

STRUCTURE AND SYNTHESIS OF MENISPORPHINE, A NEW TYPE OF ISOQUINOLINE ALKALOID

ALKALOIDS OF *MENISPERMUM DAURICUM* DC. (9)¹

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(Received in Japan 11 December 1982)

Abstract—The structure of an unknown yellow base from *Menispermum dauricum* DC. (Menispermaceae) was determined to be 5,6,9-trimethoxy-7H-dibenzo[de, h]quinolin-7-one from various spectral data and synthesis, and was named menisporphine. This is a new isoquinoline-type alkaloid having a 7H-dibenzo[de, h]quinolin-7-one skeleton for which the general term "oxoisoporphine" is proposed.

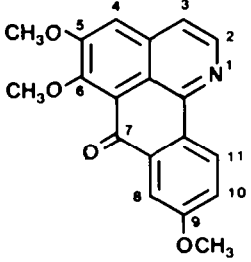
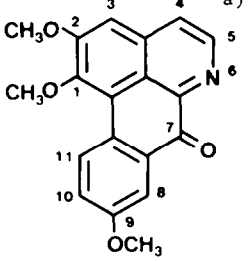
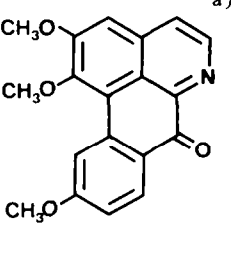
The previous paper reported the isolation of six unknown yellow alkaloids together with three known isoquinoline alkaloids (cheilanthifoline, stepholidine and stepharine) from the rhizome of *Menispermum dauricum* DC. (Menispermaceae) collected in Kyoto, Japan.¹ This paper describes the characterization, structural establishment and synthesis of the tentatively named Base II reported in the previous paper. This yellow alkaloid was named menisporphine.

Menisporphine forms yellow needles from CH₂Cl₂-Me₂CO, m.p. 199.5–200.5°, and elemental analyses and MS established the formula as C₁₉H₁₅NO₄. Its IR spectrum (KBr) showed a conjugated CO band at 1660 cm⁻¹. The UV spectrum (Table) indicated a highly conjugated system similar to that of oxoaporphine-type alkaloids.^{2,3} The MS data also supported this alkaloid type.³ The ¹H NMR spectrum (CDCl₃) showed the presence of characteristic *ortho*-coupling protons at C₄-H and C₃-H [δ 7.55 (1H, d, J = 5.5 Hz), 8.65 (1H, d, J = 5.5 Hz)] of isoquinoline skeleton and four aromatic protons with three OMe groups. Based on these data, the structure of 1,2,9- or 1,2,10-trimethoxyoxoaporphine (1 or 2)⁴ was predicted, but neither seemed to be correct as can be seen from the Table. The possible structure for menisporphine according to several pieces of spectral data was assumed to be that of trimethoxy-7H-dibenzo[de, h]quinolin-7-one which is related to the isomer of trimethoxyoxoaporphine-type alkaloids. In order to determine the position of the three OMe groups, the NOE and internuclear double resonance (INDOR) were used. In the INDOR experiments of this alkaloid, the signal of the aromatic proton at δ 7.40 was observed as a singlet upon irradiation at the frequency of aromatic proton at C₄-H (δ 7.55) of the isoquinoline skeleton. Furthermore, the NOE effect was also detected, i.e. irradiation at the frequency of C₃-H (δ 7.55) in menisporphine enhanced by ca 10% the peak area of the C₄-H signal (δ 7.40). Consequently, the signal of the aromatic proton as a singlet at δ 7.40 was assigned to the C₄-H of the 7H-dibenzo[de, h]quinolin-7-one skeleton, and the

positions of two of the three OMe groups were determined to be at C-5 and C-6 of this skeleton. The third OMe group was found to be at C-9 or C-10 according to the AMX type splitting and the coupling constant of the signals of the residual three aromatic protons in the ¹H NMR spectrum. The proton at C₁₁-H in this type of skeleton is found appreciably downfield due to ring current effect of aromatized isoquinoline ring similarly as C₁₁-H in benzanthrone derivatives⁵ or oxoaporphine-type alkaloids. The signals of *ortho*-aromatic protons at δ 7.33 and δ 8.79 were assigned to C₁₀-H and C₁₁-H, respectively. The position of the remaining OMe group must be C-9. These results suggested that menisporphine would be 5,6,9-trimethoxy-7H-dibenzo[de, h]quinolin-7-one (3).

Final evidence for this structure came from its synthesis. Many compounds having the 7H-dibenzo[de, h]quinolin-7-one skeleton are used as dyes and can be synthesized by various methods, but the positions of the substituent groups are still uncertain.⁶ The desired compound (3) was synthesized as shown in Chart 1. The starting material, N(3', 4', β -trimethoxyphenethyl)-2-bromo-4-methoxybenzamide (6a), was obtained by the Schotten-Baumann reaction of 3,4, β -trimethoxyphenethylamine and 2-bromo-4-methoxybenzoyl chloride (5a). The Bischler-Napieralski reaction of this benzamide derivative (6a) with phosphorus oxychloride afforded 1-(2'-bromo-4'-methoxyphenyl)-6,7-dimethoxyisoquinoline (7a). This compound (7a) on reaction with cuprous cyanide gave the corresponding cyano-derivative (8a) in high yield. The cyano compound (8a) was hydrolyzed to afford the corresponding carboxylic acid (9a), which is soluble in water. Confirmation of 9a was carried out by the formation of its methyl ester. The second ring cyclization of the 9a with polyphosphoric acid afforded 6-hydroxy-5,9-dimethoxy-7H-dibenzo[de, h]quinolin-7-one (10a) which demethylated the OMe group at C-6. Treatment of this compound (10a) with methyl iodide in the presence of silver oxide produced the desired compound (3) as yellow needles,

Table I. The data of menisporphine and trimethoxyoxoaporphine

				
	menisporphine (3)	(1)	(2)	
mp (°C)	199.5-200.5	201-203	200-201	
Anal ^{b)}	C ₁₉ H ₁₅ NO ₄			
UV λ _{max} ^{EtOH} (log ε)	254, 288 sh, 310 sh, 319, 334 sh, 368, 420 (4.72, 4.13, 3.96, 3.97, 3.94, 3.91, 3.97)	244, 271, 292 sh, 377, 444 (4.46, 4.44, 4.16, 3.68, 3.62)	242, 272, 284 sh, 312, 351, 387 (4.45, 4.44, 4.19, 3.84, 4.07, 4.00)	
IR ν _{max} ^{KBr}	1660 cm ⁻¹	1680 cm ⁻¹	1665 cm ⁻¹	
¹ H NMR (CDCl ₃) δ: (J: Hz)	OCH ₃	3.98, 4.08, 4.15	3.98, 3.98, 4.03	3.96, 3.99, 4.03
	arom. H	7.33(d.d, J=2.5, 9.0), 7.40(s), 7.55(d, J=5.5), 7.86(d, J=2.5), 8.65(d, J=5.5), 8.79(d, J=9.0)	7.19(s, C ₃ -H), 7.28(d.d, J=3.0, 9.0, C ₁₀ -H), 7.72(d, J=6.0, C ₄ -H), 8.01(d, J=3.0, C ₈ -H), 8.81(d, J=6.0, C ₅ -H), 8.99(d, J=9.0, C ₁₁ -H)	7.03(d.d, J=3.0, 9.0, C ₉ -H), 7.08(s, C ₃ -H), 7.62(d, J=6.0, C ₄ -H), 8.48(d, J=9.0, C ₈ -H), 8.63(d, J=3.0, C ₁₁ - H) 8.77(d, J=6.0, C ₅ -H)
MS (m/z)	321(M ⁺ , base peak), 306, 293, 278, 261	321(M ⁺), 320(base peak), 306, 305, 278	321(M ⁺ , base peak), 306, 278, 263	

a) These data cited from reference 4.

b) Menisporphine (3): Anal. Calcd: C, 71.02; H, 4.71; N, 4.36.

Found: C, 71.10; H, 4.63; N, 4.44

m.p. 199-200°. It was identified by direct comparison of its spectra, (UV, IR, ¹H NMR and MS) and TLC with those of natural product, menisporphine. From the reaction product of O-methylation, the corresponding enol ether (11), which is related to the isomer of compound 3 was also obtained in low yield.

This isoquinoline-type alkaloid has an entirely new skeleton (7H-dibenzo[de, h]quinolin-7-one) and we propose to name it "oxoisoaporphine" because of its relationship to the isomer oxoaporphine. Biogenesis for oxoisoaporphine-type alkaloids in plants probably is as Chart 2.

The precursor seemed to be a papaverinol derivative. The biogenetic route may involve the formation of isoquinoline derivative containing a cyclobutane ring from the precursor by intramolecular oxidative coupling, followed by a dienone enol rearrangement with fission of the cyclobutane ring. Finally, electrophilic substitution to the aromatic ring of the aldehyde leads to this new skeleton ring.

5,6,10-Trimethoxy-7H-dibenzo[de, h]quinolin-7-one (4), which is an isomer of menisporphine (3), was also synthesized by the same method and the desired 4 was obtained as pale yellow needles, m.p. 195-196°. In the ¹H NMR (CDCl₃) of 4, the signal of aromatic proton at C₁₁-H (δ 8.35) is present somewhat upfield than that at C₈-H (δ 8.37). Oppositely, the signal of aromatic proton at C₁₁-H (δ 8.79) of menisporphine (3) shifts appreciably downfield in the comparison with that at C₈-H (δ 7.86). The reason for this fact seems to be due to the positional difference of the OMe substituents (C₉- or C₁₀-position) of both 3 and 4, as a similar relationship between the signals of the aromatic protons of C₈-H and C₁₁-H in the trimethoxyoxoaporphines 1 and 2 was observed.

EXPERIMENTAL

All m.ps are uncorrected. ¹H NMR spectra were recorded on a JNM-FX 200 spectrometer in CDCl₃ with TMS as an internal standard. MS spectra were recorded on a direct inlet system at 70 eV using a Hitachi RMU-6 spectrometer. All organic solutions were dried over MgSO₄.

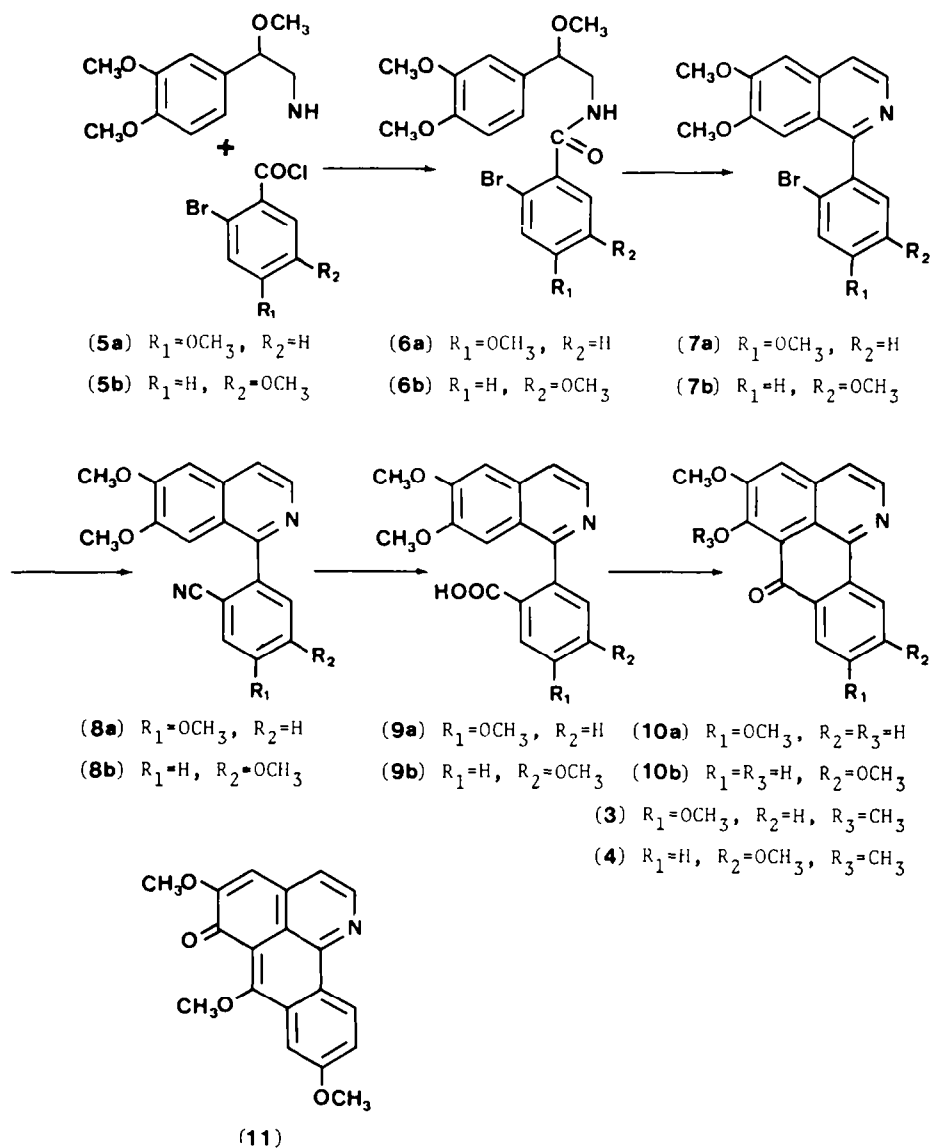


Chart 1.

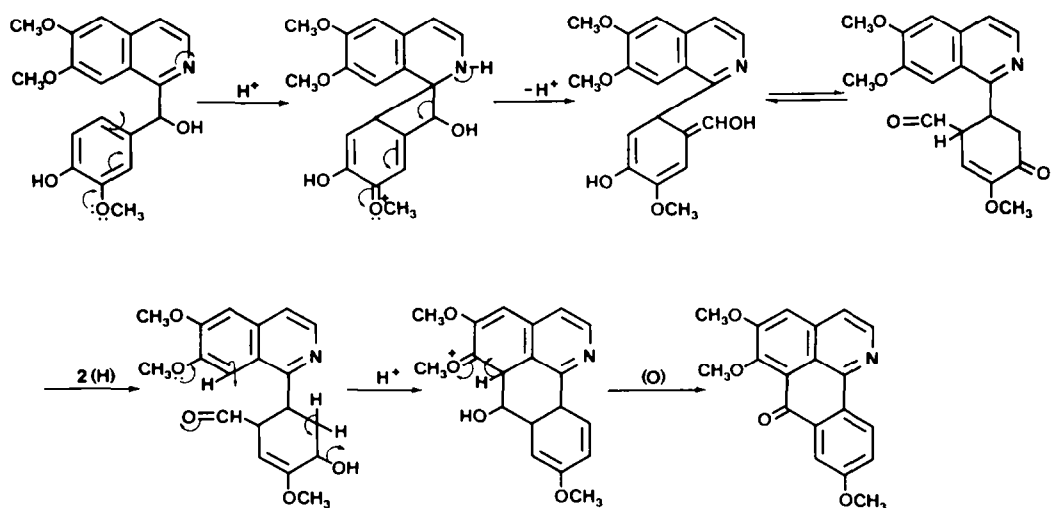


Chart 2. The biogenetic route of oxoisosporphine-type alkaloid.

(a) *Synthesis of 5,6,9-trimethoxy-7H-dibenzo[de, h]quinolin-7-one (3)*

N-(3', 4', β -Trimethoxyphenethyl)-2-bromo-4-methoxybenzamide (**6a**). To a soln of 3,4, β -trimethoxyphenethylamine (14.21 g) in 300 ml Et₂O and 480 ml of 10% NaOH aq, **5a** was added dropwise with stirring at 0–5° in anhyd. Et₂O. Compound **5a** was formed from 2-bromo-4-methoxybenzoic acid⁷ (15.5 g) and excess SOCl₂ in the usual way. Stirring was continued for 1 hr. The ppt was filtered off and dissolved in CH₂Cl₂. The CH₂Cl₂ layer was washed with 10% HCl aq and water, and dried. Removal of the solvent by evaporation and recrystallization from Et₂O-MeOH gave **6a** (25.92 g, 91.2%) as colorless needles, m.p. 114–116°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 232 (4.23), 279 (3.64), 289 (3.53). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1655, 3450. ¹H NMR δ : 3.28, 3.83, 3.89, 3.90 (3H \times 4, each s, OCH₃ \times 4), 3.38, 3.90 (2H, C₆-H \times 2), 4.34 (1H, d, J = 4.0, 9.0 Hz, C₈-H), 6.52 (1H, s, NH), 6.86 (1H, d, J = 2.5, 8.5 Hz, C₅-H), 6.89 (3H, C₂-H, C₃-H and C₆-H), 7.12 (1H, d, J = 2.5 Hz, C₃-H), 7.56 (1H, d, J = 8.5 Hz, C₆-H). MS m/z (%): 425 (1.6), 423 (M⁺, 1.6), 215 (3.1), 213 (CH₃O-BrC₆H₃CO⁺, 3.1), 195 ((CH₃O)₂C₆H₃CH(OCH₃)CH₂⁺, 4.7), 194 (38.8), 182 (13.4), 181 ((CH₃O)₂C₆H₃CHOCH₃⁺, base peak), 166 (181-CH₃, 6.5). (Found: C, 53.62; H, 5.26; N, 3.07. Calc for C₁₉H₂₂BrNO₅: C, 53.82; H, 5.23; N, 3.30%).

1-(2'-Bromo-4'-methoxyphenyl)-6,7-dimethoxyisoquinoline (**7a**). Compound **6a** (2.12 g) was heated with POCl₃ (9 ml) and anhyd toluene (15 ml) at 120° for 2.5 hr. The solvent and the excess reagent were removed by evaporation *in vacuo*, and residual reagent was decomposed by adding MeOH and 5% HCl aq. The acidic soln was washed once with Et₂O, made alkaline with 10% NH₄OH aq and extracted with CH₂Cl₂. The extract was washed with H₂O, dried and the solvent was evaporated. The residue was purified by column chromatography on silica gel (eluted by Et₂O). Recrystallization from MeOH gave 1.21 g (64.7%) of **7a** as colorless plates, m.p. 123–124°; UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 243 (4.69), 281 (sh, 3.77), 287 (sh, 3.70), 316 (sh, 3.49), 329.5 (3.61). ¹H NMR δ : 3.83, 3.89, 4.05 (3H \times 3, each s, OCH₃ \times 3), 6.87 (1H, s, C₅-H), 7.01 (1H, d, J = 2.5, 8.5 Hz, C₅-H), 7.13 (1H, s, C₈-H), 7.27 (1H, d, J = 2.5 Hz, C₃-H), 7.38 (1H, d, J = 8.5 Hz, C₆-H), 7.55 (1H, d, J = 5.5 Hz, C₄-H), 8.48 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 375 (79.5), 373 (M⁺, 79.5), 360 (375-CH₃, 20.5), 358 (M⁺-CH₃, 21.4), 294 (M⁺-Br, base peak), 279 (294-CH₃, 18.8), 278 (16.1), 250 (278-CO, 20.5), 236 (250-CH₃, 20.5). (Found: C, 57.86; H, 4.30; Calc for C₁₈H₁₆BrNO₅: C, 57.77; H, 4.31; N, 3.74%).

1-(2'-Cyano-4'-methoxyphenyl)-6,7-dimethoxyisoquinoline (**8a**). Compound **7a** (2.17 g) was heated with cuprous cyanide (772 mg) in 25 ml DMF at 180° for 5 hr. The mixture was poured into 50 ml ice water, made alkaline with 10% NH₄OH aq and extracted with CH₂Cl₂. The extract was thoroughly washed with H₂O and dried. Recrystallization from Me₂CO gave 1.53 g (82.4%) of **8a** as colorless needles, m.p. 158–158.5°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 241 (4.73), 332 (3.85). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 2250 cm⁻¹ (CN). ¹H NMR δ : 3.86, 3.93, 4.05 (3H \times 3, each s, OCH₃ \times 3), 6.99, 7.15 (1H \times 2, each s, C₅-H and C₈-H), 7.26 (1H, d, J = 3.0, 9.0 Hz, C₅-H), 7.35 (1H, d, J = 3.0 Hz, C₃-H), 7.57 (1H, d, J = 5.5 Hz, C₄-H), 7.60 (1H, d, J = 9.0 Hz, C₆-H), 8.51 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 321 (M⁺ + 1, 24.3), 320 (M⁺, base peak), 319 (M⁺-1, 20.9), 305 (M⁺-CH₃, 25.2), 290 (305-CH₃, 34.8), 262 (290-CO, 12.2). (Found: C, 71.37; H, 4.93; N, 8.80. Calc. for C₁₉H₁₆N₂O₅: C, 71.24; H, 5.03; N, 8.75%).

1-(2'-Carboxy-4'-methoxyphenyl)-6,7-dimethoxyisoquinoline (**9a**). The above **8a** (2.55 g) was heated under reflux with 40% KOH aq (60 ml) and diethylene glycol (40 ml) until the evolution of NH₃ gas ceased (24 hr). The mixture was poured into water, and washed with Et₂O. The alkaline soln was neutralized to pH 7 with AcOH, extracted three times with BuOH, and the solvent was evaporated *in vacuo*. The residual crude product was recrystallized from MeOH to give 1.10 g (40.7%) of **9a** as colorless needles, m.p. 253–254°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 242 (4.81), 318 (sh, 3.92), 330 (3.97). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400 (OH), 1600 (COO⁻). ¹H NMR δ : 3.72, 3.77, 3.84 (3H \times 3, each s, OCH₃ \times 3), 7.29 (1H, s, C₅-H), 7.31 (1H, d, J = 3.0, 9.0 Hz, C₅-H), 7.50 (1H, s, C₈-H), 7.66 (1H, d, J = 5.5 Hz, C₄-H), 7.77 (1H, d, J = 9.0 Hz, C₆-H), 8.05 (1H, d, J = 3.0 Hz, C₃-H), 8.71 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 339 (M⁺, 5.2), 322 (M⁺-OH, 56.5), 295 (79.3), 294

(322-CO, 55.9), 280 (295-CH₃, base peak). (Found: C, 66.79; H, 5.31; N, 3.85. Calc for C₁₉H₁₇NO₅·1/4H₂O: C, 66.37; H, 5.13; N, 4.07%).

Methyl ester of 9a. Compound **9a** (0.5 g) in MeOH (10 ml) was treated with excess ethereal CH₂N₂ and kept at room temp overnight. After treatment in the usual way, the desired product was recrystallized from EtOAc and petroleum ether to give colorless needles, m.p. 122–123°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 240 (4.69), 330 (3.52). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1720 cm⁻¹ (COOCH₃). ¹H NMR δ : 3.41, 3.80, 3.94, 4.04 (3H \times 4, each s, OCH₃ \times 4), 6.91 (1H, s, C₅-H), 7.12 (1H, s, C₈-H), 7.19 (1H, d, J = 3.0, 8.5 Hz, C₅-H), 7.48 (1H, d, J = 8.5 Hz, C₆-H), 7.50 (1H, d, J = 5.5 Hz, C₄-H), 7.57 (1H, d, J = 3.0 Hz, C₃-H), 8.43 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 354 (M⁺ + 1, 23.0), 353 (M⁺, 93.2), 322 (M⁺-OCH₃, base peak), 294 (322-CO, 9.2). (Found: C, 67.39; H, 5.39; N, 3.78. Calc for C₂₀H₁₉NO₅: C, 67.98; H, 5.42; N, 3.96%).

6-Hydroxy-5,9-dimethoxy-7H-dibenzo[de, h]quinolin-7-one (**10a**). The above **9a** (1.0 g) was heated with polyphosphoric acid (25 ml) at 100° for 1 hr with stirring. The mixture was poured into ice water, made alkaline with 10% NH₄OH aq and extracted with CH₂Cl₂. The CH₂Cl₂ layer was washed with H₂O and dried. Recrystallization from CH₂Cl₂ gave 0.63 g (69.5%) of a product as yellow needles, m.p. 248–249°. UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 238 (sh, 4.38), 254 (4.62), 292 (sh, 3.76), 307 (3.53), 319 (3.44), 358 (sh, 3.77), 366 (3.79), 406 (sh, 3.51), 430 (3.83), 455 (3.84). This spectrum shifts to bathochromic by addition of 10% NaOH soln or 10% HCl soln. ¹H NMR δ : 4.02, 4.10 (3H \times 2, each s, OCH₃ \times 2), 5.94 (1H, s, OH), 7.29 (1H, s, C₄-H), 7.45 (1H, d, J = 3.0, 9.0 Hz, C₁₀-H), 7.58 (1H, d, J = 5.0 Hz, C₃-H), 7.92 (1H, d, J = 3.0 Hz, C₈-H), 8.74 (1H, d, J = 5.0 Hz, C₂-H), 8.95 (1H, d, J = 9.0 Hz, C₁₁-H). MS m/z (%): 308 (M⁺ + 1, 33.3), 307 (M⁺, base peak), 278 (M⁺-CO, 32.3). (Found: C, 70.14; H, 4.15; N, 4.49. Calc for C₁₈H₁₃NO₄: C, 70.35; H, 4.26; N, 4.56%).

O-Methylation of phenolic base 10a with methyl iodide in the presence of silver oxide. The base **10a** (246 mg) in MeOH (6.0 ml) and CHCl₃ (8.0 ml) were heated under reflux with Ag₂O (1.3 g) and MeI (12.0 ml) at 60° for 6 hr with stirring. The mixture was filtered, and the ppt was thoroughly washed with CHCl₃. The CHCl₃ layer was washed with H₂O and dried. The residue was purified by column chromatography on silica gel (eluted by CH₂Cl₂ containing 1% Me₂CO) to give crystallised **3** and **11**. 5,6,9-Trimethoxy-7H-dibenzo[de, h]quinolin-7-one (**3**) as yellow needles, m.p. 199–200° (41.5% yield). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 254 (4.45), 290 (sh, 4.44), 320 (3.75), 368 (3.68), 420 (3.78). $\lambda_{\text{max}}^{\text{10\% HCl EtOH}}$ nm (log ϵ): 270 (4.43), 300 (sh, 3.81), 320 (sh, 3.69), 332 (3.69), 428 (3.70). IR $\nu_{\text{max}}^{\text{KBr}}$: 1660 cm⁻¹. ¹H NMR δ : 3.99, 4.08, 4.17 (3H \times 3, each s, OCH₃ \times 3), 7.34 (1H, d, J = 2.5, 9.0 Hz, C₁₀-H), 7.38 (1H, s, C₄-H), 7.55 (1H, d, J = 5.5 Hz, C₃-H), 7.89 (1H, d, J = 2.5 Hz, C₈-H), 8.66 (1H, d, J = 5.5 Hz, C₂-H), 8.80 (1H, d, J = 9.0 Hz, C₁₁-H). MS m/z (%): 321 (M⁺, base peak), 306 (M⁺-CH₃, 30.0), 292 (M⁺-1-CO, 64.0), 278 (M⁺-CO-CH₃, 17.7), 261 (12.5). (Found: C, 71.00; H, 4.64; N, 4.15. Calc for C₁₉H₁₅NO₄: C, 71.02; H, 4.71; N, 4.36%). This compound was identified by direct comparison (UV, IR, ¹H NMR, MS, TLC and mixed m.p.) with natural menisporphine. 5,7,9-Trimethoxy-6H-dibenzo[de, h]quinolin-6-one (**11**), yellow needles, m.p. 173–175° (20.3% yield). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 241 (4.60), 281 (sh, 4.12), 287 (4.13), 362 (3.93), 398 (sh, 3.88), 448 (sh, 3.65). $\lambda_{\text{max}}^{\text{10\% HCl EtOH}}$ nm (log ϵ): 245 (4.54), 289 (sh, 4.08), 299 (4.10), 317 (sh, 3.97), 374 (sh, 3.94), 392 (3.97), 430 (3.83), 450 (3.83). IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1645 cm⁻¹. ¹H NMR δ : 4.00, 4.03, 4.23 (3H \times 3, each s, OCH₃ \times 3), 6.80 (1H, s, C₄-H), 7.47 (1H, d, J = 5.0 Hz, C₃-H), 7.52 (1H, d, J = 2.5, 9.0 Hz, C₁₀-H), 7.89 (1H, d, J = 2.5 Hz, C₈-H), 8.90 (1H, d, J = 5.0 Hz, C₂-H), 9.22 (1H, d, J = 9.0 Hz, C₁₁-H). MS m/z (%): 321 (M⁺, base peak), 306 (M⁺-CH₃, 42.7), 292 (M⁺-1-CO, 32.2), 277 (18.2), 261 (16.9), 235 (10.6). (Found: C, 66.95; H, 4.62; N, 3.81. Calc for C₁₉H₁₅N₂O₄·H₂O: C, 67.25; H, 5.05; N, 4.13%).

(b) *Synthesis of 5,6,10-trimethoxy-7H-dibenzo[de, h]quinolin-7-one (4)*

N-(3',4', β -Trimethoxyphenethyl)-2-bromo-5-methoxybenzamide (**6b**), recrystallization from Et₂O-MeOH as colorless plates, m.p. 93–94° (81.9% yield). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 210.5 (4.56), 231.5 (4.33), 284 (3.69). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3325 (NH), 1665 (NHCO). ¹H

NMR δ : 2.06 (1H, s, NH), 3.30, 3.79, 3.90 (3H \times 4, each s, OCH₃ \times 4), 3.42 (2H, s, CH₂), 4.40 (1H, q, β -H), 6.81 (1H, d, J = 3.0, 9.0 Hz, C₄-H), 6.93 (3H, each s, C₂-H, C₃-H and C₆-H), 7.08 (1H, s, J = 3.0 Hz, C₆-H), 7.47 (1H, d, J = 9.0 Hz, C₃-H). MS m/z (%): 425 (5.5), 423 (M⁺, 5.7), 215 (2.4), 213 (CH₃O⁺-BrC₆H₃CO⁺, 2.6), 195 ((CH₃O)₂C₆H₃CH(OCH₃)CH₂⁺, 8.6), 194 (67.5), 182 (30.0), 181 ((CH₃O)₂C₆H₃CHOCH₃⁺, base peak), 179 (1.0). (Found: C, 52.64; H, 5.50; N, 2.96. Calc for C₁₉H₂₂BrNO₅·1/2H₂O: C, 52.67; H, 5.35; N, 3.23%).

1-(2'-Bromo-5'-methoxyphenyl)-6,7-dimethoxyisoquinoline (7b), pale yellow oily compound (54.2% yield) which showed a single spot on TLC when it was purified by column chromatography on silica gel (eluted by CH₂Cl₂ solvent). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 242 (4.75), 287 (3.74), 317.5 (3.60), 330.5 (3.62). ¹H NMR δ : 3.82, 3.83, 4.03 (3H \times 3, each s, OCH₃ \times 3), 6.83 (1H, d, J = 1.0, 3.0 Hz, C₆-H), 6.95 (1H, d, J = 3.0, 9.0 Hz, C₄-H), 7.02 (1H, s, C₅-H), 7.13 (1H, s, C₈-H), 7.56 (1H, d, J = 5.5 Hz, C₄-H), 7.59 (1H, d, J = 1.0, 9.0 Hz, C₃-H), 8.50 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 375 (73.5), 373 (M⁺, 73.9), 295 (32.5), 294 (M⁺-Br, base peak).

1-(2'-Cyano-5'-methoxyphenyl)-6,7-dimethoxyisoquinoline (8b), colorless plates (70.9% yield), m.p. 147–149° (from Me₂CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 210 (4.28), 243 (4.66), 319 (sh, 3.55), 332 (3.61). IR ν_{\max}^{KBr} : 2230 cm⁻¹ (CN). ¹H NMR δ : 3.86, 3.88, 4.01 (3H \times 3, each s, OCH₃ \times 3), 7.02, 7.16 (1H \times 2, each s, C₅-H and C₈-H), 7.06 (1H, d, J = 3.0, 9.0 Hz, C₄-H), 7.18 (1H, d, J = 3.0 Hz, C₆-H), 7.57 (1H, d, J = 5.5 Hz, C₄-H), 7.78 (1H, d, J = 9.0 Hz, C₃-H), 8.52 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 321 (46.9), 320 (M⁺, base peak), 319 (29.3), 305 (M⁺-CH₃, 40.6), 290 (14.3), 289 (22.3). (Found: C, 71.04; H, 4.92; N, 8.46. Calc for C₁₉H₁₆N₂O₃: C, 71.24; H, 5.03; N, 8.75%).

1-(2'-Carboxy-5'-methoxyphenyl)-6,7-dimethoxyisoquinoline (9b), colorless needles (41.1% yield), m.p. 201–203.5° (from MeOH). UV $\lambda_{\max}^{\text{MeOH}}$ nm (log ϵ): 241 (4.77), 316 (3.72), 328 (3.75). IR ν_{\max}^{KBr} : 1710 cm⁻¹ (COOH). ¹H NMR δ : 3.68, 3.78, 3.88 (3H \times 3, each s, OCH₃ \times 3), 7.18 (1H, d, J = 3.0, 9.0 Hz, C₄-H), 7.30, 7.38 (1H \times 2, each s, C₅-H and C₈-H), 7.38 (1H, d, J = 3.0 Hz, C₆-H), 7.68 (1H, d, J = 5.5 Hz, C₄-H), 8.50 (1H, d, J = 9.0 Hz, C₃-H), 8.71 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 339 (M⁺, 19.0), 322 (M⁺-OH, 20.0), 295 (M⁺-CO₂, 87.1), 294 (M⁺-COOH, 61.7), 281 (295-CH₃, 22.3), 280 (294-CH₃, base peak), 265 (24.5), 264 (64.2). (Found: C, 66.08; H, 4.89; N, 3.96. Calc for C₁₉H₁₇NO₅·1/3H₂O: C, 66.07; H, 5.15; N, 4.05%). Methyl ester of 9b, colorless needles, m.p. 117–120° (from Et₂O·Me₂CO). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 239 (4.36), 315 (3.37), 328 (3.36). IR $\nu_{\max}^{\text{CHCl}_3}$: 1705 cm⁻¹ (COOCH₃). ¹H NMR δ : 3.41, 3.77, 3.88, 4.03 (3H \times 4, each s, OCH₃ \times 4), 6.84, 7.12 (1H \times 2 each s, C₅-H and C₈-H), 7.01 (1H, d, J = 2.5 Hz, C₆-H), 7.05 (1H, d, J = 2.5, 9.0 Hz, C₄-H), 7.52 (1H, d, J = 5.5 Hz, C₄-H), 8.21 (1H, d, J = 9.0 Hz, C₃-H), 8.44 (1H, d, J = 5.5 Hz, C₃-H). MS m/z (%): 354 (M⁺ - 1, 16.3), 353 (M⁺, 63.8), 323 (354-OCH₃, 22.9), 322 (M⁺-OCH₃, base

peak), 294 (322-CO, 9.5), 280 (14.1). (Found: C, 67.74; H, 5.41; N, 3.74. Calc for C₂₀H₁₉NO₅: C, 67.98; H, 5.42; N, 3.96).

6-Hydroxy-5,10-dimethoxy-7H-dibenzo[de,h]quinolin-7-one (10b), yellow needles (64.1% yield), m.p. 244–245° (from CH₂Cl₂). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 219 (4.52), 252 (4.50), 310 (3.73), 346 (3.98), 380 (3.87), 402 (3.97), 422 (4.04) (bathochromic shifts upon addition of alkali). ¹H NMR δ : 4.10 (6H, s, OCH₃ \times 2), 7.22 (1H, d, J = 3.0, 9.0 Hz, C₉-H), 7.23 (1H, s, C₄-H), 7.60 (1H, d, J = 5.5 Hz, C₃-H), 8.43 (1H, d, J = 9.0 Hz, C₈-H), 8.48 (1H, d, J = 3.0 Hz, C₁₁-H), 8.73 (1H, d, J = 5.5 Hz, C₂-H). MS m/z (%): 307 (M⁺, base peak), 306 (M⁺-1, 31.4), 278 (M⁺-CO, 38.8), 261 (26.2). (Found: C, 70.48; H, 4.19; N, 6.41. Calc for C₁₈H₁₃NO₄: C, 70.35; H, 4.26; N, 4.56%).

5, 6, 10-Trimethoxy-7H-dibenzo[de,h]quinolin-7-one (4), pale yellow needles (67.0% yield), m.p. 195–196° (from Me₂CO·CH₂Cl₂ mixed solvent). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ϵ): 217 (4.66), 254 (4.46), 262 (4.46), 270 (sh, 4.43), 280 (sh, 4.25), 302 (sh, 3.85), 315 (3.93), 346 (4.13), 376 (4.05). IR ν_{\max}^{KBr} : 1655 cm⁻¹ (C=O). ¹H NMR δ : 4.05, 4.07, 4.15 (3H \times 3, each s, OCH₃ \times 3), 7.15 (1H, d, J = 3.0, 9.0 Hz, C₉-H), 7.35 (1H, s, C₄-H), 7.58 (1H, d, J = 5.5 Hz, C₃-H), 8.35 (1H, d, J = 3.0 Hz, C₁₁-H), 8.37 (1H, d, J = 9.0 Hz, C₈-H), 8.67 (1H, d, J = 5.5 Hz, C₂-H). MS m/z (%): 321 (M⁺, base peak), 306 (M⁺-CH₃, 32.0), 292 (35.0). (Found: C, 70.90; H, 4.56; N, 4.20. Calc for C₁₉H₁₅NO₄: C, 71.02; H, 4.71; N, 4.36%).

Acknowledgement—The authors are grateful to Miss K. Suwz, Mukogawa Women's University, for elemental analyses and measurements of UV, IR, ¹H NMR and MS.

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