HETEROCYCLES, Vol 26, No 11, 1987

FACILE SYNTHESIS OF SOME OXAZOLOPYRIDINES AND THEIR N-OXIDES VIA INTRAMOLECULAR CYCLIZATION

Yoshinobu Tagawa and Yoshinobu Goto*
Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma,
Jonan-ku, Fukuoka 814-01, Japan

Abstract —— A convenient synthesis of 3-methylisoxazolo[4,5-b]-pyridine 2, 2-methyloxazolo[4,5-b]pyridine 4 and their N-oxides (12, 17 and 18) is reported. The configurations of the oximes used for the synthesis of the compounds described above are discussed through chemical and spectral studies.

In a recent paper[1] we reported that 3-methylisoxazolo[4,5-b]pyridine derivative has been obtained in the reaction of methyl 1-oxido-2-pyridyl ketone oxime (E-form) with acetic anhydride (Ac_2O). As to the synthesis of 3-methylisoxazolo-[4,5-b]pyridine derivatives, only one method[2] is reported, however the method requires the multistage reaction and seems impractical. In addition, we can not find the reports on the synthesis of N-oxides of 3-methylisoxazolo[4,5-b]pyridine 2[3] and 2-methyloxazolo[4,5-b]pyridine 4[4] at all. On the basis of previous finding[1], in this paper we present the facile synthetic approach to 2 and 4 which were prepared by ring closure of the appropriate 2,3-disubstituted pyridines and the first synthetic approach to their N-oxides (12, 17 and 18) which were prepared by the oxidative cyclization of the appropriate 2,3-disubstituted pyridines. Besides, since the configuration of oxime possesses the important influence to the reactivity and the structure of the reaction product in general, that of the oximes (1E, 5E, 9E, 9Z and 14E) used in this paper is also described.

The reaction of methyl 3-hydroxy-2-pyridyl ketone oxime 1E, which was easily prepared from 3-hydroxypyridine 1-oxide in good overall yield (90%), with thionyl chloride ($SOCl_2$)[5], trichloroacetyl isocyanate ($Cl_3CCONCO$)[6] or chlorosulfonyl isocyanate ($ClSO_2NCO$)[7] gave 2 (Scheme 1) with the good yield as shown in Table I. The result in Table I indicates particularly $Cl_3CCONCO$ is most suitable and

$ClSO_2NCO$ is unsuitable for the preparation of 2.

Scheme 1

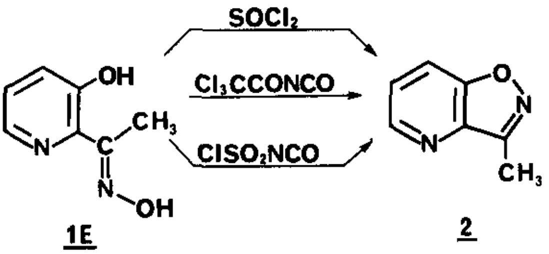
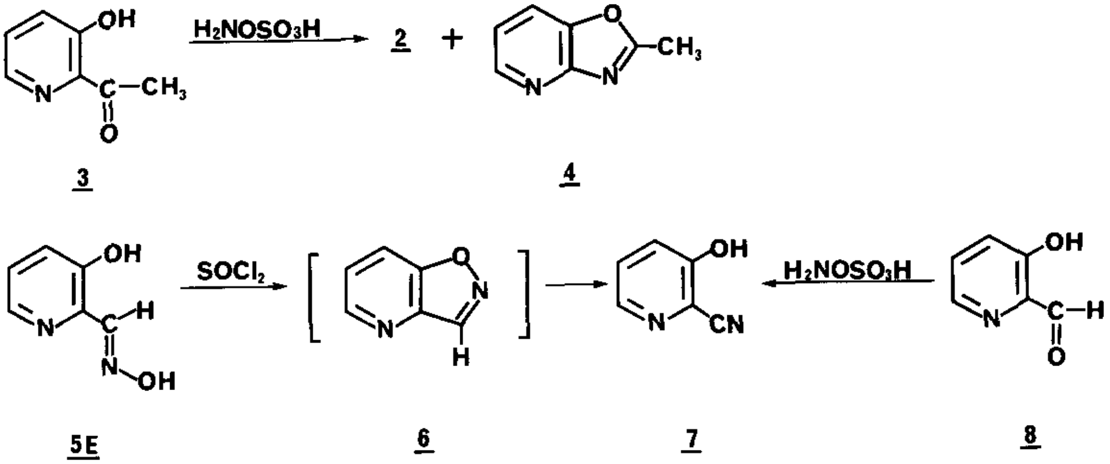


Table I. Effect of Reagents, Solvents and Temperature on the Yield of 2

Reagent	Solvent	Temp.	Time(h)	Yield(%) of 2
$SOCl_2$	ether	r.t.	2	49
	ether	reflux	2	68
	THF	r.t.	2	34
	THF	reflux	2	32
$Cl_3CCONCO$	ether	r.t.	2	73
	ether	reflux	2	78
	THF	r.t.	2	60
	THF	reflux	2	64
$ClSO_2NCO$	ether	r.t.	2	1
	THF	r.t.	2	12
	THF	reflux	2	21

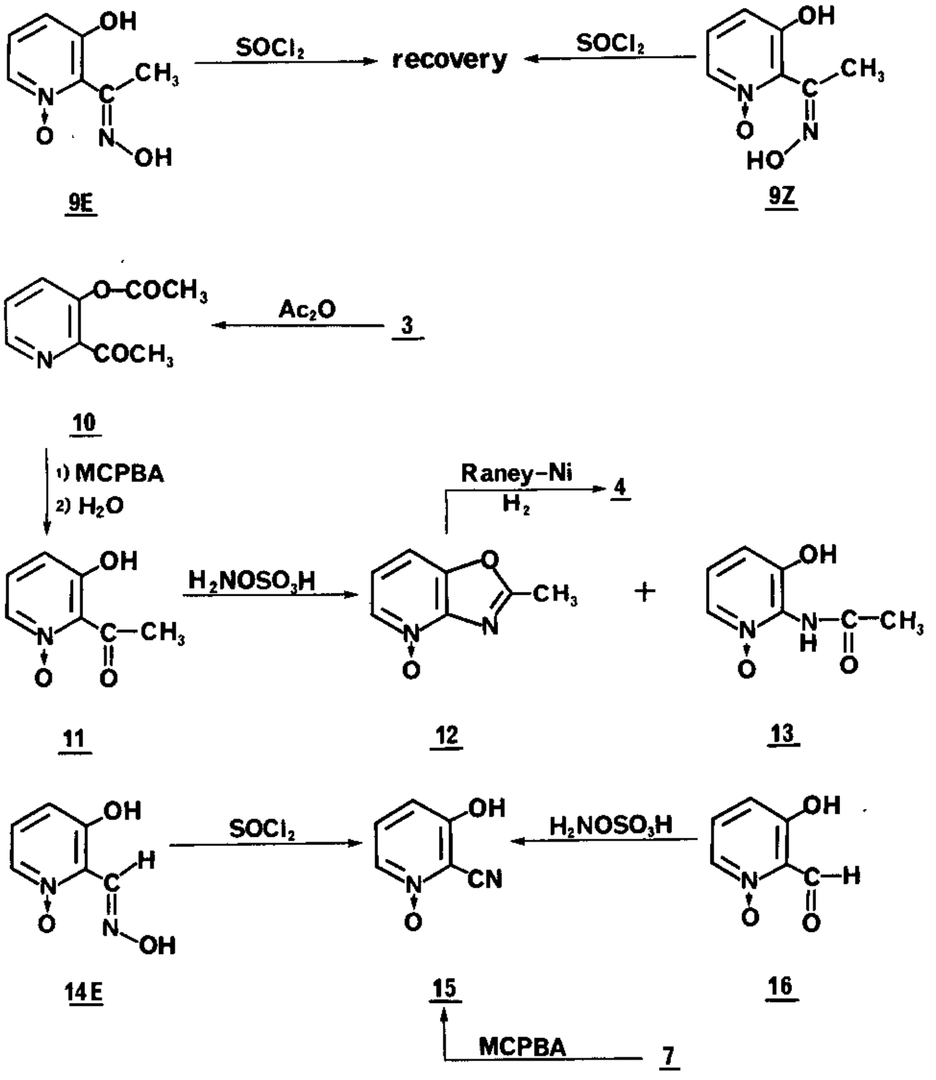
Nextly, the reaction of 2-acetyl-3-hydroxypyridine 3[8] with hydroxylamine O-sulfonic acid (H_2NOSO_3H)[9] gave 2 and 4 which formed probably as a result of a competitive Beckmann rearrangement[9] in a ratio of 1:1 (Scheme 2).

The reactions described above were carried out with the corresponding aldoxime, 3-hydroxy-2-pyridinecarboxaldehyde oxime 5E[10] and aldehyde, 3-hydroxy-2-pyridinecarboxaldehyde 8[10]. Consequently only 2-cyano-3-hydroxypyridine 7[11], which was considered as a result of dehydration reaction, in both reactions was obtained without cyclized compound (Scheme 2). However, in the case of the reaction of 5E with $SOCl_2$ the sample, immediately after the reaction, was subjected to gc-ms measurement to afford the peak based on 7 and the another peak which has the molecular ion and the fragmentation pattern the same as those of 7. This peak is assumed to be isoxazolo[4,5-b]pyridine 6, however, after the subsequent treatment of the resulting mixture, its peak disappeared and only 7 was obtained. This fact indicates that while 6 would be formed, it readily converts into 7 on account of the unstability (Scheme 2).



Scheme 2

In order to obtain the N-oxides of 2 and 4, the reaction of the N-oxides of the oximes and ketones with the foregoing reagents was carried out (Scheme 3). The reaction of methyl 3-hydroxy-1-oxido-2-pyridyl ketone oxime (9E and 9Z) with $SOCl_2$ afforded only the starting oximes, the more improved reaction conditions about this reaction would be required to obtain the desired cyclized compound. The reaction of 2-acetyl-3-hydroxypyridine 1-oxide 11 which was readily synthesized through 3-acetoxy-2-acetylpyridine 1-oxide 10 from 3 with H_2NOSO_3H afforded 2-methyloxazolo[4,5-b]pyridine 4-oxide 12 and 2-acetylamino-3-hydroxypyridine 1-oxide 13 which were both formed as a result of Beckmann rearrangement. Compound 12 was readily deoxygenated with Raney-Ni reduction to give 4. On the other hand, in the reaction of 3-hydroxy-1-oxido-2-pyridinecarboxaldehyde oxime 14E with $SOCl_2$ and the reaction of 3-hydroxy-2-pyridinecarboxaldehyde 1-oxide 16[12] with H_2NOSO_3H both reactions resulted in the formation of 2-cyano-3-hydroxypyridine 1-oxide 15 which was prepared from 7 by use of m-chloroperoxybenzoic acid (MCPBA) (Scheme 3).



Scheme 3

Therefore, in order to obtain N-oxides of 2 the reaction of 1E and 9E(or 9Z) with sodium hypochlorite (NaOCl) or lead(IV) acetate ($Pb(OAc)_4$) used in the synthesis of 1,2-benzisoxazole 2-oxides[13] was investigated (Scheme 4). The reaction of 1E with NaOCl(or $Pb(OAc)_4$) afforded mono-N-oxide, 3-methylisoxazolo[4,5-b]pyridine 2-oxide 17 in good yield as shown in Table II. Moreover, in the reaction of 9E (or 9Z) with NaOCl(or $Pb(OAc)_4$) di-N-oxide, 3-methylisoxazolo[4,5-b]pyridine 2,4-

dioxide 18 was obtained with the yield as shown in Table II and deoxygenated with phosphorus trichloride (PCl$_3$) to give 17. It is estimated that the low yield of 18 is responsible for the solubility of the oximes 9E and 9Z. However, as also observed in the preparation of 1,2-bezisoxazole 2-oxides[13], attempts to isolate the 3-unsubstituted compound by the reaction of 5E with NaOCl resulted in the recovery of starting oxime. Since there is no difference in the yield of 18

Scheme 4

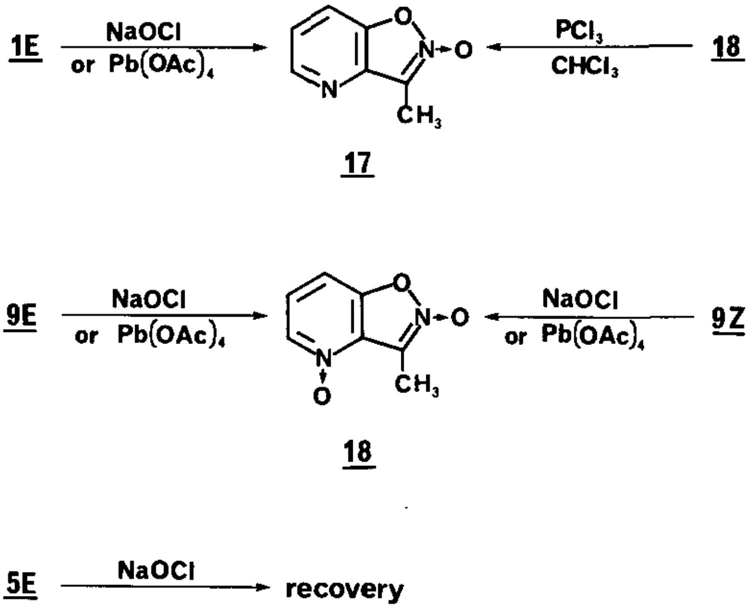


Table II. Reaction of Oximes with Oxidants

Oxime	Oxidant	Product	Yield(%)
1E	NaOCl	17	70
	Pb(OAc)$_4$	17	90
9E	NaOCl	18	11
	Pb(OAc)$_4$	18	37
9Z	NaOCl	18	31
	Pb(OAc)$_4$	18	21

between 9E and 9Z, it seems likely that the configuration of the oxime is unimportant to the formation mechanism of 18 in this case (Scheme 4).

The configuration of the oximes described in this paper was determined in the following way (Scheme 5). The reaction of 1E with trimethylsilyl polyphosphate (PPSE)[14] which is a useful reagent for the Beckmann rearrangement gave 2-acetylamino-3-hydroxypyridine 19[15] as a main product, which indicated 1E having E-form, along with 2 and 4 which had been unexpected to form. In the Beckmann rearrangement of oximes using PPSE, while the product corresponding to 4 which cyclizes via dehydration after Beckmann rearrangement was also observed in the preparation of 2-methylbenzisoxazole[16], no reports on the product corresponding to 2 which cyclizes merely via dehydration without Beckmann rearrangement were found. Therefore, this reaction was performed at room temperature or reflux temperature to give the result as shown in Table III which indicates that the yield of 19

Scheme 5

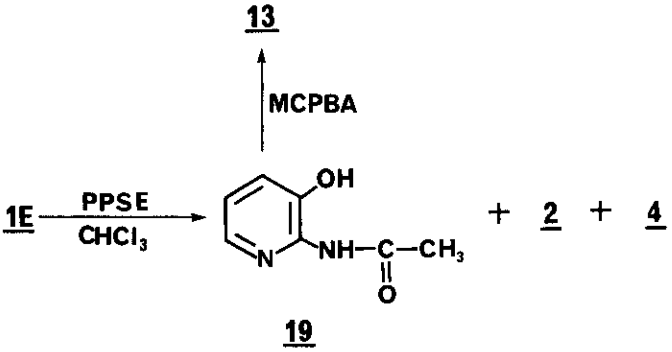


Table III. Effect of Temperature on the Yield of 2, 4 and 19

Compound	Temp.	Yield(%)
19	r.t.	11
	reflux	23
2	r.t.	7
	reflux	trace
4	r.t.	8
	reflux	4

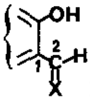
increases at reflux temperature and that of 2 and 4 increases at room temperature. *In addition*, 19 was easily oxidized to 13 with MCPBA (Scheme 5). In the case where E- and Z-form are both present, the configuration of the oximes can be easily determined based on the chemical shift difference of α carbon attributable to steric compression effect *in carbon-13 nuclear magnetic* resonance spectroscopy (^{13}C-nmr)[17] and that of the hydroxyl proton of oxime in proton nuclear magnetic resonance (^{1}H-nmr)[18] (Table IV).

Table IV. The nmr Parameters for the Establishment of the Configuration of oximes

Parameter[a)]	Compound			
	5E	**9E**	**9Z**	**14E**
$\Delta_{\underline{C}H_3}$(ppm)[b)]	—	13.5	17.5	—
$\delta_{O\underline{H}}$ (ppm)	11.8	11.3	10.7	12.2
Δ^1J_{C1C2}[c)] (Hz)	10.4	—	—	—[d)]
$\delta_{O\underline{H}} - \delta_{-C\underline{H}=N-}$(ppm)	3.5	—	—	3.5

a) All spectra were measured in DMSO-d_6 using TMS as an internal standard.

b) $\Delta_{CH_3} = \delta_{ketone-\underline{C}H_3} - \delta_{ketoxime-\underline{C}H_3}$

c) 

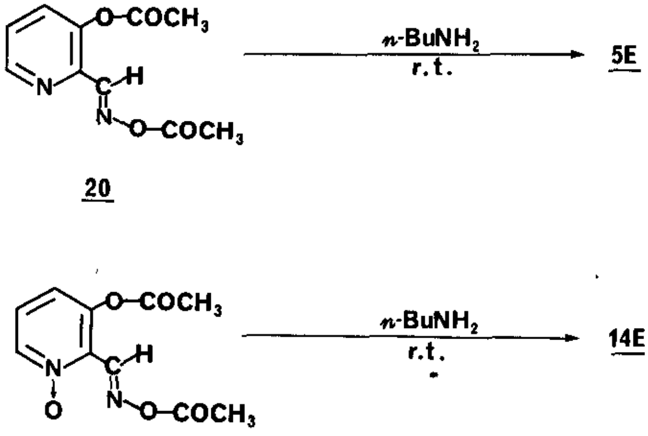
X=O or NOH

$$\Delta^1J_{c1c2} = {}^1J_{c1c2(aldoxime)} - {}^1J_{c1c2(aldehyde)}$$
$$= 72.23 - 61.80 \doteq 10.4\ \text{Hz}$$

d) It was impossible to determine $^1J_{c1c2}$ of 16 because of the instability of 16 in DMSO-d_6.

From the result of the determination as shown in Table IV, it is clear that 9E *and* 9Z are assigned to E-form and Z-form, respectively. In the case where only one isomer is obtainable, we can not use the methods as described above, however the magnitude of $\delta_{O\underline{H}} - \delta_{C\underline{H}=N-}$ can be utilized as a criterion for assigning aldoxime configuration[18]. However, *as shown in Table IV the both magnitudes of* 5E and 14E allow ambiguous configuration assignment of those oximes, therefore, in addition recently reported ^{13}C-^{13}C spin-spin coupling constants ($^{1}J_{cc}$)[19] as a configurational probe in unambiguous assignment of oximes was determined to give the result as shown in Table IV which indicates that 5E has an E-form undoubtedly, but in the case of 14E the determination of $^{1}J_{cc}$ was impossible owing to the instability of 16 in dimethylsulfoxide-d_6 (DMSO-d_6). Finally, hydrolysis of acetates of 5E and 14E, *i.e.*, 3-acetoxy-2-pyridinecarboxaldehyde O-acetyloxime 20 and 3-acetoxy-1-oxido-2-pyridinecarboxaldehyde O-acetyloxime 21 by use of mild base, n-butylamine[20] was investigated to afford the starting oximes in both hydrolysis. This result indicates that both 5E and 14E have E-forms (Scheme 6).

Scheme 6



20

21

The mechanism of the formation of 2, 4 and 12 in the reaction of the ketones and the ketoximes used in this investigation with $SOCl_2$, $Cl_3CCONCO$, $ClSO_2NCO$ and H_2NOSO_3H may be rationalized by an intramolecular nucleophilic substitution based on the activated imino nitrogen involving the Beckmann rearrangement in the case of 4 and 12. As to the mechanism of formation of 17 and 18, that *via* the nitroso quinonemethide[13] proposed as a reaction intermediate in the preparation of 1,2-benzisoxazole 2-oxide may be supported since there is no difference between 9E and 9Z in the yield of 18. Some trials to synthesize 3-unsubstituted cyclized compounds of 2 and the N-oxides, *i.e.*, isoxazolo[4,5-b]pyridine and isoxazolo-[4,5-b]pyridine 2-oxide were all unsuccessful to give the only nitriles, instead. With respect to these compounds the kinetic and thermodynamic stability may have to be discussed based on the quantum chemical calculation. However, these methods used in this paper may be sufficiently applicable also to the preparation of cyclized compounds which bear the substituent groups in pyridine nuclei. In the near future, the paper about the reaction of new and interesting compounds, i.e., 12, 17 and 18 with nucleophiles and electrophiles would be reported.

EXPERIMENTAL

Melting points were measured on a Yanagimoto micro melting point apparatus and are uncorrected. Spectral data were recorded on the following spectrometers: ultraviolet (uv) spectra, Hitachi 556; infrared (ir) spectra, JASCO IR-810; ^{1}H-nmr spectra, JEOL FX-100(100MHz) and JEOL GX-400(400MHz); ^{13}C-nmr spectra, JEOL FX-100(25.1MHz) and JEOL GX-400(100.5MHz); mass spectra (ms), JEOL JMS-DX300. High-performance thin layer chromatography (HPTLC) about the yields as shown in Table I, II and III was conducted on a Shimadzu high speed thin layer chromatoscanner (CS-920) with the detector set at uv 254nm. Gc-ms analysis was performed on a JEOL JMS-DX300. gc-ms conditions: column, 1.5% Silicon OV-17, 2mm 1m; column temperature 115°C; flow rate, He gas 20ml/min. Column chromatography was carried out with Kieselgel 60(70-230mesh, Merck). $^1J_{cc}$ was measured using JEOL GX-400 mostly according to the reference 19 and the sample was the 50% solution in DMSO-d_6 involving 0.6% of chromium tris-acetylacetonate as a relaxant.

Synthesis of Methyl 3-Hydroxy-2-pyridyl Ketone Oxime 1E —— A mixture of 2-acetyl-3-hydroxypyridine^8 (1g, 7.3mmol) in 99%EtOH (30ml) and hydroxylamine hydrochloride (0.51g, 7.4mmol dissolved in the minimum amount of water) was heated in the presence of sodium acetate (1.05g, 12.8mmol) for 3 h at reflux temperature. The solution was cooled in ice-water and the resulting precipitate was filtered off and washed with water. The product was purified by dissolving it in a minimum amount of EtOH, by treating with Norite, and by adding a large volume of water at room temperature to give colorless prisms, mp 179-181°C, 1.0g(90% yield). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.18; H, 5.32; N, 18.19. Uv λ_{max}^{EtOH}nm(logϵ): 306(4.44). Ir ν_{max}^{KBr}cm^{-1}: 3200-2800(OH), 1635(C=N), 1450, 1300, 1016, 737. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$(100MHz): 2.36(3H,s,CH_3), 7.30-7.33(2H,m, H-4 and H-5), 8.15-8.21(1H,m,H-6), 11.63(1H,s,phenolic OH), 11.90(1H,s,hydroxyimino OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$(25.1MHz): 9.96(q,CH_3), 123.71(d,C-4), 124.66(d,C-5), 136.48(s,C-2), 139.79(d,C-6), 154.02(s,C-3), 159.90(s,C=N). Ms m/z(rel.int.):

152(M^+,100), 135(75), 120(30), 98(28). High-resolution ms Calcd for $C_7H_8N_2O_2(M^+)$: 152.059. Found: 152.058.

General Procedure for the Reaction of the Oximes with $SOCl_2$ —— To a mixture of oxime (2mmol) in anhydrous ether (or anhydrous THF)(10ml) and dry pyridine (20mmol, $SOCl_2$ (2mmol) was added dropwise with stirring under ice-cooling.

Reaction of 1E with $SOCl_2$ —— The resulting mixture was further stirred for 2 h at the temperature as shown in Table I. After removal of solvent, 2 was separated from the residue by sublimation (at 45°C and 0.3mmHg) to give the yield as shown in Table I. The mp, ^{1}H- and ^{13}C-nmr and ir spectra coincided with those of an authentic sample 2[2,3].

Reaction of 3-Hydroxy-2-pyridinecarboxaldehyde Oxime 5E with $SOCl_2$ —— After the resulting mixture was further stirred for 2 h under ice-cooling (at this time, a part of this mixture was investigated by gc-ms to afford the molecular ion peak and the fragmentation to be estimated as those of 6), the solvent was evaporated off and $CHCl_3$ was added to the residue. Insoluble substance to $CHCl_3$ was filtered off and the substance was recrystallized from CH_3COOEt to give colorless crystals, 0.19g(80% yield). The mp and ir spectrum coincided with those of an authentic sample 7[11].

Reaction of Methyl 3-Hydroxy-1-oxido-2-pyridyl Ketone Oxime 9 (E- and Z-form, vide infra) with $SOCl_2$ —— After the resulting mixture was further stirred for 2 h at room temperature, the solvent was evaporated off to dryness and the residue was recrystallized from EtOH to give the starting oxime 9E (or 9Z), 0.25g(73% recovery) (or 0.27g, 80% recovery in the case of 9Z).

Reaction of 3-Hydroxy-1-oxido-2-pyridinecarboxaldehyde Oxime 14E (vide infra) with $SOCl_2$ —— After the resulting mixture was further stirred for 2 h, the solvent was evaporated off to dryness and $CHCl_3$ was added to the residue. Insoluble product to $CHCl_3$ was filtered off and recrystallized from boiling water to give colorless prisms, 0.22g(80% yield). The mp and ir spectrum coincided with those of an authentic sample 15 (vide infra).

General Procedure for the Reaction of 1E with $Cl_3CCONCO$ (or $ClSO_2NCO$) —— $Cl_3CCONCO$ (0.26g, 1.38mmol. or $ClSO_2NCO$, 0.20g, 1.38mmol) in anhydrous ether (10ml, or anhydrous THF 10ml) was added dropwise to a solution of 1E (0.2g, 1.32mmol) in anhydrous ether (10ml, or anhydrous THF 10ml) with stirring at room temperature. After further stirring for 0.5 h at room temperature, K_2CO_3 (0.2g, 1.45mmol) was added in a small portion to the solution. The resulting mixture was further stirred for 2 h at the temperature as shown in Table I. After removal of solvent, a little water was added to the residue and the solution was extracted with $CHCl_3$. After the $CHCl_3$ layer was dried over $MgSO_4$ and evaporated off to dryness, 2 was separated from the residue by sublimation to give the yield as shown in Table I.

General Procedure for the Reaction of the Ketones or the Aldehydes with H_2NOSO_3H —— The ketone (or aldehyde)(10mmol) was dissolved in a solution of H_2NOSO_3H (12 mmol) in water (15ml) with stirring and ether (20ml) was added to the solution. To the solution $NaHCO_3$ (38mmol) was added in a small portion under ice-cooling with vigorous stirring. When the addition was completed, the mixture was stirred for 5 h at room temperature.

Reaction of 2-Acetyl-3-hydroxypyridine 3 with H_2NOSO_3H —— After the resulting mixture was extracted with ether thoroughly and the ether layer was dried over $MgSO_4$, the solvent was evaporated off completely and the residue was subjected to column chromatography on silica gel to give 2 (with benzene as the eluent) and 4 (with $CHCl_3$ as the eluent). Compound 2 was purified by sublimation (at 45°C and 0.3mmHg) to give colorless prisms, 0.62g(46% yield). Compound 4 was recrystallized from petr. ether to give colorless prisms, 0.58g(43% yield). Those mps and ir spectra coincided with those of the authentic samples.

Reaction of 3-Hydroxy-2-pyridinecarboxaldehyde 8 with H_2NOSO_3H —— After removal of the solvent (the organic layer and aqueous layer), the residue was recrystallized from CH_3COOEt to give colorless crystals, mp 211°C(decomp.), 1.03g(86% yield). The mp and ir spectrum coincided with those of an authentic sample 7[11].

Reaction of 2-Acetyl-3-hydroxypyridine 1-Oxide 11 (*vide infra*) with H_2NOSO_3H —— After the resulting mixture was extracted with water and the solvent was completely evaporated off, MeOH was added to the residue and insoluble substance to MeOH was filtered off. The filtrate was subjected to column chromatography on silica gel using mixed solvent of $CHCl_3$:MeOH=50:1 as the eluent to give 2-methyloxazolo-[4,5-b]pyridine 4-oxide 12 and 2-acetylamino-3-hydroxypyridine 1-oxide 13 successively. Compound 12 was recrystallized from ether-acetone to give colorless prisms, mp 170-171°C(decomp.), 0.69g(46% yield). Anal. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.98; H, 4.00; N, 18.66. Uv λ_{max}^{EtOH}nm(logϵ): 228(4.89), 288(4.59). Ir ν_{max}^{KBr}cm^{-1}: 3072, 1600, 1459, 1433, 1239(N→O), 1065, 801. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(400MHz): 2.74(3H,s,CH_3), 7.22(1H,dd,J=8.3 and 6.8Hz,H-6), 7.44(1H, d J=8.3Hz,H-7), 8.25(1H,d J=6.8Hz,H-5). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$(100MHz): 14.69(q,CH_3), 108.71(d,C-7), 120.34(d,C-6), 135.93(d,C-5), 146.87(s,C-7a), 146.92(s,C-3a), 166.47(s,C-2). Ms m/z(rel.int.): 150(M^+,100), 134(13), 108(42). High-resolution ms Calcd for $C_7H_6N_2O_2$(M^+): 150.043. Found: 150.042. Compound 13 was recrystallized from ether-acetone to give colorless prisms, mp 204°C, 0.76g(45% yield). *Anal*. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.00; H, 4.75; N, 16.41. Uv λ_{max}^{EtOH}nm(logϵ): 236(4.78). Ir ν_{max}^{KBr}cm^{-1}: 3200-2600(OH), 1668(C=O), 1529, 1494, 1488, 1380, 1238(N→O), 1055, 791, 708. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(100MHz): 2.41 (3H,s,CH_3), 6.95-6.99(2H,m,H-4,H-5 overlapped), 7.89(1H,dd J=4.2 and 3.7Hz,H-6), 10.45(1H,br s,NH), 11.20(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 24.00(q,CH_3), 118.38 (d,C-4), 120.06(d,C-5), 129.17(d,C-6), 135.23(s,C-2), 145.79(s,C-3), 171.89(s, C=O). Ms m/z(rel.int.): 168(M^+,62), 126(49), 109(100), 81(35). High-resolution ms Calcd for $C_7H_8N_2O_3$(M^+): 168.053. Found: 168.053.

Reaction of 3-Hydroxy-2-pyridinecarboxaldehyde 1-Oxide 16 with H_2NOSO_3H —— After removal of the solvent, a little amount of water was added to the residue. The aqueous solution was mildly acidified with 10% HCl aqueous solution and the resulting precipitate was filtered off followed by washing with water. Recrystallization from boiling water gave colorless prisms, 0.71g(51% yield). The mp and ir spectrum coincided with those of an authentic sample 15 (*vide infra*).

General Procedure for the Reaction of the Oximes (1E, 5E, 9E and 9Z) with NaOCl —— A solution of aqueous NaOCl solution (commercial grade, available chlorine 5% minimum: 5.8g, 4.0mmol) was added dropwise to a solution of the oxime (3.3mmol) in ether (50ml) with vigorous stirring under ice-cooling. The resulting solution was continuously stirred for 1 day at room temperature, and then extracted with ether. The ether solution was dried over $MgSO_4$ and evaporated to dryness.

Reaction of 1E with NaOCl —— The residue was subjected to column chromatography on silica gel using ether as the eluent to give 3-methylisoxazolo[4,5-b]pyridine 2-oxide 17, colorless prisms (from petr. ether), mp 99-100°C, 0.33g(70% yield). *Anal*. Calcd for $C_7H_6N_2O_2$: C, 56.00; H, 4.03; N, 18.66. Found: C,56.25; H, 3.97; N, 18.56. Uv λ_{max}^{EtOH}nm(logϵ): 260(4.22), 311(4.61). Ir ν_{max}^{KBr}cm^{-1}: 1606, 1568, 1457, 1432, 1208(N→O), 1194, 803, 782, 669. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(100MHz): 2.51(3H,s,CH_3), 7.40-7.43(2H,m,H-6,H-7 overlapped), 8.54(1H,dd J=3.7 and 2.4Hz,H-5). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 8.62(q,CH_3), 113.30(d,C-7), 115.09(s,C-3a), 122.52(d, C-6), 140.62(s,C-7a), 145.43(s,C-3), 146.77(d,C-5). Ms m/z(rel.int.): 150(M^+, 100), 120(91), 92(44), 65(94), 39(91). High-resolution ms Calcd for $C_7H_6N_2O_2$(M^+): 150.043. Found: 150.043.

Reaction of 9E (or 9Z) with NaOCl —— The residue was subjected to column chromatography on silica gel using $CHCl_3$ as the eluent to give 3-methylisoxazolo[4,5-b]-pyridine 2,4-dioxide 18, pale yellow prisms (from ether-acetone), mp 148-149°C (decomp.), 0.06g(11% yield) in the case of 9E and 0.17g(31% yield) in the case of 9Z. Anal. Calcd for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.60; H, 3.56; N, 16.66. Uv λ_{max}^{EtOH}nm(logϵ): 263(4.57), 321(4.76). Ir ν_{max}^{KBr}cm^{-1}: 1596, 1445, 1244(N→O), 1073, 567. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(100MHz): 2.75(3H,s,CH_3), 7.05(1H,d J=8.5Hz, H-7), 7.33(1H,dd J=8.5 and 6.4Hz,H-6), 8.08(1H,d J=6.4Hz.H-5). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$ (100MHz): 10.82(q,CH_3), 104.33(d,C-7), 112.98(s,C-3a), 123.74(d,C-6), 130.81(s, C-7a), 135.50(d,C-5), 147.36(s,C-3). Ms m/z(rel.int.): 166(M^+,100), 120(69), 91 (33). High-resolution ms Calcd for $C_7H_6N_2O_3(M^+)$: 166.038. Found: 166.038.

Reaction of 5E with NaOCl —— The residue was recrystallized from boiling water to give the starting oxime 5E, 0.39g(86% recovery).

General Procedure for the Reaction of the Oximes (1E, 9E and 9Z) with $Pb(OAc)_4$ — The ground $Pb(OAc)_4$ (1.75g, 4mmol) was added in a small portion to a solution of the oxime (3.3mmol) in anhydrous ether (50ml) with vigorous stirring under ice cooling. The resulting solution was further stirred for 1 day at room temperature. After the precipitated lead(II) acetate was filtered off, the filtrate was dried over $MgSO_4$ and the solvent was evaporated to dryness.

Reaction of 1E with $Pb(OAc)_4$ —— The residue was treated in the same manner as in the case of the reaction of 1E with NaOCl to give 17, 0.45g(90% yield).

Reaction of 9E (or 9Z) with $Pb(OAc)_4$ —— The residue was treated in the same manner as in the case of the reaction of 9E (or 9Z) with NaOCl to give 18, 0.2g(37% yield) in the case of 9E and 0.12g(21% yield) in the case of 9Z.

Synthesis of 9E and 9Z —— A mixture of 11 (2.23g, 14.6mmol vide infra) in 99% EtOH and hydroxylamine hydrochloride (1.02g, 14.7mmol) dissolved in the minimum amount of water was heated in the presence of sodium acetate (2.09g, 25.5mmol) for 3 h at reflux temperature. The EtOH was evaporated off, cold water was added, and the resulting precipitate was filtered off and washed with water. The crude oxime was recrystallized from EtOH to give a mixture of 9E and 9Z (with a ratio of 1:1 from ^{1}H-nmr), 2.2g(89% yield). 9E and 9Z were separated by fractional recrystallization from water. 9E : mp 235-237°C. Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 49.95; H, 4.86; N, 16.51. Uv λ_{max}^{EtOH}nm(logϵ): 228 (4.68), 240(4.68). Ir ν_{max}^{KBr}cm^{-1}: 3200-2800(OH), 1480, 1322, 1273, 1233, 1198, 1045.

^{1}H-Nmr $\delta_{\rm ppm}^{\rm DMSO\text{-}d_6}$(100MHz): 1.97(3H,s,$CH_3$), 6.91(1H,d J=8.6Hz,H-4), 7.14-7.29(1H,m, H-5), 7.85(1H,d J=6.1Hz,H-6), 10.56(1H,s,phenolic OH), 11.30(1H,s,hydroxyimino OH) ^{13}C-Nmr $\delta_{\rm ppm}^{\rm DMSO\text{-}d_6}$(25.1MHz): 13.49(q,$CH_3$), 113.33(d,C-4), 124.96(d,C-5), 130.69(d, C-6), 135.68(s,C-2), 146.83(s,C-3), 154.08(s,C=N). Ms m/z(rel.int.): 168(M^+,43), 151(100), 120(50). High-resolution ms Calcd for $C_7H_8N_2O_3$(M^+): 168.053. Found: 168.054. **9Z**: mp 238-240°C. *Anal*. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66 Found: C, 49.99; H, 4.82; N, 16.55. Uv $\lambda_{\rm max}^{\rm EtOH}$nm(log$\epsilon$): 226(4.76). Ir $\nu_{\rm max}^{\rm KBr}$cm^{-1}: 3200-2500(OH), 1574, 1438, 1256, 1207(N→O), 1044, 1030, 1013, 809. ^{1}H-Nmr $\delta_{\rm ppm}^{\rm DMSO\text{-}d_6}$(100MHz): 2.00(3H,s,$CH_3$), 6.85(1H,d J=8.6Hz,H-4), 7.19(1H,dd J=8.6 and 6.4 Hz,H-5), 7.79(1H,d J=6.4Hz,H-6), 10.66(2H,s,OH,OH overlapped). ^{13}C-Nmr $\delta_{\rm ppm}^{\rm DMSO\text{-}d_6}$ (25.1MHz): 17.45(q,CH_3), 112.53(d,C-4), 124.87(d,C-5), 130.48(d,C-6), 134.19(s, C-2), 144.54(s,C-3), 152.83(s,C=N). Ms m/z(rel.int.): 168(M^+,62), 151(100), 120 (70). High-resolution ms Calcd for $C_7H_8N_2O_3$(M^+): 168.054. Found: 168.054.

Synthesis of 2-Acetyl-3-acetoxypyridine **10** —— Compound **3** (8.0g, 58.4mmol) was mixed with Ac_2O (6.3g, 61.7mmol) and pyridine (21ml). The mixture was heated to dissolve **3** at 60-70°C for 3 h and stood overnight. The reaction mixture was concentrated *in vacuo* to give a colorless oil, which was dissolved in ether. The ether layer was dried over $MgSO_4$ after washing with $NaHCO_3$ solution and water. After the solvent was evaporated, the residue was distilled to give a colorless oil, bp 105°C (5mmHg), 9.9g(95% yield). *Anal*. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.05; H, 5.00; N, 7.79. Uv $\lambda_{\rm max}^{\rm EtOH}$nm(log$\epsilon$): 227(4.28), 274(4.06). Ir $\nu_{\rm max}^{\rm neat}$cm^{-1}: 1775($-\underline{CO}-CH_3$), 1703($-O-\underline{CO}-CH_3$), 1189. ^{1}H-Nmr $\delta_{\rm ppm}^{\rm CDCl_3}$ (100MHz): 2.37(3H,s,$-OCOC\underline{H}_3$), 2.68(3H,s,$COC\underline{H}_3$), 7.48-7.52(2H,m,H-4,H-5 overlapped) 8.34-8.63(1H,m,H-6). ^{13}C-Nmr $\delta_{\rm ppm}^{\rm CDCl_3}$(100MHz): 20.93(q,$-OCO\underline{C}H_3$), 27.47(q,$CO\underline{C}H_3$), 127.79(d,C-5), 132.16(d,C-4), 145.89(s,C-2), 146.08(s,C-3), 146.08(d,C-6), 169.23 (s,$-O\underline{C}OCH_3$), 199.23(s,$\underline{C}OCH_3$). Ms m/z(rel.int.): 179(M^+,17), 137(100), 122(15), 109(28), 95(27). High-resolution ms Calcd for $C_9H_9NO_3$(M^+): 179.058. Found: 179.058.

Synthesis of **11** —— MCPBA (18.76g, 0.11mol) dissolved in $CHCl_3$ (250ml) was added to a solution of **10** (13.0g, 72.6mmol) in $CHCl_3$ (50ml), and the mixture was allowed to stand for 1.5 day at room temperature. After the solvent was evaporated off to dryness, the residue was extracted with hot water several times. The combined aqueous layers were completely evaporated and the residue (ca.14g) was subjected to column chromatography on silica gel using $CHCl_3$ as the eluent to give **11**, colorless prisms (from ether-acetone), mp 161-163°C, 6.0g(67% yield). *Anal*. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.81; H, 4.62; N, 9.13. Uv λ_{max}^{EtOH}nm(logϵ): 225(4.61). Ir ν_{max}^{KBr}cm^{-1}: 3200-2400(OH), 1719(C=O), 1434, 1248, 1199, 1040. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$(100MHz): 2.47(3H,s,CH_3), 6.95(1H,d J=8.8Hz,H-4), 7.30 (1H,dd J=8.8 and 6.4Hz,H-5), 7.83(1H,d J=6.4Hz,H-6), 11.03(1H,s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$(25.1MHz): 30.03(q,CH_3), 114.09(d,C-4), 126.15(d,C-5), 130.69(d,C-6), 136.48(s,C-2), 152.56(s,C-3), 195.50(s,C=O). Ms m/z(rel.int.): 153(M$^+$,55), 136 (40), 108(31), 94(100). High-resolution ms Calcd for $C_7H_7NO_3$(M$^+$): 153.042. Found: 153.041.

The Catalytic Reduction of 12 with Raney Ni —— Raney Ni, prepared from 1g of nickel-aluminum alloy, was added to a solution of 12 (0.23g, 1.53mmol) dissolved in MeOH (30ml) and the mixture was shaken in a hydrogen stream at atmospheric pressure. The reduction stopped when about 35ml of hydrogen had been absorbed. After removal of the catalyst by filtration, MeOH was evaporated from the filtrate and the residue was subjected to column chromatography on silica gel using $CHCl_3$ as the eluent to give colorless prisms (from petr. ether), 0.17g (83% yield). The mp and ir spectrum coincided with those of 4.

Synthesis of 14E —— A mixture of 16 (0.5g, 3.6mmol) in 99%EtOH and hydroxylamine hydrochloride (0.25g, 3.6mmol) dissolved in the minimum amount of water was heated in the presence of sodium acetate (0.52g, 6.34mmol) for 2 h at reflux temperature. After the reaction mixture was concentrated in vacuo and then cooled in an ice bath, the resulting precipitate was filtered off and washed with water. The crude product was recrystallized from acetone-MeOH to give pale yellow prisms, mp 214-216°C(decomp.), 0.41g (75% yield). Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.68; H, 3.88; N, 17.97. Uv λ_{max}^{EtOH}nm(logϵ): 248(4.82). Ir ν_{max}^{KBr}cm^{-1}: 3200-2400(OH), 1461, 1212(N$\rightarrow$O), 1008. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$(100MHz): 6.98 (1H,d J=8.8Hz,H-4), 7.29(1H,dd J=8.8 and 6.4Hz,H-5), 7.94(1H,d J=6.4Hz,H-6), 8.70 (1H,s,imino H), 10.80(1H,br s,phenolic OH), 12.17(1H,br s,hydroxyimino OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$(25.1MHz): 113.54(d,C-4), 125.69(d,C-5), 129.75(s,C-2), 131.14 (d,C-6), 143.60(d,imino C), 155.21(s,C-3). Ms m/z(rel.int.): 154(M$^+$,100),137(76), 120(33), 94(24), 66(29), 39(42). High-resolution ms Calcd for $C_6H_6N_2O_3$(M$^+$): 154.038 Found: 154.038.

Synthesis of 2-Cyano-3-hydroxypyridine 1-Oxide 15 —— Compound 7 (3.0g, 25mmol) was dissolved in MeOH (20ml) and $CHCl_3$ (50ml). To this solution was added MCPBA (6.47g, 37.5mmol) dissolved in $CHCl_3$ (150ml), and the mixture was left standing at room temperature for 2 days. The product was obtained by filtration and washed with $CHCl_3$. Recrystallization from boiling water gave colorless prisms, mp 288-289°C(decomp.), 1.57g(46% yield). Anal. Calcd for $C_6H_4N_2O_2$: C, 52.95; H, 2.96; N, 20.58. Found: C, 52.95; H, 2.87; N, 20.30. Uv λ_{max}^{EtOH}nm(logϵ): 218(4.54), 235 (4.49), 279(4.10), 343(4.03). Ir ν_{max}^{KBr}cm^{-1}: 3200-2400(OH), 2250(CN), 1580, 1440, 1200(N→O), 1040, 800. ^{1}H-Nmr $\delta_{ppm}^{DMSO-d_6}$(400MHz): 7.01(1H,d J=8.8Hz,H-4), 7.48(1H, dd J=8.8 and 6.4Hz,H-5), 7.99(1H,d J=6.4Hz,H-6), 12.36(1H,br s,OH). ^{13}C-Nmr $\delta_{ppm}^{DMSO-d_6}$(100MHz): 110.90(s,CN), 113.38(d,C-4), 114.97(s,C-2), 129.33(d,C-5), 131.41(d,C-6), 160.30(s,C-3). Ms m/z(rel.int.): 136(M^+,100), 120(22), 93(17), 55(20). High-resolution ms Calcd for $C_6H_4N_2O_2(M^+)$: 136.027. Found: 136.027

Deoxygenation of 18 with PCl_3 —— PCl_3 (0.9g, 6.6mmol) in $CHCl_3$ (10ml) was added dropwise to a solution of 18 (0.2g, 1.2mmol) dissolved in $CHCl_3$ (10ml) under ice cooling. The reaction mixture was heated under reflux on a water bath for 1 h, treated with ice water, the acid solution was basified with 10%Na_2CO_3 aqueous solution and then extracted with $CHCl_3$. After the $CHCl_3$ layer was dried over $MgSO_4$, the solvent was evaporated off to dryness and the residue was subjected to column chromatography on silica gel using benzene and $CHCl_3$ in turn as the eluent to give colorless prisms (from petr. ether), 0.11g(63% yield). The mp and ir spectrum coincided with those of 17.

The Beckmann Rearrangement of 1E using PPSE —— Compound 1E (0.3g, 1.97mmol) was dissolved in $CHCl_3$ solution (10ml) of PPSE with stirring at room temperature. The reaction mixture was stirred for 1 day at room temperature (or in the case of the reaction at reflux temperature, the one was heated with stirring for 3 h.). The resulting mixture was treated with water (15ml) and then extracted with $CHCl_3$ under weak acidic, neutral and weak basic conditions using aqueous 10%$NaHCO_3$ solution. After the combined $CHCl_3$ layer was dried over $MgSO_4$, the solvent was evaporated off to dryness and the residue was subjected to column chromatography using $CHCl_3$ as the eluent to give 2, 4 and 2-acetylamino-3-hydroxypyridine 19 in turn with the yields as shown in Table III. Compound 19 was recrystallized from petr. ether to give colorless prisms, the mp and ir spectrum coincided with those of an authentic sample[15].

Synthesis of 13 using 19 —— MCPBA (1.70g, 9.9mmol) dissolved in $CHCl_3$ (20ml) was added to a solution of 19 (1.0g, 6.6mmol) in $CHCl_3$ (10ml) and the mixture was stood for 1 day at room temperature. After the solvent was evaporated off to dryness, the residue was subjected to column chromatography using $CHCl_3$ as the eluent to give 13, 0.81g(74% yield).

Synthesis of 3-Acetoxy-2-pyridinecarboxaldehyde O-Acetyloxime 20 —— Compound 5E (0.15g, 1.1mmol) was mixed Ac_2O (4ml) and the mixture was heated to dissolve 5E at 50-60°C and stood at room temperature for several hours. After ice water was added to the reaction mixture in order to decompose Ac_2O, the resulting mixture was made pH 6.2-6.4 using 10%Na_2CO_3 aqueous solution and then extracted with $CHCl_3$ The $CHCl_3$ layer was dried over $MgSO_4$ and then evaporated off to dryness. The residue was recrystallized from petr. ether-ether to give colorless prisms, mp 97-98°C, 0.18g(74% yield). Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.06; H, 4.54; N, 12.61. Found: C, 53.95; H, 4.42; N, 12.66. Uv λ_{max}^{EtOH}nm(logϵ): 239(4.51), 281(4.33). Ir ν_{max}^{KBr}cm^{-1}: 1766(C=O), 1753(C=O), 1218, 1198. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(100MHz): 2.22(3H,s,$\underline{CH_3}$-CO-O-N=C-), 2.47(3H,s,$\underline{CH_3}$-CO-), 7.35-7.51(2H,m,H-4 and H-5), 8.45(1H,s,-C$\underline{H}$=N), 8.58(1H,dd J=4.2 and 1.7Hz,H-6). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$(25.1MHz): 19.40(q,$\underline{C}H_3$-CO-O-N=C), 21.01(q,CH_3), 125.81(d,C-5), 131.87(d,C-4), 142.57(s,C-2), 146.83(s,C-3), 147.22 (d,C-6), 154.78(d,-$\underline{C}$H=N-), 167.48(s,CH_3-$\underline{C}$O-O-N=C-), 169.40(s,C=O). Ms m/z(rel. int.): 222(M^+,10), 180(63), 138(75), 120(44), 93(40). High-resolution ms Calcd for $C_{10}H_{10}N_2O_4(M^+)$: 222.064. Found: 222.064.

Hydrolysis of 20 —— Compound 20 (0.05g, 0.23mmol) was added in a small portion to a solution of n-butylamine (2ml) with stirring under ice-cooling. After the resulting solution was stood for 3 h at room temperature, a little amount of water was added to the solution and the solvent was evaporated off to dryness. The residue was recrystallized from boiling water to give 5E, 0.017g(55% yield). The mp and ir spectrum coincided with those of an authentic sample.

Synthesis of 3-Acetoxy-1-oxido-2-pyridinecarboxaldehyde O-Acetyloxime 21 —— The reaction was carried out as described for the synthesis of 20. The resulting residue was recrystallized from ether-acetone to give colorless prisms, mp 118-120°C, 0.21g(80% yield from 14E, 0.17g, 1.1mmol). Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.40; H, 4.14; N, 11.50. Uv λ_{max}^{EtOH}nm(logϵ): 245 (4.90), 283(4.54). Ir ν_{max}^{KBr}cm^{-1}: 1773(C=O), 1428, 1279(N$\rightarrow$O), 1207, 1194. ^{1}H-Nmr $\delta_{ppm}^{CDCl_3}$(100MHz): 2.21(3H,s,CH_3-CO-C-N=C-), 2.44(3H,s,CH_3-CO-), 7.05-7.42(2H,m,H-4 and H-5), 8.18(1H,dd J=6.6 and 1.2Hz,H-6), 8.99(1H,s,-CH=N-). ^{13}C-Nmr $\delta_{ppm}^{CDCl_3}$ (25.1MHz): 19.28(q,$\underline{C}H_3$-CO-O-N=C-), 20.83(q,CH_3), 121.25(d,C-5), 126.12(d,C-4), 136.64(s,C-2), 137.51(d,C-6), 147.47(d,-CH=N-), 148.59(s,C-3), 167.15(s,CH_3-$\underline{C}$O-O-N=C-), 168.81(s,C=O). Ms m/z(rel.int.): 238(M^+,27), 196(89), 154(91), 137(88). High-resolution ms Calcd for $C_{10}H_{10}N_2O_5(M^+)$: 238.059. Found: 238.058.

Hydrolysis of 21 —— Hydrolysis was carried out as described for the hydrolysis of 20. The resulting residue was subjected to column chromatography on silica gel using mixed solvent ($CHCl_3$:MeOH=50:1) as the eluent to give 14E, 0.023g(71% yield from 21, 0.05g, 0.21mmol). The mp and ir spectrum coincided with those of an authentic sample.

ACKNOWLEDGEMENT

The authors are grateful to Dr. N. Honjo for her valuable advice and to Misses Y. Iwase and S. Hachiyama of the Analytical Center of the Faculty of Pharmaceutical Sciences, Fukuoka University, for $^1J_{cc}$ and gc-ms measurements, respectively.

REFERENCES AND NOTES

1. Y. Tagawa, N. Honjo, and Y. Goto, Chem. Pharm. Bull., 1986, **34**, 4984.
2. A. Camparini, F. Ponticelli, and P. Tedeschi, J. Chem. Soc., Perkin Trans. 1, 1982, 2391.
3. S. Chimichi, P. Tedeschi, A. Camparini, and F. Ponticelli, Org. Magn. Reson., 1982, **20**, 141.
4. S. Chimichi, P. Tedeschi, R. Nesi, and F. Ponticelli, Magn. Reson. Chem., 1985, **23**, 86.
5. U.R. Kalkote and D.D. Goswami, Aust. J. Chem., 1977, **30**, 1847.
6. G. Stokker, J. Org. Chem., 1983, **48**, 2613.
7. G.A. Olah, Y.D. Vankar, and A. Garcia-Luna, Synthesis, 1979, 227.
8. T. Yamazaki, K. Matoba, Y. Matsuzawa, and M. Kitagawa, Chem. Pharm. Bull., 1977, **25**, 1150. As to the preparation of 7, the reference 11 is superior to the reference cited in the reference 8.
9. A. Camparini, S. Chimichi, F. Ponticelli, and P. Tedeschi, Heterocycles, **19**, 1511(1982).
10. D. Heinert and A.E. Martell, Tetrahedron, **3**, 49(1958).
11. H. Vorbrüggen and K. Krolikiewicz, Synthesis, 1983, 316.
12. W. Loh, L.A. Cosby, and A.C. Sartorelli, J. Med. Chem., 1980, **23**, 631.
13. A.J. Boulton and P.G. Tsoungas, J. Chem. Soc., Perkin Trans. 1, 1986, 1665.
14. T. Imamoto, H. Yokoyama, and M. Yokoyama, Tetrahedron Lett., 1981, **22**, 1803.
15. H.L. Yale, J. Org. Chem., 1971, **36**, 3238.
16. K. Yamamoto and H. Watanabe, Chem. Letters, 1982, 1225.

17. G.E. Hawkes, K. Herwig, and J.D. Roberts, J. Org. Chem., 1974, 39, 1017. ; C.A. Bunnel and P.L. Fuchs, ibid., 1977, 42, 2614.

18. G.G. Kleinspehn, J.A. Jung, and S.A. Studniarz, J. Org. Chem., 1967, 32, 460.

19. L.B. Krivdin and G.A. Kalabin, Tetrahedron Lett., 1984, 25, 4817.

20. C.R. Hauser and E. Jordan, J. Am. Chem. Soc., 1936, 58, 1772.

Received, 17th June, 1987