Chem. Pharm. Bull. 26(5)1415—1425(1978)

UDC 547.854.3.03 : 541.62.04

Equilibrium Studies of 5-Substituted 4-Hydroxy-2-methylpyrimidines. V.[1] Lactim-Lactam Tautomerism in Ethereal Solvents

Takayasu Kitagawa, Kumiko Matsumoto, and Eizo Hirai

Shionogi Research Laboratory, Shionogi and Co., Ltd.[2]

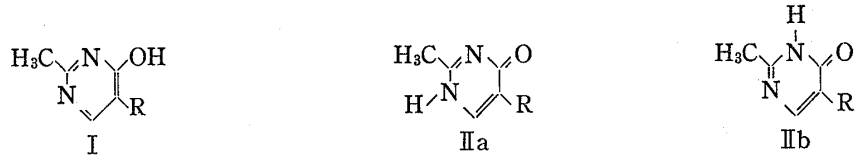
(Received September 14, 1977)

Lactim-lactam tautomerism of 5-carbethoxy-4-hydroxy-2-methylpyrimidine (**1**) was examined in the ethereal solvents (ethyl ether, *n*-propyl ether, isopropyl ether, *n*-butyl ether and *p*-dioxane). Compound **1** existed as a mixture of the lactim form (4-pyrimidinol, I) and the lactam form (4(3H)-pyrimidone, IIb) in the ethers, except *p*-dioxane. In *p*-dioxane, **1** existed mainly in the lactam form, IIb. A method was deviced to estimate spectrophotometrically the tautomeric equilibrium constant (K_t; K_t=[IIb]/[I]). The lactim form decreased with increasing the polarity of the solvent, 9.0% (IIb, 91.0%) in isopropyl ether; 10.5% (IIb, 89.5%) in *n*-propyl ether and 14.7% (IIb, 85.3%) in *n*-butyl ether.

The lactim-lactam tautomerism of 2-hydroxynicotinic acid esters (ester R; CH_3 (**5**), n-C_8H_{17} (**5'**)) and 4-hydroxynicotinic acid esters (ester R; CH_3 (**8**), n-C_8H_{17} (**8'**)) was also examined because of a structural resemblance to **1**. Compound **5** existed as a mixture of the lactim form (2-pyridinol) and the lactam form (2(1H)-pyridone) in the ethers. The lactim form of **5** existed in amounts, 10—70% (lactam form; 30—90%). Compound **8** existed mainly in the lactim form (4-pyridinol) in all the ethers. The presence of the lactim form may be resulted from an intramolecular hydrogen bonding of these compounds.

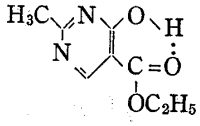
Keywords——5-carbethoxy-4-hydroxy-2-methylpyrimidine; *n*-octyl 4-hydroxy-2-methyl-5-pyrimidinecarboxylate; *n*-octyl 2-hydroxynicotinate; *n*-octyl 4-hydroxynicotinate; lactim-lactam tautomerism; UV spectrophotometry; ethereal solvents; least-squares method

In the previous papers,[1,3] it was shown that 5-substituted 4-hydroxy-2-methylpyrimidine existed in the lactam form, IIa and/or IIb, in the polar solvents (H_2O, MeOH and *n*-BuOH) and in the nonpolar solvent (*n*-hexane) except for 5-carbethoxy-4-hydroxy-2-methylpyrimidine (**1**) in *n*-hexane. The result suggests that **1** may be stabilized as a lactim form by such

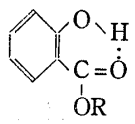


an intramolecular hydrogen bond (in III) as observed in the esters of salicylic acid (IV and V).[4] In ethereal solvents, the lactim form, III, will compete with an intermolecularly hydrogen-bonded form, VI, acting between 4-OH group of **1** and ether. Hydrogen-bond formation between phenol or benzoic acid and solvent ether was demonstrated in ethyl ether and

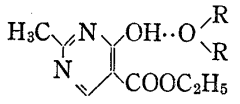
1) Part IV: T. Kitagawa, S. Mizukami, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **26**, 1403 (1978).
2) Location: *5–12–4, Sagisu, Fukushima-ku, Osaka, 553, Japan.*
3) T. Kitagawa, S. Mizukami, and E. Hirai, *Chem. Pharm. Bull.* (Tokyo), **22**, 1239 (1974).
4) L.W. Reeves, E.A. Allan, and K.O. Strømme, *Can. J. Chem.*, **38**, 1249 (1960); C.J.W. Brooks, G. Eglinton, and J.F. Morman, *J. Chem. Soc.*, **1961**, 661; R.A. Nyquist, *Spectrochim. Acta*, **19**, 1655 (1963).



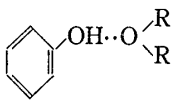
III



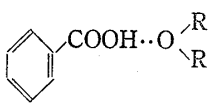
IV: R=CH_3
V: R=C_2H_5



VI



VII



VIII

p-dioxane.[5] It is presumed that without this intramolecular hydrogen-bond the lactim form will become labile to be changed into the lactam form, IIa or IIb. The lactim-lactam tautomerism was examined in a few ethereal solvents as a part of the investigations about the solvent effect on the tautomerism. Ethyl ether, *n*-propyl ether, isopropyl ether, *n*-butyl ether and *p*-dioxane were used as solvent.

Results and Discussion

Tautomerism of 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in Ethers

The tautomerism of **1** was spectrophotometrically examined by the same technique as described in the previous paper.[3] The methyl derivatives of **1**, 5-carbethoxy-4-methoxy-

Table I. UV Spectral Data of 5-Carbethoxy-4-hydroxy-2-methylpyrimidine (**1**) and Its Methyl Derivatives (**2**, **3** and **4**) in Ethers

Solvent	Compound **1**		**2**		**3**		**4**	
	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$
Ethyl ether	222.5	7.82	226	11.16	237	14.11	222	6.21
	302	6.60	262	6.69	285	6.20	302.5	7.51
n-Propyl ether	223	6.53	226	10.73	241	10.96[b]	224	5.50
	275sh[a]	3.37	263	7.05	284	5.35	303	6.83
	302	5.25						
Isopropyl ether	—[c]		—[c]		—[c]		—[c]	
	275sh	3.72	262	6.35	284.5	5.28[d]	303	7.26
	302.5	5.89						
n-Butyl ether	223	7.66	226	10.18	240.5	10.41[d]	222	5.47
	276sh	3.56	263	6.28	284.5	4.49	305	6.45
	303	4.97						
p-Dioxane	—[e]		—[e]		240	11.22	—[e]	
	302	6.65	263	6.36	287	4.69	305	6.41

a) Shoulder.
b) 10% (v/v) methanolic solution.
c) The spectrum at shorter wavelength than 250 nm was undeterminable due to the absorbance of solvent itself.
d) 5% (v/v) methanolic solution.
e) The spectrum at shorter wavelength than 230 nm was undeterminable due to the absorbance of solvent itself.

5) W.F. Forbes and A.R. Knight, *Can. J. Chem.*, **37**, 334 (1959); H.E. Ungnade and R.W. Lamb, *J. Am. Chem. Soc.*, **74**, 3789 (1952).

2-methylpyrimidine (2), 5-carbethoxy-1,2-dimethyl-4(1H)-pyrimidone (3) and 5-carbethoxy-2,3-dimethyl-4(3H)-pyrimidone (4) were used as models of the tautomers, I, IIa and IIb, respectively. The UV spectrum of **1** in ethers was compared with those of its model compounds. The spectral data are shown in Table I. The spectrum of **1** was different from those of **2** and **3**, and resembled rather better that of **4** in all the ethers. The result shows that **1** exists mainly in the lactam form, IIb, rather than the lactim form, I or the lactam form, IIa. However, a little difference in the spectra between **1** and **4** was observed in ethers except *p*-dioxane. As shown in Fig. 1, the spectrum of **1** in *n*-butyl ether had the shoulder band around 276 nm which was scarcely discernible in *p*-dioxane. It seems likely that the tautomerism is different between in ordinary ethers and in *p*-dioxane. In order to clarify the tautomerism of **1** in ethers, the tautomerism of methyl 2-hydroxynicotinate (**5**) and methyl 4-hydroxynicotinate (**8**) was examined. The tautomerism of these pyridines occurs between the lactim form (IXa and Xa) and the lactam form (IXb and Xb). Both structures of IXa

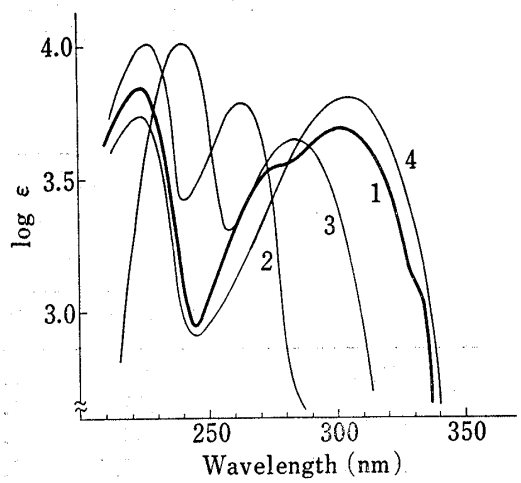
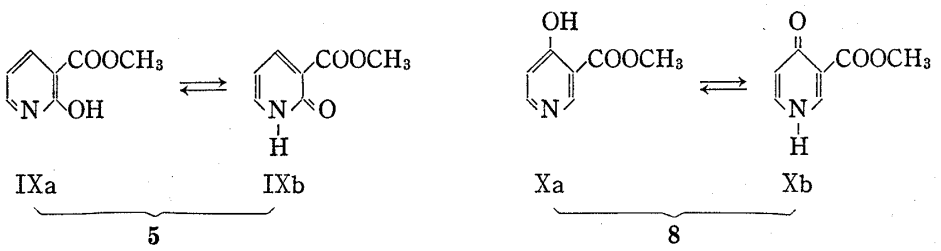


Fig. 1. UV Spectra of 5-Carbethoxy-4-hydroxy-2-methyl-pyrimidine (1), 5-Carbethoxy-4-methoxy-2-methylpyrimidine (2), 5-Carbethoxy-1,2-dimethyl-4 (1H)-pyrimidone (3) and 5-Carbethoxy-2,3-dimethyl-4 (3H)-pyrimidone (4) in *n*-Butyl Ether



and Xa are similar to that of the lactim form of **1** (I) and the structures of IXb and Xb are also similar to those of the lactam forms of **1** (IIb and IIa), respectively. Accordingly, it may be expected that the solvent effect on the tautomerism of **1** is similar to that of **5** or **8**.

The UV spectra of **5**, methyl 2-methoxynicotinate (**6**) and 3-carbomethoxy-1-methyl-2(1H)-pyridone (**7**) were shown in Table II. The spectrum of **5** had the three characteristic bands at 227.5—228, 298.5—299 and 331—332 nm in ethers except *p*-dioxane. As shown in Fig. 2, the spectrum in ethers had an intermediate character between those of **6** and **7**: the bands around 299 and 331 nm correspond to those of **6** (287 nm) and **7** (339—339.5 nm), respectively. It was considered that **5** existed in the mixtures of the lactim form (IXa) and the lactam form (IXb). In *p*-dioxane, however, the spectrum of **5** resembled that of **7**, excepting the shoulder band around 299 nm. It may be considered, therefore, that **5** exists mainly in the lactam form (IXb) containing a small amount of the lactim form (IXa) in this solvent. Table III shows the UV spectral data of **8**, methyl 4-methoxynicotinate (**9**) and 3-carbomethoxy-1-methyl-4(1H)-pyridone (**10**). The spectra of **8** in ethers are illustrated in Fig. 3. In this case, the spectrum of **8** resembled that of **9**. It was found that **8** existed in the lactim form (Xa) in all the ethers. These observations on methyl hydroxynicotinates (**5** and **8**) will lead to a conclusion that the lactim form of **1** may exist with the lactam form, IIb. It is reasonable to consider that the band around 276 nm in the spectrum of **1** is due

Table II. UV Spectral Data of Methyl 2-Hydroxynicotinate (**5**), Methyl 2-Methoxynicotinate (**6**) and 3-Carbomethoxy-1-methyl-2(1H)-pyridone (**7**) in Ethers

Solvent	Compound **5** λ_{max} (nm)	$\varepsilon(10^{-3})$	Compound **6** λ_{max} (nm)	$\varepsilon(10^{-3})$	Compound **7** λ_{max} (nm)	$\varepsilon(10^{-3})$
Ethyl ether	228	5.21	226	7.62	233	5.79
	299	4.25	287	6.22	339.5	6.45
	332	2.76				
n-Propyl ether	227.5	5.12	227	5.91	233	4.38
	298.5	4.65	287	5.68	339	6.56
	331	2.21				
Isopropyl ether	—[a]		—[a]		—[a]	
	298.5	4.34	287	4.90	339	6.87
	331.5	2.30				
n-Butyl ether	227.5	4.75	226	5.43	232	4.12
	298.5	4.66	287	5.40	339.5	6.10
	331	1.68				
p-Dioxane	231.5	5.37	226	6.56	232	5.17
	299.5sh[b]	2.77	287	5.54	338	7.09
	335.5	4.65				

a) See footnote *c* in Table I.
b) Shoulder.

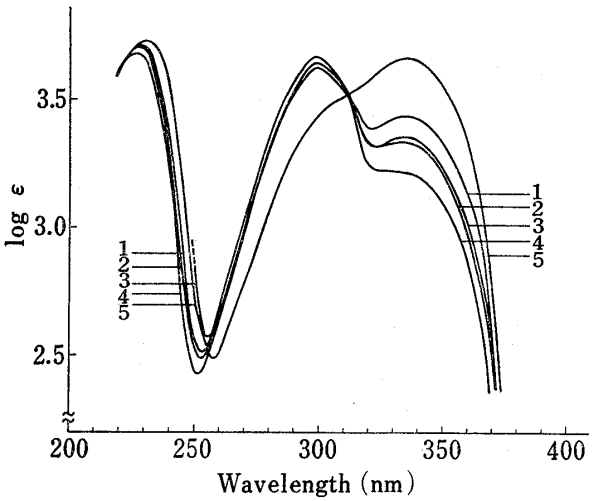


Fig. 2. UV Spectra of Methyl 2-Hydroxynicotinate (**5**) in Ethyl Ether (1), *n*-Propyl Ether (2), Isopropyl Ether (3), *n*-Butyl Ether (4) and *p*-Dioxane (5)

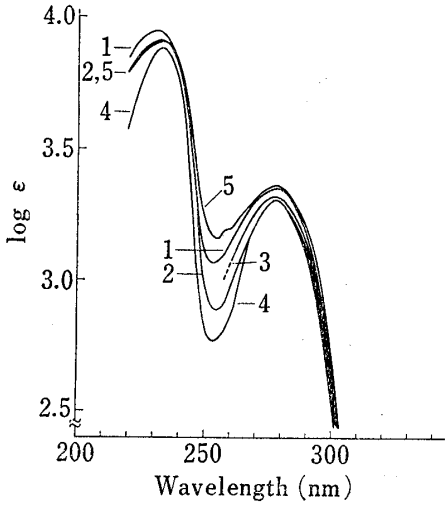


Fig. 3. UV Spectra of Methyl 4-Hydroxynicotinate (**8**) in Ethyl Ether (1), *n*-Propyl Ether (2), Isopropyl Ether (3), *n*-Butyl Ether (4) and *p*-Dioxane (5)

to some extent of the lactim form.

In the previous paper,[1] we reported that in *n*-hexane the lactim form of **1**, **5** and **8** (III, IXa and Xa) was changed into the lactam form (IIb, IXb and Xb) by addition of MeOH. The same effect of MeOH may be also expected for the ethereal solutions of these compounds.

Table III. UV Spectral Data of Methyl 4-Hydroxynicotinate (**8**), Methyl 4-Methoxynicotinate (**9**) and 3-Carbomethoxy-1-methyl-4(1H)-pyridone (**10**) in Ethers

Solvent	Compound **8**		**9**		**10**	
	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$	λ_{max} (nm)	$\varepsilon(10^{-3})$
Ethyl ether	231.5	9.00	227	7.58	251sh[a]	6.10
	277.5	2.32	268	1.61	257.5	7.94
					265	7.44
					298	2.88
n-Propyl ether	233	8.30	227	6.68	257	8.13[b]
	278	2.02	269	1.49	263	7.96
					291	2.84
Isopropyl ether	—[c]		—[c]		257.5	7.80
	277.5	2.13	268	1.71	264	7.35
					297	2.78
n-Butyl ether	233	7.47	228	6.99	257.5	7.76
	279	1.97	268	1.81	265	7.15
					296	2.75
p-Dioxane	232.5	8.53	228	7.37	258	7.80
	257sh	1.53	269	1.53	265	7.28
	277.5	2.30			298	2.54

a) Shoulder.
b) 5% (v/v) methanolic solution.
c) See footnote *c* in Table I.

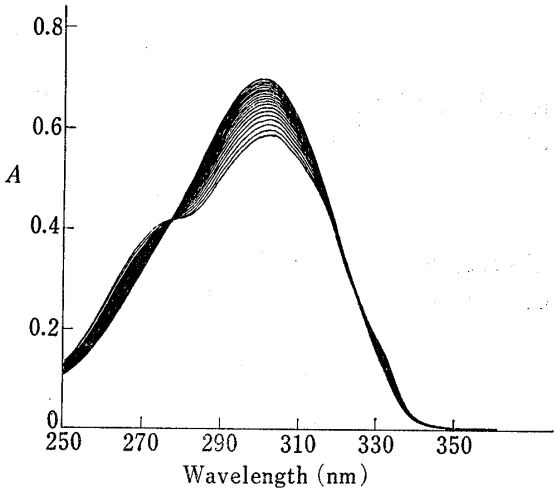


Fig. 4. Spectral Change on Addition of MeOH for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in *n*-Butyl Ether (C_{MeOH}: 0.02—0.44 M)

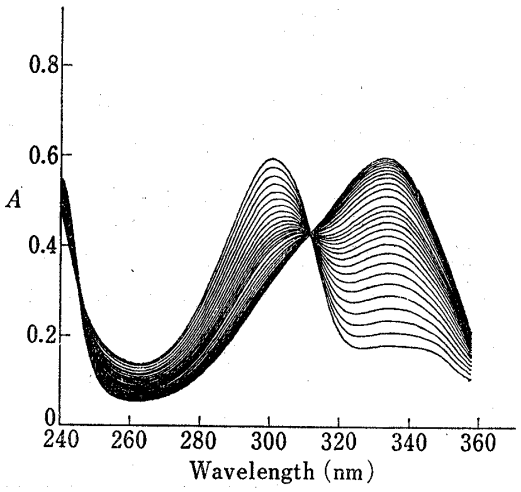


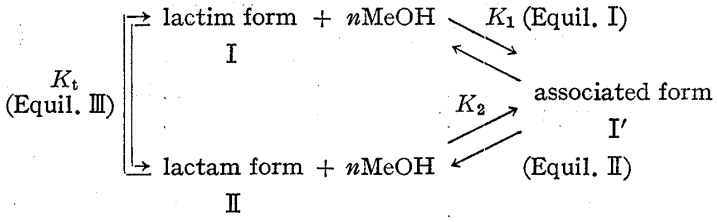
Fig. 5. Spectral Change on Addition of MeOH for Methyl 2-Hydroxynicotinate in *n*-Butyl Ether (C_{MeOH}: 0.05—1.53 M)

The UV spectra of **1** and **5** in *n*-butyl ether containing various amounts of MeOH are shown in Fig. 4 and 5, respectively. Each spectrum changed passing through the isosbestic point. With addition of MeOH, both 276 nm band of **1** and the 299 nm band of **5** disappeared gradually. The same spectral change was observed in other ethers. Although a similar change

in the spectra was also observed for **8**, a much larger amount of MeOH (>50%) than that used for **5** had to be added in the ethereal solutions. The results supported the above conclusion that a small amount of the lactim form, I, was mixed in the lactam form, IIb.

Estimation of the Tautomeric Equilibrium Constant of 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in Ethers

In order to analyze the tautomerism of **1** and **5** in ethereal solutions, a linearization method[6] was attempted. When MeOH is added to the ethereal solution, the equilibria between **1** or **5** and MeOH molecule may be described as follows:



It was found that one molecule of **1**, **5** or **8** associated with two molecules of MeOH[1] in *n*-hexane. Therefore, we also assumed $n=2$ in ethereal solutions. On the basis of these equilibria, a relationship was formulated.

$$R = \frac{\varepsilon-\varepsilon_{\mathrm{I}}}{\varepsilon_{\mathrm{II}}-\varepsilon} = K_1[\mathrm{MeOH}]^2 + \frac{K_1}{K_2} \tag{1}$$

where ε_{I} and $\varepsilon_{\mathrm{II}}$ 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. The equilibrium constants are

$$K_1 = \frac{[\mathrm{I}']}{[\mathrm{I}][\mathrm{MeOH}]^2} \tag{2}$$

$$K_2 = \frac{[\mathrm{I}']}{[\mathrm{II}][\mathrm{MeOH}]^2} \tag{3}$$

$$K_t = \frac{[\mathrm{II}]}{[\mathrm{I}]} \tag{4}$$

If the lactim form does not absorb at the wavelength, and the concentration of MeOH is much larger than that of the sample, eq(1) becomes

$$\frac{\varepsilon}{\varepsilon_{\mathrm{II}}-\varepsilon} = K_1 C_{\mathrm{MeOH}}^2 + \frac{K_1}{K_2} \tag{5}$$

where C_{MeOH} is the total concentration of MeOH. As a total concentration of **1** or **5** is constant through all measurements of UV spectra, eq(5) is converted into

$$\frac{A}{A_{\mathrm{II}}-A} = K_1 C_{\mathrm{MeOH}}^2 + \frac{K_1}{K_2} \tag{6}$$

Eq(6) is transformed into

$$A = A_{\mathrm{II}}\left(1-\frac{K_2}{K_1+K_2+K_1K_2C_{\mathrm{MeOH}}^2}\right) \tag{7}$$

In order to estimate K_1 and K_2, eq(7) was solved by means of the linearization method. The unknown parameters, α's are adjusted by the minimization of the function, S, as shown

$$S = \sum_{i=1}^{k}(y_i - f(x_i, \alpha))^2 \tag{8}$$

where y_i is the experimentally observed value; $f(x_i, \alpha)$ means the theoretical value calculated

6) N.R. Draper and H. Smith, "Applied Regression Analysis," John Wiley and Sons, Inc., New York, 1966.

from the relation, $y=f(x, \alpha)$; k is the number of the data points. The terms, y and $f(x, \alpha)$ correspond to A and eq(7) (a function of C_{MeOH} with three parameters, A_{II}, K_1 and K_2), respectively. The values, A_{II}, K_1 and K_2 were determined by use of the experimental A values and C_{MeOH}, so that the function, S, was minimized by a linear least-squares treatment. The iterative procedure for minimization was made using computer.

The approximate values for the parameters, A_{II}, K_1 and K_2 were estimated using the following manner. Of these values, A_{II} could be estimated directly from the spectrum which was obtained by adding an enough amount of MeOH to remove the lactim band (276 nm for **1**; 299 nm for **5**). Since eq(6) means that plot of $A/(A_{II}-A)$ against C^2_{MeOH} yields a straight line with a slope equal to K_1 and an intercept equal to K_1/K_2, the constants, K_1 and K_2, may be estimated by the plot. The results of the plot for **1** and **5** (n-butyl ether) are shown in Fig. 6 and **7** (for both; curve 1), respectively. Linear regression was made for both plots

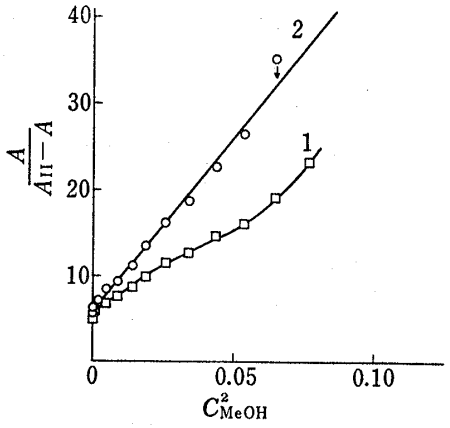


Fig. 6. Plot of $A/(A_{II}-A)$ against C^2_{MeOH} for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in n-Butyl Ether

(1) A_{II}; estimated from the spectrum.
(2) A_{II}; estimated by computation.
$A/(A_{II}-A)=5.65+415.66\ C^2_{MeOH}$; $s=1.13$; $n=12$.

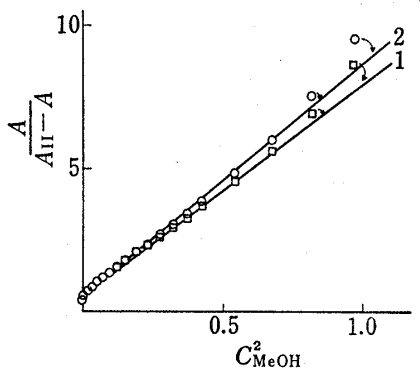


Fig. 7. Plot of $A/(A_{II}-A)$ against C^2_{MeOH} for Methyl 2-Hydroxynicotinate in n-Butyl Ether

(1) A_{II}; estimated from the spectrum.
(2) A_{II}; estimated by computation.
$A/(A_{II}-A)=0.516+8.265\ C^2_{MeOH}$; $s=0.123$; $n=19$.

according to the usual least-squares method. The approximate values of K_1 and K_2 were determined from the slope and the intercept of the regression lines. The approximate values for those parameters were put into eq(7). Iterative computation was performed until the values, A_{II}, K_1 and K_2, converged. The results of the computation for **1** and **5** in n-butyl

Table IV. The Result of the Computation of A_{II}, K_1 and K_2 for 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in n-Butyl Ether

No.	A_{II}	K_1	K_2	$S^{a)}$ (10^4)
0	0.70600	219.20	40.370	1.3928
1	0.68822	354.69	61.588	1.2035
2	0.69089	400.84	69.557	1.1890
3	0.69055	410.73	71.224	1.1885
4	0.69045	412.72	71.531	1.1885
5	0.69043	413.09	71.586	1.1885
6	0.69043	413.15	71.595	1.1885
7	0.69043	413.16	71.597	1.1885
S.E.$^{b)}$	0.45638×10^{-2}	74.712	11.135	

a) Defined as eq(8).
b) Standard error.

Table V. The Result of the Computation of A_{II}, K_1 and K_2 for Methyl 2-Hydroxynicotinate in *n*-Butyl Ether

No.	A_{II}	K_1	K_2	$S^{a)}$ (10^3)
0	0.64000	7.9900	16.140	2.8372
1	0.63505	8.6242	17.141	2.8185
2	0.63435	8.7359	17.381	2.8179
3	0.63418	8.7529	17.421	2.8179
4	0.63416	8.7554	17.426	2.8179
5	0.63415	8.7558	17.427	2.8179
S.E.[b)]	0.85276×10^{-2}	0.70021	1.6417	

a) Defined as eq(8).
b) Standard error.

ether are shown as an example in Table IV and V, respectively. The three values converged after 5 and 7 iterations. These values were estimated with good precision, *i.e.*, standard error is within 0.01 for A_{II} and 0.1 log K unit for K_1 and K_2. Plots of eq(6) for **1** and **5** were made using the computed A_{II} values, which were shown in Fig. 6 and 7 (for both; curve 2), respectively. The constants, K_1 and K_2, in various ethers were summarized in Table VI and VII. The tautomeric equilibrium constants of **1** and **5** were

Table VI. Equilibrium Constants, K_1, K_2 and K_t, of 5-Carbethoxy-4-hydroxy-2-methylpyrimidine in Ethers

Solvent	K_1	K_2	K_t
p-Dioxane	—	—	—[a)]
Ethyl ether	—	—	—[b)]
Isopropyl ether	244.4(47.7)[c)]	24.3 (3.7)	10.1
n-Propyl ether	319.0(80.6)	37.7 (7.6)	8.5
n-Butyl ether	413.2(74.7)	71.6(11.1)	5.8

a) Undeterminable due to the predominance of the lactam form.
b) Trace amount of the lactim form was recognized.
c) ( ): standard error.

Table VII. Equilibrium Constants, K_1, K_2 and K_t, of Methyl 2-Hydroxynicotinate in Ethers

Solvent	K_1	K_2	K_t
p-Dioxane	37.98(10.8)[a)]	3.43(0.89)[a)]	11.07
Ethyl ether	12.82 (1.92)	7.93(0.90)	1.61
n-Propyl ether	11.31 (1.30)	10.58(1.10)	1.07
Isopropyl ether	4.62 (0.51)	5.97(0.61)	0.77
n-Butyl ether	8.76 (0.70)	17.43(1.64)	0.50

a) ( ): standard error.

calculated from eq(4) ($K_t=K_1/K_2$) using the estimated K_1 and K_2 values. Table VI shows that the lactim form of **1** increased in Isopropyl ether, *n*-propyl ether and *n*-butyl ether in that order. The equilibrium constant, K_t, could not be determined in *p*-dioxane and ethyl ether, since an amount of the lactim form was too small to detect spectrophotometrically. In the case of **5**, the lactim form existed more largely than that of **1**, as shown in Table VII. It was found that the lactim form increased in *p*-dioxane, ethyl ether, *n*-propyl ether, Isopropyl ether and *n*-butyl ether in that order. It seems likely that the lactim-lactam tautomerism of these compounds is affected by a polarity of solvent.

Infrared Spectra of Esters of 4-Hydroxy-2-methyl-5-pyrimidinecarboxylic Acid, 2-Hydroxynicotinic Acid and 4-Hydroxynicotinic Acid

It was assumed that **1**, **5** and **8** formed an intramolecular hydrogen bond between OH group and the adjacent carbethoxy or carbomethoxy group, being stabilized as a lactim form in nonpolar or weak polar solvents such as *n*-hexane[1] or ethers. In order to support such an assumption, an infrared spectroscopic examination was attempted. Because of the poor solubility of these compounds in these solvents, the corresponding *n*-octyl esters (**1′**, **5′** and **8′**) were synthesized and CCl_4 was chosen as a nonpolar solvent. The infrared spectra were shown in Fig. 8. In the case of methyl salicylate (**11**) in the same solvent, the 3210 cm^{-1} band has been assigned as an intramolecularly hydrogen-bonded OH group.[7] Both the 3180 cm^{-1} band for **5′** and the 3150 cm^{-1} band for **8′**, therefore, will be assigned as the same type of OH group as observed in **11**. The wavenumber, molar extinction coefficient (ε), half-intensity width ($\Delta\nu_{1/2}$) and integral intensity (A) approximated to those of **11**. The result shows that the lactim forms of **5′** and **8′** exist as XIV and XV, respectively.

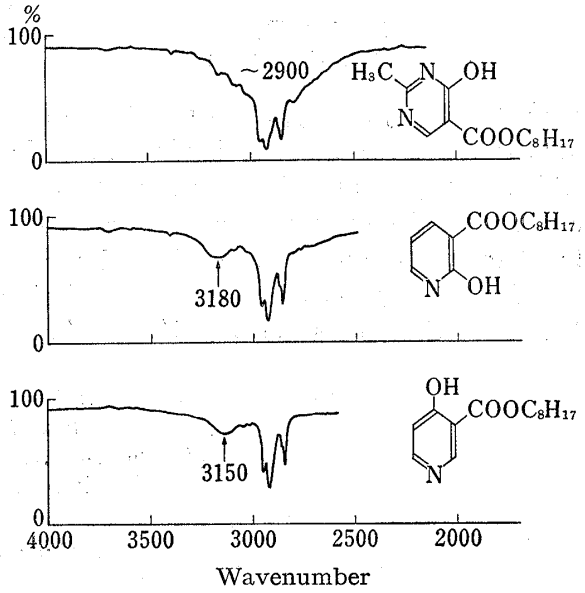
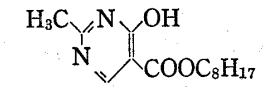
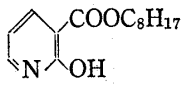
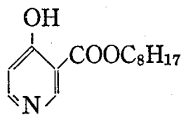
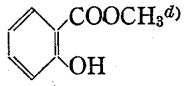


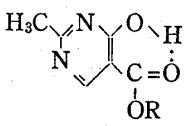
Fig. 8. IR Spectra of *n*-Octyl 4-Hydroxy-2-methyl-5-pyrimidinecarboxylate, *n*-Octyl 2-Hydroxynicotinate and *n*-Octyl 4-Hydroxynicotinate in CCl_4

TABLE VIII. IR Spectral Data of *n*-Octyl 4-Hydroxy-2-methyl-5-pyrimidinecarboxylate (**1′**), *n*-Octyl 2-Hydroxynicotinate (**5′**) and *n*-Octyl 4-Hydroxynicotinate (**8′**) in CCl_4

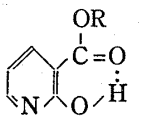
Compound (Concentration)	OH-Band $\nu_{max}^{CCl_4}$ (cm^{-1})	ε[a] (mol^{-1} 1 cm^{-1})	$\Delta\nu_{1/2}$[b] (cm^{-1})	A[c] (mol^{-1} 1 cm^{-2}) (10^{-4})	CO-Band $\nu_{max}^{CCl_4}$ (cm^{-1})
1′  (2.583×10^{-3} M)	2900				1747, 1713, 1674
5′  (2.143×10^{-3} M)	3180	50.0	130.9	2.37	1742, 1703, 1684, 1661
8′  (1.622×10^{-3} M)	3150	62.0	146.2	3.28	1682
11 	3210	71.7	125.0	3.24	1683

a) Molar extinction coefficient.
b) Half-intensity width.
c) Integral intensity (A) was calculated from Ramsay's equation (D.A. Ramsay, *J. Am. Chem. Soc.*, **74**, 72 (1952)).
d) C.J.W. Brooks, G. Eglinton, and J.F. Morman, *J. Chem. Soc.*, **1961**, 661.

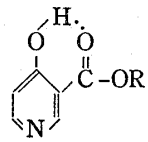
7) See footnote *d* in Table VIII.



$R=C_2H_5$ (III)
$R=n\text{-}C_8H_{17}$ (XIII)



$R=CH_3$ (XI)
$R=n\text{-}C_8H_{17}$ (XIV)



$R=CH_3$ (XII)
$R=n\text{-}C_8H_{17}$ (XV)

Unfortunately, the ν_{OH} band for **1'** could not be distinctly decided, although the band which appeared around 2900 cm^{-1} might be assigned as that band. The ν_{CO} bands of **1'**, **5'** and **8'** which appeared at 1650—1750 cm^{-1} were examined. The ν_{CO} band of **8'** (1682 cm^{-1}) coincided with the hydrogen bonding ν_{CO} band of **11** (1683 cm^{-1}). In the case of **1'** and **5'**, a few bands were observed in this region.

In order to know the structure of **1'** and **5'**, UV spectra were measured in CCl_4. Table IX shows that the spectra of **1'** and **5'** have a shoulder band at 292 nm and 340 nm, respec-

Table IX. UV Spectral Data of *n*-Octyl 4-Hydroxy-2-methyl-5-pyrimidinecarboxylate (**1'**), *n*-Octyl 2-Hydroxynicotinate (**5'**) and *n*-Octyl 4-Hydroxynicotinate (**8'**) in *n*-Hexane and CCl_4

Compound	*n*-Hexane		CCl_4	
	λ_{max} (nm)	ε (10^{-3})	λ_{max} (nm)	ε (10^{-3})
1'	273	5.58	272	5.25
	292sh[a]	3.84	292sh	4.02
5'	227	5.85	—[b]	
	297	6.41	299.5	7.16
	340sh	0.16	340sh	0.34
8'	232.5	10.34	—[b]	
	279	2.92	279	2.34

a) Shoulder.
b) Spectrum at shorter wavelength than 250 nm was undeterminable due to the absorbance of solvent itself.

tively. The fact indicates that these compounds existed as a mixture of the lactim form (XIII for **1'**; XIV for **5'**) and the lactam form (IIb type for 1'; IXb type for 5'). The bands at 1650—1750 cm^{-1} will reveal the two free ν_{CO} bands corresponding to the ester group and the ring carbonyl group (4-oxy for **1'**; 2-oxy for **5'**) in the lactam form in addition to the hydrogen bonding ν_{CO} band in the lactim form. The bands, ν_{NH} and ν_{OH}, may be overlapped in the 2900 cm^{-1} region. It was evidenced that the lactim form of **5'** and **8'** existed in the form, XIV and XV, respectively. It is reasonable to consider that the lactim form of **1** and **1'** also existed in the intramolecularly hydrogen-bonded forms, III and XIII, respectively.

Experimental

Materials——The solvents except *p*-dioxane was purified by the distillation of the commercial goods of the reagent grade. The commercial available *p*-dioxane ("Spectrosol" of Dozindo Laboratories) was used without purification. Water contents of the solvents were: ethyl ether; 0.077% (w/v), *n*-propyl ether; 0.058% (w/v), isopropyl ether; 0.120% (w/v), *n*-butyl ether; 0.026% (w/v) and *p*-dioxane; 0.070% (w/v).

5-Carbethoxy-4-hydroxy-2-methylpyrimidine and its methyl derivatives, and methyl 2-hydroxy- and 4-hydroxynicotinate, and their methyl derivatives were prepared in the same manner as described in the previous papers.[1,3]

Preparation of *n*-Octyl 4-Hydroxy-2-methyl-5-pyrimidinecarboxylate (1')——To a suspended solution of 0.5 g of 4-hydroxy-2-methyl-5-pyrimidinecarboxylic acid[3] in 6 ml of *n*-octyl alcohol was added 0.5 ml of

H_2SO_4. The solution was heated at 160° for 5 hr. After removal of the solvent below 160° under reduced pressure, the residue was poured into water containing ice and neutralized by K_2CO_3. The solution was extracted with ethyl acetate. The extract was dried and evaporated under reduced pressure. Recrystallization from ethyl ether: MeOH (1: 1) gave 0.29 g (34%) of colorless needles. mp 120°. *Anal.* Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 63.09; H, 8.54; N, 10.51.

Preparation of *n*-Octyl 2-Hydroxynicotinate (5′)——To a suspended solution of 0.2 g of 2-hydroxynicotinic acid in 2.5 ml of *n*-octyl alcohol was added 0.2 ml of H_2SO_4. The solution was heated on the steam-bath for 7 hr. After removal of the solvent at 120° under reduced pressure, the residue was poured into water containing ice and neutralized by K_2CO_3. The deposited crystals were recrystallized from acetone–H_2O (1: 1) to give 0.17 g (47%) of colorless needles, mp 74—75°. *Anal.* Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.15; H, 8.31; N, 5.37.

Preparation of *n*-Octyl 4-Hydroxynicotinate (8′)——To a suspended solution of 0.18 g of 4-hydroxynicotinic acid in 2.5 ml of *n*-octyl alcohol was added 0.2 ml of H_2SO_4. The solution was heated on the steam-bath for 3 hr. After removal of the solvent at 120° under reduced pressure, the residue was poured into water containing ice and neutralized by K_2CO_3. The solution was extracted with ethyl acetate. The extract was dried and evaporated to dryness under reduced pressure. Recrystallization from CCl_4 gave 0.1 g (31%) of colorless prisms. mp 168—172°. *Anal.* Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.95; H, 8.33; N, 5.75.

Measurement of UV Spectra——UV spectra were measured using a Hitachi 323 spectrophotometer. The measurements were carried out at sample concentrations of 0.5×10^{-4}—1.5×10^{-4} M. The compounds, **3** and **10**, were not soluble in some ethers, so the spectra were measured in 5—10% methanolic solvents.[8]

Estimation of the K_t Values of 1 and 5——The UV spectra of **1** and **5** were measured in the ethers (20—24 ml) using 100 mm cell. To the ethereal solutions of **1** and **5** were added 20—50 μl and 20—100 μl portions of MeOH, respectively. The additions of MeOH were repeated until the concentrations attained to 1.8—2.0% (v/v) and 3.8—8.1% (v/v), respectively. From the spectra of **1** and **5**, A values were read at 303 and 335 nm, respectively. The observed A values 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 ethers and the volume of MeOH, respectively. The approximate A_{II} values of the lactam forms of **1** and **5** were obtained from the spectra which were written at the highest concentrations of MeOH. In order to estimate the approximate values of K_1 and K_2, plot of eq (6) was made using the observed A and A_{II} values, and the concentrations of MeOH (C_{MeOH}). The real values of K_1, K_2 and A_{II} were estimated by the linearization method using their approximate values. Computation was carried out using a Facom 270—30 digital computer (Fuji Electric Co., Ltd.).

Acknowledgement The authors wish to express their deep appreciation to Prof. T. Uno of Kyoto University for his valuable discussions and his useful suggestions. They also wish to thank Dr. H. Otsuka, Director of this laboratory, for his helpful advice and encouragement. Thanks are also given to Dr. Y. Matsui and Mr. M. Takasuka for IR spectral measurement and to Mr. N. Yoshitani for computer calculation.

8) See footnotes, *b* and *d* in Table I, and *b* in Table III.