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Synthesis of zwitterionic 4-hydroxy-2(1*H*)-quinolinone derivatives

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Abstract

Zwitterionic 4-hydroxy-2(1*H*)-quinolinone derivatives were synthesized through a unique reaction of 4-hydroxy-2(1*H*)-quinolinone with *p*-benzoquinone and *N*-heterocyclic aromatics. The zwitterions possessed astropisomeric nature. A possible mechanism of the reaction was presented.

Keywords: 4-Hydroxy-2(1*H*)-quinolinone; Zwitterion; *p*-Benzoquinone

1. Introduction

A broad number of fascinating pharmacological activities have been associated with 2-quinolinone derivatives. The quinolinone alkaloids, isolated from the *Rutaceae* family of plants, have been shown to exhibit a variety of biological properties[1] including antibacterial, antifungal, and antiviral. 3-Halo-2(1*H*)-quinolinones have been used as cardiac stimulants and as herbicides.[2] Several 2-quinolones fused to sulfur-containing heterocycles have been proposed to exert cytostatic against a broad range of malignant cell lines.[3] 3-Aryl-4-hydroxy-2(1*H*)-quinolinones have been found to serve as key intermediates in the synthesis of non-peptide GnRH receptor antagonists.[4] In addition, some 4-hydroxy-2(1*H*)-quinolinone derivatives have been reported to show a broad spectrum of activity against both wild-type HIV-1 and key NNRTI-relevant mutant viruses.[5]

In a recent communication,[6] we reported the synthesis of the zwitterionic 4-hydroxycoumarin derivatives **1** (Fig. 1) through a unique reaction of 4-hydroxycoumarins with *p*-benzoquinone and pyridine in aqueous acetone. Apparently, the reaction involved the nucleophilic addition of 4-hydroxycoumarin to *p*-benzoquinone. 4-Hydroxy-2(1*H*)-quinolinone is similar to 4-hydroxycoumarin in the nucleophilicity of C-3. For example, nucleophilic substitution of 4-hydroxy-2(1*H*)-quinolinone and prenyl bromide in aqueous sodium hydroxide has been carried out to generate diprenylated quinolone[7] **2** (Fig. 1). Thus, we envisioned that 4-hydroxy-2(1*H*)-quinolinone would also react with *p*-benzoquinone and pyridine to yield the corresponding zwitterionic compound. We describe here the synthesis of zwitterionic 4-hydroxy-2(1*H*)-quinolinone derivatives starting from 4-hydroxy-2(1*H*)-quinolinone and several *N*-heterocyclic aromatic compounds, and the astropisomeric nature of these zwitterionic compounds.

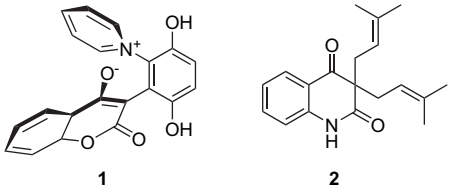

Figure 1.

2. Results and discussion

Shah et al.[8] have reported a simple and potential method to synthesize 4-hydroxycoumarins using phenols and malonic acid. Considering some similar chemical properties between

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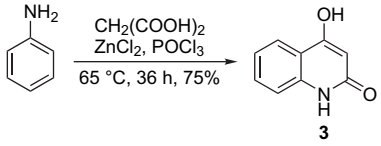
aniline and phenol, 4-hydroxy-2(1*H*)-quinolinone **3** would also be synthesized following Shah's procedure. Treating aniline with an equimolar proportion of malonic acid in the presence of a mixture of 2–3 mol each of anhydrous zinc chloride and phosphorus oxychloride as the condensing agent at 65 °C for 36 h, we obtained 4-hydroxy-2(1*H*)-quinolinone in 75% yield (Scheme 1).

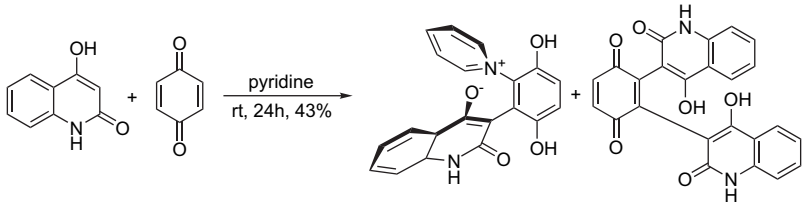


Scheme 1. Synthesis of 4-hydroxy-2(1*H*)-quinolinone.

When the mixture of 4-hydroxy-2(1*H*)-quinolinone **3**, 2 equiv of *p*-benzoquinone, and 2 equiv of pyridine in 30 ml aqueous acetone (v/v=1:1) was stirred at room temperature for 24 h, the zwitterion **4a** was generated in 43% yield after column chromatography (Scheme 2). The assignment of compound **4a** was confirmed by ^{1}H NMR analysis of the expected chemical shifts and geminal coupling constants. To optimize the yield of **4a**, we studied the effect of several factors on the outcome of this reaction, including (i) reaction temperature (rt, 40, 50 °C), (ii) the ratio of the reactants (4-hydroxy-2(1*H*)-quinolinone/*p*-benzoquinone/pyridine=1:2:2, 1:2:3, 1:2:4 (mol/mol)), and (iii) solvent (methanol, ethanol), but the yield of **4a** has not been improved effectively. It was due to a existing competitive reaction, which afforded 2,3-disubstituted-1,4-benzoquinone **5**.[9]

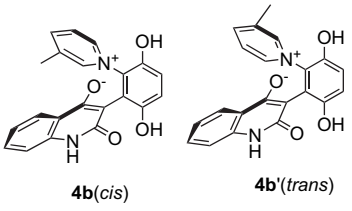
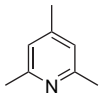
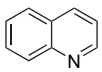
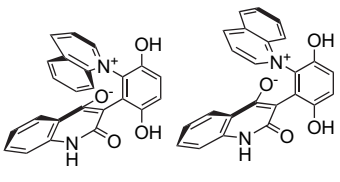
The different shift of the two α-protons located on the pyridine ring of **4a**, at δ 8.94 and 8.45 ppm, respectively, displayed that the pyridine ring could not rotate freely along the C–N bond. This restricted rotation made the compound exist as atropisomers. It is worth noting that atropisomeric compounds are of considerable interest due to their presence in a number of biologically active natural products and their utility as directing groups in asymmetric synthesis.[10] Thus, if other *N*-heterocyclic aromatics, which did not have a C_2-symmetric axis through the nitrogen atom, such as 3-methylpyridine and quinoline, were treated with 4-hydroxy-2(1*H*)-quinolinone and *p*-benzoquinone, both cis and trans products were obtained. The results of the reaction using 3-methylpyridine, 2,4,6-trimethylpyridine, or quinoline instead of pyridine as reactant were summarized in Table 1.

The results showed that the yield of quinoline zwitterion (Table 1, entry 3) was much lower than that of pyridine zwitterion and 3-methylpyridine zwitterion (Table 1, entry 1), and any trace of the 2,4,6-trimethylpyridine zwitterion (Table 1, entry 2) was not detected by TLC under the similar reaction



Scheme 2. Synthesis of compound **4a**.

Table 1
Reaction of 4-hydroxy-2(1*H*)-quinolinone with *p*-benzoquinone and *N*-heterocyclic aromatics

Entry	Heteroaromatics	Yield[a] (%)	Product **4**	cis/trans[b]
1		39	 **4b**(*cis*) **4b'**(*trans*)	1.4:1
2		0		
3		17	 **4d**(*cis*) **4d'**(*trans*)	1:1.6

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectra.

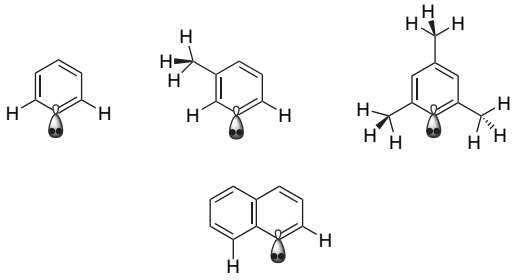


Figure 2.

conditions. The apparent difference in the yield of these zwitterions disclosed that the surrounding space of the two unshared electrons in the N-sp^2 orbital had a profound effect on the outcome of the reaction. The larger the surrounding space, the better yield would be obtained. Because the occupied nonbonding N-sp^2 orbital is parallel to C8–H bond, the surrounding space of the nonbonding N-sp^2 of quinoline is less than that of pyridine and 3-methylpridine (Fig. 2). The less space resulted in the difficulty of the nucleophilic attack of quinoline and the low yield of quinoline zwitterion. For 2,4,6-trimethylpyridine, the two methyl groups adjacent to the nitrogen atom seriously prevented the nucleophilic attack and led to no generation of 2,4,6-trimethylpyridine zwitterion.

For 3-methylpyridine and quinoline zwitterions (Table 1, entries 1 and 3), due to the restricted rotation about the C–N bond, both cis and trans products were obtained, which could not be separated by column chromatography (silica gel). The assignment of the cis and trans stereochemistry and their ratio could be determined by ^{1}H NMR spectra (Fig. 3). For 3-methylpyridine zwitterion, only the α-proton next to the methyl group on the pyridine ring was predicted to show single peak in the aromatic region. The appearance of the two aromatic singlets, at δ 8.94 and 8.39 ppm, respectively, implied that both cis and trans isomers might be generated. Furthermore the two aromatic singlets had a total integrated area corresponding to 1H, which was consistent with the mixture of the two isomers. The peak at δ 8.79 ppm was attributed to the α-proton (H2′) adjacent to the methyl group of cis isomer,

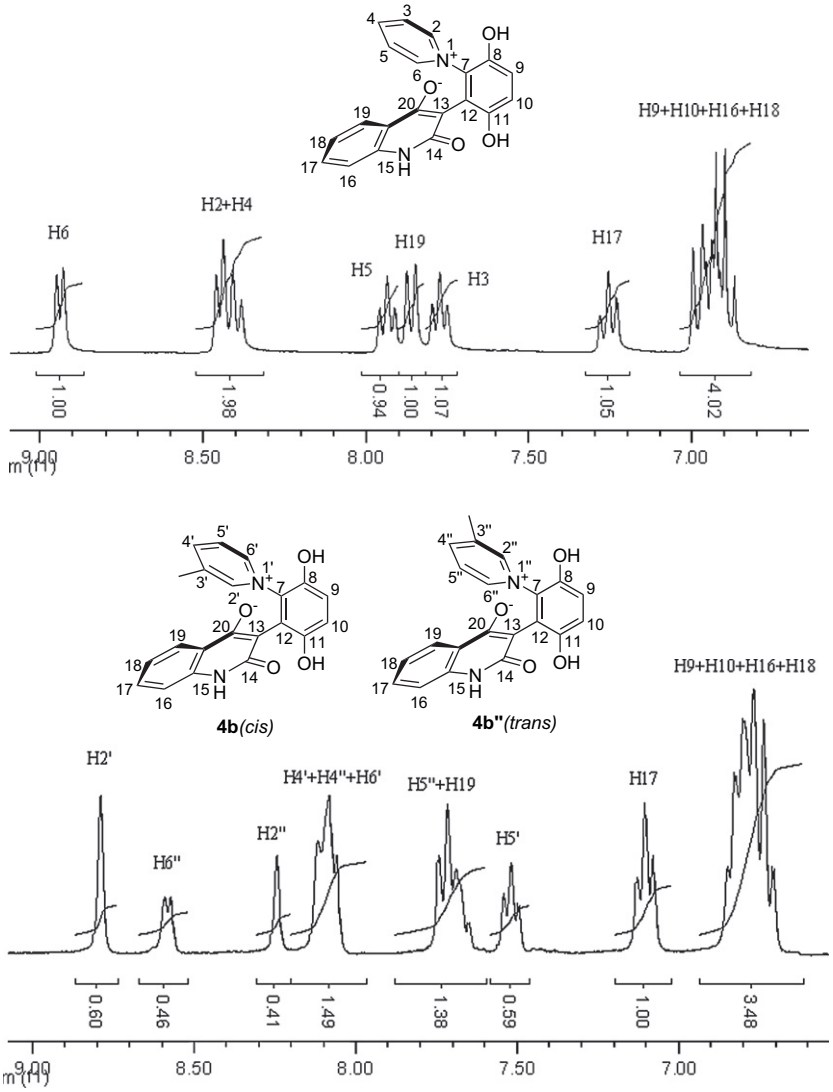


Figure 3. The ^{1}H NMR spectra of compounds **4a**, **4b**, and **4b′**.

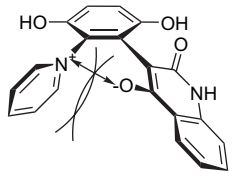


Figure 4.

in which H2′ was far away from the shielding region of the oxyanion, and came at low fields relative to H2′ of the trans isomer. Thus the area ratio of 1.4:1 of the two aromatic singlets represented the ratio of cis and trans isomers. It was interesting to note that there was more trans isomer than cis isomer in the quinoline zwitterion (cis/trans=1:1.6, Table 1, entry 3).

The restricted rotation about the C–N bond was considered to be caused from both the intramolecular ion pair attraction and the steric interaction (Fig. 4). The ion pair attraction made the 4-hydroxy-2(1*H*)-quinolinone ring tilt toward the *N*-heterocyclic aromatic ring until the equilibration between the ion pair attraction and the steric interaction. Conversely, the tilting 4-hydroxy-2(1*H*)-quinolinone ring limited the heterocyclic aromatic ring to rotate freely by the steric interaction.

A possible mechanism of the formation is presented in Figure 5. The Michael addition of 4-hydroxy-2(1*H*)-quinolinone with *p*-benzoquinone first gives intermediate **6**, which is subsequently autooxidized to generate quinone derivative **7**. Quinone derivative **7** is attacked by pyridine at the 3-position to form **4a**, which is in a hydroquinone form due to the electron-withdrawing effect of the pyridinium moiety.

In summary, the synthesis of the zwitterionic 4-hydroxy 2(1*H*)-quinolinone derivatives through a unique reaction was described. The astropisomeric nature was determined by ^{1}H NMR spectra. A possible mechanism of the formation of zwitterions was presented.

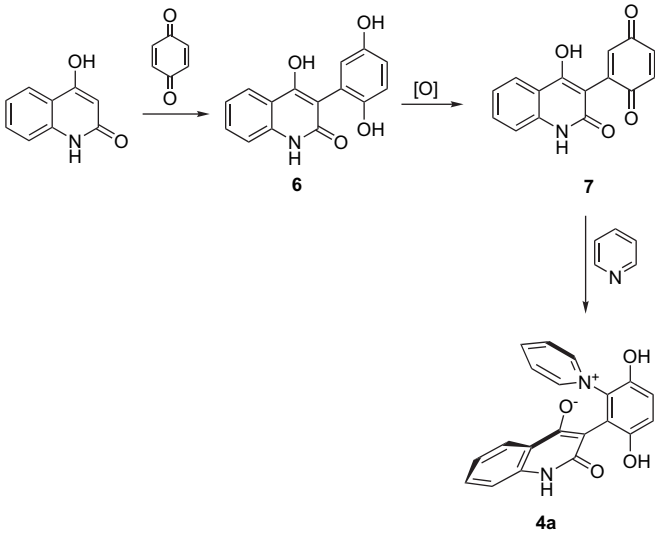


Figure 5.

3. Experimental

3.1. General

^{1}H NMR, ^{13}C NMR spectra were measured on a Varian UNITY INOVA 300 MHz spectrometer using TMS as an internal standard. For the electrospray (ESI) MS analysis, a Finnigan LCQ Deca XP ion trap mass spectrometer equipped with a Microsoft Windows NT data system and an ESI interface was used. Elemental analysis was recorded on an Elementar Vario EL elementary analysis device. IR absorption was recorded on a Bruker TENSOR 37 spectrophotometer.

3.2. The synthesis of 4-hydroxy-2(1H)-quinolinone

A mixture of aniline (27.9 g, 0.3 mol), malonic acid (31.2 g, 0.3 mol), anhydrous zinc chloride (122.7 g, 0.9 mol),

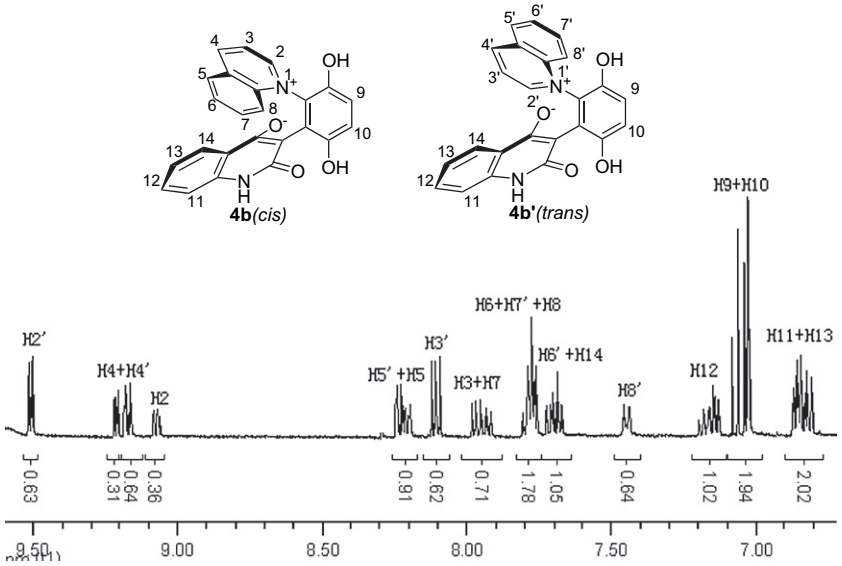


Figure 6. The ^{1}H NMR spectra of compounds **4d** and **4d′**.

and phosphorus oxychloride (90 ml) was heated with stirring at 65 °C for 36 h, cooled and decomposed with ice and water, and allowed to stand. The resulting crude 4-hydroxy-2(1*H*)-quinolinone was collected as solid by filtration, dissolved in 10% sodium carbonate, and acidified to about the neutral point. The collected precipitate was crystallized from methanol to afford 4-hydroxy-2(1*H*)-quinolinone (36 g) in 75% yield as yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.30 (1H, s), 11.18 (1H, s), 7.75 (1H, d, J=8.1 Hz), 7.46 (1H, t, J=6.9 Hz), 7.24 (1H, d, J=8.1 Hz), 7.11 (1H, t, J=7.8 Hz), 5.72 (1H, s) ppm; ^{13}C NMR (DMSO-d_6) δ 164.10, 162.96, 139.80, 131.45, 123.29, 121.27, 115.76, 115.63, 98.94 ppm; IR (KBr) 2859, 1668, 1507, 1464, 1415, 1333 cm^{-1}; ESI-MS (*m*/*z*): 162 $(M-1)^+$. Anal. Calcd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69. Found: C, 66.92; H, 4.25; N, 8.81.

3.3. General procedure of the synthesis of zwitterionic 4-hydroxy-2(1H)-quinolinone derivatives

A mixture of 4-hydroxy-2-(1*H*)-quinolinone **3** (0.82 g, 5 mmol), *p*-benzoquinone (1.08 g, 10 mmol), and pyridine (0.79 g, 10 mmol) in 30 ml aqueous acetone (v/v=1:1) was magnetically stirred at room temperature for 24 h. The reaction mixture was filtered to afford a brown crude product, which was purified by column chromatography (silica gel, methanol/trichloromethane=1:10) to give the yellow compound.

3.3.1. Compound *4a*

Yield 43%, yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.13 (1H, s), 8.94 (1H, d, J=6.3 Hz), 8.45 (1H, d, J=6.3 Hz), 8.40 (1H, d, J=7.8 Hz), 7.94 (1H, t, J=6.9 Hz), 7.86 (1H, d, J=7.5 Hz), 7.77 (1H, t, J=7.2 Hz), 7.26 (1H, t, J=7.8 Hz), 6.89–6.99 (4H, m) ppm; ^{13}C NMR (DMSO-d_6) δ 173.26, 163.46, 151.83, 151.30, 147.55, 145.75, 143.05, 139.54, 131.29, 130.09, 126.40, 126.03, 125.45, 123.54, 121.68, 121.26, 120.32, 115.14, 119.94, 100.72 ppm; IR (KBr) 2931, 1628, 1581, 1348 cm^{-1}; ESI-MS (*m*/*z*): 347 $(M-1)^+$. Anal. Calcd for $C_{20}H_{14}N_2O_4$: C, 69.36; H, 4.07; N, 8.09. Found: C, 69.21; H, 4.03; N, 8.15.

3.3.2. Compounds *4b* and *4b′*

Yield 39%, yellow solid, **4b/4b′**=1.4:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.17 (0.6H, s), 10.08 (0.4H, s), 2.40 (3H, s) ppm; IR (Bruker) 2927, 1631, 1582, 1393, 1277 cm^{-1}; ESI-MS (*m*/*z*): 361 $(M-1)^+$. Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 70.27; H, 4.56; N, 7.87 (^{1}H NMR spectra shown in Fig. 3).

3.3.3. Compounds *4d* and *4d′*

Yield 17%, yellow solid, **4d/4d′**=1:1.6. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.00 (0.64H, s), 9.84 (0.36H, s), 9.59 (1H, s) ppm; IR (Bruker) 3368, 1577, 1385 cm^{-1}; ESI-MS (*m*/*z*): 397 $(M-1)^+$. Anal. Calcd for $C_{24}H_{16}N_2O_4$: C, 72.72; H, 4.07; N, 7.07. Found: C, 72.53; H, 4.11; N, 7.35 (^{1}H NMR spectra shown in Fig. 6).

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.052.

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