THE SYNTHESIS OF 3,4-DIHYDROXY-2-METHOXYBENZALDEHYDE: THE USE OF METHYLENEDIOXY AS A PROTECTING GROUP

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The substance 3,4-dihydroxy-2-methoxybenzaldehyde (X) is not easily accessible and has not hitherto been prepared, although the isomeric compound 2,3-dihydroxy-4-methoxybenzaldehyde (XII) has been wrongly described under the above name.[1] Since formylation of 1-methoxy-2,3-methylenedioxybenzene was reported[2,3] to produce in good yield 2-methoxy-3,4-methylenedioxybenzaldehyde (II), a possible route to the desired substance was available provided the methylenedioxy group in the latter could be hydrolysed satisfactorily without affecting the methoxyl. We have therefore examined the recorded methods for inserting and removing a methylene ether group: hitherto the formation of 1,3-benzodioxoles has been a sealed-tube reaction which gives low yields and has not been an attractive preparative procedure, but with recent improvements[4] and with modifications in the method for their hydrolysis, we have found that this group could be used with advantage for blocking a catechol group even in the presence of a methoxyl.

The methylenation of several catechols was studied by Campbell *et al.*,[2] who obtained improved yields by the use of methylene bromide and Tobin bronze in methanolic potash, and the procedure was considerably improved by Aoyagi and Tomita[4] by using a cupric oxide catalyst and dimethylformamide as solvent. In our hands the latter procedure not only gave a greatly improved yield of 1-methoxy-2,3-methylenedioxybenzene (80%), but also proved far simpler than previous methods, since it can be carried out under reflux conditions.

From several experiments on the Vilsmeier–Haack formylation of the above-mentioned compound,[3] we obtained a mixture containing about 70% of 2-methoxy-3,4-methylenedioxybenzaldehyde (II) and 30% of the isomeric 4-methoxy-2,3-methylenedioxybenzaldehyde, the formation of which as a by-product of the reaction was observed by Wagner *et al.*[5] The mixture could be separated with some difficulty by chromatography on alumina.

The most effective method for cleavage of 1,3-benzodioxoles to the corresponding catechols has been via the dichloromethylene ethers formed by treatment with

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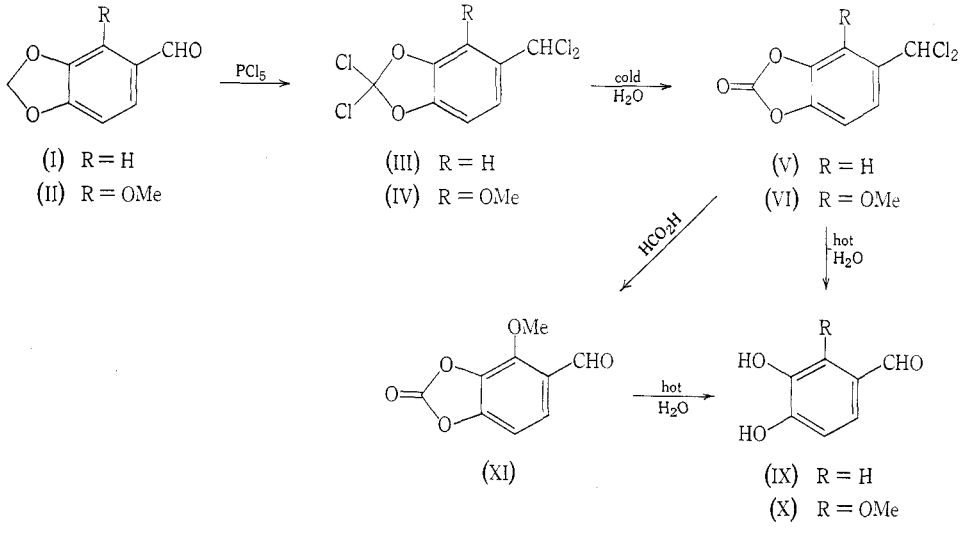
[1] Mauthner, F., *J. prakt. Chem.*, 1936, **145**, 313 (*Chem. Abstr.*, 1936, **30**, 5958).
[2] Campbell, K. N., Hopper, P. F., and Campbell, B. K., *J. org. Chem.*, 1951, **16**, 1737.
[3] Brownell, W. B., and Weston, A. W., *J. Am. chem. Soc.*, 1951, **73**, 4971; Govindachari, T., Rayadurai, S., Ramades, C., and Viswanathan, N., *Chem. Ber.*, 1960, **93**, 360.
[4] Aoyagi, Y., and Tomita, M., *Chem. pharm. Bull., Tokyo*, 1968, **16**, 525.
[5] Wagner, A. F., Walton, E., Wilson, A. N., Rodin, J. O., Holly, F. W., Brink, N. G., and Folkers, K., *J. Am. chem. Soc.*, 1959, **81**, 4983.

phosphorus pentachloride.[6,7] If an aldehyde group is present, the latter treatment converts it into the corresponding benzal chloride, and thus for piperonal (I), the product 3,4-dichloromethylenedioxybenzal chloride (III) is formed.[6] This can be hydrolysed in two stages: cold water yields the carbonyldioxybenzal chloride (V) (incorrectly represented in the *Organic Syntheses* preparation of protocatechuic aldehyde (IX) as the carbonyldioxybenzaldehyde (VII)[6]), and the hydrolysis of the benzal and carbonyldioxy groups is then effected with hot water. These reactions are shown in Scheme 1.



Scheme 1

Chlorination of 2-methoxy-3,4-methylenedioxybenzaldehyde (II) with phosphorus pentachloride produced the dichloromethylenedioxybenzal chloride (IV), which with cold water gave the carbonyldioxybenzal chloride (VI); both reactions proceeded in good yield, and the latter compound showed strong carbonyl absorptions in its i.r. spectrum at 1855 and 1830 cm^{-1} characteristic of a cyclic carbonate,[8] and a singlet at τ 2·92 in the n.m.r. spectrum corresponding to the benzal proton; no peaks could be observed in the n.m.r. or i.r. spectra which could be attributed to an aldehydic proton or carbonyl respectively, and these data thus demonstrate that the partial hydrolysis product has structure (VI) rather than (VIII), in agreement with Barger's[7] observations on the analogous compound (V) formed from piperonal (I).

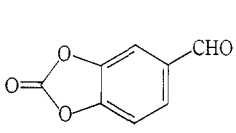
To complete the hydrolysis, the product (VI) was treated with hot water, but the desired 3,4-dihydroxy-2-methylenedioxybenzaldehyde (X) was obtained in poor yield, due presumably to the hydrolysis of the methoxyl group by the hydrochloric acid produced in the reaction. However, it was found that (VI) could be converted into the corresponding carbonyldioxybenzaldehyde (XI) with anhydrous formic

[6] Buck, S., and Zimmermann, F., *Org. Synth.*, 1943, Coll. Vol. II, 549, and references therein.

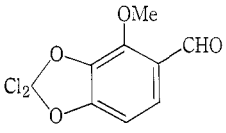
[7] Barger, G., *J. chem. Soc.*, 1908, **93**, 563.

[8] Hales, J. L., Jones, J. I., and Kynaston, W., *J. chem. Soc.*, 1957, 618.

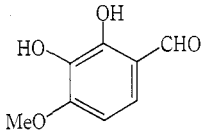
acid, and this could then be hydrolysed with boiling water to the required compound (X). The same compound could also be obtained, although in poorer yield, by direct hydrolysis of 3,4-dichloromethylenedioxy-2-methoxybenzal chloride (III) in two stages with cold and warm formic acid.



(VII)



(VIII)



(XII)

The same sequence of reactions applied to 4-methoxy-2,3-methylenedioxybenzaldehyde gave the corresponding 2,3-dihydroxy-4-methoxybenzaldehyde (XII), a compound first prepared by Mauthner[1] by a Gattermann formylation, but wrongly recorded as 3,4-dihydroxy-2-methoxybenzaldehyde (X). The same compound, correctly named, was subsequently prepared by Campbell *et al.*[2] by a slightly different procedure. The two substances in question are easily distinguished by their u.v. spectra, particularly in alkaline solution, owing to the presence of a hydroxyl *para* to a carbonyl in (X),[9] and by their i.r.[10] and n.m.r.[11] spectra, in which the effects of chelation of the carbonyl with the *ortho* hydroxyl in (XII) are clearly evident.

The difficulty in separating the abovementioned mixture produced on formylation of 1-methoxy-2,3-methylenedioxybenzene led us to examine the effect of hydrolysing the mixture of isomers by the steps described above. It was found that the resulting phenolic products, 3,4-dihydroxy-2-methoxy- and 2,3-dihydroxy-4-methoxy-benzaldehyde, could readily be separated by chromatography on silica gel. They were accompanied by very small amounts of a non-phenolic, highly fluorescent compound which gave positive tests for a methylenedioxy group. Its mass spectrum showed the presence of chlorine, and the molecular ion fitted the formula $C_9H_7ClO_4$, indicating the substitution of chlorine in one of the isomeric starting materials. The i.r. and u.v. spectra resembled those of the original methoxymethylenedioxybenzaldehydes, and likewise the n.m.r. spectrum, except for the presence of only one aromatic proton resonance, which was not coupled with the aldehydic proton, as in other examples in this series with an unsubstituted position *ortho* to the carbonyl. The substance is evidently 6-chloro-4-methoxy-2,3-methylenedioxybenzaldehyde, since it differs in n.m.r. spectrum from both the isomers produced by nuclear chlorination of 2-methoxy-3,4-methylenedioxybenzaldehyde; however, its n.m.r. spectrum showed minor peaks corresponding to the presence of one of these latter isomeric chlorination products. Thus the chlorination of the original mixture appears to produce minor amounts of a further product, which from the fact that its single aromatic proton resonates at comparatively low field and is not coupled with the aldehydic proton is considered to be 6-chloro-2-methoxy-3,4-methylenedioxybenzaldehyde.

[9] Scott, A. I., "Interpretation of the Ultraviolet Spectra of Natural Products." p. 109. (Pergamon: London 1964.)

[10] Bellamy, L. J., "The Infrared Spectra of Complex Molecules." pp. 103 *et seq.* (Methuen: London 1960.)

[11] Forsén, S., and Åkermark, B., *Acta. chem. scand.*, 1963, **17**, 1907.

Experimental

Melting points are uncorrected. Unless otherwise stated, ultraviolet spectra were measured on a Perkin–Elmer 400A Spectracord in methanol; infrared spectra were determined with a Perkin–Elmer 221 instrument in Nujol mulls; proton magnetic resonance spectra were recorded at 100 Mc/s for *c.* 5% solutions in deuterochloroform containing tetramethylsilane as internal reference on a Jeolco JNM-4H-100 spectrometer. Mass spectra were measured on an AEI MS9 instrument at 70 eV. Microanalyses are by the Australian Microanalytical Service.

1-Methoxy-2,3-methylenedioxybenzene

2,3-Dihydroxy-1-methoxybenzene[12] (5 g) was dissolved in deoxygenated anhydrous dimethylformamide (30 ml). To this solution was added methylene bromide (7 g), anhydrous potassium carbonate (10 g), and cupric oxide (0·5 g). The resulting mixture was refluxed, with stirring, under a nitrogen atmosphere for 7 hr. The cold solution was filtered, and the filtrate, together with the washings of the precipitate, was freed from solvent under vacuum. The oily residue was dissolved in ether and the solution washed with aqueous sodium hydroxide (5%) and with water. The dried ethereal solution on evaporation left a light orange solid which was distilled under vacuum, b.p. 52°/0·2 mm, to afford a product (4·5 g) identical with that prepared by the method of Campbell *et al.*,[2] m.p. 40–41° (lit. 41–42°).

2-Methoxy-3,4-methylenedioxy- and 4-Methoxy-2,3-methylenedioxy-benzaldehydes

1-Methoxy-2,3-methylenedioxybenzene was formylated with phosphorus oxychloride and dimethylformamide according to the method of Govindachari *et al.*[3] The crude crystalline material so obtained (16 g) was chromatographed on aluminium oxide (type H, Light & Co., 1·5 kg). The column was eluted with 20% chloroform in benzene to yield 2-methoxy-3,4-methylenedioxybenzaldehyde (II) (8 g), which crystallized from aqueous ethanol as long white needles, m.p. 107–108° (lit. 103°). Elution with 50% chloroform in benzene yielded 4-methoxy-2,3-methylenedioxybenzaldehyde (3·5 g) which crystallized from aqueous ethanol in white needles, m.p. 84–86° (lit.[2] 81–82°). A mixture of the isomers (1 g) was also recovered from the column. It was found that prolonged contact of the aldehydes with alumina caused decomposition to a yellow oil.

3,4-Dichloromethylenedioxy-2-methoxybenzal Chloride (IV)

2-Methoxy-3,4-methylenedioxybenzaldehyde (II) (18 g) was treated in small portions, under ice cooling, with phosphorus pentachloride (63 g). The reaction mixture initially liquefied, but towards the end of the addition the reaction became sluggish. After standing an hour at room temperature, the reaction mixture was refluxed gently for a further 2 hr, then freed from volatile by-products by distillation under vacuum at 10 mm. The residue was distilled from a Claisen flask fitted with a Vigreux column to yield the product (20 g) as a clear liquid, b.p. 104–105°/0·04 mm, which solidified in cubic prisms, m.p. 42–43°. τ 5·87 (singlet, $-OCH_3$), 3·24 (doublet, J 8 c/s, *ortho* H), 2·47 (doublet, J 8 c/s, *ortho* H), 2·96 (singlet, $ArCHCl_2$) (Found: C, 35·5; H, 2·1; Cl, 46·0. Calc. for $C_9H_6Cl_4O_3$: C, 35·6; H, 2·0; Cl, 46·7%).

3,4-Carbonyldioxy-2-methoxybenzal Chloride (VI)

3,4-Dichloromethylenedioxybenzal chloride (IV) (19 g) was poured into water (250 ml) and the mixture allowed to stand overnight. The resulting white solid was removed, triturated with water, filtered, and dried under vacuum. The dry mass was extracted with boiling hexane, and on cooling the solution afforded the product (14 g) as white dentate crystals, which after sublimation under vacuum had m.p. 71–72°. ν_{max} 1855, 1830 cm^{-1} (–O–CO–O–); τ 5·77 (singlet, OCH_3), 3·03 (doublet, J 8 c/s, *ortho* H), 2·29 (doublet, J 8 c/s, *ortho* H), 2·92 (singlet, $ArCHCl_2$) (Found: C, 43·2; H, 2·6; Cl, 28·1. Calc. for $C_9H_6Cl_2O_4$: C, 43·7; H, 2·6; Cl, 28·5%).

3,4-Carbonyldioxy-2-methoxybenzaldehyde (XI)

The above compound (VI) (10 g) was dissolved in anhydrous formic acid (50 ml) and the solution was refluxed for 1 hr, then poured into cold water (250 ml). The pale pink precipitate

[12] Surry, A., *Org. Synth.*, 1955, Coll. Vol. III. 759.

was filtered off and dried. Extraction of this solid with boiling hexane afforded the product (6 g) as pale yellow needles which after sublimation under vacuum had m.p. 118–120°. The compound was unstable and decomposed rapidly on storing. ν_{max} 1850, 1820 (–O–CO–O–), 1685 cm^{-1} (ArCHO); τ 5·70 (singlet, OCH_3), 3·02 (broad doublet, $J_{H,CHO}$ 0·8 c/s, J 8 c/s, *ortho* H), 2·24 (doublet, J 8 c/s, *ortho* H), −0·3 (broad singlet, $J_{H,CHO}$ 0·8 c/s, CHO).

Reaction of 3,4-Dichloromethylenedioxybenzal Chloride with Anhydrous Formic Acid

3,4-Dichloromethylenedioxybenzal chloride (IV) (6 g) was dissolved in anhydrous formic acid (20 ml). A vigorous reaction accompanied by evolution of hydrogen chloride occurred almost immediately; when it had subsided, the reaction mixture was warmed under reflux, whereupon a second vigorous reaction, also accompanied by evolution of hydrogen chloride, was observed. After 30 min the mixture was cooled and poured into water (300 ml). The brown precipitate was filtered off and dried under vacuum. Extraction of the dry product with boiling anhydrous hexane afforded 3,4-carbonyldioxy-2-methoxybenzaldehyde (VI) (2·5 g) identical (i.r.) with a sample produced by the method described above. A considerable quantity of tarry by-product remained from the hexane extraction.

3,4-Dihydroxy-2-methoxybenzaldehyde (*X*)

The above aldehyde (XI) (3 g) was suspended in deoxygenated water (30 ml) and heated in an inert atmosphere on a steam-bath until a clear solution was obtained. The solution was concentrated and allowed to cool, whereupon the product crystallized as long white needles (2 g) which were filtered off and washed with benzene to remove traces of non-phenolic material. They could be recrystallized from water or chloroform. After sublimation, the product had m.p. 128–129°. λ_{max} 290 (calc. 289 [9]), 237, (MeOH–NaOH) 347 (calc. 355 [9]), 255 mμ; ν_{max} 3420, 3325, 3120 (broad, ArOH), 1665, 1659 cm^{-1} (ArCHO); (10 mg/ml in $CHCl_3$), 1681 (unbonded ArCHO); τ (CD_3OD) 6·08 (singlet, OCH_3), 4·99 (broad singlet, HOD or 2OH), 3·34 (broad doublet, $J_{H,CHO}$ 0·8 c/s, J 8 c/s, *ortho* H), 2·78 (doublet, J 8 c/s, *ortho* H), −0·4 (broad singlet, $J_{H,CHO}$ 0·8 c/s, CHO). Solutions of the substance are unstable, and spectra were run as soon as possible after preparation.

2,3-Dihydroxy-4-methoxybenzaldehyde (*XII*)

Prepared according to Mauthner[1] from 2,3-dihydroxy-1-methoxybenzene, m.p. 116–117° (lit. 117–118°). λ_{max} 290 (calc. 289 [9]), 236, (MeOH–NaOH) 301 (calc. 306, dianion), 245; ν_{max} 3370 (broad, bonded OH), 1650 (ArCHO); (in $CHCl_3$), 1650, 1643 (chelated ArCHO, concentration invariant); τ 6·04 (singlet, OCH_3), 4·45 (broad singlet, non-bonded OH), 0·29 (singlet, CHO), −1·05 (singlet, chelated OH).

Formation and Separation of 2,3-Dihydroxy-4-methoxy- and 3,4-Dihydroxy-2-methoxy-benzaldehydes from the Mixed Methylenedioxy Analogues

The above isomeric mixture of methoxymethylenedioxybenzaldehydes was treated with phosphorus pentachloride, cold water, anhydrous formic acid, and boiling water in a manner similar to that outlined for the pure isomer 2-methoxy-3,4-methylenedioxybenzaldehyde. The product obtained by evaporation of the final aqueous solution was dried (P_2O_5) and chromatographed on a 30-fold quantity of silica gel (200–300 mesh, Light & Co.) in benzene. Benzene eluted a small quantity of substance identified as 6-chloro-4-methoxy-2,3-methylenedioxybenzaldehyde (see below), followed by 2,3-dihydroxy-4-methoxybenzaldehyde (XII), identical (i.r.) with material prepared as above by Mauthner's[1] method. Further elution with benzene–chloroform (4 : 1) yielded 3,4-dihydroxy-2-methoxybenzaldehyde (X) as a light brown solid, identical (i.r.) with material obtained previously.

6-Chloro-4-methoxy-2,3-methylenedioxybenzaldehyde

This substance, obtained as above as a highly fluorescent compound which crystallized from aqueous ethanol, m.p. 147–148°, was non-phenolic and gave positive tests with chromotropic and gallic acids for a methylenedioxy group. λ_{max} 284, 227, unchanged by addition of alkali;

ν_{max} 1685 cm^{-1} (ArCHO); τ 5·85 (singlet, OCH_3), 3·89 (singlet, $-O-CH_2-O-$), 2·68 (singlet, ArH), 0·04 (singlet, CHO) (Found: C, 50·8; H, 3·6; Cl, 16·0. Calc. for $C_9H_7ClO_4$: C, 50·4; H, 3·3; Cl, 16·6%).

Chlorination of 2-Methoxy-3,4-methylenedioxybenzaldehyde

2-Methoxy-3,4-methylenedioxybenzaldehyde (2 g) was dissolved in glacial acetic acid (12 ml) and a stream of chlorine was passed through the resulting solution for 30 min. The yellow solution was then poured into water (100 ml), and the precipitated yellow oil, dissolved in ether, was washed with aqueous sodium carbonate (10%) and with water, then extracted with saturated aqueous sodium bisulphite. Decomposition of the bisulphite extract yielded a white solid which was shown by t.l.c. (silica gel) to consist of approximately equal amounts of two components. The two components could be distinguished by n.m.r. spectroscopy and tentatively identified as 6-chloro-2-methoxy-3,4-methylenedioxybenzaldehyde [τ 5·89 (singlet, OCH_3), 3·88 (singlet, $-O-CH_2-O-$), 2·56 (singlet, ArH), −0·17 (singlet, CHO)] and 5-chloro-2-methoxy-3,4-methylenedioxybenzaldehyde [τ 5·92 (singlet, OCH_3), 3·97 (singlet, $-O-CH_2-O-$), 3·37 (singlet, ArH), and −0·32 (singlet, CHO)].

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