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The Structure of 2,3-Dihydromenisporphine and the Synthesis of Dauriporphine, Oxoisoaporphine Alkaloids from *Menispermum dauricum* DC.[1)]

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Two structurally unidentified alkaloids (tentatively named bases III and IV[2)]), isolated from *Menispermum dauricum* DC. (Menispermaceae), were found to be dauriporphine (**1**), a known oxoisoaporphine-type alkaloid, and 2,3-dihydromenisporphine (**3**), a new alkaloid of the same type, respectively. The structure of dauriporphine was confirmed by synthesis of 4,5,6,9-tetramethoxy-7*H*-dibenzo[*de*, *h*]quinolin-7-one (**1**).

Keywords——*Menispermum dauricum;* Menispermaceae; oxoisoaporphine alkaloid; 7*H*-dibenzo[*de*, *h*]quinolin-7-one; 2,3-dihydromenisporphine; dauriporphine synthesis

The product, tentatively named base II, isolated from the rhizomes of *Menispermum dauricum* DC. (Menispermaceae) together with five other yellow alkaloids (base III—VII),[2)] was determined from its spectral data to have the structure **2**, and this was confirmed by synthesis. Thus, base II is a new type of isoquinoline alkaloid having a 7*H*-dibenzo[*de*, *h*]quinolin-7-one skeleton, and was named menisporphine.[3)] Since the alkaloid possessed a new skeletal structure, the name of the "oxoisoaporphine-type alkaloids" was proposed for compounds having this new skeleton. Menisporphine (**2**) was the first example of the oxoisoaporphine-type alkaloids.

This paper describes the characterization and the structural establishment of other two alkaloids, tentatively named base III and base IV,[2)] which were also found to be members of this new class of alkaloids.

Identification of Base III as Dauriporphine (1) and Its Synthesis

An authentic sample of base III[2)] was obtained as yellow needles, mp 161—163 °C. This alkaloid was presumed to be identical with the known oxoisoaporphine-type alkaloid dauriporphine[4)] (=bianfugenine[5)]) (**1**) from its spectral data (Table I).

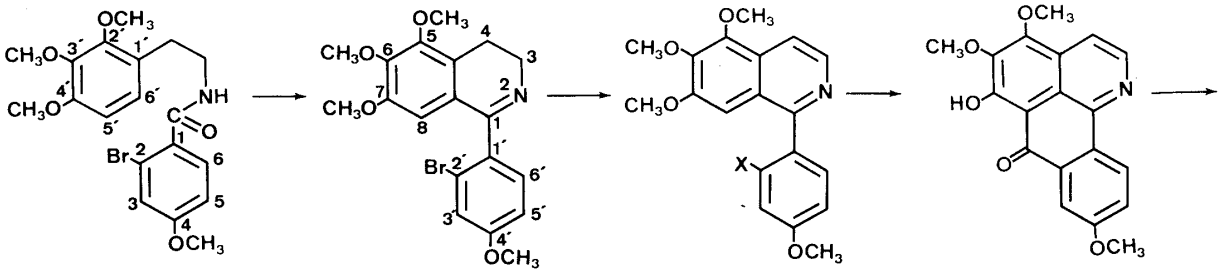
Dauriporphine had been isolated from the vines of the same plant. Although its structure had been deduced to be **1** from its physical data, especially proton nuclear magnetic resonance (^{1}H-NMR) spectral data.[4)] More definite, however, was required for this structural assignment to dauriporphine. An attempt was therefore made to synthesize dauriporphine (=4,5,6,9-tetramethoxy-7*H*-dibenzo[*de*, *h*]quinolin-7-one) (**1**). This synthesis was completed through a similar route to that previously described for **2** (Chart 1).[3)]

Schotten–Baumann reaction of 2,3,4-trimethoxyphenethylamine[6)] and 2-bromo-4-methoxybenzoyl chloride[3)] afforded an 86.9% yield of *N*-(2′,3′,4′-trimethoxyphenethyl)-2-bromo-4-methoxybenzamide (**4**), which was then transformed into 1-(2′-bromo-4′-methoxyphenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (**5**) in 89.5% yield through the standard Bischler–Napieralski reaction. Treatment of **5** with cuprous cyanide in dimethylformamide (DMF) afforded the corresponding cyano-isoquinoline derivative (**6**) in 89.2% yield. This result suggested that dehydrogenation at the 3,4-position of the isoquinoline skeleton

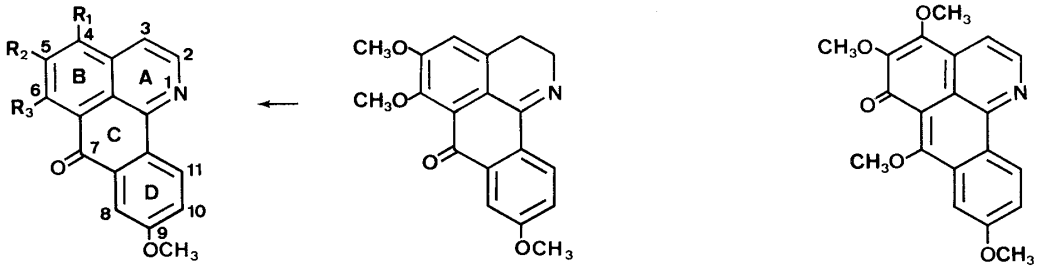
TABLE I. Physicochemical Properties of Oxoisoaporphine Alkaloids

	1 (Base III)	2[a]	3 (Base IV)
mp (°C)	161—163	199.5—200.5	177—180
Molecular formula	$C_{20}H_{17}NO_5$	$C_{19}H_{15}NO_4$	$C_{19}H_{17}NO_4$
UV λ_{max}^{EtOH} (log ε)	210 (4.36), 227 (sh, 4.23), 260 (4.47), 290 (sh, 3.81), 315 (sh, 3.57), 345 (sh, 3.62), 414 (3.78)	254 (4.72), 288 (sh, 4.13), 310 (sh, 3.96), 319 (3.97), 334 (sh, 3.94), 368 (3.91), 420 (3.97)	225 (4.37), 255 (sh, 4.31), 274 (4.42), 372 (3.76)
IR ν_{max}^{KBr} cm^{-1} (conj. C=O)	1640	1660	1665
^{1}H-NMR ($CDCl_3$) δ			
OCH_3	3.98, 4.05, 4.17, 4.27	3.98, 4.08, 4.15	3.93, 3.96, 3.98
$ArCH_2CH_2N$–	—	—	2.83 (2H×2, t, J=7.5 Hz)
Aromatic protons			
C-2	8.68 (d, J=5.7 Hz)	8.65 (d, J=5.5 Hz)	—
C-3	7.93 (d, J=5.7 Hz)	7.55 (d, J=5.5 Hz)	—
C-4	—	7.40 (s)	7.00 (s)
C-8	7.87 (d, J=2.8 Hz)	7.86 (d, J=2.5 Hz)	7.68 (d, J=3.5 Hz)
C-10	7.32 (dd, J=2.8, 8.9 Hz)	7.33 (dd, J=2.5, 9.0 Hz)	7.28 (dd, J=3.5, 8.5 Hz)
C-11	8.79 (d, J=8.9 Hz)	8.79 (d, J=9.0 Hz)	8.24 (d, J=8.5 Hz)
MS m/z (%)	352, 351 (M^+, base peak), 350, 337, 336 (M^+-CH_3), 322 ($M^+ +1-OCH_2$), 306 ($336-OCH_2$), 293 ($M^+ -OCH_2CO$)	321 (M^+, base peak), 306 (M^+-CH_3), 293 ($M^+ -CO$), 278 ($306-CO$), 261	323 (M^+, base peak), 321, 308 (M^+-CH_3), 306, 294 ($M^+ +1-OCH_2$, 292, 280 ($308-CO$), 278, 263

a) These data are cited from reference 3.



4 5 6 : X=CN 7 : X=COOH 8 : X=$COOCH_3$ 9



1 : R_1=R_2=R_3=OCH_3
2 : R_1=H, R_2=R_3=OCH_3
10 : R_1=R_3=H, R_2=OCH_3
11 : R_1=H, R_2+R_3=OCH_2O

3 12

Chart 1

and substitution of the bromine atom by the cyano group occurred concurrently. The cyano compound (**6**) was hydrolyzed to give the corresponding carboxylic acid (**7**), which was an amino acid soluble in water. For purification, the crude amino acid (**7**) was converted into its methyl ester by treatment with diazomethane ethereal solution. Recrystallization of the crude ester give the pure ester (**8**), colorless plates, mp 131.5—134.5 °C, in 54.7% overall yield from **6**. Hydrolysis of the ester (**8**) regenerated the carboxylic acid (**7**). The second cyclization of this carboxylic acid (**7**) with polyphosphoric acid afforded 6-hydroxy-4,5,9-trimethoxy-7*H*-dibenzo[*de*, *h*]quinolin-7-one (**9**), which was produced by cyclization and demethylation of a methoxyl group at the C-6 position. The compound (**9**), without purification, was methylated with methyl iodide in the presence of silver oxide to give two yellow isomers, **1**, mp 159—161.5 °C and **12**, mp 201—203.5 °C in 38.1% and 10.3% yields, respectively. In their ^{1}H-NMR spectra, the aromatic proton signals of the A ring of the latter appeared somewhat upfield from those of the former. Furthermore, the aromatic proton signals of the D ring of the latter appeared downfield from those of the former. These observations could be rationalized by assuming a shielding effect of the carbonyl group. Accordingly, the former is represented by the formula (**1**), 4,5,6,9-tetramethoxy-7*H*-dibenzo[*de*, *h*]quinolin-7-one and the latter by the formula (**12**), 4,5,7,9-tetramethoxy-6*H*-dibenzo[*de*, *h*]quinolin-6-one, which is the enol methyl ether of **9**. The compound (**1**) was identical with dauriporphine from the natural source on the basis of direct comparison of their ultraviolet (UV) spectra, infrared (IR) spectra, mass spectra (MS), ^{1}H-NMR, thin-layer chromatograms (TLC), and mixed melting point determination. Therefore, the structure of dauriporphine is unequivocally represented by the formula (**1**).

Structure of 2,3-Dihydromenisporphine (=Base IV) (3)

Next, the structure of base IV was examined, base IV forms yellow needles, mp 177—180 °C from acetone.[2] Since only a very small amount of this alkaloid was available, elemental analysis could not be performed. The molecular formula ($C_{19}H_{17}NO_4$), however, was established by the MS measurement and the number of protons in its ^{1}H-NMR spectrum. The highly conjugated carbonyl chromophore like those of **2** and **1** was suggested by the UV and IR spectra. The ^{1}H-NMR spectrum of base IV showed four aromatic proton signals due to 1,2,4-trisubstituted and pentasubstituted benzene ring systems like those of **2**. However, a marked difference was observed between the ^{1}H-NMR spectrum of base IV with that of **2**. In the spectrum of base IV, two aromatic proton signals characteristic of the C-2 and C-3 protons of the 7*H*-dibenzo[*de*, *h*]quinolin-7-one skeleton were absent and four methylene proton signals, which are absent in the spectrum of **2**, were observed. These observations suggested that base IV is the 2,3-dihydro derivative (**3**) of **2**. This deduction was also supported by the MS data. In order to obtain more direct evidence for the structure of base IV, dehydrogenation of base IV was carried out; treatment of base IV with chromium trioxide in acetic acid gave **2**. Thus, base IV can be represented by the formula **3**, 5,6,9-trimethoxy-2,3-dihydro-7*H*-dibenzo[*de*, *h*]quinolin-7-one, and we propose the name 2,3-dihydromenisporphine for base IV.

This new alkaloid (**3**) is the fifth example of the oxoisoaporphine-type alkaloids; the others are **2**,[3] **1**, bianfugecine (**10**) and bianfugedine (**11**).[5]

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian A-60 or JNM-FX 200 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Abbreviations used: s=singlet, d=doublet, t=triplet, m=multiplet, and dd=double doublet. MS were determined using a Hitachi RMU-6E instrument with a direct inlet system. Column chromatography was carried out using Merck Silica gel 60 (70—230 mesh). TLC was carried out on glass plates using 0.25-mm thick Merck

Silica gel 60F-254.

Identification of Base III with 1——Base III was recrystallized from acetone–ether mixture to give yellow needles, mp 161—163 °C.[2] The data [UV, IR (KBr), ^{1}H-NMR and MS] are shown in Table I. *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.52; H, 5.01; N, 3.72. Base III was identical with authentic samples of both natural and synthetic dauriporphine **1**.

Synthesis of 1

***N*-(2′,3′,4′-Trimethoxyphenethyl)-2-bromo-4-methoxybenzamide (4)**——An ether solution of 2-bromo-4-methoxybenzoyl chloride, which was formed from the corresponding carboxylic acid (6.02 g) and excess $SOCl_2$ in the usual way, and 200 ml of 10% aqueous NaOH solution were alternately added dropwise to a 300 ml Et_2O solution of the amine obtained from 2,3,4-trimethoxyphenethylamine oxalate (6.05 g), with stirring in an ice bath. Stirring was continued for 1 h at the same temperature. The precipitates were filtered off and the ether layer of the filtrate was evaporated to leave the residue. The precipitates and the residue were combined and dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed successively with 10% aqueous HCl solution, 10% aqueous NaOH solution and water, and dried over $MgSO_4$. Removal of the solvent by evaporation left the residue, which was recrystallized from ethyl acetate–petroleum ether to furnish the corresponding benzamide derivative (**4**), colorless plates, mp 89—91 °C [yield 9.58 g (86.9%)]. UV λ_{max}^{EtOH} nm (log ε): 232.5 (sh, 4.20), 251.5 (sh, 3.86), 277.5 (3.47). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1655 (CONH). ^{1}H-NMR ($CDCl_3$) δ: 2.89 (2H, t, J=6.6 Hz, C_β-H×2), 3.61—3.79 (2H, m, C_α-H×2), 3.81, 3.85, 3.85, 3.90 (3H×4, each s, OCH_3×4), 6.30—6.33 (1H, s, NH), 6.63 (1H, d, J=8.5 Hz, $C_{5'}$-H), 6.84 (1H, dd, J=2.4, 8.5 Hz, C_5-H), 6.90 (1H, d, J=8.5 Hz, $C_{6'}$-H), 7.08 (1H, d, J=2.4 Hz, C_3-H), 7.49 (1H, d, J=8.5 Hz, C_6-H). MS *m/z* (%): 425 (11.6), 423 (M^+, 11.5), 215 (14.4), 213 ($CH_3O\cdot Br\cdot C_6H_3CO^+$, 14.4), 195 ($(CH_3O)_3C_6H_2CH_2CH_2^+$, 22.9), 194 (base peak), 181 ($(CH_3O)_3C_6H_2CH_2^+$, 15.9), 179 (21.2), 166 (181-CH_3, 9.7). *Anal.* Calcd for $C_{19}H_{22}BrNO_5$: C, 53.78; H, 5.23; N, 3.30. Found: C, 53.65; H, 5.22; N, 3.07.

1-(2′-Bromo-4′-methoxyphenyl)-5,6,7-trimethoxy-3,4-dihydroisoquinoline (5)——A mixture of the benzamide (**4**) (1.27 g) and $POCl_3$ (6.38 ml) in dry toluene (20 ml) was refluxed for 2.5 h at 120—140 °C. Evaporation of excess reagent and the solvent left the residue, which was thoroughly washed with petroleum ether. The residual excess reagent was decomposed by addition of MeOH (2 ml). Then, the methanol solution was diluted with 10% aqueous HCl, and the acidic solution was washed twice with Et_2O, made alkaline with 10% aqueous NH_4OH, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and the solvent was evaporated off to give a brownish-yellow oil showing a single spot on TLC [yield 1.10 g (90.2%)]. UV λ_{max}^{EtOH} nm (log ε): 222.5 (sh, 4.54), 279 (4.09), 318.5 (sh, 3.54); $\lambda_{max}^{EtOH+5\%HCl}$ nm (log ε): 329 (4.12). ^{1}H-NMR ($CDCl_3$) δ: 2.81 (2H×2, t, J=2.0 Hz, CH_2×2), 3.66, 3.85, 3.89, 3.92 (3H×4, each s, OCH_3×4), 6.28 (1H, s, C_8-H), 6.93 (1H, dd, J=2.7, 8.3 Hz, $C_{5'}$-H), 7.15 (1H, d, J=2.7 Hz, $C_{3'}$-H), 7.30 (1H, d, J=8.3 Hz, $C_{6'}$-H). MS *m/z* (%): 408 (10.0), 407 (41.2), 406 (M^+, 20.5), 405 (43.7), 404 (11.0), 392 (M^+-CH_2, 12.1), 390 (404-CH_2, 13.4), 327 (21.5), 326 (M^+-Br, base peak), 310 (11.0), 296 (15.2), 265 (15.2). The hydrochloride was obtained as colorless needles, mp 182—184.5 °C, from Me_2CO. *Anal.* Calcd for $C_{19}H_{20}BrNO_4\cdot HCl$: C, 51.54; H, 4.78; N, 3.16. Found: C, 51.59; H, 4.68; N, 3.18.

1-(2′-Cyano-4′-methoxyphenyl)-5,6,7-trimethoxyisoquinoline (6)——A solution of oily free amine (**5**), obtained from the above hydrochloride (1.2 g), and cuprous cyanide (0.44 g) in DMF (13 ml) was heated for 5 h at 180 °C. The mixture was poured into 100 ml of ice water, made alkaline with 10% aqueous NH_4OH solution and extracted five times with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$ and evaporated. The dark brown residue in ether was chromatographed on silica gel, and elution of the column with ether gave a powder. Trituration of the powder with EtOH gave crystals, which were recrystallization from EtOH to afford **6** as colorless needles, mp 134—137.5 °C [yield 0.923 g (89.2%)]. UV λ_{max}^{EtOH} nm (log ε): 243 (4.65), 296 (sh, 3.83), 343 (3.80). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2250 (CN). ^{1}H-NMR ($CDCl_3$) δ: 3.83, 3.93, 4.03, 4.08 (3H×4, each s, OCH_3×4), 6.81 (1H, s, C_8-H), 7.26 (1H, dd, J=2.7, 8.5 Hz, $C_{5'}$-H), 7.35 (1H, d, J=2.7 Hz, $C_{3'}$-H), 7.58 (1H, d, J=8.5 Hz, $C_{6'}$-H), 7.91 (1H, d, J=5.6 Hz, C_4-H), 8.54 (1H, J=5.6 Hz, C_3-H). MS *m/z* (%): 351 (22.8), 350 (M^+, base peak), 336 (M^+-CH_2, 16.1), 335 (M^+-CH_3, 36.2), 307 (335−CO, 47.6), 292 (307−CH_3, 36.2), 264 (292−CO, 26.8), 249 (264−CH_3, 38.2), 221 (249−CO, 26.1). *Anal.* Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.43; H, 5.08; N, 7.78.

1-(2′-Methoxycarbonyl-4′-methoxyphenyl)-5,6,7-trimethoxyisoquinoline (8)——A solution of the cyano derivative (**6**) (5.80 g) in 30 ml of 40% ethanolic KOH solution was heated under reflux until the evolution of NH_3 gas ceased (about 40 h). The solution was neutralized to pH 7 with concentrated hydrochloric acid, and ethanol was evaporated off *in vacuo*. The concentrated solution was extracted with butanol five times, and the butanol was evaporated off *in vacuo*. The residue was dissolved in a small volume of MeOH, and excess CH_2N_2 solution in ether was added. The mixture was left overnight, the excess reagent and solvents were removed by evaporation, and the residue was dissolved in 10% aqueous HCl, then washed with H_2O and ether. The acidic layer was made alkaline with 10% aqueous NH_4OH solution and extracted repeatedly with ether. The ethereal extract was washed with H_2O and dried over anhyd. $MgSO_4$, and the solvent was evaporated off. The residue in ether was purified by silica gel column chromatography; elution with ether gave crystals, which were recrystallized from petroleum ether–ethyl acetate mixture to afford **8** as colorless plates, mp 131.5—134.5 °C [yield 3.47 g (54.7%)]. UV λ_{max}^{EtOH} nm (log ε): 243 (4.97), 341 (3.95); $\lambda_{max}^{EtOH+5\%HCl}$ 214 (4.73), 262 (4.66), 305 (4.05), 360 (3.86). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1290, 1130 ($ArCOOCH_3$). ^{1}H-NMR ($CDCl_3$) δ: 3.45 (3H, s, $ArCOOCH_3$), 3.77, 3.94, 4.01, 4.07 (3H×4, each s, OCH_3×4), 6.73 (1H, s, C_8-H), 7.18

(1H, dd, J=2.7, 8.5 Hz, C_5-H), 7.44 (1H, d, J=8.5 Hz, C_6-H), 7.58 (1H, d, J=2.7 Hz, C_3-H), 7.82 (1H, d, J=5.6 Hz, C_4-H), 8.45 (1H, d, J=5.6 Hz, C_3-H). MS m/z (%): 384 (24.8), 383 (M^+, base peak), 368 (M^+-CH_3, 10.1), 353 (13.7), 352 (M^+-OCH_3, 52.8), 337 (352−CH_3, 11.6), 310 (13.1), 309 (337−CO, 4.0), 294 (309−CH_3, 13.4). *Anal.* Calcd for $C_{21}H_{21}NO_6$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.60; H, 5.45; N, 3.40.

4,5,6,9-Tetramethoxy-7*H*-dibenzo[*de*, *h*]quinolin-7-one (=Dauriporphine) (1) and Its Isomer (12)——A mixture of the methyl ester (**8**) (4.23 g) and 80 ml of concentrated hydrochloric acid was heated under reflux for 2.5 h. The whole was poured into H_2O, neutralized to pH 7 with 10% aqueous KOH solution and thoroughly extracted with butanol. The solvent was evaporated off *in vacuo* and a solution of the unpurified residual crude product (**7**) in 20 ml of polyphosphoric acid was heated at 130 °C for 2 h. The mixture was poured into ice water, made alkaline with 10% aqueous NH_4OH solution, and extracted five times with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O, dried over $MgSO_4$ and evaporated to dryness to leave the crude residue (**9**). A solution of the residue (**9**) (410 mg) in MeOH (7.8 ml) and $CHCl_3$ (11.5 ml) was heated under reflux with Ag_2O (1.87 g) and methyl iodide (17.4 ml) at 60 °C for 12 h with stirring. The reaction mixture was filtered and the collected precipitate was thoroughly washed with hot $CHCl_3$. The filtrate and washing were combined, washed with H_2O and dried. The solvent was evaporated off to leave the residue, which was taken up in CH_2Cl_2 and chromatographed on a silica gel column. Elution of the column with hexane–CH_2Cl_2 (1 : 1) mixture gave two kinds of yellow crystals, **1** and its isomer **12**, 4,5,7,9-tetramethoxy-6*H*-dibenzo[*de*, *h*]quinolin-6-one. The former yellow crystals were recrystallized from MeOH to afford yellow needles, mp 159—161.5 °C [yield 1.48 g (38.1%)], which were shown to be identical with natural dauriporphine **1** by direct comparison [UV (EtOH), IR (KBr), ^{1}H-NMR ($CDCl_3$), MS and TLC]. *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.29; H, 4.77; N, 4.09. The latter yellow needles (from MeOH), mp 201—203 °C [yield 0.40 g (10.3%)]. UV λ_{max}^{EtOH} nm (log ε): 218 (sh, 4.45), 239 (4.60), 283 (sh, 4.15), 307 (sh, 3.87), 361 (4.08), 421 (sh, 3.65). IR ν_{max}^{KBr} cm^{-1}: 1615 (conj. C=O). ^{1}H-NMR ($CDCl_3$) δ: 4.02, 4.03, 4.23, 4.30 (3H×4, each s, OCH_3×4), 7.76 (1H, dd, J=3.0, 9.0 Hz, C_{10}-H), 8.12 (1H, d, J=3.0 Hz, C_8-H), 8.19 (1H, d, J=4.5 Hz, C_3-H), 8.98 (1H, d, J=4.5 Hz, C_2-H), 9.12 (1H, d, J=9.0 Hz, C_{11}-H). MS m/z (%): 351 (M^+, base peak), 337 (53.2), 336 (M^+-CH_3, 90.7), 322 (M^++1−OCH_2, 33.7), 306 (336−OCH_2, 22.8), 293 (M^+-OCH_2-CO, 38.7). *Anal.* Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.14; H, 4.63; N, 3.91.

Identification of the Dehydrogenated Product of Base IV (=2,3-Dihydromenisporphine) (3) as 2 by TLC——An authentic sample of base IV was obtained by recrystallization from acetone as yellow needles, mp 177—180 °C, and its spectral data are shown in Table I. The TLC was performed on glass plates after treatment of base IV (**3**) with CrO_3 in acetic acid. The spot of the dehydrogenated product exhibited the same *Rf* value as that of authentic menisporphine (**2**). A mixture of AcOEt and $CHCl_3$ (1 : 5) was used as the developing solvent.

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References and Notes

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