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The convenient synthesis of zinc chloride-free 3,7-bis(dialkylamino)phenoxazinium salts

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Abstract

Zinc chloride-free 3,7-bis(dialkylamino)phenoxazinium salts carrying different anions (chloride, bromide, hydrosulfate, tosylate, perchlorate and nitrate) were synthesized with the yields up to 84%. Their structures were determined by spectroscopy and elemental analyses.

Keywords: Zinc chloride-free 3,7-bis(dialkylamino)phenoxazinium salts; Synthesis; Phenoxazinium

1. Introduction

Phenoxazinium is the oxidized state of phenoxazine. Comparing with phenoxazinium itself, benzophenoxazinium had been studied well, since benzophenoxazinium dyes, such as Meldola's blue, Nile red, and Nile blue, were used as biologically active reagents [1], fluorescent dyes [2] and so on. A well-known phenoxazinium derivative is Basic blue 3, which was reported by Moores and co-workers in 1969 [3]. Recently, further interest has been focused on phenoxazinium derivatives on the basis of a number of reasons [4]. The highest purity of commercially available Basic blue 3 is about 60%, and it is an inhomogeneous mixture of 3,7-bis(diethylamino)phenoxazinium chloride, zinc chloride and other impurities. It is now obvious that the low purity limits this compound's application and the synthesis of zinc chloride-free phenoxazinium salts with a high purity would be very important.

During the study of active candidates for tropical disease, we found that several phenoxazinium salts showed good activities in in vitro and in vivo tests against malaria parasites [5]. It seems that phenoxazinium derivatives with high purity are too difficult to obtain; the help of zinc chloride usually purifies them. But we have found that symmetric and unsymmetric 3,7-bis(dialkylamino)phenoxaziniums with high purity could be obtained by chromatography followed by crystallization in large scale. The synthetic 3,7-bis(diethylamino)phenoxazinium chloride with about 95% purity showed about three times activity and selectivity against *Plasmodium falciparum* parasite than commercially available Basic blue 3 [5]. In this paper, we would like to report synthesis of high pure 3,7-bis(dialkylamino)phenoxazinium salts with various anions such as chloride, bromide, hydrosulfate, tosylate, perchlorate, and nitrate.

2. Results and discussion

2.1. Synthesis of *N*,*N*-dialkylaminophenol and *N*,*N*-dialkyl-3-methoxy-4-nitrosoaniline (Scheme 1)

N,*N*-Dialkylaminophenols **1a–d** and *N*,*N*-dialkyl-3-methoxy-4-nitrosoanilines **3a–d** are important intermediates for 3,7-bis(dialkylamino)phenoxaziniums. Compounds **1a** and **1d** are commercially available. 3-(Dipropylamino)phenol **1b** could be easily prepared by N-alkylation of 3-aminophenol [6]. 3-(Pyrrolidin-1-yl)phenol **1c** was obtained by the cleavage

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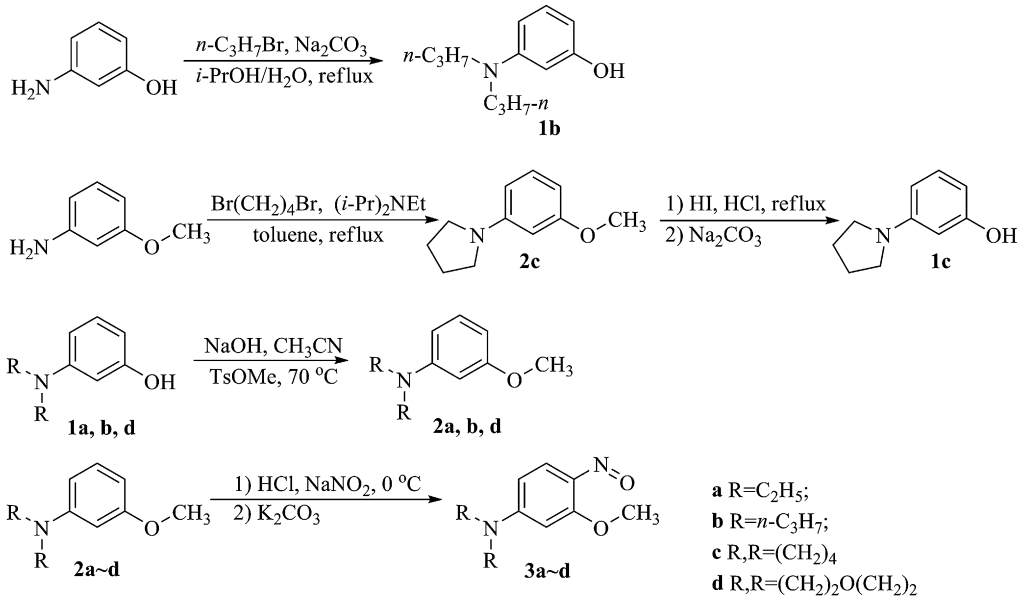
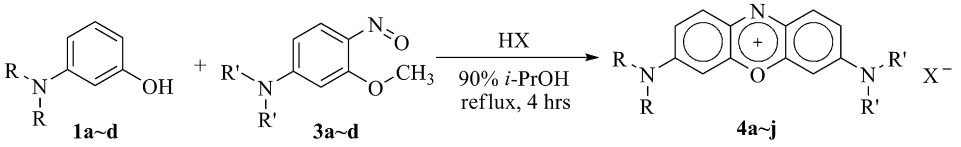


Scheme 1. Synthesis of *N*,*N*-dialkylaminophenol and *N*,*N*-dialkyl-3-methoxy-4-nitrosoaniline.

of 1-(3-methoxyphenyl) pyrrolidine **2c** [7] with hydroiodic acid in hydrochloric acid [8]. *N*,*N*-Dialkyl-3-methoxyanilines **2a**, **2b** and **2d** were prepared by the reactions of corresponding *N*,*N*-dialkylaminophenols and methyl *p*-toluenesulfonate in the presence of sodium hydroxide in acetonitrile. After the reaction of **2a**–**d** with sodium nitrite in a diluted hydrochloric acid solution, potassium carbonate was added to obtain the free bases of *N*,*N*-dialkyl-3-methoxy-4-nitrosoanilines **3a**–**d**.

2.2. Synthesis of 3,7-bis(dialkylamino)phenoxazinium salts (Scheme 2)

3,7-Bis(dialkylamino)phenoxazinium salts **4a**–**j** were obtained by the reaction of *N*,*N*-dialkyl-3-methoxy-4-nitrosoanilines **3a**–**d** and *N*,*N*-dialkylaminophenols **1a**–**d** in the acidic solutions. The yields were up to 84% and the yield of **4d** (34%) was the lowest among them; this might be due to that



Entry	R, R'	1a~d	3a~d	X	4a~j	yield(%) (purity(%))*
1	R=R'=C_2H_5	**1a**	**3a**	Cl	**4a**	60 (>99)
2	R=R'=C_2H_5	**1a**	**3a**	Br	**4b**	71 (>99)
3	R=R'=C_2H_5	**1a**	**3a**	HSO_4	**4c**	51 (>99)
4	R=R'=C_2H_5	**1a**	**3a**	TsO	**4d**	34 (>99)
5	R=R'=C_2H_5	**1a**	**3a**	ClO_4	**4e**	46 (>99)
6	R=R'=C_2H_5	**1a**	**3a**	NO_3	**4f**	84 (>99)
7	R=R'=C_3H_7-*n*	**1b**	**3b**	Cl	**4g**	60 (~99)
8	R, R=R', R'= -$(CH_2)_4$-	**1c**	**3c**	Cl	**4h**	63 (>99)
9	R, R=R',R'= -$(CH_2)_2O(CH_2)_2$-	**1d**	**3d**	Cl	**4i**	51 (>99)
10	R=C_2H_5; R', R'= -$(CH_2)_4$-	**1a**	**3c**	Cl	**4j**	82 (>99)

* By a Shimadzu LC-10Avp HPLC on an ODS-80TM (4.6 x 250 mm) column with a pre-column filter (ODS-80TM), eluted with CH_3CN-H_2O (70:30, v/v) containing trifluoroacetic acid (1 mL/L) at a flow rate of 1 ml/min with UV detection at 650 nm.

Scheme 2. Synthesis of 3,7-bis(dialkylamino)phenoxazinium salts.

p-toluenesulfonic acid was not strong enough compared with other acids. Products **4a–j** were purified by chromatography with a short silica gel column, eluted by $CHCl_3$/MeOH from 10:1 to 10:3 (v/v); after evaporation of the solvents, the remaining crude products were crystallized by treatments with alcohol and then ethyl acetate to remove the impurities. Compound **4a** was successfully synthesized in a 50-g scale under laboratory conditions. Acetic acid and benzoic acid had been used in this reaction, but phenoxazinium salt could not be obtained.

2.3. Structure of 3,7-bis(dialkylamino)phenoxazinium salts

Three structures **IIa–c** (Scheme 3) are possible for phenoxazinium derivatives. A typical ^{13}C NMR (CPD) spectrum of symmetric phenoxazinium **4a** and ^{13}C NMR (APT) spectrum of unsymmetric phenoxazinium **4j** are shown in Fig. 1. Six signals due to aromatic carbons were observed in ^{13}C NMR spectrum of **4a**, while 12 signals were detected in the region of aromatic carbons of **4j**. They clearly indicate that **IIa–c** are resonance structures. In the consideration of the electronegativity of the oxygen atom, **Ia** is a more reasonable description than **IIb**. Three heterocyclic frameworks provide a π conjugated system, and p–π electron donating conjugated effect of two nitrogen atoms makes a stable resonance structure.

2.4. Photophysical properties

The maximum UV–vis peaks of 3,7-bis(dialkylamino)phenoxazinium salts in methanol are absorbed in the region of 643–652 nm, and a UV absorption is found at 260–263 nm. Fluorescence quantum-yields (Φ_q) are listed in Table 1. Φ_q did not change with different anion (Entry 1–6). With five-member pyrrolidine ring, **7g** (Entry 7) showed the best quantum-yield $\Phi_q = 0.10$.

3. Conclusions

In summary, highly pure 3,7-bis(dialkylamino)phenoxazinium salts with an alterable anion, chloride, bromide, hydrosulfate, tosylate, perchlorate, and nitrate were synthesized with yields up to 84%. The maximum fluorescence quantum-yield of these compounds was 0.10.

4. Experimental

4.1. Instruments and reagents

Starting materials were obtained from Wako and Aldrich Company and used as received. Melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were recorded on a Jeol-270 or Bruker 400 NMR spectrometer, TMS was used as an internal standard for ^1H NMR and solvent peak was used as an internal standard for ^{13}C NMR. Fluorescence spectra were recorded at a Shimadzu RF-5300PC spectroscope. Absorption spectra were taken on Jasco V-550 UV–vis spectrophotometer. IR spectra were determined on a JASCO FT/IR-200. LC-MS (ESI^+) spectra were recorded with a Shimadzu LCMS-2010EV spectroscope. The elemental analysis was performed with Yanano CHN corder MT-5 element analyzer.

4.2. Synthesis

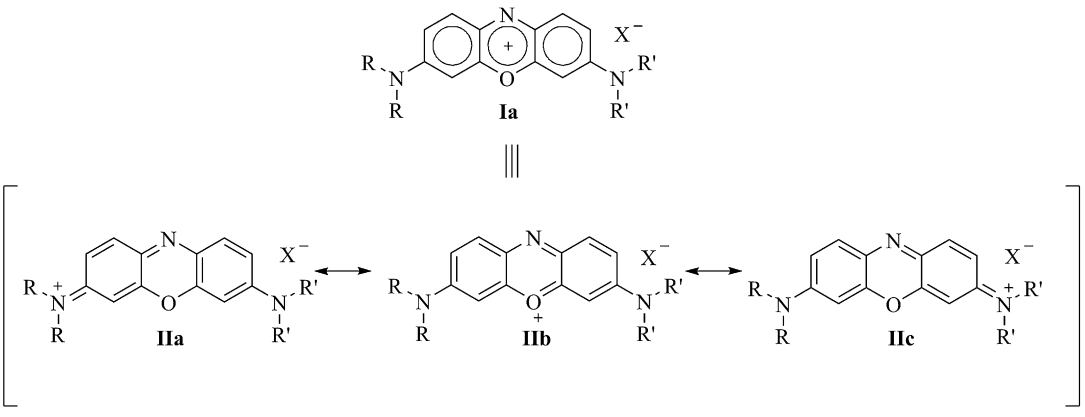
4.2.1. Preparation of N,N-dialkylaminophenol and N,N-dialkyl-3-methoxy-4-nitroso-aniline

Compounds **1b** and **2c** were synthesized according to the literature [6,8] and purified by bulk–bulk distillation; **1c** was obtained by the application of known method [7].

3-(Dipropylamino)phenol (**1b**): yield 88%, ^1H NMR (270 MHz, $CDCl_3$) δ_{ppm}: 0.90 (t, 6H, $J = 7.6$ Hz, $2 \times CH_3$), 1.52–1.66 (m, 4H, $2 \times CH_2$), 3.18 (t, $J = 7.8$ Hz, 4H, $2 \times CH_2N$), 6.07–7.06 (m, 4H, Ar–*H*).

1-(3-Methoxyphenyl)pyrrolidine (**2c**): yield 87%, ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.99–2.02 (m, 4H, $2 \times CH_2$), 3.26–3.29 (m, 4H, $2 \times CH_2N$), 3.81 (s, 3H, OCH_3), 6.06–7.10 (m, 4H, Ar–*H*).

3-(Pyrrolidin-1-yl)phenol (**1c**): yield 74%, ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.98–2.02 (m, 2H, CH_2), 3.26–3.29 (m, 4H, $2 \times CH_2N$), 6.06–7.10 (m, 4H, Ar–*H*).



Scheme 3. Structures of phenoxazinium salts.

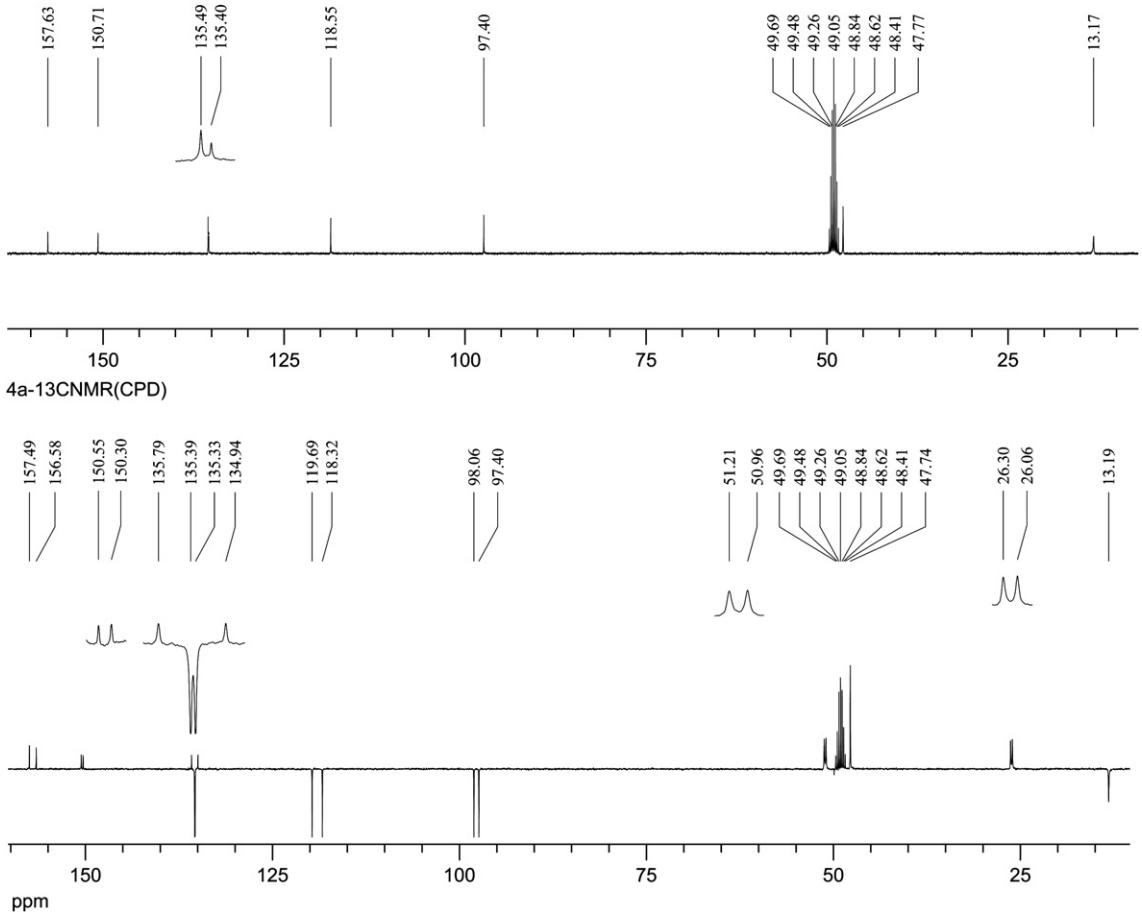


Fig. 1. ^{13}C NMR spectra of **4a** and **4j**.

*4.2.2. General method of preparation of **2a**, **2b** and **2d***

A mixture of 3-(dialkylamino)phenol (20 mmol) and NaOH (20 mmol) in MeCN (30 mL) was stirred for 1 h. After addition of methyl *p*-toluenesulfonate (20 mmol), the reaction mixture was stirred at 40 °C for 4 h, filtrated and then washed with MeCN. The filtrate was evaporated. The residue was dissolved in 5% HCl (60 mL) and washed by Et_2O (2 × 20 mL). K_2CO_3 was slowly added to basicify at about pH 9 and the water solution was extracted by Et_2O (3 × 30 mL). The organic layer was washed by 1 N NaOH solution (2 × 20 mL) and NaCl solution (4 × 30 mL), and then dried over Na_2SO_4. Evaporation of the solvent gave the oil, which was used in next step without further purification.

N,N-Diethyl-3-methoxyaniline (**2a**): yield 90%, ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.15 (t, 6H, $J = 7.1$ Hz, 2 × CH_3), 3.33 (q, $J = 7.1$ Hz, 4H, 2 × CH_2), 3.79 (s, 3H, OCH_3), 6.20–7.13 (m, 4H, Ar–*H*).

N,N-Dipropyl-3-methoxyaniline (**2b**): yield 88%, ^1H NMR (270 MHz, CD_3OD) δ_{ppm}: 0.89 (t, 6H, $J = 7.4$ Hz, 2 × CH_3), 1.49–1.63 (m, 4H, 2 × CH_2), 3.18 (t, $J = 7.7$ Hz, 4H, 2 × CH_2N), 3.70 (s, 3H, OCH_3), 6.14–7.05 (m, 4H, Ar–*H*).

4-(3-Methoxyphenyl)morpholine (**2d**): yield 85%, ^1H NMR (270 MHz, $CDCl_3$) δ_{ppm}: 3.13–3.17 (m, 4H, 2 × CH_2), 3.79 (s, 3H, OCH_3), 3.83–3.87 (m, 4H, 2 × CH_2), 6.42–6.22 (m, 4H, Ar–*H*).

Table 1
Fluorescence quantum-yields (Φ_q) and emission wavelength

Entry	Sample	Φ_q	$\lambda_{Emission}$[a]/nm
1	**4a**	0.03	656
2	**4b**	0.03	657
3	**4c**	0.03	658
4	**4d**	0.03	657
5	**4e**	0.03	656
6	**4f**	0.03	658
7	**4g**	0.10	657
8	**4h**	<0.01	668
9	**4i**	<0.01	665
10	**4j**	0.05	657

[a] Excited at 600 nm in MeOH. Cresyl violet perchlorate was used as a stand sample ($\Phi_q = 0.54$).

*4.2.3. General method of preparation of **3a–d***

A mixture of *N,N*-dialkyl-3-methoxyaniline (**2a–d**, 10 mmol) and HCl (40 mmol) in H_2O (30 mL) was stirred in an ice bath. $NaNO_2$ (14 mmol) was slowly added to the mixture for 60 min and then the resulting mixture was stirred in ice bath for another 1 h. After addition of K_2CO_3 powder to basicify the above solution until pH ~9, the mixture was filtrated and the green mass was washed with water. The mass was ultrasonicated in Et_2O and filtrated to give nitroso compounds **3a–d**.

N,N-Diethyl-3-methoxy-4-nitrosoaniline (**3a**): yield 72%, mp 72–73 °C; IR ν (neat, cm^{-1}): 2980, 2930 (alkyl-CH), 1605, 1540, 1520 (Ar C=C), 1260, 1210 (Ar–O–CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 1.28 (t, $J = 7.2$ Hz, 6H, $2 \times CH_3$), 3.50 (q, $J = 7.2$ Hz, 4H, $2 \times CH_2$), 4.16 (s, 3H, OCH_3), 6.11–6.19 (m, 3H, Ar–*H*); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.0 ($2 \times CH_3$), 46.8 (OCH_3), 56.6 ($2 \times CH_2$), 92.9 (Ar *C*H), 107.3 (Ar *C*H), 115.7 (Ar *C*H), 156.2 (Ar *C*), 159.1 (Ar *C*H), 166.9 (Ar *C*H); MS (LC-ESI$^+$): *m/z*: 209.3 $[M + H]^+$; Anal. calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45; found: C, 63.47; H, 7.71; N, 13.44.

3-Methoxy-4-nitroso-N,N-dipropylaniline (**3b**): yield 65%, mp 79–80 °C; IR ν (neat, cm^{-1}): 2965, 2875 (alkyl-CH), 1605, 1540, 1520 (Ar C=C), 1225, 1215 (Ar–O–CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 0.99 (t, 6H, $J = 7.4$ Hz, $2 \times CH_3$), 1.66–1.76 (m, 4H, $2 \times CH_2$), 3.71–3.41 (m, 4H, $2 \times CH_2$), 4.15 (s, 3H, OCH_3), 6.09–6.68 (m, 3H, Ar–*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_{ppm}: 11.3 ($2 \times CH_3$), 20.7 ($2 \times CH_2$), 53.3 (OCH_3), 56.0 ($2 \times CH_2$), 93.1 (Ar *C*H), 104.2 (Ar *C*H), 112.9 (Ar *C*H), 155.9 (Ar *C*), 156.4 (Ar *C*H), 164.7 (Ar *C*H); MS (LC-ESI$^+$): *m/z*: 237.2 $[M + H]^+$; Anal. calcd. for $C_{20}H_{26}N_4O_4$: C, 66.07; H, 8.53; N, 11.85; found: C, 66.01; H, 8.45; N, 11.98.

1-(3-Methoxy-4-nitrosophenyl)pyrrolidine (**3c**): yield 68%, mp 136–137 °C; IR ν (neat, cm^{-1}): 2970, 2870 (alkyl-CH), 1610, 1540, 1525 (Ar C=C), 1270, 1210 (Ar–O–CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm}: 2.06–2.10 (m, 4H, $2 \times CH_2$), 3.42–3.46 (m, 4H, $2 \times CH_2N$), 4.13 (s, 3H, CH_3), 5.96 (d, $J = 2.2$ Hz, 1H, Ar–*H*), 5.98 (dd, $J = 9.32$, 2.2 Hz, 1H, Ar–*H*), 6.65 (br, 1H, Ar–*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_{ppm}: 25.1 ($2 \times CH_2$), 48.3 (OCH_3), 56.0 ($2 \times CH_2N$), 92.3 (Ar *C*H), 105.0 (Ar *C*H), 112.8 (Ar *C*H), 155.4 (Ar *C*), 156.2 (Ar *C*H), 165.3 (Ar *C*H); MS (LC-ESI$^+$): *m/z*: 207.3 $[M + H^-]^+$; Anal. calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58; found: C, 64.06; H, 6.91; N, 13.54.

4-(3-Methoxy-4-nitrosophenyl)morpholine (**3d**): yield 87%, mp 175–176 °C; IR ν (neat, cm^{-1}): 2980, 2850 (alkyl-CH), 1610, 1540, 1510 (Ar C=C), 1210 (Ar–O–CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ_{ppm} 3.56–3.43 (m, 2H, $2 \times CH_2$), 3.90–3.81 (m, 2H, $2 \times CH_2$), 4.18 (s, 3H, CH_3), 6.26 (dd, $J = 9.4$, 2.5 Hz, 1H, Ar–*H*), 6.35 (d, $J = 2.4$ Hz, 1H, Ar–*H*), 6.58 (d, $J = 9.4$ Hz, 1H, Ar–*H*); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 46.8 (OCH_3), 56.3 ($2 \times CH_2$), 66.2 ($2 \times CH_2$), 94.4 (Ar *C*H), 104.7 (Ar *C*H), 112.5 (Ar *C*H), 156.1 (Ar *C*), 157.9 (Ar *C*), 164.5 (Ar *C*); MS (LC-ESI$^+$): *m/z*: 223.2 $[M + H]^+$; Anal. calcd. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60; found: C, 59.27; H, 6.29; N, 13.50.

4.2.4. General method of preparation of *4a–j*

The mixture of *N,N*-dialkylaminophenol (**1a–d**, 1 mmol) and 90% *i*-PrOH (20 mL) was stirred at 70 °C in a 50 mL two-neck bottle with distilling apparatus filled with argon. A suspended solution of *N,N*-dialkyl-3-methoxy-4-nitrosoaniline (**3a–d**, 1 mmol) and acid (1 mmol) in 90% *i*-PrOH (20 mL) was injected with syringe to the above mixture in four portions during 45 min. The temperature rose to reflux. When about 20 mL volume of the solvent was distilled out, 20 mL of 90% *i*-PrOH was added to the reaction mixture; this procedure was repeated three times during 3–4 h. The dark blue solution was evaporated and the residue was purified by column chromatography with silica gel, eluting by $CHCl_3$/MeOH from 10:1 to 10:3 (v/v) and the dark blue solution was evaporated. To a solution of the residue EtOH or MeOH (2 mL), was added AcOEt (20 mL). After ultrasonication for 10 min, the mixture was filtrated. The powder was washed by AcOEt and Et_2O then dried in vacuum.

3,7-Bis(diethylamino)phenoxazinium chloride (**4a**): green powder, yield 60%, mp 194–195 °C; IR ν (neat, cm^{-1}): 2985, 2935 (alkyl-CH), 1595, 1500, 1405 (phenoxazinium skeleton), 1150 (C–N); UV–vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.54), 643 (5.10); ^1H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.37 (t, $J = 7.1$ Hz, 12H, $4 \times CH_3$), 3.78 (q, $J = 7.1$ Hz, 8H, $4 \times CH_2$), 6.94 (d, $J = 2.6$ Hz, 2H, $2 \times$ Ar–*H*), 7.37 (dd, $J = 9.6$, 2.6 Hz, 2H, $2 \times$ Ar–*H*), 7.74 (d, $J = 9.6$ Hz, 2H, $2 \times$ Ar–*H*); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.2 ($4 \times CH_3$), 47.8 ($4 \times CH_2$), 97.4 ($2 \times$ Ar *C*H), 118.6 ($2 \times$ Ar *C*H), 135.4 ($2 \times$ Ar *C*), 135.5 ($2 \times$ Ar *C*H), 150.7 ($2 \times$ Ar *C*), 157.7 ($2 \times$ Ar *C*); MS (LC-ESI$^+$): *m/z*: 324.1 $[M–Cl^-]^+$; Anal. calcd. for $C_{20}H_{26}ClN_3O \cdot 0.5H_2O$: C, 65.12; H, 7.38; N, 11.39; found: C, 65.01; H, 7.43; N, 11.43.

3,7-Bis(diethylamino)phenoxazinium bromide (**4b**): green powder, yield 71%, mp 213–215 °C; IR ν (neat, cm^{-1}): 2980, 2935 (alkyl-CH), 1595, 1500, 1405 (phenoxazinium skeleton), 1150 (C–N); UV–vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.55), 643 (5.10); ^1H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.36 (t, $J = 7.1$ Hz, 12H, $4 \times CH_3$), 3.79 (q, $J = 6.9$ Hz, 8H, $4 \times CH_2$), 6.95 (d, $J = 2.0$ Hz, 2H, $2 \times$ Ar–*H*), 7.38 (dd, $J = 9.4$, 1.9 Hz, 2H, $2 \times$ Ar–*H*), 7.75 (d, $J = 9.6$ Hz, 2H, $2 \times$ Ar–*H*); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.2 ($4 \times CH_3$), 47.8 ($4 \times CH_2$), 97.4 ($2 \times$ Ar *C*H), 118.6 ($2 \times$ Ar *C*H), 135.5 ($2 \times$ Ar *C*), 135.5 ($2 \times$ Ar *C*H), 150.8 ($2 \times$ Ar *C*), 157.7 ($2 \times$ Ar *C*); MS (LC-ESI$^+$): *m/z*: 324.1 $[M–Br^-]^+$; Anal. calcd. for $C_{20}H_{26}BrN_3O \cdot 0.5H_2O$: C, 58.11; H, 6.58; N, 10.17; found: C, 58.43; H, 6.51; N, 10.21.

3,7-Bis(diethylamino)phenoxazinium hydrosulfate (**4c**): green crystals, yield 51%, mp 205–206 °C; IR ν (neat, cm^{-1}): 2980, 2940 (alkyl-CH), 1595, 1500, 1405 (phenoxazinium skeleton), 1150 (C–N); UV–vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.53), 643 (5.09); ^1H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.36 (t, $J = 7.2$ Hz, 12H, $4 \times CH_3$), 3.78 (q, $J = 7.2$ Hz, 8H, $4 \times CH_2$), 6.96 (d, $J = 2.7$ Hz, 2H, $2 \times$ Ar–*H*), 7.39 (dd, $J = 9.6$, 2.7 Hz, 2H, $2 \times$ Ar–*H*), 7.79 (d, $J = 9.6$ Hz, 2H, $2 \times$ Ar–*H*); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.2 ($4 \times CH_3$), 47.8 ($4 \times CH_2$), 97.4 ($2 \times$ Ar *C*H), 118.6 ($2 \times$ Ar *C*H), 135.4 ($2 \times$ Ar *C*), 135.5 ($2 \times$ Ar *C*H), 150.7 ($2 \times$ Ar *C*), 157.6 ($2 \times$ Ar *C*); MS (LC-ESI$^+$): *m/z*: 324.1 $[M–HSO_4^-]^+$; Anal. calcd. for $C_{20}H_{27}N_3O_5S$: C, 56.99; H, 6.46; N, 9.97; found: C, 56.93; H, 6.48; N, 9.87.

3,7-Bis(diethylamino)phenoxazinium 4-methylbenzenesulfonate (**4d**): green powder, yield 34%, mp >250 °C; IR ν (neat, cm^{-1}): 2980, 2935 (alkyl-CH), 1595, 1500, 1405 (phenoxazinium skeleton), 1150 (C–N); UV–vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.53); 643 (5.09); ^1H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.35 (t, $J = 7.1$ Hz, 12H,

4 × CH_3), 2.32 (s, 3H, CH_3), 3.76 (q, $J = 7.1$ Hz, 8H, 4 × CH_2), 6.92 (d, $J = 2.6$ Hz, 2H, 2 × Ar−H), 7.17 (d, $J = 7.9$ Hz, 2H, 2 × Ar−H), 7.35 (dd, $J = 9.6$, 2.6 Hz, 2H, 2 × Ar−H), 7.68 (d, $J = 8.1$ Hz, 2H, 2 × Ar−H), 7.74 (d, $J = 9.6$ Hz, 2H, 2 × Ar−H); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.1 (4 × CH$_3$), 21.4 (C_6H_4CH$_3$), 47.7 (4 × CH$_2$), 97.4 (2 × Ar CH), 118.5 (2 × Ar CH), 127.0 (2 × Ar CH), 129.7 (2 × Ar CH), 135.5 (2 × Ar C), 135.5 (2 × Ar CH), 143.8 (2 × Ar C), 150.7 (2 × Ar C), 157.7 (2 × Ar C); MS (LC-ESI$^+$): *m/z*: 324.1 [M−TsO$^-$]$^+$; Anal. calcd. for $C_{27}H_{33}N_3O_4S$: C, 65.43; H, 6.71; N, 8.48; found: C, 65.33; H, 6.70; N, 8.35.

3,7-Bis(diethylamino)phenoxazinium perchlorate (**4e**): green crystals, yield 46%, mp 228−230 °C; IR ν (neat, cm^{-1}): 2980, 2935 (alkyl-CH), 1595, 1500, 1405 (phenoxazinium skeleton), 1165 (C−N); UV−vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.50); 643 (5.04); ^{1}H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.36 (t, $J = 7.2$ Hz, 12H, 4 × CH_3), 3.78 (q, $J = 7.1$ Hz, 8H, 4 × CH_2), 6.96 (d, $J = 2.7$ Hz, 2H, 2 × Ar−H), 7.39 (dd, $J = 9.6$, 2.7 Hz, 2H, 2 × Ar−H), 7.79 (d, $J = 9.6$ Hz, 2H, 2 × Ar−H); ^{13}C NMR (101 MHz, DMSO-d_6) δ_{ppm}: 12.8 (4 × CH$_3$), 46.1 (4 × CH$_2$), 96.0 (2 × Ar CH), 117.4 (2 × Ar CH), 133.7 (2 × Ar C), 134.0 (2 × Ar CH), 148.8 (2 × Ar C), 155.5 (2 × Ar C); MS (LC-ESI$^+$): *m/z*: 324.1 [M−ClO$_4^-$]$^+$; Anal. calcd. for $C_{20}H_{26}ClN_3O_5$: C, 56.67; H, 6.18; N, 9.91; found: C, 56.77; H, 6.23; N, 9.91.

3,7-Bis(diethylamino)phenoxazinium nitrate (**4f**): green powder, yield 84%, mp 193−194 °C; IR ν (neat, cm^{-1}): 2980, 2935 (alkyl-CH), 1595, 1500, 1405 (phenoxazinium skeleton), 1160 (C−N); UV−vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.51); 643 (5.08); ^{1}H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.36 (t, $J = 7.2$ Hz, 12H, 4 × CH_3), 3.77 (q, $J = 7.1$ Hz, 8H, 4 × CH_2), 6.93 (d, $J = 2.6$ Hz, 2H, 2 × Ar−H), 7.36 (dd, $J = 9.6$, 2.6 Hz, 2H, 2 × Ar−H), 7.73 (d, $J = 9.6$ Hz, 2H, 2 × Ar−H); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.1 (4 × CH$_3$), 47.8 (4 × CH$_2$), 97.4 (2 × Ar CH), 118.5 (2 × Ar CH), 135.4 (2 × Ar C), 135.5 (2 × Ar CH), 150.7 (2 × Ar C), 157.7 (2 × Ar C); MS (LC-ESI$^+$): *m/z*: 324.1 [M−NO$_3^-$]$^+$; Anal. calcd. for $C_{20}H_{26}N_4O_4 \cdot 0.5H_2O$: C, 60.74; H, 6.88; N, 14.17; found: C, 60.65; H, 6.94; N, 14.05.

3,7-Bis(dipropylamino)phenoxazinium chloride (**4g**): black powder, yield 62%, mp 171−172 °C; IR ν (neat, cm^{-1}): 2965, 2880 (alkyl-CH), 1595, 1495, 1400 (phenoxazinium skeleton), 1150 (C−N); UV−vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 261 (4.52); 649 (5.07); ^{1}H NMR (400 MHz, CD_3OH) δ_{ppm}: 1.06 (t, $J = 7.4$ Hz, 12H, 4 × CH_3), 1.47−2.09 (m, 8H, 4 × CH_2), 3.69 (t, 8H, 4 × CH_2N), 6.92 (d, $J = 2.5$ Hz, 2H, 2 × Ar−H), 7.38 (dd, $J = 9.6$, 2.5 Hz, 2H, 2 × Ar−H), 7.76 (d, $J = 9.6$ Hz, 2H, 2 × Ar−H); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 11.4 (4 × CH$_3$), 22.1 (4 × CH$_2$), 55.1 (2 × CH$_2$N), 97.6 (2 × Ar CH), 118.8 (2 × Ar CH), 135.4 (2 × Ar CH), 135.6 (2 × Ar C), 150.7 (2 × Ar C), 158.1 (2 × Ar C); MS (LC-ESI$^+$): *m/z*: 380.2 [M−Cl$^-$]$^+$. Anal. calcd. for $C_{24}H_{34}ClN_3O \cdot 1.5H_2O$: C, 65.07; H, 8.42; N, 9.48; found: C, 64.91; H, 8.26; N, 9.36.

3,7-Di(pyrrolidin-1-yl)phenoxazinium chloride (**4h**): green powder, yield 63%, mp >250 °C; IR ν (neat, cm^{-1}): 2975, 2875 (alkyl-CH), 1595, 1485, 1405 (phenoxazinium skeleton), 1150 (C−N); UV−vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (4.50); 644 (5.03); ^{1}H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.95−2.38 (m, 8H, 2×(CH_2)$_2$), 3.69, 3.76 (br s, 8H, 2×(CH_2)$_2$N), 6.77 (d, $J = 2.2$ Hz, 2H, 2 × Ar−H), 7.23 (dd, $J = 9.4$, 2.2 Hz, 2H, 2 × Ar−H), 7.74 (d, $J = 9.4$ Hz, 2H, 2 × Ar−H); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 26.1 (2 × CH$_2$), 26.3 (2 × CH$_2$), 50.9 (2 × CH$_2$N), 51.1 (2 × CH$_2$N), 98.0 (2 × Ar CH), 119.5 (2 × Ar CH), 135.3 (2 × Ar CH), 135.5 (2 × Ar C), 150.4 (2 × Ar C), 156.6 (2 × Ar C); MS (LC-ESI$^+$): *m/z*: 320.1 [M−Cl$^-$]$^+$. Anal. calcd. for $C_{20}H_{22}ClN_3O \cdot 1.5H_2O$: C, 62.74; H, 6.58; N, 10.74; found: C, 62.98; H, 6.52; N, 10.94.

3,7-Dimorpholinophenoxazinium chloride (**4i**): black powder, yield 51%, mp >250 °C; IR ν (neat, cm^{-1}): 2925, 2855 (alkyl-CH), 1605, 1510, 1490 (phenoxazinium skeleton), 1160 (C−N); UV−vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 262 (4.51); 640 (4.90); ^{1}H NMR (400 MHz, CD_3OD) δ_{ppm}: 3.89 (m, 16H, 4×(CH_2)$_2$), 7.15 (d, $J = 2.7$ Hz, 2H, 2 × Ar−H), 7.56 (dd, $J = 9.7$, 2.7 Hz, 2H, 2 × Ar−H), 7.82 (d, $J = 9.7$ Hz, 2H, 2 × Ar−H); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 49.5 (4 × CH$_2$), 67.6 (4 × CH$_2$), 98.2 (2 × Ar CH), 118.9 (2 × Ar CH), 135.6 (2 × Ar CH), 136.5 (2 × Ar C), 151.0 (2 × Ar C), 158.9 (2 × Ar C); MS (LC-ESI$^+$): *m/z*: 352.1 [M−Cl$^-$]$^+$. Anal. calcd. for $C_{20}H_{22}ClN_3O_3 \cdot 1.5H_2O$: C, 57.90; H, 6.07; N, 10.13; found: C, 57.75; H, 6.21; N, 10.03.

3-Diethylamino-7-pyrrolidin-1-ylphenoxazinium chloride (**4j**): green powder, yield 82%, mp >250 °C; IR ν (neat, cm^{-1}): 2980, 2875 (alkyl-CH), 1605, 1505, 1430 (phenoxazinium skeleton), 1155 (C−N); UV−vis (MeOH): λ (nm) (log ε/L mol^{-1} cm^{-1}): 260 (1.77), 640 (3.84); ^{1}H NMR (400 MHz, CD_3OD) δ_{ppm}: 1.36 (t, $J = 7.2$ Hz, 6H, 2 × CH_3), 2.17 (t, $J = 6.7$ Hz, 4H, 2 × CH_2), 3.72−3.80 (m, 8H, 4 × CH_2), 6.81 (d, $J = 2.5$ Hz, 1H, Ar−H), 6.95 (d, $J = 2.7$ Hz, 1H, Ar−H), 7.26 (dd, $J = 9.5$, 2.5 Hz, 1H, Ar−H), 7.37 (dd, $J = 9.6$, 2.7 Hz, 1H, Ar−H), 7.77 (d, $J = 9.5$ Hz, 1H, Ar−H), 7.78 (d, $J = 9.6$ Hz, 1H, Ar−H); ^{13}C NMR (101 MHz, CD_3OD) δ_{ppm}: 13.2 (2 × CH$_3$), 26.1 (CH$_2$), 26.3 (CH$_2$), 47.7 (2 × CH$_2$), 51.0 (CH$_2$), 51.2 (CH$_2$), 97.4 (Ar CH), 98.1 (Ar CH), 118.3 (Ar CH), 119.7 (Ar CH), 134.9 (Ar C), 135.3 (Ar CH), 135.4 (Ar CH), 135.8 (Ar C), 150.3 (Ar C), 150.5 (Ar C), 156.6 (Ar C), 157.5 (Ar C); MS (LC-ESI$^+$): *m/z*: 322.1 [M−Cl$^-$]$^+$; Anal. calcd. $C_{20}H_{24}ClN_3O \cdot 0.5MeOH \cdot 0.5H_2O$: C, 64.30; H, 7.11; N, 10.97; found: C, 64.09; H, 6.98; N, 10.62.

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