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1-ALKYL-4-(3-PYRIDINYLAMINO)QUINOLINIUM-3-THIOLATES AND THEIR TRANSFORMATION INTO NEW DIAZAPHENOTHIAZINE DERIVATIVES [#]

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Abstract - The reactions of 5,12-dialkylthioquinantrenediinium bis-salts (**1**) with 3-aminopyridine yield 1-alkyl-4-(3-pyridinylamino)quinolinium-3-thiolates (**2**). In the presence of oxygen and hydrogen chloride, the compounds (**2**) undergo cyclization to 1,4-thiazine derivatives having the structure of 5-alkyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium salts (**4**). The structure of 3-thiolates (**2**) was analyzed using ^{1}H NMR (NOE) and ^{15}N NMR spectral methods. The structure of compound (**4**) was confirmed by X-Ray analysis.

INTRODUCTION

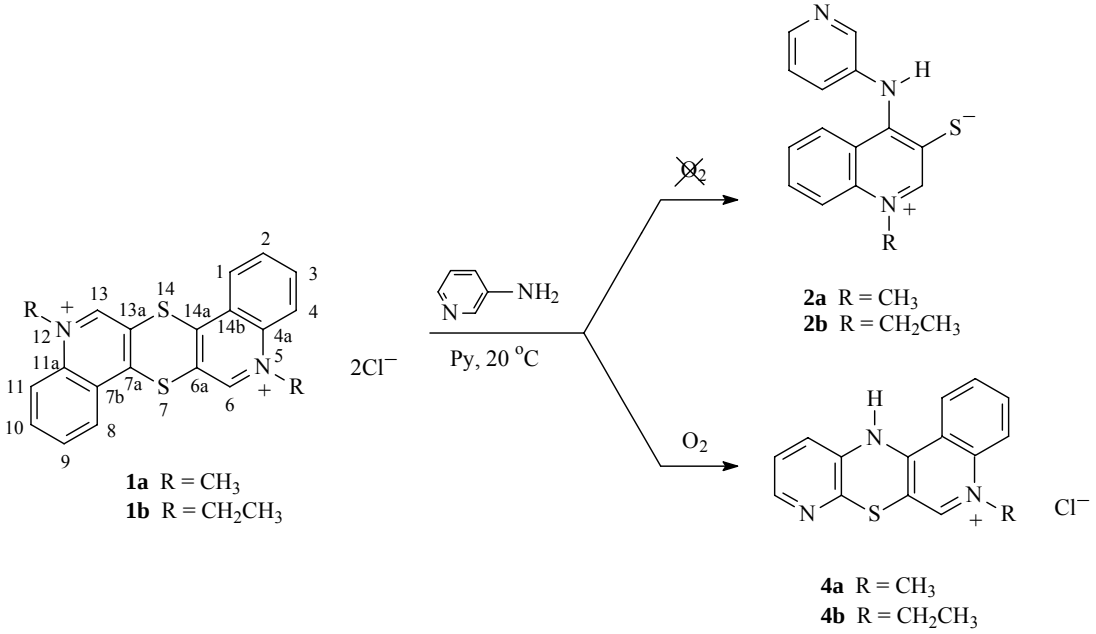
Many phenothiazine derivatives have been used as drugs. Modifications of the main structural fragment of phenothiazine drugs reveal interesting chemical properties and potent biological activity.[1-3] Extensive research has been conducted on new methods of synthesizing potentially useful phenothiazine derivatives with pharmacological activity.[4,5] New applications of phenothiazine derivatives have also been found.[6,7]

We earlier described the reaction of bis-salts (**1**) with primary aliphatic amines [8] and aniline derivatives.[9] These reactions led to 1-alkyl-4-aminoquinolinium-3-thiolates. 1-Alkyl-4-arylaminoquinonolinium-3-thiolates in the presence of oxygen and hydrogen chloride undergo cyclization to quino[1,4]benzothiazine derivatives. This reaction is a new method of synthesizing phenothiazine derivatives.[9] We here report the

results of our studies involving reactions of 5,12-dialkylthioquinantrenediinium bis-salts (**1**) with aminopyridines**.**

RESULTS AND DISCUSSION

5,12-Dialkyltioquinantrenediinium bis-salts[10] (**1**) were obtained by alkylating thioquinantrene (1,4-dithiino[2,3-*c*;5,6-*c*']diquinoline).[11] Reactions of salts (**1**) with three isomeric 2-, 3- and 4-aminopyridines were investigated.

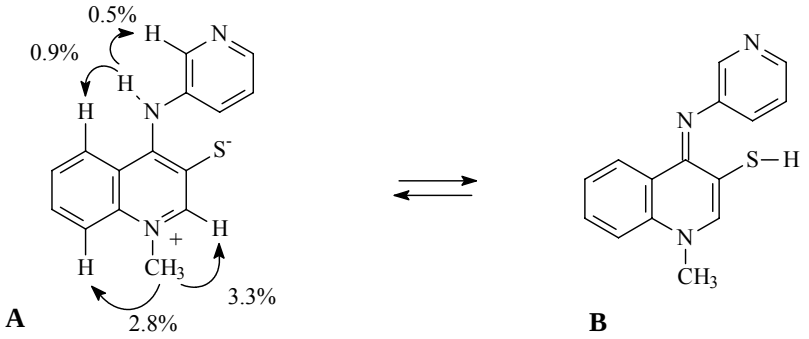


Scheme 1

Reactions of salts (**1**) with 3-aminopyridine, carried out in pyridine solution at room temperature, occur with complete consumption of salts (**1**). The reactions occur by nucleophilic attack of *exo*cyclic nitrogen atom of 3-aminopyridine on *aza*-activated positions 7a and 14a of salt (**1**), which leads to the opening of 1,4-dithiin ring of salt (**1**). Our studies have demonstrated that the structure of reaction products depends on the presence of oxygen in the reaction mixture (Scheme 1). When such mixture was prevented from atmospheric oxygen, this led to the precipitation of 1-alkyl-4-(3-pyridinylamino)quinolinium-3-thiolates (**2**). Contrarily, oxygen presence and additional intensive mixing of the mixture caused the reaction to continue and led to 5-alkyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4**). No reaction was observed between bis-salts (**1**) and 2- and 4-aminopyridine.

The structure of compounds (**2**) was analyzed by NOE ^{1}H-^{1}H homonuclear experiment (Scheme 2) and ^{15}N NMR spectra carried out for **2a** in the $CDCl_3$ solution (Figure 1). Irradiation of the NH amino proton (δ = 10.18 ppm) causes enhancement of the quinolinium proton signal H5 (multiplet, δ = 8.44-8.52 ppm) by 0.9 % and pyridine proton signal H2 (singlet, 8.48 ppm) by 0.5 %. It was also observed that irradiation

of the methyl group attached to the *endo*cyclic nitrogen atom (δ = 4.15 ppm) causes enhancement of the quinolinium proton signal H8 (multiplet, δ = 7.64-7.74 ppm) by 2.8% and quinolinium proton signal H2 (singlet, δ = 8.67 ppm) by 3.3 %. No NOE was observed between NH and the pyridine H4 proton.



2a

Scheme 2

The ^{15}N NMR spectrum of thiolate (**2a**) revealed three resonances at δ_N = – 66.8, – 230.8 and – 265.6 ppm. They were assigned with the help of the ^{1}H–^{15}N HSQC and HMBC spectra (Figure 1). In the case of the quinoline *endo*cyclic nitrogen atom (δ_N = – 230.8 ppm) three-bond correlation with H8 (δ_H = 7.64-7.74 ppm) and the two-bond correlation with H2 (δ_H = 8.72 ppm) was observed. For the pyridine *endo*cyclic nitrogen atom (δ_N = – 66.8 ppm) the two-bond correlation with H2 pyridine proton (δ_H = 8.48 ppm) was observed. A one-bond correlation between the *exo*cyclic nitrogen atom (δ_N = – 265.6 ppm) and the NH proton (δ_H = 10.18 ppm, $^{1}J_{N\text{-}H}$ = 89 Hz) was also detected.

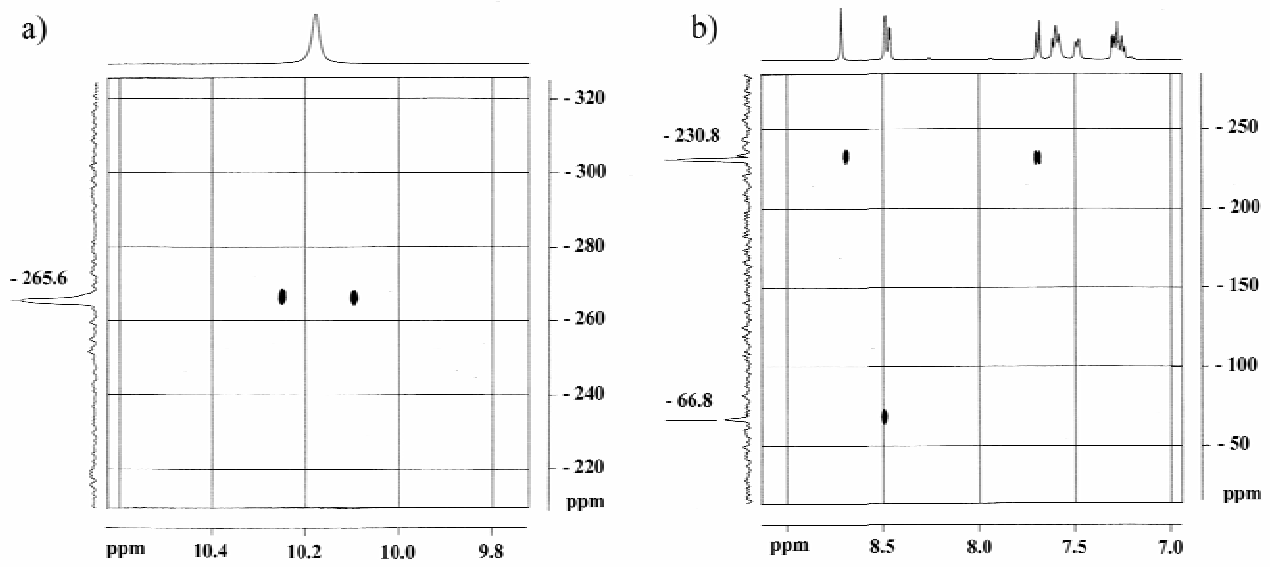
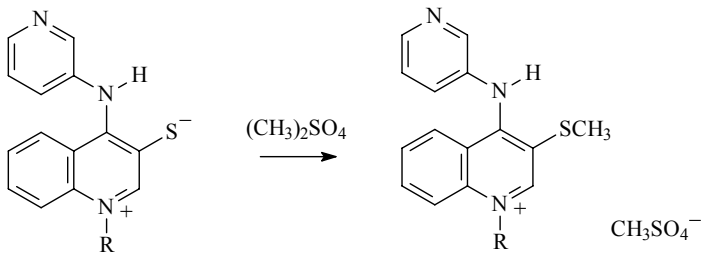


Figure 1. Two-dimensional ^{1}H-^{15}N NMR spectra of 1-methyl-4-(3-pyridinylamino)quinolinium-3-thiolate (**2a**); a) HSQC, b) HMBC

Such magnitude of the coupling constant $^{1}J_{N\text{-}H}$ provides the evidence for NH group presence.[12] These spectral data are consistent with the betaine-type structure **A** of compouds (**2**).

Thiolate anions are known to be reactive nucleophiles. Structure of betaines (**2**) was confirmed by alkylation to the 1-alkyl-3-methylthio-4-(3-pyridinylamino)quinolinium methylsulfates (**3**). The reaction of **2** with dimethyl sulfate at room temperature proceeded as *S*-alkylation and gave almost quantitatively the expected salts (**3**).

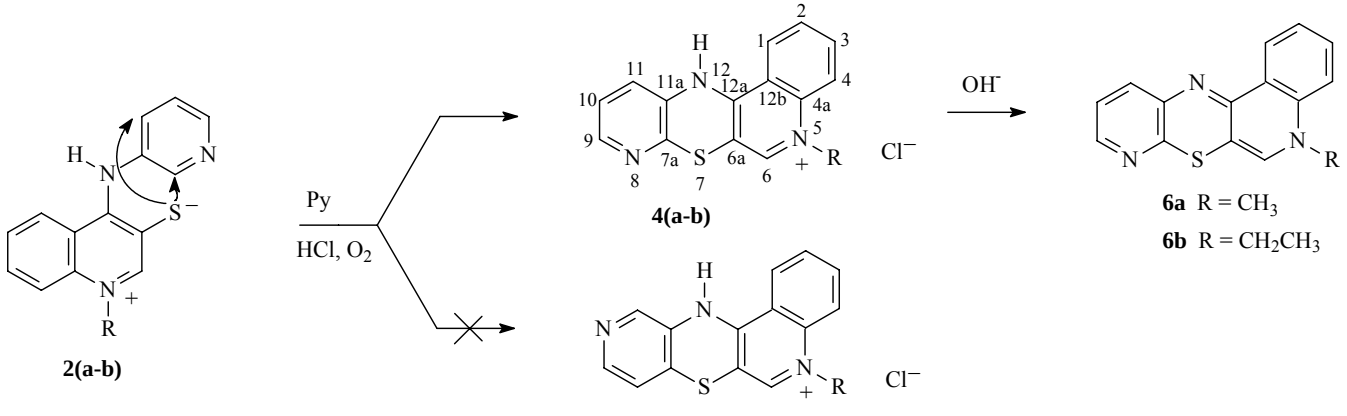


2(a - b) **3a** R = CH_3
3b R = CH_2CH_3

Scheme 3

In the presence of hydrogen chloride donor (e.g. aniline hydrochloride) and atmospheric oxygen, 3-thiolates (**2**) undergo cyclization to 1,4-thiazine (**4**) derivatives. Identical products result from the reaction of bis-salts (**1**) with 3-aminopyridine, when the reaction mixture is not prevented from oxygen access; this shows that 3-thiolates (**2**) are intermediate products of these reactions. The formation of 1,4-thiazine ring can occur *via* hydrogen atom substitution with sulfur atom at positions 2- or 4- of the pyridine ring. Our results show that the only product forming is the isomer (**4**); this occurs *via* substitution at the 2-position of the pyridine ring. The isomer (**5**) resulting from substitution at the 4-position has not been observed.

In the presence of a base, compounds (**4**) were dehydrochlorinated to 5-alkyl-5(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazine (**6**) with quantitative yield.



2(a-b) **4(a-b)** **5**

6a R = CH_3
6b R = CH_2CH_3

Scheme 4

Table 1. Preparation of 5-alkyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4**) from bis-salts (**1**) (procedure A) and from thiolates (**2**) (procedure B).

Substrate	Procedure	Product	Yield[%]
bis-salt (**1a**)	A	**4a**	60
bis-salt (**1b**)	A	**4b**	66
thiolate (**2a**)	B	**4a**	67
thiolate (**2b**)	B	**4b**	69

The structure of compounds (**4**) was confirmed by ^{1}H NMR spectral data. Especially the doublet of doublets structure of proton H10 (pyridine ring) signal and the magnitude of its coupling are of diagnostic value for the structure assignment. These constants values (**4a** δ_{H10} = 7.13 ppm, ^3J = 8.1 Hz, ^3J = 4.8 Hz; **4b** δ_{H10} = 7.18 ppm, ^3J = 8.1 Hz, ^3J = 4.5 Hz) are typical of vicinal coupling constants for 2,3-disubstituted pyridine ring protons. Compounds (**4**) feature the structural fragment shown above, whereas compounds (**5**) contains the 3,4-disubstituted pyridine fragment (Scheme 4). The signals of protons H9 and H11 were overlapped with benzene ring protons of quinoline part; coupling constants could not be determined.

The structure of compounds (**4**) was additionally confirmed by the ^{1}H NMR spectra of derivatives (**6a**) and (**6b**), showing three well separated signals of pyridine protons (H9,H10 and H11). Each proton signal is split by coupling with both other protons. Thus, each proton gives the quartet pattern shown.

Table 2. The chemical shifts and coupling constants of protons H9, H10 and H11 compounds (**6**).

	δ_{H9} [ppm]	δ_{H10} [ppm]	δ_{H11} [ppm]	$^3J_{H9\text{-}H10}$ [Hz]	$^3J_{H10\text{-}H11}$ [Hz]	$^4J_{H9\text{-}H11}$ [Hz]
6a	7.68	6.84	6.89	4.5	8.1	1.5
6b	7.75	6.88	6.96	4.8	8.1	1.5

Structure of compound (**4b**) was determined by X-Ray crystallography. The 5-ethyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium cation is planar (max. deviation from the planarity 0.068(7) Å) except of the terminal methyl group of the ethyl substituent which deviates from the plane of the rest of the atoms by 1.464(7) Å. The counter ion Cl^- is hydrogen bonded to N12 [geometry of N-H···Cl hydrogen bond: $d_{N\cdots Cl}$ = 3.227(5) Å, $d_{H\cdots Cl}$ = 2.34(6) Å, angle $_{N\text{-}H\cdots Cl}$ = 170(5)°] and lies in plane of cation (deviation from the plane 0.032(2) Å). Furthermore, the structural parameters of compound (**4b**) are in good agreement with the described earlier structure of 5-methyl-12(*H*)-quino[3,4-*b*][1,4]benzothiazinium chloride.[9]

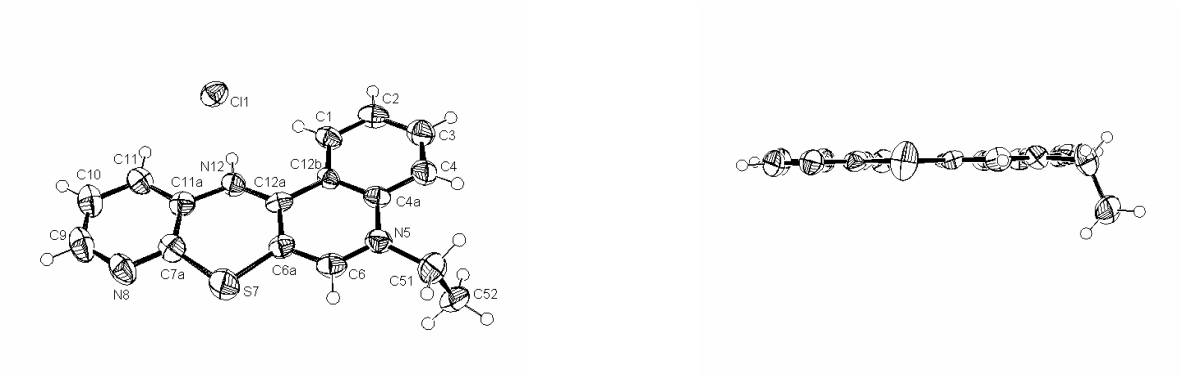


Figure 2. View of the molecule of 5-ethyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4b**)

Table 3. Selected bond lengths [Å] and angle values [º] for compound (**4b**)

Bond lengths [Å]			
C4a-N5	1.381(7)	C11a-C12	1.414(7)
N5-C6	1.336(7)	C12-C12a	1.340(7)
C6-C6a	1.371(8)	C12a-C6A	1.395(7)
C6a-S7	1.765(6)	C7a-N8	1.328(7)
S7-C7a	1.750(6)	N8-C9	1.349(8)
C7a-C11a	1.396(8)	N5-C51	1.499(7)
Bond angles [º]			
C4a-N5-C6	120.0(5)	C11a-N12-C12a	126.6(5)
C6a-S7-C7a	101.5(3)	N12-C12a-C6a	121.4(5)
C7-C7a-C11a	122.7(5)	C12a-C6a-S7	125.0(5)
C7a-C11a-N12	122.8(6)	C7a-N8-C9	117.5(6)

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra (at 300 MHz) were recorded using a Varian VXR 300 spectrometer. Proton chemical shifts are reported relative to TMS (δ = 0.0) as internal standards. ^{15}N NMR spectra were recorded using a Bruker AM 500 spectrometer at 50.698 MHz. ^{1}H NMR spectra and NOE ^{1}H-^{1}H homonuclear experiment were carried out for (**2a**) in the $CDCl_3$ solution at 500 MHz. EI MS spectra were determined using an LKB GC MS 20091 spectrometer at 75 eV.

X-Ray data were collected on a Nonius KappaCCD diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å). Diffractometer control program Collect,[13] unit cell parameters and data reduction with Denzo and Scalepak.[14] The structure was solved by direct methods SHELXS-97[15] and refined by full-matrix least-squares minimization based on all unique F^2 (SHELXL-97[16]).

Crystal data: $C_{16}H_{14}N_3ClS$, M = 315.81, red needle, 0.40 × 0.10 × 0.07 mm, monoclinic, space group $P2_1/n$ (No. 14), a = 8.0040(5), b = 18.498(1), c = 9.9610(7) Å, β = 96.959(4)°, V = 1463.9(2) Å^3, Z = 4,

D_c = 1.433 g/cm^3, $F(000)$ = 656, μ = 0.399 mm^{-1}, T = 293(2)K, $2\theta_{max}$ = 41.6º. 7333 reflections collected, 1507 unique (R_{int} = 0.037). Final *GooF* = 1.38, R = 0.074, wR = 0.128, R indices based on 1387 reflections with $I > 2\sigma(I)$ for 195 parameters and 0 restraints.

1-Alkyl-4-(3-pyridinylamino)quinolinium-3-thiolates (**2**):

Argon was passed through the suspension of bis-salts (**1**) (1 mmol) in dry pyridine (15 mL) at rt over 15 min. 3-Aminipyridine (235 mg, 2.5 mmol) was added and argon passed for further 15 min. The mixture was then stirred at rt for 7 days. The solid product was filtered off and washed with dry ether. The raw product was purified through recrystallization from ethanol.

1-Methyl-4-(3-pyridinylamino)quinolinium-3-thiolate (**2a**): yield 63%. mp 187 ^{o}C. EI MS, (m/z): 265 (M^+- 2, 100%). ^{1}H NMR ($CDCl_3$) δ: 4.15(s, 3H, CH_3), 7.20-7.33(m, 3H, H_{arom}), 7.44-7.52(m, 1H, $H5_{quinolinyl}$), 7.54-7.63(m, 1H, $H6_{quinolinyl}$), 7.64-7.74(m, 1H, $H8_{quinolinyl}$), 8.44-8.47(m, 1H, H_{arom}), 8.48(s, 1H, $H2_{pyridinyl}$), 8.72(s, 1H, $H2_{quinolinyl}$), 10.18(s, 1H, NH). *Anal*. Calcd for $C_{15}H_{13}N_3S$: C 67.39, H 4.90, N 15.72, S 11.99. Found: C 67.32, H 4.96, N 15.63, S 11.90.

1-Ethyl-4-(3-pyridinylamino)quinolinium-3-thiolate (**2b**): yield 70%. mp 149 ^{o}C. EI MS, (m/z) 279(M^+- 2, 100%). ^{1}H NMR ($CDCl_3$) δ: 1.65(t, J=7 Hz, 3H, CH_3CH_2), 4.52(q, J=7 Hz, 2H, CH_3CH_2), 7.19-7.35 (m, 3H, H_{arom}), 7.42-7.52(m, 1H, H_{arom}), 7.52-7.68(m, 2H, H_{arom}), 7.68-7.78(m, 1H, H_{arom}), 8.43-8.55(m, 1H, H_{arom}), 8.71(s, 1H, H2), 10.30(s, 1H, NH). *Anal*. Calcd for $C_{16}H_{15}N_3S$: C 68.30, H 5.37, N 14.93, S 11.39. Found: C 68.35, H 5.32, N 14.89, S 11.34.

1-Alkyl-3-methylthio-4(3-pyridinylamino)quinolinium methyl sulfates (**3**):

The mixture of 1-alkyl-4-(3-pyridylamino)quinolinium 3-thiolates (**2**) (1 mmol) and dimethyl sulfate (630 mg, 5 mmol) was mixed at rt for 2 h. The obtained methylsulfate was filtered off and washed with ether. The product was purified through recrystallization from ethanol.

1-Methyl-3-methylthio-4-(3-pyridinylamino)quinolinium methyl sulfates (**3a**): yield 100%. ^{1}H NMR ($CDCl_3$) δ: 2.56(s, 3H, SCH_3), 3.69(s, 3H, CH_3SO_4), 4.43(s, 3H, NCH_3), 7.24-7.32(m, 1H, H_{arom}), 7.33-7.48(m, 3H, H_{arom}), 7.86-8.02(m, 3H, H_{arom}), 9.18(s, 1H, $H\text{-}2_{quinolinyl}$), 9.41 (s, 1H, NH). *Anal*. Calcd for $C_{17}H_{19}N_3O_4S_2$: C 51.89, H 4.87, N, 10.68, S 16.30. Found: C 51.82, H 4.80, N 10.71, S, 16.39.

1-Ethyl-3-methylthio-4-(3-pyridinylamino)quinolinium methyl sulfates (**3b**): yield 100%. ^{1}H NMR ($CDCl_3$) δ: 1.82(t, J=7.5 Hz, 3H, CH_3CH_2), 2.39(s, 3H, SCH_3), 3.68(s, 3H, CH_3SO_4), 4.95(q, J=7.5 Hz,

2H, CH_3CH_2), 7.62-7.80(m, 1H, H_{arom}), 7.83-8.00(m, 1H, H_{arom}), 8.08-8.20(m, 3H, H_{arom}), 8.55-8.57(m, 1H, H_{arom}), 8.58-8.60(m, 2H, H_{arom}), 9.00(s, 1H, $H2_{quinolinyl}$). 11.64 (s, 1H, NH). *Anal*. Calcd for $C_{18}H_{21}N_3O_4S_2$: C 53.05, H 5.19, N 10.31, S 15.73. Found: C 53.01, H 5.12, N 10.25, S 15.81.

5-Alkyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4**):

Procedure A

3-Aminopyridine (235 mg, 2.5 mmol) was added to the mixture of bis-chloride (**1**) (1 mmol) in 10 mL of dry pyridine and the whole was mixed at 70°C for 2 h. The mixture was cooled down to rt, the product was filtered off and washed with ether. The raw product was purified through recrystallization from ethanol.

Procedure B

Aniline hydrochloride (155 mg, 1.2 mmol) was added to the mixture of 3-tiolate (**2**) (1 mmol) in 10 mL of dry pyridine and the whole was mixed at 70°C for 2 h. After cooling it down to rt the product was filtered off and washed with ether. The raw product was recrystallized from ethanol.

5-Methyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4a**)**:** mp 254 °C. EI MS, (m/z): 265 (M^+- 1, 100%). ^{1}H NMR (DMSO-d_6) δ: 4.13(s, 3H, CH_3), 7.13(dd, ^3J=8.1 Hz, ^3J=4.5 Hz, 1H, H10), 7.76-7.88(m, 2H, H_{arom}), 8.02-8.08(m, 3H, H_{arom}), 8.67(s, 1H, H6), 8.93-9.00(m, 1H, H_{arom}), 11.08(s, 1H, NH). *Anal*. Calcd for $C_{15}H_{12}N_3ClS$: C 59.70, H 4.01, N 13.92, Cl 11.75, S 10.62. Found. C 59.74, H 4.01, N 13.87, Cl 11.68, S 10.57.

5-Ethyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4b**): mp 274 °C. EI MS, (m/z): 279(M^+- 1, 100%). ^{1}H NMR (DMSO-d_6) δ: 1.50(t, *J*=7.2 Hz, 3H, CH_3CH_2), 4.66(q, *J*=7.2 Hz, 2H, CH_3CH_2), 7.18 (dd, ^3J=8.1 Hz, ^3J=4.8 Hz, 1H, H10), 7.80-7.98 (m, 2H, H_{arom}), 8.00-8.15(m, 3H, H_{arom}), 8.19-8.30(m, 1H, H_{arom}), 8.74(s, 1H, H6); 8.95-9.12(m, 1H, H_{arom}), 11.30(s, 1H, NH). *Anal.* Calcd for $C_{16}H_{14}N_3ClS$: C 60.85, H 4.47, N 13.31, Cl 11.23, S 10.15. Found. C 60.88, H 4.43, N 13.27, Cl 11.27, S 10.19.

5-Alkyl-5(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazine (**6**):

5-Alkyl-12(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazinium chloride (**4**) (1mmol) was dissolved in 50 mL of water. The solution was filtered off from the solid suspension and alkalized with 5% sodium hydroxide (10 mL). The solid product was filtered off and washed with water. The raw product was recrystallized from ethanol.

5-Methyl-5(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazine (**6a**): yield 100%. mp 160 °C. EI MS, (m/z): 265 (M^+, 100%). ^{1}H NMR (DMSO-d_6) δ: 3.52(s, 3H, CH_3), 6.84(dd, ^3J=8.1 Hz, ^3J=4.5 Hz, 1H, H10), 6.89(dd, ^3J=8.1 Hz, ^4J=1.5 Hz, 1H, H11), 7.15(s, 1H, H6), 7.22-760(m, 1H, H_{arom}), 7.28-7.36(m, 1H, H_{arom}), 7.52-7.60(m, 1H, H_{arom}), 7.68 (dd, ^3J=4.5 Hz, ^4J=1.5 Hz, 1H, H9), 8.12-8.18(m, 1H, H_{arom}). *Anal.* Calcd for $C_{15}H_{11}N_3S$: C 67.90, H 4.18, N 15.84, S 12.08. Found: C 67.85, H 4.16, N 15.84, S 12.03.

5-Ethyl-5(*H*)-pyrido[2,3-*e*]quino[3,4-*b*][1,4]thiazine (**6b**): yield 100%. mp 152 °C. EI MS, (m/z): 279(M^+, 100%). ^{1}H NMR (DMSO-d_6) δ: 1.25(t, J=7.5Hz, 3H, CH_3CH_2), 4.05(q, J=7.5Hz, 3H, CH_3CH_2) 6.88(dd, ^3J=8.1 Hz, ^3J=4.8 Hz, 1H, H10), 6.96(dd, ^3J=8.1 Hz, ^4J=1.5 Hz, 1H, H11), 7.21(s, 1H, H6); 7.24-7.32(m, 1H, H_{arom}) 7.42-7.48(m, 1H, H_{arom}), 7.56-7.64(m, 1H, H_{arom}), 7.75(dd, ^3J=4.8 Hz, ^4J=1.5 Hz, 1H, H9), 8.20-8.26(m, 1H, H_{arom}). *Anal*. Calcd for $C_{16}H_{13}N_3S$: C 68.79, H 4.69, N 15.04, S 11.48. Found: C 68.74, H 4.72, N 15.06, S 11.53.

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