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Lactams. X.[1] The Alkaline Ferricyanide Oxidation of 3-Substituted 1-(3,4-Dimethoxyphenethyl)pyridinium Salts: Effects of Functional Substituents[2]

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In the alkaline ferricyanide oxidation at 32° of 3-substituted 1-(3,4-dimethoxyphenethyl)pyridinium bromides (type **3**), the hydroxymethyl, N,N-dimethylaminomethyl, carbamoyl, and 1,1-ethylenedithioethyl groups at the 3-position have been found to orient the oxidation to both the 2- (type **4**) and the 6-position (type **5**) in ratios of 70: 30, 26: 74, 50: 50, and 4: 96. The carboxyl or 1,1-ethylenedioxyethyl group at the 3-position has oriented the oxidation to the 6-position exclusively, and possible factors in determining the regioselectivity in the ferricyanide oxidation of the 1,3-disubstituted pyridinium salts are discussed. For preparation of additional pyridone derivatives, 1-(3,4-dimethoxyphenethyl)-5-carboxy-2(1*H*)-pyridone (**5d**) was esterified with methanolic hydrogen chloride to the methyl ester (**5h**), and 1-(3,4-dimethoxyphenethyl)-5-(1,1-ethylenedioxyethyl)-2(1*H*)-pyridone (**5e**) was converted into the methyl ketone (**5i**) by acid hydrolysis. The structures of the pyridones (**4a,b,c,f, 5a—i**) thus prepared have been assigned on the basis of their ultraviolet, infrared, and nuclear magnetic resonance spectra.

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

The alkaline ferricyanide oxidation of pyridinium salts[4] constitutes one of the useful and efficient methods of generating 6-membered lactams through α-pyridones.[1,5] Although much is known about the effects of 3-substituents in the pyridine ring upon orientation of this oxidation,[6] only a relatively small amount of the recorded knowledge[5c,7] deals with quantitative analyses to determine the isomer ratios in those cases where a mixture of products (types **4** and **5**)[8] is obtained. This paucity of information is largely due to the lack of a simple and convenient analytical method for the determination of these isomeric pyridones. During investigations into the synthesis of benzo[*a*]quinolizidine alkaloids, we have devoted some attention to quantitative analytical work on the alkaline ferricyanide oxidation of 3-substituted 1-(3,4-dimethoxyphenethyl)pyridinium bromides (type **3**). Previous papers[5c,7d,e] in this series reported the effects of various hydrocarbon substituents observed

1) Paper IX in this series, T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **25**, 2336 (1977).
2) Presented in part at the 8th Congress of Heterocyclic Chemistry, Kyoto, October 23, 1975.
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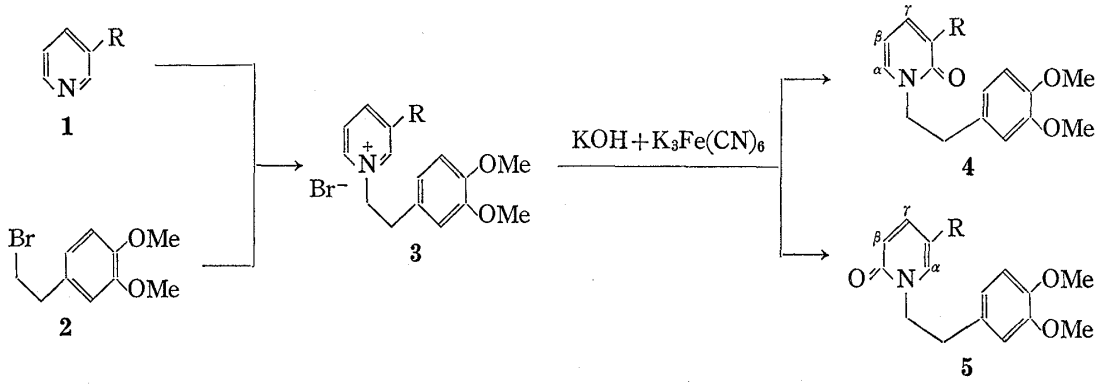
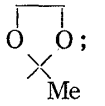
4) *a*) H. Decker, *Ber. Dtsch. Chem. Ges.*, **25**, 443 (1892); *b*) *Idem*, *J. Prakt. Chem.* [2], **47**, 28 (1893).
5) See, for example, *a*) T. Fujii and S. Yoshifuji, *Tetrahedron*, **26**, 5953 (1970); *b*) T. Fujii, S. Yoshifuji, and A. Tamai, *Chem. Pharm. Bull.* (Tokyo), **19**, 369 (1971); *c*) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *ibid.*, **21**, 2695 (1973).
6) See, for example, ref. 7 in ref. 5*c*.
7) *a*) H. Möhrle and H. Weber, *Tetrahedron*, **26**, 2953 (1970); *b*) *Idem*, *Chem. Ber.*, **104**, 1478 (1971); *c*) R.A. Abramovitch and A.R. Vinutha, *J. Chem. Soc.* (B), **1971**, 131; *d*) T. Fujii, S. Yoshifuji, K. Yoshida, M. Ohba, S. Ikegami, and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **23**, 993 (1975); *e*) T. Fujii, K. Yoshida, M. Ohba, M. Mitsukuchi, I. Tanaka, S. Yoshifuji, and M. Kirisawa, *ibid.*, **25**, 2072 (1977).
8) A γ-pyridone has also been obtained in a certain case.[7c]

in that study and the present paper describes the effects of several functional groups at the 3-position.

The pyridinium salts (**3**) selected for the present work were those which carry the hydroxymethyl, N,N-dimethylaminomethyl, carbamoyl, carboxyl, 1,1-ethylenedioxyethyl, or 1,1-ethylenedithioethyl group at the 3-position, and they were prepared from the appropriate pyridine bases (**1**) by quaternization with 3,4-dimethoxyphenethyl bromide (**2**) in boiling benzene or hot N,N-dimethylformamide (DMF) solution. By analogy with the monoquaternization of nicotine reported by Sugasawa and Tatsuno,[9] the N,N-dimethylaminomethyl derivative (**3b**·HCl) was obtained from the monohydrochloride of **1b**. The 3-carboxy derivative (**3d**) was derived from the methoxycarbonyl derivative (**3h**) by alkaline hydrolysis.



a, R=CH_2OH; **b**, R=$CH_2N(Me)_2$; **c**, R=$CONH_2$; **d**, R=CO_2H; **e**, R=  ;

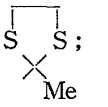
f, R=  ; **g**, R=CHO; **h**, R=CO_2Me; **i**, R=COMe

Chart 1

For uniformity and comparison with earlier data, all the alkaline ferricyanide oxidations (32°±0.1°, 5 hr) of the quaternary salts (**3a—f**) were effected according to the previously reported standard procedure,[5c] and the quantitative analytical work to determine the isomer

Table I. The Ferricyanide Oxidation of 3-Substituted Pyridinium Salts

Pyridinium salt		Product[a]		
No.	R	Combined yield (%)	% 2-Pyridone (4)	% 6-Pyridone (5)
3a	CH_2OH	80[b]	70 (**4a**)	30 (**5a, 5g**)
3b	CH_2NMe_2	50[c]	26 (**4b**)	74 (**5b**)
3c	$CONH_2$	47	50 (**4c**)	50 (**5c**)
		70[d]	43 (**4c**)[d]	57 (**5c**)[d]
3d	CO_2H	64[e]	0 (**4d**)	100 (**5d**)
3e	$C(OCH_2CH_2O)Me$	68	0 (**4e**)	100 (**5e**)
3f	$C(SCH_2CH_2S)Me$	76[f]	4 (**4f**)	96 (**5f**)

a) All isomer ratios were determined by chromatographic analysis as reported previously.[5c]
b) The yield of **5g** was 8%.
c) Based on the pyridine base (**1b**) used in the preceding quaternization.
d) From slightly modified experiments in which the reaction mixture was covered with AcOEt instead of benzene during the reaction.
e) Based on the pyridinium salt (**3h**) used in the preceding alkaline hydrolysis.
f) Based on the pyridine base (**1f**) employed in the foregoing quaternization.

9) S. Sugasawa and T. Tatsuno, *Yakugaku Zasshi*, **72**, 248 (1952). For an unusual example of competitive nitrogen alkylation, see J. I. Seeman and J. F. Whidby, *J. Org. Chem.*, **41**, 3824 (1976).

ratio of the resulting pyridones (**4** and **5**) also followed that procedure. Table I summarizes the results. The assignment of individual structures to the isomeric pyridones thus obtained was based on the spectral data assembled in Tables II and III. It has been known[5c,7b,d,e] that 1,3-dialkyl-2-pyridones can be distinguished from the corresponding 6-pyridone isomers by a hypsochromic shift in the long-wavelength ultraviolet spectra (UV) absorption band (at 300—315 nm) by *ca.* 10 nm. By analogy the isomeric pyridones with no extra conjugation (**4a, b, f, 5a, b, f**) were differentiated as shown in Table II. The differentiation between the isomers with extended conjugation (**4c, 5c**) and the assignment of the 6-pyridone structure

Table II. Ultraviolet and Infrared Spectra of Pyridones

Compound	UV spectrum[a]						IR spectrum[b]
	Short-wavelength band		Medium-wavelength band		Long-wavelength band		
	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	$\nu_{C=O}$ (cm^{-1})
2-Pyridones							
4a	231	14.0	287	6.92	304	6.69	1649
4b	231	13.1	287	6.08	309	6.57	1649
4c	230.5	13.6	281	3.61	332	9.65	1671—1682[c]
4f	231.5	12.5	287	6.77	312.5	8.37	1644
6-Pyridones							
5a	232	17.4	287	5.71	311	6.01	1666
5b	232	15.4	287	4.74	312	4.90	1666
5c	228	12.8	261	15.7	305[d]	5.25	1658—1688[c]
5d	231	10.5	262	16.4	307[d]	5.26	1643[e]
5e	232	16.3	287	5.61	309	5.80	1666
5f	234	19.6	281.5	4.56	313.5	4.90	1662
			286	4.53			
5g	230[d]	9.80	280	21.4	—	—	1663

a) Measured in abs. EtOH.
b) Determined in $CHCl_3$ solution at 0.2 M concentration.
c) Overlapped with the carbamoyl CO stretching vibration band.
d) Shoulder.
e) Determined in Nujol mull because of the poor solubility of **5d** in $CHCl_3$.

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	6.91 (d-d)	6.06 (t)	7.31 (d-m)[b]	6.7	2.0	6.7
4b	6.90 (d-d)	6.04 (t)	7.37 (d-m)[b]	6.8	2.0	6.8
4c	7.08 (d-d)	6.20 (t)	8.46 (d-d)	6.8	2.2	6.8
4f	6.90 (d-d)	5.97 (t)	7.85 (d-d)	6.8	2.0	6.8
6-Pyridones						
5a	7.00 (d)	6.60 (d)	7.40 (d-d)	—	2.6	9.2
5b	6.76 (d)	6.56 (d)	7.30 (d-d)	—	2.5	9.0
5c	7.95 (d)	6.58 (d)	7.77 (d-d)	—	2.5	9.3
5d[c]	8.28 (d)	6.45 (d)	7.79 (d-d)	—	2.6	9.3
5e	6.84 (d)	6.53 (d)	7.32 (d-d)	—	2.6	9.2
5f	6.99 (d)	6.54 (d)	7.58 (d-d)	—	2.6	9.5
5g	7.47 (d)	6.63 (d)	7.80 (d-d)	—	2.5	9.5

a) Measured on 5% (w/v) $CDCl_3$ solution. The letter in parentheses designates the multiplicity or shape of the signal with the abbreviations appeared at the top of Experimental part.
b) The multiplicity of the signal is most probably due to long-range coupling between H_γ and the side-chain $C_{(\alpha)}$-protons.[5c,7d]
c) Measured on 3% (w/v) Me_2SO-d_6 solution.

to **5d** were also based on the previous observation[7b,e] that 2-pyridones of this type display the long-wavelength band in a longer wavelength region than do the corresponding 6-pyridones. In addition, the differences in the CO stretching vibration band position included in Table II also served as good criterion[5c,7b,d,e] for distinguishing between both isomers except for the cases of **5d** and a pair of **4c** and **5c** where no solution IR spectrum was available or the identification of the pyridone CO band was hampered by the presence of the carbamoyl CO band. The most conclusive evidence for the assigned pyridone structures was finally provided by the splitting patterns of pyridone-ring proton resonances, as shown in Table III, which were in general agreement with our previous experience.[5c,7d,e] In all cases where two isomers were obtained, the 2-pyridone isomer (**4**) had a higher *Rf* value than did the 6-pyridone isomer (**5**) on an alumina thin-layer chromatography (TLC) plate. This chromatographic behavior was also consistent with that[5c,7e] observed for a pair of pyridone isomers carrying a hydrocarbon substituent at the 3-position. For preparation of additional pyridone derivatives, **5d** was esterified with methanolic hydrogen chloride to the methyl ester (**5h**), and **5e** was converted into the methyl ketone (**5i**) by acid hydrolysis.

It may be seen from Table I that in the alkaline ferricyanide oxidation of the quaternary pyridinium bromides (**3d**, **3e**), which carry the carboxyl or a cyclically ketalized acetyl group at the 3-position, the oxidation at the 6-position was favored exclusively over that at the 2-position. This regioselectivity was in general agreement with that[5b,7b,10,11] observed previously for a similar oxidation of analogous quaternary salts. The 1,1-ethylenedithioethyl group as in **3f** oriented the oxidation to the 6-position predominantly over the 2-position, but not so exclusively as reported[11] for a similar oxidation of 1-methyl-3-(1,1-ethylenedithioethyl)pyridinium salt. In the case of **3c**, the formation of an approximately 1:1 mixture of both isomeric pyridones (**4c**, **5c**) paralleled the previously reported results[12] with 1-methyl-3-carbamoylpyridinium iodide. The N,N-dimethylaminomethyl group at the 3-position as in **3b** exerted an increased regioselectivity, favoring the 6-oxidation over the 2-oxidation in a

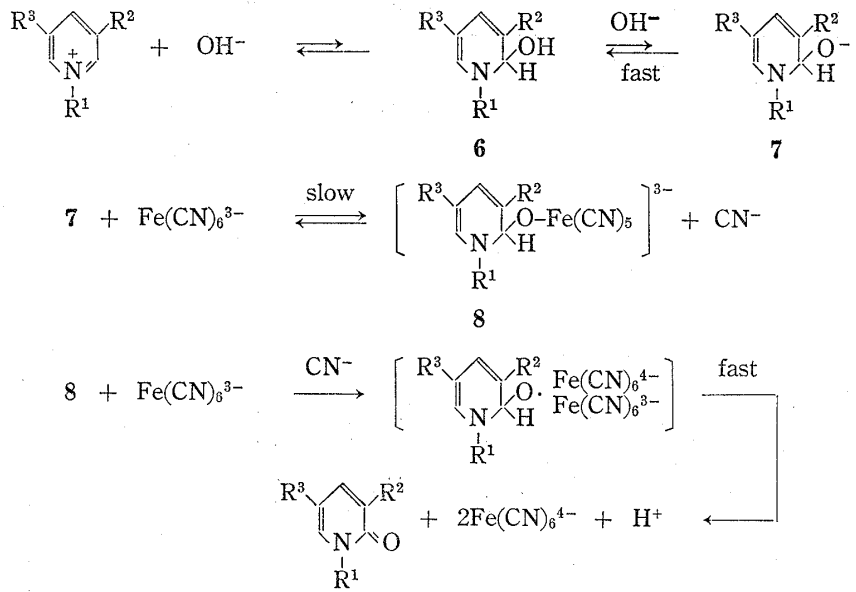


Chart 2

10) *a*) H.L. Bradlow and C.A. Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951); *b*) S. Sugasawa, K. Sakurai, and T. Okayama, *Yakugaku Zasshi*, **62**, 77 (1942); *c*) S. Sugasawa, S. Akahoshi, S. Toda, and H. Tomisawa, *ibid.*, **72**, 192 (1952); *d*) A.G. Anderson, Jr. and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958); *e*) M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **7**, 35 (1959).

11) S. Sugasawa and M. Kirisawa, *Pharm. Bull.* (Japan), **3**, 190 (1955).

12) *a*) M.E. Pullman and S.P. Colowick, *J. Biol. Chem.*, **206**, 121 (1954); *b*) R.F. Dawson, D.R.Christman, A. D'Adamo, M.L. Solt, and A.P. Wolf, *J. Am. Chem. Soc.*, **82**, 2628 (1960).

ratio of 74: 26. In the oxidation of **3a**, the 2-pyridone (**4a**) and a mixture of the 6-pyridones (**5a**, **5g**) were obtained in the ratio 70: 30. We have noticed that both the 2- (**4a**) and the 6-pyridone (**5a**) are unstable under these ferricyanide oxidation conditions, but the latter is more unstable than the former, producing **5g** and other unidentified products. Accordingly, the actual regioselectivity with the hydroxymethyl group may be somewhat lower than that recorded.

Abramovitch and Vinutha[7c] have suggested that the alkaline ferricyanide oxidation of a pyridinium salt undergoes through the complex (**8**) formed from the first one molecule of potassium ferricyanide and the alkoxide (**7**) produced from the corresponding pseudo-base (**6**) (see Chart 2) and that the formation of the complex (**8**) is rate-determining. On the basis of this mechanism, the regioselectivity with some 3-substituents observed by them[7c] and that observed previously by us with various hydrocarbon substituents[7e] have been best interpreted in terms of the balance of the three effects, namely, attractive dispersion force, steric hindrance, and electrostatic repulsion, which would be operative between the 3-substituent (R^2) and the ferricyanide ion in the rate-determining step.

If the same mechanism is operative in our present cases, the results summarized in Table I may be explained as follows. The 3-methyl group has been known to orient the ferricyanide oxidation to the 2- and the 6-position in a ratio of 94: 6.[5c] Therefore, the increase of the extent of the 6-oxidation observed for **3a** and **3b** may be due to an enhancement of steric hindrance and electrostatic repulsion (operating between the 3-substituent and the ferricyanide ion), which would have been caused by introduction of the bulky and electronegative hydroxyl or dimethylamino group into the methyl group. Möhrle and Sieker[13] have recently reported that N-methylnicotinium iodide is oxidized with ferricyanide to give a 15: 85 mixture of the corresponding 2- and 6-pyridones.[14,15] This increased regioselectivity would be due to an additional steric requirement caused by chain branching.

On the other hand, the absence of attack at $C_{(2)}$ in the oxidation of **3d** suggests steric hindrance to the approach of the bulky ferricyanide ion to this position and electrostatic repulsion between the negatively charged ion and the carboxyl group that existed as the carboxylate ion during the oxidation. While both effects would also have been present with the 3-carbamoyl group, this substituent is about the same in size and would have a smaller electrostatic influence. This would account for the *ca.* 1: 1 ratio of the 2- (**4c**) to the 6-pyridone (**5c**) with **3c**. A similar steric hindrance and electrostatic repulsion explanation would be applicable to the results obtained with **3e** and **3f**, which carry a highly branched 3-substituent with electronegative hetero atoms.

In conclusion, our present and earlier studies have provided quantitative data on the orienting effect of various 3-substituents in the ferricyanide oxidation of 3-substituted 1-(3,4-dimethoxyphenethyl)pyridinium bromides (type **3**). It is hoped that these results will help towards the generation of synthetic plans for 1,3- or 1,5-disubstituted 2-pyridones and the corresponding piperidones and for the benzo[*a*]quinolizidine system with a variety of substituents at the 1- or 3-position.

Experimental

All melting points are corrected; boiling points, uncorrected. Infrared (IR) spectra were measured in Nujol mulls or in $CHCl_3$ solutions at 0.2 M concentration. See also ref. 7*e* for details of instrumentation

13) H. Möhrle and K. Sieker, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **309**, 197 (1976).
14) In their earlier semi-quantitative work on the ferricyanide oxidation of N-(2-arylethyl)nicotinium salts, Sugasawa and Tatsuno[9] have isolated but the 6-pyridone derivatives (type **5**), which might not have been so pure isomerically as reported.
15) For results of the ferricyanide oxidation of the methiodide salts of cotinine and N′-acetylanabasine, see H. Möhrle and K. Sieker, *Pharmazie*, **31**, 540 (1976).

and measurement. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, d-m=doublet-of-multiplets, m=multiplet, s=singlet, sh=shoulder, t=triplet.

1-(3,4-Dimethoxyphenethyl)-3-hydroxymethylpyridinium Bromide (3a)——A stirred solution of 3-pyridinemethanol (**1a**) (3.27 g, 30 mmol) and 3,4-dimethoxyphenethyl bromide (**2**) (8.09 g, 33 mmol) in dry benzene (40 ml) was refluxed for 24 hr. The precipitate that resulted was collected by filtration and washed with benzene (40 ml) to give a first crop. The combined filtrate and washings were concentrated to a small volume (*ca.* 25 ml) and the resulting solution was refluxed with stirring for 6 hr to give a colorless precipitate, which was isolated as described for the first crop. The first and the second crop were combined and recrystallized from EtOH–acetone (1: 1, v/v) to produce **3a** (9.44 g, 89%) as pale yellowish prisms, mp 164—165°; UV $\lambda_{max}^{abs.EtOH}$ 270 nm (ε 5950). *Anal.* Calcd. for $C_{16}H_{20}BrNO_3$: C, 54.25; H, 5.69; N, 3.95. Found: C, 54.18; H, 5.60; N, 3.93.

1-(3,4-Dimethoxyphenethyl)-3-(N,N-dimethylaminomethyl)pyridinium Bromide (3b)——3-(N,N-Dimethylaminomethyl)pyridine (**1b**)[16] (2.04 g, 15 mmol) was dissolved in 10% ethanolic hydrogen chloride (30 ml) and the solution was evaporated to dryness *in vacuo*. To the residue was added abs. EtOH (40 ml) and the mixture was again evaporated to dryness *in vacuo*. This cycle was repeated five times. The resulting colorless solid and an additional amount (2.04 g, 15 mmol) of **1b** were dissolved in abs. EtOH (40 ml), and the homogeneous solution was evaporated to dryness *in vacuo*, leaving the monohydrochloride of **1b** as a colorless solid, mp 179—182°. The total amount of **1b**·HCl and **2** (8.09 g, 33 mmol) were heated in DMF (50 ml) at 115—120° (bath temp.) for 28 hr, and the solvent was removed by vacuum distillation. The residual brownish thick oil was washed with four 30-ml portions of ether and dissolved in a mixture of 2 N aq. NaOH (16 ml) and H_2O (10 ml). The aqueous solution was then washed with five 20-ml portions of benzene and neutralized with 10% aq. HCl (*ca.* 2 ml). After addition of H_2O (17 ml), the brownish solution was directly used in the ferricyanide oxidation described below.

1-(3,4-Dimethoxyphenethyl)-3-carbamoylpyridinium Bromide (3c)——A solution of nicotinamide (**1c**) (9.77 g, 80 mmol) and **2** (21.6 g, 88.1 mmol) in DMF (80 ml) was stirred at 80° (bath temp.) for 24 hr. The solvent was removed by vacuum distillation and the residual solid was washed with ether to give crude **3c** (21.0 g, 72%), mp 205—210°. Recrystallization from 95% aq. EtOH provided an analytical sample as yellowish scales, mp 213—214°; UV $\lambda_{max}^{abs.EtOH}$ 269.5 nm (ε 5620); IR ν_{max}^{Nujol} cm^{-1}: 3265, 3110 (NH_2), 1697 ($CONH_2$). *Anal.* Calcd. for $C_{16}H_{19}BrN_2O_3$: C, 52.33; H, 5.22; N, 7.63. Found: C, 52.06; H, 5.25; N, 7.57.

1-(3,4-Dimethoxyphenethyl)-3-carboxypyridinium Bromide (3d)——A solution of the methyl ester (**3h**) (2.29 g, 6 mmol) in 2 N aq. NaOH (12 ml) was stirred at 50—55° (bath temp.) for 2 hr. After acidification with 10% aq. HCl, the solution was evaporated *in vacuo*, and H_2O (10 ml) was added to the residue. The resulting solution was again evaporated to dryness *in vacuo* to leave an orange solid, which showed no ester CO stretching vibration band in its IR spectrum. The solid was used directly in the next oxidation step without further purification.

1-(3,4-Dimethoxyphenethyl)-3-(1,1-ethylenedioxyethyl)pyridinium Bromide (3e)——A stirred solution of 3-(1,1-ethylenedioxyethyl)pyridine (**1e**)[11] (13.2 g, 80 mmol) and **2** (21.6 g, 88.1 mmol) in dry benzene (100 ml) was refluxed for 24 hr. The oily salt that formed was separated from the benzene solution by decantation and dissolved in H_2O (100 ml). After having been washed with benzene, the aqueous solution was evaporated under diminished pressure to leave an orange, glassy substance (**3e**) (16.8 g, 51%). The benzene solution from the decantation and the benzene washings described above were combined and heated at reflux for 60 hr. From this reaction mixture was obtained a second crop (6.72 g, 20%). The first and the second crop were combined and used directly in the next oxidation reaction without further purification.

1-(3,4-Dimethoxyphenethyl)-3-(1,1-ethylenedithioethyl)pyridinium Bromide (3f)——3-(1,1-Ethylenedithioethyl)pyridine (**1f**)[11] was allowed to react with **2** in a manner similar to that described above for **3e**, and crude **3f** was obtained as a light orange, thick oil (88% yield), which was directly used in the ferricyanide oxidation without further purification.

1-(3,4-Dimethoxyphenethyl)-3-methoxycarbonylpyridinium Bromide (3h)——Methyl nicotinate (**1h**) and **2** were allowed to react as described above for **3a**, giving crude **3h**, mp 186—189° (dec.), in 95% yield. Recrystallization from MeOH furnished an analytical sample as pale yellowish granules, mp 190—192° (dec.); UV $\lambda_{max}^{abs.EtOH}$ 269 nm (ε 5590); IR ν_{max}^{Nujol} 1745 cm^{-1} (ester CO). *Anal.* Calcd. for $C_{17}H_{20}BrNO_4$: C, 53.42; H, 5.27; N, 3.66. Found: C, 53.38; H, 5.18; N, 3.55.

The Alkaline Ferricyanide Oxidation of the Pyridinium Salts (3a—f)——The oxidations of the quaternary salts (**3a—f**) were carried out at 32°±0.1° for 5 hr according to the previously reported procedure.[5c] Unless otherwise stated, isolation of the pyridones (**4** and/or **5**) that formed and determination of the isomer ratios (by chromatographic analysis) also followed that procedure. For isolation of **4a**, **5a**, and **5g**, the products were extracted successively with benzene and AcOEt, and the extracts were chromatographed on a silica gel column using $CHCl_3$–EtOH (20: 1, v/v) as eluent. For the chromatographic separation of **4b** and **5b**, alumina and ether–EtOH (30: 1, v/v) were used. In the oxidation of **3c**, the products were extracted successively with benzene and AcOEt and chromatographed on alumina using AcOEt or AcOEt–EtOH (25: 1, v/v) as

16) H. Erdtman, F. Haglid, I. Wellings, and U. S. von Euler, *Acta Chem. Scand.*, **17**, 1717 (1963).

eluent. In all cases where both isomeric pyridones were obtained, the 2-pyridone (type **4**) was eluted faster than the 6-pyridone (type **5**) in the chromatographic analysis.

The results of these oxidation experiments are assembled in Table I, and the pyridones isolated were characterized as follows.

1-(3,4-Dimethoxyphenethyl)-3-hydroxymethyl-2(1*H*)-pyridone (4a)——Recrystallized from AcOEt to slightly yellowish plates, mp 108—110.5°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1649 (pyridone CO); UV (Table II); NMR ($CDCl_3$) δ: 3.02 (2H, t, J=7.2 Hz, $ArC\underline{H}_2$), 3.44 (1H, b, OH), 3.84 and 3.88 (3H each, s, two MeO's), 4.16 (2H, t, J=7.2 Hz, NCH_2), 4.61 (2H, s, $C\underline{H}_2OH$), 6.6—6.9 (3H, m, aromatic protons), pyridone-ring protons (Table III). *Anal.* Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.38; H, 6.45; N, 4.73.

1-(3,4-Dimethoxyphenethyl)-3-(N,N-dimethylaminomethyl)-2(1*H*)-pyridone (4b)——Obtained as a faintly yellowish, thick oil, MS *m/e*: 316 (M^+); NMR ($CDCl_3$) δ: 2.30 (6H, s, NMe_2), 3.00 (2H, t, J=7.5 Hz, $ArC\underline{H}_2$), 3.42 (2H, s, $C\underline{H}_2NMe_2$), 3.81 and 3.85 (3H each, s, two MeO's), 4.13 (2H, t, J=7.5 Hz, $ArCH_2C\underline{H}_2$), 6.6—6.85 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-3-carbamoyl-2(1*H*)-pyridone (4c)——Crystallized from H_2O–EtOH (4: 1, v/v) in colorless prisms, mp 152—153°; MS *m/e*: 302 (M^+); NMR ($CDCl_3$) δ: 3.04 (2H, t, J=6.6 Hz, $ArC\underline{H}_2$), 3.80 and 3.87 (3H each, s, two MeO's), 4.22 (2H, t, J=6.6 Hz, NCH_2), 6.15 and 9.45 (1H each, b, $CONH_2$).[17] 6.55—6.85 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II); solubility: 150 mg/100 ml benzene at 32°, 347 mg/100 ml AcOEt at 32°. *Anal.* Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.32; H, 5.87; N, 9.28.

1-(3,4-Dimethoxyphenethyl)-3-(1,1-ethylenedithioethyl)-2(1*H*)-pyridone (4f)——Recrystallized from hexane–benzene (3: 1, v/v) to slightly yellowish prisms, mp 97—98°; MS *m/e*: 377 (M^+); NMR ($CDCl_3$) δ: 2.17 (3H, s, CMe), 3.00—3.55 (4H, m, $SC\underline{H}_2C\underline{H}_2S$), 3.02 (2H, t, J=7.2 Hz, $ArC\underline{H}_2$), 3.78 and 3.83 (3H each, s, two MeO's), 4.13 (2H, t, J=7.2 Hz, NCH_2), 6.55—6.85 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II). *Anal.* Calcd. for $C_{19}H_{23}NO_3S_2$: C, 60.45; H, 6.14; N, 3.71. Found: C, 60.69; H, 6.10; N, 3.59.

1-(3,4-Dimethoxyphenethyl)-5-hydroxymethyl-2(1*H*)-pyridone (5a)——Recrystallized from AcOEt to colorless needles, mp 125—126°; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1666 (pyridone CO); UV (Table II); NMR ($CDCl_3$) δ: 2.60 (1H, b, OH), 3.00 (2H, t, J=7.5 Hz, $ArC\underline{H}_2$), 3.86 and 3.90 (3H each, s, two MeO's), 4.13 (2H, t, J=7.5 Hz, NCH_2), 4.38 (2H, s, $C\underline{H}_2OH$), 6.68—6.90 (3H, m, aromatic protons), pyridone-ring protons (Table III). *Anal.* Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.84; H, 6.63; N, 4.67.

1-(3,4-Dimethoxyphenethyl)-5-(N,N-dimethylaminomethyl)-2(1*H*)-pyridone (5b)——An almost colorless oil, MS *m/e*: 316 (M^+); NMR ($CDCl_3$) δ: 2.11 (6H, s, NMe_2), 3.02 (2H, s, $C\underline{H}_2NMe_2$), 3.02 (2H, t, J=7 Hz, $ArCH_2$), 3.82 and 3.85 (3H each, s, two MeO's), 4.11 (2H, t, J=7 Hz, NCH_2), 6.6—6.85 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-5-carbamoyl-2(1*H*)-pyridone (5c)——Crystallized from AcOEt in colorless needles, mp 154—155°; MS *m/e*: 302 (M^+); NMR ($CDCl_3$) δ: 3.05 (2H, t, J=7.2 Hz, $ArC\underline{H}_2$), 3.88 and 3.91 (3H each, s, two MeO's), 4.22 (2H, t, J=7.2 Hz, NCH_2), 6.35 (2H, b, $CONH_2$), 6.7—6.95 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II); solubility: 15.7 mg/100 ml benzene at 32°, 247 mg/100 ml AcOEt at 32°. *Anal.* Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.49; H, 5.98; N, 9.01.

1-(3,4-Dimethoxyphenethyl)-5-carboxy-2(1*H*)-pyridone (5d)——The ferricyanide oxidation of **3d** (6 mmol) was carried out according to the previously described procedure,[5c] but without covering the reaction mixture with benzene during the oxidation. The pH of the resulting mixture was adjusted to *ca.* 3 with conc. aq. HCl and the brownish yellow precipitate that deposited was collected by filtration, washed with H_2O (20 ml) and dried to give crude **5d** (1.36 g), shown to be homogeneous on a thin-layer chromatography plate. The filtrate and the washings were combined and extracted with AcOEt by using a Soxhlet extractor. After having been dried over anhyd. Na_2SO_4, the AcOEt solution was evaporated to dryness *in vacuo* to leave a second crop. Recrystallization of the crude sample from 90% aq. EtOH (charcoal) gave colorless prisms, mp 207—208.5° (lit. mp 204—206°,[10e] mp 207.5—209°[18]); NMR (Me_2SO-d_6) δ: 2.89 (2H, t, J=7.2 Hz, $ArC\underline{H}_2$), 3.74 (6H, s, two MeO's), 4.18 (2H, t, J=7.2 Hz, NCH_2), 6.6—7.0 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

1-(3,4-Dimethoxyphenethyl)-5-(1,1-ethylenedioxyethyl)-2(1*H*)-pyridone (5e)——A colorless, thick oil, bp 180—184° (0.01 mmHg): MS *m/e* 345 (M^+); NMR ($CDCl_3$) δ: 1.45 (3H, s, CMe), 3.01 (2H, t, J=6.5 Hz, $ArC\underline{H}_2$), 3.35—4.0 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 3.78 and 3.83 (3H each, s, two MeO's), 4.10 (2H, t, J=6.5 Hz, NCH_2), 6.45—6.85 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II).

17) The observed non-equivalence of the NH_2 protons is probably due to restricted rotation about the central C–N bond in the carbamoyl group. The neighboring pyridone CO group seems to have enhanced such non-equivalence by the formation of intramolecular hydrogen bonding with one of the carbamoyl hydrogens.

18) R. H. Wiley, N. R. Smith, and L. H. Knabeschuh, *J. Am. Chem. Soc.*, **75**, 4482 (1953).

1-(3,4-Dimethoxyphenethyl)-5-(1,1-ethylenedithioethyl)-2(1*H*)-pyridone (5f)——Recrystallized from AcOEt–hexane (1: 1, v/v) to colorless prisms, mp 116—117°; MS *m/e*: 377 (M^+); NMR ($CDCl_3$) δ: 1.84 (3H, s, CMe), 3.00 (2H, t, J=6.5 Hz, $ArC\underline{H}_2$), 2.8—3.5 (4H, m, $SC\underline{H}_2C\underline{H}_2S$), 3.78 and 3.83 (3H each, s, two MeO's), 4.11 (2H, t, J=6.5 Hz, NCH_2), 6.5—6.85 (3H, m, aromatic protons), pyridone-ring protons (Table III); other spectra (Table II). *Anal.* Calcd. for $C_{19}H_{23}NO_3S_2$: C, 60.45; H, 6.14; N, 3.71. Found: C, 60.26; H, 6.09; N, 3.56.

1-(3,4-Dimethoxyphenethyl)-5-formyl-2(1*H*)-pyridone (5g)——In the column chromatographic separation of the products from the oxidation of **3a**, compound **5g** was isolated from first fractions and recrystallized from AcOEt–hexane (1: 1, v/v) to yellowish plates, mp 118—119° (lit.[10e] mp 117—118°); MS *m/e*: 287 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (sh) (CHO), 1663 (pyridone CO); UV (Table II); NMR ($CDCl_3$) δ: 3.06 (2H, t, J=7 Hz, $ArC\underline{H}_2$), 3.82 and 3.86 (3H each, s, two MeO's), 4.21 (2H, t, J=7 Hz, NCH_2), 6.6—6.9 (3H, m, aromatic protons), 9.43 (1H, s, CHO), pyridone-ring protons (Table III). *Anal.* Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.50; H, 5.81; N, 4.60.

1-(3,4-Dimethoxyphenethyl)-5-methoxycarbonyl-2(1*H*)-pyridone (5h)——A suspension of **5d** (303 mg, 1 mmol) in 10% methanolic hydrogen chloride (5 ml) was heated at reflux for 6 hr. The resulting clear solution was evaporated to dryness *in vacuo* to leave a slightly yellowish solid, which was dissolved in $CHCl_3$ (20 ml). The $CHCl_3$ solution was washed successively with sat. aq. $NaHCO_3$ and sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give **5h** as a slightly yellowish solid (308 mg, 97%). Recrystallization from ether–hexane (1: 1, v/v) produced an analytical sample as pale yellowish prisms, mp 88—90.5°; MS *m/e*: 317 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1717 (ester CO), 1664 (pyridone CO); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231 (10200), 265 (17300), 307 (sh) (5260); NMR ($CDCl_3$) δ: 3.02 (2H, t, J=7 Hz, $ArC\underline{H}_2$), 3.83, 3.84, and 3.86 (3H each, s, three MeO's), 4.17 (2H, t, J=7 Hz, NCH_2), 6.55—6.9 (3H, m, aromatic protons), 6.54 (1H, d, J=9.5 Hz, H_β), 7.81 (1H, d-d, J=9.5 and 2.5 Hz, H_γ), 7.86 (1H, overlapped with part of the H_γ signal, H_α). *Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.34; H, 6.09; N, 4.66.

1-(3,4-Dimethoxyphenethyl)-5-acetyl-2(1*H*)-pyridone (5i)——A mixture of **5e** (691 mg, 2 mmol), EtOH (10 ml), and 10% aq. HCl (1.5 ml) was refluxed for 1.5 hr. The solvent was removed by vacuum distillation and H_2O (5 ml) was added to the residue. The aqueous solution was made basic with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving a pale yellowish, thick oil (588 mg, 98%), which solidified on trituration with ether. Recrystallization from hexane–AcOEt (2: 1, v/v) furnished **5i** as colorless prisms, mp 90.5—91.5°; MS *m/e*: 301 (M^+); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1689 (sh), 1678 (sh), 1660 (COMe, pyridone CO); UV $\lambda_{max}^{abs.EtOH}$ 278 nm (ε 20100); NMR ($CDCl_3$) δ: 2.24 (3H, s, COMe), 3.01 (2H, t, J=7 Hz, $ArC\underline{H}_2$), 3.80 and 3.84 (3H each, s, two MeO's), 4.18 (2H, t, J=7 Hz, NCH_2), 6.55—6.9 (3H, m, aromatic protons), 6.54 (1H, d, J=9.5 Hz, H_β), 7.62 (1H, d, J=2.6 Hz, H_α), 7.83 (1H, d-d, J=9.5 and 2.6 Hz, H_γ). *Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.84; H, 6.36; N, 4.68.

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