

## New Pyridyl-Substituted Pyrazine Ligands as Spectrophotometric Reagents for Copper and Iron

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**Summary:** Twelve new Pyridyl-substituted dihydropyrazine and pyrazine ligands have been prepared by condensation of dioxo-1-phenyl-2-(2'-pyridyl), 2,2'-pyridil and 6,6'-dimethyl-2,2'-pyridil with ethylenediamine, 2,3-diaminobutane, 2-methyl-1,2-diaminopropane and meso-stilbenediamine. The reagents have been assessed for solvent extraction and spectrophotometric determinations of copper and iron. The reagents 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethyl-5,6-dihydropyrazine and 2,3-bis-[2'-(6'-methylpyridyl)]-5,6-dimethylpyrazine are particularly found useful with analytical selectivity similar to neocuproine.

### Introduction

Pyridyl-substituted dihydropyrazine and pyrazine compounds containing ferriin and cuproin reactive atomic groupings are of considerable interest because of their close resemblance to 1,10-phenanthroline and 2,2'-bipyridine, but relatively less work has been reported on these compounds [1-9]. Therefore, twelve new ligands have been prepared by simple synthetic routine to assess them as spectrophotometric reagents.

### Experimental

#### *Preparation of Reagents*

Equimolar solution of 1,2-diaminoethane, 2,3-diaminobutane, 1,2-diamino-2-methylpropane and meso-1,2-diamino-1,2-diphenylethane in ethanol was slowly added to the refluxing solution of 1,2-dioxo-1-phenyl-2-(2'-pyridyl), 2,2'-pyridil and 6,6'-dimethyl-2,2'-pyridil in ethanol. The solution were refluxed for 1-2 hr, and half of ethanol was distilled out and remaining solution was cooled at -5°C overnight. Precipitate was recrystallised from ethanol. In case of 2,3-bis[2'-(6'-methylpyridyl)]-5,5-dimethyl-5,6-dihydropyrazine the residue was dissolved in benzene and solvent was removed on rotary evaporator under reduced pressure. The fresh solvent was again introduced and this process was repeated several times with a mixture of benzene and petroleum ether (60-80°); then with petroleum ether (60-80°) only. The solid so obtained was recrystallised from petroleum ether (60-80°). The results of elemental analyses with melting points are summarized in Table-I.

The reagents, I, II, III, IV & V were dehydrogenated to respective pyrazine compounds as follows:-

1.0g of the compound was dissolved in 15ml of mesitylene containing Palladium charcoal (10%, w/w, 0.15g). The reaction mixture was refluxed for 32 hr. and filtered while hot. The filtrate was concentrated to 5ml and 5ml of n-hexane was added to the mixture. The mixture was cooled to -5°C and the solid so obtained was recrystallized from mixture of benzene and petroleum spirit (60-80°) or petroleum spirit (60-80°) only.

1,2-Dioxo-1-phenyl-2-(2'-pyridyl) [10], 6,6-dimethyl-2,2'-pyridil [11], meso-1,2-diamino-1,2-diphenylethane [12] were prepared by reported methods and 2,2'-pyridil (Aldrich) is commercially available. Solution (0.2%, W/V) of organic reagents were prepared in appropriate amount of water ethanol (1:1). A few drops of hydrochloric acid 5N were added if required to facilitate dissolution.

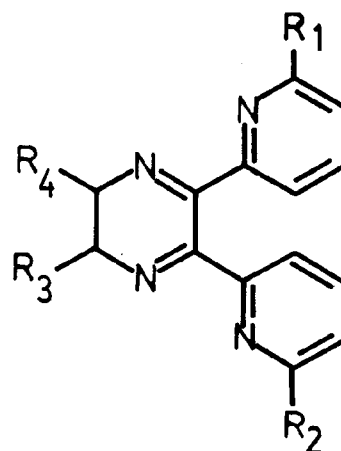
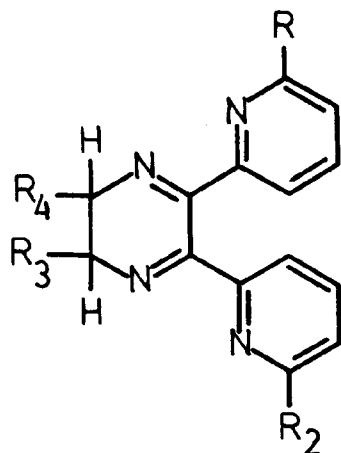
#### *Analytical Procedure*

Exactly 1.0 ml of metal ion solution was transferred to a 25ml volumetric flask and 1ml of freshly prepared (1% W/V) ascorbic acid, 2 ml of appropriate buffer solution followed by 5 ml of organic reagent were added. The contents were diluted to volume with ethanol or water and absorption spectrum of the solution was recorded against reagent blank in appropriate solvent.

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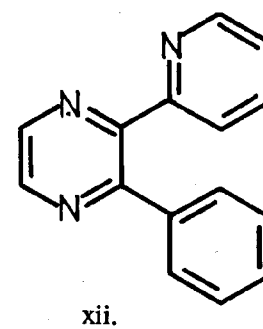
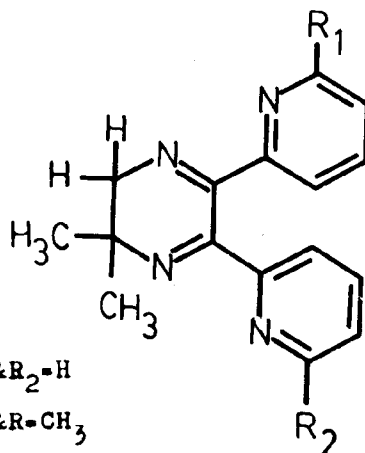
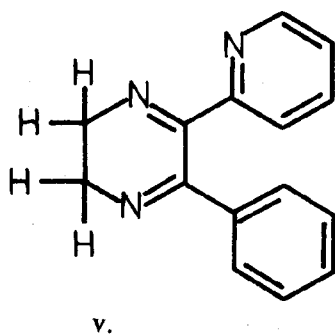
Table-I

Reagent	Mol Formula	m.p. °C	C	H	N	Expected %	Found %
I 2,3-Bis(2'-Pyridyl)-5,6-dimethyl-5,6-dihydropyrazine.	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub>	132	72.87	6.06	20.07	73.1	6.0 21.4
II 2,3-Bis(2'-pyridyl)meso-5,6-diphenyl-5,6-dihydro-pyrazine.	C <sub>26</sub> H <sub>20</sub> N <sub>4</sub>	259	80.4	5.2	14.4	80.3	4.5 14.4
III 2,3-Bis[2'-(6'-methylpyridyl)]meso-5,6-diphenyl-5,6-dihydro-pyrazine.	C <sub>28</sub> H <sub>24</sub> N <sub>4</sub>	158	80.76	5.77	14.46	80.95	5.5 13.8
IV 2,3-Bis(2'-(6'-methylpyridyl))-5,6-dimethyl-5,6-dihydropyrazine	C <sub>18</sub> H <sub>20</sub> N <sub>4</sub>	117	73.94	6.89	19.16	73.9	6.8 19.4
V 2-Phenyl-3-(2'-Pyridyl)-5,6-dihydropyrazine	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub>	142	76.59	5.53	17.87	76.5	5.7 17.7
VI 2,3-Bis(2'-Pyridyl)-5,5-dimethyl-5,6-dihydropyrazine	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub>		72.87	6.06	21.07	73.0	5.9 21.2
VII 2,3-Bis(2'-Pyridyl)-5,6-dimethylpyrazine	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub>	154	73.26	5.38	21.36	73.0	5.3 21.2
VIII 2,3-Bis(2'-Pyridyl)-5,6-dimethylpyrazine	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub>	154	73.26	5.38	21.36	73.0	5.3 21.2
IX 2,3-Bis(2'-pyridyl)-meso-5,6-diphenyl-pyrazine	C <sub>26</sub> H <sub>18</sub> N <sub>4</sub>	260	80.81	4.69	14.8	80.73	4.68 14.68
X 2,3-Bis(2'-(6'-methylpyridyl))-meso-5,6-diphenyl-pyrazine	C <sub>28</sub> H <sub>22</sub> N <sub>4</sub>	156	81.16	5.31	13.54	81.2	5.25 13.5
XI 2,3-Bis(2'-(6'-methylpyridyl))-5,6-dimethylpyrazine	C <sub>18</sub> H <sub>18</sub> N <sub>4</sub>	113	74.46	6.25	19.3	74.8	6.2 19.5
XII 2-phenyl-3-(2'-pyridyl) pyrazine	C <sub>15</sub> H <sub>11</sub> N <sub>3</sub>	109-10	77.25	4.7	18.0	77.1	4.4 18.0



- i. R<sub>1</sub> & R<sub>2</sub> = H; R<sub>3</sub> & R<sub>4</sub> = CH<sub>3</sub>
- ii. R<sub>1</sub> & R<sub>2</sub> = H, R<sub>3</sub> & R<sub>4</sub> = C<sub>6</sub>H<sub>5</sub>
- iii. R<sub>1</sub> & R<sub>2</sub> = CH<sub>3</sub>, R<sub>3</sub> & R<sub>4</sub> = C<sub>6</sub>H<sub>5</sub>
- iv. R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> = CH<sub>3</sub>
- vi. R<sub>1</sub> & R<sub>2</sub> = H

- vii. R<sub>1</sub> & R<sub>2</sub> = CH<sub>3</sub>
- viii. R<sub>1</sub> & R<sub>2</sub> = H; R<sub>3</sub> & R<sub>4</sub> = CH<sub>3</sub>
- ix. R<sub>1</sub> & R<sub>2</sub> = H, R<sub>3</sub> & R<sub>4</sub> = C<sub>6</sub>H<sub>5</sub>
- x. R<sub>1</sub> & R<sub>2</sub> = CH<sub>3</sub>, R<sub>3</sub> & R<sub>4</sub> = C<sub>6</sub>H<sub>5</sub>
- xi. R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> = CH<sub>3</sub>



- vi R<sub>1</sub> & R<sub>2</sub> = H
- vii R<sub>1</sub> & R<sub>2</sub> = CH<sub>3</sub>

Where measurements were carried out in a solvent other than ethanol or water, the following procedure was used. The metal ion solution was placed in 100 ml separating funnel, followed by other reagents as above; 2% of solid sodium perchlorate monohydrate was then added and chelate was extracted in 7-8 ml of extracting solvent. The organic layer was collected in 25 ml volumetric flask and the extraction was repeated twice with 5 ml of extracting solvent. (In case of 1,2-dichloroethane, chloroform and amylalcohol 2 ml of ethanol were added to the flask before dilution to volume, where the extracts were collected over 1 g anhydrous sodium sulphate, addition of ethanol was not need and the absorbances were measured after 10 min. The nitrobenzene extracts were filtered before spectrophotometric measurements).

The absorption spectra in visible region were measured on Cecil 505 and Beckmann BD Spectrophotometer with 1 cm silica cells.

### Results and Discussion

The results of quantitative absorptiometric data are summarized in Table-II. The reagents I, V, VI, XII react with copper(I) and iron(II) to form coloured complexes but the reagents II, III, IV, VII, VIII, IX, X and XI, react only with copper(I) to form purple to orange complexes of analytical utility and their reactions towards iron(II) are prevented owing to the presence of methyl or phenyl groups in the pyridyl and pyrazine rings adjacent to imine nitrogen atoms. The reagent 2,3-bis(2'-pyridyl)-5,6-dimethyl-5,6-dihydropyrazine(I) containing methyl group near to donor nitrogen atoms in dihydropyrazine ring surprisingly reacted with iron(II) and copper(I); when excess of reagent is added to the metal solution, which is easily extractable in 1,2-dichloroethane as perchlorate ion association complexes in a characteristic fashion as compared to 2,3-bis(2'-pyridyl)-5,6-dimethylpyrazine(VIII) and 2,3-bis(2'-pyridyl)-5,6-diphenyl-5,6-dihydropyrazine(II) which react only with copper(I) as expected.

Examination of the structural formulae of 2,3-bis(2'-pyridyl)-5,6-dimethyl-5,6-dihydropyrazine(I) indicates that the carbon atoms

at position 5 and 6 in the dihydropyrazine ring have tetrahedral configuration as compared to 2,3-bis(2'-pyridyl)-5,6-dimethylpyrazine(VIII), which contains same carbon atoms in the aromatic pyrazine ring with trigonal hybridization. Therefore it could be that the hydrogen atoms in less rigid, more flexible and possibly puckered dihydropyrazine ring are pushing the methyl groups on the side from the direct exposure to iron(II), in order to accommodate three molecules around iron(II) to form an octahedral complex, particularly in 1,2-dichloroethane as perchlorate ion association complex. However the bulky phenyl groups in dihydropyrazine ring near imine nitrogen in 2,3-bis(2'-pyridyl)-5,6-dimethyl-5,6-dihydropyrazine(II) are introducing a measure of steric hinderance to form tris-iron(II) complex.

The reagent 2-phenyl-3-(2'-pyridyl)-5,6-dihydropyrazine (V) show highest sensitivity for iron(II) ( $\epsilon 1.67 \times 10^4 \text{ mole}^{-1} \text{ cm}^{-1}$  at 600 nm among the series when extracted in nitrobenzene as perchlorate ion association complex. This higher sensitivity could be due to the replacement of pyridyl group in the dihydropyrazine ring with phenyl group, but the reagent shows poor solution stability for both copper(I) and iron(II) complexes. The reagent 2-phenyl-3-(2'-pyridyl)-5,6-dihydropyrazine(V) when dehydrogenated to 2-phenyl-3-(2'-pyridyl) Pyrazine(XII), it retains its reactivity towards copper(I) and iron(II) with improvement of solution stability of iron(II) complex particularly when the extracts in 1,2-dichloroethane as perchlorate ion pair are collected over anhydrous sodium sulphate. However there is a decrease in sensitivity of both of copper and iron reactions.

Stephen [5] has indicated that the dihydropyrazine ligands behave similarly to the pyrazine ligands to form metal complexes. Moreover in 2,3-bis(2'-pyridyl)-5,5-dimethyl-5,6-dihydropyrazine(VI) and 2,3-bis[2'-(6'-methylpyridyl)]-5,5-dimethyl-5,6-dihydropyrazine(VII) ligands, the "dihydro" state is stabilised due to the substitution of both hydrogen atoms at position "5" in the pyrazine ring with two methyl groups. The molecule of 2,3-bis(2'-pyridyl)-5,5-dimethyl-5,6-dihydropyrazine(VI) contains on one reactive side ferrioin and on the other cuprioin functionalities.

Table-II: Quantitative Absorptiometric data for Iron(II) and Copper(II) reactions at pH 4.6

Reagent	Solvent	Copper Complex			Iron Complex				
		$\lambda$ -max nm	$\epsilon$ , l mole <sup>-1</sup> cm <sup>-1</sup>	Colour of the complex	Solution Stability	$\lambda$ -max nm	$\epsilon$ , l mole <sup>-1</sup> cm <sup>-1</sup>	Colour of the complex	Solution Stability
1 2,3-bis(2'-pyridyl)5,5-dimethyl-5,6-dihydropyrazine (vi)	Ethanol	534	9848	Purple	1 hr	622	10471	Greenish	5-10 min, the absorbances decrease with some bathochromatic shift.
	Water	-	-	-	-	610	13403	Blue	30 min, absorbance decreases slowly.
	1,2-dichloroethane	530	9848	Purple	1 hr	606	14520	Blue	2 h.r
2 2,3-bis(2'-Pyridyl)-5,6-dimethyl-5,6-dihydropyrazine (i)	1,2-dichloroethane over anhydrous Na <sub>2</sub> SO <sub>4</sub>	530	9848	Purple	1 hr	606	14799	Blue	20 hr.
	Ethanol	540	10484	Purple	1 hr	640	2293	Bluish green	-
	Water	550	10960	Purple	1 hr	625	2513	Bluish green	-
	1,2-dichloroethane	536	9848	Purple	20-30 min	600	12007	Blue	20-30 min.

Continued Table II:

Reagent	Solvent	Copper Complex			Iron Complex			Solution Stability	
		$\lambda$ -max nm	$\epsilon$ :l mole <sup>-1</sup> cm <sup>-1</sup>	Colour of the complex	Solution Stability	$\lambda$ -max nm	$\epsilon$ :l.mole <sup>-1</sup> cm <sup>-1</sup>		Colour of the complex
3 2-Phenyl-3-(2'-Pyridyl)-5,6-dihydropyrazine (v)	1,2-dichloroethane over anhydrous Na <sub>2</sub> SO <sub>4</sub>	536	9848	Purple	20-30 min	600	12288	Blue	1hr.
	Water	520	7700	Purple absorbance decreases slowly	15 min.	595	15100	Blue	5 min. Absorbance decreased to 10800 with shift in $\lambda$ max to 630 nm after 30 min.
	Ethanol	520	7900	Purple	30 min	635	14300	Bluish Green	The absorbance decreased to 10400 at 634 nm after 30 min.
4 2-Phenyl-3-(2'-pyridyl)-pyrazine (xii)	1,2-dichloroethane	522	8100	Purple	30 min	593	15200	Blue	10 min. Absorbance decreased to 12200 with bathochromic shift in $\lambda$ -max at 630 after 1 hr.
	Nitrobenzene	-	-	-	-	600	16700	Blue	4 hr.
	1,2-dichloroethane over anhydrous Na <sub>2</sub> SO <sub>4</sub>	455	5559	Brown	30 min	528	10750	Reddish Pink	5 days

Table III: Quantitative absorptiometric properties of Copper(I) complexes, with Cuproin reagent.

Reagent	Solvent	$\lambda$ -max nm	$\epsilon$ , l mole <sup>-1</sup> cm <sup>-1</sup>	Colour of the complex	Solution stability
1 2,3-Bis(2'-Pyridyl)-meso-5,6-diphenyl-5,6-dihydropyrazine(ii)	Ethanol	500	3600	Brown	2 hr.
	1,2-dichloroethane.	560	3000	Purple	2 hr.
2 2,3-Bis[2'-(6'-methylpyridyl)]-meso-5,6-diphenyl-5,6-dihydropyrazine (iii)	Ethanol	492	5100	Brown	5 hr.
3 2,3-Bis[2'-(6'-methylpyridyl)]-5,6-dimethyl-5,6-dihydropyrazine (iv)	Water	543	11600	Red-purple	5 hr.
	1,2-dichloroethane	539	11468	Red-purple	6 hr.
4 2,3-[2'-(6'-methyl-pyridyl)]-5,5-dimethyl-5,6-dihydropyrazine (vii).	Water	555	12787	Red-purple	6 hr.
	1,2-dichloroethane	540	11913	Red-purple	4 hr.
5 2,3-Bis(2'-Pyridyl)-5,6-methylpyrazine (viii)	Ethanol	450	6350	Orange brown	6 hr.
	1,2-dichloroethane	450	6350	Orange brown	2 days.

Continued Table III:

Reagent	Solvent	$\lambda$ -max nm	$\epsilon$ , l. mole <sup>-1</sup> cm <sup>-1</sup>	Colour of the complex	Solution stability
6 2,3-Bis[2-(2-Pyridyl)-meso-5,6-diphenyl-pyrazine (ix),	Ethanol	487	3300	Brown	2 hr.
		560	3200		
	1,2-dichloroethane	565	3800	Purple	2 hr.
7 2,3-Bis[2-(6-methylpyridyl)]-meso-5,6-diphenyl-pyrazine (x)	Ethanol	487	4200	Brown	6 hr.
	1,2-dichloroethane	487	4000	Brown	6 hr.
8 2,3-Bis[2-(6-methylpyridyl)]-5,6-dimethyl-pyrazine (xi)	Ethanol	455	7225	Orange	24 hr.
	Water	461	7466	Orange	4 days.
	1,2-dichloroethane	453	7148	Orange	4 days



The reagent as expected reacts with both copper(I) and iron(II) to give characteristic red purple and blue complexes respectively. The solution stability of iron(II) complex enhances considerably when the extract in 1,2-dichloroethane is collected over anhydrous sodium sulphate. The reagent could be used for simultaneous determinations of copper and iron in a single aliquot, but it requires to solve a simultaneous equation to determine the amounts of copper and iron in a solution.

The reagents II, III, IX and X react with copper(II) only, but their colour reactions are relatively less sensitive, this decrease in sensitivity could be due to the steric hindrance introduced by the bulky phenyl groups substituted near to imine nitrogen in pyrazine ring, and this steric hindrance is neutralizing all the favourable electronic factors introduced by phenyl substitution.

The reagents 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethyl-5,6-dihydropyrazine(IV) and 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethylpyrazine(XI) containing double cuproin atomic groupings have considerable promise as analytical reagents for copper. The reagents react only with copper(I) to form red-purple and orange complexes in slightly acidic to neutral solution (pH 3.5-7.5) which are extractable in 1,2-dichloroethane and amyl alcohol as perchlorate ion association complexes. The effect of the increasing concentration of copper(I) on the extraction of the complex in 1,2-dichloroethane was investigated and the colour of the complexes of 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethyl-5,6-dihydropyrazine and 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethylpyrazine obey the Beer's law in the range of 0.5-7.0  $\mu\text{g/ml}$  and 1.0-12.0  $\mu\text{g/ml}$  of copper respectively.

The effect of  $\text{Co}^{2+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Ru}^{2+}$ , citrate, tartrate and phosphate ions for their possible interference on the extraction of copper(I) chelate in 1,2-dichloroethane was investigated for both (VI & XI) reagents and their ten times the concentrations of copper(I) did not interfere.

## Conclusion

The reagents exemplify the group action in the molecule and the colour reactions of 2,3-bis(2'-pyridyl)-5,6-dimethylpyrazine towards iron(II) is prevented owing to the presence of methyl groups adjacent to imine nitrogens in pyrazine ring, but the corresponding dihydropyrazine compound 2,3-bis(2'-pyridyl)-5,6-dihydropyrazine retains its characteristic reaction towards iron(II).

Symmetrically tetramethyl-substituted ligands 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethyl-5,6-dihydropyrazine and 2,3-bis[2'-(6'-methylpyridyl)]-5,6-dimethylpyrazine show similar sensitivity and analytical selectivity that of neocuproine and are particularly useful as analytical reagents for copper. The reagents recommended in the present work are simple and easy to prepare from less expensive chemicals.

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