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Synthesis of Cularine Type Compounds[1] (Studies on the Syntheses of Heterocyclic Compounds. CCXXXVI[2])

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1-(4-Hydroxy-3-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-8-ol (V) was oxidized with potassium ferricyanide to dienone (VI), which was subjected to dienone-phenol rearrangement with hydrochloric acid in acetic acid to give the cularine type compound (XXI). These reactions provide a possible model for biogenesis of cularine and related alkaloids. Moreover, this paper described the preparation of V.

A hypothetical intermediate in the biogenesis of cularine (I)[4] and related alkaloids is 1,2,3,4-tetrahydroisoquinoline derivative (II). Thus, oxidation of II would lead to either the cularine type of compound (III) or dienone (IV). Further conversion of the latter compound (IV) into III would involve wellknown dienone-phenol rearrangement.

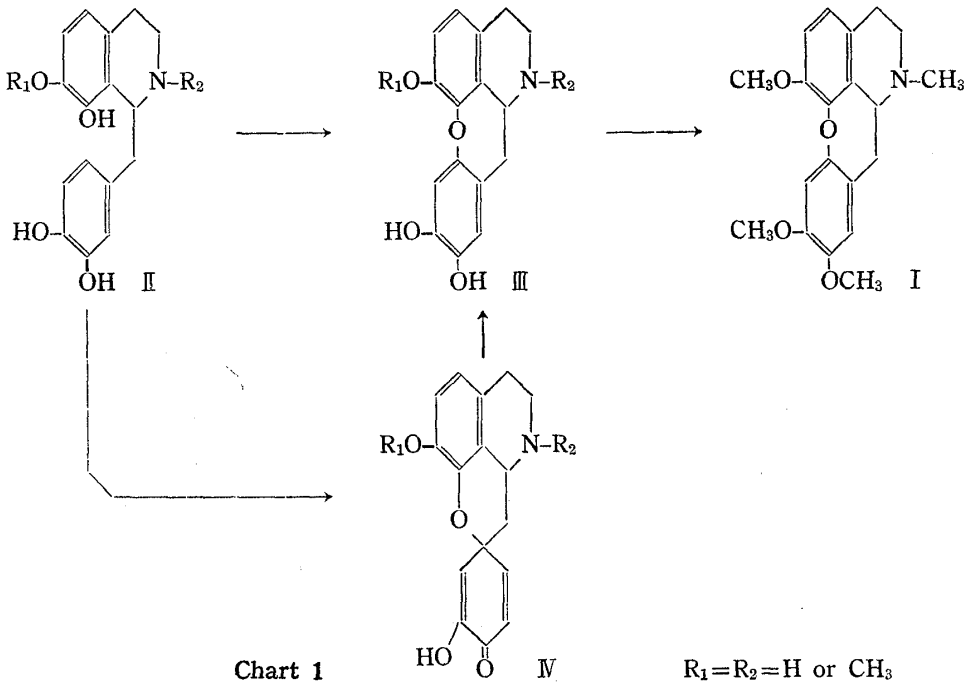
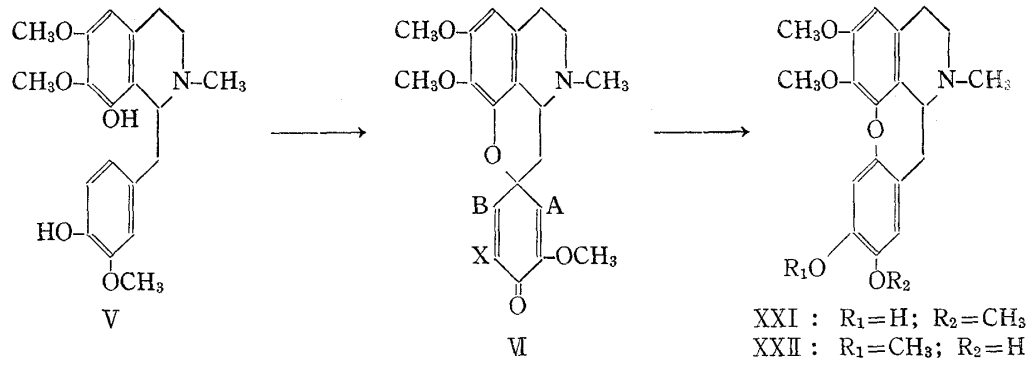


Chart 1 $R_1=R_2=H$ or CH_3

We now provide a laboratory analogy for the latter biogenetic route to a cularine type of compound. The oxidation of V was effected with potassium ferricyanide in the presence of ammonium acetate at room temperature with stirring for 3 hr in a current of nitrogen. The product formed as the hydrochloride, in 3% yield, having mp 173—175° can be assigned the formula (VI) on the basis of the following evidence. Mass-spectral data verified the

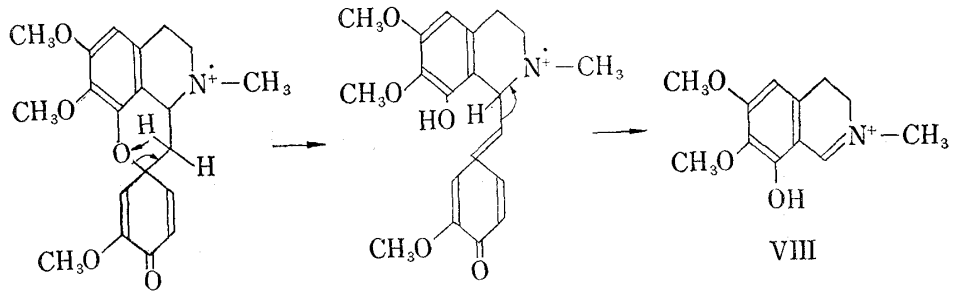
1) Preliminary communication was reported in *Chem. Comm.*, **1967**, 546.
2) Part CCXXXIV: T. Kametani, T. Kobari, and S. Takano, *Yakugaku Zasshi*, **88**, 782 (1968); Part CCXXXV: T. Kametani, K. Fukumoto, H. Yagi, H. Iida, and T. Kikuchi, *J. Chem. Soc.* (C), **1968**, 1178.
3) Location: *No. 85, Kita-4-bancho, Sendai.*
4) R.H.F. Manske, *J. Am. Chem. Soc.*, **72**, 55 (1950); T. Kametani and K. Fukumoto, *J. Chem. Soc.*, **1963**, 4289; T. Kametani, S. Shibuya, S. Seino, and K. Fukumoto, *J. Chem. Soc.*, **1964**, 4146; T. Kametani and S. Shibuya, *J. Chem. Soc.*, **1965**, 5565.



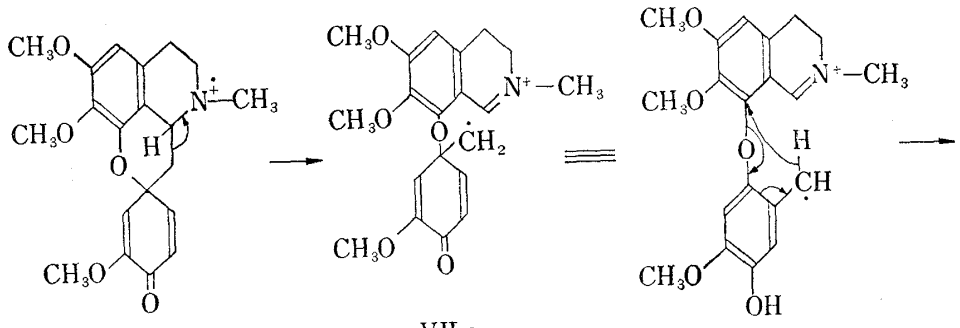
V Ⅵ

XXI : $R_1=H$; $R_2=CH_3$
XXII : $R_1=CH_3$; $R_2=H$

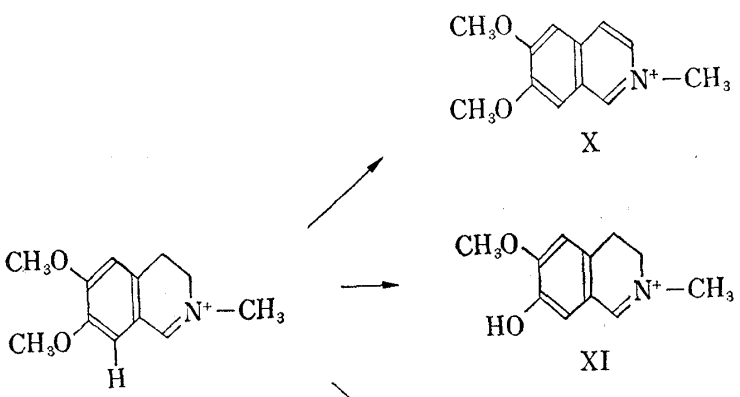
Chart 2



VII VII a VIII



VII b VII c VII d



X

IX XI

XII

Chart 3

formula $C_{20}H_{23}O_5N$, and the infrared [ν_{max} (in $CHCl_3$) 1675/(C=O), 1650 (C=C) cm^{-1}] and ultraviolet (λ_{max}^{MeOH} 231 mμ (log ε=4.42)] spectra were in accord with a dienone structure. The NMR spectrum (in $CDCl_3$) revealed a singlet aromatic proton (3.65 τ), olefinic protons (H_A; 4.08 τ, doublet, $J_{H_AH_B}$=2.5 cps), H_X; 3.90 τ, doublet, $J_{H_BH_X}$=12.5 cps) and (H_B; 3.03, quartet, $J_{H_AH_B}$=2.5 cps, $J_{H_BH_X}$=12.5 cps), O-methyl singlets (6.25, 6.22, and 6.16 τ), N-methyl singlet (7.60 τ), and broad multiplets of methylene groups (6.50—7.30 τ), unambiguously cofirming the structure (VI). Although there can be two isomers as the coupling products in this oxidation, both isomers could not be separated.

Moreover, mass spectrum showed the peaks at the following positions; *m/e* 357 (M^+), 222 (M^+–135), 221 (M^+–136), 220 (M^+–137), 206 (M^+–151, base peak), 204 (M^+–153), 192 (M^+–165), 190 (M^+–167), 178 (M^+–179), 175 (M^+–182), 162 (M^+–195), and 149 (M^+–208). The ion (VIII), M^+–135 peak, is due to the loss of a dienone moiety at 1-position in the isoquinoline ring by way of concerted migration of β-hydrogen to an ethereal oxygen from the molecular ion (VII). Furthermore, α-cleavage of (VII-b), followed by concerted migration of γ-hydrogen in molecular ion (VII-d) gives the ion (IX) (*m/e*; 206), from which the ions, (X) (*m/e*; 204) and (XI) (*m/e*; 192) and the radical ion (XII), seem to be derived by a usual manner.

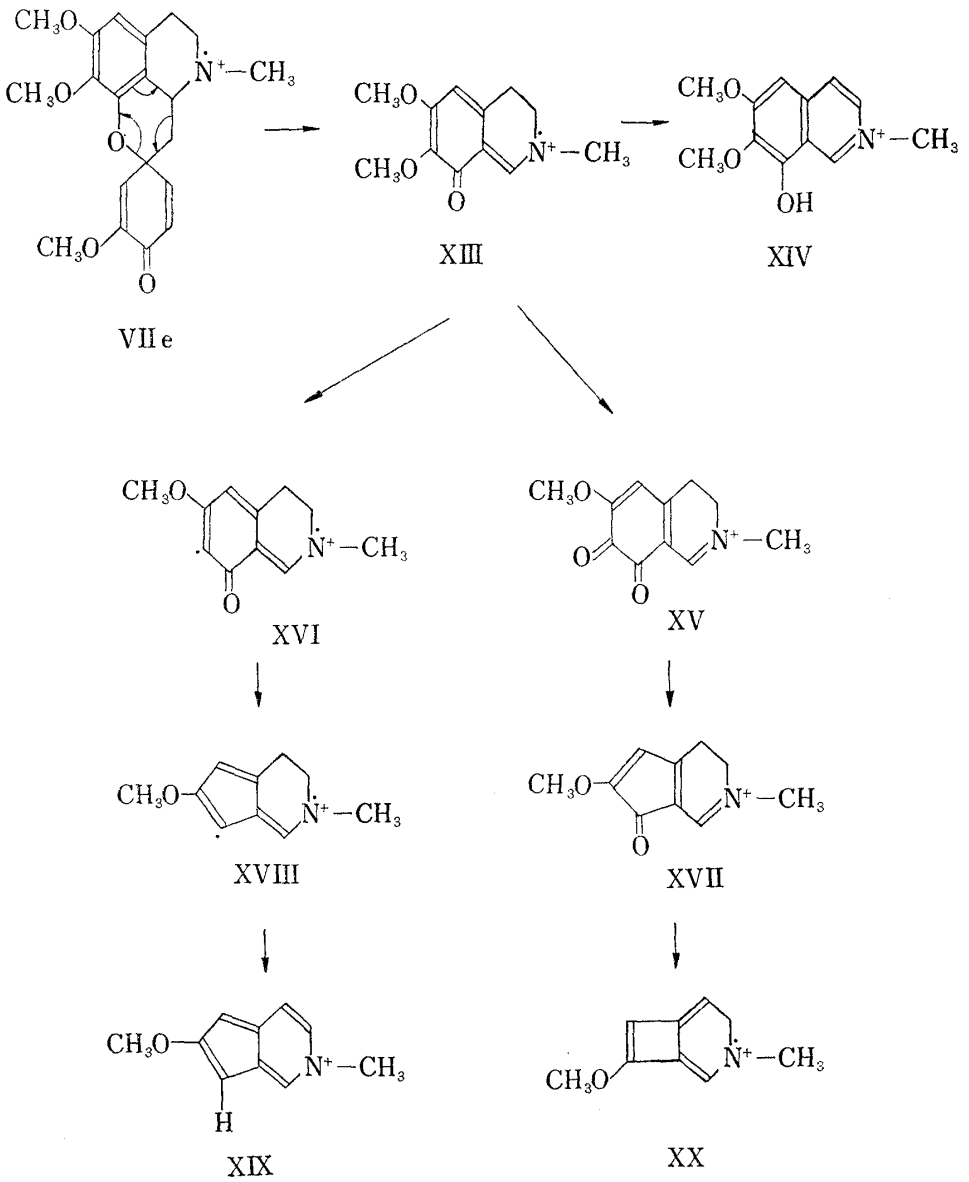


Chart 4

The third mode of stabilization which is the most characteristic fragmentation for this type of compound seems to be due to the retro Diels–Alder reaction of the dihydropyran ring. The resulting radical ion (XIII) (*m/e*; 221) gives the stable ion (XIV) (*m/e*; 220) by the loss of hydrogen in the isoquinoline ring. On the other hand, the loss of methyl or methoxyl radical gives the ion (XV) (*m/e*; 206) and biradical ion (XVI) (*m/e*; 190), respectively, and these ions lose the carbon monoxide to afford the ion (XVII) (*m/e*; 178) and the biradical ion (XVIII) (*m/e*; 162). Moreover, the latter is stabilized by aromatization to give the ion (XIV) (*m/e*; 161), and the former ion (XVII) also gives the strong peak, M–149 (XX) (*m/e* 149) by the loss of hydrogen and carbon monoxide.

Rearrangement of VI with concentrated hydrochloric acid in glacial acetic acid with stirring at room temperature in a current of nitrogen was carried out to give the cularine type isoquinoline (XXI), mp 188—189°. This structure was tentatively assigned as XXI from the spectral evidence below.

The IR spectrum showed ν_{max} (in $CHCl_3$) 3500 (OH) cm^{-1}, and NMR (in $CDCl_3$) spectrum revealed three singlet aromatic protons (3.82, 3.34, and 3.27 τ), three O-methyl singlets (6.21, 6.19, and 6.14 τ), and an N-methyl singlet (7.61 τ). The chemical shift of methyl protons at C_9– and the C_{10}–methoxyl groups in cularine and cularidine were assigned as 6.16 and 6.21 τ by spectral comparison with those of 6,10–O,O–demethylcularine.[5,6] Since the chemical

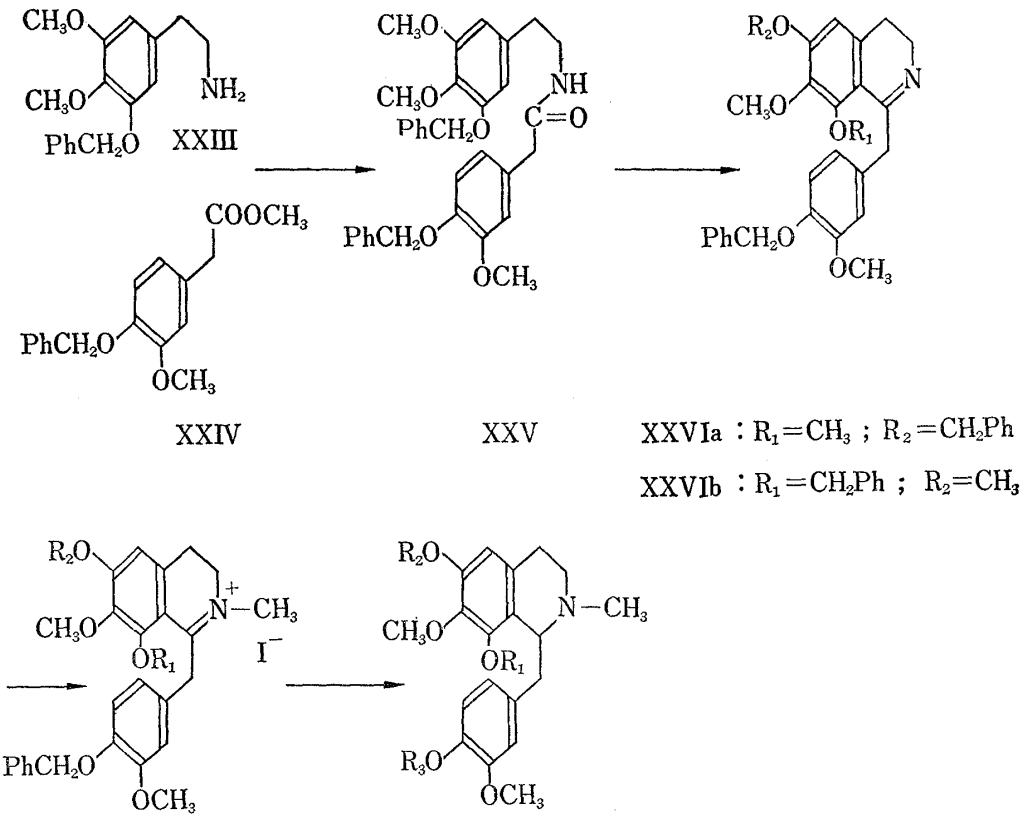


Chart 5

5) T. Kametani, S. Shibuya, C. Kibayashi, and S. Sasaki, *Tetrahedron Letters*, **1966**, 3215.
6) T. Kametani, S. Shibuya, and S. Sasaki, *Yakugaku Zasshi*, **87**, 198 (1967).

shift of O-methyl groups of our product was 6.21 τ but not 6.16 τ, the rearrangement product seemed to be XXI rather than XXII.

The starting material (V) in this oxidation was synthesized as follows; the amide (XXV), prepared by condensation of the amine (XXIII) with the ester (XXIV) was subjected to Bischler–Napieralski reaction, and a mixture of the resulting 3,4-dihydroisoquinoline derivatives (XXVIa) and (XXVIb) was methylated with methyl iodide. Furthermore, reduction of the preceding methiodides (XXVIIa) and (XXVIIb) with sodium borohydride gave 1,2,3,4-tetrahydroisoquinoline derivatives (XXVIIIa) and (XXVIIIb). Thin-layer chromatography of these isoquinoline derivatives as above showed one spot, and the isomers could not be separated even at this stage.

The mixture of XXVIIIa and XXIIIb was debenzylated with concentrated hydrochloric acid in ethanol to afford two phenolic bases, which were separated as the oxalates in the final stage. The expected base (V) formed a crystalline oxalate, mp 225—227°, but the compound (Va) was obtained as an oil, which was characterized as its hydrochloride, mp 198—200°.

The above oxidation, followed by rearrangement with acid, serves as a possible model for the biogenetic route to the cularine type alkaloids, and study of another route leading directly to III from II is in progress.

Experimental[7]

N-(5-Benzyloxy-3,4-dimethoxyphenethyl)-2-(4-benzyloxy-3-methoxyphenyl)acetamide (XXV)——A mixture of 3 g of 3-benzyloxy-4,5-dimethoxyphenethylamine (XXIII)[8] and 2.8 g of methyl 4-benzyloxy-3-methoxyphenylacetate[9] was heated in an oil-bath at 180° for *ca.* 8 hr to afford, on cooling, a viscous syrup whose recrystallization from benzene gave 4.0 g of the amide (XXV) as colorless needles, mp 75—77°. *Anal.* Calcd. for $C_{33}H_{35}O_6N$: C, 73.17; H, 6.51; N, 2.59. Found: C, 73.08; H, 6.61; N, 2.57. IR cm^{-1} ($CHCl_3$): ν_{NH} 3500, $\nu_{C=O}$ 1670.

6-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-7,8-dimethoxy-3,4-dihydroisoquinoline (XXVIa) and 8-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (XXVIb)——A mixture of 3 g of the preceding amide (XXV), 5 g of $POCl_3$, and 30 ml of dry benzene was heated on a water-bath for 4 hr, to which an excess of *n*-hexane was added after cooling. After the resultant mixture had been allowed to stand at room temperature overnight, the solvent layer was removed by decantation to afford a viscous syrup, which was washed fully with *n*-hexane several times. A solution of the preceding syrup in a small amount of MeOH was poured into an excess of cooled 5% NH_4OH aq. solution, and a viscous syrup separated was extracted with ether. The extract was washed with water, dried on K_2CO_3, and distilled to give 2.8 g of a syrup, whose picrolonate was recrystallized from EtOH to give yellow prisms, mp 160—162°. *Anal.* Calcd. for $C_{33}H_{33}O_5N \cdot C_{10}H_8O_5N_4$: C, 65.56; H, 5.25; N, 8.89. Found: C, 65.48; H, 5.33; N, 8.63. IR cm^{-1} ($CHCl_3$): $\nu_{C=N}$ 1620.

6-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-7,8-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (XXVIIIa) and 8-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (XXVIIIb)——To a solution of 1.5 g of the above cyclized compound in 40 ml of MeOH–Me_2CO (1:1) was added 10 ml of MeI, and the mixture was heated on a water-bath for 5 hr. After the reaction, removal of the solvent afforded the residue, which was washed with ether. This substance (XXVIIa and XXVIIb) could not be crystallised and therefore was used in the following reaction without purification.

To a solution of the above mixture in 50 ml of MeOH was added gradually 1.2 g of $NaBH_4$ at room temperature, and the mixture was heated on a water-bath for further 1 hr. After removal of the solvent, the residue was dissolved in 5% NaOH aq. solution and extracted with ether. The extract was washed with water, dried on K_2CO_3, and distilled to give 1.2 g of a mixture of XXVIIIa and XXVIIIb as a syrup, showing one spot in thin-layer chromatogram. These compounds could not be separated under a variety of conditions. Therefore, the mixture was used in the following reaction without purification. IR cm^{-1} ($CHCl_3$): ν_{N-Me} 2750.

7) All melting points were not corrected..

8) Y. Inubushi and N. Fujitani, *Yakugaku Zasshi*, **78**, 486 (1958).

9) T. Kametani and J. Serizawa, *Yakugaku Zasshi*, **72**, 1084 (1952).

Debenzylation of XXVIIIa and XXVIIIb and Separation of Both Debenzylated Compounds——A mixture of 1.0 g of the above compound (XXVIIIa and XXVIIIb) and 40 ml of conc. HCl–EtOH (1:1) was heated on a water-bath for 2 hr. After the reaction, removal of the solvent in a current of N_2 under reduced pressure afforded the residue, which was dissolved in 5% NaOH aq. solution and washed with benzene several times. The resulting alkaline solution was neutralized with an excess of crystalline NH_4Cl, and extracted with ether. The extract was washed with water, dried on K_2CO_3, and distilled to give a viscous syrup, to whose solution in a small amount of ethanol was added a saturated ethanolic oxalic acid solution. Collection of the oxalate by filtration and recrystallization from EtOH afforded 300 mg of 8-hydroxy-1,2,3,4-tetrahydroisoquinoline (V) oxalate as colorless prisms, mp 225—227°. *Anal.* Calcd. for $C_{20}H_{25}O_5N \cdot C_2H_2O_4$: C, 58.79; H, 6.06; N, 3.12. Found: C, 58.97; H, 6.15; N, 3.25. IR cm^{-1} ($CHCl_3$): ν_{OH} 3500. NMR (τ)[10] ($CDCl_3$): 7.63(3H, singlet, N-C$\underline{H}_3$), 6.23, 6.21, 6.14 (9H, 3 singlets, O-C$\underline{H}_3$), 3.83 (1H, singlet, C_5-H),[11] 3.23 (3H, aromatic protons).

On the other hand, the substance, which was obtained by concentration of the filtrate from recrystallization of the above oxalate, was made basic with saturated $NaHCO_3$ aq. solution and extracted with ether. The extract was washed with ether, dried on K_2CO_3, and distilled to give the residue, to whose solution in 20 ml of ether was added an ethereal solution saturated with dry HCl gas. Recrystallization of the oil separated from EtOH afforded 300 mg of 6-hydroxy-1,2,3,4-tetrahydroisoquinoline (Va) hydrochloride as colorless needles, mp 198—200°. *Anal.* Calcd. for $C_{20}H_{25}O_5N \cdot HCl \cdot H_2O$: C, 58.04; H, 6.82; N, 3.38. Found: C, 57.73; H, 7.18; N, 3.75. IR cm^{-1} ($CHCl_3$): ν_{OH} 3500. NMR (τ) ($CDCl_3$): 7.69 (3H, singlet, N-C$\underline{H}_3$), 6.24, 6.20, 6.18 (9H, singlets, O-C$\underline{H}_3$), 3.63 (1H, singlet, C_5-H), 3.30 (3H, aromatic protons).

Phenolic Oxidative Coupling Reaction of Compound (V) with Potassium Ferricyanide (Formation of Dienone (VI))——A solution of 3 g of the preceding oxalate of V in 300 ml of 8% NH_4OAc aq. solution was added gradually within 1 hr with stirring to a mixture of 15 g of $K_3Fe(CN)_6$, 700 ml of 8% $AcONH_4$ aq. solution, and 300 ml of $CHCl_3$. After three hours' stirring, the solvent layer was separated from the reaction mixture, and the aqueous layer was extracted with $CHCl_3$ several times. The combined $CHCl_3$ layers were washed with saturated NaCl aq. solution, dried on Na_2SO_4, and distilled to give a residue, which was again dissolved in 800 ml of ether. The extract was washed with 5% NaOH aq. solution, dried over Na_2SO_4, and distilled to give 100 mg of VI as an oil. IR cm^{-1} ($CHCl_3$): $\nu_{C=O}$ 1675, $\nu_{C=O}$ 1650 (dienone). Since this dienone could not be crystallized, it was characterized as its HCl salt, which was recrystallized from ether to give colorless needles, mp 173—175°. *Anal.* Calcd. for $C_{20}H_{23}O_5N \cdot HCl \cdot 2.5H_2O$: C, 54.73; H, 6.66. Found: C, 54.25; 6.44.

2,3,12,12a-Tetrahydro-9-hydroxy-5,6,10-trimethoxy-1-methyl-1*H*-[1]benzoxepino[2,3,4-*ij*]isoquinoline (XXI) (Rearrangement of the Dienone with Acid)——A mixture of 60 mg of the crude dienone (VI), 40 ml of glacial AcOH, and a few drops of conc. HCl was stirred at room temperature for 45 hr in the presence of N_2, and the resulting reaction mixture was made basic with conc. NH_4OH aq. solution and extracted with $CHCl_3$. The extract was washed with water, dried over K_2CO_3, and distilled to give a syrup, whose recrystallization from ether afforded 15 mg of XXI as colorless needles, mp 188—189°. *Anal.* Calcd. for $C_{20}H_{23}O_5N \cdot H_2O$: C, 63.99; H, 6.71. Found: C, 64.08; H, 7.17.

Acknowledgement We are grateful to Miss R. Kobayashi, Miss R. Hasebe, and Miss T. Yamaki for microanalyses.

10) The NMR spectrum was determined on a Varian A-60 spectrophotometer with deuteriochloroform as solvent and tetramethylsilane as internal reference.
11) This value agrees with that of C_5-H of corpaverine.[12]
12) T. Kametani, K. Ohkubo, and I. Noguchi, *J. Chem. Soc.* (C), **1966**, 715.