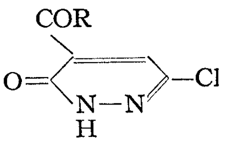
*UDC 547.852.2: 544.621*

## **111. Tsukasa Kuraishi:** 4, 5-Substituted Pyridazines. VI.[1] Infrared Absorption and Structure of 4- and 5-Carboxy-6-chloro-3-pyridazinol.

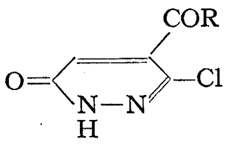
(*Pharmaceutical Faculty, University of Nagasaki**)

In connection with the synthesis of pyridazine derivatives, structural studies on these compounds have also become of increasing importance in the last few years. Previously, the infrared and Raman spectra of three isomeric diazines were measured and fundamental vibrational frequencies were reported briefly,[2] but the infrared spectra of simple pyridazine compounds have not been reported.[3]

In this paper will be presented the infrared spectra in crystalline state and ultraviolet absorption spectra of 4- and 5-carboxy-6-chloro-3-pyridazinols (I and II) and their esters (IE and IIE).



( I ) R=OH, (IE) $R=OC_2H_5$

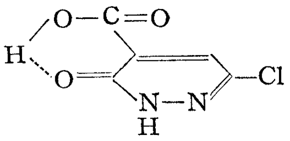


(II) R=OH, (IIE) $R=OC_2H_5$

The preparation of these compounds was reported in the preceding paper[4] with the only exception of (IIE) which is given in the experimental section.

The interpretation of infrared absorption spectra of these complex molecules is often based in the first instance upon analogy with similar molecules because of the difficulty in anticipating the frequencies. As a preliminary to the consideration of infrared frequencies of these compounds, assignments were evaluated for a number of fundamental vibrations in pyridazine itself cited in an earlier work.[2]

Nevertheless, the purpose of this paper is not to consider the individual bands strictly, but to compare the bands of each isomer in respect to intramolecular hydrogen bonding which would be expected in 4-carboxy-6-chloro-3-pyridazinol (I) like (I′).



(I′)

Therefore, little systematic work was undertaken in the present study to assign the individual bands, but experimental results obtained to date show good agreement with the above consideration. The observed infrared frequencies of strong and medium lines are presented in Table I. The infrared and ultraviolet absorption spectra of these compounds are shown in Figs. 1∼3.

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* Schowa-machi, Nagasaki (倉石 典).

[1] Part V: This Bulletin, **6**, 331(1958).

[2] M. Ito, R. Shimada, T. Kuraishi, W. Mizushima: J. Chem. Phys., **25**, 597(1956).

[3] During the preparation of this paper, infrared spectra of 3- and 4-hydroxypyridazines, etc., were reported by S. F. Mason (J. Chem. Soc., **1957**, 4874).

[4] Part III: This Bulletin, **5**, 587(1957).

Discussions and comparison between them will be made below.

**Infrared Absorptions of 4- and 5-Carboxy-6-chloro-3-pyridazinols (I and II)** The infrared spectra were obtained in the $2\sim15\,\mu$ region, using potassium bromide pellets. It was presumed from infrared measurements that, under this condition, (II) would form an intermolecular hydrogen bonding since the broad absorptions in the region of $2300\sim2700\,\text{cm}^{-1}$ and $976\,\text{cm}^{-1}$ in (II) are absent in the spectrum of (I). The bands in the former region may arise from a combination of O-H stretching frequency with lattice vibration or with low frequency associated with the dimeric ring resulting from its carboxyl group of the type shown in (A), and those of the latter correspond to the out-of-plane vibration of the dimeric ring (A).

Fig. 1. Infrared Absorption Spectra of 4-and 5-Carboxy-6-chloro-3-pyridazinol and their Esters

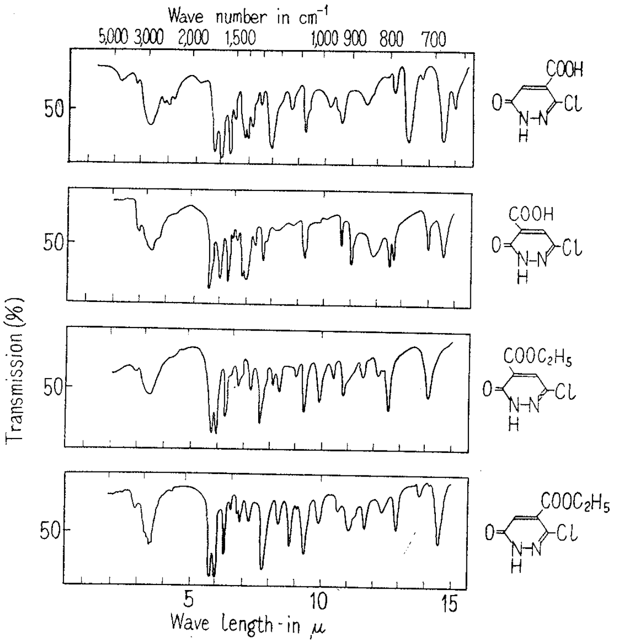
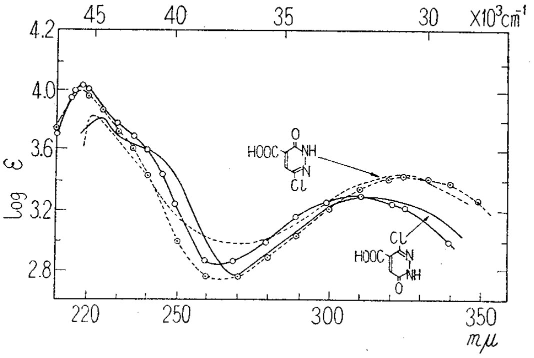


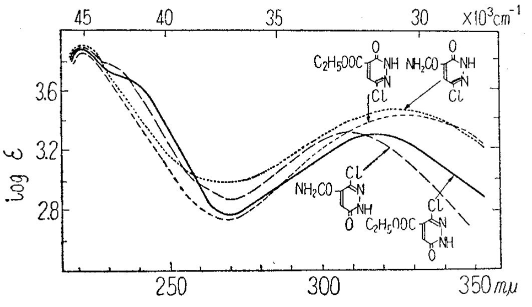
Fig. 2. Ultraviolet Absorption Spectra of 4- and 5-Carboxy-6-chloro-3-pyridazinol



Solvent:

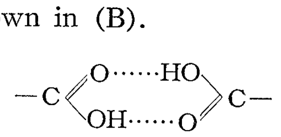
Dioxane {- - - (I), —— (II)} EtOH {······ (I), -o-o- (II)}

Fig. 3. Ultraviolet Absorption Spectra of 4- and 5-Ethoxycarbonyl-6-chloro-3-pyridazinol, and 4- and 5-Carbamoyl-6-chloro-3-pyridazinol

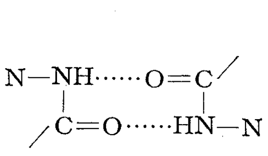


Solvent: Dioxane

There is also another dimeric type to be considered for an intermolecular hydrogen bonding as shown in (B).



(A)



(B)

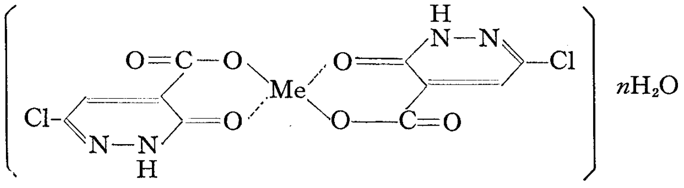
Although many workers studied the frequencies of associated N-H band, characterized in the type (B), located in the region of $3060\sim3450\,\text{cm}^{-1}$, satisfactory assignment of this band has not been given yet.[5] In addition, infrared absorptions obtained in this study appeared in the region of $2800\sim3300\,\text{cm}^{-1}$ and $3400\sim3500\,\text{cm}^{-1}$ in all cases, even in (I). Accordingly, the existence of an intermolecular hydrogen bonding of the type (B) cannot clearly be demonstrated but such bonding would be possible in the cases of (II), (I$_E$), and (II$_E$).

On the other hand, it is well known that the strong hydrogen bonding that occurs in a carboxylic acid dimer generally lowers the carbonyl frequency from that of monomeric acid. The lowered frequency of the COOH group (1704 cm$^{-1}$) in (II) could result from internal hydrogen bonding of the dimeric type (A).

On the other hand, there is no evidence of any dimer band due to the carbonyl group in the spectrum of (I) in this region.

The presence of an intramolecular hydrogen bonding in (I) has been supported by the lowering of frequency of the carbonyl in 3-position of the pyridazine ring (1658 cm$^{-1}$) from that of the ester (1682 cm$^{-1}$), and there is a strong band at 1767 cm$^{-1}$ due to a monomeric COOH group. This situation is similar to that of pyridinecarboxylic acids which also show carbonyl frequencies in the range of 1709~1727 cm$^{-1}$ (in Nujol).[6] Actually, intramolecular hydrogen bonding for picolinic acid, which showed the highest value among their isomers, was suggested by Sponer, *et al.* from their ultraviolet[7] and kinetic studies.[8] Therefore, it is supposed that the dimerization of this molecule has been prevented by intramolecular hydrogen bonding.

Furthermore, chemical evidences also support the foregoing results. For example, when a solution of copper, nickel, or manganese acetate is added to an ethanolic solution of (I), the colored precipitate sparingly soluble in organic solvents is obtained and the structure of these products is presumed from their analytical data as shown by (C).



(C)

**Infrared Absorptions of 4- and 5-Ethoxycarbonyl-6-chloro-3-pyridazinol ($I_E$ and $II_E$)** Infrared spectra of these esters show some differences in this region, especially in the lower frequencies. ($I_E$) showed an absorption at 1706 cm$^{-1}$ due to the C=O stretching frequency resulting from COOEt group and at 1682 cm$^{-1}$, from the carbonyl in 3-position of the pyridazine ring, and they are appreciably lower than those (1730 cm$^{-1}$ and 1695 cm$^{-1}$) of ($II_E$).

The reason of this difference is not clearly understood. The strong lines at 1017 and 1199 cm$^{-1}$ in ($I_E$), and at 1016 and 1198 cm$^{-1}$ in ($II_E$) were found to be the characteristic frequencies of the esters.

As seen in Fig. 1, the broad bands near 820~860 cm$^{-1}$ for each of the compounds are considered to arise from the N-H out-of-plane deformation vibration of the ring. Although the C-Cl stretching and C-H out-of-plane vibrations are also expected in the region of about 600 and 900 cm$^{-1}$, respectively, this point will not be taken up in the present work.

**Ultraviolet Absorption Spectra** Ultraviolet spectra of these compounds and amides (4- and 5-carbamoyl-6-chloro-3-pyridazinol, R=$NH_2$), which were measured for comparison, are shown in Figs. 2 and 3, and their absorption maxima are given in Table II.

By the comparison of the absorption spectra of esters and amides, it becomes clear that the spectrum is very similar to that of the corresponding acid. All show an extremely strong band near 220 m$\mu$, and a weak band ($\pi$-$\pi^*$) at about 310~330 m$\mu$ in dioxane and ethanol solution. As seen in Figs. 2 and 3, a strong band near 230 m$\mu$ appears as a shoulder in dioxane solution in the spectra of (II), ($II_E$), and ($II_{Amide}$).

In general, $\pi$-$\pi^*$ transition is known to produce a bathochromic shift by the solvation

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5) cf. W. West: "Chemical Applications of Spectroscopy," 515(1956).
6) H. Shindo: This Bulletin, **5**, 472(1957).
7) H. P. Stephenson, H. Sponer: J. Am. Chem. Soc., **79**, 2050(1957).
8) N. H. Cantwell, E. V. Brown: *Ibid.*, **74**, 5967(1952).

effect.[9] In this cases, however, a large hypsochromic shift in going from dioxane to water is considered to be due to the formation of a hydrogen bond, with the solvent acting as a proton donor, with the exception of (I) in ethanol solution where the $\pi$-$\pi^*$ transition appears in nearly the same position as that in dioxane solution.

Therefore, it may be possible to consider that (I) exists in a chelated (I′) in dioxane or ethanol solution because the situation seems similar to the case of picolinic acid N-oxide for which a chelated form was recently suggested by reason of the small solvent effect and the presence of absorption maximum in almost the same position as that in picolinic acid itself.[10]

The writer expresses his sincere thanks to Prof. M. Yanai for his encouragement throughout this work and to Mr. H. Shindo of Takamine Research Laboratory, Sankyo Co., Ltd., for recording the infrared spectra and for giving valuable suggestions. The writer also acknowledges a Grant in Aid for Scientific Research from the Ministry of Education.

## Experimental

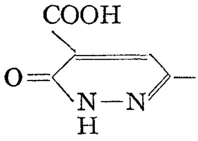
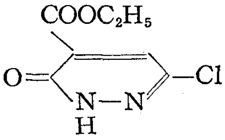
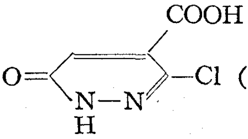
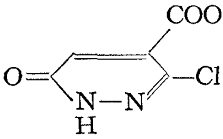
(All m.p.s are uncorrected)

**5-Ethoxycarbonyl-6-chloro-3-pyridazinol (IIE)**—A mixture of 5.8 g. of 5-carboxy-6-chloro-3-pyridazinol (II) in 80 cc. of dehyd. EtOH containing HCl (ca. 15%) was refluxed on a water bath for 5 hrs. and 5.2 g. of white crystals formed after partial evaporation of the solvent and cooling. Recrystallized from water. m.p. 112°. *Anal.* Calcd. for $C_7H_7O_2N_2Cl$: C, 41.48; H, 3.46. Found: C, 41.48; H, 3.63.

**5-Carbamoyl-6-chloro-3-pyridazinol** ($\text{II}_{\text{Amide}}$)—2.7 g. of (IIE) was placed in a sealed tube with dehyd.

TABLE I.

Infrared Frequencies of (I), (II), and their Esters

|  (I) |  (IE) |  (II) |  (IIE) |
|---|---|---|---|
| 685 (6) | | 667 (5) | 692 (6) |
| 713 (5) | 711 (5) | 687 (8) | |
| | | 757 (8) | |
| | | 786 (3) | 777 (5) |
| 793 (5) | | | |
| 802 (6) | 802 (6) | | |
| 838 (6) broad | 825 (4) broad | 856 (5) broad | 816 (3) broad |
| | 868 (4) | | 860 (5) |
| 902 (6) | | | 903 (5) |
| 938 (5) | 927 (5) | 936 (6) | |
| | | | 937 (3) |
| | | 945 (5) | |
| | | 976 (5) broad | |
| | 1017 (6) | | 1016 (5) |
| 1080 (6) | 1080 (7) | 1074 (7) | 1068 (8) |
| | 1115 (4) | | |
| | | 1139 (5) | 1143 (7) |
| | 1199 (5) | | 1198 (5) |
| 1227 (4) | 1238 (4) | | |
| 1300 (6) | 1316 (8) | 1250 (9) | 1289 (9) |
| | | 1307 (5) | |
| 1366 (5) | 1376 (5) | 1380 (6) | 1376 (5) |
| 1419 (8) | 1462 (4) | 1414 (7) | 1449 (4) |
| 1447 (8) | 1479 (5) | 1431 (7) | 1473 (3) |
| 1585 (8) | 1586 (7) | 1577 (9) | 1594 (9) |
| 1658 (8) | 1682 (9) | 1645 (10) | 1695 (10) |
| 1767 (9) | 1706 (9) | 1704 (9) | 1730 (10) |
| | | 2300~2700 (5) | |
| 3050~3130 (6) | 2850~3050 (6) | 2900~3050 (7) | 2860~2920 (6) |

Relative intensities are given in parentheses.

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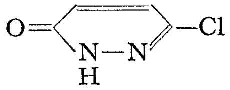
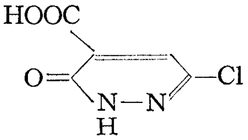
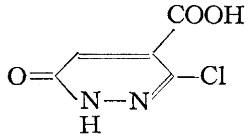
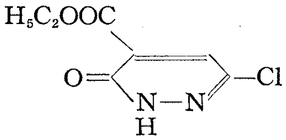
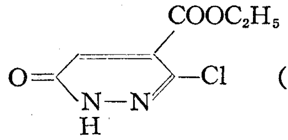
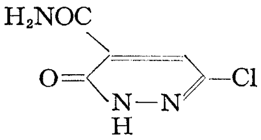
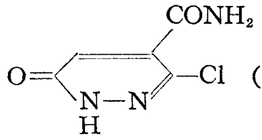
9) G. J. Brealy, M. Kasha: *Ibid.*, **77**, 4462 (1955).
10) N. Hata: Bull. Chem. Soc. Japan, **31**, 255 (1958).

## Table II.

Ultraviolet Absorption Maxima of Some Pyridazine Compounds in Various Solvents

| Solvent | <br>λmax (mμ) | log ε |
|---|---|---|
| Dioxane | 232 | 3.53 |
| | 302～305 | 3.30 |
| EtOH | 213 | 3.81 |
| | 226 | 3.66 |
| | 300 | 3.27 |
| |  (I) | |
| Dioxane | 223 | 3.93 |
| | 323 | 3.49 |
| EtOH | 218 | 4.01 |
| | 325 | 3.43 |
| Water | 213 | 4.10 |
| | 302 | 3.45 |
| |  (II) | |
| Dioxane | 226<br>shoulder | 3.78 |
| | 317 | 3.30 |
| EtOH | 218 | 4.03 |
| | 309～311 | 3.30 |
| Water | 217 | 4.14 |
| | 292 | 3.35 |
| |  (I$_E$) | |
| Dioxane | 221 | 3.86 |
| | 332 | 3.41 |
| |  (II$_E$) | |
| Dioxane | 223<br>shoulder | 3.87 |
| | 320 | 3.27 |
| |  (I$_{Amide}$) | |
| Dioxane | 220 | 3.93 |
| | 326 | 3.48 |
| |  (II$_{Amide}$) | |
| Dioxane | 221<br>shoulder | 3.89 |
| | 310～311 | 3.30 |

EtOH saturated with $NH_3$ and the mixture was heated in a water bath for 1 hr. After partial evaporation of the solvent, the separated crystals were collected and recrystallized from water. Yield, 1.7 g. of m.p. 259~260°(decomp.). *Anal.* Calcd. for $C_5H_4O_2N_3Cl$: C, 34.63; H, 2.31. Found: C, 34.61; H, 2.27.

**Preparation of Metal Chelate Compounds**—A typical procedure of the preparation of metal chelate compound of (I) was as follows: 1.1 moles of metal acetate (Ni, Cu, Mn) in EtOH containing a few drops of AcOH was added to EtOH solution of 1 mole of (I), and the mixture was heated on a water bath for 30 mins. The precipitate that formed was collected, washed with hot water and EtOH, and recrystallized from glacial AcOH.

| | Analysis (%) | | | |
|---|---|---|---|---|
| Formula | Calcd. | | Found | |
| | C | H | C | H |
| $C_{10}H_4O_6N_4Cl_2Ni\cdot 3H_2O$ | 26.12 | 2.18 | 26.23 | 2.26 |
| $C_{10}H_4O_6N_4Cl_2Cu\cdot {}^1/_2H_2O$ | 28.60 | 1.19 | 29.04 | 1.30 |
| $C_{10}H_4O_6N_4Cl_2Mn\cdot 2H_2O$ | 27.40 | 1.83 | 26.89 | 1.86 |

Infrared spectra were measured with a Perkin-Elmer Model 21 double-beam spectrophotometer equipped with a NaCl prism and the ultraviolet spectra were obtained with a Shimadzu spectrophotometer Type QB-50 with 1-cm. quartz cells.

## Summary

Infrared and ultraviolet absorption spectra of 4- and 5-carboxy-6-chloro-3-pyridazinol (I and II) and of their esters ($I_E$ and $II_E$) were measured. It was found that (I) exists in a chelated form in its crystalline state and that (II) forms an intermolecular hydrogen bonding. Metal chelate compounds of (I) with nickel, copper, or manganese were reported. The preparation and ultraviolet absorption spectrum of 5-carbamoyl-6-chloro-3-pyridazinol ($II_{Amide}$) were described.

(Received May 15, 1958)

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UDC 547.864.6—156 : 541.486 : 541.651

# 112. **Yoshinori Kidani**: Studies on Metal Chelate Compounds of Phenazine Derivatives. I. Spectrophotometric Studies on Copper Chelate Compounds of 1-Hydroxyphenazine and its Di-N-oxide.

(*International Christian University**)

Metal chelates were originally developed in the field of analytical chemistry and they recently have begun to play a very important rôle in the field of pharmaceutical sciences. One of the main reasons is that an enzyme is a kind of polymolecular chelate compounds and it has been found that chelating agents and metal chelates themselves are very closely related to the growth-inhibitory action of bacteria.

For example, 8-hydroxyquinoline (oxine), which had originally been used as an analytical reagent, shows antibacterial action and, inversely, some of the chemotherapeutics and antibiotics were found to be chelating agents.

Albert, Rubbo, and others[1] reported studies on oxine derivatives and they showed that metal chelates of organic compounds have a close relation to antibacterial action. When the growth-inhibitory action against *Staphylococcus aureus* was examined by adding a trace of iron or copper to oxine solution, the action increased markedly compared with that without the addition of metals. When hydroxyl in oxine was alkylated, or, when hydroxyl groups in oxine isomers are blocked except at the 8-position, they have no chelating ability and therefore such a compound did not show any effect from metals. From these results,

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* 1500 Osawa, Mitaka-shi, Tokyo (喜谷喜徳).

[1] A. Albert, D. Magrath: J. Biochem., **41**, 534(1947); A. Albert, S. D. Rubbo, R. J. Goldace, B. G. Balfour: Brit. J. Exptl. Pathol., **28**, 69(1947); S. D. Rubbo, A. Albert, M. I. Gibson: *Ibid.*, **31**, 4125(1950).