

Lactams. VIII.¹⁾ The Alkaline Ferricyanide Oxidation of 3-Substituted 1-(3,4-Dimethoxyphenethyl)pyridinium Salts: Effects of Hydrocarbon Substituents on Orientation of the Oxidation²⁾

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The alkaline ferricyanide oxidation at 32° of 1-(3,4-dimethoxyphenethyl)pyridinium bromides (3c–f) carrying the *n*-butyl, isopropyl, benzyl, and phenyl group at the 3-position has been found to produce the corresponding 2- (4c–f) and 6-pyridones (5c–f) in ratios of 74:26, 71:29, 69:31, and 13:87. In the case of the 3-benzyl derivative (3e), 1-(3,4-dimethoxyphenethyl)-5-benzoyl-2(1*H*)-pyridone (5g) has also been obtained in 1% yield. On the basis of the present and earlier data, possible factors in determining the orientation in the ferricyanide oxidation of 1,3-disubstituted pyridinium salts are discussed.

Keywords—pyridinium salt; pyridone; Decker oxidation; isomer ratio; effect of hydrocarbon substituent; chromatographic analysis; UV; IR; NMR

Previous papers^{4,5)} in this series described a comparative study of the mercuric acetate-EDTA and the ferricyanide oxidation methods for synthesis of 1-(2-arylethyl)-3-alkyl-2- and -6-piperidones. In view of the great synthetic utility of both methods for placing substituent groups in ring C of the benzo[*a*]quinolizidine system, we have tried to extend the scope of both oxidation reactions.^{6–9)} This paper reports the results of the alkaline ferricyanide oxidation of 1-(3,4-dimethoxyphenethyl)pyridinium salts carrying various hydrocarbon groups at the 3-position with particular emphasis on the effect of the substituent upon the position of oxidation.

The hydrocarbon substituents we selected for the present work were the *n*-butyl, isopropyl, benzyl, and phenyl group, and the pyridine bases (1c–f) were converted into the pyridinium bromides (3c–f) by quaternization with 3,4-dimethoxyphenethyl bromide (2) in hot benzene, toluene, or *N,N*-dimethylformamide (DMF) solution. All the alkaline ferricyanide oxidations (32±0.1°, 5 hr) of the quaternary bromides (3c–f) and the quantitative analytical work to determine the isomer ratio of the resulting pyridones (4 and 5) were carried out according to the previously reported standard procedure.⁵⁾ The results are summarized in Table I.

- 1) Paper VII in this series, T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.* (Tokyo), **23**, 2094 (1975).
- 2) Presented in part at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 4, 1974.
- 3) Location: 13-1 Takara-machi, Kanazawa 920, Japan; a) Address correspondence to this author at Kanazawa University; b) 1-8 Kanda-surugadai, Chiyoda-ku, Tokyo 101, Japan.
- 4) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **20**, 1451 (1972).
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- 7) T. Fujii, M. Ohba, and S. Yoshifuji, Abstracts of Papers, the 8th Congress of Heterocyclic Chemistry, Kyoto, October, 1975, p. 134.
- 8) T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731.
- 9) S. Yoshifuji and T. Fujii, *Tetrahedron Lett.*, **1975**, 1965.

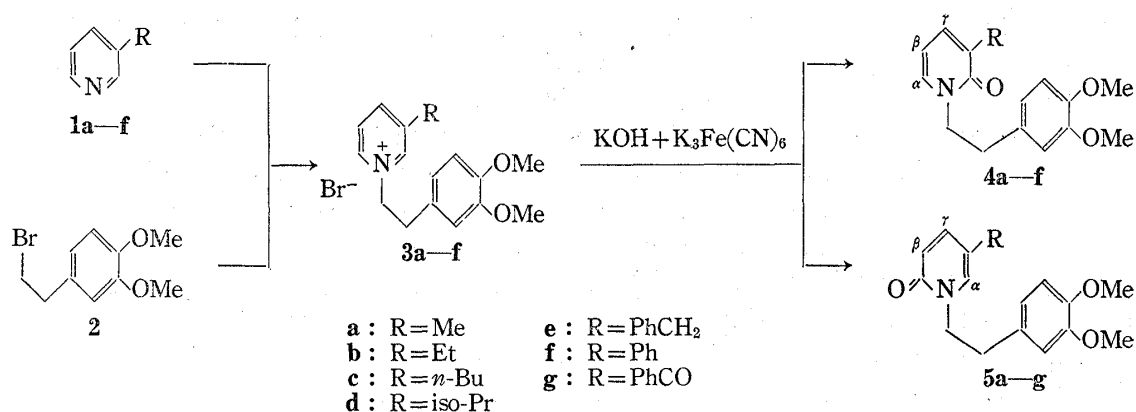


Chart 1

TABLE I. Alkaline Ferricyanide Oxidation of 3-Substituted Pyridinium Salts

No.	Pyridinium salt		Product ^{a)}		
	R		Combined yield (%)	% 2-Pyridone (4)	% 6-Pyridone (5)
3a	Me		76 ^{b)}	94 (4a) ^{b)}	6 (5a) ^{b)}
3b	Et		71 ^{b)}	88 (4b) ^{b)}	12 (5b) ^{b)}
3c	<i>n</i> -Bu		44 ^{c)}	74 (4c)	26 (5c)
3d	iso-Pr		79 ^{c)}	71 (4d)	29 (5d)
3e	PhCH ₂		71 ^{d)}	69 (4e)	31 (5e)
3f	Ph		50 ^{e)}	13 (4f)	87 (5f)

a) All isomer ratios were determined by column chromatographic analysis as reported previously.⁵⁾

b) From ref. 5.

c) Overall yield from the corresponding pyridine base (type 1) used in the preceding quaternization.

d) In addition, **5g** was obtained in 1% yield.

TABLE II. Ultraviolet and Infrared Spectra of Pyridones

Compound	UV spectrum ^{a)}						IR spectrum ^{b)} ν _{C=O} (cm ⁻¹)
	Short-wavelength band		Medium-wavelength band		Long-wavelength band		
	λ _{max} (nm)	log ε	λ _{max} (nm)	log ε	λ _{max} (nm)	log ε	
2-Pyridones							
4a ^{c)}	231	4.12	286	3.84	302	3.83	1651
4b ^{c)}	232	4.08	286	3.81	303	3.81	1650
4c	231.5	4.09	287	3.82	303	3.82	1648
4d	232	4.12	287	3.84	303	3.84	1649
4e	231.5	4.18	287.5	3.85	307.5	3.89	1647
4f	—	—	286	3.70	324	4.04	1647
6-Pyridones							
5a ^{c)}	231	4.17	284	3.66	314	3.74	1667
5b ^{c)}	232	4.19	284	3.68	313	3.76	1668
5c	232	4.21	286.5	3.66	314	3.76	1668
5d	231	4.18	286.5	3.68	313	3.74	1667
5e	232	4.31	287	3.69	316	3.79	1666
5f	228 ^{d)}	4.27	268	4.33	323.5	3.67	1664

a) Determined in abs. EtOH.

b) Measured in CHCl₃ solution at 0.2 M concentration.

c) From ref. 5.

d) Shoulder.

The spectral data collected in Tables II and III have definitely confirmed the structures of the pyridones thus produced. All the pyridones with aliphatic hydrocarbon substituents fulfilled the previously described four criteria^{5,6,10} for distinguishing between 1,3-dialkyl-2- and -6-pyridones, namely, isomer ratio, long-wavelength ultraviolet (UV) absorption band position, CO stretching vibration band position, and splitting pattern of pyridone-ring proton resonances, but the 3-phenylpyridones (**4f** and **5f**) did not satisfy the first and the second criteria, as anticipated from earlier observations.¹⁰⁻¹² It is of interest, however, to note that in all cases the 2-pyridone isomer (**4**) had a higher *R_f* value than that of the 6-pyridone isomer (**5**) on an alumina thin-layer chromatography (TLC) plate. This chromatographic behavior is consistent with that⁵ of the 3-methyl- (**4a** and **5a**) and the 3-ethylpyridones (**4b** and **5b**), allowing to set up a fifth criterion for distinguishing between 1,3-disubstituted 2- and 6-pyridones. Similar observations have also been made by Möhrle and Weber¹⁰ on several pairs of isomeric pyridones.

TABLE III. Pyridone-Ring Proton Resonances

Compound	Chemical shift (δ) ^a			Coupling constant (Hz)		
	H _{α}	H _{β}	H _{γ}	J _{$\alpha\beta$}	J _{$\alpha\gamma$}	J _{$\beta\gamma$}
2-Pyridones						
4a ^b	6.85 (d-d)	5.96 (t)	7.16 (d-m) ^c	6.5	2.0	6.5
4b ^b	6.82 (d-d)	5.96 (t)	7.11 (d-m) ^c	6.5	2.2	6.5
4c	6.88 (d-d)	5.96 (t)	7.18 (d-m) ^c	6.5	1.9	6.5
4d	6.81 (d-d)	5.97 (t)	7.12 (d-m) ^c	6.5	2.0	6.5
4e ^d	6.84 (d-d)	5.94 (t)	7.00 (d-m) ^c	6.8	2.0	6.8
4f	6.90 (d-d)	6.06 (t)	7.1-7.8 ^e	6.2	1.9	6.2
6-Pyridones						
5a ^b	6.6-6.7 ^e	6.53 (d)	7.18 (d-d)	— ^f	2.5	9.3
5b ^b	6.58 (d)	6.54 (d)	7.18 (d-d)	ca. 1	2.3	9.0
5c	6.55-6.95 ^e	6.55 (d)	7.18 (d-d)	— ^f	2.5	9.0
5d	6.46-6.88 ^e	6.53 (d)	7.21 (d-d)	— ^f	2.5	9.2
5e ^d	6.60 (d)	6.53 (d)	7.15 (d-d)	— ^f	2.5	9.5
5f	6.94-7.43 ^e	6.50-6.94 ^e	7.58 (d-d)	—	2.8	9.0
5g	7.2-7.6 ^e	6.64 (d)	7.94 (d-d)	— ^f	2.5	9.5

a) Measured on 10% (w/v) CDCl₃ solution. The letter in parentheses designates the multiplicity or shape of the signal with the abbreviations appeared at the top of Experimental part.

b) From ref. 5.

c) The multiplicity of the signal is most probably due to long-range coupling between H _{γ} and the side-chain C _{α} -proton(s).^{5,6}

d) Measured on 5% (w/v) CDCl₃ solution.

e) Overlapped with the signals of the aromatic protons.

f) Unmeasurably small.

It may be seen from Table I that in the alkaline ferricyanide oxidation of the quaternary pyridinium bromides (**3a-e**), which carry an alkyl or aralkyl group at the 3-position, the oxidation at the 2-position is much favored over that at the 6-position. This preference is in general agreement with that^{10,13-15} observed for a similar oxidation of 3-methyl- and 3-ethyl-1-methylpyridinium salts. A higher and/or bulkier 3-alkyl substituent, however, causes the extent of the 6-pyridone (type **5**) formation to increase. On the contrary, the phenyl group

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12) S. Sugawara and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **3**, 187 (1955).

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15) R. A. Abramovitch and A. R. Vinutha, *J. Chem. Soc. (B)*, **1971**, 131.

at the 3-position orients the oxidation to the 6-position predominantly over the 2-position, but not so exclusively as reported¹²⁾ for a similar oxidation of 1-methyl- or 1-phenethyl-3-phenylpyridinium salt.

In the mechanism of alkaline ferricyanide oxidation of pyridinium salts suggested by Abramovitch and Vinutha,¹⁵⁾ the rate-determining step has been assumed to be the formation of the complex (7) from the first one molecule of potassium ferricyanide and the alkoxide (6) produced from the corresponding pseudo-base (Chart 2). They have explained that the pre-

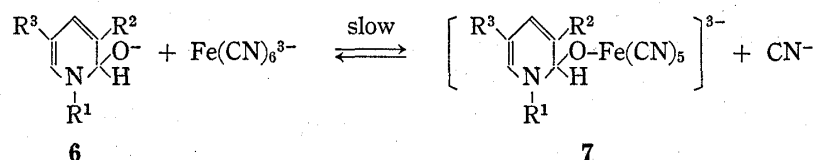


Chart 2

ferred orientation at the 2-position observed for the oxidation of 1,3-dimethylpyridinium iodide¹⁵⁾ may be due to an attractive dispersion force between the 3-methyl group in the alkoxide (6, R¹=R²=Me; R³=H) and the highly polarizable ferricyanide ion. If the same mechanism is operative in our present cases, one logical explanation for the 2-oxidation decreasing effect with a higher and/or bulkier 3-alkyl substituent is that steric hindrance to the approach of the bulky ferricyanide ion to the alkoxide [6, R¹=3,4-(MeO)₂C₆H₃CH₂CH₂; R²=alkyl; R³=H] is also operative. Comparison of the quantitative data on the effects of the 3-isopropyl and the 3-phenyl group in Table I suggests that electrostatic repulsion between the electronegative substituent and the ferricyanide ion may also be an important factor in determining the orientation in the oxidation of 3f. Thus, the isomer ratios obtained in the present study appear to reflect the balance of the three effects, namely, attractive dispersion force, steric hindrance, and electrostatic repulsion, with regard to the 3-substituents tested.

Further interest in the ferricyanide oxidation stems from the finding that besides the expected pyridones (4e and 5e) the 5-benzoyl-2-pyridone derivative (5g) was formed also from the 3-benzylpyridinium salt (3e) in 1% yield. Proof of the correctness of structure 5g was provided by the nuclear magnetic resonance (NMR) spectrum (Table III) and elemental analyses of the third product and also by its physical properties which were in agreement with those reported.¹⁶⁾ Since both the benzyl pyridones (4e and 5e) have been found to be stable under these oxidation conditions, the formation of 5g would not be due to the secondary oxidation of 5e once formed. It is, therefore, most likely that the 3-benzylpyridinium salt (3e) was first oxidized to the 3-benzoylpyridinium salt and the electronegative 3-benzoyl group then oriented the ring oxidation to the 6-position. Work on effects of various functional substituents upon orientation of the oxidation will be reported elsewhere shortly.

Experimental

All melting points are corrected; boiling points, uncorrected. Spectra reported herein were measured with a Hitachi Model 323 UV spectrophotometer, a JASCO-IRA-2 IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a JEOL-JNM-C-60H or -JNM-PS-100 NMR spectrometer at 23° using tetramethylsilane as an internal standard. The following abbreviations are used: d=doublet, d-d=doublet-of-doublets, d-m=doubt-of-multiplets, m=multiplet, s=singlet, sh=shoulder, t=triplet.

1-(3,4-Dimethoxyphenethyl)-3-butylpyridinium Bromide (3c)—A solution of 3-butylpyridine (1c)¹⁷⁾ (5.21 g, 38.5 mmol) and 3,4-dimethoxyphenethyl bromide (2) (8.58 g, 35 mmol) in DMF (35 ml) was heated at 100° for 18 hr. The solvent was evaporated *in vacuo* to leave a dark reddish, viscous oil, which was dissolved in H₂O (50 ml). The aq. solution was washed with three 20-ml portions of benzene, treated with

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charcoal, and evaporated to dryness *in vacuo*, leaving a yellow sirup (3c). The crude quaternary salt was directly used in the next oxidation reaction without further purification.

1-(3,4-Dimethoxyphenethyl)-3-isopropylpyridinium Bromide (3d)—A stirred solution of 3-isopropylpyridine (1d)¹⁸ (3.64 g, 30 mmol) and 2 (8.09 g, 33 mmol) in dry benzene (30 ml) was heated at reflux for 48 hr. The oily salt that formed was extracted with H₂O (100 ml). The aq. solution was washed with two 50-ml portions of benzene and then concentrated to dryness *in vacuo* to give crude 3d as a yellowish brown, thick oil, which was directly used in the next oxidation step without further purification.

1-(3,4-Dimethoxyphenethyl)-3-benzylpyridinium Bromide (3e)—A stirred mixture of 3-benzylpyridine (1e)¹⁹ (5.08 g, 30 mmol), 2 (8.09 g, 33 mmol), and dry benzene (40 ml) was refluxed for 48 hr. The precipitate that resulted was collected by filtration, washed with benzene (40 ml), and recrystallized from hexane-EtOH (2:1, v/v) to produce 3e (11.3 g, 89%), mp 154–156°. Further recrystallization from EtOH-ether (1:1, v/v) yielded an analytical sample as almost colorless scales, mp 156.5–158° (dried over P₂O₅ at room temp. and 3 mmHg for 24 hr); UV $\lambda_{\text{max}}^{\text{abs. EtOH}}$ 231 nm (sh) (log ϵ 4.06), 269 (3.78), 275 (3.77). *Anal.* Calcd. for C₂₂H₂₄BrNO₂·1/2H₂O: C, 62.42; H, 5.95; N, 3.31. Found: C, 62.66; H, 5.87; N, 3.55.

1-(3,4-Dimethoxyphenethyl)-3-phenylpyridinium Bromide (3f)—The quaternization of 3-phenylpyridine (1f)²⁰ with 2 was accomplished in a manner similar to that described above for 3d but in toluene instead of benzene. The resulting caramel-like salt was directly used in the next step without further purification.

Ferricyanide Oxidation of the Pyridinium Salts (3)—The oxidation of the quaternary salts (3c–f) was carried out at 32° ± 0.1° for 5 hr according to the previously reported standard procedure.⁵ Isolation of the isomeric pyridones (4 and 5) that formed and determination of the isomer ratios (by column chromatographic analysis) also followed that procedure. In all cases, 2-pyridone 4 was eluted faster than 6-pyridone 5 in the chromatographic analysis.

The results of these oxidation experiments are summarized in Table I, and the physical properties of the pyridones are recorded in the following.

1-(3,4-Dimethoxyphenethyl)-3-butyl-2(1H)-pyridone (4c)—Obtained as a pale yellowish, thick oil, bp 220–240° (bath temp.) (0.15 mmHg); MS *m/e*: 315 (M⁺); NMR (CDCl₃) δ : 0.7–1.10 (3H, unresolved t, CH₂Me), 1.10–1.80 (4H, m, CH₂CH₂Me), 2.56 (2H, dull t, CH₂Pr), 2.97 (2H, t, *J* = 7 Hz, ArCH₂), 3.78 and 3.83 (6H, s each, two MeO's), 4.10 (2H, t, *J* = 7 Hz, NCH₂), 6.60–6.80 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-3-isopropyl-2(1H)-pyridone (4d)—Obtained as a pale yellowish, thick oil, bp 150–152° (0.01 mmHg); MS *m/e*: 301 (M⁺); NMR (CDCl₃) δ : 1.20 (6H, d, *J* = 7 Hz, CHMe₂), 2.98 (2H, t, *J* = 7 Hz, ArCH₂), 3.25 (1H, m, CHMe₂), 3.80 and 3.85 (6H, s each, two MeO's), 4.10 (2H, t, *J* = 7 Hz, NCH₂), 6.55–6.75 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-3-benzyl-2(1H)-pyridone (4e)—Recrystallized from hexane-ether (1:2, v/v) to colorless pillars, mp 57.5–59°; MS *m/e*: 349 (M⁺); NMR (CDCl₃) δ : 3.01 (2H, t, *J* = 7 Hz, ArCH₂), 3.79 and 3.87 (6H, s each, two MeO's), 3.91 (2H, s, C₆H₅CH₂), 4.13 (2H, t, *J* = 7 Hz, NCH₂), 6.60–6.85 (m, aromatic protons), 7.15–7.4 (5H, m, C₆H₅), pyridone-ring protons (Table III); other spectra (Table II). *Anal.* Calcd. for C₂₂H₂₃NO₃: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.58; H, 6.67; N, 3.99.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-2(1H)-pyridone (4f)—A pale yellowish, thick oil, MS *m/e*: 335 (M⁺); NMR (CDCl₃) δ : 3.01 (2H, t, *J* = 7 Hz, ArCH₂), 3.78 and 3.81 (6H, s each, two MeO's), 4.14 (2H, t, *J* = 7 Hz, NCH₂), 6.52–6.78 (3H, m, aromatic protons), 7.1–7.8 (m, C₆H₅), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-5-butyl-2(1H)-pyridone (5c)—A pale yellowish, thick oil, bp 230–240° (bath temp.) (0.01 mmHg); MS *m/e*: 315 (M⁺); NMR (CDCl₃) δ : 0.65–1.0 (3H, unresolved t, CH₂Me), 1.0–1.75 (4H, m, CH₂CH₂Me), 2.21 (2H, dull t, CH₂Pr), 2.98 (2H, t, *J* = 7 Hz, ArCH₂), 3.78 and 3.83 (6H, s each, two MeO's), 4.08 (2H, t, *J* = 7 Hz, NCH₂), 6.55–6.95 (m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-5-isopropyl-2(1H)-pyridone (5d)—A pale yellowish, thick oil, bp 158–160° (0.03 mmHg); MS *m/e*: 301 (M⁺); NMR (CDCl₃) δ : 1.04 (6H, d, *J* = 7 Hz, CHMe₂), 2.50 (1H, m, CHMe₂), 2.99 (2H, t, *J* = 7 Hz, ArCH₂), 3.80 and 3.86 (6H, s each, two MeO's), 4.08 (2H, t, *J* = 7 Hz, NCH₂), 6.46–6.88 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-5-benzyl-2(1H)-pyridone (5e)—Crystallized from hexane-AcOEt (1:1, v/v) in colorless prisms, mp 95–96°; MS *m/e*: 349 (M⁺); NMR (CDCl₃) δ : 3.00 (2H, t, *J* = 7 Hz, ArCH₂), 3.56 (2H, s, C₆H₅CH₂), 3.77 and 3.87 (6H, s each, two MeO's), 4.09 (2H, t, *J* = 7 Hz, NCH₂), 6.45–6.85 (m, aromatic protons), 6.9–7.4 (5H, m, C₆H₅), pyridone-ring protons (Table III); other spectra (Table II). *Anal.* Calcd. for C₂₂H₂₃NO₃: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.74; H, 6.53; N, 3.97.

1-(3,4-Dimethoxyphenethyl)-5-phenyl-2(1H)-pyridone (5f)—Recrystallized from hexane-AcOEt (1:1, v/v) to colorless pillars, mp 99–100°; MS *m/e*: 335 (M⁺); NMR (CDCl₃) δ : 3.06 (2H, t, *J* = 7 Hz, ArCH₂),

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3.82 and 3.86 (6H, s each, two MeO's), 4.22 (2H, t, $J=7$ Hz, NCH_2), 6.50—6.94 (m, aromatic protons), 6.94—7.43 (m, C_6H_5), pyridone-ring protons (Table III); other spectra (Table II). *Anal.* Calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.39; H, 6.36; N, 4.21.

1-(3,4-Dimethoxyphenethyl)-5-benzoyl-2(1H)-pyridone (5g)—In the column chromatographic separation of the products from the oxidation of **3e**, compound **5g** was isolated from middle fractions and recrystallized from hexane-AcOEt (1:1, v/v) to give pale yellowish prisms, mp 156—157° (lit.¹⁰) mp 154.5—156°; MS m/e : 363 (M^+); IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 1662 and 1632 (CO's); UV $\lambda_{\text{max}}^{\text{abs. EtOH}}$ 231 nm (sh) ($\log \epsilon$ 4.14), 250 (sh) (3.99), 288 (4.27); NMR (CDCl_3) δ : 3.05 (2H, t, $J=7$ Hz, ArCH_2), 3.81 and 3.87 (6H, s each, two MeO's) 4.14 (2H, t, $J=7$ Hz, NCH_2), 6.55—6.9 (3H, m, aromatic protons), 7.2—7.6 (5H, m, $\text{C}_6\text{H}_5\text{CO}$), pyridone-ring protons (Table III). *Anal.* Calcd. for $\text{C}_{22}\text{H}_{21}\text{NO}_4$: C, 72.71; H, 5.82; N, 3.85. Found: C, 72.76; H, 5.71; N, 3.90.

Stability of 4e and 5e toward Alkaline Ferricyanide Oxidation—The benzyl pyridones (**4e** and **5e**) (349 mg, 1 mmol) were separately dissolved in benzene (4 ml). To each solution were added a solution of $\text{K}_3\text{Fe}(\text{CN})_6$ (1.96 g, 6 mmol) in H_2O (5 ml) and a solution of KOH (0.9 g, 16 mmol) in H_2O (4 ml). The mixture was stirred at 32° for 20 hr in a thermoregulated constant temperature bath (accurate to $\pm 0.1^\circ$). No change of the pyridone in the benzene solution was shown by a single spot on a TLC plate. The benzene solution was separated and the aq. solution was extracted with four 5-ml portions of benzene. The combined benzene extracts were dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*, leaving the starting material. The recovery of each pyridone was 95—96%.

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