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185. Osamu Yamauchi,[*1] Hisashi Tanaka, and Toyozo Uno[*2] : Studies on Imidazole Derivatives as Chelating Agents. III.[*3] Syntheses of Schiff Bases and 4(5)-Aminomethyl Derivatives and Their Reactions with Metal Ions.

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The Schiff bases from 4(5)-imidazolecarboxaldehyde and aromatic amines (type [A]), those from 4(5)-amino-5(4)-methylimidazole and aromatic aldehydes (type [B]), and 4(5)-aminomethylimidazoles (type [C]) were prepared. The compounds [A] and [C] react with Fe(III), Cu(II), Pd(II), Pt(IV), Au(III), etc. to give green～brown colors, whereas the compounds [B] give only faint colors with Cu(II), Pt(IV), and Au(III). The copper chelates of type Cu (ligand)$_2$Br$_2$, where the ligands are the compounds [A] and [C], were isolated, and the binding site of the imidazole nucleus was determined to be the pyridine nitrogen by comparing the IR spectra with those of the deuteration products and of the copper chelate of type Cu (ligand)$_2$. The reactivities of the compounds [A] and [C] suggest that they behave as bidentate ligands.

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The Schiff bases and their reduction products containing the imidazole nucleus are expected to exhibit chelating abilities as bidentate ligands. From this point of view, Schiff bases from 4(5)-imidazolecarboxaldehyde and primary aromatic amines (type [A]), those from 4(5)-amino-5(4)-methylimidazole and aromatic aldehydes (type [B]), and 4(5)-aminomethylimidazoles (type [C]) were prepared, and their reactions with metal ions were investigated by spot tests at various pH values. Isolations and the structural studies of the copper chelates of the compounds [A] and [C] were also made.

4(5)-Imidazolecarboxaldehyde condenses with primary amines, but only a few Schiff bases, such as N-[4(5)-imidazolylmethylene]aniline[1)] and N,N'-bis[4(5)-imidazolylmethylene]ethylenediamine,[2)] have been reported. The aldehyde, prepared by oxidation of 4(5)-hydroxymethylimidazole[3)] with nitric acid by the method of Pyman,[4)] was refluxed in aqueous ethanol with *p*-toluidine, *p*-anisidine, *p*-chloroaniline, *p*-dimethylaminoaniline, and 1-aminonaphthalene to give the corresponding Schiff bases I, II, III, IV, and V in good yields (Chart 1). The reactions with butylamine and with *o*-toluidine gave oily substances, from which no products were isolated in the pure state.

The Schiff bases of the type [B] were prepared from 4(5)-amino-5(4)-methylimidazole[5,6)] and aromatic aldehydes. Condensation of the amine with *p*-tolualdehyde, *p*-anisaldehyde, *p*-chlorobenzaldehyde, and salicylaldehyde in aqueous methanol afforded the corresponding Schiff bases VII, VIII, IX, and X. The reactions proceeded easily without sufficient heating.

Apart from the Schiff bases, Holmes and Jones,[7)] and Schaeg, *et al.*[8,9)] investigated the chelating ability of 4(5)-aminomethylimidazole and determined the stability constants

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[*3] Part II : This Bulletin, **14**, 952 (1966).

1) W. Hubball, F.L. Pyman : J. Chem. Soc., **1928**, 25.
2) W. Langenbeck, G. Reinisch, K. Schönzart : Ber., **92**, 2040 (1959).
3) R.M. Silverstein, E.E. Ryskiewicz, C. Willard : "Organic Syntheses," Coll. Vol., III, 831 (1963).
4) F.L. Pyman : J. Chem. Soc., **109**, 186 (1916).
5) R.G. Fargher : *Ibid.*, **117**, 668 (1920).
6) R. Weidenhagen, R. Herrmann : Ber., **68**, 2205 (1935).
7) H. Holmes, F. Jones : J. Chem. Soc., **1960**, 2398.
8) G. Weitzel, W. Schaeg, F. Schneider : Ann., **632**, 124 (1960).
9) W. Schaeg, F. Schneider : Hoppe-Seyler's Z. physiol. Chem., **326**, 40 (1961).

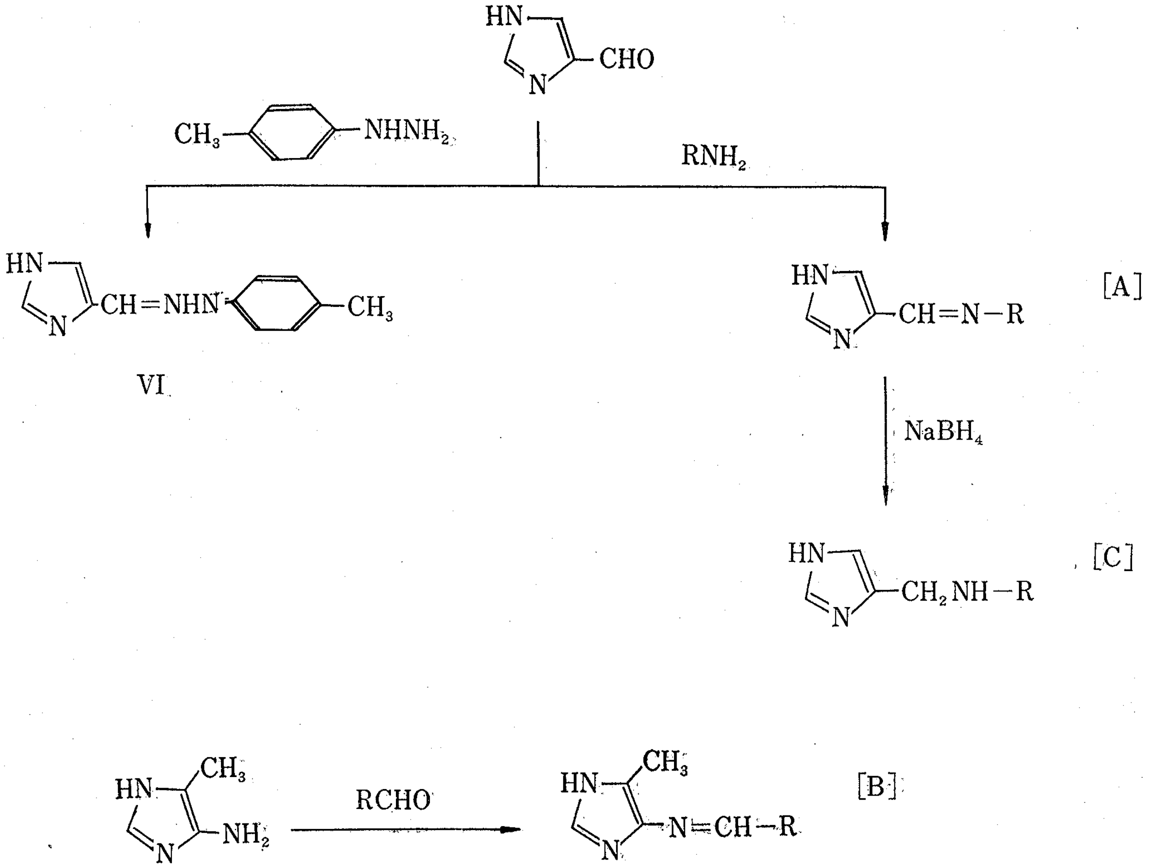


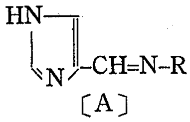
Chart 1.

of some of its metal chelates. Therefore, the 4(5)-aminomethylimidazole derivatives, XI, XII, XIII, and XIV (type [C]) were prepared from the Schiff bases I, II, III, and V (type [A]), respectively, by reduction with sodium borohydride. The reduction was carried out in methanol at room temperature, and when the Schiff base was sparingly soluble in methanol, a suspension in methanol was treated analogously. However, the Schiff base VII (type [B]) was not reduced with sodium borohydride under the conditions employed.

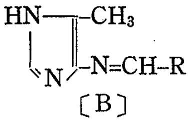
The melting points, the yields, and the analytical data of the compounds prepared are given in Table I.

The IR spectra of the Schiff bases [A] show a strong band in the region 1620~1634 cm^{-1}, whereas N,N′-bis[4(5)-imidazolylmethylene]ethylenediamine which has no benzene ring has a strong band at 1651 cm^{-1}. These bands may be assigned to the C=N stretching vibration of the side chain, because most Schiff bases obtained from aromatic aldehydes have the νC=N near 1620 cm^{-1}. The Schiff bases [B], however, show no clear νC=N near 1630 cm^{-1}, and only weak or medium bands are observed at 1610 cm^{-1} and 1670 cm^{-1}. Since imidazole shows a weak band near 1670 cm^{-1}, the νC=N of the side chain is possibly overlapping with the νC=C of the benzene ring. Owing to the strong hydrogen bond, the N-H stretching band of the imidazole nucleus is observed near 3000 cm^{-1} as a broad band. The deuteration product of I shows the νN-D in the region 2180~2300 cm^{-1}, and consequently the original νN-H is calculated to be in the region 3000~3100 cm^{-1}. On reduction of the Schiff bases [A], the C=N stretching band near 1630 cm^{-1} disappears, and a sharp band appears near 3455 cm^{-1}, which is probably due to the N-H stretching mode of the side chain. The deuteration product of XI shows two N-D stretching bands at 2500 cm^{-1} and 2100~2200 cm^{-1}.

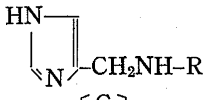
Table I. Schiff Bases and 4(5)-Aminomethylimidazole Derivatives



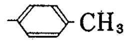
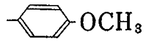
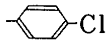
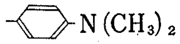
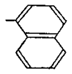
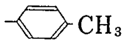
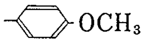
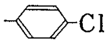
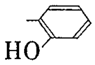
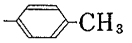
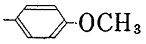
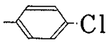
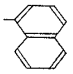
[A]



[B]



[C]

Compound No.	[Type]	R	m.p. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	[A]		172~173 (decomp.)	73	$C_{11}H_{11}N_3$	71.33	5.98	22.69	71.33	6.26	22.97
II	[A]		161~162	80	$C_{11}H_{11}ON_3$	65.66	5.51	20.89	65.88	5.81	20.99
III	[A]		183~184	75	$C_{10}H_8N_3Cl$	58.41	3.92	20.44	58.70	4.11	20.60
IV	[A]		196~198	71	$C_{12}H_{14}N_4$	67.26	6.59	26.15	67.01	6.78	26.35
V	[A]		218~220 (decomp.)	87	$C_{14}H_{11}N_3$	76.00	5.01	18.99	75.86	5.31	18.88
VII	[B]		200~201	68	$C_{12}H_{13}N_3$	72.33	6.57	21.09	72.21	6.74	20.69
VIII	[B]		194~195 (decomp.)	74	$C_{12}H_{13}ON_3$	66.95	6.09	19.53	67.08	6.09	19.14
IX	[B]		192~194 (decomp.)	65	$C_{11}H_{10}N_3Cl$	60.15	4.65	19.13	59.87	4.65	19.44
X	[B]		227~230 (decomp.)	55	$C_{11}H_{11}ON_3$	65.66	5.51	20.89	65.48	5.62	21.20
XI	[C]		109~111	73	$C_{11}H_{13}N_3$	70.57	7.00	22.44	70.68	7.30	22.18
XII	[C]		108~110	70	$C_{11}H_{13}ON_3$	65.00	6.45	20.68	65.18	6.65	20.76
XIII	[C]		133~135	80	$C_{10}H_{10}N_3Cl$	57.83	4.86	20.23	58.12	5.07	20.06
XIV	[C]		170~171	78	$C_{14}H_{13}N_3$	75.31	5.87	18.82	75.39	6.05	18.56

The reactivities of the imidazole derivatives with various metal ions were investigated by spot tests in weakly acid, neutral, and weakly alkaline solutions. The compounds of the type [A] gave brown, yellow, or green colors by the reactions with Fe(III), Co(II), Ni(II), Cu(II), Pd(II), Au(III), etc. Fe(III) formed a chloroform-insoluble brown precipitate, whereas Pd(II) and Au(III) formed chloroform-soluble yellow~yellowish brown precipitates. Cu(II) reacted with all the reagents studied to give deep green~brown colors. The substituents in the benzene ring other than the $N(CH_3)_2$ group do not affect the color reactions remarkably. It is worth mentioning that the complexing tendency of the Schiff bases [A] is similar to that of the previously reported Schiff bases of pyrrole series.[10] On the other hand, the Schiff bases of the type [B] reacted to give only faint colors with Cu(II) (grayish green), Pt(IV) (yellow), Au(III) (brown), etc. The weak reactivities of the compounds [B] might be explained by the fact that they can only form an unstable four-membered chelate ring in comparison with the compounds [A] which can form a stable five-membered ring.

Reactions of the hydrazone (VI) of 4(5)-imidazolecarboxaldehyde with metal ions were like those of the Schiff bases [A].

4(5)-Aminomethylimidazoles [C] also may form a five-membered chelate ring, and in fact they were found to react with such metal ions as Fe(III), Cu(II), Pd(II), and

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[10] H. Tanaka, O. Yamauchi: This Bulletin, **9**, 588 (1961).

Au(III) in acid and neutral solutions. They formed green～greenish brown copper complexes that were more deeply colored than those of the compounds [A].

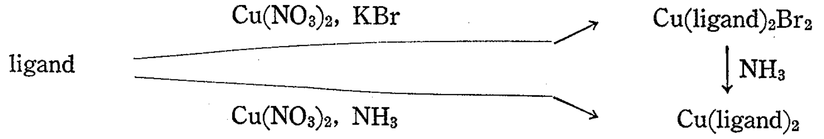
The results of the spot tests in acid, neutral, and alkaline solutions are summarized in Table II.

Table II. Spot Tests

Compound		Metal Ion	Reaction		
[Type]	No.		acid	neutral	alkaline
[A]	I, II, III, V	Fe (III)	brown$^{a)}$	brown$^{a)}$	
		Co (II)	light brown	yellow	pink～brown$^{a)}$
		Ni (II)	yellowish green	yellowish green	
		Cu (II)	green	yellowish green	green$^{a)}$
		Pd (II)	yellow$^{a)}$	pale yellow$^{a)}$	
		Pt (IV)			light brown
		Au (III)	dark brown$^{a)}$	dark brown$^{a)}$	dark brown$^{a)}$
	IV	Fe (III)	red$^{b)}$	red$^{b)}$	
		Cu (II)	brown	brown	
		Pd (II)	brown$^{a)}$	brown$^{a)}$	
		Ag (I)		brown$^{a)}$	
		Pt (IV)	reddish violet	reddish violet	
		Au (III)	dark brown	dark brown	
[C]	XI, XIII	Fe (III)	orange	orange	
		Cu (II)	green	green	
		Pd (II)	yellow$^{a)}$	yellow$^{a)}$	
		Pt (IV)		yellow$^{a)}$	
		Au (III)	brown～reddish brown	reddish brown$^{a)}$	
	XII	Fe (III)	dark brown	violet	
		Cu (II)	green	green	
		Ag (I)	bluish black		
		Pt (IV)		brown	
		Au (III)	dark brown$^{a)}$	brown$^{a)}$	
	XIV	Cu (II)		reddish brown	
		Pd (II)	yellow	yellow	
		Au (III)	deep green$^{a)}$	dark green$^{a)}$	

a) Precipitation occurred.
b) The color was transient and faded in a few minutes.

In order to obtain informations about the contributions of the pyridine-like nitrogen and the pyrrole-like NH group to complexation with metals, isolations of the copper complexes of the compounds [A] and [C] were attempted. When the ligands were caused to react with cupric nitrate in aqueous ethanol containing ammonia, grayish green complexes, which were insoluble in water and other solvents, were obtained. But when they were caused to react with cupric nitrate in aqueous ethanol, water-soluble complexes were formed, and these were isolated as bromides or nitrates. In acid or neutral solutions the reactions at various ligand : copper ratios between 1:1 and 4:1 always gave the same complex, the composition of which was determined to be $Cu(ligand)_2Br_2$ by elemental analysis. A complex of the type $Cu(ligand)_2(NO_3)_2$ was also isolated. The grayish green complexes obtained in alkaline solution were found to have the composition $Cu(ligand)_2$, although purification of the complexes was not complete because of their insolubilities. The water-soluble complexes could be converted to the water-insoluble complexes $Cu(ligand)_2$ by ammonia. These experimental results show that the above mentioned reactions follow the courses :



The reaction of the Schiff base IX (type [B]) with Cu(II) in neutral solution gave a grayish brown precipitate whose IR spectrum showed a weak band near 1700 cm^{-1}, and isolation of the complex was not successful. IX may be hydrolyzed to the aminoimidazole and *p*-chlorobenzaldehyde by the reaction with Cu(II).

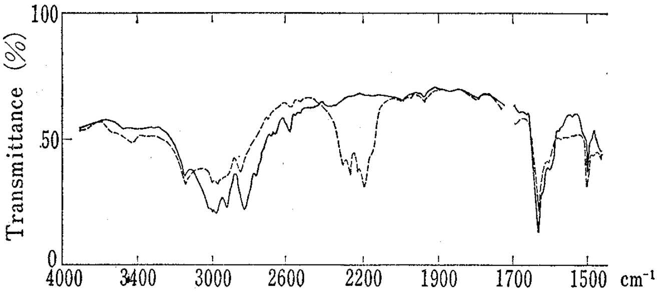


Fig. 1. Infrared Spectra of Cu(II)-I Chelate (solid line) and Its Deuteration Product (broken line)
4000~1700 cm^{-1}: HCB mull
1700~1500 cm^{-1}: Nujol mull

Several studies have been reported as to the binding site of the imidazole nucleus. Comparing the stability constants of the copper complexes of imidazole and 1-methylimidazole, Li, *et al.*[11] assumed the coordination through the pyridine nitrogen. Weitzel, *et al.*,[12] and Bauman and Wang[13] also investigated the binding site of imidazole derivatives.

The IR spectrum of Cu(ligand)$_2$Br$_2$ (Fig. 1) shows absorptions in the region 3000~3100 cm^{-1}. On deuteration, the N-D stretching bands arise in the region 2200~2300 cm^{-1} with the decrease in the intensities of the absorptions in the region 3000~3100 cm^{-1}. Consequently, the νN-H is estimated to be found between 3000 and 3100 cm^{-1}, and it becomes evident that the compound I coordinates to copper through the pyridine nitrogen of the imidazole nucleus. However, coordination to copper causes no large shift of the νC=N of the side chain. As to the copper complex of XI, the νN-H of the ligand observed at 3455 cm^{-1} shifts to lower frequencies, and deuteration gives rise to the N-D stretching bands in the region 2200~2300 cm^{-1} (Fig. 2). Although the presence of the pyrrole-like NH group is somewhat ambiguous owing to the side chain NH group, the composition of the complex and its solubility in water support the coordination through the pyridine nitrogen. On the other hand, the IR spectrum of the Cu(II)-III complex of the type Cu(ligand)$_2$ exhibits no νN-H, and this fact is indicative of the participation of the NH group of the imidazole nucleus in binding with copper. In this case, binding with copper causes a frequency shift of the νC=N of the side chain from 1634 cm^{-1} to 1610 cm^{-1}.

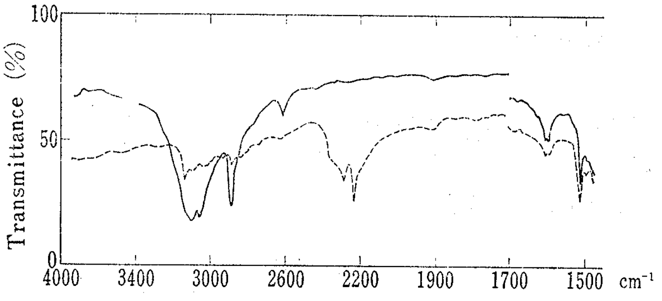


Fig. 2. Infrared Spectra of Cu(II)-XI Chelate (solid line) and Its Deuteration Product (broken line)
4000~1700 cm^{-1}: HCB mull
1700~1500 cm^{-1}: Nujol mull

The absorption spectra (in 50v/v% EtOH-H_2O) of the copper chelates of the type Cu(ligand)$_2$Br$_2$ are shown in Fig. 3 and 4. The chelates have the absorption peaks in the region 675~710 mμ with ε=60~85 (ligand: I, II, and III) and 660~710 mμ with ε=140~230 (ligand: XI, XII, and XIII). The maximum wavelengths vary with the properties of the substituents in the para-position of the benzene ring.

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11) N.C. Li, J.M. White, E. Doody: J. Am. Chem. Soc., **76**, 6219 (1954).

12) G. Weitzel, A.M. Fretzdorff: Hoppe-Seyler's Z. physiol. Chem., **305**, 1 (1956); G. Weitzel, *et al.*: *Ibid.*, **307**, 14 (1957).

13) J.E. Bauman, J.C. Wang: Inorg. Chem., **3**, 368 (1964).

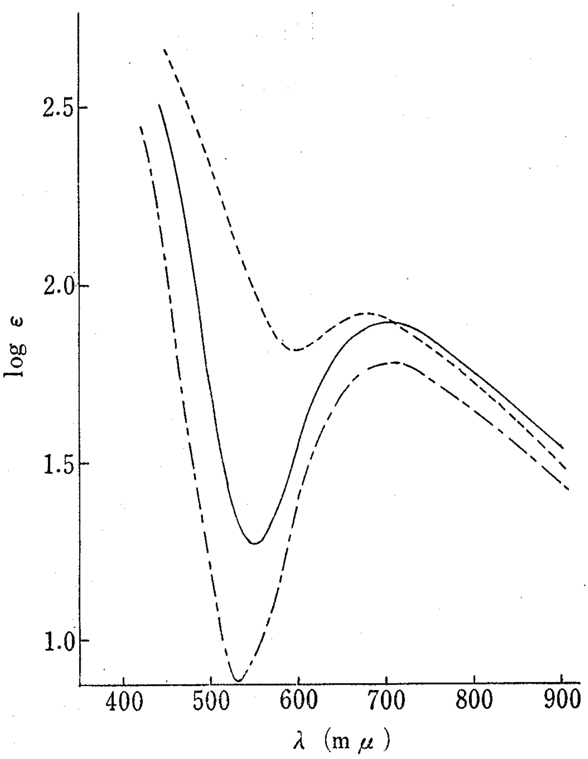


Fig. 3. Absorption Spectra of the Copper Chelates of the Schiff Bases [A]
Chelate: Cu(ligand)$_2$Br$_2$
Solvent: 50v/v% EtOH-H$_2$O
Ligand: I ———— ; II -------- ; III —-—-—

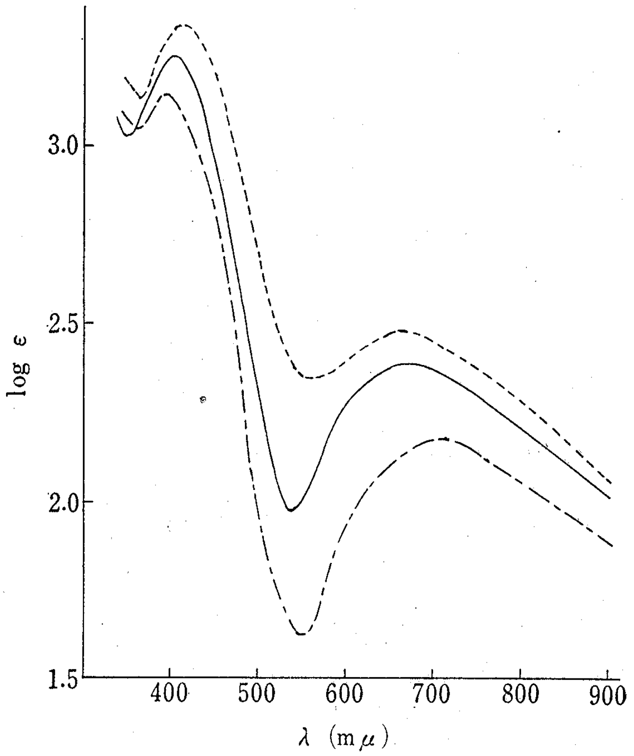
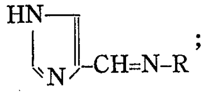


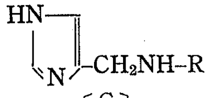
Fig. 4. Absorption Spectra of the Copper Chelates of the 4(5)-Aminomethylimidazoles
Chelate: Cu(ligand)$_2$Br$_2$
Solvent: 50v/v% EtOH-H$_2$O
Ligand: XI ———— ; XII -------- ; XIII —-—-—

TABLE III. Copper Chelates

Ligands:



[A]



[C]

Chelates: Cu(ligand)$_2$X$_2$; Cu(ligand)$_2$

Ligand (No.)	Formula	m.p. (°C) (decomp.)	Appearance	Analysis (%)							
				Calcd.				Found			
				C	H	N	Cu	C	H	N	Cu
I	Cu(C$_{11}$H$_{11}$N$_3$)$_2$Br$_2$	235～236	green powder	44.50	3.73	14.15		44.77	3.95	13.87	a)
II	Cu(C$_{11}$H$_{11}$ON$_3$)$_2$Br$_2$	231～232	green powder	42.22	3.54	13.43		42.06	3.59	13.58	a)
III	Cu(C$_{10}$H$_8$N$_3$Cl)$_2$Br$_2$	228～229	green prisms	37.85	2.54	13.25		37.55	2.68	13.32	a)
XI	Cu(C$_{11}$H$_{13}$N$_3$)$_2$Br$_2$	189～191	greenish brown prisms	44.20	4.38	14.06		44.46	4.52	14.25	a)
XI	Cu(C$_{11}$H$_{13}$N$_3$)$_2$(NO$_3$)$_2$	227～228	green rods	47.01	4.66	19.94	11.31	47.28	4.96	19.84	11.51
XII	Cu(C$_{11}$H$_{13}$ON$_3$)$_2$Br$_2$	189～191	dark green leaves	41.95	4.16	13.34		42.05	4.46	13.51	a)
XIII	Cu(C$_{10}$H$_{10}$N$_3$Cl)$_2$Br$_2$	193～194	brown prisms	37.61	3.15	13.16		37.61	3.39	12.79	a)
III	Cu(C$_{10}$H$_7$N$_3$Cl)$_2$ b)	286～287	grayish green powder	50.80	2.98	17.78		49.00	3.03	17.35	a)

a) Analysis of copper was impossible.
b) Purification was not complete because of the insolubility.

The melting points and the analytical data of the copper chelates are listed in Table III.

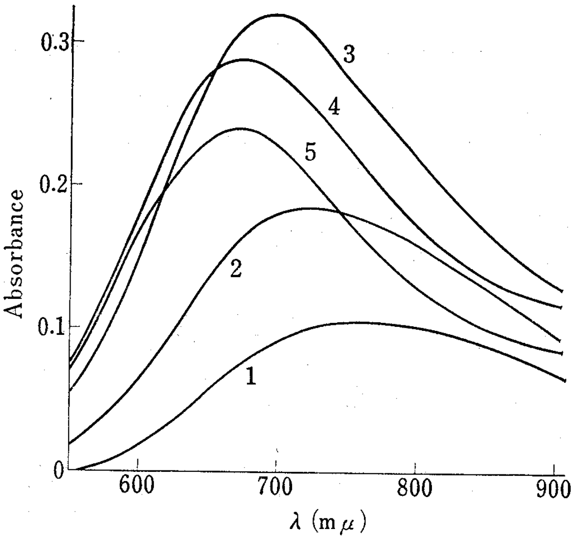


Fig. 5. Absorption Spectra of I in the Presence of Cu(II)

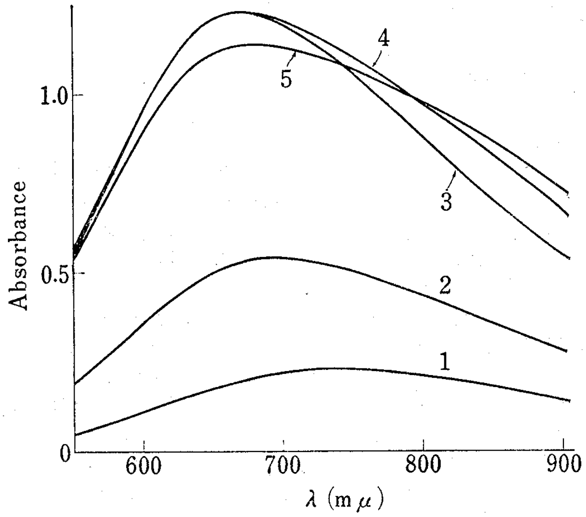
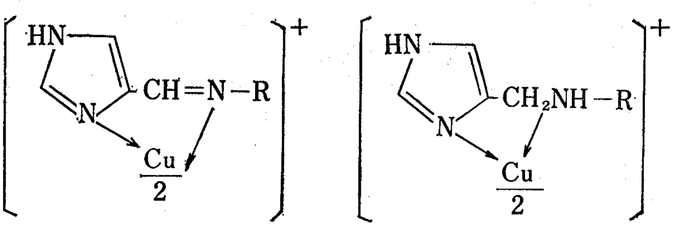


Fig. 6. Absorption Spectra of XI in the Presence of Cu(II)

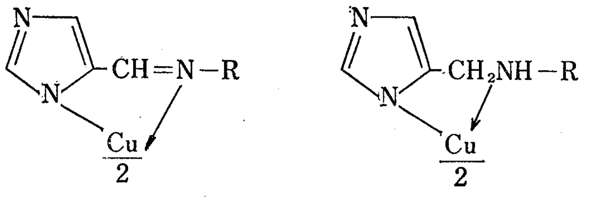
Concentration of Cu (II): $5\times10^{-3}M$
Solvent: 50v/v% EtOH-H_2O
Ligand : Cu (II) ratio: 0.4:1 (curve 1) 3:1 (curve 4)
1:1 (curve 2) 4:1 (curve 5)
2:1 (curve 3)

Fig. 5 and 6 show the absorption spectra of I and XI, respectively, in the presence of Cu(II) at various ligand : copper ratios. It is apparent from the curves that the absorption peak of the Cu(II)-I complex shifts to shorter wavelengths as the ratio increases, whereas the peak of the Cu(II)-XI complex shifts only when the ratio is less than 2. In both cases the absorbances are greatest when the ratio equals 2. These spectral behaviors suggest that, when the ligand : copper ratio in solution is greater than 2, complexes of the Schiff bases [A] other than Cu(ligand)$_2$X$_2$ (X=Br^-, NO_3^-, etc.) may also be formed to some extent, whereas the 4(5)-aminomethylimidazoles [C] form the chelates of the type Cu(ligand)$_2$X$_2$ almost exclusively.



Cu(ligand)$_2$X$_2$ (X=Br^-, NO_3^-, etc.)

Although the small frequency shifts of the C=N stretching band of the side chain observed on complex formation and the above mentioned spectral behaviors do not reject the possible unidentate character of the Schiff bases [A], contribution of the side chain nitrogen of the Schiff bases to coordination to copper with the consequent formation of a chelate ring as bidentate ligands is compatible with the weak reactivities of the Schiff bases [B] which are unlikely to form a chelate ring.



Cu (ligand)$_2$

From the present experimental results, coordination of the imidazole derivatives to copper, at least in the crystalline state, may be safely expressed by the above structures.

Experimental[*4]

Syntheses of the Compounds

The following examples illustrate the syntheses of the Schiff bases [A] and [B], and the 4(5)-aminomethylimidazoles [C].

N-[4(5)-Imidazolylmethylene]-*p*-toluidine(I)——4(5)-Imidazolecarboxaldehyde (1.5 g.) and *p*-toluidine (1.8 g.) dissolved in aq. EtOH was refluxed on a water bath for 1 hr. After evaporation of the solvent, the residue was recrystallized from EtOH to give 2.1g. (73%) of I as colorless prisms, m.p. 172~173° (decomp.).

4(5)-Imidazolecarboxaldehyde *p*-methylphenylhydrazone(VI)——4(5)-Imidazolecarboxaldehyde(0.5 g.) and *p*-methylphenylhydrazine hydrochloride (0.80 g.) were treated analogously to give 0.7 g. (67%) of Ⅵ as colorless prisms, m.p. 186~188° (decomp.). *Anal.* Calcd. for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.95; H, 6.23; N, 27.95.

4(5)-Methyl-5(4)-(*p*-methylbenzylidene)aminoimidazole (VII)——To a solution of 4(5)-amino-5(4)-methylimidazole dihydrochloride (2.0 g.) and *p*-tolualdehyde (1.4 g.) in aq. MeOH was added an aq. solution of Na_2CO_3 (1.2 g.), and the mixture was warmed on a water bath for 10~20 min., when colorless crystals separated. The mixture was cooled in ice-water, and the crystals were filtered and recrystallized from aq. EtOH to give 1.6 g. (68%) of Ⅶ as colorless prisms, m.p. 200~201° (decomp.).

4(5)-(*p*-Tolylaminomethyl)imidazole (XI)——To a solution of I (0.41 g.) in MeOH was added dropwise a solution of $NaBH_4$ (0.17 g.) in MeOH at room temperature. After the mixture was kept standing for 0.5 hr., the solvent was removed, and H_2O was added to the residue, when an oily substance separated and was crystallized with a spatula. Recrystallization of the crystals from aq. EtOH gave 0.3 g. (73%) of Ⅺ as colorless crystals, m.p. 109~111°. Dinitrate: colorless leaflets, m.p. 166~168° (decomp.). *Anal.* Calcd. for $C_{11}H_{15}O_6N_5$: C, 42.17; H, 4.83; N, 22.36. Found: C, 42.45; H, 5.04; N, 22.63.

General Procedure of the Spot Tests

Reagents——The Schiff bases and the 4(5)-aminomethylimidazoles were used as 3% solutions in EtOH.

Standard Solutions of Metal Ions——Metal acetates, nitrates, sulfates, or chlorides were dissolved in distilled water, and the concentrations of the metal ions were adjusted to 10 mg./ml.

Spot Tests——One drop of a metal ion solution, 5 drops of a buffer solution (pH=3.6, 6.7, or 8.9), and 2~3 drops of a reagent were mixed on a plate, and the color development was observed. The colors of the reagents alone were also observed at each pH.

General Procedures of Isolations of the Copper Chelates

1) **$Cu(ligand)_2Br_2$**——To a solution of a ligand (0.0005 *M*) in EtOH was added $Cu(NO_3)_2 \cdot 3H_2O$ (0.00025 *M*) in aq. EtOH with stirring, and after a few minutes 2~5 ml. of 50% KBr solution was added to the mixture. There separated green crystals, which were filtered, washed with a small volume of aq. EtOH, and dried.

The reaction of Ⅺ with $Cu(NO_3)_2$ in EtOH without addition of KBr gave the copper chelate of the type $Cu(ligand)_2(NO_3)_2$.

2) **$Cu(ligand)_2$**——A ligand (0.001 *M*) and $Cu(NO_3)_2 \cdot 3H_2O$ (0.0005 *M*) were mixed in aq. EtOH, and 28% ammonia water (2~5 drops) was added to the mixture. The grayish green precipitate was collected, washed with EtOH and H_2O, and dried.

The copper chelates of this type are not sufficiently pure, because they are insoluble in H_2O and most organic solvents. In Table Ⅲ only the copper chelate of Ⅲ is listed.

The authors are grateful to the members of the Microanalysis Center of Kyoto University for microanalyses.

[*4] All melting points are uncorrected.