Quinolizidines. XVII.\(^1\) A New Access to 9,10-Dimethoxy- and 8-Hydroxy-9,10-dimethoxybenz[a]quinolizidine-Type \textit{Alangium} Alkaloids from 3-Acetylpyridine

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New syntheses of the ipecac and \textit{Alangium} alkaloids possessing the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenz[a]quinolizidine skeletons (types 1 and 2) have now become possible through generally applicable routes starting from 3-acetylpyridine (5). The routes involve the mercuric acetate–edetic acid oxidation of the 3-acetylpyridine derivatives 9a, b or the alkaline ferricyanide oxidation of the quaternary salts (26a, b and 27a, b) of 3-acetylpyridine equivalents, Wolff–Kishner reduction of the acetyl group or reductive desulfurization of the thioketal group, sullenlylation–dehydroxylation of the lactams 12a, b, Michael reaction of the \(\alpha,\beta\)-unsaturated lactams 15a, b, and de-ethoxyconversion of the Michael adducts 16a, b as the main operations.

Keywords—ipecac alkaloid synthesis; \textit{Alangium} alkaloid synthesis; piperidine mercuric acetate–edetic acid oxidation; lactam sulfonylation–dehydroxylation; \(\alpha,\beta\)-unsaturated lactam Michael reaction; malonic ester de-ethoxyconversion; pyridinium salt ferricyanide oxidation; thioketal reductive desulfurization; \(O\)-benzyl group hydrogenolysis; phenethyl alcohol bromination

Up to now, the Indian medicinal plant \textit{Alangium lamarckii} THW. (Alangiaceae) has been found to contain eighteen benz[a]quinolizidine alkaloids, which are structurally related to the ipecac bases, as well as ten other alkaloids.\(^2,3\) We have already shown that these benz[a]quinolizidine-type \textit{Alangium} alkaloids may be classified into four groups (1–4) according to their substitution patterns in the aromatic ring A,\(^4\) and that the racemic synthesis of all of these types of alkaloids is possible through a “lactim ether route” and the chiral synthesis, through a “cincholoipon-incorporating route.”\(^5\) In the present study, an alternative route starting from 3-acetylpyridine (5) was generated for the racemic synthesis, and its feasibility was demonstrated in the syntheses of some ipecac and \textit{Alangium} alkaloids having the 9,10-dimethoxy- and 8-hydroxy-9,10-dimethoxybenz[a]quinolizidine skeletons (1 and 2).\(^6\) These syntheses utilized mercuric acetate–edetic acid (EDTA) oxidation or alkaline ferricyanide oxidation for construction of the lactam carbonyl function at the 6-position of 3-acetylpyridine equivalents, and the resulting lactam carbonyl group played an important role.

\[\text{Diagram with structures 1, 2, 3, and 4} ]

\(R = \text{CH}_2\text{OH, CO}_2\text{H, or a heterocyclic ring}\)
in the introduction of the acetate chain into the 4-position and in the formation of ring B at later steps.

**The Route through Hg(OAc)₂–EDTA Oxidation**

For the synthesis of the 1-type alkaloids, 3-acetylpyridine (5) was first converted into the ketonic lactam 11a via the intermediates 6, 7a, 8a, 9a, and 10a according to the previously reported procedure. In the Hg(OAc)₂–EDTA oxidation of 9a, the enamine 21a, probably derived from the initially formed iminium salt, was obtained in 9% yield besides the main product 10a (81% yield). The minor product has not been isolated in our previous experiments, and it is now disclosed that oxidation of 9a also occurs at the 2-position in the form of dehydrogenation and that the ratio of the 6- to the 2-oxidation is 90:10, and not

![Chemical diagram](image-url)
100% as reported previously,\textsuperscript{2b,7a} however, regioselectivity is still high in this reaction. Wolff-Kishner reduction of 11a was then effected by means of the Huang–Minlon modification to give the lactam 12a in 82% yield. Although the same lactam 12a had previously been prepared from 3-ethylpyridine through a parallel sequence of conversions,\textsuperscript{9} its overall yield had been much lower than that in the present route. This is apparently owing to the low regioselectivity in the Hg(OAc)\textsubscript{2}–EDTA oxidation of the ethyl analogue 22, whereby the 6-piperidone 23 and the 2-piperidone 24 are produced in a ratio of 54 : 46.\textsuperscript{2b,7b,8} Sulfonylation\textsuperscript{9} of 12a in tetrahydrofuran (THF) with diphenyl disulfide in the presence of lithium diisopropylamide and hexamethylphosphoramidate (HMPA) at –78°C furnished 13a in 91% yield as a diastereomeric mixture. The mixture 13a was then oxidized with sodium metaperiodate in aqueous MeOH at room temperature, and thermolysis of the resulting sulfoxide 14a in boiling toluene in the presence of CaCO\textsubscript{3} afforded the \(\alpha,\beta\)-unsaturated lactam 15a in 91% overall yield from 13a, concluding the dehydroxysulfonylation of 13a. The conversion of 12a to 15a via 13a and 14a by a similar method has been reported by Takano \textit{et al.}\textsuperscript{10} and the analogous introduction of \(\alpha,\beta\)-unsaturation into a six-membered lactam, by Grieco \textit{et al.}\textsuperscript{11}

The Michael addition of diethyl malonate to 15a was carried out according to the previously reported procedure,\textsuperscript{12} and the diester 16a (presumed to be a 13 : 87 mixture of the \textit{cis} and \textit{trans} isomers) was obtained in 69% yield. The adduct 16a was de-ethoxycarbonylated by heating with NaCl in moist dimethyl sulfoxide\textsuperscript{10,13} to produce the monoester 18a (85% yield), which was shown to be a 9 : 91 mixture of the \textit{cis} and \textit{trans} isomers on carbon-13 nuclear magnetic resonance (\textsuperscript{13}C-NMR) spectroscopic analysis. Hydrolysis of the mixture 18a with NaOH in aqueous EtOH at room temperature and purification of the products by recrystallization gave the \textit{trans}-lactam acid (\(\pm\))-19a in 84% yield. The structure and stereochemistry of (\(\pm\))-19a were confirmed by its identity with an authentic sample, which was prepared from 15a through 16a and 17a by the method of Battersby and Turner.\textsuperscript{12,14}

In view of the previous conversions of (\(\pm\))-19a into (\(-\))-emetine,\textsuperscript{14} (\(+\))-O-methylphysostigmine,\textsuperscript{14} (\(+\))-cephaeline,\textsuperscript{15} (\(+\))-tubulosine,\textsuperscript{16} (\(+\))-deoxytubulosine,\textsuperscript{17} (\(+\))-protoemetine,\textsuperscript{14} (\(+\))-protoemetine,\textsuperscript{15} and (\(+\))-emetamine\textsuperscript{18} through the ethyl ester (\(\pm\))-20a, the above synthesis of (\(\pm\))-19a from 3-acetylpyridine (5) is formally tantamount to new syntheses of these ippecac and/or \textit{Alangium} alkaloids having the 9,10-dimethoxybenz[a]quinolizidine skeleton (type 1).

Next, the synthesis of the 2-type alkaloids was tried by means of a parallel series of conversions, which started with quaternization of 6 with 2-benzylxoy-3,4-dimethoxyphenacyl bromide. The resulting quaternary salt 7b (99% yield) was reduced first with hydrogen over Adams catalyst and then with NaBH\textsubscript{4} to give 8b in 81% yield as a diastereomeric mixture. Deketalization of 8b with 1 N hydrochloric acid at 40°C produced the ketone 9b (98% yield), which was oxidized with Hg(OAc)\textsubscript{2}–EDTA according to the previously reported standard procedure,\textsuperscript{8,19} affording the 6-piperidone 10b (as a diastereomeric mixture) and the enamine 21b in 82% and 10% yields, respectively. Catalytic hydrogenolysis of the mixture 10b and Wolff–Kishner reduction of the resulting phenolic ketone 11c (89% yield) provided the
phenolic lactam 12c in 84% yield. Compound 12c was benzylated with benzyl bromide in boiling acetone containing K₂CO₃ to give the benzyl ether 12b (96% yield), which was then converted into the trans-lactam ester (+)-20b in 43% overall yield (from 12b) through the intermediates 13b, 14b, 15b, 16b (cis:trans = 12:88), 18b (cis:trans = 11:89), and (+)-19b in a manner similar to that described above for the a-series. A by-pass from 16b to (+)-19b (54% overall yield from 15b) consisted of alkaline hydrolysis of the former and decarboxylation of the resulting dicarboxylic acid 17b in boiling 60% aqueous AcOH.

Since the lactam ester (+)-20b thus prepared was identical with an authentic sample synthesized by us²⁰ through a “lactim ether route” and since (+)-20b has already been converted into (+)-ankorine,²⁰ (±)-alangicine,²¹ and (±)-alangimarckine,²² the above synthesis of (+)-20b formally constitutes new racemic syntheses of these three Alangium alkaloids possessing the 8-hydroxy-9,10-dimethoxybenz[a]quinolizidine skeleton (type 2).

The Route through Alkaline Ferricyanide Oxidation

In view of the intermediary function of the ketonic lactam 11a in the foregoing synthesis of the 1-type alkaloids, the previously reported preparation of 11a²⁷,²³ from the ketal 6 and 3,4-dimethoxyphenethyl bromide through the route involving alkaline ferricyanide oxidation [6→26a→28a→30a→11a (Chart 3)] represents alternative formal syntheses of these alkaloids. In much the same sense, the lactam 12a was synthesized in 84% yield by reductive desulfurization (Raney Ni, boiling 70% aqueous EtOH) of 29a, which was available from initial quaternization of the thioketal 25 with 3,4-dimethoxyphenethyl bromide and subsequent alkaline ferricyanide oxidation of the resulting pyridinium salt 27a according to the
previously reported procedure,\textsuperscript{23a} thus concluding yet another formal synthesis of the 1-type alkaloids. The same lactam 12\textsubscript{a} had previously been prepared from 3-ethylpyridine \textit{via} the quaternary salt 31 and the 6-pyridone 32, but in a much less efficient manner.\textsuperscript{8} This inefficiency is attributed to the high regioselectivity in the alkaline ferricyanide oxidation of 31, which is in favor of the formation of the undesired 2-pyridone 33 (32 : 33 = 12 : 88).\textsuperscript{8,23b}

Interestingly, these formal syntheses of the 1-type alkaloids from 6 or 25 amount to the realization of the idea of Professor Sugasawa, who attempted to utilize the alkaline ferricyanide oxidation of 1-substituted 3-ethylpyridinium salt or its equivalents for the synthesis of the ipecac alkaloid emetine (type 1) in the early 1950's.\textsuperscript{24}

The scope of this synthetic strategy was then extended to include the syntheses of the 2-type \textit{Alangium} alkaloids. We first prepared 2-benzzyloxy-3,4-dimethoxyphenethyl bromide (39), one of the requisite starting materials, from the ketone 34 by the following 5-step synthesis. Treatment of 34 with sulfur and morpholine under Willgerodt–Kindler reaction conditions produced the thiomorpholine 35 (62\% \textsubscript{y} yield), which was hydrolyzed with KOH in boiling aqueous EtOH to give the carboxylic acid 36 in 93\% \textsubscript{y} yield. On esterification with ethanolic HCl, 36 afforded the ester 37 in 97\% \textsubscript{y} yield, and the subsequent LiAlH\textsubscript{4} reduction of 37 in ether furnished the alcohol 38 in 97\% \textsubscript{y} yield. The desired bromide 39 was obtained from 38 in 88\% \textsubscript{y} yield by treatment with N-bromosuccinimide/Ph\textsubscript{3}P reagent\textsuperscript{25b} in benzene.

The pyridinium salts 26\textsubscript{b} and 27\textsubscript{b} were then prepared from 6 and 25, respectively, by quaternization with 39 in benzene. The alkaline ferricyanide oxidations of 26\textsubscript{b} and 27\textsubscript{b} were effected under the standard conditions described previously,\textsuperscript{8,23a} giving the 6-oxidation products 28\textsubscript{b} (83\% \textsubscript{y} overall yield from 6) and 29\textsubscript{b} (42\% \textsubscript{y} overall yield from 25), respectively. In both oxidations, no 2-oxidation products were obtained, in general agreement with the previous results\textsuperscript{2b,23a} from the a-series. On catalytic hydrogenation over Raney Ni and subsequent acid hydrolysis, the 6-pyridone 28\textsubscript{b} was converted into the phenolic lactam 11\textsubscript{e} in 95\% \textsubscript{y} yield through 30\textsubscript{c}, whereas desulfurization of 29\textsubscript{b} with Raney Ni in boiling aqueous EtOH followed by catalytic hydrogenation (Raney Ni/H\textsubscript{2}) provided 12\textsubscript{c} in 82\% \textsubscript{y} yield. The observed hydrogenolysis of the O-benzyl group over Raney Ni catalyst in the above two cases is rather unusual, but some precedents have been found in the literature.\textsuperscript{26} Since the phenolic lactams 11\textsubscript{e} and 12\textsubscript{c} have already been led to the 2-type \textit{Alangium} alkaloids by the route shown in Chart 1, the above syntheses of 11\textsubscript{e} and 12\textsubscript{c} from 6 and 25 utilizing alkaline ferricyanide oxidation represent additional new formal syntheses of these alkaloids.

**Conclusion**

The present work has shown that the 1- and 2-types of benzo[\textit{a}]quinolizidine alkaloids can be synthesized either from the ketal 6 by employing Hg(OAc)\textsubscript{2}–EDTA oxidation or from 6 or the thiohketal 25 by utilizing alkaline ferricyanide oxidation. Since the starting material 6 or 25 is easily obtainable from 3-acetylpiperidine (5),\textsuperscript{24c} the routes used for the above syntheses may be generalized under the name of the "3-acetylpiperidine route." Such a route is probably applicable to the syntheses of the remaining 3- and 4-type \textit{Alangium} alkaloids, and work along this line is in progress in our laboratory.
**Experimental**

**General Notes**—All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected; boiling points are uncorrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. See ref. 27 for details of instrumentation and measurements. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doubles, dt = doublet-of-triplets, m = multiplet, q = quartet, s = singlet, sh = shoulder, t = triplet.

1-(2-Benzoyloxy-3,4-dimethoxyphenacyl)-3-(1,1-ethylenedioxyethyl)pyridinium Bromide (7b)—A solution of 6$^{24,25}$ (1.82 g, 11 mmol) and 2-benzoyloxy-3,4-dimethoxyphenacyl bromide$^{26}$ (3.65 g, 10 mmol) in dry benzene (30 ml) was stirred at room temperature for 1.5 h. The precipitate that resulted was filtered off, washed with benzene (20 ml), and dried to give 7b (3.19 g) as a colorless solid, mp 167.5—168.5 °C (dec.). The filtrate and washings were combined, concentrated to a volume of ca. 10 ml, and kept at room temperature overnight to yield a second crop (2.08 g) of 7b. The total yield of 7b was 5.27 g (99.9%). Recrystallization of crude 7b from EtOH furnished an analytical sample as colorless minute needles, mp 169—169.5 °C (dec.); IR ν$_{max}$ cm$^{-1}$: 1685 (CO); $^1$H-NMR (CDCl$_3$) δ: 1.70 (3H, s, CMe), 3.91 and 3.97 (3H each, s, two OMe's), 5.50 (2H, s, OCH$_2$Ph), 6.53 (2H, s, ArCOCH$_3$), 6.81 (1H, d, J = 9.0 Hz, H$_{2a}$), 7.25—7.7 (5H, m, Ph), 7.73 (1H, d, J = 9.0 Hz, H$_{5a}$), 8.02 (1H, dd, J = 7.5 and 6.0 Hz, H$_{5b}$), 8.41 (1H, s, H$_{2b}$), 8.46 (1H, d, J = 7.5 Hz, H$_{5a}$), 9.37 (1H, d, J = 6.0 Hz, H$_{5b}$). Anal. Calc'd for C$_{26}$H$_{24}$BrNO$_4$: C, 58.88; H, 5.32; N, 2.64. Found: C, 58.75; H, 5.25; N, 2.92.

1-(2-Benzoyloxy-3,4-dimethoxyphenacyl)-2-[3-(1,1-ethylenedioxyethyl)piperidinol]ethanol (8b)—A solution of 7b (28.6 g, 54 mmol) in 50% aqueous EtOH (250 ml) was hydrogenated over Adams catalyst (500 mg) at room temperature and atmospheric pressure for 18 h, absorbing ca. 3.1 mol eq of H$_2$. The catalyst was removed by filtration and the filtrate was concentrated to 2 ml aqueous NaOH (27 ml). The resulting solution was stirred at room temperature overnight, during which time NaBH$_4$ (2.04 g, 54 mmol) was added portionwise. The reaction mixture was concentrated in vacuo, and the residue was partitioned by extraction with a mixture of H$_2$O and benzene. The benzene extracts were washed with H$_2$O, dried over anhydrous K$_2$CO$_3$, and concentrated to leave a faintly yellow oil (24.3 g). Purification of the oil by column chromatography [alumina, hexane-AcOEt (2:1, v/v)] gave 8b (20.0 g, 81% yield) as an almost colorless oil (presumed to be a diastereomeric mixture), MS m/e: 457 (M$^+$); IR ν$_{max}$ cm$^{-1}$: 3410 (OH); $^1$H-NMR (CDCl$_3$) δ: 1.23 (3H, s, CMe), 3.87 (6H, s, two Me's), 4.8—5.05 (1H, m, ArCH$_2$OH), 5.03 and 5.13 (2H, AB type d's, J = 11.0 Hz, OCH$_3$Ph), 6.72 (1H, d, J = 8.8 Hz, H$_{5a}$), 7.21 (1H, d, J = 8.8 Hz, H$_{5b}$), 7.2—7.5 (5H, m, Ph).

1-[2-(Benzyloxy-3,4-dimethoxyphenacyl)-2-hydroxyethyl]-3-piperidinyl Methyl Ketone (9b)—A solution of 8b (19.2 g, 42 mmol) in 1% aqueous HCl (120 ml) was stirred at 40 °C for 2 h. The reaction mixture was made basic (pH 10) with K$_2$CO$_3$ and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried (K$_2$CO$_3$), and concentrated to leave 9b (17.0 g, 98% yield) as a faintly yellow oil. A portion of the oil was purified by column chromatography [alumina, hexane-AcOEt (1:1, v/v)] to afford a colorless oil (presumed to be a diastereomeric mixture), MS m/e: 413 (M$^+$); IR ν$_{max}$ cm$^{-1}$: 3410 (OH), 1706 (CO); $^1$H-NMR (CDCl$_3$) δ: 2.13 (3H, s, COMe), 3.83 and 3.89 (6H, s each, two OMe's), 4.8—5.0 (1H, m, ArCH$_2$OH), 5.04 and 5.15 (2H, AB type d's, J = 11.0 Hz, OCH$_3$Ph), 6.72 (1H, d, J = 8.8 Hz, H$_{5a}$), 7.19 (1H, d, J = 8.8 Hz, H$_{5b}$), 7.2—7.5 (5H, m, Ph).

1-[3-(3,4-Dimethoxyphenacyl)-2-hydroxyethyl]-1,2,3,4-tetrahydro-5-pyridyl Methyl Ketone (21a)—The Hg(OAc)$_2$—EDTA oxidation of 9a and column chromatographic separation of the products were carried out as described previously, and besides the known 6-piperidone 10a$^{27}$ (81% yield), the enamine 21a having a thin-layer chromatographic (TLC) mobility lower than that of 10a was isolated in 9% yield as a faintly yellowish oil, MS m/e: 305 (M$^+$); IR ν$_{max}$ cm$^{-1}$: 3320 (OH), 1618 and 1570 (vinyllogous amide);$^{28}$ $^1$H-NMR (CDCl$_3$) δ: 1.6—1.95 (2H, m, H$_{2a}$), 2.03 (3H, s, COMe), 2.1—2.4 (2H, m, H$_{2b}$), 3.05—3.65 (5H, m, H$_{2c}$'s and ArCH$_2$OH), 3.85 (6H, s, two OMe's), 4.7—4.9 (1H, m, ArCH$_2$OH), 6.75—7.0 (3H, m, aromatic protons), 7.24 (1H, s, H$_{5b}$).

The Hg(OAc)$_2$—EDTA Oxidation of 9b—According to the previously reported standard procedure, 9b was oxidized with Hg(OAc)$_2$—EDTA in boiling 10% aqueous AcOH and the reaction mixture was worked up to give the 6-piperidone 10b (as a diastereomeric mixture) and the enamine 21b in 82% and 10% yields, respectively. Separation of the two products was accomplished by means of column chromatography using silica gel and CHCl$_3$, and 10b was eluted faster than 21b. They were characterized as described below.

5-Acetyl-1-[2-(benzoyloxy-3,4-dimethoxyphenacyl)-2-hydroxyethyl]-2-piperidone (10b)—This diastereomeric mixture was isolated as a faintly yellowish solid, mp 95—99 °C; MS m/e: 410 (M$^+$—OH); IR ν$_{max}$ cm$^{-1}$: 3340 (OH), 1714 (CO), 1619 (lactam CO); $^1$H-NMR (CDCl$_3$) δ: 2.07 and 2.10 (3H each, diastereomeric COMe's), 3.88 and 3.90 (6H each, two OMe's), 4.68 (d, J = 5.1 Hz) and 4.81 (d, J = 4.4 Hz) (1H, diastereomeric OH's), a pair of 4.94 and 5.26 (AB type d's, J = 10.9 Hz) and a pair of 4.98 and 5.29 (AB type d's, J = 11.0 Hz) (2H, diastereomeric OCH$_3$Ph's), 4.95—5.15 (1H, m, ArCH$_2$OH), 6.72 (1H, d, J = 8.8 Hz, H$_{5a}$), 7.1—7.5 (6H, m, H$_{5b}$, Ph). Recrystallization of the solid from the solvent (AcOEt—AcEtO 1:1, v/v) yielded an analytical sample, shown to be stereochimically still impure, as colorless needles, mp 99—101 °C; IR ν$_{max}$ cm$^{-1}$: 3360 (OH), 1713 (CO), 1623 (lactam CO); $^1$H-NMR (CDCl$_3$), identical with that of the above crude sample. Anal. Calc'd for C$_{24}$H$_{23}$NO$_4$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.14; H, 6.88; N, 3.30.
1-(2-Benzylxylo-3,4-dimethoxyphenyl)-2-hydroxyethyl]-1,2,3,4-tetrahydro-5-pyridyl Methyl Ketone (21b) —
This was recrystallized from EtOH to give an analytical sample as finely yellowish scales, mp 164.5—165.5°C; MS
m/e: 411 (M⁺); IR νmax/cm⁻¹: 3290 (OH), 1616 and 1550 (vinyllogous amide).²⁻¹H-NMR (CDCl₃) δ: 1.5—1.8 (2H,
m, H₃(2)×3), 2.00 (3H, s, COMe), 2.23 (2H, t, J = 6.3 Hz, H₃(4)×2), 2.69 (1H, d, J = 4.6 Hz, OH), 2.99 (2H,
t, J = 5.5 Hz, H₂(3), 3.1—3.3 [2H, m, Ar(CHO)CH₃], 3.89 (6H, s, two OMe's), 4.8—5.0 (1H, m, Ar(CHO)H), 5.06 and 5.24 (2H,
AB type d's, J = 11.0 Hz, OCH₂Ph), 6.71 (1H, d, J = 8.8 Hz, H₃(6)), 7.10 (1H, s, H₃(7)), 7.10 (1H, d, J = 8.8 Hz, H₃(8)),
7.25—7.5 (5H, m, Ph). Anal. Caled for C₂₉H₃₀NO₃: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.97; H, 7.27; N, 3.34.

5-Acetyl-1-(3,4-dimethoxyphenyl)-2-piperidone (11c) — A solution of 10b (12.8 g, 30 mmol) in EtOH (200 ml)
containing 70%, aqueous HClO₄ (3 ml) was hydrogenated over 10% Pd·C (4.0 g) at room temperature and
atmospheric pressure for 6 h. Removal of the catalyst by filtration and concentration of the filtrate under reduced
pressure left a pale yellowish oil, which was partitioned between H₂O and CHCl₃. The CHCl₃ extracts were washed
successively with saturated aqueous NaHCO₃ and saturated aqueous NaCl, dried, and concentrated to leave
11c (8.54 g, 89%). mp 119—122°C. Recrystallization from AcOEt yielded an analytical sample as colorless needles,
mp 123—124°C; IR νmax/cm⁻¹: 1700 (CO), 1631 (lactam CO), 1'H-NMR (CDCl₃) δ: 2.17 (3H, s, COMe), 3.83 and 3.89
(3H each, s, two OMe's), 6.35 (1H, s, OH), 6.39 (1H, d, J = 8.8 Hz, H₃(6)), 6.80 (1H, d, J = 8.8 Hz, H₃(7)). Anal. Caled
for C₁₆H₁₉NO₂: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.25; H, 7.24; N, 4.41.

1-(3,4-Dimethoxyphenyl)-5-ethyl-2-piperidine (12a) — A mixture of 11a (305 mg, 1 mmol), ethylene glycol
(2 ml), 80% aqueous hydrizidine hydrate (188 mg, 3 mmol), and KOH (200 mg) was placed in a flask equipped with a
descending condenser. The mixture was heated in an oil bath at 120°C for 1 h with stirring. Then, the temperature of
the oil bath was slowly raised to 190°C in 30 min, and the mixture was further heated with stirring at 190—195°C for
3 h to give a light distillate. After cooling, the reaction mixture was diluted with H₂O (5 ml), neutralized with
10% aqueous HCl, and extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried,
and concentrated to leave a colorless oil (256 mg). Purification of the oil by column chromatography [alumina, hexane:AcOEt (1:1, v/v)] furnished 12a (238 mg, 82%) as a colorless oil. The infrared (IR) spectrum (neat) and TLC
behavior of this sample were identical with those of authentic 12a.²⁻¹

1-(3,4-Dimethoxyphenyl)-5-ethyl-2-piperidine (12c) — A mixture of 11c (3.21 g, 10 mmol), ethylene glycol
(20 ml), 80%, aqueous hydrizidine hydrate (1.25 g, 20 mmol), and KOH (200 mg) was allowed to react as
described above for 12a. The reaction mixture was poured into H₂O (50 ml), and the resulting solution was acidified
with 10% aqueous HCl to pH 2—3 and extracted with benzene. The benzene extracts were washed with saturated
aqueous NaCl, dried, and concentrated to leave a slightly brownish solid, mp 115—118°C. Recrystallization of the
solid from AcOEt gave 12c (2.25 g) as pale yellow plates, mp 119—120°C. Evaporation of the solvent from the
resulting mother liquor and column chromatography [silica gel, CHCl₃:MeOH (20:1, v/v)] furnished 12c (0.33 g) of 12c.
The yield was 2.58 g (84%). Further recrystallizations from AcOEt afforded an analytical sample as colorless needles,
mp 119.5—120.5°C; IR νmax/cm⁻¹: 3550 (OH), 1620 (lactam CO), 1'H-NMR (CDCl₃) δ: 0.88 (3H, t, J = 6Hz, CCH₂Me), 3.80 and 3.85 (3H each, s, two OMe's), 6.32 (1H, d, J = 8.5 Hz, H₃(6)),
6.73 (1H, d, J = 8.5 Hz, H₃(7)). Anal. Caled for C₁₆H₂₁NO₂: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.48; H, 8.32; N,
4.39.

1-(2-Benzylxylo-3,4-dimethoxyphenyl)-5-ethyl-2-piperidine (12b) — A stirred mixture of 12c (615 mg,
2 mmol) and benzyl bromide (410 mg, 2.4 mmol) in acetonitrile (10 ml) containing anhydrous K₂CO₃ (332 mg, 2.4 mmol)
was heated under reflux for 24 h. The solvent was removed from the reaction mixture by vacuum distillation, and
the residue was partitioned by extraction with a mixture of benzene and H₂O. The benzene extracts were washed
successively with H₂O, 5% aqueous KOH, and H₂O, dried, and concentrated to leave a yellow oil, which was
dissolved in a mixture of benzene (5 ml) and pyridine (1 ml). After the resulting solution had been kept at room
temperature overnight, the solvents were evaporated under reduced pressure. The residue was dissolved in benzene (60 ml),
and the benzene solution was washed successively with H₂O, 5% aqueous HCl, and saturated aqueous NaCl, dried,
and concentrated to leave a yellow oil. This material was purified on a 10-g silica gel column (AcOEt) to provide
12b (767 mg, 96%) as a colorless oil, MS m/e: 397 (M⁺); IR νmax/cm⁻¹: 1624 (lactam CO); 1'H-NMR (CDCl₃) δ: 0.83 (3H,
t, J = 7 Hz, CCH₃Me), 3.86 and 3.88 (3H each, s, two OMe's), 5.09 (2H, s, OCH₂Ph), 6.62 (1H, d, J = 8.5 Hz, H₃(6)),
6.90 (1H, d, J = 8.5 Hz, H₃(7)), 7.2—7.5 (5H, m, Ph).

1-(3,4-Dimethoxyphenyl)-5-ethyl-3-phenylthio-2-piperidine (13a) — A stirred solution of disopropylamine
(1.53 ml, 10.9 mmol) in dry THF (10 ml) was cooled to −78°C in an atmosphere of N₂, and 1.7 m solution (6.41 ml,
10.9 mmol) of butyllithium in hexane was added dropwise. After the mixture had been stirred at the same temperature
for 20 min, a solution of 12a (1.27 g, 4.36 mmol) in dry THF (2 ml) was added dropwise in 10 min, stirring was
continued for 30 min, and a solution of diphenyl disulfide (952 mg, 4.36 mmol) in dry THF (2 ml) containing
hexamethylphosphoramide (0.76 ml, 4.4 mmol) was added dropwise in 5 min. The resulting mixture was further
stirred at −78°C for 2 h, brought to room temperature after addition of saturated aqueous NH₄Cl (6 ml), and
extracted with benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated
to leave a yellow oil (2.21 g). Purification of the oil by column chromatography [alumina, hexane:AcOEt (3:1, v/v)]
afforded 13a (1.59 g, 91%) as a pale yellow oil (presumed to be a diastereomeric mixture), MS m/e: 399 (M⁺); IR νmax/cm⁻¹:
1633 (lactam CO); 1'H-NMR (CDCl₃) δ: 0.82 and 0.85 (3H, t, each, J = 7 Hz, diastereomeric
CCH₂Me₃), 3.85, 3.88, and 3.90 (6H, s each, diastereomeric OMe's), 6.65—6.85 (3H, m, aromatic protons), 7.1—7.65 (5H, m, Ph).

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-5-ethyl-3-phenylthio-2-piperidine (13b)—Sulfenylation of 12b was effected as described above for 13a, and the crude oily product was purified on an alumina column [hexane-AcOEt (5:1, v/v)] to give 13b in 94% yield as a faintly yellowish oil (presumed to be a diastereomeric mixture), MS m/e 505 (M⁺); IR ν(CHCl₃ cm⁻¹ : 1633 (lactam CO); ¹H-NMR (CDCl₃) δ : 0.77 and 0.81 (3H, t each, J = 7 Hz, diastereomeric CCH₂Me³), 3.86 and 3.89 (6H, s each, two OMe's), 5.09 (2H, s, OCH₂Ph), 6.62 and 6.64 (1H, d each, J = 8.5 Hz, diastereomeric H₆α), 6.88 and 6.93 (1H, d each, J = 8.5 Hz, diastereomeric H₆β), 7.1—7.65 (10H, m, SPh and OCH₂Ph).

1-(3,4-Dimethoxyphenyl)-5-ethyl-5,6-dihydro-2(1H)-pyridinone (15a)—A stirred solution of 13a (1.36 g, 3.4 mmol) in MeOH (25 ml) was cooled in an ice bath, and a solution of NaI₀₃ (800 mg, 3.7 mmol) in H₂O (5 ml) was added dropwise in 5 min. After the mixture had been stirred at room temperature for 18 hr, the insoluble material that resulted was filtered off and washed with MeOH (10 ml). The filtrate and washings were combined and concentrated in vacuo, and the residue was dissolved in benzene (50 ml). The benzene solution was washed with saturated aqueous NaCl, dried, and concentrated to leave the sulfide 14a (1.44 g) as an almost colorless oil. A solution of this oil in toluene (40 ml) containing CaCO₃ (1.02 g, 10.2 mmol) was then heated under reflux in an atmosphere of N₂ for 1 hr. The reaction mixture was filtered, and the filtrate was washed with saturated aqueous NaCl, dried, and concentrated to leave a yellowish oil. Purification of the oil by column chromatography [silica gel, CH₂Cl₂-AcOEt (6:1, v/v)] gave 15a (896 mg, 91%), overall yield from 13a) as a colorless oil, MS m/e: 289 (M⁺); IR ν(CHCl₃ cm⁻¹ : 1662 (C = O), 1606 (lactam CO); ¹H-NMR (CDCl₃) δ : 0.90 (3H, t, J = 7.2 Hz, CCH₂Me), 1.2—1.6 (2H, m, CCH₂Me), 2.05—2.4 (1H, m, H₆α), 3.86 and 3.87 (3H each, s, two OMe's), 5.89 (1H, dd, J = 9.8 and 2.0 Hz, H₆β), 6.44 (1H, dd, J = 9.8 and 3.5 Hz, H₆γ), 6.7—6.9 (3H, m, aromatic protons). The IR and ¹H-NMR spectra of this sample were identical with those of authentic 15a prepared by the method of Battersby and Turner.¹⁴

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-5-ethyl-5,6-dihydro-2(1H)-pyridinone (15b)—The sulfide 13b was dehydroxysulfenylated via the sulfoxide 14b in a manner similar to that described above for 15a, and 15b was obtained in 88% overall yield (from 13b) as a pale yellow oil, MS m/e: 395 (M⁺); IR ν(CHCl₃ cm⁻¹ : 1661 (C = O), 1605 (lactam CO); ¹H-NMR (CDCl₃) δ : 0.85 (3H, t, J = 7.2 Hz, CCH₂Me), 1.1—1.5 (2H, m, CCH₂Me), 1.95—2.35 (1H, m, H₆α), 3.86 and 3.89 (3H each, s, two OMe's), 5.10 (2H, s, OCH₂Ph), 5.84 (1H, dd, J = 9.8 and 2.0 Hz, H₆β), 6.39 (1H, dd, J = 9.8 and 3.3 Hz, H₆γ), 6.62 (1H, d, J = 8.4 Hz, H₆δ), 6.91 (1H, d, J = 8.4 Hz, H₆α), 7.2—7.55 (5H, m, Ph).

1-(3,4-Dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidinemalonamic Acid Diethyl Ester (16a)—The following procedure is a modification of that reported in the literature.¹⁴ A solution of 15a (810 mg, 2.8 mmol) in abs. EtOH (3 ml) was added dropwise in 30 min in an atmosphere of N₂ to a stirred solution of diethyl malonate (897 mg, 5.6 mmol) in a mixture of Na (97 mg, 4.2 mg-atoms) and abs. EtOH (5 ml). The resulting solution was heated at 70°C for 2 hr and then under reflux for 6 hr. After addition of Ac₂O (0.3 ml), the reaction mixture was concentrated in vacuo, and the residue was partitioned by extraction with a mixture of H₂O and benzene. The benzene extracts were washed successively with 5% aqueous Na₂CO₃ and saturated aqueous NaCl, dried, and concentrated to leave a pale yellow oil (1.46 g). The excess of diethyl malonate was removed from this oil by vacuum distillation (100—110°C bath temp. 2 mm Hg, 1 hr), and the pale yellow oil (1.1 g) that remained was purified by column chromatography (silica gel, AcOEt) to yield 16a (865 mg, 69%) as a colorless oil, MS m/e: 449 (M⁺); IR ν(CHCl₃ cm⁻¹ : 1750 (sh) and 1728 (ester CO), 1641 (lactam CO); ¹H-NMR (CDCl₃) δ : 0.83 (3H, t, J = 7.0 Hz, CCH₂Me), 1.27 (6H, t, J = 7.1 Hz, two OCH₂Me's), 3.85 and 3.88 (3H each, s, two OMe's), 4.20 (4H, q, J = 7.1 Hz, two OCH₂Me's), 6.55—6.9 (3H, m, aromatic protons). On the basis of the results of ¹³C-NMR spectroscopic analysis,¹² this sample was estimated to be a 13:87 mixture of the 4,5-cis isomer [¹³C-NMR (CDCl₃) δ : 12.3 (CCH₂Me), 17.7 (CCH₂Me)] and the 4,5-trans isomer [δ : 11.1 (CCH₂Me), 24.0 (CCH₂Me)].

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidinemalonamic Acid Diethyl Ester (16b)—The Michael addition of diethyl malonate to 15b was carried out as described above for 16a, giving 16b in 71% yield as a colorless oil, MS m/e: 555 (M⁺); IR ν(CHCl₃ cm⁻¹ : 1750 (sh) and 1730 (ester CO), 1632 (lactam CO); ¹H-NMR (CDCl₃) δ : 0.77 (3H, t, J = 7.2 Hz, CCH₂Me), 1.26 and 1.27 (6H, t each, J = 7.1 Hz, two OCH₂Me's), 3.86 and 3.89 (3H each, s, two OMe's), 4.19 (4H, q, J = 7.1 Hz, two OCH₂Me's), 5.10 (2H, s, OCH₂Ph), 6.63 (1H, d, J = 8.5 Hz, H₆β), 6.89 (1H, d, J = 8.5 Hz, H₆γ), 7.2—7.5 (5H, m, Ph). The ¹³C-NMR spectroscopic analysis¹² of this sample suggested that it was a 12:88 mixture of the 4,5-cis isomer [¹³C-NMR (CDCl₃) δ : 12.3 (CCH₂Me), 17.6 (CCH₂Me)] and the 4,5-trans isomer [δ : 11.1 (CCH₂Me), 23.9 (CCH₂Me)].

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidinemalonamic Acid (17b)—A crude sample (1.54 g) of 16b obtained from 15b (1.19 g, 3 mmol) as described above was dissolved in EtOH (6 ml) containing 2N aqueous NaOH (3 ml). The resulting solution was stirred at 50°C for 20 hr and then concentrated in vacuo. The residue was partitioned between H₂O (30 ml) and benzene, and the aqueous extracts were acidified with 10% aqueous HCl to pH 2 and extracted with CHCl₃. The CHCl₃ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave 17b (1.10 g, 73% from 15b) as a colorless glass, IR ν(CHCl₃ cm⁻¹ : 1726 (CO₂H), 1598 (lactam CO); ¹H-NMR (CDCl₃) δ : 3.84 and 3.87 (3H each, s, two OMe's), 5.08 (2H, s, OCH₂Ph), 6.62 (1H, d, J = 8.5 Hz, H₆β), 6.84 (1H, d, J = 8.5 Hz, H₆γ), 11.0 (2H, br, two CO₂H's). The ¹³C-NMR spectroscopic analysis of this
sample suggested that it was a 13:87 mixture of the 4,5-cis isomer $[^1]^{13}$C-NMR (CDCl$_3$) $\delta$: 12.2 (CCH$_2$Me) and the 4,5-trans isomer $\delta$: 10.4 (CCH$_2$Me).

1-(3,4-Dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (18a)—A solution of 16a (450 mg, 1 mmol) in Me$_2$SO (2 ml) containing powdered NaCl (12 mg, 0.2 mmol) and H$_2$O (36 mg, 2 mmol) was heated in an atmosphere of N$_2$ at 160–165 °C (bath temp.) for 8 h. After cooling, the reaction mixture was diluted with H$_2$O (20 ml) and extracted with ether. The ether extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave an orange oil (373 mg). Purification of the oil by column chromatography [silica gel, hexane–AcOEt (1:2, v/v)] produced 18a (322 mg, 85% yield) as a pale yellow oil. Although the IR (neat) and $^1$H-NMR (CDCl$_3$) spectra of this sample were virtually identical with those of authentic 18a, the $^1$C-NMR spectrum suggested this oil to be a 9:91 mixture of the 4,5-cis isomer $[^1]^{13}$C-NMR (CDCl$_3$) $\delta$: 11.9 (CCH$_2$Me), 20.8 (CCH$_3$Me) and the 4,5-trans isomer $\delta$: 10.9 (CCH$_2$Me), 23.6 (CCH$_3$Me). In a separate experiment, it was confirmed that a pure sample of the 4,5-trans isomer of 18a did not isomerize to the cis isomer at all under the above de-ethoxyacetylation conditions.

1-(2-Benzoxy-3,4-dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (18b)—The diester 16b was de-ethoxyacetylated by 7 h as described above for 18a. The crude product was purified on a silica gel column [hexane–AcOEt (1:1, v/v)] to furnish 18b in 88% yield as a pale yellow oil. Although the IR (neat) and $^1$H-NMR (CDCl$_3$) spectra of this oil were virtually identical with those of authentic 18b, the $^1$C-NMR spectrum suggested the oil to be an 11:89 mixture of the 4,5-cis isomer $[^1]^{13}$C-NMR (CDCl$_3$) $\delta$: 11.9 (CCH$_2$Me), 20.9 (CCH$_3$Me) and the 4,5-trans isomer $\delta$: 10.9 (CCH$_2$Me), 23.5 (CCH$_3$Me).

(+)-1-(3,4-Dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidineacetic Acid (19a)—A solution of 18a (189 mg, 0.5 mmol) in EtOH (3 ml) containing 1 N aqueous NaOH (1.5 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo, and the oily residue was partitioned between H$_2$O (10 ml) and ether. The aqueous extracts were made acid to Congo red with 10% aqueous HCl and extracted with CHCl$_3$. The CHCl$_3$ extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave a colorless solid. Recrystallization of the solid from 50% aqueous acetone gave 19a (147 mg, 84% yield) as colorless pillar, mp 154–155.5 °C. This sample was identical by [by mixture melting point test and by comparison of IR (Nujol), $^1$H-NMR (CDCl$_3$), and $^{13}$C-NMR (CDCl$_3$) spectra] with authentic 19a.

(-)-1-(2-Benzoxy-3,4-dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidineacetic Acid (19b)—From 18b: Alkaline hydrolysis of 18b was effected as described above for 19a, and the crude product was recrystallized from AcOEt to afford 19b in 85% yield as colorless scales, mp 124–126 °C. The sample was identical by [by mixture melting point test and by comparison of IR (Nujol) spectrum] with the one prepared by method (ii) (see below).

(i) From 17b: A solution of 17b (800 mg, 1.6 mmol) in 60% aqueous AcOH (20 ml) was heated under reflux for 6 h. The reaction mixture was concentrated in vacuo to leave a yellow oil, which was dissolved in CHCl$_3$ (50 ml). The CHCl$_3$ solution was washed with H$_2$O, dried, and concentrated, leaving a pale yellow solid (724 mg; mp 114–121 C). This was presumed to be a 19:81 mixture of the cis and trans isomers on the basis of $^{13}$C-NMR spectroscopic analysis. Two recrystallizations of the solid from AcOEt yielded stereochemically pure 19b (543 mg, 74% yield), mp 125–127 °C. For analysis, this sample was further recrystallized from AcOEt to give colorless scales, mp 126–128 °C; $^1$H-NMR (CDCl$_3$) $\delta$: 1710 (CO·H), 1593 (lactam CO), 3040 (H-NMR (CDCl$_3$), identical with that of authentic (+)-19b. Analytical Caled. For C$_{35}$H$_{42}$N$_2$O$_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.35; H, 7.40; N, 3.23.

(±)-1-(2-Benzoxy-3,4-dimethoxyphenyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (20b)—A solution of 19b (137 mg, 0.3 mmol) in 10% (w/v) ethanolic HCl (3 ml) was stirred at room temperature for 24 h. The mixture was concentrated in vacuo, and the residue was partitioned by extraction with a mixture of benzene (10 ml) and H$_2$O (5 ml). The benzene extracts were washed sequentially with H$_2$O, saturated aqueous NaHCO$_3$, and saturated aqueous NaCl, dried, and concentrated to afford 20b (141 mg, 97% yield) as a colorless oil. This sample was identical by [by comparison of the IR (neat or in CHCl$_3$) spectrum and TLC mobility] with authentic 20b.

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-3-(1,1-ethylenedioxyethoxy)pyridinium Bromide (26b)—A mixture of 6 (3.7 g, 62.4 mmol) and 39 (24.0 g, 68.3 mmol) in dry benzene (57 ml) was heated under reflux for 72 h. After cooling, the reaction mixture was extracted with H$_2$O (85 ml), and the aqueous extracts of 26b were used in the next oxidation step without further purification.

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-3-(1,1-ethylenedioxyethoxy)pyridinium Bromide (27b)—A mixture of 28 (2.67 g, 13.5 mmol) and 39 (5.22 g, 14.9 mmol) in dry benzene (10 ml) was heated under reflux for 72 h. After cooling, the reaction mixture was diluted with benzene (10 ml) and extracted with H$_2$O (30 ml). Evaporation of the aqueous extracts under reduced pressure and drying of the residue gave crude 27b (7.01 g, 94% yield) as an orange oil, which was used in the next oxidation step without further purification.

1-(2-Benzoxyl-3,4-dimethoxyphenyl)-5-(1,1-ethylenedioxyethoxy)-2(1H)-pyridinone (28b)—The foregoing aqueous solution of 26b was subjected to alkaline ferricyanide oxidation according to the previously reported standard procedure, and crude 28b (23.5 g, 83% yield from 6) was obtained as a reddish-brown oil, which was shown to be isomer-free by a single spot on TLC analysis. A portion of this oil was purified on a silica gel column [hexane–AcOEt (3:7, v/v)] to afford a pale orange oil, MS $m/e$: 451 (M$^+$); UV $\lambda_{max}^{EtOH}$ 283.5 nm (sh) (6350); 309 (5300); IR $\nu_{max}^{CN}$ cm$^{-1}$: 1666 (pyridone); $^1$H-NMR (CDCl$_3$) $\delta$: 1.44 (3H, s, CMe), 2.92 (2H, t, $J$ = 6.7 Hz, ArCH$_2$), 3.45–4.0 Hz.
(4H, m, OCH₂CH₂O), 3.82 and 3.90 (3H each, s, two OMe's), 4.02 (2H, t, J = 6.7 Hz, ArCH₂Cl₂), 5.10 (2H, s, OCH₂Ph), 6.51 (1H, d, J = 8.5 Hz, H₅), 6.52 (1H, d, J = 9.4 Hz, H₂), 6.64 (1H, d, J = 8.5 Hz, H₆), 6.86 (1H, d, J = 2.4 Hz, H₅), 7.31 (1H, dd, J = 9.4 and 2.4 Hz, H₆). 7.2–7.55 (5H, m, Ph).

1-(2-Benzoyloxy-3,4-dimethoxyphenethyl)-5-(1,1-ethylenedithioethyl)-2(1H)-pyridine (29b) — The foregoing crude 27b was oxidized in the same manner as described above for 28b, giving the crude product (5.75 g) as a dark red oil. Purification of the oil on a silica gel column [hexane–AcOEt (2:3, v/v) or CH₂Cl₂–AcOEt (5:1, v/v)] furnished 29b (2.74 g, 42%), overall yield from 29a as an orange oil. The oil was crystallized from hexane–AcOEt (3:2, v/v) to afford yellow prisms (mp 72–74 °C), which turned to an oil on drying over P₂O₅, at 2 mmHg and room temperature for 20 h. When allowed to stand in a vessel saturated with H₂O, the oil again crystallized to form 29b–1/2H₂O, mp 72–74 °C; MS m/e: 483 (M⁺), UV εmax 227.5 nm (sh) (λ = 19200), 281.5 (2900), 313.5 (4800); IR νmax 1662 cm⁻¹ (pyridone); ¹H-NMR (CDCl₃): δ: 1.82 (3H, s, CMe), 2.19 (1H, s, 1/2H₂O), 2.91 (2H, t, J = 6.7 Hz, ArCH₂), 3.0–3.5 (4H, m, SCh₂CH₂S), 3.84 and 3.90 (3H each, s, two OMe's), 4.01 (2H, t, J = 6.7 Hz, ArCH₂CH₂), 5.10 (2H, s, OCH₂Ph), 6.52 (1H, d, J = 8.5 Hz, H₅), 6.55 (1H, d, J = 9.5 Hz, H₆), 6.63 (1H, d, J = 8.5 Hz, H₆), 6.98 (1H, d, J = 2.4 Hz, H₅). 7.2–7.5 (5H, m, Ph). 7.61 (1H, dd, J = 9.5 and 2.4 Hz, H₆). Anal. Caled for C₂₇H₂₇NO₄S₂·1/2H₂O: C, 63.39; H, 6.14; N, 2.84. Found: C, 63.42; H, 6.24; N, 2.97.

1-(3,4-Dimethoxy-2-hydroxyphenethyl)-5-(1,1-ethylenedithioethyl)-2-piperidine (30c) — A solution of 28b (6.49 g, 14.4 mmol) in EtOH (150 ml) was hydrogenated over Raney Ni-W-2 catalyst (7 ml) at atmospheric pressure at room temperature for 1 h and then at 35 °C for 12 h. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure afforded a colorless oil, which was dissolved in CHCl₃ (200 ml). The CHCl₃ solution was dried and concentrated to leave 30c (5.24 g, 100%), as a colorless solid. Recrystallization from AcOEt yielded an analytical sample as colorless prisms, mp 99–101 °C; MS m/e: 365 (M⁺); IR νmax 1601 (lactam CO); ¹H-NMR (CDCl₃): δ: 1.22 (3H, s, CMe), 3.83 and 3.89 (3H each, s, two OMe's), 6.39 (1H, d, J = 8.5 Hz, H₅), 6.79 (1H, d, J = 8.5 Hz, H₆). Anal. Caled for C₂₇H₂₇NO₄S·C₇H₅: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.44; H, 7.37; N, 3.96.

Deketalization of 30c — A solution of 30c (194 mg, 0.53 mmol) in EtOH (1 ml) containing 10% aqueous HCl (0.4 ml) was heated under reflux for 2 h. The reaction mixture was concentrated in vacuo, and the residue was extracted with CHCl₃ (5 ml) and subsequent neutralization with NaHCO₃. The CHCl₃ extracts were dried and concentrated to leave 11e (163 mg, 95%), as a yellow powder, mp 120–122 °C. Recrystallization from AcOEt gave a pure sample as colorless needles, mp 124–125 °C. This sample was identical [by mixture melting point test and comparison of the IR (Nujol) spectrum] with authentic 11c obtained via the foregoing alternative route.

Reductive Desulfurization of 29a — A mixture of 29a (9 mg, 5 mmol), 70% (v/v) aqueous EtOH (100 ml), and Raney Ni (33) (20 ml) was heated under reflux for 3 h. The catalyst was removed by filtration. The filtrate was washed and combined and concentrated in vacuo, and the residue was partitioned between H₂O (20 ml) and benzene. The benzene extracts were washed with saturated aqueous NaCl, dried, and concentrated to leave 12a (1.22 g, 84%), as a colorless oil. The IR (neat) spectrum and TLC behavior of this oil were identical with those of authentic 12a. 8)

Reductive Desulfurization of 29b — A mixture of 29b·1/2H₂O (300 mg, 0.61 mmol), 70% (v/v) aqueous EtOH (20 ml), and Raney Ni (33) (3 ml) was heated under reflux for 6 h. Removal of the catalyst by filtration and concentration of the filtrate left an oil, which was dissolved in benzene (50 ml). The benzene solution was washed with H₂O, dried, and concentrated to leave a colorless oil, which was hydrogenated in EtOH (15 ml) over Raney Ni-W-2 catalyst (0.5 ml) at atmospheric pressure and room temperature for 3.5 h. The usual work-up of the reaction mixture gave 12c (154 mg, 82%), as a colorless solid, mp 114–118 °C. Recrystallization of the solid from AcOEt yielded colorless needles (mp 119–120 °C), which were identical [by mixture melting point test and comparison of IR (Nujol) and ¹H-NMR (CDCl₃) spectra and TLC mobility] with authentic 12c prepared by the foregoing alternative method.

4-[2-(Benzyloxy-3,4-dimethoxyphenyl)-1-thioethoxyethyl]morpholine (35) — A mixture of 34 (60.0 g, 0.21 mol), sulfur (10.1 g, 0.315 mol), and morpholine (27.5 g, 0.316 mol) was heated at 80 °C for 1 h and then under reflux for 4 h. Removal of the excess morpholine from the reaction mixture by vacuum distillation left a reddish-brown oil, which was crystallized from EtOH to afford 35 (50.1 g, 62%), as a yellow powder, mp 103–108 °C. Recrystallization from EtOH gave an analytical sample as yellow plates, mp 110–111 °C: MS m/e: 387 (M⁺); IR νmax 1500 [C(S)N]; ¹H-NMR (CDCl₃): δ: 3.87 and 3.89 (3H each, s, two OMe's), 4.08 (2H, s, ArCH₂), 5.09 (2H, s, OCH₂Ph), 6.66 (1H, d, J = 8.7 Hz, H₅), 7.08 (1H, d, J = 8.7 Hz, H₆), 7.37 (5H, m, Ph). Anal. Caled for C₃₇H₄₉N₂O₄S·C₇H₅: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.83; H, 6.53; N, 3.65.

2-Benzyl-3,4-dimethoxypyruvic Acid (36) — A mixture of 35 (42.0 g, 0.108 mol) and 50% aqueous KOH (140 ml) in EtOH (420 ml) was heated under reflux for 9 h. The reaction mixture was concentrated in vacuo to leave an orange oil, which was partitioned by extraction with a mixture of H₂O (500 ml) and benzene. The aqueous extracts were made acid to Congo red with conc. aqueous HCl and extracted with benzene. The benzene extracts were washed with H₂O, dried, and concentrated to leave 36 (30.5 g, 93%), as a yellow powder. Recrystallization from hexane–AcOEt (3:2, v/v) produced an analytical sample as colorless prisms, mp 113–114 °C; MS m/e: 302 (M⁺); IR νmax 1700 (CO₂H); ¹H-NMR (CDCl₃): δ: 3.52 (2H, s, ArCH₂), 3.87 (6H, s, two OMe's), 5.09 (2H, s, OCH₂Ph), 6.65 (1H, d, J = 8.5 Hz, H₅), 6.89 (1H, d, J = 8.5 Hz, H₆), 7.25–7.55 (5H, m, Ph), 8.9 (1H, br, CO₂H). Anal. Caled for C₁₈H₁₄O₅: C, 67.54; H, 6.00. Found: C, 67.26; H, 5.98.
2-Benzoxy-3,4-dimethoxyphenylnalacte Acid Ethyl Ester (37)—A mixture of 36 (45.0 g, 0.149 mol) and 10% (w/w) ethanolic HCl (90 ml) in abs. EtOH (90 ml) was stirred at room temperature for 20 h. The reaction mixture was concentrated in vacuo to leave a yellow oil, which was dissolved in benzene (500 ml). The benzene solution was washed successively with H2O, 4% aqueous NaOH, and H2O, dried, and concentrated to afford 37 (47.8 g, 97%) as a pale yellow oil, bp 185–187 °C (3 mmHg); MS m/e: 330 (M+); IR v\text{\textsubscript{max}} cm\textsuperscript{-1}: 1735 (ester CO); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ: 1.19 (3H, t, J = 7.1 Hz, OCH\textsubscript{3}Me), 3.53 (2H, s, ArCH\textsubscript{2}), 3.86 and 3.87 (3H each, s, two OMe's), 4.08 (2H, q, J = 7.1 Hz, OCH\textsubscript{2}Me), 5.08 (2H, s, OCH\textsubscript{2}Ph), 6.65 (1H, d, J = 8.5 Hz, H\textsubscript{5}), 6.91 (1H, d, J = 8.5 Hz, H\textsubscript{6}), 7.2–7.55 (5H, m, Ph).

2-Benzoxo-3,4-dimethoxyphenyl Alcohol (38)—A solution of 37 (45.0 g, 0.136 mol) in dry ether (200 ml) was added dropwise in 1 h to a stirred, chilled (0–5 °C) suspension of LiAlH\textsubscript{4} (5.17 g, 0.136 mol) in dry ether (200 ml). After the mixture had been stirred at room temperature for 4 h, H2O (5.2 ml), 15% aqueous NaOH (5.2 ml), and H2O (15 ml) were successively added dropwise under ice-cooling and stirring. The insoluble material that resulted was filtered off, and the filtrate was dried and concentrated to leave 38 (38.2 g, 97%) as a faintly yellow oil, bp 180–190 °C (0.08 mmHg); MS m/e: 288 (M+); IR v\text{\textsubscript{max}} cm\textsuperscript{-1}: 3420 (OH); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ: 1.82 (1H, s, OH), 2.77 (2H, t, J = 6.4 Hz, ArCH\textsubscript{2}), 3.73 (2H, t, J = 6.4 Hz, CH\textsubscript{2}OH), 3.86 and 3.88 (3H each, s, two OMe's), 5.08 (2H, s, OCH\textsubscript{2}Ph), 6.64 (1H, d, J = 8.5 Hz, H\textsubscript{5}), 6.87 (1H, d, J = 8.5 Hz, H\textsubscript{6}), 7.2–7.55 (5H, m, Ph).

2-Benzoxo-3,4-dimethoxyphenyl Bromide (39)—Triphenylphosphine (27.3 g, 0.104 mol) was added portionwise to a stirred, ice-cooled solution of 38 (30.0 g, 0.104 mol) in benzene (160 ml). N-Bromosuccinimide (18.5 g, 0.104 mol) was then added portionwise at such a rate that the inner temperature did not exceed 10 °C. After having been stirred at room temperature for 2 h, the reaction mixture was filtered. The filtrate was washed successively with 5% aqueous Na2S\textsubscript{2}O\textsubscript{3}, 0.5N aqueous NaOH, and saturated aqueous NaCl, dried, and concentrated. The residue was triturated with hexane–AcOEt (5:1, v/v) (20 ml) and the mixture was filtered in order to remove the insoluble material. The filtrate was then passed through a column packed with silica gel (60 g). Concentration of the eluate under reduced pressure left 39 (32.3 g, 89%) as an orange solid. For analysis, the solid was recrystallized from hexane to give colorless prisms, mp 45.5–47 °C; MS m/e: 352, 350 (M+); \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) δ: 3.02 (2H, t, J = 7.2 Hz, ArCH\textsubscript{2}), 3.43 (2H, t, J = 7.2 Hz, CH=Br), 3.86 and 3.88 (3H each, s, two OMe's), 5.10 (2H, s, OCH\textsubscript{2}Ph), 6.62 (1H, d, J = 8.5 Hz, H\textsubscript{5}), 6.85 (1H, d, J = 8.5 Hz, H\textsubscript{6}), 7.2–7.55 (5H, m, Ph). Anal. Calcd for C\textsubscript{17}H\textsubscript{15}BrO\textsubscript{3}: C, 58.13; H, 5.45.

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References and Notes

5) For the two synthetic routes, see references cited in ref. 4.
24) a) S. Sugawara and Y. Ban, Yakugaku Zasshi, 72, 1336 (1952); b) S. Sugawara and M. Kirisawa, Chem. Pharm. Bull., 4, 139 (1956); c) Idem, ibid., 3, 190 (1955).
32) We have already observed that the N-benzyl analogue of 19b is transformed into the 4,S-cis isomer to the extent of 9%, under similar reaction conditions. For details, see T. Fujii, S. Yoshifuji, and M. Ohba, Chem. Pharm. Bull., 26, 645 (1978).