

0040-4020(95)00614-1

A Novel Ring Cleavage and Recyclization of *N*-Cyanomethyl-1,2,3,4-tetrahydroisoquinolinium Methiodides: A Biomimetic Synthesis of Litebamine

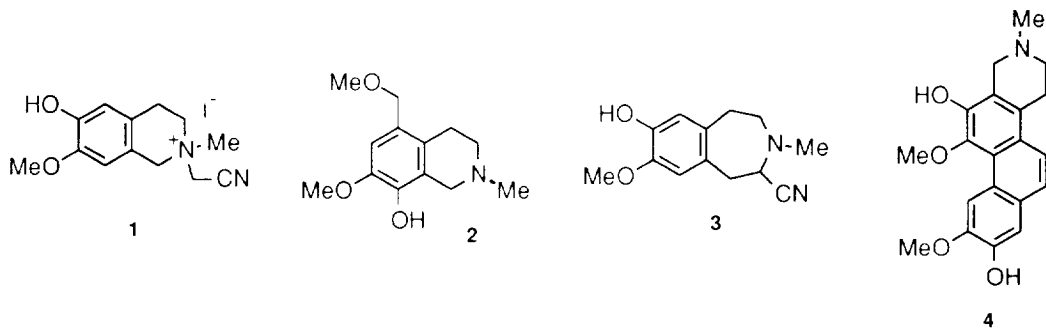
Hiroshi Hara,* Ken-ichi Kaneko, Masaki Endoh,

Hideharu Uchida, and Osamu Hoshino*

*Faculty of Pharmaceutical Sciences, Science University of Tokyo,
 12 Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan*

Summary Treatment of *N*-cyanomethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolinium methiodide (**1**) with NaOMe in MeOH caused C1-N fission and simultaneous recyclization to give 8-hydroxy-5-methoxymethyl-1,2,3,4-tetrahydroisoquinoline (**2**). By using of the rearrangement synthesis of litebamine (**4**) was carried out.

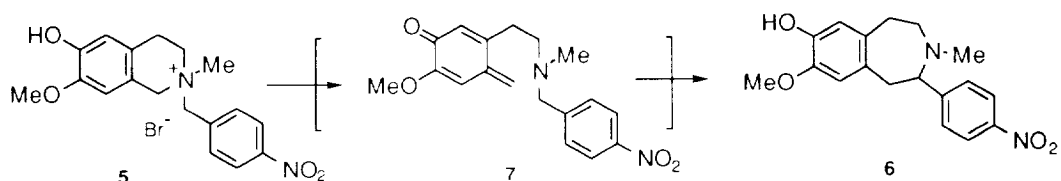
Numerous C1-N fission reactions of 1,2,3,4-tetrahydroisoquinoline skeletons have been developed for structural determination of the related alkaloids¹ or exploration of pharmacologically active compounds.² Recently,³ we found a novel rearrangement of *N*-cyanomethyl-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinolinium methiodides (**1**) into 8-hydroxy-7-methoxy-5-methoxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (**2**) under refluxing with sodium methoxide (NaOMe) in MeOH, during effort to invent a new ring expansion reaction of **1** to 3-benzazepine (**3**). We wish to report here full details of the novel reaction including a biomimetic synthesis of litebamine (**4**) and new reductive cleavage and recyclization on 1,2,3,4-tetrahydroisoquinoline rings.



Results and Discussion

A Novel Rearrangement of Phenolic Quaternary Ammonium Salts of Tetrahydroisoquinolines

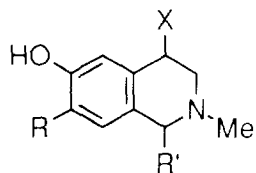
Shamma *et al.*⁴ have reported a unique ring expansion reaction from a tetrahydroisoquinolinium methobromide (5) into the corresponding 2-aryl-3-benzazepine (6) under basic conditions. A key intermediate (7) is generated with C1-N bond fission promoted by electron-donation of phenolate anion, in which *p*-nitrobenzyl substituent is indispensable to form carbanion at an adequate site for recyclization to seven membered ring (Scheme 1). Therefore, the ring expansion is useful for preparation of 2-aryl-3-benzazepines.



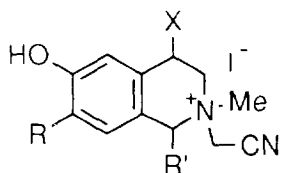
Scheme 1

In order to invent more general method for the ring expansion, we employed cyanomethyl group instead of the benzyl substituent. Cyano group has ability to generate the carbanion at the α position and can be readily removed⁵ after ring expansion. The tetrahydroisoquinolinium methiodide (**1**) was easily prepared by the reaction of isocorypalline (**8**) and iodoacetonitrile (ICH₂CN) in acetonitrile at room temperature. Attempts to create the new rearrangement under various basic conditions (*t*-BuOK, NaH, LDA, DBU, Dabco, etc) missed our aim. However, when **1** was refluxed with NaOMe in MeOH for 2 h, the reaction proceeded to unexpected direction to furnish the 8-hydroxytetrahydroisoquinoline (**2**), quantitatively, hydroxyl and methoxyl groups in which were substituted in the pattern different from those in the starting isoquinoline (**8**). ¹H-NMR spectrum of the product showed *N*-methyl protons (δ 2.48), two singlets of methoxyl protons (δ 3.36 and 3.85), two singlets of methylene protons (δ 3.57 and 4.34), and one aromatic proton (δ 6.74, singlet), suggesting the structure of **2**. To determine unambiguously the substitution pattern on **2**, an authentic sample was prepared from 8-hydroxy-7-methoxy-2-methyltetrahydroisoquinoline (**9**). Refluxing of **9** with 35% formalin and 50% aqueous KOH⁶ in MeOH gave the 5-methoxymethyl derivative, ¹H-NMR and IR spectra of which were coincident with those of the rearranged product (**2**).

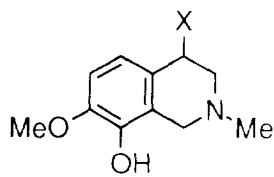
Scheme 2 depicts a plausible mechanism to generate **2**. Electron-donation from phenolate (**1'**) cleaves C1-N bond to form *p*-quinone methide (**10**), on which conjugated addition by methoxide anion generates the methoxy-methylphenolate anion (**11'**). Finally, recyclization with release of cyanide takes place to give the 8-hydroxy-5-methoxymethyl congener (**2**). This assumption was confirmed by isolation of an intermediary (**11**). Namely,



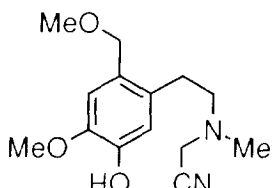
- 8 : R = OMe, R' = X = H
 51 : R = OMe, R' = Me, X = H
 52 : R = OMe, R' = CH₂Ph, X = H
 53 : R = OMe, R' = veratryl, X = H
 54 : R = OMe, R' = H, X = Ph
 55 : R = R' = X = H



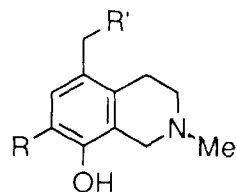
- 13 : R = R' = X = H
 20 : R = OMe, R' = Me, X = H
 21 : R = OMe, R' = H, X = Ph
 23 : R = OMe, R' = CH₂Ph, X = H
 24 : R = OMe, R' = veratryl, X = H



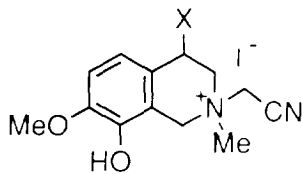
- 9 : X = H
 26 : X = Ph



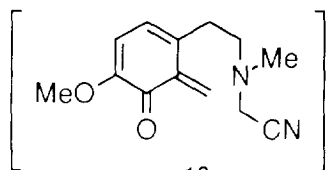
11



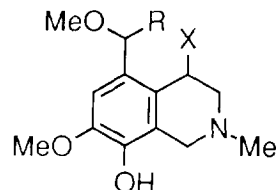
- 12 : R = OMe, R' = OEt
 14 : R = H, R' = OMe
 44 : R = R' = H



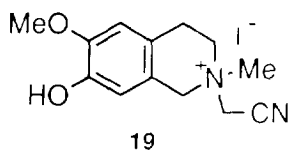
- 15 : X = H
 22 : X = Ph



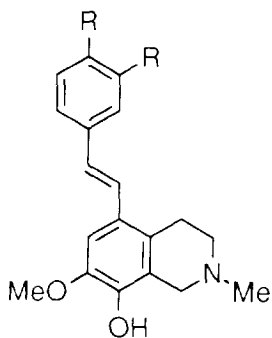
16



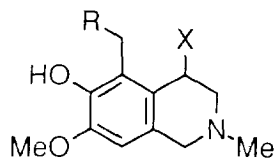
- 18 : R = H, X = Ph
 25 : R = Me, X = H



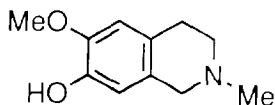
19



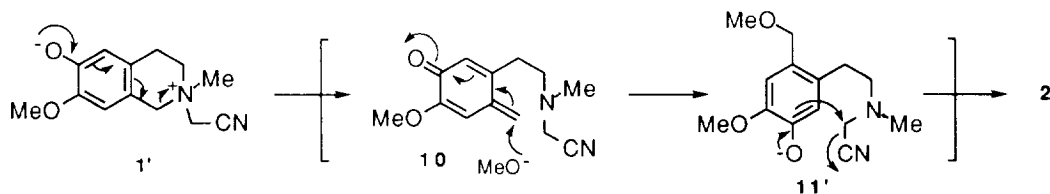
- 28 : R = H
 29 : R = OMe



- 17 : R = OMe, X = H
 27 : R = OMe, X = Ph
 45 : R = X = H
 48 : R = H, X = Ph



56



Scheme 2

treatment of **1** with NaOMe (10 eq.) at room temperature for 2.5 h afforded **11** (62%) together with **2** (12%). Structure of the fragmented compound (**11**) was determined by $^1\text{H-NMR}$ [δ 2.41 (NMe), 3.38 (Aliph. OMe), 3.56 (CH_2CN), 3.85 (Ar. OMe), 4.36 (ArCH_2O), 6.74, 6.80 (each ArH)], mass spectrum [m/z 264 (M^+)] and elemental analysis. Then, **11** was heated with NaOMe (3 eq.) in MeOH to give the final product (**2**) in the yield of 87%.

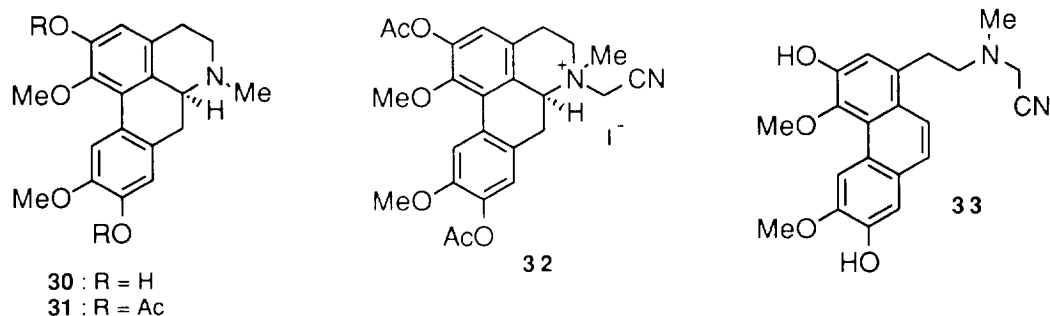
Next we examined scope and limitation of this novel rearrangement. Analogously, the reaction of **1** with NaOEt in EtOH furnished the 5-ethoxymethyl-8-hydroxytetrahydroisoquinoline (**12**) in 91% yield. Substrate (**13**) bearing no methoxyl group on the 7 position was also rearranged to yield the 8-hydroxy-5-methoxymethyl derivative (**14**) in 59% yield. Structures of both products (**12** and **14**) were spectroscopically decided. On the other hand, 8-hydroxy-7-methoxy-2-methyltetrahydroisoquinolinium salt (**15**) seems to be a precursor of the *o*-quinone methide (**16**). Actually, treatment of **15**, derived from **9**, with NaOMe gave 6-hydroxy-7-methoxy-5-methoxymethyltetrahydroisoquinoline (**17**) in the yield of 49%. The substitution pattern of the product was confirmed by identification with an authentic sample prepared from isocorypalline (**8**) in a manner similar to that noted for **2**.

However, the reaction of corypallinium cyanomethiodide (**19**), a regio isomer of **1**, under the same basic conditions did not occur. Thus, existence of the hydroxyl group on the 6- or 8-position is indispensable to the rearrangement.

Then, this novel rearrangement was applied to variously substituted 6- or 8-hydroxytetrahydroisoquinolinium salts (**20** - **24**). The reaction of the former three congeners (**20** - **22**) with NaOMe in MeOH gave the corresponding products (**25**, **18**, and **27**) in good yields. In the case of the latter two (**23** and **24**), elimination of MeOH occurred simultaneously with the rearrangement to furnish *trans*- β -arylvinyltetrahydroisoquinolines (**28** and **29**) in 67 and 52% yields, respectively. $^1\text{H-NMR}$ spectra of **28** and **29** showed a peak as each one doublet (δ 6.85, $J = 16.2$ Hz and 6.73, $J = 16$ Hz) assigning protons of *trans* olefin, respectively.

A Biomimetic Synthesis of Litebamine

Construction of the stilbene moiety in the novel rearrangement took our attention to synthesis of litebamine (**4**), which has been isolated from *Litsea Cubeba* Persoon (Lauraceae)⁷ and firstly synthesized from boldine (**30**)⁸ by Wu and Lee's group. The alkaloid (**4**) could be biogenetically formed from (*S*)-boldine (**30**) because of coexisting (*S*)-**30** in the same plant.⁷

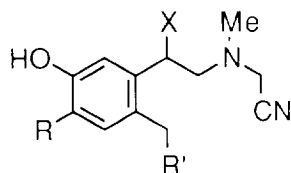


To prepare the cyanomethiodide of (*S*)-boldine (**30**) as a starting material, direct quaternarization of **30** with ICH₂CN occurred by no means. It might be owing to lower basicity of the diphenolic amine. Actually, quaternarization was successfully carried out after protection of the hydroxyl groups. Thus, the reaction of (*S*)-*O,O*-diacetylboldine (**31**) with ICH₂CN in CH₂Cl₂ afforded the cyanomethiodide (**32**) in 41% yield, which was refluxed with NaOMe in MeOH to give litebamine (**4**) in the yield of 69%. Physical data of the product were completely consistent with those reported in the literature.^{7,8} Acid treatment (c.HCl, MeOH, reflux) also severed the piperidine ring of **31** to form a methine base (**33**), which should be an intermediate closing to litebamine (**4**). The highly strained tetracyclic system might cause the ring cleavage,⁹ because no reaction occurred with the bicyclic one (**1**) under the same conditions. Heating of the methine base (**33**) with NaOMe in MeOH furnished the recycled product (**4**) in 83% yield. Thus, a biomimetic synthesis of litebamine (**4**) starting from (*S*)-boldine (**30**) was accomplished.

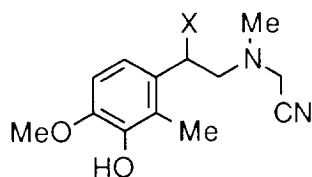
Reductive Cleavage of The Quaternary Ammonium Salts of Tetrahydroisoquinolines and Recyclization to Tetrahydroisoquinolines

As mentioned above, the *p*-quinone methide (**10**), generated from **1**, was attacked by methoxide anion to form a key intermediate (**11**) (Scheme 2). This findings suggest that reductive cleavage² seemed to occur when hydride reagent was employed. Use of NaBH₄ as hydride donor, in fact, realized the speculated cleavage. A mixture of **1** and NaBH₄ in *iso*-PrOH was stirred at room temperature to give the expected cyanomethylamine (**34**) in the yield of 91%. ¹H-NMR spectrum of the product showed a singlet (δ 2.24) assigned to aromatic methyl protons, and mass spectrum (MS) [m/z 234 (M^+)] and elemental analysis also supported the structure of **34**.

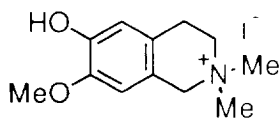
Similarly, cyanomethiodide (**13** or **15**) of 6- or 8-hydroxytetrahydroisoquinoline was reduced to give the corresponding amine (**35** or **36**). However, no reaction was observed with 7-hydroxy congener (**19**) or



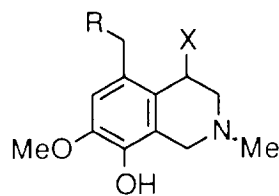
- 34** : R = OMe, R' = X = H
35 : R = R' = X = H
38 : R = OMe, R' = Me, X = H
39 : R = OMe, R' = H, X = Ph
41 : R = OMe, R' = CH₂Ph, X = H
42 : R = OMe, R' = veratryl, X = H



- 36** : X = H
40 : X = Ph



37



- 43** : R = X = H
46 : R = Me, X = H
47 : R = H, X = Ph
49 : R = CH₂Ph, X = H
50 : R = veratryl, X = H

isocorypallinium methiodide (**37**) even under reflux conditions. Therefore, existence of both substituents (6- or 8-hydroxyl and *N*-cyanomethyl groups) are requisite in the present reaction. To examine the generality on the reaction, a various types of cyanomethiodides (**20** - **24**) were treated with NaBH₄ in *iso*-PrOH. All of substrates were reduced accompanying by ring-opening to give the cyanomethylamines (**38** - **42**) in 55-96% yields, respectively. These structures were supported by their physical data (¹H-NMR, MS, elemental analyses), respectively. It is noticed that the present reaction should be available to determination of the position of hydroxyl group in isoquinoline alkaloids.

N-Cyanomethylamines thus obtained might be recycled to afford the corresponding hydroxytetrahydroisoquinolines, because cyano group serves as a pseudo halogen. Thus, recycling reaction of the cleaved amines was performed. The cyanomethylamine (**34**) was treated under the basic conditions (NaOMe, MeOH, reflux) to afford 8-hydroxy-7-methoxy-5-methyltetrahydroisoquinoline (**43**) in 86% yield, structure of which was chemically decided. That is, demethoxylation of **2** by reduction (NaBH₄, NaOMe, MeOH, reflux) gave 5-methyl derivative (**43**), which was identical with the recycled product. Similarly, other cyanomethylamines (**35**, **36**, **38-42**) were subjected to the recycling to furnish successfully the 5-alkyltetrahydroisoquinolinols (**44-50**), respectively. Furthermore, the reactions (reductive cleavage and recycling) of **1** proceeded in one pot to afford the final product (**43**) in 88% yield. Similarly, one pot conversion of the quaternary ammonium salts (**13**, **20**, **23**, and **24**) into the corresponding tetrahydroisoquinolines (**44**, **46**, **49**, and **50**) was accomplished in 68-89% yields.

Conclusion

Proper arrangement of electron push and pull functions on quaternary ammonium salt of tetrahydroisoquinoline caused a novel C-N fragmentation and subsequent recyclization under basic conditions. These contributions are concerned with practical synthesis of a various types of tetrahydroisoquinolines having carbon substituent on the 5 position and with recognition of the oxygenated pattern in isoquinoline alkaloids.

Acknowledgement

The authors are indebted to Ms. N. Sawabe, Mrs. F. Hasegawa, and Mr. H. Igarashi of this Faculty for ^1H -NMR and mass spectral measurement and elemental analyses.

Experimental

Melting points were determined on Büchi 510 apparatus and are uncorrected. ^1H -NMR spectra were recorded on JEOL model FX-100 and FX-270 spectrometers in CDCl_3 solution, unless otherwise noted and chemical shifts are expressed in ppm (δ) relative to tetramethylsilane as internal standard. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). IR spectra were taken with Hitachi model 260-10 spectrometer in CHCl_3 solution, unless otherwise noted. Mass spectra were recorded on JEOL model D-300 and Hitachi model M-80 spectrometers. Preparative TLC was performed on 20 x 20 cm plates coated with 0.5 mm thickness of Merck Kieselgel 60F254 (Art 5744).

General Procedure for Quaternarization of Tetrahydroisoquinolines with Cyanoacetonitrile

Phenolic tetrahydroisoquinolines (**8**,¹¹ **9**,¹² **26**,¹³ **51**,¹⁴ **52**,¹⁴ **53**,¹⁵ **54**,¹³ **55**,¹⁶ and **56**¹⁷) were dissolved into CH_3CN at room temperature or by heating, and ICH_2CN (excess) was added. Then, the whole was stirred at room temperature or refluxed until starting amine diminished on TLC. Evaporation of the solvent gave the corresponding products (**1**, **13**, **15**, **19** - **24**) as crystals or oil, which were recrystallized directly or after purification by silica gel column chromatography.

2-Cyanomethyl-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (**1**):

Colorless crystals (81 %). mp 191-192 °C (CH_3CN). IR (KBr) 3370 cm^{-1} (OH). ^1H -NMR (CD_3OD): δ 2.93-3.46 (2H, m, 4-H), 3.37 (3H, s, NCH_3), 3.46-4.04 (2H, m, 3-H), 3.84 (3H, s, OCH_3), 4.45-4.91 (2H, m, 1-H), 4.68 (2H, s, CH_2CN), 6.71, 6.73 (each 1H, s, Ar-H), 7.86 (1H, s, OH). *Anal.* Calcd for $\text{C}_{13}\text{H}_{17}\text{IN}_2\text{O}_2$: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.16; H, 4.75; N, 7.86.

2-Cyanomethyl-6-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (13): Yellow needles (80%), mp 179.5-181.5 °C (CH₃CN). ¹H-NMR (DMSO-D₆) δ 3.14 (2H, t, J = 7 Hz, 4-H), 3.24 (3H, s, NCH₃), 3.82 (2H, t, J = 7Hz, 3-H), 4.63 (2H, s, 1-H), 4.95 (2H, s, CH₂CN), 6.60-6.76 (2H, m, 5- and 7-H), 7.02 (1H, d, J = 8 Hz, 8-H), 7.58 (1H, s, OH). *Anal.* Calcd for C₁₂H₁₅IN₂O: C, 43.65; H, 4.58; N, 8.49. Found: C, 43.77; H, 4.53; N, 8.65.

2-Cyanomethyl-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (15): Yellow needles (98%), mp 178-180 °C (EtOH-hexane). *Anal.* Calcd for C₁₃H₁₇IN₂O₂: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.18; H, 4.72; N, 7.62.

2-Cyanomethyl-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (19): Colorless crystals (65 %), mp 193-194 °C (CH₃CN). *Anal.* Calcd for C₁₃H₁₇IN₂O₂: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.18; H, 4.78; N, 7.70.

2-Cyanomethyl-6-hydroxy-7-methoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (20): Colorless needles (62%), mp 167 °C (EtOH). Low MS: *m/z* 246 (M⁺-1). HRMS: Calcd for C₁₄H₁₈N₂O₂: *m/z* 246.1367 (M⁺-1). Found: 246.1372.

2-Cyanomethyl-6-hydroxy-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolinium Iodide (21): Yellow amorphous mass (86%), mp 118-124 °C. Low MS: *m/z* 308 (M⁺-1). HRMS: Calcd for C₁₉H₂₀N₂O₂: *m/z* 308.1523 (M⁺-1). Found: 308.1513.

2-Cyanomethyl-8-hydroxy-7-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolinium Iodide (22): This compound was subjected to reactions without purification, because of its instability.

1-Benzyl-2-cyanomethyl-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (23): Yellow prisms (93%), mp 111-113 °C (CH₂Cl₂). Low MS: *m/z* 322 (M⁺-1). HRMS: Calcd for C₂₀H₂₂N₂O₂: *m/z* 322.1679 (M⁺-1). Found: 322.1667. Picrate, mp 164-165 °C (MeOH). *Anal.* Calcd for C₂₆H₂₅N₅O₉: C, 56.62; H, 4.57; N, 12.70. Found: C, 56.56; H, 4.42; N, 12.66.

2-Cyanomethyl-6-hydroxy-7-methoxy-2-methyl-1-veratryl-1,2,3,4-tetrahydroisoquinolinium Iodide (24): Yellow prisms (90%), mp 144-145 °C (CH₂Cl₂). Low MS: *m/z* 382 (M⁺-1). HRMS: Calcd for C₂₂H₂₆N₂O₄: *m/z* 382.1891 (M⁺-1). Found: 382.1898.

General Procedure for Formation of 6- (17, 27) or 8-Hydroxy- (2, 14, 18, 25) 5-methoxy-methyl-2-methyl-1,2,3,4-tetrahydroisoquinolines and 8-Hydroxy-7-methoxy-2-methyl-5-β-styryl-1,2,3,4-tetrahydroisoquinolines (28, 29) by the Reaction of 2-Cyanomethyl-6- (1, 13, 20, 21, 23, 24) or 8-hydroxy-1,2,3,4-tetrahydroisoquinolinium Iodides (15, 22) with Sodium Methoxide

A mixture of cyanomethiodide (0.2 mmol) and NaOMe (2 mmol) in MeOH (10 ml) was refluxed for 2 h. The solvent was removed *in vacuo* and saturated aqueous NH₄Cl solution was added to the residue. The product was extracted with CH₂Cl₂ and the organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent under reduced pressure gave a crude product, which was purified by preparative TLC with CHCl₃-MeOH (8 : 1 - 20 : 1).

8-Hydroxy-7-methoxy-5-methoxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (2): From **1**; pale brown oil (97 %). $^1\text{H-NMR}$: δ 2.48 (3H, s, NCH_3), 2.52-2.92 (4H, m, 3- and 4-H), 3.36 (3H, s, CH_2OCH_3), 3.57 (2H, s, 1-H), 3.85 (3H, s, ArOCH_3), 4.34 (2H, s, ArCH_2O), 6.74 (1H, s, 6-H). IR: 3560 cm^{-1} (OH). Low MS: m/z 237 (M^+). HRMS: Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_3$: m/z 237.1364 (M^+). Found: 237.1367.

8-Hydroxy-5-methoxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (14): From **13**; pale brown oil (59 %). $^1\text{H-NMR}$: δ 2.46 (3H, s, NCH_3), 2.60-3.02 (4H, m, 3- and 4-H), 3.28 (3H, s, CH_2OCH_3), 3.54 (2H, s, 1-H), 4.28 (2H, s, ArCH_2O), 6.32, 6.85 (each 1H, d, $J = 8\text{ Hz}$, 6- and 7-H). Low MS: m/z 207 (M^+).

8-Hydroxy-7-methoxy-5-methoxymethyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (18): From **21**; pale brown oil (66 %). $^1\text{H-NMR}$: δ 2.34 (3H, s, NCH_3), 2.76 (2H, d, $J = 4\text{ Hz}$, 3-H), 3.16 (3H, s, CH_2OCH_3), 3.31, 3.97 (each 1H, d, $J = 15\text{ Hz}$, 1-H), 3.74, 4.12 (each 1H, d, $J = 12\text{ Hz}$, ArCH_2O), 3.84 (3H, s, ArOCH_3), 4.23 (1H, t, $J = 4\text{ Hz}$, 4-H), 6.76 (1H, s, 6-H), 6.96-7.20 (5H, m, PhH). IR: 3570 cm^{-1} (OH). Low MS: m/z 313 (M^+). HRMS: Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_3$: m/z 313.1676 (M^+). Found: 313.1674.

8-Hydroxy-7-methoxy-5- α -methoxyethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (25): From **20**; pale brown oil (80 %). $^1\text{H-NMR}$: δ 1.34 (3H, d, $J = 6\text{ Hz}$, OCHCH_3), 2.52 (3H, s, NCH_3), 2.54-2.84 (4H, m, 3- and 4-H), 3.17 (3H, s, CHOCH_3), 3.63 (2H, s, 1-H), 3.85 (3H, s, ArOCH_3), 4.44 (1H, q, $J = 6\text{ Hz}$, OCHCH_3), 6.80 (1H, s, 6-H). Low MS: m/z 251 (M^+). HRMS: Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_3$: m/z 251.1520 (M^+). Found: 251.1514.

6-Hydroxy-7-methoxy-5-methoxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (17): From **15**; pale brown oil (49 %). $^1\text{H-NMR}$: δ 2.48 (3H, s, NCH_3), 2.64-3.00 (4H, m, 3- and 4-H), 3.35 (3H, s, CH_2OCH_3), 3.57 (2H, s, 1-H), 3.81 (3H, s, ArOCH_3), 4.54 (2H, s, ArCH_2O), 6.44 (1H, s, 8-H). Low MS: m/z 237 (M^+). HRMS: Calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_3$: m/z 237.1363 (M^+). Found: 237.1359.

6-Hydroxy-7-methoxy-5-methoxymethyl-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (27): From **22**; pale brown oil (61 %). $^1\text{H-NMR}$: δ 2.29 (3H, s, NCH_3), 2.78 (2H, d, $J = 4\text{ Hz}$, 3-H), 3.12 (3H, s, CH_2OCH_3), 3.32, 3.82 (each 1H, d, $J = 15\text{ Hz}$, 1-H), 3.85 (3H, s, ArOCH_3), 4.10, 4.30 (each 1H, d, $J = 12\text{ Hz}$, ArCH_2O), 4.24 (1H, t, $J = 4\text{ Hz}$, 4-H), 6.54 (1H, s, 8-H), 6.96-7.20 (5H, m, PhH). Low MS: m/z 313 (M^+).

8-Hydroxy-7-methoxy-2-methyl-5-*trans*- β -phenylvinyl-1,2,3,4-tetrahydroisoquinoline (28): From **23**; red amorphous mass (67 %). $^1\text{H-NMR}$: δ 2.50 (3H, s, NCH_3), 2.72, 2.95 (each 2H, t, $J = 5.9\text{ Hz}$, 3- and 4-H), 3.61 (2H, s, 1-H), 3.92 (3H, s, ArOCH_3), 6.85 (1H, d, $J = 16.2\text{ Hz}$, olefinic H). Low MS: m/z 295 (M^+). HRMS: Calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_2$: m/z 295.1570 (M^+). Found: 295.1568.

8-Hydroxy-7-methoxy-2-methyl-5-*trans*- β -(3,4-dimethoxyphenyl)vinyl-1,2,3,4-tetrahydroisoquinoline (29): From **24**; brown oil (52 %). $^1\text{H-NMR}$: δ 2.52 (3H, s, NCH_3), 2.64-3.04 (4H, m, 3- and 4-H), 3.63 (2H, s, 1-H), 3.86, 3.88, 3.91 (each 3H, s, ArOCH_3), 6.73 (1H, d, $J = 16\text{ Hz}$, olefinic H), 6.84 (1H, s, 6-H), 6.88-7.16 (4H, m, olefinic and ArH). Low MS: m/z 355 (M^+). HRMS: Calcd for $\text{C}_{21}\text{H}_{25}\text{NO}_4$: m/z 355.1782 (M^+). Found: 355.1787.

Formation of 5-Ethoxymethyl-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (12) by the Reaction of 2-Cyanomethyl-6-hydroxy-1,2,3,4-tetrahydroisoquinolinium Iodide (1) with Sodium Ethoxide

A NaOEt solution [Na (12 mg, 0.5 mgatom) / EtOH (5 ml)] was added to a solution of cyanomethiodide (**1**) (36 mg, 0.1 mmol) in EtOH (5 ml), and the whole was refluxed for 2.5 h. The solvent was removed *in vacuo* and saturated aqueous NH₄Cl solution was added to the residue. The product was extracted with CH₂Cl₂ and the organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent *in vacuo* gave a brown oil (35 mg), which was purified by preparative TLC with CHCl₃-MeOH (8 : 1) to give a pale brown oil (23 mg, 91 %). ¹H-NMR: δ 1.22 (3H, t, J = 7 Hz, OCH₂CH₃), 2.47 (3H, s, NCH₃), 2.52-2.92 (4H, m, 3- and 4-H), 3.50 (2H, q, J = 7 Hz, OCH₂CH₃), 3.56 (2H, s, 1-H), 3.84 (3H, s, ArOCH₃), 4.38 (2H, s, ArCH₂O), 6.74 (1H, s, 6-H). IR: 3550 cm⁻¹ (OH). Low MS: *m/z* 251 (M⁺). HRMS: Calcd for C₁₄H₂₁NO₃: *m/z* 251.1519 (M⁺). Found: 251.1513.

Reaction of 2-Cyanomethyl-6-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Iodide (1) with Sodium Methoxide at Room Temperature

NaOMe (108 mg, 2 mmol) was added to a solution of cyanomethiodide (**1**) (72 mg, 0.2 mmol) in MeOH (10 ml). The whole was stirred for 2.5 h at 24 °C. The solvent was removed *in vacuo* and saturated aqueous NH₄Cl solution was added to the residue. The product was extracted with CH₂Cl₂ and the organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent *in vacuo* gave a brown oil (54 mg), which was separated by preparative TLC with CHCl₃-MeOH (15 : 1) to afford **11** and **2**.

N-Cyanomethyl-*N*-β-(5-hydroxy-4-methoxy-2-methoxymethyl)ethylmethylamine (**11**): Colorless needles (33 mg, 62 %), mp 78-78.5 °C (AcOEt-hexane). ¹H-NMR: δ 2.41 (3H, s, NCH₃), 2.68 (4H, s, ArCH₂CH₂N), 3.38 (3H, s, CH₂OCH₃), 3.56 (2H, s, NCH₂CN), 3.85 (3H, s, ArOCH₃), 4.36 (2H, s, ArCH₂O), 6.74, 6.80 (each 1H, s, ArH). Low MS: *m/z* 264 (M⁺). HRMS: Calcd for C₁₄H₂₀N₂O₃: *m/z* 264.1472 (M⁺). Found: 264.1468. *Anal.* Calcd for C₁₄H₂₀N₂O₃: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.50; H, 7.68; N, 10.34.

8-Hydroxy-7-methoxy-5-methoxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (2): Pale brown oil (5.6 mg, 12 %), spectral data of which were coincident with those of a sample obtained by heating of **1** with NaOMe in MeOH.

Recyclization of *N*-Cyanomethyl-*N*-β-(5-hydroxy-4-methoxy-2-methoxymethyl)ethylmethylamine (11) to 8-Hydroxy-7-methoxy-5-methoxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline (2)

A solution of **11** (36 mg, 0.14 mmol) and NaOMe (22 mg, 0.4 mmol) in MeOH (5 ml) was refluxed for 3 h.

Usual work-up as above gave **2** (29 mg, 87 %) as a pale brown oil. spectral data of which were coincident with those of a sample obtained from **1**.

Preparation of Authentic Specimens (**2** and **17**)

For 2; a mixture of **9** (194 mg, 1 mmol), 35 % formalin (1.5 ml), 50 % aqueous KOH solution (2 ml) and MeOH (3 ml) was refluxed for 4 h. Usual work-up as above gave **2** (pale brown oil, 29 mg, 12 %), spectral data of which were coincident with those of a sample obtained from **1**.

For 17; a mixture of isocorypalline (**8**) (194 mg, 1 mmol), 35 % formalin (1.5 ml), 50 % aqueous KOH solution (2 ml) and MeOH (3 ml) was refluxed for 4 h. Usual work-up as above gave **17** (pale brown oil, 20 mg, 9 %), spectral data of which were coincident with those of a sample obtained from **15**.

Synthesis of Litebamine (**4**)

(*S*)-*O,O*-Diacetylboldine (**31**)

(+)-Boldine (**30**) hydrochloride¹⁰ (364 mg, 1 mmol) was neutralized with aqueous ammonia solution, and the free base was extracted with CH₂Cl₂. Organic layer was washed with brine and dried over MgSO₄. Evaporation of the solvent *in vacuo* gave colorless plates (331 mg), to CH₂Cl₂ (6 ml) solution of which was added Ac₂O (306 mg, 3 mmol) and pyridine (318 mg, 4 mmol). The whole was stirred overnight at room temperature. After water was added to the mixture, the product was extracted with CH₂Cl₂. Organic layer was washed with brine and dried over K₂CO₃. Evaporation of the solvent gave lemon-yellow amorphous mass (439 mg), which was purified by column chromatography [silica gel (12 g), eluent: CHCl₃] to afford lemon-yellow amorphous mass (**31**) (373 mg, 91 %). ¹H-NMR: δ 2.34, 2.36 (each 3H, s, COCH₃), 2.55 (3H, s, NCH₃), 2.97 - 3.25 (4H, m, 4- and 5-H), 3.59, 3.84 (each 3H, s, OCH₃), 6.81, 6.96 (each 1H, s, 3- and 8-H), 8.06 (1H, s, 11-H). IR (KBr): 1775 cm⁻¹ (ArOCOCH₃). Low MS: *m/z* 411 (M⁺). HRMS: Calcd for C₂₃H₂₅NO₆: *m/z* 411.1680 (M⁺). Found: 411.1686. **Methiodide**: mp 225-225.5 °C (EtOH). *Anal.* Calcd for C₂₄H₂₈INO₆: C, 52.09; H, 5.10; N, 2.53. Found: C, 51.84; H, 4.98; N, 2.47.

(*S*)-*O,O*-Diacetylboldine Cyanomethiodide (**32**)

A solution of **31** (1.63 g, 4 mmol) and ICH₂CN (6.6 g, 40 mmol) in CH₂Cl₂ (8 ml) was stirred at room temperature for 18 h to liberate white crystals, which were collected by filtration. A small amount of ether was added to the filtrate to give white precipitate. Both deposits were combined and recrystallized from MeOH to afford colorless needles (**32**) (945 mg, 41 %), mp 178 °C (dec.). ¹H-NMR (DMSO-*d*₆): δ 2.29, 2.36 (each 3H, s, COCH₃), 3.20 (3H, s, NCH₃), 3.63, 3.80 (each 3H, s, OCH₃), 4.86 (1H, dd, *J* = 11, 3 Hz, 6aH), 5.06, 5.40 (each 1H, d, *J* = 16 Hz, NCH₂CN), 7.09, 7.17 (each 1H, s, 3- and 8-H), 7.90 (1H, s, 11-H). IR (KBr): 1765 cm⁻¹ (ArOCOCH₃). Low MS: *m/z* 451 (M⁺). *Anal.* Calcd for C₂₅H₂₇IN₂O₆: C, 51.92; H, 4.71; N, 4.84. Found: C, 51.73; H, 4.85; N, 4.88.

1-(β -*N*-Cyanomethyl-*N*-methylamino)ethyl-3,7-dihydroxy-4,6-dimethoxyphenanthrene (33)

Concentrated HCl solution (67 mg, 0.6 mmol) was added to a suspension of the cyanomethiodide (32) (118 mg, 0.2 mmol) in MeOH (3 ml) and the whole was refluxed for 1 h. Water (5 ml) and NaHCO₃ (84 mg, 1 mmol) was added to the cooled reaction mixture and the product was extracted with CH₂Cl₂. Organic layer was washed with brine and dried over MgSO₄. Evaporation of the solvent *in vacuo* gave pale orange-yellow amorphous mass (73 mg), which was purified by column chromatography [silica gel (7g), eluent: CHCl₃] to yield pale yellow crystals (33) (72 mg, 96 %), mp 167-168 °C (EtOH). ¹H-NMR (DMSO-*d*₆): δ 2.40 (3H, s, NCH₃), 2.52 - 2.84, 3.00 - 3.28 (each 2H, m, ArCH₂CH₂N), 3.78 (2H, s, NCH₂CN) 3.82, 3.99 (each 3H, s, OCH₃), 7.12, 7.24 (each 1H, s, 2- and 8-H), 7.45, 7.69 (each 1H, d, J = 9 Hz, 9- and 10-H), 9.04 (1H, s, 5-H). IR (KBr): 1620 cm⁻¹. Low MS: *m/z* 366 (M⁺). Anal. Calcd for C₂₁H₂₂N₂O₄: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.76; H, 5.88; N, 7.49.

Litebamine (4):

From 32; a mixture of the cyanomethiodide (32) (57.8 mg, 0.1 mmol), NaOMe (30 mg, 0.55 mmol) and MeOH (10 ml) was refluxed for 6 h. To an ice-cooled reaction mixture was added dry ice (ca. 1g) and then the solvent was evaporated *in vacuo*. The residue was directly subjected to column chromatography [silica gel (20g), eluent; CHCl₃-MeOH (15 : 1)] to give brown crystals (4) (23.5 mg, 69 %), mp 218-219 °C (MeOH) (lit.⁶ mp 218-220 °C). ¹H-NMR (DMSO-*d*₆): δ 2.43 (3H, s, NCH₃), 2.67, 3.09 (each 2H, bt, J = 5.7 Hz, 11- and 12-H), 3.53 (2H, s, 14-H) 3.72, 3.94 (each 3H, s, OCH₃), 7.16 (1H, s, 8-H), 7.40, 7.59 (each 1H, d, J = 9 Hz, 9- and 10-H), 8.90 (1H, s, 5-H). IR (KBr): 1600 cm⁻¹. Low MS: *m/z* 341 (M⁺+2, 2), 340 (M⁺+1, 16), 339 (M⁺, 70), 338 (26), 296 (100), 281 (40), 253 (16). Anal. Calcd for C₂₀H₂₁NO₄: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.59; H, 6.31; N, 3.99.

From 33; a mixture of the methine base (33) (74.1 mg, 0.2 mmol), NaOMe (337 mg, 6 mmol) and MeOH (10 ml) was refluxed for 6 h. Treatment similar to that noted for 32 gave brown crystals (4) (57 mg, 83 %), mp 218-219 °C (MeOH), spectral data of which were coincident with those of litebamine (4) obtained from 32.

General Procedure for Formation of *N*-Cyanomethyl-*N*- β -(5-hydroxy-2-methylphenyl)ethylamines (34, 35, 38, 39, 41, 42) and *N*-Cyanomethyl-*N*- β -(3-hydroxy-2-methylphenyl)ethylmethylamines (36, 40): Reductive Cleavage of 2-Cyanomethyl-6- (1, 13, 20, 21, 23, 24) and 8-hydroxy-1,2,3,4-tetrahydroisoquinolinium Iodides (15, 22) with Sodium Borohydride

NaBH₄ (2 mmol) was added to a suspension of cyanomethiodide (1 mmol) in *i*-PrOH (20 ml). The whole was stirred for 0.5 h at room temperature. The solvent was removed *in vacuo* and water was added to the residue. The product was extracted with CHCl₃ and the organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent *in vacuo* followed by purification on preparative TLC with CHCl₃-MeOH (20 : 1) afforded the title compounds.

***N*-Cyanomethyl-*N*- β -(5-hydroxy-4-methoxy-2-methylphenyl)ethylmethylamine (34):** From 1; colorless needles (91 %), mp 87 °C (*i*-PrOH). ¹H-NMR: δ 2.24 (3H, s, ArCH₃), 2.41 (3H, s, NCH₃), 2.62

(4H, s, ArCH₂CH₂N), 3.55 (2H, s, NCH₂CN), 3.82 (3H, s, OCH₃), 6.60, 6.68 (each 1H, s, ArH). IR: 3570 cm⁻¹ (OH). Low MS: *m/z* 234 (M⁺). Anal. Calcd for C₁₃H₁₈N₂O₂: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.56; H, 7.64; N, 11.80.

***N*-Cyanomethyl-*N*-β-(5-hydroxy-2-methylphenyl)ethylmethylamine (35)**: From **13**; colorless needles (91 %), mp 80-82 °C (EtOH-hexane). ¹H-NMR: δ 2.22 (3H, s, ArCH₃), 2.42 (3H, s, NCH₃), 2.66 (4H, s, ArCH₂CH₂N), 3.56 (2H, s, NCH₂CN), 6.56 (1H, dd, *J* = 8, 3 Hz, 4-H), 6.59 (1H, d, *J* = 3 Hz, 6-H), 7.00 (1H, d, *J* = 8 Hz, 3-H). IR: 3380 cm⁻¹ (OH). Low MS: *m/z* 204 (M⁺). HRMS: Calcd for C₁₂H₁₆N₂O: *m/z* 204.1261 (M⁺). Found: 204.1265.

***N*-Cyanomethyl-*N*-β-(3-hydroxy-4-methoxy-2-methylphenyl)ethylmethylamine (36)**: From **15**; pale yellow oil (66 %). ¹H-NMR: δ 2.20 (3H, s, ArCH₃), 2.40 (3H, s, NCH₃), 2.44-2.84 (4H, m, ArCH₂CH₂N), 3.54 (2H, s, NCH₂CN), 3.82 (3H, s, OCH₃), 6.60 (2H, s, ArH). Low MS: *m/z* 234 (M⁺). HRMS: Calcd for C₁₃H₁₈N₂O₂: *m/z* 234.1368 (M⁺). Found: 234.1370.

***N*-Cyanomethyl-*N*-β-(2-ethyl-5-hydroxy-4-methoxyphenyl)ethylmethylamine (38)**: From **20**; colorless needles (84 %), mp 80-80.5 °C (*i*-PrOH). ¹H-NMR: δ 1.20 (3H, t, *J* = 7.5 Hz, ArCH₂CH₃), 2.42 (3H, s, NCH₃), 2.57 (2H, q, *J* = 7.5 Hz, ArCH₂CH₃), 2.64 (4H, s, ArCH₂CH₂N), 3.56 (2H, s, NCH₂CN), 3.84 (3H, s, OCH₃), 6.62, 6.68 (each 1H, s, ArH). IR: 3570 cm⁻¹ (OH). Low MS: *m/z* 248 (M⁺). Anal. Calcd for C₁₄H₂₀N₂O₂: C, 67.72; H, 8.12; N, 11.28. Found: C, 67.75; H, 8.32; N, 11.15.

***N*-Cyanomethyl-*N*-[β-(5-hydroxy-4-methoxy-2-methylphenyl)-β-phenyl]ethylmethylamine (39)**: From **21**; pale yellow oil (96 %). ¹H-NMR: δ 2.21 (3H, s, ArCH₃), 2.37 (3H, s, NCH₃), 2.96 [2H, d, *J* = 8 Hz, NCH₂CH(Ph)Ar], 3.44 (2H, s, NCH₂CN), 3.80 (3H, s, OCH₃), 4.20 [1H, t, *J* = 8 Hz, NCH₂CH(Ph)Ar], 6.59, 6.79 (each 1H, s, ArH), 7.00-7.32 (5H, m, PhH). Low MS: *m/z* 310 (M⁺). HRMS: Calcd for C₁₉H₂₂N₂O₂: *m/z* 310.1679 (M⁺). Found: 310.1676.

***N*-Cyanomethyl-*N*-[β-(3-hydroxy-4-methoxy-2-methylphenyl)-β-phenyl]ethylmethylamine (40)**: From **22**; pale yellow oil (55 %). ¹H-NMR: δ 2.16 (3H, s, ArCH₃), 2.38 (3H, s, NCH₃), 2.99 [2H, observed as dd, *J* = 8, 2 Hz, NCH₂CH(Ph)Ar], 3.48 (2H, s, NCH₂CN), 3.83 (3H, s, OCH₃), 4.25 [1H, t, *J* = 8 Hz, NCH₂CH(Ph)Ar], 6.69 (2H, s, ArH), 7.00-7.32 (5H, m, PhH). Low MS: *m/z* 310 (M⁺). HRMS: Calcd for C₁₉H₂₂N₂O₂: *m/z* 310.1680 (M⁺). Found: 310.1685.

***N*-Cyanomethyl-*N*-β-[2-β-(phenyl)ethyl-5-hydroxy-4-methoxyphenyl]ethylmethylamine (41)**: From **23**; colorless oil (74 %). ¹H-NMR: δ 2.39 (3H, s, NCH₃), 2.59 (4H, s, ArCH₂CH₂N), 2.84 (4H, s, ArCH₂CH₂Ph), 3.51 (2H, s, NCH₂CN), 3.78 (3H, s, OCH₃), 6.52, 6.68 (each 1H, s, ArH), 7.00-7.36 (5H, m, PhH). Low MS: *m/z* 324 (M⁺). HRMS: Calcd for C₂₀H₂₄N₂O₂: *m/z* 324.1837 (M⁺). Found: 324.1838.

***N*-Cyanomethyl-*N*-β-[2-β-(3,4-dimethoxyphenyl)ethyl-5-hydroxy-4-methoxyphenyl]ethylmethylamine (42)**: From **24**; pale yellow oil (76 %). ¹H-NMR: δ 2.39 (3H, s, NCH₃), 2.57 (4H, s, ArCH₂CH₂N), 2.80 (4H, s, ArCH₂CH₂Ar), 3.51 (2H, s, NCH₂CN), 3.79, 3.80, 3.83 (each 3H, s, OCH₃),

6.54, 6.60 (each 1H, s, ArH), 6.64-6.84 (3H, m, ArH). IR: 3570 cm^{-1} (OH). Low MS: m/z 384 (M^+). HRMS: Calcd for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_4$: m/z 384.2048 (M^+). Found: 384.2055.

General Procedure for Formation of 6- (45, 48) and 8-Hydroxy-5-alkyl-1,2,3,4-tetrahydroisoquinolines (43, 44, 46, 47, 49, 50): Recyclization of *N*-Cyanomethyl-*N*- β -(3-hydroxy-2-methylphenyl)ethylamines (36, 40) and *N*-Cyanomethyl-*N*- β -(5-hydroxy-2-methylphenyl)-ethylmethylamines with Sodium Methoxide (34, 35, 38, 39, 41, 42) (Method A)

A solution of *N*-cyanomethyl-*N*- β -arylethylmethylamine (0.2 mmol) and NaOMe (0.6 mmol) in MeOH (10 ml) was refluxed for 2 h. The solvent was removed *in vacuo* and saturated aqueous NH_4Cl solution was added to the residue. The product was extracted with CHCl_3 and the organic layer was washed with brine and dried over Na_2SO_4 . Evaporation of the solvent *in vacuo* followed by purification on preparative TLC with CHCl_3 -MeOH (15 : 1) afforded the title compounds.

8-Hydroxy-7-methoxy-2,5-dimethyl-1,2,3,4-tetrahydroisoquinoline (43): From 34; colorless needles (86 %), mp 120-121 $^\circ\text{C}$ (AcOEt-hexane). $^1\text{H-NMR}$: δ 2.14 (3H, s, ArCH_3), 2.47 (3H, s, NCH_3), 2.68 (4H, s, 3- and 4-H), 3.56 (2H, s, 1-H), 3.81 (3H, s, ArOCH_3), 6.55 (1H, s, 6-H). IR: 3590 cm^{-1} (OH). Low MS: m/z 207 (M^+). HRMS: Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2$: m/z 207.1258 (M^+). Found: 207.1264.

8-Hydroxy-2,5-dimethyl-1,2,3,4-tetrahydroisoquinoline (44): From 35; colorless oil (86 %). $^1\text{H-NMR}$: δ 2.09 (3H, s, ArCH_3), 2.56 (3H, s, NCH_3), 2.64-2.98 (4H, m, 3- and 4-H), 3.64 (2H, s, 1-H), 6.46, 6.78 (each 1H, d, $J = 8$ Hz, 6- and 7-H). Low MS: m/z 177 (M^+).

6-Hydroxy-7-methoxy-2,5-dimethyl-1,2,3,4-tetrahydroisoquinoline (45): From 36; colorless oil (71 %). $^1\text{H-NMR}$: δ 2.11 (3H, s, ArCH_3), 2.43 (3H, s, NCH_3), 2.69 (4H, s, 3- and 4-H), 3.48 (2H, s, 1-H), 3.81 (3H, s, ArOCH_3), 6.36 (1H, s, 8-H). Low MS: m/z 207 (M^+).

5-Ethyl-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (46): From 38; colorless needles (90 %), mp 109-110 $^\circ\text{C}$ (AcOEt-hexane). $^1\text{H-NMR}$: δ 1.15 (3H, t, $J = 7$ Hz, ArCH_2CH_3), 2.48 (3H, s, NCH_3), 2.50 (2H, q, $J = 7$ Hz, ArCH_2CH_3), 2.60-2.88 (4H, m, 3- and 4-H), 3.57 (2H, s, 1-H), 3.81 (3H, s, OCH_3), 6.53 (1H, s, 6-H). IR: 3540 cm^{-1} (OH). Low MS: m/z 221 (M^+).

8-Hydroxy-7-methoxy-2,5-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (47): From 39; pale brown oil (79 %). $^1\text{H-NMR}$: δ 1.82 (3H, s, ArCH_3), 2.33 (3H, s, NCH_3), 2.76 (2H, d, $J = 4$ Hz, 3-H), 3.28, 3.97 (each 1H, d, $J = 15$ Hz, 1-H), 3.81 (3H, s, OCH_3), 6.50 (1H, s, 6-H), 6.88-7.32 (5H, m, PhH). IR: 3550 cm^{-1} (OH). Low MS: m/z 283 (M^+).

6-Hydroxy-7-methoxy-2,5-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (48): From 40; pale brown oil (71 %). $^1\text{H-NMR}$: δ 1.78 (3H, s, ArCH_3), 2.35 (3H, s, NCH_3), 2.85 (2H, d, $J = 4$ Hz, 3-H), 3.39, 3.87 (each 1H, d, $J = 15$ Hz, 1-H), 3.85 (3H, s, OCH_3), 4.12 (1H, J = 4 Hz, 4-H), 6.45 (1H, s, 8-H),

6.84-7.28 (5H, m, PhH). Low MS: m/z 283 (M^+).

8-Hydroxy-7-methoxy-2-methyl-5- β -phenylethyl-1,2,3,4-tetrahydroisoquinoline (49): From **41**; pale brown oil (73 %). $^1\text{H-NMR}$: δ 2.46 (3H, s, NCH₃), 2.60 - 2.88 (8H, m, 3- and 4-H and ArCH₂CH₂Ph), 3.57 (2H, s, 1-H), 3.75 (3H, s, OCH₃), 6.44 (1H, s, 6-H), 7.00-7.40 (5H, m, PhH). Low MS: m/z 297 (M^+). HRMS: Calcd for C₁₉H₂₃NO₂: m/z 297.1728 (M^+). Found: 297.1728.

5- β -(3,4-Dimethoxyphenyl)ethyl-8-hydroxy-7-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (50): From **42**; pale brown oil (88 %). $^1\text{H-NMR}$: δ 2.48 (3H, s, NCH₃), 2.52 - 2.84 (8H, m, 3- and 4-H and ArCH₂CH₂Ar'), 3.58 (2H, s, 1-H), 3.76, 3.81, 3.83 (each 3H, s, OCH₃), 6.44 (1H, s, 6-H), 6.56-6.84 (3H, m, ArH). Low MS: m/z 357 (M^+). HRMS: Calcd for C₂₁H₂₇NO₄: m/z 357.1938 (M^+). Found: 357.1923.

One-pot reaction (Method B)

NaBH₄ (6 mmol) was added to a suspension of cyanomethiodide (0.2 mmol) in MeOH (10 ml). After stirring for 1 h at room temperature, NaOMe (6 mmol) was added to the mixture. The whole was refluxed for 2 h and the solvent was evaporated *in vacuo*. Treatment similar to that noted in Method A afforded **43** (83 %), **44** (68 %), **46** (71 %), **49** (89 %), and **50** (86 %), respectively. They were identical in all respects with compounds prepared by Method A.

REFERENCES AND NOTE

1. Stermitz F. R.; Lwo S.-Y.; Kellos G. *J. Amer. Chem. Soc.* **1963**, *85*, 1551; Bick I. R. C.; Douglas D. K. *Aust. J. Chem.* **1965**, *18*, 1997; Kupchan S. M.; Yoshitake A. *J. Org. Chem.* **1969**, *34*, 1062; Kametani T.; Takemura M.; Takahashi K.; Takeshita M.; Ihara M.; Fukumoto K. *Heterocycles* **1974**, *2*, 653.
2. Nagata W.; Okada K. *Chem. Pharm. Bull.* **1975**, *23*, 2878.
3. Hara H.; Endoh M.; Kaneko K.; Hoshino O. *Heterocycles* **1993**, *36*, 249.
4. Smith, Jr. S.; Elango V.; Shamma M. *J. Org. Chem.* **1984**, *49*, 581.
5. Akimoto H.; Yamada S. *Tetrahedron Lett.* **1969**, 3105; Akimoto H.; Okamura K.; Yui M.; Shioiri T.; Kuramoto M.; Kikugawa Y.; Yamada S. *Chem. Pharm. Bull.* **1974**, *22*, 2615; Konda M.; Shioiri T.; Yamada S. *ibid.* **1975**, *23*, 1025; *idem.*, *ibid.* **1975**, *23*, 1063; Bonin M.; Romero J. R.; Grierson D.S.; Husson H-P. *Tetrahedron Lett.* **1982**, *23*, 3369.
6. Kharasch M. S.; Joshi B. S. *J. Org. Chem.* **1957**, *22*, 1435.
7. Wu Y. C.; Liou J. Y.; Duh C. Y.; Lee S. S.; Lu S. T. *Tetrahedron Lett.* **1991**, *32*, 4169.
8. Lee S. S.; Lin Y. J.; Chen M. Z.; Wu Y. C.; Chen C. H. *Tetrahedron Lett.* **1992**, *33*, 6309.
9. Recently, Lee's group reported cleavage of C-N bond of 2-hydroxyaporphines by refluxing in propionic acid: Lee S. S.; Chiou C. M.; Lin H. Y.; Chen C. H. *Tetrahedron Lett.* **1995**, *36*, 1531.
10. (*S*)-Boldine hydrochloride was purchased from Aldrich Chemical Co. Inc..
11. Bobbitt J. M.; Roy D. N.; Marchand A.; Allen C. W. *J. Org. Chem.* **1967**, *32*, 2225.

12. Bobbitt J. M.; Dutta C. P. *J. Org. Chem.* **1969**, *34*, 2001.
13. Hara H.; Shirai R.; Hoshino O.; Umezawa B. *Chem. Pharm. Bull.* **1985**, *33*, 3107.
14. Hoshino O.; Ohyama K.; Taga M.; Umezawa B. *Chem. Pharm. Bull.* **1974**, *22*, 2587.
15. Hoshino O.; Taga M.; Umezawa B. *Heterocycles* **1973**, *1*, 223.
16. Marchant A.; Pinder A. R. *J. Chem. Soc.* **1956**, 327.
17. Tomita M.; Watanabe H. *Yakugaku Zasshi* **1938**, *58*, 783.

(Received in Japan 4 July 1995; accepted 24 July 1995)