c*]-quinoline (IVb). Yield 0.33 g (69%), mp 77–79°C, R_f 0.62 (B). ^{1}H NMR spectrum, δ, ppm: 2.40 σ (3H, CH_3), 2.70 s (3H, $NCCH_3$), 3.60 s (3H, OCH_3), 4.60 s (2H, CH_2), 7.0 s (1H, CH), 7.6–8.2 m ($3H_{arom}$). Found, %: C 74.80; H 6.08; N 5.70. $C_{15}H_{15}NO_2$. Calculated, %: C 74.69; H 6.22; N 5.81.

4-Methyl-2-(methoxymethyl)-6-methoxyfuro-[3.2-*c*]quinoline (IVc). Yield 0.36 g (70%), mp 115–117°C, R_f 0.60 (B). ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, $NCCH_3$), 3.65 s (3H, OCH_3), 3.93 s (3H, OCH_3), 4.65 s (2H, CH_2), 7.0 s (1H, CH), 7.5–8.1 m ($3H_{arom}$). Found, %: C 70.13; H 5.71; N 5.59. $C_{15}H_{15}NO_3$. Calculated, %: C 70.04; H 5.71; N 5.45.

4,8-Dimethyl-2-(ethoxymethyl)furo[3.2-*c*]-quinoline (Va). Yield 0.37 g (72%), mp 69–70°C, R_f 0.67 (C). ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, OCH_2CH_3), 2.30 s (3H, CH_3), 2.65 s (3H, $NCCH_3$), 3.40 q (2H, OCH_2CH_3), 3.85 s (2H, CH_2), 6.8 s (1H, CH), 7.1–8.2 m ($3H_{arom}$). Found, %: C 75.41; O 6.49; N 5.57. $C_{16}H_{17}NO_2$. Calculated, %: C 75.29; H 6.66; N 5.49.

4,6-Dimethyl-2-(ethoxymethyl)furo[3.2-*c*]quinoline (Vb). Yield 0.41 g (81%), mp 63–65°C, R_f 0.60 (B). ^{1}H NMR spectrum, δ, ppm: 1.13 t (3H, OCH_2CH_3), 2.22 s (3H, CH_3), 2.60 s (3H, $NCCH_3$), 3.45 q (2H, OCH_2CH_3), 3.80 s (2H, CH_2), 6.60 s (1H, CH), 7.0–8.0 m ($3H_{arom}$). Found, %: C 75.16; O 6.78; N 5.61. $C_{16}H_{17}NO_2$. Calculated, %: C 75.29; H 6.66; N 5.49.

4-Methyl-6-methoxy-2-(ethoxymethyl)furo-[3.2-*c*]quinoline (Vc). Yield 0.42 g (78%), mp 103–104°C, R_f 0.63 (C). ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, OCH_2CH_3), 2.70 s (3H, $NCCH_3$), 3.40 q (2H, OCH_2CH_3), 3.85 s (2H, CH_2), 4.0 s (3H, OCH_3), 6.8 s (1H, CH), 7.3–8.2 m ($3H_{arom}$). Found, %: C 70.75; O 6.40; N 5.27. $C_{16}H_{17}NO_3$. Calculated, %: C 70.83; H 6.32; N 5.16.

2-(Isopropoxymethyl)-4,8-dimethylfuro[3.2-*c*]-quinoline (VIa). Yield 0.44 g (82%), mp 75–77°C, R_f 0.65 (B). ^{1}H NMR spectrum, δ, ppm: 1.20 d (6H, $2CH_3$), 2.40 s (3H, CH_3), 2.75 s (3H, $NCCH_3$), 3.80 m (1H, CH), 4.65 s (2H, CH_2), 6.90 s (1H, CH), 7.5–8.2 m ($3H_{arom}$). Found, %: C 75.90; H 7.04; N 5.34. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20.

2-(Isopropoxymethyl)-4,6-dimethylfuro[3.2-*c*]-quinoline (VIb). Yield 0.43 g (80%), mp 54–55°C, R_f 0.70 (A). ^{1}H NMR spectrum, δ, ppm: 1.17 d (6H, $2CH_3$), 2.33 s (3H, CH_3), 2.65 s (3H, $NCCH_3$), 3.75 m (1H, CH), 4.60 s (2H, CH_2), 6.80 s (1H, CH), 7.3–8.1 m ($3H_{arom}$). Found, %: C 75.74; H 7.20; N 5.11. $C_{17}H_{19}NO_2$. Calculated, %: C 75.81; H 7.11; N 5.20.

2-(Isopropoxymethyl)-4-methyl-6-methoxyfuro-[3.2-*c*]quinoline (VIc). Yield 0.39 g (68%), mp 80–81°C, R_f 0.54 (B). ^{1}H NMR spectrum, δ, ppm: 1.20 d (6H, $2CH_3$), 2.30 s (3H, CH_3), 2.70 s (3H, $NCCH_3$), 3.85 m (1H, OCH), 4.60 s (2H, CH_2), 6.80 s (1H, CH), 7.3–8.0 m ($3H_{arom}$). Found, %: C 71.67; H 6.58; N 5.02. $C_{17}H_{19}NO_3$. Calculated, %: C 71.56; H 6.71; N 4.91.

Substituted 4-methyl-2-[(diethylamino)methyl]-furo[3.2-*c*]quinolines VIIa–VIIc. To a solution of 2 mmol of compound **IIa–IIc** in 10 ml of DMF was added 0.65 ml of (6 mmol) diethylamine, and the mixture was boiled for 3 h. Then DMF was distilled off at a reduced pressure. The residue was dissolved in dilute hydrochloric acid, filtered, and the filtrate was alkalinized to pH 8. The separated oily layer was extracted with benzene. On removing benzene a crystalline substance was obtained.

4,8-Dimethyl-2-[(diethylamino)methyl]furo-[3.2-*c*]quinoline (VIIa). Yield 0.43 g (77%), mp 44–45°C, R_f 0.59 (A). ^{1}H NMR spectrum, δ, ppm: 1.15 m (6H, $2CH_3$), 2.20 s (3H, CH_3), 2.55 s (4H, $2CH_2$), 2.75 s (3H, $NCCH_3$), 4.80 s (2H, CH_2), 2.20 s (3H, CH_3), 6.70 s (1H, CH), 7.3–8.1 m ($3H_{arom}$). Found, %: C 76.64; O 7.73; N 9.84. $C_{18}H_{22}N_2O$. Calculated, %: C 76.56; H 7.85; N 9.93.

4,6-Dimethyl-2-[(diethylamino)methyl]furo-[3.2-*c*]quinoline (VIIb). Yield 0.37 g (67%), mp 40–41°C, R_f 0.50 (A). ^{1}H NMR spectrum, δ, ppm: 1.20 m

(6H, $2CH_3$), 2.22 s (3H, CH_3), 2.60 s (4H, $2CH_2$), 2.80 s (3H, $NCCH_3$), 4.80 s (2H, CH_2), 6.75 s (1H, CH), 7.2–8.1 m ($3H_{arom}$). Found, %: C 76.48; O 7.93; N 9.85. $C_{18}H_{22}N_2O$. Calculated, %: C 76.56; H 7.85; N 9.93.

4-Methyl-6-methoxy-2-[(diethylamino)methyl]-furo[3.2-*c*]quinoline (VIIc). Yield 0.46 g (78%), mp 49–50°C, R_f 0.47 (A). ^{1}H NMR spectrum, δ, ppm: 1.12 m (6H, $2CH_3$), 2.60 s (4H, $2CH_2$), 2.80 s (3H, $NCCH_3$), 4.0 s (3H, OCH_3), 4.85 s (2H, CH_2), 6.80 s (1H, CH), 7.4–8.2 m ($3H_{arom}$). Found, %: C 72.54; O 7.37; N 9.46. $C_{18}H_{22}N_2O_2$. Calculated, %: C 72.46; H 7.43; N 9.39.

Substituted 4-methyl-2-(morpholinomethyl)furo-[3.2-*c*]quinolines VIIIa–VIIIc. To a solution of 2 mmol of compound **IIa–IIc** in 10 ml of DMF and 0.5 ml of anhydrous pyridine was added 0.2 ml (2 mmol) of morpholine, and the mixture was boiled for 3 h. Then DMF was distilled off at a reduced pressure. The residue was dissolved in dilute hydrochloric acid, filtered, and the filtrate was alkalinized to pH 8. The separated oily layer was extracted with ethere. On removing ether an oily substance was obtained.

4,8-Dimethyl-2-(morpholinomethyl)furo[3.2-*c*]quinoline (VIIIa). Yield 0.41 g (70%), R_f 0.60 (B). ^{1}H NMR spectrum, δ, ppm: 2.50 t [4H, $N(CH_2)_2$], 2.75 s (3H, $NCCH_3$), 3.65 t [4H, $O(CH_2)_2$], 6.80 s (1H, CH), 7.1–8.0 m ($3H_{arom}$). Found, %: C 72.86; O 6.91; N 9.00. $C_{18}H_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45.

4,6-Dimethyl-2-(morpholinomethyl)furo[3.2-*c*]quinoline (VIIIb). Yield 0.43 g (74%), R_f 0.62 (B). ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.52 t [4H, $N(CH_2)_2$], 2.80 s (3H, $NCCH_3$), 3.60 t [4H, $O(CH_2)_2$], 6.83 s (1H, CH), 7.4–8.4 m ($3H_{arom}$). Found, %: C 73.06; O 6.71; N 9.34. $C_{18}H_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45.

4-Methyl-6-methoxy-2-(morpholinomethyl)furo-[3.2-*c*]quinoline (VIIIc). Yield 0.42 g (70%), R_f 0.64 (A). ^{1}H NMR spectrum, δ, ppm: 2.50 t [4H, $N(CH_2)_2$], 2.75 s (3H, $NCCH_3$), 3.60 t [4H, $O(CH_2)_2$], 4.10 s (3H, OCH_3), 6.80 m (1H, CH), 7.4–8.3 m ($3H_{arom}$). Found, %: C 69.11; O 6.55; N 8.89. $C_{18}H_{20}N_2O_3$. Calculated, %: C 69.21; H 6.45; N 8.97.

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