

Lactams. IV.¹⁾ The Synthesis of Benzo[*a*]quinolizine Derivatives from Piperidine through 1-Substituted 2-Piperidones²⁾

TOZO FUJII and SHIGEYUKI YOSHIFUJI

Faculty of Pharmaceutical Sciences, Kanazawa University³⁾

(Received December 13, 1971)

The mercuric acetate—(ethylenedinitrilo)tetraacetic acid oxidation of aminoalcohol III furnished lactamalcohol V in 73% yield and its O-acetyl derivative (VI) as a minor product. Treatment of V with phosphoryl chloride gave tetrahydrobenzo[*a*]quinolizinium salt X in 87% yield, whereas hydrogenolysis of V in the presence of perchloric acid and ring-closure of the resulting lactam VIII afforded hexahydrobenzo[*a*]quinolizinium salt IX, which produced benzo[*a*]quinolizidine Ia on hydrogenation. When treated with perchloric acid, lactamalcohol V yielded oxazolinium salt VIIa in a good yield. The facile hydrogenolysis of VIIa to VIII has suggested the possibility that the perchloric acid-accelerated, direct hydrogenolysis of V may proceed through VIIa.

The starting aminoalcohol III was synthesized either by the sodium borohydride reduction of aminoketone II obtained from piperidine and 3,4-dimethoxyphenacyl bromide or by reduction of quaternary salt IV from pyridine and 3,4-dimethoxyphenacyl bromide.

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (Ia) possesses the parental carbon skeleton common to the benzoquinolizidine fragments of most of the Ipecacuanha alkaloids.⁴⁾ Since 1931 several methods for synthesizing compounds of a I-type have been reported in the literature: (a) intramolecular quaternization of 1-(4-chlorobutyl)-3,4-dihydro-6,7-dimethoxyisoquinoline followed by reduction;⁵⁾ (b) a Pschorr-type cyclization of 1-substituted pyridinium salts followed by hydrogenation;⁶⁾ (c) the Bischler-Napieralski reaction of 1-substituted 2-piperidones, prepared from any of glutaric anhydride,⁷⁾ δ -valerolactone,⁸⁾ 1-substituted 2-pyridone,⁹⁾ or δ -valerolactam,¹⁰⁾ and reduction of the resulting 1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium salts (type IX). Now we report the synthesis of Ia from piperidine, which may fall under the category (c), through the use of the mercuric acetate—(ethylenedinitrilo)tetraacetic acid (EDTA) method¹¹⁾ developed by Möhrle;¹²⁾ a parallel synthesis of hitherto unknown 9,10-dimethoxy-1,2,3,4-tetrahydrobenzo[*a*]quinolizinium salts (X) is also included.

The starting piperidine derivative (III) was prepared in an excellent yield by the sodium borohydride reduction of 3',4'-dimethoxy-2-piperidinoacetophenone (II), derived from the reaction of piperidine with 3,4-dimethoxyphenacyl bromide in the presence of potassium

- 1) Paper III in this series, T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.* (Tokyo), **19**, 1051 (1971).
- 2) Presented in part at the 32nd Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, June 26, 1971. This article is dedicated to Emeritus Professor, Dr. Shigehiko Sugasawa of University of Tokyo on the occasion of his 75th birthday.
- 3) Location: 13-1 Takara-machi, Kanazawa, 920, Japan.
- 4) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids," Hirokawa Publishing Co., Inc., Tokyo, 1968, pp. 160—166, pp. 253—255.
- 5) R. Child and F.L. Pyman, *J. Chem. Soc.*, **1931**, 36.
- 6) S. Akaboshi, T. Kato, and A. Saiga, *Chem. Pharm. Bull.* (Tokyo), **11**, 1446 (1963).
- 7) S. Sugasawa, K. Sakurai, and N. Sugimoto, *Yakugaku Zasshi*, **59**, 247 (1939).
- 8) S. Sugasawa, S. Akaboshi, and M. Yamada, *Yakugaku Zasshi*, **71**, 1341 (1951).
- 9) a) S. Sugasawa and K. Mizukami, *Chem. Pharm. Bull.* (Tokyo), **6**, 359 (1958); b) S. Akaboshi, T. Kutsuma, and K. Achiwa, *ibid.*, **8**, 14 (1960).
- 10) T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 591 (1958).
- 11) J. Knabe, *Arch. Pharm.*, **292**, 416 (1959).
- 12) H. Möhrle, *Arch. Pharm.*, **297**, 474 (1964).

carbonate. Alternatively, reduction of the quaternary salt (IV) from pyridine and 3,4-dimethoxyphenacyl bromide also furnished III in a good yield.

In the mercuric acetate oxidation of III to lactamalcohol V, the presence of the hydroxyl group at the benzylic position proved of great value, as observed on 1-phenyl-2-piperidinoethanol.¹²⁾ When heated in dilute acetic acid with a combination of mercuric acetate and the disodium salt of EDTA, amine III produced V in 73% yield together with its O-acetyl derivative (VI) (7%). The minor product (VI) was characterized by mass spectrum [m/e 321 (M^+)], correct analysis for $C_{17}H_{23}O_5N$, infrared (IR) spectrum [$\nu_{\max}^{CHCl_3}$ cm^{-1} : 1740 (ester CO), 1633 (lactam CO)], nuclear magnetic resonance (NMR) spectrum, and alkaline hydrolysis leading to formation of lactamalcohol V. In view of the postulated mechanism by Leonard *et al.*¹³⁾ for the mercuric acetate oxidation of 3-hydroxyethyl-3-azabicyclo[3.3.1]nonane to give 3-hydroxyethyl- and 3-acetoxyethyl-2-keto-3-azabicyclo[3.3.1]nonane, it is reasonable to consider that the oxidation of III to V proceeded through the intermediate bicyclic oxazolinium compound (VII) and that attack of VII by acetate ion in the reaction medium on $C_{(5)}$ of the oxazoline moiety cleaved the ring to form VI, whereas attack by water at $C_{(2)}$ (or $C_{(5)}$) of the same moiety resulted in the formation of the major product (V).

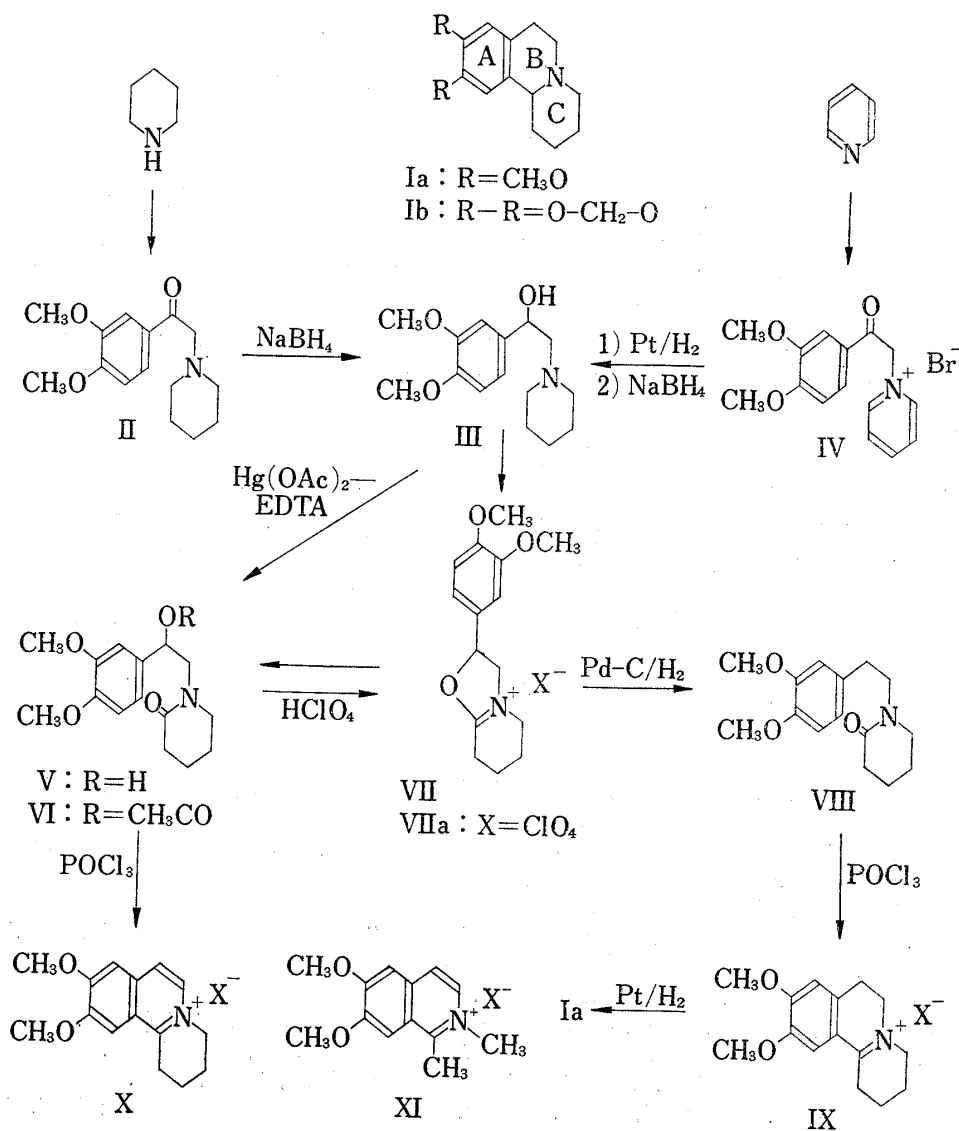


Chart 1

13) N.J. Leonard, K. Conrow, and R.R. Sauer, *J. Am. Chem. Soc.*, **80**, 5185 (1958).

The next step was removal of the hydroxyl group from V. Thus, V was hydrogenated in ethanol or acetic acid over 10% palladium-on-charcoal at 50° and few atmospheric pressure; the hydrogenolysis progressed only slowly and took from one to few days for its completion. Addition of a small amount of perchloric acid, however, speeded up the deoxygenation remarkably even at 25°, reducing reaction time to just a few hours, and it was possible to isolate lactam VIII in a solid state, mp 56—57°, for the first time in 94% yield. Although it is well known that palladium catalysts can be markedly activated for the hydrogenolysis of alcohols of the type ArCH(OH)- by addition of a small amount of perchloric acid,¹⁴⁾ this may be not necessarily all responsible for the acceleration of the hydrogenolysis described. We may consider the possibility that V is first converted by the action of perchloric acid into the oxazolinium perchlorate (VIIa), which then undergoes a rapid hydrogenolysis to give VIII. For this reason VIIa was separately prepared from V according to a general method recommended by Leonard, *et al.*,¹³⁾ and its hydrogenolysis in ethanol at 20° was investigated. The reaction was found to proceed as rapidly as the perchloric acid-accelerated, direct hydrogenolysis of V and afforded lactam VIII in 93% yield.

The final stage was the formation of the tricyclic skeleton, and this was conducted by treating VIII with phosphoryl chloride. The resulting immonium salt (IX)^{5,15)} was then converted into Ia^{5-8,9a,10)} by catalytic hydrogenation. Thus, these transformations also served to support the assigned structures V, VIIa, and VIII.

Since acylated aminomethylphenylcarbinols have been known to yield isoquinolines by the Pictet-Gams modification¹⁶⁾ of the Bischler-Napieralski reaction, lactam-alcohol V carrying the hydroxyl group at the benzylic position is of special interest. On being heated with phosphoryl chloride, it produced, after treatment with potassium iodide, quaternary salt X (X=I) in 87% yield. The assignment of structure X was based on correct analysis for C₁₅H₁₈O₂NI, ultraviolet (UV) spectrum similar to that of 6,7-dimethoxy-1,2-dimethylisoquinolinium iodide (XI: X=I)¹⁷⁾ (see Fig. 1), and conversion into the corresponding perchlorate (X: X=ClO₄) which also gave satisfactory analysis and exhibited almost identical UV spectrum to that of 6,7-dimethoxy-1,2-dimethylisoquinolinium perchlorate (XI: X=ClO₄).¹⁷⁾ The NMR spectrum of iodide X (X=I) in deuterated dimethyl sulfoxide revealed a pair of AB type doublets for H₍₇₎ and H₍₆₎ at 1.94 and 1.66 τ (1H each, $J=7$ cps), indicating also that ring B in X was fully aromatized. The difference in the

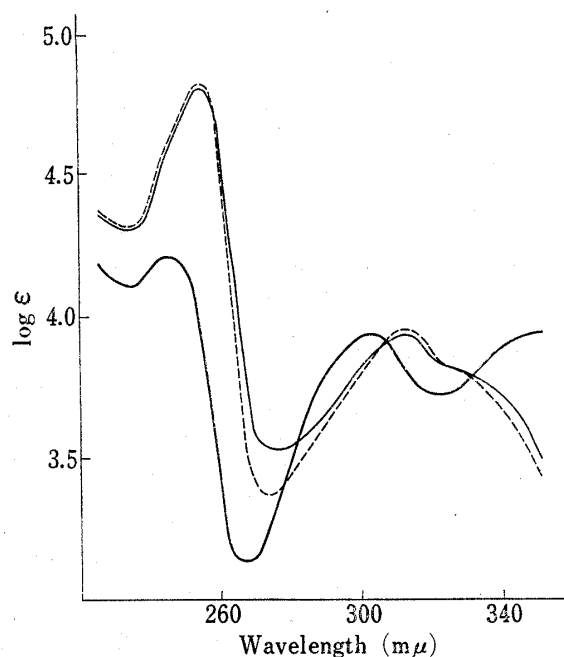


Fig. 1. UV Spectra of 9,10-Dimethoxy-1,2,3,4,6,7-hexahydro- (IX: X=I) and -1,2,3,4-tetrahydrobenzo[*a*]quinolinium Iodide (X: X=I) and 6,7-Dimethoxy-1,2-dimethylisoquinolinium Iodide (XI: X=I) in 99% Aq. Ethanol

—: IX (X=I); —: X (X=I); ----: XI (X=I)

- 14) a) K.W. Rosenmund and E. Karg, *Chem. Ber.*, **75**, 1850 (1942); b) W.H. Hartung and R. Simonoff, "Organic Reactions," Vol. VII, ed. by R. Adams, John Wiley & Sons, Inc., New York, 1953, pp. 290—291.
- 15) a) Y. Ban, O. Yonemitsu, and M. Terashima, *Chem. Pharm. Bull.* (Tokyo), **8**, 183 (1960); b) D.W. Brown, S.F. Dyke, M. Sainsbury, and W.G.D. Lugton, *Tetrahedron*, **26**, 4985 (1970).
- 16) W.M. Whaley and T.R. Govindachari, "Organic Reactions," Vol. VI, ed. by R. Adams, John Wiley & Sons, Inc., New York, 1951, pp. 76—77.
- 17) J. Knabe and N. Ruppenthal, *Arch. Pharm.*, **299**, 159 (1966).

UV spectrum between the tetrahydro- (X: X=I) and hexahydrobenzo[*a*]quinolizinium salt (IX: X=I) thus obtained is visualized in Fig. 1.

In conclusion, the facile synthesis of Ia and X from piperidine described above has demonstrated the great utility of the hydroxyl group in aminoalcohol III in introducing the lactam carbonyl function and in producing additional C=C unsaturation later on. It has also suggested that this method may be applicable to synthesis of ring C-substituted benzo[*a*]quinolizine derivatives from properly substituted piperidines. Pursuit along this line is now in progress.

Experimental¹⁸⁾

3',4'-Dimethoxy-2-piperidinoacetophenone (II)—To a stirred mixture of piperidine (4.26 g, 50 mmoles), anhyd. K_2CO_3 (6.91 g, 50 mmoles), and abs. benzene (130 ml) was added 3,4-dimethoxyphenacyl bromide¹⁹⁾ (13.0 g, 50 mmoles), and the resulting mixture was heated with stirring in an oil bath kept at 95° for 4 hr. After cooling, the reaction mixture was filtered to remove an insoluble solid. The filtrate was evaporated *in vacuo*, leaving a light brown oil, which was dissolved in 20% aq. HCl (40 ml) under cooling. The aq. solution was washed with benzene, made basic with 40% aq. NaOH, and extracted with benzene. The extracts were washed with sat. aq. NaCl, dried over anhyd. K_2CO_3 , and evaporated *in vacuo* to leave crude II as a light brown, viscous oil (12.6 g, 96%). Since thin-layer chromatography (TLC) revealed that this sample was contaminated with minute amounts of impurities, it was purified through the corresponding hydrobromide as shown below.

To a solution of the total amount of the free base (II) in 99% aq. ethanol (100 ml) was added under cooling 47% aq. HBr until the solution became acid to Methyl Orange paper. The mixture was concentrated *in vacuo* to give faintly brownish scales (15.2 g, 88% based on the piperidine used). Recrystallization from ethanol-ethyl acetate (1:1, v/v) yielded an analytical sample of II·HBr as colorless scales, mp 201–202°; UV $\lambda_{max}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 232.5 (16800), 281.5 (11000), 311.5 (9200); IR ν_{max}^{KBr} 1680 cm^{-1} (CO). *Anal.* Calcd. for $C_{15}H_{22}O_2NBr$: C, 52.53; H, 6.44; N, 4.06. Found: C, 52.77; H, 6.55; N, 4.01.

Basification of an aq. solution of pure II·HBr (10.19 g) followed by extraction with benzene produced the free base (II) (7.50 g) as an almost colorless oil, UV $\lambda_{max}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 229 (14100), 276.5 (8500), 306 (sh) (6200); IR $\nu_{max}^{CHCl_3}$ 1688 cm^{-1} (CO); NMR ($CDCl_3$) τ : 8.1–8.7 (6H, m, three ring- CH_2 's), 7.3–7.6 (4H, m, two ring-N CH_2 's), 6.26 (2H, s, $COCH_2N$), 6.06 (6H, s, two CH_3O 's), 3.12 (1H, d, $J=9$ cps, $H_{(5')}$), 2.35 (1H, unresolved d, $H_{(2')}$), 2.26 (1H, d-d, $J=9$ and 2 cps, $H_{(6')}$).

The hydrochloride (II·HCl) was prepared from II and conc. aq. HCl in the same way as described above for II·HBr. Recrystallization from ethanol-ethyl acetate (1:5, v/v) furnished colorless scales, mp 199–200°; UV $\lambda_{max}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 232.5 (16700), 281.5 (10900), 311.5 (9100); IR ν_{max}^{KBr} 1680 cm^{-1} (CO). *Anal.* Calcd. for $C_{15}H_{22}O_2NCl$: C, 60.01; H, 7.40; N, 4.67. Found: C, 60.19; H, 7.39; N, 4.82.

1-(3,4-Dimethoxyphenyl)-2-piperidinoethanol (III)—i) From Aminoketone II: To a stirred solution of II (7.50 g, 28.5 mmoles) in 99% aq. ethanol (100 ml) was added in small portions $NaBH_4$ (1.08 g, 28.5 mmoles) under cooling. The mixture was stirred at room temp. for 8 hr, allowed to stand overnight, and evaporated *in vacuo* to dryness to leave a colorless solid mass. The solid was treated with H_2O (60 ml), separating an oil, which was collected in chloroform. The extracts were washed with sat. aq. NaCl, dried over anhyd. Na_2SO_4 , and evaporated *in vacuo* to leave a colorless solid (7.26 g, 96%), mp 106–108°, shown to be homogeneous on a TLC plate. Recrystallization from 99% aq. ethanol gave an analytical sample of III as colorless pillars, mp 108–109°; UV $\lambda_{max}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 230.5 (8600), 279 (2700); IR $\nu_{max}^{CHCl_3}$ 3375 cm^{-1} (b, OH); NMR ($CDCl_3$) τ : 8.1–8.8 (6H, m, three ring- CH_2 's), 7.1–7.9 (6H, m, three N CH_2 's), 6.11 and 6.08 (3H each, s, two CH_3O 's), 5.77 (1H, s, OH), 5.2–5.5 [1H, m, ArCH(OH)], 3.0–3.25 (3H, m, aromatic protons). *Anal.* Calcd. for $C_{25}H_{33}O_3N$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.63; H, 8.75; N, 5.24.

The hydrobromide (III·HBr) was prepared in the following manner: To a solution of the free base (III) (1.33 g) in 99% aq. ethanol (10 ml) was added dropwise 47% aq. HBr until the solution was acid to Methyl Orange paper. Addition of ether (10 ml) to the mixture produced almost colorless crystals (1.69 g), which were recrystallized from ethanol-ethyl acetate (1:1, v/v) to give colorless needles, mp 180–181°; IR ν_{max}^{NaCl} 3175 cm^{-1} (b, OH). *Anal.* Calcd. for $C_{15}H_{24}O_3NBr$: C, 52.03; H, 6.99; N, 4.05. Found: C, 52.16; H, 7.10; N, 3.99.

18) All melting points were obtained on a Yamato MP-1 capillary melting point apparatus and are corrected. Spectra reported herein were determined with a Hitachi EPS-2U UV spectrophotometer, a JASCO-DS-402G IR spectrophotometer, a JEOL-JMS-01SG mass spectrometer, or a JEOL-JNM-C-60H NMR spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: b=broad, d=doublet, DMSO=dimethyl sulfoxide, m=multiplet, s=singlet, sh=shoulder.

19) C. Mannich and F.L. Hahn, *Chem. Ber.*, **44**, 1549 (1911).

ii) From Pyridinium Salt IV: A mixture of IV (18.0 g, 53.2 mmoles) and 99% aq. ethanol (400 ml) was hydrogenated over Adams catalyst (300 mg) at 50° and atmospheric pressure; the reaction was almost complete within 14 hr, absorbing first three equivalent mole of H₂ smoothly and then one more equivalent of H₂ very slowly. After cooling, the reaction mixture was transferred to a 1-liter flask with the aid of a little ethanol and stirred under cooling, and NaBH₄ (3.90 g, 103 mmoles) was added in small portions. After having been stirred at room temp. for 16 hr, the reaction mixture was filtered to remove the Pt catalyst. Evaporation of the ethanol from the filtrate left a colorless solid mass, which was treated with H₂O (60 ml) to separate an oil. The mixture was extracted with chloroform, and the extracts were washed with sat. aq. NaCl, dried over anhyd. Na₂SO₄, and evaporated *in vacuo* to dryness, leaving a slightly brownish solid (12.9 g, 91%), mp 104—106°. This was recrystallized from 99% aq. ethanol to yield colorless pillars, mp 108—109°, identical (by mixed melting-point test, TLC, and IR spectrum) with the sample of III obtained by method-(i).

1-(3,4-Dimethoxyphenacyl)pyridinium Bromide (IV)—A stirred mixture of pyridine (5.54 g, 70 mmoles), 3,4-dimethoxyphenacyl bromide¹⁹ (18.1 g, 70 mmoles), and abs. benzene (650 ml) was heated at reflux for 8 hr. After cooling, the mixture was filtered to collect the colorless precipitates that formed. Yield of crude IV, mp 255—257° (decomp.), was 22.6 g (96%). Recrystallization from 90% aq. ethanol furnished an analytical sample as colorless needles, mp 256—257° (decomp.); UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 233.5 (18200), 269 (sh) (11300), 281 (12100), 312 (9400); IR $\nu_{\text{max}}^{\text{KBr}}$ 1681 cm⁻¹: (CO); NMR (CF₃CO₂H) τ : 5.96 and 5.93 (3H each, s, two CH₃O's), 3.47 (2H, s, COCH₂N⁺), 2.80 (1H, d, $J=8$ cps, H_(5')), 2.28 (1H, d, $J=2$ cps, H_(2')), 2.03 (1H, d-d, $J=8$ and 2 cps, H_(6')), 1.05—1.9 (5H, m, pyridine protons). *Anal.* Calcd. for C₁₅H₁₆O₃NBr: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.42; H, 4.80; N, 3.90.

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-2-piperidone (V) and 1-(3,4-Dimethoxyphenyl)-2-(2-oxopiperidino)ethyl Acetate (VI)—To a solution of aminoalcohol III (9.02 g, 34 mmoles) in 1% aq. acetic acid (250 ml) were added mercuric acetate (21.7 g, 68 mmoles) and (ethylenedinitrilo)tetraacetic acid disodium salt dihydrate (25.3 g, 68 mmoles), and the resulting mixture was heated with stirring in an oil bath kept at 110° for 1.5 hr. After cooling, the reaction mixture was filtered to remove metallic Hg. The dark orange filtrate was extracted with four successive 40-ml portions of chloroform. The combined extracts were washed successively with 10% aq. HCl, H₂O, sat. aq. Na₂CO₃, and H₂O, dried over anhyd. Na₂SO₄, and evaporated *in vacuo* to dryness to leave an almost colorless solid (9.6 g). The solid was dissolved in chloroform (30 ml), and the solution was passed through a column packed with alumina (30 g). The column was further eluted with chloroform (100 ml). The eluate was evaporated *in vacuo*, and the residual solid (8.06 g) was recrystallized from ethyl acetate-isopropyl ether (1:1, v/v) to give colorless pillars (6.57 g) of mp 105—107°. Repeated recrystallization afforded an analytical sample of V as colorless pillars, mp 106—107°; UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 230.5 (9500), 280 (2700); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3325 (b, OH), 1615 (lactam CO); NMR (CDCl₃) τ : 8.0—8.6 (4H, m, two ring-CH₂'s), 7.4—7.8 (2H, m, CH₂CON), 6.7—7.1 (2H, m, ring-CH₂NCO), 6.3—6.55 and 4.9—5.2 [ABX type m, CH(OH)CH₂N and ArCH(OH)CH₂], 6.14 and 6.12 (3H each, s, two CH₃O's), 5.10 (s, OH), 3.0—3.25 (3H, s, aromatic protons). *Anal.* Calcd. for C₁₅H₂₁O₄N: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.78; H, 7.54; N, 5.02.

Next the mother liquor of the first recrystallization of V was evaporated *in vacuo* to leave a light brown oil (1.49 g), which showed two main spots on a TLC plate. The oil was then chromatographed on a column packed with silica gel (150 g). The column was eluted first with ethanol-ethyl acetate (5:95, v/v) (500 ml), then with ethanol-ethyl acetate (10:90, v/v). From fractions eluted later, a second crop (325 mg) of V, mp 103—104°, was obtained, total yield 6.89 g (73%). On the other hand, earlier fractions afforded acetate VI (660 mg, 7%), mp 73—75°. Recrystallization from benzene-hexane (1:1, v/v) produced a pure sample of VI as colorless prisms, mp 76—77°; UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 233 (9800), 280 (3000); IR and Mass Spectrum, see Theoretical Part; NMR (CDCl₃) τ : 8.05—8.45 (4H, m, two ring-CH₂'s), 7.93 (3H, s, CH₃CO), 7.45—7.85 (2H, m, NCOCH₂CH₂), 6.5—6.9 (2H, m, CH₂CH₂NCO), 6.2—6.45 and 3.8—4.15 [ABX type m, CH(OAc)CH₂N and ArCH(OAc)CH₂], 6.14 and 6.11 (3H each, s, two CH₃O's), 3.0—3.2 (3H, aromatic protons). *Anal.* Calcd. for C₁₇H₂₃O₅N: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.33; H, 7.22; N, 4.53.

Hydrolysis of Acetate VI—A mixture of a solution of VI (45 mg, 0.14 mmole) in 99% aq. ethanol (0.5 ml) and 20% aq. NaOH (2 ml) was allowed to stand at room temp. for 48 hr. The reaction mixture was neutralized with 10% aq. HCl, concentrated *in vacuo* to ca. 2 ml, made alkaline with 20% aq. NaOH, and extracted with chloroform. The chloroform solution was dried over anhyd. Na₂SO₄ and evaporated *in vacuo* to dryness to leave a colorless solid (28 mg, 72%), identified with the sample of lactamalcohol V described above by means of TLC and IR spectrum.

2-(3,4-Dimethoxyphenyl)-2,3,5,6,7,8-hexahydrooxazolo[3,2-*a*]pyridinium Perchlorate (VIIa)—To a solution of lactamalcohol V (1.00 g, 3.6 mmoles) in abs. ethanol (10 ml) was added 70% aq. HClO₄ (0.35 ml, ca. 4 mmoles), and the mixture was evaporated *in vacuo* to leave a colorless solid (ca. 1.3 g), mp 145—147°. A portion (850 mg) of the solid was dissolved in boiling abs. ethanol (50 ml), and the solution concentrated to ca. 25 ml, and hot hexane (25 ml) was added. The mixture was allowed to stand at room temp. overnight, and the colorless needles that resulted were collected by filtration, washed with a little abs. ethanol, and dried, mp 154—155°, yield 495 mg. Further recrystallization in the same way did not raise their melting point; UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ $m\mu$ (ϵ): 232 (9500), 280 (3050); IR $\nu_{\text{max}}^{\text{KBr}}$ 1680 cm⁻¹ (C=N⁺); NMR (DMSO-*d*₆) τ : 7.7—

8.3 (4H, m, two CH₂'s), 7.0—7.4 (m, CH₂C=N⁺), 6.0—6.5 (m, CH₂N⁺), 6.22 and 6.20 (3H each, s, two CH₃O's), 5.4—6.0 and 3.6—4.1 [ABX type m, CH(O)-CH₂N⁺] and ArCH(O)-CH₂, 2.6—2.95 (m, aromatic protons). *Anal.* Calcd. for C₁₅H₂₀O₇NCl: C, 49.80; H, 5.58; N, 3.87. Found: C, 49.94; H, 5.58; N, 3.85.

1-(3,4-Dimethoxyphenethyl)-2-piperidone (VIII)—i) Direct Hydrogenolysis of Lactamalcohol V: A solution of V (1.00 g, 3.6 mmoles) in 99% aq. ethanol (60 ml) and 70% aq. HClO₄ (0.5 ml) was hydrogenated over 10% palladium-on-charcoal (1.2 g) at 25° and 3.6 atmospheric pressure; one equivalent mole of H₂ was taken up within 4 hr. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to leave a yellowish syrup. The residue was dissolved in chloroform, and the solution was washed successively with H₂O, 5% aq. NaOH, and H₂O, dried over anhyd. Na₂SO₄, and evaporated *in vacuo* to dryness to leave VIII as a slightly yellowish solid mass (895 mg, 94%), mp 48—53°, shown to be homogeneous by means of TLC. The solid was dissolved in hot ethanol and treated with charcoal. Filtration of the mixture and evaporation of the filtrate left an almost colorless solid, which was recrystallized from isopropyl ether as colorless plates, mp 56—57°; UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ m μ (ϵ): 230 (9000), 281 (2750); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ 1628 cm⁻¹ (lactam CO); NMR (CDCl₃) τ : 8.0—8.45 (4H, m, two ring-CH₂'s), 7.45—7.8 (2H, m, CH₂CON), 7.05—7.4 and 6.25—6.65 (A₂B₂ type m, ArCH₂CH₂ and CH₂CH₂NCO), 6.7—7.05 (m, ring-CH₂NCO), 6.14 and 6.13 (3H each, s, two CH₃O's), 3.23 (3H, s, aromatic protons). *Anal.* Calcd. for C₁₅H₂₁O₃N: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.56; H, 8.19; N, 5.60.

ii) Hydrogenolysis of Oxazolinium Salt VIIa: A mixture of VIIa (1.30 g, 3.6 mmoles) and abs. ethanol (60 ml) was hydrogenated over 10% palladium-on-charcoal (1.2 g) at 20° and 3.7 atmospheric pressure; the reaction ceased after having taken one equivalent mole of H₂ within 4 hr. Treatment of the reaction mixture in the same way as described above [method-(i)] furnished colorless plates (880 mg, 93%), mp 56—57°, undepressed upon mixture with the sample of VIII obtained by method-(i). The IR spectra of both samples were also identical.

9,10-Dimethoxy-1,2,3,4,6,7-hexahydrobenzo[a]quinolizinium Iodide (IX:X=I)—The cyclization of VIII to IX was carried out according to the procedure reported by Ban, *et al.*,^{15a} and crude IX (X=I) was obtained in 98% yield. Recrystallization from 99% aq. ethanol yielded yellow needles, mp 202—204° (decomp.) (lit.^{15a} mp 203—205°); UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ m μ (ϵ): 246 (16900), 304 (8750) (Fig. 1); IR $\nu_{\text{max}}^{\text{KBr}}$ 1648 cm⁻¹ (C=N⁺). *Anal.* Calcd. for C₁₅H₂₀O₂NI: C, 48.27; H, 5.40; N, 3.75. Found: C, 48.56; H, 5.41; N, 4.00.

The corresponding picrate was prepared from the iodide by dissolving it in 99% aq. ethanol and adding a solution of picric acid in 99% aq. ethanol. Recrystallization from 90% aq. ethanol gave yellow scales, mp 184—185° (lit.^{5,10} mp 185—186°), identical (by mixed melting-point test and IR spectrum) with an authentic specimen.¹⁰

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizine (Ia)—Iodide IX (X=I) was converted into the corresponding chloride IX (X=Cl) with AgCl, and the chloride was hydrogenated over Adams catalyst according to the reported procedure.^{15a} Thus, base Ia was obtained in 79% yield and afforded the picrate as yellow pillars, mp 173—174° (lit.⁵ mp 172—174°), undepressed upon mixture with authentic picrate.¹⁰ The IR spectra of both samples were also superimposable. *Anal.* Calcd. for C₂₁H₂₄O₉N₄: C, 52.94; H, 5.08; N, 11.76. Found: C, 52.91; H, 5.26; N, 11.79.

9,10-Dimethoxy-1,2,3,4-tetrahydrobenzo[a]quinolizinium Salt (X)—A mixture of V (1.96 g, 7 mmoles), abs. benzene (6 ml), and POCl₃ (6 ml) was refluxed for 2.5 hr. After cooling, the solvent and the excess of POCl₃ were removed by evaporation, and the residual oil was dissolved in H₂O (10 ml). To the aq. solution was added KI (6.0 g, 36 mmoles), and the mixture was triturated. The precipitates that resulted were filtered off, washed with a little H₂O, and dried to give crude X (X=I) (2.26 g, 87%), mp 220—228° (decomp.). For analysis it was recrystallized from H₂O to produce faintly greenish yellow, minute needles, mp 227—228° (decomp.); UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ m μ (ϵ): 255.5 (65100), 312 (8600) (Fig. 1). *Anal.* Calcd. for C₁₅H₁₈O₂NI: C, 48.53; H, 4.89; N, 3.77. Found: C, 48.33; H, 4.88; N, 3.91.

The perchlorate (X: X=ClO₄) was prepared as described below: To a hot solution of iodide X (X=I) (642 mg, 1.73 mmoles) in H₂O (70 ml) was added a solution of AgClO₄ (394 mg, 1.9 mmoles) in H₂O (5 ml). The precipitates that formed immediately were removed by filtration, and the filtrate was evaporated *in vacuo* to dryness to leave silky needles (590 mg, 99%), mp 241—244° (decomp.). Recrystallization from H₂O produced an analytical sample as colorless, minute needles, mp 242—244° (decomp.); UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ m μ (ϵ): 255.5 (65200), 312 (8100). *Anal.* Calcd. for C₁₅H₁₈O₆NCl: C, 52.41; H, 5.28; N, 4.08. Found: C, 52.14; H, 5.31; N, 3.96.

6,7-Dimethoxy-1,2-dimethylisoquinolinium Perchlorate (XI: X=ClO₄)—This was prepared in 99% yield from the corresponding iodide (XI: X=I)¹⁷ and AgClO₄ in a manner similar to that described above for X (X=ClO₄). An analytical sample was recrystallized from H₂O as colorless micro-needles, mp 288—289° (decomp.) (lit.¹⁷ mp 280—281°); UV $\lambda_{\text{max}}^{99\% \text{ aq. EtOH}}$ m μ (ϵ): 255.5 (64700), 313 (8850). *Anal.* Calcd. for C₁₃H₁₆O₆NCl: C, 49.14; H, 5.08; N, 4.41. Found: C, 49.42; H, 5.19; N, 4.58.

Acknowledgement The support of this work by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan is gratefully acknowledged. We also wish to thank Professor Y. Ban of Hokkaido University for his warm encouragement and Mr. Y. Itatani and Misses M. Imai, S. Toyoshima, and T. Tsuji at Kanazawa University for microanalyses and NMR and mass spectral data.