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105. Toyozo Uno, Katsunosuke Machida, and Kazuhiko Hanai: Infrared Spectra of Sulfonamide Derivatives. II.*1 Thiophene, Thiadiazole, and Isoxazole Derivatives.

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Infrared spectra have been applied to the studies on the amido-imido tautomerism of sulfonamide derivatives containing heterocyclic rings such as pyridine,[1~3] pyrimidine,[1,3] thiazole,[1,3] thiadiazole,[1] and pyrazole.[4] Jones and Katritzky[2] have shown from the spectral similarity between sulfonamidopyridines and their endocyclic N-methyl derivatives that 2- and 4-methylsulfonamidopyridines exist in the imido-form. Sheinker and his co-workers[1] have concluded from the comparison with various methyl derivatives in the fixed tautomeric forms that 2-phenylsulfonamidothiazole, -thiadiazole, -pyridine, and -pyrimidine have the imido-form in the solid state.

In the first paper[3] of this series we discussed the amido-imido tautomerism of sulfonamides on the basis of the spectral change on N-deuteration and pointed out that 2-phenylsulfonamidopyridine and N'-2-pyrimidylsulfanilamide (sulfadiazine) are in the amido-form in the solid state, contrary to Sheinker's conclusion.[1] Since the spectral change on N-deuteration affords quite obvious distinction between the amido-form and the imido-form, we have extended its application to thiadiazole and isoxazole derivatives. Intending to confirm the heterocyclic ring frequencies of the amido-form in the region 1650 to 1500 cm^{-1}, we have also investigated the infrared spectra of N-substituted carboxylic acid amides containing 2-thienyl, 3-isoxazolyl, and 5-isoxazolyl groups as the N-substituents. The present paper deals with the results of these investigations.

Experimental

Materials*3

$SnCl_4$ Salt of 2-Aminothiophene Hydrochloride——According to the directions described by Babasinian,[5] 28 g. of thiophene in 120 ml. of Ac_2O was nitrated with 27 g. of fuming HNO_3 (sp. gr. 1.52) dissolved in 200 ml. of AcOH, giving 39.2 g. of 2-nitrothiophene, which gave needles, m.p. 42~43.5°, on recrystallization from petr. ether. Thirteen grams of 2-nitrothiophene was reduced with Sn-HCl to 18.6 g. of the $SnCl_4$ salt of 2-aminothiophene hydrochloride. Without isolating the free base which is susceptible to oxidation,[6] the salt was subjected to condensation with benzenesulfonyl chloride, acetic anhydride, and benzoyl chloride under the presence of alkali.

2-Phenylsulfonamidothiophene (2-PSTp)——To a solution of 6 g. of the 2-aminothiophene salt dissolved in 25 ml. of H_2O a solution of 4 g. of benzenesulfonyl chloride in 10 ml. of ether was added. To the mixture an aqueous solution of NaOH (7 g. in 10 ml. of H_2O) was added gradually under ice-cooling and stirring. The reaction mixture was acidified by HCl, and the product was extracted with ether. After washing with

*1 Part I. T. Uno, K. Machida, K. Hanai, M. Ueda, S. Sasaki: This Bulletin, **11**, 704 (1963).

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*3 All melting points are uncorrected.

1) Yu. N. Sheinker, I. Ya. Postovskii, N. M. Voronina, V. V. Kushkin: Zhur. Fiz. Khim. S. S. S. R., **31** 1745 (1957); Yu. N. Sheinker, I. K. Kuznetsova: *Ibid.*, **31**, 2656 (1957); Yu. N. Sheinker, E. M. Peresleny, N. P. Zosimova, Yu. I. Pomerantsev: *Ibid.*, **33**, 2096 (1959); Yu. N. Sheinker: Doklady Akad. Nauk S. S. S. R., **113**, 1080 (1957).

2) R. A. Jones, A. R. Katritzky: J. Chem. Soc., **1961**, 378.

3) T. Uno, K. Machida, K. Hanai, M. Ueda, S. Sasaki: This Bulletin, **11**, 704 (1963).

4) J. Seydel, E. Krüger-Thiemer: Arzneimittel-Forsch., **14**, 1294 (1964).

5) V. S. Babasinian: J. Am. Chem. Soc., **50**, 2748 (1928).

6) W. Steinkopf: Ann., **403**, 17 (1914).

Table I. Sulfonamide Derivatives

$R\text{-}SO_2NH\text{-}R'$

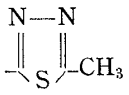
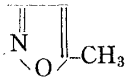
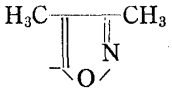
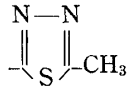
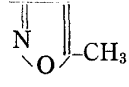
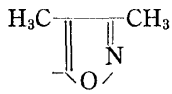
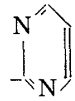
Abbreviations of compounds	R	R′	m.p. (°C)	Recryst. solvents	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
2-PSTp	C_6H_5–		84.5～85	CCl_4	$C_{10}H_9O_2N_1S_2$	50.19	3.79	5.85	49.92	4.00	6.00
2-PSTd	〃		179.5～180.5	40% EtOH	$C_9H_9O_2N_3S_2$	42.34	3.55	16.46	42.38	3.75	16.70
3-MSIx	CH_3–		130.5～131.5	C_6H_6	$C_5H_8O_3N_2S_1$	34.08	4.58	15.90	34.28	4.75	16.19
3-PSIx	C_6H_5–	〃	112.5	iso-PrOH	$C_{10}H_{10}O_3N_2S_1$	50.41	4.23	11.76	50.48	4.46	12.05
5-PSIx	〃		157.5～158.5 (decomp.)	C_6H_6	$C_{11}H_{12}O_3N_2S_1$	52.37	4.79	11.10	52.08	5.01	11.13

Table II. Carboxylic Acid Amide Derivatives

$R\text{-}CONH\text{-}R'$

Abbreviations of compounds	R	R′	m.p. (°C)	Recryst. solvents	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
2-AcTp	CH_3–		160.5～161	C_6H_6	$C_6H_7O_1N_1S_1$	51.04	5.00	9.92	51.33	4.96	9.73
2-BzTp	C_6H_5–	〃	174.5～175	〃	$C_{11}H_9O_1N_1S_1$	65.00	4.46	6.89	64.85	4.34	6.86
2-AcTh	CH_3–		204～205	sublimat.	$C_5H_6O_1N_2S_1$	42.24	4.25	19.70	42.08	4.15	19.71
2-BzTh	C_6H_5–	〃	152～153	EtOH	$C_{10}H_8O_1N_2S_1$	58.80	3.95	13.72	58.73	4.05	13.67
2-AcTd	CH_3–		297～297.5 (decomp.)	〃	$C_5H_7O_1N_3S_1$	38.21	4.49	26.73	38.20	4.72	26.94
2-BzTd	C_6H_5–	〃	245～246	〃	$C_{10}H_9O_1N_3S_1$	54.78	4.14	19.16	54.66	4.33	19.21
3-AcIx	CH_3–		179.5～181	〃	$C_6H_8O_2N_2$	51.42	5.75	19.99	51.72	5.89	19.94
3-BzIx	C_6H_5–	〃	162～163	C_6H_6	$C_{11}H_{10}O_2N_2$	65.34	4.99	13.85	65.53	5.00	13.94
5-AcIx	CH_3–		113～113.5	CCl_4	$C_7H_{10}O_2N_2$	54.53	6.54	18.17	54.83	6.70	18.22
5-BzIx	C_6H_5–	〃	97～97.5	〃	$C_{12}H_{12}O_2N_2$	66.65	5.59	12.96	66.88	5.82	12.73
2-AcPm	CH_3–		146～147	AcOEt	$C_6H_7O_1N_3$	52.55	5.15	30.64	52.62	5.40	30.47
2-BzPm	C_6H_5–	〃	140.5～141.5	C_6H_6	$C_{11}H_9O_1N_3$	66.32	4.55	21.10	66.04	4.46	21.23

H_2O, the ether extract was dried over Na_2SO_4. Evaporation of ether left 1.3 g. of the crude product, which was purified by repeated extraction with petr. benzin. Recrystallization from CCl_4 gave needles, m.p. 83.5～84.5°.

2-Acetamidothiophene (2-AcTp)——To a solution of 9 g. of the 2-aminothiophene salt in 25 ml. of H_2O a solution of 6.5 g. of Ac_2O in 10 ml. of ether was added under ice-cooling. To the mixture an aqueous solution of NaOH (11 g. in 11 ml. of H_2O) was added gradually under ice-cooling and stirring. The crude product was collected by filtration and washed with H_2O. The filtrate was neutralized with HCl and shaken with ether. After the ether extract was washed with H_2O and dried over Na_2SO_4, the solvent was removed. Total yield, 3.7 g. Recrystallization from benzene gave crystals of m.p. 160.5～160°.

2-Benzamidothiophene (2-BzTp)——To a mixture of an aqueous solution of 9 g. of the 2-aminothiophene salt and 80 ml. of ether 4.9 g. of benzoyl chloride and an aqueous solution of NaOH (8 g. in 40 ml. of H_2O) were added dropwise under ice-cooling and stirring. The ether layer was separated, washed with H_2O and dried over Na_2SO_4. Evaporation of the solvent gave 2.5 g. of the crude product, which was purified by recrystallization from benzene with charcoal, m.p. 174.5～175°.

The other sulfonamide and carboxylic acid amide derivatives were synthesized from amino heterocyclic compounds and sulfonyl chloride, acetic anhydride, or benzoyl chloride according to general methods. Melting points and microanalytical data are given in Tables I and II.

The sulfanilamide derivatives were those from commercial source.

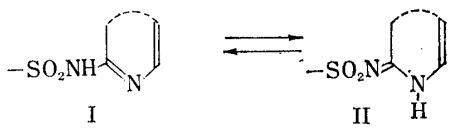
The N-deuterated compounds were prepared by the exchange reaction with heavy water in dioxane or acetone solutions. The infrared spectra of these N-deuterated species were compared with those of the undeuterated species which were treated with ordinary water under the same condition. For 3-PSIx, however, we encountered quite fortuitous occurrences of different crystal forms without any appreciable change in the crystallization procedure. The N-H stretching absorption is a single sharp band for some crystals and split into several broad bands for others. Accordingly the crystal forms of the undeuterated and the deuterated samples of 3-PSIx were identified by comparing the infrared spectrum of the undeuterated sample with that of the deuterated sample placed in moist atmosphere for a few days. Fortunately, the polymorphism observed for 3-PSIx does not cause any serious trouble in this study because the absorption bands discussed in the following are commonly observed for different crystal forms.

Measurements

The measurements were carried out with the instrument and the technique described in the previous paper.[3]

Results and Discussion

Previously we pointed out that a prominent spectral change on N-deuteration occurs in the region 1600 to 1400 cm^{-1} for the imido-form and in the region 1000 to 700 cm^{-1} for the amido-form. The spectral change in the region 1600 to 1500 cm^{-1} was observed for methylsulfonamidopyridines by Jones and Katritzky[2]. The difference in the pattern of the spectral change between the amido- and the imido-forms may be related to the difference in the position of N-H group between these two forms. The N-H group is inside and outside the heterocyclic ring for the imido-form (II) and the amido-form (I), respectively.



I II

One may suppose therefore that the NH or ND deformation vibrations couple with the ring stretching vibrations in the imido-form and with the S-N or the N-C stretching vibrations in the amido-form. Figures 1 to 4 show the infrared spectra of 2-phenylsulfonamidothiophene (2-PSTp), 2-phenylsulfonamido-5-methyl-1,3,4-thiadiazole (2-PSTd), 3-phenylsulfonamido-5-methylisoxazole (3-PSIx), 3,4-dimethyl-5-phenylsulfonamidoisoxazole (5-PSIx), and their N-deuterated compounds. Table III shows the frequencies and the relative intensities of the absorption bands to be discussed in the following. The compounds previously treated are also included in Table III for comparison.

2-PSTp can be used as a model compound of the amido-form just as methanesulfonanilide and benzenesulfonanilide in the previous paper. The absorption bands of 2-PSTp, 3-MSIx, 3-PSIx, and 5-PSIx between 1650 to 1500 cm^{-1} remain almost unchanged on N-deuteration, while a prominent spectral change occurs in the same

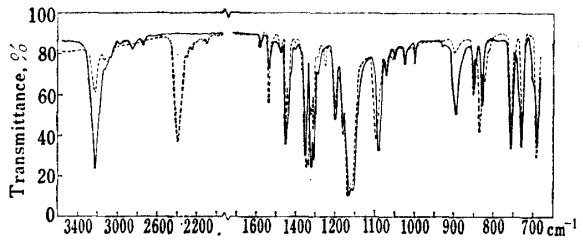


Fig. 1. Infrared Spectra of 2-PSTp (solid line) and 2-PSTp-*d* (broken line)

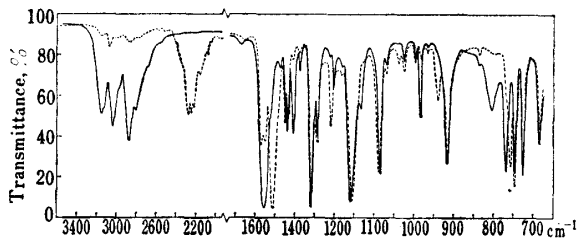


Fig. 2. Infrared Spectra of 2-PSTd (solid line) and 2-PSTd-*d* (broken line)

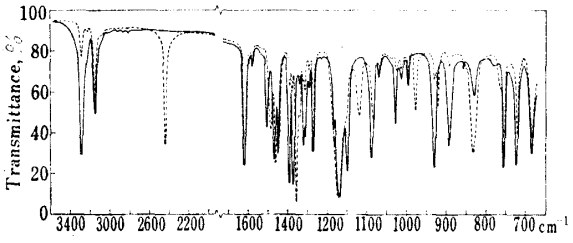


Fig. 3. Infrared Spectra of 3-PSIx (solid line) and 3-PSIx-*d* (broken line)

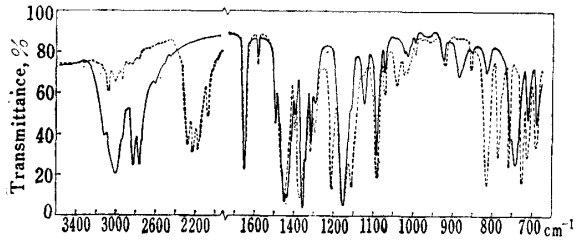


Fig. 4. Infrared Spectra of 5-PSIx (solid line) and 5-PSIx-*d* (broken line)

region on N-deuteration of 2-PSTd. The spectral change in the double bond stretching region, similar to that observed for 2-PSTd, has been reported for the compounds which are in the lactam form in the solid state. Nakamura[7] has assigned a strong band around 1600 cm^{-1} of 2(1*H*)-pyridone to the in-plane NH bending vibration on the basis of N-deuteration and dichroism measurement. Hirano and his co-workers[8] have suggested that the spectral change in the region 1660 to 1500 cm^{-1} for 6-hydroxypyrimidine derivatives is attributed to the effect of the deuteration of ring NH on the ring vibration. The ring structural part, $=\overset{|}{C}-NH-$, seems to be essential for the spectral change on N-deuteration around 1600 cm^{-1}. The above result suggests therefore that 2-PSTd takes the imido-form, while 3-MSIx, 3-PSIx, and 5-PSIx take the amido-form in the crystalline state.

The amido- and the imido-forms may also be distinguished from each other by the examination of the region 950 to 880 cm^{-1}. The band at 917 cm^{-1} of 2-PSTd remains unshifted, whereas the bands around 900 cm^{-1} of 2-PSTp, 3-MSIx, 3-PSIx, and 5-PSIx disappear or shift to lower frequencies on N-deuteration. The characteristic bands of sulfonamides around 900 cm^{-1} have been discussed by several authors. For the imido-form Sheinker and his co-workers[1] have observed a band in the region 915 to 990 cm^{-1} and attributed it to the structure, $-SO_2-N=\overset{|}{C}-N<$. This band does not shift on N-deuteration. On the other hand, Tanaka and Tanaka[9] have observed a band between 950 to 850 cm^{-1} (the Band B in their paper) which shifts to lower frequencies by 30 to 100 cm^{-1} on N-deuteration for many sulfonamides and assigned it to the S-N stretching vibration of the structure, $-SO_2-NH-$. Although the possibility of the amido-imido tautomerism has not been discussed by Tanaka and Tanaka, it is obvious that the Band B occurs only for the amido-form. Among the frequencies between 950 and 850cm^{-1} in Figs. 1 to 4 that of 2-PSTd corresponds to Sheinker's band of the imido-form, while those of 2-PSTp, 3-PSIx, and 5-PSIx correspond to Tanaka's Band B of the amido-form. This means that the conclusion from the region 1650 to 1500 cm^{-1} agrees with that from the region 950 to 850 cm^{-1}. It should

7) K. Nakamura: Nippon Kagaku Zasshi, **80**, 231 (1959).
8) H. Hirano, H. Yonemoto, H. Kamio: Yakugaku Zasshi, **76**, 239 (1956).
9) Y. Tanaka, Y. Tanaka: This Bulletin, **13**, 399 (1965).

be noted here that the N-deuteration is useful to distinguish Sheinker's band from Tanaka's Band B and to reach the correct conclusion on the amido-imido tautomerism.

Comparison with Acid Amides——The infrared spectra of N-substituted acetamide and benzamide derivatives, which contain the same heterocyclic N-substituents as the sulfonamides discussed above, were measured for both the undeuterated and the N-deuterated compounds in the solid state. Besides the amide I band, the amide II and III bands were clearly identified for each of these N-substituted amides by referring to the spectral change on N-deuteration. The presence of these bands shows that each amide investigated exists in the usual amide form, R-CONH-R′, in the solid state. One may therefore expect that the acid amides and the sulfonamides having the same N-substituents show similar heterocyclic ring stretching bands if

Table III. The Absorption Bands due to Heterocyclic Rings in the Region 1650~1500 cm^{-1} (in cm^{-1})

	Sulfonamides[a]			Carboxylic acid amides[a]	
	NH-compd.	ND-compd.		NH-compd.	ND-compd.
			2-AcTp	— [b]	1537 s
2-PSTp	1537 w	1537 m	2-BzTp	— [b]	1536 s
2-MSTh	1568 vs 1536 vs	1527 vs	2-AcTh	— [b]	1520 s
2-PSTh	1567 s 1525 s	1502 vs	2-BzTh	— [b]	1512 s
			2-AcTd	— [b]	1515 s
2-PSTd	1553 vs	1510 vs	2-BzTd	— [b]	1511 s
3-MSIx	1615 s	1611 s	3-AcIx	1624 vs	1610 vs
3-PSIx	1619 s	1616 s	3-BzIx	1623 vs	1617 vs
			5-AcIx	1660 vs	1641 vs
5-PSIx	1651 s	1649 s	5-BzIx	1651 s	1640 vs
2-MSPy	1632 vs 1617 s 1529 m	1628 s 1561 s 1501 vs	2-AcPy	1602 s 1580 vs	1594 vs 1571 s
2-PSPy	1631 vs 1604 s 1526 m	1623 s 1560 m 1503 vs	2-BzPy	1610 vs 1582 vs	1603 s 1583 s
			2-AcPm	1580 vs	1575 vs
2-PSPm	1580 vs	1568 s	2-BzPm	1589 vs	1568 vs

a) MS, PS, Ac and Bz mean methylsulfonamido-, phenylsulfonamido-, acetamido- and benzamido-, respectively. Tp, Th, Td, Ix and Pm are the heterocyclic rings given in Tables I and II. Py means pyridine ring.
b) The first ring stretching band is overlapped by the strong amide II band around 1550 cm^{-1}.

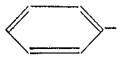
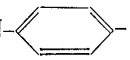
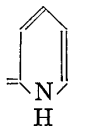
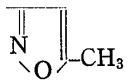
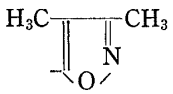
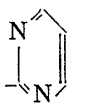
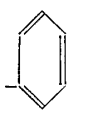
the sulfonamides are in the amido-form. Table III shows the frequencies and the relative intensities of the bands in the region 1650 to 1500 cm^{-1} due to the heterocyclic rings in the sulfonamides and the acid amides. These frequencies could be picked up easily by referring to the characteristic ring stretching frequencies of the corresponding heterocyclic nuclei in literature.[10] Both the frequencies and the intensities in Table III are quite similar to those in the corresponding sulfonamides for 3-AcIx, 3-BzIx, 5-AcIx, 5-BzIx, 2-AcPm, and 2-BzPm. This is also the case for 2-AcTp and 2-BzTp as expected. We exclude the data of the undeuterated carboxylic acid amides for which one of the ring absorptions is obscured by overlapping of the strong amide II band. On the other hand, the agreement between the sulfonamides and the acid amides is very poor for thiadiazole, thiazole, and pyridine derivatives irrespective of

10) A. R. Katritzky: "Physical Methods in Heterocyclic Chemistry," Vol. II, 161 (1963). Academic Press, New York and London.

N-deuteration. This suggests that the sulfonamides with these heterocyclic rings are not in the amido-form, but in the imido-form. This result agrees with the conclusion based on the pattern of the spectral change on N-deuteration of the sulfonamides.

Sulfanilamide Derivatives——We have also investigated the tautomeric forms of sulfamethylthiadiazole, sulfisomezole, and sulfisoxazole by means of both the N-deuteration and the comparison with the acid amides. The presence of the bands due to the NH_2 (ND_2) group for these sulfanilamides (sulfanilamides-d_3) does not obscure the characteristic features of the amido- and the imido-forms in their infrared spectra, because the NH_2 group frequencies have been well established and can be easily identified by deuterating the NH_2 group. The result seems to show that sulfamethylthiadiazole takes the imido-form, and sulfisomezole and sulfisoxazole take the amido-form in the solid state, as in the case of the corresponding benzenesulfonamides. The SO_2 symmetric stretching frequencies of the benzenesulfonamides and the sulfanilamides studied in the present paper are given in Table Ⅳ together with those of the previously

Table Ⅳ. The SO_2 Symmetric Stretching Frequencies of Sulfonamide Derivatives (in cm^{-1})

	R′	R : 	H_2N- 
R-SO_2-N=R′ (Imido-form)		1159	1128
		1148	1135
		1136	1125
R-SO_2-NH-R′ (Amido-form)		1163	
		1171	1157 1144
		1174	1162
		1167	1155
		1155	1152

treated compounds.[3] As previously pointed out[3] the SO_2 symmetric stretching frequencies of the sulfanilamides in the imido-form are lower than those of the sulfanilamides in the amido-form. The similar tendency is observed also for the benzenesulfonamides, although the distinction in the frequency region between the two forms is less obvious. The same conclusion has been reported for methylsulfonamidopyridines, its various methyl derivatives, and methanesulfonanilides by Jones and Katritzky.[2]

The authors are indebted to the members of the Microanalytical Center of Kyoto University for the analytical data.

Summary

Infrared spectra were applied to the studies on the amido-imido tautomerism of the sulfonamide derivatives containing the heterocyclic rings such as thiadiazole and isoxazole. 2-Phenylsulfonamidothiophene was used as a model compound of the amido-form. From the pattern of the spectral change on N-deuteration and the comparison with the corresponding carboxylic acid amides in the region 1650~1500 cm^{-1}, it was found that 2-sulfonamidothiadiazoles exist in the imido-form, while 3- and 5-sulfonamidoisoxazoles exist in the amido-form in the solid state.

For most of the sulfonamides the SO_2 symmetric stretching frequencies of the imido-form were found to be lower than those of the amido-form.

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106. Masatomo Hamana and Hiroshi Noda: Studies on Tertiary Amine Oxides. XXVII.*1 Reactions of Aromatic N-Oxides with Enamines of Cyclohexanone in the Presence of Acylating Agents. (2)*2: Reaction of α- and γ-Methyl-pyridine and -quinoline N-Oxides.

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Recently we have shown that the acyl-adducts of N-oxides of pyridine series readily react with enamines of cyclohexanone to give the corresponding 2-(α-heterocyclyl)cyclohexanones (I, II and III) in good yields after hydrolysis of the reaction mixtures.*2 In order to explore the scope and limitations of the reaction, studies were carried out with a variety of derivatives of aromatic N-oxides. The present communication describes the reactions of α- and γ-methyl-pyridine and -quinoline N-oxides with enamines of cyclohexanone in the presence of an acylating agent.

When benzoyl chloride (1.2 equiv.) was added with stirring to an ice-cooled solution of 2-picoline 1-oxide (IV) and morpholine enamine of cyclohexanone (2 equiv.) in chloroform, an exothermic reaction occurred and the solution turned to light orange. The reaction mixture was allowed to stand at room temperature for further three days, followed by treatment with 20% hydrochloric acid to afford a yellow oil as a basic fraction. It was distilled under reduced pressure to give 2-(6-methyl-2-pyridyl)cyclohexanone (VI), $b.p_{0.2}$ 115~120°, in 82% yield.

Similarly 4-picoline 1-oxide (V) gave 2-(4-methyl-2-pyridyl)-cyclohexanone (VII), $b.p_{0.12}$ 115~120°, in 72% yield.

The structures of VI and VII were deduced from their conversions by hydrogen peroxide-acetic acid oxidation to the corresponding picolinic acid 1-oxides (VIII[1] and IX)

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*1 Part XXVI. M. Hamana, T. Nagayoshi: This Bulletin, **14**, 319 (1966).
*2 Part I. M. Hamana, H. Noda: This Bulletin, **13**, 912 (1965).
*3 Katakasu, Fukuoka (浜名政和, 野田浩司).
1) W. Baker, K. M. Buggle, J. F. W. McOmie, D. A. M. Watkins: J. Chem. Soc., **1958**, 3594; J. Szafran: Roczniki. Chem., **38**, 1793 (1964) (C. A., **62**, 10403 (1965)).