Substituent Effects on Tautomerism of 4-Pyridinethiones

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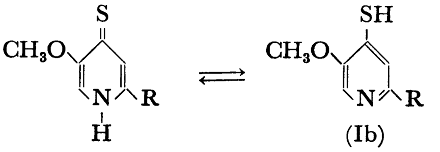
The tautomeric constants K_t of several 4-pyridinethiones were determined by measurement of pK_a values. For 2-substituted 5-methoxy-4-pyridinethiones, the K_t values are correlated to the substituent constants σ, by the equation $\log K_t = 4.00 + 3.99\sigma_m - 7.33\sigma_o$.

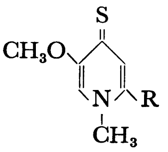
Two tautomers, enethiol and thione forms, are possible for the tautomerism of 4-pyridinethiones. Ross[1] found by means of UV spectra that 4-pyridinethione exists predominantly in the thione form in ethanolic solution. Jones and Katritzky,[2] and Albert and Barlin[3] concluded by measurement of pK_a values that the thione form predominates in aqueous solution by factors of *ca.* 10^4 by comparative studies of 4-pyridinethione and both alkylated compounds. It was shown by means of IR,[4] NMR,[5] and UV[6] that polyhalogenated 4-pyridinethiones exist mostly in the enethiol form.

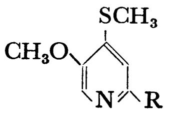
In the previous paper, we reported the substituent effects of 2-substituted 5-methoxy-4-pyridones in aqueous solution on tautomerism.[7] We hereby report the tautomerism of 2-substituted-5-methoxy-4-pyridinethiones by a similar treatment to that of 2-substituted 5-methoxy-4-pyridones.

Results and Discussion

Dissociation Constants. The dissociation constants of 4-pyridinethiones (I), *N*-methyl-4-pyridinethiones (II), and 4-methylthiopyridines (III) were determined spectrophotometrically in water at 25 °C. The results are summarized in Table 1, where pK_1 represents the first dissociation constants for 4-pyridinethiones (I), pK_{NCH_3} and pK_{SCH_3} corresponding to the dissociation constants for *N*-methyl-4-pyridinethiones (II) and 4-methylthiopyridines (III), respectively.


(Ia) (Ib)


(II)


(III)

Since activity coefficients were not introduced into the calculation, the dissociation constants do not represent thermodynamic terms, giving only a relative measure of base strength.

The pK_a values of 4-pyridinethiones (I) and *N*-methyl-4-pyridinethiones (II) are smaller than those of 4-pyridones and *N*-methyl-4-pyridones, since electronegativity of sulfur atom is smaller than that of oxygen atom. The pK_a values of I, II, and III decrease by electron-withdrawing groups attached to 2-position similarly to those of 4-pyridones.

TABLE 1. DISSOCIATION CONSTANTS

Substituent	pK_1	pK_{NCH_3}	pK_{SCH_3}
CH_3	1.90	1.82	6.50
H	1.69		
CH_2OH	1.64	1.53	5.38
CH_2OCH_3		1.44	
CHO			3.86

Tautomeric Ratio. The tautomeric constants K_t which represent the ratio of NH-form (Ia) to SH-form (Ib), are given by the following equation:[8] (Table 2).

$$\log K_t = pK_{SCH_3} - pK_{NCH_3} \qquad (1)$$

TABLE 2. TAUTOMERIC CONSTANTS

Substituent	log K_t	
	4-Pyridinethiones	4-Pyridones
CH_3	4.7	3.7
CH_2OH	3.9	2.8

The K_t values for 4-pyridinethiones are affected by the substituents in the 2-position, decreasing by electron-withdrawing groups. It is concluded that the thione forms predominate in aqueous solution by factors of *ca.* 10^5 for 5-methoxy-2-methyl-4-pyridinethione and *ca.* 10^4 for 5-methoxy-2-hydroxymethyl-4-pyridinethione.

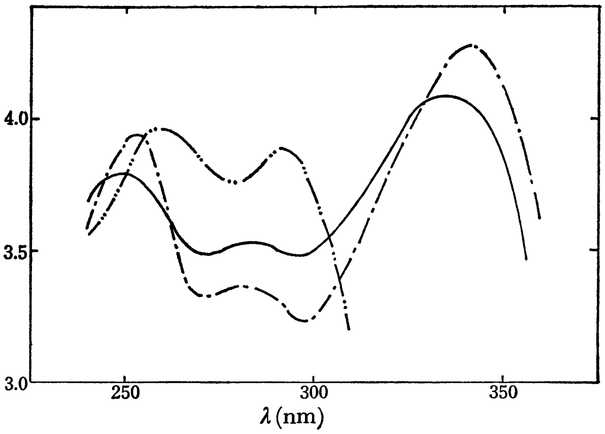


Fig. 1. The UV spectra of the neutral species of 5-methoxy-2-hydroxymethyl-4-pyridinethione series
—— 5-methoxy-2-hydroxymethyl-4-pyridinethione;
—·— 5-methoxy-2-hydroxymethyl-1-methyl-4-pyridinethione;—··— 5-methoxy-2-hydroxymethyl-4-methylthiopyridine.

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UV Spectra. The UV spectra of the neutral species of 5-methoxy-4-pyridinethiones (I) having the methyl and hydroxymethyl group in the 2-position are similar to those of their *N*-methyl derivatives (II), but differ a great deal from those of their *S*-methyl derivatives (III). Figure 1 shows the UV spectra of the neutral species of 5-methoxy-2-hydroxymethyl-4-pyridinethione series, the thione form being seen to exist predominantly.

Substituent Effects. Clark and Perrin[9] obtained the substituent constants σ_o for ortho-substituted pyridines from their dissociation constants. We also obtained the substituent constants σ_o and σ_m for the hydroxymethyl group.[7] When the pK_a values of 2-substituted 5-methoxy-4-pyridinethiones (I), pK_1, are plotted against the substituent constants σ_m,[10,11] a straight line is obtained, giving the following equation by the least-square methods:

$$pK_1 = 1.68 - 3.16\sigma_m \quad (r=0.998). \qquad (2)$$

For the proton gain of 2-substituted 5-methoxy-1-methyl-4-pyridinethiones (II) and the proton loss of 2-substituted 5-methoxy-4-methylthiopyridines (III), Eqs. 3 and 4, respectively, are obtained.

$$pK_{NCH_3} = 1.54 - 3.99\sigma_m \quad (r=0.992), \qquad (3)$$

$$pK_{SCH_3} = 5.54 - 7.33\sigma_o \quad (r=0.999). \qquad (4)$$

When Eqs. 3 and 4 are substituted into Eq. 1, we have

$$\log K_t = 4.00 + 3.99\sigma_m - 7.33\sigma_o. \qquad (5)$$

We have obtained a similar equation for 2-substituted 5-methoxy-4-pyridones:[7]

$$\log K_t = 2.98 + 2.93\sigma_m - 6.18\sigma_o. \qquad (6)$$

The ρ-value 2.93 for the substituent constants σ_m indicates the decrease of the hydroxy form by electron-withdrawing groups in the 2-position. In contrast, the ρ-value −6.18 for the substituent constants σ_o shows that the ratio of the hydroxy form increases electron-withdrawing group in the 2-position. It is possible to explain the tautomerism of 2-substituted 5-methoxy-4-pyridinethiones in a similar manner to that above. In Eq. 5, the ρ-value 3.99 for σ_m indicates the decrease of the enethiol form (Ib) by the electron-withdrawing group in the 2-position. In contrast, the ρ-value −7.33 for σ_o shows that the ratio of (Ib) increases with electron-withdrawing group in the 2-position. The substituent effects on the tautomerism of 2-substituted 5-methoxy-4-pyridinethiones are similar to those of 2-substituted 5-methoxy-4-pyridones.

It is concluded that the thione forms for 4-pyridinethione-4-mercaptopyridine tautomerism predominate by factors of *ca.* 10 the keto forms for 4-pyridone-4-hydroxypyridine tautomerism.

Experimental

All the melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were taken on a JASCO IRA-1 spectrophotometer, and the NMR spectra on a Hitachi-Perkin-Elmer R-24 spectrometer (60 MHz) with tetramethylsilane as an internal reference.

The pK_a values of 4-pyridinethiones (I), *N*-methyl-4-pyridinethiones (II), and 4-(methylthio)pyridines (III) were measured spectrophotometrically in water at 25 °C by the method of Albert and Serjeant.[12] The absorption spectra were taken on a Hitachi EPS-3T spectrophotometer, while the pH values were measured with a Hitachi-Horiba F-7 pH meter.

Materials. 4-Pyridinethiones (I) and *N*-methyl-4-pyridinethiones (II) were obtained by the reaction of 4-pyranthiones with ammonia and methylamine. All 4-pyranthiones were prepared by the reaction of the corresponding 4-pyrones with phosphorus pentasulfide in dry benzene.

3-Methoxy-4-pyranthione: Yield, 36%; mp 110—114 °C (from carbon tetrachloride); IR (KBr) 1604 cm^{-1}; NMR ($CDCl_3$) δ: 7.45 (d, 1H, J=4.7 Hz), 7.45 (s, 1H), 7.26 (d, 1H, J=4.7 Hz), 3.83 (s, 3H). Found: C, 50.49; H, 4.26%. Calcd for $C_6H_6O_2S$: C, 50.71; H, 4.26%.

5-Methoxy-2-methyl-4-pyranthione: Yield, 40%; mp 98.5—100 °C (from carbon tetrachloride); IR (KBr) 1615 cm^{-1}; NMR ($CDCl_3$) δ: 7.43 (s, 1H), 7.22 (s, 1H), 3.82 (s, 3H), 2.24 (s, 3H). Found: C, 53.55; H, 5.06%. Calcd for $C_7H_8O_2S$: C, 53.82; H, 5.17%.

5-Methoxy-2-acetoxymethyl-4-pyranthione: Yield, 54%; mp 152.5—153.5 °C (from benzene); IR (KBr) 1750, 1630 cm^{-1}; NMR ($CDCl_3$) δ: 7.45 (s, 1H), 7.32 (s, 1H), 4.88 (s, 2H), 3.85 (s, 3H), 2.15 (s, 3H). Found: C, 50.40; H, 4.60%. Calcd for $C_9H_{10}O_4S$: C, 50.47; H, 4.67%.

5-Methoxy-2-methoxymethyl-4-pyranthione: Yield, 37%; mp 56—56.5 °C (from benzene–petroleum ether); IR (KBr) 1635 cm^{-1}; NMR ($CDCl_3$) δ: 7.43 (s, 1H), 7.36 (s, 1H), 4.24 (s, 2H), 3.86 (s, 3H), 3.46 (s, 3H). Found: C, 51.48; H, 5.33%. Calcd for $C_8H_{10}O_3S$: C, 51.59; H, 5.42%.

3-Methoxy-4-pyridinethione: Yield, 44%; mp 149—152 °C (from methanol); IR (KBr) 3160, 2800, 1602 cm^{-1}; NMR (CF_3COOH) δ: 8.3—7.7 (m, 3H), 4.20 (s, 3H). Found: C, 50.80; H, 5.02; N, 9.94%. Calcd for C_6H_7NOS: C, 51.06; H, 5.02; N, 9.93%.

5-Methoxy-2-methyl-4-pyridinethione: Yield, 66%; mp 156—158 °C (from ethyl acetate); IR (KBr) 3245, 2800, 1615 cm^{-1}; NMR (CF_3COOH) δ: 7.9—7.5 (m, 2H), 4.15 (s, 3H), 2.69 (s, 3H). Found: C, 54.04; H, 5.78; N, 8.90%. Calcd for C_7H_9NOS: C, 54.19; H, 5.81; N, 9.03%.

5-Methoxy-1,2-dimethyl-4-pyridinethione: Yield, 60%; mp 200—202 °C (dec) (from methanol); IR (KBr) 3450, 3370, 1615 cm^{-1}; NMR (CF_3COOH) δ: 7.92 (s, 1H), 7.64 (s, 1H), 4.17 (s, 3H), 4.12 (s, 3H), 2.69 (s, 3H). Found: C, 56.66; H, 6.53; N, 8.25%. Calcd for $C_8H_{11}NOS$: C, 56.79; H, 6.55; N, 8.28%.

5-Methoxy-2-hydroxymethyl-4-pyridinethione was obtained by the reaction of 5-methoxy-2-acetoxymethyl-4-pyranthione with ammonia: Yield, 41%; mp 154—156 °C (from methanol); IR (KBr) 3210, 1600, 1585 cm^{-1}; NMR (CF_3COOH) δ: 8.2—7.6 (m, 2H), 5.13 (s, 2H), 4.18 (s, 3H). Found: C, 48.78; H, 5.35; N, 8.08%. Calcd for $C_7H_9NO_2S$: C, 49.08; H, 5.30; N, 8.19%.

5-Methoxy-2-hydroxymethyl-1-methyl-4-pyridinethione was obtained by the reaction of 5-methoxy-2-acetoxymethyl-4-pyranthione with methylamine: Yield, 65%; mp 199.5—201.5 °C (from methanol); IR (KBr) 3300, 1615 cm^{-1}; NMR (CF_3COOH) δ: 7.99 (br, s, 2H), 5.14 (s, 2H), 4.27 (s, 3H), 4.16 (s, 3H). Found: C, 51.29; H, 6.07; N, 7.58%. Calcd for $C_8H_{11}NO_2S$: C, 51.85; H, 5.98; N, 7.57%.

5-Methoxy-2-methoxymethyl-1-methyl-4-pyridinethione: Yield, 70%; mp 166—168 °C (dec) (from methanol); IR (KBr) 1615 cm^{-1}; NMR (CF_3COOH) δ: 8.00 (s, 1H), 7.86 (s, 1H), 4.78 (s, 2H), 4.26 (s, 3H), 4.16 (s, 3H), 3.65 (s, 3H). Found: C, 54.08; H, 6.58; N, 7.01%. Calcd for $C_9H_{13}NO_2S$: C, 54.26; H, 6.58; N, 7.03%.

5-Methoxy-2-methyl-4-(methylthio)pyridine was obtained by the methylation of 5-methoxy-2-methyl-4-pyridinethione with methyl iodide: Yield, 54%; mp 58—59 °C (from petroleum ether); IR (KBr) 1575 cm^{-1}; NMR (CCl$_4$) δ: 7.75 (s, 1H), 6.66 (s, 1H), 3.85 (s, 3H), 2.37 (s, 3H), 2.31 (s, 3H). Found: C, 56.79; H, 6.62; N, 8.30%. Calcd for $C_8H_{11}NOS$: C, 56.79; H, 6.55; N, 8.28%.

5-Methoxy-2-hydroxymethyl-4-methylthiopyridine was obtained by the methylation of 5-methoxy-2-hydroxymethyl-4-pyridinethione with methyl iodide: Yield, 53%; mp 108 °C (from carbon tetrachloride); IR (KBr) 3200, 1580 cm^{-1}; NMR (CDCl$_3$) δ: 7.97 (s, 1H), 7.02 (s, 1H), 4.69 (s, 2H), 3.95 (s, 3H), 2.43 (s, 3H), 4.3—3.3 (br, 1H). Found: C, 51.44; H, 5.95; N, 7.67%. Calcd for $C_8H_{11}NO_2S$: C, 51.85; H, 5.98; N, 7.57%.

5-Methoxy-2-formyl-4-(methylthio)pyridine was obtained by manganese dioxide oxidation of 5-methoxy-2-hydroxymethyl-4-methylthiopyridine: Yield, 62%; mp 116—117 °C (from petroleum ether); IR (KBr) 1720, 1550 cm^{-1}; NMR (CDCl$_3$) δ: 9.96 (s, 1H), 8.19 (s, 1H), 7.73 (s, 1H), 4.06 (s, 3H), 2.51 (s, 3H). Found: C, 52.35; H, 5.03; N, 7.55%. Calcd for $C_8H_9NO_2S$: C, 52.46; H, 4.95; N, 7.65%.

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