Oxonium heterocyclic quinone in the synthesis of some cyanine dyes and their antimicrobial activity

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1. Introduction

Cyanine dyes have found various applications in different fields, such as antimicrobial agents [1-4], photographic sensitizers, heat developable photosensitizing materials [5-7], and color photography [8]. Cyanine dyes also used as optical recording materials [9-15], in manufacturing of blue filter to laminate of an organic electroluminescent element, and color filter showed highly pure light emission [16] and antioxidants [17]. Cyanine dyes are colorant compounds used in staining of internal limiting membrane (ILM) [18] and used as fluorescent dyes in DNA detection [19-23]. Quinone derivatives are widely used as fungicides [24,25], and antibacterial agent [25-29]. This paper reports the synthesis and characterization of a series of new monomethine, trimethine and styryltrimethine cyanine dyes, and also their structure-property relationship of these dyes from their visible absorption spectra.

2. Experimental

2.1. Instrumentation

All melting points are uncorrected. Elemental analysis was carried out at the Micro Analytical Center (Cairo University). The IR (KBr) spectra were determined with Perkin-Elmer Infrared 127B Spectrophotometer (Cairo University). 1H NMR spectra were recorded with a Bruker AMX-250 spectrometer. The electronic absorption spectra were recorded within the wavelength range (350-700 nm) on 6405 UV-Visible recording spectrophotometer, Faculty of Science, Aswan, Egypt. Mass spectra were recorded on an HPms 6988 spectrometer (Cairo University).

2.2. Synthesis of 2-acetyl-3-amino-1,4-naphthoquinone (2)

This compound was prepared according to references described earlier (Scheme 1) [30,31].

2.3. Synthesis of N-(3-acetyl 1,4-dioxo-1,4-dihydro naphthalen-2-yl)acetamide (3)

A pure sample of compound 2 was dissolved in acetic anhydride and the reaction mixture was refluxed for 3-5 h, filtered, concentrated and cooled. The product 3 was precipitated on dilution with water and crystallized from ethanol (Scheme 1). Color: Red. Yield: 80%. Mp: 258-260 °C. FT-IR (KBr, ν, cm⁻¹): 3400-3100 (NH), 1713-1620 (Acyclic C=O), 1650 (Quinone ring), 1355 (C-N). 1H NMR (400 MHz, DMSO-d₆, δ, ppm): 7.89-7.26 (m, 4H, Ar-H), 6.97 (s, 1H, NH), 2.54 (m, 6H, 2CH₃), MS (EL, m/z): 257, 59. Anal. calcd. for C₃₉H₂₃NO₇: C, 65.36; H, 4.28; N, 5.44. Found: C, 65.36; H, 4.27; N, 5.66%.
2.4. Synthesis of 2,4-dimethyl-5,10-dioxo-5,10-dihydro naphtho[2,3-d][1,3]oxazin-3-ium chloride (4)

A pure sample of compound 3 was dissolved in ethanol (30 mL), and then hydrochloric acid (1 mL) was added. The reaction mixture was refluxed for 2 h; filtered hot, concentrated and cooled. The product 4 was precipitated on dilution with water and crystallized from ethanol (Scheme 1). Color: Brownish red. Yield: 75%. M.p: 217-220 °C. FT-IR (KBr, ν, cm⁻¹): 2921 (Chloride salt), 1634 (Quinone ring), 1480 (C=N), 1350 (C–N), 1150 (C–O–C cyclic). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 8.01–6.93 (m, 4H, Ar–H), 1.69 (s, 3H, CH₃ at C4), 1.31 (s, 3H, CH₃ at C2). MS (El, m/z): 275.5, 132. Anal. calcd. for C₁₄H₁₀NO₃Cl: C, 60.98; H, 3.62; N, 5.08. Found: C, 60.99; H, 3.62; N, 5.09%.

2.5. Synthesis of 1,2,4-trimethyl-5,10-dioxo-5,10-dihydro naphtho[2,3-d][1,3]oxazine-1,3-diium chloride iodide (5)

A pure sample of compound 4 was suspended in excess of ethyl (methyl) iodide and heated in a sealed tube at 140 °C for 3 h. The sealed tube was cooled, opened and the product 5 was collected, washed with ether and crystallized from ethyl alcohol to give brown crystals (Scheme 1). Color: Dark black. Yield: 70%. M.p.: 188-190 °C. FT-IR (KBr, ν, cm⁻¹): 1155 (C=O-C cyclic), 1489 (C=O, Quinone), 2917 (quaternary salt). ¹H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.10 (s, 3H, CH₃ (Methyl iodide)), 3.53 (s, 6H, 2CH₃), 7.43-8.52 (m, 4H, Ar–H). MS (El, m/z): 417.5, 156. Anal. calcd. for C₁₅H₁₃NO₃ClI: C, 43.11; H, 3.11; N, 3.35. Found: C, 43.10; H, 3.12; N, 3.35%.

2.6. Synthesis of compound 6a-c dyes

An ethanolic solution of equimolar amount of compound 5 and 1-ethyl-[pyridinium, quinolinium and/or iso-quinolinium] salts (0.01 mol) were refluxed for 7-8 h in the presence of piperidine (3-5 drops), filtered hot, concentrated and acidified with acetic acid. The precipitated products after dilution with water filtered off and crystallized from ethanol to give the corresponding products (Scheme 1 and 2).

4-{(1-Ethylpyridin-1-ium-4-yl)methylene}-1,2-dimethyl-5,10-dioxo-5,10-dihydro-4H-naphtho[2,3-d][1,3]oxazin-1-ium iodide (6a): Color: Red. Yield: 70%. M.p: 223-225 °C. MS (El, m/z): 614, 77. Anal. calcd. for C₂₁H₂₀N₂O₃: C, 43.02; H, 3.28; N, 4.56. Found: C, 42.93; H, 3.20; N, 4.43%.
2.7. Synthesis of 4-(2,2-diethoxyethyl)-1,2-dimethyl-5,10-dioxo-5,10-dihydro-4H-naphtho[2,3-d][1,3]oxazine-1,3-dium chloride iodide (7)

A mixture of the quaternary compound 5 (0.01 mol) and (0.01 mol) of triethyl-ortho-formate was dissolved in ethanol (50 mL) containing piperidine (3-5 drops) and refluxed for 4 h, filtered hot to remove unreacted materials, concentrated to one half its initial volume, cooled, acidified with acetic acid, and precipitated by cold water, filtered off and crystallized from ethanol to give the corresponding product 7 (Scheme 3). Color: Red. Yield: 65%. M.p.: 200-210 °C. MS (El, m/z): 664, 170. Anal. calcd. for C_{28}H_{24}N_{2}O_{3}: C, 48.72; H, 3.50; N, 4.06. Found: C, 48.60; H, 3.42; N, 4.09%.

2.8. Synthesis of compound 8a-c dyes

Equimolar amounts of compound 7 and 2-methyl quaternary salts (α(γ)-piperidine and/or quinaldine) ethyl iodide (0.01 mol) were dissolved in ethanol (30 mL) then piperidine (3-5 drops) was added. The reaction mixture was refluxed for 8 h, filtered hot, concentrated, cooled and acidified with acetic acid. The precipitated products (8a-c) after dilution with water were collected and crystallized from aqueous ethanol (Scheme 3).
2.9. Synthesis of compound 9a-c dyes

An equimolar amounts of heterocyclic quaternary salt (5, 0.01 mol) and aromatic aldehydes (benzaldehyde, p-nitro benzaldehyde and/or N-dimethyl benzaldehyde (0.01 mol) were dissolved in absolute ethanol (30 mL), then piperidine (1 mL) was added. The reaction mixture was refluxed for 8-10 h, filtered hot, concentrated, acidified with water. The precipitated styrylcyanines (9a-c) were filtered, washed several times with cooled water and then crystallized from the appropriate solvent (Scheme 3).

1,2-Dimethyl-5,10-dioxo-4-styryl-5,10-dihydronaphtho(2,3-d)[1,3]oxazine-1,3-diium chloride iodide (9a): Color: Red. Yield: 70%. M.p.: 218-220 °C. MS (EI, m/z): 505.5, 156. Anal. calcd. for C22H16N2O5ClI: C, 52.25; H, 3.39; N, 5.10. Found: C, 52.80; H, 3.41; N, 5.11.0%.

1,2-Dimethyl-4-(4-nitrostyryl)-5,10-dihydronaphtho(2,3-d)[1,3]oxazine-1,3-diium chloride iodide (9b): Color: Pale red. Yield: 82%. M.p.: >300 °C. FT-IR (KBr, ν, cm⁻¹): 1160-1030 (C-O-C cyclic), 1350 (C-N), 1484 (C=N), 1595 (C=C), 1650 (C=0 Quinone), 2957 (quaternary salt). 1H NMR (400 MHz, DMSO-d₆, δ, ppm): 1.19 (s, 3H, CH₃ [Methyl iodide]), 3.35 (s, 3H, CH₃), 7.81-8.21 (m, 8H, Ar-H), 5.04-4.05 (m, 2H, H=CH).

3. Results and discussion

3.1. Synthesis

Reaction of equimolar ratio of 1,2,4-trimethyl-5,10-dioxo-5,10-dihydronaphtho[2,3-d][1,3]oxazine-1,3-diium chloride iodide (5) with heterocyclic quaternary salts of pyridinium, quinolinium and isoquinolinium ethyl iodide in the presence of piperidine as basic catalysis afforded the desired compound 6a-c dyes (Scheme 1).
Treating on the latter compound 6a-c by conc. H₂SO₄ resulted in liberating iodine vapor on warming. This is due to that the above reaction between the compound 5 and heterocyclic quaternary salts of pyridinium, quinolinium and/or isoquinolinium ethyl iodide was suggested to proceed through liberation of hydrogen chloride (dehydrohalogenation) and hydrogen molecule.

Additionally, interaction of equimolar ratios of compound 5 with triethylorthoformate in ethanol containing few drops of hydrogen molecule. Through liberation of hydrogen chloride (dehydrohalogenation) and/or isoquinolinium ethyl iodide was suggested to proceed through liberation of hydrogen chloride (dehydrohalogenation) and hydrogen molecule.

Condensation reaction of equimolar ratios of compound 5 and benzaldehyde, p-nitrobenzaldehyde and/or N-dimethyl benzaldehyde between the active methyl group of the former compound and formyl group of the latter ones in the presence of piperidine as basic catalyst and ethyl alcohol as solvent gave the corresponding compound 9a-c dyes (Scheme 3).

The newly synthesized cyanine dyes (6a-c), (8a-c) and (9a-c) are highly colored compounds, easily soluble in polar organic solvents given green fluorescence but sparingly soluble in non-polar solvents and soluble in conc. H₂SO₄ liberating iodine vapor on warming.

3.2. Spectral behavior

The electronic absorption spectrum features (λmax and εmax values) of the newly synthesized cyanine dyes (6a-c), (8a-c) and (9a-c) in ethanol solution are depicted in Table 2.

The visible absorption spectra of compound 6a-c dyes in 95% ethanol undergo bathochromic or hypsochromic shifts depending on the nature of the quaternary salts residue and its linkage position. Thus, the electronic absorption spectra of compound 6a which incorporating a heterocyclic of N-ethyl pyridin-4-i um, showed λmax at 450 nm. Substitution of a heterocyclic of N-ethyl pyridin-4-r iumd in compound 6a by a heterocyclic of N-ethyl quinolin-4-i um in compound 6b resulted in a bathochromic shift of λmax = 15 nm, so compound 6b, exhibited λmax = 465 nm. This is due to the more extensive π-delocalization and extra conjugation within the extra phenyl ring in quinolinium ring in compound 6b [32,33].

Additionally, changing the linkage position from 4-i um in compound 6b which incorporating a heterocyclic N-ethyl quinolin-4-i um to 1-i um in compound 6c which incorporating a heterocyclic of N-ethyl isoquinolin-1-i um causes a hypsochromic shift of λmax = 5 nm, so compound 6c showed λmax = 460 nm. This is due to the more extensive π-delocalization within 4-i um rather than 1-i um linkage position (Table 2).

The visible absorption spectra of compound 8a-c dyes in 95% ethanol showed absorption band undergo batho(hypo)chromically shifted depending upon the heterocyclic quaternary residue, and their linkage position. Thus, the absorption spectra of compound 8a quaternary heterocyclic residue of 1-ethyl pyridin-2-ium ethyl iodide showed λmax = 460 nm. Substituting of heterocyclic quaternary residue 1-ethyl pyridin-2-ium ethyl iodide in compound 8a by quaternary heterocyclic residue of 1-ethyl quinolin-2-ium ethyl iodide in compound 8b exhibited λmax = 520, 565 and 605 nm. This is due to the more extensive π-delocalization within the extra phenyl ring in compound 8b.

Additionally, changing the linkage position from 2-i um linkage position in compound 8a, quaternary heterocyclic residue of 1-ethyl pyridin-2-ium ethyl iodide to 4-i um in compound 8c, quaternary heterocyclic residue of 1-ethyl pyridin-4-ium ethyl iodide resulted in a remarkable bathochromic shift of λmax = 5 nm, if compared with compound 8a, (8c, λmax = 465 nm). This is due to the increasing of the extension conjugation of 4-linkage pyridine moiety better than 2-linkage analogous (Table 2).

Finally, the visible absorption spectra of compound 9a-c dyes in 95% ethanol showed absorption bands influenced by aryl substituents [34]. Thus, styryl cyanine dye 9a show single absorption band located at λmax = 445 nm. Substituting benzaldehyde in dye 9a by p-nitro benzaldehyde in dye 9b resulted in a hypsochromic shift of λmax = 40 nm (9b, λmax = 405 nm).

### Table 1. Biological activity of some newly synthesized compounds.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mean diameter inhibition zone (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacillus subtilis</td>
</tr>
<tr>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>20.5</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>4</td>
<td>21.5</td>
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<td>5</td>
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<td>19</td>
</tr>
<tr>
<td>6c</td>
<td>20</td>
</tr>
<tr>
<td>8a</td>
<td>18</td>
</tr>
<tr>
<td>8b</td>
<td>31.5</td>
</tr>
</tbody>
</table>

* Standard which is Methylparol at conc. 1 mg/mL for Gram positive bacteria, while Kellex was used as standard for Gram negative bacteria at concentration 1 mg/mL. Flucorai was used as standard for fungi at concentration 1 mg/mL. Amikacin was used as standard at concentration 1 mg/mL for *Canadida albicans*.

### Table 2. The electronic absorption spectra of new synthesized cyanine dyes (6a-c), (8a-c) and (9a-c) in 95% EtOH.

<table>
<thead>
<tr>
<th>Compound</th>
<th>λmax, nm</th>
<th>εmax, mol⁻¹ cm⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>460</td>
<td>665</td>
</tr>
<tr>
<td>6b</td>
<td>605, 565, 520</td>
<td>1100, 1650, 1200</td>
</tr>
<tr>
<td>6c</td>
<td>460</td>
<td>460</td>
</tr>
<tr>
<td>εmax, mol⁻¹ cm⁻¹</td>
<td>1727</td>
<td>1235</td>
</tr>
<tr>
<td>8a</td>
<td>445</td>
<td>405</td>
</tr>
<tr>
<td>8b</td>
<td>1770</td>
<td>1990</td>
</tr>
<tr>
<td>9a</td>
<td>1770</td>
<td>1990</td>
</tr>
<tr>
<td>9b</td>
<td>1770</td>
<td>1990</td>
</tr>
<tr>
<td>9c</td>
<td>1770</td>
<td>1990</td>
</tr>
</tbody>
</table>
nm). This is due to the strong electron withdrawing effect of p-NO₂ group. Also, substituting p-nitro-benzaldehyde in dye 9b by N-dimethyl benzaldehyde is dye 9c causes a bathochromic shift of λmax = 55 nm, (9c, λmax = 460 nm). This is due to the electron donating effect of two methyl groups (Table 2).

3.3. Antimicrobial activity

Structure-antimicrobial activity relation-ship for some selectively synthesized quinone compounds 3, 4, 5, 6a-c, 8a, 8b, 9a and 9b were studied and determined against some bacterial and fungi strains (Table 1). The data obtained are expressed as size (mm) of inhibition zone. Diameter of the inhibition zones were high (22-18 mm), moderate (17-12 mm), slight (11-1 mm), no response (-). The final conclusion from this work is that these novel compounds showed significant antibacterial activity according to the following factors: (i) Increasing and/or decreasing conjugation in the dye molecule; (ii) Increasing and/or decreasing the number of the methine group; (iii) The presence of either electron donating and/or accepting group.

4. Conclusion

New unsymmetrical cyanine dyes have been prepared incorporating heterocyclic quinone and were identified by chemical and spectroscopic evidences (Elemental analysis, UV-Vis, IR, 1H NMR and MS spectra). Also, antimicrobial activity of few selected compounds against some bacterial strains was tested.

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References