2,5-dinitrobenzoic acid, respectively, showing that quinolines were oxidized to carbostyrils, considered as a kind of acylamino compounds, via their 1-oxide and further oxidation of the carbostyrils to nitrobenzoic acids takes place.

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90. Nobuo Ikekawa and Yoshihiro Sato : Studies on the Coal Tar Bases. IX.[1] Methylpyridine 1-Oxides and their Ultraviolet Absorption Spectra.

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Some years ago, one of the authors (Ikekawa) took part in a study on the separation of pyridine bases in coal tar by fractional distillation of their 1-oxides.[2] It was found from the study that in methylpyridine 1-oxides the methyl groups exhibit more different character by their position than in the original methylpyridines. The present study was undertaken to investigate the structures of methylpyridine 1-oxides and the spectral properties of the methyl groups in pyridine 1-oxide ring.

Pyridine 1-oxide and nine kinds of methylpyridine 1-oxides were compared in regard to their physical constants and ultraviolet absorption spectra. As reported in the previous paper[1] of this series, the methyl group in the γ-position of methylpyridine series exhibited a hypsochromic effect and that in α- or β-position, a bathochromic in the ultraviolet absorption spectra. In this study it was found that in their 1-oxides only the methyl group in α-position exhibited a hypsochromic effect and that in β- or γ-position a bathochromic effect.

Methylpyridine 1-oxide There are some literatures[2~5] on six kinds of methylpyridine 1-oxide shown in Table I. In addition, 1-oxides of 2,3-lutidine, 2,4,5- and 2,3,4-collidine were newly synthesized. Although most methylpyridine 1-oxides were hygroscopic crystals, it was noticed that the 1-oxide possessing two methyl groups in α- and

Table I. Physical Constants of Methylpyridine 1-Oxides

1-Oxide of	b.p$_4$ °C	m.p., °C	Picrate		Analyses found		
			m.p., °C	Crystal form	C%	H%	N%
Pyridine[5]	113~114	hygro. cryst.	179~181	yellow needles			
2-Picoline[3]	110	—	125	yellow needles			
3-Picoline[2]	111~112	41~42	134.5~135.5	yellow needles			
4-Picoline[2,4]	125	181~182	155	yellow plates			
2,6-Lutidine[2,3]	93~94	—	123.5~124.5	yellow plates			
2,3-Lutidine	95~98	82~85	114~115	yellow needles	44.50	3.48	15.95[a]
2,4-Lutidine[2,3]	115~117	—	141	yellow plates			
2,4,6-Collidine[3]	105	—	168~169	yellow needles			
2,3,4-Collidine	127~130	hygro. cryst.	122~123	orange plates or yellow needles	46.08	3.71	15.25[b]
2,4,5-Collidine	132	65~66	123~124	orange plates	45.52	3.81	15.10[b]

a) Calcd. for $C_7H_9ON \cdot C_6H_3O_7N_3$ (lutidine 1-oxide picrate) : C, 44.31; H, 3.41; N, 15.99.
b) Calcd. for $C_8H_{11}ON \cdot C_6H_3O_7N_3$ (collidine 1-oxide picrate) : C, 45.90; H, 3.82; N, 15.30.

* Hakata, Fukuoka (池川信夫, 佐藤良博).

1) Part Ⅷ : This Bulletin, **2**, 209(1954).
2) E. Ochiai, M. Ikehara, T. Kato, N. Ikekawa : J. Pharm. Soc. Japan, **71**, 1385(1951).
3) M. Ishikawa, Z. Sai : *Ibid.*, **63**, 78(1943).
4) E. Ochiai, M. Ishikawa, Z. Sai : *Ibid.*, **65**, 72(1945).
5) E. Ochiai, Z. Sai : *Ibid.*, **65**, 73(1945).

α'-positions, e.g. 2,6-lutidine and 2,4,6-collidine 1-oxides, were a liquid at a room temperature and exhibited lower boiling point than other methylpyridine 1-oxides. α-Picoline and 2,4-lutidine 1-oxides could not be obtained as crystals in spite of repeated purification. γ-Picoline 1-oxide showed an extraordinary high melting point.

Ultraviolet absorption spectra The absorption spectra of 10 kinds of 1-oxide were measured in ether and 95%, 50%, and 10% EtOH solution. The absorption spectra of all isomers in these solutions are similar in shape as shown in Fig. 1. Generally, by the N-oxidation of methylpyridines, λ_{max} of spectrum shifted to the longer wave length region. These results were summarized in Fig. 2 and Table II.

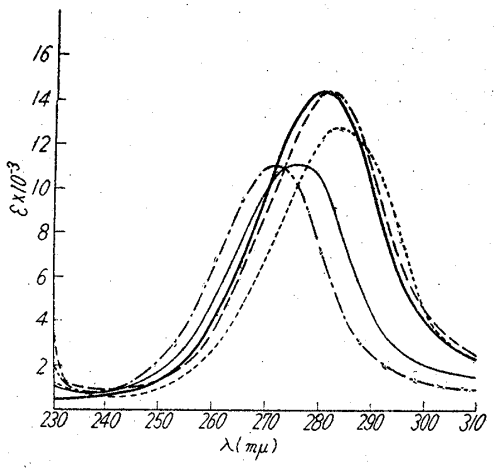


Fig. 1. Absorption Spectra of Methylpyridine 1-Oxides (in ether)

——— pyridine 1-oxide
——— α-picoline 1-oxide
– – – – β-picoline 1-oxide
····· γ-picoline 1-oxide
–·–·– 2,6-lutidine 1-oxide

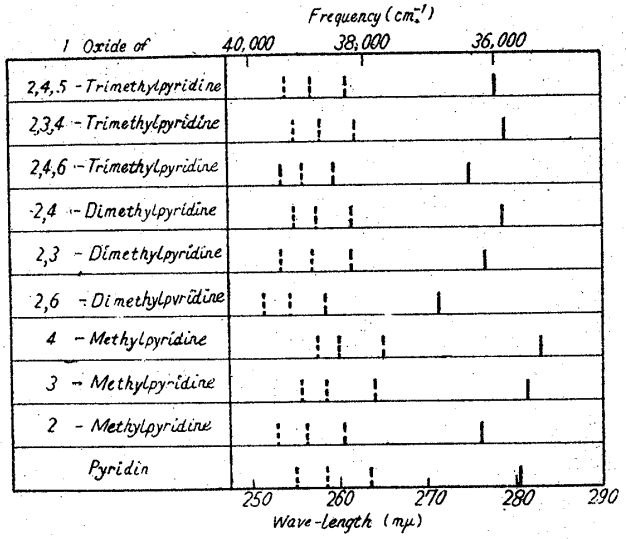


Fig. 2. Position of Absorption Maximum of Methylpyridine 1-Oxides

in ether	in 95% EtOH
in 50% EtOH	in 10% EtOH

Table II. Ultraviolet Absorption Characteristics of Methylpyridine 1-Oxides (mμ)

1-Oxide of	in ether		in 95% EtOH		in 50% EtOH		in 10% EtOH	
	λ_{max}	ε_{max}	λ_{max}	ε_{max}	λ_{max}	ε_{max}	λ_{max}	ε_{max}
Pyridine	280.5	14,780	263.5	12,440	258.5	10,500	255	10,900
2-Picoline	276	11,230	260.5	10,360	255.5~256	9,840	253	10,240
3-Picoline	281~282	14,500	264	9,920	258~259	9,580	255~255.5	9,240
4-Picoline	283	12,660	265	11,240	259.5~260.5	10,600	257.5	11,480
2,6-Lutidine	271.5	11,090	258.5	9,020	254.5	9,300	251.5	8,620
2,3-Lutidine	276.5~277	11,750	261.5	9,560	257	9,160	253.5	9,200
2,4-Lutidine	278.5~279	12,190	261~262	13,600	257.5	12,940	255	11,240
2,4,6-Collidine	275	11,550	259.5	11,180	256	10,100	253.5	10,380
2,3,4-Collidine	279	13,220	261.5~262.5	12,920	258	12,240	255	13,120
2,4,5-Collidine	278	16,050	261	12,720	257	12,360	254	12,400

Hirayama and Kubota[6] measured the ultraviolet spectra of pyridine 1-oxide and its derivates in various solvents and described that λ_{max} of the 1-oxides shifted to a shorter wave length region in polar solvents. As shown in Fig. 2, λ_{max} of methylpyridine 1-oxides shifted to a shorter wave length by ca. 16 mμ in 95% EtOH, ca. 20 mμ in 50% EtOH, and ca. 23 mμ in 10% EtOH, than in ether solution. An introduction of methyl group into the β- or γ-position of pyridine 1-oxide ring produces a bathochromic shift, but in the α-position a hypsochromic shift, which is very marked in ether. Consequently, the

6) H. Hirayama, T. Kubota : Ann. Repts. Shionogi Research Lab., **2**, 121 (1952).

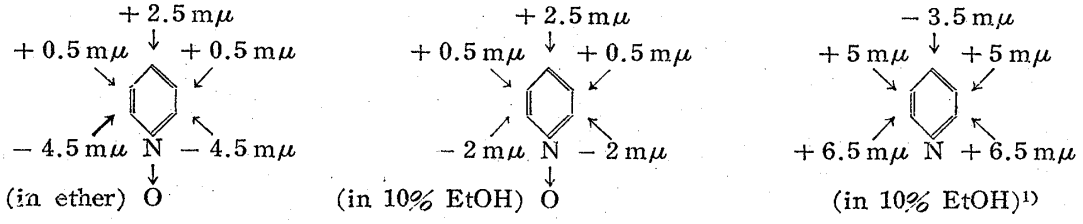
λ_{max} of 2,6-lutidine 1-oxide exists in the shortest wave length region. The effects of solvent and of methyl group on intensity of spectra were not so remarkable.

As seen in methylpyridine,[1] contributions of the individual methyl groups are almost additive in the absorption spectra of methylpyridine 1-oxide. On the basis of these data, it will be assumed that the introduction of a methyl group into α-, β-, or γ-position of pyridine 1-oxide would cause a shift of $-4.5\,m\mu$, $+0.5\,m\mu$, $+2.5\,m\mu$ in ether and $-2\,m\mu$, $+0.5\,m\mu$, $+2.5\,m\mu$ in 10% EtOH, respectively. Utilizing these values, calculated values of λ_{max} in 2,4,6-collidine 1-oxide are:

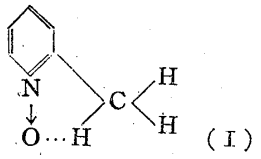
$$280.5 + (-4.5 \times 2) + 2.5 = 274\,m\mu \text{ (Found : } 275\,m\mu \text{ in ether)}$$
$$255 + (-2 \times 2) + 2.5 = 253.5\,m\mu \text{ (Found : } 253.5\,m\mu \text{ in EtOH)}$$

In other isomers, the calculated values also agree perfectly with observed values, and therefore, the λ_{max} of spectra in polymethylpyridine 1-oxide may be predictable.

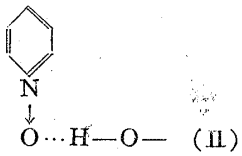
Fig. 3. Shift of λ_{max} by the Introduction of Methyl Groups



Discussion As shown in Fig. 3, spectral property of the methyl group in methylpyridine is changed by the introduction of an oxygen atom in the pyridine ring. In methylpyridine 1-oxide the spectral properties of β- and γ-methyl groups show no remarkable difference, while that of α-methyl group exhibits a hypsochromic effect, which is most apparent in ether. These results may suggest that the resonance of pyridine 1-oxide will be hindered by the formation of a weak intramolecular hydrogen bond between the oxygen atom and hydrogen atom of the α-methyl group (I). This consideration may be supported by the decreasing effect of α-methyl group on the boiling point and melting point.



(I)



(II)

Moreover, as Hirayama and Kubota[6] explained, the blue shift of 1-oxide in polar solvent may also be caused by the solvation, namely, hydrogen bond between oxygen atom of 1-oxide and hydrogen atom of the solvent (II).

The authors express their gratitude to Prof. K. Tsuda for his constant guidance during the course of this work.

Experimental

Synthesis of Methylpyridine 1-Oxides—Pure pyridine and α-picoline were obtained by fractional distillation of commercial pyridine and α-picoline. 2,6- and 2,4-Lutidine and 2,4,6-collidine isolated from coal tar base were purified by recrystallisation of their picrates. 2,3-Lutidine and 2,3,4- and 2,4,5-collidine were synthesized as previously reported. 1-Oxides of these bases were synthesized by the following usual method. To a solution of 2 g. of methylpyridine in 20 cc. glacial AcOH, 4 g. of ca. 30% H_2O_2 was added in small portions and the mixture was heated at 80~90° for 12 hrs. Then it was condensed to 10 cc. under diminished pressure and was made alkaline with Na_2CO_3. The resulting mixture was extracted with $CHCl_3$, dried over Na_2SO_4, and $CHCl_3$ was distilled off. The residue was distilled under a reduced pressure. The yield was ca. 70% in the case of most bases but ca. 40% in the case of 2,6-lutidine and 2,4,6-collidine. This low yield may be due to the steric hindrance of the two methyl groups in α- and α'-positions. The m.p. of pyridine and

2,3,4-collidine 1-oxides could not be measured because of their great hygroscopic character. The samples were redistilled under a reduced pressure before use.

Ultraviolet Absorption Spectra—The absorption spectra were determined using a Shimazu Spectrophotometer type QB-50, with quartz cells of 10-mm. optical depth, in the region of 225~320 mμ. Density measurements were never made at intervals of more than 2 mμ, while in the neighbourhood of maxima the interval was decreased to 0.5 mμ. Solvent water was purified by repeated distillation, and ether and ethanol were carefully purified by the usual procedures. The concentrations of the solutions were 0.05 *mM*. The temperature was at 20°±2°.

Summary

The ultraviolet absorption spectra of pyridine 1-oxide and nine kinds of methylpyridine 1-oxide were measured in ether and in 95%, 50%, and 10% ethanol. The methyl group in the α-position exhibits a hypsochromic effect and in the β- or γ-position a bathochromic effect. These spectral results and physical constants of methlpyridine 1-oxides suggest the presence of a weak hydrogen bond between the oxygen atom and the hydrogen atom of the α-methyl group.

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91. Tadakazu Tsuji: Researches on Chemotherapeutic Drugs against Viruses. XVII.* Synthesis and Antiviral Properties of Urazoles and Related Compounds.

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It was found by Toyoshima[1] in the screening tests of enzyme-inhibitors on influenza viruses that both sodium azide and melamine exerted a weak inhibitory activity against the influenza A virus. Later several benzimidazole derivatives were reported to possess weak inhibitory activities on the influenza A virus.[2]

On the basis of these findings, a number of heterocyclic compounds containing nitrogen and related compounds were synthesized and examined as to their antiviral activities. This paper describes the synthesis and antiviral activities of 4-alkylphenylurazoles, dialkylphenylureas, 4-alkylurazoles, acylurazoles, 1-substituted biureas, and 1,6-disubstituted biureas.

Synthesis of Urazole and Related Compounds Several of the known five- and six-membered ring compounds, as illustrated in Table VI, were prepared and screened as to their activities against the Nakayama strain of *Encephalitis japonica* and PR-8 strain of influenza A virus. In these preliminary examinations, urazole and 4-phenylurazole among the above compounds were found to possess a weak activity against the virus. Consequently, urazole and its related compounds were taken up in the search for antiviral drugs.

4-Alkylphenylurazole is not known yet, but its parent compound, 4-phenylurazole was synthesized by Thiele[3] and by Arndt,[4] along with diphenylurea as a by-product, on

* T. Ueda, S. Toyoshima: Researches on Chemotherapeutic Drugs against Viruses. XVII. Part XVI: This Bulletin, **1**, 379(1953).

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2) I. Tamm, K. Folkers, C. H. Shunk, F. L. Horsfall: J. Exptl. Med., **98**, 245(1953); *Ibid.*, **99**, 227 (1954).

3) Thiele, Stange: Ann., **283**, 45(1894).

4) F. Arndt, L. Löwe, A. Tarlan-Akõn: C. A., **42**, 8190(1948).