

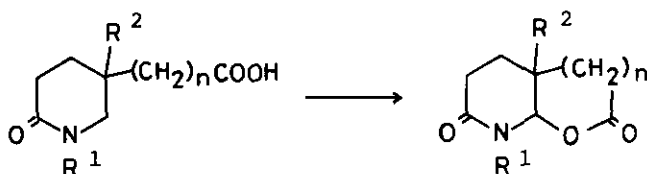
TOTAL SYNTHESIS OF (±)-EBURNAMONINE AND (±)-EPIEBURNAMONINE

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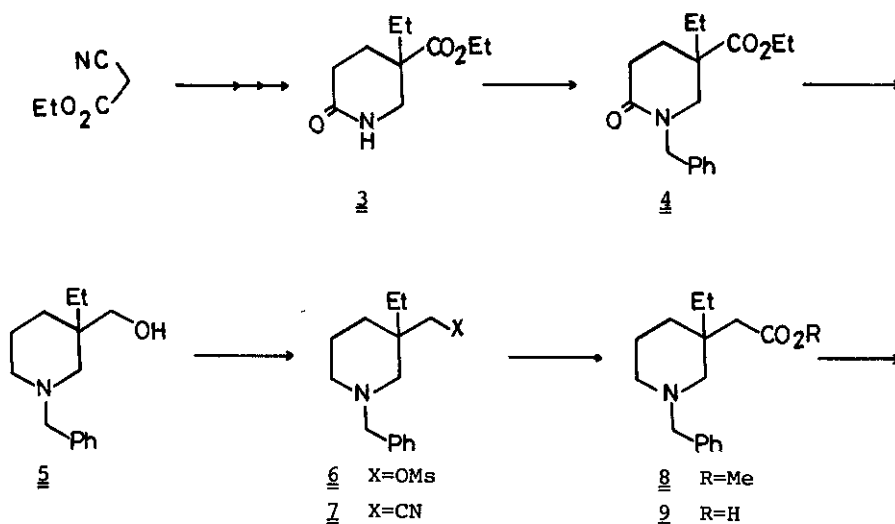
Abstract---Anodic oxidation of N-carbomethoxy-3-ethylpiperidine-3-acetic acid(11) provided the corresponding lactone(12) in good yield, from which were synthesized (±)-eburnamonine and (±)-epieburnamonine by the modified procedure.

In the previous paper, we reported that the anodic oxidation of 2-piperidinone-carboxylic acids(1a-1e) provided the corresponding lactam-lactones(2a-2e), respectively. The formation of lactones took place stereoselectively at ring junction, and was applied to a formal synthesis of an indole alkaloid, (±)-eburnamonine(16).¹ This route, however, involved the tedious processes for conversion of lactam-lactone(2e) to amino-lactone(13), a key intermediate in Wenkert's synthesis of the above alkaloid,² in an unsatisfactory yield. We now wish to report a modified total synthesis of (±)-eburnamonine(16) and (±)-epieburnamonine(15) through the other lactone(12) obtained by anodic oxidation of N-carbomethoxypiperidine-carboxylic acid derivative(11).

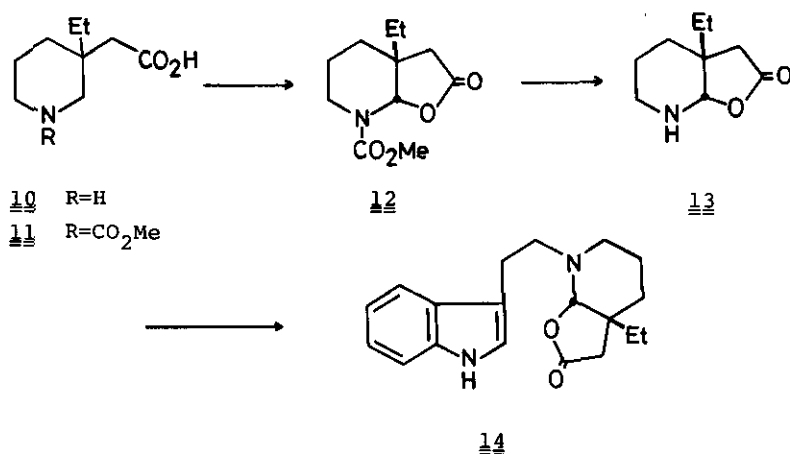


- 1 a. R¹=H, n=2, R²=Et
 b. R¹=H, n=2, R²=CH₂OAc
 c. R¹=H, n=2, R²=COOMe
 d. R¹=Et, n=1, R²=Et
 e. R¹=H, n=1, R²=Et

- 2 a. R¹=H, n=2, R²=Et
 b. R¹=H, n=2, R²=CH₂OAc
 c. R¹=H, n=2, R²=COOMe
 d. R¹=Et, n=1, R²=Et
 e. R¹=H, n=1, R²=Et

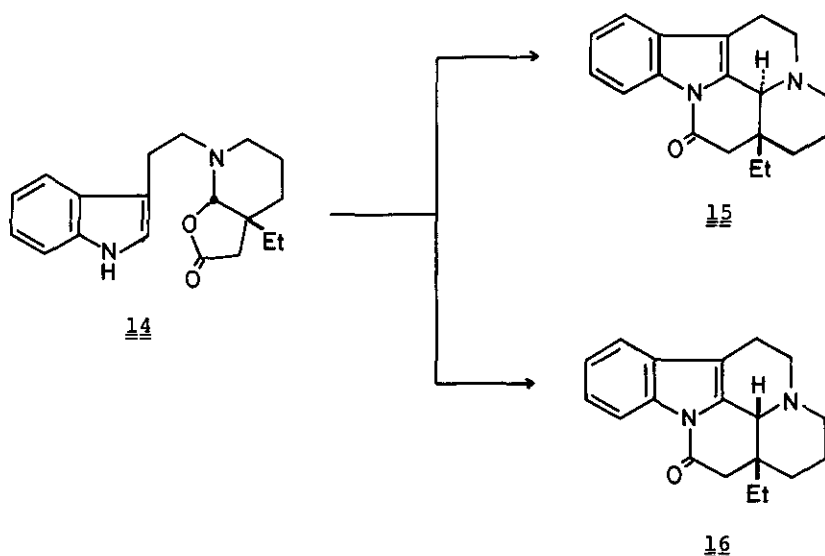


5-Ethyl-5-carboethoxy-2-piperidinone(3) prepared from ethyl cyanoacetate through three steps, was converted to N-benzyl derivative(4) (anhydrous DMF, NaH, benzyl bromide, room temperature) [bp_{0.2} 183-188°C; IR(film): ν 1720, 1640cm⁻¹; NMR(CDCl₃): δ 0.77(3H, t, J=7.3Hz), 1.17(3H, t, J=7.1Hz), 1.58(2H, q, J=7.3Hz), 1.66-1.88(1H, m), 2.08-2.63(3H, m), 3.03(1H, d, J=12Hz), 3.62(1H, dd, J=12 and 2Hz), 3.88-4.25(2H, m), 4.44, 4.74(2H, dd, J_{AB}=14.6Hz), 7.28(5H, s); MS: m/e 289(M⁺), 216, 142, 132, 113, 91(100%), 64] in 81.5% yield, which was reduced with LiAlH₄ in anhydrous ether at room temperature to give 1-benzyl-3-ethyl-3-hydroxymethylpiperidine(5) [bp_{4.0} 137-139°C; IR(film): ν 3380cm⁻¹; NMR(CDCl₃): δ 0.77(3H, t, J=7Hz), 1.00-2.20(8H, m), 2.56-2.90(2H, m), 3.44(2H, s), 3.64(2H, s), 7.29(5H, s); MS:m/e 233(M⁺), 232, 204, 185, 146, 142, 134, 120, 91(100%)] in 98% yield. The alcohol(5) in anhydrous ether containing triethylamine was treated with methanesulfonyl chloride, at 5-10°C to yield the mesylate(6), which without purification, was reacted with sodium cyanide in refluxing aq. ethanol for 3h to furnish 1-benzyl-3-ethyl-3-cyanomethylpiperidine(7) [bp_{1.0} 160°C; IR(film): ν 2240cm⁻¹; NMR(CDCl₃): δ 0.83(3H, t, J=7.4Hz), 1.10-1.76(6H, m), 1.80-2.20(2H, m), 2.24-2.86(4H, m), 3.44(2H, s), 7.28(5H, s); MS: m/e 242(M⁺), 216, 213, 202, 165, 151, 146, 134, 91(100%)] in 83% yield. Hydrolysis of the nitrile(7) in methanol with conc. sulfuric acid (refluxing for 48h) gave methyl 1-benzyl-3-ethylpiperidine-3-acetate(8) [bp_{6.0} 156-160°C; IR(film): ν 1735cm⁻¹; NMR(CDCl₃): δ 0.78(3H, t, J=7Hz), 1.00-1.70(4H, m), 1.75-



2.35 (4H, m), 2.37–2.60 (2H, m), 3.40 (2H, s), 3.55 (3H, s), 7.24 (5H, s); MS: m/e 275 (M^+), 260, 247, 245, 202, 184, 146, 134, 91 (100%)] in 57% yield. The ester (**8**) was saponified with sodium hydroxide in aq. ethanol to afford the crude amino acid (**9**) in 97% yield. Debenzylation of the amino acid (**9**) was carried out in ethanol with 10% Pd/C at H₂ atmosphere using Parr apparatus (60 psi, overnight) to give the amino acid (**10**) [MS: m/e 171 (M^+), 143, 124, 112, 111, 96, 82, 70, 68, 67, 57, 56, 55, 45, 44, 43, 41, 39] as a viscous oil in quantitative yield. 3-Ethylpiperidine-3-acetic acid (**10**) thus obtained was dissolved in 10% NaOH solution, which was cooled to 0–5°C and treated with methyl chloroformate to provide N-carbomethoxy-3-ethylpiperidine-3-acetic acid (**11**) [MS: m/e 229 (M^+), 170, 169 (100%), 154, 140, 110, 103, 102, 88, 67, 59, 58, 42, 41] in 75% yield. The anodic oxidation of N-carbomethoxy-3-ethylpiperidine-3-acetic acid (**11**) was carried out as follows.

In the reaction vessel (undivided cell) equipped with Pt electrodes (2cm x 1cm), added the acid (**11**) (344mg, 1.5mmol), tetraethylammonium perchlorate (115mg, 0.5 mmol), acetonitrile (5ml), and stirred homogeneously with a magnetic stirrer. The solution was electrolyzed with constant current (30mA) at room temperature till the acid (**11**) was consumed. The reaction was completed after 2.7F/mol of charge was passed through the solution. The solvent was removed in vacuo to leave the residue



which was purified on silica gel column chromatography to give the lactone(12) (285mg, mp66-67.5°C, recrystallized from isopropyl ether) [IR(CHCl₃): ν 1770, 1710 cm⁻¹; NMR(CDCl₃): δ 0.93(3H, t, J=7.5Hz), 1.30-1.90(6H, m), 2.32, 2.51(2H, dd, J_{AB}=16.9Hz), 2.80-3.20(1H, m), 3.77(3H, s), 3.80-4.20(1H, m), 6.03(1H, bs); MS: m/e 227(M⁺), 199, 183, 154, 110, 97, 96(100%), 81, 67, 59, 55, 41] in 84% yield. Hydrolysis of the lactone(12) (930mg, 4.09mmol) was effected on refluxing in aq. KOH-dioxane(dioxane 60ml, KOH 2g, H₂O 20ml, 100°C, 1.5h) containing a catalytic amount of 18-crown-6 to give 3-ethyl-2-hydroxypiperidine-3-acetic acid lactone(13) (620mg, mp74-76°C, recrystallized from isopropyl ether-n-hexane) [IR(CHCl₃): ν 3380, 1745cm⁻¹; NMR(CDCl₃): δ 0.91(3H, t, J=7.4Hz), 1.10-2.00(6H, m), 2.25, 2.38(2H, dd, J_{AB}=16.6Hz), 2.60-3.16(3H, m), 5.11(1H, s); MS: m/e 169(M⁺), 126, 125, 110, 109, 97, 96(100%), 81, 71, 67, 59, 55, 41] in 89.5% yield. The spectral data and tlc of this lactone(13) were completely identical with those of the lactone which was previously prepared by the other method.¹ The amino-lactone (13) (20mg) was condensed with tryptophyl bromide(26mg) and K₂CO₃(21mg) in anhydrous dioxane(2ml) at reflux under N₂ atmosphere for 6h. After the reaction was completed, the solution was filtered and the solvent was removed off. The residue was purified on preparative tlc(SiO₂, CHCl₃:EtOH=20:1) to furnish the tryptophyl-

amino-lactone(14) (22.8mg, mp112-113°C, recrystallized from iso-PrOH) [IR (CHCl₃): ν 3480, 1740cm⁻¹; NMR(CDCl₃): δ 0.83(3H, t, J=7.5Hz), 1.28-1.90(6H, m), 2.20, 2.39(2H, dd, J_{AB}=16.7Hz), 2.68-2.92(2H, m), 2.92-3.30(4H, m), 5.09(1H, s), 6.92-7.50(4H, m), 7.50-7.70(1H, m), 7.96(1H, bs); MS: m/e 312(M⁺), 268, 240, 239, 183, 182(100%), 144, 143, 138, 130, 96; UV(MeOH): $\lambda_{\max}$ 221, 281, 290nm; Anal. Calcd. for C₁₉H₂₄N₂O₂: C, 73.05 H, 7.74 N, 8.97 Found: C, 72.77 H, 7.85 N, 8.71] in 62% yield. The final step for the synthesis of (±)-eburnamonine was effected by treatment of tryptophylamino-lactone(14) with acetic acid although the lactone (14) was submitted to thermolysis by Wenkert, who obtained (±)-eburnamonine in 60% yield.² In the present procedure, tryptophylamino-lactone(14) (80mg, 0.256mmol) was dissolved in acetic acid(2ml) and the solution was refluxed for 21h. After the usual work up, the preparative tlc(SiO₂, CHCl₃:EtOH=20:1) of the residue gave two products of isomers, (±)-epieburnamonine(15) (34.4mg, upper part on tlc) [mp 138-139°C, recrystallized from isopropyl ether; IR(CHCl₃): ν 2800, 2750, 1700, 1660cm⁻¹; NMR(CDCl₃): δ 0.70-0.90(3H, m), 1.00-2.12(6H, m), 2.12-3.26(9H, m), 7.20-7.50(3H, m), 8.24-8.40(1H, m); MS: m/e 295, 294(M⁺), 293(100%), 265, 263, 237, 180, 167, 115, 41; UV(MeOH): $\lambda_{\max}$ 242, 264, 294, 301nm; Anal. Calcd. for C₁₉H₂₂N₂O: C, 77.52 H, 7.53 N, 9.52 Found: C, 77.52 H, 7.53 N, 9.43] and (±)-eburnamonine (16) (30.6mg, under part on tlc) [mp202-205°C, recrystallized from ethanol; IR(CHCl₃): ν 1700, 1630cm⁻¹; NMR(CDCl₃): δ 0.93(3H, t, J=7.3Hz), 1.10-3.12(12H, m), 3.16-3.44(2H, m), 3.99(1H, s), 7.30-7.50(3H, m), 8.28-8.46(1H, m); MS: m/e 295, 294(M⁺) (100%), 293, 266, 238, 180, 115, 41; UV(MeOH): $\lambda_{\max}$ 242, 267, 295, 302nm; Anal. Calcd. for C₁₉H₂₂N₂O: C, 77.52 H, 7.53 N, 9.52 Found: C, 77.72 H, 7.61 N, 9.27] in 45.6 and 40.6% yields, respectively. Thus the total synthesis of (±)-eburnamonine³ was achieved by utilization of the modified method. Further investigations in line with this principle are in progress.

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