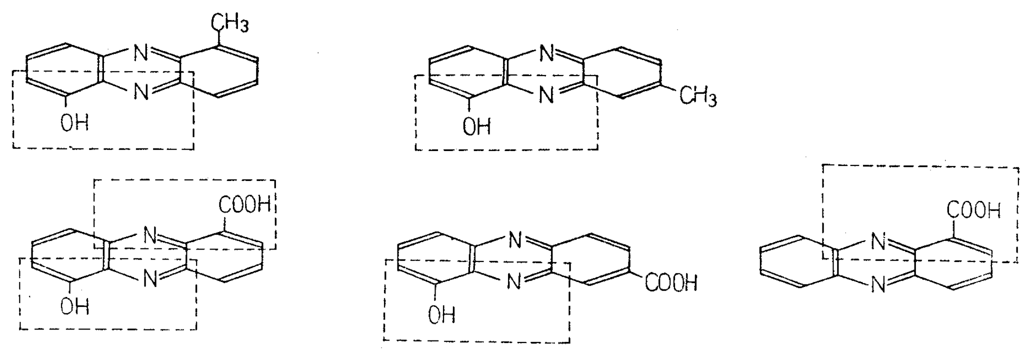
UDC 547.864-156:

16. Yoshinori Kidani: Studies on Metal Chelate Compounds of Phenazine Derivatives. IV.[1] Spectrophotometric Study of Copper Chelate Compounds of 1-Hydroxy-6-methyl- and 1-Hydroxy-8-methyl-phenazines, 6-Hydroxyphenazine-1-carboxylic Acid and 9-Hydroxyphenazine-2-carboxylic Acids, and Phenazine-1-carboxylic Acid.

(*International Christian University**)

In several previous papers, it was observed that α-hydroxyphenazine derivatives, which have an oxine-like structure, form chelates with copper. When hydroxyl group is located in the β-position, the compounds have no chelating ability, but they have individual chemical properties. Such properties give some influence upon bacteria.



In the present series of work, examinations were made on the copper chelate formation of α-hydroxyphenazine derivatives, which have one oxine-like functional group in common, but with one other group such as a methyl group as a lipophilic radical and a carboxylic acid group as a hydrophilic radical, at α- or β-position. As to the hydroxyl group, studies have already been made on 1-hydroxy-6-methyl- and 1-hydroxy-8-methylphenazines, and 6-hydroxyphenazine-1- and 9-hydroxyphenazine-2-carboxylic acids. Introduction of a methyl or a carboxylic acid group into α-hydroxyphenazine derivatives gave very interesting results which are described in this paper. In case of 1-hydroxyphenazine-6-carboxylic acid, from the spectrophotometric study applied in this series of experiments, it seems rather difficult to distinguish whether it is a real chelate compound or just a simple metal salt, and therefore copper chelate of phenazine-1-carboxylic acid was also studied. Like the oxine-like functional group, α-carboxylic acid group has a similar capacity to form chelates. By the infrared analysis of the copper chelate of phenazine-1-carboxylic acid, which was isolated, this substance was determined to be a real chelate and not a simple salt.

Results

I. Copper Chelates of 1-Hydroxy-6-methylphenazine and 1-Hydroxy-8-methylphenazine

1. Absorption Spectra—As is shown in Figs. 1 and 2, the Cu chelate of 1-hydroxy-6-methylphenazine has λ_{max} at 540 mμ in acid, at 560 mμ in neutral, and at 500 mμ in alkaline solutions. The Cu chelate of 1-hydroxy-8-methylphenazine has λ_{max} at 550 mμ in both acid and neutral solutions.

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1) Part III: This Bulletin, **7**, 68 (1959).

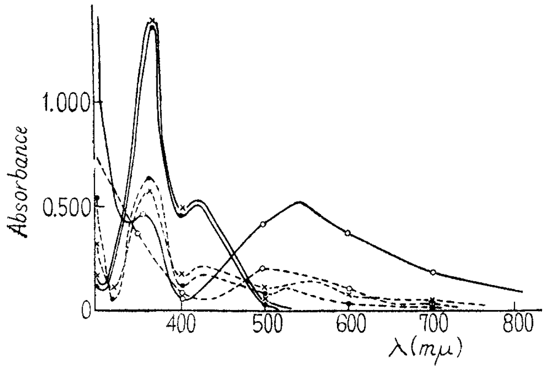


Fig. 1. Absorption Spectra of 1-Hydroxy-6-methylphenazine-Copper Chelate

(The solution contains $1\times10^{-4}M$ of 1-hydroxy-6-methylphenazine)

	Reag.	Complex
Acid	——●——	---●---
Neut.	——×——	---×---
Alkali	——○——	---○---

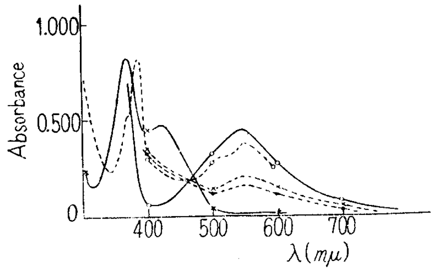


Fig. 2. Absorption Spectra of 1-Hydroxy-8-methylphenazine-Copper Chelate

(The solution contains $2\times10^{-4}M$ of 1-hydroxy-8-methylphenazine)

	Reag.	Complex
Acid	——●——	---●---
Neut.	——×——	---×---
Alkali	——○——	---○---

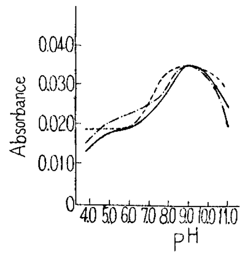


Fig. 3. Effect of pH Change on 1-Hydroxy-6-methylphenazine-Copper Chelate

(Measured at 500 mμ, 540 mμ, and 560 mμ. The solution contains $5\times10^{-5}M$ of 1-hydroxy-6-methylphenazine)

———— 500 mμ
------ 540 mμ
—•—•— 560 mμ

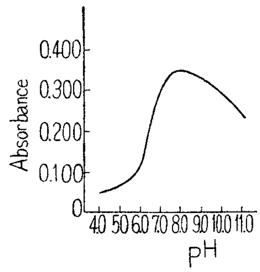


Fig. 4. Effect of pH Change on 1-Hydrcxy-8-methylphenazine-Copper Chelate

(Measured at 550 mμ. The solution contains $5\times10^{-5}M$ of 1-hydroxy-8-methylphenazine)

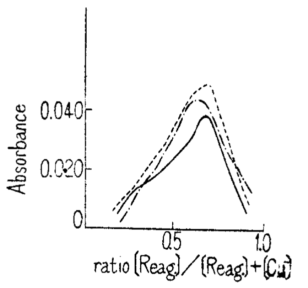


Fig. 5. Absorption Curves of 1-Hydroxy-6-methylphenazine-Copper Chelate (Job Method)

(Measured at 500 mμ, 540 mμ, and 560 mμ, at pH 8.0. The total concentration is $5\times10^{-5}M$)

———— 500 mμ
------ 540 mμ
—•—•— 560 mμ

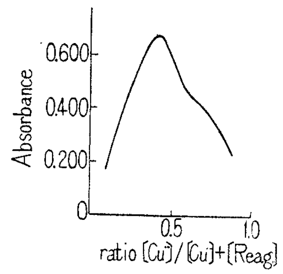


Fig. 6. Absorption Curve of 1-Hydroxy-8-methylphenazine-Copper Chelate (Job Method)

(Measured at 550 mμ and at pH 8.0. The total concentration is $5\times10^{-5}M$)

2. Effect of pH Change—The absorptions of 1-hydroxy-6-methylphenazine- and 1-hydroxy-8-methylphenazine-copper chelates in EtOH solution in various pH are shown in Figs. 3 and 4, respectively. In the solution of the chelates, the maximum absorption is shown at pH of about 8.0～9.0, measured at 500, 540, and 560 mμ for the former compound, and at pH of about 8.0 and at 550 mμ for the latter compound, and decreases markedly in absorption if the pH is increased or decreased.

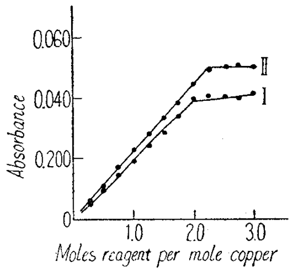


Fig. 7. Absorption Curves of 1-Hydroxy-6-methylphenazine-Copper Chelate (Molar Ratio Method)

(Measured at 560 mμ (I) and 540 mμ (II), at pH 8.0. The concentration of copper is $5\times10^{-5}M$)

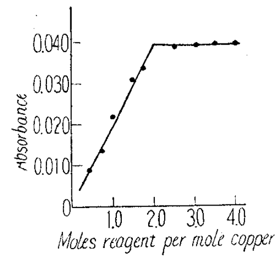


Fig. 8. Absorption Curve of 1-Hydroxy-8-methylphenazine-Copper Chelate (Molar Ratio Method)

(Measured at 550 mμ and at pH 8.0. The concentration of copper is $5\times10^{-5}M$)

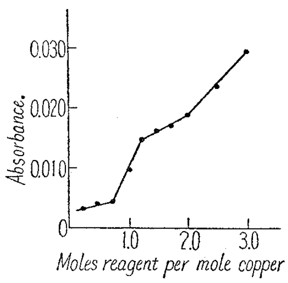


Fig. 9. Absorption Curve of 1-Hydroxy-6-methylphenazine-Copper Chelate (Molar Ratio Method)

(Measured at 500 mμ and at pH 4.9. The concentration of copper is $5\times10^{-5}M$)

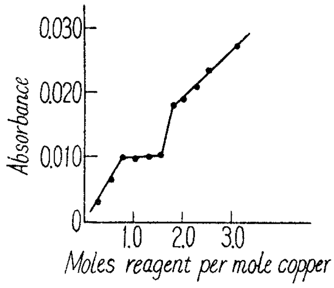


Fig. 10. Absorption Curve of 1-Hydroxy-8-methylphenazine-Copper Chelate (Molar Ratio Method)

(Measured at 550 mμ and at pH 4.9. The concentration of copper is $5\times10^{-5}M$)

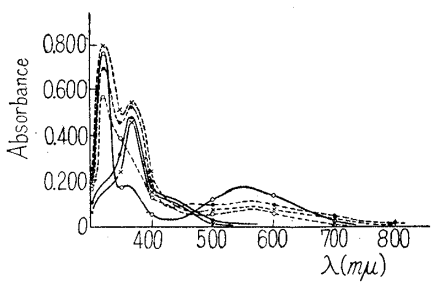


Fig. 11. Absorption Spectra of 9-Hydroxyphenazine-2-carboxylic acid-Copper Chelate

(The solution contains $2\times10^{-4}M$ of 9-hydroxyphenazine-2-carboxylic acid)

	Reag.	Complex
Acid	——●——	---●---
Neut.	——×——	---×---
Alkali	——○——	---○---

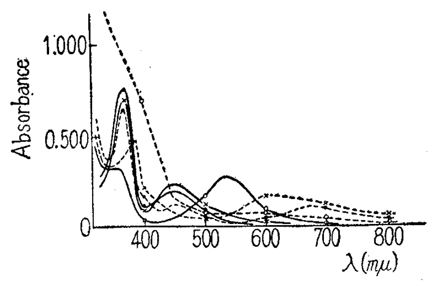


Fig. 12. Absorption Spectra of 6-Hydroxyphenazine-1-carboxylic Acid-Copper Chelate

(The solution contains $2\times10^{-4}M$ of 6-hydroxyphenazine-1-carboxylic acid)

	Reag.	Complex
Acid	——●——	---●---
Neut.	——×——	---×---
Alkali	——○——	---○---

3. Composition of the Chelates in Solution—The measurements were made by the two methods, (i) Job's Continuous Variation Method and (ii) Molar Ratio Method. Both compounds showed the molar ratio 2:1 of reagent to copper, a normal complex, measured at a wave length of 500, 540, and 560 mμ in the former compound, and at 550 mμ in the latter compound, at pH 8.0, as shown in Figs. 5 and 6, measured by the Job's method, and in Figs. 7 and 8 by the Molar Ratio Method. When the measurements were made in acid solution, at pH 4.9, both compounds showed a break, which was also observed at the 1-hydroxyphenazine. This suggests a formation of cation complex in a ratio of 1:1 (Figs. 9 and 10) in solution.

II. Copper Chelate Compounds of 9-Hydroxyphenazine-2-carboxylic Acid and 6-Hydroxyphenazine-1-carboxylic Acid

1. Absorption Spectra—The curves of the two compounds formed with copper in three kinds of solutions are shown in Figs. 11 and 12. In 9-hydroxyphenazine-2-carboxylic acid, λ_{max} was determined at 580 mμ, but in 6-hydroxyphenazine-1-carboxylic acid, curves different from other compounds were obtained. In acid solution, λ_{max} was at 680 mμ and that of neutral was at 600 mμ.

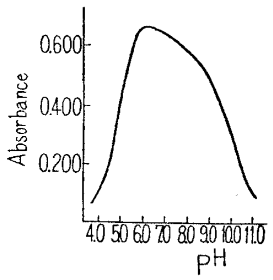


Fig. 13. Effect of pH Change on 9-Hydroxyphenazine-2-carboxylic Acid-Copper Chelate

(Measured at 580 mμ. The solution contains $1\times10^{-4}M$ of 1-hydroxyphenazine-2-carboxylic acid)

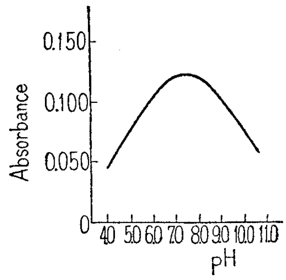


Fig. 14. Effect of pH Change on 9-Hydroxyphenazine-2-carboxylic Acid-Copper Chelate

(Measured at 650 mμ. The solution contains $1\times10^{-4}M$ of 6-hydroxyphenazine-1-carboxylic acid)

2. Effect of pH Change—The absorption of 9-hydroxyphenazine-2-carboxylic acid-copper chelate in EtOH solution of various pH is shown in Fig. 13. The solution of the chelate shows maximum absorption at pH of about 6.3 at 580 mμ. The absorption of 6-hydroxyphenazine-1-carboxylic acid-copper chelate solution shows a maximum at pH of about 6.7～8.0 at 650 mμ, which is shown in Fig. 14. Absorption decreases in both if the pH is increased or decreased.

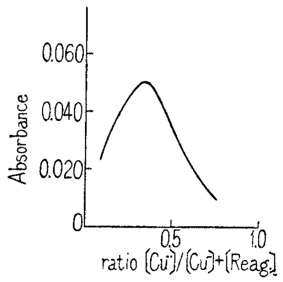


Fig. 15. Absorption Curve of 9-Hydroxyphenazine-2-carboxylic Acid-Copper Chelate (Job Method)

(Measured at 580 mμ and at pH 6.5. The total concentration is $1\times10^{-4}M$)

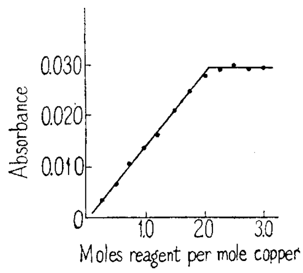


Fig. 16. Absorption Curve of 9-Hydroxyphenazine-2-carboxylic-Acid Copper Chelate (Molar Ratio Method)

(Measured at 580 mμ and at pH 6.5. The concentration of copper is $1\times10^{-4}M$).

3. Composition of the Chelates in Solution—The composition of 9-hydroxyphenazine-2-carboxylic acid-copper chelate was determined by the two methods. The measurements were made at a wave length of 580 mμ and at pH 6.5, and the normal complex 2 : 1 (Reag.: Cu) was determined (Figs. 15 and 16). 6-Hydroxyphenazine-1-carboxylic acid showed a normal complex 2:1 (Reag.: Cu) at 610 and 640 mμ, and at pH 8.0, by both methods (Figs. 17～19). When the measurements were made at pH 6.2 and a wave length of 670 mμ, the same 2:1 normal complex was observed by the two methods (Figs. 20 and 21).

4. Degree of Dissociation (α) and Dissociation Constant (K)

From the data obtained by the molar ratio method, α and -log K calculated from the formulae (1) and (3)[*1] are shown in Table I.

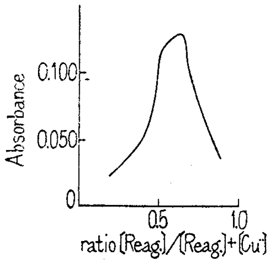


Fig. 17. Absorption Curve of 6-Hydroxyphenazine-1-carboxylic Acid-Copper Chelate (Job Method)

(Measured at 610 mμ and at pH 8.0. The total concentration is $1\times10^{-4}M$)

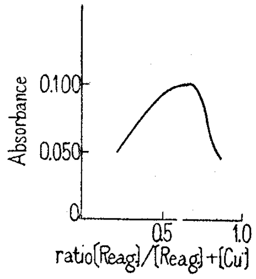


Fig. 18. Absorption Curve of 6-Hydroxyphenazine-1-carboxylic Acid-Copper Chelate (Job Method)

(Measured at 640 mμ and at pH 8.0. The total concentration is $1\times10^{-4}M$)

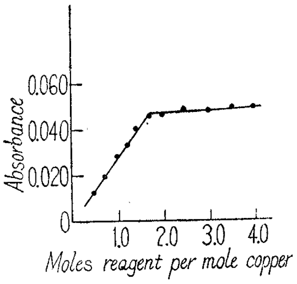


Fig. 19. Absorption Curve of 6-Hydroxyphenazine-1-carboxylic Acid-Copper Chelate (Molar Ratio Method)

(Measured at 640 mμ and at pH 8.0. The concentration of copper is $1\times10^{-4}M$)

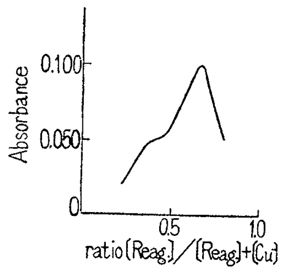


Fig. 20. Absorption Curve of 6-Hydroxyphenazine-1-carboxylic Acid-Copper Chelate (Job Method)

(Measured at 670 mμ and at pH 6.2. The total concentration is $1\times10^{-4}M$)

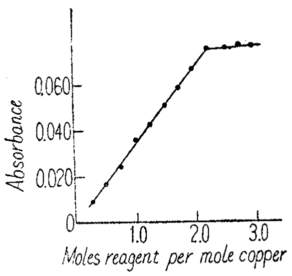


Fig. 21. Absorption Curve of 6-Hydroxyphenazine-1-carboxylic Acid-Copper-Chelate (Molar Ratio Method)

(Measured at 670 mμ and at pH 6.2. The concentration of copper is $1\times10^{-4}M$)

TABLE I.

Compound	α	-log K	pH
1-Hydroxy-6-methylphenazine	0.19	11.07	8.0
1-Hydroxy-8-methylphenazine	0.27	9.58	8.0
6-Hydroxyphenazine-1-carboxylic acid	0.19	9.81	8.0
	0.17	9.63	6.2
9-Hydroxyphenazine-2-carboxylic acid	0.22	8.99	6.5

6-Hydroxyphenazine-1-carboxylic acid-copper chelate was expected to be 1 : 1 normal chelate, because it has two chelating functional groups, but such chelate was not observed. Then the following investigation on phenazine-1-carboxylic acid-copper chelate was carried out. Absorption spectra of phenazine-1-carboxylic acid is shown in Fig. 22. The first and second maximum absorption regions were seen at 570 and 390 mμ.

*1 Part I: This Bulletin, **6**, 556 (1958).

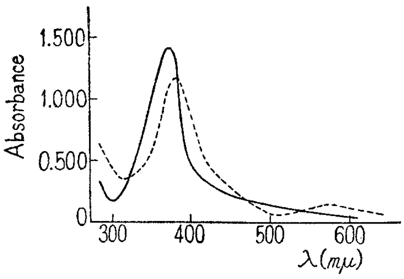


Fig. 22. Absorption Spectra of Phenazine-1-carboxylic Acid-Copper Chelate

(The solution contains $1\times10^{-4}M$ of phenazine-1-carboxylic acid)

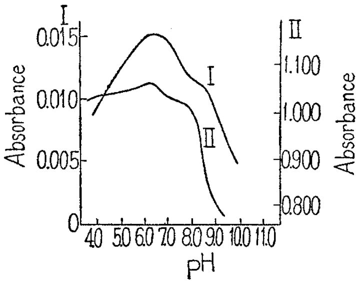


Fig. 23. Effect on pH Change of Phenazine-1-carboxylic Acid-Copper Chelate

(Measured at 570 mμ (I) and 390 mμ (II). The solution contains $1\times10^{-4}M$ (I) and $2\times10^{-4}M$ (II) of phenazine-1-carboxylic acid)

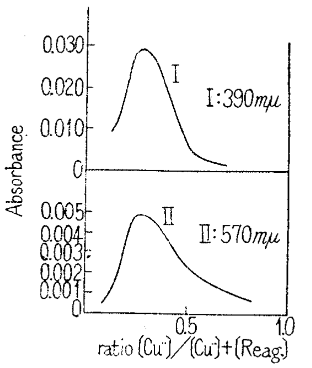


Fig. 24. Absorption Curves of Phenazine-1-carboxylic Acid-Copper Chelate (Job Method)

(Measured at 390 mμ (I) and 570 mμ (II) at pH 7.0. The total concentration is $1\times10^{-4}M$)

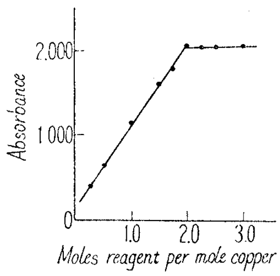
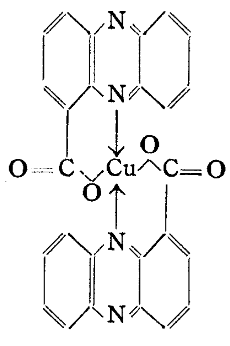


Fig. 25. Absorption Curve of Phenazine-1-carboxylic Acid-Copper Chelate (Molar Ratio Method)

(Measured at 390 mμ and at pH 6.2. The concentration of copper is $1\times10^{-3}M$)

Maximum absorption when the pH is varied was at about 6.2~7.2, at 570 mμ (Fig. 23). The composition of this compound was 2 : 1 (Reag.: Cu) when it was measured by both Job's Continuous Variation and Molar Ratio method, at pH 7.0 (Figs. 24 and 25). Under these conditions, the degree of dissociation (α) and the dissociation constant (K) were $\alpha=0.01$ and $-\log K=10.79$, measured by the molar ratio method. The structure of this chelate is shown below:

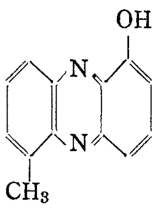


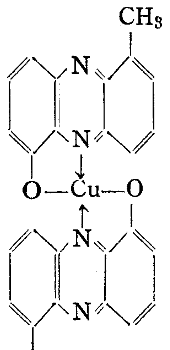
From the above obtained results, it seemed inadequate to determine only the formation of chelates and, therefore, an infrared absorption analysis of this compound was carried out separately. Phenazine-1-carboxylic acid shows the characteristic absorption band at 1740 cm^{-1}, and in its copper chelate, the absorption band shifted to 1650 cm^{-1}, which indicates the presence of hydrogen bonding. No absorption of COO^- was observed which showed the formation of a metal chelate. Considering these experimental data, it could be explained that in the chelate of 6-hydroxyphenazine-1-carboxylic acid, each functional group has its own optimum pH and the two functional groups do not work at the same time. In acid medium, chelate is supposed to form in carboxylic acid group while in neutral solution, the hydroxyl group functions.

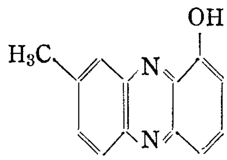
5. Structures and Discussions

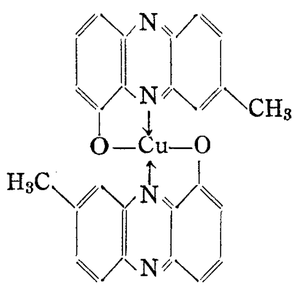
When CH_3 or COOH group is introduced into phenazine compounds, they form a fairly stable metal chelate of a five-membered ring. 1-Hydroxy-6-methylphenazine and 1-hydroxy-8-methylphenazine showed a formation of 1:1 cation complex, which is observed in acid solution. Their structures are described below.

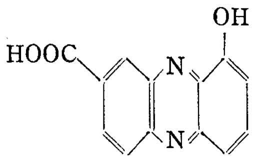
(Ia) indicates the copper chelate of 1-hydroxy-6-methylphenazine (I), and (IIa) shows the copper chelate of 1-hydroxy-8-methylphenazine (II). In the case of carboxylic acid compounds of phenazine derivative, (IIIa) shows the copper chelate of 9-hydroxyphenazine-2-carboxylic acid (III), and (IVa) and (IVb) are the copper chelates of 6-hydroxyphenazine-1-carboxylic acid (IV).

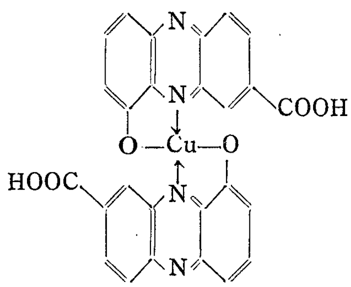

(I)

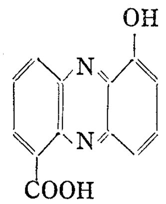

(Ia)

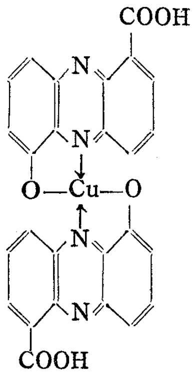

(II)

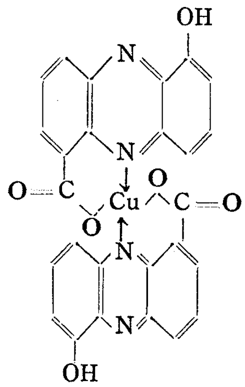

(IIa)


(III)


(IIIa)


(IV)


(IVa)


(IVb)

Expreimental

Materials—A $1\times10^{-4}M$ solution was prepared by dissolving 2.10 mg. of 1-hydroxy-6-methylphenazine or 1-hydroxy-8-methylphenazine in 100 cc. of dehyd. EtOH.

A $1\times10^{-4}M$ solution was prepared by dissolving 2.40 mg. of 6-hydroxyphenazine-1-carboxylic acid or 9-hydroxyphenazine-2-carboxylic acid in 100 cc. of dehyd. EtOH.

A $1\times10^{-4}M$ solution was prepared by dissolving 2.24 mg. of phenazine-1-carboxylic acid in 100 cc. of dehyd. EtOH.

Phenazine-1-carboxylic Acid-Copper Chelate—To EtOH solution of phenazine-1-carboxylic acid (ca. 0.5 g.), $CuSO_4$ (0.2 g. in 2 cc. of H_2O) was added. The precipitated deposit was washed with water to remove excess of $CuSO_4$, collected, and dried *in vacuo*. Greenish yellow precpitate was obtained.

Conclusion

In a previous work, copper chelates of α-hydroxyphenazine derivatives were studied spectrophotometrically, and it has been found that the oxine-like functional group formed a fairly stable chelate with copper, in EtOH solution.

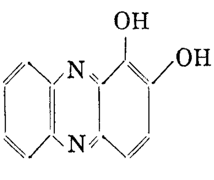
Yosioka[2] reported the experimental data of applying α-hydroxyphenazine derivatives against *Staphylococcus aureus* 209P, as well as *Mycobacterium Smegmatis*, and he recognised the influence of copper, as was proposed by Albert and Erlenmeyer, *et al.*

Comparison of his data with the present results showed some interesting findings in the mode of action of the chelate.

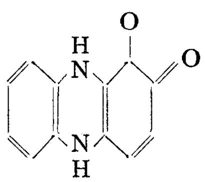
If the data of bacterial test were summarized on top of this, 1,2-, 1,4-, 1,7-, and 1,9-dihydroxyphenazines, as well as 1-carboxylic acid are ineffective. As to the first test against *Staphylococcus aureus* 209P by di-N-oxide, it was said to be ineffective, and the reason was that the di-N-oxide itself has a very strong activity and even if di-N-oxide may show its effect with copper, its activity being less than the reagent itself and copper effect is masked. Therefore, there seemed to be no influence, but later, bacterial experiments against *Mycobacterium Smegmatis* showed that there was an influence of copper with a shake culture.

1-Hydroxyphenazine methyl derivatives were much more effective than those without methyl group. The data mentioned above will be discussed below:

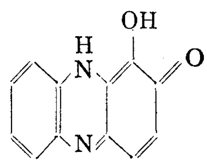
(1) Yosioka[2] reported that it was impossible to test 1,2- and 1,4-dihydroxyphenazines because a certain kind of decomposition or deformation might take place. As described before, they are able to form a chelate when pH is adjusted suitably, but they are easily converted to the *ortho*- or *para*-quinoid forms, which still retain the ability to form chelates.



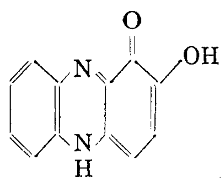
(a)



(b)

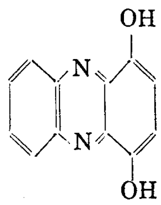


(c)

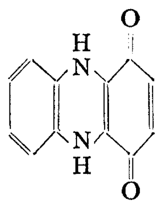


(d)

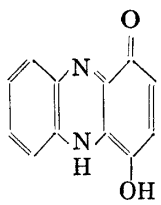
In 1,2-dihydroxyphenazine, (a) and (b) may chelate but (c) and (d), which are considered to be a kind of semi-quinoid form, are unable to form a chelate.



(e)



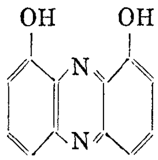
(f)



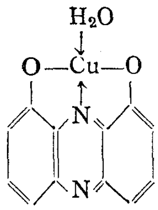
(g)

In 1,4-dihydroxyphenazine, the first two may chelate but not the last one. For these reasons, they are supposed to be ineffective. This may be explained by the experimental data by Otomasu[3] that in the case of 5,10-dihydrophenazine derivatives which possess a methoxyl at the α- or β-position, only monoacyl compound was obtained. 1,2-Dihydroxyphenazine possesses one oxine-like chelating functional group and one hydroxyl which does not take part in chelation. 1,4-Dihydroxyphenazine possesses two functional groups. The properties do not seem to be quite the same, but these two compounds showed nearly the same antibacterial activity. Therefore, they are supposed to belong to the same category.

2) I. Yosioka, S. Uehara: Yakugaku Zasshi, **78**, 351 (1958).
3) H. Otomasu: Reported at the 11th Annual Meeting of the Pharmaceutical Society of Japan, April, 1958.



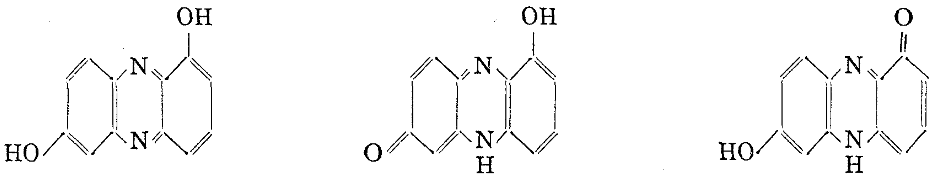
(h)



(i)

(2) 1,9-Dihydroxyphenazine: This compound may form a chelate but the structure (i) is proposed in which one molecule of H_2O is coordinated and this cannot form a 1:1 cation complex. That is the main reason why this compound does not show any strengthening effect from copper.

(3) 1,7-Dihydroxyphenazine: Yosioka reported the ineffectiveness of this compound. This substance may be able to chelate in alkaline solution, at pH 9.2. Neutrality in bacterial tests seems to correspond to an apparent pH of about 8.0, which was named neutral in these series of reports only because it is between the acid and alkaline solutions, though the measurement was carried out in EtOH.



(j) (k) (l)

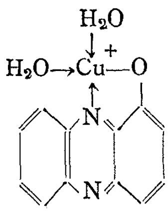
In (j) and (k), they still retain chelating function which is supposed to operate at pH 9.2 but (l) has no such function. In this compound, no diketo form is considered and it always shows a semi-quinoid form. As was mentioned above, it was found that these four α-hydroxyphenazines have no strengthening effect by copper.

(4) Phenazine-1-carboxylic acid does not show any effect, even though it has chelating function.

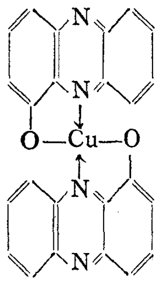
Concluding this series of study, the following facts have been revealed of phenazine derivatives: (i) Chelation takes place with copper with the functional group of hydroxyl *peri* to a ring-nitrogen; (ii) although di-N-oxide has a functional group capable of forming a six-membered ring, and the addition of copper increases its activity, the mechanism apparently takes a different route from that revealed by the present study, and (iii) introduction of a methyl group increases the efficacy.

It has been shown that the introduction of hydrophilic group such as OH or COOH seems to weaken the efficacy, while the introduction of lipophilic group such as CH_3 strengthens its efficacy. Therefore, this efficacy appears after the chelates transfer into the cell where the effect takes place. In the di-N-oxide derivatives, cation complex was measured and in some of the α-hydroxyphenazine derivatives, the presence of cation complex was presumed from measurement, in acid medium, by the molar ratio method.

The author wholly agrees with the hypothesis of the formation of cation complex, postulated by Albert, *et al.* In biological aspect, there exists a strong relationship between the efficacy and both the concentration and pH. From these facts, it may be assumed that, [A] is formed first from 1-hydroxyphenazine, in which two molecules of H_2O are coordinated at the copper site, and this makes the formation of cation complex easier, as proposed by Albert.



[A]



[B]

This is not so stable compared with the normal complex [B]. [A] seems to be more easily formed in acid medium. At the same time, the formation of [A] is easier in a very dilute solution than in a highly concentrated solution. As the concentration increases, [A] is converted faster into [B] in order to stabilize. This fact coincides well with the view of Albert that, although it is ineffective at a concentration of $1\times10^{-4}M$, efficacy is exhibited at the concentration of $2\times10^{-6}M$.

Finally, the following interpretation is proposed. In dilute concentrations, cation complex is formed and this penetrates into the cell membrane, and after that the cation complex will combine with the enzymatic protein, or in other cases deprive the trace metal element or decompose the enzyme, and combine with the central metal. In this case, copper is the most stable metal.

TABLE II. Dissociation Constants of Chelate Compounds of Phenazines

Compound	α	-log K	pH
1-Hydroxyphenazine[b]	0.34	8.68	8.0
1-Hydroxyphenazine di-N-oxide[b]	0.18[a] 0.30	5.89 8.62	6.0 8.0
1,6-Dihydroxyphenazine[b]	0.18	5.41	8.0
1,6-Dihydroxyphenazine di-N-oxide[b]	0.13[a] 0.06	3.57 7.12	5.0 9.0
1,4-Dihydroxyphenazine	0.04	6.78	8.0
1,9-Dihydroxyphenazine	0.30	4.90	8.0
1,2-Dihydroxyphenazine	0.16	10.34	6.0
1,7-Dihydroxyphenazine	0.20	8.80	9.2
1-Hydroxy-6-methylphenazine[b]	0.19	11.07	8.0
1-Hydroxy-8-methylphenazine[b]	0.27	9.58	8.0
6-Hydroxyphenazine-1-carboxylic acid	0.19 0.17	9.81 9.63	8.0 6.2
9-Hydroxyphenazine-2-carboxylic acid	0.22	8.99	6.5
Phenazine-1-carboxylic acid	0.01	10.79	6.2

a) Forms a cation complex.
b) Has antibacterial effect.

On the other hand, it is thought to be natural that the action of strengthening the efficacy is parallel to the value of dissociation constants.

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Summary

Properties and compositions, as well as the dissociation constants of the copper chelates of α-hydroxyphenazine derivatives, which possess CH_3 or COOH group at the α- or β-position, have been investigated by spectrophotometric method. The COOH group *peri* to a ring-nitrogen is also capable of forming a chelate, and copper chelate of phenazine-1-carboxylic acid has also been studied. In concluding this study of the series of copper chelates of α-hydroxyphenazine derivatives, some findings on the mode of action were made from the standpoint of chelate chemistry.

1) The fortifying effect by copper is caused by the formation of chelate compounds, which are required to possess at least one oxine-like functional group at the α-position.

2) Di-N-oxide derivatives are fairly effective.

3) Introduction of lipophilic radical strengthens the effect.

4) The antibacterial effects depend upon the degree of the binding power between phenazine derivatives and copper.

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