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Lactams. XIX.[1] The Alkaline Ferricyanide Oxidation of 1,3-Disubstituted Pyridinium Salts: Effects of Branched Alkyl Groups at the 3-Position[2]

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In the oxidation of 3-substituted 1-methylpyridinium salts (type III) with potassium ferricyanide and KOH at 32°C, the isopropyl and the *tert*-butyl group at the 3-position were found to orient oxidation to both the 2- (type IV) and the 6-position (type V) in ratios of 71: 29 and 14: 86, respectively. In the oxidation of the 1-methyl-3-*tert*-butylpyridinium salt (IIIl), replacement of the 1-methyl group by an aralkyl group along the series benzyl, phenethyl, and 3,4-dimethoxyphenethyl decreased the extent of the 2-pyridone formation along the series.

Keywords——Decker oxidation; pyridinium salt; pyridone; regioselectivity; *tert*-butyl group; isopropyl group; steric effect; UV; IR; NMR

The oxidation of quaternary pyridinium salts by ferricyanide ion[3] offers many possibilities for preparing 6-membered lactams through α-pyridones.[1,4] We investigated the alkaline ferricyanide oxidation of 1,3-disubstituted pyridinium salts (type III) which can afford in principle isomeric 2- and 6-pyridones (types IV and V) in a variety of ratios, and the effects of various 3-substituents on the regioselectivity in the pyridone formation were catalogued[4f,5] in terms of the observed isomer ratios. However, the effect of the 3-*tert*-butyl group, a highly branched, bulky hydrocarbon substituent, has remained undetermined because of some difficulty in obtaining pure 3-*tert*-butylpyridine (I),[6] a precursor for the required pyridinium salt (IIIl or IIIo). Our recent discovery[7] of a new synthetic route to I from α-*tert*-butylacrolein has now made it possible to determine the effect of this substituent.

Quaternization of I with an excess of MeI in benzene at room temperature produced the methiodide IIIl (X=I)[8] in 99% yield. The quaternary salt was then oxidized with potassium ferricyanide and KOH at 32±0.1°C for 5 h according to the previously reported[4f] standard procedure, giving the 2-pyridone IVl and the 6-pyridone Vl in a combined yield of 89%. The assignment of the two pyridone structures was based on the spectral data shown in Tables I and II and a difference in chromatographic mobility between IVl and Vl, which all fulfilled the previously described criteria[4f,5a,b] for distinguishing between 1,3-dialkyl-2- (type IV) and -6-pyridones (type V). The oxidation reaction was run in triplicate and analysis of the products was carried out as reported previously[4f,5] or by means of high performance liquid chromatography (HPLC); the average isomer ratio of the pyridones thus obtained was IVl: Vl =14: 86.

On the other hand, a similar ferricyanide oxidation of 1-(3,4-dimethoxyphenethyl)-3-*tert*-butylpyridinium bromide (IIIo: X=Br), prepared by quaternization of I with 3,4-dimethoxyphenethyl bromide, was found to furnish only one pyridone isomer, namely, the 6-pyridone Vo, in 57% overall yield (from I), and no 2-pyridone isomer (IVo) was detected in the crude product. When the 1-phenethyl (IIIn: X=Br) and the 1-benzyl (IIIm: X=Br) analogs, synthesized from I by quaternizations with phenethyl bromide and benzyl bromide, were likewise oxidized, both pyridone isomers were produced in ratios of IVn: Vn=2: 98 (65% yield) and IVm: Vm=9: 91 (74% yield), respectively. These changes in the isomer ratio seemed significant, since we had already observed[4f,5a] that in similar oxidations of 1-substituted 3-methyl- and 3-ethylpyridinium ions the effect of a slender N-alkyl or N-aralkyl group

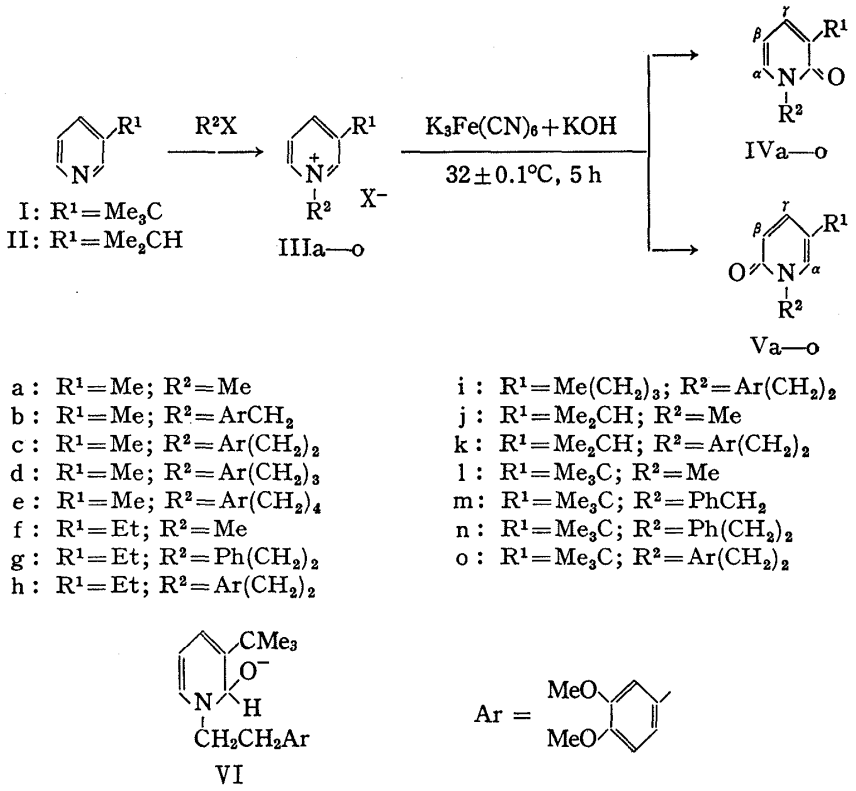

Chart 1

on the regioselectivity in the nucleus oxidation was negligibly small (see, for example, Table III). This led us to examine a similar oxidation of 1-methyl-3-isopropylpyridinium iodide (IIIj: X=I) in order to compare its result with that reported[5b] for the 1-(3,4-dimethoxyphenethyl) analog (IIIk: X=Br).

Treatment of 3-isopropylpyridine (II)[6] with an excess of MeI in benzene at room temperature yielded the methiodide (IIIj: X=I)[9] as a hygroscopic solid. On oxidation in the

Table I. Ultraviolet and Infrared Spectral Data for Pyridones

Compound No.	R^1	R^2	UV spectrum[a] Short-wavelength band λ_{max} (nm)	log ε	Long-wavelength band λ_{max} (nm)	log ε	IR spectrum[b] ν_{CO} (cm^{-1})
2-Pyridones							
IVj	Me_2CH	Me	234	3.74	303	3.83	1646
IVl	Me_3C	Me	233	3.75	301	3.83	1650
IVm	Me_3C	$PhCH_2$	235	3.73	302.5	3.84	1647
IVn	Me_3C	$Ph(CH_2)_2$	234	3.72	301	3.79	1645
6-Pyridones							
Vj	Me_2CH	Me	231	3.92	311	3.72	1665
Vl	Me_3C	Me	230	3.96	309	3.75	1663
Vm	Me_3C	$PhCH_2$	231	3.93	312	3.74	1665
Vn	Me_3C	$Ph(CH_2)_2$	230.5	3.88	312	3.71	1663
Vo	Me_3C	$Ar(CH_2)_2$[c]	230	4.18	312	3.76[d]	1660

a) Measured in abs. EtOH.
b) Determined in $CHCl_3$ solution at 0.2 M concentration.
c) The symbol Ar stands for the 3,4-dimethoxyphenyl group.
d) In addition, a medium-wavelength band was observed at 286 nm (log ε 3.70).

same manner as described above, the crude methiodide gave the 2-pyridone IVj as well as the 6-pyridone Vj in a combined yield of 88% (from II). The isomer ratio was determined to be IVj: Vj=71: 29, and it was in good agreement with that observed[5b] for the corresponding 1-(3,4-dimethoxyphenethyl)pyridinium salt (IIIk: X=Br) (IVk: Vk=71: 29).

The structures of the pyridones IVj,m,n and Vj,m—o thus obtained were assigned in the same way as described above for IVl and Vl. Tables I and II list their spectral features. It may be seen from Table II that the H_α and the H_β signals of the 2-pyridone IVn and the H_α and the *tert*-butyl proton signals (see "Experimental") of the 6-pyridones Vn,o appear upfield

Table II. 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						
IVj	7.16 (d-d)	6.11 (t)	7.16 (d-d)	6.8	—[b]	6.8
IVl	7.16 (d-d)[c]	6.04 (t)	7.20 (d-d)[c]	6.6	2.0	6.6
IVm	7.11 (d-d)	6.05 (t)	7.11 (d-d)	6.8	2.0	6.8
IVn	6.78 (d-d)	5.83 (t)	7.0—7.4[d]	6.8	2.0	6.8
6-Pyridones						
Vj	7.04 (d)	6.54 (d)	7.28 (d-d)	—[b]	2.6	9.5
Vl	7.09 (d)	6.53 (d)	7.42 (d-d)	—[b]	3.0	9.5
Vm	7.07 (d)	6.57 (d)	7.39 (d-d)	—[b]	3.0	9.5
Vn	6.50 (d)	6.58 (d)	7.38 (d-d)	—[b]	3.0	9.5
Vo	6.52 (d)	6.56 (d)	7.38 (d-d)	—[b]	3.0	9.5

a) Measured as 5% (w/v) $CDCl_3$ solution. The letter(s) in parentheses designate(s) the multiplicity of the signal; the abbreviations are given in "Experimental."
b) Unmeasurably small.
c) The distinction between the H_α and the H_γ signals is tentative.
d) Overlapped with the signals of the aromatic protons.

Table III. The Alkaline Ferricyanide Oxidation of 1,3-Disubstituted Pyridinium Salts

Pyridinium salt (III)[a]				Product[b]		
No.	R^1	R^2	X	Combined yield (%)	% 2-Pyridone (IV)	% 6-Pyridone (V)
IIIa	Me	Me	I	82	93 (IVa)[c]	7 (Va)[c]
IIIb	Me	$ArCH_2$	Cl	68	92 (IVb)	8 (Vb)
IIIc	Me	$Ar(CH_2)_2$	Br	76	94 (IVc)	6 (Vc)
IIId	Me	$Ar(CH_2)_3$	Br	50[d]	92 (IVd)	8 (Vd)
IIIe	Me	$Ar(CH_2)_4$	Br	50[d]	91 (IVe)	9 (Ve)
IIIf	Et	Me	I	86	87 (IVf)[c]	13 (Vf)[c]
IIIg	Et	$Ph(CH_2)_2$	Br	86	85 (IVg)	15 (Vg)
IIIh	Et	$Ar(CH_2)_2$	Br	71	88 (IVh)	12 (Vh)
IIIi	$Me(CH_2)_3$	$Ar(CH_2)_2$	Br	44[d]	74 (IVi)	26 (Vi)
IIIj	Me_2CH	Me	I	88[d]	71 (IVj)[e]	29 (Vj)[e]
IIIk	Me_2CH	$Ar(CH_2)_2$	Br	79[d]	71 (IVk)	29 (Vk)
IIIl	Me_3C	Me	I	89	14 (IVl)[e]	86 (Vl)[e]
IIIm	Me_3C	$PhCH_2$	Br	74	9 (IVm)	91 (Vm)
IIIn	Me_3C	$Ph(CH_2)_2$	Br	65	2 (IVn)	98 (Vn)
IIIo	Me_3C	$Ar(CH_2)_2$	Br	57[d]	0 (IVo)	100 (Vo)

a) The symbol Ar designates the 3,4-dimethoxyphenyl group.
b) Unless otherwise noted, isomer ratios were determined by column chromatographic analysis as reported previously.[4f] The results for IIIa,b,d—f are taken from ref. 5*a*; those for IIIc,g,h, from ref. 4*f*; those for IIIi,k, from ref. 5*b*.
c) Determined by gas–liquid chromatographic analysis.
d) Overall yield from the corresponding pyridine base used in the preceding quaternization reaction.
e) Analysis by means of HPLC gave identical results.

from the corresponding signals of other analogs. Such upfield shifts have already been observed[5a] for the corresponding protons of IVc and Vc, 2- and 6-pyridones of an N-phenethyl type, and were interpreted in terms of contributions of conformers folded in such a manner that these protons lie above the plane of the benzene ring.[5a]

For ready comparison, the results of the present oxidation study are summarized in Table III together with some of the previous results. It may be seen that the oxidation at the 2-position is greatly favored over that at the 6-position when the quaternary pyridinium ions (type III) carry a *n*-alkyl or isopropyl group at the 3-position. However, a higher and/or bulkier 3-alkyl group tends to increase the extent of the 6-pyridone formation, and the bulky 3-*tert*-butyl group causes a reversal of the regioselectivity in oxidation. Interestingly, the greatest reversal is the case of the 1-(3,4-dimethoxyphenethyl)-3-*tert*-butyl derivative IIIo (X=Br), where the highest degree of steric hindrance to the approach of the bulky ferricyanide ion[10] to the 2-position of the postulated intermediate 2-alkoxide (VI)[5b,c,11] (Chart 1) should be produced by the cooperation of both the bulky 3- and the 1-substituents. In this approach, however, simultaneous occurrence of electrostatic repulsion[5b,c] between the 3,4-dimethoxyphenyl ring of the 1-substituent and the ferricyanide ion (though limited in extent) is also suggested by comparison with the oxidation data on the 1-phenethyl analog IIIn (X=Br) whose phenyl ring lacks electron-donating methoxyl groups.

In conclusion, the present results offer striking examples of the steric effect operating in the ferricyanide oxidation of 1,3-disubstituted pyridinium salts. It is hoped that they will further help to unravel the mechanism of this complicated reaction.

Experimental

General Notes——All melting points are corrected; boiling points are uncorrected. See ref. 1 for details of instrumentation and measurements. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, s=singlet, sh=shoulder, t=triplet. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University.

1-Methyl-3-(1-methylethyl)pyridinium Iodide (IIIj: X=I)——A solution of 3-isopropylpyridine (II)[6] (1.23 g, 10 mmol) and MeI (4.3 g, 30 mmol) in dry benzene (5 ml) was stirred at room temp. for 5 h. The reaction mixture was partitioned between H_2O (50 ml) and benzene (30 ml). The aqueous extracts were washed with benzene, concentrated *in vacuo*, and dried to give IIIj (X=I) as a yellowish, hygroscopic solid (lit.[9] mp 85°C), which was directly used in the next oxidation step without further purification.

1-Methyl-3-(1,1-dimethylethyl)pyridinium Iodide (IIII: X=I)——A solution of 3-*tert*-butylpyridine (I)[7] (2.23 g, 16.5 mmol) and MeI (7.0 g, 49 mmol) in dry benzene (8 ml) was stirred at room temp. for 36 h. The crystals that resulted were filtered off, washed with ether, and dried to provide IIII (X=I) (4.52 g, 99%), mp 169—170.5°C. Recrystallization from acetone furnished an analytical sample as colorless needles, mp 169.5—170.5°C (lit.[8] mp 168.2—169.4°C); UV $\lambda_{max}^{abs.\ EtOH}$ 265.5 nm (log ε 3.74), 273 (sh) (3.62); NMR ($CDCl_3$) δ: 1.48 (9H, s, Me_3C), 4.73 (3H, s, NMe), 8.02 (1H, d-d, J=8.0 and 6.4 Hz, $H_{(5)}$), 8.43 (1H, d, J=8.0 Hz, $H_{(4)}$), 9.13 (1H, d, J=6.4 Hz, $H_{(6)}$), 9.17 (1H, s, $H_{(2)}$). *Anal.* Calcd for $C_{10}H_{16}IN$: C, 43.34; H, 5.82; N, 5.05. Found: C, 43.61; H, 5.89; N, 4.84.

1-Benzyl-3-(1,1-dimethylethyl)pyridinium Bromide (IIIm: X=Br)——A solution of I[7] (1.66 g, 12 mmol) and benzyl bromide (4.2 g, 25 mmol) in dry benzene (6 ml) was stirred at room temp. for 3 h. The reaction mixture was worked up as described above for IIIj (X=I), yielding IIIm (X=Br) (3.88 g, 97%) as a solid of mp 120—124°C. Recrystallization from acetone produced a monohydrate of the salt as colorless needles, mp 120—124°C (dried over P_2O_5 at 2 mmHg and room temp. for 24 h); $\lambda_{max}^{abs.\ EtOH}$ 266 nm (log ε 3.69), 274 (sh) (3.55); IR ν_{max}^{Nujol} cm^{-1}: 3460, 3400 (H_2O); NMR ($CDCl_3$) δ: 1.42 (9H, s, Me_3C), 2.17 (b, H_2O), 6.35 (2H, s, $NC\underline{H}_2Ph$), 7.15—7.80 (5H, m, Ph), 7.87 (1H, d-d, J=7.6 and 5.8 Hz, $H_{(5)}$), 8.25 (1H, d, J=7.6 Hz, $H_{(4)}$), 9.34 (1H, d, J=5.8 Hz, $H_{(6)}$), 9.58 (1H, s, $H_{(2)}$). *Anal.* Calcd for $C_{16}H_{20}BrN\cdot H_2O$: C, 59.26; H, 6.84; N, 4.32. Found: C, 59.23; H, 6.59; N, 4.39.

1-Phenethyl-3-(1,1-dimethylethyl)pyridinium Bromide (IIIn: X=Br)——A stirred solution of I[7] (1.36 g, 10 mmol) and phenethyl bromide (3.7 g, 20 mmol) in dry benzene (10 ml) was heated under reflux for 18 h. After cooling, the reaction mixture was worked up in a manner similar to that described above for IIIj (X=I) to afford a slightly yellowish solid, mp 63.5—65.5°C. On recrystallization from acetone–ether (1:1, v/v), the solid yielded a monohydrate of IIIn (X=Br) as colorless prisms, mp 65.5—67°C (dried over P_2O_5 at 2 mmHg and room temp. for 24 h); UV $\lambda_{max}^{abs.\ EtOH}$ 266 nm (log ε 3.70), 273 (sh) (3.64); IR ν_{max}^{Nujol} cm^{-1}: 3500, 3440 (H_2O); NMR ($CDCl_3$) δ: 1.25 (9H, s, Me_3C), 3.34 (2H, t, J=6.8 Hz, $NCH_2C\underline{H}_2Ph$), 3.97 (2H, s, H_2O), 5.32 (2H, t, J=6.8 Hz, $NC\underline{H}_2CH_2Ph$), 7.12 (5H, s, Ph), 7.93 (1H, d-d, J=8.0 and 5.6 Hz, $H_{(5)}$), 8.27 (1H, d,

J=8.0 Hz, $H_{(4)}$), 8.60 (1H, s, $H_{(2)}$), 9.30 (1H, d, J=5.6 Hz, $H_{(6)}$). *Anal.* Calcd for $C_{17}H_{22}BrN \cdot H_2O$: C, 60.36; H, 7.15; N, 4.14. Found: C, 60.48; H, 7.13; N, 4.43.

1-(3,4-Dimethoxyphenethyl)-3-(1,1-dimethylethyl)pyridinium Bromide (IIIo: X=Br)——A stirred solution of I[7] (1.36 g, 10 mmol) and 3,4-dimethoxyphenethyl bromide (2.85 g, 12 mmol) in dry benzene (10 ml) was refluxed for 52 h. After cooling, the reaction mixture was partitioned between H_2O (100 ml) and benzene (20 ml). The aqueous extracts were washed with benzene and concentrated *in vacuo* to leave IIIo (X=Br) as a yellow glass, which was used in the next oxidation reaction without further purification.

Ferricyanide Oxidation of the Quaternary Salts (IIIj,l—o)——The oxidations of the pyridinium salts IIIj,l (X=I) and IIIm,n,o (X=Br) were effected at 32±0.1°C for 5 h according to the previously reported[4f] standard procedure. Isolation of the isomeric pyridones that were formed and determination of the isomer ratios by column chromatographic analysis also followed the previous procedure. In all cases, the 2-pyridone (type IV) was eluted faster than the 6-pyridone (type V). Each oxidation reaction was run in duplicate or triplicate and the mean value of the isomer ratios was obtained. In the cases of IIIj (X=I) and IIIl (X=I), the isomer ratios were alternatively obtained by HPLC analysis of the crude products. The HPLC analyses were carried out on a Waters ALC/GPC 204 liquid chromatograph [Corasil II, $CHCl_3$–EtOH (98: 2, v/v), 250 p.s.i.], and the peak height of each isomer was determined. The isomer ratio was then estimated from calibration curves which had been constructed with analytical samples of the pyridone isomers.

The results thus obtained are summarized in Table III, and the isolated pyridones were characterized as described below.

1-Methyl-3-(1-methylethyl)-2(1*H*)-pyridone (IVj)——This compound was isolated as a colorless oil, bp 106°C (5 mmHg); MS *m/e*: 151 (M^+); NMR ($CDCl_3$) δ: 1.18 (6H, d, J=7.0 Hz, $\underline{Me}_2CH$), 3.22 (1H, septet, J=7.0 Hz, $Me_2C\underline{H}$), 3.55 (3H, s, NMe), pyridone-ring protons (Table II); other spectra (Table I).

1-Methyl-3-(1,1-dimethylethyl)-2(1*H*)-pyridone (IVl)——This was purified by sublimation at 75—85°C (bath temp.) and 18 mmHg to give colorless scales, mp 78.5—79.5°C; MS *m/e*: 165 (M^+); NMR ($CDCl_3$) δ: 1.36 (9H, s, Me_3C), 3.52 (3H, s, NMe), pyridone-ring protons (Table II); other spectra (Table I). *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.68; H, 9.26; N, 8.61.

1-Benzyl-3-(1,1-dimethylethyl)-2(1*H*)-pyridone (IVm)——Recrystallized from hexane as colorless needles, mp 76—77.5°C; MS *m/e*: 241 (M^+); NMR ($CDCl_3$) δ: 1.36 (9H, s, Me_3C), 5.13 (2H, s, $NC\underline{H}_2Ph$), 7.20—7.36 (5H, m, Ph), pyridone-ring protons (Table II); other spectra (Table I). *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.68; H, 8.19; N, 6.01.

1-Phenethyl-3-(1,1-dimethylethyl)-2(1*H*)-pyridone (IVn)——Obtained as a reddish, thick oil, MS *m/e*: 255 (M^+); NMR ($CDCl_3$) δ: 1.35 (9H, s, Me_3C), 3.00 (2H, t, J=7.4 Hz, $NCH_2C\underline{H}_2Ph$), 4.07 (2H, t, J=7.4 Hz, $NC\underline{H}_2CH_2Ph$), 7.0—7.4 (m, Ph), pyridone-ring protons (Table II); other spectra (Table I).

1-Methyl-5-(1-methylethyl)-2(1*H*)-pyridone (Vj)——A colorless oil, bp 124°C (5 mmHg); MS *m/e*: 151 (M^+); NMR ($CDCl_3$) δ: 1.16 (6H, d, J=7.0 Hz, $\underline{Me}_2CH$), 2.66 (1H, septet, J=7.0 Hz, $Me_2C\underline{H}$), 3.52 (3H, s, NMe), pyridone-ring protons (Table II); other spectra (Table I).

1-Methyl-5-(1,1-dimethylethyl)-2(1*H*)-pyridone (Vl)——Crystallized from hexane as colorless scales, mp 91.5—92.5°C; MS *m/e*: 165 (M^+); NMR ($CDCl_3$) δ: 1.24 (9H, s, Me_3C), 3.54 (3H, s, NMe), pyridone-ring protons (Table II); other spectra (Table I). *Anal.* Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.56; H, 9.38; N, 8.39.

1-Benzyl-5-(1,1-dimethylethyl)-2(1*H*)-pyridone (Vm)——Recrystallized from hexane as faintly yellowish needles, mp 99—101°C; MS *m/e*: 241 (M^+); NMR ($CDCl_3$) δ: 1.19 (9H, s, Me_3C), 5.11 (2H, s, $NC\underline{H}_2Ph$), 7.22—7.32 (5H, m, Ph), pyridone-ring protons (Table II); other spectra (Table I). *Anal.* Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.72; H, 8.03; N, 5.70.

1-Phenethyl-5-(1,1-dimethylethyl)-2(1*H*)-pyridone (Vn)——Obtained as a reddish, thick oil, MS *m/e*: 255 (M^+); NMR ($CDCl_3$) δ: 1.04 (9H, s, Me_3C), 3.04 (2H, t, J=7.0 Hz, $NCH_2C\underline{H}_2Ph$), 4.14 (2H, t, J=7.0 Hz, $NC\underline{H}_2CH_2Ph$), 7.0—7.3 (5H, m, Ph), pyridone-ring protons (Table II); other spectra (Table I).

1-(3,4-Dimethoxyphenethyl)-5-(1,1-dimethylethyl)-2(1*H*)-pyridone (Vo)——A reddish, thick oil, MS *m/e*: 315 (M^+); NMR ($CDCl_3$) δ: 1.06 (9H, s, Me_3C), 3.00 (2H, t, J=6.5 Hz, $NCH_2C\underline{H}_2Ar$), 3.76 and 3.84 (3H each, s, two MeO's), 4.12 (2H, t, J=6.5 Hz, $NC\underline{H}_2CH_2Ar$), pyridone-ring protons (Table II); other spectra (Table I).

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