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Substituent Effects on the Dissociation Constants of 1-Aryl-5-hydroxy-2-hydroxymethyl-4-pyridones

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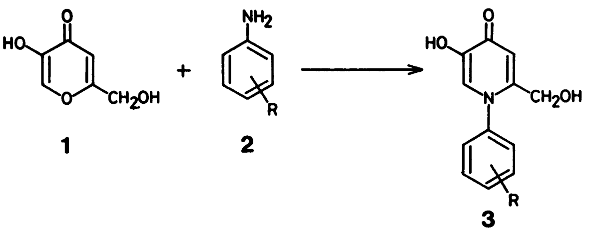
Synopsis. Six new 1-aryl-5-hydroxy-2-hydroxymethyl-4-pyridones were synthesized and their dissociation constants were measured. Hammett analysis of pK_a values for proton gain and proton loss gave the following equations: pK_1= 2.74−0.34σ and pK_2=8.80−0.36σ, respectively.

Hahn *et al.*[1,2] obtained 1-aryl-3-hydroxy-4-pyridones by the reactions of comenic acid and meconic acid with aniline derivatives. However, there is no further investigation in a detailed manner.

In the present work, we wish to report the synthesis of 1-aryl-5-hydroxy-2-hydroxymethyl-4-pyridones from kojic acid and the effects of the substituent in the benzene ring on the dissociation constants.

Results and Discussion

Synthesis. Condensation of kojic acid (**1**) with six anilines (**2a**—**f**) were respectively carried out, according to the Hahn's method,[1,2] to afford 1-aryl-5-hydroxy-2-hydroxymethyl-4-pyridones (**3a**—**f**). However, their yields were not necessarily good. All of the 4-pyridones gave a violet color with iron(III) chloride solution.



a R=H d R=*m*-OCH$_3$
b R=*p*-CH$_3$ e R=*p*-Cl
c R=*p*-OCH$_3$ f R=*p*-COCH$_3$

Dissociation Constants. The dissociation constants of six 1-aryl-5-hydroxy-2-hydroxymethyl-4-pyridones were determined spectrophotometrically in water at 25 °C. The results are summarized in Table 1, where pK_1 and pK_2 values represent respectively the dissociation constants for the proton gain and proton loss of the 4-pyridones. Both pK_1 and pK_2 values are respectively smaller than those of 6-substituted 3-hydroxy-1-methyl-4-pyridones,[3] because of inductive effect of the aryl group. When these pK values were plotted against Hammett σ constants,[4] the following equations were obtained by the least-square method.

TABLE 1. DISSOCIATION CONSTANTS

R	pK_1	pK_2
p-OCH$_3$	2.85	8.89
p-CH$_3$	2.82	8.86
H	2.64	8.82
m-OCH$_3$	2.76	8.78
p-Cl	2.39	8.69
p-COCH$_3$	2.57	8.62

$$\mathrm{p}K_1 = 2.74 - 0.34\sigma \quad (r=0.867,\ s=0.04)$$

$$\mathrm{p}K_2 = 8.80 - 0.36\sigma \quad (r=0.980,\ s=0.02)$$

The ratio of the ρ value for **3** against the ρ value for 1-methyl-3-hydroxypyridones[3] is 0.29 for the proton gain and 0.34 for the proton loss. These values are comparable to the transmission factor (π=0.3) for *m*- and *p*-phenylene groups.[5]

Experimental

All the melting points were measured on a Yanagimoto MP-S2 melting point measuring apparatus and are uncorrected. The IR and UV spectra were taken on a JASCO IRA-1 and on a Hitachi EPS-3T spectrophotometer, respectively. The pH values were measured by a Hitachi-Horiba F-5 pH meter. The pKa determination was carried out according to the method of Albert and Serjeant.[6]

5-Hydroxy-2-hydroxymethyl-1-phenyl-4-pyridone (3a). A mixture of kojic acid (**1**) (1.0 g) and aniline (**2a**) (1.3 ml) in water (3.3 ml) was heated in the presence of 12 M (1 M=1 mol dm^{-3}) hydrochloric acid (0.5 ml) in a sealed tube on a water bath for 4 h. Water (6.7 ml) was added to the mixture to precipitate **3a** (280 mg, 18.3%). Mp 231 °C (from methanol); IR (KBr) 1653 cm^{-1}; UV (CH$_3$OH) 224 (sh, log ε 4.33), 287 nm (4.25). Found: C, 66.15; H, 5.18; N, 6.44%. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45%.

*5-Hydroxy-2-hydroxymethyl-1-(*p*-methylphenyl)-4-pyridone (3b).* A mixture of kojic acid (**1**) (1.5 g) and *p*-toluidine (**2b**) (2.4 g) in water (3.5 ml) was treated in the presence of 12 M hydrochloric acid (0.5 ml) and worked up, as mentioned above, to afford **3b** (240 mg, 9.8%). Mp 215—217 °C (from methanol); IR (KBr) 1635 cm^{-1}; UV (CH$_3$OH) 227 (log ε 4.32), 288 nm (4.28). Found: C, 67.41; H, 5.67; N, 6.08%. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06%.

*5-Hydroxy-2-hydroxymethyl-1-(*p*-methoxyphenyl)-4-pyridone (3c).* A mixture of kojic acid (**1**) (1.5 g) and *p*-anisidine (**3c**) (2.6 g) in water (3.5 ml) was treated in the presence of 12 M hydrochloric acid (0.5 ml) and worked up, as mentioned above, to afford **3c** (130 mg, 5.0%). Mp 231—233 °C (from methanol); IR (KBr) 1635 cm^{-1}; UV (CH$_3$OH) 244 (log ε 4.43), 288 nm (4.30). Found: C, 63.24; H, 5.23; N, 5.72%. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67%.

*5-Hydroxy-2-hydroxymethyl-1-(*m*-methoxyphenyl)-4-pyridone (3d)* A mixture of kojic acid (**1**) (1.4 g) and *m*-anisidine (**2d**) (1.5 g) in water (1.0 ml) was heated in the presence of 12 M hydrochloric acid (0.5 ml) in a sealed tube at 130—150 °C for 14 h. The reaction mixture was worked up, as mentioned above, to give **3d** (170 mg, 7.0%). Mp 206—208 °C (from methanol); IR (KBr) 1645 cm^{-1}; UV (CH$_3$OH) 222 (log ε 4.46), 288 nm (4.29). Found: C, 63.10; H, 5.29; N, 5.73%. Calcd for

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$C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67%.

*1-(*p*-Chlorophenyl)-5-hydroxy-2-hydroxymethyl-4-pyridone (3e).* A mixture of kojic acid (**1**) (1.5 g) and *p*-chloroaniline (**2e**) (4.0 g) in water (8 ml) was treated in the presence of 12 M hydrochloric acid (0.2 ml), as mentioned above, to give **3e** (30 mg, 1.1%). Mp 230—233 °C (from water); IR (KBr) 1636 cm^{-1}; UV (CH_3OH) 224 (sh, log ε 4.40), 290 nm (4.27). Found: C, 57.14; H, 3.97; N, 5.45%. Calcd for $C_{12}H_{10}ClNO_3$: C, 57.27; H, 4.01; N, 5.57%.

*1-(*p*-Acetylphenyl)-5-hydroxy-2-hydroxymethyl-4-pyridone (3f).* A mixture of kojic acid (**1**) (1.0 g) and *p*-aminoacetophenone (**2f**) (2.7 g) in water (8 ml) was treated in the presence of 12 M hydrochloric acid (0.3 ml), as mentioned above, to give **3f** (560 mg, 30.7%). Mp 240—243 °C (from methanol); IR (KBr) 1703, 1737 cm^{-1}; UV (CH_3OH) 228 (log ε 4.31), 292 nm (4.27). Found: C, 65.09; H, 5.07; N, 5.40%. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40%.

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