

[Chem. Pharm. Bull.]
31(4)1191-1198(1983)

1,6-Dihydro-3(2*H*)-pyridinones. V.¹⁾ Total Synthesis of (±)-Eburnamonine²⁾

TAKESHI IMANISHI, KEN-ICHI MIYASHITA, AKIRA NAKAI,
MAKOTO INOUE, and MIYOJI HANAOKA*

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

(Received September 17, 1982)

3-Ethyl-3-methoxycarbonylmethylpiperidine (**20**) was prepared *via* the unsaturated aldehyde (**12**) derived from benzyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**5b**). *N*-Chlorination of **20** and subsequent exposure to a base afforded *rel*-(2*S*,3*R*)-3-ethyl-2-hydroxypiperidine-3-acetic acid γ -lactone (**3**) in a good yield. According to the known method, the lactone (**3**) was converted into (±)-eburnamonine (**1**) and (±)-epieburnamonine (**31**). A possible pathway from **20** to **3** is also discussed.

Keywords—dihydropyridinone; total synthesis; indole alkaloid; eburnamonine; epieburnamonine; *N*-chlorination; lactone formation; sodium hypochlorite; isomerization of imine

Indole alkaloids having a 1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]naphthylidine framework, *e.g.* eburnamonine and vincamine, have received much attention from synthetic organic chemists because of their significant pharmacological activities.

Eburnamonine (**1**), first isolated from *Hunteria eburnea* Pichon,³⁾ is known to show cerebrovascular activity.⁴⁾ Since the first synthesis of (±)-eburnamonine by Bartlett and Taylor,^{5*a*)} several investigators have achieved its total synthesis.⁵⁾ Among the successful synthetic strategies for eburnamonine, Wenkert and his co-workers presented an elegant route.^{5*f*)} Namely, the cyclopropanecarboxylate (**2**) was subjected to basic hydrolysis to afford the amino lactone (**3**), which was condensed with tryptophyl bromide followed by thermolysis to furnish (±)-eburnamonine (**1**). More recently, an alternative synthesis of the same lactone (**3**) was reported by Irie and Ban^{5*g*)} using anodic oxidation of the urethane (**4**).

In a previous paper¹⁾ of this series we described a synthesis of (±)-tabersonine, one of the Aspidosperma alkaloids, starting from ethyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (**5a**) *via* the key compound (**6**), which could also serve as a potential intermediate for the amino lactone (**3**). As a continuation of our studies on general alkaloid syntheses starting from

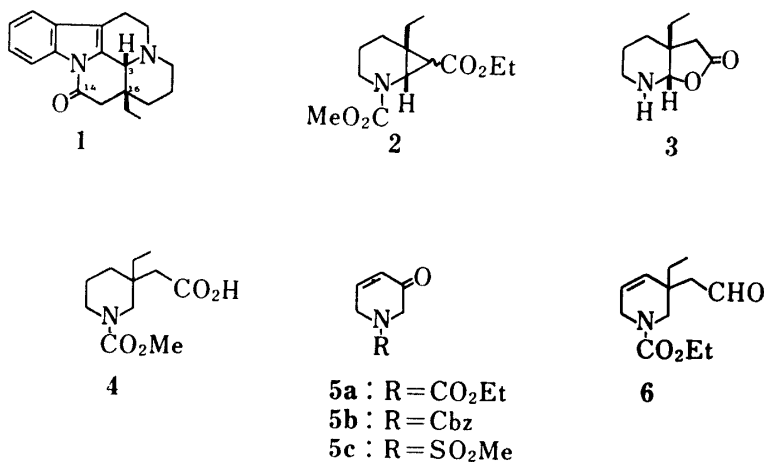


Chart 1

the same synthon, the dihydropyridinone (5), this paper describes a successful synthesis of ($\pm$)-eburnamonine (1) utilizing a novel method for amino lactone formation.

Basic hydrolysis of the allylic alcohol (7)⁶ followed by treatment with carbobenzoxy chloride yielded the benzyl urethane (8), which was oxidized to benzyl 1,6-dihydro-3(2*H*)-pyridinone-1-carboxylate (5b) in 86% overall yield from 7. The aldehyde (12), the benzyl urethane analogue of compound 6, was prepared from 5b according to the previously reported procedures¹ as follows. Exposure of 5b to an excess of ethylmagnesium bromide in ether, followed by chromatographic separation, gave the 1,2-adduct (9) and the 1,4-adduct (10) in 57 and 16% yields, respectively. Upon treatment with 1% hydrochloric acid in acetone allylic rearrangement of the hydroxyl group of the former (9) occurred easily to give the isomeric alcohol (11) in 61% yield. The proton nuclear magnetic resonance (¹H-NMR) spectrum of 11 exhibited a one-proton multiplet at 5.57 ppm and a pair of signals at 1.03 (3H, t, *J* = 7 Hz) and 2.02 ppm (2H, q, *J* = 7 Hz) due to the C₄-H and C₅-ethyl protons, respectively. Heating of 11 with ethyl vinyl ether in the presence of mercuric acetate⁸ in a sealed tube at 200°C provided the labile aldehyde (12).

Catalytic hydrogenation of its acetal (13) over platinum oxide in ethyl acetate gave the saturated urethane (14) in 69% yield. Acidic hydrolysis of 14 gave the aldehyde (15), which was then oxidized to the carboxylic acid (16) with *in situ*-generated silver(I) oxide⁹ in 75% yield from 14. Esterification of 16 with diazomethane and subsequent hydrogenolysis over 5% palladium on carbon in methanol afforded the amino ester (20) in 72% yield. The infrared (IR) spectrum of 20 showed an NH band and an ester carbonyl band at 3350 and 1720 cm⁻¹, respectively, and its mass spectrum showed a parent peak at *m/e* 185. The same amino ester (20) was

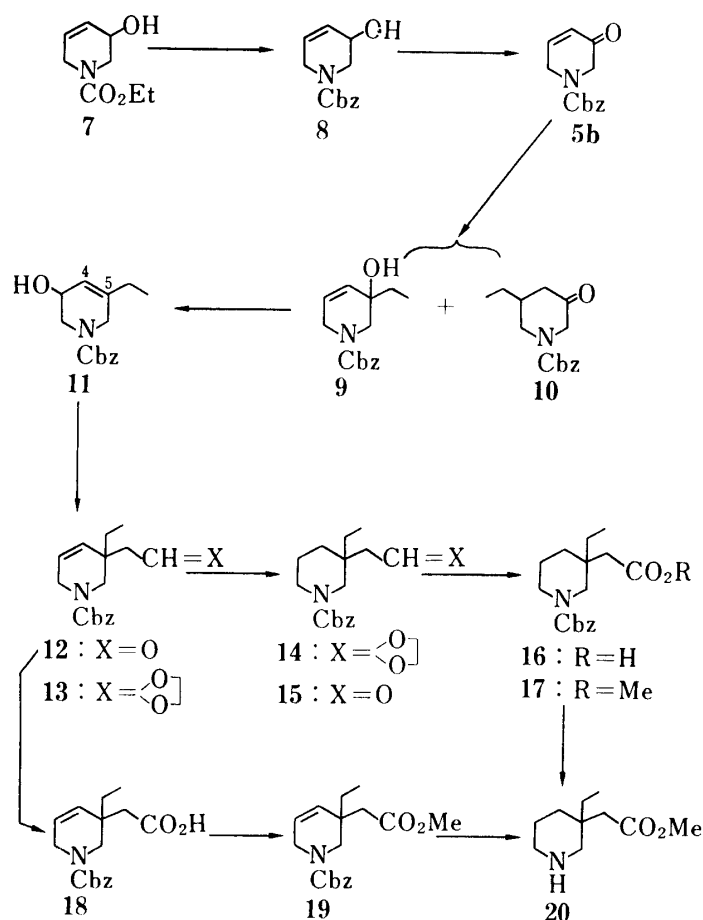


Chart 2

also obtained from the allylic alcohol (**11**) by an alternative and shorter sequence. Namely, the Claisen rearrangement of **11** using ethyl vinyl ether was immediately followed by oxidation with silver(I) oxide to provide the carboxylic acid (**18**) in 46% yield. Treatment of **18** with diazomethane afforded the methyl ester (**19**), which was subjected to catalytic hydrogenation over 5% palladium on carbon in methanol to give the amino ester (**20**) in 19% overall yield from **11**.

The desethyl analogue (**25**) of **20** was prepared from the alcohol (**7**) as follows. The carboxylic acid (**21**), obtained by the Claisen rearrangement with ether vinyl ether and oxidation with silver(I) oxide, was hydrogenated and then treated with potassium hydroxide in boiling aqueous ethanol and subsequently with carbobenzoxy chloride to afford the benzyl urethane (**23**), which was esterified with diazomethane and successively hydrogenolyzed to yield **25**.

Next, oxidative cyclization of **20** or **25** was examined. After some unsuccessful attempts, *N*-chlorination with sodium hypochlorite¹⁰⁾ was found to be suitable for our present purpose. On two-phase reaction of **20** with sodium hypochlorite in a water-dichloromethane system under ice cooling, exclusive formation of the chloramine (**26**) was easily recognized by thin-layer chromatography (TLC). Without isolation of the product (**26**), the solvent was exchanged from dichloromethane to dioxane and the solution was treated with aqueous potassium hydroxide to furnish the desired lactone (**3**) in 85% yield. The structure of **3** was easily elucidated from spectral evidence. The IR spectrum showed a lactone carbonyl band at 1745 cm^{-1} in chloroform and the $^1\text{H-NMR}$ spectrum exhibited a singlet at 5.13 ppm due to $\text{C}_2\text{-H}$ and an AB-quartet at 2.21 and 2.42 ppm ($J=16.5\text{ Hz}$) attributable to the methylene protons adjacent to the carbonyl function. These data and the melting point ($73\text{--}75^\circ\text{C}$) were in good accord with the reported values⁵ⁱ⁾ for **3**. On the other hand, the same treatment of the desethyl analogue (**25**) failed to yield the corresponding lactone (**27**).

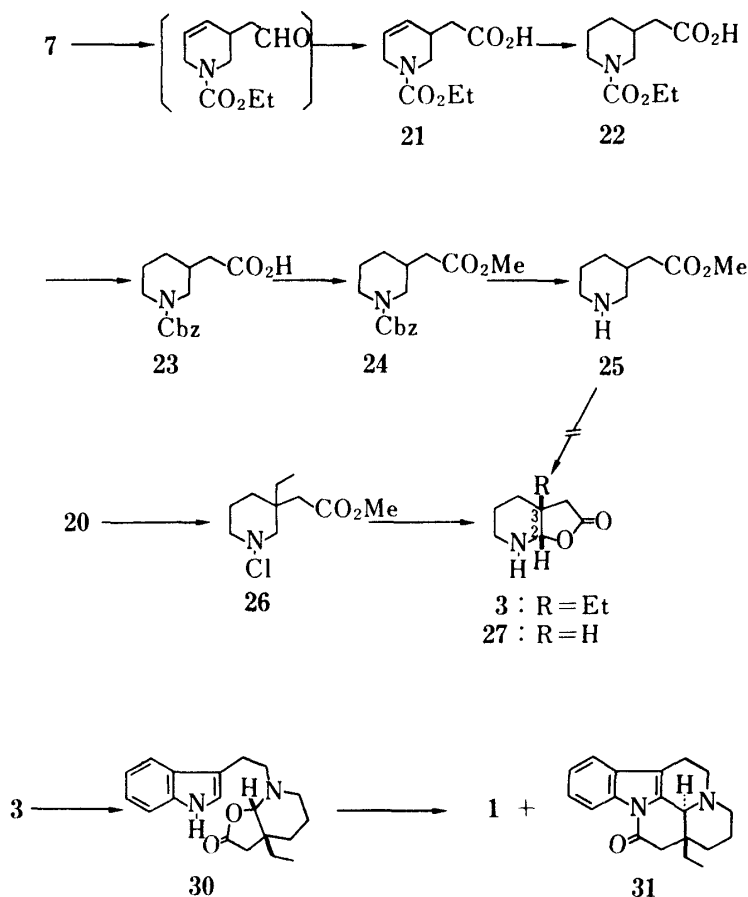


Chart 3

The exclusive formation of the amino lactone (3) from 20 can be interpreted as follows. The amino ester (20) is oxidized with sodium hypochlorite to the chloramine (26), which is subjected to ester hydrolysis and dehydrochlorination to give the interconvertible¹¹⁾ imino carboxylates (28a and 28b). On the assumption of participation of the carboxylate group at the C-3 position, only the imino carboxylate (28a) may be formed, as shown in 29. The imino carboxylate (28a) is expected to exist as a mixture of two conformers (A and B) because of the almost equal steric bulkiness of the ethyl and carboxymethyl groups both attached at the C-3 position. From the viewpoint of a perpendicular attack of the carboxylate group on the imino double bond, the intramolecular reaction of the imino carboxylate (28a) into the amino lactone (3) must take place only in the conformer A. In the case of the desethyl series, however, owing to the small contribution of the requisite quasi-axial orientation of the carboxymethyl group in the corresponding imino carboxylate, none of the lactone (27) is obtained.

Finally, according to the procedures given in the literature,⁵ⁱ⁾ the amino lactone (3) was converted into ($\pm$)-eburnamonine (1) and ($\pm$)-epiburnamonine (31) via the intermediate 30. The synthetic ($\pm$)-eburnamonine was proved to be identical with natural eburnamonine by means of TLC and spectral comparisons.

Thus, a novel method for preparing the amino lactone (3) using the oxidation of amine with sodium hypochlorite has been developed, and by utilizing this method, a total synthesis of ($\pm$)-eburnamonine (1) has been achieved.

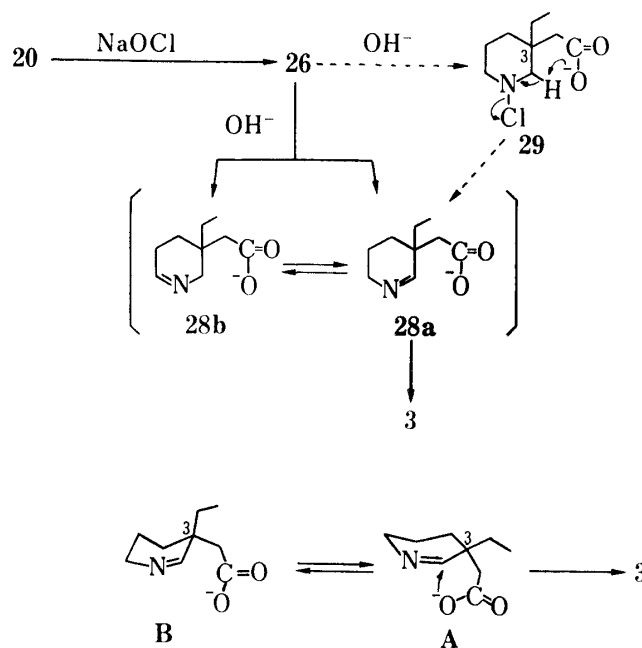


Chart 4

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 75 eV). ¹H-NMR spectra were recorded on a JEOL PMX-60 or FX-100 spectrometer with CDCl₃ as a solvent and tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet, and br=broad. All organic extracts were dried over anhydrous sodium sulfate and concentrated with a rotary evaporator *in vacuo*. Column chromatography was performed on Silica gel 60 (70–230 mesh, Merck) or Alumina 90 (70–230 mesh, Merck).

Benzyl 3-Hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (8)—Aqueous 15% KOH solution (15 ml) was added to a solution of the ethyl urethane (7; 2.15 g) in EtOH (15 ml), and the mixture was refluxed with stirring for 27 h. Ethanol was evaporated off and the remaining aqueous solution was washed with ether (10 ml × 2) in order to remove the unchanged starting material. Carbobenzoxy chloride (3.8 ml) and then CHCl₃ (40 ml) were added to the resulting aqueous layer and the whole was stirred at room temperature for 2 h. The CHCl₃ layer was separated and the aqueous layer was extracted with CHCl₃ (30 ml × 3). The combined extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in CHCl₃ to afford 2.89 g (99%) of the benzyl urethane (8) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3560 (OH), 1680 (NCOO), 1650 (C=C), 690 (aromatic). ¹H-NMR δ : 2.27 (1H, s, OH), 3.58 (2H, m, C₂-H), 3.93 (2H, m, C₆-H), 4.42 (1H, m, C₃-H), 5.12 (2H, s, CH₂Ar), 5.82 (2H, m, C₄- and C₅-H), 7.33 (5H, s, Ar-H). MS *m/e* (%): 233 (2, M⁺), 181 (2), 91 (100). High resolution MS. Calcd for C₁₃H₁₅NO₃: 233.1051. Found: 233.1062.

Benzyl 1,6-Dihydro-3(2H)-pyridinone-1-carboxylate (5b)—The Jones reagent⁷⁾ (8 N; 2.6 ml) was added dropwise to a stirred solution of the alcohol (8; 1.6 g) in purified acetone (7 ml) under ice cooling over a period

of 1 h. Excess reagent was decomposed with MeOH and the resulting mixture was diluted with water. The mixture was extracted with CHCl_3 (15 ml $\times$ 3) and the extract was washed with brine and dried. The solvent was evaporated off to give 1.32 g (87%) of the dihydropyridinone (**5b**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1685 (CO and NCOO), 1625 (C=C), 690 (aromatic). $^1\text{H-NMR}$ δ : 4.12 (2H, s, $\text{C}_2\text{-H}$), 4.22 (2H, dd, $J=3$ and 2.5 Hz, $\text{C}_6\text{-H}$), 5.12 (2H, s, CH_2Ar), 6.05 (1H, dt, $J=10$ and 2.5 Hz, $\text{C}_4\text{-H}$), 6.92 (1H, dt, $J=10$ and 3 Hz, $\text{C}_5\text{-H}$), 7.25 (5H, s, Ar-H). The semicarbazone of **5b**: mp 192–193°C (from EtOH). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.03; H, 5.59; N, 19.63.

Benzyl 3-Ethyl-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (9) and Benzyl 5-Ethyl-3-oxopiperidine-1-carboxylate (10)—A solution of the ketone (**5b**; 4.25 g) in dry ether (30 ml) was added dropwise to a stirred solution of EtMgBr in dry ether [prepared from Mg (1.2 g) and EtBr (4.0 ml) in dry ether (30 ml)] at -15°C over a period of 20 min and the mixture was further stirred at the same temperature for 2 h. Aqueous sat. NH_4Cl solution was added to the mixture and the organic layer was separated. The aqueous layer was extracted with ether (50 ml $\times$ 3). The combined ethereal extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in CHCl_3 . The first fraction afforded 790 mg (16%) of the 1,4-adduct (**10**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1715 (CO), 1685 (NCOO), 690 (aromatic). $^1\text{H-NMR}$ δ : 0.95 (3H, t, $J=7$ Hz, $\text{C}_5\text{-CH}_2\text{CH}_3$), 1.33 (2H, qn, $J=7$ Hz, $\text{C}_5\text{-CH}_2\text{CH}_3$), 3.90 (1H, d, $J=17$ Hz, $\text{C}_2\text{-H}$), 4.10 (1H, d, $J=17$ Hz, $\text{C}_2\text{-H}$), 5.12 (2H, s, CH_2Ar), 7.10 (5H, s, Ar-H). MS m/e (%): 261 (4, M^+), 188 (3), 108 (18), 91 (100). High resolution MS. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$: 261.1364. Found: 261.1368. The second fraction afforded 2.73 g (57%) of the 1,2-adduct (**9**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3560 (OH), 1680 (NCOO), 1650 (C=C), 695 (aromatic). $^1\text{H-NMR}$ δ : 0.93 (3H, t, $J=7$ Hz, $\text{C}_3\text{-CH}_2\text{CH}_3$), 1.60 (2H, q, $J=7$ Hz, $\text{C}_3\text{-CH}_2\text{CH}_3$), 2.12 (1H, s, OH), 3.43 (1H, d, $J=15$ Hz, $\text{C}_2\text{-H}$), 3.60 (1H, d, $J=15$ Hz, $\text{C}_2\text{-H}$), 3.90 (1H, br d, $J=15$ Hz, $\text{C}_6\text{-H}$), 4.05 (1H, br d, $J=15$ Hz, $\text{C}_6\text{-H}$), 5.12 (2H, s, CH_2Ar), 5.72 (2H, br s, $\text{C}_4\text{-}$ and $\text{C}_5\text{-H}$), 7.30 (5H, s, Ar-H). MS m/e (%): 261 (2, M^+), 205 (1), 164 (14), 98 (31), 91 (100). High resolution MS. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$: 261.1364. Found: 261.1364.

Benzyl 5-Ethyl-3-hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (11)—A mixture of the tertiary alcohol (**9**; 1.14 g), 1% HCl (3 ml), and purified acetone (15 ml) was refluxed for 10 h. Acetone was evaporated off and the residue was extracted with CHCl_3 (20 ml, 15 ml $\times$ 2). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in CHCl_3 to afford 691 mg (61%) of the secondary alcohol (**11**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3555 (OH), 1680 (NCOO), 1660 (C=C), 690 (aromatic). $^1\text{H-NMR}$ δ : 1.03 (3H, t, $J=7$ Hz, $\text{C}_5\text{-CH}_2\text{CH}_3$), 2.02 (2H, q, $J=7$ Hz, $\text{C}_5\text{-CH}_2\text{CH}_3$), 3.53 (2H, d, $J=4$ Hz, $\text{C}_2\text{-H}$), 4.60 (1H, s, OH), 5.07 (2H, s, CH_2Ar), 5.57 (1H, m, $\text{C}_4\text{-H}$), 7.22 (5H, s, Ar-H). MS m/e (%): 261 (1, M^+), 188 (1), 164 (18), 91 (100). High resolution MS. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$: 261.1364. Found: 261.1367.

Benzyl 3-Ethyl-3-(2-ethylenedioxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (13)—A mixture of the alcohol (**11**; 690 mg), $\text{Hg}(\text{OAc})_2$ (350 mg), and ethyl vinyl ether (5 ml) was heated in a sealed tube at 200°C for 48 h. After evaporation of the solvent, the residue was dissolved in C_6H_6 (50 ml) and the C_6H_6 solution was washed with 10% HCl and water. This C_6H_6 solution of the crude aldehyde (**12**) was concentrated to 3/4 of the original volume and then ethylene glycol (1.0 ml) and $p\text{-TsOH}$ (trace) were added to the remainder. The resulting mixture was refluxed with stirring for 1.5 h while the water formed was removed azeotropically using a Dean-Stark apparatus. The reaction mixture was washed with sat. NaHCO_3 and brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in C_6H_6 to afford 410 mg (47% from **11**) of the acetal (**13**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1680 (NCOO). $^1\text{H-NMR}$ δ : 0.83 (3H, t, $J=7$ Hz, $\text{C}_3\text{-CH}_2\text{CH}_3$), 1.32 (2H, q, $J=7$ Hz, $\text{C}_3\text{-CH}_2\text{CH}_3$), 1.70 (2H, d, $J=4.5$ Hz, $\text{CH}_2\text{CH}(\text{O})$), 3.38 (2H, s, $\text{C}_2\text{-H}$), 3.8–3.9 (6H, m, $\text{C}_6\text{-H}$ and $\text{OCH}_2\text{CH}_2\text{O}$), 4.78 (1H, t, $J=4.5$ Hz, $\text{CH}(\text{O})$), 5.07 (2H, s, CH_2Ar), 5.57 (2H, br s, $\text{C}_4\text{-}$ and $\text{C}_5\text{-H}$), 7.22 (5H, s, Ar-H). MS m/e (%): 331 (7, M^+), 91 (100).

Benzyl 3-Ethyl-3-(2-ethylenedioxyethyl)piperidine-1-carboxylate (14)—A solution of the olefin (**13**; 615 mg) in AcOEt (13 ml) was hydrogenated over platinum oxide (30 mg) under atmospheric pressure of H_2 at room temperature for 6 h. The catalyst was filtered off and the filtrate was concentrated to leave an oily residue, which was chromatographed on alumina in $\text{CHCl}_3\text{-C}_6\text{H}_6$ (1: 1) to afford 430 mg (69%) of the saturated urethane (**14**) as a colorless oil. $^1\text{H-NMR}$ δ : 0.82 (3H, t, $J=7$ Hz, $\text{C}_3\text{-CH}_2\text{CH}_3$), 1.30–1.58 (6H, m, $\text{C}_3\text{-CH}_2\text{CH}_3$, $\text{C}_4\text{-}$, and $\text{C}_5\text{-H}$), 1.63 (2H, d, $J=5$ Hz, $\text{CH}_2\text{CH}(\text{O})$), 3.24–3.45 (4H, m, $\text{C}_2\text{-}$ and $\text{C}_6\text{-H}$), 3.73–3.92 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 4.91 (1H, t, $J=5$ Hz, $\text{CH}(\text{O})$), 5.11 (2H, s, CH_2Ar), 7.34 (5H, s, Ar-H).

Benzyl 3-Carboxymethyl-3-ethylpiperidine-1-carboxylate (16)—A mixture of the acetal (**14**; 430 mg), 6% HCl (5.5 ml), and purified acetone (30 ml) was refluxed for 6 h. Acetone was evaporated off and the residue was extracted with CHCl_3 (30 ml, 20 ml $\times$ 2). The extract was washed with brine, dried, and concentrated to leave 317 mg (85%) of the crude aldehyde (**15**), which was used for the next step without purification. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 2720 (CHO), 1710 (CO), 1680 (NCOO). A solution of KOH (330 mg) in distilled water (5 ml) was added dropwise to a stirred mixture of the crude aldehyde (**15**; 317 mg), AgNO_3 (330 mg), water (5 ml), and EtOH (5 ml) under ice cooling over a period of 2–3 min, and the whole was further stirred for 20 min

at the same temperature. The reaction mixture was acidified to pH 1 with conc. HCl and then extracted with CHCl_3 (15 ml $\times$ 4). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in CHCl_3 -EtOH (50:1) to afford 250 mg (75%) of the carboxylic acid (**16**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3550–2400 (COOH), 1700 (CO), 1680 (NCOO). $^1\text{H-NMR}$ δ : 0.87 (3H, t, $J=7$ Hz, C_3 - CH_2CH_3), 1.20–1.72 (6H, m, C_3 - CH_2CH_3 , C_4 -, and C_5 -H), 2.27 (2H, s, CH_2COOH), 3.13–3.63 (4H, m, C_2 - and C_6 -H), 5.07 (2H, s, CH_2Ar), 7.23 (5H, s, Ar-H). MS m/e (%): 305 (8, M^+), 91 (100).

Benzyl 3-Ethyl-3-methoxycarbonylmethylpiperidine-1-carboxylate (17)—A solution of CH_2N_2 in ether (ca. 2% solution; 20 ml) was added dropwise to a stirred solution of the carboxylic acid (**16**; 313 mg) in ether (5 ml) under ice cooling over a period of 5 min. The mixture was further stirred for 1 h under cooling and then allowed to stand at room temperature overnight. Evaporation of the solvent left an oily residue, which was chromatographed on alumina in CHCl_3 to afford 299 mg (91%) of the ester (**17**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1725 (CO), 1680 (NCOO). $^1\text{H-NMR}$ δ : 0.83 (3H, t, $J=6.5$ Hz, C_3 - CH_2CH_3), 1.07–1.80 (6H, m, C_3 - CH_2CH_3 , C_4 -, and C_5 -H), 2.25 (2H, s, CH_2COOMe), 3.13–3.73 (4H, m, C_2 - and C_6 -H), 3.57 (3H, s, OCH_3), 5.05 (2H, s, CH_2Ar), 7.22 (5H, s, Ar-H). MS m/e (%): 319 (2.4, M^+), 184 (100).

Benzyl 3-Carboxymethyl-3-ethyl-1,2,3,6-tetrahydropyridine-1-carboxylate (18)—A mixture of the alcohol (**11**; 1.02 g), $\text{Hg}(\text{OAc})_2$ (580 mg), and ethyl vinyl ether (12 ml) was heated in a sealed tube at 200°C for 48 h. The solvent was evaporated off and the residue was dissolved in C_6H_6 (50 ml). The C_6H_6 solution was washed with 10% HCl and water, dried, and concentrated to leave the crude aldehyde (**12**). A mixture of the crude product, AgNO_3 (0.80 g), distilled water (8 ml), and EtOH (15 ml) was treated with a solution of KOH (0.80 g) in distilled water (8 ml) in the same manner as described for **16**. The crude product was chromatographed on silica gel in CHCl_3 to afford 540 mg (46% from **11**) of the carboxylic acid (**18**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3500–2400 (COOH), 1700 (CO), 1680 (NCOO). $^1\text{H-NMR}$ δ : 0.87 (3H, t, $J=7$ Hz, C_3 - CH_2CH_3), 1.55 (2H, q, $J=7$ Hz, C_3 - CH_2CH_3), 2.33 (2H, s, CH_2COOH), 3.33 (1H, d, $J=13$ Hz, C_2 -H), 3.55 (1H, d, $J=13$ Hz, C_2 -H), 3.99 (2H, br s, C_6 -H), 5.08 (2H, s, CH_2Ar), 5.63 (2H, br s, C_4 - and C_5 -H), 7.23 (5H, s, Ar-H).

Benzyl 3-Ethyl-3-methoxycarbonylmethyl-1,2,3,6-tetrahydropyridine-1-carboxylate (19)—A solution of CH_2N_2 in ether (ca. 2% solution; 8 ml) was added dropwise to a stirred solution of the carboxylic acid (**18**; 453 mg) in ether (20 ml) under ice cooling over a period of 10 min, and the mixture was allowed to stand at room temperature for 1 h. Evaporation of the solvent left an oily residue, which was chromatographed on alumina in CHCl_3 - C_6H_6 (1:1) to afford 0.40 g (84%) of the ester (**19**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1725 (CO), 1690 (NCOO). $^1\text{H-NMR}$ δ : 0.85 (3H, t, $J=7$ Hz, C_3 - CH_2CH_3), 1.50 (2H, q, $J=7$ Hz, C_3 - CH_2CH_3), 2.30 (2H, s, CH_2COOMe), 3.35 (1H, d, $J=13$ Hz, C_2 -H), 3.52 (1H, d, $J=13$ Hz, C_2 -H), 3.55 (3H, s, OCH_3), 3.87 (2H, br s, C_6 -H), 5.07 (2H, s, CH_2Ar), 5.62 (2H, br s, C_4 - and C_5 -H), 7.23 (5H, s, Ar-H). MS m/e (%): 317 (3, M^+), 91 (100).

3-Ethyl-3-methoxycarbonylpiperidine (20)—a) From **17**: A solution of **17** (246 mg) in abs. MeOH (5 ml) was hydrogenated over 5% Pd-C (70 mg) under atmospheric pressure of H_2 at room temperature for 20 min. The catalyst was filtered off and the filtrate was concentrated to leave an oily residue, which was chromatographed on alumina in CHCl_3 to afford 112 mg (79%) of the amine (**20**) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3350 (NH), 1720 (CO). $^1\text{H-NMR}$ δ : 0.83 (3H, t, $J=6.5$ Hz, C_3 - CH_2CH_3), 2.35 (2H, s, CH_2COOMe), 2.52–2.88 (4H, m, C_2 - and C_6 -H), 3.58 (3H, s, OCH_3). MS m/e (%): 185 (36, M^+), 44 (100). The picrate of **20**: mp 132 – 134°C (from ether-EtOH). Anal. Calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_2 \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 46.37; H, 5.35; N, 13.52. Found: C, 46.30; H, 5.21; N, 13.70.

b) From **19**: A solution of **19** (350 mg) in abs. MeOH (20 ml) was hydrogenated over 5% Pd-C (200 mg) under atmospheric pressure of H_2 at room temperature for 1 h, and work-up as usual afforded 0.10 g (49%) of the amine (**20**).

Ethyl 3-Carboxymethyl-1,2,3,6-tetrahydropyridine-1-carboxylate (21)—A mixture of allylic alcohol (**7**; 1.01 g), $\text{Hg}(\text{OAc})_2$ (820 mg), and ethyl vinyl ether (8 ml) was heated in a sealed tube at 210°C for 43 h.¹²⁾ Work-up as usual gave the crude aldehyde, which was oxidized with AgNO_3 -KOH in the same manner as described for **18**. The reaction mixture was washed with CHCl_3 in order to remove some neutral impurities and then acidified to pH 1 with conc. HCl. The acidic aqueous layer was extracted with CHCl_3 (30 ml $\times$ 3) and the extract was washed with brine. The dried extract was concentrated to give 750 mg (60%) of the carboxylic acid (**21**), which was homogeneous on TLC, as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3600–2400 (COOH), 1700 (CO), 1680 (NCOO), 1650 (C=C). $^1\text{H-NMR}$ δ : 1.25 (3H, t, $J=7$ Hz, OCH_2CH_3), 2.37 (2H, d, $J=6$ Hz, CH_2COOH), 3.48 (2H, m, C_2 -H), 3.86 (2H, br s, C_6 -H), 4.12 (2H, q, $J=7$ Hz, OCH_2CH_3), 5.68 (2H, br s, C_4 - and C_5 -H), 8.88 (1H, s, COOH). MS m/e (%): 213 (21, M^+), 153 (30), 140 (47), 102 (100). High resolution MS. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_4$: 213.0999. Found: 213.0951.

Benzyl 3-Methoxycarbonylmethylpiperidine-1-carboxylate (24)—A solution of the carboxylic acid (**21**; 750 mg) in abs. MeOH (7.5 ml) was hydrogenated over platinum oxide (60 mg) under atmospheric pressure of H_2 at room temperature for 30 min. The catalyst was filtered off and the filtrate was concentrated to afford 590 mg of crude ethyl 3-carboxymethylpiperidine-1-carboxylate (**22**) as a colorless oil.

A mixture of **22** (crude; 590 mg), KOH (620 mg), water (13 ml), and EtOH (13 ml) was refluxed with stirring for 43 h. Ethanol was evaporated off and then carbobenzoxy chloride (0.5 ml) was added to the

residue. The resulting mixture was stirred at room temperature for 10 h and washed with CHCl_3 (30 ml) in order to remove neutral substances. The aqueous layer was acidified to pH 1 with conc. HCl and extracted with CHCl_3 (25 ml $\times$ 4). The dried extract was concentrated to leave 413 mg of benzyl 3-carboxymethylpiperidine-1-carboxylate (23) as a colorless oil. $^1\text{H-NMR}$ δ : 2.18 (2H, d, $J=6$ Hz, CH_2COOH), 5.05 (2H, s, CH_2Ar), 7.22 (5H, s, Ar-H), 9.80 (1H, br s, COOH).

A solution of CH_2N_2 in ether (ca. 2% solution; 3.5 ml) was added dropwise to a stirred solution of 23 (410 mg) in ether (20 ml) under ice cooling over a period of 10 min. Stirring was continued for 40 min with cooling and the solvent was evaporated off to leave an oily residue, which was chromatographed on silica gel in CHCl_3 to afford 393 mg (38% from 21) of the ester (24) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1720 (CO), 1680 (NCOO). $^1\text{H-NMR}$ δ : 2.13 (2H, d, $J=6$ Hz, CH_2COOMe), 3.55 (3H, s, OCH_3), 3.63—4.13 (4H, m, C_2 - and C_6 -H), 5.00 (2H, s, CH_2Ar), 7.17 (5H, s, Ar-H). MS m/e (%): 291 (0.6, M^+), 91 (100).

Methyl Piperidine-3-acetate (25)—A solution of 24 (380 mg) in abs. MeOH (7 ml) was hydrogenated over 5% Pd-C (110 mg) under atmospheric pressure of H_2 at room temperature for 3 h. The catalyst was filtered off and the filtrate was concentrated to leave an oily residue, which was chromatographed on alumina in CHCl_3 to afford 112 mg (55%) of the amine (25) as a colorless oil. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3125 (NH), 1725 (CO). $^1\text{H-NMR}$ δ : 1.91 (1H, s, NH), 2.19 (2H, d, $J=5.5$ Hz, CH_2COOMe), 3.66 (3H, s, OCH_3). MS m/e (%): 157 (16, M^+), 83 (100).

rel-(2S,3R)-3-Ethyl-2-hydroxypiperidine-3-acetic Acid γ -Lactone (3)—Aqueous NaOCl solution (5%; 1.5 ml) was added dropwise to a stirred solution of the amine (20; 62 mg) in distilled CH_2Cl_2 (4 ml) under ice cooling over a period of 1 min. The resulting mixture was vigorously stirred for 6 h under cooling. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (5 ml $\times$ 2). The combined extract was washed with brine and diluted with dioxane (5 ml). Dichloromethane was evaporated off *in vacuo* at room temperature and a solution of KOH (0.30 g) in water (1.5 ml) was added to the remainder. The resulting mixture was refluxed with stirring for 2.5 h and acidified with 10% HCl (1.5 ml). The solvent was evaporated off and the residue was made basic with sat. NaHCO_3 . The mixture was extracted with CHCl_3 (8 ml $\times$ 4) and the extract was dried. Evaporation of the solvent left 48 mg (85%) of the lactone (3) as colorless plates, mp 73—75°C (from hexane) (lit.⁵¹) mp 74—75°C). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3400 (NH), 1745 (CO). $^1\text{H-NMR}$ δ : 0.91 (3H, t, $J=7.5$ Hz, C_3 - CH_2CH_3), 1.08—2.00 (6H, m, C_3 - CH_2CH_3 , C_4 -, and C_5 -H), 2.21 (1H, d, $J=16.5$ Hz, CH_2CO), 2.41 (1H, d, $J=16.5$ Hz, CH_2CO), 2.58 (1H, s, NH), 2.67—3.16 (2H, m, C_6 -H), 5.13 (1H, s, C_2 -H). MS m/e (%): 169 (10, M^+), 96 (100). High resolution MS. Calcd for $\text{C}_9\text{H}_{15}\text{NO}_2$: 169.1102. Found: 169.1103.

Attempt to prepare the Lactone (27)—Aqueous NaOCl solution (5%; 3 ml) was added dropwise to a stirred solution of the amine (25; 0.10 g) in CH_2Cl_2 (7 ml) under ice cooling over a period of 1 min, and the mixture was vigorously stirred for another 2 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 ml $\times$ 2). The extract was washed with brine and diluted with dioxane (10 ml). Dichloromethane was evaporated off and a solution of KOH (0.60 g) in water (3 ml) was added to the remainder. The resulting mixture was refluxed with stirring for 3.5 h. Work-up as usual gave none of the desired product (27).

rel-(2S,3R)-3-Ethyl-2-hydroxy-1-[2-(3- β -indolyl)ethyl]piperidine-3-acetic Acid γ -Lactone (30)—A mixture of the lactone (3; 40 mg), tryptophyl bromide¹³¹ (110 mg), K_2CO_3 (100 mg), and dry dioxane (5 ml) was refluxed with stirring for 6 h according to the procedure of Irie and Ban.⁵¹ The inorganic substances were filtered off and the filtrate was concentrated to leave a residue, which was chromatographed on silica gel in CHCl_3 -EtOH (50: 1). The first fraction afforded 34 mg (46%) of the tertiary amine (30), mp 111—113°C (from iso-PrOH) (lit.⁵¹) mp 112—113°C). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3470 (NH), 1745 (CO). $^1\text{H-NMR}$ δ : 0.80 (3H, t, $J=7.5$ Hz, C_3 - CH_2CH_3), 2.17 (1H, d, $J=17$ Hz, CH_2CO), 2.35 (1H, d, $J=17$ Hz, CH_2CO), 5.07 (1H, s, C_2 -H), 6.88—7.40 (4H, m, Ar-H), 7.44—7.64 (1H, m, Ar-H), 8.37 (1H, br s, NH). MS m/e (%): 312 (13, M^+), 182 (100). High resolution MS. Calcd for $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2$: 312.1836. Found: 312.1851. The second fraction yielded 9 mg of the starting material. The yield of 30 based on the consumed starting material was 59%.

($\pm$)-Eburnamonine (1) and ($\pm$)-Epieburnamonine (31)—A solution of 30 (24 mg) in glac. AcOH (1.5 ml) was refluxed for 30 h according to the known procedure⁵¹ and the solvent was evaporated off. The residue was made basic with sat. NaHCO_3 and extracted with CHCl_3 (7 ml $\times$ 4). The extract was dried and concentrated to leave a residue, which was chromatographed on silica gel in CHCl_3 -EtOH (50: 1). The first fraction afforded 6.5 mg (29%) of ($\pm$)-epieburnamonine (31), mp 135—138°C (from iso-Pr₂O) (lit.⁵¹) mp 138—139°C). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1700, 1655 (CO). $^1\text{H-NMR}$ δ : 0.68—0.90 (3H, m, C_{16} - CH_2CH_3), 1.08—1.36 (2H, m, C_{16} - CH_2CH_3), 7.12—7.44 (3H, m, Ar-H), 8.20—8.36 (1H, m, Ar-H). MS m/e (%): 294 (83, M^+), 293 (100). High resolution MS. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$: 294.1730. Found: 294.1700. The second fraction afforded 6.4 mg (28%) of ($\pm$)-eburnamonine (1), mp 202—204°C (from EtOH) (lit.⁵¹) mp 202—205°C). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1695, 1630 (CO). $^1\text{H-NMR}$ δ : 0.93 (3H, t, $J=7$ Hz, C_{16} - CH_2CH_3), 3.97 (1H, s, C_3 -H), 7.16—7.48 (3H, m, Ar-H), 8.24—8.44 (1H, m, Ar-H). MS m/e (%): 294 (100, M^+). High resolution MS. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$: 294.1730. Found: 294.1725. The synthetic ($\pm$)-eburnamonine was found to be identical with natural eburnamonine by means of TLC [silica gel, CHCl_3 -EtOH (50: 1)], IR (CHCl_3), and $^1\text{H-NMR}$ (CDCl_3) comparisons.

Acknowledgement We wish to thank Prof. E. Wenkert, University of California, San Diego, for a generous supply of natural eburnamonine.

References and Notes

- 1) Part IV: T. Imanishi, H. Shin, N. Yagi, A. Nakai, and M. Hanaoka, *Chem. Pharm. Bull.*, **31**, 1183 (1983).
- 2) A part of this work was published in a preliminary communication: T. Imanishi, K. Miyashita, A. Nakai, M. Inoue, and M. Hanaoka, *Chem. Pharm. Bull.*, **30**, 1521 (1982).
- 3) M.F. Bartlett, W.I. Taylor, and Raymond-Hamet, *C.R. Acad. Sci., Ser. C*, **249**, 1259 (1959) [*Chem. Abstr.*, **54**, 16473e (1960)].
- 4) E.A. Trutneva and V.V. Berezhinskaya, *Farmakol. Toksikol.*, **29**, 171 (1966) [*Chem. Astr.*, **65**, 6123a (1966)].
- 5) a) M.F. Bartlett and W.I. Taylor, *J. Am. Chem. Soc.*, **82**, 5941 (1960); b) E. Wenkert and B. Wichberg, *ibid.*, **87**, 1580 (1965); c) D. Cartier, J. Levy, and J. Le Men, *Bull. Soc. Chim. Fr.*, **1976**, 1961; d) G. Costerousse, J. Buendia, E. Torromanoff, and J. Martel, *ibid.*, **1978**, 11-355; e) F. Klatte, U. Rosentretter, and E. Winterfeldt, *Angew. Chem. Int. Ed. Engl.*, **16**, 878 (1978); f) E. Wenkert, T. Hudlicky, and H.D.H. Showalter, *J. Am. Chem. Soc.*, **100**, 4893 (1978); g) J.L. Herrmann, R.J. Cregge, J.E. Richman, G.R. Kieczkowski, S.N. Normandin, M.L. Quesada, C.L. Semmelhack, A.J. Poss, and R.H. Schlessinger, *ibid.*, **101**, 1540 (1979); h) E. Bolsing, F. Klatte, U. Rosentretter, and E. Winterfeldt, *Chem. Ber.*, **112**, 1902 (1979); i) K. Irie and Y. Ban, *Heterocycles*, **15**, 201 (1981); j) E. Wenkert, T.D.J. Halls, L.D. Kwart, G. Magnusson, and H.D.H. Showalter, *Tetrahedron*, **37**, 4017 (1981).
- 6) T. Imanishi, I. Imanishi, and T. Momose, *Synth. Commun.*, **8**, 99 (1978); T. Imanishi, H. Shin, M. Hanaoka, T. Momose, and I. Imanishi, *Chem. Pharm. Bull.*, **30**, 3617 (1982).
- 7) A. Bowers, T.G. Halsall, E.R.H. Jones, and A.J. Lemin, *J. Chem. Soc.*, **1953**, 2548.
- 8) W.G. Dauben and T.J. Dietche, *J. Org. Chem.*, **37**, 1212 (1972).
- 9) M. Shamma and H.R. Rodriguez, *Tetrahedron*, **24**, 6583 (1968).
- 10) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, John Wiley and Sons, Inc., New York, 1967, pp. 1084—1087.
- 11) Cf. S.W. Pelletier, W.H. De Camp, and N.V. Mody, *J. Am. Chem. Soc.*, **100**, 7976 (1978).
- 12) T. Imanishi, N. Yagi, H. Shin, and M. Hanaoka, *Chem. Pharm. Bull.*, **30**, 4052 (1982).
- 13) J.L. Neumeyer, U.V. Moyer, and J.E. Leonard, *J. Med. Chem.*, **12**, 450 (1969).