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1-ALKYL-3-ETHYLTHIO-4-(*N*-BENZOYL-*N*-PHENYLAMINO)-QUINOLINIUM SALTS — SYNTHESIS AND TRANSFORMATIONS[#]

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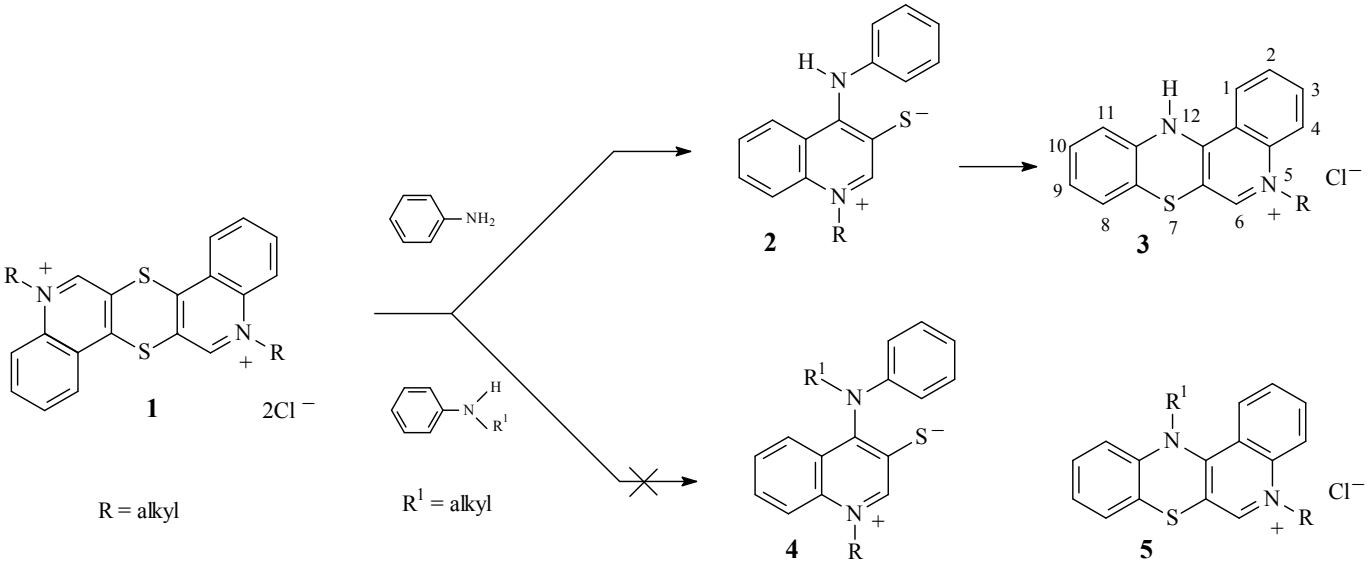
Abstract – The reaction of 1-alkyl-4-(phenylamino)quinolinium 3-thiolates (**2**) with benzoyl chloride leads to 1-alkyl-3-benzoylthio-4-(phenylamino)quinolinium chloride (**6**). In the presence of DABCO, compounds (**6**) split off hydrogen chloride yielding 1-alkyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7**). Alkylation of 4-(phenylimino)quinoline (**7**) with ethyl bromide leads to 1-alkyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromide (**10**). The structure of the obtained compounds were analyzed using ^{1}H NMR (NOE) and ^{15}N NMR spectral methods. The structure of compound (**10a**) was confirmed by X-ray analysis.

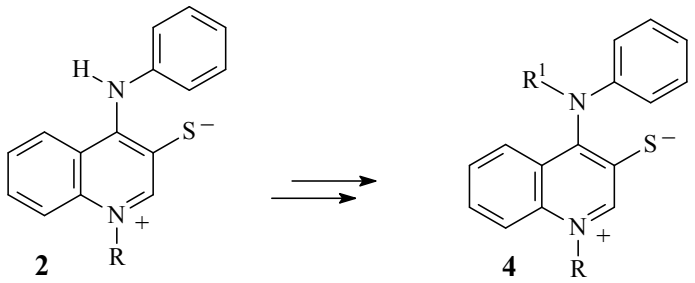
INTRODUCTION

Phenothiazine derivatives exhibit interesting chemical properties and pharmaceutical activities.[1] Many phenothiazine derivatives with the substituent attached to the thiazine nitrogen have been used as neuroleptic and antihistaminic drugs.[2,3] In our earlier reports we described a two-step synthesis of 5-alkyl-12*H*-quino[3,4-*b*][1,4]benzothiazinium chloride[4,5] **3** from thioquinantrenediinium bis-salts[6] **1** *via* 1-alkyl-4-(phenylamino)quinolinium 3-thiolates **2** (Scheme 1). This reaction is a new method of synthesis of the 1,4-thiazine systems. Adaptation of the described procedure to obtain the 3-thiolates **4** and 12-substituted quino[3,4-*b*][1,4]benzothiazine derivatives (**5**) in the reaction of thioquinantrenediinium bis-salts (**1**) with secondary amines was unsuccessful (Scheme 1).



Scheme 1

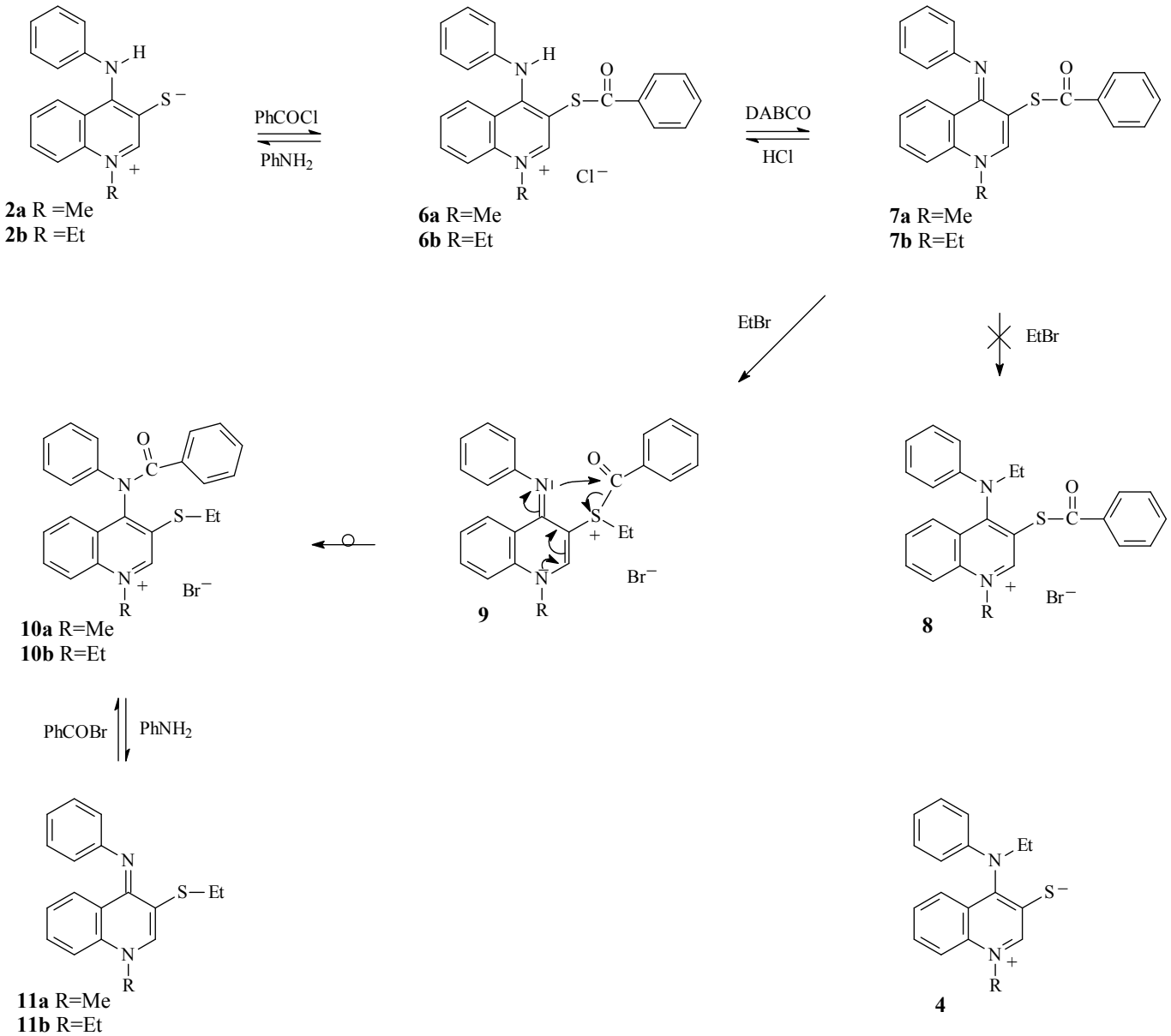
The present study was aimed at using of 1-alkyl-4-(phenylamino)quinolinium 3-thiolates (**2**) as a source of 1-alkyl-4-(*N*-alkyl-*N*-phenylamino)quinolinium 3-thiolates (**4**). Cyclization of the 3-thiolates (**4**) could possibly lead to the expected 12-substituted quino[3,4-*b*][1,4]benzothiazine derivatives (**5**).



RESULTS AND DISCUSSION

The thiolate function in 1-alkyl-4-aminoquinolinium 3-thiolates can be protected as a thioester, from which it is regenerated by aminolysis reaction.[7] The reactions of 1-alkyl-4-(phenylamino)quinolinium 3-thiolates (**2**) with benzoyl chloride (Scheme 2) occur easily as *S*-acylation and led to 1-methyl-3-benzoylthio-4-(phenylamino)quinolinium chlorides (**6**). The structure of compounds **6** was confirmed by ^{1}H and ^{15}N NMR spectra. In ^{1}H NMR spectra of compounds (**6a-b**) in $CDCl_3$ solution, the signal of NH amine proton occurs in a typical range at δ = 11.80 and 11.97 ppm. The ^{15}N NMR spectrum of the compound (**6a**) in DMSO-d_6 revealed two resonances at δ_N = – 220.3 and – 254.4. They were assigned with the help of the ^{1}H–^{15}N HSQC and HMBC spectra. In the case of the quinoline endocyclic nitrogen atom (δ_N = – 220.3), a three-bond correlation with the H8 proton (δ_H = 8.24-8.29) and a two-bond

correlation with the H2 proton (δ_H = 9.12) were observed. A one-bond correlation between the exocyclic nitrogen atom (δ_N = – 254.4) and the NH proton (δ_H = 11.52, $^1J_{N\text{-}H}$ = 92 Hz) was also detected. These results provided the evidence for NH group being present at the 4-position in the quinoline ring.[8]



Scheme 2

The reaction of salt **6** with aniline occurs *via* nucleophilic attack of the amine nitrogen atom on the carboxylic carbon atom and results in restitution of the thiolate function at the 3-position in the quinoline ring.

Table 1. Preparation of 1-alkyl-4-(phenylamino)quinolinium 3-thiolates (**2**) from 1-alkyl-3-benzoylthio-4-(phenylamino)quinolinium chloride (**6**).

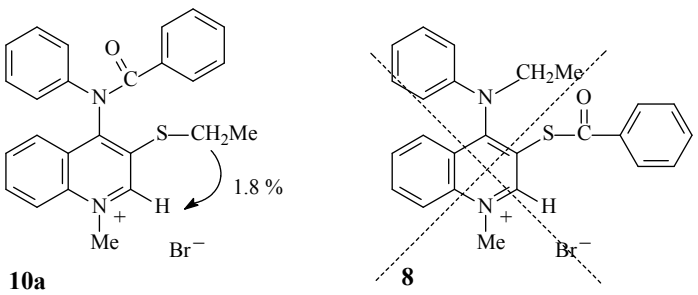
Substrate	Product	Yield[%]
6a	**2a**	74
6b	**2b**	62

In the presence of a base (DABCO), the compounds (**6**) were dehydrochlorinated to 1-alkyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7**) with quantitative yield. On the other hand, the reaction of 4-(phenylimino)quinolines (**7**) with hydrogen chloride led with quantitative yield to 4-(phenylamino)quinoline derivatives (**6**). The course of these reactions confirms the imine structure of compounds (**7**).

In our earlier report, we described reactions of 1-alkyl-3-alkylthio-1,4-dihydro-4-(phenylimino)-quinolines with alkylating agents, which occurred as *N*-alkylation at the imine nitrogen atom and led to 1-alkyl-3-alkylthio-4-(*N*-alkyl-*N*-phenylamino)quinoline salts.[4] We expected that 1-alkyl-3-benzoylthio-4-(*N*-ethyl-*N*-phenylamino)quinolinium bromide (**8**) can be obtained in the same way. A cleavage of the thioester group in the presence of aniline could possibly lead to the expected 3-thiolates (**4**).

Contrary to expectation the reactions of the 4-iminochinolines (**7**) with ethyl bromide led to 1-alkyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromides (**10**). The reaction of compounds (**10**) with aniline led to 1-alkyl-3-ethylthio-1,4-dihydro-4-(phenylimino)quinolines (**11**) (Scheme 2).

A two-step reaction mechanism is proposed in order to explain the formation of compounds (**10**) following alkylation of compounds (**7**) with ethyl bromide. In the first step the compound (**7**) undergoes *S*-alkylation to give intermediate of the sulfonium salt structure (**9**). Then the sulfonium salt (**9**) undergoes intramolecular rearrangement to give compounds (**10**) by acylation at imine nitrogen atom. This hypothesis is supported by reaction 4-(phenylimino)quinolines (**11**) with benzoyl bromide. The structure of compounds (**10**) was studied using NOE ^{1}H-^{1}H homonuclear experiment (Scheme 3) as well as X-ray analysis (Figure 1).



10a **8**

Scheme 3

Irradiation of methylene protons (δ = 3.34 - 3.40) in $MeCH_2$ group of the compound (**10a**) increased the intensity of quinoline H2 signal (δ = 8.52, 1.8 %) (Scheme 3). This rules out the expected compound (**8**) to be the product of the reaction considered as its ethyl group is linked to the exocyclic nitrogen atom in the 4-position of quinoline.

X-Ray analysis of the derivative (**10a**) demonstrated definitely that the examined compound has the structure of 1-methyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromide (Figure 1).

The quinoline moiety is planar, maximum deviation from planarity is 0.024(4) Å for atom C3 and the methyl group at the endocyclic nitrogen atom is in the quinoline plane. The valence angle C8A-N1-C2 is equal to 121.8(3)° which is a value typical of azine salts. The bond length between the carbonyl carbon atom and exocyclic nitrogen atom N2 is equal to 1.383(5) Å.

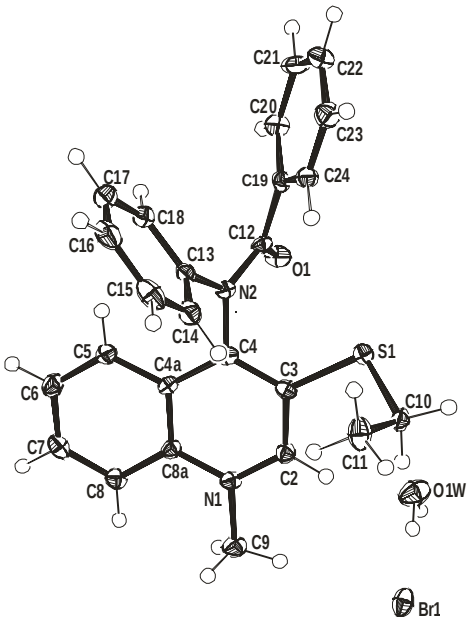


Figure 1. View of 1-methyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromide **10a.**

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra (at 300 MHz) were recorded using a Varian VXR 300 spectrometer at 303 K. Proton chemical shifts are reported relative to TMS (δ = 0.0) as internal standards. ^{15}N NMR spectra were recorded in the DMSO solution using a Bruker AM 500 spectrometer at 50.698 MHz. NOE ^{1}H-^{1}H homonuclear experinent was carried out for (**10a**) in the $CDCl_3$ solution at 500 MHz. EI MS spectra were recorded using an LKB GC MS 20091 spectrometer at 75 eV.

X-Ray data were collected on a Bruker KappaApexII diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å). Diffractometer control program Collect,[9] unit cell parameters and data reduction with Denzo and Scalepak.[10] The structure was solved by direct methods SHELXS-97[11] and refined by full-matrix least-squares minimization based on all unique F^2 (SHELXL-97[12]).

Crystal data: $C_{25}H_{23}N_2OS^+ \cdot Br^- \cdot H_2O$, M = 497.44, light-yellow block, 0.50 × 0.30 × 0.30 mm, orthorhombic, space group *Pbca*, a = 13.26(3), b = 9.4976(5), c = 36.548(1) Å, V = 4605.8(3) Å^3, Z = 8, D_c = 1.435 g/cm^3, $F(000)$ = 2048, μ = 1.900 mm^{-1}, T = 100(2)K, $2\theta_{max}$ = 55.0º. 23818 reflections collected, 5041 unique (R_{int} = 0.044). Final *GooF* = 1.08, R = 0.059, wR = 0.102, R indices based on 3975 reflections with $I > 2\sigma(I)$ for 288 parameters and 0 restraints.

The crystallographic data for the structure (**10a**) have been deposited at the Cambridge Crystallographic Data Center (depository number CCDC-689038).

1-Alkyl-3-benzoylthio-4-(phenylamino)quinolinium chloride (**6**):

A. From 1-alkyl-4-(phenylamino)quinolinium 3-thiolates (**2**)

The mixture of 1-alkyl-4-(phenylamino)quinolinium 3-thiolates (**2**) (1 mmol) and benzoyl chloride (702 mg, 5 mmol) was mixed at rt for 2 h. The obtained chloride (**6**) was filtered off and washed with Et_2O. The raw product was purified through recrystallization from EtOH.

B. From 1-alkyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7**)

Hydrogen chloride was passed through the solution of 4-(phenylimino)quinoline (**7**) (1 mmol) in dry benzene (15 mL) at rt over 5 min. The solid product was filtered off and washed with dry benzene. The raw product was purified through recrystallization from EtOH.

1-Methyl-3-benzoylthio-4-(phenylamino)quinolinium chloride (**6a**): yield: (A) 92 %, (B) 89 %. ^{1}H NMR ($CDCl_3$) δ: 4.27(s, 3H, NMe), 7.02-7.16(m, 3H, H_{arom}), 7.18-7.26(m, 2H, H_{arom}), 7.29-7.42(m, 3H, H_{arom}), 7.49-7.58(m, 3H, H_{arom}), 7.82-7.93(m, 2H, H_{arom}), 8.61(s, 1H, $H2_{quinolinyl}$), 9.37-9.48(m, 1H, $H5_{quinolinyl}$), 11.80(s, 1H, NH). *Anal*. Calcd for $C_{23}H_{19}ClN_2OS$: C 67.89, H 4.71, Cl 8.71, N 6.88, S 7.88. Found: C 67.81, H 4.64, Cl 8.62, N 6.81, S 7.95.

1-Ethyl-3-benzoylthio-4-(phenylamino)quinolinium chloride (**6b**): yield: (A) 90%, (B) 86%. ^{1}H NMR ($CDCl_3$) δ: 1.62-1.81(t, J=7.5 Hz, 3H, NCH_2Me), 4.14-4.26(q, J=7.5 Hz, 2H, $NC\underline{H_2}Me$), 7.05-7.23(m. 3H, H_{arom}), 7.25-7.48(m, 5H, H_{arom}), 7.52-7.64(m, 3H, H_{arom}), 7.85-8.07(m, 2H, H_{arom}), 8.75(s, 1H, $H2_{quinolinyl}$), 9.41-9.51(m, 1H, $H5_{quinolinyl}$), 11.97(s, 1H, NH). *Anal*. Calcd for $C_{24}H_{21}ClN_2OS$: C 68.48, H 5.03, Cl 8.42, N 6.65, S 7.62. Found: C 68.43, H 5.12, Cl 8.29, N 6.57, S 7.69.

1-Alkyl-4-(phenylamino)quinolinium-3-thiolate (**2**) from chloride (**6**):

Aniline (280 mg, 3 mmol) was added to the mixture of chloride (**6**) (1 mmol) in dry pyridine (10 mL) and the whole was mixed at 70 °C for 2 h. The solid product was filtered off and washed with dry Et_2O. The raw product was purified through recrystallization from EtOH.

1-Alkyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7**):

The solution of DABCO (135 mg, 1.2 mmol) in MeOH (5 mL) was added to the mixture of chloride (**6**) (1 mmol) in MeOH (10 mL) and the whole was mixed at rt for 1 h. The product was filtered off and washed with MeOH. The raw product was purified through recrystallization from EtOH.

1-Methyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7a**): yield 84%. oil. EI MS, (m/z): 370(M^+, 60%), 265(M^+-105, 65%). ^{1}H NMR ($CDCl_3$) δ: 4,17(s, 3H, NMe), 7.05-7.32(m, 7H, H_{arom}), 7.43-7.60(m, 3H, H_{arom}), 7.62-7.80(m, 3H, H_{arom}), 7.86-7.95(m, 1H, $H5_{quinolinyl}$), 9.12(s, 1H, $H2_{quinolinyl}$). *Anal*. Calcd for $C_{23}H_{18}N_2OS$: C 74.57, H 4.90, N 7.56, S 8.65. Found: C 74.55, H 4.97, N 7.48, S 8.72.

1-Ethyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7b**): yield 75%. oil EI MS, (m/z): 384(M^+, 72%), 279(M^+-105, 68%). ^{1}H NMR ($CDCl_3$) δ: 1.73-1.88(t, *J*=7.1 Hz, 3H, NCH_2Me), 4.11-4.25(q, *J*= 7.1 Hz, 2H, $NC\underline{H_2}Me$), 7.05-7,45(m, 7H, H_{arom}), 7.48-7.59(m, 3H, H_{arom}), 7.60-7.79(m, 3H, H_{arom}), 8.12-8.20(m, 1H, $H5_{quinolinyl}$), 9.17(s, 1H, $H2_{quinolinyl}$) (*Anal*. Calcd for $C_{24}H_{20}N_2OS$: C 74.97, H 5.24, N 7.29, S 8.34. Found: C 74.94, H 5.18, N 7.22, S 8.32.

1-Alkyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromide (**10**):

A. From 1-alkyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7**)

The mixture of 1-alkyl-3-benzoylthio-1,4-dihydro-4-(phenylimino)quinoline (**7**) (1 mmol) and ethyl bromide (545 mg, 5 mmol) was mixed at 50 °C for 2 h. The mixture was cooled down to rt, the product was filtered off and washed with Et_2O. The raw product was purified through recrystallization from EtOH.

B. From 1-alkyl-3-ethylthio-1,4-dihydro-4-(phenylimino)quinolines (**11**)

The mixture of compound (**11**) (1 mmol) and benzoyl bromide (555 mg, 3 mmol) was mixed at 70 °C for 4 h. The obtained bromide (**10**) was filtered off and washed with Et_2O. The raw product was purified through recrystallization from EtOH.

1-Methyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromide (**10a**: yield: (A) 87%, (B) 91%. ^{1}H NMR (DMSO-d_6) δ: 1.18-35(t, *J*=7.0 Hz, 3H, SCH_2Me), 3.34-3.40(q, *J*=7.0 Hz, 2H, $SC\underline{H_2}Me$), 4.72(s, 3H, NMe), 7.06-7.66(m, 10H, H_{arom}), 7.93-8.10(m, 1H, H_{arom}), 8.12-8.19(m, 1H, H_{arom}), 8.28-8.36(m, 1H, H_{arom}), 8.52(s, 1H, $H2_{quinolinyl}$), 9.78-9.90(m, 1H, $H5_{quinolinyl}$). *Anal*. Calcd for $C_{25}H_{23}BrN_2OS$: C 62.63, H 4.84, N 5.84, S 6.62. Found: C 62.57, H 4.93, N 5.79, S 6.67.

1-Ethyl-3-ethylthio-4-(*N*-benzoyl-*N*-phenylamino)quinolinium bromide (**10b**): yield: (A) 91%, (B) 94 %.

^{1}H NMR (DMSO-d_6) δ: 1.25-1.34(t, *J*=7.2 Hz, 3H, SCH_2Me), 1.54-1.79(t, *J*=7.5 Hz, 3H, NCH_2Me), 3.35-3.47(q, *J*=7.2 Hz, 2H, $SC\underline{H}_2Me$), 5.05-5.24(q, *J*=7.5 Hz, 2H, $NC\underline{H}_2Me$), 7.05-7.82(m, 10H, H_{arom}), 7.82-7.98(m, 1H, H_{arom}), 8.11-8.23(m, 1H, H_{arom}), 8.32-8.41(m, 1H, H_{arom}), 8.61(s, 1H, $H2_{quinolinyl}$), 9.69-9.86(m, 1H, $H5_{quinolinyl}$). *Anal*. Calcd for $C_{26}H_{25}BrN_2OS$: C 63.28, H 5.11, N 5.68, S 6.50. Found: C 63.23, H 5.07, N 5.59, S 6.55.

1-Alkyl-3-ethylthio-1,4-dihydro-4-(phenylimino)quinoline (**11**):

Aniline (140 mg, 1.2 mmol) was added to the mixture of bromide (**10**) (1 mmol) in dry pyridine (10 mL) and the whole was mixed at 70 °C for 4 h. After cooling down to rt the mixture was poured into water (50 mL). The resulting solid was filtered off and washed with water. The product was dehydrated in a vacuum exsiccator over calcium chloride. The raw product was recrystallized from EtOH.

1-Methyl-3-ethylthio-1,4-dihydro-4-(phenylimino)quinoline (**11a**): yield 76%. mp 106-108 °C. EI MS, (m/z): 294(M^+, 82%). ^{1}H NMR ($CDCl_3$) δ: 0.99-1.04(t, *J*=7.4 Hz, 3H, SCH_2Me), 2.49-2.55(q, *J*=7.4 Hz, 2H, $SC\underline{H}_2Me$), 3.66(s, 1H, NMe), 6.64-6.72(m, 2H, H_{arom}), 6.81-6.85(m, 1H, H_{arom}), 7.05-7.10(m, 1H, $H6_{quinolinyl}$), 7.14-7.19(m, 2H, H_{arom}), 7.40-7.43(m, 1H, $H8_{quinolinyl}$), 7.49-7.54(m, 1H, $H7_{quinolinyl}$), 7.64(s, 1H, $H2_{quinolinyl}$), 7.93-7.99(m, 1H, $H5_{quinolinyl}$). *Anal*. Calcd for $C_{18}H_{18}N_2S$: C 73.43, H 6.16, N 9.51, S 10.89. Found: C 73.40, H 6.19, N 9.42, S 10.96.

1-Ethyl-3-ethylthio-1,4-dihydro-4-(phenylimino)quinoline (**11b**): yield 84%. oil. EI MS, (m/z): 308(M^+, 87%). ^{1}H NMR ($CDCl_3$) δ: 1.05-1.15(t, *J*=7.4 Hz, 3H, SCH_2Me), 1.40-1.49(t, *J*=7.5 Hz, 3H, NCH_2Me), 2.52-2.67(q, *J*=7.4 Hz, 2H, $SC\underline{H}_2Me$), 4.01-4.12(q, *J*=7.5 Hz, 2H, $NC\underline{H}_2Me$), 6.84-6.90(m, 2H, H_{arom}), 6.92-6.99(m, 1H, H_{arom}), 7.02-7.11(m, 1H, H_{arom}), 7.19-7.31(m, 3H, H_{arom}), 7.42-7.48(m, 1H, H_{arom}), 7.52(s, 1H, $H2_{quinolinyl}$), 8.02-8.19(m, 1H, $H5_{quinolinyl}$). *Anal*. Calcd for $C_{19}H_{20}N_2S$: C 73.99, H 6.54, N 9.08, S 10.39. Found: C 73.94, H 6.49, N 9.01, S 10.34.

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