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Two new fluorescent heterocyclic perimidines: first syntheses, crystal structure, and spectral characterization

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ABSTRACT

An efficient one-pot synthesis of two new heterocyclic perimidines 4-(2,3-dihydro-1*H*-perimidin-2-yl)-2-methoxyphenol and 2-(quinoxalin-2-yl)-2,3-dihydro-1*H*-perimidine in good yields is presented. This methodology provides a simple, straightforward synthetic route to these interesting classes of heterocycles. Crystal structure, solvatochromism, and antibacterial activity of these organic compounds are discussed.

The 1*H*-perimidine system has been known since 1874, when it was obtained by de Aguiar.[1] These peri-naphtho-fused pyrimidines have the characteristics both of π-deficient and π-excessive systems.[2] They have long been used as dye intermediates and coloring materials for polymers[3], polyester fibers[4], and more recently as a source of a novel carbene ligand.[5] Perimidines are of wide interest[6,7] because they exhibit a diverse range of biological activities, for example, their potential to act as anti-fungal, anti-microbial, anti-ulcer, and anti-tumor agents.[4,8]

Synthetic method[4] for the preparation of perimidines is the condensation reaction of 1,8-diaminonaphthalene with various carbonyl groups. Acyl chlorides[9] and anhydrides, carboxylic acids[10,11] afford the mono-amide derivatives, and these undergo acid-catalyzed cyclization to 2-substituted perimidines. Although a wide range of 2-alkyl-, aryl-, and heterocycle-substituted perimidines have been prepared by these approaches, there have been no examples synthesized with quinoxaline-2-carboxaldehyde or with 4-hydroxy-3-methoxybenzaldehyde so far. Quinoxaline[12a–c] derivatives are an important class of nitrogen-containing heterocycles in medicinal chemistry.[13a–d] For example, quinoxaline is a part of various antibiotics such as echinomycin, levomycin, and actinoleutin that are known to inhibit the growth of Gram-positive bacteria[13c], and are active against various transplantable tumors.[13d] 1,8-Diaminonaphthalene possesses excellent fluorescence properties.[14] Photoluminescence is an intrinsic molecular property of great interest for the preparation of advanced materials required for applications such as organic light-emitting devices or liquid crystal displays.[15] It has previously been shown[16] that usually perimidine formation needs special reagent or vigorous reaction conditions, but here we have succeeded in preparing the perimidines, 4-(2,3-dihydro-1*H*-perimidin-2-yl)-2-methoxyphenol (compound **1**) and 2-(quinoxalin-2-yl)-2,3-dihydro-1*H*-perimidine (compound **2**) by very simple and efficient procedure in good yield without any other byproducts.

Compound **1** (Scheme 1) was synthesized by refluxing 0.16 g (1 mmol) of purified 1,8-diaminonaphthalene[17,18] and 0.15 g (1 mmol) of 4-hydroxy-3-methoxy benzaldehyde in methanol. It was refluxed for 3 h under nitrogen atmosphere. The product was collected by removing the solvent with rotavapor. The crude product was purified by chromatography on silica gel with hexane/ethyl acetate (80/20 mixture) to get colorless crystals in 80% yield. The crystal suitable for X-ray crystallography was obtained by keeping the solution of the compound in methanol for 4–5 days. Compound **2** (Scheme 1) was synthesized by following the same procedure given above except that the reaction was carried out at room temperature to obtain orange crystals in 85% yield.

The reaction involves two steps. The first step is the condensation to form Schiff's base and the second step is the intramolecular nucleophilic attack of the amino group at the imino carbon to bring

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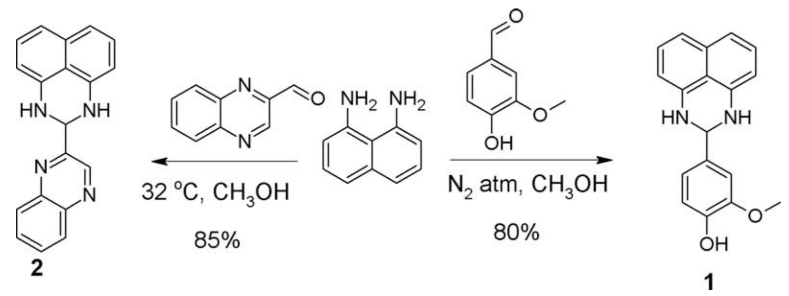

Scheme 1. Synthesis of compound **1** and **2**.

about the C–N coupling. The imino (or azomethine, C=N) carbon is partially positively charged, and therefore is susceptible to intermolecular or intramolecular nucleophilic attack[19], as illustrated in Scheme 1 in Supplementary data. In particular the intramolecular reactions give five- or six-membered heterocycles.

Spectroscopic characterizations of the perimidines were carried out by ^{1}H, ^{13}C NMR, IR as well as by elemental analysis. IR spectrum of compound **1** exhibits broad absorption bands at 3167 (NH) and 3367 (OH) cm^{-1}. Compound **2** exhibits bands at 3284 (NH) and 1599 (C=N, quinoxaldehyde ring) cm^{-1}. The ^{1}H and ^{13}C NMR spectra of compound **1** show signals at δ_H 4.50 (2H, NH), 5.37 (1H, OH), 5.79 (1H, C8), and δ_c 132.0 (C4), 68.3 (C8) and the spectra of the compound 2 exhibit signals at δ_H 5.01 (2H, NH), 5.83 (1H, C9), 9.25 (1H, C7) and δ_c 154.1 (C8), 67.2 (C9). Also the purity of these compounds in methanol (10^{-5} mol L^{-1}) is checked by HPLC. The HPLC chromatogram (For figures: see Supplementary data) gave only one peak with retention times 3.10 min and 3.35 min for compounds **1** and **2**, respectively. Corresponding UV–vis spectra of the HPLC peaks of the compounds **1** and **2** are given in Supplementary data.

Further structural information for **1** and **2** was rendered by the single crystal X-ray diffraction analyses (Table 1; Figs. 1 and 2). Compound **1** crystallized in an orthorhombic system. The asymmetric unit of compound **1** contains two crystallographically independent molecules. The naphthalene moiety of perimidine ring and benzene ring of 3-methoxy-4-hydroxybenzaldehyde is nearly perpendicular with an angle of 86.53°. The loss of planarity of the perimidine ring is worth mentioning. The C8 atom lies 0.578 Å above the plane of perimidine ring and hence there is a large deviation. Compound **1** is stabilized by intermolecular O–H···O hydrogen bonding.

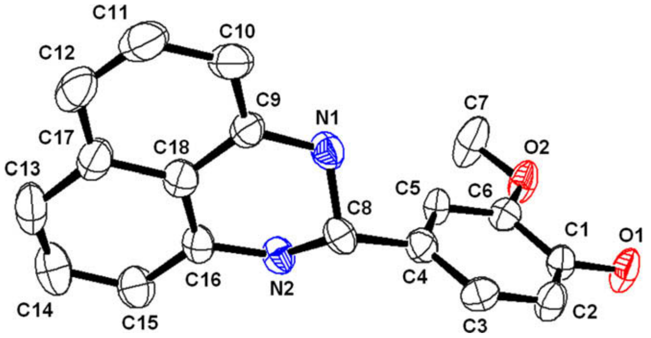

Figure 1. ORTEP drawing of compound **1** at 50% probability level.

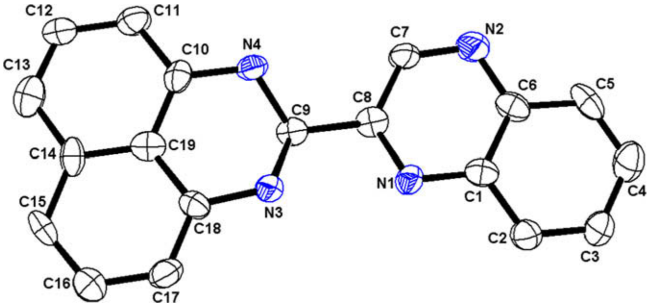

Figure 2. ORTEP drawing of compound **2** at 50% probability level.

Table 1
Crystal data of the compounds **1** and **2**

Crystal data		
Parameters	Compound **1**	Compound **2**
Empirical formula	$C_{18}H_{16}N_2O_2$	$C_{19}H_{14}N_4$
Formula weight	292.33	298.34
Temperature (K)	298(2)	298(2)
Crystal system	Orthorhombic	Monoclinic
Space group	$Pna2_1$	$P2_1/c$
a (Å)	8.7813 (15)	13.729 (4)
b (Å)	7.4057 (12)	5.3352 (15)
c (Å)	45.282 (8)	20.104 (5)
α (°)	90	90
β (°)	90	97.530
γ (°)	90	90
V (Å^3)	2944.8 (9)	1459.9 (7)
Z	8	4
D_{calcd} (Mg/m^3)	1.319	1.357
M (mm^{-1})	0.09	0.08
F (0 0 0)	1232	624
T_{min}	0.971	0.977
T_{max}	0.990	0.991
Number of reflections with $I > 2\sigma(I)$	2713	1662
$R[F^2 > 2\sigma(F^2)]$	0.061	0.129
$wR(F^2)$	0.157	0.257

Compound **2** crystallizes in a monoclinic system. The naphthalene moiety of the perimidine ring and quinoxaline ring of compound **2** is nearly parallel. The loss of planarity of the compound is affected by the position of C9 which is 0.559 Å above the plane of quinoxaline ring. There is no classical hydrogen bonding observed in compound **2**. The CH···π interaction of C9–H9 with symmetry-related naphthalene ring at a distance of 2.46 Å contributes to the stability of crystal packing. In both the crystals, the carbon atoms C8 and C9 lie 0.578–0.559 Å above the perimidine ring plane. This feature of both crystals closely parallels that of the trimethylsilyl analogue[20] in which the Si atom lies 0.88 Å above the plane of the naphthalene ring.[21] There are no reports of organic compounds in which loss of planarity of perimidine ring moiety is mentioned.

The UV–vis absorption spectra of the compounds **1** and **2** in methanol exhibit well-defined $\pi\rightarrow\pi^*$ transition absorption bands with the wavelength maximum at 337 and 345 nm, respectively (Fig. 3a). In the electronic spectrum of compound **2** absorption at 322 nm is due to the $n\rightarrow\pi^*$ transition of the –C=N group in

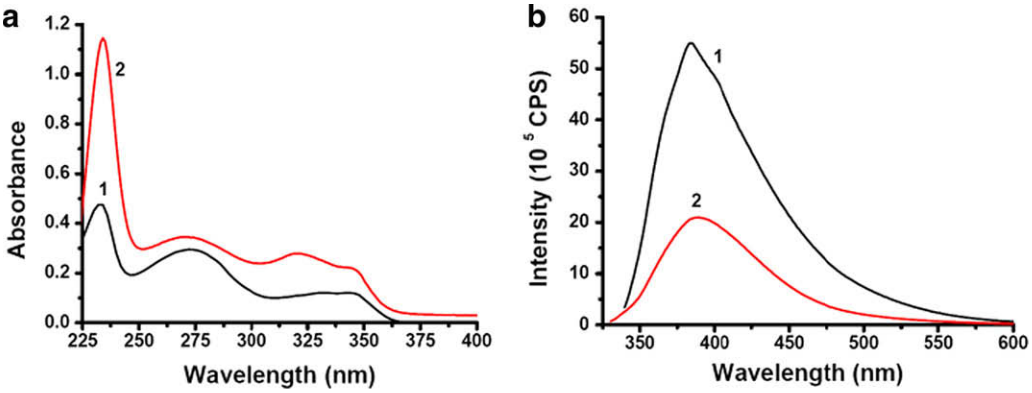

Figure 3. UV–vis absorption spectra and fluorescence spectra of the compounds **1** and **2** in methanol.

quinoxaline ring.[22] The UV–vis spectra corresponding to the peaks in the HPLC chromatogram of compounds **1** and **2** in methanol (10^{-5} mol L^{-1}) and UV–vis spectra of the compounds in methanol (10^{-5} mol L^{-1}) are almost identical to each other. The effect of various solvents on the absorption spectra of these compounds is studied (Table 2). For compound **1**, the absorption spectra are bathochromically shifted in going from cyclohexane to acetonitrile, but are hypsochromically shifted in methanol (polar solvents).[14] This positive solvatochromism in non-hydrogen bonding solvents may be due to the effect of dipole moment changes in the excited state; whereas the negative solvatochromism in polar solvents may be due to the combined effect of dipole moment changes and hydrogen bonding.[12a] In the case of compound **2**, the obtained results showed no solvatochromic effect suggesting that UV–vis spectrum of the compound is independent[23] of the solvent polarity.

The fluorescence band maxima of these compounds at longer wavelengths (Table 2) are compared with that of literature reports of 1,8-diaminonaphthalene.[14] Fluorescence spectra of compounds **1** and **2** in methanol are shown in Figure 3b. In compound **1**, hypsochromic shift (negative fluorescent solvatochromism)[24] is noticed on changing the nature of solvent from non-polar to polar suggesting that this may be due to the apparent stabilization of the ground state through dipole–dipole interaction or a possible hydrogen bonding in polar solvents. On the other hand, a constant bathochromic shift[25] (positive fluorescent solvatochromism) is noticed in the fluorescence spectra of compound **2**. This might be due to the absence of hydroxyl group in compound **2** and consequent hydrogen bonding interactions. The Stokes shift observed in the case of compound **2** is smaller than that observed for compound **1**. The fluorescence quantum yields were determined using a solution of quinine sulfate in 1 N H_2SO_4 (aq) with a concentration of 1×10^{-5} mol L^{-1} as the reference standard ($\Phi_F = 0.546$)[26] (see Supplementary data). Here solvents have only minor effects on the excitation spectra but a strong impact on the emission. In compound **1**, the fluorescence efficiencies in non-polar solvents (chloroform and ethyl acetate) are very high (Φ_F = 0.32 and 0.81) but are moderate in polar hydrogen bonding and non-hydrogen bonding donor solvents (Φ_F = 0.21–0.07). Whereas in compound **2**, the fluorescence efficiencies in non-polar solvents are moderate ($\Phi_F = 0.31$) but are high in polar non-hydrogen bonding donor solvents (acetonitrile and dioxane) (Φ_F = 0.22 and 0.82).

Table 2
UV–vis absorption data, fluorescence spectral data, Stokes shift, and quantum yield of compound **1** and **2** in various solvents

Solvent	Absorption (nm) ($\varepsilon_{max} \times 10^{-5}$ (L mol^{-1} cm^{-1}))	Emission (nm)	Stokes shift (nm)	Quantum yield (Φ_F)
*Compound **1***				
Cyclohexane	332 (0.31)	376	44	0.07
Dioxane	345 (0.13)	387	42	0.13
Tetrahydrofuran	346 (0.26)	388	42	0.14
Ethyl acetate	346 (0.06)	386	40	0.81
Acetonitrile	348 (0.08)	386	38	0.11
Methanol	337 (0.12)	384	47	0.21
Ethanol	335 (0.24)	385	50	0.07
Dichloromethane	335 (0.31)	389	54	0.08
Chloroform	329 (0.06)	389	60	0.32
*Compound **2***				
Cyclohexane	—[a]	—[a]	—[a]	—[a]
Dioxane	346 (0.04)	382	36	0.82
Tetrahydrofuran	345 (0.28)	375	30	0.07
Ethyl acetate	—[a]	—[a]	—[a]	—[a]
Acetonitrile	345 (0.08)	383	38	0.24
Methanol	345 (0.21)	389	44	0.04
Ethanol	345 (0.21)	388	43	0.01
Dichloromethane	345 (0.11)	385	40	0.05
Chloroform	315 (0.17)	373	58	0.31

[a] Due to the weak fluorescence, the evaluation of photophysical properties of compound **2** in cyclohexane and ethyl acetate was not possible.

Table 3
Evaluation of antibiotic sensitivity of *Staphylococcus aureus*

Name	Diameter of zone of inhibition (mm)
Ciprofloxacin (10 μg)	12
Ampicillin (10 μg)	8
Tetracycline (30 μg)	13
Erythromycin (15 μg)	15
Gentamicin (30 μg)	14
Pencillin G (10 μg)	0
Amikacin (30 μg)	17
Compound **1** (30 μg)	25
Compound **2** (30 μg)	21

These perimidines were screened for their antibacterial activities and a comparative study was made with antibiotics of known potencies. Antibacterial activities of compounds were checked against clinical isolates of *Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa* by well diffusion method (see Supplementary data). Both the compounds are more active toward *Staphylococcus aureus* than antibiotic discs of known potency (Table 3).

In conclusion, we have achieved a practical and simple procedure for the synthesis of new highly fluorescent antibacterial heteroaromatic compounds in good yield.

Acknowledgments

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Supplementary data

Supplementary data (details regarding various experimental methods and spectroscopic data, single crystal XRD data and antibacterial studies. Crystallographic data for the structures of compounds **1** and **2** have been deposited in the Cambridge Crystallographic Data Centre as CCDC 726819 and CCDC 726820) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.077.

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