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The Synthesis of 2,3-Dimethoxy-5-methyl-*p*-benzoquinone and Related Compounds[1)]

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2,3-Dimethoxy-5-methyl-*p*-benzoquinone (IV), a synthetic intermediate of ubiquinones was prepared in excellent yield by oxidation of 2,3-dimethoxy-5-methyl-*p*-phenylenediamine dihydrochloride (XIV) obtained *via* 3,4-dimethoxy-2,5-dinitrobenzaldehyde (XII) from vanillin. A number of *p*-benzoquinones related to IV were also synthesized for biological evaluation.

2,3-Dimethoxy-5-methyl-*p*-benzoquinone (IV) is the nucleus component of ubiquinones[3)] and utilized as a synthetic intermediate for these quinones. The compound (IV) was first prepared by Raistrick, *et al.*[4)] in the course of structural determination of fumigatin, a fungus metabolite, and thereafter alternative syntheses were described by Seshadri, *et al.*[5)] and in patents.[6)] An improved synthesis of IV and related compounds, which were required for biological studies, was investigated in this Laboratory and the results are herein reported.

In the study of Raistrick, *et al.*, the quinone (IV) was obtained from vanillin (I) by the sequence (I→II→III→IV) shown in Chart 1. By tracing these steps, it was observed that the original procedure of preparing the nitro compound (IIb) by nitration of 2-methoxy-*p*-cresol (IIa) was improved by the use of benzoyl nitrite instead of nitric acid but the drastic oxidation of the amino compound (IIIb) with potassium dichromate in the presence of sulfuric acid gave IV in poor yield. Since mild oxidation of a *p*-diamino compound with ferric chloride to a quinone seemed preferable, vanillin was transformed to the diamine (XIV), *via* the dinitro derivative (XII). The two dinitro derivatives (VIIa, XVII) isomeric to XII were also prepared and characterized. The diamine (XIV) was found to be convertible in excellent yield to the quinone by the above mild oxidation. The synthetic routes are illustrated in Chart 1.

An attempted nitration of 5-nitrovanillin (Va)[7)] with various nitrating agents resulted in the recovery of the unchanged material or formation of polymerized products; however, the methyl ether (VIb) of Va, prepared *via* the dimethyl acetal (Vb), was nitrated smoothly with fuming nitric acid to afford the dinitro compound (VIIa) melting at 97°. This (VIIa) was transformed into the methyldiamino derivative (VIIc) through chlorination with phosphorous pentachloride to VIIb and subsequent reduction with tin and hydrochloric acid. Oxidation of VIIc with ferric chloride furnished the amino quinone (VIII). The light absorption maxima at 274 mμ and 500 mμ of VIII coincided with those (at 273 mμ and 492 mμ) of 2-amino-3,6-dimethyl-*p*-benzoquinone[8)] and the infrared spectra of both compounds were

1) A preliminary account was reported in *Chem. Pharm. Bull.* (Tokyo), **11**, 404 (1963).
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3) C.H. Shunk, B.O. Linn, E.L. Wong, P.E. Witterreich, F.M. Robinson and K. Folkers, *J. Am. Chem. Soc.*, **80**, 4753 (1958).
4) W.K. Anslow, J.N. Ashley and H. Raistrick, *J. Chem. Soc.*, **1938**, 439.
5) K. Agboramurthy, M.K. Ramanathan and T.R. Seshadri, *Chem. Ind.* (London), **1954**, 1327.
6) *a*) F. Hoffmann-La Roche & Co., A.-G., Brit. Patent 889704 (1962) [*C.A.*, **57**, 4596 (1962)]; *b*) Kyowa Fermentation Industry Co., Ltd., Japan. Patent 22574 (1963) [*C.A.*, **60**, 2847 (1964)]; *c*) L. Blaha and J. Weichet, Czech. Patent **110938** (1964) [*C.A.*, **62**, 1601 (1965)].
7) P. Traynard and A. Robert, *Bull. Soc. Chim. France*, **1954**, 1364.
8) H. Teuber and M. Hasselbach, *Chem. Ber.*, **92**, 674 (1959).

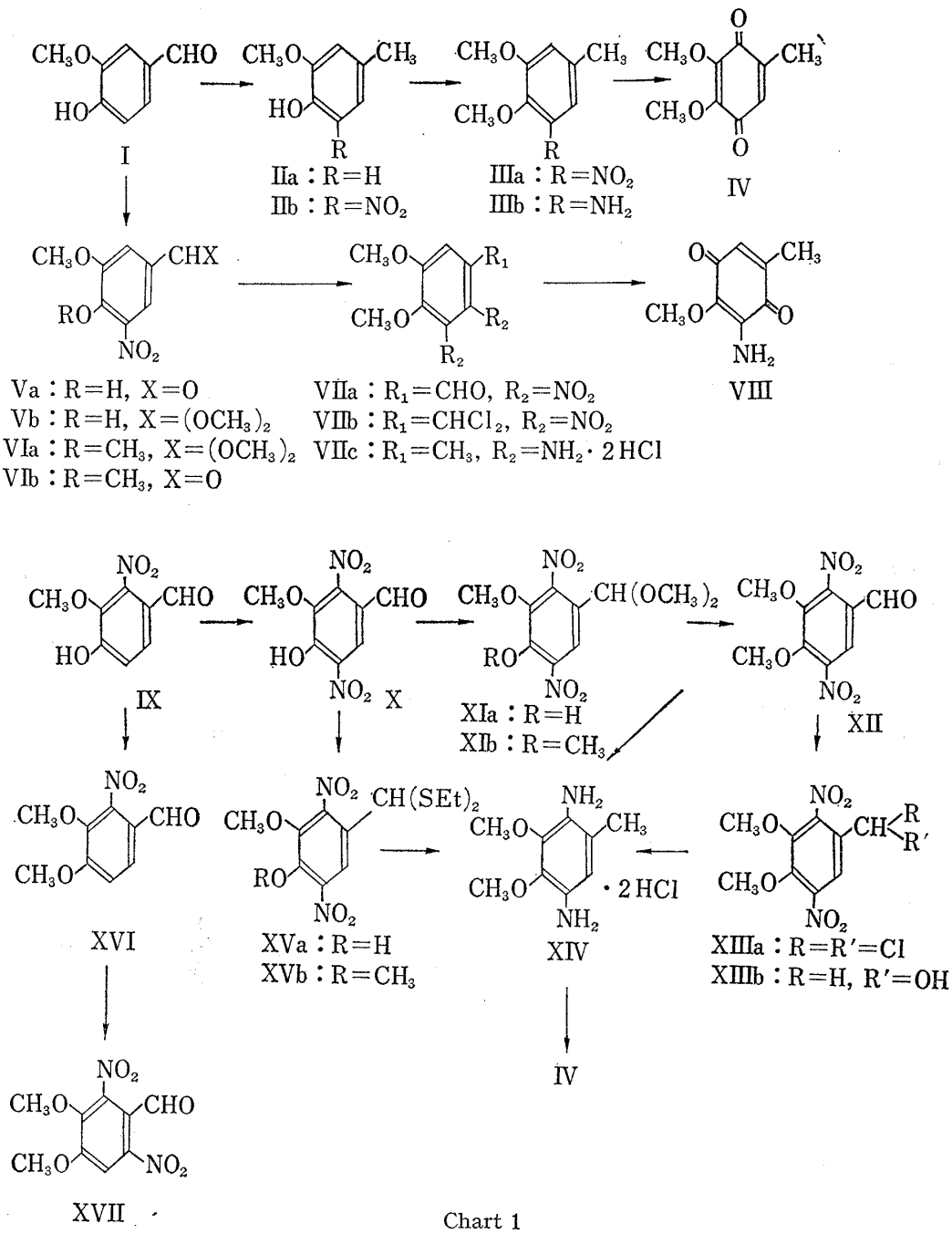

Chart 1

also similar. The structure of VIII and therefore the location of the two nitro groups of VIIa in *ortho* positions were thus established.

Nitration of 2-nitrovanillin (IX)[9] with fuming nitric acid in acetic acid under ice-cooling formed another dinitro compound (X) melting at 102°, whose *p*-dinitro structure was proved by converting ultimately into the quinone (IV) as described below. On the other hand, nitration of the corresponding methyl ether (XVI) with fuming nitric acid without solvents at room temperature gave the third dinitro derivative (XVII), mp 123° and its *m*-dinitro structure was concluded from the non-identity with the *o*- and *p*-isomers.

Methylation of the *p*-dinitro compound (X) gave the methyl ether (XII) in low yield, whereas the acetal (XIa) of X was methylated smoothly with dimethyl sulfate and alkali

9) *a*) R. Pschorr and C. Sumuleanu, *Chem. Ber.*, **32**, 3405 (1899); *b*) D. Hey and L. Labo, *J. Chem. Soc.*, **1954**, 2246.

to afford the uncrystallizable acetal methyl ether (XIb) which was hydrolyzed to XII. The poor reactivity of X toward methylation is explained by the electron attractive effect of the aldehyde group combined with that of the two nitro groups. Similar results were observed in the case of Va described above.

2,3-Dimethoxy-5-methyl-*p*-phenylenediamine dihydrochloride (XIV) was produced (i) by chlorination of XII to XIIIa followed by reduction with tin and hydrochloric acid or with palladium, (ii) by Meerwein–Pondorf reduction of XII to XIIIb followed by catalytic reduc-

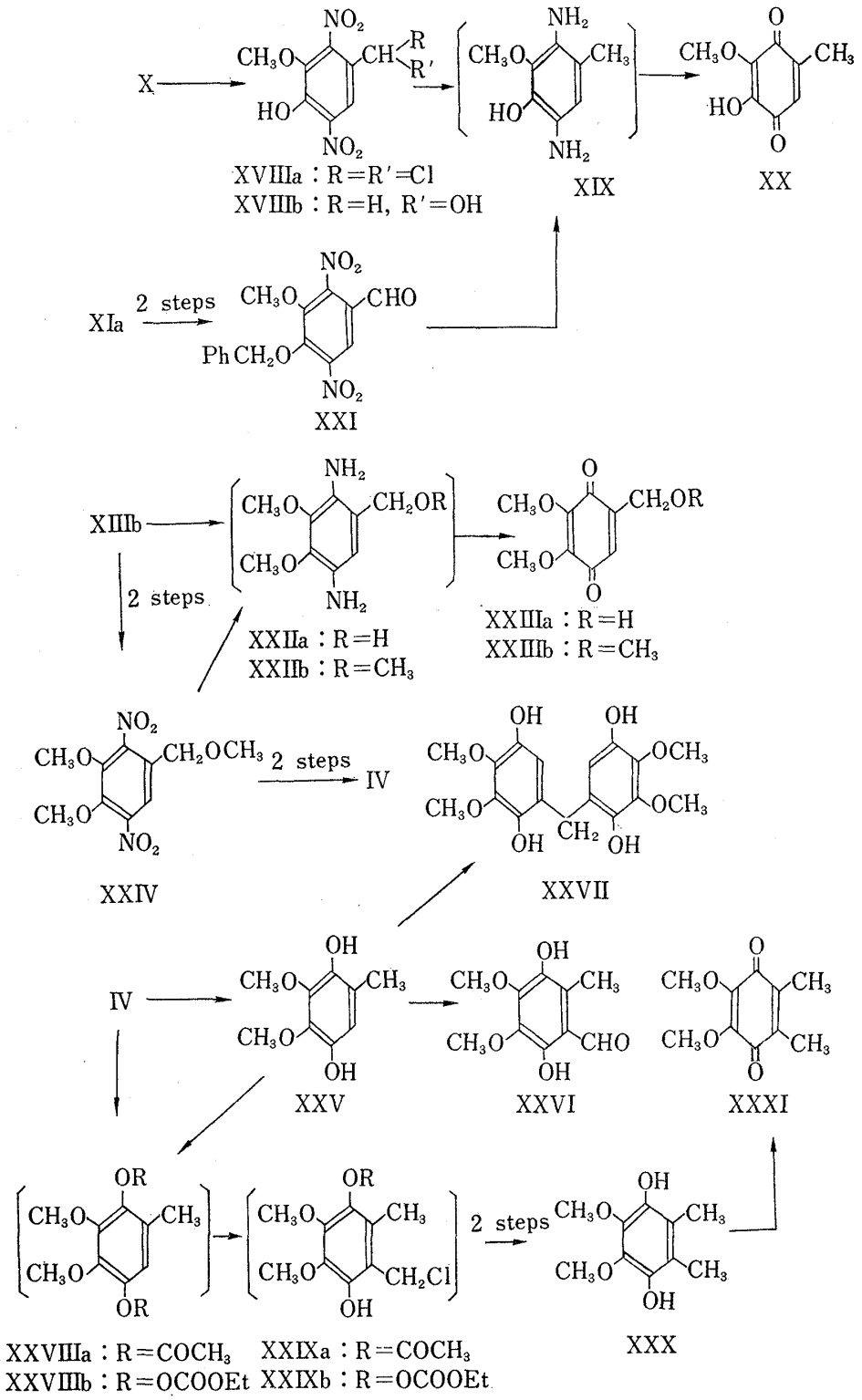

Chart 2

tion, or (iii) by conversion of X to the diethyl thioacetal (XVb) followed by reduction with Raney nickel. The second method was most suitable. An attempted catalytic hydrogenation of XII directly to the diamine (XIV) resulted in low yield. By oxidation of XIV with ferric chloride, the desired quinone (IV) was obtained without difficulty and a total yield of 47% from I was realized.

A number of related compounds were prepared in a similar manner. 2,5-Dinitrovanillin (X) was converted, *via* the dichloride (XVIIIa) or the alcohol (XVIIIb), into the methyl diamine (XIX) which without isolation was oxidized to give 2-hydroxy-3-methoxy-5-methyl-*p*-benzoquinone (XX), an isomer of fumigatin. Alternatively, the benzyl ether aldehyde (XXI) derived from the acetal (XIa) was hydrogenated with palladium to furnish the diamine (XIX) which was oxidized to the quinone (XX).

Hydrogenation of 3,4-dimethoxy-2,5-dinitrobenzyl alcohol (XIIIb) with Raney nickel or palladium in neutral methanol, followed by oxidation of the resultant diamine (XXIIa) with ferric chloride gave the hydroxymethyl dimethoxy quinone (XXIIIa). On the other hand, hydrogenation of XIIIb with palladium in acidic methanol, followed by oxidation provided a mixture of XXIIIa and the methoxymethyl derivative (XXIIIb). The latter was also synthesized from XIIIb through chlorination with phosphorous pentachloride, methoxylation with sodium methoxide to XXIV, hydrogenation in a neutral solution to the diamine and oxidation. Hydrogenation of XXIV in acidic medium, followed by oxidation resulted in the formation of the quinone (IV).

Synthesis of aurantiogliocladin (XXXI) from IV was further undertaken. This quinone (XXXI) is also a fungus metabolite and has been prepared previously by Baker, *et al.*[10] and Seshadri, *et al.*[11] The method of the latter authors involved formylation of the hydroquinone (XXV) with hexamethylenetetramine and hydrochloric acid but the yield of the aldehyde (XXVI) was unsatisfactory. By chloromethylation of XXV with formaldehyde and hydrochloric acid under mild conditions, the diphenylmethane derivative (XXVII) was isolated as the sole product, while the diacetate (XXVIIIa) and the diethoxycarbonate (XXVIIIb) of XXV were converted smoothly into the non-crystalline chloromethyl derivatives (XXIXa and b), respectively. The products showed a positive colour reaction with ferric chloride and infrared absorption due to a hydroxyl group, indicating the presence of a phenolic hydroxyl group which is most likely located at the *ortho* position to the chloromethyl group. The literature[12] includes similar results due to elimination of the acetyl group, during chloromethylation, from the acetate in the *ortho* position of the chloromethyl group. Hydrogenation of the chloromethyl derivatives with palladium afforded the oily *vic*-dimethyl derivatives which were hydrolyzed to the hydroquinone (XXX). Subsequent oxidation gave aurantiogliocladin (XXXI).

Experimental[13]

Preparation of 2,3-Dimethoxy-5-methyl-*p*-benzoquinone (IV) by Modification of Raistrick's Method—To a solution of 2-methoxy-*p*-cresol (IIa) (2.8 g) in $CHCl_3$ (30 ml) was added freshly prepared benzoyl nitrite (4.0 g) in the same solvent (1.5 ml) and the mixture was allowed to stand overnight at room temperature. After evaporation of the solvent the residue was treated with benzene (10 ml) and the separated benzoic acid was removed by filtration. The filtrate was concentrated, the crude 5-nitro derivative (IIb) obtained was dissolved in toluene (50 ml) and the solution was refluxed with Me_2SO_4 (20.5 g) and K_2CO_3 (13.0 g) for 3 hr. The cooled reaction mixture was treated with benzene and the benzene layer was washed with

10) W. Baker, J. McOmie, and O. Miles, *J. Chem. Soc.*, **1953**, 820.
11) T. Seshadri and G. Venkatasubramanian, *J. Chem. Soc.*, **1959**, 1660.
12) L. Smith and R. Carlin, *J. Am. Chem. Soc.*, **64**, 524 (1942).
13) Melting points are uncorrected. Unless otherwise described, IR spectra were measured in a KBr disc, and UV spectra in EtOH. Microanalyses were performed by Mr. B. Kurihara and his associates in this Laboratory.

2% aqueous NaOH (150 ml) and H_2O, dried and concentrated. Distillation of the residue gave benzoic acid and then 3,4-dimethoxy-5-nitrotoluene (IIIa) (2.46 g; 62% from IIa), bp 135—137° (3 mmHg), mp 52—55°. The latter was dissolved in MeOH (19 ml) and hydrogenated catalytically with Raney Ni (W-5, 0.63 g). Removal of the catalyst and evaporation of the solvent gave crude 3-amino-4,5-dimethoxytoluene (IIIb) (2.08 g), a portion of which was benzoylated with benzoyl chloride and pyridine to afford the benzamide derivative of IIIb, prisms (from MeOH) mp 80°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.66; H, 6.21; N, 5.06. The crude amine (IIIb) (2.0 g) was added dropwise to 40% H_2SO_4 (20 ml) cooled to −15°. A solution of $Na_2Cr_2O_7$ (3.6 g) in H_2O (12 ml) was then added and the mixture was stirred at the same temperature for 4 hr. After being allowed to stand at room temperature overnight the reaction mixture was extracted with ether (50 ml × 3) to give the crude quinone (IV) (0.66 g) which was dissolved in ether and passed through a column of alumina (6.0 g; deactivated with 10% H_2O). Recrystallization from petr. ether furnished a pure sample as deep crimson needles (0.38 g; 9.3% from IIa), mp 58—59° (lit. mp 59°[4]).

5-Nitrovanillin Dimethyl Acetal (Vb)——A solution of 5-nitrovanillin (Va) (30.0 g) in MeOH (300 ml) was refluxed for 2 hr. Evaporation of the solvent gave the crude acetal (Vb). A portion of the product was recrystallized from MeOH to afford an analytical sample as yellow needles, mp 62°. *Anal.* Calcd. for $C_{10}H_{13}O_6N$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.40; H, 5.46; N, 5.76. This was slowly hydrolyzed to Va by exposure to atmospheric moisture.

3,4-Dimethoxy-5-nitrobenzaldehyde (VIb)——The above crude acetal in acetone (300 ml) was heated under reflux with anhydrous K_2CO_3 (11.0 g) and Me_2SO_4 (28.8 g) for 3 hr. After evaporation of the solvent the residue was partitioned between ether (200 ml) and 2% aqueous NaOH (500 ml). The organic layer was washed with H_2O, dried and evaporated to afford a mixture of VIb and its acetal (VIa). The mixture was warmed with AcOH (60 ml) and 10% H_2SO_4 (120 ml) at 70° for 1 hr. After being cooled, a precipitated solid was filtered, washed with H_2O and dried to give VIb (25.5 g), mp 86—89° (lit. mp 90—91°[14]).

4,5-Dimethoxy-2,3-dinitrobenzaldehyde (VIIa)——Powdered VIb (25.5 g) was added in small portions to fuming HNO_3 (51.0 ml) cooled to 5°. After 5 min the reaction mixture was poured into ice–water and a precipitated solid was filtered, washed with H_2O and dried. The solid (27.8 g) was recrystallized from ether to give pale yellow plates of VIIa, mp 97°. *Anal.* Calcd. for $C_9H_8O_7N_2$: C, 42.19; H, 3.15; N, 10.94. Found: C, 42.16; H, 3.49; N, 11.09.

3-Dichloromethyl-5,6-dimethoxy-1,2-dinitrobenzene (VIIb)——To VIIa (5.0 g) in benzene (100 ml) was added PCl_5 (4.1 g) and the solution was warmed at 60° for 2 hr. The reaction mixture was concentrated *in vacuo* and the resulting solid was recrystallized from ether to give plates of VIIb (4.65 g), mp 108°. *Anal.* Calcd. for $C_9H_8O_6N_2Cl_2$: C, 34.74; H, 2.59; N, 9.01. Found: C, 35.03; H, 2.89; N, 8.99.

2,3-Diamino-4,5-dimethoxytoluene Dihydrochloride (VIIc)——To a suspension of VIIb (2.0 g) in conc. HCl (40 ml) was added granular tin (15 g) and the mixture was stirred at 80° for 5 hr. Additional tin (5 g) and conc. HCl (10 ml) were then added and the stirring was continued further for 4 hr. After being basified with 10% aqueous NaOH, the reaction mixture was extracted with ether. The ethereal layer was back-extracted with 5% aqueous HCl. Evaporation of the aqueous solution *in vacuo* at 60° and recrystallization of the residue (1.16 g) from MeOH–ether (1:9) afforded VIIc, mp 203° (decomp.). *Anal.* Calcd. for $C_9H_{15}O_2N_2Cl_2$: C, 42.78; H, 6.32; N, 10.98. Found: C, 42.85; H, 6.12; N, 11.02.

2-Amino-3-methoxy-6-methyl-*p*-benzoquinone (VIII)——To a solution of the above amine hydrochloride (VIIc) (0.40 g) in 5% aqueous hydrochloric acid (10 ml) was added $FeCl_3 \cdot 10H_2O$ in H_2O (5 ml) at 0°, the mixture was extracted with ether and evaporation of the solvent gave the crude quinone which was recrystallized from petr. ether to separate needles of VIII (0.08 g), mp 91°. UV λ_{max} mμ (ε): 274 (10100), 500 (2000). IR ν_{max} cm^{-1}: 3440, 3330 (NH), 1669, 1642 (C=O), 1588 (NH). *Anal.* Calcd. for $C_8H_9O_3N$: C, 57.45; H, 5.42; N, 8.38. Found: C, 57.29; H, 5.47; N, 8.38.

2,5-Dinitrovanillin (X)——To a stirred suspension of 2-nitrovanillin (IX)[7] (5.00 g) in AcOH (10 ml) was added dropwise fuming HNO_3 (3.55 g) in AcOH (5 ml) at 10—15°. After 30 min, the reaction mixture was poured into ice–water and the precipitate was filtered, washed well with H_2O and dried (5.20 g, 84.7%). Recrystallization from ether gave pale yellow needles of X, mp 102°. *Anal.* Calcd. for $C_8H_6O_7N_2$: C, 39.67; H, 2.50; N, 11.57. Found: C, 39.64; H, 2.70; N, 11.41.

3,4-Dimethoxy-2,5-dinitrobenzaldehyde (XII)——A solution of X (22.0 g) in MeOH (100 ml) was refluxed for 40 min. The cooled reaction mixture separated the dimethyl acetal of X (XIa) (26.0 g) as yellow prisms, mp 120—123°. An analytical sample recrystallized from MeOH melted at 123°. *Anal.* Calcd. for $C_{10}H_{12}O_8N_2$: C, 41.67; H, 4.20; N, 9.72. Found: C, 41.45; H, 3.98; N, 10.01.

To the acetal (12.0 g) in acetone (80 ml) were added Me_2SO_4 (7.9 g) and K_2CO_3 (3.16 g) and the mixture was refluxed for 2 hr. After removal of inorganic salts by filtration, the solvent was evaporated *in vacuo*, the residue was partitioned between ether and H_2O, and the ethereal layer was washed with 2% aqueous NaOH and then H_2O. Concentration of the ethereal solution gave a crude liquid of 3,4-dimethoxy-2,5-dinitrobenzaldehyde dimethyl acetal (XIb) which failed to crystallize. A solution of the crude acetal in a

14) P. Pschorr and W. Stoehrer, *Chem. Ber.*, **35**, 4393 (1902).

mixture of AcOH (25 ml) and 10% H_2SO_4 (50 ml) was stirred at 80° for 3 hr. After being chilled with ice, the separated crystals were collected and dried. This (9.80 g; mp 103—105°) was recrystallized from AcOEt to afford prisms of XII, mp 105°. *Anal.* Calcd. for $C_9H_8O_7N_2$: C, 42.19; H, 3.15; N, 10.94. Found: C, 42.32; H, 3.34; N, 11.02.

2-Dichloromethyl-5,6-dimethoxy-1,4-dinitrobenzene (XIIIa)——To XII (3.00 g) in anhydrous benzene (30 ml) was added PCl_5 (2.56 g) and the mixture was refluxed gently with occasional shaking for 45 min. The reaction mixture was washed with ice-water, dried and evaporated to dryness to afford a crystalline solid (3.60 g, mp 135—140°) which was recrystallized from ether to give XIIIa, mp 144°. *Anal.* Calcd. for $C_9H_8O_6N_2Cl_2$: C, 34.75; H, 2.59; N, 9.01. Found: C, 35.05; H, 2.85; N, 8.88.

3,4-Dimethoxy-2,5-dinitrobenzyl Alcohol (XIIIb)——To a solution of aluminium isopropoxide (4.4 g) in iso-PrOH (60 ml) was added XII (15.0 g) and the mixture was heated with stirring at 90—95°(bath temperature) until the distillate no longer showed positive test with 2,4-dinitrophenylhydrazine for acetone. The solvent was evaporated *in vacuo* and the residual semisolid was treated with 5% aqueous HCl (120 ml) under ice-cooling. Extraction with benzene gave a solid (14.9 g) which was recrystallized from petr. ether to separate XIIIb as needles, mp 49°. *Anal.* Calcd. for $C_9H_{10}O_7N_2$: C, 41.86; H, 3.90; N, 10.85. Found: C, 41.67; H, 3.98; N, 10.87.

2,5-Dinitrovanillin Diethyl Thioacetal (XVa)——To a mixture of anhydrous $ZnCl_2$ (1.0 g), anhydrous Na_2SO_4 (2.0 g) and ethanethiol (5.0 g), was added X (1.0 g). After being allowed to stand overnight, the mixture was extracted with ether, H_2S was introduced into the ethereal extract and the precipitated ZnS was removed. Evaporation of the solvent gave a crystalline solid which was recrystallized from petr. ether to afford yellow prisms of XVa (0.8 g), mp 62°. *Anal.* Calcd. for $C_{12}H_{16}O_6N_2S_2$: C, 41.38; H, 4.63; N, 8.04. Found: C, 41.59; H, 4.86; N, 8.02.

2,5-Diamino-3,4-dimethoxytoluene Dihydrochloride (XIV)——a) A mixture of XVa (0.50 g) in acetone (5 ml), Me_2SO_4 (0.40 g) and K_2CO_3 (0.11 g) was refluxed for 3 hr, the solvent was removed, H_2O was added to the residue and the product was taken up into ether. The ethereal solution was washed with 2% aqueous NaOH and then H_2O and dried. Removal of the solvent afforded crude liquid (0.52 g) of 3,4-dimethoxy-2,5-dinitrobenzaldehyde diethyl thioacetal (XVb) which failed to crystallize. The same compound (XVb) was obtained by thioacetalization of XII in a similar manner as described for XVa.

A mixture of XVb (0.43 g) in EtOH (40 ml) and Raney Ni (W-5; 3.0 g) was refluxed for 2 hr, Raney Ni was removed by filtration, and the filtrate was concentrated. The oily residue (0.20 g) was dissolved in ether and treated with dry HCl to give XIV. Recrystallization from MeOH–ether gave an analytical sample as prisms, mp 245° (decomp.). *Anal.* Calcd. for $C_9H_{16}O_2N_2Cl$: C, 42.37; H, 6.32; N, 10.98. Found: C, 42.37; H, 6.48; N, 11.17.

b) To a suspension of XIIIa (4.0 g) in conc. HCl (80 ml) was added granular tin (2.0 g) and the mixture was heated at 80° for 2 hr. Additional tin (12 g) and conc. HCl (30 ml) was then added and heating was continued further for 8 hr. The reaction mixture was basified with aqueous NaOH and extracted with a mixture of benzene and ether. The extracted product (2.0 g) was dissolved in ether and treated with dry HCl to give XIV. Catalytic hydrogenation of XIIIa in MeOH with Pd-C for 16 hr also gave XIVa in 85% yield.

c) A suspension of XIIIb (20.0 g) in 2% aqueous HCl (350 ml) was hydrogenated with 10% Pd-C (5.0 g) under atmospheric pressure until 7 mole equiv. of H_2 were absorbed. The catalyst was removed by filtration and the resultant solution of XIV was used for the oxidation of the next step (as below) to afford IV.

2,3-Dimethoxy-5-methyl-*p*-benzoquinone (IV)——To a solution of XIV (14.0 g) in 3% aqueous HCl (250 ml) was added $FeCl_3 \cdot 10H_2O$ (81.0 g) in H_2O (50 ml) and the solution was shaken at room temperature for 20 min. The mixture was extracted with benzene to afford a solid (8.9 g), mp 56—58°. Recrystallization from petr. ether separated IV as red needles, mp 59° (lit. mp 59°,[4] 56—58°,[5] 58—59°,[6a] 61°,[6b] 59—60°[6c]). UV λ_{max} mμ (ε): 265 (11950), 365 (700). IR ν_{max} cm^{-1}: 1672, 1658, 1643, 1605. *Anal.* Calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.42; H, 5.50.

3,4-Dimethoxy-2,6-dinitrobenzaldehyde (XVII)——3,4-Dimethoxy-2-nitrobenzaldehyde[9] (XVI) (0.50 g) was added in small portions to fuming HNO_3 (3 ml) at 15°. The mixture was poured into ice-water to separate a crude product which was filtered, washed with H_2O and dried (0.50 g; 82.2%). Recrystallization from MeOH gave needles of XVII, mp 123°. *Anal.* Calcd. for $C_9H_8O_7N_2$: C, 42.19; H, 3.15; N, 10.94. Found: C, 42.13; H, 3.20; N, 11.13.

4-Dichloromethyl-2-methoxy-3,6-dinitrophenol (XVIIIa)——A solution of X (3.0 g) and PCl_5 (2.6 g) in anhydrous benzene (45 ml) was allowed to stand overnight. Evaporation of the solvent at 40° *in vacuo* and crystallization of the residue (3.7 g) from petr. ether afforded yellow needles of XVIIIa (1.85 g). Further recrystallization gave an analytical sample, mp 64°. *Anal.* Calcd. for $C_8H_6O_6N_2Cl_2$: C, 32.34; H, 2.04; N, 9.43. Found: C, 32.42; H, 2.16; N, 9.43.

4-Hydroxymethyl-2-methoxy-3,6-dinitrophenol (XVIIIb)——To a solution of aluminium isopropoxide (3.1 g) in iso-PrOH (20 ml) was added X (5.0 g). The mixture was stirred at 90—92°, acetone slowly distilled off during 4 hr, the solution concentrated to dryness, and the residue treated with 5% aqueous HCl (70 ml). The product was extracted with benzene and the benzene solution was washed with 2% aqueous $NaHCO_3$, and H_2O, dried and concentrated. Recrystallization of the residue gave pale yellow needles of XVIIIb

(4.7 g) mp 92°. *Anal.* Calcd. for $C_8H_8O_7N_2$: C, 39.35; H, 3.30; N, 11.47. Found: C, 39.39; H, 3.28; N, 11.30.

4-Benzyloxy-3-methoxy-2,5-dinitrobenzaldehyde (XXI)——A mixture of XIa (28.8 g) in anhydrous acetone (170 ml), benzyl chloride (19.0 g), anhydrous K_2CO_3 (10.3 g) and KI (3.0 g) was refluxed for 10 hr. The inorganic materials were filtered, the filtrate was concentrated to dryness and the residue was partitioned between ether and H_2O. The ethereal phase was washed with 2% aqueous NaOH and H_2O, dried and evaporated. Recrystallization of the residue (33.0 g) from MeOH afforded the dimethyl acetal of XXI, mp 78°. *Anal.* Calcd. for $C_{17}H_{18}O_8N_2$: C, 53.97; H, 4.80; N, 7.40. Found: C, 54.18; H, 4.89; N, 7.35.

The acetal (16.5 g) in a mixture of AcOH (70 ml) and 25% H_2SO_4 (270 ml) was heated at reflux temperature for 2 hr. The solution was extracted with benzene and the extract was washed with aqueous $NaHCO_3$ and H_2O and dried. Evaporation of the solvent and recrystallization of the residue (13.5 g) from benzene–cyclohexane (1:1) afforded needles of XXI, mp 114°. *Anal.* Calcd. for $C_{15}H_{12}O_7N_2$: C, 54.21; H, 3.64; N, 8.43. Found: C, 53.96; H, 3.94; N, 8.37.

2-Hydroxy-3-methoxy-5-methyl-*p*-benzoquinone (XX)——a) A suspension of XVIIIb (1.0 g) in 5% aqueous HCl (30 ml) was hydrogenated with 10% Pd-C (1.0 g). The absorption of H_2 ceased after consumption of 80% of the theoretical amount. The catalyst was removed by filtration, $FeCl_3 \cdot 10H_2O$ (2.4 g) in H_2O (5 ml) added to the filtrate, and the mixture extracted with ether. The residue obtained from the ethereal solution was recrystallized from cyclohexane to afford XX (0.05 g), mp 80°. IR ν_{max} cm^{-1}: 3350 (OH), 1650, 1612 (C=O). *Anal.* Calcd. for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.43; H, 4.78.

b) To a suspension of XVIIIa (0.5 g) in conc. HCl (10 ml) was added granular tin (3.0 g) and the mixture was heated with stirring at 65° for 3 hr. Tin (1.5 g) and conc. HCl (5.0 ml) were added and heating was continued further for 1 hr. To the reaction mixture was added $FeCl_3 \cdot 10H_2O$ (25 g) in H_2O under ice-cooling. Extraction with ether and crystallization from petr. ether of the extracted product afforded XX (0.02 g), mp 80°, identical with the specimen described in a).

c) A suspension of XXI (1.0 g) in 5% aqueous HCl was hydrogenated with 40% Pd-C (1.0 g) until it no longer absorbed H_2 (about 30 min were required.). The hydrogenated product was oxidized with $FeCl_3 \cdot 10H_2O$ (2.4 g) as described for a) to give XX (0.18 g), mp 80°, identical with that described above.

Methylation of XX (60 mg) in acetone (5.0 ml) with Me_2SO_4 (90 mg) and K_2CO_3 (50 mg) at reflux temperature for 1.5 hr and crystallization of the product from petr. ether afforded the quinone (IV) (50 mg), mp 56—58°, identical with the specimen described in the paragraph for IV.

2-Hydroxymethyl-5,6-dimethoxy-*p*-benzoquinone (XXIIIa) and Its Methyl Ether (XXIIIb)——a) A solution of XIIIb (1.0 g) in MeOH (40 ml) was hydrogenated with Raney Ni (1.0 g) until it no longer absorbed H_2 (about 7 hr). The catalyst was removed and the solvent was evaporated at 30° *in vacuo*. The residual crude diamine (XXIIa) was dissolved in 2% aqueous HCl (15 ml) and $FeCl_3 \cdot 10H_2O$ (10 g) in H_2O (10 ml) was added thereto. The mixture was extracted with ether and a solid product from the ethereal solution was recrystallized from petr. ether to give orange needles of XXIIIa, mp 70°. *Anal.* Calcd. for $C_9H_{10}O_5$: C, 54.54; H, 5.05. Found: C, 54.28; H, 4.96.

b) A solution of XIIIb (0.5 g) in a mixture of MeOH (15 ml) and 10% aqueous HCl (3.0 ml) was hydrogenated with 5% Pd-C (1.0 g). The catalyst was removed and the resultant solution was oxidized with $FeCl_3$ as described above to give a solid (0.22 g) melting at 40—50°, which was fractionally recrystallized from petr. ether to afford the less soluble hydroxymethyl quinone (XXIIIa) (0.03 g; 7.8%) and the more soluble methoxymethyl quinone (XXIIIb) (0.16 g; 39.0%) identical with that described below.

c) To a solution of XIIIb (5.0 g) in benzene (100 ml) was added PCl_5 (4.3 g). The mixture was heated at 70° for 30 min cooled and washed well with ice–water. A solid (5.0 g) obtained from the benzene solution was recrystallized from cyclohexane to afford needles of 3,4-dimethoxy-2,5-dinitrobenzyl chloride, mp 62°. *Anal.* Calcd. for $C_9H_9O_6N_2Cl$: C, 39.07; H, 3.28; N, 10.13. Found: C, 39.25; H, 3.36; N, 10.33. A mixture of the chloride (4.0 g) in anhydrous MeOH (40 ml) and sodium methoxide in MeOH (0.34 g of Na in 50 ml) was refluxed for 4 hr. After removal of the solvent *in vacuo*, the residue was partitioned between ether (50 ml) and H_2O (20 ml). The residue (3.6 g) from the ethereal layer was purified by molecular distillation to give 3,4-dimethoxy-2,5-dinitrobenzyl methyl ether (XXIV) (3.1 g) as a liquid. *Anal.* Calcd. for $C_{10}H_{12}O_7N_2$: C, 44.12; H, 4.44; N, 10.29. Found: C, 44.41; H, 4.60; N, 10.03. A suspension of XXIV (0.85 g) in H_2O (25 ml) was hydrogenated with 20% Pd-C (0.5 g). After removal of the catalyst, the solution was oxidized with $FeCl_3 \cdot 10H_2O$ (2.0 g) and the product was taken up into ether. The solid (0.43 g) obtained was recrystallized from petr. ether to afford XXIIIb, mp 53°. UV λ_{max} $m\mu$ (ε): 261 (10400), 420 (90). IR ν_{max} cm^{-1}: 1676, 1657, 1605. *Anal.* Calcd. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.72; H, 5.59. When XXIV (0.82 g) was hydrogenated with 20% Pd-C in 2% aqueous HCl, and then oxidized, the product was IV (0.32 g).

2,5-Dihydroxy-3,4-dimethoxy-6-methylbenzaldehyde (XXVI)——The quinone (IV) in an ethereal solution was reduced by shaking with an aqueous $Na_2S_2O_3$ solution to give the corresponding hydroquinone (XXV), mp 77—78° (lit. 77—78°[3]), in almost quantitative yield. A solution of XXV (2.0 g) and hexamethylenetetramine (9.2 g) in AcOH (30 ml) was treated at 90° for 5 hr, thereto was added a boiling solution of 20% aqueous HCl and the mixture was kept at the same temperature for 5 min. The cooled mixture was poured into ice–water, NaCl was added, and the product was taken up into benzene. A solid (0.61 g) obtained

was recrystallized from cyclohexane to afford pale yellow prisms of XXVI (0.48 g; 20.80%), mp 129—130° (lit. mp 130°[11]). IR ν_{max} cm^{-1}: 3200, 1650, 1590.

2,5,2′,5′-Tetrahydroxy-3,4,3′,4′-tetramethoxy-6,6′-dimethyldiphenylmethane (XXVII)——A stirred solution of 37% aqueous formaldehyde (5 ml) was saturated with dry HCl at 10—15°, XXV (0.5 g) was added and HCl was introduced at 15—20° for 10 min. The reaction mixture was poured into ice–water, and the precipitate was filtered, washed with H_2O, and dried. Recrystallization from benzene separated XXVII (0.30 g) as needles, mp 190—195° (decomp.). IR ν_{max} cm^{-1}: 3540 (OH), 3400, 1618, 1580. *Anal.* Calcd. for $C_{19}H_{24}O_8$: C, 59.99; H, 6.36. Found: C, 60.23; H, 6.18.

2,3-Dimethoxy-5,6-dimethylhydroquinone (XXX)——a) From IV *via* XXVIIIa: To a solution of IV (0.20 g) in a mixture of AcOH (0.5 ml) and Ac_2O (10 ml) were added anhydrous NaOAc (0.3 g) and Zn–dust (0.4 g) and the mixture was refluxed for 2 hr. The inorganic materials were filtered and washed with AcOH. The filtrate and washings were combined, diluted with H_2O and extracted with benzene. Concentration of the benzene solution gave 2,5-diacetoxy-3,4-dimethoxytoluene (XXVIIIa) (0.26 g) as an oil, which failed to crystallize. IR ν_{max}^{liq} cm^{-1}: 1770 (acetoxy), 1620, 1580, 1490, 1200. A mixture of 37% aqueous formaldehyde (1.5 ml) and conc. HCl (2.0 ml) was saturated with dry HCl at 15—20° and added to the above acetate (XXVIIIa). Dry HCl was introduced thereto with stirring for 1.5 hr. The reaction mixture was poured into ice–water and the solution was extracted with ether. From the ethereal solution was obtained the crude chloromethyl derivative (presumably 2-acetoxy-6-chloromethyl-5-hydroxy-3,4-dimethoxytoluene (XXIXa) as a red liquid (0.24 g) which gave brown color with $FeCl_3$ and deposited AgCl with $AgNO_3$ in MeOH. IR ν_{max}^{liq} cm^{-1}: 3400 (OH), 1760, 1615. This crude chloromethyl derivative (0.20 g) in MeOH (10 ml) was hydrogenated with 10% Pd–C (0.30 g). The catalyst was removed by filtration, 2 drops of conc. H_2SO_4 in MeOH (2 ml) added, and the solution refluxed under N_2 for 30 min. After addition of H_2O (6 ml), the solution was concentrated *in vacuo* and extracted with ether. The product obtained from the ethereal solution was crystallized from cyclohexane to give needles of XXX (0.02 g). mp 80—81° (lit. mp 84° [11]), identical with that obtained from XXVI by the known procedure.

b) From XXV *via* XXVIIIb: To a solution of XXV (1.70 g) and NaOH (0.90 g) in H_2O (10 ml) was added dropwise ethyl chlorocarbonate (1.20 g) under cooling. After 1 hr, the product was taken up into ether and the crude 2,5-bis(ethoxycarboxy)-3,4-dimethoxytoluene (XXVIIIb) was obtained as an oil (1.79 g) which failed to crystallize. IR ν_{max}^{liq} cm^{-1}: 1760, 1650, 1605, 1270, 1230. The crude oil (1.70 g) was chloromethylated similarly as described for a) to afford the chloromethyl derivative (presumably 2-chloromethyl-6-ethoxycarboxy-3-hydroxy-4,5-dimethoxytoluene (XXIXb)) as a viscous liquid (1.5 g) which gave positive $FeCl_3$–test and precipitate of AgCl with $AgNO_3$ in MeOH. IR ν_{max}^{liq} cm^{-1}: 3450 (OH), 1765, 1650, 1610, 1270, 1230. The crude chloromethyl derivative (1.4 g) in MeOH (30 ml) was hydrogenated with 10% Pd–C (1.0 g) to give the crude dechlorinated product (presumably 3-ethoxycarboxy-6-hydroxy-4,5-dimethoxy-*o*-xylene) as a liquid (1.2 g). This liquid (0.8 g) in ether was shaken with 5% aqueous NaOH at room temperature for 5 min. The aqueous phase was separated, acidified with 10% aqueous HCl and extracted with ether. The product obtained from the ethereal solution was crystallized from cyclohexane to give XXX (0.35 g), identical with the sample described above, mp 80—81°.

2,3-Dimethoxy-4,5-dimethylbenzoquinone (XXXI)——A solution of XXX (0.35 g) in ether (20 ml) was shaken with 20% aqueous $FeCl_3$ (10 ml), the ethereal layer was separated, and the aqueous solution was extracted with ether. From the ethereal solution, the crude product (0.34 g) was obtained and recrystallized from petr. ether to afford orange needles of XXXI (0.25 g), mp 63.5—64° (lit. mp 62.0—62.5°,[10] 63°.[11]). UV λ_{max} mμ (ε): 275 (14200), 420 (600). IR ν_{max} cm^{-1}: 1660, 1640, 1608. *Anal.* Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.43; H, 6.40.

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