Lactams. XI. Construction of Lactam Carbonyl Function in 1,3-Disubstituted Piperidines by Mercuric Acetate-EDTA Oxidation : Effects of Carbonyl and Related Groups at the 3-Position

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Lactams. XI.[1] Construction of Lactam Carbonyl Function in 1,3-Disubstituted Piperidines by Mercuric Acetate–EDTA Oxidation: Effects of Carbonyl and Related Groups at the 3-Position[2]

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1-(3,4-Dimethoxyphenyl)-2-(3-substituted piperidino)ethanols (**3a**—**d**), which carry the carbamoyl, methoxycarbonyl, acetyl, and 1,1-ethylenedioxyethyl group as the 3-substituent in the piperidine ring, have been prepared from 3-substituted pyridines (type **1**) through 1-(3,4-dimethoxyphenacyl)pyridinium bromides (type **2**). In the mercuric acetate–EDTA oxidation of **3a**—**d**, these 3-substituents have been found to orient the lactam carbonyl formation to the 6-position almost exclusively. It is suggested that the 3-substituents exert both steric and electronic effects.

Keywords——1,3-disubstituted piperidines; mercuric acetate-EDTA oxidation; piperidones; isomer ratio; effect of carbonyl and related groups; chromatographic analysis; hydrogenolysis; pyridones; hydrogenation

Previous reports[4] from this laboratory described the results of the mercuric acetate–(ethylenedinitrilo)tetraacetic acid (EDTA) oxidation[5] of 1,3-disubstituted piperidines (type **3**) with particular emphasis on the effects of various hydrocarbon groups at the 3-position upon regioselectivity in the formation of the lactam carbonyl function. Considering its actual and potential utility in the synthesis of 1- or 3-substituted benzo[*a*]quinolizidines[4a,6] and related alkaloids,[7] we have tried to extend the scope of this oxidation reaction. This paper is concerned with the orienting effects of the carbonyl and related groups at the 3-position in the piperidine ring.

The 1-aryl-2-piperidinoethanols (**3**) we selected for the present work were those which carry the carbamoyl, methoxycarbonyl, acetyl, or 1,1-ethylenedioxyethyl group at the 3-position, and they were synthesized from the appropriate pyridine bases (type **1**). Quaternization of **1a,b,d** with 3,4-dimethoxyphenacyl bromide in benzene or N,N-dimethylformamide gave the corresponding pyridinium salts (**2a,b,d**) in good yields. Treatment of these quaternary salts with hydrogen and Adams catalyst followed by sodium borohydride furnished the piperidinoethanols (**3a,b,d**), and acid hydrolysis of the ketal derivative (**3d**) produced the 3-acetyl derivative (**3c**) in a good yield. Although each of the piperidinoethanols (**3a**—**d**) thus obtained was presumed to be a mixture of the two possible diastereoisomers, they all were directly used in the next oxidation step because of the difficulty in purification.

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2) Presented in part at the 8th Congress of Heterocyclic Chemistry, Kyoto, October 23, 1975.
3) Location: *13-1 Takara-machi, Kanazawa, 920, Japan.*
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5) *a*) J. Knabe, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, **292**, 416 (1959); *b*) H. Möhrle, *ibid.*, 297, 474 (1964); *c*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **20**, 1451 (1972).
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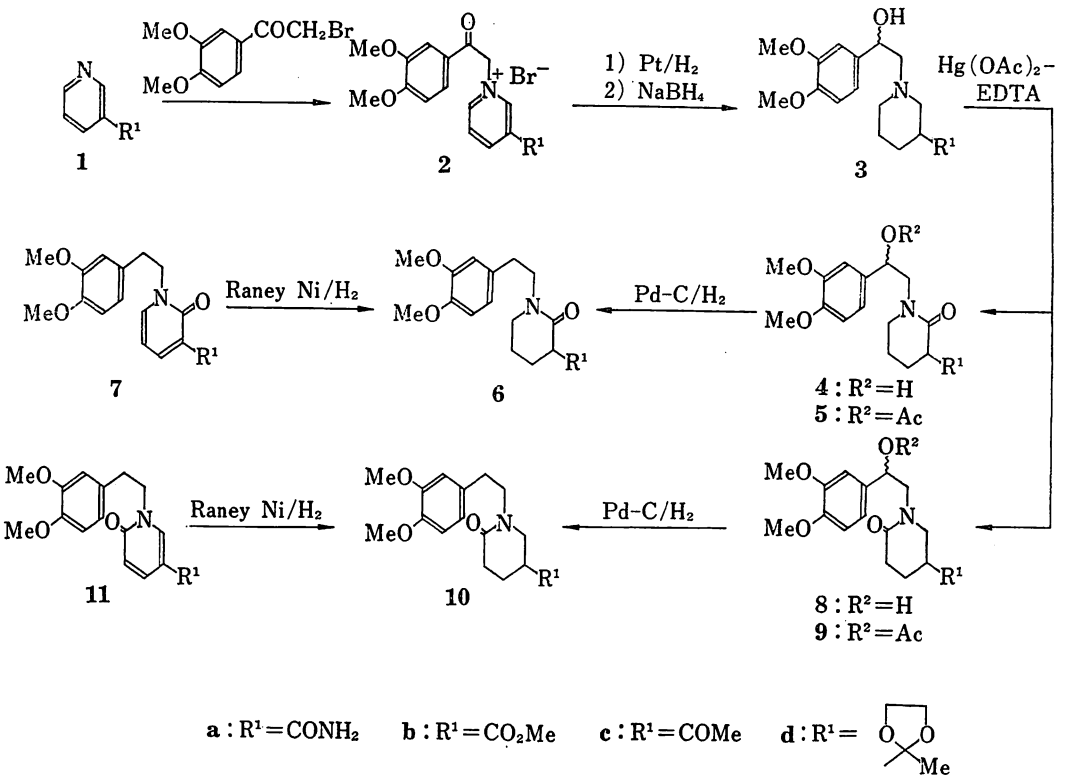

Chart 1

For uniformity and comparison with our earlier data[4] on the orienting effect of hydrocarbon substituents at the 3-position, all the mercuric acetate–EDTA oxidations (in boiling 1% aqueous AcOH, 1.5 hr) of **3a—d** were carried out according to the previously recorded standard procedure.[4a] In these oxidation reactions, the concomitant formation of small amounts of the O-acetyl derivatives (types **5** and/or **9**) was to be anticipated[4,5c] and was actually suggested by means of thin-layer chromatography (TLC) of the reaction mixtures. However, the post-treatment with sodium hydroxide or sodium carbonate, included in the standard procedure,[4a] should have converted them, if any, into the corresponding lactam alcohols (types **4** and/or **8**). In the oxidation of **3c** and **3d**, determination of the ratio of the 2- to the 6-oxidation was accomplished at this stage by chromatographic analysis in a manner similar to that reported previously.[4a] On the other hand, the products from the oxidations of **3a** and **3b** were directly subjected to catalytic hydrogenolysis using hydrogen and palladium-on-charcoal in the presence of a little perchloric acid, and the isomer ratios were determined by a similar chromatographic analysis of the resulting lactams (types **6** and **10**). This modified process not only prevented the hydrolysis of the carbamoyl and methoxycarbonyl groups, but also should have hydrogenolyzed the O-acetyl derivatives (types **5** and **9**), if any, as well as the lactam alcohols (types **4** and **8**) to the corresponding lactams (types **6** and **10**).

The results of the mercuric acetate–EDTA oxidation of the piperidinoethanols (**3a—d**) are summarized in Table I. Each of **8c** and **8d** thus obtained was presumably a diastereoisomeric mixture. On hydrogenolysis (Pd-C/H_2, EtOH–70% aq. $HClO_4$), they produced the lactam derivative (**10c**). The direct formation of **10c** from **8d** is probably due to the hydrolysis of the ketal group under the reaction conditions employed. Since the piperidones (**6a, 10a—c**) derived from the mercuric acetate–EDTA oxidation products were found to be identical with those

Table I. The Mercuric Acetate–EDTA Oxidation of 1,3-Disubstituted Piperidines (3)

Starting material	Substituent R^1	Product[a]		
		Combined yield (%)	% 2-Oxidation	% 6-Oxidation
3a	$CONH_2$	71[b]	4 (**6a**)	96 (**10a**)
3b	CO_2Me	80[b]	0 (**6b**)	100 (**10b**)
3c	COMe	81	0 (**4c**)	100 (**8c**)
3d	$C(OCH_2CH_2O)Me$	66[c]	0 (**4d**)	100 (**8d**, **8c**)[c]

a) All isomer ratios were determined as described in the text.
b) Overall yield from the piperidinoethanol stage (type **3**) to the lactam stage (type **6**, **10**) through the lactam alcohol stage (type **4**,**5**,**8**,**9**).
c) The yields of **8c** and **8d** were 60% and 6%.

prepared from the known pyridones (**7a**, **11a**,**b**,**d**)[1] by catalytic hydrogenation (Raney Ni/H_2) followed, in the case of **11d**, by acid hydrolysis, the chemical correlations described permitted the assignments of the 2-piperidone structure to **6a**, and the 6-piperidone structure to **8c**,**d** and **10a**—**d**.

It may be seen from Table I that in all cases generation of the lactam carbonyl function occurred rather smoothly and every substituent at the 3-position oriented the oxidation to the 6-position almost exclusively. The formation of the acetyl derivative (**8c**) in the oxidation of the ketal derivative (**3d**) may be due to the hydrolysis of **8d** once formed as well as the oxidation of **3c** which might have been formed from **3d** by hydrolysis. In view of the instability which is expected from the β-dicarbonyl or equivalent structure of **4a**—**d**, we can not exclude the possibility that the 2-piperidones (**4a**—**d**) once formed might have been lost partly or completely during the oxidation reaction. Accordingly, the actual regioselectivity with these functional groups might be somewhat lower than that observed. Thus, it may be safe to regard the regioselectivity recorded in Table I as not so exclusive but rather high and higher than that[4] observed for a 3-alkyl group.

On the basis of the postulated mechanism of the mercuric acetate oxidation of cyclic amines[8] and piperidinoalcohols,[5c,9] we have suggested[4b] that in a similar oxidation of 1-aryl-

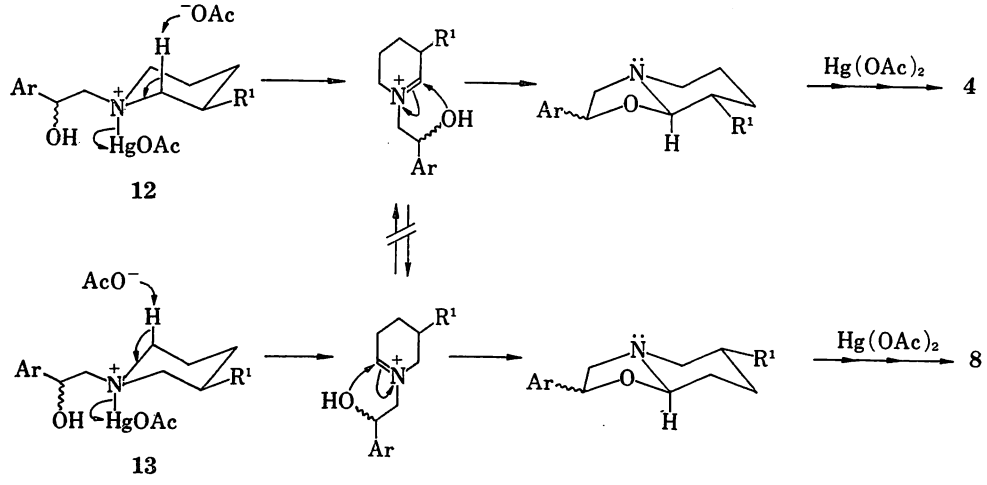

Chart 2

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2-(3-substituted piperidino)ethanols (type **3**) possible factors in determining the regioselectivity may be steric and electrostatic repulsions, which would be operative between the 3-substituent (R^1) and the acetate ion approaching to the axial $C_{(2)}$-proton of the mercurated complex (**12**) formed at the first stage (see Chart 2). The 3-isopropyl group as in **3** (R^1=*iso*-Pr) has been found to orient the mercuric acetate–EDTA oxidation to the 2- and the 6-position in a ratio of 29: 71.[4b] While the carbamoyl and the acetyl group are smaller than the isopropyl group and the methoxycarbonyl group is roughly comparable in size, these functional groups would have a much larger electrostatic influence. This would account for rather a high regioselectivity with **3a**—**c** in favor of the 6-oxidation. A similar steric hindrance and electrostatic repulsion explanation would be applicable to the result obtained with **3d**, which carries a highly branched 3-substituent containing electronegative oxygen atoms.

The present work described above has extended the scope of the mercuric acetate–EDTA oxidation of 1-aryl-2-(3-substituted piperidino)ethanols (type **3**) to include those with the carbonyl and related groups at the 3-position. As illustrated in Chart 1, the 1,3-disubstituted piperidones (**6**, **10**) can be synthesized alternatively from the corresponding pyridones (**7**, **11**) which are easily prepared by the alkaline ferricyanide oxidation[1,4a,10] of 1,3-disubstituted pyridinium salts. In recent work,[1] we have revealed that in this oxidation similar functional groups (*e. g.*, 1,1-ethylenedioxyethyl and carboxyl groups) at the 3-position orient the oxidation to the 6-position exclusively with the exception of the very low regioselectivity with the 3-carbamoyl group. It is, therefore, interesting to note that for the synthesis of compounds of (**10b**—**d**)-type we can choose between the two oxidation methods for the alternative of acidic or alkaline reaction conditions, which are often important factors in keeping other reactive sites inert during the desired chemical transformation.

Experimental

All melting points are corrected; boiling points, uncorrected. IR spectra were measured in Nujol mulls, in KBr discs, or in $CHCl_3$ solutions at 0.2 M concentration. See also ref. 10*b* for details of instrumentation and measurement. The following abbreviations are used: b=broad, m=multiplet, s=singlet.

1-(3,4-Dimethoxyphenacyl)-3-carbamoylpyridinium Bromide (2a)——A solution of nicotinamide (**1a**) (9.40 g, 77 mmol) and 3,4-dimethoxyphenacyl bromide[11] (18.1 g, 70 mmol) in N,N-dimethylformamide (120 ml) was stirred at room temp. for 6 hr. The precipitate that resulted was filtered off, washed with ether, and dried to give crude **2a** (25.6 g, 96%), mp 240—241° (dec.). Recrystallization from 70% aq. EtOH furnished an analytical sample as colorless, minute needles, mp 244—245° (dec.); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231.5 (20900), 278.5 (15300), 312 (10600); IR ν_{max}^{Nujol} 1680 cm^{-1} (CO, $CONH_2$). *Anal.* Calcd. for $C_{16}H_{17}BrN_2O_4$: C, 50.41; H, 4.49; N, 7.35. Found: C, 50.16; H, 4.78; N, 7.17.

1-(3,4-Dimethoxyphenacyl)-3-methoxycarbonylpyridinium Bromide (2b)——A stirred solution of methyl nicotinate (**1b**) (9.05 g, 66 mmol) and 3,4-dimethoxyphenacyl bromide[11] (15.55 g, 60 mmol) in dry benzene (100 ml) was kept at room temp. for 48 hr. The precipitate that resulted was collected by filtration and washed with benzene (30 ml) to give a first crop (13.2 g). The combined filtrate and washings were concentrated to a small volume (*ca.* 50 ml) and the resulting solution was stirred again at room temp. for 24 hr to produce a second crop (8.35 g), total yield 21.55 g (91%). The crude sample, mp 162.5—164.5° (dec.), was recrystallized from MeOH–acetone (1: 1, v/v) to colorless plates, mp 167—168° (dec.); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 232 (20000), 278 (14300), 313 (10700); IR ν_{max}^{Nujol} cm^{-1}: 1735 (ester CO), 1687 (CO). *Anal.* Calcd. for $C_{17}H_{18}BrNO_5$: C, 51.53; H, 4.58; N, 3.54. Found: C, 51.72; H, 4.67; N, 3.58.

1-(3,4-Dimethoxyphenacyl)-3-(1,1-ethylenedioxyethyl)pyridinium Bromide (2d)——3-(1,1-Ethylenedioxyethyl)pyridine (**1d**)[12] was allowed to react with 3,4-dimethoxyphenacyl bromide[11] in a manner similar to that described above for **2b**, giving crude **2d**, mp 195—196° (dec.), in 91% yield. Recrystallization from EtOH provided an analytical sample as colorless, minute needles, mp 198—199° (dec.); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 232.5 (19100), 275 (14500), 311.5 (10800); IR ν_{max}^{Nujol} 1682 cm^{-1} (CO). *Anal.* Calcd. for $C_{19}H_{22}BrNO_5$: C, 53.79; H, 5.23; N, 3.30. Found: C, 53.60; H, 5.07; N, 3.51.

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1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-piperidinecarboxamide (3a)——A solution of **2a** (15.3 g, 40 mmol) in 50% aq. EtOH (400 ml) was hydrogenated over Adams catalyst (350 mg) at 25° and atmospheric pressure for 12.5 hr, absorbing *ca.* 3.1 molar equivalents of H_2. The catalyst was removed by filtration and the filtrate was neutralized with 2 N aq. NaOH (20 ml). The resulting solution was stirred with $NaBH_4$ (1.52 g, 40 mmol) at room temp. for 5 hr. After having been kept standing at room temp. overnight, the reaction mixture was evaporated to dryness *in vacuo* and the residue was treated with H_2O (80 ml) and $CHCl_3$ (150 ml). The aqueous layer was separated from the $CHCl_3$ layer, saturated with NaCl, and extracted with five 100-ml portions of $CHCl_3$. All the $CHCl_3$ extracts were combined, dried over anhyd. K_2CO_3, and evaporated *in vacuo*, leaving a pale yellowish solid. The solid was chromatographed on a 100-g alumina column using $CHCl_3$ (1.5 l) as eluent to give **3a** (12.0 g, 97%) as a colorless solid (presumed to be a diastereoisomeric mixture), mp 140—172°; MS *m/e*: 308 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (8550), 279 (2800); IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1687, 1665 ($CONH_2$); NMR ($CDCl_3$) δ: 1.55—2.0 (4H, m, two ring-CH_2's), 2.2—3.2 (7H, m, three NCH_2's and ring-CH), 3.36 (1H, s, OH), 3.89 and 3.91 (3H each, s, two MeO's), 4.6—4.95 [1H, m, ArC<u>H</u>(OH)], 5.6—6.1 and 6.6—7.15 (b each, $CONH_2$), 6.75—7.05 (m, aromatic protons). Repeated recrystallizations of a small sample of crude **3a** from EtOH yielded colorless scales, possibly one of the diastereoisomers, mp 191—193°; MS *m/e*: 308 (M^+); IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1684, 1663 ($CONH_2$). *Anal.* Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08. Found: C, 62.39; H, 7.89; N, 8.87.

Methyl 1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-piperidinecarboxylate (3b)——A suspension of **2b** (13.5 g, 34 mmol) in abs. MeOH (150 ml) was hydrogenated over Adams catalyst (250 mg) at 20° and atmospheric pressure; *ca.* 3 molar equivalents of H_2 was taken up within 12 hr. After removal of the catalyst by filtration, the methanolic filtrate was neutralized with 2 N aq. NaOH (17 ml) and stirred at room temp. with $NaBH_4$ (1.29 g, 34 mmol) for 2 hr, then with an additional amount (643 mg, 17 mmol) of $NaBH_4$ for 1.5 hr. The reaction mixture was evaporated to dryness *in vacuo* and H_2O (40 ml) was added to the residue. The resulting mixture was extracted with benzene, and the benzene solution was dried over anhyd. K_2CO_3 and evaporated *in vacuo*, leaving a yellow oil. Purification of the oil on a 80-g alumina column using AcOEt–hexane (1: 2, v/v) (400 ml) as eluent gave **3b** (9.64 g, 88%) as a colorless, thick oil, presumed to be a diastereoisomeric mixture, MS *m/e*: 323 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 231 (8420), 280 (2980); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (OH), 1726 (ester CO); NMR ($CDCl_3$) δ: 1.4—2.1 (4H, m, two ring-CH_2's), 2.2—3.4 (8H, m, three NCH_2's, ring-CH, and OH), 3.72 (3H, s, CO_2Me), 3.87 and 3.91 (3H each, s, two MeO's), 4.6—4.8 [1H, m, ArC<u>H</u>(OH)], 6.85—7.05 (3H, m, aromatic protons).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3-piperidyl Methyl Ketone (3c)——A solution of the ketal derivative (**3d**, see below) (8.79 g, 25 mmol) in 5% aq. HCl (50 ml) was stirred at 50—55° (bath temp.) for 1 hr. The solution was made basic with K_2CO_3 and extracted with four 50-ml portions of benzene. The combined benzene extracts were washed with sat. aq. NaCl, dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo*, leaving **3c** (7.62 g, 99%) as a pale yellowish, thick oil, MS *m/e*: 307 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (9230), 278.5 (2970); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1705 (CO); NMR ($CDCl_3$) δ: 2.16 and 2.18 (3H, s each, diastereoisomeric MeCO's), 1.2—3.3 (11H, m, two ring-CH_2's, -CH, three NCH_2's), 3.4—4.0 (1H, b, OH), 3.87 and 3.89 (3H each, s, two MeO's), 4.6—4.8 [1H, m, ArC<u>H</u>(OH)], 6.8—7.0 (3H, m, aromatic protons).

1-(3,4-Dimethoxyphenyl)-2-[3-(1,1-ethylenedioxyethyl)piperidino]ethanol (3d)——A solution of **2d** (29.7 g, 70 mmol) in 50% aq. EtOH (250 ml) was hydrogenated over Adams catalyst (350 mg) at 30° and atmospheric pressure for 14 hr, absorbing *ca.* 3.2 molar equivalents of H_2. The mixture was worked up in a manner similar to that described above for **3b**, giving **3d** (18.7 g, 76%) as a colorless, thick oil, presumed to be a diastereoisomeric mixture, MS *m/e*: 351 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230.5 (8870), 279 (2950); IR $\nu_{max}^{CHCl_3}$ 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ: 1.24 and 1.26 (3H, s each, diastereoisomeric Me's), 1.45—3.35 [11H, m, piperidine-ring protons, ArCH(OH)C<u>H</u>$_2$], 3.67 (1H, b, OH), 3.87 and 3.91 (3H, each, s, two MeO's), 3.8—4.0 (4H, m, two OCH_2's), 4.55—4.80 [1H, m, ArC<u>H</u>(OH)], 6.7—7.0 (3H, m, aromatic protons).

The $Hg(OAc)_2$–EDTA Oxidation of the Piperidinoethanols (3a—d)——All the oxidations of **3a—d**, which were presumably diastereoisomeric mixtures, were carried out in boiling 1% aq. AcOH for 1.5 hr according to the previously reported standard procedure,[4a] but with the following modification in the post-treatment. The reaction mixtures were neutralized with $NaHCO_3$, saturated with NaCl, and extracted with five 20-ml portions of $CHCl_3$. The combined extracts were dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo*, leaving oily or solid substances (types **4**, **5** and/or **8**, **9**), which were dissolved in $CHCl_3$ and decolorized by passing the solutions through alumina columns as in the standard procedure.[4a] However, the latter decolorizing process was not applied to the product obtained from **3a**. In the cases of the oxidation products from **3a** and **3b**, the residues thus obtained were separately subjected to catalytic hydrogenolysis and the ratio of the resulting lactams (**6**: **10**) was determined by chromatographic analysis (see below).

In the cases of the oxidation products from **3c** and **3d**, the oily residues were dissolved in EtOH (50 ml) and the solutions were stirred with anhyd. Na_2CO_3 (2.5 g) at room temp. for 3 hr for the hydrolysis of substances presumed to be the O-acetyl derivatives (types **5** and/or **9**) to the lactam alcohols (types **4** and/or **8**). The mixtures were filtered and the filtrates were evaporated to dryness *in vacuo*. Each of the resulting residues was dissolved in $CHCl_3$ (50 ml) and the $CHCl_3$ solution was washed with two 15-ml portions of sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo*, leaving an orange, thick oil. For

analysis, the oil was chromatographed on a 250-g silica gel column using $CHCl_3$–EtOH (10: 1, v/v) or $CHCl_3$–MeOH (30: 1, v/v) as eluent.

In all cases, the $Hg(OAc)_2$–EDTA oxidation was run in triplicate and the isomer ratios obtained were averaged. The results are summarized in Table I, and the isolated lactam alcohols (**8c, d**), presumed to be diastereoisomeric mixtures, were characterized as follows.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-acetyl-2-piperidone (8c)——Crystallized from AcOEt–hexane (2: 1, v/v) in colorless prisms, mp 83.5—85°; MS *m/e*: 321 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (11000), 279 (3190); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1713 (CO), 1623 (lactam CO); NMR ($CDCl_3$) δ: 2.14 and 2.19 (s each, diastereoisomeric MeCO's), 1.65—2.25 (m, $H_{(4)}$'s), 2.35—2.55 (2H, m, $H_{(3)}$'s), 2.55—3.0 (1H, m, $H_{(5)}$), 3.05—3.75 [4H, m, $H_{(6)}$'s and ArCH(OH)C$\underline{H}_2$], 3.87 and 3.89 (3H each, s, two MeO's), 3.94 (1H, s, OH), 4.85—5.05 [1H, m, ArC$\underline{H}$(OH)], 6.75—7.0 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.31; H, 7.18; N, 4.24.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-5-(1,1-ethylenedioxyethyl)-2-piperidone (8d)——Crystallized from AcOEt–hexane (1: 2, v/v) in colorless, minute prisms, mp 108—110.5°; MS *m/e*: 365 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (9330), 279 (2900); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3340 (OH), 1615 (lactam CO); NMR ($CDCl_3$) δ: 1.17 and 1.23 (3H, s each, diastereoisomeric Me's), 1.4—2.2 (3H, m, $H_{(4)}$'s and $H_{(5)}$), 2.3—2.75 (2H, m, $H_{(3)}$'s), 3.85 and 3.89 (s each, two MeO's), 4.08 (1H, s, OH), 4.85—5.05 [1H, m, ArC$\underline{H}$(OH)], 6.8—7.05 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.37; H, 7.42; N, 3.91.

Hydrogenolysis of the Lactam Alcohols (8c, d) and Crude Products from the $Hg(OAc)_2$–EDTA Oxidation of 3a and 3b——All the hydrogenolytic reactions were effected [10% Pd-C/H_2, EtOH (MeOH for the methyl ester derivative)–70% aq. $HClO_4$, 3.1—3.9 atm, 15—20 hr] by a procedure similar to that reported before[4a] for the hydrogenolysis of **4** (R^1=Me) to **6** (R^1=Me). The resulting reaction mixtures were worked up as described below under the names of the lactams (**6a, 10a—c**) formed.

1-(3,4-Dimethoxyphenethyl)-2-oxo-3-piperidinecarboxamide (6a) and 1-(3,4-Dimethoxyphenethyl)-2-oxo-5-piperidinecarboxamide (10a)——The reaction mixture from the hydrogenolysis of the crude oxidation product (2.35 g) derived from **3a** (2.47 g, 8.0 mmol) was filtered and the filtrate was neutralized with 2 N aq. NaOH. Evaporation of the solvent under diminished pressure left a pale brownish, glassy substance, which was purified on a 20-g silica gel column using $CHCl_3$–MeOH (10: 1, v/v) (200 ml) as eluent. The resulting colorless solid (2.19 g) was recrystallized from AcOEt–EtOH (5: 1, v/v) (80 ml) to give **10a** (1.095 g) as colorless prisms, mp 187—188°; MS *m/e*: 306 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 229 (9510), 280 (2900); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3550, 3425 (NH_2), 1690 ($CONH_2$), 1634 (lactam CO); NMR ($CDCl_3$) δ: 1.8—2.7 (5H, m, $H_{(3)}$'s, $H_{(4)}$'s, and $H_{(5)}$), 2.65—3.0 and 3.4—3.7 (m, ArC$\underline{H}_2$CH$_2$ and ArCH$_2$C$\underline{H}_2$), 3.86 and 3.88 (3H each, s, two MeO's), 5.76 (2H, b, $CONH_2$), 6.80 (3H, s, aromatic protons). *Anal.* Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.73; H, 7.25; N, 9.14.

The mother liquor from the first recrystallization of the crude hydrogenolyzed product was evaporated *in vacuo*, and the residual solid (1.09 g) was chromatographed on a 109-g silica gel column using $CHCl_3$–MeOH (20: 1, v/v) as eluent; later fractions yielded an additional amount of **10a** and earlier fractions gave **6a** as a solid. Recrystallization of the solid (**6a**) from benzene–hexane (1: 1, v/v) provided an analytical sample as colorless scales, mp 111.5—112.5°; MS *m/e*: 306 (M^+); UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 228.5 (9320), 280 (2610); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3515, 3370 (NH_2), 1687 ($CONH_2$), 1632 (lactam CO); NMR ($CDCl_3$) δ: 1.45—2.55 (4H, m, $H_{(4)}$'s and $H_{(5)}$'s), 2.6—3.0 (2H, m, ArC$\underline{H}_2$CH$_2$), 3.0—3.9 (5H, m, ArCH$_2$C$\underline{H}_2$, $H_{(6)}$'s, and $H_{(3)}$), 3.83 and 3.85 (3H each, s, two MeO's), 5.63 and 7.49 (1H each, b, $CONH_2$),[13] 6.5—6.9 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.53; H, 7.28; N, 9.03.

Methyl 1-(3,4-Dimethoxyphenethyl)-2-oxo-5-piperidinecarboxylate (10b)——The hydrogenolysis reaction mixture of the crude oxidation product (1.34 g) obtained from **3b** (1.29 g, 4.0 mmol) was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with H_2O (20 ml) and an insoluble oil was extracted with four 20-ml portions of $CHCl_3$. The combined extracts were washed with sat. aq. NaCl, dried over anhyd. Na_2SO_4, and evaporated *in vacuo*, to leave a pale yellowish solid (1.03 g, 80% from **3b**), shown to be homogeneous by a single spot on a TLC plate. Recrystallization of this sample from AcOEt–hexane (1: 1, v/v) provided **10b** as colorless, minute scales, mp 98—100°; MS *m/e*: 321 (M^+): UV $\lambda_{max}^{abs.EtOH}$ nm (ε): 230 (9220), 280 (2870); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1731 (ester CO), 1629 (lactam CO); NMR ($CDCl_3$) δ: 1.8—3.0 (7H, m, $H_{(3)}$'s, $H_{(4)}$'s, $H_{(5)}$, and ArC$\underline{H}_2$CH$_2$), 3.3—3.8 (m, $H_{(6)}$'s and ArCH$_2$C$\underline{H}_2$), 3.71 (s, CO_2Me), 3.84 and 3.87 (3H each, s, two MeO's), 6.65—7.0 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.69; H, 7.10; N, 4.15.

1-(3,4-Dimethoxyphenethyl)-5-acetyl-2-piperidone (10c)——i) From **8c**: The hydrogenolysis reaction mixture of **8c** (321 mg, 1.0 mmol) described above was filtered and the filtrate was concentrated *in vacuo*. To the residue was added H_2O (10 ml), and the mixture was extracted with benzene after neutralization with $NaHCO_3$. The benzene solution was dried over anhyd. Na_2SO_4 and evaporated *in vacuo* to leave a pale yellowish oil, which was purified by means of chromatography [alumina (30 g), AcOEt–hexane (1: 1 v/v)] or vacuum distillation [bp 178—182° (0.01 mmHg)] to a colorless solid, mp 57—60°. Recrystallization from

13) For an additional example of enhanced non-equivalence of the NH_2 protons, see footnote 17 in ref. 1.

ether provided an analytical sample of **10c** as colorless prisms, mp 59.5—61°; MS *m/e*: 305 (M^+); UV $\lambda_{max}^{abs.\,EtOH}$ nm (ε): 229.5 (10800), 280.5 (3210); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (CO), 1631 (lactam CO); NMR ($CDCl_3$) δ: 2.20 (s, MeCO), 2.7—3.0 and 3.5—3.75 (m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 3.91 and 3.93 (3H each, s, two MeO's), 6.88 (3H, s, aromatic protons). *Anal.* Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 67.08; H, 7.57; N, 4.52.

ii) From **8d**: The hydrogenolysis reaction mixture of the ketal derivative (**8d**) (73 mg, 0.2 mmol) described above was worked up similarly to give **10c** (48 mg, 79% from **8d**), identical with an authentic sample.

iii) By Hydrolysis of **10d**: A solution of a sample (1.40 g, 4.0 mmol) of **10d** derived from **11d**[1] (see below) in a mixture of EtOH (10 ml) and 10% aq. HCl (3 ml) was refluxed for 1.5 hr. The reaction mixture was concentrated to dryness *in vacuo* and H_2O was added to the residue. The resulting mixture was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extracts were worked up in a manner similar to that described under method-(i), yielding a colorless solid (1.20 g, 98%), mp 57—60°, identical (by TLC, IR spectrum, and mixed melting-point test) with the sample obtained by method-(i) or method-(ii).

Hydrogenation of the Pyridones (7a, 11a, b, d) to the Lactams (6a, 10a, b, d)——The catalytic hydrogenations of the pyridones (**7a, 11a, b, d**)[1] were performed [Raney Ni W-2 catalyst/H_2, EtOH (MeOH for **11b**), room temp., 2—6 hr] as described previously[4a] for the conversion of **7** (R^1=Me) into **6** (R^1=Me), producing the corresponding lactams (**6a, 10a, b, d**) in 88—97% yields. Lactams **6a, 10a**, and **10b** were identified (by TLC, IR spectrum, and mixed melting-point test) with the samples obtained by the above-mentioned hydrogenolysis of the corresponding lactam alcohols. Lactam **10d** was characterized as follows.

1-(3,4-Dimethoxyphenethyl)-5-(1,1-ethylenedioxyethyl)-2-piperidone (10d)——Obtained as a colorless, thick oil, bp 172—178° (10^{-3} mmHg); MS *m/e*: 349 (M^+); UV $\lambda_{max}^{abs.\,EtOH}$ nm (ε): 229.5 (9700), 280.5 (2970); IR $\nu_{max}^{CHCl_3}$ 1627 cm^{-1} (lactam CO); NMR ($CDCl_3$) δ: 1.23 (3H, s, Me), 1.4—2.2 (3H, m, $H_{(4)}$'s and $H_{(5)}$), 2.25—2.55 (2H, m, $H_{(3)}$'s), 2.75—3.0 and 3.45—3.75 (4H, m, $ArC\underline{H}_2CH_2$ and $ArCH_2C\underline{H}_2$), 3.0—3.3 (2H, m, $H_{(6)}$'s), 3.90 and 3.92 (s each, two MeO's), 3.75—4.1 (m, two OCH_2's), 6.84 (3H, s, aromatic protons).

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