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Lactams. IX.[1] Generation of Lactam Carbonyl Function in 1,3-Disubstituted Piperidines by Mercuric Acetate-EDTA Oxidation: Effects of Hydrocarbon Substituents at the 3-Position[2]

Tozo Fujii, Kiyoshi Yoshida, Masashi Ohba, and Shigeyuki Yoshifuji

Faculty of Pharmaceutical Sciences, Kanazawa University[3]

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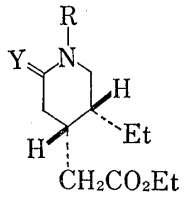
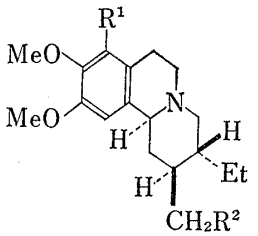
The mercuric acetate–(ethylenedinitrilo)tetraacetic acid oxidation of 1-(3,4-dimethoxyphenyl)-2-(3-substituted piperidino)ethanols (**7c—f**), which carry the *n*-butyl, isopropyl, benzyl, and phenyl group as the 3-substituent in the piperidine ring, has been found to produce the corresponding 2- (**8c—f**) and 6-piperidones (**12c—f**) in good yields in ratios of 41 : 59, 29 : 71, 26 : 74, and 15 : 85. It is suggested that the 3-substituents exert both steric and electronic effects. The structures of the lactam alcohols (**8c—f**, **12c—f**) have been confirmed by the chemical correlation with the known pyridones (**11c—f**, **15c—f**) through the lactams (**10c—f**, **14c—f**). The starting piperidinoethanols (**7c—f**) have been synthesized from the 3-substituted pyridines (**5c—f**) by quaternization with 3,4-dimethoxyphenacyl bromide followed by catalytic and sodium borohydride reductions.

Keywords——1,3-disubstituted piperidines; mercuric acetate–EDTA oxidation; piperidones; isomer ratio; effect of hydrocarbon substituent; chromatographic analysis; IR

Our recent success in synthetic incorporation of cincholoipon ethyl ester (**1**), a degradation product from the major cinchona alkaloids, into the ipecac alkaloids (**3**)[4] and the *Alangium lamarckii* alkaloid ankorine (**4**)[5] through the piperidone intermediate (type **2**) has exemplified the actual usefulness of the mercuric acetate–(ethylenedinitrilo)tetraacetic acid (EDTA) oxidation method[6,7] for generation of the lactam carbonyl function in the piperidine ring. Since the unsymmetrical structural feature of **1** required some preliminary experiments to reveal the effects of the 3-ethyl group upon the position of the functionalization, we carried out, prior



1 : R=H; Y=H$_2$
2 : R=2-arylethyl; Y=O



3 : R^1=H; R^2=CHO or a heterocyclic moiety
4 : R^1=OH; R^2=CH$_2$OH

Chart 1

1) Paper VIII in this series, T. Fujii, K. Yoshida, M. Ohba, M. Mitsukuchi, I. Tanaka, S. Yoshifuji, and M. Kirisawa, *Chem. Pharm. Bull.* (Tokyo), **25**, 2072 (1977).
2) Presented in part at the 94th Annual Meeting of Pharmaceutical Society of Japan, Sendai, April 4, 1974.
3) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*
4) T. Fujii and S. Yoshifuji, *Tetrahedron Lett.*, **1975**, 731.
5) S. Yoshifuji and T. Fujii, *Tetrahedron Lett.*, **1975**, 1965.
6) J. Knabe, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **292**, 416 (1959).
7) H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **297**, 474 (1964).

to the above alkaloid syntheses, a quantitative analytical work to determine the isomer ratios of the 3-substituted 2- (type **8**) and 6-piperidones (type **12**) produced by the mercuric acetate–EDTA oxidation of 1-aryl-2-(3-substituted piperidino)ethanols (type **7**).[8] A previous paper[9] in this series described the effect of a 3-alkyl substituent (Me, Et) observed in that study and the present paper reports the effects of various hydrocarbon groups at the 3-position.

The quaternization of the pyridine bases (**5c—f**) with 3,4-dimethoxyphenacyl bromide in benzene furnished the corresponding pyridinium salts (**6c—f**) in excellent yields. Conversion of these salts into the piperidinoethanols (**7c—f**) was readily achieved by means of catalytic hydrogenation over Adams catalyst followed by sodium borohydride reduction. Although each of the piperidinoethanols thus produced was presumed to be a mixture of the two possible diastereoisomers, it was directly used in the next oxidation step because of the difficulty in purification.

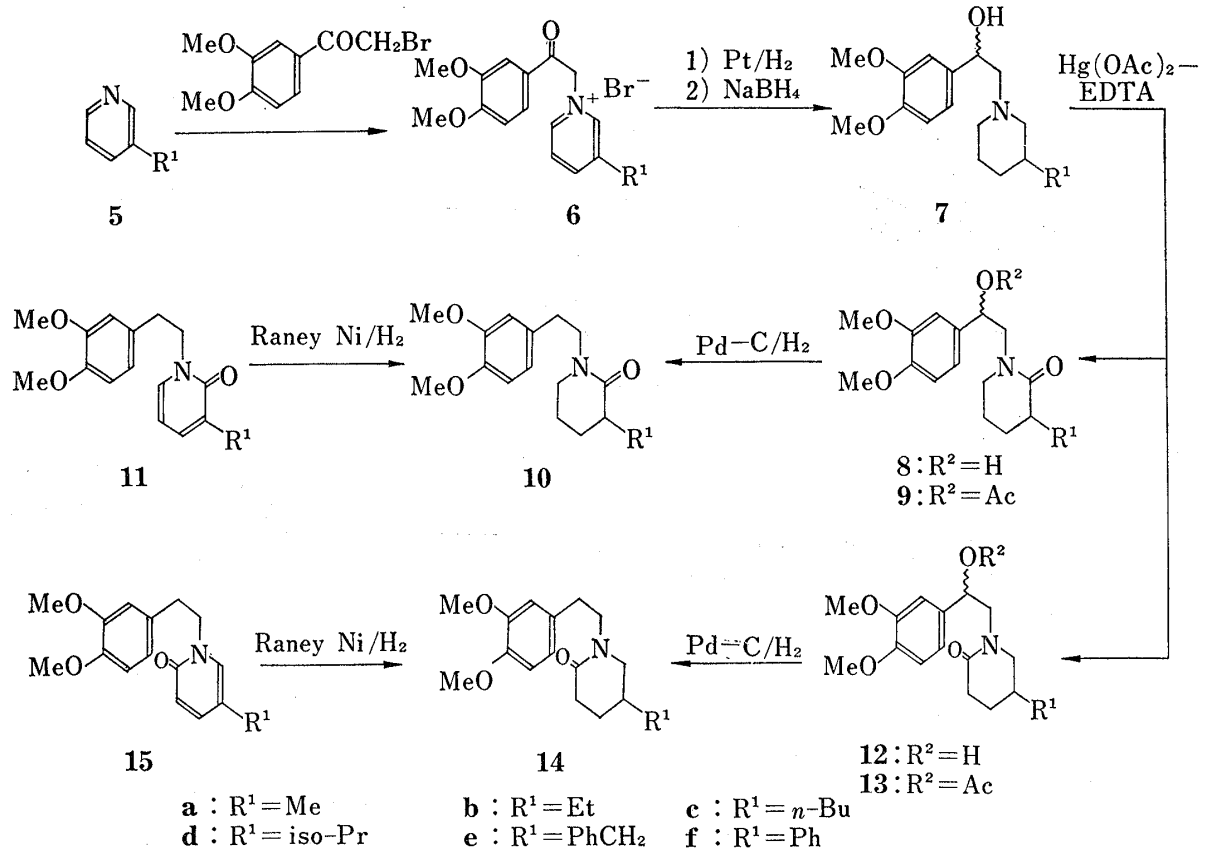


Chart 2

All the mercuric acetate–EDTA oxidations (in boiling 1% aqueous AcOH, 1.5 hr) of **7c—f** and the determination of the isomer ratio of the resulting piperidones (**8**, **12**) were carried out according to the previously reported standard procedure.[9] In these oxidation reactions, the concomitant formation of small amounts of the O-acetyl derivatives (types **9** and **13**) could be anticipated[9,10] and was actually suggested by means of thin-layer chromatography (TLC) of the reaction mixtures. However, the post-treatment with alkali, included in the standard procedure, should have converted them, if any, into the corresponding lactam alcohols (types

8) T. Fujii, M. Ohba, and S. Yoshifuji, Abstracts of Papers, the 8th Congress of Heterocyclic Chemistry, Kyoto, October, 1975, p. 134.
9) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **21**, 2695 (1973).
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TABLE I. The Mercuric Acetate–EDTA Oxidation of 1,3-Disubstituted Piperidines (7)

Starting material	Substituent R^1	Product[a]		
		Combined yield (%)	% 2-oxidation	% 6-oxidation
7a	Me	75[b]	45 (8a)[b]	55 (12a)[b]
7b	Et	76[b]	46 (8b)[b]	54 (12b)[b]
7c	*n*-Bu	82	41 (8c)	59 (12c)
7d	iso-Pr	86	29 (8d)	71 (12d)
7e	$PhCH_2$	84	26 (8e)	74 (12e)
7f	Ph	71	15 (8f)	85 (12f)

a) All isomer ratios were determined by chromatographic analysis as reported previously.[9]
b) From ref. 9.

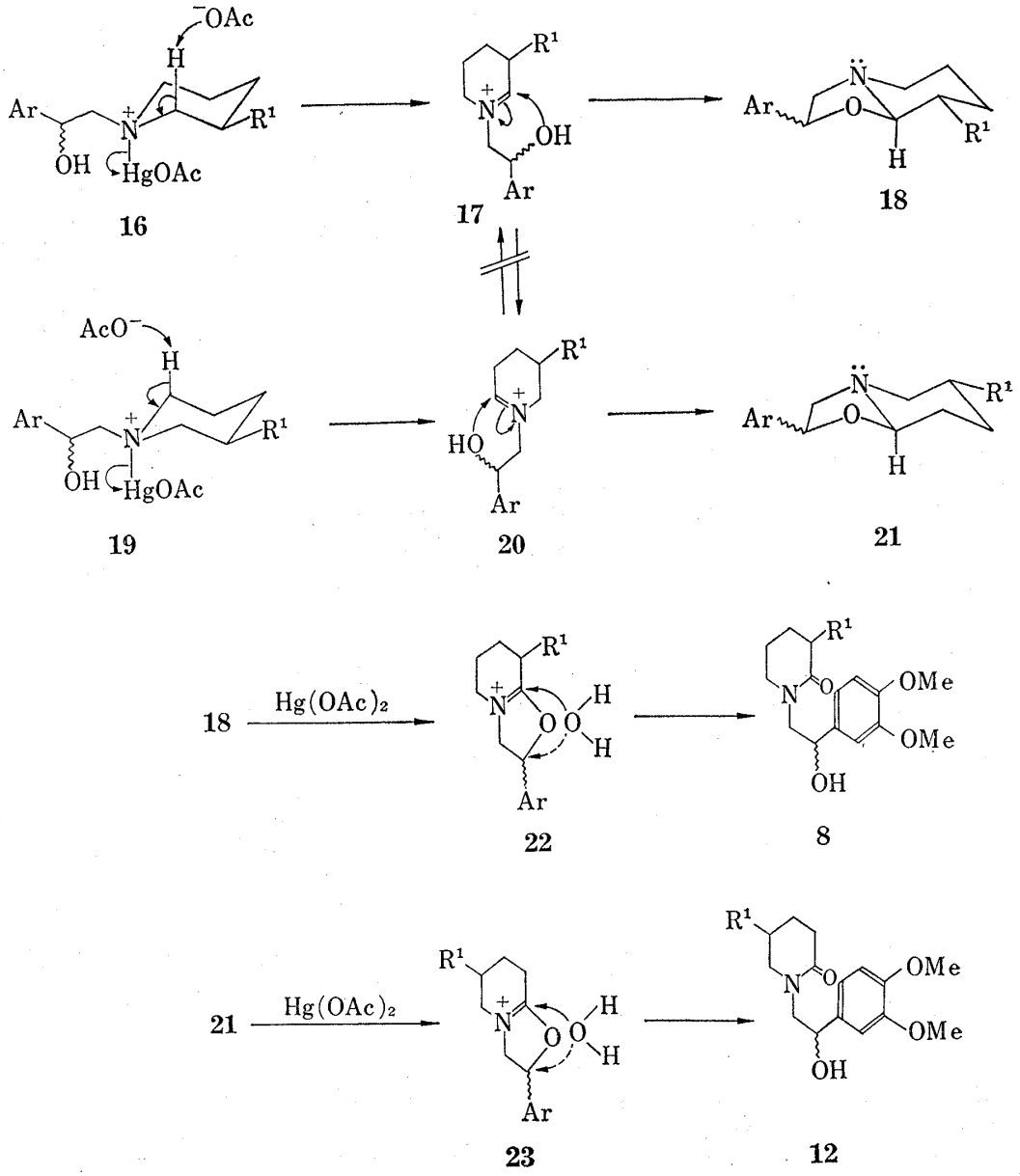

Chart 3

8 and **12**). Each of **8c—f** and **12c—f** thus obtained was presumably a diastereoisomeric mixture and the location of the lactam carbonyl group was established by hydrogenolysis using hydrogen and palladium-on-charcoal in the presence of a little perchloric acid, which led to the 2-piperidone derivative (type **10**) or 6-piperidone derivative (type **14**) identical with a sample prepared from the known 2- (type **11**)[1] or 6-pyridone derivative (type **15**)[1] by catalytic hydrogenation.

The results of the oxidation of the piperidinoethanols (**7a—f**) are summarized in Table I. It may be seen that in all cases the reaction proceeds smoothly and a hydrocarbon group at the 3-position orients the oxidation to both the 2- and the 6-position but with an advantage to the latter position. A higher and/or bulkier 3-substituent tends to increase the extent of the 6-oxidation and the 3-phenyl group is the one with which a marked preference for the 6-oxidation has been noticed.

On the basis of the postulated mechanism of the mercuric acetate oxidation of cyclic amines[11] and piperidinoalcohols,[10,12–14] the observed orientation of the oxidation may be interpreted as follows (Chart 3). The abstraction of the axial proton from $C_{(2)}$ of the mercurated complex (**16**) by the acetate ion could be a concerted process with cleavage of the nitrogen–mercury bond. The resulting iminium ion (**17**) would undergo intramolecular cyclization to give the oxazolidine derivative (**18**), which could be similarly dehydrogenated by a second molecule of mercuric acetate to the oxazolinium ion (**22**). Attack of **22** by water at $C_{(2)}$ (or $C_{(5)}$) of the oxazoline moiety would result in the formation of the 2-piperidone derivative (**8**). For the formation of the 6-piperidone derivative (**12**), a parallel sequence starting with the abstraction of the axial proton from $C_{(6)}$ of the mercurated complex (**19**) may be formulated (**19**→**20**→**21**→**23**→**12**). Since the isomerization of one iminium salt to the other (**17**, **20**) would not occur under the reaction conditions employed,[15,16] the unfavored oxidation at the 2-position shown in Table I may be due to steric repulsion between the hydrocarbon group (R^1) at the 3-position and the acetate ion approaching to the axial $C_{(2)}$-proton (type **16**). This steric hindrance explanation is also preferred for understanding the 2-oxidation decreasing effect of the higher and/or bulkier 3-substituents. In addition, comparison of the quantitative data on the effects of the 3-isopropyl and the 3-phenyl group in Table I suggests that electrostatic repulsion between the electronegative substituent and the acetate ion may also be operative.

As illustrated in Chart 2, the 1,3-disubstituted piperidones (**10**, **14**) can be prepared alternatively from the corresponding pyridones (**11**, **15**) which are easily obtained by the alkaline ferricyanide oxidation of 1,3-disubstituted pyridinium salts. In recent work,[1] we have revealed that in this oxidation various alkyl groups at the 3-position orient the oxidation to the 2-position predominantly. Consequently, the mercuric acetate–EDTA and the alkaline ferricyanide oxidation methods serve as complementary one to the other in regard to the efficiency of synthesizing the isomeric piperidones (**10**, **14**) from 3-alkylpyridines (**5**).

Now that several pairs of the isomeric piperidones (**10**, **14**) are available, we are able to examine whether any convenient diagnostic method exists for differentiating between both isomers. It has been found that in their infrared (IR) spectra in $CHCl_3$ solution at 0.2 M concentration all the 2-piperidones (**10a—f**) display the CO stretching vibration in the 1619—1629 cm^{-1} region, and the 6-piperidones (**14a—f**), in the range 1623—1630 cm^{-1}. Although the partial overlapping of the two regions makes the general differentiation of both isomers difficult, the fact that a higher shift of the CO frequency of the 6-piperidone derivative (type **14**) by *ca.* 5 cm^{-1} is observed for every pair of the isomeric piperidones (**10a—e**, **14a—e**), except

11) N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, **77**, 439 (1955).
12) N. J. Leonard, K. Conrow, and R. R. Sauers, *J. Am. Chem. Soc.*, **80**, 5185 (1958).
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16) H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **299**, 295 (1966).

the pair of the 3-phenyl derivatives (**10f, 14f**) which show their CO bands at almost identical positions, may find ways to be utilized as criterion for distinguishing between 1,3-disubstituted 2- and 6-piperidones in certain cases. A similar relation has also been found to hold for the CO stretching vibration band positions of the isomeric pairs of the lactam alcohols (**8a—f, 12a—f**).

Experimental

All melting points are corrected; boiling points, uncorrected. IR spectra were measured in Nujol mulls, in liquid films, or in $CHCl_3$ solutions at 0.2 M concentration. See also ref. 1 for details of instrumentation and measurement. The following abbreviations are used: b=broad, d=doublet, d-d=doublet-of-doublets, m=multiplet, s=singlet, sh=shoulder, t=triplet.

Quaternization of the Bases (5c—f) to the Pyridinium Salts (6c—f)——A solution of a pyridine base (**5c**,[17] **5d**,[18] **5e**,[19] or **5f**[20]) (44 mmol) and 3,4-dimethoxyphenacyl bromide[21] (10.36 g, 40 mmol) in dry benzene (100 ml) was stirred at room temp. for 48 hr. The resulting colorless precipitate was filtered off, washed with benzene, and dried to give the corresponding quaternary salt (**6c**, **6d**, **6e**, or **6f**) in 98%, 97%, 95%, or 85% yield. The salts (**6c—f**) thus produced were recrystallized from appropriate solvents and characterized as described below.

1-(3,4-Dimethoxyphenacyl)-3-butylpyridinium Bromide (**6c**)——Recrystallized from EtOH–ether (20: 1, v/v) to colorless, minute needles, mp 171—171.5° (dec.); ultraviolet spectrum (UV) $\lambda_{max}^{abs.EtOH}$ nm (ε): 232.5 (19500), 276.5 (16500), 311 (11000); IR ν_{max}^{Nujol} 1670 cm^{-1} (CO); nuclear magnetic resonance spectrum (NMR) (Me_2SO-d_6) δ: 0.97 (3H, unresolved t, $\underline{Me}CH_2$), 1.15—2.2 (4H, m, $MeC\underline{H}_2C\underline{H}_2$), 2.95 (2H, t, J=7 Hz, $PrC\underline{H}_2$), 3.86 and 3.91 (3H each, s, two MeO's), 6.54 (2H, s, NCH_2CO), 7.18 (1H, d, J=9 Hz, $H_{(5')}$), 7.52 (1H, d, J=2 Hz, $H_{(2')}$), 7.76 (1H, d-d, J=9 and 2 Hz, $H_{(6')}$), 8.17 (1H, d-d, J=8 and 6 Hz, $H_{(5)}$), 8.63 (1H, b, d, J=8 Hz, $H_{(4)}$), 8.94 (1H, b, d, J=6 Hz, $H_{(6)}$), 9.06 (1H, b, s, $H_{(2)}$). *Anal.* Calcd. for $C_{19}H_{24}BrNO_3$: C, 57.88; H, 6.14; N, 3.55. Found: C, 57.70; H, 6.19; N, 3.82.

1-(3,4-Dimethoxyphenacyl)-3-isopropylpyridinium Bromide (**6d**)——Recrystallized from acetone–EtOH (10: 1, v/v) to colorless prisms, mp 153—155° (dec.); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 232.5 (19000), 275.5 (15700), 311 (10700); IR ν_{max}^{Nujol} 1683 cm^{-1} (CO); NMR (Me_2SO-d_6) δ: 1.33 (6H, d, J=7 Hz, $\underline{Me}_2CH$), 2.21 (1H, m, $Me_2C\underline{H}$), 3.87 and 3.92 (3H each, s, two MeO's), 6.59 (2H, s, NCH_2CO), 7.22 (1H, d, J=9 Hz, $H_{(5')}$), 7.55 (1H, d, J=2 Hz, $H_{(2')}$), 7.78 (1H, d-d, J=9 and 2 Hz, $H_{(6')}$), 8.21 (1H, d-d, J=8 and 6 Hz, $H_{(5)}$), 8.70 (1H, b, d, J=8 Hz, $H_{(4)}$), 8.94 (1H, b, d, J=6 Hz, $H_{(6)}$), 9.14 (1H, b, s, $H_{(2)}$).

1-(3,4-Dimethoxyphenacyl)-3-benzylpyridinium Bromide (**6e**)——Crystallized from EtOH in colorless needles, mp 179—180.5° (dec.); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 232.5 (22300), 280 (16400), 312 (10900); IR ν_{max}^{Nujol} 1680 cm^{-1} (CO). *Anal.* Calcd. for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.89; H, 5.12; N, 3.23.

1-(3,4-Dimethoxyphenacyl)-3-phenylpyridinium Bromide (**6f**)——Crystallized from EtOH in colorless prisms, mp 215—216.5° (dec.); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 234 (29700), 278 (20500), 307 (15600); IR ν_{max}^{Nujol} 1688 cm^{-1} (CO). *Anal.* Calcd. for $C_{21}H_{20}BrNO_3$: C, 60.88; H, 4.87; N, 3.38. Found: C, 61.16; H, 5.00; N, 3.25.

Reduction of the Quaternary Salts (6c—f) to the Piperidinoethanols (**7c—f**)——Solutions of the salts (**6c—f**) in EtOH (in the cases of **6c** and **6d**) or 95% aq. EtOH (in the case of **6e**) or 50% aq. EtOH (in the case of **6f**) were separately subjected to catalytic hydrogenation (Pt/H_2) followed by $NaBH_4$ reduction in a manner similar to that described previously[9] for the conversion of **6a** into **7a**. The resulting **7c**, **7d**, **7e**, and **7f**, presumed to be diastereoisomeric mixtures, were isolated in 97%, 98%, 98%, and 95% yields and characterized as follows.

1-(3,4-Dimethoxyphenyl)-2-(3-butylpiperidino)ethanol (**7c**)——A colorless, thick oil, bp 168—174° (10^{-3}—10^{-4} mmHg); MS *m/e*: 321 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231 (8600), 279 (2700); IR $\nu_{max}^{CHCl_3}$ 3360 cm^{-1} (OH); NMR ($CDCl_3$) δ: 0.6—1.0 (3H, m, diastereiosomeric $\underline{Me}CH_2$'s), 1.0—2.2 (11H, m, $MeC\underline{H}_2C\underline{H}_2C\underline{H}_2$, two ring-$CH_2$'s, and -CH), 2.3—3.3 (6H, m, three NCH_2's), 3.88 and 3.91 (3H each, s, two MeO's), 3.99 (1H, s, OH), 4.47—4.88 [1H, m, $ArC\underline{H}(OH)$], 6.7—7.0 (3H, m, aromatic protons).

1-(3,4-Dimethoxyphenyl)-2-(3-isopropylpiperidino)ethanol (**7d**)——A colorless, thick oil, bp 152—153° (0.04 mmHg); MS *m/e*: 307 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (8750), 279 (2970); IR ν_{max}^{film} 3430 cm^{-1} (OH); NMR ($CDCl_3$) δ: 0.7—1.2 (6H, m, diastereoisomeric $\underline{Me}_2CH$'s), 1.2—3.2 [12H, unresolved m, nine ring-protons, $NC\underline{H}_2CH(OH)$, $Me_2C\underline{H}$], 3.88 and 3.92 (3H each, s, two MeO's), 3.70—3.92 (1H, b, OH), 4.54—4.78 [1H, m, $ArC\underline{H}(OH)$], 6.76—7.02 (3H, m, aromatic protons).

1-(3,4-Dimethoxyphenyl)-2-(3-benzylpiperidino)ethanol (**7e**)——A colorless, thick oil, MS *m/e*: 355

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18) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).
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20) H. Rapoport, M. Look, and G. J. Kelly, *J. Am. Chem. Soc.*, **74**, 6293 (1952).
21) C. Mannich and F. L. Hahn, *Ber. Dtsch. Chem. Ges.*, **44**, 1542 (1911).

(M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231 (7930), 280 (2930); IR $\nu_{max}^{CHCl_3}$ 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ: 1.55—2.1 (5H, m, two ring-CH_2's and -CH), 2.3—2.9 (6H, m, three NCH_2's), 3.05 (2H, d, J=8.5 Hz, $C_6H_5C\underline{H}_2$), 3.35 (1H, b, OH), 3.87 and 3.89 (3H each, s, two MeO's), 4.55—4.75 [1H, m, ArC$\underline{H}$(OH)], 6.8—7.0 (3H, m, aromatic protons), 7.1—7.45 (5H, m, C_6H_5).

1-(3,4-Dimethoxyphenyl)-2-(3-phenylpiperidino)ethanol (7f)——A colorless, thick oil, bp 220—225° (0.3 mmHg); MS *m/e*: 341 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 229.5 (10700), 278.5 (3360); IR $\nu_{max}^{CHCl_3}$ 3390 cm^{-1} (OH); NMR ($CDCl_3$) δ: 1.3—2.2 (5H, m, two ring-CH_2's and -CH), 2.2—3.5 (6H, m, three NCH_2's), 3.91 and 3.94 (3H each, s, two MeO's), 3.8—4.1 (1H, b, OH), 4.45—4.90 [1H, m, ArC$\underline{H}$(OH)], 6.8—7.05 (3H, m, aromatic protons), 7.15—7.45 (5H, m, C_6H_5).

Mercuric Acetate-EDTA Oxidation of the Piperidinoethanols (7c—f)——The oxidation of **7c—f**, which were presumably diastereoisomeric mixtures, was carried out in boiling 1% aq. AcOH for 1.5 hr according to the previously reported standard procedure.[9] The post-treatment of the reaction mixtures and determination of the isomer ratios (**8**: **12**) by chromatographic analysis also followed that procedure. In all cases, 2-piperidone **8** was eluted faster than 6-piperidone **12** in the chromatographic analysis.

The results of these oxidation experiments are summarized in Table I, and the isolated piperidones (**8c—f, 12c—f**), presumed to be diastereoisomeric mixtures, were characterized as follows.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-butyl-2-piperidone (8c)——Crystallized from petroleum ether-ether (1: 1, v/v) in colorless needles, mp 59—63.5°, which turned oil on drying in a desiccator; MS *m/e*: 335 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230.5 (9450), 278.5 (2810); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1608 (lactam CO); NMR ($CDCl_3$) δ: 0.65—1.1 (3H, unresolved m, $\underline{Me}CH_2$), 1.1—2.05 (10H, m, $MeC\underline{H}_2C\underline{H}_2C\underline{H}_2$, $H_{(4)}$'s, $H_{(5)}$'s), 2.05—2.55 (1H, b, m, $H_{(3)}$), 2.75—3.35 (2H, m, $H_{(6)}$'s), 3.45—3.7 [2H, m, ArCH(OH)C$\underline{H}_2$], 3.86 and 3.88 (3H each, s, two MeO's), 4.08 (1H, b, OH), 4.80—5.08 [1H, m, ArC$\underline{H}$(OH)], 6.70—6.98 (3H, m, aromatic protons).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-isopropyl-2-piperidone (8d)——Recrystallized from hexane-AcOEt (1: 1, v/v) to colorless prisms, mp 99—100.5°; MS *m/e*: 321 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (9580), 279 (2690); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (OH), 1606 (lactam CO); NMR ($CDCl_3$) δ: 0.83 and 0.94 (3H each, d, J=7 Hz, $\underline{Me}_2CH$), 1.23—1.95 (4H, m, $H_{(4)}$'s, $H_{(5)}$'s), 2.10—2.75 (2H, m, $Me_2C\underline{H}$, $H_{(3)}$), 2.75—3.35 (2H, m, $H_{(6)}$'s), 3.50—3.70 [2H, m, ArCH(OH)C$\underline{H}_2$], 3.87 and 3.88 (3H each, s, two MeO's), 4.63 (1H, s, OH), 4.85—5.0 [1H, m, ArC$\underline{H}$(OH)], 6.70—7.00 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.40; H, 8.38; N, 4.39.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-benzyl-2-piperidone (8e)——Recrystallized from AcOEt to colorless prisms, mp 109—110°; MS *m/e*: 369 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231 (sh) (10600), 280 (3000); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1608 (lactam CO); NMR ($CDCl_3$) δ: 1.2—2.0 (4H, m, $H_{(4)}$'s, $H_{(5)}$'s), 1.89 [1H, s, $1/2H_2O$ (hydrate)], 2.5—3.8 [7H, m, $C_6H_5C\underline{H}_2$, $H_{(3)}$, $H_{(6)}$'s, ArCH(OH)C$\underline{H}_2$], 3.89 and 3.91 (3H each, s, two MeO's), 4.7—5.1 [2H, m, ArC$\underline{H}$(O$\underline{H}$)], 6.85—7.1 (3H, m, aromatic protons), 7.15—7.4 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{22}H_{27}NO_4 \cdot 1/2H_2O$: C, 69.82; H, 7.46; N, 3.70. Found: C, 70.07; H, 7.41; N, 3.64.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-phenyl-2-piperidone (8f)——Crystallized from hexane-AcOEt (1: 1, v/v) in colorless prisms, mp 160—161.5°; MS *m/e*: 355 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 228 (10960), 279 (2990); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1620 (lactam CO); NMR ($CDCl_3$) δ: 3.72 (s, OH), 3.88 (6H, s, two MeO's), 4.87—5.2 [1H, m, ArC$\underline{H}$(OH)], 6.83—7.05 (3H, m, aromatic protons), 7.13—7.52 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.72; H, 7.10; N, 4.07.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-butyl-2-piperidone (12c)——A pale yellowish oil, MS *m/e*: 335 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230.5 (8950), 278 (2750); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH), 1615 (lactam CO); NMR ($CDCl_3$) δ: 0.65—1.05 (3H, unresolved m, $\underline{Me}CH_2$), 1.05—1.35 (6H, m, $MeC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.35—2.1 (3H, m, $H_{(4)}$'s, $H_{(5)}$), 2.1—2.75 (2H, m, $H_{(3)}$'s), 2.75—3.35 (2H, m, $H_{(6)}$'s), 3.35—3.80 [2H, m, ArCH(OH)-C$\underline{H}_2$], 3.89 and 3.92 (3H each, s, two MeO's), 4.48 (1H, b, OH), 4.8—5.2 [1H, m, ArC$\underline{H}$(OH)], 6.82—7.08 (3H, m, aromatic protons).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-isopropyl-2-piperidone (12d)——Recrystallized from AcOEt to colorless pillars, mp 115—117°; MS *m/e*: 321 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (8950), 279 (2900); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3320 (OH), 1614 (lactam CO); NMR ($CDCl_3$) δ: 0.72—1.04 (6H, m, $\underline{Me}_2CH$), 1.20—1.96 (4H, m, $H_{(4)}$'s, $Me_2C\underline{H}$, $H_{(5)}$), 2.27—2.56 (2H, m, $H_{(3)}$'s), 2.74—3.2 (2H, m, $H_{(6)}$'s), 3.2—3.8 [2H, m, ArCH(OH)-C$\underline{H}_2$], 3.88 and 3.90 (3H each, s, two MeO's), 4.54 (1H, s, OH), 4.84—5.04 [1H, m, ArC$\underline{H}$(OH)], 6.73—7.04 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.17; H, 8.27; N, 4.18.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-benzyl-2-piperidone (12e)——Recrystallized from hexane-AcOEt (1: 1, v/v) to colorless prisms, mp 111—112°; MS *m/e*: 369 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231 (9000), 280 (2850); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3350 (OH), 1614 (lactam CO); NMR ($CDCl_3$) δ: 1.3—2.2 (3H, m, $H_{(4)}$'s, $H_{(5)}$), 2.3—2.7 (4H, m, $H_{(3)}$'s, $C_6H_5C\underline{H}_2$), 2.85—3.76 [4H, m, $H_{(6)}$'s, ArCH(OH)C$\underline{H}_2$], 3.88 (6H, s, two MeO's), 4.86 (1H, s, OH), 4.8—5.05 [1H, m, ArC$\underline{H}$(OH)], 6.8—7.4 (8H, m, aromatic protons, C_6H_5). *Anal.* Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.29; H, 7.33; N, 3.92.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-phenyl-2-piperidone (12f)——Crystallized from AcOEt-EtOH (8: 1, v/v) in colorless, minute needles, mp 156—158°; MS *m/e*: 355 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 229.5 (9460), 279 (2850); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3370 (OH), 1619 (lactam CO); NMR ($CDCl_3$) δ: 3.88 (6H, s, two MeO's), 4.08 (1H, s, OH), 4.8—5.15 [1H, ArC$\underline{H}$(OH)], 6.78—7.0 (3H, aromatic protons), 7.0—8.4 (5H, m, C_6H_5).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: 70.78; H, 7.08; N, 4.01.

Hydrogenolysis of the Lactam Alcohols (8c—f, 12c—f) to the Lactams (10c—f, 14c—f)——The lactam alcohols (**8c—f**, **12c—f**) were separately reduced (10% Pd–C/H_2, EtOH–70% aq. $HClO_4$, 3.6—3.8 atm) in a manner similar to that reported previously[9] for the hydrogenolysis of **8a** to **10a**. The results are summarized in the following.

1-(3,4-Dimethoxyphenethyl)-3-butyl-2-piperidone (10c)——Obtained in 87% yield as a slightly yellowish oil, MS *m/e*: 319 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 229 (9170), 280 (2850); IR $\nu_{max}^{CHCl_3}$ 1620 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 0.6—1.05 (3H, unresolved t, $\underline{Me}CH_2$), 2.6—3.0 and 3.35—3.75 (m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 3.90 and 3.92 (3H each, s, two MeO's), 6.75 (3H, s, aromatic protons).

1-(3,4-Dimethoxyphenethyl)-3-isopropyl-2-piperidone (10d)——Isolated in 87% yield as a colorless oil, MS *m/e*: 305 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 229.5 (9440), 280.5 (2920); IR $\nu_{max}^{CHCl_3}$ 1619 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 0.80 and 0.93 (3H each, d, $J=7$ Hz, $\underline{Me}_2CH$), 2.7—2.9 and 3.26—3.74 (m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 3.84 and 3.86 (3H each, s, two MeO's), 6.74 (3H, s, aromatic protons).

1-(3,4-Dimethoxyphenethyl)-3-benzyl-2-piperidone (10e)——Obtained in 89% yield and recrystallized from hexane–AcOEt (4: 1, v/v) to colorless needles, mp 69—70.5°; UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (sh) (9720), 280 (2940); IR $\nu_{max}^{CHCl_3}$ 1620 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.2—1.95 (4H, m, $H_{(4)}$'s, $H_{(5)}$'s), 1.85 [*ca.* 1/2H, s, $1/4H_2O$ (hydrate)], 2.66—2.96 and 3.36—3.7 (m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 3.87 and 3.89 (3H each, s, two MeO's), 6.78 (3H, s, aromatic protons), 7.1—7.45 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{22}H_{27}NO_3 \cdot 1/4H_2O$: C, 73.82; H, 7.74; N, 3.91. Found: C, 73.85; H, 7.53; N, 3.80.

1-(3,4-Dimethoxyphenethyl)-3-phenyl-2-piperidone (10f)——Obtained in 86% yield as a slightly yellowish oil, MS *m/e*: 339 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 228 (sh) (9920), 280 (2830); IR $\nu_{max}^{CHCl_3}$ 1629 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 2.68—3.06 and 3.46—3.76 (m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 3.87 and 3.90 (3H each, s, two MeO's), 6.87 (3H, s, aromatic protons), 7.0—7.45 (5H, m, C_6H_5).

1-(3,4-Dimethoxyphenethyl)-5-butyl-2-piperidone (14c)——Obtained in 81% yield as a slightly yellowish oil, MS *m/e*: 319 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 229.5 (8860), 280 (2850); IR $\nu_{max}^{CHCl_3}$ 1625 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 0.65—1.08 (3H, unresolved t, $\underline{Me}CH_2$), 2.58—3.35 (4H, m, $H_{(6)}$'s, $ArC\underline{H}_2CH_2$), 3.35—3.85 (2H, m, $ArCH_2C\underline{H}_2$), 3.90 and 3.92 (3H each, s, two MeO's), 6.78 (3H, s, aromatic protons).

1-(3,4-Dimethoxyphenethyl)-5-isopropyl-2-piperidone (14d)——Recrystallized from petroleum ether–ether (2: 1, v/v) to colorless plates, mp 37.5—43°; 88% yield; MS *m/e*: 305 (M^+): UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (9210), 280.5 (2940); IR $\nu_{max}^{CHCl_3}$ 1624 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 0.82 and 0.86 (3H each, d, $J=7$ Hz, $\underline{Me}_2CH$), 2.2—2.49 (2H, m, $H_{(3)}$'s), 2.67—3.13 (4H, m, $H_{(6)}$'s, $ArC\underline{H}_2CH_2$), 3.41—3.62 (2H, m, $ArCH_2C\underline{H}_2$), 3.83 and 3.85 (3H each, s, two MeO's), 6.72 (3H, s, aromatic protons).

1-(3,4-Dimethoxyphenethyl)-5-benzyl-2-piperidone (14e)——Isolated in 83% yield as a colorless oil, bp 230—240° (bath temp.) (0.2 mmHg); MS *m/e*: 353 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (8620), 281 (2990); IR $\nu_{max}^{CHCl_3}$ 1623 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.2—2.1 (3H, m, $H_{(4)}$'s, $H_{(5)}$), 2.55 (d, $J=7$ Hz, $C_6H_5C\underline{H}_2$), 2.25—2.6 (m, $H_{(3)}$'s), 2.65—3.15 (4H, m, $H_{(6)}$'s, $ArC\underline{H}_2CH_2$), 3.40—3.60 (2H, m, $ArCH_2C\underline{H}_2$), 3.86 (6H, s, two MeO's), 6.70—6.85 (3H, m, aromatic protons), 7.0—7.4 (5H, m, C_6H_5).

1-(3,4-Dimethoxyphenethyl)-5-phenyl-2-piperidone (14f)——Isolated in 79% yield and recrystallized from hexane–AcOEt (5: 1, v/v) to colorless plates, mp 106—108°; MS *m/e*: 339 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 228.5 (9200), 280 (2910); IR $\nu_{max}^{CHCl_3}$ 1630 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 2.83—3.11 (m, $ArC\underline{H}_2CH_2$), 3.43—3.80 (m, $ArCH_2C\underline{H}_2$), 3.90 (6H, s, two MeO's); 6.83 (3H, s, aromatic protons), 7.02—7.58 (5H, m, C_6H_5). *Anal.* Calcd. for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.21; H, 7.44; N, 4.32.

Hydrogenation of the Pyridones (11c—f, 15c—f) to the Lactams (10c—f, 14c—f)——The hydrogenations of the pyridones (**11c—f**, **15c—f**)[1] were effected (Raney Ni W-2 catalyst/H_2, EtOH, room temp.) as described previously[9] for the catalytic reduction of **11a** to **10a**, giving the corresponding lactams (**10c—f**, **14c—f**) in 81—95% yields. Each of the lactams thus produced was identical [by TLC, IR spectrum, and mixed melting-point test (for a solid sample)] with a sample prepared by the above-mentioned hydrogenolysis of the corresponding lactam alcohol (type **8** or **12**).

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