ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 4, pp. 601–605. © Pleiades Publishing, Ltd., 2018.
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Halocyclization of 1-Allyl-6(7)-methylquinolin-2(1*H*)-ones

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Received July 19, 2017

Abstract—Oxidation of 1-allyl-6- and -7-methylquinolinium iodides with potassium hexacyanoferrate(III) gave 1-allyl-6(7)-methylquinolin-2(1*H*)-ones which reacted with halogens to afford 2-halomethyl-7(8)-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium halides.

DOI: 10.1134/S1070428018040140

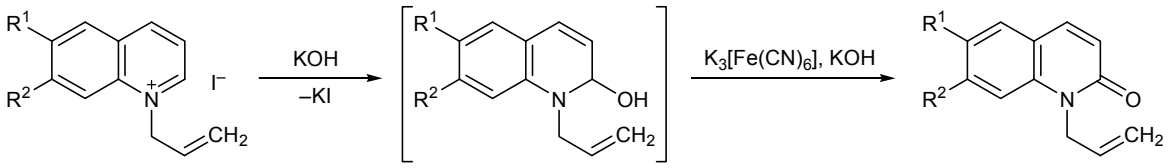
Quinolinium salts exhibit high physiological activity, and many of them have found practical application [1]. However, oxazoloquinolinium salts with bridgehead nitrogen atom remain poorly studied. Heterocyclizations of some 1-allylquinolin-2(1*H*)-ones by the action of iodine and bromine have been reported [2–5]. In this work we studied for the first time reactions of 1-allyl-6- and -7-methylquinolin-2(1*H*)-ones **2a** and **2b** with iodine, bromine, and chlorine with the goal of synthesizing new 1,2-dihydro[1,3]oxazolo[3,2-*a*]-quinolinium salts.

Compounds **2a** and **2b** were not reported previously. They were synthesized by oxidation of 1-allyl-6(7)-methylquinolinium iodides **1a** and **1b** with $K_3[Fe(CN)_6]$ according to [6] (Scheme 1). The IR spectra of **2a** and **2b** displayed a strong carbonyl stretching band at 1650 cm^{-1}, and their ^1H NMR spectra contained signals typical of allyl group. In the mass spectra of **2a** and **2b**, the molecular ion peaks $[M]^+$ had relative intensities of 41 and 49%, respectively, whereas the base peak was that of the $[M - CH_3]^+$ ion resulting from elimination of methyl radical with formation of aromatic oxazolo[3,2-*a*]quinolinium system. Elimination of allene molecule from the molecular ion gave methylquinolin-2(1*H*)-one radical cation with *m/z* 159 $[M - 40]^+$ (Scheme 2).

Allylquinolinones **2a** and **2b** reacted with iodine to give 2-iodomethyl-7(8)-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium triiodides **3a** and **3b** regardless of the reactant ratio (1 : 1 or 1 : 2). Triiodide **3a** was also synthesized by oxidative iodocyclization of 1-allyl-6-methylquinolin-2(1*H*)-one **2a** (Scheme 3); in this case, compound **2a** was dissolved in excess 57% aqueous HI, and 30% hydrogen peroxide was then added.

The reaction of **2a** with bromine gave 2-bromomethyl-7-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quin-

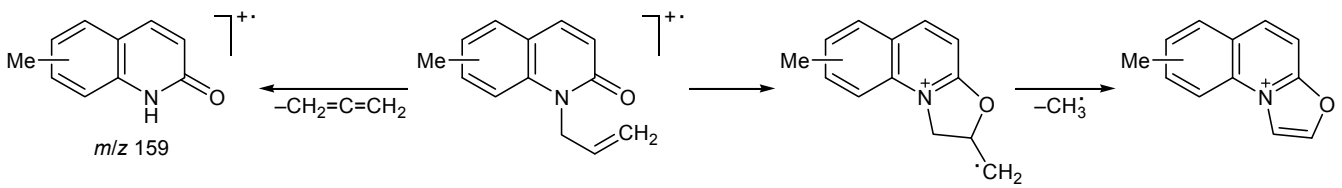
Scheme 1.



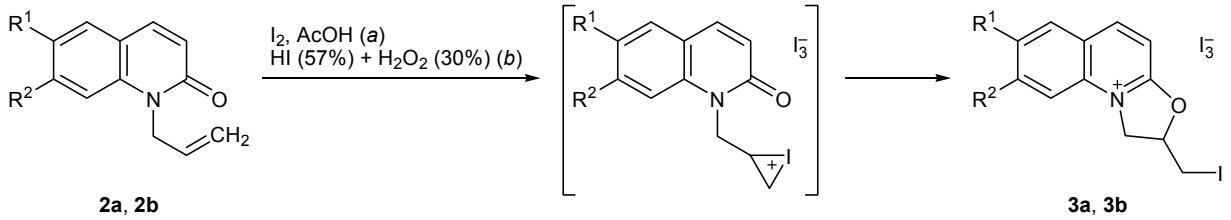
1a, **1b** **2a**, **2b**

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

Scheme 2.

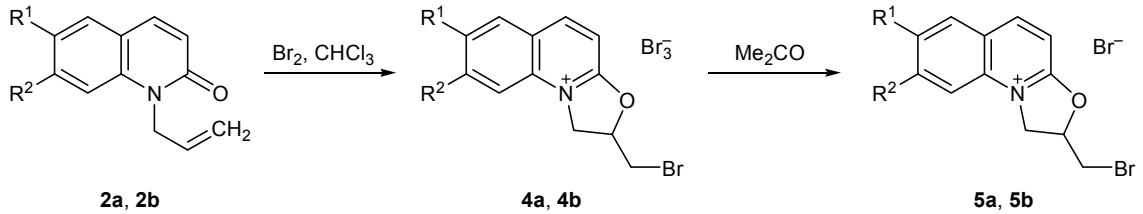


Scheme 3.



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

Scheme 4.



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

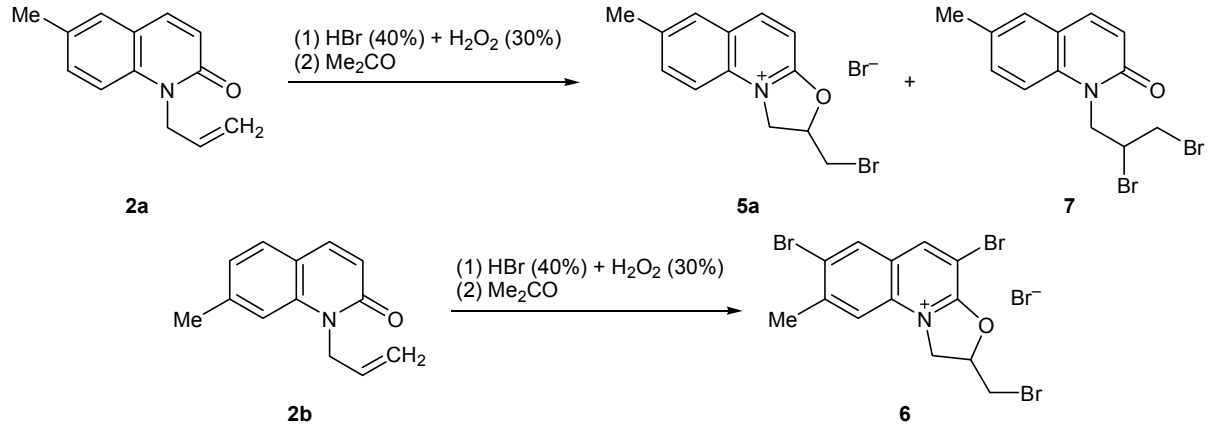
olinium tribromide (**4a**) which was converted to bromide **5a** by treatment with acetone (Scheme 4). The structure of **4a** was determined by X-ray analysis (Fig. 1). The tricyclic system of molecule **4a** is planar, while the Br–Br bond lengths in almost linear tribromide ion Br_3^- [$\angle Br^1Br^2Br^3$ 178.31(8)°] somewhat differ from each other [2.511(2) and 2.567(2) Å].

Tribromide **4b** obtained by bromination of **2b** was treated with acetone to afford 2-bromomethyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium bromide **5b**. We also made an attempt to synthesize bromide **5b** by oxidative bromocyclization of **2b** under the action of HBr–H_2O_2. However, instead of expected compound **5b**, we isolated 4,7-dibromo-2-bromomethyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium bromide (**6**); i.e., the heterocyclization was accompanied by electrophilic substitution in the aromatic fragment (Scheme 5). The ^{1}H NMR spectrum of **6** contained three aromatic proton singlets at δ 8.16, 8.52, and 9.34 ppm.

Unlike quinolinone **2b**, no electrophilic substitution was observed in the reaction of **2a** with HBr–H_2O_2. According to the ^{1}H NMR data, the products were compound **5a** and 1-(2,3-dibromopropyl)-6-methylquinolin-2(1*H*)-one **7** at a ratio of 1:0.5 (Scheme 5). Compound **7** is the product of bromine addition to the double bond of the allyl substituent. In the ^{1}H NMR spectrum of **7**, the CHBr proton resonated at δ 4.62 ppm, and the NCH_2 and CH_2Br proton signals were located at δ 4.85 and 4.09 ppm, respectively.

Under conditions of oxidative halocyclization quinolinones **2a** and **2b** could be converted to the corresponding hydrohalides. We studied the reaction of 1-allyl-6-methylquinolin-2(1*H*)-one **2a** with hydro-

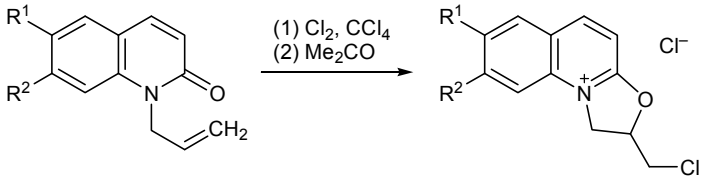
Scheme 5.



Scheme 6.

2a **8**

Scheme 7.



2a, **2b** **9a**, **9b**

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

bromic acid in acetone and found that the substrate was protonated at the oxygen atom with formation of 1-allyl-2-hydroxy-6-methylquinolinium bromide hydrate **8** (Scheme 6).

The structure of **8** was proved by X-ray analysis (Fig. 2). The $C^2 \cdots O^1$ distance [1.306(2) Å] is shorter than the sum of the covalent radii of carbon and oxygen atoms (1.51 Å) [7] but is longer than the C=O bond in aldehyde and ketone carbonyl groups [1.215(5) Å] [8]. In the crystal structure of **8**, the OH proton is involved in H-bonding with the oxygen atom of the hydration water molecule ($H_2O \cdots H$ 1.67 Å).

1-Allylquinolinones **2a** and **2b** reacted with chlorine according to the halocyclization path to produce 2-chloromethyl-7(8)-methyl-1,2-dihydro[1,3]oxazolo-[3,2-*a*]quinolinium chlorides **9a** and **9b** (Scheme 7).

In the ^{1}H NMR spectra of oxazoloquinolinium halides **3**–**5** and **9a**, signals from protons in the quinoline fragment are located significantly downfield (~1 ppm) from those of the initial quinolinones due to the presence of a positive charge on the nitrogen atom.

Thus, the reaction of 1-allyl-6(7)-methylquinolin-2(1*H*)-ones with halogens involves heterocyclization with formation of 2-halomethyl-7(8)-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium halides, whereas their oxidative bromination with $HBr–H_2O_2$ is accompanied by other transformations.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance-500 spectrometer at 500 MHz using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were obtained on a Shimadzu QP2010 Ultra GC/MS instrument. The IR spectra were measured in KBr on Bruker Tensor 27 and Varian 800FT-IR Scimitar Series spectrometers. The elemental compositions were determined on a Carlo Erba 1108 automated analyzer. The X-ray diffraction data for compounds **4a** and **8** were acquired on a D8 QUEST automated four-circle diffractometer with a CCD detector [Mo K_α radiation, graphite monochromator, ω-scanning with a step of 1°; 296(2) K]; the results were deposited as cif files to the Cambridge Crystallographic Data Centre [CCDC entry nos. 1477008 (**4a**) and 1477694 (**8**)].

Compounds 2a and b (*general procedure***).** Allyl iodide, 0.01 mol, was added to a solution of 0.01 mol of 6- or 7-methylquinoline in 20 mL of acetone. The mixture was kept for 24 h, the precipitate was filtered

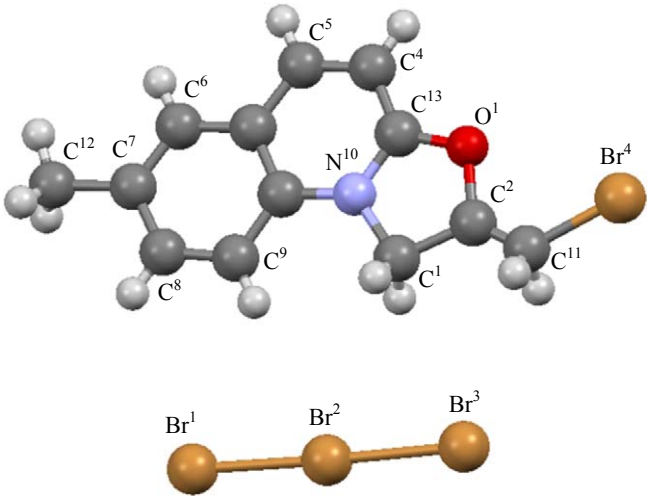


Fig. 1. Structure of the molecule of 2-bromomethyl-7-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium tribromide (**4a**) according to the X-ray diffraction data.

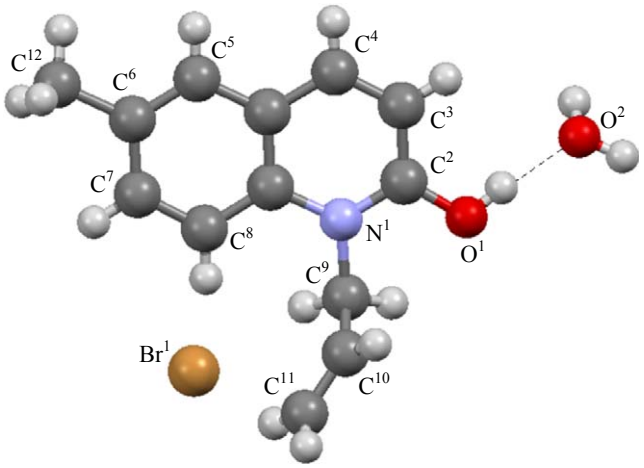


Fig. 2. Structure of the molecule of 1-allyl-2-hydroxy-6-methylquinolinium bromide hydrate (**8**) according to the X-ray diffraction data.

off and dissolved in 70 mL of water, a solution of 16.8 g (0.03 mol) of potassium hydroxide in 30 mL of water and a solution of 65.8 g (0.02 mol) of potassium hexacyanoferrate(III) in 150 mL of water were added, and the mixture was stirred for 5 h at 0–5°C. The mixture was extracted with 100 mL of diethyl ether, the solvent was distilled off from the extract, and the residue was distilled under reduced pressure.

1-Allyl-6-methylquinolin-2(1*H*)-one (2a). Yield 0.756 g (38%), bp 175–180°C (6.7×10^6 Pa), mp 35°C (from petroleum ether). IR spectrum: ν 1650 cm^{-1}, s (C=O). ^{1}H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 4.87 d.t (2H, 1′-H, ^3J = 4.7 Hz), 4.93 d.d.t (1H, 3′-H, ^3J = 17.3 Hz), 5.12 d.d.t (1H, 3′-H, ^3J = 10.5 Hz), 5.92 d.d.t (1H, 2′-H, ^3J = 17.3, 10.5, 4.6 Hz), 6.61 d (1H, 3-H, ^3J = 9.5 Hz), 7.34 d (1H, 7-H, ^3J = 8.5 Hz), 7.41 d (1H, 8-H, ^3J = 8.7 Hz), 7.52 s (1H, 5-H), 7.87 d (1H, 4-H, ^3J = 9.5 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 199 (49) $[M]^+$, 184 (100) $[M - CH_3]^+$, 159 (7) $[M - 40]^+$, 143 (10), 115 (2), 103 (5), 77 (8), 63 (3), 39 (5). Found, %: C 78.15; H 6.45; N 7.45. $C_{13}H_{13}NO$. Calculated, %: C 78.36; H 6.58; N 7.03. *M* 199.25.

1-Allyl-7-methylquinolin-2(1*H*)-one (2b). Yield 0.701 g (35%), bp 170–175°C (6.7×10^6 Pa), mp 31°C (from petroleum ether). IR spectrum: ν 1655 cm^{-1}, s (C=O). ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H, CH_3), 4.85 d (2H, 1′-H, ^3J = 4.7 Hz), 4.96 d.d (1H, 3′-H, ^3J = 17.3 Hz), 5.14 d.d (1H, 3′-H, ^3J = 10.5 Hz), 5.94 d.d.t (1H, 2′-H, ^3J = 17.3, 10.5, 4.6 Hz), 6.56 d (1H, 3-H, ^3J = 9.5 Hz), 7.08 d (1H, 5-H, ^3J = 7.9 Hz), 7.26 s (1H, 8-H), 7.61 d (1H, 6-H, ^3J = 7.9 Hz), 7.89 d (1H, 4-H, ^3J = 9.5 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 199 (41) $[M]^+$, 184 (100) $[M - CH_3]^+$, 170 (6) $[M - 29]^+$, 159 (4) $[M - 40]^+$, 142 (15), 115 (11), 103 (5), 89 (4), 77 (8), 39 (8). Found, %: C 78.21; H 6.39; N 7.15. $C_{13}H_{13}NO$. Calculated, %: C 78.36; H 6.58; N 7.03. *M* 199.25.

Triiodides 3a and 3b (*general procedure*). *a*. A solution of 0.051 g (0.2 mmol) of iodine in 5 mL of glacial acetic acid was added to a solution of 0.1 mmol of compound **2a** or **2b** in 3 mL of the same solvent. The precipitate was filtered off, washed with diethyl ether, and dried.

b. Aqueous HI (57%), 1 mL, was added to 0.2 mmol of compound **2a**, and 1 mL of 30% hydrogen peroxide was then added dropwise. The precipitate was filtered off, washed with diethyl ether, and dried.

2-Iodomethyl-7-methyl-1,2-dihydro[1,3]oxazolo-[3,2-*a*]quinolinium triiodide (3a). Yield 0.066 g (94%) (*a*), 0.120 g (85%) (*b*), mp 95°C. ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, CH_3), 3.79 d.d and 3.82 d.d (1H each, CH_2I, ^2J = 10.8, ^3J = 5.9 Hz), 4.75 d.d (1H, 1-H, ^2J = 11.9, ^3J = 7.3 Hz), 5.19 d.d (1H, 1-H, ^2J = 11.8, ^3J = 9.8 Hz), 5.79 m (1H, 2-H), 7.81 d (1H, 4-H, ^3J = 9.2 Hz), 8.01 m (2H, 8-H, 9-H), 8.12 s (1H, 6-H), 9.00 d (1H, 5-H, ^3J = 9.2 Hz). Found, %: C 22.05; H 1.92; N 1.96. $C_{13}H_{13}I_4NO$. Calculated, %: C 22.09; H 1.85; N 1.98.

2-Iodomethyl-8-methyl-1,2-dihydro[1,3]oxazolo-[3,2-*a*]quinolinium triiodide (3b). Yield 0.059 g (83%) (*a*), mp 110°C. ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 3.82 d (2H, CH_2I, ^3J = 5.9 Hz), 4.73 d.d (1H, 1-H, ^2J = 11.8, ^3J = 7.2 Hz), 5.17 d.d (1H, 1-H, ^2J = 11.8, ^3J = 9.8 Hz), 5.77 m (1H, 2-H), 7.72 d (1H, 7-H, ^3J = 8.4 Hz), 7.74 d (1H, 4-H, ^3J = 9.2 Hz), 7.95 s (1H, 9-H), 8.22 d (1H, 6-H, ^3J = 8.2 Hz), 9.03 d (1H, 5-H, ^3J = 9.2 Hz). Found, %: C 22.03; H 1.87; N 1.94. $C_{13}H_{13}I_4NO$. Calculated, %: C 22.09; H 1.85; N 1.98.

2-Bromomethyl-7-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium tribromide (4a). A solution of 0.2 mmol (0.01 mL) of bromine in 3 mL of chloroform was added to a solution of 0.1 mmol of quinolinone **2a** in 3 mL of chloroform. The precipitate was filtered off and dried. Yield 0.040 g (76%), mp 85°C.

Bromides 5a and 5b (*general procedure*). A solution of 0.2 mmol (0.01 mL) of bromine in 3 mL of glacial acetic acid or chloroform was added to a solution of 0.1 mmol of quinolinone **2a** or **2b** in 3 mL of the same solvent. The precipitate was filtered off, treated with 3 mL of acetone, and dried.

2-Bromomethyl-7-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium bromide (5a). Yield 0.023 g

(65%), mp 194°C. ^{1}H NMR spectrum, δ, ppm: 2.57 s (3H, CH_3), 4.12 d.d (1H, CH_2Br, ^2J = 11.4, ^3J = 5.9 Hz), 4.15 d.d (1H, CH_2Br, ^2J = 11.4, ^3J = 4.6 Hz), 4.87 d.d (1H, 1-H, ^2J = 11.9, ^3J = 7.2 Hz), 5.23 d.d (1H, 1-H, ^2J = 11.8, ^3J = 10.0 Hz), 5.94 m (1H, 2-H), 7.82 d (1H, 4-H, ^3J = 9.2 Hz), 7.99 m (2H, 8-H, 9-H), 8.15 s (1H, 6-H), 9.03 d (1H, 5-H, ^3J = 9.3 Hz). Found, %: C 43.45; H 3.67; N 3.93. $C_{13}H_{13}Br_2NO$. Calculated, %: C 43.49; H 3.65; N 3.90.

2-Bromomethyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium bromide (5b). Yield 0.024 g (68%), mp 135°C. ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 4.11 d.d (1H, CH_2Br, ^2J = 11.4, ^3J = 5.8 Hz), 4.15 d.d (1H, CH_2Br, ^2J = 11.4, ^3J = 4.7 Hz), 4.86 d.d (1H, 1-H, ^2J = 11.9, ^3J = 7.0 Hz), 5.17 d.d (1H, 1-H, ^2J = 11.8, ^3J = 10.0 Hz), 5.93 m (1H, 2-H), 7.72 d (1H, 7-H, ^3J = 8.4 Hz), 7.76 d (1H, 4-H, ^3J = 9.2 Hz), 7.94 s (1H, 9-H), 8.23 d (1H, 6-H, ^3J = 8.2 Hz), 9.04 d (1H, 5-H, ^3J = 9.2 Hz). Found, %: C 43.47; H 3.62; N 3.92. $C_{13}H_{13}Br_2NO$. Calculated, %: C 43.49; H 3.65; N 3.90.

4,7-Dibromo-2-bromomethyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium bromide (6). Aqueous HBr (40%), 2 mL, was added to 0.2 mmol of quinolinone **2b**, and 2 mL of 30% hydrogen peroxide was then added dropwise. The precipitate was filtered off, washed with 3 mL of acetone, and dried. Yield 0.072 g (70%), mp 189°C. ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 4.12 d (2H, CH_2Br, ^3J = 5.5 Hz), 4.96 d.d (1H, 1-H, ^2J = 12.1, ^3J = 7.2 Hz), 5.27 d.d (1H, 1-H, ^2J = 12.2, ^3J = 9.9 Hz), 5.99 m (1H, 2-H), 8.16–9.34 m (3H, 5-H, 6-H, 9-H). Found, %: C 30.23; H 2.17; N 2.75. $C_{13}H_{11}Br_4NO$. Calculated, %: C 30.21; H 2.15; N 2.71.

1-Allyl-2-hydroxy-6-methylquinolinium bromide hydrate (8). Compound **2a**, 0.1 mmol, was dissolved in 1 mL of acetone, 1 mL of 40% aqueous HBr was added, and the mixture was left to stand for 24 h. The precipitate was filtered off and dried. Yield 84%, mp 157°C. Found, %: C 52.42; H 5.32; N 4.65. $C_{13}H_{16}BrNO_2$. Calculated, %: C 52.36; H 5.37; N 4.70.

Chlorides 9a and 9b (*general procedure*). Gaseous chlorine was passed through a solution of 0.4 mmol of compound **2a** or **2b** in 5 mL of carbon tetrachloride until a solid no longer separated. The precipitate was filtered off, washed with acetone, and dried.

2-Chloromethyl-7-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium chloride (9a). Yield 0.052 g (48%), mp 120°C. ^{1}H NMR spectrum, δ, ppm: 2.57 s (3H, CH_3), 4.32 m (2H, CH_2Cl), 4.95 m and 5.25 m (1H each, 1-H), 5.96 m (1H, 2-H), 7.84 d (1H, 4-H, ^3J = 9.2 Hz), 8.01 m (2H, 8-H, 9-H), 8.15 s (1H, 6-H), 9.05 d (1H, 5-H, ^3J = 9.2 Hz). Found, %: C 57.83; H 4.82; N 5.13. $C_{13}H_{13}Cl_2NO$. Calculated, %: C 57.80; H 4.85; N 5.18.

2-Chloromethyl-8-methyl-1,2-dihydro[1,3]oxazolo[3,2-*a*]quinolinium chloride (9b). Yield 0.034 g (31%), mp 137°C. ^{1}H NMR spectrum, δ, ppm: 2.65 s (3H, CH_3), 4.26 d.d (1H, CH_2C, ^2J = 12.4, ^3J = 5.6 Hz), 4.29 d.d (1H, CH_2Cl, ^2J = 12.4, ^3J = 4.0 Hz), 4.90 d.d (1H, 1-H, ^2J = 11.9, ^3J = 7.1 Hz), 5.19 d.d (1H, 1-H, ^2J = 11.6, ^3J = 10.0 Hz), 5.95 m (1H, 2-H), 7.72 d (1H, 7-H, ^3J = 8.4 Hz), 7.76 d (1H, 4-H, ^3J = 9.2 Hz), 7.93 s (1H, 9-H), 8.24 d (1H, 6-H, ^3J = 8.2 Hz), 9.06 d (1H, 5-H, ^3J = 9.2 Hz). Found, %: C 57.83; H 4.87; N 5.15. $C_{13}H_{13}Cl_2NO$. Calculated, %: C 57.80; H 4.85; N 5.18.

This study was performed under financial support by the Government of the Russian Federation (resolution no. 211, March 16, 2013; contract no. 02.A03.21.0011) and in the framework of state assignment no. 4.9665.2017/BCh.

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