Phenolic Oxidative Coupling Reaction of 1,2,3,4-Tetrahydro-7-hydroxy-1-(2-hydroxy-4,5-methylenedioxybenzyl)-6-methoxy-2-methylisoquinoline with Ferric Chloride (Studies on the Syntheses of Heterocyclic Compounds. CCLXV)\textsuperscript{1)}

TETSUJI KAMETANI and ISAO NOGUCHI\textsuperscript{2)}

Pharmaceutical Institute, Tohoku University School of Medicine\textsuperscript{3)}

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Phenolic oxidation of 1, 2, 3, 4-tetrahydro-7-hydroxy-1-(2-hydroxy-4, 5-methylenedioxybenzyl)-6-methoxy-2-methylisoquinoline (Ib) afforded the dienone (IIb) in 3.2\% yield, which was characterized by its microanalysis and spectral determination.

In a previous paper,\textsuperscript{3)} the present authors reported that the phenolic oxidative coupling of 1,2,3,4-tetrahydro-7-hydroxy-(2-hydroxybenzyl)-6-methoxy-2-methylisoquinoline gave the 2,4-dienone (IIa), whose reduction with sodium borohydride, followed by rearrangement of the corresponding dienol (III) in acidic media, to give (\pm)-N-methylcaaverine (IVA). On the other hand, Jackson and Martin\textsuperscript{4)} have already reported that the oxidation of the diphenol (Ic) with potassium ferricyanide afforded the 2,4-dienone (IIc).

We now wish to report the oxidation with ferric chloride of 1,2,3,4-tetrahydro-7-hydroxy-(2-hydroxy-4,5-methylenedioxybenzyl)-6-methoxy-2-methylisoquinoline (Ib) in order to investigate whether the methylenedioxy group in the 1-benzyl group would give the influence for the formation of the ortho-cyclohexadienone, or not.

![Chemical Structures](chart1.png)

The starting material (Ib) was synthesized as follows. Chlorination with thionyl chloride of the carbinal (Vb), which was obtained by reduction of 2-benzoxyl-4,5-methylenedioxybenzaldehyde (Va)\textsuperscript{3)} with sodium borohydride, afforded the chloride (Vc). Cyanation of Vc, followed by hydrolysis of the resulting cyanide (Vd), gave the 2-benzoyl-4,5-methylenedioxyphenylacetic acid (Ve), which was converted into the amide (VII) by heating with 4-benzoyloxy-3-methoxyphenethylamine (VI) at 180—190\(^\circ\) for 3 hr. Methylation of the 3,4-dihydroisoqui-

\textsuperscript{2)} Location: No. 85, Kita-4-bancho, Sendai.
noline (VIII) with methyl iodide, which was obtained by Bischler-Napieralski reaction with phosphoryl chloride, afforded the methiodide (IX). Reduction of IX with sodium borohydride gave 1,2,3,4-tetrahydroisoquinoline (X), whose debenzylation with ethanolic concentrated hydrochloric acid solution gave the desired diphenol (Ib), mp 206—207° (decomp.) as colorless needles. The structure of this diphenol was determined by microanalysis and spectral data.

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\begin{align*}
\text{Va} : & \quad R = \text{CHO} \\
\text{Vb} : & \quad R = \text{CH}_2\text{OH} \\
\text{Vc} : & \quad R = \text{CH}_2\text{Cl} \\
\text{Vd} : & \quad R = \text{CH}_2\text{CN} \\
\text{Ve} : & \quad R = \text{CH}_3\text{CO}_2\text{H}
\end{align*}
\]

\[
\begin{align*}
\text{MeO}- & \quad \text{PhCH}_2 \quad \text{NHR} \\
\text{VI} : & \quad R = \text{H} \\
\text{VII} & \quad \text{R} = -\text{COCH}_2
\end{align*}
\]

Chart 2

Secondly, a solution of the hydrochloride of Ib was oxidized with 6 molar equivalents of ferric chloride hexahydrate at 10—15° for 10 hr with stirring in a current of nitrogen. The usual work up gave a brownish syrup, which was chromatographed on silica gel. Evaporation of the chloroform eluate containing 2% methanol afforded an expected 2,4-diene as colorless prisms, mp 260°, in 3.2% yield. Its IR spectrum (CHCl₃) showed the hydroxy (3500 cm⁻¹), N-methyl (2780 cm⁻¹), carbonyl (1630 cm⁻¹), and methylenedioxy absorptions (2760 and 940 cm⁻¹), respectively. Furthermore, the nuclear magnetic resonance (NMR) spectrum of the compound (IIb) showed a singlet due to the aromatic proton at 6.50 ppm, two singlets attributable to two vinyl protons at 5.79 and 5.59 ppm, methylenedioxy—protons at 5.81 ppm, methoxy—protons at 3.73 ppm and a N-methyl group at 2.28 ppm as singlets, respectively. These facts were closely similar to the spectral data of the Jackson's “slow” diene (IIc), which was one conformer showing no chelation between the carbonyl and hydroxy groups. The ultraviolet (UV) spectrum of IIb (in MeOH) showed λmax 257 [shoulder], 290, and 310 mμ (shoulder). In addition, the bathochromic shift of the benzenoid bands to 307 mμ was observed by addition of sodium hydroxide solution.⁶ On the other hand, the mass spectrum of the dienone (IIb) showed a molecular ion peak at m/e 341. In addition, a fragment at m/e 298 (M⁺—43) (XIII) due to retro—Diels—Alder cleavage of the molecular ion species was shown and the other fragments in details were observed in Chart 3.

These facts also support that the structure of the dienone (IIb) would be correct. Finally, borohydride reduction of IIb, followed by dienol—benzene rearrangement of the resulting dienol as usual, gave a basic compound, whose UV spectrum showed the characteristic absorptions of 1,2,8,9-tetraalkoxy—substituted aporphine.⁷,⁸ This compound was tentatively assigned to 1-hydroxy-2-methoxy-8,9-methylenedioxyaporphine (IVb) from the UV spectral

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point of view, but its structure has not yet been confirmed. Further determination is under examination. Regarding the conformation of the dienone (IIb), Dreiding model of the stereo-isomeric dienone (IIb) shows that in one racemic compound (IIb–A and IIb–B) hydrogen bonding between the hydroxy and carbonyl groups is possible, whereas the above two groups are at a long distance in the other racemic compound (IIb–C and IIb–D). Jackson and Martin⁴ reported that borohydride reduction of the dienone (IIc) would be inhibited by the slightly greater steric hindrance of the carbonyl group against the attack by the borohydride in one conformer which showed the chelation between carbonyl and hydroxy groups. Therefore, the conformation of the dienone (IIb), whose structure is closely similar to the Jackson and Martin’s dienone (IIc), would be assumed to be the conformers (IIb–C and IIb–D). In the latter conformers the chelation with hydroxy group seems to be difficult.

It is of great interest that oxidation of Ib with ferric chloride has led to the formation of the ortho–dienone, which seems to be one of a very few examples and, furthermore, the first one in case of 1-benzyl rest having methylenedioxy group.
Experimental

2-Benzylxy-4,5-methylenedioxybenzyl Alcohol (Vb) —— To a solution of 5 g of 2-benzylxy-4,5-methylenedioxybenzaldehyde (Va)\(^9\) in 50 ml of MeOH was added in small portions with stirring 2 g of NaBH\(_4\) at room temperature. After standing for 1 hr, the solvent was evaporated to yield a colorless gum, which was diluted with 5 ml of water and extracted with CHCl\(_3\). The extract was washed with water, dried over K\(_2\)CO\(_3\) and evaporated to give a colorless gum, which was recrystallized from CHCl\(_3\)-hexane to afford 3.7 g of 2-benzylxy-4,5-methylenedioxybenzyl alcohol (Vb) as colorless needles, mp 111—112\(^\circ\). Anal. Calcd. for C\(_{24}\)H\(_{22}\)O\(_7\): C, 69.75; H, 5.46. Found: C, 70.09; H, 5.51. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OH}}\) 3340, \(\nu\)\(_{\text{OCBO}}\) 2793, 932, \(\delta\)_CH 738, 697 (monosubstituted benzene).

2-Benzylxy-4,5-methylenedioxybenzyl Cyanide (Vd) —— The alcohol (Vb) (3.0 g) in 20 ml of dry ether was refluxed with 10 g of SO\(_4\)_\(_2\) for 2 hr. The excess of the reagent was removed by distillation to give the chloride (Ve) as a yellow oil, whose solution in 100 ml of EtCOME was stirred at 70—75\(^\circ\) with 3.5 g of NaCN and 3 g of NaI for 18 hr. The resulting yellow solution was diluted with 20 ml of water and the organic solvent layer was separated. The solvent was washed with water, dried over K\(_2\)CO\(_3\) and evaporated to give a yellow gum which was recrystallized from ether to afford 2.1 g of 2-benzylxy-4,5-methylenedioxybenzyl cyanide (Vd) as colorless needles, mp 116—117\(^\circ\). Anal. Calcd. for C\(_{24}\)H\(_{22}\)O\(_7\)N: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.79; H, 4.90; N, 4.90. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OCBO}}\) 2780, \(\nu\)\(_{\text{CH}}\) 2242.

2-Benzylxy-4,5-methylenedioxyphenylelacetic Acid (Ve) —— A mixture of 0.5 g of the foregoing cyanide (Vd), 10 ml of MeOH, 10 ml of dioxane and 8 ml of 25% KOH solution was refluxed for 20 hr. After evaporation of the solvent, the residue was mixed with 20 ml of water and extracted with ether (2×10 ml). The resultant aqueous layer was acidified with dil. HCl and extracted with CHCl\(_3\). The extract was washed with water, dried over Na\(_2\)SO\(_4\) and evaporated to give a oil which was recrystallized from benzene to give 350 mg of 2-benzylxy-4,5-methylenedioxyphenylelacetic acid (Ve) as colorless prisms, mp 122—123\(^\circ\). Anal. Calcd. for C\(_{24}\)H\(_{22}\)O\(_7\)N: C, 67.12; H, 4.93. Found: C, 67.12; H, 5.00. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OCBO}}\) 2790, 929, \(\nu\)\(_{\text{CH}}\) 1706.

N-(4-Benzylxy-3-methoxyphenethyl)-2-benzylxy-4,5-methylenedioxyphenyleacetaamide (VII) —— A mixture of 10 g of 2-benzylxy-4,5-methylenedioxyphenyleacetic acid (Ve) and 10 g of 4-benzylxy-3-methoxyphenethylamine (VI) was heated at 180—190\(^\circ\) for 3 hr. On cooling, the residue was dissolved in CHCl\(_3\) and the solvent layer separated was acidified with dil. HCl and then dil. NaOH solution. The extract was dried over K\(_2\)CO\(_3\) and evaporated to dryness, a residual oil being solidified on scratching. Recrystallization from MeOH gave 14.5 g of the amide (VII) as colorless needles, mp 153—154\(^\circ\). Anal. Calcd. for C\(_{31}\)H\(_{28}\)O\(_2\)N: C, 73.03; H, 6.14; N, 2.66. Found: C, 73.23; H, 5.95; N, 2.68. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OH}}\) 3300, \(\nu\)\(_{\text{OCBO}}\) 2800, 940, \(\nu\)\(_{\text{CH}}\) 1650.

7-Benzylxy-1-(2-benzylxy-4,5-methylenedioxybenzyl)-3,4-dihydro-6-methoxysquinoquinone (VIII) Hydrochloride —— A mixture of 12 g of the amide (VII), 200 ml of dry benzene and 15 ml of POCl\(_3\) was heated under reflux for 2 hr. After the reaction mixture was poured into hexane (1:1) and kept at room temperature for 16 hr, the precipitate was collected and recrystallized from EtOH to give 9.1 g of the 3,4-dihydroisquinoquinone (VIII) hydrochloride as yellow needles, mp 192—193\(^\circ\). Anal. Calcd. for C\(_{34}\)H\(_{31}\)O\(_4\)N.HCl: C, 70.65; H, 5.56; N, 2.58. Found: C, 70.73; H, 5.80; N, 2.68. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OH}}\) 3450, 2700—2600, \(\nu\)\(_{\text{CH}}\) 1650.

7-Benzylxy-1-(2-benzylxy-4,5-methylenedioxybenzyl)-3,4-dihydro-6-methoxysquinoquinone Methiodide (IX) —— A solution of the above base (obtained from 8.5 g of its hydrochloride of VIII as usual) in 25 ml of MeI was kept at room temperature for 1 hr. The precipitate was collected and recrystallized from MeOH to give 8 g of methiodide as pale yellow needles, mp 207—208\(^\circ\). Anal. Calcd. for C\(_{38}\)H\(_{34}\)O\(_4\)N.M.I: C, 60.97; H, 4.96; N, 2.16. Found: C, 60.84; H, 4.96; N, 2.17. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OH}}\) 1630.

7-Benzylxy-1-(2-benzylxy-4,5-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6-methoxy-2-methylsquinoquinone (X) —— To a solution of 7.5 g of the methiodide (IX) in 200 ml of MeOH and 50 ml of CHCl\(_3\) was added portionwise 2.5 g of NaBH\(_4\) at room temperature with stirring. The resulting colorless solution was evaporated to dryness, and the residue was decomposed by addition of dil. AcOH solution, which was extracted with benzene. The extract was dried over K\(_2\)CO\(_3\) and evaporated to give the solid, whose crystallization from ether—hexane afforded 4.2 g of 1,2,3,4-tetrahydrosquinoquinine (X) as colorless needles, mp 105—106\(^\circ\). Anal. Calcd. for C\(_{30}\)H\(_{29}\)O\(_3\): C, 75.84; H, 6.35; N, 2.67. Found: C, 75.84; H, 6.34; N, 2.71. IR cm\(^{-1}\) (KBr): \(\nu\)\(_{\text{OH}}\) 3280. NMR (ppm) (CDCl\(_3\)): 7.31, 7.28 (10H, two singlets, \(2\times\) C\(_{6}\)H\(_5\)), 6.52 (2H, broad singlet, C\(_{6}\)H\(_5\)), 6.50 (1H, singlet, C\(_{6}\)H\(_5\)), 6.02 (1H, singlet, C\(_{6}\)H\(_5\)), 5.90 (2H, singlet, \(-\text{OC}_{6}\text{H}_{5}\)), 4.83, 4.65 (4H, two singlets, 2\times\text{OC}_{6}\text{H}_{5}, 3.76 (3H, singlet, \(-\text{OC}_{6}\text{H}_{5}\)), 2.35 (3H, singlet, N-CH\(_3\)).

9) All melting points were measured in a sulfuric acid bath and uncorrected. NMR spectra were determined on a Hitachi H-60 spectrometer in CDCl\(_3\) with TMS as an internal standard. Mass spectra were determined on a Hitachi RMU-6D spectrometer.

10) Since this compound was labile, it was dried on P\(_2\)O\(_5\) at 50—60\(^\circ\) for 20 hr under reduced pressure.

11) Wakogel B-5 and a solution of CHCl\(_3\)-MeOH (10:1) as an eluent were used and the spot was detected with I\(_2\) vapor.
1,2,3,4-Tetrahydro-7-hydroxy-1-(2-hydroxy-4,5-methylenedioxybenzyl)-6-methoxy-2-methylisoquinoline (Ib)—A mixture of 200 mg of the tetrahydroisoquinoline (X), 20 ml of EtOH and 20 ml of conc. HCl solution was refluxed for 2 hr. The solution was evaporated to give a colorless powder, which was washed with ether. A suspension of the resulting crude hydrochloride in 20 ml of AcOEt was basified with 10% NH₄OH aq. solution. The organic solvent layer was separated, dried over Na₂SO₄ and evaporated to give a syrup which was crystallized from ether to afford 220 mg of the desired phenolic tetrahydroisoquinoline (Ib) as colorless prisms, mp 206—207°. Anal. Calcd. for C₃₉H₃₁O₂N: C, 66.45; H, 6.15; N, 4.07. Found: C, 66.03; H, 6.35; N, 4.12. IR cm⁻¹: vOH, 3300; vC=O, 2800 vCH₃, 940. NMR (ppm) (CDCl₃): 6.63, 6.43, 6.35, 6.32 (4H, four singlets, Ar-CH), 5.73 (2H, singlet, -OCH₂O-), 3.78 (3H, singlet, OCH₃), 2.52 (3H, singlet, NCH₃). TLC: RF 0.69 [Wakogel B-5; CHCl₃-MeOH (10:1); the spot was detected by I₂ vapor].

Oxidation of 1,2,3,4-Tetrahydro-7-hydroxy-1-(2-hydroxy-4,5-methylenedioxybenzyl)-6-methoxy-2-methylisoquinoline (Ib)—To a solution of the dihydropenic base (Ib) hydrochloride (obtained from 500 mg of Ib as usual) 50 ml of water was added dropwise a solution of 2.3 g of FeCl₃·6H₂O [6 molar equivalents] in 10 ml of water and the mixture was stirred at room temperature for 6 hr. The dark violet reaction mixture was basified with 10% NH₄OH aq. solution and extracted with AcOEt. The extract was dried over Na₂SO₄ and evaporated to give 160 mg of a brown gum, which was purified by column chromatography on 15 g of silica gel. Removal of the CHCl₃ eluate containing 10% methanol afforded a pale yellow gum which was crystallized from CHCl₃-hexane to give 16 mg (3.2%) of the diene (IIb) as colorless needles, mp 260° (decomp.). Anal. Calcd. for C₃₉H₃₁O₂N·½H₂O: C, 65.20; H, 5.76; N, 4.00. Found: C, 65.40; H, 5.74; N, 3.79. IR cm⁻¹ (KBr): vOH, 3250; vC=O, 2780; vCH₃, 2770, 945; vC=O, 1610; IR cm⁻¹ (CHCl₃): vOH, 3500; vC=O, 1630. UV λmax μ: 257 (shoulder) (3.83), 289 (3.67), 310 (shoulder) (3.51): λmax (MeOH-MeOH): 255 (shoulder) (3.91), 293 (3.72), 307 (3.69). NMR (ppm) (CDCl₃): 6.50 (1H, singlet, C₆-CH), 5.81 (2H, singlet, -OCH₂O-), 5.79, 5.59 (2H, two singlets, vinyl proton), 3.73 (3H, singlet, OCH₃), 2.28 (3H, singlet, N-CH₃). TLC Rf 0.45. Mass (m/e): 341 (M+·71), 340 (M+·72), 328 (M+·17) (100), 312 (M+·29) (14), 298 (M+·43) (40).

Reduction of the Dienone (IIb) to the Dienol and Rearrangement to the Aporphine (IVb)—A solution of 14 mg of the diene (IIb) in 10 ml of iso-ProOH was treated with 35 mg of NaBH₄ as usual and the mixture was kept at room temperature for 20 hr. After the solvent had been evaporated, 15 ml of water was added to the resultant residue and extracted with CHCl₃. The extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave 10 mg of the dienol as a pale yellow gum. IR cm⁻¹ (CHCl₃): 3450, 2925, 2805, 2730, 1930, 1530.

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