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Dimerization of Diphenolic Benzylisoquinolines by Phenolic Oxidative Coupling (Studies on the Syntheses of Heterocyclic Compounds. CXXVIII[1])

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Ferric chloride oxidative coupling of 1,2,3,4-tetrahydro-7-hydroxy-1-(2-hydroxybenzyl)-6-methoxyisoquinoline (IIb) afforded two dimeric benzylisoquinolines, III in 1.6% yield and V in 1.1% yield, respectively. Eschweiler–Clarke reaction of III gave the corresponding N-methyl derivative (IV), which was identified with authentic sample.

Ferricyanide oxidative coupling of 1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (IId) also gave the dimeric benzylisoquinoline (VI) in 0.4% yield, which was characterized by microanalysis and spectral data.

In the preceding paper,[3] the present authors reported that the oxidative coupling of 1,2,3,4-tetrahydro-7-hydroxy-1-(2-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (IIc) resulted in the formation of the diphenyl ether derivative (IV). Here we wish to report on the phenolic oxidative coupling of 1,2,3,4-tetrahydro-7-hydroxy-1-(2-hydroxybenzyl)-6-methoxyisoquinoline (IIb) and 1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxybenzyl)-6-methoxy-2-methylisoquinoline[4] (IId), in order to examine whether the formation of diphenyl ether linkage in case of these compounds would be possible or not.

The starting material (IIb) was synthesized as follows. 7-Benzyloxy-1-(2-benzyloxybenzyl)-3,4-dihydro-6-methoxyisoquinoline[3] (I) was reduced with sodium borohydride to afford 7-benzyloxy-1-(2-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (IIa), which was debenzylated with ethanolic concentrated hydrochloric acid solution to give the desired diphenol (IIb).

A solution of the hydrochloride of the diphenol (IIb) was treated with 7.5 molar equivalents of ferric chloride hexahydrate at 30—40° for 40 hr. After working up as usual, column chromatography of the resultant brownish gum using silicic acid was carried out, to give two phenolic fractions ("Fast Dimer" and "Slow Dimer") although in low yields. These are

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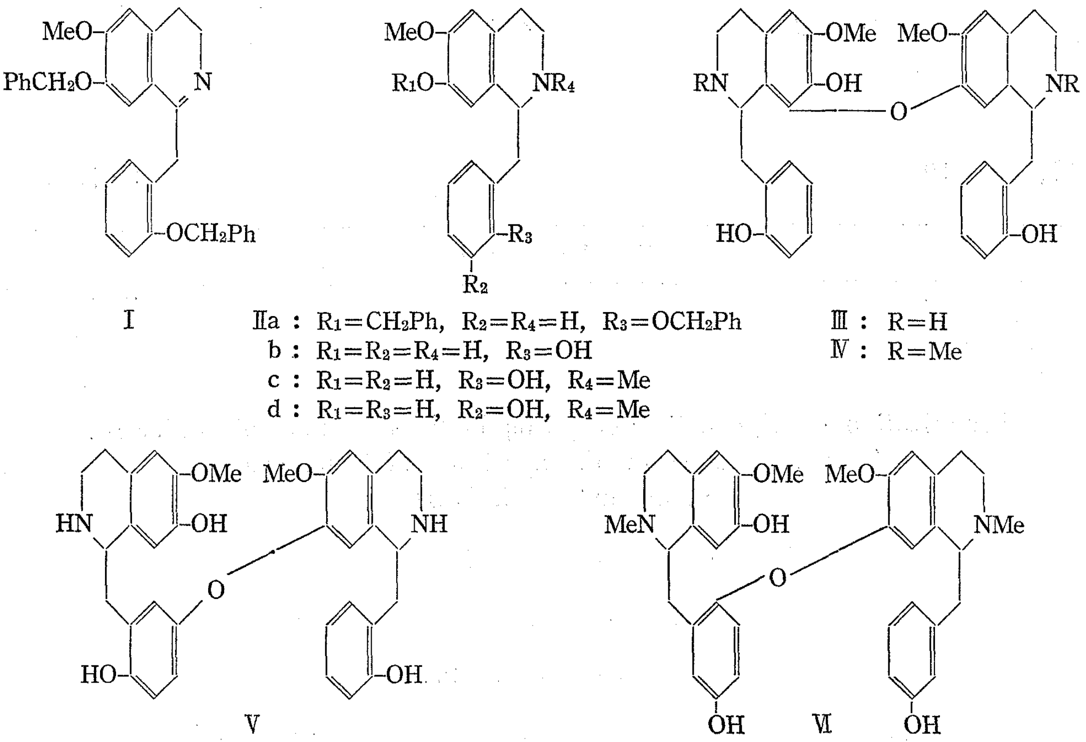
[1] Part CXXVII: T. Kametani, T. Sugahara, and K. Fukumoto, *Chem. Ind.* (London), **1969**, 833.
[2] Location: *Aobayama, Sendai.*
[3] T. Kametani and I. Noguchi, *J. Chem. Soc.* (*C*), **1969**, 502.
[4] I. Baxter, L.T. Allan, and G.A. Swan, *J. Chem. Soc.*, **1965**, 3645.

named due to the behavior of chromatography. Namely the former eluant means "Fast Dimer" and the latter is "Slow Dimer." These compounds were assigned to the structures, (V and III), respectively.



I

IIa : $R_1=CH_2Ph$, $R_2=R_4=H$, $R_3=OCH_2Ph$
b : $R_1=R_2=R_4=H$, $R_3=OH$
c : $R_1=R_2=H$, $R_3=OH$, $R_4=Me$
d : $R_1=R_3=H$, $R_2=OH$, $R_4=Me$

III : R=H
IV : R=Me

V

VI

Chart 1

One of the phenolic fractions, "Fast Dimer," mp 151°, had the molecular formula of $C_{34}H_{36}O_6N_2$ on the basis of microanalysis and mass spectrometry (*m/e* 568, M^+; *m/e* 284, M^{2+}) and its infrared (IR) spectrum showed the hydroxy (3500 cm^{-1}), NH (3300 cm^{-1}), and C–O–C stretching (1110 cm^{-1})[3,5] absorptions. Nuclear magnetic resonance (NMR) spectrum[6–8] of the compound showed four singlets due to aromatic protons at 6.55, 6.53, 6.23, and 6.21 ppm and two singlets due to two methoxyl groups at 3.88 and 3.83 ppm. Furthermore, a complex pattern due to seven aromatic protons at 7.25—6.10 ppm and a multiplet corresponding to two NH and three hydroxy groups were observed at 6.00—5.10 ppm. The signal at 6.00—5.10 ppm disappeared on treatment with deuterium oxide. These facts reveal that this compound has three hydroxy groups and that it shows the dimeric structure containing a C–O–C linkage. The mass spectrum[9] of the "Fast Dimer" showed a molecular ion peak at *m/e* 568. In addition, a strong peak at *m/e* 461 (M^+-107) seems to be formed through radical cleavage at the C_1-benzyl position and further cleavage at another benzyl position forms strong four ion species at *m/e* 283 (M^+-285), *m/e* 282 (M^+-286), *m/e* 178 (M^+-390), and *m/e* 163 (M^+-405).[10,11] These fragmentations were supported by the appearance of each metastable ion species. Considering the position of the diphenyl ether linkage at the benzylic group, the coupling at the *para* position to hydroxy group is less hindered than at the *ortho* position. Moreover, the ultraviolet (UV) spectrum[6] of the compound showed λ_{max} 283 mμ (log ε 4.04). These facts reveal the "Fast Dimer" to be a head to tail type dimeric benzylisoquinoline which is represented by the planar structural formula (V).

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5) B. Franck and G. Blaschke, *Ann.*, **668**, 145 (1963).
6) M. Tomita, H. Furukawa, T.H. Yang, and T.J. Lin, *Chem. Pharm. Bull.* (Tokyo), **13**, 39 (1965).
7) H. Furukawa, *Yakugaku Zasshi*, **86**, 883 (1966).
8) H. Furukawa, *Yakugaku Zasshi*, **85**, 335 (1965).
9) D.C. DeJongh, S.R. Shrader, and M.P. Cava, *J. Am. Chem. Soc.*, **88**, 1052 (1966).

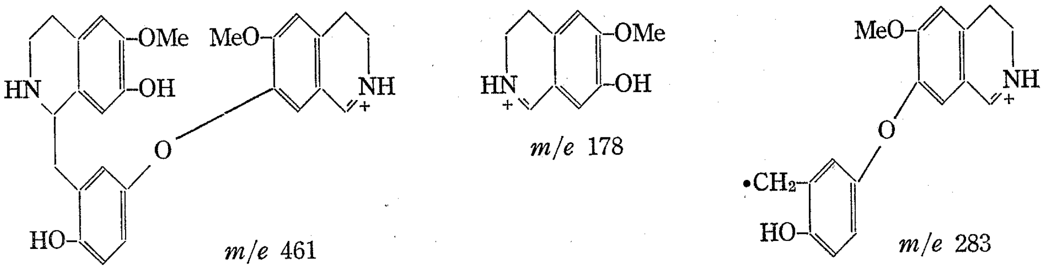
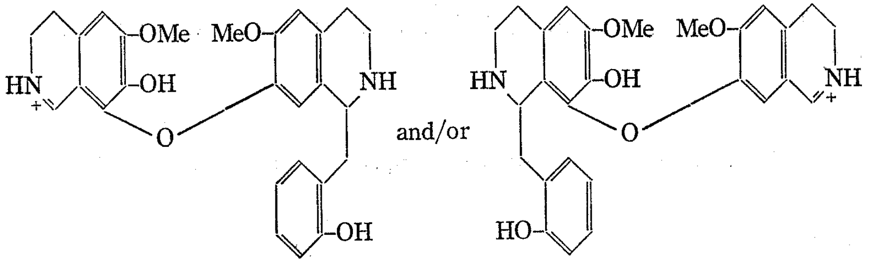

m/e 461 m/e 178 m/e 283

Chart 2

The second compound, "Slow Dimer", mp 157°, showed hydroxy (3500 cm^{-1}), NH (3300 cm^{-1}), and C–O–C stretching (1110 cm^{-1}) absorptions in its IR spectrum.[3,5] The NMR spectrum[3] of this compound showed three singlets due to three aromatic protons at 6.52, 6.51, and 6.20 ppm and two singlets corresponding to two methoxyl groups at 3.89 and 3.81 ppm. Furthermore, a multiplet due to two NH and three hydroxy groups at 5.50—4.50 ppm was observed and disappeared on treatment with deuterium oxide.

Mass spectrum[9–12] of the "Slow Dimer" (III) showed a molecular ion peak at *m/e* 568. In addition, a fragment at *m/e* 461 (M^{+}-107) appeared through the loss of one benzylic group, and a doubly charged ion at *m/e* 177 (M-214)$^{2+}$ as the base peak was shown with an isotopic peak at *m/e* 177.5 due to the loss of another benzylic group.[10,11] These facts were closely similar to those of IV.[3] These fragmentation patterns have been also observed in case of alkaloids of *Demerara Greenheart*.[12]


m/e 461

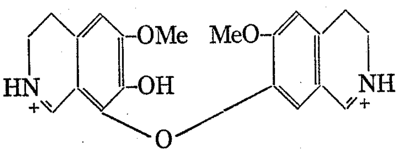

m/e 177

Chart 3

Furthermore, Eschweiler–Clarke reaction of III afforded N-methyl derivative, mp 157°, and its IR (CHCl$_3$), NMR, and UV spectra and thin–layer chromatography (*Rf*) were identical with those of the preceding diastereoisomeric mixture[3] with the planar structural formula (IV).

In case of Franck's work[5] *dl*-magnocurarine iodide has been oxidized to the corresponding diquarternary diphenyl ether derivative. It is interesting that the conversion of the diphenol (IIb) to the compounds having a diphenyl ether linkage by phenolic oxidation has been achieved successfully, since no attempts to oxidize the 1,2,3,4-tetrahydrobenzylisoquinoline derivatives having NH group have been carried out.

On the other hand, the oxidative coupling of 1,2,3,4-tetrahydro-7-hydroxy-1-(3-hydroxy benzyl)-6-methoxy-2-methylisoquinoline (IId) has been studied under a variety of condi-

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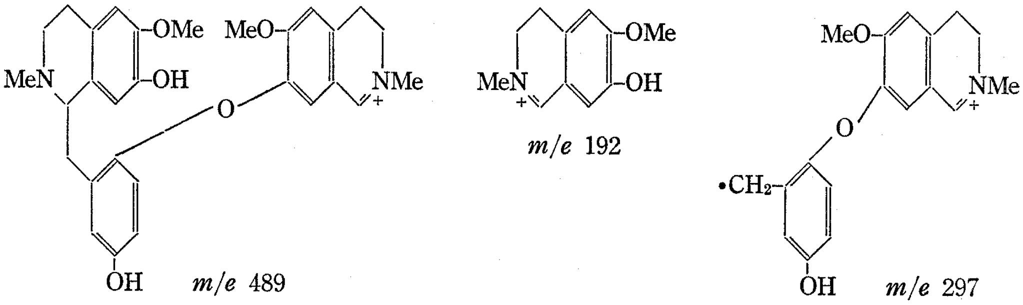
10) H. Budzikiewicz, C. Djerassi, and D.H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry*, Vol. I, Holden-Day, Inc., San Francisco, Calif., 1964, p. 174.

11) C. Djerassi, H.W. Brewer, C. Clarke, and L.J. Durham, *J. Am. Chem. Soc.*, **84**, 3210 (1962).

12) K.C. Charn, M.T.A. Evans, C.H. Hassall, and A.M.W. Sangster, *J. Chem. Soc.* (*C*), **1967**, 2479.

tions.[13-16] Although polymeric products had been often produced according to Jackson and Martin's method,[17] the dimeric benzylisoquinoline (VI) was obtained in poor yield (0.4%) with aqueous potassium ferricyanide buffered with ammonium acetate in our case. The dimer (VI) was found to have the molecular formula of $C_{36}H_{40}O_6N_2$ on the basis of microanalysis and mass spectrometry, and its IR spectrum (KBr) also showed hydroxy (3400 cm^{-1}), N-methyl (2805 cm^{-1}), and C–O–C stretching (1120 cm^{-1}) absorptions. Furthermore, the NMR spectrum[6] of the compound (VI) showed two singlets due to two methoxyl groups at 3.86 and 3.83 ppm and two singlets corresponding to two N-methyl groups at 2.39 and 2.23 ppm.



m/e 489 m/e 192 m/e 297

Chart 4

Furthermore, in its high resolution mass spectrum[9,18] the fragmentations in details were summarized in Table I and these calculated data supported the fragmentation pattern as shown in Chart 4.

Table I. High Resolution Mass Spectrum of the Dimer (VI)

Ion	m/e (Found)	m/e (Calcd.)	Relative intensity (%)
$C_{29}H_{33}O_5N_2$	489.240	489.239	12
$C_{29}H_{31}O_5N_2$	487.224	478.223	7
$C_{18}H_{19}O_3N$	297.133	297.136	8
$C_{18}H_{20}O_2N$	282.146	282.146	6
$C_{11}H_{14}O_2N$	192.105	192.102	76
$C_{10}H_{10}ON$	160.007	160.076	100

Considering the position of the diphenyl ether linkage at the benzylic group, the resulting radical at the *para* position to the hydroxy group was assumed to be more stable than that at the *ortho* position. The above results also support that the planar structural formula of the dimer (VI) would be correct. Tomita and co-workers[18b] reported that the potassium ferricyanide oxidation of *dl*-4′-O-methyl-N-methylcoclaurine afforded two stereoisomers of the head to head type diphenyl ether derivative. It is very interesting that a variety of bisbenzylisoquinoline alkaloids would be synthesized by phenolic oxidative coupling.

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13) A.H. Jackson and J.A. Martin, *J. Chem. Soc.* (*C*), **1966**, 2222.
14) W.W. Chan and P. Maitland, *J. Chem. Soc.* (*C*), **1966**, 753.
15) T. Kametani and I. Noguchi, *J. Chem. Soc.* (*C*), **1967**, 1440.
16) T. Kametani and I. Noguchi, *J. Chem. Soc.* (*C*), **1968**, 480.
17) A.H. Jackson and J.A. Martin, *J. Chem. Soc.* (*C*), **1966**, 2061.
18) *a*) B. Willhalm, A.F. Thomas, and E. Gautschi, *Tetrahedron*, **20**, 1185 (1964); *b*) M. Tomita, Y. Masaki, K. Fujitani, and Y. Sakatani, *Chem. Pharm. Bull.* (Tokyo), **16**, 688 (1968).

Experimental[19]

7-Benzyloxy-1-(2-benzyloxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (IIa)——To a solution of 3.0 g of the 3,4-dihydroisoquinoline (I) hydrochloride in 50 ml of MeOH was added portionwise 1.0 g of $NaBH_4$, and the mixture was allowed to stand at room temperature for 30 min. After one hour's refluxing, removal of the solvent gave the residue, which was treated with 20 ml of water and extracted with benzene. The extract was washed with water, dried over K_2CO_3, and evaporated to give 2.2 g of the 1,2,3,4-tetrahydroisoquinoline (IIa) as a colorless syrup. IR cm^{-1} ($CHCl_3$): ν_{NH} 3350. NMR (ppm) ($CDCl_3$): 7.34 (10H, broad singlet, $2\times C_6\underline{H}_5$), 6.58 (1H, singlet, C_5–$\underline{H}$), 5.02, 4.78 (4H, two singlets, $2\times OC\underline{H}_2C_6H_5$), 3.78 (3H, singlet, $OC\underline{H}_3$), 1.75 (1H, multiplet, $N\underline{H}$).

It formed a picrate, mp 151—153°, as yellow prisms (from MeOH–ether). *Anal.* Calcd. for $C_{31}H_{31}O_3N\cdot C_6H_3O_7N_3$: C, 63.94; H, 4.93; N, 8.06. Found: C, 64.02; H, 5.10; N, 7.58. IR cm^{-1} (KBr): ν_{NO_2} 1530, 1330.

1,2,3,4-Tetrahydro-7-hydroxy-1-(2-hydroxybenzyl)-6-methoxyisoquinoline (IIb)——A solution of 1.8 g of the foregoing tetrahydroisoquinoline (IIa) in 60 ml of EtOH and 60 ml of conc. HCl was heated under reflux for 4 hr and the solvent was evaporated to dryness. After the residue had been washed with ether, recrystallization from MeOH–ether afforded 0.9 g of the desired diphenolic tetrahydroisoquinoline (IIb) hydrochloride as colorless prisms, mp 266—268° (decomp.). *Anal.* Calcd. for $C_{17}H_{19}O_3N\cdot HCl$: C, 63.41; H, 6.26; N, 4.35. Found: C, 63.30; H, 6.30; N, 4.09. IR cm^{-1} (KBr): ν_{OH} 3500, $\nu^{+}{}_{NH_2}$ 2800—2500.

A suspension of 0.8 g of the above hydrochloride in 100 ml of AcOEt was basified with 10% aq. NH_4OH solution carefully and the organic layer was separated. The solvent was dried over Na_2SO_4 and distilled to give 0.6 g of the free base (IIa) as a colorless powder. Recrystallization from ether gave the phenolic base (IIb) as colorless prisms, mp 171—172°. *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.55; H, 6.71; N, 4.91. Found: C, 71.71; H, 6.99; N, 4.55. IR cm^{-1} (KBr): ν_{OH} 3400, ν_{NH} 3300. NMR (ppm) ($CDCl_3$): 6.49 (1H, singlet, C_5–$\underline{H}$), 6.15—5.50 (3H, multiplet, $2\times O\underline{H}$, $N\underline{H}$), 3.83 (3H, singlet, $OC\underline{H}_3$).

Oxidation of 1,2,3,4-Tetrahydro-7-hydroxy-1-(2-hydroxybenzyl)-6-methoxyisoquinoline (IIb)——A solution of 9.9 g of ferric chloride hexahydrate in 30 ml of water was added dropwise with stirring to a solution of 1.6 g of the diphenolic isoquinoline (IIb) hydrochloride [obtained from (IIb) as usual] in 200 ml of water at room temperature in a current of nitrogen. In this case the solution became dark green. After stirring at 30—40° for further 40 hr, the reaction mixture was basified with 10% aq. NH_4OH solution and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 840 mg of a pale brownish gum which was chromatographed on 16.0 g of silicic acid under inspection by thin–layer chromatography. Evaporation of the first $CHCl_3$ (containing 2% MeOH) eluate gave a colorless glass, which was crystallized from $CHCl_3$–hexane to afford 32 mg of the "head to tail" dimeric benzylisoquinoline (V) (1.1%) as a colorless powder, mp 151°. *Anal.* Calcd. for $C_{34}H_{36}O_6N_2\cdot 1/2H_2O$[20]: C, 70.65; H, 6.45; N, 4.85. Found: C, 70.97; H, 6.32; N, 4.49. IR cm^{-1} ($CHCl_3$): ν_{OH} 3500, ν_{NH} 3300, $\nu_{=C-O-C=}$ 1110. UV λ_{max}^{MeOH} mμ (log ε): 283 (4.04), 295 (shoulder) (3.76). NMR (ppm) ($CDCl_3$): 6.55, 6.53 (2H, two singlets, C_5– and C_5'–$\underline{H}$), 6.23, 6.21 (2H, two singlets, C_8– and C_8'–$\underline{H}$), 7.25—6.10 (7H, complex pattern, aromatic protons), 6.00—5.10 (5H, multiplet, $3\times O\underline{H}$, $2\times N\underline{H}$), 3.88, 3.83 (6H, two singlets, $2\times OC\underline{H}_3$). Mass (*m/e*): 568 ($M^+$), 461 ($M^+$–107), 300 ($M^+$–268), 284 ($M^{2+}$ or M^+–284), 283 (M^+–285), 282 (M^+–286), 178 (base peak) (M^+–390), 163 (M^+–405), 107 (tropilium ion). TLC[21] *Rf* 0.32.

Evaporation of the second $CHCl_3$ eluate containing 3% MeOH gave a colorless glass, which was crystallized from $CHCl_3$–hexane to afford 46 mg of the "head to head" dimeric benzylisoquinoline (III) (1.6%) as pale yellow grains, mp 157°. *Anal.* Calcd. for $C_{34}H_{36}O_6N_2\cdot 1/2H_2O$[20]: C, 70.65; H, 6.45; N, 4.85. Found: C, 70.94; H, 6.64; N, 4.71. IR cm^{-1} ($CHCl_3$): ν_{OH} 3500, ν_{NH} 3300, $\nu_{=C-O-C=}$ 1110. UV ${}_{max}^{MeOH}$ mμ (log ε): 283 (3.98), 295 (shoulder) (3.76). NMR (ppm) ($CDCl_3$): 6.52, 6.51 (2H, two singlets, C_5– and C_5'–$\underline{H}$), 6.20 (1H, singlet, C_8–$\underline{H}$), 5.50—4.50 (5H, multiplet, $3\times O\underline{H}$, $2\times N\underline{H}$), 3.89, 3.81 (6H, two singlets, $2\times OC\underline{H}_3$). Mass (*m/e*): 568 ($M^+$), 461 ($M^+$–107), 354 ($M^+$–214), 353 ($M^+$–215), 351 ($M^+$–217), 339 ($M^+$–229), 300 ($M^+$–268), 284 ($M^{++}$ or M^+–284), 268 (M^+–300), 177 (base peak) $(M–214)^{++}$, 107 (tropilium ion). TLC[21] *Rf* 0.17.

Eschweiler-Clarke Reaction of (III)——A mixture of 16 mg of the foregoing "head to head" dimeric benzylisoquinoline (III), 0.6 ml of 100% HCOOH and 0.6 ml of 37% HCHO was heated at 90—95° for 3 hr. The reaction mixture was basified with 10% aq. NH_4OH solution and extracted with AcOEt. The extract was washed with water, dried over Na_2SO_4 and evaporated to give a pale yellow gum, which was chromatographed on 1.0 g of silica gel using $CHCl_3$ containing 2% MeOH as an eluant to afford 8 mg of a

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19) All melting points were measured in a sulfuric acid bath and uncorrected. NMR spectra were determined on a Hitachi H–60 spectrometer in $CDCl_3$ and pyridine with TMS as an internal standard. Mass spectra were determined on a Hitachi RMU–6D and a JEOL JMS–OISP high resolution spectrometer.

20) Since its mass spectrum supports the molecular formula with no water of crystallization, this formula as hydrate is correct.

21) Thin–layer chromatography: Wakogel B–5 and the solvent ($CHCl_3$:acetone:MeOH=50:40:1) were used; the spots were detected with iodine vapor.

colorless glass. Recrystallization from $CHCl_3$–hexane gave 6 mg of the desired N-methyl-derivative (IV) as a colorless powder, mp 157°. The IR ($CHCl_3$), NMR and UV spectra and thin-layer chromatography (*Rf*) were identical with those of the authentic diastereoisomeric mixture[3] with the planar structural formula (IV).

Oxidation of 1,2,3,4-Tetrahydro-7-hydroxy-1-(3-hydroxybenzyl)-6-methoxy-2-methylisoquinoline (IId)—— A solution of 10.0 g of potassium ferricyanide in 200 ml of 8% aq. NH_4OAc solution was added dropwise with stirring to a solution of 2.5 g of the diphenol (IId) hydrochloride in 600 ml of 8% aq. NH_4OAc solution. The mixture was kept for 48 hr at room temperature, then basified with 10% aq. NH_4OH solution, and extracted with AcOEt. The extract was dried over Na_2SO_4 and evaporated to give 0.6 g of a brownish powder, which was chromatographed on 20.0 g of silicic acid under inspection by thin-layer chromatography. Evaporation of the $CHCl_3$ eluate containing 6% MeOH gave a pale yellow glass, which was crystallized from MeOH–ether–hexane to afford 19 mg (0.4%) of the dimer (VI) as a pale yellow powder, mp 192°. *Anal.* Calcd. for $C_{36}H_{40}O_6N_2 \cdot H_2O$[20]: C, 70.34; H, 6.88; N, 4.95. Found: C, 70.83; H, 6.49; N, 4.98. IR cm^{-1} (KBr): ν_{OH} 3400, ν_{NCH_3} 2805, $\nu_{=C-O-C=}$ 1120. UV λ_{max}^{MeOH} mμ (log ε): 283 (3.87). NMR (ppm) (pyridine): 3.86, 3.83 (6H, two singlets, $2 \times OC\underline{H}_3$), 2.39, 2.23 (6H, two singlets, $2 \times NC\underline{H}_3$), TLC[22] *Rf* 0.53.

Mass (*m/e*): 596 (M^+), 489 (M^+-107), 487 (M^+-109), 474 (M^+-122), 314 (M^+-282), 298 (M^{2+} or M^+-298), 297 (M^+-299), 282 (M^+-314), 192 (M^+-404), 177 (M^+-419), 175 (M^+-421), 174 (M^+-422), 160 (base peak) (M^+-436), 107 (tropilium ion).

Acknowledgement We thank Miss R. Hasebe for microanalysis, Miss Y. Tadano of Pharmaceutical Institute for NMR spectral determination. We also thank Department of Chemistry, Tohoku University for mass spectral determination, and Nippon Electronics Co., Ltd. for high resolution mass spectral determination.

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[22] A mixture of $CHCl_3$–acetone–MeOH (4:3:2) was used as solvent; the spots were detected with iodine vapor.