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Synthesis and Fluorescence Properties 2-*N*-Piperidinopyrazines

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2-*N*-Piperidinopyrazine, 2-*N*-(3-methyl)piperidinopyrazine and 2-*N*-(4-methyl)piperidinopyrazine were synthesized by reacting 2-chloropyrazine with piperidine, 3-methylpiperidine, 4-methylpiperidine respectively. The structures of these compounds were confirmed by spectroscopic methods. Fluorescence studies were carried out in tetrahydrofuran, acetonitrile, ethyl acetate and ethanol. 2-*N*-Piperidinopyrazine showed the highest fluorescence intensity in tetrahydrofuran followed by 2-*N*-4-methylpiperidinopyrazine. The fluorescence intensity decreases as the polarity of the solvent increases.

Key Words: 2-*N*-Piperidinopyrazine, 2-*N*-(3-Methyl)piperidinopyrazine, 2-*N*-(4-Methyl)piperidinopyrazine, Fluorescence.

INTRODUCTION

Pyrazine represents an important class of heterocyclic compounds[1-4]. The structural unit is found in many natural products. They are important flavour ingredient in food[5,6], which also occur as flavour constituents of peas, coffee, capsicum peppers and wines[7]. Although present in very small amounts, they are extremely odorous and can be detected at concentration as low as 0.00001 ppm. Pyrazine is an aromatic heterocycles, therefore it undergoes electrophilic aromatic substitution. However, nucleophilic substitution of pyrazine has been reported[8,9]. The nucleophilic reagents can attack at the 2, 3, 5 and 6 positions of the pyrazine ring. Studies have shown that the nucleophiles attacked the ring becomes easier in the presence of at least one powerful electron releasing group such as NH_2, OH, SH in another position on the ring.

The fluorescence characteristic of heterocyclic compounds in general and pyrazine in particular is less studied. However, our group has reported on the fluorescence characteristics of pyridines, pyrimidines and purines[9-12]. In this paper, the fluorescence characteristics of 2-piperidinopyrazines will be reported.

EXPERIMENTAL

Organic solvents were distilled prior to use. Thin Layer Chromatography (TLC) was performed using MERCK 25 TLC plates 20 20 cm silica gel 60 F_{254} precoatedaluminium plate. Nuclear magnetic resonance (NMR) spectra were taken in deuterated chloroform on the JEOL FT-NMR Lambda 400 MHz and FT-NMR ECA 400 MHz spectrometers, IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR or a Perkin-Elmer RX1 FT-IR spectrophotometer. Melting point was carried out in glass capillaries recorded on a melting point apparatus Fargo MP-ID and are uncorrected. Mass spectroscopic analyses were performed at a Hewlett-Packard HP 6890 Series of GC System with mass selective indicator and GCMS QP5050A Shimadzu. Fluorescence spectra were recorded using Fluorescence Spectrometer, Model F2000, Hitachi and Luminescence Spectrometer, Model LS 50B, Perkin Elmer. The measurements were recorded at room temperature at the same setting in quartz cells.

2-*N*-Piperidinopyrazine: 2-Chloropyrazine (0.40 mL) was added to a solution of piperidine (5.00 mL) in ethanol and the mixture was refluxed for 2 h. The mixture was then cooled and the solvent was evaporated off. The residue was dissolved in water and then extracted with diethyl ether (3 × 10 mL). The ether extracts were washed with water (3 × 10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave the product, a yellowish liquid which was purified by washing with several portions of diethyl ether. (0.5606 g, 76 %); IR (KBr, ν_{max}, cm^{-1}): 1672 (C=N), 1517 (C=C), 2935 (C-H); ^{1}H NMR (ppm, 400 MHz, $CDCl_3$) δ_H: 8.05 (1H, d, J = 1.4 Hz, H-3), 7.96 (1H, dd, J = 2.6 Hz, 1.4 Hz, H-5), 7.69 (1H, d, J = 2.6 Hz, H-6), 3.49 (4H, s, H-2', H-6'), 1.55 (6H, s, H-3', H-4', H-5'); ^{13}C NMR (ppm, 100 MHz, $CDCl_3$) δ_C: 155.0 (C-2), 141.6 (C-3), 131.7 (C-5), 130.9 (C-6), 45.4 (C-2', C-6'), 25.0 (C-5',C-3'), 24.4 (C-4'); GCMS: Found M^+ = 163.00; $C_9H_{13}N_3$ requires M^+ = 163.22.

2-*N*-(3-Methyl)piperidinopyrazine: 2-Chloropyrazine (0.20 mL) was added to 3-methylpiperidine (1.33 mL) and refluxed in oil bath at 120-140 ºC. The reaction was stopped when starting material could no longer be detected on TLC. The mixture was then cooled and dissolved in 10 mL of water. The aqueous layer was extracted with ether (3 × 10 mL). The ethereal layer was washed twice with water (10 mL) and dried over anhydrous sodium sulphate. Filtration and evaporation of the solvent gave the crude mixture which was purified using preparative thin layer chromatography. Ethyl acetate-hexane mixture (1:2) was used as the solvent system. (0.1337 g, 34 %); IR (KBr, ν_{max}, cm^{-1}): 1673 (C=N), 1517 (C=C), 2927 (C-H); ^{1}H NMR (ppm, 400 MHz, $CDCl_3$) δ_H: 8.04 (1H, d, *J* = 1.4 Hz, H-3), 7.94 (1H, dd, *J* = 2.6Hz, 1.4 Hz, H-5), 7.66 (1H, d, *J* = 2.6 Hz, H-6), 4.10 (2H, d, *J* = 12 Hz, H-6'), 2.73 (1H, td, *J* = 12.6 Hz, 2.9 Hz, H-2'), 2.41 (1H, t, *J* = 10.9 Hz, H-2'), 1.42 (4H, m, H-5', H-4'), 1.03 (1H, m, H-3'), 0.86 (3H, d, *J* = 6.5 Hz, CH_3); ^{13}C NMR (ppm, 100 MHz, $CDCl_3$) δ_C: 155.0 (C-2), 141.7 (C-3), 131.8 (C-5), 131.1 (C-6), 52.2 (C-6'), 45.0 (C-2'), 33.1 (C-5'), 30.6 (C-4'), 24.8 (C-3'), 19.3 (CH_3); GCMS: Found M^+ = 177.00; $C_{10}H_{15}N_3$ requires M^+ = 177.25.

2-*N*-(4-Methyl)piperidinopyrazine: 2-Chloropyrazine (0.20 mL) was added to 4-methylpiperidine (2.20 mL). The reaction mixture was refluxed in an oil bath for 2 h. The mixture was then cooled and the solvent was evaporated off. The reaction mixture was dissolved in water and then extracted with diethyl ether (3 × 10 mL). The ether extracts were washed with water and dried over anhydrous sodium sulphate. Evaporation of solvent gave 2-*N*-(4-methyl) piperidinopyrazine, a yellowish liquid. (0.3049 g, 77 %); IR (KBr, ν_{max}, cm^{-1}): 1673 (C=N), 1518 (C=C), 2924 (C-H); ^{1}H NMR (ppm, 400 MHz, $CDCl_3$) δ_H: 8.08 (1H, d, *J* = 1.4 Hz, H-3), 7.98 (1H, dd, *J* = 2.6 Hz, 1.4 Hz, H-5), 7.69 (1H, d, *J* = 2.6 Hz, H-6), 4.22 (2H, d, *J* = 12 Hz, H-2'), 2.79 (2H, td, *J* = 12.6 Hz, 2.4 Hz, H-6'), 2.60 (2H, d, *J* = 12 Hz, H-3'), 1.54 (1H, m, H-4'), 0.99 (2H, m, H-5'), 0.85 (3H, d, *J* = 4 Hz, CH_3); ^{13}C NMR (ppm, 100 MHz, $CDCl_3$) δ_C: 155.1 (C-2), 141.7 (C-3), 131.9 (C-5), 131.2 (C-6), 45.0 (C-2', C-6'), 33.6 (C-3', C-5'), 31.0 (C-4'), 21.9 (CH_3); GCMS: Found M^+ = 177.00; $C_{10}H_{15}N_3$ requires M^+ = 177.25.

Fluorescence studies: Fluorescence spectra were recorded using fluorescence spectrometer, Model F2000, Hitachi (with the sensitivity is 2) and Luminescence Spectrometer, Model LS 50B, Perkin Elmer using 2.5 mm slits. Quinine sulphate (10 ppm in 0.1 N sulphuric acid) was used as the standard. All spectra were recorded at room temperature and are corrected for phototuberesponse and by substraction of the solvent background. The fluorescence spectra of all the compounds were measured in tetrahydrofuran acetonitrile, ethyl acetate and ethanol of concentrations of 10^{-6} M in capped and uncapped conditions.

RESULTS AND DISCUSSION

2-*N*-Piperidinopyrazine (**1**), 2-*N*-(3-methyl)piperidinopyrazine (**2**) and 2-*N*-(4-methyl)piperidinopyrazine (**3**) were obtained when 2-chloropyrazine were treated with piperidine, 3-methylpiperidine and 4-methylpiperidine respectively as shown in Fig. 1.

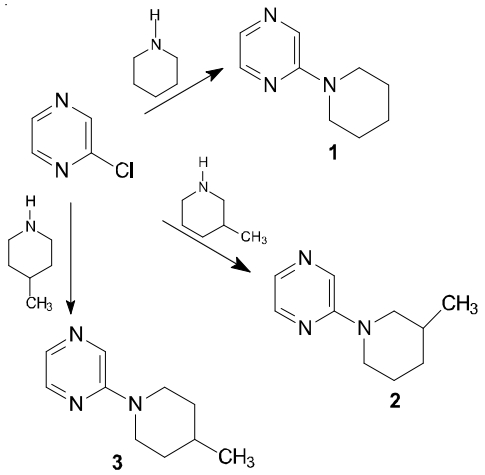


Fig. 1. Formation of 2-*N*-piperidinopyrazine (**1**), 2-*N*-(3-methyl) piperidinopyrazine (**2**) and 2-*N*-(4-methyl)piperidinopyrazine (**3**) from 2-chloropyrazine

The structure of 2-*N*-piperidinopyrazine (**1**), 2-*N*-(3-methyl)piperidinopyrazine (**2**) and 2-*N*-(4-methyl) piperidinopyrazine were confirmed by spectroscopic methods. In general, the presence of the adjacent electron withdrawing nitrogen atom in pyrazine makes the 2-position of pyrazine ring activated towards the nucleophilic attack. Thus, nucleophilic substitution reaction occurs at this position. The detail

TABLE-1
FLUORESCENCE EMISSION PEAKS PIPERIDINOPYRAZINE DERIVATIVES IN TETRAHYDROFURAN, ACETONITRILE, ETHYL ACETATE AND ETHANOL

2-Y-Pyrazine	Solvent	Excitation wavelength (nm)	Fluorescence wavelength (nm)	Intensity
-N-Piperidino (**1**)	Tetrahydrofuran	345	403	62.27
	Acetonitrile	348	411	51.64
	Ethyl acetate	344	404	26.3
	Ethanol	349	422	4.183
-N-3-Methylpiperidino (**2**)	Tetrahydrofuran	347	402	27.42
	Acetonitrile	347	414	11.31
	Ethyl acetate	345	401	15.32
	Ethanol	348	424	3.37
-N-4-Methylpiperidino (**3**)	Tetrahydrofuran	345	402	29.62
	Acetonitrile	347	411	17.80
	Ethyl acetate	343	404	21.88
	Ethanol	348	425	2.56

assignments of protons and carbons of compounds **1**, **2** and **3** are given in experimental section.

Fluorescence studies: Table-1 shows the fluorescence emission peaks of piperidinopyrazine derivatives in tetrahydrofuran, acetonitrile, ethyl acetate and ethanol respectively. It can be seen from Table-1 that all compounds showed the highest fluorescence intensity in tetrahydrofuran followed by acetonitrile, ethyl acetate and ethanol.

The fluorescence spectrum of 2-*N*-piperidinopyrazine in various solvents is as shown in Fig. 2.

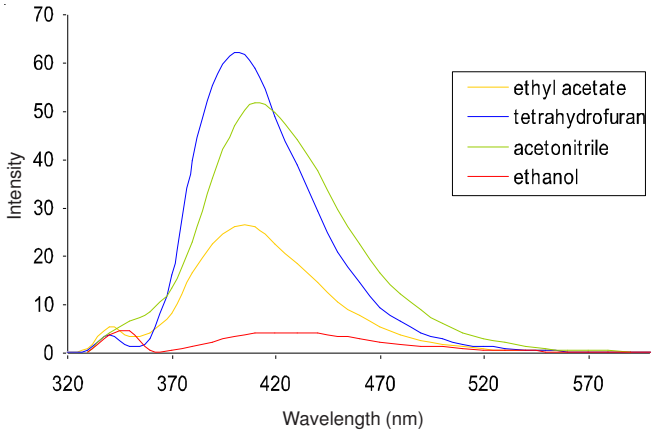
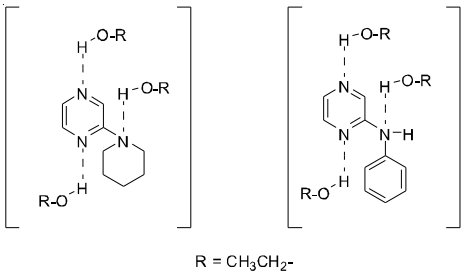


Fig. 2. Fluorescence spectra of 2-*N*-piperidinopyrazine in various solvents

Table 1 and Fig. 2 show that there is a shift in fluorescence maxima in polar solvents for all compounds. This observation is due to the fact that in most polar molecules, the excited state is more polar than the ground state. Hence, an increase in the polarity of the solvent produces a greater stabilization of the excited state than of the ground state. Consequently, a shift in fluorescence spectra to longer wavelength is observed as the polarity and dielectric constant of the solvents increases[13]. 2-*N*-Piperidinopyrazine showed a higher shifting of fluorescence peak in THF and acetonitrile which both are polar aprotic solvents and have higher dielectric constant. This observation is in the agreement with the work done by Drobnik and Augenstein[14,15].

2-*N*-Piperidinopyrazine showed the lowest fluorescence intensities in ethanol. The observations are believed to be due to the quenching effect from the "hydrogen bonded solvents" associated with the lone pair of electrons on the pyrazine ring and the amino group. As the result, it is not available to move around the system, thus low fluorescence intensity was observed. It is also believed that both compounds formed complex with the solvent as shown in Fig. 3, whereby the intramolecular charge transfer transitions *via* hydrogen bonding are formed.



R = CH_3CH_2-

Fig. 3. Formation of hydrogen bonding with the solvent

This phenomenon is also explained by Weisstuch and Testa[16] which they had reported that in some aromatic heterocyclic compounds with hydrogen bonding formation quenched the fluorescence intensity. The formation of hydrogen bond which is capable of conjugating with the π-electron system of the heterocyclic ring, results in the mobility of the π-electron been disturbed and caused the fluorescence intensity to be reduced. This phenomenon also favours the low lying $n \rightarrow \pi^*$ transitions which refers to the excitation of a non-bonding electron to an antibonding orbital It was pointed out that $n \rightarrow \pi^*$ transitions are usually not observed in fluorescence spectra and when present are weak[16]. As the results, a decrease in fluorescence intensity was observed. Similar observation was recorded with 2-*N*-(3-methyl)piperidinopyrazine and 2-*N*-(4-methyl)-piperidinopyrazine.

Both 2-*N*-(3-methyl)piperidinopyrazine and 2-*N*-(4-methyl)piperidinopyrazine showed lower fluorescence intensity in all solvents compared to 2-*N*-piperidinopyrazine. The reduced fluorescence intensity observed is probably due to the reduction in the rigidity of the piperidino ring. The presence of methyl group on the piperidino ring increases the vibrational amplitudes of thering, thus energy absorbed was dissipated as heat. This phenomena was in agreement with the work done by Yang *et al.*[17] and Joshi nee Pant *et al.*[18].

Table-2 shows the fluorescence intensity of 2-*N*-piperidinopyrazine, 2-*N*-(3-methyl)piperidinopyrazine and 2-*N*-(4-methyl)piperidinopyrazine in tetrahydrofuran and acetonitrile at different concentrations.

TABLE-2
FLUORESCENCE INTENSITY OF, 2-*N*-(3-METHYL)PIPERIDINOPYRAZINE AND 2-*N*-(4-METHYL)PIPERIDINOPYRAZINE IN TETRAHYDROFURAN, AND ACETONITRILE AT DIFFERENT CONCENTRATIONS

Solvent	Concentration (M)			Fluorescence wavelength (nm)			Intensity		
	$\times 10^{-4}$	$\times 10^{-5}$	$\times 10^{-6}$	10^{-4}	10^{-5}	10^{-6}	$\times 10^{-4}$	$\times 10^{-5}$	$\times 10^{-6}$
2-*N*-Piperidinopyrazine									
THF	6.127	6.127	6.127	401	402	403	560.0	382.7	62.27
CH_3CN	6.127	6.127	6.127	419	415	411	460.6	262.4	51.64
2-*N*-(3-Methyl)piperidinopyrazine									
THF	5.578	5.578	5.578	401	404	402	505.4	235.3	27.42
CH_3CN	5.578	5.578	5.578	414	414	414	364.8	84.34	11.31
2-*N*-(4-Methyl)piperidinopyrazine									
THF	5.578	5.578	5.578	403	400	402	518.5	208.0	29.62
CH_3CN	5.578	5.578	5.578	415	415	411	399.6	130.3	17.80

It can be seen that the fluorescence intensity increases with increasing concentration at relatively low concentrations. This observation was in agreement with the work reported earlier, where by at higher concentrations, the fluorescence intensity reaches its limiting value which normally results in concentration quenching and sometime accompanied by a shift in fluorescence wavelength[19].

Conclusion

2-*N*-Piperidinopyrazine, 2-*N*-(3-methyl)piperidinopyrazine and 2-*N*-(4-methyl)piperidinopyrazine were successfully prepared and fluorescence characteristics of these compounds were studied in various solvents. 2-*N*-Piperidinopyrazine showed the highest fluorescence intensity amongst the piperidino derivatives and the highest fluorescence intensity was recorded in tetrahydrofuran. The fluorescence intensity of all the derivatives decreases with decreasing concentrations.

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