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128. Osamu Yamauchi, Hisashi Tanaka, and Toyozo Uno:

Studies on Imidazole Derivatives as Chelating Agents. I. Syntheses of Azoimidazoles and Their Reactions with Metal Ions.*1

(*Faculty of Pharmaceutical Sciences, Kyoto University**2)

Imidazole is known to form complexes with various metal ions through its pyridine-like nitrogen or its pyrrole-like imino group. The reactivity with metal ions and the biochemical importance of imidazole prompted the studies on imidazole itself, alkylimidazoles, histidine, histamine and some aminoalkylimidazoles, and some other related compounds. As to imidazole derivatives in general, however, the literature offers no sufficient knowledge of their reactions with metal ions and their analytical applicabilities.

The authors intended systematic studies on imidazole derivatives having such structures as are expected to form metal chelates in order to obtain some knowledge of their chelating abilities and, if possible, apply them to determinations of metals.

Since the appearance of 1-(2-pyridylazo)-2-naphthol (PAN) as a useful metallochromic indicator,1) properties of many other ortho-hydroxyazo compounds with heterocyclic components, such as pyridine, quinoline, and thiazole, have been investigated, and many of them proved to be applicable to determinations of metals by chelatometric titrations or by solvent extractions.

Considering the complexing ability of imidazole and scanty knowledge of the reactions of azoimidazoles with metal ions, the authors synthesized several azoimidazoles containing an ortho-hydroxy group, a dimethylamino group, or both groups and studied their reactions with metal ions by spot tests.

Many azoimidazoles were prepared by coupling of diazo derivatives of aromatic amines with imidazoles, and their structures were established by Fargher and Pyman.2) Because of the labile character of the amino group in the 4(5)-position of imidazole, diazotization and subsequent coupling with phenols or aromatic amines for the synthesis of azoimidazoles did not seem to be feasible. However, Fargher3) found that 4(5)-amino-5(4)-methylimidazole can be isolated as dihydrochloride (I), which Weidenhagen and Herrmann4) later obtained in better yield. They found that it gives a reddish brown color with 1- and 2-naphthols and resorcinol after treatment with nitrous acid. Recently Shealy, *et al.*5) obtained azoimidazoles by coupling of diazotized 4(5)-aminoimidazole-5(4)-carboxamide with 2-naphthol, N-methylaniline, and N,N-dimethylaniline.

The authors used 4(5)-amino derivative (I) as a diazo component and synthesized four azoimidazoles by coupling the diazotized amine with 2-naphthol, *p*-methoxyphenol, N,N-dimethyl-*m*-aminophenol, and N,N-dimethylaniline. Diazotization of I was effected by sodium nitrite in acid solution at temperatures below 5°. The diazo derivative

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*1 Some of this work has been briefly reported in a preliminary publication (H. Tanaka, O. Yamauchi: This Bulletin, **12** 1268 (1964)).

*2 Yoshidashimoadachi-cho, Sakyo-ku, Kyoto (山内　脩, 田中　久, 宇野豊三).

1) K.L. Cheng, R.H. Bray: Anal. Chem., **27**, 782 (1955).

2) R.G. Fargher, F.L. Pyman: J. Chem. Soc., **115**, 217 (1919).

3) R.G. Fargher: *Ibid.*, **117**, 675 (1920).

4) R. Weidenhagen, R. Herrmann: Ber., **68**, 2207 (1935).

5) Y.F. Shealy, C.A. Krauth, J.A. Montgomery: J. Org. Chem., **27**, 2150 (1962).

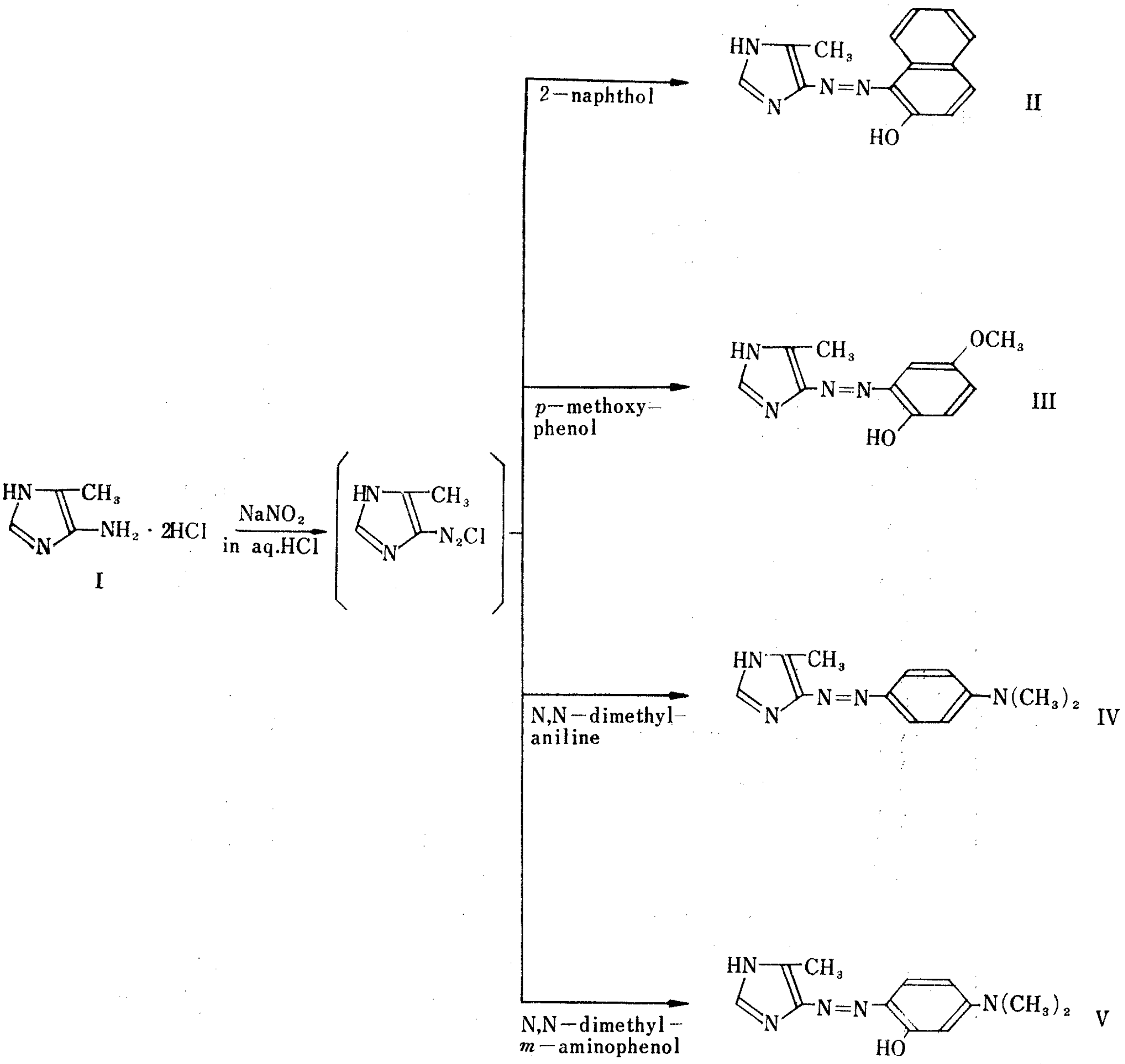

Chart 1. Synthesis of Azoimidazoles

was then coupled with 2-naphthol and *p*-methoxyphenol in alkaline solution to give 1-[4(5)-methyl-5(4)-imidazolylazo]-2-naphthol (II) and 2-[4(5)-methyl-5(4)-imidazolylazo]-4-methoxyphenol (III), respectively. Coupling of the diazotized amine with N,N-dimethylaniline in acid solution afforded 4(5)-methyl-5(4)-(*p*-dimethylaminophenylazo)imidazole (IV). As diazotized aromatic amines generally couple with N,N-dimethyl-*m*-aminophenol in acid solution in the position *para* to the dimethylamino group,[6] the compound obtained by coupling with the phenol in acid solution is supposed to be 3-dimethylamino-6-[4(5)-methyl-5(4)-imidazolylazo]phenol (V). The infrared spectrum also suggests 1,2,4-substitution of the benzene ring.[*3] Although the diazo derivative of I coupled with 2-naphthol or N,N-dimethylaniline easily, it coupled with *p*-methoxyphenol slowly, and the yield of the azo derivative was a little lower. The azo derivative of *p*-cresol could not be isolated in the pure state under the conditions employed. Coupling of diazotized 2-aminopyridine and N,N-dimethyl-*p*-phenylenediamine with imidazole or 2-methylimidazole was not successful.

[*3] That the hydroxy group is in the position *ortho* to the azo group is suggested by its acid dissociation constant, which will be reported in the following paper.

6) C. Bülow, H. Wolfs: Ber., **31**, 488 (1898).

Table I. Reactions of the Azoimidazoles with Metal Ions and Extractions of the Chelates with Organic Solvents

Compound	Metal ion	Color[a]		Extraction[b]
		acid	neutral	
Ⅱ	Fe (III)	deep red	deep red	insoluble
	Co (II)	reddish brown	reddish brown	$CHCl_3$; iso-Am[c]
	Ni (II)	orange red	orange red	iso-Am
	Cu (II)	deep red	reddish violet	$CHCl_3$; iso-Am
	Zn (II)	orange	orange red	〃
	Pd (II)	brown	brown	iso-Am
	Ag (I)	yellowish brown	〃	insoluble
	Cd (II)	orange red	red	$CHCl_3$; iso-Am
	Pb (II)	orange	pink	iso-Am
	Bi (III)	red		〃
	VO (II)	reddish violet	brown	$CHCl_3$; iso-Am
	UO_2 (II)	red	red	iso-Am
Ⅲ	Fe (III)	brown	brown	insoluble
	Co (II)	violet	reddish violet	$CHCl_3$; iso-Am
	Ni (II)	orange red	〃	iso-Am
	Cu (II)	violet	violet	$CHCl_3$; iso-Am
	Zn (II)	orange	pink	〃
	Zr (IV)	red	red	iso-Am
	Pd (II)	greenish brown	greenish brown	$CHCl_3$; iso-Am
	Cd (II)	yellow	pink	〃
	Au (III)	brown	brown	〃
	Pb (II)	yellow	reddish violet	iso-Am
	Bi (III)	violet	dark violet	insoluble
	VO (II)	〃	violet	iso-Am
Ⅳ	Fe (III)	reddish brown	reddish brown	insoluble
	Co (II)	deep red	〃	$CHCl_3$; iso-Am
	Ni (II)	red	orange red	$CHCl_3$[d]
	Cu (II)	deep red	reddish brown	$CHCl_3$; iso-Am
	Zn (II)		〃	$CHCl_3$[d]
	Zr (IV)		yellowish brown	insoluble
	Pd (II)	dark brown	dark brown	$CHCl_3$
	Cd (II)		orange	insoluble
	Au (III)	dark brown	dark brown	$CHCl_3$
	Hg (II)	red	reddish brown	$CHCl_3$; iso-Am
	Pb (II)		orange	insoluble
	UO_2 (II)		yellowish brown	〃
Ⅴ	Fe (III)	brown	brown	insoluble
	Co (II)	orange red	red	$CHCl_3$; iso-Am
	Ni (II)	〃	orange red	〃
	Cu (II)	red	red	〃
	Zn (II)		〃	iso-Am
	Zr (IV)	pink	pink	$CHCl_3$
	Pd (II)	brown	brown	$CHCl_3$; iso-Am
	Cd (II)		orange	$CHCl_3$
	Au (III)	brown	brown	$CHCl_3$; iso-Am
	Pb (II)	orange red	red	iso-Am
	Bi (III)	reddish violet	reddish violet	$CHCl_3$
	VO (II)	brown	brown	$CHCl_3$; iso-Am[d]

Reagent: 0.1% solution of an azoimidazole in EtOH.

a) A test solution contained 2 drops of a reagent, 1 drop of a metal ion solution (10 mg./ml.), and 5 drops of a buffer solution (pH 3.6 (acid); pH 7.1 (neutral)).

b) Extraction of a colored chelate was examined by shaking a weakly acid or a neutral solution with chloroform or iso-amyl alcohol.

c) iso-Am=iso-Amyl alcohol.

d) Extraction was not complete.

The colors of the solutions of the compounds (Ⅱ and Ⅲ) are yellow (acid), orange yellow (neutral), and orange red (alkaline), whereas the compounds containing a dimethylamino group in the position *para* to the azo group (Ⅳ and Ⅴ) are orange in acid or neutral solution and yellow in alkaline solution. The infrared spectra of these compounds show on free OH and NH stretching bands owing to the strong hydrogen bonds. Since deuteration of Ⅲ in acetone gives rise to a broad band near 2100 cm^{-1}, the original OH and NH bands can be estimated to exist in the region 2900~3000 cm^{-1}.

The reactions of the compounds with various metal ions were investigated by spot tests in acid, neutral, and alkaline solutions. The significant color changes or formations of intensely colored precipitates in acid and neutral solutions are shown in Table I. All the azo compounds react with Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Pd (II), and Pb (II) to produce reddish violet~brown colors. In alkaline solution Ⅲ reacts with Ca (II) (red), Mg (II) (pink), and Hg (II) (violet) in addition to these metal ions. EDTA blocks most of the color formations. It is interesting that Ⅱ and Ⅲ form violet or reddish violet copper chelates as compared with the red or reddish brown copper chelates of Ⅳ and Ⅴ. Many of the colored chelates can be extracted from neutral solutions into organic solvents, such as chloroform and iso-amyl alcohol. These facts indicate that the azoimidazoles can be applied to determinations of metals as metallochromic indicators and as extractants.

Experimental*4

1-[4(5)-Methyl-5(4)-imidazolylazo]-2-naphthol (II)——A solution of $NaNO_2$ (0.2 g.) in 5 ml. of H_2O was added dropwise to 0.5 g. of I dissolved in 8 ml. of H_2O containing 3 ml. of 1*N* HCl. Excessive $NaNO_2$ was decomposed with sulfamic acid. Coupling was effected by adding the solution of the diazotized amine to a stirred solution of 1.0 g. of 2-naphthol in a mixture of 20 ml. of 50% EtOH-H_2O and 3~4 ml. of 28% ammonia water in ca. 20 min. The temperature was maintained at 5° throughout the reaction. A reddish brown precipitate was formed during the reaction. The reaction mixture was kept standing overnight, and the precipitate was filtered. Recrystallization from EtOH gave 0.3 g. of Ⅱ as reddish brown needles, m.p. 226~227° (decomp.) *Anal.* Calcd. for $C_{14}H_{12}ON_4$: C, 66.65; H, 4.79; N, 22.21. Found : C, 66.93; H, 5.08; N, 22.04.

2-[4(5)-Methyl-5(4)-imidazolylazo]-4-methoxyphenol (III)——An aqueous solution of I (1.0 g.) was diazotized with 0.4 g. of $NaNO_2$ according to the procedure described above and added with stirring to 2.5 g. of *p*-methoxyphenol dissolved in 20 ml. of 50% EtOH-H_2O containing 4 ml. of 28% ammonia water. The addition took ca. 1 hr. The brown precipitate was separated and recrystallized from EtOH to give 0.3 g. of Ⅲ as a yellowish brown powder, m.p. 232~233° (decomp.). *Anal.* Calcd. for $C_{11}H_{12}O_2N_4$: C, 56.89; H, 5.21; N, 24.13. Found : C, 57.18; H, 5.42; N, 24.41.

4(5)-Methyl-5(4)-(*p*-dimethylaminophenylazo)imidazole (IV)——An aqueous solution of I (1.8 g.) was similarly diazotized with $NaNO_2$ (0.7 g.). The solution of the diazotized amine was added in ca. 40 min. to a stirred solution of 2.4 g. of N,N-dimethylaniline in a mixture of 30 ml. of EtOH, 10 ml. of 1*N* HCl, and 20 ml. of H_2O. Careful neutralization of the deep red reaction mixture with 1*N* NaOH afforded a yellowish brown precipitate, which on recrystallization from EtOH gave 1.3 g. of Ⅳ as brown black needles, m.p 222~224° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}N_5$: C, 62.85; H, 6.59; N, 30.55. Found : C, 62.77; H, 6.77; N, 30.49.

3-Dimethylamino-6-[4(5)-methyl-5(4)-imidazolylazo]phenol(V)——An aqueous solution of I (0.5 g.) was diazotized with 0.2 g. of $NaNO_2$ and added to a solution of 1.0 g. of N,N-dimethyl-*m*-aminophenol in 10 ml. of 50% EtOH-H_2O containing 2~3 ml. of 1*M* AcOH. The reaction mixture, from which a reddish brown precipitate separated, was kept standing overnight, and the pH of the solution was adjusted to 4.5 with 1*N* NaOH. The precipitate (0.25 g.) was separated, washed with 50% EtOH-H_2O, and dissolved in 3~5 ml. of 1*N* HCl. Neutralization of the solution and washing of the precipitate with 50% EtOH-H_2O gave a yellowish brown powder, m.p. 247~249° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}ON_5$: C, 58.76; H, 6.16; N, 28.56. Found: 58.67; H, 6.43; N, 28.26. IR ν_{max}^{Nujol} cm^{-1} : 816 (C-H out of plane bend.).

This compound was also obtained by coupling reaction in alkaline solution.

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*4 All melting points are uncorrected.

Summary

As part of the systematic studies on imidazole derivatives as chelating agents, four azoimidazoles having an ortho-hydroxy group, a dimethylamino group, or both groups were prepared from 4(5)-amino-5(4)-methylimidazole as a diazo component and 2-naphthol, *p*-methoxyphenol, N,N-dimethylaniline, and N,N-dimethyl-*m*-aminophenol as coupling components: 1-[4(5)-methyl-5(4)-imidazolylazo]-2-naphthol; 2-[4(5)-methyl-5(4)-imidazolylazo]-4-methoxyphenol; 4(5)-methyl-5(4)-(*p*-dimethylaminophenylazo)imidazole; 3-dimethylamino-6-[4(5)-methyl-5(4)-imidazolylazo]phenol. The reactions of the azo derivatives with various metal ions were studied by spot tests in acid, neutral, and alkaline solutions. All the azo derivatives react with metal ions, such as Fe (III), Co (II), Ni (II), Cu (II), Zn (II), Pd (II) and Pb (II), to give intensely colored chelates which are usually extracted into chloroform or iso-amyl alcohol. These results indicate that the azoimidazoles can be used as metallochromic indicators or as extractants for determinations of metal ions by chelatometric titrations or by solvent extractions.

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129. Osamu Yamauchi, Hisashi Tanaka, and Toyozo Uno:

Studies on Imidazole Derivatives as Chelating Agents. II.[*1] Spectrophotometric and Potentiometric Investigations of Acid-base Equilibria of Azoimidazoles.

(*Faculty of Pharmaceutical Sciences, Kyoto University*[*2])

In the preceding paper[*1] the authors reported the syntheses of some azoimidazoles having an ortho-hydroxy group, a dimethylamino group, or both groups, along with their remarkable color formations with a number of metal ions. Most of their colored chelates are decomposed by EDTA, and the fact indicates the possibilities of their applications as metallochromic indicators in chelatometric titrations. Just as other azo compounds with a dimethylamino group or a hydroxy group generally exhibit color changes as the pH of the solution varies, these azoimidazoles show spectral changes owing to the equilibria that are dependent on the pH of the solution.

The groups contributing to the acid-base equilibria of the azoimidazoles concerned are the pyridine-like nitrogen and the pyrrole-like imino group of the imidazole nucleus, the hydroxy group, and the dimethylamino group, and protonation of the azo group does not occur in the usual pH range. As a basis of their applications to chelatometric titrations and calculations of the stability constants of their metal chelates, the authors investigated the pH dependence of the spectra and determined the acid dissociation constants by spectrophotometric and potentiometric methods.

[*1] Part I: This Bulletin, **14**, 948 (1966).

[*2] Yoshidashimoadachi-cho, Sakyo-ku, Kyoto (山内 脩, 田中 久, 宇野豊三).