

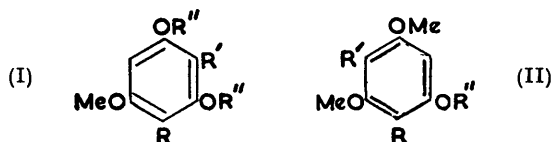
383. *Griseofulvin. Part X.* The Orientation of Some Derivatives of 5-Methoxyresorcinol.*

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Mononitro-, monochloro-, and dichloro-derivatives of 5-methoxyresorcinol have been prepared, and their structures established.

ORIENTATION of the monochloro-derivatives of 5-methoxyresorcinol (I; R = R' = R'' = H) was required in connection with synthetic work related to the structure of griseofulvin and in problems arising out of the biological degradation of griseofulvin. The methods employed were similar to those used by Grove, MacMillan, Mulholland, and Zealley¹ for the orientation of the monochloro-derivatives of 3 : 5-dimethoxyphenol.

5-Methoxyresorcinol in ether or boiling chloroform with sulphuryl chloride gave the 4-chloro-compound (I; R = Cl, R' = R'' = H), m. p. 183°, and, in low yield, the 2-chloro-



derivative (I; R' = Cl, R = R'' = H), m. p. 74°; in chloroform suspension at room temperature the 2 : 4-dichloro-compound (I; R = R' = Cl, R'' = H) was also formed. The same dichloro-compound was produced by further chlorination with sulphuryl chloride of both the 4- and the 2-chloro-derivative. The structure of the 2 : 4-dichloro-compound was established by the last reaction and confirmed by the unambiguous synthesis of the 4 : 6-dichloro-derivative (see below). The structures of the monochloro-compounds were established in three ways, as follows.

First, chlorination of methyl 2 : 6-dihydroxy-4-methoxybenzoate (I; R' = CO₂Me, R = R'' = H) gave the 3-chloro-ester which was hydrolysed by sulphuric acid at 70° to the corresponding acid, which on decarboxylation with copper chromite in quinoline afforded 4-chloro-5-methoxyresorcinol, m. p. 183°.

Secondly, the mononitro-5-methoxyresorcinols were prepared and orientated and related to the chloro-derivatives. Nitration of 5-methoxyresorcinol gave the steam-volatile 2-nitro-compound (I; R' = NO₂, R = R'' = H); the 4-nitro-compound (I;

* Part IX, *J.*, 1954, 2585.

¹ Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967.

R = NO₂, R' = R'' = H) was also isolated from the material not volatile in steam. Reduction of the 4-nitro-compound gave the amine whose structure as the 4-amino-derivative was confirmed by oxidation with ferric chloride to 2-hydroxy-6-methoxy-*p*-benzoquinone.² No product could be isolated on oxidation of the 2-amino-derivative under identical conditions. Direct conversion of the amino-derivatives into the chloro-compounds was not attempted. Attempts to convert the amine (I; R = H, R' = NH₂, R'' = CH₂Ph), obtained by reduction of the dibenzyl ether of the 2-nitro-compound, into the dibenzyl ether of 2-chloro-5-methoxyresorcinol by the Sandmeyer reaction were unsuccessful, but the nitro- and the chloro-5-methoxyresorcinol were linked by the following reactions. Chlorination of 2 : 6-diethoxy-4-methoxynitrobenzene (I; R = H, R' = NO₂, R'' = Et), obtained by ethylation of 5-methoxy-2-nitroresorcinol, gave the 3-chloro-derivative (I; R = Cl, R' = NO₂, R'' = Et) which was reduced by dithionite to 3-chloro-2 : 6-diethoxy-4-methoxyaniline (I; R = Cl, R' = NH₂, R'' = Et). Diazotisation, followed by elimination of the amino-group gave 1-chloro-2 : 4-diethoxy-6-methoxybenzene (I; R = Cl, R' = H, R'' = Et), identical with the compound obtained by ethylation of 4-chloro-5-methoxyresorcinol.

Finally, methylation of 4-chloro-5-methoxyresorcinol with one mol. of diazomethane in ether gave, as sole product, 4-chloro-3 : 5-dimethoxyphenol (II; R = R'' = H, R' = Cl) of established structure.¹

Further chlorination of methyl 3-chloro-2 : 6-dihydroxy-4-methoxybenzoate with sulphuryl chloride in chloroform at 80° or in chloroform containing 1% of ethanol at room temperature (cf. Barnes, Hirschler, and Bluestein³) gave the 3 : 5-dichloro-ester. Loss of halogen during decarboxylation of the corresponding acid with copper chromite in quinoline at 180° led to 4-chloro-5-methoxyresorcinol. 4 : 6-Dichloro-5-methoxyresorcinol was, however, obtained in good yield by heating 3 : 5-dichloro-2 : 6-dihydroxy-4-methoxybenzoic acid in nitrogen at the melting point. 4 : 6-Dichloro-5-methoxyresorcinol was not identical with the dichloro-derivative obtained by direct chlorination of 5-methoxyresorcinol.

Grove *et al.*¹ isolated and identified the 2- and the 4-nitro-derivative and 2 : 6-dimethoxy-*p*-benzoquinone among the products of nitration of 3 : 5-dimethoxyphenol; two other nitro-compounds were also obtained in very low yield and have now been identified as 2- and 4-nitro-5-methoxyresorcinol. They are presumed to have been produced by nitration of 5-methoxyresorcinol present as impurity in the 3 : 5-dimethoxyphenol, rather than by demethylation during the reaction.

Acetylation of amino-phloroglucinol ethers under reflux with acetic anhydride frequently leads to the formation of *NN*-diacetyl derivatives. Where interpretation of the analytical data is difficult, infrared spectra can be used to distinguish between the monoacetyl and the diacetyl structures. Thus the former type shows an >NH stretching frequency close to 3300 cm.⁻¹ (solid state) and C=O absorption near 1650 cm.⁻¹ (amide C=O), while the latter type has no >NH absorption and the C=O absorption is displaced to *ca.* 1715 cm.⁻¹. By this means the acetyl derivatives of 2- and 4-amino-3 : 5-dimethoxyphenol¹ have been shown to be the triacetyl compounds (II; R = NAc₂, R' = H, R'' = Ac) and (II; R = H, R' = NAc₂, R'' = Ac), respectively.

EXPERIMENTAL

Microanalyses are by Messrs. W. Brown and A. G. Olney. M. p.s are corrected. In chromatography, B.D.H. alumina was rendered alkali-free (pH 4) and activated at 250°/15 mm. for 2 hr. Infrared spectra (Nujol "mulls") were determined by Dr. L. A. Duncanson. Ultraviolet data refer to EtOH solutions.

Chlorination of 5-Methoxyresorcinol.—(a) *In ether at room temperature.* 5-Methoxyresorcinol (5.0 g.) in dry ether (75 ml.) was treated dropwise with stirring with sulphuryl chloride (5.3 g.) in ether (20 ml.). After 6 hr., concentration of the clear solution afforded (i) a solid (3.8 g., 61%; m. p. 183°), and (ii) a gum which was dissolved in benzene–light petroleum (b. p. 60–80°)

² Pollak and Gans, *Monatsh.*, 1902, **23**, 947.

³ Barnes, Hirschler, and Bluestein, *J. Amer. Chem. Soc.*, 1952, **74**, 4091.

(10 : 1; 100 ml.) and chromatographed on alumina (20 × 1.5 cm.). The oily fractions eluted with benzene–light petroleum (b. p. 60–80°) (10 : 1; 50 ml.), benzene (50 ml.), and benzene–methanol (99 : 1; 100 ml.) were combined and twice distilled; the colourless distillate, b. p. 86–89°/0.1 mm., solidified after 1 week at 0° and crystallised from light petroleum (b. p. 60–80°) in needles, m. p. 74° (20 mg., 0.3%), of 2-chloro-5-methoxyresorcinol (I; R' = Cl, R = R'' = H) (Found : C, 48.3; H, 4.1; Cl, 20.0. C₇H₇O₃Cl requires C, 48.2; H, 4.0; Cl, 20.3%). Ultraviolet absorption max. : 273 mμ (ε 610). The *dibenzyl ether* formed prisms, m. p. 97–98°, from light petroleum (b. p. 60–80°) (Found : C, 70.7; H, 5.4; Cl, 10.1. C₂₁H₁₉O₃Cl requires C, 71.1; H, 5.4; Cl, 10.0%); it was insoluble in 2N-sodium hydroxide.

The solid (i) was sublimed at 110–130°/0.1 mm. and crystallised from benzene–methanol, giving 4-chloro-5-methoxyresorcinol (I; R = Cl, R' = R'' = H) as prisms, m. p. 183° (Found : C, 47.9; H, 4.1; Cl, 21.1; OMe, 18.1. C₇H₇O₃Cl requires C, 48.2; H, 4.0; Cl, 20.3; OMe, 17.8%). Ultraviolet absorption max. : 275 mμ (ε 670). The *dibenzyl ether* crystallised from ethanol in prisms, m. p. 74–75° (Found : C, 71.3; H, 5.6; Cl, 10.0%); it was insoluble in 2N-sodium hydroxide.

(b) *In chloroform at 61°*. 5-Methoxyresorcinol (2.5 g.) in boiling chloroform (30 ml.) was treated dropwise with sulphuryl chloride (2.5 g.) in chloroform (10 ml.) during 30 min. After 4 hours' heating under reflux the mixture was left at room temperature for 48 hr. and the insoluble 4-chloro-derivative (1.75 g., 56%; m. p. 175–180°) was collected. The filtrate was washed with water (3 × 10 ml.) and dried, and the solvent removed. The residual gum was treated with hot water, insoluble material rejected, and the soluble portion recovered by evaporation under reduced pressure. Distillation of the product (623 mg.) at 87–90°/0.1 mm. afforded a pasty distillate (442 mg.) which was combined with a similar fraction (281 mg., obtained by evaporation of the aqueous washings) and sublimed at 50–60°/0.1 mm. The colourless gummy sublimate crystallised from light petroleum (b. p. 60–80°) in needles of the 2-chloro-derivative (m. p. 73–74°; 433 mg., 14%).

(c) *In chloroform suspension at room temperature*. 5-Methoxyresorcinol (5.0 g.), suspended in dry chloroform (75 ml.), was vigorously stirred while sulphuryl chloride (5.3 g.) in chloroform (10 ml.) was added during 30 min. After 6 hr., the solution was filtered from crude 4-chloro-5-methoxyresorcinol [(i) 3.1 g., m. p. 178–180°]; concentration of the filtrate afforded (ii) a solid (0.1 g.), m. p. 140–165°, and (iii) a gum (2.2 g.).

Crystallisation of fractions (i) and (ii) from benzene afforded 4-chloro-5-methoxyresorcinol, m. p. 181–183° (3.1 g., 50%). The gum (iii) in benzene–light petroleum (b. p. 60–80°) (10 : 1) was chromatographed on alumina, affording (iv) a solid (83 mg.) and, on elution with benzene, (v) a gum (1.7 g.). Fraction (iv) crystallised from benzene in needles, m. p. 115–116°, of 2 : 4-dichloro-5-methoxyresorcinol (I; R = R' = Cl, R'' = H) (Found : C, 40.15; H, 3.15; Cl, 33.8. C₇H₆O₃Cl₂ requires C, 40.2; H, 2.9; Cl, 33.9%). Crystallisation from water gave the *dihydrate*, needles, m. p. (tube) 106°, partly melting at 80°, (Köfler block) 106°. On cooling, the melt reset and remelted at 115° (Found, after drying for 2 hr. *in vacuo* at 20° over P₂O₅ : C, 34.2; H, 4.6; Cl, 29.7, 28.1. C₇H₈O₃Cl₂·2H₂O requires C, 34.3; H, 4.1; Cl, 28.9%). Ultraviolet absorption max. : 280 mμ (ε 860). Anhydrous material, m. p. 106°, was obtained when the dihydrate was dried for 6 hr. *in vacuo* over sulphuric acid at 20° (Found : C, 40.2; H, 3.0%) and, when cooled and reheated, was converted into the higher-melting form, m. p. 115°. It is concluded that two crystalline modifications of the anhydrous compound exist; the dihydrate readily loses water, and, if heated slowly, melts at the m. p. of the lower-melting anhydrous modification. On one occasion the higher-melting form was obtained on drying the hydrate *in vacuo* at 63° over phosphoric oxide for 4 hr.

The *dibenzyl ether* crystallised from light petroleum (b. p. 60–80°) in prisms, m. p. 106° (Found : C, 65.0; H, 4.8; Cl, 17.9. C₂₁H₁₈O₃Cl₂ requires C, 64.8; H, 4.7; Cl, 18.2%). It was insoluble in 2N-sodium hydroxide.

Distillation of fraction (v) at 100°/0.1 mm. and extraction of the oily distillate with light petroleum (b. p. 60–80°) left an insoluble residue which on crystallisation from benzene afforded the above dichloro-derivative, m. p. 115° (150 mg.). The total yield of dichloro-compound was 233 mg. (3%).

Chlorination of 4-Chloro-5-methoxyresorcinol.—Sulphuryl chloride (0.78 g.) in ether (15 ml.) was added slowly with stirring to a solution of the chlorophenol (1.0 g.) in ether (50 ml.). Stirring was continued for 5 hr. and the solution set aside for 15 hr. Removal of the ether left a brown gum which was chromatographed in benzene–light petroleum (b. p. 60–80°) (1 : 1; 100 ml.) on alumina (15 × 1.5 cm.): the following eluates were collected : (i) benzene–light petroleum (b. p. 60–80°) (4 : 1; 75 ml.), furnishing 2 : 4-dichloro-5-methoxyresorcinol, m. p.

115° (45 mg.); (ii) benzene-methanol (49 : 1; 50 ml.), giving unchanged starting material, m. p. 180—182° (800 mg.).

Chlorination of 2-Chloro-5-methoxyresorcinol.—Sulphuryl chloride (10⁻³ ml. × 8) in chloroform (5 ml.) was added with stirring during 10 min. to a solution of the chlorophenol (15 mg.) in chloroform (8 ml.). After 48 hr. at room temperature the chloroform was washed with water, dried, and evaporated. Crystallisation of the product from light petroleum (b. p. 60—80°) afforded prisms (9 mg.), 114—115°, of 2 : 4-dichloro-5-methoxyresorcinol identified by mixed m. p. determination and comparison of the infrared spectrum with that of material obtained directly by chlorination of 5-methoxyresorcinol.

Methyl 2 : 6-Dihydroxy-4-methoxybenzoate.—Methylation of phloroglucinolcarboxylic acid with 2 mol. of diazomethane in ether⁴ and crystallisation of the product from methanol gave methyl 2 : 6-dihydroxy-4-methoxybenzoate, m. p. 114—115° (Found : C, 54.2; H, 5.1; OMe, 31.0. Calc. for C₉H₁₀O₅ : C, 54.5; H, 5.1; 2OMe, 31.3%).

Methyl 3-Chloro-2 : 6-dihydroxy-4-methoxybenzoate (I; R = Cl, R' = CO₂Me, R'' = H).—Sulphuryl chloride (530 mg.) in chloroform (10 ml.) was added during 30 min. to the above ester (708 mg.) in chloroform (30 ml.). Stirring was continued for 6 hr. and the solution set aside overnight. After being washed with water, the dried chloroform solution was concentrated, giving the 3-chloro-compound (800 mg., 96%), m. p. 178—180°, raised to 183—184° (needles) by crystallisation from ethyl acetate (Found : C, 46.3; H, 4.0; Cl, 15.0. C₉H₉O₅Cl requires C, 46.5; H, 3.9; Cl, 15.2%). It dissolved in 2N-sodium hydroxide and in sodium carbonate solution, but was only slightly soluble in sodium hydrogen carbonate. It gave an intense greenish-blue colour with ferric chloride in ethanol. It was unusually stable to hydrolytic reagents and was recovered unchanged after 2 hr. under reflux with 2N-sulphuric acid diluted with an equal volume of ethanol, 2 hr. at room temperature in concentrated sulphuric acid, 2 hr. under reflux with 2N-sodium hydroxide, or 1 hr. under reflux with N-alcoholic potassium hydroxide.

3-Chloro-2 : 6-dihydroxy-4-methoxybenzoic Acid.—The above chloro-ester (0.1 g.) in concentrated sulphuric acid (1 ml.) was heated for 2 hr. at 70°, cooled, and the solution poured over crushed ice. The precipitate was collected [85 mg.; m. p. 185—190° (decomp.)], sublimed at 150°/0.1 mm., and crystallised from benzene (in which it was only sparingly soluble) in prisms of 3-chloro-2 : 6-dihydroxy-4-methoxybenzoic acid, m. p. 202° (decomp.) (Found : C, 44.0; H, 3.5; OMe, 13.8. C₈H₇O₅Cl requires C, 43.9; H, 3.2; OMe, 14.2%). It gave an intense greenish-blue colour with ferric chloride in ethanol.

Decarboxylation of 3-Chloro-2 : 6-dihydroxy-4-methoxybenzoic Acid.—The acid (82 mg.) was heated in quinoline (5 ml.) with copper chromite (0.1 g.) in a stream of carbon dioxide-free nitrogen. Evolution of carbon dioxide was complete in 30 min. at a bath temperature of 180° (total CO₂ evolved, 1.06 mol.). After removal of the catalyst the filtrate was poured into 2N-hydrochloric acid (25 ml.) and extracted continuously with ether for 24 hr. The ethereal extract was washed with 2N-hydrochloric acid, extracted with sodium hydrogen carbonate solution, and dried. Evaporation left a tar which sublimed at 70—130°/0.1 mm. The colourless oily sublimate crystallised from benzene in prisms, m. p. 180—182° (19 mg.), of 4-chloro-5-methoxyresorcinol identified by mixed m. p. and infrared absorption spectrum.

The sodium hydrogen carbonate extract on acidification and recovery afforded starting material (2 mg.), m. p. and mixed m. p. 202° (decomp.).

Methylation of 4-Chloro-5-methoxyresorcinol.—Diazomethane (1.05 millimole) in ether (12 ml.) was added to the chlorophenol (174 mg., 1 millimole) in ether (2 ml.). After 6 hr. at room temperature the ether was removed and the oily residue extracted with light petroleum (b. p. 60—80°). The soluble fraction (3 mg.), m. p. ca. 120°, contained no 2-chloro-3 : 5-dimethoxyphenol. The insoluble solid (146 mg.) was crystallised from benzene, giving (i) unchanged starting material, m. p. 170—180° (90 mg.), and (ii) 4-chloro-3 : 5-dimethoxyphenol, m. p. 122—130° raised to m. p. 128—130° (20 mg.) after three crystallisations from benzene. Identification was established by mixed m. p. determination and the infrared spectrum.¹

Methyl 3 : 5-Dichloro-2 : 6-dihydroxy-4-methoxybenzoate.—(a) Sulphuryl chloride (150 mg.) in chloroform (5 ml.) was added dropwise to a stirred solution of methyl 3-chloro-2 : 6-dihydroxy-4-methoxybenzoate (200 mg.) in chloroform (10 ml.) and ethanol (0.1 ml.) at room temperature. Stirring was continued for 4 hr. and the solution was set aside for 40 hr. and then washed with water, and dried, and the solvent removed. The product crystallised from ethanol in hexagonal plates or prisms of methyl 3 : 5-dichloro-2 : 6-dihydroxy-4-methoxybenzoate (160 mg.), m. p.

⁴ Sonn and Winzer, *Ber.*, 1928, **61**, 2305.

144—145° (Found : C, 40.1; H, 3.1; Cl, 26.5. $C_9H_8O_5Cl_2$ requires C, 40.45; H, 3.0; Cl, 26.5%). It was insoluble in sodium hydrogen carbonate and gave an intense green colour in ethanol with ferric chloride.

Chlorination in pure chloroform or in ether-methylene chloride was less satisfactory and only very low yields of the desired ester were obtained.

(b) Methyl 3-chloro-2 : 6-dihydroxy-4-methoxybenzoate (100 mg.) was suspended in chloroform (0.7 ml.); sulphuryl chloride (0.3 ml.) was added and the mixture warmed at 80° until reaction ceased (5 min.). Chloroform and excess of sulphuryl chloride were removed *in vacuo*, and the product was crystallised from ethanol, giving the crude 3 : 5-dichloro-ester (100 mg.; m. p. 138—145°). Use of a greater excess of sulphuryl chloride led to contamination of the product by a yellow impurity.

3 : 5-Dichloro-2 : 6-dihydroxy-4-methoxybenzoic Acid.—The above ester (100 mg.) was dissolved in concentrated sulphuric acid (1 ml.). After 48 hr. at room temperature, the brown solution was poured into water, set aside at 0° for some hours, and the precipitate collected and extracted with sodium hydrogen carbonate. A little insoluble material (2 mg.) was identified as unchanged chloro-ester. The acid fraction [m. p. 186—192° (decomp.)], recovered by acidification and filtration of the precipitate, crystallised from benzene (25 ml.) in needles of 3 : 5-dichloro-2 : 6-dihydroxy-4-methoxybenzoic acid (76 mg.), m. p. 200—204° (decomp.) (Found : C, 37.6; H, 2.5; Cl, 27.4%; equiv., 231. $C_9H_6O_5Cl_2$ requires C, 37.9; H, 2.4; Cl, 28.0%; equiv., 253). It gave an intense green colour with ferric chloride in ethanol. The 3-chloro-acid [202° (decomp.)] was depressed in m. p. on admixture with the 3 : 5-dichloro-acid.

Hydrolysis of the chloro-ester with concentrated sulphuric acid for 1 hr. at 70° led to an impure product in reduced yield.

Decarboxylation of 3 : 5-Dichloro-2 : 6-dihydroxy-4-methoxybenzoic Acid.—(a) The acid (22 mg.) was heated in quinoline (1.5 ml.) with copper chromite (20 mg.) as described above for the monochloro-acid. Evolution of carbon dioxide (1.1 mol.) was complete after 1 hr. at 180°. The fraction insoluble in sodium hydrogen carbonate was sublimed at 125°/0.1 mm. and the sublimate washed with light petroleum (b. p. 60—80°) and crystallised from benzene. The first fraction (4 mg.) consisted of prisms, m. p. 180—182°, identified as 4-chloro-5-methoxyresorcinol by a mixed m. p. determination and its infrared spectrum. Subsequent fractions, m. p. ca. 140—150°, were gummy and intractable.

(b) The acid (100 mg.) was heated in a small tube at 210° in nitrogen. A vigorous evolution of carbon dioxide took place from the melt and was complete in 5 min. The dark residue sublimed at 70°/0.1 mm. (59 mg.; m. p. 105—112°). Crystallisation from benzene gave 4 : 6-dichloro-5-methoxyresorcinol, prismatic needles, m. p. 117° (Found : C, 40.3; H, 3.2; Cl, 34.0. $C_7H_6O_3Cl_2$ requires C, 40.2; H, 2.9; Cl, 33.9%). The mixed m. p. with the 2 : 4-dichloro-derivative obtained by direct chlorination of 5-methoxyresorcinol showed a large depression.

Nitration of 5-Methoxyresorcinol.—To a stirred solution of 5-methoxyresorcinol (37.5 g.) in acetic acid (150 ml.) and acetic anhydride (75 ml.) at -4°, there was added dropwise (1½ hr.) nitric acid (*d* 1.42; 24 g.) in acetic acid (60 ml.). After 2 hr. at room temperature the solution was poured over cracked ice (800 g.), and the mixture steam-distilled (10 l.). The steam-volatile 5-methoxy-2-nitroresorcinol (I; R = R'' = H, R' = NO₂) crystallised from ethanol in orange-yellow needles, m. p. 154° (6.5 g., 13%) (Found : C, 45.2; H, 3.8; N, 7.8; OMe, 17.2. $C_7H_7O_5N$ requires C, 45.4; H, 3.8; N, 7.6; OMe, 16.8%). The diacetate, insoluble in 2N-sodium hydroxide, crystallised from ethanol in almost colourless needles, m. p. 117° (Found : C, 49.6; H, 4.4; N, 5.2. $C_{11}H_{11}O_7N$ requires C, 49.1; H, 4.1; N, 5.2%). The dibenzyl ether formed pale yellow needles, m. p. 101°, from ethanol (Found : C, 68.9; H, 5.4; N, 4.25. $C_{21}H_{19}O_5N$ requires C, 69.0; H, 5.2; N, 3.8%).

The residual tar from the steam-distillation was dried and extracted with benzene. Insoluble material (11 g.) was discarded. The benzene extract was concentrated until orange crystals (a) (4.0 g.; m. p. 182—186°) were deposited, and the mother-liquors were chromatographed on alumina (30 × 3 cm.). Elution of the orange band with benzene furnished an orange-red solid (b) (0.52 g.; m. p. 170—183°) which was combined with (a) and recrystallised from benzene-ethanol. 5-Methoxy-4-nitroresorcinol (I; R = NO₂, R' = R'' = H) was obtained as orange needles, m. p. 191° (4.3 g., 8.7%) (Found : C, 45.7; H, 3.9; N, 7.9; OMe, 16.8. $C_7H_7O_5N$ requires C, 45.4; H, 3.8; N, 7.6; OMe, 16.8%). It readily sublimed at 140°/0.1 mm. The diacetate formed prisms, m. p. 80°, from methanol (Found : C, 49.5; H, 4.1; N, 5.5. $C_{11}H_{11}O_7N$ requires C, 49.1; H, 4.1; N, 5.2%), slowly dissolving in 2N-sodium hydroxide to an orange solution.

Nitration of 3 : 5-dimethoxyphenol (50 g.) has been described by Grove *et al.*¹ Chromatography on alumina of the benzene-soluble portion of the residual pitch after removal of 3 : 5-dimethoxy-2-nitrophenol by steam-distillation afforded 2 : 6-dimethoxy-*p*-benzoquinone, some additional 3 : 5-dimethoxy-2-nitrophenol and 3 : 5-dimethoxy-4-nitrophenol as already described.¹ The following additional bands were obtained and were eluted with benzene-methanol (99 : 1) : (iv) orange yellow band, giving on recovery an orange solid (70 mg.; m. p. 153—160°) from which 5-methoxy-2-nitroresorcinol, m. p. and mixed m. p. 153°, was obtained by crystallisation from benzene-ethanol; (v) deep orange band, furnishing 5-methoxy-4-nitroresorcinol (830 mg.), m. p. and mixed m. p. 189—191°.

2-Amino-5-methoxyresorcinol.—5-Methoxy-2-nitroresorcinol (0.2 g.) in ethanol (50 ml.) was shaken with hydrogen at room temperature in the presence of Raney nickel (0.1 g.) (absorption : 3 mol. in 15 min.). After filtration and removal of the solvent under reduced pressure in nitrogen, the residual brown solid was sublimed at 110—140°/10⁻⁴ mm. The colourless sublimate (41 mg.) consisted of *2-amino-5-methoxyresorcinol*, m. p. 170—175° (decomp.) (Found : C, 54.2; H, 6.0; N, 8.7. C₇H₉O₃N requires C, 54.2; H, 5.85; N, 9.0%). *2-Amino-5-methoxyresorcinol* dissolved in 2*N*-sodium hydroxide and in 2*N*-hydrochloric acid. It gave an intense blue colour with ferric chloride in ethanol; the colour rapidly faded in air to olive-green and then slowly intensified to dark brown. The *tetra-acetyl derivative*, obtained by 2 hours' heating with acetic anhydride, crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 85—86° (Found : C, 56.0; H, 5.7; OMe, 9.9; Ac, 55.7. C₁₅H₁₇O₇N requires C, 55.7; H, 5.3; OMe, 9.6; 4Ac, 53.2%). The infrared spectrum showed the absence of >NH; C=O absorption bands were present at 1770 (phenyl acetate) and 1717 cm.⁻¹ (—NAC₂). The derivative was insoluble in 2*N*-hydrochloric acid.

Reduction of 5-Methoxy-2-nitroresorcinol Dibenzyl Ether.—To the benzyl ether (0.1 g.) in boiling ethanol (4 ml.) and water (4 ml.) was added sodium hydrosulphite (dithionite) (0.25 g.) in portions during 10 min. The solution was heated under reflux for a further 20 min., the ethanol removed *in vacuo*, and the residue made alkaline with sodium hydroxide and extracted with ether. Rapid removal of the ether in nitrogen left a red oil which solidified at 0° and distilled at 120—140°(bath)/10⁻⁴ mm. The colourless *amine* (I; R = H, R' = NH₂, R'' = CH₂Ph) (25 mg.) formed prisms, m. p. 94—95°, from light petroleum (b. p. 60—80°) (Found : C, 75.1; H, 6.4; N, 4.5. C₂₁H₂₁O₃N requires C, 75.2; H, 6.3; N, 4.2%). It was only weakly basic and diazotisation by the "direct" method was unsatisfactory. Diazotisation by the glacial acetic acid-nitrosylsulphuric acid and the glacial acetic acid-concentrated hydrochloric acid method was successful, but the Sandmeyer reaction as carried out on the amine (II; R = NH₂, R' = H, R'' = CH₂Ph)¹ failed.

The *diacetyl derivative*, formed by heating with acetic anhydride for 1 hr., was obtained as prisms, m. p. 102°, from light petroleum (b. p. 60—80°) (Found : C, 71.7; H, 6.2; Ac, 20.5. C₂₅H₂₅O₅N requires C, 71.6; H, 6.0; 2Ac, 20.6%). The infrared spectrum showed the absence of >NH; a C=O absorption band occurred at 1710 cm.⁻¹ (—NAC₂). The derivative was insoluble in 2*N*-hydrochloric acid.

4-Amino-5-methoxyresorcinol.—5-Methoxy-4-nitroresorcinol (0.2 g.) was reduced with hydrogen in the presence of Raney nickel as described for the 2-nitro-compound (absorption : 3 mol. in 1½ hr.). The free amine (41 mg.), obtained by sublimation at 130—160°/10⁻⁴ mm., chars above 160°. It was converted into the *hydrochloride*, prisms, decomp. >190°, from concentrated hydrochloric acid containing a trace of stannous chloride (Found : C, 43.6; H, 5.8. C₇H₉O₃N.HCl requires C, 43.85; H, 5.3%). The *tetra-acetyl derivative* formed prismatic needles (from ethanol), m. p. 130° [Found : C, 55.6; H, 5.3%; M (Rast), 310. Calc. for C₁₅H₁₇O₇N : C, 55.7; H, 5.3%; M, 323.3]. Pollak and Gans² give m. p. 129°. The infrared spectrum showed the absence of >NH; C=O absorption bands were found at 1778 (phenyl acetate), and 1730 and 1705 cm.⁻¹ (—NAC₂ doublet).

4-Amino-5-methoxyresorcinol was soluble in 2*N*-sodium hydroxide and in 2*N*-hydrochloric acid; it was very much more sensitive to atmospheric oxidation than the 2-amino-isomer, and was stored under nitrogen or as the hydrochloride. It gave a reddish-brown colour in ethanol with ferric chloride; the colour faded slowly.

Oxidation of 2- and 4-Amino-5-methoxyresorcinols.—The aminophenol (17 mg.) in 2 drops of 16% hydrochloric acid was oxidised with hydrated ferric chloride (60 mg.) in 2 drops of 16% hydrochloric acid. The solution was shaken for 15 min., and extracted with benzene and, after dilution with water, with chloroform.

(a) *4-Amino-compound.* The deep yellow benzene extract on concentration deposited orange needles (2 mg.) of 2-hydroxy-6-methoxy-*p*-benzoquinone³ which gave a violet colour

with 2*N*-sodium hydroxide. The chloroform extract furnished a red solid from which a little more of the quinone was obtained by sublimation *in vacuo*.

(b) *2-Amino-compound*. The colourless benzene extract of the mixture, which was much darker than that obtained by oxidation of the 4-amino-compound, only furnished a trace of gum on evaporation. The chloroform extract only yielded a trace of a dark solid.

Infrared Spectra of Acetyl Derivatives.—Acetylation of 2- and 4-amino-3:5-dimethoxyphenol gave the acetyl derivatives, m. p. 93° and 169° respectively.¹ Acetyl determinations employing an improved method of hydrolysis now indicate both compounds to be the *triacetyl derivatives* (II; R = NAc₂, R' = H, R'' = Ac) and (II; R = H, R' = NAc₂, R'' = Ac) respectively (Found: Ac, 44.3, 43.3% respectively. C₁₄H₁₇O₆N requires 3Ac, 43.7%). The *mono-* (m. p. 146—147°) and the *di-acetyl* (m. p. 117—118°) derivative of (II; R = NH₂, R' = H, R'' = CH₂Ph) gave correct analyses (Found: Ac, 13.4, 24.2% respectively. C₁₇H₁₉O₄N requires Ac, 14.3. C₁₈H₂₁O₅N requires 2Ac, 25.1%).

Infrared spectra.

Compound	NH	OAc	C=O NAc ₂	NHAc
(II; R = NHAc, R' = H, R'' = CH ₂ Ph)	3280	—	—	1653
(II; R = NAc ₂ , R' = H, R'' = CH ₂ Ph)	—	—	1716 1696	—
(II; R = NAc ₂ , R' = H, R'' = Ac)	—	1763	1719 1706	—
(II; R = H, R' = NAc ₂ , R'' = Ac)	—	1769	1715	—

2:6-Diethoxy-4-methoxynitrobenzene (I; R = H, R' = NO₂, R'' = Et).—5-Methoxy-2-nitroresorcinol (580 mg.) in ether (200 ml.) at 0° was treated with excess of ethereal diazoethane. After 24 hr. at room temperature the ether and excess of diazoethane were removed *in vacuo*. Sublimation of the dark brown residue at 80—95°/10⁻⁴ mm. afforded *2:6-diethoxy-4-methoxynitrobenzene* (590 mg.), yellow needles, m. p. 115° [from light petroleum (b. p. 60—80°)] (Found: C, 55.0; H, 6.5. C₁₁H₁₅O₅N requires C, 54.8; H, 6.3%). Ethylation by diethyl sulphate and sodium hydroxide was less satisfactory.

3-Chloro-2:6-diethoxy-4-methoxynitrobenzene (I; R = Cl, R' = NO₂, R'' = Et).—The above nitro-compound (387 mg.) in chloroform (6 ml.) was treated dropwise with sulphuryl chloride (0.165 ml.). A vigorous reaction with gas evolution took place after the addition of each drop, and when the reaction had subsided (5 min.) the solution was warmed on the water-bath for 5 min. and the solvent and excess of sulphuryl chloride were removed *in vacuo*. Sublimation of the solid residue at 70—85°/10⁻⁴ mm. furnished *3-chloro-2:6-diethoxy-4-methoxynitrobenzene* (255 mg.), lemon-yellow plates, m. p. 90—91° [from light petroleum (b. p. 60—80°)] [Found: C, 47.65; H, 5.4%; M (Rast), 298. C₁₁H₁₄O₅NCl requires C, 47.9; H, 5.1%; M, 275.7].

3-Chloro-2:6-diethoxy-4-methoxyaniline (I; R = Cl, R' = NH₂, R'' = Et).—The chloro-nitro-compound (200 mg.) was heated under reflux in aqueous ethanol (50%; 16 ml.) while sodium dithionite (300 mg.) was added during 2 min. After 10 min. a further quantity of dithionite (500 mg.) was added and heating continued for 20 min. After removal of the ethanol *in vacuo* (concentration to 5 ml.), 2*N*-sodium hydroxide (5 ml.) was added and the solution extracted with ether. Recovery and sublimation of the product at 55—70°/10⁻⁴ mm. furnished *3-chloro-2:6-diethoxy-4-methoxyaniline* (113 mg.), needles, m. p. 60—61° [from light petroleum (b. p. 40—60°)] (Found: C, 53.5; H, 6.6; N, 6.1. C₁₁H₁₆O₃NCl requires C, 53.8; H, 6.6; N, 6.0%).

1-Chloro-2:4-diethoxy-6-methoxybenzene (I; R = Cl, R' = H, R'' = Et).—(a) *By ethylation of 4-chloro-5-methoxyresorcinol*. The resorcinol derivative (200 mg.) in 3*N*-sodium hydroxide (10 ml.) was stirred during the addition of diethyl sulphate (0.5 ml.) and then heated under reflux for 1 hr. A further portion of diethyl sulphate (0.5 ml.) was then added and heating continued for a further 6 hr. The cooled mixture was extracted with ether, and the oily extract crystallised from methanol in prisms of *1-chloro-2:4-diethoxy-6-methoxybenzene* (110 mg.), m. p. 87° (Found: C, 57.35; H, 6.7. C₁₁H₁₅O₃Cl requires C, 57.2; H, 6.6%).

(b) *From 3-chloro-2:6-diethoxy-4-methoxyaniline*. The amine (50 mg.) in ethanol (200 mg.) and concentrated sulphuric acid (100 mg.) at 0° was diazotised by the addition of sodium nitrite (16 mg.) in water (0.05 ml.). The solution was warmed on the water-bath until evolution of gas ceased, diluted with water (10 ml.), and extracted with ether. The ethereal extract was concentrated and extracted with 2*N*-sodium hydroxide. The phenolic fraction, on recovery, was negligible. The neutral fraction on sublimation at 50—60°/0.1 mm. and crystallisation

of the oily sublimate from light petroleum (b. p. 40—60°) furnished 1-chloro-2 : 4-diethoxy-6-methoxybenzene (26 mg.), m. p. and mixed m. p. with the specimen prepared as in (a) 83—86°. Identity was confirmed by comparison of the infrared spectra.

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