U.D.C. 547.821.4 : 544.621

86. **Hideyo Shindo**: Studies on the Infrared Spectra of Heterocyclic Compounds. III.[1] Infrared Spectra of Alkylpyridine 1-Oxides.

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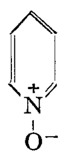
Pyridine 1-oxide and its derivatives show chemical properties so vastly different from those of the corresponding pyridines, the reactivity of their 4-position was studied by Ochiai and his school[2] on a wide scale, and the result of such studies has offered one of important means in the syntheses of pyridine derivatives.[3] In 1940, Linton[4] indicated, from the fact that the value of the dipole moment of pyridine 1-oxide was far lower than that calculated from the group moment of the N-oxide function and the moment of pyridine, that there was a contribution of structures (II) to (IV) in the resonance system of pyridine 1-oxide. This fact is now used to explain the more facile substitution of electrophilic reagents in pyridine 1-oxide than in pyridine and the occurrence of such substitutions in the 4- and 2-positions. More recently, further physicochemical studies, mainly through ultraviolet absorption and pKa, have been carried out by Hirayama and Kubota,[5~8] Jaffé, *et al.*,[9~11] and Ito, *et al.*,[12] all proving stabilization of the compound by the contribution of such mesomeric structures.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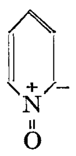
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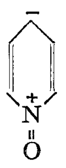
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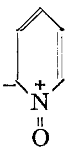
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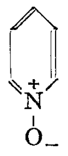
(V)

However, practically no examination has been made of their infrared spectra and characteristic absorption bands for the N-oxide group has not been clearly established as yet. Costa, *et al.*[13] assigned the absorption at around 1250 cm^{-1} in some 4-substituted pyridine 1-oxides for their N-O stretching frequency, while Ito, *et al.*[14] assigned for it the absorption at 830 cm^{-1} in pyridine 1-oxide, but neither have sufficient basis.

In the present series of experiments, infrared spectra of pyridine 1-oxide and 15 kinds of its alkyl derivatives were measured, characteristic absorption band for the N-oxide group was established by comparing these spectra with those of the corresponding alkylpyridines reported earlier,[15] and the effect of ring substituents on the N-O frequency and the effect of the introduction of N-oxide function on the ring vibration are

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1) Part II. H. Shindo, S. Tamura: This Bulletin, **4**, 292(1956).
2) E. Ochiai: J. Org. Chem., **18**, 534(1953).
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11) H. H. Jaffe: *Ibid.*, **77**, 4451(1955).
12) M. Ito, N. Hata: Bull. Chem. Soc. Japan, **28**, 260(1955).
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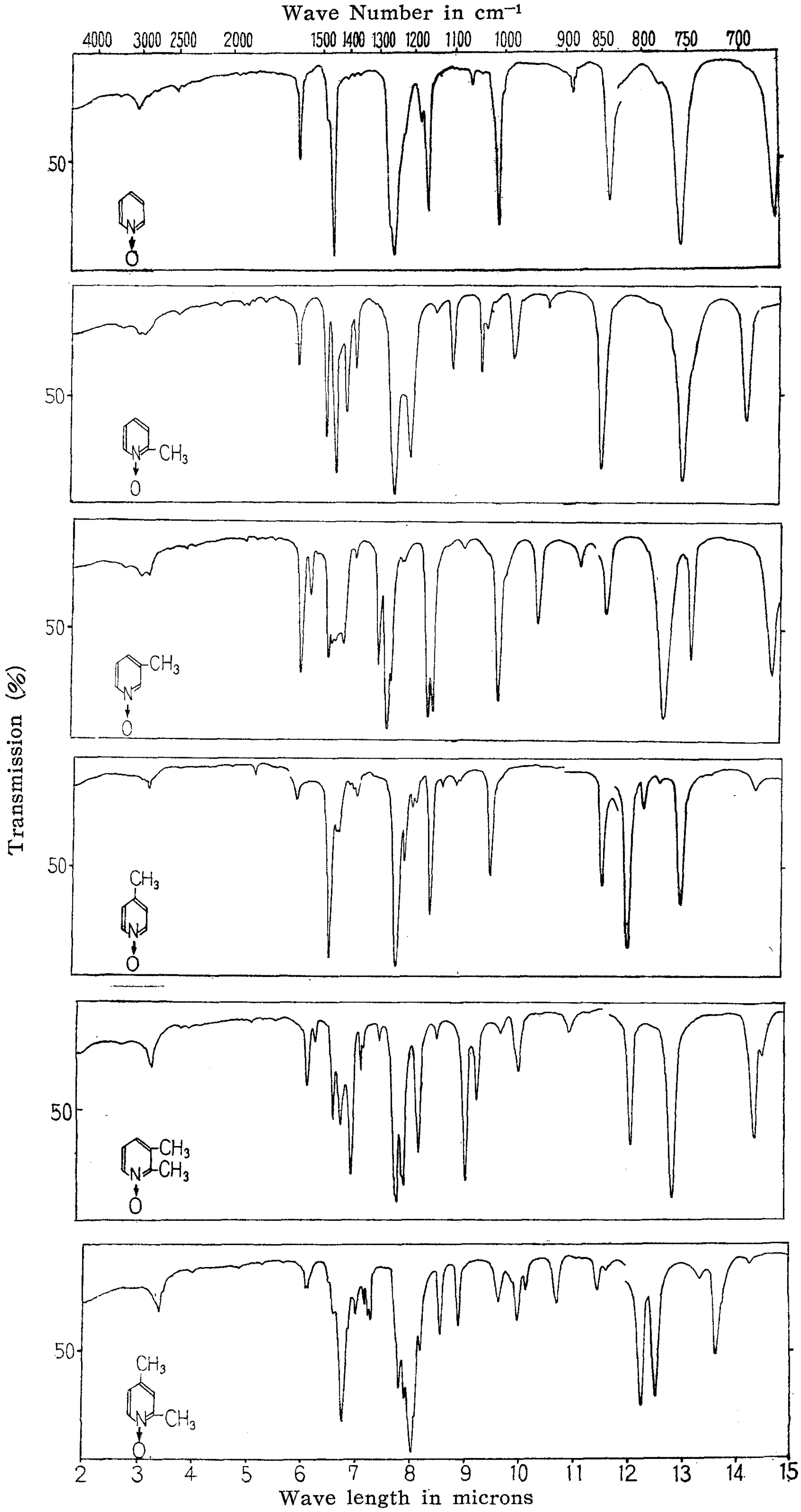

Fig. 1. Infrared Absorption Spectra of Alkylpyridine 1-Oxides (1)

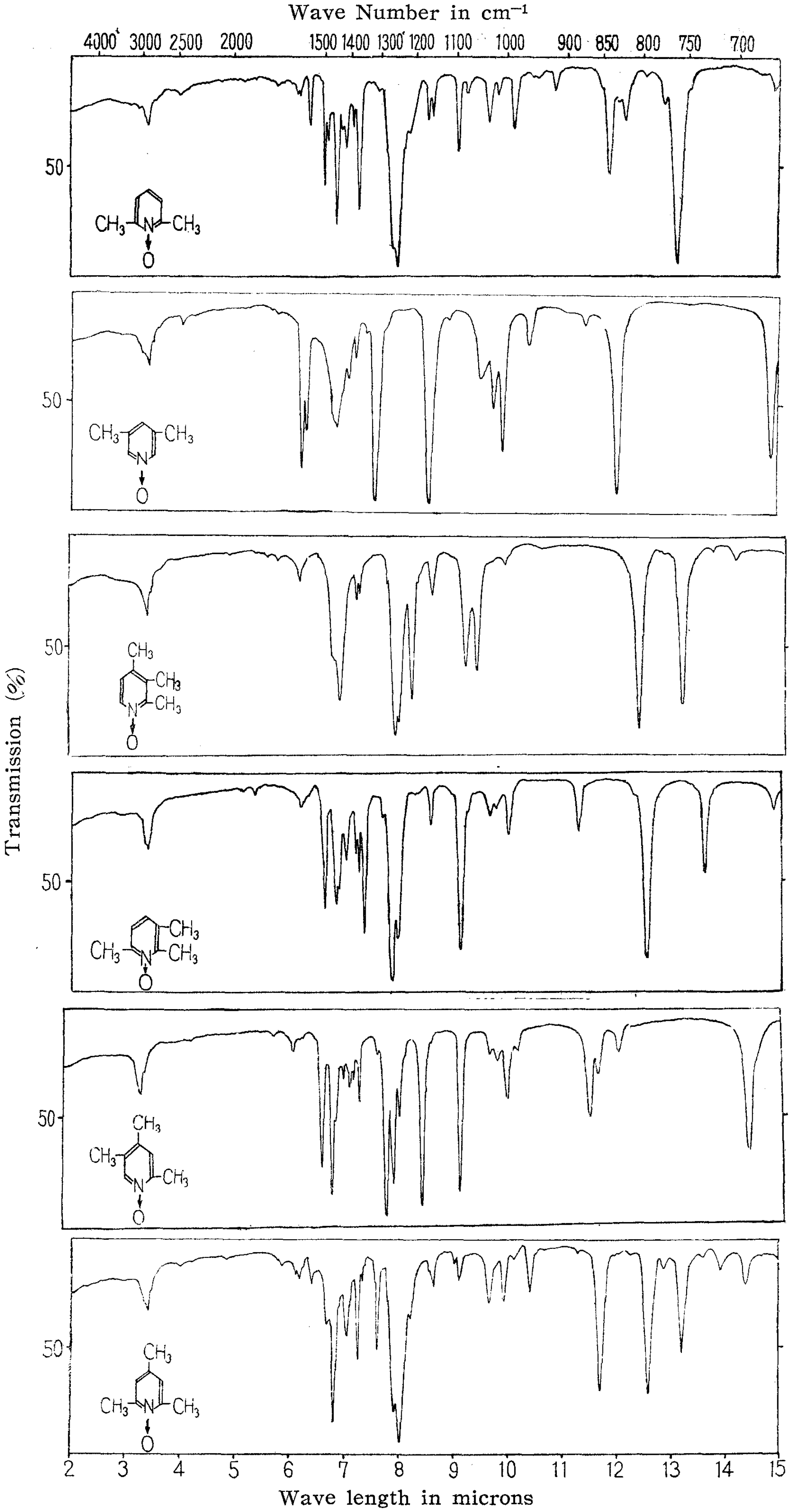

Fig. 1. Infrared Absorption Spectra of Alkylpyridine 1-Oxides (2)

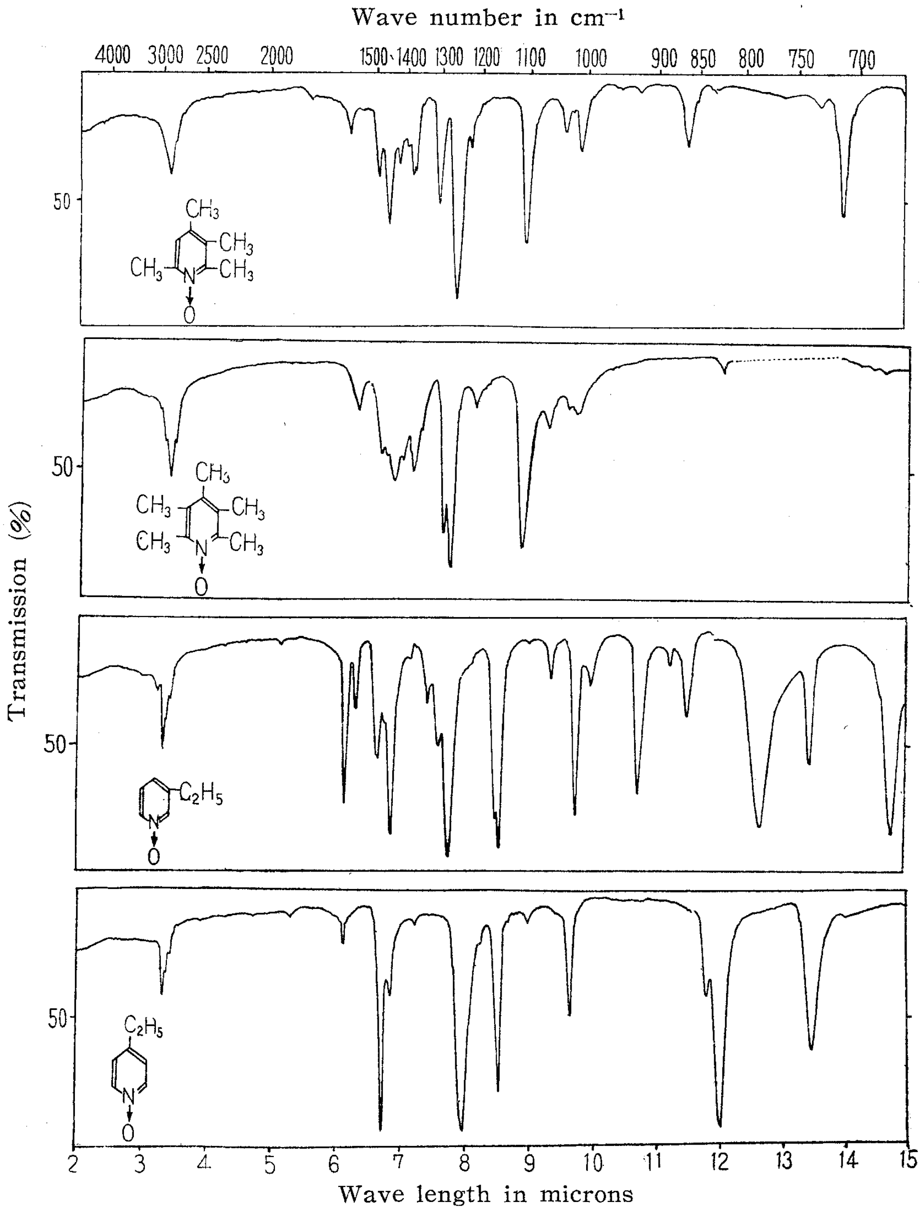

Fig. 1. Infrared Absorption Spectra of Alkylpyridine 1-Oxides (3)

discussed in this paper. The ultraviolet spectra of nine kinds of methylpyridine 1-oxides were described earlier by Ikekawa, *et al.*[16]

I. Characteristic Frequencies of N-Oxide Group

Spectra of pyridine 1-oxide derivatives taken in nonpolar solvent are shown in Fig. 1. It is seen from these spectra that there are more absorptions of strong intensity between 850 and 1300 cm^{-1}, compared to those of the corresponding pyridines, and they can be divided into the following regions :

(1) Intense absorptions between 1200 and 1300 cm^{-1}
(2) Variable absorptions, usually two or three, between 1000 and 1200 cm^{-1}
(3) Moderate to weak absorption at around 850 cm^{-1}

The observed frequencies are summarized in Table I.

Of these, the absorptions at 1200~1300 cm^{-1} are the most characteristic and these were assigned to the N-O stretching band from the following properties :

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[16] N. Ikekawa, Y. Sato : *Ibid.*, **2**, 400(1954).

Table I. Characteristic Frequencies of N-Oxide Group

	N-Oxide of	1200~1300 cm^{-1} region[a] (in cm^{-1})			$\Delta\gamma$	800~1200 cm^{-1} region (cm^{-1} in CCl_4 or CS_2)		
		in CCl_4 or CS_2	Condensed phase[b]	in 10% MeOH/CCl_4		near 1200 cm^{-1}	1000~ 1100 cm^{-1}	near 850 cm^{-1}
(I)	Pyridine	1264	1250 (*m*)	1235	29	1168 s (1172)[c]	1016 s	841 s (836)
(II)	2-Picoline	1261	1250 (*l*)	1220	41	1217 s	1111 1049 w (1113)	854 s (850)
(III)	3-Picoline	1283	1275 (*m*)	1268	15	1170 1159 s (1160)	1008 s	847m
(IV)	4-Picoline	1261	1250	1227	34	1170m (1178)	1037m	855m (855)
(V)	2,3-Lutidine	1276, 1255	1262	1245	31	1212m (1218)	1101 s (1098)	825m (825)
(VI)	2,4-Lutidine	1246	1236 (*l*)	1227	21	1168w (1166)		873w (874)
(VII)	2,6-Lutidine	1255	1246 (*l*)	1230	25		1101w (1103)	844m (840)
(VIII)	3,5-Lutidine	1319	1310	1312	7	1170 s (1163)	1010m	876 vw
(IX)	2,3,4-Collidine	1269, 1256	1250	1244	25	1221m (1225)	1092 m (1088) 1070 m (1065)	
(X)	2,4,5-Collidine	1285, 1263	1280	—	—	1188 s	1100 s	860w
(XI)	2,3,6-Collidine	1274, 1256	1270	—	—		1098 s	887w
(XII)	2,4,6-Collidine	1247	1240 (*l*)	1221	26			(855 s)[d] (854)
(XIII)	2,3,4,6-Tetramethylpyridine	1261	—	—	—		1110 s	
(XIV)	Pentamethylpyridine	1282	—	—	—		1120 s	828vw
(XV)	3-Ethylpyridine	1276	1265	—	—	1159 s	1017 s	863w
(XVI)	4-Ethylpyridine	1253	1238	—	—	1172 s	1036m	

a) All the absorptions are of very strong intensity.

b) (*m*) melted film, (*l*) liquid film. Others as Nujol mull. All the compounds are extremely hygroscopic, absorb moisture during measurement, and exhibit a broad absorption of water at around 3300 and 1700 cm^{-1}.

c) Values in parentheses are frequencies of the same compound in 10% MeOH/CCl_4.

d) This is assumed to be the out-of-plane bending vibration of ring hydrogen.

i) This band always appears in all N-oxide compounds with the same strong intensity.

ii) Only this band clearly shifts to a lower frequency in the presence of a small amount of methanol.

iii) Extremely sensitive relationship exists between the frequency of this absorption and the position of alkyl group in the ring.

iv) Absorption region is appropriate from the double-bond nature of the N-O bond.

v) A reasonable relationship exists between substituents other than alkyls and the frequency of this absorption.

The foregoing points can be explained satisfactorily on the basis of contribution of the structures (II) to (IV) and further discussions will be made on each point.

i) Considering the large dipole of N-O bond, the dipole moment of the molecule may be expected to undergo a large change during N-O stretching vibration and this would result in the appearance of a strong absorption in the infrared spectrum. This absorption appears usually as the most intense band in the region of 900~1700 cm^{-1} in the spectrum. The fact that a strong absorption also appears in pentamethylpyridine 1-oxide indicates that this absorption is independent of ring hydrogen and contradicts the assignment of this absorption to C-H in-plane bending vibration by Ito, *et al.*[14] Absorption at around 850 cm^{-1} is weak and becomes weaker and indistinct with increasing number of substituents.

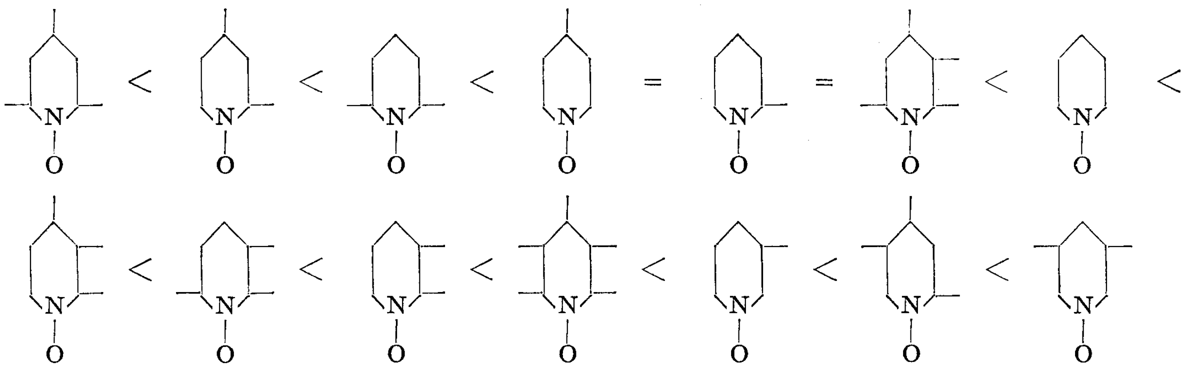
In a condensed phase, the absorption always appears in about 10 cm^{-1} lower frequency than that in a nonpolar solvent, and this is assumed to be due to intermolecular dipolar association (cf. Table I).

ii) Hirayama and Kubota[5,7] reported that the ultraviolet spectra of pyridine 1-oxides shifted to a shorter wave length in polar solvent and that their maxima approached closer to that of pyridine as the polarity of the solvent increases, explaining this phenomenon as the solvation effect of the solvent. They suggested that the formation of a hydrogen bond between oxygen of the N-oxide group and hydrogen of the solvent had prevented mesomerism between N-O and the ring. This would result in the decrease of a double-bond character of the N-O bond and the N-O stretching frequency may be expected to shift to a lower frequency region. Measurement of the infrared spectra in carbon tetrachloride, containing 10% of methanol, indicated that the band in 1200~1300 cm^{-1} alone always showed a shift to the lower frequency region, while no such distinct shift was observed in other bands, as can be seen from Table I.

As a comparison, effect of acetone, which does not possess active hydrogen but has a large dielectric constant, was examined. The absorption band of pyridine 1-oxide in carbon tetrechloride containing 10% of acetone appeared at 1259 cm^{-1}, showing a lowering of only 5 cm^{-1}. Therefore, the lowering of 29 cm^{-1} by methanol is clearly due to the formation of a hydrogen bonding and this also endorses the assignment of this absorption to the N-O stretching frequency.

iii) It is anticipated that the alkyl group in 2- and 4-positions of the pyridine ring, from its electron-donating nature, would prevent the contribution of (II) to (IV) structures than that in 3-position. From the comparison of N-O frequency in methyl derivatives, it was found that the introduction of a methyl group in 2- and 4-positions causes displacement of N-O frequency to a lower frequency region and that of a methyl in 3-position to a higher frequency, these effects appearing additively in each compound as shown in Chart 1.

Chart 1. N-O Frequency Order of Methylpyridine 1-Oxides

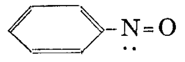


However, the effect of the methyl in 3-position is predominantly large and all the compounds possessing methyl group in 3-position absorbed at a higher frequency than pyridine 1-oxide. Such a marked effect cannot be explained easily. For example, pKa values,[10] which are considered to correspond to the bond order of N-O, are in the order of 0.79 for pyridine 1-oxide, 1.08 for 3-picoline 1-oxide, and 1.29 for 4-picoline 1-oxide. Therefore, the N-O stretching frequency should be in parallel with these pKa values and the methyl group at 3-position should also show a rather lowering effect on the N-O frequency. It follows that these frequencies cannot be taken *per se* as indicating the size of N-O bond order, especially in the case of 3-alkyl derivatives.

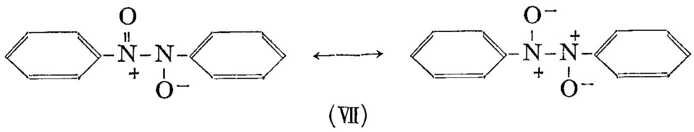
This phenomenon may have been caused by the coupling of this frequency with other mode of vibration in this region. Since these absorptions are always accompanied by one weaker absorption in 50~100 cm^{-1} lower region, which is especially strong and distinct in 3-picoline and 3,5-lutidine 1-oxides, it may be assumed that a vibrational coupling with these frequencies is present and the degree of coupling is greater in the 3-alkyl derivatives.

In any case, such a close connection between the structure and absorption frequency cannot be expected in absorptions other than that based on N-O mode.

iv) The N–O stretching frequency in aliphatic tertiary amine N–oxides is assigned to the region of 950 cm^{-1},[17] and that of the oxime also at 930~950 cm^{-1},[18] and the region of 1200~1300 cm^{-1} is far to the higher frequency compared to them. On the other hand, the N–O stretching frequency of aromatic nitroso compounds is in 1380~1340 cm^{-1} region in the monomer (VI) and in 1270~1260 cm^{-1} region when the double–bond character of N–O bond is reduced to below 50% on forming a dimer (VII).[19] Since the N–O bond in pyridine 1–oxides is expected to have a far greater double–bond character than that in aliphatic tertiary amine N–oxides by mesomerism with the ring, the fact that its frequency agrees approximately with that of dimerized nitroso group seems to be appropriate.



(VI)



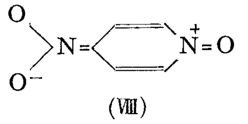
etc.

(VII)

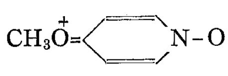
v) Pyridine 1–oxides possessing substituents other than alkyl also exhibit this absorption with a strong intensity. The N–O frequencies of some 4–substituted pyridine 1–oxides are compared with those[19] of the corresponding *para*–substituted nitrosobenzenes and nitrobenzenes in Table II. These three groups of compounds show entirely parallel displacements of their N–O frequencies and this displacement can reasonably be explained from the electronical nature of the substituents. For example, the high frequency of the N–O band in 4–nitropyridine 1–oxide, which corresponds to the increased double–bond character of the N–O bond, may be understood from the contribution of the ionic structure (VIII) by the powerful electron–attracting nature of the nitro group, while the low frequency in the 4–methoxy compound, which corresponds to the increased ionic nature of the N–O bond, may be due to the contribution of the ionic structure (IX) by the strong electron–donating nature of the methoxyl group.

Table II. Relationship between the *para*–Substituted Groups and N–O Stretching Frequencies in Pyridine 1–Oxides and Nitroso– and Nitrobenzenes (cm^{-1}, Nujol mull)

para–Subst. group	N–O Frequency	N=O Frequency	NO_2 asym. frequency
NO_2	1269	1375	1564
Cl	1246	1369	1533
CH_3	1250	1369	1530
OCH_3	1205	—	—
$N(CH_3)_2$	—	1344	—
NH_2	1192	—	1473



(VIII)



(IX)

Absorptions in regions other than 1200~1300 cm^{-1} are varied in both frequency and intensity and do not indicate any distinct connection with the structure. It is assumed that these include ring vibrations intensified by the introduction of N–O function.

II. Out-of-plane Bending Vibrations of Ring C-H

The strong absorptions in the region of 700~900 cm^{-1} can be assigned to the out–of–plane bending vibration of ring hydrogen. These frequencies of alkylpyridine 1–oxides and of corresponding pyridines are listed in Table III. It was suggested in Part I of this series[15] that the out–of–plane C–H vibration in alkylpyridines could be considered

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17) R. Mathis-Noel, R. Wolf, F. Gallais: Compt. rend., **242**, 1873(1956).

18) A. Palm, H. Werbin: Can. J. Chem., **32**, 858(1954).

19) K. Nakamoto, R.E. Rundle: J. Am. Chem. Soc., **78**, 1113(1956).

Table III. C–H Out-of-plane Bending Frequencies of Alkylpyridine 1-Oxides and corresponding Pyridines

N-Oxide of	C-H Frequency (cm^{-1}, in CS_2)			No. of adjacent free H atom
		$\Delta\gamma$		
Pyridine	759 (744)	+15	669 (701)	5
2-Picoline	757 (749)	+ 8	695 (726)	4
3-Picoline	778 (782)	− 4	674 (709)	3
3-Ethylpyridine	785 (805)	−20	675 (611)	3
2, 3-Lutidine	777 (784)	− 7	694 (726)	3
2, 6-Lutidine	762 (770)	− 8		3
4-Picoline	823 (793)	+30	761	2
4-Ethylpyridine	833 (818)	+15	734 (766)	2
2, 4-Lutidine	816 (814)	+ 2	799	2
2, 3, 4-Collidine	812 (821)	− 9	763 (733)	2
2, 3, 6-Collidine	798 (814)	−16	736	2
3, 5-Lutidine	832 (856)	−24	673 (709)	1
2, 4, 6-Collidine	855 (839)	+16	794, 758	1
2, 4, 5-Collidine	875 (861)	+14	697	1
2, 3, 4, 6-Tetramethylpyridine	868 (857)	+11	715	1

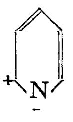
Values in parentheses indicate frequency of corresponding alkylpyridines.

as analogous to substituted benzenes. As compared in Table III, the same analysis is possible for the 1-oxides and they approximately correspond with the usual range of substituted benzenes listed by Bellamy²⁰⁾ by the number of adjacent hydrogen on the ring, but displacement from the corresponding pyridines is extremely varied.

Recently, Kross, *et al.*²¹⁾ indicated that the depletion of π-electron density in the ring due to the effect of substituents in substituted benzenes results in the displacement of C-H out-of-plane bending vibrations to a higher frequency. In N-oxide compounds, π-electron density of the ring must have increased over that of corresponding pyridines due to mesomerism and their C-H frequencies are expected to be lower than those of the corresponding pyridines. Actually, however, they did not show any shift in a definite direction, as indicated in Table III, and it was noticed that six out of seven compounds showing such lowering possess alkyl group in 3-position and that the absorption of 3, 5-lutidine 1-oxide was 24 cm^{-1} lower than that of 3, 5-lutidine. This fact seems to bear some relation to the specific effect of an alkyl group in 3-position to the N-O frequency.

III. Ring Double-bond Vibration

Absorptions in the region of 1450 to 1650 cm^{-1} are assigned to the stretching frequencies of ring C=C and C=N bond. Absorptions in this range are generally weak in N-oxide compounds and it is sometimes impossible to detect the presence of an aromatic ring from this region. However, comparison of intensity of absorptions between 1560 and 1620 cm^{-1} in 1-oxides and corresponding pyridines gives interesting result. In 1-oxides, compounds possessing an alkyl in 4-position do not show any strong absorption in this region while those with an alkyl in 3-position show distinct absorption, same as the usual substituted benzenes. In alkylpyridines, on the other hand, those with a methyl in 4-position show absorptions similar to ordinary substituted benzenes while those with a methyl in 3-position exhibit extremely abnormal absorption.¹⁵⁾ It follows that the absorption in this region tends to show an entirely reverse behavior when pyridines



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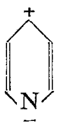

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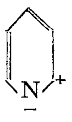

(XII)

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20) L. J. Bellamy : "The Infrared Spectra of Complex Molecules," Methuen & Co., London, 59(1954).

21) R. D. Kross, V. A. Fassel, M. Nargoshes : J. Am. Chem. Soc., **78**, 1332(1956).

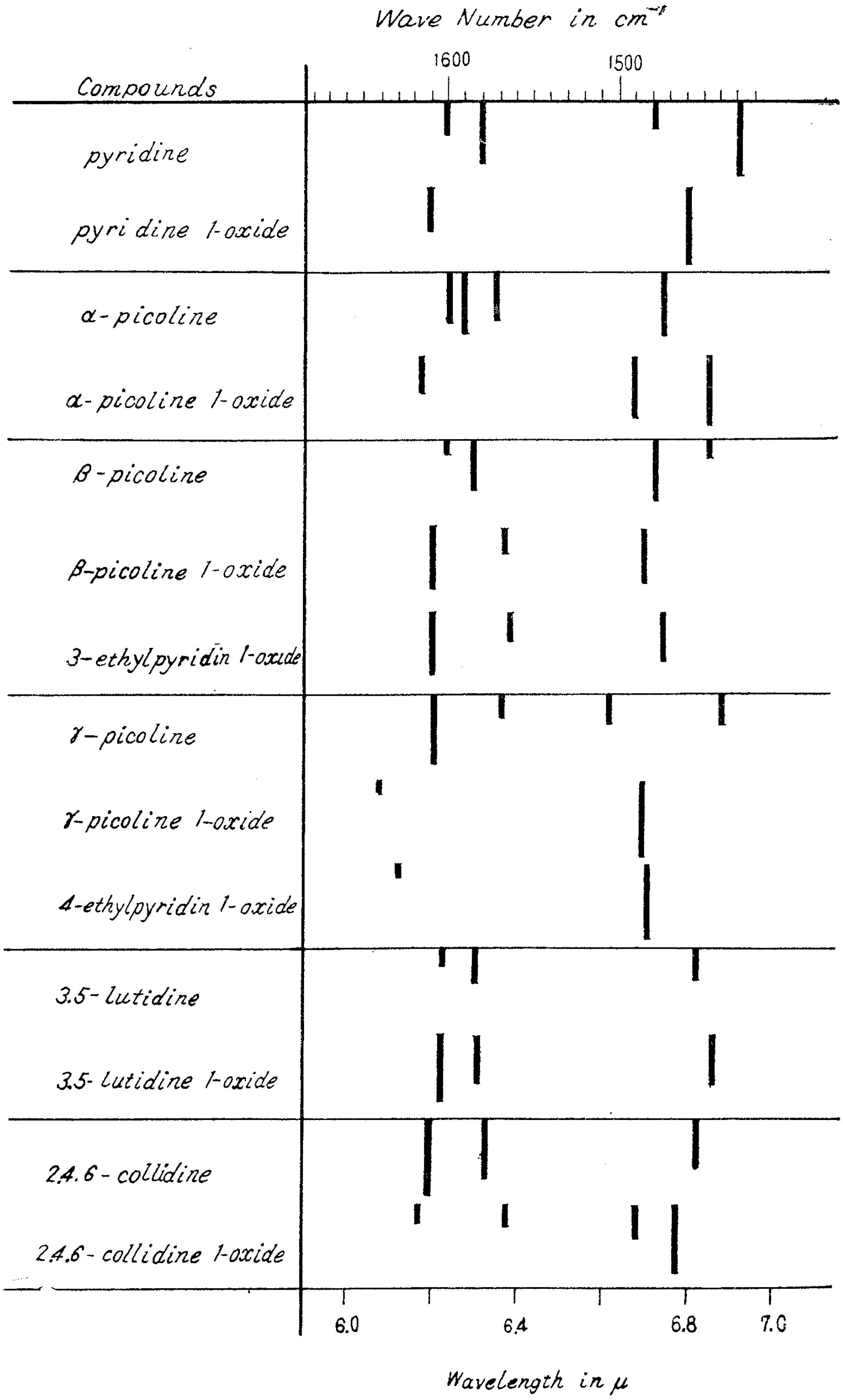

Fig. 2.

are converted to their N-oxides. Some examples of this are shown in Fig. 2. Considering the electron distribution in the ring, this seems to be related to the fact that such distribution in 1-oxide compounds is entirely reverse of those (X to XII) of pyridines due to the contribution of structures (II) to (IV).

The writer expresses his deep gratitude to Prof. Kyosuke Tsuda of the University of Tokyo for kind guidance throughout the course of this work, to Dr. Takehiko Shimanouchi of the University of Tokyo for valuable advices, to Mr. Ikekawa of the Institute of Microbiology, University of Tokyo, for technical assistance in the preparation of samples, to Messrs. Sakai and Kaneko of the Pharmaceutical Institute, University of Tokyo, for supplying some of the samples, and to Mr. Minoru Suzuki of this Laboratory for helpful encouragements.

Experimental

Materials—The 1-oxide compounds of pyridine, 2-, 3-, and 4-picolines, 2, 3-lutidine, 2, 3, 4-collidine, and 2, 4, 5-collidine used were those prepared earlier by Ikekawa, *et al.*[16] Other alkylpyridine 1-oxides were prepared from corresponding pyridines by oxidation with H_2O_2 according to the method of Ochiai.[2] The pyridine bases used as the starting material, other than 2, 4-lutidine, were pure samples prepared or isolated by Ikekawa and others and used in the experiments reported in Part I of this series.[15] 2, 4-Lutidine 1-oxide was prepared in the following manner. Commercial 2, 4-lutidine containing 2, 3-lutidine was derived to the N-oxide, fractionated, and its picrate was recrystallized twice from MeOH. The picrate was warmed with 10% NaOH to liberate the 1-oxide compound and this was distilled to remove 2, 3-lutidine 1-oxide completely.

The yield of 2, 3, 4, 6-tetramethylpyridine and pentamethylpyridine 1-oxides was extremely poor, about 400 mg. of the base affording about 20 mg. of white crystals by low-pressure distillation, barely enough for the infrared measurement.

The compounds not described in any literature to date are 3, 5-lutidine 1-oxide (picarte : Yellow plates, m.p. 138~139°. *Anal.* Calcd. for $C_{13}H_{12}O_8N_4$: C, 44.32; H, 3.43; N, 15.91. Found : C, 44.26; H, 3.58; N, 15.85) and 2, 3, 6-collidine 1-oxide (picrate : Yellow plates, m.p. 102°. *Anal.* Calcd. for $C_{14}H_{14}O_8N_4$: C, 45.90; H, 3.85; N, 15.30. Found : C, 46.03; H, 3.85; N, 15.52). The data for picrates of other compounds agreed with those given in the literature.

All the samples were purified by low-pressure distillation, redistilled immediately prior to measurement, and stored over P_2O_5. They were weighed rapidly and measured in a dry room so as to avoid inclusion of water.

Four 4-substituted pyridine 1-oxides were prepared in the Pharmaceutical Institute of the University of Tokyo.

Method—Infrared spectra were measured with a Perkin-Elmer Model 21 double-beam spectrophotometer provided with a NaCl prism. The solvent used was CCl_4 or CS_2. Measurements in the 850~5000 cm^{-1} region were made as a solution of 5% concentration in CCl_4 with a 0.1-mm. cell and those in the region of 670~850 cm^{-1} as approx. 0.5% solution in CS_2 with a 1.0-mm. cell. 4-Picoline 1-oxide is insoluble in CCl_4 that it was measured over the whole region as approx. 0.5% solution in CS_2, and the regions of 1400~1700 and 850~900 cm^{-1}, as a $CHCl_3$ solution.

The absorption of MeOH, when it was added, was extinguished by compensation of the same solvent but this hardly affected the region of 1100~1300 cm^{-1}.

Summary

Infrared absorption spectra of pyridine 1-oxide and 15 kinds of its alkyl derivatives were measured and characteristic absorption band for the N-oxide group was established. The effect of ring substituents on the N-O frequency and the effect of the introduction of N-O function on ring vibration were discussed in comparison with the spectra of corresponding pyridine bases. The absorption of strong intensity always appearing in the region between 1200 and 1300 cm^{-1} in these compounds were assigned to that based on the N-O stretching mode. This absorption was always displaced to lower frequencies in the presence of methanol, thereby proving its solvation effect. The frequencies of this absorption showed sensitive relationship to the position of the alkyl group in the ring, the effect being especially marked in 3-alkyl group which caused a shift to the higher frequency. A reasonable relation was found to exist between N-O frequency and electronical nature of the substituents in several of the 4-substituted pyridine 1-oxides. There was no marked relationship between the out-of-plane bending frequencies of ring hydrogen in 1-oxides and those in corresponding pyridines. The behavior of the ring double-bond vibration in 1-oxide compounds was contrasting to that of the corresponding pyridines.

(Received July 25, 1956)