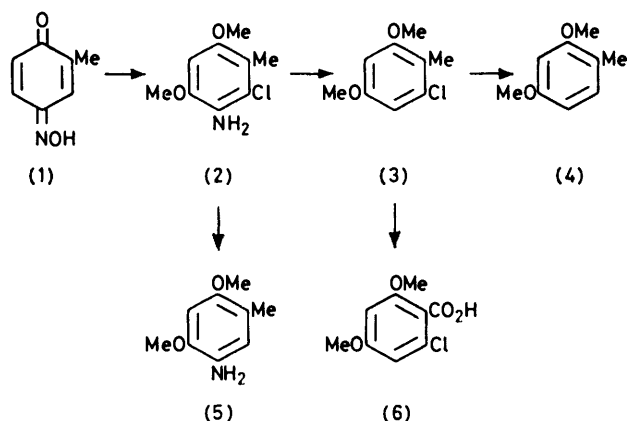


## Reaction of Some 1,4-Benzoquinone Mono-oximes with Methanolic Hydrogen Chloride

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When 2-methyl-1,4-benzoquinone 4-oxime (1) reacted with methanolic hydrogen chloride at 25–30 °C the product was 2-chloro-4,6-dimethoxy-3-methylaniline (2). Similarly 1,4-benzoquinone 4-oxime (7) gave 2-chloro-4,6-dimethoxyaniline (8), 3-methyl-1,4-benzoquinone 4-oxime (11) gave 2-chloro-4-methoxy-6-methoxymethylaniline (12) and 2-chloro-4-methoxy-6-methylaniline (13), and 2-methoxy-1,4-benzoquinone 4-oxime (19) gave 2-chloro-4,5-dimethoxyaniline (20).

IN connection with some synthetic work it appeared that a convenient source of 2-chloro-4-methoxy-5-methylaniline, m.p. 66 °C, would be the reaction of 2-methyl-1,4-benzoquinone 4-oxime (1) with methanolic hydrogen chloride.<sup>1</sup> Repetition of this reaction at 25–30 °C

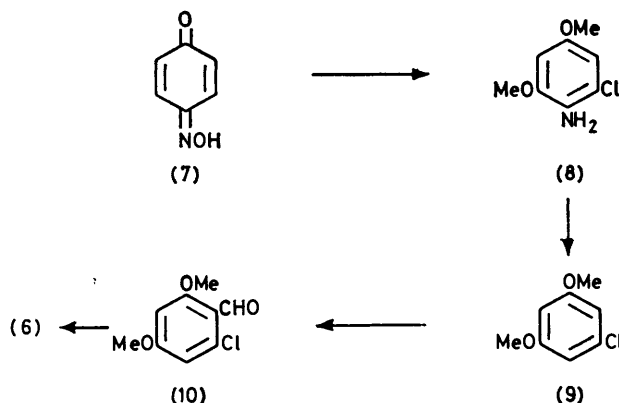


SCHEME 1

gave an aniline derivative in good yield with m.p. 67–68 °C, which was not that claimed by the Italian workers. Its elemental analysis and mass spectrum were in agreement with the molecular formula  $C_9H_{12}ClNO_2$ , and its <sup>1</sup>H n.m.r. spectrum exhibited signals due to a methyl group, two methoxy-groups, and an aromatic proton. Hydrogenolytic dechlorination yielded a new dimethoxytoluidine, m.p. 86–87 °C, in which the aromatic protons were in a *para*-orientation (<sup>1</sup>H n.m.r.). On deamination by reduction of the diazonium salt of the aniline, m.p. 67–68 °C, with phosphinous acid, a new chlorodimethoxytoluene, m.p. 28–29 °C, was obtained. The <sup>1</sup>H n.m.r. spectrum of this compound revealed that its aromatic protons were in a *meta*-orientation. On hydrogenolytic dechlorination the chlorodimethoxytoluene afforded 2,4-dimethoxytoluene (4), identical with a sample obtained by the method of Cram.<sup>2</sup> Oxidation of the chlorodimethoxytoluene with permanganate in aqueous pyridine gave 2-chloro-4,6-dimethoxybenzoic acid (6), identical with a sample prepared by an alternative route (see later). The initial aniline is therefore 2-chloro-4,6-dimethoxy-3-methylaniline (2) (Scheme 1),

and the dimethoxytoluidine and the chlorodimethoxytoluene are thus compounds (5) and (3), respectively.

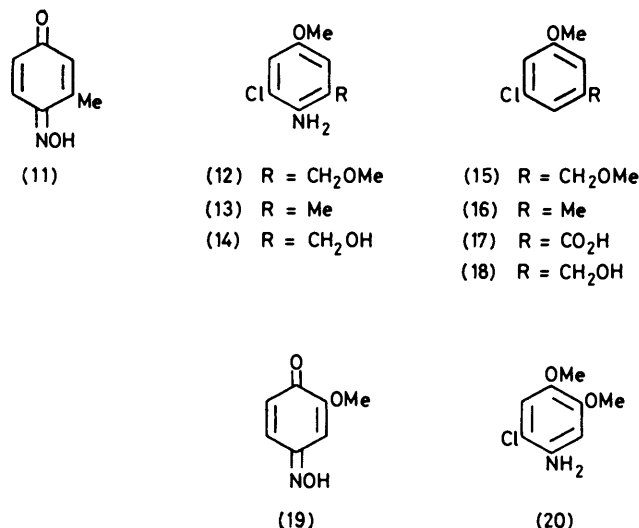
In agreement with the results of Goldschmidt and Suchanek,<sup>3</sup> treatment of 1,4-benzoquinone mono-oxime (7) with methanolic hydrogen chloride at 25–30 °C gave exclusively 2-chloro-4,6-dimethoxyaniline (8) (Scheme 2). Deamination of the latter afforded 1-chloro-3,5-dimethoxybenzene (9). Vilsmeier–Haack formylation of 1-chloro-3,5-dimethoxybenzene (9), like that of the bromo-analogue,<sup>4</sup> gave predominantly one isomer: 2-chloro-4,6-dimethoxybenzaldehyde (10). On oxidation this benzaldehyde afforded the benzoic acid (6), identical with that obtained by degradation of 2-chloro-4,6-dimethoxy-3-methylaniline (2).



SCHEME 2

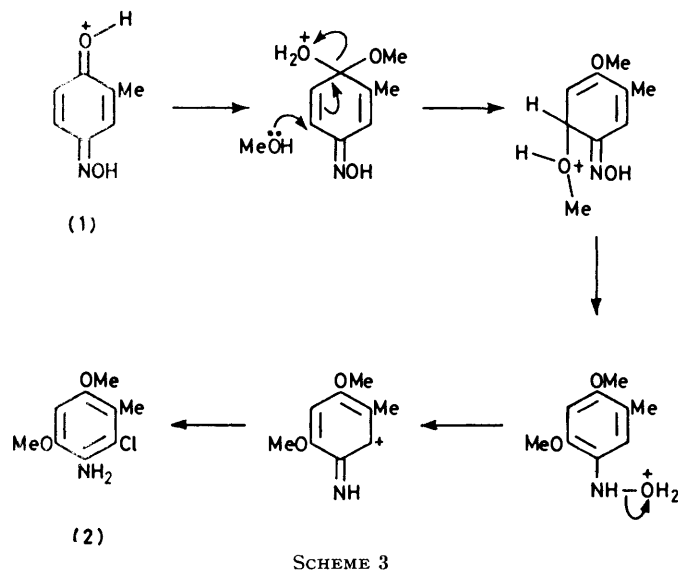
Angeletti and Oliviero<sup>1</sup> reported that treatment of 3-methyl-1,4-benzoquinone 4-oxime (11) with methanolic hydrogen chloride yielded solely 2-chloro-4-methoxy-6-methoxymethylaniline (13). In my hands this reaction afforded a steam-volatile mixture of 2-chloro-4-methoxy-6-methoxymethylaniline (12) and 2-chloro-4-methoxy-6-methylaniline (13) in the ratio *ca.* 3 : 1 (<sup>1</sup>H n.m.r. and g.l.c.–mass spectrometry). Deamination of the mixture afforded 3-chloro- $\alpha$ ,5-dimethoxytoluene (15) and 3-chloro-5-methoxytoluene (16), which were separated by chromatography and readily identified by their spectroscopic properties (see Experimental section). Oxidation of the mixture of compounds (15) and (16) gave 3-chloro-5-methoxybenzoic acid (17) in high yield. The non-

steam-volatile residue from the foregoing reaction gave a little 2-chloro-6-hydroxymethyl-4-methoxyaniline (14), presumably from demethylation of the hydrochloride of compound (12) during steam distillation. On deamination the aniline (14) yielded the benzyl alcohol (18).



Treatment of 2-methoxy-1,4-benzoquinone 4-oxime (19) with methanolic hydrogen chloride gave the known 2-chloro-4,5-dimethoxyaniline (20)<sup>5</sup> in poor yield. It was readily identified from its spectroscopic data.

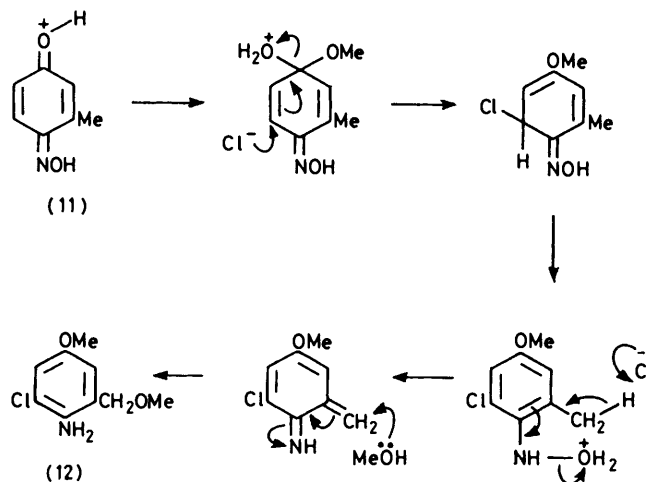
The formation of compounds (2) and (8) in the above reactions is readily explained by the mechanism shown in Scheme 3 for the formation of compound (2). The



SCHEME 3

reaction is initiated by protonation of the carbonyl group and subsequent hemiacetalisation followed by the conjugate addition of methanol. The intermediate phenylhydroxylamine then undergoes a reaction of the Bamberger type.<sup>6</sup> The production of compound (12) must involve a methide-type intermediate as shown in

Scheme 4. The formation of compounds (13) and (20) is not readily explained without invoking a redox reaction. It may be relevant, however, that nitroso-benzene is reported to yield some *p*-chloroaniline as well as 2,4-dichloroaniline on treatment with hydrogen chloride.<sup>7</sup>



SCHEME 4

## EXPERIMENTAL

General directions have been given before.<sup>8</sup>

*Reaction of 2-Methyl-1,4-benzoquinone 4-Oxime (1) with Methanolic Hydrogen Chloride.*—The quinone oxime (1)<sup>9</sup> (15.0 g) in anhydrous methanol (375 ml) was cooled in an ice-salt bath and a stream of dry hydrogen chloride was passed through the solution at 25–30 °C. After some time a precipitate appeared. The solution was saturated with hydrogen chloride and was then set aside at 5 °C for 18 h. The methanol was removed by steam distillation and the residue was cooled in ice and basified with aqueous sodium hydroxide. Steam distillation and isolation with ethyl acetate gave 2-chloro-4,6-dimethoxy-3-methylaniline (2) (15.1 g) as plates (from light petroleum), m.p. 67–68 °C (Found: C, 53.75; H, 5.95; Cl, 17.65; N, 6.7%; *M*<sup>+</sup>, 201/203. C<sub>9</sub>H<sub>12</sub>ClNO<sub>2</sub> requires C, 53.6; H, 6.0; Cl, 17.6; N, 6.95%; *M*, 201/203); δ(CDCl<sub>3</sub>; 90 MHz) 2.20 (3 H, s, Me), 3.74 and 3.81 (each 3 H, s, OMe), and 6.38 (1 H, s, ArH); the NH<sub>2</sub> resonance was obscured by the OMe signal.

*2,4-Dimethoxy-5-methylaniline (5).*—The amine (2) (3.4 g) in ethanol (75 ml) containing triethylamine (2 ml) was stirred with Engelhard 10% palladium-charcoal (500 mg) under hydrogen until absorption ceased. The catalyst was separated by filtration and washed with ethanol. The residue left after removal of the solvent was dissolved in chloroform and washed with water, and then with saturated brine. The aniline (5) (2.5 g) formed plates (from light petroleum), m.p. 86–87 °C (Found: C, 64.6; H, 7.95; N, 8.35%; *M*<sup>+</sup>, 167. C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub> requires C, 64.65; H, 7.85; N, 8.4%; *M*, 167); δ(CDCl<sub>3</sub>; 90 MHz) 2.10 (3 H, s, *W*<sub>1</sub> 1.5 Hz, Me), 3.38b (2 H, NH<sub>2</sub>), 3.74 and 3.80 (each 3 H, s, Me), 6.42 (1 H, s, 3-H), and 6.48 (1 H, s, *W*<sub>1</sub> 2.0 Hz, 6-H); irradiation at δ 2.10 sharpened the 6-H resonance.

*2-Chloro-4,6-dimethoxytoluene (3).*—The aniline (2) (12.5 g) in dioxan (100 ml) and water (100 ml) was stirred and concentrated hydrochloric acid (20 ml) was added. The

suspension was stirred and cooled to 0 °C and sodium nitrite (4.5 g) in water (75 ml) was added dropwise at 0 °C. After a further 15 min at 0 °C, phosphinous acid (50%; 75 ml) was added dropwise over 1 h at 0 °C. The solution was stirred for 1 h at 0 °C, set aside at 0 °C for 18 h, and then extracted with ether. The extract was washed in turn with water, dilute aqueous sodium hydroxide, dilute hydrochloric acid, water, and finally saturated brine. The crude product on distillation under reduced pressure afforded the chlorotoluene (3) (9.1 g) as an oil, b.p. 137–138 °C at 22 mmHg, which eventually solidified. A sample formed plates (from cold light petroleum), m.p. 28–29 °C (Found: C, 57.45; H, 5.9; Cl, 18.8%;  $M^+$ , 186/188.  $C_9H_{11}ClO_2$  requires C, 57.9; H, 5.95; Cl, 19.0%;  $M$ , 186/188);  $\delta(CDCl_3)$ ; 90 MHz) 2.16 (3 H, s, Me), 3.71 and 3.74 (each 3 H, s, OMe), and 6.30 and 6.49 (2 H, AB,  $J$  2.5 Hz,  $2 \times$  ArH).

**2,4-Dimethoxytoluene (4).**—Hydrogenolytic dechlorination of the chlorotoluene (3) as described for compound (2) gave 2,4-dimethoxytoluene (4) (92%) as an oil, b.p. 125 °C (kugelrohr) at 7 mmHg (lit.,<sup>3</sup> 104–105 °C at 12 mmHg), identical (t.l.c., n.m.r., and mass spectra) with a sample prepared by the method of Cram.<sup>2</sup>

**2-Chloro-4,6-dimethoxybenzoic Acid (6).**—The chlorotoluene (3) (7.5 g) in pyridine (90 ml) and water (90 ml) was stirred and heated on a steam-bath during the addition in portions of potassium permanganate (12.7 g) over 1.5 h. The mixture was stirred on a steam-bath for a further 2 h and then poured into an excess of cold dilute hydrochloric acid. The manganese dioxide was destroyed by the addition of sodium pyrosulphite. Extraction with ethyl acetate and isolation with sodium hydrogen carbonate solution in the usual way gave the acid (6) (7.0 g) as prisms (from dichloromethane–light petroleum), m.p. 150–152 °C (Found: C, 49.75; H, 4.2; Cl, 16.8%;  $M^+$ , 216/218.  $C_9H_9ClO_4$  requires C, 49.9; H, 4.2; Cl, 16.35%;  $M$ , 216/218). The methyl ester was obtained as a thick oil, b.p. 140° (kugelrohr) at 0.01 mmHg (Found: C, 51.9; H, 4.9; Cl, 15.55%;  $M^+$ , 230/232).  $C_{10}H_{11}ClO_4$  requires C, 52.1; H, 4.8; Cl, 15.35%;  $M$ , 230/232);  $\delta(CDCl_3)$ ; 90 MHz) 3.78 (6 H, s,  $2 \times$  OMe), 3.90 (3 H, s, OMe), and 6.35 and 6.49 (2 H, AB,  $J$  2.1 Hz,  $2 \times$  ArH).

**Reaction of 1,4-Benzoquinone Mono-oxime (7) with Methanolic Hydrogen Chloride.**—Carried out by the method described for compound (1) this oxime<sup>10</sup> afforded 2-chloro-4,6-dimethoxyaniline (8) (87%), which formed plates [from light petroleum (charcoal)], m.p. 44–45 °C (lit.,<sup>3</sup> 46 °C) (Found: C, 51.2; H, 5.5; Cl, 19.1; N, 7.3%;  $M^+$  187/189. Calc. for  $C_8H_9ClNO_2$ : C, 51.2; H, 5.35; Cl, 18.9; N, 7.45%;  $M$ , 187/189);  $\delta(CDCl_3)$ ; 90 MHz) 3.70 (3 H, s, OMe), 3.76b (2 H,  $D_2O$ -exchangeable  $NH_2$ ), 3.80 (3 H, s, OMe), and 6.37 and 6.43 (2 H, AB,  $J$  2.4 Hz,  $2 \times$  ArH).

**1-Chloro-3,5-dimethoxybenzene (9).**—Deamination of the aniline (8) by the method described for compound (2) afforded the chlorobenzene (9) (92%), which formed laths (from cold light petroleum), m.p. 34–35 °C (lit.,<sup>3</sup> 36 °C) (Found: C, 55.55; H, 5.35; Cl, 20.8%;  $M^+$ , 172/174. Calc. for  $C_8H_9ClO_2$ : C, 55.65; H, 5.25; Cl, 20.55%;  $M$ , 172/174);  $\delta(CDCl_3)$ ; 90 MHz) 3.75 (6 H, s,  $2 \times$  OMe), 6.32 (1 H, t,  $J$  2.1 Hz, 4-H), and 6.48 (2 H, d,  $J$  2.1 Hz, 2- and 6-H).

**2-Chloro-4,6-dimethoxybenzaldehyde (10).**—A stirred solution of 1-chloro-3,5-dimethoxybenzene (9) (3.1 g) in *N,N*-dimethylformamide (20 ml) was cooled to 0 °C and treated dropwise with phosphoryl chloride (5 ml). The solution

was then stirred at room temperature for 0.5 h and then heated on a steam-bath for 3 h. The solution was poured into water and ice and the mixture was set aside overnight. Next day the precipitate was separated by filtration, washed with water, and dried *in vacuo*. The aldehyde (10) (2.0 g) formed plates [from dichloromethane–light petroleum (charcoal)], m.p. 79–80 °C (Found: C, 53.75; H, 4.5; Cl, 17.75%;  $M^+$ , 200/202.  $C_9H_9ClO_3$  requires C, 53.9; H, 4.5; Cl, 17.65%;  $M$ , 200/202);  $\delta(CDCl_3)$ ; 90 MHz) 3.86 and 3.88 (each 3 H, s, OMe), 6.38 and 6.50 (2 H, AB,  $J$  2.1 Hz,  $2 \times$  ArH), and 10.36 (1 H, s, CHO). On oxidation with potassium permanganate in aqueous pyridine as described for compound (3), it afforded 2-chloro-4,6-dimethoxybenzoic acid (6) (88%) as prisms (from dichloromethane–light petroleum), m.p. 150–152 °C, identical (mixed m.p., n.m.r., and mass spectra) with the sample already described.

**Reaction of 3-Methyl-1,4-benzoquinone 4-Oxime (11) with Methanolic Hydrogen Chloride.**—Treated as described for compound (1), this oxime (11)<sup>11</sup> (10.0 g) afforded from the steam distillate a mixture (7.7 g) of 2-chloro-4-methoxy-6-methoxymethylaniline (12) (72 mol % by n.m.r.),  $\delta(CCl_4)$ ; 60 MHz) 3.16 and 3.51 (each 3 H, s, OMe), 3.88 (2 H, s,  $NH_2$ ), 4.19 (2 H, s,  $CH_2$ ), and 6.34 and 6.58 (2 H, AB,  $J$  2.5 Hz,  $2 \times$  ArH),  $m/z$  90 (11%), 91 (9), 92 (9), 99 (11), 126 (18), 127 (26), 128 (9), 129 (8), 134 (23), 142 (9), 168 (30), 169 (100), 170 (40), 171 (35), 172 (12), 201 (42,  $M^+$ ), and 203 (15,  $M^+$ ); and 2-chloro-4-methoxy-6-methylaniline (13) (28 mol %)  $\delta(CCl_4)$ ; 60 MHz) 2.00 (3 H, s, Me), 3.51 (3 H, s, OMe), 3.88 (2 H, s,  $NH_2$ ), and 6.29 and 6.47 (2 H, AB,  $J$  2.5 Hz,  $2 \times$  ArH),  $m/z$  92 (15%), 93 (21), 127 (7), 128 (12), 156 (100), 158 (33), 171 (47,  $M^+$ ), and 173 (15,  $M^+$ ). The mixture was analysed using a Hewlett-Packard 5986 g.l.c.–mass spectrometer system with a 0.31 mm i.d.  $\times$  25 m OV-101 wall-coated open tubular capillary column at a helium flow rate of 7 ml  $min^{-1}$ , an injector temperature of 200 °C, and a column temperature of 100 °C rising at 20 °C  $min^{-1}$  to 200 °C after a delay of 1 min. Under these conditions compound (13) had a retention time of 3.6 min and compound (12) 4.4 min. This mixture of amines (4.1 g) was deaminated by the method described for compound (2), and afforded a crude product (3.7 g). A portion of this mixture (2.0 g) was oxidised with potassium permanganate in aqueous pyridine as described for compound (3). This afforded 3-chloro-5-methoxybenzoic acid (17) (1.8 g), which formed plates (from methanol), m.p. 178–179 °C (Found: C, 51.55; H, 3.85; Cl, 19.1%;  $M^+$ , 186/188.  $C_8H_7ClO_3$  requires C, 51.5; H, 3.8; Cl, 19.0%;  $M$ , 186/188);  $\delta(CDCl_3)$ ; 80 MHz) 3.86 (3 H, s, OMe), 7.14 (1 H, narrow t, ArH), 7.50 (1 H, narrow m, ArH), and 7.68 (1 H, narrow m, ArH). Chromatography of the remaining mixture over silica gel with 0–5% ethyl acetate–light petroleum as eluant afforded 3-chloro-5-methoxytoluene (16) as an oil, b.p. 100 °C (kugelrohr) at 0.8 mmHg (Found: C, 61.25; H, 5.95%;  $M^+$ , 154/156.  $C_8H_9ClO$  requires C, 61.35; H, 5.8%;  $M$ , 154/156);  $\delta(CDCl_3)$ ; 90 MHz) 2.27 (3 H, apparent d, Me), 3.74 (3 H, s, OMe), and 5.44–5.49 (3 H, m,  $3 \times$  ArH); irradiation at  $\delta$  2.27 caused collapse of the aromatic proton signals to ABX pattern. This was followed by 3-chloro- $\alpha$ ,5-dimethoxytoluene (15) as an oil, b.p. 90 °C (kugelrohr) at 0.01 mmHg (Found: C, 58.2; H, 6.1; Cl, 18.5%;  $M^+$  186/188.  $C_9H_{11}ClO_2$  requires C, 57.9; H, 5.95; Cl, 19.0%;  $M$ , 186/188);  $\delta(CDCl_3)$ ; 90 MHz) 3.37 and 3.77 (each 3 H, s, OMe), 4.38 (2 H, s,  $CH_2$ ), and 6.72–6.83 (3 H, m,  $3 \times$  ArH); irradiation at  $\delta$  4.38 caused collapse of the aromatic proton signals to an ABX pattern. The

aqueous residue from the steam distillation was decanted from some tar; on cooling it deposited needles of 2-chloro-6-hydroxymethyl-4-methoxyaniline (14) (1.0 g) which crystallized from ether–light petroleum (charcoal) as needles, m.p. 75–76 °C (Found: C, 51.4; H, 5.4; Cl, 19.05; N, 7.65%;  $M^+$ , 187/189.  $C_8H_{10}ClNO_2$  requires C, 51.2; H, 5.35; Cl, 18.9; N, 7.45%;  $M$ , 187/189);  $\delta(CDCl_3$ ; 90 MHz) 3.88b (1 H,  $D_2O$ -exchangeable OH), 3.68 (3 H, s, OMe), 4.22b (2 H,  $D_2O$ -exchangeable  $NH_2$ ), 4.52 (2 H, s,  $W_{\frac{1}{2}}$  3.8 Hz,  $CH_2$ ), and 6.54 and 6.78 (2 H, AB,  $J$  3.0 Hz, 2 ArH).

3-Chloro-5-methoxybenzyl Alcohol (18).—The amine (14) was deaminated as described for compound (2) and afforded the benzyl alcohol (14) (54%) as an oil, b.p. 130 °C (Kugelrohr) at 0.2 mmHg, which eventually solidified and formed prisms (from ether–light petroleum), m.p. 37–38 °C (Found: C, 55.4; H, 5.15; Cl, 20.35%;  $M^+$ , 172/174.  $C_8H_9ClO_2$  requires C, 55.65; H, 5.25; Cl, 20.55%;  $M$ , 172/174);  $\delta(CDCl_3$ ; 90 MHz) 2.91br (1 H,  $D_2O$ -exchangeable OH), 3.74 (3 H, s, OMe), 4.53 (2 H, s,  $CH_2$ ), and 6.68–6.93 (3 H, m, 3  $\times$  ArH).

Reaction of 2-Methoxy-1,4-benzoquinone 4-Oxime (19) with Methanolic Hydrogen Chloride.—The oxime (19)<sup>12</sup> (5.0 g) in anhydrous methanol (50 ml) and anhydrous ether (50 ml) was saturated with dry hydrogen chloride at 25–30 °C. The mixture was set aside at 5 °C for 15 h and the precipitate was separated by filtration and washed with ether. It was treated with dilute aqueous sodium hydroxide and extracted with ether. This gave 2-chloro-4,5-dimethoxyaniline (20)

(1.7 g), which formed needles [from light petroleum (charcoal)], m.p. 72–73 °C (lit.,<sup>5</sup> 73–74 °C) (Found: C, 51.2; H, 5.4; Cl, 19.0; N, 7.3%;  $M^+$ , 187/189. Calc. for  $C_8H_{10}ClNO_2$ : C, 51.2; H, 5.35; Cl, 18.9; N, 7.45%;  $M$ , 187/189);  $\delta(CDCl_3$ ; 90 MHz) 3.78 and 3.80 (each 3 H, s, OMe), 6.34 (1 H, s, ArH), and 6.78 (1 H, s, ArH).

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#### REFERENCES

- <sup>1</sup> A. Angeletti and A. Oliviero, *Gazz. Chim. Ital.*, 1940, **70**, 789.
- <sup>2</sup> D. J. Cram, *J. Am. Chem. Soc.*, 1948, **70**, 4240.
- <sup>3</sup> S. Goldschmidt and L. Suchanek, *Chem. Ber.*, 1957, **90**, 19.
- <sup>4</sup> M. V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 1981, 403.
- <sup>5</sup> R. R. Holmes, J. Conrady, J. Guthrie, and R. McKay, *J. Am. Chem. Soc.*, 1954, **76**, 2400.
- <sup>6</sup> J. March, 'Advanced Organic Chemistry: Reactions, Mechanisms, and Structure,' 2nd ed., McGraw-Hill Kogakusha, Tokyo, 1977, p. 616.
- <sup>7</sup> E. Bamberger, H. Büsdorf, and B. Szolayski, *Ber.*, 1899, **32**, 210.
- <sup>8</sup> R. Jongen, T. Sala, and M. V. Sargent, *J. Chem. Soc., Perkin Trans. I*, 1979, 2588.
- <sup>9</sup> W. T. Sumerford and D. N. Dalton, *J. Am. Chem. Soc.*, 1944, **66**, 1330.
- <sup>10</sup> N. J. Leonard and J. W. Curry, *J. Org. Chem.*, 1952, **17**, 1071.
- <sup>11</sup> C. F. Koelsch, *J. Am. Chem. Soc.*, 1944, **66**, 2019.
- <sup>12</sup> H. Rupe, *Ber.*, 1897, **30**, 2444.