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Equilibrium Studies of 5-Substituted 4-Hydroxy-2-methylpyrimidines. IV.[1] Lactim-Lactam Tautomerism in Methanol, *n*-Butanol and *n*-Hexane

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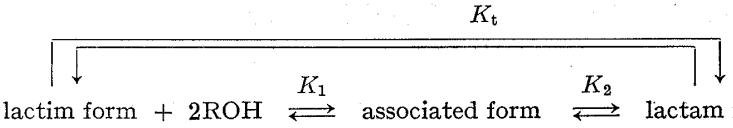
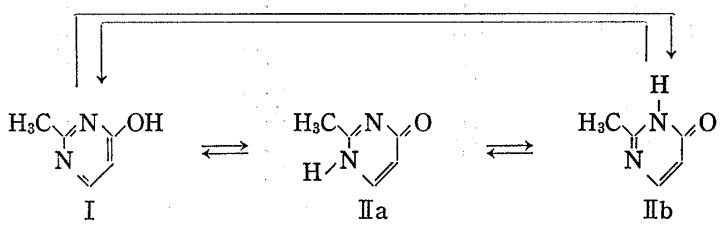
Lactim-lactam tautomerism of 5-substituted 4-hydroxy-2-methylpyrimidines (R; H, CH_3, OCH_3 and $COOC_2H_5$) was examined in MeOH, *n*-BuOH and *n*-hexane. All the compounds existed mainly in the lactam form (4(3H)-pyrimidone, IIb) in the alcohols. No substituent effect at 5-position on the tautomerism in the alcohols was observed. In *n*-hexane, 5-H and 5-CH_3 derivatives also existed mainly in the lactam form, IIb. 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (**4**), however, existed mainly in the lactim form (4-pyrimidinol, I). The lactim form of **4** in *n*-hexane was changed into the lactam form, IIb, on addition of MeOH and *n*-BuOH to the solution. The conversion to the lactam form may be explained as a result of an association of two molecules of alcohol to **4**, *i.e.*,



The association was investigated quantitatively by ultraviolet spectrophotometry: K_1= 1483±29 (MeOH-association) and K_1=1279±19 (*n*-BuOH-association). The tautomeric equilibrium constant (K_t; K_t=[IIb]/[I]) in pure *n*-hexane was estimated to be less than 0.02.

Keywords——5-substituted 4-hydroxy-2-methylpyrimidine; 5-carbethoxy-4-hydroxy-2-methylpyrimidine; methyl 2-hydroxynicotinate; methyl 4-hydroxynicotinate; lactim-lactam tautomerism; UV spectrophotometry; association equilibria with alcohols

4-Hydroxypyrimidines have the possibility of exhibiting tautomeric equilibria. Three tautomers were referred to by the lactim form, I and the two lactam forms, IIa and IIb. In



the previous paper on the lactim-lactam tautomerism of 4-hydroxy-2-methylpyrimidines,[3] it was clarified that the compounds existed mainly as a mixture of both lactam forms, IIa and IIb, in aqueous solution. Lardenois, *et al.*[4] pointed out that the main species of 4-hydroxy-2-methylpyrimidine in EtOH was the lactam form, IIb. Bauer, *et al.*[5] reached the same conclusion for 4-hydroxypyrimidine in dimethyl sulfoxide as that in EtOH. However, the effects of solvent and substituent on the tautomerism have not been elucidated yet. The

1) Part III: T. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 66 (1978).
2) Location: *5–12–4, Sagisu, Fukushima-ku, Osaka, 553, Japan.*
3) T. Kitagawa, S. Mizukami, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **22**, 1239 (1974).
4) P. Lardenois, M. Sélim, and M. Sélim, *Bull. Soc. Chim. France*, **1971**, 1858.
5) L. Bauer, G.E. Wright, B.A. Mikrut, and C.L. Bell, *J. Heterocycl. Chem.*, **2**, 447 (1965).

authors attempted to examine a solvent effect on the tautomerism of 4-hydroxy-2-methylpyrimidines with substituent at 5-position. Methanol and *n*-BuOH as polar solvents, and *n*-hexane as nonpolar solvent were used.

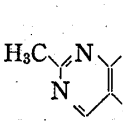
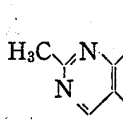
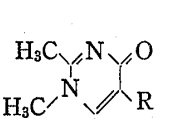
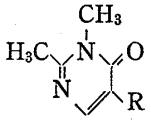
Results and Discussion

Tautomerism in MeOH and *n*-BuOH

The tautomerism of the 4-hydroxypyrimidines was examined using the dissociation constant method and the ultraviolet (UV) spectroscopic method. It has generally been recognized that the physical characters of the tautomer, such as dissociation constant and UV-absorption spectrum do not change significantly by substituting an alkyl group for the tautomeric hydrogen atom.[6] So the form of the tautomer, if one of the tautomers exists predominantly, may be estimated by the comparison of both characters between the tautomeric compound and the alkyl derivative. The methyl derivatives of 4-hydroxy-2-methylpyrimidine (**1**), 4-methoxy-2-methylpyrimidine (**1a**), 1,2-dimethyl-4(1H)-pyrimidone (**1b**) and 2,3-dimethyl-4(3H)-pyrimidone (**1c**), were used as the corresponding models of the tautomers, I, IIa and IIb. The dissociation constant of **1** was compared with those of the methyl derivatives. These constants in MeOH and *n*-BuOH were already determined in the previous paper.[1,7] The dissociation constant of **1** approximated more closely to that of **1c** than that of **1a** or **1b**. Such an approximation was also found between the dissociation constants of all the 4-hydroxypyrimidines and those of the corresponding 4(3H)-pyrimidones (Table I).

Table I. Dissociation Constants (pK_{BH}^{ROH}) of 5-Substituted 4-Hydroxy-2-methylpyrimidine and Its Methyl Derivatives in Alcohols

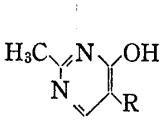
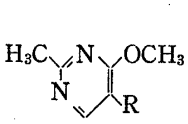
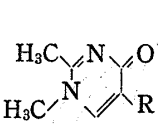
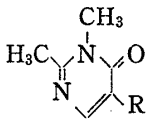
$$BH^+ \overset{K_{BH}^{ROH}}{\rightleftarrows} H^+ + B \left(K_{BH}^{ROH} = \frac{[H^+][B] f_H}{[BH^+] f_{BH}} \right)$$

	Solvent	 (1, 2, 3, 4)	 (1a, 2a, 3a, 4a)	 (1b, 2b, 3b, 4b)	 (1c, 2c, 3c, 4c)
R=H	MeOH	4.01	4.80	4.61	4.04
	n-BuOH	3.71	4.10	4.97	3.68
R=CH_3	MeOH	4.55	5.90	5.79	4.48
	n-BuOH	4.26	4.69	5.67	4.24
R=OCH_3	MeOH	4.08	5.04	4.76	4.07
	n-BuOH	3.76	4.40	4.91	3.68
R=$COOC_2H_5$	MeOH	2.66	3.29	3.36	2.59

The UV spectra of 5-substituted 4-hydroxy-2-methylpyrimidines (R; H(**1**), CH_3(**2**), OCH_3(**3**) and $COOC_2H_5$(**4**)) were compared with those of their three methyl derivatives in Table II. The UV spectra of four 4-hydroxy-2-methylpyrimidines in MeOH and *n*-BuOH were closely similar to those of the corresponding 2,3-dimethyl-4(3H)-pyrimidones. These results, therefore, show that 5-substituted 4-hydroxy-2-methylpyrimidines exist predominantly in the lactam form, IIb, in the alcoholic solvents and that the tautomerism of 4-hydroxypyrimidines in these solvents is different from that in water, *i.e.*, these pyrimidines in water exist as a mixture of approximately equal amounts of the two lactam forms, IIa and IIb.[3]

6) A.R. Katritzky and J.M. Lagowski, "Advances in Heterocyclic Chemistry," Vol. 1, ed. by A.R. Katritzky, Academic Press Inc., New York, 1963, pp. 311—338.
7) T. Kitagawa and S. Mizukami, *Chem. Pharm. Bull.* (Tokyo), **26**, 53 (1978).

TABLE II. UV Spectra of 5-Substituted 4-Hydroxy-2-methylpyrimidine and Its Methyl Derivatives in MeOH, *n*-BuOH and *n*-Hexane

	Solvent	 (1, 2, 3, 4)		 (1a, 2a, 3a, 4a)		 (1b, 2b, 3b, 4b)		 (1c, 2c, 3c, 4c)	
		λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$
R=H	MeOH	221	7.83	214.5	6.80	240	14.23	222	6.70
		272.5	4.48	250.5	3.89			276	4.77
	n-BuOH	222	7.39	215	6.33	241	13.46	222.5	7.30
		273.5	4.40	250	3.48			277.5	4.49
	n-Hexane	220	8.57	212.5	6.36	240	13.68[a]	221	5.43
		272.5	4.54	249	3.63			284.5	3.98
R=CH_3	MeOH	228	6.22	218.5	7.25	246	13.93	226	5.73
		274	5.75	256	4.66			275	5.88
	n-BuOH	226	6.36	217.5	7.61	246.5	12.24	228	5.25
		275	5.52	255	4.41			277	5.57
	n-Hexane	224.5	6.98	215	7.45	246	11.80[a]	225.5	4.82
		272	5.00	254.5	4.22			282.5	5.28
R=OCH_3	MeOH	238	7.17	227	8.33	264	12.46	239	6.41
		275	7.39	269	5.20			278	7.16
	n-BuOH	238	6.68	227	7.83	263	11.24	238.5	5.78
		277.5	6.96	269	5.20			279	6.60
	n-Hexane	—[b]		223	7.40	263	10.96[a]	235	4.92
				265	4.30			282	5.95
R=$COOC_2H_5$	MeOH	225.5	7.73	227.5	10.23	240	13.11	226	5.92
		297	7.24	263	6.16	283	5.46	302	7.87
	n-BuOH	225.5	6.88	227.5	9.45	241	11.84	225	5.92
		299	6.66	263	5.96	284	4.75	303	7.04
	n-Hexane	228	9.43	225.5	9.57	240	12.62[a]	223.5	4.39
		271	6.81	262.5	5.92	283	4.97	304	5.87
		300sh[c]	0.74						

a) 5% (v/v) methanolic solution.
b) Insoluble in *n*-hexane.
c) Shoulder.

Tautomerism in *n*-Hexane

The UV spectra of **1** and **2** in *n*-hexane were compared with those of the methyl derivatives. In the case that 5-substituent is H or CH_3, the spectra of 4-hydroxy-2-methylpyrimidines are different largely from those of the corresponding 4-methoxy-2-methylpyrimidines and 1,2-dimethyl-4(1H)-pyrimidones, but they resemble those of the corresponding 2,3-dimethyl-4(3H)-pyrimidones, as shown in Fig. 1(5-H). These spectral similarity shows that 4-hydroxy-2-methylpyrimidines (**1** and **2**) exist predominantly in the lactam form, IIb, in *n*-hexane as well as in the alcoholic solvents. However, in the case of 5-carbethoxy derivative (**4**), the tautomerism in *n*-hexane is significantly different from that of the above pyrimidines, **1** and **2**. Fig. 2 shows the UV spectra of **4** and its three methyl derivatives. The spectral similarity was not observed between **4** and 5-carbethoxy-2,3-dimethyl-4(3H)-pyrimidone (**4c**). The spectrum rather resembled that of 5-carbethoxy-4-methoxy-2-methylpyrimidine (**4a**). It seems, therefore, that the tautomeric behavior of **4** in *n*-hexane is different from that in alcoholic solvents. From the spectral similarity, a main tautomer of **4** in *n*-hexane may be expected to be lactim type, I.

In order to clarify the tautomer of **4**, we examined the lactim-lactam tautomerism of the compounds, the structures of which are similar to **4**: methyl 2-hydroxynicotinate (**7**) and

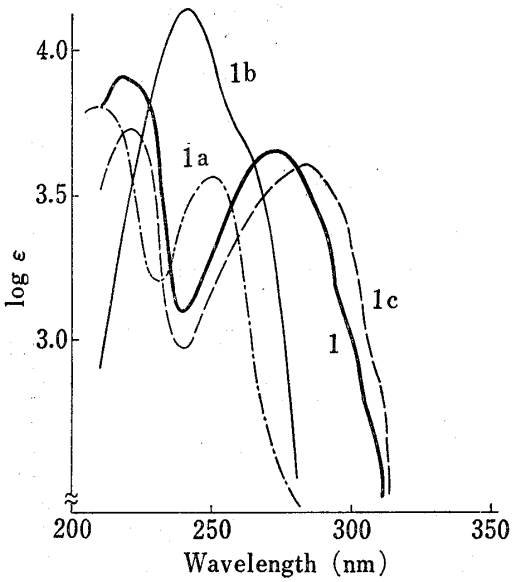


Fig. 1. UV Spectra of 4-Hydroxy-2-methylpyrimidine (**1**), 4-Methoxy-2-methylpyrimidine (**1a**), 1,2-Dimethyl-4(1H)-pyrimidone (**1b**) and 2,3-Dimethyl-4(3H)-pyrimidone (**1c**) in *n*-Hexane

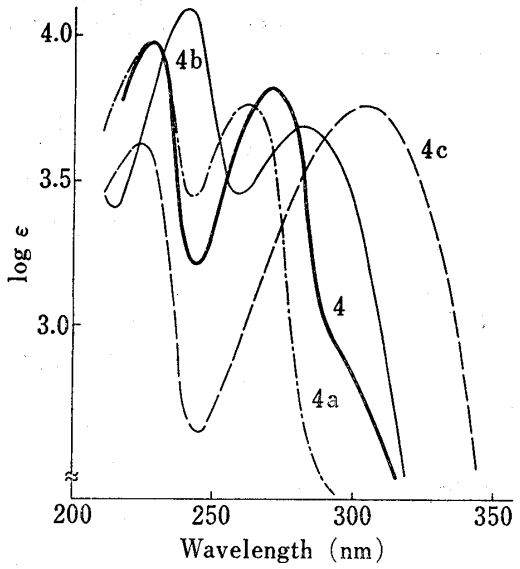
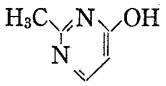
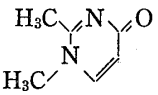
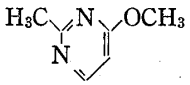
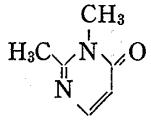
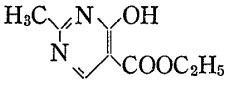
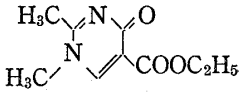
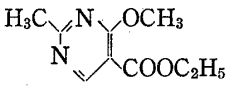
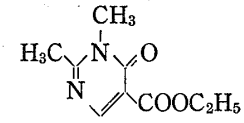


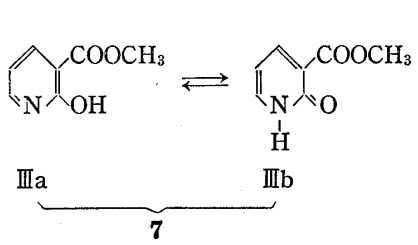
Fig. 2. UV Spectra of 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (**4**), 5-Carbethoxy-4-methoxy-2-methylpyrimidine (**4a**), 5-Carbethoxy-1,2-dimethyl-4(1H)-pyrimidone (**4b**) and 5-Carbethoxy-2,3-dimethyl-4(3H)-pyrimidone (**4c**) in *n*-Hexane

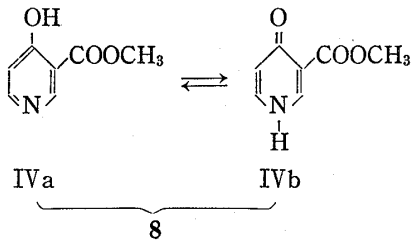
1  **1b** 

1a  **1c** 

4  **4b** 

4a  **4c** 





methyl 4-hydroxynicotinate (**8**). The tautomerism of these pyridines occurs between the lactim form (IIIa and IVa) and the lactam form (IIIb and IVb). Both structures of IIIa and IVa are similar to that of the lactim form, I, of **4**, and the structures of IIIb and IVb are also similar to those of the lactam forms, IIb and IIa, of **4**, respectively. Accordingly, it may be expected that the solvent effect on the tautomerism of **4** is similar to that of **7** or **8**.

The UV spectra of **7** and **8** in *n*-hexane were measured and were compared with those of their methyl derivatives. These spectra are shown in Fig. 3 and 4. Methyl 2-methoxynicotinate (**7a**) and 3-carbomethoxy-1-methyl-2(1H)-pyridone (**7b**) were used as models of IIIa and IIIb, respectively and methyl 4-methoxynicotinate (**8a**) and 3-carbomethoxy-1-methyl-4(1H)-pyridone (**8b**) were used as models of IVa and IVb, respectively. Spectral data of **7**, **8** and their methyl derivatives are shown in Table III and IV. The spectrum of **7** resembles that of **7a** rather than that of **7b**. Both spectra of **7** and **7a** have two absorption maxima. Both bands at the shorter wavelengths situate at almost the same positions and those bands

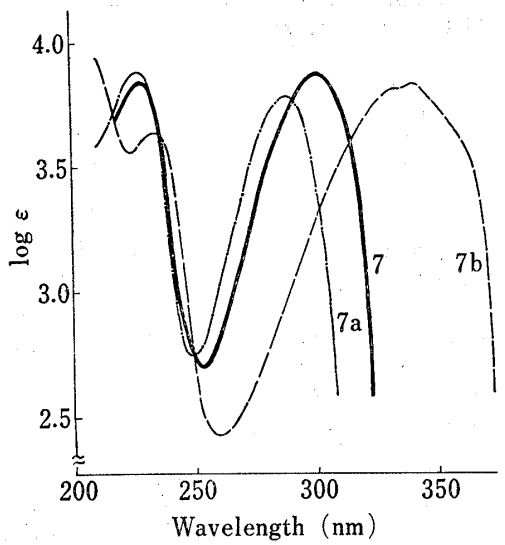
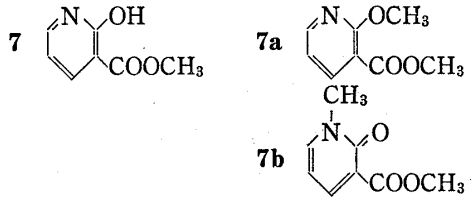


Fig. 3. UV Spectra of Methyl 2-Hydroxynicotinate (7), Methyl 2-Methoxynicotinate (7a) and 3-Carbomethoxy-1-methyl-2(1H)pyridone (7b) in *n*-Hexane



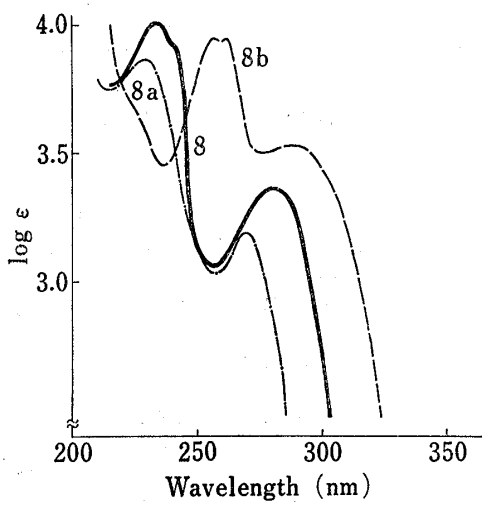


Fig. 4. UV Spectra of Methyl 4-Hydroxynicotinate (8), Methyl 4-Methoxynicotinate (8a) and 3-Carbomethoxy-1-methyl-4(1H)pyridone (8b) in *n*-Hexane

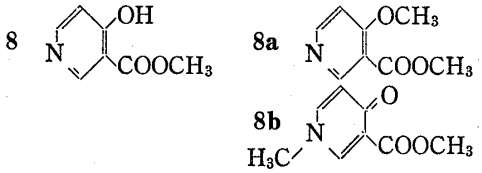
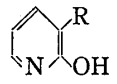
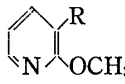
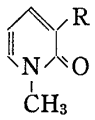


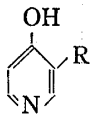
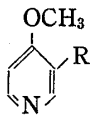
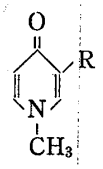
TABLE III. UV Spectral Data of 2-Hydroxypyridine, Methyl 2-Hydroxynicotinate and Their Methyl Derivatives in MeOH and *n*-Hexane

	Solvent	 (5, 7)		 (5a, 7a)		 (5b, 7b)	
		λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$
R=H	MeOH	227	7.88	214.5	8.15	228.5	6.51
		299	5.33	271	4.17	302	5.16
				280sh[a]	2.67		
	n-Hexane	228—231	7.93—7.96	215	5.84	234.5	5.68
		298.5	3.92	269.5—273	3.67—3.85	239.5[b]	4.22
				279.5[b]	2.95	308	4.34
						318[b]	4.12
						333[b]	2.01
R=$COOCH_3$	MeOH	235	7.35	226.5	7.34	235.5	5.09
		328	8.09	287.5	5.87	331	7.83
	n-Hexane	229	6.73	226.5	7.44	233.5	4.32
		300	7.24	287.5	6.03	342	6.47

a) Shoulder.
b) Absorption with fine structure.

at the longer wavelengths show the deviation: the wavelength for **7** is longer by 12.5 nm than that of **7a**. In the case of **8**, **8a** and **8b**, spectral resemblance was also found between **8** and **8a**. The spectral behaviors found for **7** and **8** were compared with that of **4**. Both bands of **4** and 5-carbethoxy-4-methoxy-2-methylpyrimidine (**4a**) at the shorter wavelengths

Table IV. UV Spectral Data of 4-Hydroxypyridine, Methyl 4-Hydroxynicotinate and Their Methyl Derivatives in MeOH and *n*-Hexane

	Solvent	 (6, 8)		 (6a, 8a)		 (6b, 8b)	
		λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$
R=H	MeOH	256	15.25	219	8.39	263.5	16.67
				245sh[a]	0.89		
	n-Hexane	—[b]		213.5	6.63	—[b]	
				237—241	0.64		
R=$COOCH_3$	MeOH	250.5	12.24	229	7.67	256.5	8.42
		256	12.36	271	1.74	261.5	8.42
		281	4.72			286	2.90
	n-Hexane	232.5	10.03	228	7.33	257.5	8.78[c]
		282	2.32	269	1.43	261.5	8.72
						288	3.47

a) Shoulder.
b) Insoluble in *n*-hexane.
c) 5% (v/v) methanolic solution.

situate at almost the same positions and the band of **4** at the longer wavelength situates by 8.5 nm longer than **4a** does. Three kinds of hydroxy compounds, **4**, **7** and **8** showed characters similar to those of the corresponding methoxy derivatives, **4a**, **7a** and **8a**, models of the lactim form, I, IIIa and IVa, respectively.[8] The results indicate that **4** exists predominantly in the lactim form, I, in *n*-hexane.

The UV spectrum of **4** in *n*-hexane was remarkably affected by the presence of alcohols. As shown in Fig. 5, the spectrum was changed with adding MeOH or *n*-BuOH through an isosbestic point (for both solvents: 280 nm). However, the spectrum of **4** remained constant in *n*-hexane solution containing MeOH of more than 0.7% (v/v) or *n*-BuOH of more than 1.7% (v/v). Both the final spectra are closely similar to those of MeOH solution and *n*-BuOH solution, respectively, and are essentially different from that in *n*-hexane. These spectra resemble those of **4c** in MeOH and *n*-BuOH. The results indicate that a main tautomer of **4** in *n*-hexane was changed into the lactam form, IIb, from the lactim form, I, by adding alcohols.

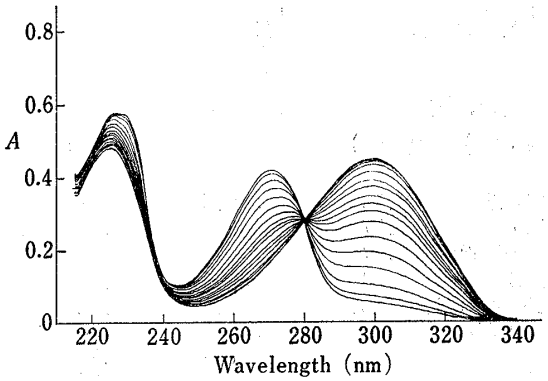


Fig. 5. Spectral Change on Addition of MeOH to *n*-Hexane Solution of 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (4) (C_{MeOH}: 0.005—0.18 M)

The effect of alcohols on the tautomerism in *n*-hexane was also demonstrated for **7** and **8**. The spectra obtained by addition of MeOH and *n*-BuOH were similar to the corresponding N_1-methylpyridones, **7b** and **8b**. Fig. 6 and 7 show an effect of MeOH on the spectra of **7** and **8**. The tautomers of **7** and **8** were changed into the lactam forms, IIIb and IVb, respectively, in the same manner as observed for **4**.

8) The UV spectrum of 2-hydroxypyridine (**5**) showed that the compound existed in the lactam form (2(1H)-pyridone) in *n*-hexane or MeOH (Table III).

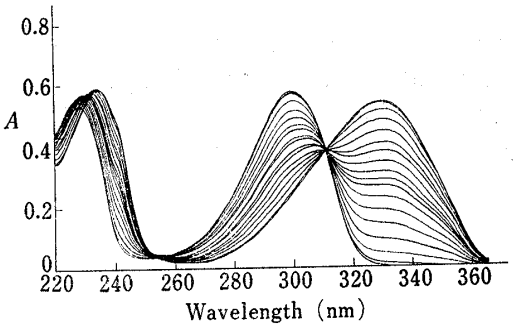


Fig. 6. Spectral Change on Addition of MeOH to *n*-Hexane Solution of Methyl 2-Hydroxynicotinate (7) (C_{MeOH}: 0.009—0.48 M)

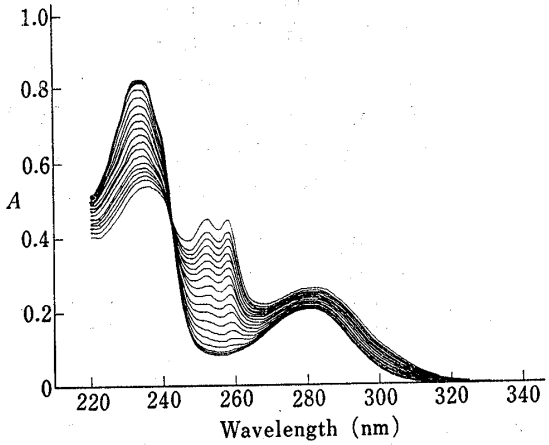
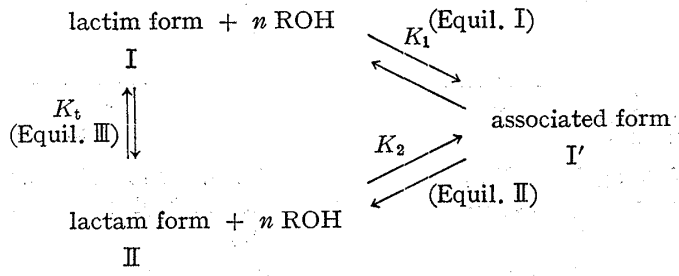


Fig. 7. Spectral Change on Addition of MeOH to *n*-Hexane Solution of Methyl 4-Hydroxynicotinate (8) (C_{MeOH}: 0.29—1.73 M)

It was concluded that the 4-hydroxypyrimidine existed predominantly in the lactim form, I, in *n*-hexane. Such a lactim-lactam tautomerism that the main tautomer is the lactim form has not been found for 4-hydroxypyrimidine. However, the tautomerism was revealed for 5-carbethoxy derivative of the compound in *n*-hexane that the lactim form existed predominantly. It is clear that the lactim-lactam tautomerism depends on the kind of substituent and solvent.

Solvent Effect on the Tautomerism

Since all spectra of **4**, **7** and **8** in Fig. 5, 6 and 7 passed through the isosbestic point (s) (280 nm, 253 and 312 nm, and 242.5 nm for each compound), equilibria in such solutions may be expressed by a lactim form, a lactam form and an alcohol. The following equilibria were assumed. Here, we assumed an associated form, I′, as an intermediate which was formed



by association of alcohol to **4**, **7** or **8**. Alcohols, MeOH and *n*-BuOH, were written as ROH. The equilibrium constants in equilibria, I, II and III, are defined as K_1, K_2 and K_t, respectively. The constants, K_1, K_2 and K_t, are written as

$$K_1 = \frac{[I']}{[I][ROH]^n} \quad (1)$$

$$K_2 = \frac{[I']}{[II][ROH]^n} \quad (2)$$

$$K_t = \frac{[II]}{[I]} \quad (3)$$

The ratio of the concentration of the lactam form to that of the lactim form observed on the UV spectra was defined as R. Assuming that the UV spectrum of the associated form is approximately identical with that of the lactam form, R is expressed

$$R = \frac{[I']+[II]}{[I]} = \frac{\varepsilon-\varepsilon_I}{\varepsilon_{II}-\varepsilon} \quad (4)$$

where ε_I and ε_{II} are the molar extinction coefficient at a given wavelength of the lactim and the lactam form, respectively, and ε is the coefficient at the same wavelength apparently observed for the test solution. As a total concentration of each compound in **4**, **7** and **8** is constant through all measurements of UV spectra. Eq(4) is converted into

$$\frac{\varepsilon-\varepsilon_I}{\varepsilon_{II}-\varepsilon} = \frac{A-A_I}{A_{II}-A} \quad (5)$$

Introducing eq(1) and (2) into eq(4) yields

$$R = K_1[\mathrm{ROH}]^n + \frac{K_1}{K_2} \quad (6)$$

Eq(6) means that plot of R against $[\mathrm{ROH}]^n$ yields a straight line. Its slope and intercept correspond to K_1 and K_1/K_2, respectively. The concentration of the alcohol ([ROH]) is much larger than that of the sample, so [ROH] can be replaced by the total concentration of the alcohol, C_{ROH}. When [ROH] approaches zero, R will approach K_1/K_2. From eq(1) and (2), K_1/K_2 corresponds to the tautomeric equilibrium constant, K_t (eq(3)). The equilibrium constant, K_t, is an independent value of alcohol content in n-hexane. It is concluded

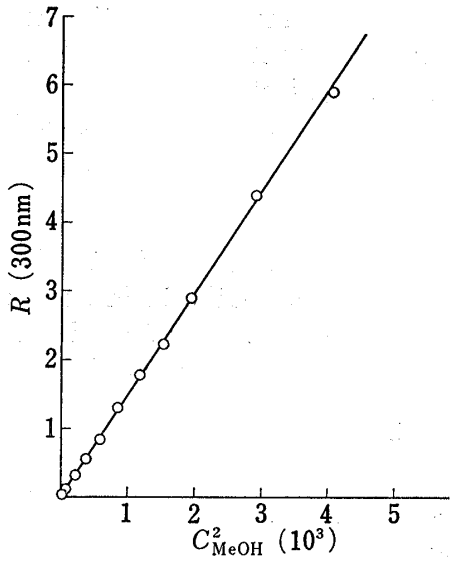


Fig. 8. Plot of R against C^2_{MeOH} for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (**4**)

R=0.004+1483 C^2_{MeOH}; s=0.052; n=11.

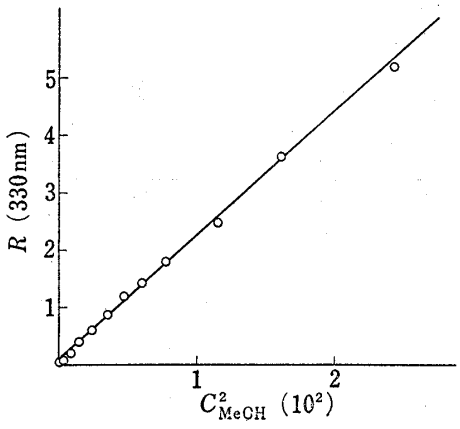


Fig. 9. Plot of R against C^2_{MeOH} for Methyl 2-Hydroxynicotinate (**7**)

R=0.086+215.0 C^2_{MeOH}; s=0.082; n=12.

TABLE V. Results of the Plot of R against C^2_{ROH} for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (**4**), Methyl 2-Hydroxynicotinate (**7**) and Methyl 4-Hydroxynicotinate (**8**)

Compound	MeOH					*n*-BuOH				
	Slope	Intercept	r[a]	Std. dev.	*n*	Slope	Intercept	r[a]	Std. dev.	*n*
4	1483(±29)[b]	0.004	0.9997	0.052	11	1279(±19)[b]	0.014	0.9998	0.082	13
7	215.0(±7.4)	0.086	0.9988	0.082	12	149.9(±6.4)	0.131	0.9987	0.428	10
8	0.377(±0.005)	0.014	0.9997	0.008	16	—[c]				

a) Correlation coefficient.
b) 95% confidence interval.
c) The spectrum of the lactam form could not be measured by the addition of *n*-BuOH (See footnote 9).

from UV spectral examination as mentioned above that K_t is a very small value. Accordingly, n may be approximately estimated from eq(7).

$$\log R = n \log C_{ROH} + \log K_1 \quad (7)$$

When plots of log R against log C_{ROH} were attempted for **4** and **7**, it was found for both plots that $n=2$.

Plot of R against C^2_{MeOH} for **4** was found to be linear, which was shown in Fig. 8. The same plot for **7** yielded a straight line, which was shown in Fig. 9. The K_1 and K_1/K_2 values which are calculated by the method of least-squares are listed in Table V. The results show that the lactam forms of **4** and **7** were formed through the equilibria, I, II and III.

The conclusion, however, was drawn on the basis of the assumption that the UV spectrum of the associated form was approximately identical with that of the lactam form (expressed as eq(4)). If the spectrum of the associated species is identical with that of the lactim form, the ratio, R, is written as

$$R = \frac{[\text{II}]}{[\text{I}]+[\text{I}']} \quad (8)$$

Introducing eq(1) and (2) into eq(8) yields eq(9).

$$\frac{1}{R} = K_2[\text{ROH}]^n + \frac{K_2}{K_1} \quad (9)$$

Eq(9) means that plot of $1/R$ against $[\text{ROH}]^n$ will give a straight line with a slope equal to K_2 and an intercept equal to K_2/K_1. In all of the cases of $n=1$, 2 and 3, however, no linear relationships were gained. Thus, it was confirmed that eq(8) was not applicable.

It seems likely that eq(6) is also available for compound **8**. However, the spectral change of **8** could not be analyzed by the plot of eq(6). Since the association of **8** with alcohols was so weak that the spectrum of the lactam form could not be measured by the addition of a certain amount of alcohols.[9] Then, in order to estimate A_{II} value, the following method was deviced. One spectrum which was measured in a given amount of the alcohol was chosen. When the absorbance at a given wavelength in the spectrum and the alcohol content are shown as A_0 and C_0, respectively, eq(6) is

$$\frac{A_0-A_I}{A_{II}-A_0} = \frac{K_1}{K_2} + K_1C_0^2 \quad (10)$$

Subtracting eq(10) from eq(6) yields

$$\frac{A-A_I}{A_{II}-A} - \frac{A_0-A_I}{A_{II}-A_0} = K_1(C^2-C_0^2) \quad (11)$$

Eq(11) is transformed in the form

$$A = A_{II} + \frac{1}{K_1}\frac{A_{II}-A_I}{A_0-A_{II}}\frac{A-A_0}{C^2-C_0^2} \quad (12)$$

Eq(12) means that plot of A against $(A-A_0)/(C^2-C_0^2)$ yields a straight line with a slope equal to $(A_{II}-A)/\{K_1(A_0-A_{II})\}$ and an intercept equal to A_{II}. This plot was attempted using the data in Fig. 7. The spectrum which was obtained at $C_{MeOH}=1.734$ (M) was chosen, and A_0 and C_0 were determined. A linear relationship existed. Estimated A_{II} value at 258 nm was shown in Fig. 10. The K_1 and K_1/K_2 values were then evalu-

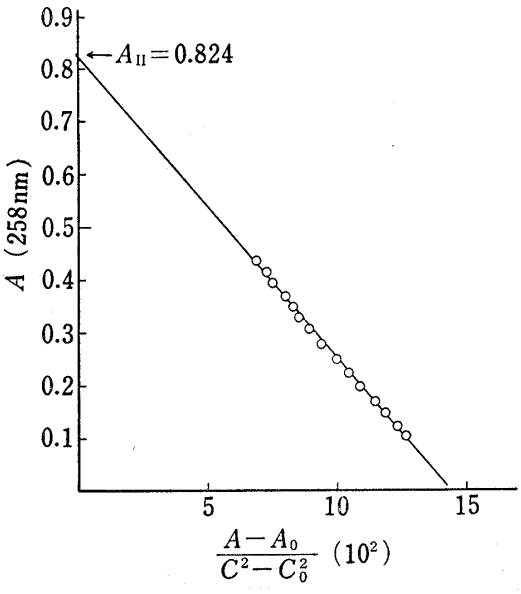


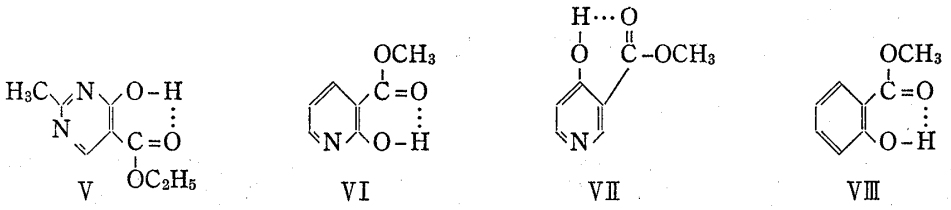
Fig. 10. Plot of A against $(A-A_0)/(C^2-C_0^2)$ for Methyl 4-Hydroxynicotinate (**8**)
$A=0.824-5.690\,(A-A_0)/(C^2-C_0^2)$; $s=0.007$; $n=15$.

9) If alcohols are added to obtain the final spectrum, the solvent system will change largely. The spectra were not followed in amount more than 7% (v/v).

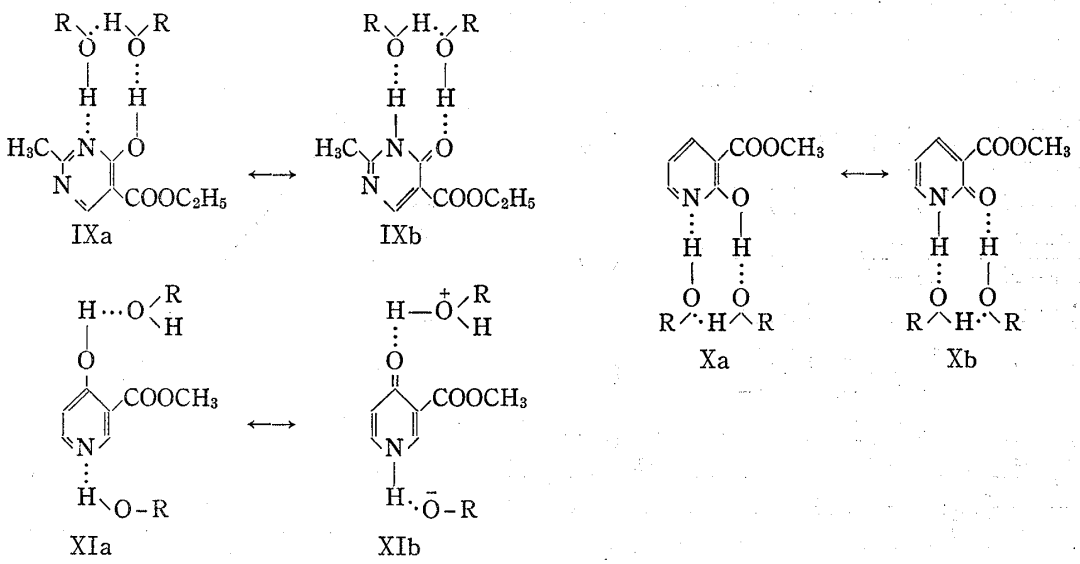
ated according to the above plot (eq(6)) by use of this A_{II} value (Table V). Thus, eq(6) was also applicable to the formation of the lactam form of **8**. In the case of the reaction of **8** with *n*-BuOH, only a small change of the absorbance (0.058 *A* unit) was observed even by addition of larger amount of *n*-BuOH (13%(v/v)). Equilibria of **8** with *n*-BuOH could not be followed. From these results, therefore, it may be concluded that **4**, **7** and **8** exist in the equilibria, I, II and III, in a *n*-hexane solution containing alcohols.

The equilibrium constant, K_t, is constant, regardless of alcohol content in *n*-hexane. These values for **4**, **7** and **8** were calculated to be almost zero.[10] Accordingly, it is concluded that these compounds exist predominantly in the lactim form in *n*-hexane. This conclusion agrees with that estimated qualitatively by the UV spectrophotometry.

Since the hydroxyl group is adjacent to the carbomethoxy or carbethoxy group, **4**, **7** and **8** may be stabilized as a lactim form by an intramolecular hydrogen bonding in an inert solvent such as *n*-hexane, *i.e.*, V, VI and VII. Such an intramolecular hydrogen bonding was found for methyl salicylate (VIII) in CCl_4.[11]



When a large amount of alcohol was added to the solution of **4**, **7** and **8**, the intramolecular hydrogen bonding may be cleaved by attack of the hydroxyl group of alcohol molecule. The association of two molecules of alcohol to one molecule of the species was found from the experimental result as described above. Thus, the associated form may be assumed as follows:



The lactam form, IXb, Xb or XIb, may be considered as a favorable one of two canonical forms for each compound, because eq(4) is applicable to the equilibria, I, II and III. Moreover, the K_1 values of **4** and **7** were much larger than that of **8** (**4**; 3900 times, **7**; 570 times). The result suggests that **4** and **7** exist in more stable forms than **8** does. A cyclic intramolecu-

10) Regarded as zero for **4**.
11) L.W. Reeves, E.A. Allan, and K.O. Strømme, *Can. J. Chem.*, **38**, 1249 (1960).

lar hydrogen bonding by association of two molecules of alcohol was considered for **4** and **7**, but could not be for **8**.

Experimental

Measurement of UV Spectra——UV Spectra were measured using a Hitachi EPS-3T spectrophotometer. The measurements were carried out at *ca.* $0.5\times10^{-4}-1.5\times10^{-4}$ M in concentration for the compounds easily soluble in solvents. Some samples of the hydroxy pyrimidine and pyridine derivatives were not sufficiently soluble in *n*-hexane. The spectrum of such compounds was measured for the saturated solution or done after dilution to appropriate concentration. In the case that the solution did not still attain to a sufficient concentration for the measurement (*e.g.*, **4** and **8**), 100 mm cell (total volume: 25 ml) was used. The measurement in more dilute solution of $0.5\times10^{-5}-1.5\times10^{-5}$ M was possible by the use of this cell. The concentration of the saturated *n*-hexane solution was measured by analyzing the MeOH solution which was prepared by evaporating a certain volume of *n*-hexane solution, followed by addition of MeOH. However, the UV spectra of 4-hydroxypyridine, 1-methyl-4(1H)-pyridone and 5-substituted 1,2-dimethyl-4(1H)-pyrimidone (H, CH_3, OCH_3 and $COOC_2H_5$) in *n*-hexane could not be measured by using such a method as above. Then, the spectra of some of the compounds were measured in 5% (v/v) methanolic solution.

Estimation of K_1 and K_t of 4, 7 and 8——The UV spectra of **4**, **7** and **8** were measured in *n*-hexane using 100 mm cell. The alcohol was added to the *n*-hexane solution. In order to observe the change of the absorbance (0.02 *A* unit or above), 5—10 μl, 10—50 μl and 100 μl portions of the alcohol (MeOH and *n*-BuOH) were added to the *n*-hexane solutions of **4**, **7** and **8**, respectively. The addition of alcohol was repeated until no more change of the absorbance occurred. About 10 spectra were recorded in various concentrations of alcohols. The concentrations of MeOH ranged from 5×10^{-3} M to 2 M and that of *n*-BuOH ranged from 5×10^{-3} M to 0.4 M. From the spectra of **4**, **7** and **8**, *A* values were read at 300, 330 and 258 nm, respectively. Since the content of MeOH ranged from 1.2% (v/v) to 7.1% (v/v), the observed *A* values for **8** were corrected according to the equation

$$A_{\text{corrected}} = A_{\text{observed}}\frac{V_0+V}{V_0}$$

where V_0 and V are the initial volume of the *n*-hexane solution and the volume of MeOH, respectively.

Materials——Commercial available MeOH and *n*-BuOH (both: analytical grade) were purified by the same methods as described in the previous papers.[7,12] The commercial available *n*-hexane ("Spectrosol" of Dozindo Laboratories) was distilled. The distillate was collected at 68.5—69°. Water contents of MeOH, *n*-BuOH and *n*-hexane were 0.013—0.018, 0.005—0.010 and 0.002—0.003% (w/v), respectively.

5-Substituted 4-hydroxy-2-methylpyrimidine and its methyl derivatives were prepared in the same manner as described in the previous paper.[3] Methyl 2-hydroxynicotinate (**7**) was prepared according to the cited reference; mp 154—155° (lit.,[13] 143—153°).

Methyl 2-Methoxynicotinate (7a)——To a solution of 1 g of 2-methoxynicotinic acid[14] in 25 ml of MeOH was added dropwise 2 ml of thionyl chloride. The mixture was allowed to stand for 8 hr at room temperature. It was then evaporated on the water bath (60°) under reduced pressure to give a white crystalline solid. To the solid was added 20 g of ice and the solution was neutralized by 2 N NaOH to pH 4. The solution was extracted with ether. The extract was dried and evaporated. The residue was distilled, giving a 90% yield of product, bp 130—131° (35 mmHg). IR ν_{max}^{liq} cm^{-1}: 1735, 1713. *Anal.* Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.26; H, 5.39; N, 8.31.

3-Carbomethoxy-1-methyl-2(1H)-pyridone (7b)——To a solution of diazomethane which was prepared from 10 g of nitrosomethylurea was added 2.2 g of **7**. The mixture was allowed to stand for 24 hr at room temperature. It was then evaporated under reduced pressure to a yellow oil. Chromatography on alumina using ether as eluent gave 0.4 g (17%) of **7b**, colorless needles, mp 156—158°. IR ν_{max}^{Nujol} cm^{-1}: 1746, 1648. *Anal.* Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.36; H, 5.45; N, 8.30.

Methyl 4-Hydroxynicotinate (8)——To 3.5 mol of HCl in MeOH was added 1.47 g of 4-hydroxynicotinic acid.[15] The mixture was refluxed on the steam bath for 5 hr. The solution was evaporated under reduced pressure to give an oily residue. The aqueous solution of the residue which was obtained by addition of ice was neutralized with Na_2CO_3 to pH 7. Recrystallization of the deposited crystals from water gave 1.0 g (62%) of colorless needles, mp 231—232.° IR ν_{max}^{Nujol} cm^{-1}: 1705, 1640. *Anal.* Calcd. for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.02; H, 4.62; N, 9.15.

Methyl 4-Methoxynicotinate (8a)——Compound **8a** was synthesized from 2 g of 4-methoxynicotinic acid[15] by the same method as described for **7a**. The crude product which was obtained from the ethereal extract

12) T. Kitagawa, *Chem. Pharm. Bull.* (Tokyo), **26**, 59 (1978).
13) J.D. Crum and C.H. Fuchsman, *J. Heterocycl. Chem.*, **3**, 252 (1966).
14) K. Shimizu, I. Sakamoto, and S. Fukushima, *Yakugaku Zasshi*, **87**, 672 (1967).
15) W.C.J. Ross, *J. Chem. Soc.*, (*C*), **1966**, 1816.

was purified by recrystallization from *n*-hexane to give 0.7 g (32%) of colorless needles, mp 84—85°. IR ν_{max}^{Nujol} cm^{-1}: 1713. *Anal.* Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.50; H, 5.42; N, 8.23.

3-Carbomethoxy-1-methyl-4(1H)-pyridone (8b)——To 0.1 mol of NaOMe in 20 ml of MeOH was added 0.30 g of **8**. The mixture was dissolved on the water bath (60°) and then evaporated to dryness on the same bath. To the residue was added a mixture of 10 ml of CH_3I and 1 ml of MeOH. The solution was refluxed on the water bath (90°) for 2 hr. After removal of the solvent, the crystalline residue was chromatographed on a silica gel column (3 × 9 cm) with acetone. After all NaI was eluted using about 1 l of acetone, MeOH was flown through the column, giving 0.14 g of oil. Recrystallization from $CHCl_3$–ether gave 0.1 g (31%) of colorless needles which were very hygroscopic. IR ν_{max}^{Nujol} cm^{-1}: 1729, 1647. The hydrochloride was obtained by introducing dry HCl gas into $CHCl_3$ solution of the above crystals. The solution was concentrated to give colorless needles, mp 254°. IR ν_{max}^{Nujol} cm^{-1}: 1719, 1649. *Anal.* Calcd. for $C_8H_9NO_3 \cdot HCl$: C, 47.19; H, 4.95; N, 6.88; Cl, 17.41. Found: C, 47.12; H, 4.93; N, 6.60; Cl, 17.11.

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