UDC 547.861.8 : 547.826.1

32. **Shigeru Yoshida and Motoji Asai**: Infrared Spectra of Pyrazine- and Pyridine-carboxylic Acid and Their Derivatives.[1]

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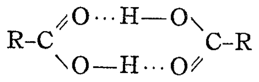
There are numerous works on the infrared absorption spectra of carboxylic acids, the representatives among them being the works of Flett,[2] Hadži and Sheppard,[3] and Corish.[4] However, most of these concerns aliphatic carboxylic acid and benzoic acid, and no detailed study has been made on the infrared absorption spectra of nitrogenous heterocyclic carboxylic acids like pyrazine- and pyridine-carboxylic acids. Therefore, detailed examination of infrared spectra of such carboxylic acids and their deuterated analogs was carried out.

According to the work of Sheppard and others, ordinary carboxylic acids possess characteristic absorptions as listed in Table I and are present as a dimer (I) in the solid.

Table I. Characteristic Absorptions of Ordinary Carboxylic Acids (cm^{-1})

	Ordinary acid		Deuterated acid
ν_{OH}	3000	ν_{OD}	3200
Main satellite bands	2650		2100
$\nu_{C=O}$	1720±30		1720±30
$\delta_{OH(\text{in-plane})}$	1420±20	$\delta_{OD(\text{in-plane})}$	1350±50
ν_{C-O}	1300±15	ν_{C-O}	1050±10
$\delta_{OH(\text{out-of-plane})}$	935±15	$\delta_{OD(\text{out-of-plane})}$	675±25


(I)

The infrared spectra of pyridine- and pyrazine-carboxylic acids are entirely different from those of the foregoing carboxylic acids (Table II and Fig. 1).

It may be noted from Fig. 1 that there is a broad absorption centered around 2450 and 1900 cm^{-1} in these heterocyclic carboxylic acids. Such broad absorptions are present around 2451 and 1894[5] cm^{-1} in pyrazine-carboxylic acid, around 2408 and 1960~1850 cm^{-1} in isonicotinic acid, around 2450 and 1930 cm^{-1} in nicotinic acid, around 2152 and 2062~1850 cm^{-1} in picolinic acid, and around 2450 and 1880 cm^{-1} in 2-chloroisonicotinic acid. These absorptions are absent in ordinary carboxylic acids. The conspicuous absorption of O-H out-of-plane deformation vibration at around 935 cm^{-1} is entirely absent in these heterocylic carboxylic acids. In order to clarify the characteristic absorptions of these carboxylic acids, the acids were deuterated and shifts of absorption by deuteration were examined. Results of this examination are listed in Table II and characteristic differences from ordinary carboxylic acids are as follows:

(a) The broad absorption band with a peak at 2450 cm^{-1} shifts to around 1900 cm^{-1} by deuteration but the broad absorption band with a peak at 1900 cm^{-1} does not.

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* Nishi-Shinagawa, Shinagawa-ku, Tokyo (吉田 茂, 浅井素次).

1) Paper presented at the 4th Symposium on Infrared and Raman Spectra in Tokyo, October 12, 1957.

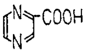
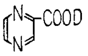
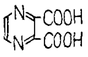
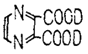
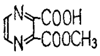
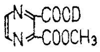
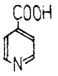
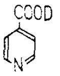
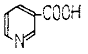
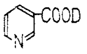
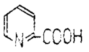
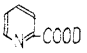
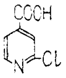
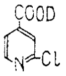
2) M. St. C. Flett: J. Chem. Soc., **1951**, 962.

3) D. Hadži, N. Sheppard: Proc. Roy. Soc.(London), A, **216**, 274(1953); Spectrochim. Acta, 8, 249 (1956).

4) P. J. Corish, D. Chapman: J. Chem. Soc., **1957**, 1746; cf. R. G. Sinclair, A. F. McKay, R. N. Jones: J. Am. Chem. Soc., **74**, 2570(1952).

5) A brief report has been made on the absorption of pyrazinic acid at 1880 cm^{-1} (I. A. Solomons: J. Am. Chem. Soc., **75**, 679(1953)).

Table II. Characteristic Frequencies of Pyrazinic Acid, Pyridinecarboxylic Acid, and their Derivatives (in Nujol)

Compounds	3500~1800 cm^{-1} region	$\nu_{C=O}$	ν_{C-O}	$\delta_{OH(OD)}$(in-plane)	$\delta_{C\genfrac{}{}{0pt}{}{O}{O}}$
	2800(br.), 2602, 2451(br.), 1894(br.)	1718(s. br.)	1273	1311	710
	2198, 2170, 1925(br.), 1870(br.)	1712(s. br.)	1080	1342	
	3280, 2610, 2460, 1900~1800	1760, 1715, 1690	1276, 1259	1357	693
	2445(s.), 2150(br.), 2000(br.)	1755, 1722, 1690	1035, 1022	1367	
	2565, 2495	1745, 1712	1260	1302	
	2150, 1980	1736, 1703	1035, 1022	1337	
	3200~2700(br.), 2408(br.), 1960~1850	1712	1300	1338	698
	2350, 1960~1850(br.)	1707	1052	1346	
	3100, 2900, 2850, 2450(br.), 1930(br.)	1710	1300	1320	680
	2448, 2200, 1925(br.), 1850(br.)	1695	1082	1342	
	2570(br.), 2152, 2062~1850	1720(br.), 1660(w.), Nujol 1720(w.), 1660(s.), KBr	1310		683
	2045(br.), 1890	1700, 1664	1065	1367 1351	
	2765(br.), 2450(br.), 1880(br.)	1715	1263	1289	667
	2150(br.), 1960(br.), 1890(br.)	1712	1056	1342	

Therefore, the band at around 1900 cm^{-1} is overlapped by deuteration, appearing as a broad absorption or a doublet.

(b) The absorption band of O–H in-plane deformation vibration is present in a lower frequency region than that of ordinary carboxylic acids, appearing at 1340~1300 cm^{-1}, and shifts to 1360~1340 cm^{-1} by deuteration. This absorption of O–H in-plane deformation and its shift are entirely specific in heterocyclic carboxylic acids.

(c) The absorption band at 1310~1260 cm^{-1} for C–O stretching vibration shifts to 1080~1020 cm^{-1} by deuteration and this displacement is the same as that in ordinary carboxylic acids.

(d) There is no absorption band for O–H out-of-plane deformation and its shift cannot be observed by deuteration.

(e) The absorption band for $C\genfrac{}{}{0pt}{}{O}{O}$ is present at around 700 cm^{-1}, same as in ordinary carboxylic acids.

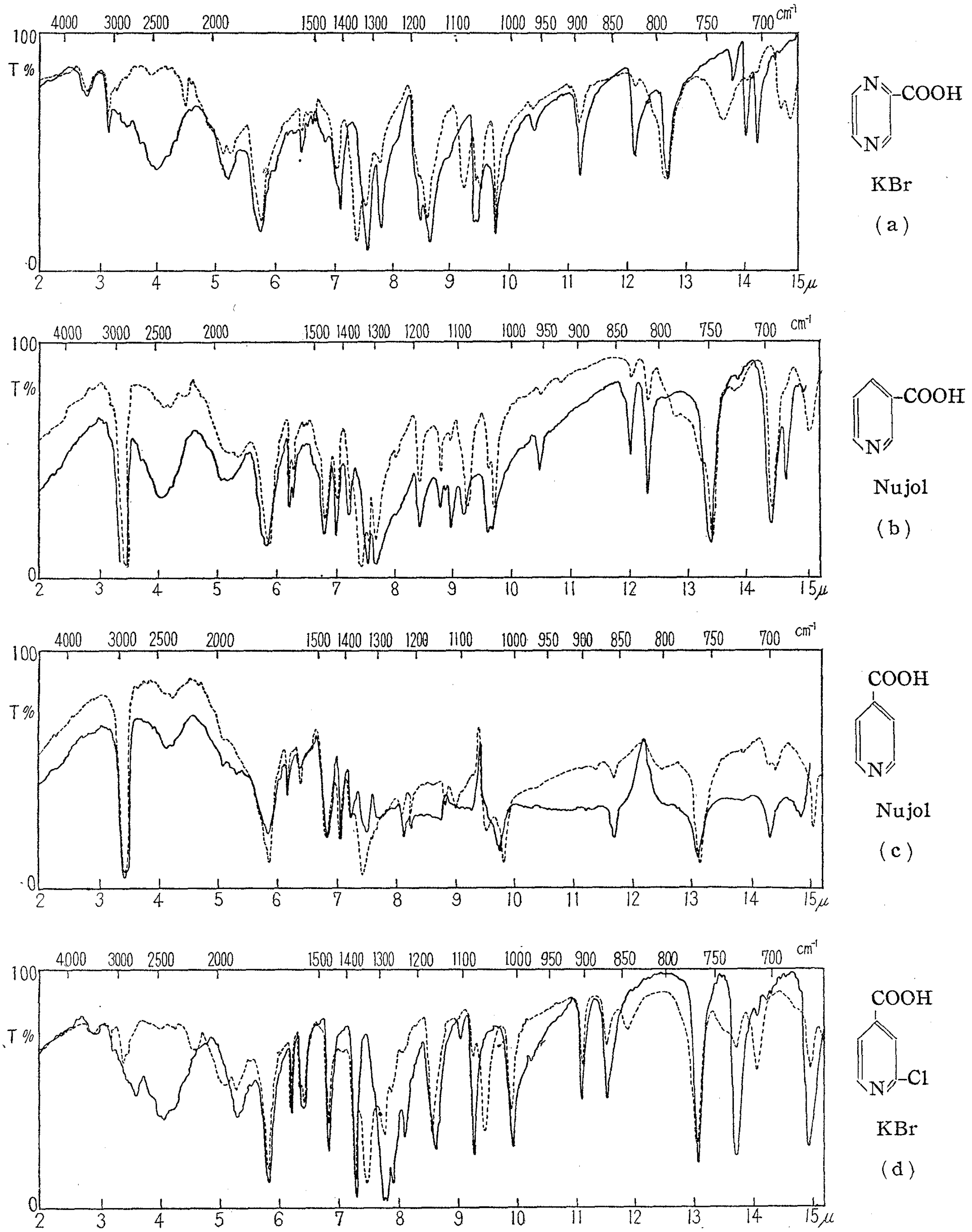


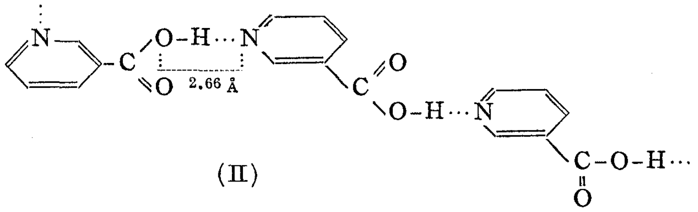
Fig. 1.

(a) Pyrazinic acid
(b) Nicotinic acid
(c) Isonicotinic acid
(d) 2-Chloroisonicotinic acid

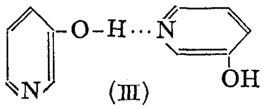
(a), (d) KBr —— Normal acid
(b), (c) Nujol ------ Deuterated acid

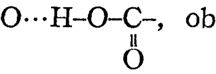
The most striking feature of the foregoing differences is the fact that one of the absorptions at 2450 and 1950 cm^{-1} shifts by deuteration while the other does not, the shift of O–H in-plane absorption being from 1340∼1300 cm^{-1} to 1360∼1340 cm^{-1}, and the absence of absorption for O–H out-of-plane deformation mode.

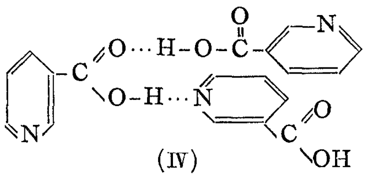
Pyrazine- and pyridine-carboxylic acids exhibit such characteristic absorptions as described above and these cannot be interpreted by the known structure (I) of a dimer. Of these carboxylic acids, crystal structure of nicotinic acid has been examined in detail by X-ray diffraction[6] and nicotinic acid is known to form the following intermolecular hydrogen bond of N···H–O– type (II).


(II)

Result of X-ray diffraction analysis of nicotinic acid enabled the explanation of the result of infrared spectral absorptions, and isonicotinic acid is thought to have the same structure. The broad absorptions around 2450 and 1900 cm^{-1} are assumed to be due to the hydrogen bonding between OH in carboxylic acid and nitrogen in the ring. This absorption by hydrogen bonding seems probable from the fact that other compound, such as 3-hydroxypyridine, also exhibits the same absorption for hydrogen bonding by forming a structure of the type (III).[7]


(III)

There are the works of Nakamoto, Pimentel, and others[8] on the hydrogen bonding of N···H–O type. According to studies by Wright,[6] the distance between nitrogen and oxygen is 2.66 Å and this does not agree with the value calculated from the two broad absorption bands appearing at 2450 and 1900 cm^{-1}. Since the band of C=O stretching mode is not sharp but generally broad, it may be assumed that the looser dimeric bonding (IV) by bonding of  $-\mathrm{C{=}O\cdots H{-}O{-}\underset{\underset{O}{\|}}{C}{-}}$, observed in ordinary molten carboxylic acids, is also present to a small extent.


(IV)

The characteristic absorptions of pyridine- and pyrazine-carboxylic acids can easily be explained by hydrogen bonding structure of the type (II). According to the work of Corish and others,[9] the dimer (I) breaks up on melting to take a looser-type hydrogen bonding such as that of the structure (I′), and the absorptions at 1430 cm^{-1} for O–H in-plane deformation and at 930 cm^{-1} for O–H out-of-plane deformation disappear. Farmer[10] showed that benzoic acid was adsorbed principally as a monomer on

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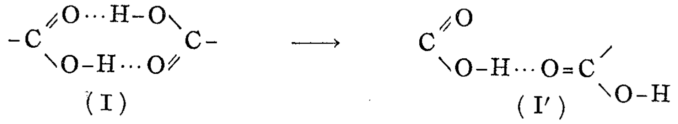
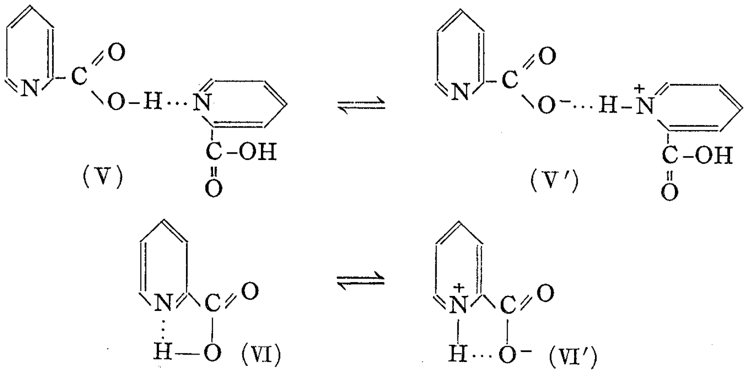
6) W. B. Wright: Acta Cryst., **6**, 305(1952).
7) H. Shindo: Private communication. Data will be published at a later date.
8) a) K. Nakamoto, *et al.*: J. Am. Chem. Soc., **77**, 6480(1955); b) G. C. Pimentel, C. H. Cederholm: J. Chem. Phys., **24**, 639(1950); c) D. G. Cannon: Spectrochim. Acta, **10**, 341(1958).
9) P. J. Corish, W. H. Davison: J. Chem. Soc., **1955**, 2431.
10) V. C. Farmer: Spectrochim. Acta, **8**, 374(1957).

alkali halide so that spectral changes result in the shift of absorption of O–H in-plane deformation at 1424 cm^{-1} to 1383 cm^{-1} and disappearance of the absorption for O–H out-of-plane deformation, while the O–H in-plane deformation absorption also disappears in liquid state.[4)] These facts agree well with the above results of the foregoing carboxylic acids. For example, the absorption for O–H in-plane deformation in these carboxylic acids shifts to a lower frequency region by taking the structure like (II) and there is no absorption for O–H out-of-plane deformation. It is still obscure why the absorption for OH in-plane deformation shifts by deuteration from 1340∼1300 cm^{-1} to 1360∼1340 cm^{-1}, but it may be due to the coupling of δ_{OH} and ν_{C-O}. The displacement factor is ca. 0.98 in this case.



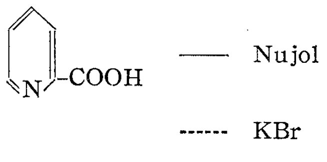
In the case of picolinic acid, two kinds of structure are possible, the intermolecular hydrogen bonding (V) and intramolecular hydrogen bonding (VI).



The C=O absorption of picolinic acid differs from that of isonicotinic, nicotinic, or pyrazinecarboxylic acid and the absorptions appear at 1720 (br.) and 1660 (w) cm^{-1} in Nujol, and at 1720 (w) and 1660 (s) cm^{-1} in KBr (Fig. 2). The absorption at 1660 cm^{-1} is in a rather low frequency for $\nu_{C=O}$ by hydrogen bonding, and is assumed to be the absorption of a carboxylic ion. This absorption is that of C=O stretching vibration of the proton charge transfer state in hydrogen bonding. In (VI), the hydrogen

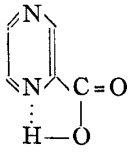
Fig. 2.

Infrared Spectra of Picolinic Acid

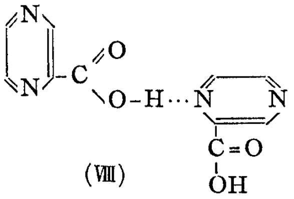


bonding results in formation of a five-membered ring, causing resonance, and proton charge transfer takes place more easily than in (V), so that picolinic acid takes the hydrogen-bonding structure[11] (VI) which converts to (VI′) by transfer of proton charge when measured in KBr and the absorption at 1660 cm^{-1} appears in strong intensity. In the case of isonicotinic and nicotinic acids, there is no absorption of carboxyl ion at around 1660 cm^{-1} and therefore there is no need to consider the structure (II) with transfer of proton charge.

Intramolecular hydrogen bonding structure (VII) can also be considered for pyrazinecarboxylic acid as in the case of picolinic acid. In this case, the band around 2450 and 1950 cm^{-1} in pyrazinecarboxylic acid is extremely similar to that of nicotinic and isonicotinic acids, and, since the basicity of nitrogen in the pyrazine ring is weaker than that in picolinic acid, the structure (VIII) with intermolecular hydrogen bonding would seem possible but, as will be shown later, there are two absorptions, entirely identical with those of picolinic acid, when measured in chloroform or dioxane solution. Therefore, it seems appropriate to assume the structure (VII) with intramolecular hydrogen bonding.



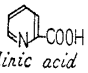
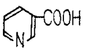
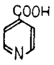
(VII)



(VIII)

The absorptions for $\nu_{C=O}$ for pyridine- and pyrazine-carboxylic acids in chloroform and dioxane solutions are listed in Table III and in Fig. 3. As is clear from Table III, picolinic acid and pyrazinecarboxylic acid having carboxyl in the position *alpha* to ring nitrogen show two absorption bands for $\nu_{C=O}$ and one of them is in a higher frequency region. In chloroform solution, these appear at 1776 (s) and 1718 (w) cm^{-1} in picolinic acid, and the absorption at 1718 cm^{-1} almost disappears on dilution. In dioxane solution, the absorption at 1722 cm^{-1} is stronger than that in chloroform. The absorption band in a higher frequency region in chloroform and dioxane solution in both picolinic and pyrazinic acids is due to a monomer, a state in which the intramolecular hydrogen

Table III. Carbonyl Stretching Frequencies

Compounds	$\nu_{C=O}$ (cm^{-1})	
	Chloroform	Dioxane
 *picolinic acid*	1776 (s) 1718 (w)	1761 (s) 1722 (m)
 *pyrazinic acid*	1773 (s) 1724 (m)	1754 (m) 1730 (m)
 *nicotinic acid*	1729	1730
 *isonicotinic acid*	1736	1733

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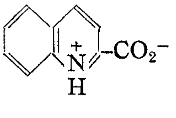
[11] Intramolecular hydrogen bonding (VI) has recently been recognized through ultraviolet absorption spectrum. cf. N. Hata : Bull. Chem. Soc. Japan, **31**, 255(1958). Flett (*loc. cit.*) gave the structure of  to quinaldic acid from the weakness of its absorption at around 1700 cm^{-1}. A detailed discussion on quinolinecarboxylic acid will be made in the following report.

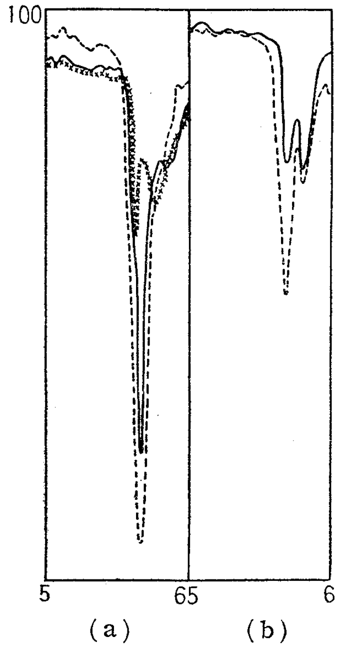


Fig. 3.
Infrared Spectra of Picolinic Acid
and Pyrazinic Acid

a) Chloroform solution

—— Picolinic acid (cell-thickness, 0.1 mm.)

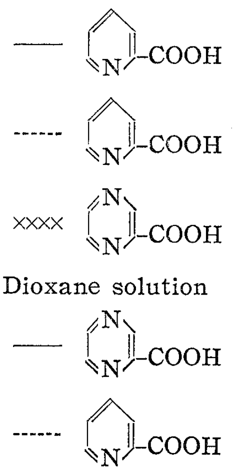
------ Picolinic acid (cell-thickness, 1 mm.)

xxxx Pyrazinic acid (cell-thickness, 0.1 mm.)

b) Dioxane solution

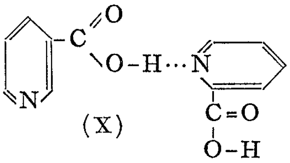
—— Pyrazinic acid

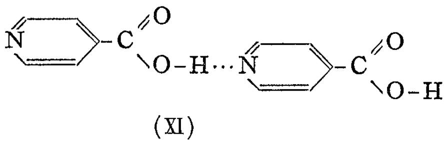
------ Picolinic acid



bonding of N···H–O– has been loosened. The absorption band in the lower frequency is thought to be due to intramolecular hydrogen bonding (Ⅵ and Ⅶ). The fact that the band in the higher frequency region is due to a monomer is clear, since dilution of a chloroform solution results in weakening of the band in lower frequency region and intensification of that in the higher frequency region.

The absorption of $\nu_{C=O}$ in nicotinic and isonicotinic acids is considered to be due to intramolecular hydrogen bonding (X and XI),12) since this absorption in dioxane solution is almost the same as that in chloroform solution. The absorption of the monomer of picolinic acid and pyrazinic acids in dioxane solution shifts to a lower frequency region and this is thought to be due to hydrogen bonding between the monomer and dioxane.


(X)


(XI)

In these carboxylic acids, the absorption band for $\delta_{\mathrm{C}\begin{smallmatrix}\nearrow \mathrm{O}\\ \searrow \mathrm{O}\end{smallmatrix}}$ is present in the region of 700~660 cm^{-1} and this disappears by deuteration.

In order to examine the appropriateness of the foregoing considerations, a more detailed discussion will be made on the absorptions of pyridinecarboxylic acid hydrochloride and 2,6-disubstituted isonicotinic acid derivatives.

a) Infrared Absorption Spectrum of Pyridinecarboxylic Acid Hydrochloride: Pyridinecarboxylic acid hydrochloride has no lone-pair electrons on the ring nitrogen and cannot form intramolecular or intermolecular hydrogen bond. Therefore it would form a dimer like that of benzoic acid and probably show absorption similar to ordinary acids discussed by Hadži and others.3) These points were examined by preparation of hydrochlorides of various pyridinecarboxylic acids and deuteriochlorides of these deuterated analogs. As indicated in Table Ⅳ and Fig. 4, they all showed absorptions similar to those of ordinary carboxylic acids but O–H out-of-plane deformation absorption was extremely weak.

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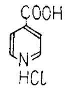
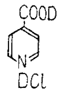
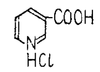
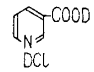
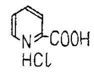
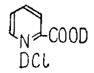
12) As a similar structure, there is a study on the structure of acetic acid and pyridine in chloroform solution. cf. G. M. Barrow: J. Am. Chem. Soc., 78, 5802(1956).

Table IV. Characteristic Frequencies of Pyridinecarboxylic Acid Hydrochloride (in Nujol)

Compound	3500~1800 cm^{-1} region	$\nu_{C=O}$	$\delta_{OH(OD)(in\text{-}plane)}$	ν_{C-O}	$\delta_{OH(out\text{-}of\text{-}plane)}$
	2700(s.), 2595(s.), 2445(s.), 2065, 1982, 1925, 1880	1730	1410	1260	902(m.)
	2175(sh.), 2110(s.), 1960(s. br.)	1715	1352	1041	
	2685, 2577, 2330(s. br.), 2200, 2070, 2000(w.), 1930(w.)	1712	1408	1289	980(w.)
	2405, 2327(s.), 2200, 2100, 1893(s.), 1780(s.)	1705	1356	1041	
	3100, 2744(s.), 2632(s.), 2488(s.), 2080(w.), 2025(w.), 1970(w.), 1850(w.)	1745	1410	1256	956(m.)
	2273(s.), 2103, 2000(s.)	1730	1370	1026	

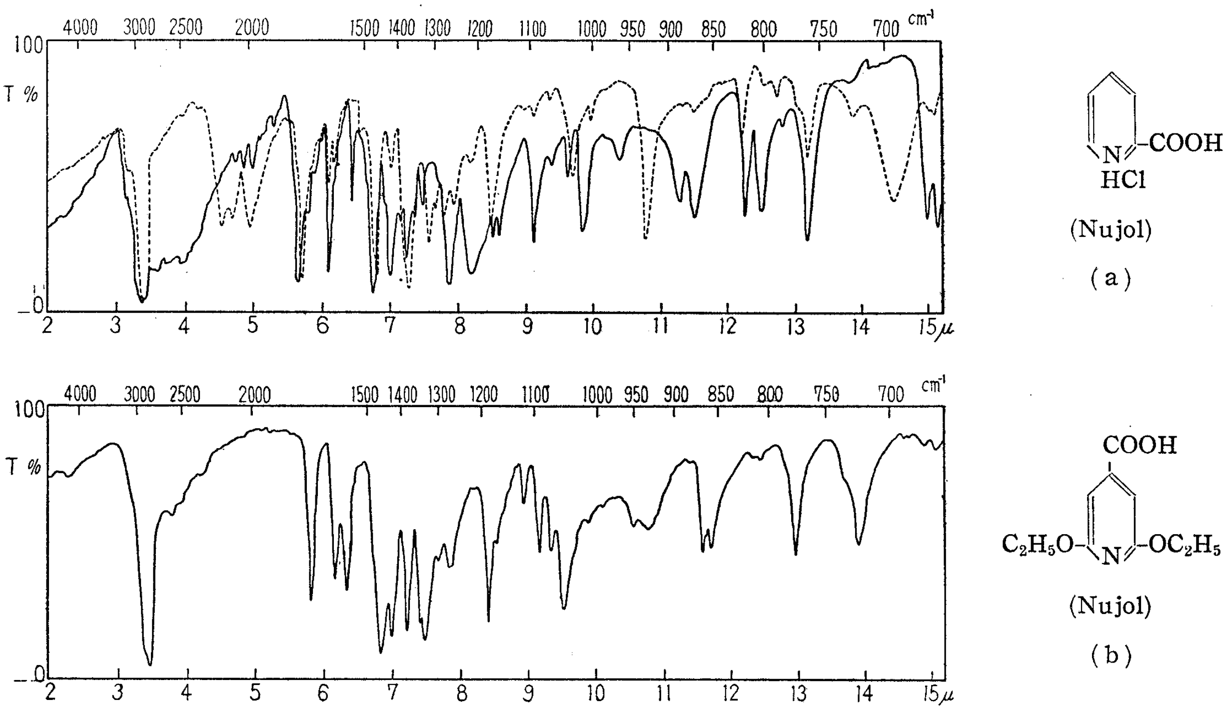


Fig. 4.

a) Picolinic acid hydrochloride ------ Deuterated acid deuteriochloride
b) 2,6-Diethoxyisonicotinic acid —— Normal acid

b) Infrared Absorption Spectrum of 2,6-Disubstituted Isonicotinic Acid: Infrared absorption spectra were examined with 2,6-disubstituted isonicotinic acids listed in Table V. These compounds possess a large substituent in the position *ortho* to ring nitrogen and the formation of hydrogen bonding between ring nitrogen and OH is thought to be difficult by steric hindrance.13) This means that there would be no

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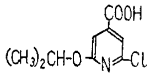
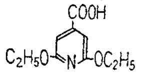
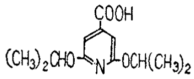
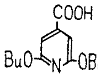
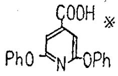
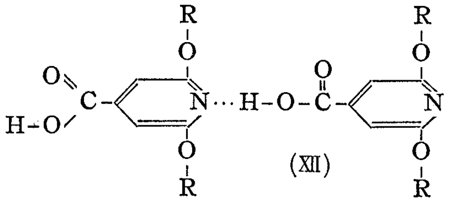
13) Examples of the presence of alcohols and phenols as monomers by steric hindrance are found in the following works: F.A. Smith, E.C. Creitz: J. Research Natl. Bur. Standards, **46**, 145 (1951); N.D. Coggeshall: J. Am. Chem. Soc., **69**, 1620(1947); W.C. Sear, L.J. Kitchen: J. Am. Chem. Soc., **71**, 4110(1949).

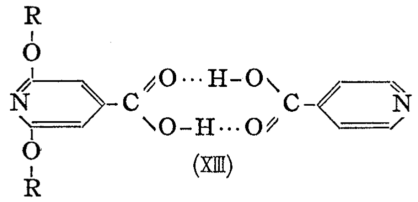
TABLE V. Absorption Frequencies of Isonicotinic Acid Derivatives (cm^{-1})

Compounds	3000~2200 cm^{-1} region	$\nu_{C=O}$	$\delta_{OH(in-plane)}$	ν_{C-O}	$\delta_{OH(out-of-plane)}$	$\delta_{C\langle^{O}_{O}}$
	3000, 2600, 2350	1710 1736(D)	1425	1325, 1308	937	710
	2990, 2630, 2525, 2350	1712 1712(chl.) 1736(D)	1426	1346, 1334	950, 930	720
	3000, 2630, 2520, 2340	1709 1734(D)	1426	1336, 1322	946	726
 ※	2650, 2540, 2350	1709 1733(D)	1425	1340	944	720
 ※	2760, 2620, 2460	1739 1739(chl.) 1736(D)	1420	1230	905	760

* Nujol mull, others in KBr
(chl.) Chloroform (D) Dioxan solution.

hydrogen bond of the type (XII) seen in isonicotinic acid in this case and a dimer (XIII) seen in ordinary carboxylic acid would probably be indicated.


(XII)


(XIII)

Actually, these substituted isonicotinic acids show absorptions for O–H in-plane deformation, C–O stretching, and OH out-of-plane deformation, as in ordinary carboxylic acids, as shown in Table V and Fig. 4–b, and this fact indicates that they take the dimeric structure (XIII). These carboxylic acids show the absorption for $\nu_{C=O}$ at around 1736 cm^{-1} in dioxane solution and this indicates that, although isonicotinic acid takes the structure of an intermolecular hydrogen bonding (XI) in dioxane solution, these substituted carboxylic acids become a monomer and take the structure of an intermolecular hydrogen bonding with dioxane. These carboxylic acids exist as a dimer in chloroform and show the absorptions identical with those of a solid. It should especially be noted that $\nu_{C=O}$ of 2,6–diphenoxyisonicotinic acid appears at 1739 cm^{-1} in Nujol and chloroform, and at 1736 cm^{-1} in dioxane, and this seems to suggest that this compound is present as a monomer in both solid and in solution.

The authors express their gratitude to Mr. M. Matui, the Director of this Laboratory, for kind encouragement. They are indebted to Messrs. H. Shindo and O. Amakasu for their help in infrared spectral measurements, and to Mrs. Ishioka for her help in arrangement of data.

Experimental

Infrared absorption spectra were measured with the Perkin-Elmer Model 21 spectrophotometer with NaCl prism. All carboxylic acids were measured as Nujol mull or KBr pellet. All the acids were sparingly soluble in $CHCl_3$ or dioxane so that their saturated solution was used. Conditions of measurement are indicated on each Table and Chart.

All the compounds used were those available in the laboratory and the isonicotinic acid derivatives listed in Table V were prepared by Okajima and Seki[14] of this Laboratory. Heavy water used for deuteration was a product of Hydro Norsk, of purity 99.77%. For deuteration, each carboxylic acid was dissolved in 3~5 volumes of heavy water, and insoluble ones were dissolved in

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[14] Y. Okajima, I. Seki: Yakugaku Zasshi, **73**, 845(1953).

dioxane. Deuteriochloride of deuterated pyridinecarboxylic acids was prepared by decomposition of the chloride of each carboxylic acid with heavy water and distillation of heavy water *in vacuo.*

Summary

Infrared absorption spectra of pyridine- and pyrazine-carboxylic acids have following characteristic absorptions.

1) There are broad absorption bands with peaks at 2450 and 1900 cm^{-1}. The former shifts to around 1900 cm^{-1} by deuteration but the latter does not.

2) Absorptions for O-H in-plane deformation and C-O stretching vibration are present at 1340∼1300 cm^{-1} and 1310∼1260 cm^{-1}, and shift respectively to 1360∼1340 cm^{-1} and 1080∼1020 cm^{-1} by deuteration.

3) There is no absorption band for O-H out-of-plane deformation and that for $\delta_{\mathrm{C}\langle^{\mathrm{O}}_{\mathrm{O}}}$ is present at around 700 cm^{-1}.

These characteristic absorptions can be explained by the structure (II) with intramolecular hydrogen bonding for nicotinic and isonicotinic acids, and the structures (VI and VII) with intramolecular hydrogen bonding for picolinic and pyrazinic acids possessing a carboxyl in the position *alpha* to ring nitrogen. The hydrochloride of pyridinecarboxylic acids and 2,6-disubstituted isonicotinic acid derivatives possess the structure (II) same as that of ordinary carboxylic acids.

(Received July 22, 1958)

〔Added in proof〕 A report on the spectra of benzoic acid and deuterated benzoic acid mixed with pyridine (1 : 1) became available during printing of this paper (D. Hadži, M. Pintar : Spectrochim. Acta, **12**, 162(1958)) and following points listed by these workers are similar to the results described in the foregoing pages.

1) The band due to OH out-of-plane vibration near 900 cm^{-1} does not appear.
2) The band near 1420 cm^{-1} is not detectable.
3) The band at 1275 cm^{-1} shifts to 1330 cm^{-1} on deuteration.

UDC 547.734

33. **Ryuichi Kimura and Takahiro Yabuuchi** : Studies on Thiophene Derivatives. II.[1] Optical Resolution of 3-Piperidino-1,1-di(2-thienyl)-1-butene.

(*Scientific Research Institute for Practical Life, University of Kyoto**)

In 1950, dithienyl-amino-butene derivatives were synthesized by Adamson and Green,[2,3] and their potent analgesic and antispasmodic actions were demonstrated. Of these derivatives, *dl*-3-piperidino-1,1-di(2-thienyl)-1-butene hydrochloride (*dl*-PBN-HCl) gave especially potent antitussive action by "Coughing Dog method" as reported by Kasé.[4]

This compound was also synthesized by the present authors and was recognized in the clinical application as a new potent antitussive, which was effective in a dose of

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* Yoshida-Konoe-cho, Sakyo-ku, Kyoto (木村隆一, 藪内隆弘).

[1] Part I : This Bulletin, **6**, 159(1958).

[2] D. W. Adamson, A. F. Green : Nature, **165**, 122(1950).

[3] D. W. Adamson, W. H. Duffin, A. F. Green : *Ibid.*, **167**, 153(1951).

[4] Y. Kasé, *et al.* : This Bulletin, **3**, 394(1955).