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Synthesis of 1-Benzyloxindole Derivatives for the Study of Phenolic Oxidative Coupling (Studies on the Syntheses of Heterocyclic Compounds. CCCXLVII[1])

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At first the synthetic method of 6-hydroxy-1-(3-hydroxy-2-methoxybenzyl)-5-methoxy-2-oxindole (IIIa) was investigated as a precursor for Amaryllidaceae alkaloids. Secondly phenolic oxidative coupling of IIIa with ferric chloride or potassium ferricyanide under a variety of conditions, but failed.

In the previous paper, we have reported the modified total synthesis of (±)-galanthamine (I) by biogenetic type synthesis in which the yield of phenolic oxidative coupling reaction have been much improved with blocking of nitrogen of the starting material (II) by amide formation.[3] Based on the above aspect, we have examined the synthesis of 1-benzyloxindole derivatives (IIIa) and IIIb as the starting materials for the synthetic approach to haemanthamine (IV and V) and lycorine type compound (VI). In the course of our investigation to synthesize IIIb, abnormal reactions have occurred. We here report these resluts.

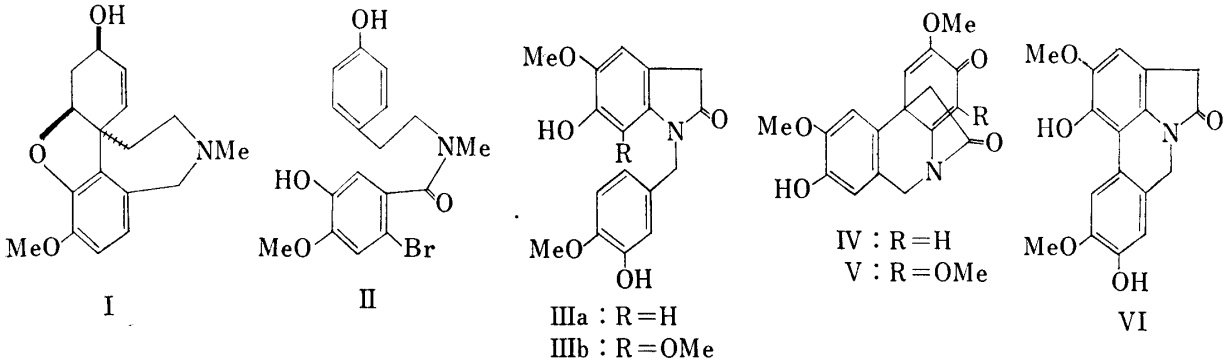
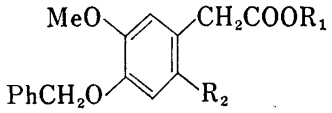


Chart 1

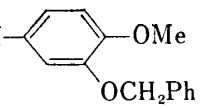
1) Part CCCXLVI: T. Kametani, K. Wakisaka, and K. Kigasawa, *Chem. Commun.*, **1970**, 277.
2) Location: *Aobayama, Sendai.*
3) T. Kametani, K. Yamaki, H. Yagi, and K. Fukumoto, *Chem. Commun.*, **1969**, 425; *J. Chem. Soc.* (*C*), **1969**, 3602.

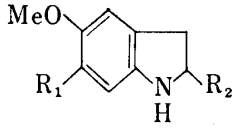
Synthesis of 6-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-5-methoxy-2-oxindole (IIIa) was carried out as follows. Esterification of 4-benzyloxy-5-methoxy-2-nitrophenylacetic acid (VII)[4] gave the ester (VIII). In order to obtain the amine derivative (IX), several hydrogenation conditions were investigated. At first, the ester (VIII) was hydrogenated in acetic acid in the presence of palladium-charcoal[5] to give the oxindole (X), whose structure was confirmed as the indole derivative (XII) through XI by the fact that benzylation, followed by lithium aluminum hydride reduction, gave XII.

Therefore, the ester (VIII) was hydrogenated in tetrahydrofuran in the presence of Adam's catalyst and the reaction mixture was treated below 10° to give the expected amine (IX). The reaction between benzylisovanillin and the amine (IX) gave the Schiff base (XIII)[6] which was hydrogenated in acetic acid using 10% palladium-charcoal afforded the oxindole derivative (IIIa).

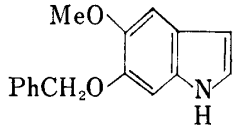


VII : R_1=H, R_2=NO_2
VIII : R_1=Et, R_2=NO_2
IX : R_1=Et, R_2=NH_2
XIII : R_1=Et, R_2=N=CH-





X : R_1=OH, R_2=O
XI : R_1=OCH_2Ph, R_2=O



XII

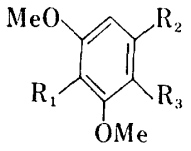
Ph=C_6H_5

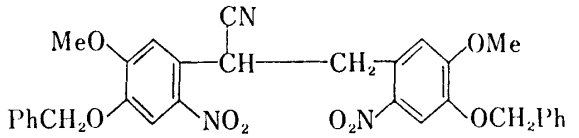
Chart 2

On the other hand, attempt to obtain another starting material (IIIb) for phenol oxidation was carried out as follows. Lithium aluminum hydride reduction of methyl 4-benzyloxy-3,5-dimethoxybenzoate (XV),[7] which was obtained by benzylation of methyl 4-hydroxy-3,5-dimethoxybenzoate (XIV), gave the carbinol (XVI), whose chlorination with thionyl chloride, followed by cyanation of XVII with sodium cyanide in ethyl methyl ketone, afforded the nitrile (XVIII). After hydrolysis of XVIII, nitration of XIX with fuming nitric acid in glacial acetic acid was carried out in order to obtain a normal nitro compound (XX), but unexpected nitro-derivative (XXI) was formed as a neutral substance, mp 77°. The nuclear magnetic resonance (NMR) spectrum (δ) of XXI showed a singlet (6H) due to two methoxy groups at 3.84 and the methylene protons at 7.40 ppm. Furthermore, the infrared (IR) spectrum showed an absorption band attributable to nitro group at 1335 cm^{-1}. Microanalysis also supported the composition of 4-benzyloxy-3,5-dimethoxynitrobenzene (XXI). Though this fact seems to be interesting, its mechanism is not clear.[8] Accordingly, hydrolysis of the nitro compound (XXII), which was obtained by nitration of the preceding compound (XV) with cupric nitrate in acetic anhydride according to William's method,[9] was examined to give the acid (XXIII), whose chlorination, followed by reduction of the resultant acid chloride (XXIV) with sodium borohydride,[10] gave our expected carbinol (XXV). After chlorination of XXV with thionyl chloride, cyanation of XXVI was carried out, but the unexpected dimer (XXVIII) was obtained instead of the compound (XXVII). The NMR spectrum (δ) showed two aromatic protons as singlets at 6.58 and 6.68, the methylene protons (4H) due to two benzyl groups

4) P.S. Clezy and D.Y.K. Lan, *Australian J. Chem.*, **19**, 437 (1966).
5) S.N. Mishra and G.A. Swan, *J. Chem. Soc.*, **1967**, 1424.
6) This compound (XIII) exhibited antithrobtic activity *in vitro* in the primary screening.
7) L. Jurd, *J. Am. Chem. Soc.*, **81**, 4606 (1959).
8) A.H. Salway, *J. Chem. Soc.*, **95**, 1155 (1909).
9) K.I.H. Williams, *J. Am. Chem. Soc.*, **82**, 3984 (1960).
10) K. Hirai, *Yakugaku Zasshi*, **80**, 1429 (1960).

as a singlet at 5.02, two methoxy resonances (6H) as two singlets at 3.87 and 3.91, the methine proton as a triplet with J 6.9 cps at 4.31, and two methylene protons as a doublet with J 6.9 cps at 3.18 ppm. Furthermore, the IR spectrum showed a weak absorption due to the cyano group at 2230 cm^{-1} and the characteristic band of nitro group at 1530 and 1370 cm^{-1}. This fact shows that the reaction similar to the Franchimont reaction[11] has been occurred to give the dimer (XXVIII) which would be formed owing to the strong I effect of nitro group. The similar reaction was also observed by Kametani.[12] In this case cyanation of XXVI with potassium cyanide in dimethyl sulfoxide also gave XXVIII, but use of ethanol and benzene recovered the starting material. The synthesis of IIIb could not be successful in the methods described above, but unusual side reactions have been found.





XXVIII

XIV : R_1=OH, R_2=COOMe, R_3=H
XV : R_1=OCH_2Ph, R_2=COOMe, R_3=H
XVI : R_1=OCH_2Ph, R_2=CH_2OH, R_3=H
XVII : R_1=OCH_2Ph, R_2=CH_2Cl, R_3=H
XVIII : R_1=OCH_2Ph, R_2=CH_2CN, R_3=H
XIX : R_1=OCH_2Ph, R_2=CH_2COOH, R_3=NO_3
XX : R_1=OCH_2Ph, R_2=CH_2COOH, R_3=NO_2
XXI : R_1=OCH_2Ph, R_2=NO_2, R_3=H
XXII : R_1=OCH_2Ph, R_2=COOMe, R_3=H
XXIII : R_1=OCH_2Ph, R_2=COOH, R_3=NO_2
XXIV : R_1=OCH_2Ph, R_2=COCl, R_3=NO_2
XXV : R_1=OCH_2Ph, R_2=CH_2OH, R_3=NO_2
XXVI : R_1=OCH_2Ph, R_2=CH_2Cl, R_3=NO_2
XXVII : R_1=OCH_2Ph, R_2=CH_2CN, R_3=NO_2

Chart 3

Finally, phenol oxidation of IIIa with ferric chloride and potassium ferricyanide was investigated but, although our expected oxidized compound was not obtained, there obtained an unexpected compound, whose structure is under examination.

Experimental[13]

Ethyl 4-Benzyloxy-5-methoxy-2-nitrophenylacetate (VIII)——A mixture of 22.0 g of 4-benzyloxy-5-methoxy-2-nitrophenylacetic acid[4] (VII), 40 ml of conc. H_2SO_4 and 1 liter of EtOH was refluxed for 4 hr and an usual work-up gave yellow needles, whose recrystallization from $CHCl_3$–EtOH (1:3) gave 20.0 g of the ester (VIII) as pale yellow needles, mp 137.5°. *Anal.* Calcd. for $C_{18}H_{19}O_6N$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.80; H, 5.80; N, 3.77.

6-Hydroxy-5-methoxy-2-oxindole (X)——A solution of 20.0 g of the ester (VIII) in 300 ml of glacial AcOH was hydrogenated in the presence of 500 mg of 7% Pd–C, a calculated amount of H_2 being absorbed for 3 hr. After filtration, the filtrate was evaporated *in vacuo* at 80° to give 8.0 g of dark green scales which were recrystallised from EtOH to give 6.0 g of the oxindole (X) as pale brown scales, mp 222—224°. *Anal.* Calcd. for $C_9H_9O_3N$: C, 60.34; H, 5.06; N, 7.82. Found: C, 60.42; H, 5.40; N, 8.18. δ (ppm in CF_3CO_2H), 3.85 (2H, singlet, CH_2CONH), 2.99 (3H, singlet, OCH_3), 6.98 (1H, singlet, C_6–H), 7.10 (1H, singlet, C_7–H), 9.67 (1H, NH).

11) A.P.N. Franchimont, *Ber.*, **5**, 1048 (1872).
12) T. Kametani, M. Hiiragi, and K. Kigasawa, *Yakugaku Zasshi*, **85**, 867 (1965).
13) Melting points are uncorrected. The IR spectra were taken in chloroform with a Hitachi EPI-S_2 spectrophotometer, and UV spectra were taken in methanol on a Hitachi EPS-3 recording spectrophotometer. NMR spectra were measured on a Hitachi H-60 in deuteriochloroform using TMS as an internal standard. Mass spectrum was measured on a Hitachi RMU-7.

6-Benzyloxy-5-methoxy-2-oxindole (XI)——A mixture of 5.0 g of the compound (X), 3.98 g of benzyl chloride, 2.5 g of K_2CO_3, and 300 ml of EtOH was refluxed for 5 hr. After filtration, evaporation of the filtrate gave the residue, which was mixed with 300 ml of water and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 5.5 g of dark green crystals, which were chromatographed on silica gel. Removal of the $CHCl_3$ eluate gave 4.0 g of gray scales, which were recrystallised from EtOH to give 3.6 g of XI as pale brown scales, mp 192°. *Anal.* Calcd. for $C_{16}H_{15}O_3N$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.61; H, 5.68; N, 5.19. δ (ppm in $CDCl_3$) 3.80 (3H, singlet, OCH_3), 3.42 (2H, singlet, CH_2CO), 5.07 (2H, singlet, $PhCH_2O$), 6.49 (1H, singlet, C_4–H), 6.84 (1H, singlet, C_7–H), 7.36 (5H, aromatic protons), 8.14 (1H, broad singlet, NH).

6-Benzyloxy-5-methoxyindole (XII)——A cooled solution of 1.0 g of XI in 70 ml of dry tetrahydrofuran was added dropwise under stirring to a suspension of 0.9 g of $LiAlH_4$ in 50 ml of dry tetrahydrofuran and the stirring was continued at 0—5° for 20 min. After stirring at room temperature for 30 min, the mixture was then refluxed for 22 hr. On decomposition of the reaction mixture with wet ether, the mixture was filtered with celite and the solvent was distilled off, to give a syrup, which was dissolved in 100 ml of ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 0.75 g of a dark green viscous syrup, which was chromatographed on silica gel. Evaporation of the chloroform eluate gave pale yellow crystals, whose recrystallisation from EtOH afforded 0.2 g of XII as colorless scales, mp 148.5°. *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.85; H, 5.97; N, 5.53. Found: C, 76.15; H, 5.93; N, 5.44. δ (ppm in $CDCl_3$), 3.87 (3H, singlet, OCH_3), 6.39 (1H, C_3–H), 6.84 (1H, singlet, C_4–H), 7.00 (1H, C_2–H), 7.10 (1H, singlet, C_7–H), 7.95 (1H, broad, NH).

Ethyl 2-Amino-4-benzyloxy-5-methoxyphenylacetate (IX)——A solution of 10 g of the nitro-ester derivative (VIII) in 300 ml of tetrahydrofuran was hydrogenated in the presence of 300 mg of Adams' platinum, a caluculated amount of H_2 being absorbed within 8 hr. After filtration, the filtrate was evaporated *in vacuo* at 5—10° to give a reddish oil, ν_{max} 3400, 3320 (NH), 1720 cm^{-1} (C=O), which was used in the following reaction without purification.

Ethyl 4-Benzyloxy-2-(3-benzyloxy-4-methoxybenzylidene)amino-5-methoxyphenylacetate (XIII)——A mixture of 3.5 g of the preceding amino-derivative (IX), 2.1 g of 3-benzyloxy-4-methoxybenzaldehyde and 100 ml of EtOH was refluxed on a water-bath for 1 hr and then cooled at room temperature. Resulting crystals were collected by filtration to give 5 g of yellowish needles, which were recrystallised from EtOH to give pale yellow needles, mp 121°. *Anal.* Calcd. for $C_{33}H_{33}O_6N$: C, 73.45; H, 6.16; N, 2.6. Found: C, 73.42; H, 6.09; N, 2.79. ν_{max} (KBr) 1725 (C=O) and 1623 cm^{-1} (C=N), δ (ppm in $CDCl_3$), 1.10 (3H, triplet, J 7.0 cps, CH_2CH_3), 3.72 (2H, singlet, $-CH_2COO-$), 3.85 (3H, singlet, OCH_3), 3.86 (3H, singlet, OCH_3), 4.02 (2H, quartet, J 7.0 cps, $-CH_2CH_3$), 5.10 (2H, singlet, CH_2Ph), 5.18 (2H, singlet, CH_2Ph), 8.12 (1H, singlet, –N=CH–).

6-Hydroxy-1-(3-hydroxy-4-methoxybenzyl)-5-methoxy-2-oxindole (IIIa)——A solution of 2 g of the preceding Schiff base (XIII) in 100 ml of glacial AcOH was hydrogenated in the presence of 500 mg of 10% Pd–C, a caluculated amount of H_2 being absorbed within 4.5 hr. After filtration, the filtrate was evaporated *in vacuo* in an oil bath at 120° to give a pale brownish solid which was taken up in 100 ml of $CHCl_3$. The extract was washed with saturated $NaHCO_3$ solution, water and dried over Na_2SO_4. Evaporation of the solvent gave 0.9 g of a pale brownish solid which was recrystallised from benzene to give the oxindole (IIIa) as colorless needles, mp 168—169°. *Anal.* Calcd. for $C_{17}H_{17}O_5N$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.75; H, 5.43; N, 4.59. ν_{max} ($CHCl_3$) 3500 (OH) and 1690 cm^{-1} (C=O), δ [ppm in $(CD_3)_2SO$] 3.45 (2H, singlet, $-CH_2CON$), 3.68 (3H, singlet, OCH_3), 3.70 (3H, singlet, OCH_3), 6.36 (1H, singlet, aromatic proton at C-7), 6.70—6.79 (4H, aromatic protons), 8.70—9.00 (2H, broad, OH, disappeared with D_2O). Mass spectrum (m/e): 315 (M^+), 137.

Methyl 4-Benzyloxy-3,5-dimethoxybenzoate (XV)[7]——A mixture of 54.0 g of methyl 4-hydroxy-3,5-dimethoxybenzoate (XIV), 440 ml of MeOH, 31.0 g of benzyl chloride and 18.5 g of K_2CO_3 was refluxed on a water-bath for 5 hr. After removal of the solvent, the residue was extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 67.0 g of the ester (XV) as a dark reddish viscous oil, bp 166—168° (0.02 mmHg), which was characterised as its hydrazide, mp 154—156°. *Anal.* Cacld. for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.43; H, 6.10; N, 9.37.

4-Benzyloxy-3,5-dimethoxybenzyl Alcohol (XVI)——To a cooled suspension of 20.0 g of $LiAlH_4$ in 300 ml of dry tetrahydrofuran was added drop by drop with stirring a solution of 67.0 g of the ester (XV) in 200 ml of dry tetrahydrofuran, and the stirring was continued for 2 hr at room temperature. The reaction mixture was decomposed with 30% NaOH solution and, after filtration, the filtrate was concentrated *in vacuo* to give the syrup, which was extracted with benzene. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 51.0 g of the carbinol (XVI) as a pale yellow oil, bp 194—196° (0.01 mmHg). *Anal.* Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.68; H, 6.75.

4-Benzyloxy-3,5-dimethoxybenzyl Chloride (XVII)——To a solution of 48.6 g of the preceding carbinol (XVI) in 250 ml of dry benzene was added dropwise 58.8 g of $SOCl_2$ under cooling, and, after standing at room temperature for 10 min, the mixture was refluxed for 0.5 hr. After removal of the reagent under reduced pressure, an excess of dry benzene was added to the residue and evaporated. This process was continued until the bulk of $SOCl_2$ had been removed and the resulting oil was extracted with $CHCl_3$. The

extract was washed with water, saturated $NaHCO_3$ solution and water, dried over $MgSO_4$ and evaporated to give 47.0 g of the chloride (XVII) as a dark reddish viscous oil, which was used without purification because of its instability.

4-Benzyloxy-3,5-dimethoxyphenylacetonitrile (XVIII)——A mixture of 47.5 g of the preceding chloride (XVII), 76.9 g of NaCN, 65.5 g of NaI and 1.3 l of MeCOEt was refluxed with stirring for 4 hr. After cooling at room temperature, 200 ml of water was added to the mixture, and the solvent layer was separated, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 28.5 g of nitrile (XVIII) as a reddish-yellow viscous oil, whose distillation afforded a yellow oil, bp 186—189° (0.6 mmHg). *Anal.* Calcd. for $C_{17}H_{17}O_3N$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.85; H, 6.34; N, 4.92.

4-Benzyloxy-3,5-dimethoxyphenyl Acetic Acid (XIX)——A mixture of 27.0 g of the nitrile (XVIII) and 150 ml of 5% ethanolic KOH solution was refluxed on a water-bath for 32 hr. After removal of the solvent, 600 ml of water was added to the resultant residue and the mixture was washed twice with 400 ml of ether. An alkaline solution was acidified with 10% HCl and a pale yellow oil separated was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 21.0 g of a brown viscous oil, which was chromatographed on silicic acid using $CHCl_3$ as an eluant. Removal of the solvent gave 8.0 g of a yellowish-brown solid, which was recrystallised from benzene–hexane (1:3) to give 6.5 g of the acid (XIX) as colorless needles, mp 104°. *Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.38; H, 6.06. δ (ppm in CCl_4) 3.76 (6H, singlet, $2\times OCH_3$), 3.47 (2H, singlet, $-CH_2CO_2H$), 6.43 (2H, singlet, C_2–H and C_7–H), 8.77 (1H, broad, CO_2H).

Nitration of XIX——To a cooled solution of 5.0 g of the preceding acid (XIX) in 35 ml of glacial AcOH was added dropwise with stirring 10 ml of fumic HNO_3 within 40 min and the stirring was continued for 0.5 hr at room temperature. The reaction mixture was poured into 300 ml of water and a colorless oil separated was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 3.3 g of a brown viscous syrup, which was chromatographed on silica gel using $CHCl_3$ as an eluant. Removal of the $CHCl_3$ eluate gave 4-benzyloxy-3,5-dimethoxynitrobenzene (XXI) as yellow needles, whose recrystallisation from EtOH afforded 1.2 g of pale yellow needles, mp 77°. *Anal.* Calcd. for $C_{15}H_{15}O_5N$: C, 62.34; H, 5.23; N, 4.85. Found: C, 62.31; H, 5.58; N, 4.69. δ (ppm in CCl_4) 3.84 (6H, singlet, $2\times OCH_3$), 5.00 (2H, singlet, $PhCH_2O$), 7.40 (2H, singlet, aromatic protons). ν_{max} ($CHCl_3$) 1335 cm^{-1} (NO_2).

Methyl 4-Benzyloxy-3,5-dimethoxy-2-nitrobenzoate (XXII)——To a cooled solution of 35.0 g of the preceding ester (XV) in 175 ml of Ac_2O was added in small portions with stirring 27.2 g of $Cu(NO_3)_2$ as a powder, which was ground in a mortar, at less than 50°, and the stirring was continued for 1 hr at room temperature. After the reaction mixture had been poured into 500 ml of water, yellowish-green crystals were separated and collected. After dryness on a filter, the crude crystals were dissolved in benzene, which was passed over 50 g of neutral alumina. Evaporation of the benzene eluate gave 27.0 g of a yellow solid which was recrystallised from EtOH to give 24.5 g of the ester (XXII) as pale yellow needles, mp 96°. *Anal.* Calcd. for $C_{17}H_{17}O_7N$: C, 58.79; H, 4.93; N, 4.03. Found: C, 59.10; H, 5.21; N, 4.06. ν_{max} (KBr) 1725 (ester C=O), 1540 and 1374 cm^{-1} (NO_2). δ (CCl_4) 3.90 (6H, singlet, $-COOCH_3$, C_3–OCH_3), 3.81 (3H, singlet, C_5–OCH_3), 5.07 (2H, singlet, $PhCH_2O$), 7.22 (1H, singlet, C_6–H).

4-Benzyloxy-3,5-dimethoxy-2-nitrobenzonic Acid (XXIII)——A solution of 7.0 g of XXII in 80 ml of 5% methanolic KOH solution was refluxed on a water-bath for 50 min and, after removal of MeOH, the residue was dissolved in 100 ml of water. The resultant alkaline solution was acidified with 10% HCl and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 6.0 g of a colorless solid, whose recrystallisation from benzene gave 5.5 g of the acid (XXIII) as colorless needles, mp 182.5°. *Anal.* Calcd. for $C_{16}H_{15}O_7N$: C, 57.65; H, 4.54; N, 4.20. Found: C, 57.55; H, 4.58; N, 3.95.

4-Benzyloxy-3,5-dimethoxy-2-nitrobenzoyl Chloride (XXIV)——A mixture of 5.5 g of the acid (XXIII), 5 ml of $SOCl_2$, and 90 ml of dry benzene was refluxed on a water-bath at 60° for 1 hr. After removal of the solvent at 60° *in vacuo*, repeated distillation with addition of an excess of dry benzene gave a syrup, which, on standing at room temperature, solidified. Collected pale brown needles (6.0 g) were used in the following reaction without purification due to its instability.

4-Benzyloxy-3,5-dimethoxy-2-nitrobenzyl Alcohol (XXV)——A solution of 6.0 g of the acid chloride (XXIV) in 50 ml of dry tetrahydrofuran was added dropwise with stirring to a suspension of 3.3 g of $NaBH_4$ in 100 ml of dry tetrahydrofuran within 0.5 hr and the stirring was continued at room temperature for 1 hr. The mixture was then heated under reflux on a water-bath for an additional 1 hr. After cooling, the reaction mixture was decomposed with water and then 5% HCl, and the solvent was removed by distillation *in vacuo*. The resulting residue was extracted with $CHCl_3$. The extract was washed with 5% K_2CO_3 solution and then water, dried over Na_2SO_4, and evaporated to give 5.0 g of the carbinol (XXV) as a dark reddish viscous syrup, which was used without purification in the following reaction.

4-Benzyloxy-3,5-dimethoxy-2-nitrobenzyl Chloride (XXVI)——To a stirred solution of 23.0 g of the above compound (XXV) in 70 ml of dry benzene was added dropwise 19.0 g of $SOCl_2$ under cooling and, after addition, the mixture was allowed to stand for 20 min at room temperature and then refluxed on a water-bath at 60° for 0.5 hr. After removal of the solvent, repeated distillation with an excess of 50 ml of dry benzene gave a syrup, which was extracted with benzene. The extract was washed with water, dried over

Na_2SO_4, and evaporated to give 19.0 g of pale yellow needles, whose recrystallisation from EtOH gave 11.0 g of the chloride (XXVI) as pale yellow needles, mp 83°. *Anal.* Calcd. for $C_{16}H_{16}O_5NCl$: C, 56.85; H, 4.74; N, 4.14. Found: C, 57.06; H, 4.92; N, 4.51. δ (ppm in $CDCl_3$) 3.93 (3H, singlet, C_3–OCH_3), 3.87 (3H, singlet, C_5–OCH_3), 4.54 (2H, singlet, $ClCH_2$–), 5.01 (2H, singlet, $PhCH_2O$), 6.77 (1H, singlet, C_6–H).

Cyanation of XXVI——A mixture of 5.0 g of the chloride (XXVI), 125 ml of MeCOEt, 6.6 g of NaCN and 5.7 g of NaI was refluxed with stirring on a water-bath for 6 hr. After the reaction, the mixture was poured into 1 liter of water and the crystals were collected by filtration. Recrystallisation of 5.0 g of the dried yellow crystals from EtOH–$CHCl_3$ (3:1) afforded 3.5 g of 1,2-bis(4-benzyloxy-3,5-dimethoxy-2-nitrophenyl) propionitrile (XXVIII) as pale yellow needles, mp 166.5°. *Anal.* Calcd. for $C_{33}H_{31}O_{10}N_3$: C, 62.95; H, 4.96; N, 6.67. Found: C, 63.12; H, 5.0; N, 6.60. ν_{max} (KBr) 2230 (C=N), 1530 and 1370 cm^{-1} (NO_2), δ (ppm in $CDCl_3$), 3.87 (3H, singlet, OCH_3), 3.91 (3H, singlet, OCH_3), 3.18 (2H, doublet, J 6.9 cps, –CH(CN)CH_2), 4.31 (1H, triplet, J 6.9 cps, –CHCN–), 5.02 (4H, singlet, $2\times PhCH_2O$), 6.58, 6.68 (1H, each, two singlets, aromatic protons).

Phenol Oxidation of IIIa——To a solution of 10.5 g of $K_3Fe(CN)_6$ in 300 ml of 5% $NaHCO_3$ solution was added dropwise a solution of 2.5 g of IIIa in 300 ml of $CHCl_3$ with vigorous stirring at room temperature for 30 min. The $CHCl_3$ layer was separated, washed with water and dried over Na_2SO_4. Evaporation of the solvent gave 1.8 g of a dark reddish caramel, which was labile on chromatography by alumina or silica gel and could not be purified by recrystallization. The structure of this compound could not be elucidated because of its unstability. Reprecipitation from $CHCl_3$–petro. ether gave a pale brownish powder, mp 153—158°. (Found: C, 64.17; H, 4.59; N, 3.82; 4.09), δ (ppm $CDCl_3$), 3.80 (3H, OCH_3), 3.87 (3H, OCH_3), 4.60 (2H, $ArCH_2N$), 5.60 (1H, doublet, J 2 cps), 6.10 (1H, singlet), 6.75 (2—3H, broad singlet), 5.70 (1H, OH, disappeared with D_2O), ν_{max} ($CHCl_3$), 3500 (OH), 1710 (CO), 1635 cm^{-1}. Mass spectrum: *m/e* 315, 137. This compound was very unstable and changed to a deep violet substance by acetylation or ethoxycarbonylation. Sodium borohydride and deuterio-sodium borohydride reduction of this compound gave the starting diphenol (IIIa) and the deuterium substitution did not occur.

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