Chem. Pharm. Bull. 21(12)2695—2704(1973)

UDC 547.759.1.057

Lactams. V.[1] Syntheses of 1-(2-Arylethyl)-3-alkyl-2- and -6-piperidones: A Comparative Study of the Mercuric Acetate-EDTA and the Ferricyanide Oxidation Methods[2]

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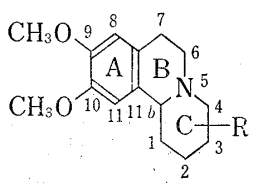
(Received April 21, 1973)

The mercuric acetate–EDTA oxidation of 1-(3,4-dimethoxyphenyl)-2-piperidinoethanol (IV: $R^1=H$; $R^2=CH_3O$) to form 1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-2-piperidone (XI: $R^1=H$; $R^2=CH_3O$) was extended to include 3-alkylpiperidine derivatives (IV: $R^1=CH_3$, C_2H_5), which were synthesized from 3-alkylpyridines (II: $R^1=CH_3$, C_2H_5) by quaternization with phenacyl bromides followed by catalytic and $NaBH_4$ reductions. It was found that the 3-methyl and 3-ethyl groups of IV almost equally oriented the oxidation to both the 2- and 6-positions but with a slight advantage to the latter position. In contrast, the alkaline ferricyanide oxidation of quaternary salts V ($R^1=CH_3$, C_2H_5) at 32° produced 2-pyridones (IX) as the main product and 6-pyridones (XIII) as the minor product. It seemed that a higher 3-alkyl substituent caused the extent of 6-pyridone formation to increase slightly (Table I). The structures of the pyridones (IX and XIII) were assigned on the basis of their ultraviolet, infrared, and nuclear magnetic resonance spectra (Tables II and III), and the chemical correlations (IX→VI←VII and XIII→X←XI) shown in Chart 2 established the structures of the hydroxypiperidones (VII and XI) obtained by the mercuric acetate–EDTA oxidation method. In alternative synthesis of Xe, 1-benzyl-5-ethyl-2-piperidone (XV) was debenzylated with sodium and liquid ammonia to give XIV. Treatment of the potassium salt of XIV with phenethyl bromide furnished Xe.

In an earlier paper[1] dealing with the synthesis of benzo[*a*]quinolizine derivatives (Ia, b,c: R=H) from piperidine through 1-substituted 2-piperidones (type XId and Xd: R^1=H), it was shown that construction of the lactam carbonyl function in the piperidine ring was readily achieved in a high yield by the mercuric acetate–(ethylenedinitrilo)tetraacetic acid (EDTA) oxidation method[4] developed by Möhrle.[5] These results appeared to offer numerous possibilities for placing substituent groups in ring C of benzo[*a*]quinolizine systems (type I) by the use of an adequately substituted piperidine as a starting material. As part of a continuing effort along these lines, it became desirable to extend the scope of the mercuric acetate–EDTA oxidation reaction to include 3-substituted piperidine derivatives which can afford in principle both of isomeric 2- and 6-piperidones in a variety of ratios. Since the same piperidones should be alternatively obtainable by the alkaline ferricyanide oxidation[6] of 3-substituted pyridinium salts followed by hydrogenation of the resulting



Ia
Ib: 5(11*b*)-dehydro derivative
Ic: 5(11*b*),6-bisdehydro derivative

Chart 1

1) Paper IV in this series, T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **20**, 1451 (1972).
2) Presented in part at the 92nd Annual Meeting of Pharmaceutical Society of Japan, Osaka, April 5, 1972 and in part at the 35th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, December 2, 1972.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) J. Knabe, *Arch. Pharm.*, **292**, 416 (1959).
5) H. Möhrle, *Arch. Pharm.*, **297**, 474 (1964).
6) *a*) H. Decker, *Chem. Ber.*, **25**, 443 (1892); *b*) *Idem*, *J. Prakt. Chem.* (2), **47**, 28 (1893).

3-substituted 2- and/or 6-pyridones,[7] it was also of interest to carry out quantitative analytical work to determine the isomer ratios of the 3-substituted pyridones produced by the ferricyanide oxidation method. In this paper we wish to report the results of the mercuric acetate–EDTA oxidation of 1-aryl-2-(3-alkylpiperidino)ethanols (IVd,e,f); quantitative data on the effect of a 3-alkyl substituent (CH_3, C_2H_5) upon the position of the ferricyanide oxidation of pyridinium salts (Vd,e,f) are also included.

The synthesis of the starting piperidine derivatives (IVd,e,f) was based on our previous experience with quaternization of pyridine with 3,4-dimethoxyphenacyl bromide followed by reduction.[1] Thus, treatment of 3-ethylpyridine (II: $R^1=C_2H_5$) with phenacyl and 3,4-dimethoxyphenacyl bromides in benzene solution furnished the corresponding quaternary salts (IIIe,f) in 90—97% yield. Likewise, quaternary bromide IIId was prepared from 3-methylpyridine (II: $R^1=CH_3$) in an excellent yield. Conversion of ketones IIId,e,f into aminoalcohols IVd,e,f was readily effected by means of catalytic hydrogenation over Adams catalyst followed by the sodium borohydride reduction. Since the piperidinoalcohols (IVd, e,f) obtained in this manner were found to be hardly separable diastereoisomeric mixtures, they were directly used in the next step without further purification. Thus, each of crude IVd,e,f was oxidized with mercuric acetate in dilute aqueous acetic acid in the presence of the disodium salt of EDTA according to the procedure described before,[1,5] and the neutral fraction of the products was treated with aqueous-ethanolic sodium hydroxide to give a mixture of two isomeric lactamalcohols (type VII and XI) in 75—78% yield. In this oxidation reaction, concomitant formation of small amounts of the O-acetyl derivatives (type VIII and XII) could be anticipated[1] and was actually suggested by means of thin-layer chromatography of the reaction mixture. However, the alkali treatment described above should have converted them, if any, into the corresponding lactamalcohols (type VII and XI). Each of VIId,e,f and XId,e,f thus obtained was presumed to be a mixture of two diastereoisomers, and in the case of VIIe,f and XIe,f the diastereoisomers could be separated by careful column chromatography. The location of the lactam carbonyl group in these hydroxypiperidones was established by hydrogenolysis using hydrogen and palladium-on-charcoal, which led to the 2-piperidone derivatives (VId,e,f) and the 6-piperidone derivatives (Xd,e,f) identical with samples synthesized *via* an unambiguous route from pyridones IXd,e,f and XIIId,e,f (see below). Moreover, compound Xe was alternatively synthesized from piperidone XV[7s,8] by debenzylation with sodium in liquid ammonia[9] followed by N-alkylation of the resulting secondary lactam (XIV) with powdered potassium and phenethyl bromide in the manner reported previously.[7n,10]

7) *a*) S. Sugasawa, K. Sakurai, and T. Okayama, *Chem. Ber.*, **74**, 537 (1941); *b*) S. Sugasawa and T. Saito, *Yakugaku Zasshi*, **65B**, 452 (1945); *c*) *Idem*, *ibid.*, **68**, 93 (1948); *d*) V. Petrow and W.R. Wragg, *J. Chem. Soc.*, **1947**, 1410; *e*) *Idem*, *ibid.*, **1950**, 3516; *f*) H.L. Bradlow and C.A. Vanderwerf, *J. Org. Chem.*, **16**, 73 (1951); *g*) S. Sugasawa and T. Tatsuno, *Yakugaku Zasshi*, **72**, 248 (1952); *h*) S. Sugasawa and H. Tomisawa, *ibid.*, **72**, 804 (1952); *i*) S. Sugasawa and Y. Ban, *ibid.*, **72**, 1336 (1952); *j*) H. Tomisawa, *ibid.*, **79**, 1173 (1959); *k*) S. Sugasawa, T. Tatsuno, and T. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **1**, 233 (1953); *l*) S. Sugasawa and T. Tatsuno, *ibid.*, **2**, 193 (1954); *m*) S. Sugasawa and M. Kirisawa, *ibid.*, **4**, 139 (1956); *n*) *Idem*, *ibid.*, **3**, 187 (1955); *o*) *Idem*, *ibid.*, **3**, 190 (1955); *p*) M. Kirisawa, *ibid.*, **7**, 35 (1959); *q*) T. Fujii, S. Yoshifuji, and A. Tamai, *ibid.*, **19**, 369 (1971); *r*) A.G. Anderson, Jr., and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958); *s*) T. Fujii and S. Yoshifuji, *Tetrahedron*, **26**, 5953 (1970); *t*) H. Möhrle and H. Weber, *ibid.*, **26**, 2953 (1970); *u*) *Idem*, *Chem. Ber.*, **104**, 1478 (1971); *v*) R.A. Abramovitch and J.G. Saha, "Advances in Heterocyclic Chemistry," Vol. 6, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York, 1966, pp. 305—307; *w*) R.A. Abramovitch and A.R. Vinutha, *J. Chem. Soc.* (B), **1971**, 131, and references cited.

8) S. Sugasawa and T. Fujii, *Proc. Japan Acad.*, **30**, 877 (1954); *idem*, *Chem. Pharm. Bull.* (Tokyo), **3**, 47 (1955).

9) *a*) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958); *b*) E. Shaw, *J. Am. Chem. Soc.*, **80**, 3899 (1958).

10) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).

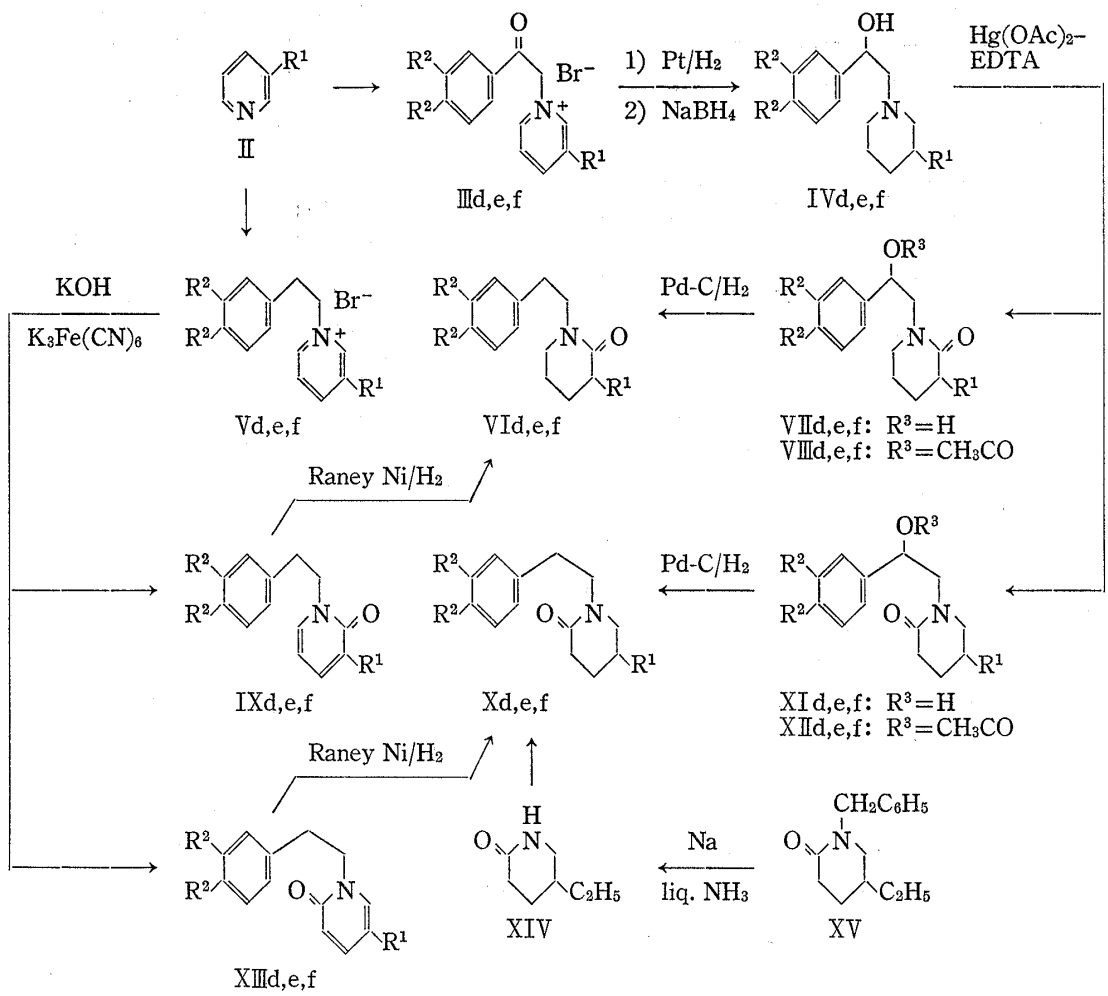


Chart 2

In order to learn the effect of a 3-alkyl substituent on the position of functionalization in the mercuric acetate–EDTA oxidation of piperidines IVd,e,f, the oxidation process in each case was run in triplicate and such isomer ratios of the produced piperidones (VII and XI) as determined by column chromatographic analysis were compared after having been averaged. It may be seen from Table I that the 3-methyl and 3-ethyl groups almost equally oriented the oxidation to both the 2- and 6-positions but with a slight advantage to the latter position. The formation of 2-piperidones (VIId,e,f) to that extent is particularly noteworthy since in his report dealing with the same oxidation of 1-phenyl-2-(3-methylpiperidino)ethanol (IV: $R^1=CH_3$; $R^2=H$) Möhrle[11] has described the occurrence of the 6-piperidone derivative (XI: $R^1=CH_3$; $R^2=H$) alone. In this connection it is also of interest to note that no appreciable change in the isomer ratio was observed when the phenyl group of substrate IVe was replaced by the 3,4-dimethoxyphenyl group. In view of the postulated mechanism of the mercuric acetate oxidation,[12] this orientation of the oxidation may be interpreted in terms of the steric influence of the 3-alkyl group. However, we prefer not to commit ourselves as to its exact nature until our further study is complete.

11) H. Möhrle, *Arch. Pharm.*, **298**, 440 (1965). See also *idem*, *ibid.*, **298**, 847 (1965).
12) *a*) N.J. Leonard, K. Conrow, and R.R. Sauers, *J. Am. Chem. Soc.*, **80**, 5185 (1958); *b*) H. Möhrle, *Arch. Pharm.*, **299**, 122 (1966); *c*) H. Möhrle and H. Weber, *Chem. Ber.*, **105**, 368 (1972).

TABLE I. Oxidation of 3-Substituted Piperidines (IV) and 3-Substituted Pyridinium Salts (V)

Starting material	Substituent		Oxidation method[a]	Product		
	R^1	R^2		Total yield (%)	% 2-oxidation[b]	% 6-oxidation[b]
IVd[c]	CH_3	CH_3O	ME	75	VIId[c] : 45	XId[c] : 55
IVe[c]	C_2H_5	H	ME	78	VIIe[c] : 46	XIe[c] : 54
IVf[c]	C_2H_5	CH_3O	ME	76	VIIf[c] : 46	XIf[c] : 54
Vd	CH_3	CH_3O	AF	76	IXd : 94	XIIId : 6
Ve	C_2H_5	H	AF	86	IXe : 85 (86[d])	XIIIe : 15 (14[d])
Vf	C_2H_5	CH_3O	AF	71	IXf : 88	XIIIf : 12

a) The symbol ME designates the mercuric acetate–EDTA oxidation method, and AF, the alkaline ferricyanide oxidation method.
b) Unless otherwise noted, all isomer ratios were determined by column chromatographic analysis.
c) A hardly separable diastereoisomeric mixture.
d) Determined by gas-liquid chromatographic analysis.

We next focused our attention on the alkaline ferricyanide oxidation of 3-alkylpyridinium salts Vd,e,f, which were readily prepared by quaternization of II (R^1=CH_3, C_2H_5) with 3,4-dimethoxyphenethyl bromide or phenethyl bromide in hot N,N-dimethylformamide or benzene solution. In a pilot experiment, an aqueous solution of quaternary salt Vf was treated at room temperature with varying amounts of potassium ferricyanide in the presence of a large excess of potassium hydroxide. Contrary to the usual quantity of the oxidizing reagent, an amount of 2—3 molar equivalents[7] seemed insufficient. It was then found that the reaction product could be obtained in a favorable yield using a molar ratio of 6: 1 of the ferricyanide to quaternary bromide Vf. Consequently, this ratio was also adopted in the oxidation of the other salts (Vd,e). All the alkaline ferricyanide oxidations were carried out at 32° for 5 hr and the ratios of amounts of the resulting two isomeric pyridones (type IX and XIII) were determined by gas-liquid chromatographic and/or column chromatographic analysis. This procedure was repeated three times in each case and the mean value of the isomer ratios was obtained. The results are included in Table I. In contrast to the results of the mercuric acetate–EDTA oxidation of IV, the oxidation at the 2-position is much favored over that at the 6-position in all cases, paralleling the experience of other workers[7i,m,t,u,w] in a similar oxidation of 3-methyl- and 3-ethyl-1-methylpyridinium salts. It seems that a higher 3-alkyl substituent causes the extent of 6-pyridone formation to increase slightly, whereas the effect of a slender N-alkyl group on the orientation of the oxidation may be little or nothing.

The structures of the pyridones (IX and XIII) were assigned on the following considerations. By analogy[7f,m,u,w] it was expected that in the alkaline ferricyanide oxidation of Vd, e,f the 2-pyridone derivatives (IXd,e,f) would predominate over the 6-pyridone derivatives (XIIId,e,f). As shown in Table II, 2-pyridones IXd,e,f had the ultraviolet (UV) absorption band due to the $n\rightarrow\pi^*$ transition (CO) at 302—303 mμ, and 6-pyridones XIIId,e,f, at 313—314 mμ. A parallel difference has been observed[7f,u,13] for several pairs of 3-alkyl-2- and -6-pyridones. In their infrared (IR) spectra IXd,e,f displayed the CO stretching vibration in the 1650—1653 cm^{-1} region, and XIIId,e,f, in the range 1667—1670 cm^{-1}. Such a higher shift of the CO frequency of 6-pyridones XIII by *ca.* 20 cm^{-1} is in general agreement with the previous finding of Tomisawa[14] and of Möhrle.[7u] The most conclusive evidence for the assigned structures was provided by nuclear magnetic resonance (NMR) spectroscopy. It can be seen from Table III that among the pyridone-ring protons of each of IX and XIII series

13) M. Barash, J.M. Osbond, and J.C. Wickens, *J. Chem. Soc.*, **1959**, 3530.
14) H. Tomisawa and T. Agatsuma, *Ann. Rept. Tohoku Coll. Pharm.* (Sendai), **8**, 25 (1961).

Table II. Ultraviolet and Infrared Spectra of Pyridones

Compound	UV spectrum[a]						IR spectrum[b] ν_{CO} (cm^{-1})
	Short-wavelength band		Medium-wavelength band		Long-wavelength band		
	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	λ_{max} (mμ)	log ε	
2-Pyridones							
IXd	231	4.12	286	3.84	302	3.83	1651
IXe	233	3.74	—	—	303	3.83	1653
IXf	232	4.08	286	3.81	303	3.81	1650
1,3-Dimethyl-2-pyridone[c]	226	3.74	—	—	299	3.68	1640[d]
3-Methyl-2-pyridone[e]	226	3.84	—	—	295	3.93	—
6-Pyridones							
XIIId	231	4.17	284	3.66	314	3.74	1667
XIIIe	232	3.96	—	—	313	3.79	1670
XIIIf	232	4.19	284	3.68	313	3.76	1668
1,3-Dimethyl-6-pyridone[c]	227	3.88	—	—	311	3.63	1659[d]
3-Methyl-6-pyridone[e]	227	3.91	—	—	303	3.79	—

a) Unless otherwise noted, the spectra were determined in abs. ethanol.
b) Measured in chloroform at 0.2M concentration.
c) From ref. 7*u*. The UV spectrum was determined in methanol.
d) The physical state of the sample for recording the spectrum has not been specified in ref. 7*u*.
e) From ref. 13. The solvent employed for measuring the spectrum was water.

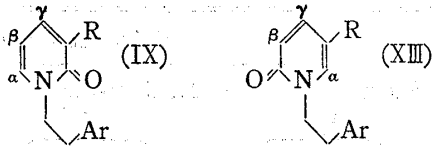
the most shielded one was H_β. As expected, the H_β signals of 2-pyridones IX resonated approximately 0.6 ppm upfield from those of 6-pyridones XIII, and were observed as an apparent triplet instead of a hypothetical doublet-of-doublets since coupling constants $J_{\alpha\beta}$ and $J_{\beta\gamma}$ were equal. It is also noteworthy that the 3-alkyl protons of IXd,e,f appeared downfield from their 6-pyridone counterparts by 0.14—0.3 ppm, probably owing to the deshielding effect of the neighboring 2-pyridone carbonyl group.[15] The H_γ signals of IXd and IXf resonated as a doublet-of-multiplets at lower field than did the H_α doublet-of-doublets. The multiplicity of the former is most probably due to long-range coupling between H_γ and the methyl or methylene protons at the 3-position.[16] In addition to the spectral evidence described, physical properties of XIIIe and XIIIf were in fair agreement with those reported.[17]

Correlation of the pyridones (IX or XIII) with the lactamalcohols (VII or XI) through the piperidones (VI or X) should unequivocally establish the location of the lactam carbonyl group in VII or XI, and the reductions of IXd,e,f and XIIId,e,f to VId,e,f and Xd,e,f were separately accomplished with Raney nickel catalyst and hydrogen, realizing satisfactory results.

The present work has revealed that in regard to the efficiency of synthesizing either 3-alkyl-2- (VI) or -6-piperidones (X) from 3-alkylpyridines (II), the alkaline ferricyanide and the mercuric acetate–EDTA methods serve as complementary one to the other. Further studies on the effect of a variety of 3-substituents other than lower alkyl groups upon the position of oxidation of the nitrogen-containing 6-membered rings will be the subject of our forthcoming papers.

15) L.M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon Press, Oxford, 1969, pp. 88—92.
16) Spin-decoupling experiments have been performed by Dr. S. Ikegami, National Institute of Radiological Sciences, and full discussion will be found in sequential papers in preparation.
17) *a*) J.A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956); *b*) J.A. Berson and J.S. Walia, *J. Org. Chem.*, **24**, 756 (1959).

Table III. NMR Spectra of 2- and 6-Pyridones



Compound	Chemical shift (τ) and coupling constant (J, cps)[a]											
	Methyl protons		Methylene protons			Aromatic protons	Pyridone protons					
	CCH_3	OCH_3	CH_3CH_2	$ArCH_2$	NCH_2		H_α	H_β	H_γ	$J_{\alpha\beta}$	$J_{\alpha\gamma}$	$J_{\beta\gamma}$
2-Pyridones												
IXd	7.82 (s)	6.14 (s), 6.17 (s)	—	7.02 (t)	5.87 (t)	3.27—3.4 (m)	3.15 (d-d)	4.04 (d-d)[b]	2.84 (d-m)	6.5	2.0	6.5
IXe	8.84 (t)[c]	—	7.45 (q)	7.03 (t)	5.94 (t)	*ca.* 2.9 (m)	3.25 (d-d)	4.12 (d-d)[b]	2.75—3.1 (m)[d]	6.5	2.0	6.5
IXf	8.82 (t)[c]	6.18 (s), 6.23 (s)	7.45 (q)	7.06 (t)	5.93 (t)	3.27—3.45 (m)	3.18 (d-d)	4.04 (d-d)[b]	2.89 (d-m)	6.5	2.2	6.5
6-Pyridones												
XIIId	8.02 (s)	6.15 (s), 6.19 (s)	—	7.03 (t)	5.92 (t)	3.25—3.37 (m)	3.3—3.4[d]	3.47 (d)	2.82 (d-d)	—[e]	2.5	9.3
XIIIe	8.98 (t)[c]	—	7.75 (q)	6.99 (t)	5.92 (t)	2.86 (m)	3.43 (d)	3.52 (d)	2.7—3.15[d]	*ca.* 1	2.0	9.0
XIIIf	8.99 (t)[c]	6.17 (s), 6.22 (s)	7.71 (q)	7.01 (t)	5.91 (t)	3.1—3.35 (m)	3.42 (d)	3.46 (d)	2.82 (d-d)	*ca.* 1	2.3	9.0

a) Measured on 10% (w/v) $CDCl_3$ solution with a JEOL-JNM-C-60H spectrometer operating at 60 Mcps. Unless otherwise stated, the letter in parentheses designates the multiplicity or shape of the signal: d=doublet, d-d=doublet-of-doublets, d-m=doublet-of-multiplets, m=multiplet, q=quartet with J=7.5 cps, s=singlet, t=triplet with J=7 cps.
b) Observed as an apparent triplet.
c) J=7.5 cps
d) Overlapped with the signals of the aromatic protons.
e) unmeasurably small

Experimental[18]

1-(3,4-Dimethoxyphenacyl)-3-methylpyridinium Bromide (IIId)——A stirred mixture of 3-methylpyridine (1.00 g, 10.7 mmoles) and 3,4-dimethoxyphenacyl bromide[19] (2.77 g, 10.7 mmoles) in abs. benzene (20 ml) was kept at room temp. for 45 hr. The colorless precipitates that resulted were collected by filtration, washed with benzene, and dried to give IIId (3.65 g, 97%), mp 227—228° (decomp.). Recrystallization from abs. ethanol yielded an analytical sample as colorless prisms, mp 228—229° (decomp.); UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 233.5 (18800), 276 (15600), 312 (10400); IR ν_{max}^{Nujol}: 1688 cm^{-1} (CO). *Anal.* Calcd. for $C_{16}H_{18}O_3NBr$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.48; H, 5.25; N, 3.99.

1-Phenacyl-3-ethylpyridinium Bromide (IIIe)——This was obtained in 90% yield from 3-ethylpyridine by treating it with phenacyl bromide as described above for IIId. Recrystallization from abs. ethanol–ether furnished IIIe as colorless, hygroscopic needles, mp 173—175°; UV $\lambda_{max}^{95\%\ aq.\ EtOH}$: 249 mμ ($\varepsilon$ 15700); IR ν_{max}^{KBr}: 1690 cm^{-1} (CO).

For characterization, a small sample (202 mg, 0.66 mmole) of IIIe was dissolved in H_2O (1 ml), and a saturated solution (12.2 ml) of picric acid in H_2O was added. The resulting precipitates were filtered off, dried, and recrystallized from abs. ethanol–benzene (1: 1, v/v) to give the corresponding picrate as yellow needles, mp 145—146°. *Anal.* Calcd. for $C_{21}H_{18}O_8N_4$: C, 55.51; H, 3.99; N, 12.33. Found: C, 55.68; H, 4.06; N, 12.16.

1-(3,4-Dimethoxyphenacyl)-3-ethylpyridinium Bromide (IIIf)——Prepared in 97% yield from 3-ethylpyridine and 3,4-dimethoxyphenacyl bromide[19] in a manner similar to that described for IIId. Recrystallization from abs. ethanol afforded IIIf as colorless needles, mp 199—200° (decomp.); UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 233

18) All melting points are corrected; boiling points, uncorrected. For details of instrumentation and measurement and the abbreviations used, see footnote 18 in ref. 1. We are indebted to Mr. Y. Itatani and Misses S. Toyoshima and T. Tsuji at Kanazawa University for microanalyses and NMR and mass spectral data.
19) C. Mannich and F.L. Hahn, *Chem. Ber.*, **44**, 1542 (1911).

(19000), 276 (15600), 311 (10300); IR ν_{max}^{KBr}: 1680 cm^{-1} (CO). *Anal.* Calcd. for $C_{17}H_{20}O_3NBr$: C, 55.75; H, 5.50; N, 3.82. Found: C, 55.87; H, 5.49; N, 4.05.

1-(3,4-Dimethoxyphenyl)-2-(3-methylpiperidino)ethanol (IVd)——A suspension of IIId (7.04 g, 20 mmoles) in 50% aq. ethanol (50 ml) was hydrogenated over Adams catalyst (200 mg) at 40° and atmospheric pressure. The salt was in solution within 30 min, and the hydrogenation was almost complete within 16 hr, absorbing first three molar equivalents of H_2 smoothly and then one more equivalent of H_2 very slowly. The catalyst was removed by filtration, and the filtrate was neutralized with 2N aq. NaOH (10 ml). To the resulting solution was added $NaBH_4$ (760 mg, 20 mmoles) in small portions. After having been stirred at room temp. overnight, the reaction mixture was evaporated *in vacuo* to leave a jelly, which was treated with H_2O (10 ml) to separate an oil. The mixture was extracted with benzene, and the benzene solution was dried over anhyd. K_2CO_3 and evaporated *in vacuo*, leaving a slightly yellowish oil (5.36 g, 96%). Distillation of the residue under reduced pressure yielded a diastereoisomeric mixture of IVd (4.87 g, 87%) as colorless, viscous oil, bp 150—151° (0.05 mm Hg), which solidified on standing at room temp., mp 56—60°; UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 230 (9200), 279 (3050); IR $\nu_{max}^{CHCl_3}$: 3385 cm^{-1} (OH); Mass Spectrum *m/e*: 279 (M^+); NMR ($CDCl_3$) τ: 9.12 and 9.10 (3H, d each, J=5.7 cps, diastereoisomeric CH_3's), 8.1—8.8 (5H, m, two ring-CH_2's and -CH), 6.65—8.1 (6H, m, three NCH_2's), 6.14 and 6.10 (3H each, s, two CH_3O's), 5.86 (1H, s, OH), 5.2—5.55 [1H, m, Ar$\underline{C}$H(OH)CH_2], 2.95—3.3 (3H, m, aromatic protons).

1-Phenyl-2-(3-ethylpiperidino)ethanol (IVe)——A mixture of IIIe (16.84 g, 55 mmoles) and abs. ethanol (120 ml) was hydrogenated over Adams catalyst (200 mg) at 20° and atmospheric pressure. When *ca.* 3.2 molar equivalents of H_2 had been taken up during the first 7 hr, the reaction was discontinued and the reaction mixture was filtered to remove the catalyst. The filtrate was treated successively with 2N aq. NaOH (27.5 ml) and $NaBH_4$ (2.08 g, 55 mmoles) in the same manner as described for IVd. The resulting solution was also worked up as described above for IVd except that chloroform was used for extraction of the free base (IVe). The crude base thus obtained was vacuum distilled to produce a colorless oil (12.11 g, 94%), bp 137° (3 mm Hg); UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 247 (sh) (221), 252 (233), 258 (249), 264 (191), 267 (sh) (125); IR ν_{max}^{film}: 3400 cm^{-1} (b) (OH); NMR ($CDCl_3$) τ: 6.8—9.35 (16H, unresolved m, $C\underline{H}_3CH_2$, $CH_3C\underline{H}_2$, two ring-CH_2's, ring-CH, three NCH_2's), 5.82 (1H, s, OH), 5.13—5.45 [1H, m, $C_6H_5C\underline{H}$(OH)CH_2], 2.67 (5H, s, C_6H_5).

For characterization, a portion (2.56 g) of the distilled oil was dissolved in abs. ethanol (20 ml) and the resulting solution was neutralized with 57% aq. HI, treated with charcoal, and evaporated *in vacuo* to leave a yellowish solid (3.57 g), mp 137—143°. Six recrystallizations of the solid from abs. ethanol–ethyl acetate (1: 4, v/v) provided colorless scales (530 mg), mp 168—169°, presumed to be the hydriodide of one of the diastereoisomers of IVe. *Anal.* Calcd. for $C_{15}H_{24}ONI$: C, 49.87; H, 6.70; N, 3.88. Found: C, 49.89; H, 6.77; N, 3.82.

1-(3,4-Dimethoxyphenyl)-2-(3-ethylpiperidino)ethanol (IVf)——A solution of IIIf (3.66 g, 10 mmoles) in 90% aq. ethanol (100 ml) was hydrogenated over Adams catalyst (100 mg) at room temp. and atmospheric pressure, absorbing *ca.* 4 molar equivalents of H_2 for periods up to 12 hr. The resulting mixture was worked up as described for IVd to furnish IVf (2.73 g, 93%) as a pale yellowish oil, UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 230 (6100), 279 (2700); IR ν_{max}^{film}: 3420 cm^{-1} (b) (OH); NMR ($CDCl_3$) τ: 9.12 (3H, t, overlapped diastereoisomeric $C\underline{H}_3CH_2$'s), 7.9—8.9 (7H, unresolved m, two ring-CH_2's, -CH, $CH_3C\underline{H}_2$), 6.7—7.9 (6H, m, three NCH_2's), 6.20 and 6.16 (3H each, s, two CH_3O's), 6.01 (1H, s, OH), 5.15—5.6 [1H, m, Ar$\underline{C}$H(OH)CH_2], 3.0—3.3 (3H, m, aromatic protons).

Mercuric Acetate-EDTA Oxidation of Piperidinoalcohols IV——Standard Procedure: To a solution of a piperidinoethanol IV (10 mmoles) in 1% aq. acetic acid (73 ml) were added (ethylenedinitrilo)tetraacetic acid disodium salt dihydrate (9.31 g, 25 mmoles) and mercuric acetate (7.97 g, 25 mmoles). The mixture was stirred for 1.5 hr in an oil bath kept at 110°, depositing metallic Hg and a yellowish oil. After cooling, the reaction mixture was extracted with four 20-ml portions of chloroform. The combined extracts were washed successively with two 15-ml portions of 10% aq. HCl, H_2O (15 ml), two 15-ml portions of 5% aq. NaOH, and two 15-ml portions of a saturated solution of NaCl in H_2O, dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to leave a brownish oil. The residue was dissolved in chloroform (20 ml) and the solution was passed through a column packed with alumina (30 g). The column was eluted with chloroform (80 ml). The eluate was evaporated *in vacuo* to give a slightly brownish oil, shown to be impure by four spots on a thin-layer chromatography (TLC) plate [alumina, hexane–ethyl acetate (1: 2, v/v)]. In order to hydrolyze substances presumed to be acetates VIII and XII, the total amount of the oil was dissolved in abs. ethanol (50 ml), and 50% aq. NaOH (6 ml) was added. After having been kept at room temp. overnight, the reaction mixture was neutralized with 10% aq. HCl and evaporated *in vacuo* to dryness. To the resulting residue was added H_2O (20 ml) and the mixture was extracted with four 15-ml portions of chloroform. The chloroform solution was washed successively with 10% aq. HCl (10 ml), H_2O (10 ml), 5% aq. NaOH (10 ml), and two 10-ml portions of H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the chloroform left a light brown oil, shown to be a mixture of VII and XI by two spots on a TLC plate. Separation of the two lactams, each of which was a diastereoisomeric mixture, was effected by means of column chromatography using alumina (250 g) and hexane–ethyl acetate as eluent. In all cases, VII came out earlier than XI. The oxidation reaction was run in triplicate, and the isomer ratios obtained were averaged. The results with IVd,e,f are collected in Table I. The physical properties of lactamalcohols VIId,e,f and XId,e,f thus formed are

recorded in the following.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-methyl-2-piperidone (VIId)——Obtained as a slightly yellowish, viscous oil (a diastereoisomeric mixture), UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 230.5 (9520), 279 (2840); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (b) (OH), 1608 (lactam CO); Mass Spectrum *m/e*: 293 (M^+); NMR ($CDCl_3$) τ: 8.76 (3H, d, J=6.8 cps, overlaid diastereoisomeric CH_3's), 7.1—8.6 (5H, unresolved m, $H_{(4)}$'s, $H_{(5)}$'s, $H_{(3)}$), 6.6—7.1 (2H, dull m, $H_{(6)}$'s), 6.3—6.55 and 4.9—5.2 [ABX type m, ArCH(OH)C$\underline{H}_2$ and ArC$\underline{H}$(OH)CH_2], *ca.* 6.15 (1H, OH), 6.15 and 6.13 (6H, two CH_3O's), 3.19 and 3.07 (3H, dull peaks, aromatic protons).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-methyl-2-piperidone (XId)——Isolated as a diastereoisomeric mixture, colorless prisms of mp 99—101°. One recrystallization from ethyl acetate yielded a sample of mp 100—103°, UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 230 (9470), 279 (2910); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (b) (OH), 1614 (lactam CO); Mass Spectrum *m/e*: 293 (M^+); NMR ($CDCl_3$) τ: 9.07 and 9.05 (3H, two d's, J=6 cps each, diastereoisomeric CH_3's), 7.95—8.8 (3H, $H_{(4)}$'s and $H_{(5)}$), 7.3—7.8 (2H, m, $H_{(3)}$'s), 6.7—7.25 (2H, m, $H_{(6)}$'s), 6.27—6.7 and 4.9—5.25 [ABX type m, ArCH(OH)C$\underline{H}_2$ and ArC$\underline{H}$(OH)CH_2], 6.14 and 6.12 (6H, s each, two CH_3O's), 5.40 (1H, s, OH), 3.0—3.25 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{23}O_4N$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.71; H, 7.86; N, 4.69.

1-(2-Phenyl-2-hydroxyethyl)-3-ethyl-2-piperidone (VIIe)——Colorless prisms of mp 59—61°. A small amount (*ca.* 1 g) of this sample was chromatographed on a 100-g alumina column using hexane–ethyl acetate (1: 1, v/v) as eluent, and 10-ml fractions were taken in a fraction collector. A material obtained from earlier fractions melted at 64—66°. Four recrystallizations from hexane yielded one of the diastereoisomers of VIIe as colorless scales, mp 75—76.5°; UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 247 (143), 252 (168), 258 (203), 264 (153), 267.5 (sh) (84); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (b) (OH), 1610 (lactam CO); Mass Spectrum *m/e*: 247 (M^+); NMR ($CDCl_3$) τ: 9.06 (3H, t, J=7 cps, $C\underline{H}_3CH_2$), 7.5—8.9 (7H, m, $CH_3C\underline{H}_2$, $H_{(4)}$'s, $H_{(5)}$'s, $H_{(3)}$), 6.7—7.35 (2H, m, $H_{(6)}$'s), 6.40 [2H, d, J=5 cps, $C_6H_5CH(OH)C\underline{H}_2$], 5.19 (1H, s, OH), 5.02 [1H, t, J=5 cps, $C_6H_5C\underline{H}(OH)CH_2$], 2.73 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.93; H, 8.73; N, 5.70.

Later fractions of the chromatography gave another diastereoisomer of VIIe as a colorless solid, mp 61—63°. Four recrystallizations from hexane produced an analytical sample as colorless prisms, mp 72—73.5°, depressed to mp 59—61° upon admixture with the first diastereoisomer; Mass Spectrum *m/e*: 247 (M^+); NMR ($CDCl_3$) τ: 9.10 (3H, t, J=7 cps, $C\underline{H}_3CH_2$), 7.5—8.9 (7H, m, $CH_3C\underline{H}_2$, $H_{(4)}$'s, $H_{(5)}$'s, $H_{(3)}$), 6.7—7.35 (2H, m, $H_{(6)}$'s), 6.3—6.5 and 4.9—5.15 [ABX type m, $C_6H_5CH(OH)C\underline{H}_2$ and $C_6H_5C\underline{H}(OH)CH_2$], 5.28 (1H, s, OH), 2.73 (5H, s, C_6H_5). *Anal.* Calcd. for $C_{15}H_{21}O_2N$: C, 72.84; H, 8.56; N, 5.66. Found: C, 73.10; H, 8.76; N, 5.84. Although the UV spectrum in abs. ethanol and the IR spectrum in chloroform (0.2M solution) of this sample were virtually identical with those of the diastereoisomer of mp 75—76.5°, the NMR spectra of both samples were not identical.

1-(2-Phenyl-2-hydroxyethyl)-5-ethyl-2-piperidone (XIe)——Obtained as a colorless oil, which was further chromatographed in the same way as described above for VIIe, being separated into two oily diastereoisomers. Their UV, IR, and mass [*m/e* 247 (M^+)] spectra were almost identical; UV $\lambda_{max}^{abs.\ EtOH}$ mμ (ε): 247 (203), 252 (218), 258 (222), 264 (155), 267.5 (sh) (88); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3325 (b) (OH), 1615 (lactam CO). However, their NMR spectra in $CDCl_3$ were not superimposable.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-2-piperidone (VIIf)——Separated into two diastereoisomers: An oily isomer, UV $\lambda_{max}^{abs.\ EtOH}$mμ (ε): 230.5 (9350), 279 (3720); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (b) (OH), 1609 (lactam CO); Mass Spectrum *m/e*: 307 (M^+); NMR ($CDCl_3$) τ: 9.07 (3H, t, J=7 cps, $C\underline{H}_3CH_2$), 7.35—8.8 (7H, m, CH_3-$C\underline{H}_2$, $H_{(4)}$'s, $H_{(5)}$'s, $H_{(3)}$), 6.6—7.35 (2H, m, $H_{(6)}$'s), 6.3—6.55 and 4.95—5.25 [ABX type m, ArCH(OH)C$\underline{H}_2$ and ArC$\underline{H}$(OH)CH_2], 6.19 (1H, s, OH), 6.15 and 6.12 (6H, s each, two CH_3O's), 2.9—3.25 (3H, m, aromatic protons). A crystalline isomer, colorless prisms of mp 70.5—77° (from pet. ether–ethyl acetate). The UV, IR, and mass spectra of this sample were virtually identical with those of the oily diastereoisomer. The NMR spectra of both samples, however, were distinguishable.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-piperidone (XIf)——Two crystalline diastereoisomers were obtained: Colorless pillars, mp 86—91° [from hexane–ethyl acetate (3: 1, v/v)]; UV $\lambda_{max}^{abs.\ EtOH}$mμ (ε): 230 (8790), 279 (4440); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (b) (OH), 1615 (lactam CO); Mass Spectrum *m/e*: 307 (M^+). *Anal.* Calcd. for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.55; H, 8.37; N, 4.66. Colorless prisms, mp 103—106° [from hexane–ethyl acetate (3: 1, v/v)]. *Anal.* Calcd. for $C_{17}H_{25}O_4N$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.09; H, 8.31; N, 4.54. Although the UV, IR, and mass spectra of the latter were almost identical with those of the former, the NMR spectra of both samples were not identical.

1-(3,4-Dimethoxyphenethyl)-3-methyl-2-piperidone (VId)——i) Hydrogenolysis of VIId: A mixture of the diastereoisomeric mixture (293 mg, 1 mmole) of VIId described above, abs. ethanol (20 ml), and 70% aq. $HClO_4$ (0.2 ml) was hydrogenated over 10% Pd-C (300 mg) at room temp. and 3.6—3.8 atmospheric pressure for 10 hr. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The resulting residue was dissolved in abs. ethanol (20 ml) and 50% aq. NaOH (2 ml) was added in order to hydrolyze a contaminant presumed from the IR spectrum (ν_{max}^{film} 1725 cm^{-1}) to be an ester. After having been kept at room temp. overnight, the reaction mixture was neutralized with 10% aq. HCl and was evaporated *in vacuo*. To the residue was added H_2O (20 ml) and an insoluble oil was extracted with benzene. The benzene solution was washed successively with 10% aq. HCl, H_2O, 10% aq. NaOH, and H_2O, dried over anhyd. Na_2SO_4, and evaporated under reduced pressure, leaving VId (222 mg, 80%) as a slightly yellowish

oil, shown to be homogeneous by a single spot on a TLC plate; UV $\lambda_{max}^{abs.EtOH}$: 229.5 (9730), 280.5 (3050); IR $\nu_{max}^{CHCl_3}$: 1620 cm^{-1} (lactam CO); Mass Spectrum *m/e*: 277 (M^+); NMR ($CDCl_3$) τ: 8.78 (3H, d, J=7 cps, CH_3), 7.05—7.4 and 6.25—6.65 (A_2B_2 type m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 6.16 (6H, s, two CH_3O's), 3.26 (3H, s, aromatic protons).

ii) Hydrogenation of IXd: A solution of pyridone IXd (672 mg, 2.46 mmoles) in abs. ethanol (15 ml) was hydrogenated over Raney Ni W-2 catalyst (2.5 ml) at room temp. and atmospheric pressure; two molar equivalents of H_2 was taken up within 2 hr. The catalyst was filtered off and the filtrate was evaporated *in vacuo* to leave an oil. The oil was dissolved in benzene, and the solution was washed successively with 5% aq. HCl, H_2O, 5% aq. NaOH, and H_2O, and dried over anhyd. Na_2SO_4. Evaporation of the resulting solution left VId (635 mg, 93%) as an almost colorless oil. The UV, IR, NMR, and mass spectra of this sample were superimposable on those of the specimen prepared by method-(i).

1-Phenethyl-3-ethyl-2-piperidone (VIe)——i) From VIIe: The diastereoisomeric mixture of VIIe described above was hydrogenated as described for VIId, and piperidone VIe was obtained in 96% yield as colorless oil, bp 155—157° (3 mm Hg); UV $\lambda_{max}^{abs.EtOH}$ mμ (ε): 247.5 (137), 253 (171), 259 (203), 261 (sh) (177), 264.5 (158), 268 (128); IR ν_{max}^{film}: 1637 cm^{-1} (lactam CO); $\nu_{max}^{CHCl_3}$: 1618 cm^{-1} (lactam CO); Mass Spectrum *m/e*: 231 (M^+); NMR ($CDCl_3$) τ: 9.10 (3H, t, J=7 cps, $C\underline{H}_3CH_2$), 6.75—7.35 (4H, m, $H_{(6)}$'s and $C_6H_5C\underline{H}_2CH_2$), 6.2—6.65 (2H, m, $C_6H_5CH_2C\underline{H}_2$), 2.77 (5H, s, C_6H_5).

ii) From IXe: Hydrogenation of pyridone IXe was carried out in a manner similar to that employed for IXd, producing VIe in 92% yield. This sample was found to be identical (by TLC, UV, IR, NMR, and mass spectra) with the one obtained by method-(i).

1-(3,4-Dimethoxyphenethyl)-3-ethyl-2-piperidone (VIf)——Prepared, in the same way as described for VId, either by the hydrogenolysis of any of the diastereoisomers of VIIf in 79—85% yield, or by the hydrogenation of pyridone IXf in 83% yield. A colorless, viscous oil, bp 190—200° (bath temp.) (0.2 mm Hg); UV $\lambda_{max}^{abs.EtOH}$ mμ (ε): 229 (9070), 280 (2690); IR $\nu_{max}^{CHCl_3}$: 1620 cm^{-1} (lactam CO); Mass Spectrum *m/e*: 291 (M^+); NMR ($CDCl_3$) τ: 9.07 (3H, t, J=7 cps, $C\underline{H}_3CH_2$), 7.05—7.4 and 6.3—6.7 (4H, m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 6.14 (6H, s, two CH_3O's), 3.25 (3H, s, aromatic protons).

1-(3,4-Dimethoxyphenethyl)-5-methyl-2-piperidone (Xd)——i) From XId: The diastereoisomeric mixture of XId described above was hydrogenated in a manner similar to that recorded above for the hydrogenolysis of VIId. The product obtained in 92% yield was recrystallized from hexane to provide an analytical sample of Xd as colorless pillars, mp 61—62°; UV $\lambda_{max}^{abs.EtOH}$ mμ (ε): 229 (9410), 280.5 (2990); IR $\nu_{max}^{CHCl_3}$: 1623 cm^{-1} (lactam CO); NMR ($CDCl_3$) τ: 9.06 (3H, d, J=6 cps, CH_3), 7.15—7.45 and 6.3—6.7 (m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 6.16 (6H, s, two CH_3O's), 3.26 (3H, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{23}O_3N$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.45; H, 8.14; N, 5.14.

ii) From XIIId: Pyridone XIIId was hydrogenated as in the case of IXd, and piperidone Xd was obtained in 84% yield.

1-Phenethyl-5-ethyl-2-piperidone (Xe)——i) Catalytic Hydrogenations of XIe and XIIIe: Either hydrogenation was accomplished as described above for VId, and piperidone Xe was produced in 80—95% yield as a colorless oil, bp 170—174° (bath temp.) (3 mm Hg); UV $\lambda_{max}^{abs.EtOH}$ mμ (ε): 248 (135), 253 (173), 259 (207), 261 (sh) (182), 264.5 (161), 268 (135); IR ν_{max}^{film}: 1644 cm^{-1} (lactam CO); $\nu_{max}^{CHCl_3}$: 1627 cm^{-1} (lactam CO); Mass Spectrum *m/e*: 231 (M^+); NMR ($CDCl_3$) τ: 9.16 (3H, t, J=7 cps, $C\underline{H}_3CH_2$), 6.7—7.35 (4H, m, $H_{(6)}$'s and C_6H_5-$C\underline{H}_2CH_2$), 6.2—6.65 (2H, m, $C_6H_5CH_2C\underline{H}_2$), 2.79 (5H, s, C_6H_5).

ii) Alkylation of XIV: To a suspension of powdered K (0.4 g, 0.01 g.-atom) in abs. xylene (5 ml) was added dropwise a solution of XIV (1.27 g, 10 mmoles) in abs. xylene (15 ml), and the mixture was then heated at 150—160° for 30 min. After cooling, a solution of phenethyl bromide (2.03 g, 11 mmoles) in abs. xylene (15 ml) was added dropwise over a period of 15 min. The resulting mixture was stirred at 150° for 12 hr in the presence of powdered Cu (0.1 g). After cooling, the Cu and KBr that precipitated were removed by filtration, and the filtrate was evaporated *in vacuo* to leave a dark brown oil. The oil was then chromatographed on a 200-g alumina column using hexane–ethyl acetate (2: 1, v/v) as eluent. Fractions containing Xe were combined and the solvent was removed by evaporation. The resulting oil was vacuum distilled and a fraction boiling at 175° (bath temp.) (3 mm Hg) was collected. Yield, 52 mg. This sample was identified (by means of TLC and IR spectrum) with a specimen prepared by method-(i). Recovery of the starting material (XIV) was 996 mg (78%).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2-piperidone (Xf)——Prepared, in the same manner as described for VId, either by the hydrogenolysis of any of the diastereoisomers of XIf in 79—82% yield, or by the hydrogenation of pyridone XIIIf in 85% yield. A colorless oil, UV $\lambda_{max}^{abs.EtOH}$ mμ (ε): 229.5 (8990), 280 (2850); IR $\nu_{max}^{CHCl_3}$: 1624 cm^{-1} (lactam CO); Mass Spectrum *m/e*: 291 (M^+); NMR ($CDCl_3$) τ: 9.10 (3H, t, J=6 cps, $C\underline{H}_3CH_2$), 6.85—7.35 (m, $H_{(6)}$'s and $ArC\underline{H}_2CH_2$), 6.3—6.65 (2H, m, $ArCH_2C\underline{H}_2$), 6.17 and 6.14 (6H, s each, two CH_3O's), 3.24 (3H, s, aromatic protons).

1-(3,4-Dimethoxyphenethyl)-3-methylpyridinium Bromide (Vd)——A stirred mixture of 3-methylpyridine (1.90 g, 20.4 mmoles) and 3,4-dimethoxyphenethyl bromide (4.90 g, 20 mmoles) in N,N-dimethylformamide (DMF) (20 ml) was kept at 100—105° for 3.5 hr and then at room temp. overnight. The mixture was evaporated *in vacuo*, and the resulting solid mass was washed with benzene and recrystallized from benzene–abs. ethanol (5: 1, v/v) to give Vd (5.50 g, 81%) as slightly yellowish prisms, mp 202—203° (decomp.); UV $\lambda_{max}^{abs.EtOH}$:

268 mμ (ε 6260). *Anal.* Calcd. for $C_{16}H_{20}O_2NBr$: C, 56.82; H, 5.96; N, 4.14. Found: C, 57.14; H, 6.01; N, 4.34.

1-Phenethyl-3-ethylpyridinium Bromide (Ve)——3-Ethylpyridine (6.43 g, 60 mmoles) and phenethyl bromide (11.1 g, 60 mmoles) were dissolved in abs. benzene (100 ml), and the solution was heated at reflux for 10 hr with stirring, depositing a light brown oil. After cooling, the mixture was extracted with H_2O (50 ml). The aq. solution was worked up as described below for Vf to afford Ve (16.1 g, 92%) as a hygroscopic solid, which was directly used in the next step without further purification.

1-(3,4-Dimethoxyphenethyl)-3-ethylpyridinium Bromide (Vf)——A mixture of 3-ethylpyridine (9.43 g, 88 mmoles), 3,4-dimethoxyphenethyl bromide (19.6 g, 80 mmoles), and DMF (50 ml) was heated at 80° for 10 hr with stirring. The DMF was removed by vacuum distillation, and the crystalline residue was dissolved in H_2O (150 ml). The aq. solution was washed with three 50-ml portions of ether, treated with charcoal, and evaporated *in vacuo*. The residue was dried over conc. H_2SO_4 at room temp. and recrystallized from abs. ethanol–ether to furnish Vf (21.2 g, 75%) as colorless prisms, mp 157—159° (decomp.); UV $\lambda_{max}^{abs.EtOH}$: 268 mμ (ε 6440). *Anal.* Calcd. for $C_{17}H_{22}O_2NBr$: C, 57.96; H, 6.29; N, 3.98. Found: C, 57.98; H, 6.34; N, 4.28.

Ferricyanide Oxidation of Pyridinium Salts V——Standard Procedure: To a cold (3—5°), stirred solution of a pyridinium salt V (12 mmoles) in H_2O (18 ml), was added dropwise a solution of $K_3Fe(CN)_6$ (23.7 g, 72 mmoles) in H_2O (70 ml) over a period of 30 min. Then, a solution of KOH (10.8 g, 192 mmoles) in H_2O (16 ml) was added in a similar manner. After the addition was complete, benzene (40 ml) was poured into the reaction flask, and the mixture was stirred at 32° for 5 hr in a thermoregulated constant temperature bath (accurate to ±0.1°). After cooling, the benzene layer was separated from the aq. layer, and the latter was extracted with four 50-ml portions of benzene. The combined benzene extracts were dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to leave a light brown oil, shown to be a mixture of two components (IX and XIII) by two spots on a TLC plate. In order to isolate both components, the oil was chromatographed on a 260-g alumina column using hexane–ethyl acetate as eluent. In all cases, 2-pyridone IX was eluted faster than 6-pyridone XIII. The oxidation reaction was run in triplicate and the mean value of the isomer ratios was obtained. The results with Vd,e,f are shown in Table I. In the case of Ve, the ratio of IXe to XIIIe was alternatively obtained by gas-liquid chromatography (GLC) of the crude product. The GLC analyses were performed on a Shimadzu GC-3AH gas chromatograph equipped with a 1.5 m×3 mm column containing 1.5% SE-30 (methyl silicone) on Chromosorb W, and the peak area of each isomer was determined. The isomer ratio was then estimated from calibration curves which had been constructed on analytical samples of IXe and XIIIe (Table I). The physical properties of pyridones thus prepared are described in the following.

1-(3,4-Dimethoxyphenethyl)-3-methyl-2(1*H*)-pyridone (IXd)——Recrystallized from hexane–benzene (10: 1, v/v) to almost colorless plates, mp 72—73°; spectra (Tables II and III). *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.11; H, 6.97; N, 5.15.

1-(3,4-Dimethoxyphenethyl)-5-methyl-2(1*H*)-pyridone (XIIId)——Obtained as a slightly yellowish oil, bp 220—230° (bath temp.) (10^{-3} mm Hg); Mass Spectrum *m/e*: 273 (M^+); other spectra (Tables II and III).

1-Phenethyl-3-ethyl-2(1*H*)-pyridone (IXe)——A pale yellowish oil, bp 145° (2 mm Hg); spectra (Tables II and III).

1-Phenethyl-5-ethyl-2(1*H*)-pyridone (XIIIe)——A pale yellowish oil, bp 160° (3 mm Hg) [lit.[17a] bp 192—195° (4 mm Hg)], which solidified on standing. Recrystallization from hexane gave colorless pillars, mp 55—56° (lit.[17a] mp 56—57°); spectra (Tables II and III). Picrate of XIIIe: Yellow pillars, mp 105—106° [from benzene–ligroin (1: 1, v/v)] (lit.[17a] mp 105—106°).

1-(3,4-Dimethoxyphenethyl)-3-ethyl-2(1*H*)-pyridone (IXf)——A pale yellowish oil, bp 160—162° (10^{-4} mm Hg); Mass Spectrum *m/e*: 287 (M^+); other spectra (Tables II and III).

1-(3,4-Dimethoxyphenethyl)-5-ethyl-2(1*H*)-pyridone (XIIIf)——A pale yellowish oil, bp 168—176° (bath temp.) (10^{-4} mm Hg), which solidified on standing. Recrystallized successively from ether and hexane–benzene (2: 1, v/v), mp 45—47° (lit.[17b] mp 57—58°); spectra (Tables II and III). *Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.26; H, 7.47; N, 4.78. Picrate: Yellow plates, mp 98—99° [from hexane–ethyl acetate (1: 1, v/v)] (lit.[17b] mp 99—100°).

5-Ethyl-2-piperidone (XIV)——To a stirred solution of 1-benzyl-5-ethyl-2-piperidone[7a,8] (XV: 2.50 g, 11.5 mmoles) in liquid NH_3 (80 ml) was added Na (540 mg, 0.023 g.-atom) in small pieces over a period of *ca.* 1 hr. The reaction mixture was worked up as described previously[9a] for similar debenzylation reactions, affording XIV (1.20 g, 82%) as colorless oil, bp 155—157° (15 mm Hg); IR ν_{max}^{film} cm^{-1}: 3300 (b) (NH), 1665 (lactam CO); Mass Spectrum *m/e*: 127 (M^+); NMR (CCl_4) τ: 9.03 (3H, t, J=5 cps, $C\underline{H}_3CH_2$), 8.0—8.9 (5H, m, $CH_3C\underline{H}_2$, $H_{(4)}$'s, $H_{(5)}$), 7.6—8.0 (2H, m, $H_{(3)}$'s), 6.5—7.4 (2H, m, $H_{(6)}$'s), 1.68 (1H, b, NH).

Acknowledgement We wish to thank Emeritus Professor Dr. S. Sugasawa, University of Tokyo, and Professor M. Kirisawa, Nihon University, for their interest and warm encouragement. We are also pleased to acknowledge the support of our research by a Grant-in-Aid for Scientific Research (A-67031, to Professor Y. Ban) from the Ministry of Education of Japan.