QUINOLIZIDINES. XXXI.[1] A SYNTHESIS OF THE DIBENZO-[*a,h*]QUINOLIZIDINE RING SYSTEM: AN APPLICATION OF THE MERCURIC ACETATE–EDETIC ACID OXIDATION METHOD TO 1,2,3,4-TETRAHYDROISOQUINOLINE†

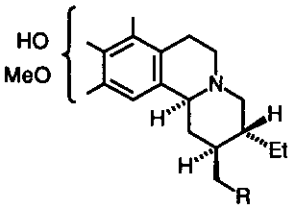
Masashi Ohba, Yoko Shinbo, Takako Ohashi, Mitsuhiro Toda, and Tozo Fujii*

Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

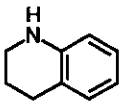
Abstract——A formal synthesis of 2,3-dimethoxydibenzo[*a,h*]quinolizidine (**25a**) has been achieved through a route including mercuric acetate–edetic acid oxidation of a benzene-fused piperidine. The route started with an initial condensation of 1,2,3,4-tetrahydroisoquinoline (**3a**) with 3,4-dimethoxyphenacyl bromide (**7**) and proceeded through the amino ketone (**8a**), amino alcohol (**9a**), lactam alcohol (**10a**), and the lactam (**15a**). A parallel sequence of reactions starting with 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**3b**) and **7** concluded a formal synthesis of the 2,3,11,12-tetramethoxy analogue (**25b**) of the tetracycle (**25a**). In the mercuric acetate–edetic acid oxidations of the amino alcohols (**9a,b**) under acidic or alkaline conditions, the oxazoloisoquinoline derivatives (**11a,b**) were obtained besides the desired lactam alcohols (**10a,b**).

Generation of the lactam carbonyl function in a piperidine ring has been found feasible enough by means of mercuric acetate–edetic acid oxidation.[2-4] This oxidation method has enjoyed its successful application to our chiral syntheses of benzo[*a*]quinolizidine-type *Alangium* alkaloids (type **1**).[4i,5] The preceding paper[1] in this series described a further application of the method to 1,2,3,4-tetrahydroquinoline (**2**), a benzene-fused piperi-

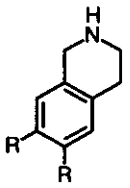
† Dedicated to Emeritus Professor Dr. Shun-ichi Yamada (University of Tokyo) on the occasion of his 77th birthday.



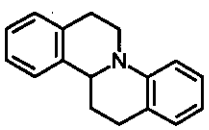
1: R = CH_2OH, CO_2H, or a heterocyclic ring



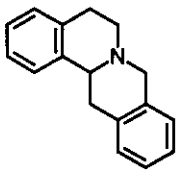
2



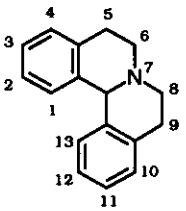
3a: R = H
3b: R = MeO



4



5



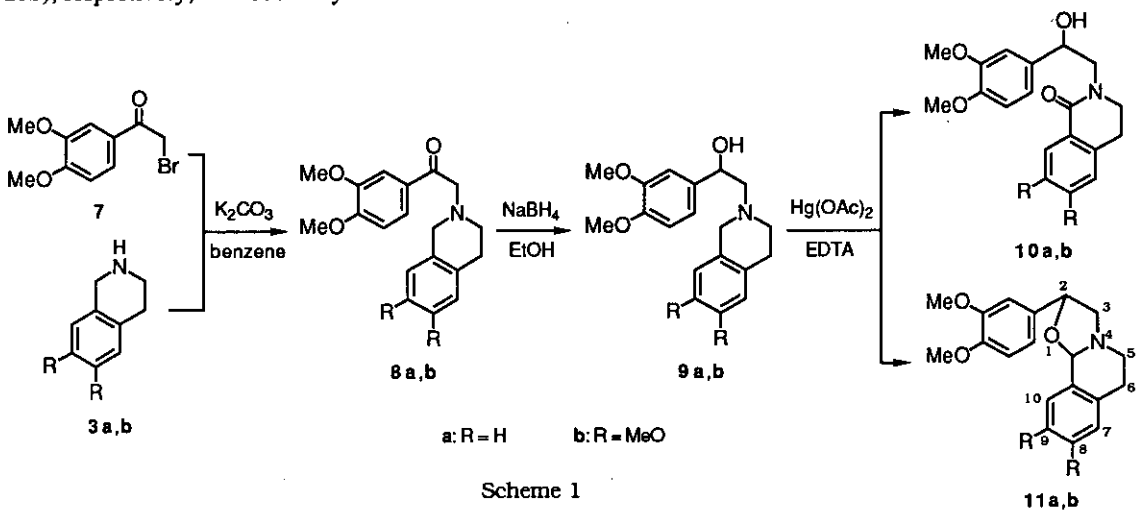
6

dine system, which led to an alternative synthesis of the dibenzo[*a,f*]quinolizidine ring system (**4**). In the present study, we sought to extend the same method to cover 1,2,3,4-tetrahydroisoquinoline (**3a**), another benzene-fused piperidine, in the hope of developing a new synthetic route to the dibenzo[*a,g*]quinolizidine (**5**) and/or the dibenzo[*a,h*]quinolizidine ring system (**6**).

Condensation of **3a** with 3,4-dimethoxyphenacyl bromide (**7**) in boiling benzene containing anhydrous K_2CO_3 for 4 h furnished the amino ketone (**8a**). The crude amino ketone (**8a**) was then subjected to the $NaBH_4$ reduction in EtOH at room temperature for 24 h to give the amino alcohol (**9a**) in 91% overall yield from **3a**. In a similar condensation followed by reduction, 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**3b**) was converted into **9b** *via* **8b** in 72% overall yield.

With the amino alcohols (**9a,b**) in hand, we next investigated the applicability of the mercuric acetate–edetic acid oxidation method. Oxidation of **9a** according to the previously reported standard procedure [2.5 molar equivalents of mercuric acetate–edetic acid (EDTA) in boiling 1% aqueous AcOH for 1.5 h][4b] produced the lactam alcohol (**10a**) and the oxazolidine (**11a**) in 38% and 50% yields, respectively, together with the concomitant formation of the isocarbostyril (**12**) in 6% yield (Table I). These results are in general agreement with those observed by Möhrle[6] for a similar oxidation of the amino alcohol (**13**) under somewhat milder conditions. Elongation of the reaction time from 1.5 h to 6 h raised the yield of **10a** to 62% while lowering that of **11a** to 33%. Interestingly, at each of these reaction times, the formation of **10b** from **9b** was less than that of

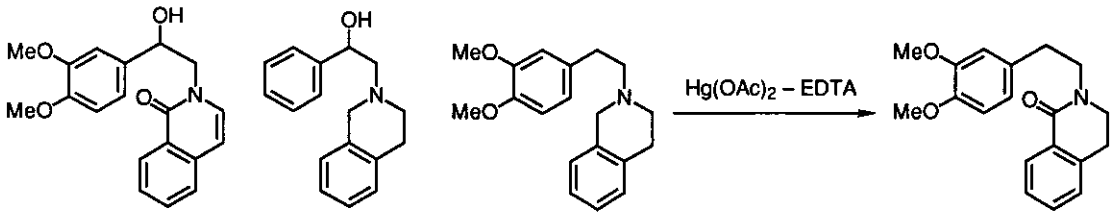
10a from **9a**. Further oxidations of the oxazolidines (**11a** and **11b**) afforded the lactam alcohols (**10a** and **10b**), respectively, in moderate yields.



Scheme 1

At this stage of the oxidation study, a recent development[7] of the procedure for oxidation of cyclic tertiary amines to lactams by mercuric acetate–edetic acid treatment at high pH prompted us to study similar conversions of **9a,b** in alkaline medium. Oxidation of the amino alcohol (**9a**) with 2.5 molar equivalents of mercuric acetate–edetic acid in boiling H_2O–2 N aqueous NaOH (3 : 2, v/v) for 3 h produced the lactam alcohol (**10a**) in 72% yield along with an appreciable amount (19% yield) of the oxazolidine (**11a**). A parallel result was also obtained with a similar oxidation of **9b**. It may be seen from Table I that the oxidation of **9a,b** in the tetrahydroisoquinoline moiety occurred at the 1-position predominantly over the 3-position under both the acidic and alkaline reaction conditions. Interestingly, the lactam alcohols (**10a,b**) were formed faster under alkaline conditions than under acidic conditions.

In the above alkaline oxidations of the amino alcohols (**9a** and **9b**), however, the reactions would not necessarily have proceeded through intramolecular participation of the side chain hydroxy group as accepted[3,4] in the cases of the acidic oxidations. Therefore, we next investigated the mercuric acetate–edetic acid oxidation of **14**,[8] which lacks hydroxy group at the benzylic position in the side chain of the tetrahydroisoquinoline moiety. Under the same alkaline oxidation conditions as those adopted for **9a,b**, **14** furnished the lactam (**15a**) in only 14% yield. Thus, it has become apparent that the hydroxy group in **9a,b** plays an important role[3,4] in the mercuric acetate–edetic acid oxidation process under the conditions in question.



12 13 14 15a

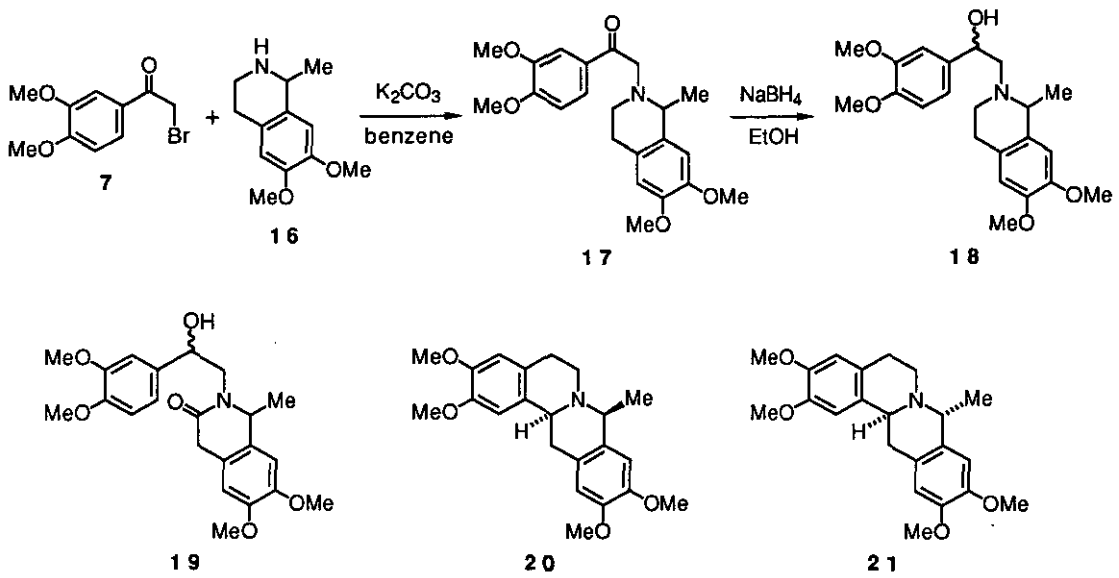
Scheme 2

TABLE I. The Mercuric Acetate–Edetic Acid Oxidation of the Amino Alcohols (**9a,b**) and the Oxazolidines (**11a,b**)

Substrate	Reaction conditions[a]		Product			
	Solvent[b]	Time (h)	No.	Yield (%)	No.	Yield (%)
9a	A	1.5	**10a**	38	**11a**	50[c]
9a	A	6	**10a**	62	**11a**	33
9a	B	3	**10a**	72	**11a**	19
9b	A	1.5	**10b**	23	**11b**	69
9b	A	6	**10b**	38	**11b**	50
9b	B	3	**10b**	60	**11b**	24
11a	A	24	**10a**	57	—[d]	
11b	A	24	**10b**	55	**11b**	31

a) For details of the reaction conditions, see "EXPERIMENTAL".
b) The letter A stands for 1% aqueous AcOH; B, H_2O–2 N aqueous NaOH (3 : 2, v/v).
c) The isocarbostyril (**12**) was also isolated in 6% yield.
d) No attempt was made to isolate **11a**.

We then studied the mercuric acetate–edetic acid oxidation of the amino alcohol (**18**) possessing a methyl group at the 1-position in the tetrahydroisoquinoline moiety. If the methyl group could orient the oxidation to the less favorable 3-position, the resulting lactam alcohol (**19**) would be useful as a key intermediate for the syntheses of coralydine (**20**)[9] and *O*-methylcorytenchirine (**21**),[9,10] both containing the dibenzo[*a*,*g*]quinolizidine ring system. Treatment of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**16**)[11] with **7** in the presence of anhydrous K_2CO_3 and subsequent reduction of the resulting amino ketone (**17**) with $NaBH_4$ produced **18**, presumed to be a mixture of the two possible diastereoisomers, in 79% overall yield from **16**. Unfortunately, oxidation of **18** with 2.5 molar equivalents of mercuric acetate–edetic acid in boiling AcOH for 6 h gave a complex mixture, from which the demethylated lactam alcohol (**10b**) was isolated in only 3% yield, and we were

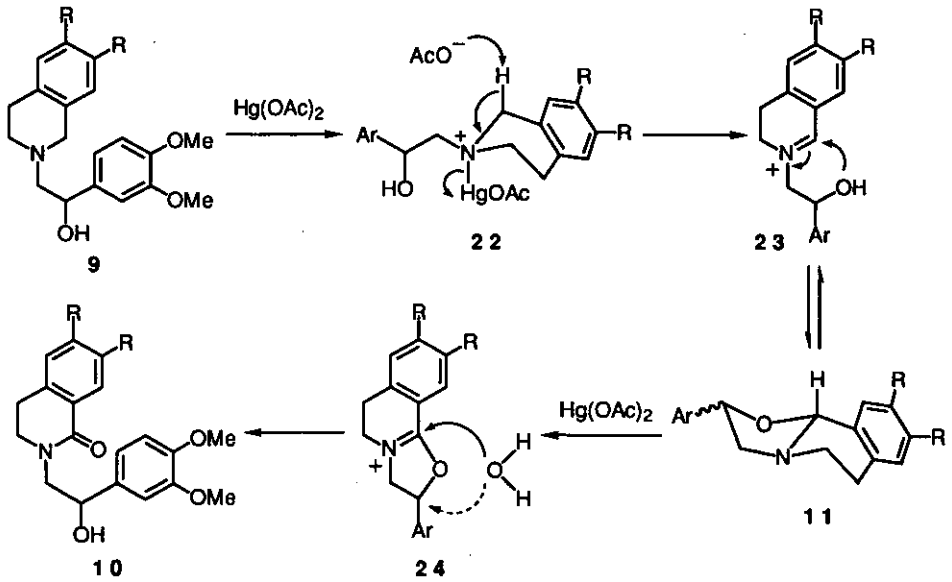


Scheme 3

unable to obtain the desired lactam alcohol (**19**). A similarly poor result was obtained under alkaline oxidation conditions. We therefore discontinued this route.

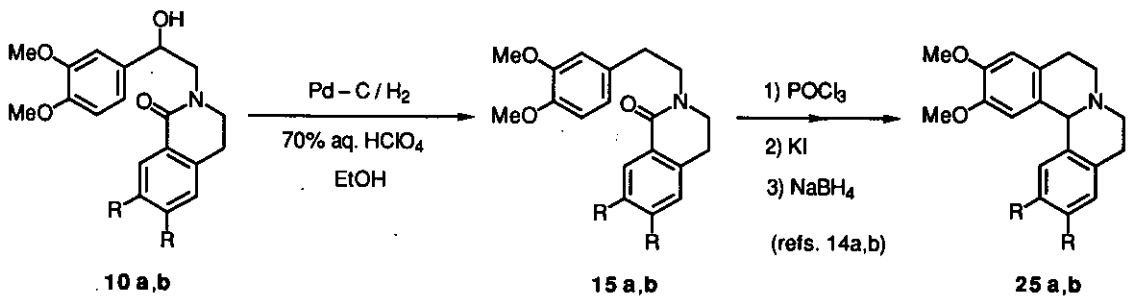
The observed orientation of the oxidation may be interpreted on the basis of the postulated mechanism of the mercuric acetate oxidation of cyclic amines[12] and amino alcohols[4a,c,d,13] (Scheme 4). The abstraction of an axial proton from C(α) (with respect to N) of the mercurated complex (**22**) by the acetate ion could occur much more easily at the more acidic benzylic position [C(1)] than at C(3). The resulting iminium ion (**23**) would undergo intramolecular cyclization to give the oxazolidine derivative (**11**), which could be similarly dehydrogenated by a second molecule of mercuric acetate to the oxazolinium ion (**24**). Attack of **24** by water would result in the formation of the lactam alcohol (**10**). Since the C=N$^+$ double bond in **23** is stabilized by resonance with the adjacent aromatic ring, the iminium–oxazolidine equilibrium (**23** $\rightleftharpoons$ **11**) in 1% aqueous AcOH would tend to shift to the left, compared with the cases lacking the aromatic ring fused to this particular side of the piperidine ring. The formations of the lactam alcohols (**10a,b**) would therefore be slow under acidic conditions. The low yield of **10b**, in comparison with that of **10a**, would be understandable in terms of resonance stabilization of the iminium ion (**23**) by the methoxy group. On the other hand, the alkaline conditions would accelerate the intramolecular cyclization of **23** to **11** through the corresponding alkoxide (**23**: O$^-$ for the benzylic OH), resulting in the faster formation of **10a,b** in good yields. Such pH-dependent shift of equilibrium was supported by the uv spectra of **11b** in acidic, neutral, and basic media: the appearance in acidic and neutral media and the absence in

basic medium of the strong absorption band at 369 nm indicated the predominant existence of the bicyclic iminium structure (**23**) in the first two media.



Scheme 4

Hydrogenolyses of the lactam alcohols (**10a,b**) were separately effected by using hydrogen and Pd–C in the presence of a little 70% aqueous $HClO_4$, giving the lactams (**15a**) (mp 108–108.5°C) and (**15b**) (mp 129–130°C) in 95% and 76% yields, respectively. The melting points and uv, ir, and ^1H nmr spectral data obtained for these samples were found to match those reported[14] for authentic **15a** and **15b**, respectively.



Scheme 5

Since the lactams (**15a,b**) have already been led to **25a,b** through Bischler–Napieralski cyclization followed by $NaBH_4$ reduction,[14a,b] the above syntheses of **15a,b** from **3a,b** represent additional new syntheses of the dibenzo[*a,h*]quinolizidine ring system (**6**)[15] in a formal sense. It should be emphasized that the scope of the mercuric acetate–edetic acid oxidation method has now been extended to cover the 1,2,3,4-tetrahydroisoquinoline system (type **3**) beyond 1,2,3,4-tetrahydroquinoline (**2**).[1] As a result, this has made the dibenzo[*a,h*]quinolizidine skeleton (**6**) readily accessible but the dibenzo[*a,g*]quinolizidine skeleton (**5**) unaccessible. The skeleton (**6**) is unique among the seven theoretically possible dibenzoquinolizidines[16] because of its U-shape molecular symmetry caused by fusion of two 1,2,3,4-tetrahydroisoquinoline units.

EXPERIMENTAL

General Notes. All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. See ref. 1 for details of instrumentation, measurements, and chromatographies. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-dd's, m = multiplet, s = singlet, sh = shoulder, t = triplet.

1-(3,4-Dimethoxyphenyl)-2-(1,2,3,4-tetrahydro-2-isoquinolinyl)ethanone (8a). A stirred mixture of 1,2,3,4-tetrahydroisoquinoline (**3a**)[17] (2.66 g, 20 mmol), anhydrous K_2CO_3 (5.53 g, 40 mmol), 3,4-dimethoxyphenacyl bromide (**7**)[18] (5.18 g, 20 mmol), and dry benzene (100 ml) was heated under reflux in an atmosphere of N_2 for 4 h. After cooling, the reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated *in vacuo* to leave **8a** (7.52 g) as a yellowish brown oil, which was used directly in the next $NaBH_4$ reduction without further purification.

In a separate experiment, a small sample of the crude oil was purified by flash chromatography[19] [hexane–AcOEt (2 : 1, v/v), then CH_2Cl_2–AcOEt (8 : 1, v/v)] to give a yellowish orange solid. Recrystallization of the solid from EtOH–H_2O (3 : 2, v/v) yielded an analytical sample of **8a** as faintly orange needles, mp 95.5–98.5°C; ms *m/z*: 311 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 228.5 nm (ε 19300), 274 (11700), 304 (8650); ir ν_{max}^{Nujol} 1676 cm^{-1} (ArCO); ^1H nmr ($CDCl_3$) δ:[20] 2.92 [4H, br s, C(3)-H's and C(4)-H's], 3.81 [2H, s, N(2)-CH_2CO or C(1)-H's], 3.93 and 3.94 [8H, s each, two MeO's and C(1)-H's or N(2)-CH_2CO], 6.87 [1H, d, J = 8.5 Hz, C(5')-H], 6.9–7.15 [4H, m, C(5)-H, C(6)-H, C(7)-H, and C(8)-H], 7.63 [1H, d, J = 2 Hz, C(2')-H], 7.77 [1H, dd, J = 8.5 and 2 Hz, C(6')-H]. *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.17; H, 6.89; N, 4.57.

1-(3,4-Dimethoxyphenyl)-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)ethanone (8b). A stirred mixture of 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (**3b**·HCl)[21] (1.15 g, 5 mmol), anhydrous K_2CO_3 (2.07 g, 15 mmol), 3,4-dimethoxyphenacyl bromide (**7**)[18] (1.30 g, 5 mmol), and dry benzene (25 ml) was heated under reflux in an atmosphere of N_2 for 8 h. The reaction mixture was then worked

up as described above for **8a**, giving **8b** (2.95 g) as a yellowish orange solid. This solid was used directly in the next reduction step without further purification.

1-(3,4-Dimethoxyphenyl)-2-(1,2,3,4-tetrahydro-6,7-dimethoxy-1-methyl-2-isoquinolinyl)-ethanone (17). A stirred mixture of 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline (**16**)[11] (6.20 g, 29.9 mmol), anhydrous K_2CO_3 (8.30 g, 60.1 mmol), 3,4-dimethoxyphenacyl bromide (**7**)[18] (7.80 g, 30.1 mmol), and dry benzene (150 ml) was heated under reflux in an atmosphere of N_2 for 4 h. The reaction mixture was worked up in a manner similar to that described above for **8a**, giving **17** (16.4 g) as a yellowish brown oil. Without further purification this oil was used directly in the next step.

α-(3,4-Dimethoxyphenyl)-3,4-dihydro-2(1*H*)-isoquinolineethanol (9a). A solution of the crude amino ketone (**8a**) (7.52 g) in EtOH (75 ml) was stirred under ice-cooling, and $NaBH_4$ (832 mg, 22 mmol) was added portionwise. After the mixture had been stirred at room temperature for 24 h, acetone (9 ml) was added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous K_2CO_3, and concentrated *in vacuo* to leave a yellow viscous oil (7.04 g). The oil crystallized from EtOH–H_2O (1 : 1, v/v) to give a first crop (5.61 g) of **9a**, mp 93–95°C. Concentration of the mother liquor from this crystallization and recrystallization of the residue from EtOH–H_2O (1 : 2, v/v) afforded a second crop (68 mg) of **9a**, mp 91–93°C. The total yield of **9a** was 5.68 g (91% from **3a**). Recrystallization of the crude **9a** from EtOH–H_2O (3 : 2, v/v) produced an analytical sample as colorless scales, mp 96.5–97°C; ms *m/z*: 313 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 229 nm (sh) (ε 10400), 274 (3040), 279 (sh) (2990); ir $\nu_{max}^{CHCl_3}$ 3430 cm^{-1} (OH); ^1H nmr ($CDCl_3$) δ:[20] 2.5–3.2 [4H, m, C(3)-H's and C(4)-H's], 2.66 (1H, d, J = 8 Hz) and 2.67 (1H, d, J = 6 Hz) [N(2)-C<u>H</u>$_2$CH(OH)], 3.69 and 3.93 [2H, AB type d's, J = 15 Hz, C(1)-H's], 3.85 (1H, br, OH), 3.88 and 3.91 (6H, s each, two MeO's), 4.81 [1H, dd, J = 8 and 6 Hz, N(2)-CH$_2$C<u>H</u>(OH)], 6.75–7.25 (7H, m, aromatic protons). *Anal.* Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.62; H, 7.66; N, 4.64.

α-(3,4-Dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-2(1*H*)-isoquinolineethanol (9b). A solution of the crude **8b** (2.95 g) in EtOH (18 ml) was kept stirring under ice-cooling, and $NaBH_4$ (208 mg, 5.5 mmol) was added portionwise. After having been stirred at room temperature for 24 h, the mixture was worked up as described above for **9a**, giving a yellowish brown viscous oil, which crystallized from EtOH–H_2O (1 : 1, v/v) to afford a first crop (937 mg) of **9b** as yellow prisms, mp 115–118°C. Concentration of the mother liquor of this crystallization and purification of the residue by means of flash chromatography[19] [$CHCl_3$–EtOH (30 : 1, v/v)] furnished a second crop (410 mg) of **9b**. The total yield of **9b** was 1.35 g (72% from **3b**). Recrystallization of the crude **9b** from EtOH–H_2O (2 : 1, v/v) produced an analytical sample as colorless prisms, mp 120.5–122.5°C; ms *m/z*: 373 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 227 nm (ε 17200), 282 (6640); ir ν_{max}^{Nujol} 3470 cm^{-1} (OH); ^1H nmr ($CDCl_3$) δ:[20] 2.5–3.2 [4H, m, C(3)-H's and C(4)-H's], 2.67 (1H, d, J = 8 Hz) and 2.68 (1H, d, J = 6 Hz) [N(2)-C<u>H</u>$_2$CH(OH)], 3.63 and 3.88 [2H, AB type d's, J = 14 Hz, C(1)-H's], 3.7 (1H, br, OH), 3.85, 3.86, 3.88, and 3.91 (12H, s each, four MeO's), 4.82 [1H, dd, J = 8 and 6 Hz, N(2)-CH$_2$C<u>H</u>(OH)], 6.54 [1H, s, C(5)-H or C(8)-H], 6.62 [1H, s, C(8)-H or C(5)-H], 6.75–7.05 [3H, m, C(2')-H, C(5')-H, and C(6')-H]. *Anal.* Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.34; H, 7.43; N, 3.73.

α-(3,4-Dimethoxyphenyl)-3,4-dihydro-6,7-dimethoxy-1-methyl-2(1*H*)-isoquinolineethanol (18). A solution of the crude **17** (16.4 g) in EtOH (100 ml) was stirred under ice-cooling, and $NaBH_4$ (1.25 g, 33 mmol) was added portionwise. After having been stirred at room temperature for 20 h, the reaction mixture was worked up in a manner similar to that described above for **9a**, giving a brown viscous oil (11.4 g). Purification of the oil by means of flash chromatography[19] [AcOEt, then $CHCl_3$–EtOH (9 : 1, v/v)] afforded **18** (9.12 g, 79% from **16**) as a yellow solid (presumed to be a diastereoisomeric mixture), mp 95–98°C; ir ν_{max}^{Nujol} 3400 cm^{-1} (OH); ^1H nmr ($CDCl_3$) δ:[20] 1.37 and 1.44 [3H, d each, J = 6.5 Hz, diastereoisomeric C(1)-Me's], 2.35–3.35 [7H, m, N(2)-C<u>H</u>$_2$CH(OH), C(3)-H's, C(4)-H's, and OH], 3.7–3.9 [1H, m, C(1)-H], 3.85, 3.86, 3.87, and 3.91 (12H, s each, four MeO's), 4.55–4.8 [1H, m, N(2)-CH_2C<u>H</u>(OH)], 6.54 [1H, s, C(5)-H or C(8)-H], 6.58 [1H, s, C(8)-H or C(5)-H], 6.7–7.0 [3H, m, C(2')-H, C(5')-H, and C(6')-H]. Repeated recrystallizations of a small sample of the crude **18** from hexane–AcOEt (5 : 1, v/v) yielded colorless needles, mp 99–100°C; ms *m/z*: 387 (M^+); ir ν_{max}^{Nujol} 3400 cm^{-1} (OH). *Anal.* Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.99; H, 7.82; N, 3.58. The ^1H nmr spectrum of this sample was identical with that of the crude **18**, indicating that it was still impure stereochemically.

2-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3,4-dihydro-1(2*H*)-isoquinolinone (10a), 2-(3,4-Dimethoxyphenyl)-2,3,6,10b-tetrahydro-5*H*-oxazolo[2,3-*a*]isoquinoline (11a), and 2-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-1(2*H*)-isoquinolinone (12). (i) Acidic Oxidation of **9a**: A stirred mixture of **9a** (1.25 g, 4 mmol), (ethylenedinitrilo)tetraacetic acid disodium salt dihydrate (EDTA·2Na·2H_2O) (3.72 g, 10 mmol), and $Hg(OAc)_2$ (3.19 g, 10 mmol) in 1% aqueous AcOH (30 ml) was heated for 1.5 h in an oil bath kept at 110°C. After cooling, the reaction mixture was brought to pH 11 with 10% aqueous NaOH and extracted with $CHCl_3$. The $CHCl_3$ solution was then washed with 10% aqueous HCl. The combined aqueous washings were made basic with 10% aqueous NaOH and extracted with $CHCl_3$ again. The resulting $CHCl_3$ extracts were combined and washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave **11a** (624 mg, 50%) as a brown caramel; ms *m/z*: 311 (M^+); ^1H nmr ($CDCl_3$) δ: 2.65–3.15 [4H, m, C(5)-H's and C(6)-H's], 3.1–3.8 (0.27 × 2H, m), 3.35 (0.73H, dd, J = 12.5 and 9 Hz), and 3.60 (0.73H, dd, J = 12.5 and 6.5 Hz) [C(3)-H's], 3.81 and 3.85 (0.27 × 6H) and 3.89 and 3.92 (0.73 × 6H) (s each, two MeO's), 4.9–5.1 (0.27H, m) and 5.10 (0.73H, dd, J = 9 and 6.5 Hz) [C(2)-H], 5.44 (0.27H) and 5.65 (0.73H) [s each, C(10b)-H], 6.7–7.55 (7H, m, aromatic protons). On the basis of the ^1H nmr spectrum, this caramel is presumed to be a 2.7 : 1 mixture of the two possible diastereoisomers.

The $CHCl_3$ solution that had been washed with 10% aqueous HCl as described above was then washed successively with H_2O, 5% aqueous NaOH, and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The brown glass thus obtained was passed through a column packed with alumina (12 g) using $CHCl_3$ as the solvent. The eluate was concentrated *in vacuo* and the resulting brown solid (664 mg) was dissolved in EtOH (20 ml). The ethanolic solution was then stirred with 50% aqueous NaOH (2.5 ml) at room temperature for 24 h. The reaction mixture was neutralized by addition of 10% aqueous HCl and then concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed successively with 10% aqueous HCl, H_2O, 5% aqueous NaOH, and H_2O, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a brownish orange solid (624 mg). Purification of the solid by means of flash chromatography[19] [$CHCl_3$–AcOEt (5 : 1, v/v)] gave **10a** (494 mg, 38%) as a slightly

yellow solid, mp 118.5–120.5°C. Recrystallization of the solid from hexane–AcOEt (1 : 1, v/v) afforded an analytical sample as colorless needles, mp 121–121.5°C; ms *m/z*: 327 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 230 nm (ε 16900), 254 (sh) (6930), 265.5 (6320), 279 (sh) (5560); ir ν_{max}^{Nujol} cm^{-1}: 3340 (OH), 1628 (lactam CO); ^1H nmr ($CDCl_3$) δ:[20] 2.84 [2H, t, J = 6.5 Hz, C(4)-H's], 3.15–3.65 [2H, m, C(3)-H's], 3.71 (1H, dd, J = 14 and 7 Hz) and 3.92 (1H, dd, J = 14 and 3.5 Hz) [N(2)-C<u>H</u>$_2$CH(OH)], 3.85 and 3.87 (6H, s each, two MeO's), 4.35 (1H, d, J = 4 Hz, OH), 5.06 [1H, ddd, J = 7, 4, and 3.5 Hz, N(2)-CH$_2$C<u>H</u>(OH)], 6.75–7.5 (6H) and 8.0–8.15 (1H) (m each, aromatic protons). *Anal.* Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.55; H, 6.55; N, 4.13.

In addition, earlier fractions of the above chromatography furnished **12** (76 mg, 6%) as a slightly yellow solid. Recrystallization of the solid from hexane–AcOEt (1 : 2, v/v) yielded an analytical sample as colorless needles, mp 144.5–146°C; ms *m/z*: 325 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 227.5 nm (ε 29500), 280 (13000), 286.5 (sh) (12300), 315 (sh) (3900), 326.5 (4550), 342 (sh) (3000); ir ν_{max}^{Nujol} cm^{-1}: 3310 (OH), 1648 (CO); ^1H nmr ($CDCl_3$) δ:[20] 2.6 (1H, br, OH), 3.81 and 3.88 (6H, s each, two MeO's), 4.01 (1H, dd, J = 13.5 and 8 Hz) and 4.45 (1H, dd, J = 13.5 and 3 Hz) [N(2)-C<u>H</u>$_2$CH(OH)], 5.16 [1H, dd, J = 8 and 3 Hz, N(2)-CH$_2$C<u>H</u>(OH)], 6.44 [1H, d, J = 7 Hz, C(4)-H], 6.75–7.0 [3H, m, C(2')-H, C(5')-H, and C(6')-H], 6.91 [1H, d, J = 7 Hz, C(3)-H], 7.4–7.75 [3H, m, C(5)-H, C(6)-H, and C(7)-H], 8.35–8.5 [1H, m, C(8)-H]. *Anal.* Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.10; H, 5.87; N, 4.42.

A similar oxidation of **9a** but with elongation of the reaction time from 1.5 h to 6 h was carried out on the same scale as that described above. The results are given in Table I.

(ii) Alkaline Oxidation of **9a**: A stirred mixture of **9a** (1.25 g, 4 mmol), EDTA·2Na·2H$_2$O (3.72 g, 10 mmol), Hg(OAc)$_2$ (3.19 g, 10 mmol), and H$_2$O (18 ml) was heated, after addition of 2 N aqueous NaOH (12 ml), under reflux for 3 h in an oil bath kept at 110°C. The reaction mixture was worked up as described above under method (i), giving **10a** (941 mg, 72%) as a yellow solid, mp 120–121.5°C, and **11a** (240 mg, 19%) as a yellowish brown caramel. The products (**10a** and **11a**) thus obtained were identical [by comparison of the tlc behavior and ir spectrum] with authentic samples obtained by method (i).

(iii) Oxidation of the Oxazolidine (**11a**): A stirred mixture of **11a** (102 mg, 0.33 mmol), EDTA·2Na·2H$_2$O (309 mg, 0.83 mmol), Hg(OAc)$_2$ (265 mg, 0.83 mmol), and 1% aqueous AcOH (3 ml) was heated under reflux for 24 h. The reaction mixture was worked up in a manner similar to that described above under method (i), giving **10a** (61 mg, 57%) as a slightly yellow solid. This sample was identical (by comparison of the tlc behavior and ir spectrum) with authentic **10a** prepared by method (i).

2-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-3,4-dihydro-6,7-dimethoxy-1(2*H*)-isoquinolinone (10b) and 2-(3,4-Dimethoxyphenyl)-2,3,6,10b-tetrahydro-8,9-dimethoxy-5*H*-oxazolo[2,3-*a*]isoquinoline (11b). (i) Acidic Oxidation of **9b**: A stirred mixture of **9b** (374 mg, 1.0 mmol), EDTA·2Na·2H$_2$O (931 mg, 2.5 mmol), Hg(OAc)$_2$ (797 mg, 2.5 mmol), and 1% aqueous AcOH (7.5 ml) was heated under reflux for 1.5 h. The reaction mixture was then worked up as described above for **10a** and **11a**, giving **10b** (91 mg, 23%) and **11b** (257 mg, 69%), which were characterized as follows.

10b: Crystallized from EtOH in faintly yellow needles, mp 206–207.5°C; ms *m/z*: 387 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 224 nm (ε 37500), 263.5 (10500), 271.5 (10700), 286 (7420), 298 (7990); ir ν_{max}^{Nujol} cm^{-1}: 3380 (OH), 1626 (lactam CO); ^1H nmr ($CDCl_3$) δ:[20] 2.76 [2H, t, J = 6.5 Hz, C(4)-H's], 3.1–3.6 [2H, m, C(3)-H's], 3.68 (1H,

dd, J = 14 and 7 Hz) and 3.92 (1H, dd, J = 14 and 3.5 Hz) [N(2)-C$\underline{H}_2$CH(OH)], 3.85, 3.88, 3.91, and 3.93 (12H, s each, four MeO's), 4.45 (1H, d, J = 4 Hz, OH), 5.05 [1H, ddd, J = 7, 4, and 3.5 Hz, N(2)-CH$_2$C$\underline{H}$(OH)], 6.60 [1H, s, C(5)-H], 6.75–7.0 [3H, m, C(2')-H, C(5')-H, and C(6')-H], 7.58 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.62. Found: C, 64.99; H, 6.62; N, 3.72.

11b: Crystallized from hexane–EtOH (4 : 1, v/v) in colorless needles, mp 138.5–139.5°C; ms *m/z*: 371 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 233.5 nm (ε 18200), 282 (6510), 313 (1550), 370 (1790); λ_{max} [50% (v/v) aq. EtOH] 249 (19800), 286 (sh) (4660), 313 (11600), 369 (12100); λ_{max} [50% (v/v) aq. EtOH (pH < 7)[22]] 249 (21100), 286 (sh) (4560), 313 (12400), 369 (12900); λ_{max} [50% (v/v) aq. EtOH (pH > 7)[23]] 233 (19000), 281 (7110); ^{1}H nmr ($CDCl_3$) δ:[20] 2.6–3.1 [4H, m, C(5)-H's and C(6)-H's], 3.1–3.8 (0.29 × 2H, m), 3.37 (0.71H, dd, J = 12.5 and 9 Hz), and 3.58 (0.71H, dd, J = 12.5 and 6.5 Hz) [C(3)-H's], 3.83, 3.85, 3.89, and 3.92 (12H, s each, four MeO's), 4.9–5.1 (0.29H, m) and 5.08 (0.71H, dd, J = 9 and 6.5 Hz) [C(2)-H], 5.37 (0.29H) and 5.62 (0.71H) [s each, C(10b)-H], 6.66 [1H, s, C(7)-H], 6.7–7.0 [3H, m, C(2')-H, C(5')-H, and C(6')-H], 6.94 [1H, s, C(10)-H]. *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.70; H, 6.88; N, 3.72. The ^{1}H nmr spectrum of this specimen indicated that it was a 2.5 : 1 diastereoisomeric mixture. The crude oxazolidine (**11b**) (mp 136–137°C) that had not been purified by recrystallization was also found to be a 2.5 : 1 diastereoisomeric mixture on ^{1}H nmr spectral analysis.

A similar oxidation but for 6 h instead of 1.5 h was also effected as described above. The results are summarized in Table I.

(ii) Alkaline Oxidation of **9b**: A stirred mixture of **9b** (374 mg, 1.0 mmol), EDTA·2Na·2H$_2$O (931 mg, 2.5 mmol), Hg(OAc)$_2$ (797 mg, 2.5 mmol), H$_2$O (4.5 ml), and 2 N aqueous NaOH (3 ml) was heated under reflux for 3 h. The reaction mixture was then worked up as described above for **10a** and **11a**, affording **10b** (234 mg, 60%) as an orange solid, mp 199–201°C, and **11b** (90 mg, 24%) as a yellow solid, mp 137–139°C. The products (**10b** and **11b**) thus isolated were identical (by comparison of the tlc behavior and ir spectrum) with authentic samples obtained by method (i).

(iii) Oxidation of the Oxazolidine (**11b**): A stirred mixture of **11b** (736 mg, 2 mmol), EDTA·2Na·2H$_2$O (1.84 g, 5 mmol), Hg(OAc)$_2$ (1.58 g, 5 mmol), and 1% aqueous AcOH (15 ml) was heated under reflux for 24 h. The reaction mixture was worked up in a manner similar to that described above for **10a** and **11a**, giving **10b** (426 mg, 55%) as an orange solid, mp 202–204°C. In this reaction, the starting material (**11b**) (228 mg, 31%) was recovered as a yellow solid. These samples of **10b** and **11b** were identical (by comparison of the tlc behavior and ir spectrum) with authentic specimens obtained by method (i).

(iv) Oxidation of **18**: A stirred mixture of **18** (388 mg, 1.0 mmol), EDTA·2Na·2H$_2$O (931 mg, 2.5 mmol), Hg(OAc)$_2$ (797 mg, 2.5 mmol), and 1% aqueous AcOH (7.5 ml) was heated under reflux for 6 h. The reaction mixture was then worked up as described above for **10a** and **11a**. The acid-soluble fraction gave an intractable mixture (274 mg) as a dark brown caramel, whereas the neutral fraction afforded **10b** (11 mg, 3%), mp 198–200°C, which was identical (by comparison of the tlc behavior and ^{1}H nmr spectrum) with authentic **10b** prepared by method (i).

In a separate experiment, **18** was oxidized in a manner similar to that described above for **9b** under alkaline conditions. However, the only product identified was **10b**, and its yield was only 2%.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-1(2*H*)-isoquinolinone (15a). (i) From the Amine (**14**): A stirred mixture of **14**[8] (297 mg, 1.0 mmol), EDTA·2Na·2H_2O (931 mg, 2.5 mmol), $Hg(OAc)_2$ (797 mg, 2.5 mmol), H_2O (4.5 ml), and 2 N aqueous NaOH (3 ml) was heated under reflux for 3 h, depositing metallic Hg and a brown oil. After cooling, the reaction mixture was made basic with 10% aqueous NaOH and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a brown oil. Purification of the oil by means of flash chromatography[19] [hexane–AcOEt (1 : 1, v/v)] furnished **15a** (44 mg, 14%) as a pale yellow solid, mp 104–106°C, which was identical (by comparison of the tlc behavior and ir spectrum) with an authentic sample prepared by method (ii) described below.

(ii) From the Lactam Alcohol (**10a**): A solution of **10a** (263 mg, 0.8 mmol) in EtOH (16 ml) containing 70% aqueous $HClO_4$ (0.16 ml) was hydrogenated over 10% Pd–C (240 mg) at 2.3–4.5 atm and 50°C for 8 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting brown oil was partitioned by extraction with a mixture of H_2O and $CHCl_3$. The $CHCl_3$ extracts were washed successively with 10% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave **15a** (238 mg, 95%) as a pale yellow solid. Recrystallization of the solid from EtOH–H_2O (1 : 2, v/v) yielded an analytical sample as colorless prisms, mp 108–108.5°C [lit. mp 109–110°C (from EtOH);[14a] mp 123–124°C (from Et_2O)[14b]]; ms *m/z*: 311 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 230 nm (ε 16900), 254 (sh) (6780), 265 (6120), 278 (5590); ir ν_{max}^{Nujol} 1636 cm^{-1} (lactam CO); ^1H nmr ($CDCl_3$) δ:[20] 2.75–3.0 [4H, m, N(2)-CH_2CH_2Ar and C(4)-H's], 3.3–3.5 [2H, m, N(2)-CH_2CH_2Ar or C(3)-H's], 3.65–3.85 [2H, m, C(3)-H's or N(2)-CH_2CH_2Ar], 3.83 and 3.86 [6H, s each, two MeO's], 6.79 [3H, s, C(2')-H, C(5')-H, and C(6')-H], 7.05–7.5 [3H, m, C(5)-H, C(6)-H, and C(7)-H], 8.0–8.15 [1H, m, C(8)-H]. *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.23; H, 6.83; N, 4.69. The uv, ir, ^1H nmr, and mass spectra of this sample were identical with those reported[14] for authentic **15a**.

2-[2-(3,4-Dimethoxyphenyl)ethyl]-3,4-dihydro-6,7-dimethoxy-1(2*H*)-isoquinolinone (15b). A mixture of **10b** (387 mg, 1.0 mmol), EtOH (20 ml), and 70% aqueous $HClO_4$ (0.2 ml) was hydrogenated over 10% Pd–C (300 mg) at 3.9–4.5 atm and 38°C for 12 h. The reaction mixture was then worked up in a manner similar to that described above for **15a**, giving a yellow viscous oil (322 mg). Crystallization of the oil from hexane–EtOH (4 : 1, v/v) afforded a first crop (253 mg, 68%) of **15b** as colorless needles, mp 128–129.5°C. Concentration of the mother liquor of this crystallization and purification of the residue by means of flash chromatography[19] [hexane–AcOEt (1 : 2, v/v)] furnished a second crop (30 mg, 8%) of **15b** as a colorless solid, mp 126.5–128.5°C. The total yield of **15b** was 283 mg (76%). For analysis, the crude **15b** was recrystallized from hexane–EtOH (4 : 1, v/v) to give colorless needles, mp 129–130°C (lit.[14a] mp 128–129°C); ms *m/z*: 371 (M^+); uv $\lambda_{max}^{99\%\ aq.\ EtOH}$ 224 nm (ε 38100), 264 (10400), 271.5 (10500), 288 (7670), 298 (7930); ir ν_{max}^{Nujol} 1645 cm^{-1} (lactam CO); ^1H nmr ($CDCl_3$) δ:[20] 2.7–3.0 [4H, m, N(2)-CH_2CH_2Ar and C(4)-H's], 3.25–3.55 [2H, m, N(2)-CH_2CH_2Ar or C(3)-H's], 3.65–3.85 [2H, m, C(3)-H's or N(2)-CH_2CH_2Ar], 3.84, 3.86, 3.90, and 3.93 (12H, s each, four MeO's), 6.60 [1H, s, C(5)-H], 6.79 [3H, s, C(2')-H, C(5')-H, and C(6')-H], 7.61 [1H, s, C(8)-H]. *Anal.* Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.99; H, 7.04; N, 3.77. The uv, ir, and ^1H nmr spectra of this sample were identical with those reported[14a] for authentic **15b**.

REFERENCES

1. Paper XXX in this series, M. Ohba, Y. Shinbo, M. Toda, and T. Fujii, *Chem. Pharm. Bull.*, 1992, **40**, in press.
2. J. Knabe, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1959, **292**, 416.
3. H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1964, **297**, 474.
4. (a) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, 1972, **20**, 1451; (b) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *ibid.*, 1973, **21**, 2695; (c) T. Fujii, K. Yoshida, M. Ohba, and S. Yoshifuji, *ibid.*, 1977, **25**, 2336; (d) T. Fujii, M. Ohba, and S. Yoshifuji, *ibid.*, 1977, **25**, 3042; (e) T. Fujii, T. Hiraga, and M. Ohba, *ibid.*, 1981, **29**, 2691; (f) T. Fujii, M. Ohba, and S. Akiyama, *ibid.*, 1985, **33**, 5316; (g) T. Fujii, M. Ohba, M. Tsuchida, K. Saito, Y. Hirano, and J. Sakaguchi, *ibid.*, 1986, **34**, 496; (h) T. Fujii, M. Ohba, and J. Sakaguchi, *ibid.*, 1987, **35**, 3628; (i) For a review, see T. Fujii, M. Ohba, and S. Yoshifuji, *Heterocycles*, 1988, **27**, 1009.
5. For earlier reviews, see (a) T. Fujii, *Yakugaku Zasshi*, 1983, **103**, 257; (b) T. Fujii and M. Ohba, 'The Alkaloids,' Vol. XXII, ed. by A. Brossi, Academic Press, New York, 1983, Chapter 1.
6. H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1966, **299**, 715.
7. (a) J. Bosch, D. Mauleón, M. Feliz, and R. Granados, *J. Org. Chem.*, 1983, **48**, 4836; (b) E. Wenkert and E. C. Angell, *Synth. Commun.*, 1988, **18**, 1331.
8. (a) K. Rehse, D. Fredrich, and W. Kehr, *Arch. Pharm. (Weinheim, Ger.)*, 1979, **312**, 670; (b) S.-I. Murahashi, K. Kondo, and T. Hakata, *Tetrahedron Lett.*, 1982, **23**, 229.
9. (a) H. Bruderer, J. Metzger, and A. Brossi, *Helv. Chim. Acta*, 1975, **58**, 1719; (b) H. Bruderer, J. Metzger, A. Brossi, and J. J. Daly, *ibid.*, 1976, **59**, 2793, and references cited therein.
10. (a) S.-T. Lu, T.-L. Su, T. Kametani, A. Ujiie, M. Ihara, and K. Fukumoto, *Heterocycles*, 1975, **3**, 459; (b) *Idem, J. Chem. Soc., Perkin Trans. 1*, 1976, 63.
11. (a) C. Viel, *Ann. Chim. (Paris)*, 1963, **8**, 515 [*Chem. Abstr.*, 1964, **60**, 11982*b*]; (b) T. Fujii, K. Yamada, S. Minami, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, 1983, **31**, 2583.
12. N. J. Leonard, A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Am. Chem. Soc.*, 1955, **77**, 439.
13. (a) N. J. Leonard, K. Conrow, and R. R. Sauers, *J. Am. Chem. Soc.*, 1958, **80**, 5185; (b) H. Möhrle, *Arch. Pharm. Ber. Dtsch. Pharm. Ges.*, 1966, **299**, 122; (c) H. Möhrle and H. Weber, *Chem. Ber.*, 1972, **105**, 368.
14. (a) D. W. Brown, S. F. Dyke, M. Sainsbury, and W. G. D. Lugton, *Tetrahedron*, 1970, **26**, 4985; (b) H. Iida, K. Kawano, T. Kikuchi, and F. Yoshimizu, *Yakugaku Zasshi*, 1976, **96**, 176; (c) S. Ruchirawat, M. Chuankamnerdkarn, and S. Thianpatanagul, *Tetrahedron Lett.*, 1984, **25**, 3479.
15. For other synthetic routes to this ring system, see F. Vlaeminck, E. De Cock, D. Tourwé, and G. Van Binst, *Heterocycles*, 1981, **15**, 1213, and references cited therein.
16. (a) S. Sugasawa, K. Kodama, and H. Inagaki, *Yakugaku Zasshi*, 1941, **61**, 491; (b) S. Sugasawa and N. Sugimoto, *Proc. Imp. Acad. Tokyo*, 1942, **18**, 658.
17. Purchased from Nakarai Chemicals Co. (Japan) and purified by vacuum distillation before use.
18. T. Fujii, S. Yoshifuji, and M. Ohba, *Chem. Pharm. Bull.*, 1978, **26**, 3218.
19. W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

20. For convenience, each skeletal atom in the isoquinoline moiety is indicated by a usual number and each aromatic carbon in the 3,4-dimethoxyphenyl moiety by a primed number.
21. Purchased from Aldrich Chemical Co., Inc.
22. Measured in 50% (v/v) aqueous EtOH containing HCl at 0.1 M concentration.
23. Measured in 50% (v/v) aqueous EtOH containing NaOH at 0.1 M concentration.

Received, 12th June, 1992