[Chem. Pharm. Bull. 22(6)1239—1255(1974)]

UDC 547.853.3.03.04 : 543.422.6

Equilibrium Studies of 5-Substituted 4-Hydroxy-2-methylpyrimidines. I. The Ionization Constants in Aqueous Solution

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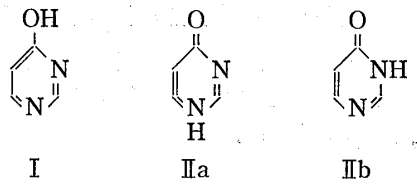
(Received August 3, 1973)

The ionization constants of 5-substituted 4-hydroxy-2-methylpyrimidines (1—11) and some of their methyl derivatives, 4-methoxy-2-methylpyrimidines, 1,2-dimethyl-4(1H)-pyrimidones and 2,3-dimethyl-4(3H)-pyrimidones were determined. From the ionization constants, the degree of lactim-lactam tautomerism in the 4-hydroxypyrimidines was estimated. It was found that each of the pyrimidines exist mainly as a mixture of lactam forms (4(1H)-pyrimidone and 4(3H)-pyrimidone) in approximately equal amounts, in aqueous solution (*ca.* 1×10^{-4}M). The results were also supported by ultraviolet absorption spectroscopy. The substituent effect on the tautomerism was discussed in connection with the Hammett equation for the basicity of the pyrimidines.

4-Hydroxypyrimidine can tautomerize to three forms, a lactim form I and lactam forms IIa and IIb.[2]



I IIa IIb

Brown and co-workers[3,4] determined the ionization constants of 4-hydroxypyrimidine and its methyl derivatives; 4-methoxypyrimidine, 1-methyl-4(1H)-pyrimidone and 3-methyl-4(3H)-pyrimidone. These methyl derivatives were applicable as models of the tautomers, I, IIa and IIb. Using the ionization constants of these compounds, Mason[5] estimated the tautomeric equilibrium of 4-hydroxypyrimidine in aqueous solution. However, such estimation for substituted 4-hydroxypyrimidines at the 5-position has not been reported. We have, therefore determined the ionization constants of some 5-substituted 4-hydroxy-2-methylpyrimidines (R; H (**1**), CH_3 (**2**), NH_2 (**3**), OCH_3 (**4**), OH (**5**), CH_2OH (**6**), $NHCOOC_2H_5$ (**7**), $COOC_2H_5$ (**8**), $CONH_2$ (**9**), COOH (**10**) and CN (**11**)), and those of some of their methyl derivatives, 4-methoxy-2-methylpyrimidines (R; H (**14**), CH_3 (**19**), OCH_3 (**24**), $COOC_2H_5$ (**29**), $CONH_2$ (**34**) and CN (**37**)), 1,2-dimethyl-4(1H)-pyrimidones (R; H (**12**), CH_3 (**17**), OCH_3 (**22**), $COOC_2H_5$ (**27**), $CONH_2$ (**32**) and CN (**35**)) and 2,3-dimethyl-4(3H)-pyrimidones (R; H (**13**), CH_3 (**18**), OCH_3 (**23**), $COOC_2H_5$ (**28**), $CONH_2$ (**33**) and CN (**36**)).

Result and Discussion

The acidic and basic ionization constants of the 5-substituted 4-hydroxy-2-methylpyrimidines are listed in Table I. The basic pK_a values (proton gained) of the compounds were determined by spectrophotometry and the acidic pK_a values (proton lost) were mostly deter-

1) Location: *Fukushima-ku, Osaka, 553, Japan.*
2) *a*) D.J. Brown, "The Pyrimidines," John Wiley & Sons, Inc., New York, 1962, Chapter XIII; *b*) 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. 368—370.
3) D.J. Brown and L.N. Short, *J. Chem. Soc.*, **1953**, 331.
4) D.J. Brown, E. Hoerger, and S.F. Mason, *J. Chem. Soc.*, **1955**, 211.
5) S.F. Mason, *J. Chem. Soc.*, **1958**, 674.

mined by potentiometric titration. The acidic ionization constants of compound (**3**, **5** and **10**), $pK_a^{II(2)}$s related to the third ionization, were obtained by spectrophotometry, because the acid strengths of the monoanions were too weak to be determined by potentiometric titration. The pK_a values were corrected thermodynamically according to the methods of Albert and Serjeant.[6]

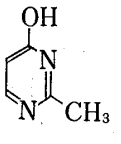
Table I. The Ionization Constants of 5-Substituted 4-Hydroxy-2-methylpyrimidines

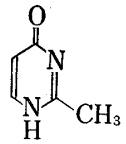
No.	5-Substituent	Basic pK_a[a]		Acidic pK_a[b]	
		$pK_a^{I(1)}$	$pK_a^{I(2)}$	$pK_a^{II(1)}$	$pK_a^{II(2)}$
1	H		2.51		9.06
2	CH_3		3.23		9.64
3	NH_2	−1.12	3.88		10.01[a]
4	OCH_3		2.58		9.05
5	OH		2.93	7.57	12.74[a]
6	CH_2OH		2.71		9.19
7	$NHCOOC_2H_5$		2.72		8.05
8	$COOC_2H_5$		1.27		7.77
9	$CONH_2$		1.32		7.59
10	COOH		0.81	4.40	9.85[a]
11	CN		−0.18		6.22

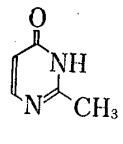
a) spectrophotometric method
b) potentiometric method except pK_a^{II}s of compound (**3**, **5** and **10**)

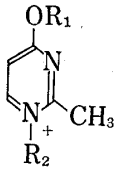
Ionization Equilibria of 4-Hydroxy-2-methylpyrimidine

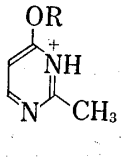
Since **1** tautomerizes to the forms I′, IIa′ and IIb′, the cations of the compound can be formulated as III and IV, III and V, and IV and V arising from protonation of I′, IIa′ and IIb′, respectively.


I′


IIa′


IIb′


III: $R_1=R_2=H$
VI: $R_1=CH_3$, $R_2=H$
VII: $R_1=H$, $R_2=CH_3$


IV: R=H
VIII: $R=CH_3$

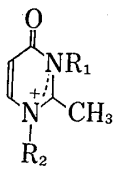

V: $R_1=R_2=H$
IX: $R_1=H$, $R_2=CH_3$
X: $R_1=CH_3$, $R_2=H$

Chart 1

As an approach to investigation of the equilibria of these cations, we have examined the protonation of 4-methoxy-2-methylpyrimidine, 1,2-dimethyl-4(1H)-pyrimidone, and 2,3-dimethyl-4(3H)-pyrimidone, compounds similar in structure to I′, IIa′ and IIb′, respectively.

6) A. Albert and E.P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, 1962, pp. 57—68.

TABLE II. The Ionization Constants and Ultraviolet Absorption Spectra of the Methyl Derivatives of 4-Hydroxy-2-methylpyrimidines

No.	Compounds	pK_a^I	Cation			Neutral species		
			λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium	λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium
12	1,2-Dimethyl-4(1H)-pyrimidone	2.69	228 260	10.51 3.72	1.0N HCl	238.5 255sh[a]	13.01 7.32	pH 6.60
13	2,3-Dimethyl-4(3H)-pyrimidone	2.74	226.5 259	8.32 3.51	1.0N HCl	222 272.5	6.70 5.00	pH 6.60
14	4-Methoxy-2-methylpyrimidine	3.99	223 244	6.93 6.31	1.0N HCl	213 252	5.82 4.23	pH 6.60
15	1,2-Dimethyl-4-methoxy-pyrimidinium perchlorate		227 244—248	8.57 7.11	H_2O			
16	1,2,3-Trimethyl-4-pyrimidonium perchlorate		231.5 265	9.70 3.39	H_2O			
17	1,2,5-Trimethyl-4(1H)-pyrimidone	3.46	238 260	9.79 5.61	1.0N HCl	246 260sh[a]	11.76 9.26	pH 6.60
18	2,3,5-Trimethyl-4(3H)-pyrimidone	3.42	234.5 260	7.71 5.27	1.0N HCl	227 272.5	5.51 6.05	pH 6.60
19	2,5-Dimethyl-4-methoxy-pyrimidine	4.79	229 250	6.36 7.32	1.0N HCl	219 257	7.05 4.95	pH 6.60
20	4-Methoxy-1,2,5-trimethyl-pyrimidinium perchlorate		232—233 255	6.98 7.67	H_2O			
21	1,2,3,5-Tetramethyl-4-pyrimidonium perchlorate		239 265—267	8.48 4.90	H_2O			
22	1,2-Dimethyl-5-methoxy-4(1H)-pyrimidone	2.79	258	11.07	1.0N HCl	265	11.53	pH 6.60
23	2,3-Dimethyl-5-methoxy-4(3H)-pyrimidone	2.72	255—257	9.54	1.0N HCl	239 277	6.45 7.32	pH 6.60
24	4,5-Dimethoxy-2-methyl-pyrimidine	4.11	239 270	6.57 7.48	1.0N HCl	226.5 269	8.01 5.53	pH 6.60
25	4,5-Dimethoxy-1,2-dimethyl-pyrimidinium perchlorate		242 274	6.57 8.53	H_2O			
26	5-Methoxy-1,2,3-trimethyl-pyrimidonium perchlorate		260	9.40	H_2O			
27	5-Carbethoxy-1,2-dimethyl-4(1H)-pyrimidone	1.50	230 282	9.26 6.00	21% H_2SO_4[b]	240 283	13.20 6.11	pH 6.60
28	5-Carbethoxy-2,3-dimethyl-4(3H)-pyrimidone	1.38	227 280	6.76 6.12	21% H_2SO_4[b]	227.5 297	6.49 8.29	pH 6.60
29	5-Carbethoxy-4-methoxy-2-methylpyrimidine	2.36	234.5 257sh[a]	9.27 5.25	1.0N HCl	228 263	9.90 6.83	pH 6.60
30	5-Carbethoxy-1,2-dimethyl-4-methoxypyrimidinium perchlorate		238 260sh[a]	11.01 6.18	10% EtOH[c]			
31	5-Carbethoxy-1,2,3-trimethyl-pyrimidonium perchlorate		231 296	17.42 11.17	10% MeOH[c]			
32	5-Carbamoyl-1,2-dimethyl-4(1H)-pyrimidone	1.44	230 281	9.35 5.43	21% H_2SO_4[b]	239 281	10.63 5.55	pH 6.60
33	5-Carbamoyl-2,3-dimethyl-4(3H)-pyrimidone	1.48	227.5 279	7.55 6.15	21% H_2SO_4[b]	226.5 295	7.48 8.23	pH 6.60
34	5-Carbamoyl-4-methoxy-2-methylpyrimidone	2.49	233 252sh[a]	10.50 6.49	1.0N HCl	226.5 262	11.06 6.19	pH 6.60
35	5-Cyano-1,2-dimethyl-4(1H)-pyrimidone	−0.01	232 285	8.20 6.34	45% H_2SO_4[d]	240.5 284.5	12.13 5.97	pH 6.60
36	5-Cyano-2,3-dimethyl-4(3H)-pyrimidone	−0.06	228.5 282.5	6.56 6.75	45% H_2SO_4[d]	227 299	5.89 8.61	pH 6.60
37	5-Cyano-4-methoxy-2-methyl-pyrimidine	0.80	238 260sh	9.20 5.82	45% H_2SO_4[d]	229—230 266	9.43 6.25	pH 6.60

a) shoulder
b) H_0 acidity function = −1.07
c) These compounds were unstable in aqueous medium, but stable at least for 2 hr in EtOH or MeOH solution. Therefore, the stock solutions of these compounds of **30** and **31** were prepared in EtOH and MeOH, respectively, and then the solutions were diluted with water (1:9) prior to spectroscopic measurement.
d) H_0 acidity function = −2.85

The ultraviolet absorption spectra of the cations of these methyl derivatives were compared with those of 1,2,3-trimethyl-4-pyrimidonium perchlorate and 1,2-dimethyl-4-methoxypyrimidinium perchlorate, which cannot tautomerize. Since it is generally recognized that the spectrum of a tautomer, although it cannot be determined directly, is approximately identical with that of the derivative obtained by substitution of an alkyl group for the tautomerizable hydrogen atom,[7] the former perchlorate can be used as a model of cations IX and X, and the latter perchlorate as a model of cation VI. When the cations of 1,2-dimethyl-4(1H)-pyrimidone and 2,3-dimethyl-4(3H)-pyrimidone exist respectively as forms IX and X, their spectra both resemble that of 4-pyrimidonium perchlorate, and when the former exists in the form VII, the spectrum resembles that of 4-pyrimidinium perchlorate. On the other hand, the spectrum of 4-methoxy-2-methylpyrimidinium cation, if it exists as the form VI, may be almost identical with that of the 4-pyrimidinium perchlorate. The ultraviolet spectral data for the cations of 5-substituted 4-methoxy-2-methylpyrimidines (**14**, **19**, **24** and **29**), 5-substituted 1,2-dimethyl-4(1H)-pyrimidones (**12**, **17**, **22** and **27**) and 5-substituted 2,3-dimethyl-4(3H)-pyrimidones (**13**, **18**, **23** and **28**), and those for 5-substituted 1,2,3-trimethyl-4-pyrimidonium perchlorates (R; H (**16**), CH_3 (**21**), OCH_3 (**26**) and $COOC_2H_5$ (**31**)) and 1,2-dimethyl-4-methoxypyrimidinium perchlorates (R; H (**15**), CH_3 (**20**), OCH_3 (**25**) and $COOC_2H_5$ (**30**)) are listed in Table II. The spectra of 1,2-dimethyl-4(1H)-pyrimidones in acidic solution resemble those of the 4-pyrimidonium perchlorates[8] and differ from those of the 4-pyrimidinium perchlorates. Such resemblance was also found between the spectra of 2,3-dimethyl-4(3H)-pyrimidonium cations and the 4-pyrimidonium perchlorates.[8] The results show that the cations of both the N-methylpyrimidones exist mainly as the structures IX and X, protonated at the ring nitrogen. When the spectra of 4-methoxy-2-methylpyrimidines in acidic solution were compared with those of the 4-pyrimidinium perchlorates, similarity was observed between the compounds. Mizukami and Hirai[9] reported that protonation of 4,5-substituted 2-methylpyrimidine occurrs at the ring nitrogen N_1, and Roth and Strelitz[10] pointed out the same position for the protonation of 4-substituted pyrimidines. Since the possibility of N_1-protonation is also considered from our results, their conclusion may also hold for 4-methoxy-2-methylpyrimidine.

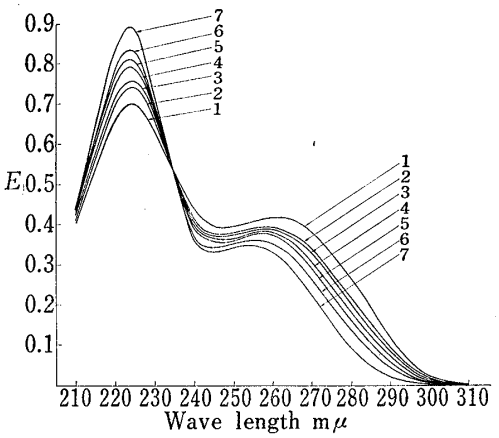


Fig. 1. Ultraviolet Absorption Spectra of 4-Hydroxy-2-methylpyrimidine in Aqueous Solutions (1.05×10^{-4}M) of Various pH

1: pH 7.00, 2: pH 3.13, 3: pH 2.99, 4: pH 2.67, 5: pH 2.51, 6: pH 2.29, 7: 1.0N HCl or 45% H_2SO_4

Thus, the results for the three types of methyl derivative of the tautomer show that the protonation equilibria for the lactam forms exist mainly between IIa′ and V, and IIb′ and V, and that the equilibrium of the lactim form may exist possibly between I′ and III.

Wagner and Philipsborn[11] pointed out that 4-hydroxypyrimidine is doubly protonated in fluorosulfuric acid (HSO_3F) and HSO_3F–SbF_5–SO_3, so-called super acid media, but monoprotonated in trifluoroacetic acid. In the present work 45% aqueous sulfuric acid was the

7) Ref. 2*b*, pp. 311—338.
8) The molar extinction coefficients of **31** at their maximum wave lengths are larger than those of each cation of **27** and **28** and the spectrum of **31** showed marked red shifts compared with those of the cations of **27** and **28**. However, similarity was found among the spectra of these analogues.
9) S. Mizukami and E. Hirai, *J. Org. Chem.*, **31**, 1199 (1966).
10) B. Roth and J. Strelitz, *J. Org. Chem.*, **34**, 821 (1969).
11) R. Wagner and W. von Philipsborn, *Helv. Chim. Acta*, **53**, 299 (1970).

most acidic medium used. The acidity of this solution ($Ho=-2.85$) is much weaker than those of HSO_3F and HSO_3F–SbF_5–SO_3,[12] and slightly stronger than that of 90% aqueous trifluoroacetic acid. The diprotonation of 4-hydroxypyrimidines would not be expected in 45% aqueous sulfuric acid.

The ultraviolet absorption spectra of 4-hydroxy-2-methylpyrimidine in aqueous solutions of various pH are shown in Fig. 1.

All of these spectra pass through one isosbestic point (*ca.* 234 mμ). The same behavior was observed with other pyrimidines in this paper. The ultraviolet absorption spectra of the pyrimidines in 45% aqueous sulfuric acid also pass through the corresponding isosbestic point. It is concluded, therefore, that the pyrimidines in the study are not doubly protonated, even in 45% aqueous sulfuric acid.

The acidic and basic ionization equilibria of 4-hydroxy-2-methylpyrimidine are shown in Chart 2.

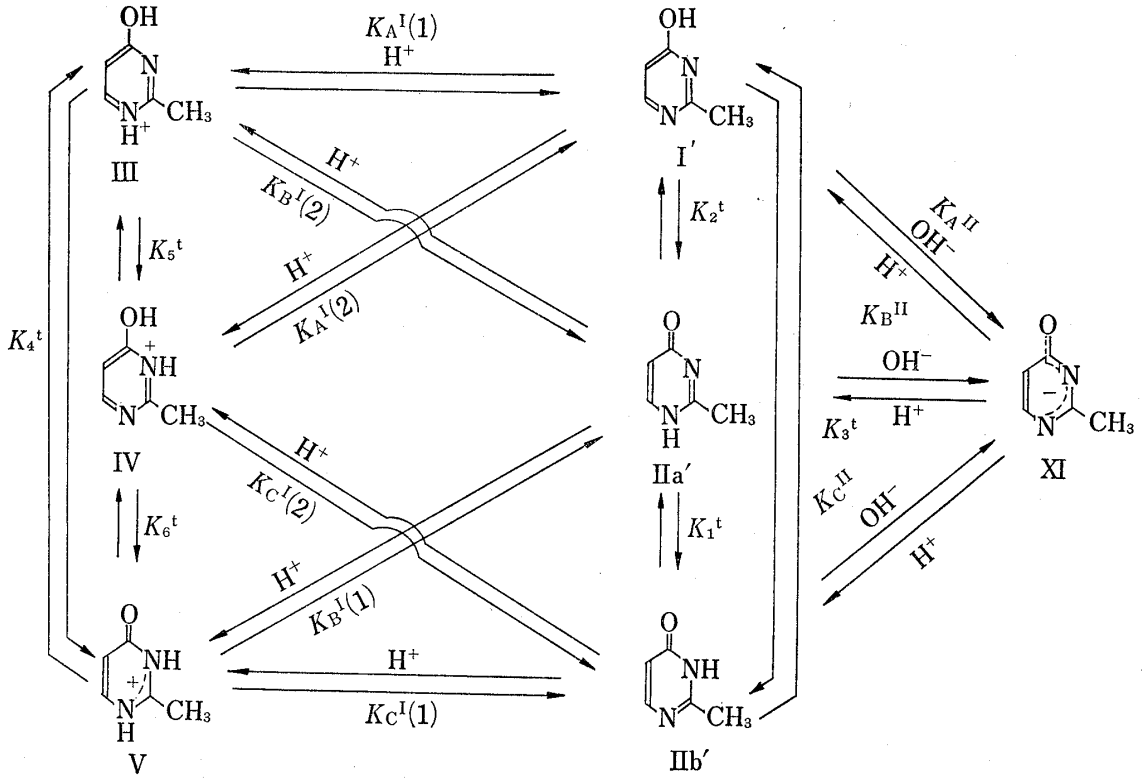


Chart 2

Tautomerism of 4-Hydroxy-2-methylpyrimidine

The tautomeric equilibrium constants, K_1^t, K_2^t, K_3^t, K_4^t, K_5^t and K_6^t as shown

$$K_1^t = \frac{[IIa']}{[IIb']} \quad (1)$$

$$K_2^t = \frac{[I']}{[IIa']} \quad (2)$$

$$K_3^t = \frac{[I']}{[IIb']} \quad (3)$$

$$K_4^t = \frac{[III]}{[V]} \quad (4)$$

12) R.J. Gillespie, *Accounts Chem. Res.*, **1**, 202 (1968).

$$K_5^t = \frac{[IV]}{[III]} \quad (5)$$

$$K_6^t = \frac{[IV]}{[V]} \quad (6)$$

Equations (1), (2) and (3) may be converted into equations (1′), (2′) and (3′), using the basic ionization constants of the tautomers, I′, IIa′ and IIb′, $K_A^{I'}$, K_B (1) and K_C (1), respectively. $K_A^{I'}$ is expressed by equation (7).

$$K_1^t = \frac{K_B^I(1)}{K_C^I(1)} \quad (1')$$

$$K_2^t = \frac{K_A^{I'}}{K_B^I(1)}(K_4^t + K_6^t) \quad (2')$$

$$K_3^t = \frac{K_A^{I'}}{K_C^I(1)}(K_4^t + K_6^t) \quad (3')$$

$$K_A^{I'} = \frac{1}{\frac{1}{K_A^I(1)} + \frac{1}{K_A^I(2)}} \quad (7)$$

The apparent basic ionization constant, K_a^I, measured for 4-hydroxy-2-methylpyrimidine is given by

$$K_a^I = \frac{[H^+]([I']+[IIa']+[IIb'])}{[III]+[IV]+[V]} \quad (8)$$

Substitution of equations (1), (2), (3), (4) and (6) into equation (8) gives

$$K_a^I = \frac{K_A^{I'}(K_4^t + K_6^t) + K_B^I(1) + K_C^I(1)}{1 + K_4^t + K_6^t} \quad (9)$$

Equations (1′), (2′) and (3′) indicate that if $K_A^{I'}$, K_B^I (1), K_C^I (1), K_4^t and K_6^t are known, estimation of K_1^t, K_2^t and K_3^t is possible. Although the basic ionization constants, cannot be determined directly, they may be approximately evaluated on the basis of the assumption that they are essentially identical with those of the compounds obtained by replacement of the mobile hydrogen atom in the tautomers by a methyl group. Such approximation has been generally used in the study of tautomerism.[7] The protonations of 1,2-dimethyl-4(1H)-pyrimidone and 2,3-dimethyl-4(3H)-pyrimidone occur at the ring nitrogen, and K_B^I (1) and K_C^I (1) are approximately identical with $K^I_{N_1\text{-}CH_3}$ and $K^I_{N_3\text{-}CH_3}$, respectively. Both constants correspond to protonations similar to those of the N-methylpyrimidones. Other constants, K_A^I (1) and K_A^I (2), are approximately identical with the basic ionization constants for 4-methoxy-2-methylpyrimidine, K_A^I (1) (OCH_3) and K_A^I (2) (OCH_3), respectively, which correspond to protonation at the N_1- and N_3-position, respectively. The over-all basic ionization constant of the lactim form I′, $K_A^{I'}$, is substituted by the apparent basicity, $K^I_{OCH_3}$. Although the tautomeric equilibrium constants, K_4^t and K_6^t, cannot be evaluated independently, the sum of the two constants is obtainable from equation (10) using the basic ionization constants of the methyl derivatives.

$$K_T^t = K_4^t + K_6^t = \frac{K^I_{N_1\text{-}CH_3} + K^I_{N_3\text{-}CH_3} - K_a^I}{K_a^I - K^I_{OCH_3}} \quad (10)$$

Where K_T^t is defined as the ratio of total lactim to lactam forms in the cations.

Thus, determination of the $K^I_{OCH_3}$, $K^I_{N_1\text{-}CH_3}$, $K^I_{N_3\text{-}CH_3}$ and K_a^I values makes possible the evaluation of the tautomeric equilibrium constants. The pK_a^I (OCH_3), pK_a^I (N_1–CH_3), pK_a^I (N_3–CH_3) and pK_a^I values determined spectrophotometrically are listed in Table I and II.

Table IV shows the tautomeric equilibrium constants of **1**, **2**, **4**, **8**, **9** and **11** estimated in this manner. The molar ratio of the three tautomers can be calculated from the equation

$$[I']:[IIa']:[IIb']=K_1^t\cdot K_2^t:K_1^t:1 \qquad (11)$$

The values are listed in Table V. It is evident from Table IV and V that all the 5-substituted 4-hydroxy-2-methylpyrimidines exist predominantly in the lactam forms, IIa′ and IIb′ and that the proportions of the respective lactam forms are almost equal to each other regardless of the kind of substituent at the 5-position, and that the cations exist largely in the lactam form V.

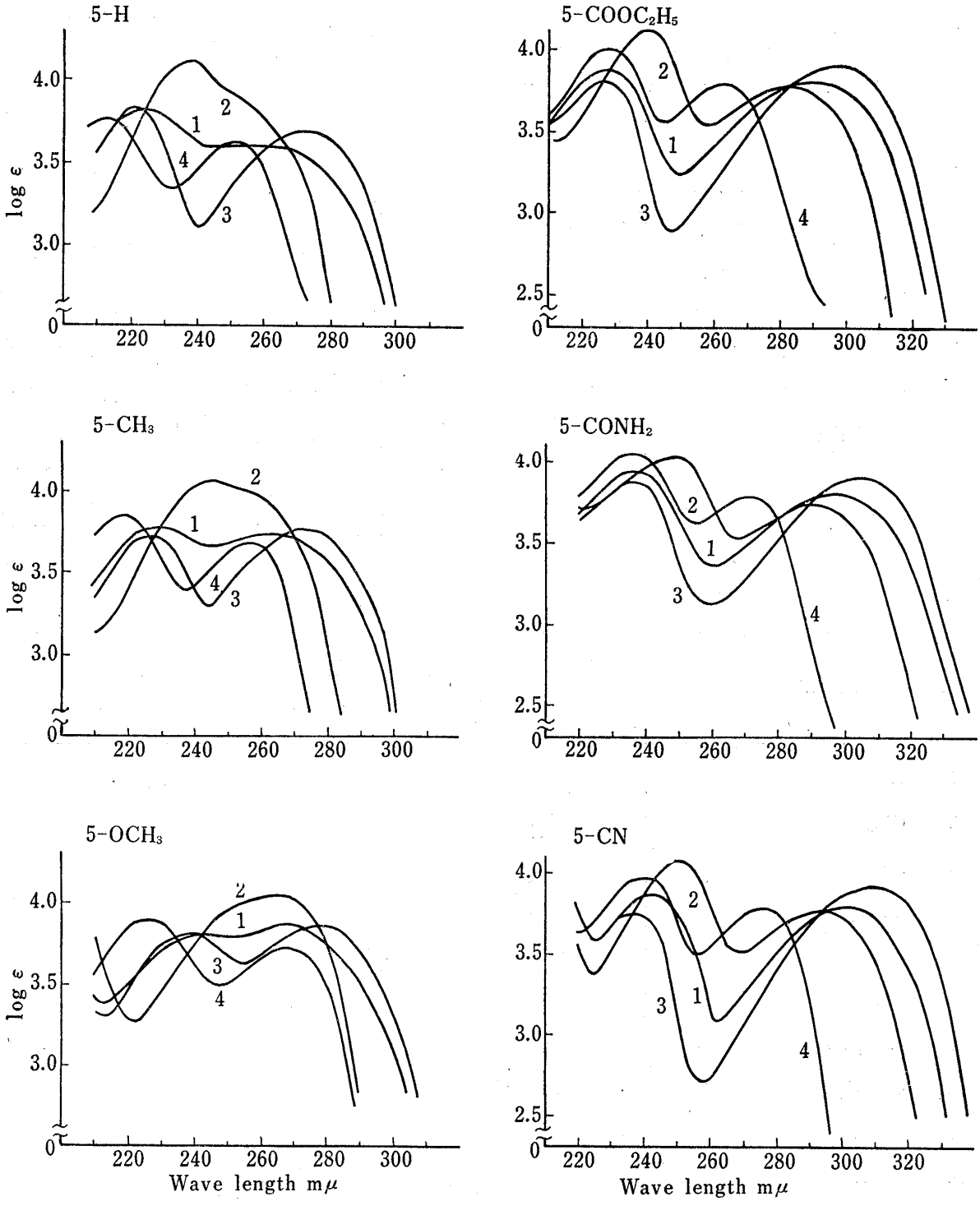


Fig. 2. Ultraviolet Absorption Spectra of 5-Substituted 4-Hydroxy-2-methylpyrimidine (1), 5-Substituted 1,2-Dimethyl-4(1H)-pyrimidone (2), 5-Substituted 2,3-Dimethyl-4-(3H)-pyrimidone (3) and 5-Substituted 4-Methoxy-2-methylpyrimidine (4)

The ultraviolet absorption spectra of the 4-hydroxy-2-methylpyrimidines, the 1,2-dimethyl-4(1H)-pyrimidones, the 2,3-dimethyl-4(3H)-pyrimidones and the 4-methoxy-2-methylpyrimidines in aqueous solution are shown in Fig. 2.

Table III. Ultraviolet Absorption Spectra of 5-Substituted 4-Hydroxy-2-methylpyrimidines

No.	Substituent	Dication			Monocation			Neutral species		
		λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium	λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium	λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium
1	H				224 255	8.43 3.59	1.0N HCl	224.5 261.5	6.65 4.14	pH 7.00
2	CH_3				233 255	8.37 5.40	1.0N HCl	229 263	6.15 5.67	pH 7.00
3	NH_2	223.5 257	7.52 4.35	60% H_2SO_4[a]	286	10.78	pH 2.00	255 286	6.26 7.23	pH 7.00
4	OCH_3				255	9.71	1.0N HCl	243 268	6.49 7.37	pH 6.60
5	OH				257	9.09	1.0N HCl	243 272	5.69 7.12	pH 5.27
6	CH_2OH				229 256	7.97 4.99	1.0N HCl	227 264	6.61 5.12	pH 6.60
7	$NHCOOC_2H_5$				260 280	9.89 11.73	1.0N HCl	251 276	8.45 9.32	pH 7.00
8	$COOC_2H_5$				224.5 275	7.92 5.76	21% H_2SO_4[c]	227.5 290	7.63 6.57	pH 6.00
9	$CONH_2$				225.5 275	8.65 5.89	21% H_2SO_4[c]	227 287	8.71 6.45	pH 7.00
10	COOH				225 275	7.21 5.22	21% H_2SO_4[c]	230 283	7.17 5.11	pH 2.40
11	CN				227 279	6.89 5.92	45% H_2SO_4[d]	233 291.5	7.49 6.44	pH 7.00

No.	Substituent	Monoanion			Dianion		
		λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium	λ_{max} mμ	$\varepsilon \times 10^{-3}$	Medium
1	H	227.5 266	8.52 4.23	0.1N NaOH			
2	CH_3	231 269	7.56 5.64	0.1N NaOH			
3	NH_2	246 285.5	6.43 6.51	0.1N NaOH			
4	OCH_3	238 273	7.16 6.41	0.1N NaOH			
5	OH	264 296	7.50 8.01	pH 9.00	258 294	7.43 7.09	2.0N NaOH[b]
6	CH_2OH	230 267	8.42 5.28	0.1N NaOH			
7	$NHCOOC_2H_5$	240 281	7.85 6.78	0.1N NaOH			
8	$COOC_2H_5$	237.5 282	7.73 5.44	0.1N NaOH			
9	$CONH_2$	233 291	8.47 7.34	0.1N NaOH			
10	COOH	227 282	6.60 5.37	pH 8.00	237 281	7.34 5.19	0.1N NaOH
11	CN	234.5 292	8.24 6.56	0.1N NaOH			

a) H_0 acidity function = −4.46, b) H_- acidity function = 14.40, c, d) See footnotes *a* and *c* in Table II.

Table IV. The Tautomeric Equilibrium Constants of 5-Substituted 4-Hydroxy-2-methylpyrimidines

No.	5-Substituent	K_1^t	K_2^t	K_3^t	K_T^t
1	H	1.12	0.013	0.015	0.26
2	CH_3	0.91	0.011	0.010	0.24
4	OCH_3	0.85	0.017	0.014	0.35
8	$COOC_2H_5$	0.76	0.055	0.042	0.40
9	$CONH_2$	1.10	0.043	0.047	0.48
11	CN	0.89	0.074	0.066	0.48

Table V. The Proportions of the Tautomeric Isomers of 5-Substituted 4-Hydroxy-2-methylpyrimidines

No.	5-Substituent	I′ (%)	IIa′ (%)	IIb′ (%)
1	H	0.7	52.5	46.8
2	CH_3	0.5	47.4	52.1
4	OCH_3	0.8	45.6	53.6
8	$COOC_2H_5$	2.3	42.2	55.5
9	$CONH_2$	2.2	51.2	46.6
11	CN	3.4	45.5	51.1

It seems that the spectrum of the 4-hydroxypyrimidine is essentially different from that of the corresponding 4-methoxypyrimidine and is intermediate between the spectra of the two corresponding pyrimidones. This spectroscopic observation suggests that the compound exists predominantly as a mixture of both lactam forms, a conclusion consistent with the result calculated from the ionization constants.

The spectrum of the cation of the 4-hydroxypyrimidine is similar to those of the cations of the corresponding 1,2-dimethyl-4(1H)- and 2,3-dimethyl-4(3H)-pyrimidone, and also to that of 1,2,3-trimethylpyrimidonium perchlorate. The spectral data are summerized in Table II and III. This shows that the cation of the compound exist predominantly in the lactam form, V. These results are in accord with those obtained by the ionization constant method.

The literature contains conflicting reports on this subject. Brown and co-workers[4] pointed out qualitatively, using the ultraviolet absorption spectra and the ionization constants, that 4-hydroxypyrimidine exists in the lactam form, IIb. Mason[5] estimated the ratio of the tautomers IIa and IIb, as 2: 3 by the ionization constant method and 2: 5 by spectrophotometry. His estimation was based on the assumption that no lactim forms exist in the neutral molecule or the cation. Albert and Spinner[13] demonstrated from Raman and infrared spectroscopy that the main species is the IIb form in more than 80%. Inoue and co-workers[14] concluded from nuclear magnetic resonance spectroscopy that the IIb form exists predominantly. Discrepancies found in these reports may have resulted either because no account was taken of the tautomers presumed in Chart 2, or because of, extreme differences in concentration among the solutions used in these methods. The present investigation was carried out taking into consideration all possible tautomers and using very dilute solutions; *ca.* 1×10^{-4}M. Our results for 5-substituted 4-hydroxy-2-methylpyrimidines agree with Mason's conclusion that the IIa form exists to some extent.

13) A. Albert and E. Spinner, *J. Chem. Soc.*, **1960**, 1221.
14) Y. Inoue, N. Furutachi, and K. Nakanishi, *J. Org. Chem.*, **31**, 175 (1966).

Application of the Hammett Equation

The Hammett equation has been successfully applied to a large number of heterocyclic compounds. The applications have been reviewed by Jaffé and Jones.[15] Mizukami and Hirai[9] found that the equation could be applied to pyrimidines. Examination of the Hammett equation for 4-hydroxypyrimidine derivatives is of interest because the compounds exist largely as a mixture of the two pyrimidones as discussed above.

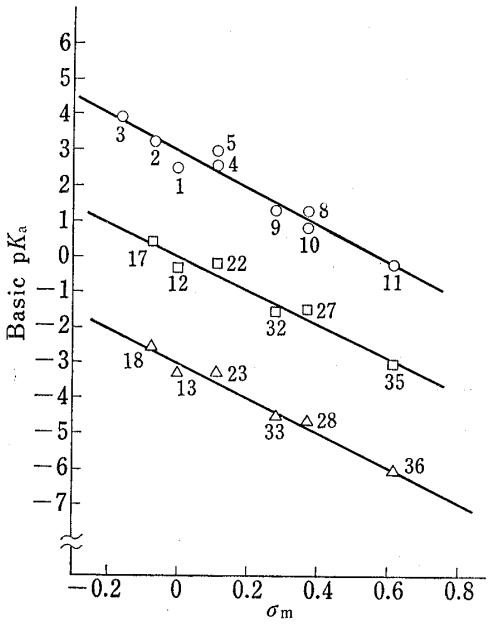


Fig. 3. Variation of Basic pK_a (proton gained) with σm for

○: 5-substituted 4-hydroxy-2-methylpyrimidines, □: 5-substituted 1,2-dimethyl-4 (1H)-pyrimidones (added −3 pK_a unit), △: 5-substituted 2,3-dimethyl-4 (3H)-pyrimidones (added −6 pK_a unit)

Plots of the basic ionization constants for the 1,2-dimethyl-4(1H)- and 2,3-dimethyl-4(3H)-pyrimidone series against the *meta* substituent constants (σm) are given in Fig. 3.

When σm values are used as a measure of the polar effect of the substituent on the pyrimidones, there is a linear correlation between the basic ionization constant and the σm value in each of the pyrimidone series without modification. The σm values are taken from those collated by McDaniel and Brown[16] except the values for CN, $CONH_2$ and O^- groups. For these groups, the values found in the literature are used: 0.28[17] for $CONH_2$, −0.71[17] for O^- and 0.615[18] for CN. It is clear that the Hammett equation can be applied to such series.

The tautomeric equilibrium constant, pK_1^t, is approximately equal to the difference between the pK_a^I values of the N-methylpyrimidones as shown

Table VI. Relationship of the pK_a Values of 5-Substituted 4-Hydroxy-2-methylpyrimidines and Their Methyl Derivatives to Hammett σ Values

Series	pK_a	Hammett ρ value	95% confidence limits (±)	Intercept[a]	95% confidence limits (±)	r[b]	Std dev	n[c]	Substituents
5-Substituted 4-hydroxy-2-methylpyrimidine	pK_a^I	5.13	1.11	2.97	0.33	0.9717	0.330	9	NH_2, CH_3, H, OCH_3, OH, $CONH_2$, COOH, $COOC_2H_5$, CN
	pK_a^{II}	4.87	0.50	9.29	0.18	0.9934	0.226	9	O^-, NH_2, COO^-, CH_3, H, OCH_3, $CONH_2$, $COOC_2H_5$, CN
5-Substituted 1,2-dimethyl-4(1H)-pyrimidone	pK_a^I	4.79	1.44	3.02	0.46	0.9774	0.296	6	CH_3, H, OCH_3, $CONH_2$, $COOC_2H_5$, CN
5-Substituted 2,3-dimethyl-4(3H)-pyrimidone	pK_a^I	4.88	1.12	3.01	0.36	0.9865	0.231	6	CH_3, H, OCH_3, $CONH_2$, $COOC_2H_5$, CN

a) intercept of regression line with ordinate ($\sigma=0$) *b*) the correlation coefficient *c*) the number of compounds

15) H.H. Jaffé and H.L. Jones, "Advances in Heterocyclic Chemistry," Vol. 3, ed. by A.R. Katritzky Academic Press Inc., New York, 1964, pp. 209—261.
16) D.H. McDaniel and H.C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
17) H.H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
18) G. Briegleb and A. Bieber, *Z. Electrochem.*, **55**, 250 (1951). The value has been corroborated by a few investigators. See, for example, references 11—13) in ref. 8.

$$K_1^t = \frac{K^I_{N_1\text{-}CH_3}}{K^I_{N_3\text{-}CH_3}} \tag{12}$$

pK_1^t may be written in the equation

$$pK_1^t = -(\rho-\rho')\sigma - (\log K_0^I(N_1{-}CH_3) - \log K_0^I(N_3{-}CH_3)) \tag{13}$$

where ρ and ρ' are the reaction constants for the 1,2-dimethyl-4(1H)- and 2,3-dimethyl-4(3H)-pyrimidone series respectively, and $K_0^I(N_1{-}CH_3)$ and $K_0^I(N_3{-}CH_3)$ mean the basic ionization constant for each respective N-methyl pyrimidone itself. The ρ and ρ' values calculated by the least square method are 4.79 ± 1.44 and 4.88 ± 1.12, respectively, as illustrated in Table VI. The fact that both ρ values are approximately identical indicates that pK_1^t can approximately coincides with the term $-(\log K_0^I(N_1{-}CH_3) - \log K_0^I(N_3{-}CH_3))$ in equation (13). Accordingly, K_1^t values may be kept constant through the series of 5-substituted 4-hydroxypyrimidines. This explains why the K_1^t values remain unaltered as shown in Table IV.

On the other hand, a Hammett plot of the basic ionization constant of the 4-hydroxypyrimidine also gave a similar linearity to that observed with the two N-methylpyrimidones series, as shown in Fig. 3.

Equation (8) is converted to the form

$$K_a^I = \frac{K_B^I(1)\left(1+\frac{1}{K_1^t}+K_2^t\right)}{1+K_T^t} \tag{14}$$

or

$$K_a^I = \frac{K_C^I(1)\{1+K_1^t(1+K_2^t)\}}{1+K_T^t} \tag{15}$$

since $K^I_{N_1\text{-}CH_3}$ and $K^I_{N_3\text{-}CH_3}$ may be substituted for K_B^I (1) and K_C^I (1), respectively, and $K_2^t \ll 1$ as shown in Table IV, equations (14) and (15) are simplified as follows:

$$pK_a^I = pK_a^I(N_1{-}CH_3) - \log\frac{1+K_1^t}{K_1^t(1+K_T^t)} \tag{16}$$

or

$$pK_a^I = pK_a^I(N_3{-}CH_3) - \log\frac{1+K_1^t}{1+K_T^t} \tag{17}$$

equations (16) and (17) may be expressed

$$pK_a^I = -4.79\sigma - \log K_0^I(N_1{-}CH_3) - \log\frac{1+K_1^t}{K_1^t(1+K_T^t)} \tag{18}$$

or

$$pK_a^I = -4.88\sigma - \log K_0^I(N_3{-}CH_3) - \log\frac{1+K_1^t}{1+K_T^t} \tag{19}$$

If the third terms of the right-hand side of equations (18) and (19) are either constant or small as compared with $\{-4.79\,\sigma - \log K_0^I(N_1{-}CH_3)\}$ and $\{-4.88\,\sigma - \log K_0^I(N_3{-}CH_3)\}$, respectively, the linear relationship between the pK_a^I value of the 4-hydroxypyrimidine and the σm value may be predicted from the equations. The values of the slope and the intercept of the straight line actually obtained for the 4-hydroxy-2-methylpyrimidine series are 5.13 ± 1.11, and 2.97 ± 0.33 pK_a unit, respectively, as shown in Table VI. Neither of those values is significantly different from the respective value observed for 1,2-dimethyl-4(1H)-pyrimidone series or the 2,3-dimethyl-4(3H)-pyrimidone series. The result shows that both the terms are very small and nearly constant, which is why the Hammett equation could be applied for the basic ionization constants of 5-substituted 4-hydroxy-2-methylpyrimidines.

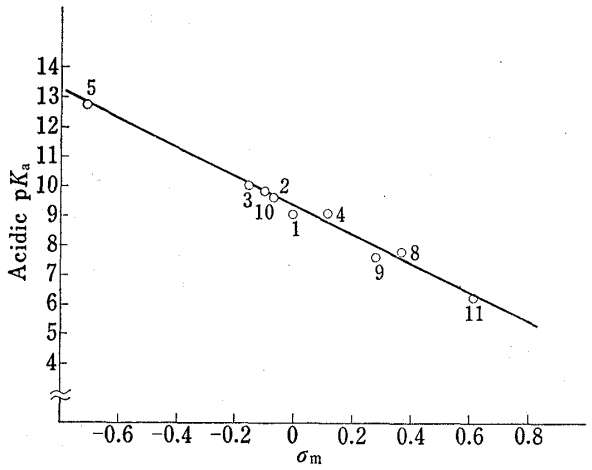


Fig. 4. Variation of Acidic pK_a (proton lost) with σm for 5-Substituted 4-Hydroxy-2-methylpyrimidines

On the other hand, plots of the acidic ionization constants, K_a^{II}s, of the 4-hydroxy-2-methylpyrimidine series against the σm constants fall on a straight line as shown in Fig. 4.

K_a^{II} is expressed by the form

$$\frac{1}{K_a^{II}} = \frac{1}{K_A^{II}} + \frac{1}{K_B^{II}} + \frac{1}{K_C^{II}} \qquad (20)$$

where K_A^{II}, K_B^{II} and K_C^{II} are the acidic ionization constants of the tautomers, I′, IIa′ and IIb′, respectively. Since the lactim form of the 4-hydroxypyrimidine exists in a negligible amount, equation (20) becomes

$$\frac{1}{K_a^{II}} = \frac{1}{K_B^{II}} + \frac{1}{K_C^{II}} \qquad (21)$$

Substitution of equation (1) into equation (21) gives

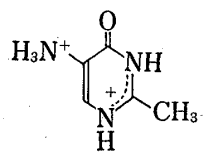
$$pK_a^{II} = pK_a^{II}(B) + \log\left(1 + \frac{1}{K_1^t}\right) \qquad (22)$$

or

$$pK_a^{II} = pK_a^{II}(C) + \log(1 + K_1^t) \qquad (23)$$

Barlin and Perrin[19] suggested that acidic ionization constants in the 2-hydroxy- and 4-hydroxypyridine series could be correlated by the Hammett equation; the compounds exist predominantly in the lactam form in aqueous solution, 2(1H)-pyridone and 4(1H)-pyridone.[20] This would further suggest the possibility of application of the equation to each of the lactam forms, IIa′ and IIb′ of the 4-hydroxypyrimidines, because the ionizations of these lactam forms are not essentially different from those of 4(1H)-pyridone and 2(1H)-pyridone, respectively. If the equation can be applied to the lactam forms, then the apparent acidity of the compounds, K_a^{II}, can be correlated with the σm constants, because it is expected that K_1^t is almost constant in the series.

That the plot of Hammett function against the pK_a values of the 4-hydroxypyrimidine gives a straight line, provides some information about the ionization equilibria of compounds with two basic and two acidic groups. 5-Amino-4-hydroxy-2-methylpyrimidine (**3**) has two basic ionization constants. The infrared spectrum of the monohydrochloride shows strong bands at 3294 cm^{-1} and 3425 cm^{-1} in the solid state. This suggests that the hydrochloride is not the cation protonated on the 5-amino group because it seems that the bands may be assigned as the symmetric and asymmetric modes of the free amino group. The ultraviolet absorption spectra of the monocation change gradually with increasing acidity of the solution. The spectra obtained in various concentrations of the acid have an isosbestic point at 252 mμ. This spectral change shows that the cation protonates further to form a dication, XII.



XII

A Hammett plot of p$K_a^{I(1)}$ against the σm (NH_2) value deviates considerably from the straight line in Fig. 3, but the plot of p$K_a^{I(2)}$ falls on the line. This shows that the protonation equilibrium of the compound corresponding to the p$K_a^{I(2)}$

19) G.B. Barlin and D.D. Perrin, *Quart, Rev.*, **20**, 75 (1966).
20) Ref. 2*b*, pp. 347—352 and references therein.

value is the same as that of the other 4-hydroxypyrimidines; the protonation occurrs at the ring nitrogen N_1.

4,5-Dihydroxy-2-methyl- (**5**) and 5-carboxy-4-hydroxy-2-methylpyrimidine (**10**) are dibasic acids. The Hammett equation for the acidic pK_a values, $pK_a^{II(1)}$ and $pK_a^{II(2)}$, was also examined. The plots of each $pK_a^{II(2)}$ value against the σm (O^-) (for **5**) and the σm (COO^-) (for **10**) values fall on the same straight line found for the pK_a^{II} values of the other 4-hydroxy-2-methylpyrimidines, as shown in Fig. 4. The results indicate that dissociation occurrs at the acidic groups of these compounds (5-OH or 5-COOH group), and then at the lactam NH group. This was proved by comparing the ultraviolet absorption spectra of the anions of 5-methoxy-4-hydroxy-2-methyl- (**4**) and 5-carbethoxy-4-hydroxy-2-methylpyrimidine (**8**) with those of the monoanions of **5** and **10**, respectively. If the latter anions are formed by dissociation at the lactam NH group, the spectra will resemble those of the anions of **4** and **8**, respectively. As shown in Table III, the spectra of the anions of **5** and **10** in fact differ from those of **4** and **8**, respectively. Therefore, it is evident that $pK_a^{II(1)}$ and $pK_a^{II(2)}$ correspond to the ionization of the substituent itself and the lactam NH group, respectively.

Experimental

Measurement of the Ionization Constants——The basic ionization constants were all determined by ultraviolet spectrophotometric method using a Hitachi EPS-2U spectrophotometer. The determinations were carried out at sample concentrations of *ca.* 0.5—1.5 × 10^{-4} M. Britton and Robinson's buffer solutions[21] were used for the stronger bases. Weaker bases with electron-attracting substituents at the 5-position, such as $COOC_2H_5$, $CONH_2$, COOH and CN, were all measured in diluted hydrochloric acid solution; 0.01—1.0 M. The hydrogen ion activity of the solution was calculated using the activity coefficient of the hydrochloric acid determined by Harned and Owen.[22] The ultraviolet absorption spectra of the cations of the weak bases were measured in 5—60% sulfuric acid solution, the acidity of which was given as the *Ho* acidity function.[23] These sulfuric acid solutions were also used on measurement of the basic pK_a value ($pK_a^{I(1)}$) of **3**. For all the compounds the spectra obtained at different solution acidities, all passed through an isosbestic point.

The acidic ionization constants were mostly measured by the potentiometric titration method using a Metrohm E436 potentiometer with a glass-calomel electrode system. However, as the acid strengths of **3** and the monoanions of **5** and **10** are too weak for the equivalence point to be detected, the constants for these species were obtained by spectrophotometry.

All the pK_a values were calculated from the equation

$$pK_a = pH - \log \frac{[B]}{[BH]} \pm \log f_{\pm} \qquad (I)$$

Where [B] and [BH] are the molar concentrations of the conjugated base and acid in the equilibria, respectively, the ratio of which is calculated from the ultraviolet absorption spectra or the potentiometric titration curve, and $f_{\pm}$ is the mean ionic activity coefficient. The plus and minus signs of the third term of the right-hand side in equation (I) are used on calculating the basic and acidic ionization constants, respectively. The term was calculated by use of the relation[6]

$$-\log f_{\pm} = \frac{0.505\sqrt{I}}{1+1.6\sqrt{I}} \qquad (II)$$

where I is the ionic strength of the solution determined. The experiments were carried out in the spectrophotometer and the titration cell maintained at 20 ± 0.2°.

Preparation of 5-Substituted 4-Hydroxy-2-methylpyrimidines——The compounds, with the exception of **3**, **9** and **10**, had the melting points and properties reported in the literature and were prepared according to the cited references: 4-hydroxy-2-methyl-(**1**), mp 211—212° (lit.,[24] mp 212°); 2,5-dimethyl-4-hydroxy-

21) H.T.S. Britton and R.A. Robinson, *J. Chem. Soc.*, **1931**, 1456.
22) H.S. Harned and B.B. Owen, "The Physical Chemistry of Electrolytic Solutions," Second ed., Reinhold Publishing Corporation, New York, 1950, p. 547.
23) M.A. Paul and F.A. Long, *Chem. Rev.*, **57**, 1 (1957).
24) S. Gabriel, *Chem. Ber.*, **37**, 3638 (1904).

(2), mp 178° (lit.,[25] mp 174°); 4-hydroxy-5-methoxy-2-methyl- (4), mp 216—217° (lit.,[26] 214—215°); 4,5-dihydroxy-2-methyl- (5), mp 280° (lit.,[27] mp 231° (decomp.)). *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.53; H, 4.90; N, 22.28. 5-Hydroxymethyl-4-hydroxy-2-methyl- (6), mp 220—221° (lit.,[28] mp 215°); 5-carbethoxyamino-4-hydroxy-2-methyl- (7), mp 264° (decomp.) (lit.,[27] 260—261° (decomp.)); 5-carbethoxy-4-hydroxy-2-methyl- (8), mp 191—192° (lit.,[29] mp 191°); 5-cyano-4-hydroxy-2-methyl- (11), mp 235° (decomp.) (lit.,[29] mp 233—235°).

5-Amino-4-hydroxy-2-methylpyrimidine (3)——A solution of 1.6 g of 5-amino-4-methoxy-2-methylpyrimidine[30] in 8 ml of 38% HCl was heated on a steam bath for 0.5 hr. The solution was neutralized by 2 N NaOH to pH 6, it was then evaporated to dryness under reduced pressure to give a brown solid. The solid was dissolved in anhydrous EtOH and filtered to separate NaCl. The filtrate was evaporated to dryness to give light brown crystalline solid. Recrystallization from *n*-BuOH gave 0.5 g (35%) light brown plates mp 237° (decomp.). *Anal.* Calcd. for $C_5H_7ON_3$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.14; H, 5.90; N, 33.27. The hydrochloride was obtained from 0.1 M HCl–EtOH solution of 3. The solution was evaporated to dryness under reduced pressure. The residue was recrystallized from MeOH, to give light yellow prisms, mp 258° (decomp.). *Anal.* Calcd. for $C_5H_7ON_3 \cdot HCl$: C, 37.16; H, 4.99; N, 26.01; Cl, 21.94. Found: C, 37.26; H, 5.10; N, 25.91; Cl, 21.67.

5-Carbamoyl-4-hydroxy-2-methylpyrimidine (9)——A solution of 2.0 g of **8** in 20 ml of 28% NH_3 was stirred for 6 hr at room temperature. The solution was evaporated to dryness under reduced pressure. The crystalline residue was dissolved in 50 ml of H_2O, acidified to pH 5 with AcOH and cooled. The deposited crystals were recrystallized from H_2O to give 1.5 g (84%) of colorless needles, mp 253—254° (decomp.). *Anal.* Calcd. for $C_6H_7O_2N_3 \cdot 1/2H_2O$: C, 44.44; H, 4.97; N, 25.92. Found: C, 44.53; H, 5.22; N, 25.85.

5-Carboxy-4-hydroxy-2-methylpyrimidine (10)——A solution of 4 g of **8** in 20 ml of 38% HCl was heated on a steam bath for 8 hr. The solution was evaporated to dryness under reduced pressure. The crystalline residue was dissolved in H_2O and the aqueous solution was neutralized to pH 6 by 1 N NaOH. After concentration of the solution under reduced pressure, the white product which separated was filtered off. Recrystallization from H_2O gave 3.2 g (94%) colorless needles, mp 201°. *Anal.* Calcd. for $C_6H_6O_3N_2$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.47; H, 4.03; N, 17.88.

Preparation of 5-Substituted 4-Methoxy-2-methylpyrimidines——To 150 ml of methanolic NaOMe (from 10—15 g of sodium) was added 0.060 mole of the corresponding 4-chloro-2-methylpyrimidine (5-H, lit.[24]; 5-CH_3, lit.[25]; 5-$COOC_2H_5$, lit.[29]; 5-CN, lit.[31]). The reaction mixture was refluxed on a steam bath for 7 hr, then neutralized by passing dry CO_2 into the solution. After removal of the solvent, the residue was poured into ice-cold H_2O and extracted with ether. The ethereal extract was dried and evaporated under reduced pressure. The residue was purified by distillation, recrystallization or chromatography. 4-Methoxy-2-methylpyrimidine (14), 93% yield, bp 157—158°. *Anal.* Calcd. for $C_6H_8ON_2 \cdot 1/5H_2O$: C, 56.42; H, 6.62; N, 21.93. Found: C, 56.32; H, 6.81; N, 22.16. Compound (14) was identified as 4-methoxy-2-methylpyrimidine picrate[9] by mixed melting point and comparison of infrared spectra with an authentic sample. 2,5-Dimethyl-4-methoxypyrimidine (19), 87% yield, bp 89—90°. (30 mmHg). *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.56; H, 7.46; N, 19.98. 4,5-Dimethoxy-2-methylpyrimidine (24), 90% yield, mp 54° (lit.,[9] mp 54°).

5-Carbethoxy-4-methoxy-2-methylpyrimidine (29)——Compound (29) was prepared using 0.060 mole of NaOMe. Recrystallization from aqueous MeOH gave 9.4 g (80%) of colorless needles, mp 48—49°. *Anal.* Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.01; H, 6.42; N, 14.27.

5-Cyano-4-methoxy-2-methylpyrimidine (37)——The yellow crystalline residue was chromatographed on silica gel with ether as an eluent. The eluate was then evaporated to dryness. Recrystallization from petroleum ether (bp 30—60°) gave 4.0 g (45%) of colorless needles, mp 79—80°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.63; H, 4.85; N, 28.38.

5-Carbamoyl-4-methoxy-2-methylpyrimidine (34)——Compound (34) was prepared from **29** (2.0 g) by a method similar to that used for preparation of **9**. Recrystallization from H_2O gave 1.6 g (94%) of colorless needles, mp 175°. *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.51; H, 5.71; N, 25.34.

Preparation of 5-Substituted 1,2-Dimethyl-4(1H)-pyrimidones——All of the substances were prepared by reaction of the corresponding 4-methoxy-2-methylpyrimidine with CH_3I followed by hydrolysis.

25) R.R. Williams and N.J. Rosell, U.S. Patent 2194190 (1940) [*A.C.*, **34**, 4866 (1940)].
26) Z. Buděšinský, V. Bydžovský, J. Kopecký, A. Šváb, and J. Vavřina, *Česk. Farm.*, **10**, 241 (1961) [*C.A.* **55**, 25973 (1961)].
27) W. Huber and H.A. Holsher, *Chem. Ber.*, **71**, 87 (1938).
28) L.R. Cerecedo and F.D. Pickel, *J. Am. Chem. Soc.*, **59**, 1714 (1937).
29) A.R. Todd and F. Bergel, *J. Chem. Soc.*, **1937**, 364.
30) R. Urban and S.O. Schnider, *Helv. Chim. Acta*, **41**, 1806 (1958).
31) P. Nesbitt and P. Sykes, *J. Chem. Soc.*, **1954**, 3057.

1,2-Dimethyl-4(1H)-pyrimidone (12)——A solution of **14** in CH_3I was allowed to stand at room temperature for several days. The deposited crystals were collected and washed repeatedly with ether. The methiodide was obtained in 93% yield, mp 118°. *Anal.* Calcd. for $C_6H_8ON_2 \cdot CH_3I$: C, 31.60; H, 4.17; N, 10.53; I, 47.69. Found: C, 31.74; H, 4.27; N, 10.75; I, 47.44. To a solution of 2.0 g of the methiodide in 100 ml of H_2O was added Amberlite IRA-400 resin (OH type) until iodide ion was completely eliminated. After filtering off the resin, the filtrate was evaporated to dryness under reduced pressure. Recrystallization from $CHCl_3$ gave 0.70 g of pale yellow prisms, mp 190°. *Anal.* Calcd. for $C_6H_8ON_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 57.78; H, 6.72; N, 22.73.

1,2,5-Trimethyl-4(1H)-pyrimidone (17)——Compound (17) was synthesized from **19** by the same method as described for **12**. The methiodide was obtained in 99% yield, mp 114°. *Anal.* Calcd. for $C_7H_{10}ON_2 \cdot CH_3I$: C, 34.30; H, 4.68; N, 10.00; I, 45.31. Found: C, 34.39; H, 4.71; N, 10.13; I, 45.10. Compound (17), 99% yield, mp 175—176° (from acetone). *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.57; H, 7.48; N, 20.10.

1,2-Dimethyl-5-methoxy-4(1H)-pyrimidone (22)——Compound (22) was synthesized from **24** by the same method as described for **12**. The methiodide was obtained in 94% yield, mp 211° (decomp.). *Anal.* Calcd. for $C_7H_{10}O_2N_2 \cdot CH_3I$: C, 32.45; H, 4.43; N, 9.46; I, 42.86. Found: C, 32.53; H, 4.64; N, 9.72; I, 42.78. Compound (22), 77% yield, mp 214° (from $CHCl_3$). *Anal.* Calcd. for $C_7H_{10}O_2N_2$; C, 54.53; H, 6.54; N, 18.17. Found: C, 54.61; H, 6.67; N, 18.08.

5-Carbethoxy-1,2-dimethyl-4(1H)-pyrimidone (27)——Compound (27) was synthesized from **29** by the same method as described for **12**. The methiodide was obtained in 70% yield, mp 163°. *Anal.* Calcd. for $C_9H_{12}O_3N_2 \cdot CH_3I$: C, 35.52; H, 4.47; N, 8.28; I, 37.53. Found: C, 35.61; H, 4.59; N, 8.20; I, 37.55. Compound (27), 50% yield, mp 187—188° (from EtOH). *Anal.* Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17; N, 14.28. Found: C, 54.86; H, 6.37; N, 13.98.

5-Carbamoyl-1,2-dimethyl-4(1H)-pyrimidone (32)——Compound (32) was prepared by the reaction of **27** (4.0 g) with 28% NH_3 by a similar method to that used in the above preparation of **9**. Recrystallization from EtOH gave 2.8 g of pale yellow needles, mp 248—249° (decomp.). *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.35; H, 5.63; N, 25.37.

5-Cyano-1,2-dimethyl-4(1H)-pyrimidone (35)——1.0 g of **37** was dissolved in 20 ml of CH_3I. The solution was refluxed on a steam bath for several days. The deposited precipitate was washed with ether. Recrystallization of the precipitate from EtOH gave 0.83 g pale yellow prisms, mp 201—202°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.63; H, 5.03; N, 28.22.

The method of Curd and Richardson[32] was also applied to the preparation of some 1,2-dimethyl-4(1H)-pyrimidones (**12** and **32**). The methiodides of 4-amino-2-methylpyrimidine[9] and 4-amino-5-carbamoyl-2-methylpyrimidine[9] were hydrolyzed by boiling for 1 hr with KOH to give the corresponding pyrimidone.

Preparation of 5-Substituted 2,3-Dimethyl-4(3H)-pyrimidones——These substances were prepared by the reaction of the corresponding 4-hydroxypyrimidines with diazomethane. 2,3-Dimethyl-4(3H)-pyrimidone (**13**) was synthesized by the method of Pfleiderer[33] giving 30% yield, mp 63—64° (lit.,[33] mp 63—65°).

2,3,5-Trimethyl-4(3H)-pyrimidone (18)——To 0.066 mole of diazomethane in 100 ml of ether was slowly added 4.7 g of **2**. The mixture was allowed to stand for 6 days at room temperature, then the unreacted pyrimidine was filtered off. The filtrate was evaporated under reduced pressure to a yellow oil. Distillation of the oil gave two fractions of bp 79—83° and bp 150—157°, at 32 mm, respectively. Chromatography of the latter fraction on alumina using ether: $CHCl_3$ (1: 1) as eluent gave 1.8 g (34%) of **18** in the form of very hygroscopic crystals. *Anal.* Calcd. for $C_7H_{10}ON_2 \cdot 1/2H_2O$: C, 57.12; H, 7.53; N, 19.04. Found: C, 57.23; H, 7.80; N, 19.33. The hydrochloride was obtained by passing HCl gas into a $CHCl_3$ solution of the pyrimidone. Recrystallization from EtOH–ether gave colorless needles, which were sublimed at 200°. *Anal.* Calcd. for $C_7H_{10}ON_2 \cdot HCl \cdot H_2O$: C, 43.64; H, 6.80; N, 14.54; Cl, 18.40. Found: C, 43.54; H, 6.83; N, 14.63; Cl, 18.51. On the other hand the former fraction was purified by distillation giving a 3.4% yield of product, bp 88—90° (30 mmHg), which was identified as **19**.

2,3-Dimethyl-5-methoxy-4(3H)-pyrimidone (23)——To 0.033 mole of diazomethane in 100 ml of ether was slowly added 1.0 g of **4**. The mixture was allowed to stand for 2 days at room temperature, then the unreacted pyrimidine was filtered off. The filtrate was evaporated to dryness under reduced pressure. Recrystallization from AcOEt gave 0.12 g of colorless needles, mp 113°. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.44; H, 6.65; N, 18.00.

5-Carbethoxy-2,3-dimethyl-4(3H)-pyrimidone (28)——To 0.047 mole of diazomethane in 130 ml of ether was added dropwise a solution of 8.5 g of **8** in 150 ml of $CHCl_3$. The solution was allowed to stand for 2 days at room temperature, then evaporated to a yellow oil. The oily residue was solidified by scratching in ether. Recrystallization from ether yielded 3.8 g of colorless needles, mp 61—62°. *Anal.* Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.31; H, 6.39; N, 14.47. The ethereal layer was evaporated to dryness. The residue was distilled and collected over the boiling range 102—108° at 4 mm. The fraction

32) F.H.S. Curd and D.N. Richardson, *J. Chem. Soc.*, **1955**, 1853.
33) W. Pfleiderer and H. Mosthaf, *Chem. Ber.*, **90**, 728 (1957).

solidified on standing at room temperature. Recrystallization from aqueous MeOH gave 0.15 g of colorless needles, mp 48°. This compound was identified as **29** by mixed melting point and comparison of infrared spectra with an authentic sample.

5-Carbamoyl-2,3-dimethyl-4(3H)-pyrimidone (33)——To a solution of 2.3 g of **9** in 100 ml of EtOH was added dropwise 0.041 mole of diazomethane in 100 ml of ether. The mixture was left for 2 days at room temperature, the deposited crystals were filtered and then washed with EtOH. Recrystallization from H_2O gave 1.7 g of colorless needles, mp 251° (decomp.). *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.17; H, 5.72; N, 25.34.

5-Cyano-2,3-dimethyl-4(3H)-pyrimidone (36)——To a solution of 1.5 g of **11** in 70 ml of EtOH was added dropwise 0.019 mole of diazomethane in 51 ml of ether. The mixture was allowed to stand for 2 days at room temperature, the unreacted pyrimidine was filtered off. The filtrate was evaporated to dryness under reduced pressure, then triturated residue was washed several times with ether and then recrystallized from *n*-BuOH to give 0.63 g of colorless prisms, mp 83°. *Anal.* Calcd. for $C_7H_7ON_3$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.08; H, 5.03; N, 28.07. On evaporating the above washing to dryness and recrystallizing the residue from petroleum ether (bp 30—60°), 0.29 g colorless needles, mp 79—80° were obtained. This compound was identified as **37** by mixed melting point and comparison of infrared spectra with an authentic sample. Some of the 5-substituted 4-methoxy-2-methylpyrimidines (**14**, **19** and **24**) were also converted to the corresponding 3-methyl-4(3H)-pyrimidone (**13**, **18** and **23**) by the thermal rearrangement which was used by Brown and co-workers[4] to obtain 3-methyl-4(3H)-pyrimidone. The rearranged products were shown to be identical with pyrimidones prepared by mixed melting point and comparison of infrared spectra.

Preparation of 5-Substituted 1,2-Dimethyl-4-methoxypyrimidinium Perchlorates and 5-Substituted 1,2,3-Trimethyl-4-pyrimidonium Perchlorates——These substances were prepared by substitution in the corresponding 1,2-dimethyl-4-methoxypyrimidinium iodide described above and in 1,2,3-trimethyl-4-pyrimidonium iodide. 5-Substituted 1,2,3-trimethyl-4-pyrimidonium iodides (R; H, CH_3, OCH_3, $COOC_2H_5$) were prepared from the corresponding 4-methoxy-2-methylpyrimidine in satisfactory yields. To a solution of 1.0 g of the 4-methoxy derivative in 4.0 ml of acetone was added 20 ml of CH_3I. The mixture was refluxed for 16 hr, then white product was separated from the solution by filtration, washed with acetone several times, and dried under vacuum. The products were identified with the methiodide obtained in the same manner from both corresponding 1,2-dimethyl-4(1H)-pyrimidone and 2,3-dimethyl-4(3H)-pyrimidone by the reaction with CH_3I. To a solution of the 1,2-dimethyl-4-methoxypyrimidinium iodide or the 1,2,3-trimethyl-4-pyrimidonium iodide in anhydrous MeOH was added an equimolar amount of $AgClO_4$. The precipitated product was separated by filtration and the filtrate was evaporated to dryness under reduced pressure. The corresponding perchlorate was obtained by recrystallization of the crystalline residue.

1,2-Dimethyl-4-methoxypyrimidinium Perchlorate (15)——Compound (**15**) was synthesized from 1,2-dimethyl-4-methoxypyrimidinium iodide, 74% yield, colorless needles, mp 102° (from EtOH). *Anal.* Calcd. for $C_7H_{11}O_5N_2Cl$: C, 35.23; H, 4.65; N, 11.74; Cl, 14.86. Found: C, 35.49; H, 4.68; N, 11.76; Cl, 15.03.

4-Methoxy-1,2,5-trimethylpyrimidinium Perchlorate (20)——Compound (**20**) was synthesized from 4-methoxy-1,2,5-trimethylpyrimidinium iodide, 67% yield, colorless needles, mp 132—133° (from EtOH–ether). *Anal.* Calcd. for $C_8H_{13}O_5N_2Cl$: C, 38.03; H, 5.19; N, 11.09; Cl, 14.03. Found: C, 38.11; H, 5.20; N, 11.14; Cl, 14.23.

4,5-Dimethoxy-1,2-dimethylpyrimidinium Perchlorate (25)——Compound (**25**) was synthesized from 4,5-dimethoxy-1,2-dimethylpyrimidinium iodide, 63% yield, colorless prisms, mp 141—142° (from EtOH). *Anal.* Calcd. for $C_8H_{13}O_6N_2Cl$: C, 35.77; H, 4.88; N, 10.43; Cl, 13.20. Found: C, 35.70; H, 4.88; N, 10.43; Cl, 13.21.

5-Carbethoxy-1,2-dimethyl-4-methoxypyrimidinium Perchlorate (30)——Compound (**30**) was synthesized from 1,2-dimethyl-5-carbethoxy-4-methoxypyrimidinium iodide, 27% yield, colorless needles, mp 187—190° (decomp.) (from acetone–ether). *Anal.* Calcd. for $C_{10}H_{15}O_7N_2Cl$: C, 38.66; H, 4.87; N, 9.02; Cl, 11.41. Found: C, 39.01; H, 4.89; N, 9.15; Cl, 11.63.

1,2,3-Trimethyl-4-pyrimidonium Perchlorate (16)——1,2,3-Trimethyl-4-pyrimidonium iodide was obtained in 80% yield, mp 219—221°. *Anal.* Calcd. for $C_7H_{11}ON_2I$: C, 31.60; H, 4.17; N, 10.53; I, 47.69. Found: C, 31.66; H, 4.10; N, 10.66; I, 47.97. Compound (**16**), 83% yield, colorless needles, mp 185° (from MeOH). *Anal.* Calcd. for $C_7H_{11}O_5N_2Cl$: C, 35.23; H, 4.65; N, 11.74; Cl, 14.86. Found: C, 35.38; H, 4.59; N, 11.82; Cl, 14.96.

1,2,3,5-Tetramethyl-4-pyrimidonium Perchlorate (21)——1,2,3,5-Tetramethyl-4-pyrimidonium iodide was obtained in 98% yield, mp 260° (decomp.). *Anal.* Calcd. for $C_8H_{13}ON_2I$: C, 34.30; H, 4.68; N, 10.00; I, 45.31. Found: C, 34.29; H, 4.79; N, 10.18; I, 45.58. Compound (**21**), 46% yield, colorless needles, mp 189° (from EtOH). *Anal.* Calcd. for $C_8H_{13}O_5N_2Cl$: C, 38.03; H, 5.19; N, 11.09; Cl, 14.03. Found: C, 38.16; H, 5.15; N, 11.07; Cl, 14.14.

5-Methoxy-1,2,3-trimethyl-4-pyrimidonium Perchlorate (26)——5-Methoxy-1,2,3-trimethyl-4-pyrimidonium iodide was obtained in 94% yield, mp 229° (decomp.). *Anal.* Calcd. for $C_8H_{13}O_2N_2I$: C, 32.45; H, 4.43; N, 9.46; I, 42.86. Found: C, 32.68; H, 4.71; N, 9.25; I, 42.92. Compound (**26**), 95% yield, colorless needles, mp 217° (decomp.) (from MeOH). *Anal.* Calcd. for $C_8H_{13}O_6N_2Cl$: C, 35.77; H, 4.88; N, 10.43; Cl, 13.20. Found: C, 35.88; H, 4.86; N, 10.42; Cl, 13.36.

5-Carbethoxy-1,2,3-trimethyl-4-pyrimidonium Perchlorate (31)——5-Carbethoxy-1,2,3-trimethyl-4-pyrimidonium iodide was obtained in 65% yield, mp 194° (decomp.). *Anal.* Calcd. for $C_{10}H_{15}O_3N_2I$: C, 35.52; H, 4.47; N, 8.28; I, 37.53. Found: C, 35.62; H, 4.58; N, 8.56; I, 37.44. Compound (31), 87% yield, colorless plates, mp 189—190° (decomp.) (from EtOH). *Anal.* Calcd. for $C_{10}H_{15}O_7N_2Cl$: C, 38.66; H, 4.87; N, 9.02; Cl, 11.41. Found: C, 38.79; H, 4.85; N, 9.14; Cl, 11.45.

Acknowledgement The authors wish to express their deep appreciation to Dr. H. Otsuka, Director of this laboratory, for his helpful advice and encouragement.