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Structure of 5-Hydroxy-2-hydroxymethyl-4-pyridones

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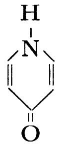
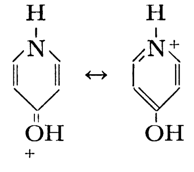
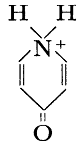
5-Hydroxy-2-hydroxymethyl-4-pyridone and its *N*-methyl, *N*-ethyl, and *N*-phenyl derivatives were prepared from kojic acid. The UV spectra in neutral, acid, and alkaline solutions showed that the neutral species and the conjugate acids existed in the pyridone and the pyridine form, respectively. The conjugate bases may exist in both forms. The acid dissociation constants and the halochromism have been measured and discussed.

In the protonation of the 4-pyridone (A), structure (B) represents the *O*-protonated form and (C) the *N*-protonated form.


(A)


(B) (B′)


(C)

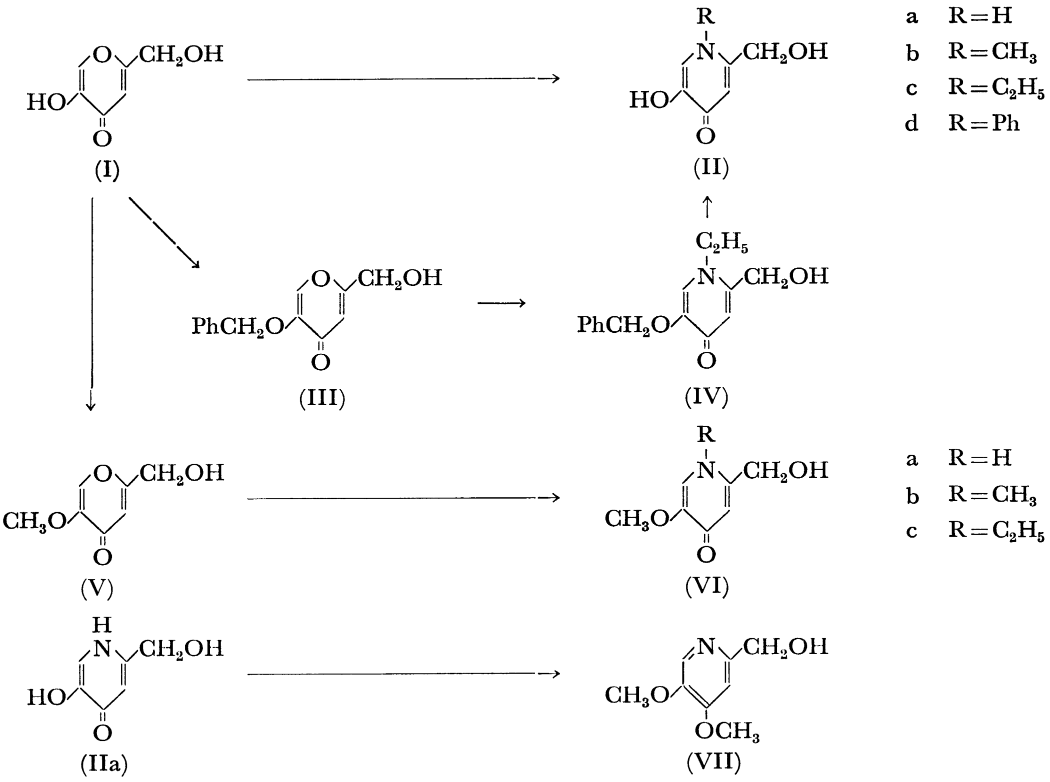
The theory of mesomerism predicts that the two cationic forms of B, B↔B′ should be greatly stabilized relative to type C, and their predominance has been assumed. The similarity among the ultraviolet spectra of the conjugate acids of 4-methoxypyridine, 1-methyl-4-pyridone, and 4-pyridone was taken to support such an assumption.[1] The NMR spectra also support the structure of type B↔B′.[2,3] However, the infrared and Raman spectra of these cations have been interpreted in favor of the structure of type C.[4,5]

The structure of 5-hydroxy-2-hydroxymethyl-4-pyridone in the acidic and alkaline solutions and the halochromism of its *N*-substituted derivatives are reported together with the acid dissociation constants.

Results and Discussion

Synthesis. 5-Hydroxy-2-hydroxymethyl-4-pyridone (IIa)[6] and its *N*-substituted derivatives (IIb[7] and IId) were obtained by the reaction of kojic acid (I) with the corresponding amines, while the *N*-ethyl-substituted compound (IIc) was prepared from I *via* 5-benzyloxy-2-hydroxymethyl-4-pyrone (III)[8] and 5-benzyloxy-1-ethyl-2-hydroxymethyl-4-pyridone (IV). 2-Hydroxymethyl-5-methoxy-4-pyridone (VIa)[9] and its *N*-substituted derivatives (VIb[9] and VIc) were obtained from kojic acid methyl ether (V)[9] by the reaction with the corresponding amines. The reaction of IIa with diazomethane gave 3,4-dimethoxy-6-hydroxymethylpyridine (VII) in 33% yield.

Acid Dissociation Constants. The acid dissociation constants of 5-hydroxy-2-hydroxymethyl-4-



Scheme 1.

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pyridones IIa—d were determined spectrophotometrically in water at 25 °C. The results are summarized in Table 1, where the pK_2 and pK_1 values represent the acid dissociation exponent (pK_a) of a neutral compound and that of its conjugate acid, respectively. The pK_1 values are comparable to the pK_a values for the conjugate acids of some 4-pyridones,[10,11] and the pK_2 values to the pK_a values for some 3-hydroxy-4-pyrones.[12] These values are increased by introduction of an electron donative substitutent on the nitrogen atom, but do not give a good Hammett relationship.

UV Spectra. The UV spectral data of the conjugate acids, neutral species, conjugate bases of 5-hydroxy-2-hydroxymethyl-4-pyridone (IIa) and its *N*-substituted derivatives (IIb—d) and 2-hydroxymethyl-5-methoxy-4-pyridone (VIa) and its *N*-substituted derivatives (VIb and VIc) are summarized in Tables 2 and 3, respectively. The spectra of 5-hydroxy-2-hydroxymethyl-4-pyridone (IIa), the *N*-methyl derivative (IIb) and 3,4-dimethoxy-6-hydroxymethyl-pyridone (VII) in water and M/10 hydrochloric acid are presented in Figs. 1 and 2 as examples. The spectra of 5-methoxy derivatives VIa and VIb are also presented together with the spectra of VII in Figs. 3 and 4.

TABLE 1. pK_a VALUES OF *N*-SUBSTITUTED 5-HYDROXY-2-HYDROXYMETHYL-4-PYRIDONES

Compd	*N*-Substituent	pK_1	pK_2
IIa	H	3.26	
IIb	CH_3	3.37	9.18
IIc	C_2H_5	3.31	8.97
IId	Ph	2.64	8.82

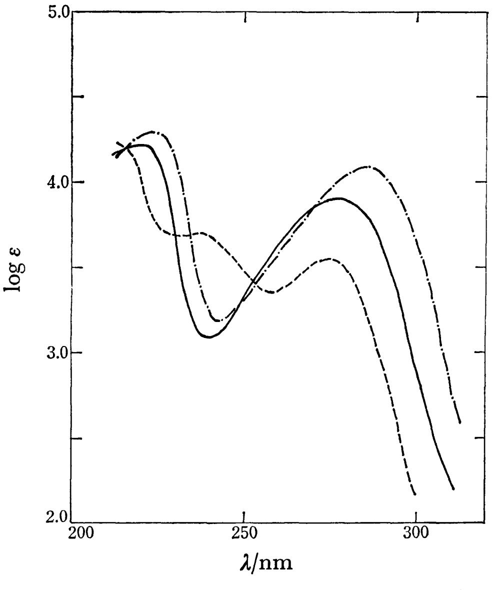

Fig. 1. The UV spectra of the neutral species. ——: IIa, —·—: IIb, ----: VII.

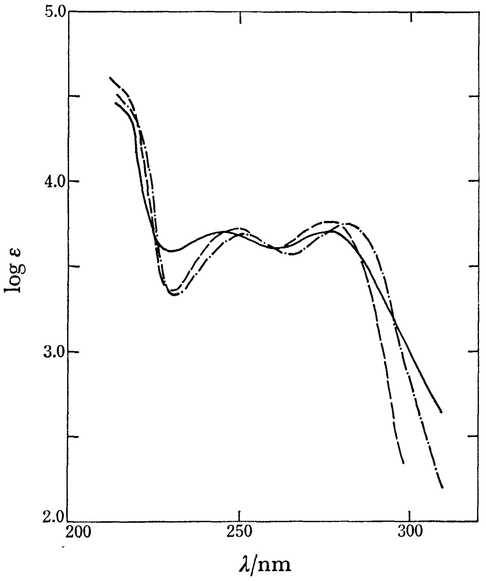

Fig. 2. The UV spectra of the cationic species. ——: IIa, —·—: IIb, ----: VII.

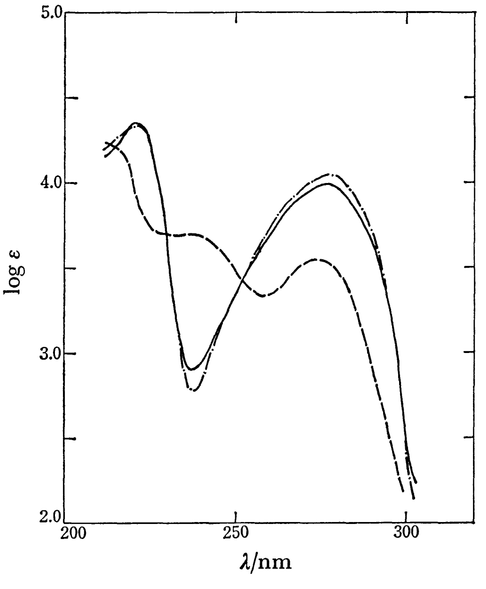

Fig. 3. The UV spectra of the neutral species. ——: VIa, —·—: VIb, ----: VII.

TABLE 2. UV SPECTRA OF *N*-SUBSTITUTED 5-HYDROXY-2HYDROXYMETHYL-4-PYRIDONES

Compd	*N*-Substituent	Conjugate acid		Neutral species		Conjugate base		$\Delta\tilde{\nu}$ / cm^{-1}
		λ_{max}/nm ($\log\varepsilon$)	$\tilde{\nu}$ / cm^{-1}	λ_{max}/nm ($\log\varepsilon$)	$\tilde{\nu}$ / cm^{-1}	λ_{max}/nm ($\log\varepsilon$)	λ / cm^{-1}	
IIa	H	276 (3.70)	36230	278 (3.90)	35970	298 (3.75)	33560	−2410
IIb	CH_3	281 (3.75)	35590	285 (4.08)	35090	312 (3.96)	32050	−3040
IIc	C_2H_5	281 (3.72)	35590	286 (4.08)	34970	312 (4.00)	32050	−2920
IId	Ph	284 (3.92)	35210	290 (4.24)	34480	316 (4.10)	31650	−2830

Table 3. UV spectra of N-substituted 2-hydroxymethyl-5-methoxy-4-pyridones

Compd	N-Substituent	Conjugate acid		Neutral species	
		$\frac{\lambda_{max}}{nm}$ (log ε)	$\frac{\tilde{\nu}}{cm^{-1}}$	$\frac{\lambda_{max}}{nm}$ (log ε)	$\frac{\tilde{\nu}}{cm^{-1}}$
VIa	H	275 (3.63)	36360	277 (3.99)	36100
VIb	CH_3	275 (3.70)	36360	278 (4.04)	35970
VIc	C_2H_5	281 (3.72)	35590	285 (4.11)	35090

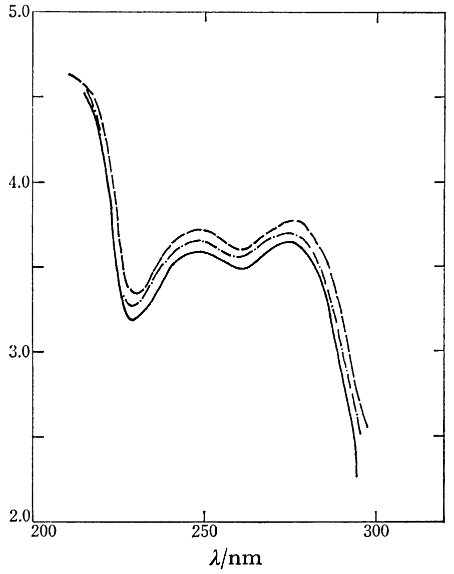

Fig. 4. The UV spectra of the cationic species.
——: VIa, —·—: VIb, ----: VII.

It may be seen from Figs. 1 and 3 that the spectra of the neutral species of IIa and VIa are similar to those of IIb and VIb, but are different from the spectrum of VII, indicating that the 4-pyridones exist predominantly in the NH-form.

As Figs. 2 and 4 illustrate, the spectra of the conjugate acids of 5-hydroxy-4-pyridones IIa and IIb and 5-methoxy-4-pyridones VIa and VIb are very similar to the spectrum of the conjugate acid of VII. This shows that the protonation of the 4-pyridones occurs at the oxygen atom at the 4-position in agreement with Katritzky and Lagowski's results.[1]

The NMR spectral data were also examined. In deuterium oxide, the positions of the peaks of the α- and β-protons of VIa (7.61 and 6.52 ppm) are considerably different from those of VII (7.93 and 7.00 ppm), while in 20% sulfuric acid those of VIa (8.72 and 7.30 ppm) are close to those of VII (8.31 and 7.57 ppm). This indicates the O-protonation to be in agreement with the results of Katritzky *et al.*[2,3]

The UV spectra of the conjugate bases of the 4-pyridones IIa and IIb are shown in Fig. 5 together with that of the neutral species of VII. As shown in Fig. 5 and Table 2, the maximum absorption band of IIa is shifted to a shorter wavelength from those of the N-substituted 4-pyridones. The spectral pattern is also different from those of the N-substituted derivatives, in that a broad shoulder exists at 270—280 nm. This shoulder closely corresponds to the maximum absorption band of the pyridine derivative VII. Thus, IIa might exist not only in the pyridone form but also in the pyridine form.

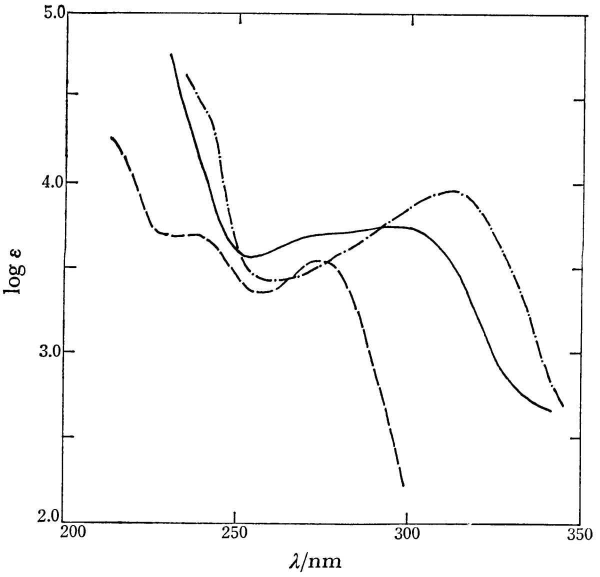

Fig. 5. The UV spectra of the anionic species.
——: IIa, —·—: IIb, ----: VII (neutral).

Halochromism. Rapoport *et al.*[13] measured the absorption spectra of 4-substituted 2-nitrophenols in neutral and alkaline solutions, and showed that the difference in wave number between the maxima of the longest-wavelength absorption bands in the two solutions is quantitatively related to the dissociation constant. The wave number shift is also proportional to the Hammett substituent constant. This phenomenon of halochromism is well documented and the degree of halochromism of a compound may be defined as the wave number difference ($\Delta\tilde{\nu}$) between the longest-wavelength band of the neutral species and that of its conjugate acid or base.

The $\Delta\tilde{\nu}$ values (Table 2) of the 4-pyridones plotted against the pK_a ($\equiv$pK_2) values, produces a straight line as shown in Fig. 6, giving the following equation by the least-square method.

$$\Delta\tilde{\nu} = -583\text{p}K_a - 2311 \qquad (r=1.000,\ s=1)$$

The slope was comparable to that reported for the phenols.[13]

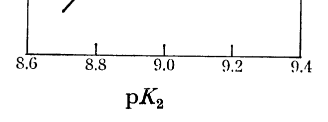

Fig. 6. The relationship between $\Delta\tilde{\nu}$ and pK_2.

Experimental

All the melting points were measured on a Yanagimoto micro-melting point apparatus and are uncorrected. The IR and NMR spectra were taken on JASCO IRA-1 spectrophotometer and a Hitachi-Perkin-Elmer R-24 (60 MHz) spectrometer, respectively. The UV spectra were recorded on a Hitachi EPS-2U and EPS-3T spectrophotometer. The pH values were measured by a Hitachi-Horiba F-5 pH meter. The pK_a determination was conducted according to Albert-Serjeant's method.[14]

Materials. All the known compounds were prepared according to the methods described in the references: IIa, mp 232—234 °C (lit,[6] 237—238 °C); IIb, mp 220 °C (lit,[7] 225—227 °C); III, mp 132 °C (lit,[8] 133 °C); V, mp 165—166 °C (lit,[9] 165 °C); VIa, mp 170 °C (lit,[9] 173—175 °C); VIb, mp 203—205 °C (lit,[9] 203—204 °C).

5-Benzyloxy-1-ethyl-2-hydroxymethyl-4-pyridone (IV). A mixture of 5-benzyloxy-2-hydroxymethyl-4-pyrone(III)[8] (2 g) and 70% ethylamine solution (4 ml) was heated in a sealed tube at 130 °C for 5 h. The excess amine was evaporated off and the residue recrystallized from methanol to afford IV (1.8 g, 80.6%) as colorless needles, mp 183 °C. Found: C, 69.25; H, 6.87; N, 5.32%. Calcd for $C_{15}H_{11}NO_3$: C, 69.48; H, 6.61; N, 5.40%. IR (KBr): 1620 cm^{-1}. UV (MeOH) λ_{max}/nm (log ε): 225 (4.35), 286 (4.16).

1-Ethyl-5-hydroxy-2-hydroxymethyl-4-pyridone (IIc). A mixture of 5-benzyloxy-1-ethyl-2-hydroxymethyl-4-pyridone (IV) (2 g) and 5% palladium carbon (0.8 g) in methanol (20 ml) was stirred for 2 h at room temperature under a hydrogen atmosphere. After removal of the catalyst the solvent was evaporated off and the residue recrystallized from ethanol to afford IIc (0.9 g, 69.0%) as colorless needles, mp 187 °C. Found: C, 56.68; H, 6.67; N, 8.18%. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28%. IR (KBr): 1640 cm^{-1}. UV (MeOH) λ_{max}/nm (log ε): 226 (4.22), 290 (4.10).

5-Hydroxy-2-hydroxymethyl-1-phenyl-4-pyridone (IId). A mixture of kojic acid (I) (1.5 g) and aniline (2 ml) in water (5 ml) was heated on a water-bath in the presence of 12 M hydrochloric acid (0.7 ml) in a sealed tube for 3 h. Water was added to the reaction mixture, which gave a red-brown precipitate. This precipitate was recrystallized from methanol to afford IId (0.85 g, 37.1%) as colorless needles, mp 238 °C. Found: C, 66.00; H, 5.33; N, 6.44%. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45%. IR (KBr): 1645 cm^{-1}. UV (MeOH) λ_{max}/nm (log ε): 292 (4.24).

1-Ethyl-2-hydroxymethyl-5-methoxy-4-pyridone (VIc). 2-Hydroxymethyl-5-methoxy-4-pyrone (V)[9] (1.5 g) was heated with 70% ethylamine solution (3 ml) in a sealed tube at 140 °C for 4 h. After evaporation of the excess amine and water, the residue was recrystallized from methanol to give VIc (1.6 g, 90.9%) as colorless needles, mp 177 °C. Found: C, 58.93; H, 7.22; N, 7.81%. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65%. IR (KBr): 1635 cm^{-1}. UV (MeOH) λ_{max}/nm (log ε): 224 (4.21), 287 (4.13).

3,4-Dimethoxy-6-hydroxymethylpyridine (VII). An excess of diazomethane in ether was added to a solution of 5-hydroxy-2-hydroxymethyl-4-pyridone (IIa) (1 g) in methanol (600 ml), and the mixture allowed to stand in a refrigerator until the purple color with iron(III) chloride disappeared. After evaporation of the solvents, the residue was recrystallized from ethanol and sublimed to afford VII (0.4 g, 33%) as colorless needles, mp 121—122 °C. Found: C, 56.61; H, 6.55; N, 8.20%. Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28%. IR (KBr): 1595 cm^{-1}. UV (MeOH) λ_{max}/nm (log ε): 234 (3.77), 274 (3.44). NMR ($CDCl_3$): 3.90 (s, 6H), 4.66 (s, 2H), 6.91 (1H), 7.97 (s, 1H).

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