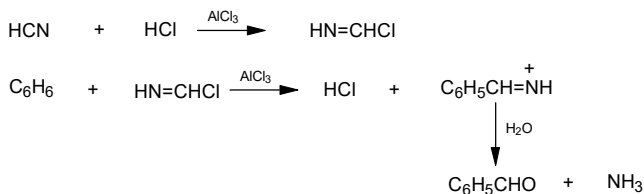


Aldehydes

Aldehydes (aromatic) are prepared by the following methods.

GATTERMANN FORMYLATION

This reaction is also known as Gatterman Aldehyde synthesis. It consists in the treatment of aromatic substance (phenols and phenolic ether) with hydrogen cyanide in the presence of lewis acid catalysts (zinc chloride, aluminium chloride). The reaction is believed to proceed as follows.

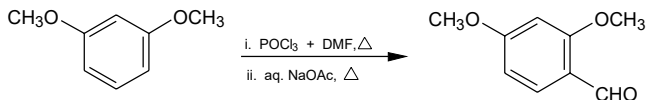


In this reaction hydrogen cyanide is generated in situ by passing dry hydrogen chloride gas into a mixture of the organic compound, zinc cyanide and or aluminium chloride in anhydrous ether.

Following aldehydes have been prepared by this method 2,2, 5, 14, 17, 19, 20, 23, 27, 28, 30, 35.

VILSMEIER-HAAK REACTION

This method is used for the preparation of aromatic aldehydes. It consists in heating the substrate (phenolic ethers) with dimethyl formamide in the presence of phosphorous oxychloride. The formed complex $\text{ArCH} = \text{N}^+(\text{CH}_3)_2\text{Cl}^-$ on heating with aqueous sodium acetate give the aldehyde in good yield.



Step (i) m-Nitrobenzaldehyde

Fuming nitric acid (125 g, 83.7 ml, d, 1.49-1.50) is added fairly rapidly to stirred concentrated sulphuric acid (650 ml, d, 1.84); the mixture is cooled by ice-bath so that the temperature of the mixed acid remains $< 10^{\circ}$. The mixture is stirred at $5-10^{\circ}$ and benzaldehyde (101.5 g, 1 mole) is added during 2-3 hr. After the addition is complete the reaction mixture is allowed to stand overnight at room temperature. The mixture is poured carefully into ice (1.5 kg) with stirring. The separated product is filtered, washed with cold water and pressed as dry as possible. A small amount of oily liquid consisting of the ortho- and meta-isomers passes through the filter and is discarded. Further removal of water is accomplished by dissolving in warm benzene (75 ml) in a separatory funnel. The clear benzene solution is concentrated on a steam bath. The residual m-nitrobenzaldehyde is sufficiently pure. Yield 135.2 g (82.5 %).

Pure m-nitrobenzaldehyde is obtained by diluting the above benzene solution with additional benzene (total volume approx. 200 ml) and washing with aqueous sodium bicarbonate solution until the washings are alkaline. Incomplete washing of the product results in explosion during distillation; all remaining acid must be removed before distillation is attempted. The benzene solution is dried (sodium sulphate) and distilled. The residual oily product is distilled at $119-123^{\circ}/4$ mm. Yield 123 g (75%) (lit.³ b.p. $119-23^{\circ}/4$ mm).

Step (ii) m-Hydroxybenzaldehyde

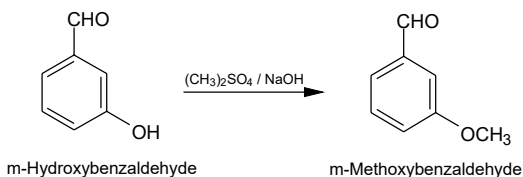
m-Nitrobenzaldehyde (50 g, 0.33 mole) is added in one lot to a cooled and stirred mixture (5° , ice-salt bath) of powdered stannous chloride dihydrate (250 g, 1 mole) and concentrated hydrochloric acid (300 ml). After the addition, the mixture is removed from the cooling mixture of ice-salt and stirring continued. The temperature rises slowly to $25-30^{\circ}$ in about 5 minutes; it rises further to about 100° . At this stage the reaction mixture is again cooled (ice-salt). The stirring is continued. The formed m-aminobenzaldehyde dissolves and a red solution is obtained. The solution is cooled with slow stirring in ice-salt mixture for 2-2.5 hr. The orange red paste of stannic chloride and m-aminobenzaldehyde is filtered preferably using a sintered glass funnel. It is used as such for the next step.

To a cooled and stirred suspension of the above product in concentrated hydrochloric acid (75 ml) (ice-salt bath) is added a solution of sodium nitrite (23 g in 75 ml water) through a separating funnel, with its

stem below the surface of the suspension; the temperature of the mixture is kept at 4-5°. After the addition of sodium nitrite solution is complete (1 hr), stirring is continued for 1 hr more. During this time the stannic chloride of the diazonium salt crystallises out. It is filtered using a sintered glass funnel.

The above product is added in small portions during 40 min to boiling water (900 ml). The reaction is treated with decolourising charcoal (4 g), boiled for 3-4 min, filtered and cooled (10-12 hr in ice box). The separated *m*-hydroxybenzaldehyde is filtered. Yield 48 g (59%). M.p. 99-101°. It is finally crystallised from benzene using decolourising charcoal as light tan crystals. M.p. 101-102°. (lit.⁴ m.p. 101-102°).

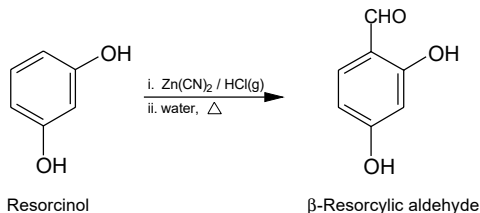
2.4 *m*-METHOXYBENZALDEHYDE



m-Hydroxybenzaldehyde (2.3) (60.4 g, 0.4 mole) is dissolved in sodium hydroxide solution (2N, 225 ml). To the dark coloured stirred solution is added dropwise dimethyl sulphate (63 g, 47.5 ml, 0.5 mole) and the temperature of the reaction mixture is maintained at 40-45°. After the addition is over, the mixture is stirred for 10 min more. Sodium hydroxide solution (2N, 137 ml) is added in one lot and dimethyl sulphate (31.5 g, 23.8 ml) is added as before, this time the temperature of the reaction mixture is allowed to rise to 50°. The mixture is stirred for 30 min at 50°, cooled and extracted with ether (2 × 150 ml). The ether solution is dried over anhydrous sodium sulphate (6 hr), filtered and distilled. *m*-Methoxybenzaldehyde is obtained as pale yellow liquid. Yield 86 g (63.0%). B.p. 88-90°/3 mm. (lit.⁵ b.p. 88-9°/3 mm).

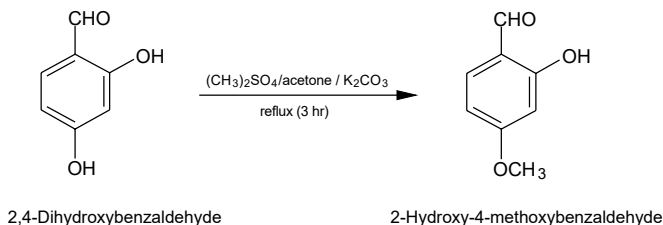
2.5 2,4-DIHYDROXYBENZALDEHYDE (β -RESORCYLIC ALDEHYDE)

An ice cold solution (0-10°) of dry resorcinol (10 g, 0.09 mole) and zinc cyanide (40 g, 0.34 mole) in dry ether (175 ml) is saturated with dry hydrogen chloride gas for 4-5 hr under anhydrous conditions. The separated imine hydrochloride is allowed to stand for 3 hr. Ether is



decanted and the solid product washed with dry ether (2×50 ml) and is hydrolysed by heating with water (70 ml) on a water bath at $60-75^\circ$ for 15 min. and the solution cooled. The separated product is filtered. It is crystallised from water as colourless needles. Yield 9 g (71.8%). M.p. $136-7^\circ$ (lit.⁶ m.p. $136-7^\circ$).

2.6 2-HYDROXY-4-METHOXYBENZALDEHYDE

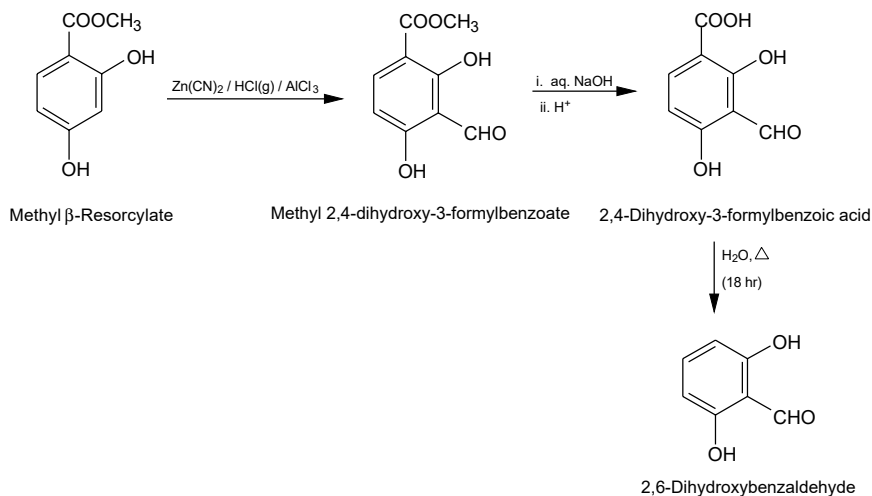


2,4-Dihydroxybenzaldehyde (2.5) (10 g, 0.072 mole) is dissolved in dry acetone (150 ml) and refluxed for 3 hr (water bath) with dimethyl sulphate (12.61 g, 9.5 ml, 0.1 mole) and ignited potassium carbonate (25 g) under anhydrous conditions. The potassium salts are filtered and the residue washed with hot acetone (2×25 ml). The combined acetone is distilled. 2-Hydroxy-4-methoxybenzaldehyde is obtained as the steam volatile product. It is crystallised from alcohol as colourless needles. Yield 2.5 g (22.7%). M.p. 41° (lit.⁷ m.p. $40-2^\circ$).

2.7 2,4-DIMETHOXYBENZALDEHYDE



2.10 2,6 DIHYDROXYBENZALDEHYDE (γ -RESORCYLIC ALDEHYDE)



Step (i) Methyl 2,4-dihydroxy-3-formylbenzoate

To a cooled solution of anhydrous aluminium chloride (8 g, 0.06 mole) in dry ether (100 ml) is added methyl β -resorcyate (3.7) (5 g, 0.03 mole) and anhydrous zinc cyanide (7 g, 0.06 mole). The mixture is cooled to 0° (ice-salt mixture) and dry hydrogen chloride gas is passed through the stirred suspension for 5 hr under anhydrous conditions. The ether is decanted from the separated oily product and washed with more ether (2×50 ml). The remaining oily product is treated with water (70 ml) (caution) and the mixture is heated for 30 min at 100° (water bath) with occasional shaking. The separated product is filtered while hot. It is crystallised from alcohol as colourless needles. Yield 3 g (51.5%). M.p. $138-140^\circ$ (lit.¹¹ m.p. $138-140^\circ$). The aqueous filtrate on cooling gave unchanged methyl β -resorcyate (0.5 g).

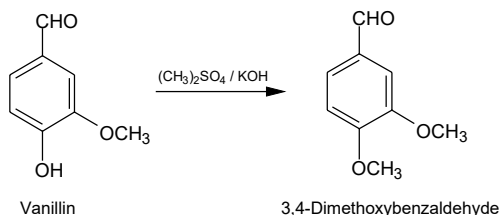
Step (ii) 2,4-Dihydroxy-3-formyl Benzoic Acid

The above ester (5 g, 0.025 mole) is dissolved in aqueous sodium hydroxide (N, 84 ml) and left at room temperature for 45 hr. The brownish solution is acidified with hydrochloric acid. It is extracted with ether and the ether distilled. The oily product is titrated with benzene (50 ml) to remove the unchanged ester. It is crystallised from the aqueous methanol as colourless needles. Yield 3.5 g (75.4%). M.p. $193-94^\circ$ (lit.¹¹ m.p. $193-94^\circ$).

Step (iii) 2,6- Dihydroxybenzaldehyde

2,4-Dihydroxy-3-formyl benzoic acid (2 g, 0.011 mole) is heated with water (30 ml) at 100° (water bath) for 18 hr in a sealed tube. The mixture is cooled and extracted once with ether. The remaining reddish oily residue is separated. It is crystallised from boiling water as colourless needles. Yield 0.3 g (19.8%). M.p. 155-56° (lit.¹¹ m.p. 155-56°).

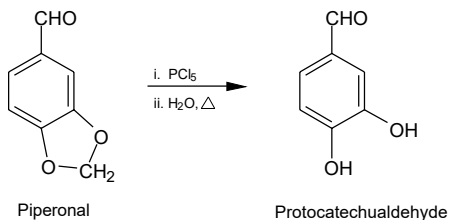
2.11 3,4-DIMETHOXYBENZALDEHYDE (VERATRALDEHYDE)



Vanillin (76 g, 0.5 mole) is melted by warming on a steam bath in a three necked flask (500 ml capacity) fitted with a mechanical stirrer and two separatory funnels. A solution of potassium hydroxide (46 g, 0.75 mole) in water (75 ml) is added dropwise through a separatory funnel. Simultaneously dimethyl sulphate (80 g, 60 ml, 0.063 mole) is added dropwise through the second separatory funnel to the vigorously stirred mixture. The external heating is stopped after a few minutes and the mixture continues to reflux by the heat of the reaction. The addition of both the reagents is completed in 20-25 min. It is ascertained that the reaction mixture remains alkaline throughout the reaction. The reaction mixture is transferred to a large beaker and allowed to cool over night. The hard crystalline mass of veratraldehyde is removed, ground in a mortar with ice- cold water (200 ml) and filtered. It is crystallised from petroleum ether as colourless needles. Yield 79 g (95%). M.p. 42-43° (lit.¹² m.p. 43°).

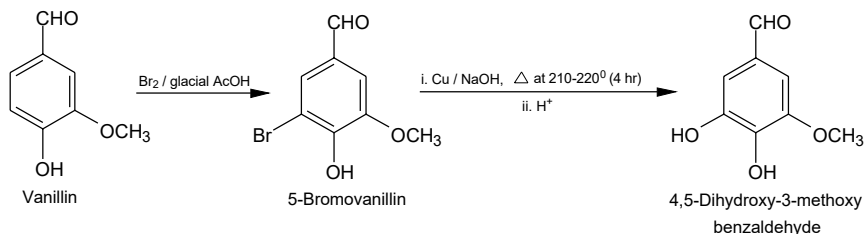
2.12 3,4 DIHYDROXYBENZALDEHYDE (PROTocatechualdehyde)

Phosphorous pentachloride (113 g, 0.54 moles) is added in small lots during 30 min under anhydrous conditions to piperonal (27 g, 0.18 mole) in 1 L R.B. flask. The reaction is vigorous in the beginning, the flask is cooled (ice) during the initial stage. The resulting mixture is gently heated over a small flame for about 45 min to expel hydrogen chloride. The



mixture is heated for 30 min on a steam bath under reduced pressure to remove the volatile material. It is poured into water (1000 ml) with caution. An oily product is formed, which becomes solid after 1-2 hr. The mixture is left overnight and heated gently for 3 hr. It is charcoaled and the clear solution concentrated in vacuo to about 150 ml. The solution is allowed to stand overnight at 0°. The separated protocatechualdehyde is filtered and washed with water. It is crystallised from water, yield 15 g (60-61%), m.p. 153-54° (decomp.) (lit.¹³ m.p. 153-54°).

2.13 4,5-DIHYDROXY-3-METHOXYBENZALDEHYDE

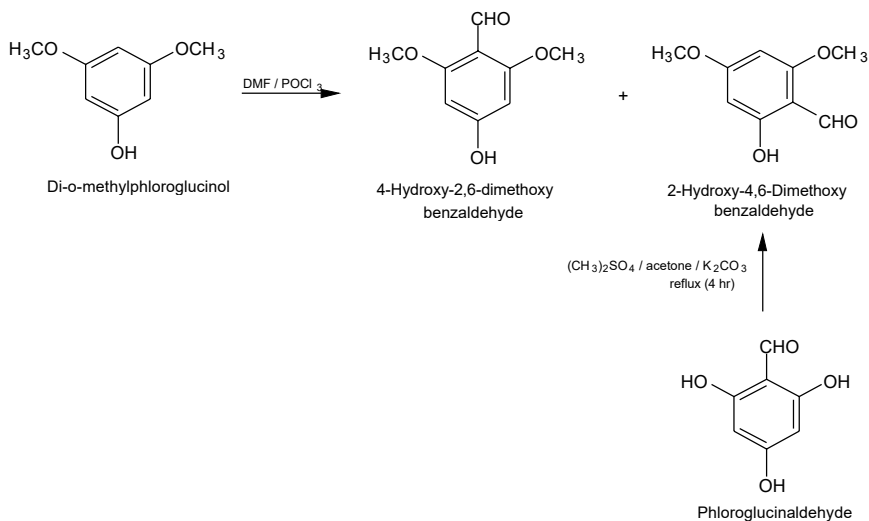


Step (i) 3-Methoxy-4-hydroxy-5-bromobenzaldehyde (5-Bromovanillin)

A solution of bromine (16 g, 5.16 ml, 0.1 mole) in glacial acetic acid is added to vanillin (15 g, 0.1 mole) dissolved in glacial acetic acid (30 ml). The bromo vanillin separates out immediately. It is filtered, washed with water and crystallised from alcohol as cubic crystals. Yield 16 g (70.2%). M.p. 163-64° (lit.¹⁴ m.p. 164°).

Step (ii) 4,5 Dihydroxy-3-methoxybenzaldehyde

A mixture of 5-bromovanillin (9.2 g, 0.04 mole), copper bronze (3.6 g) and aqueous sodium hydroxide (8%, 140 ml) is heated for 4 hr in a sealed tube at 210-220° (oil bath). The mixture is cooled, filtered and acidified with dilute sulphuric acid. The clear filtrate is concentrated in vacuo and extracted with ether (5 × 50 ml). The ether solution is distilled and the



crystallised from methanol as colourless needles of 4-hydroxy-2,6-dimethoxybenzaldehyde. Yield 4 g (38%). M.p. 223-24° (lit.¹⁷ m.p. 223-24°).

The ethyl acetate extract (M) is dried (sodium sulphate). It is filtered and treated with petroleum ether to remove the impurities. The clear solution is evaporated. The residual product is crystallised from benzene-petroleum ether as colourless needles of 2-hydroxy-4,6-dimethoxybenzaldehyde. Yield 4.1 g (34.7%). M.p. 69-70° (lit.¹⁷ m.p. 69-70°).

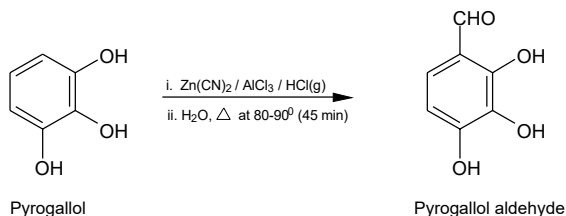
2-Hydroxy-4,6-dimethoxybenzaldehyde (2.16) is also obtained by refluxing phloroglucinaldehyde (5 g, 0.03 mole) in dry acetone (100 ml) with ignited potassium carbonate (20 g) and dimethyl sulphate (10 g, 7.5 ml, 0.08 mole) for 4 hr. The mixture is worked up in the usual way. The product obtained is crystallised from methanol as colourless needles. Yield 4 g (67.8%). M.p. 69-70°.

2.17 2,4-DIHYDROXY-6-METHOXYBENZALDEHYDE

A mixture of phloroglucinol monomethyl ether (1.12) (10g, 0.07 mole), anhydrous zinc cyanide (10 g, 0.085 mole) and dry ether (100 ml) is saturated with dry hydrogen chloride gas for 4 hr at 0° (under anhydrous conditions). The reaction mixture is left overnight at room temperature. The ether layer is decanted and the remaining semi-solid viscous mass washed with dry ether (2 × 50 ml). Cold water (100 ml) is added to the oily

A current of dry hydrogen chloride gas is passed through a stirred mixture of mesitylene (20.4 g, 23.6 ml, 0.17 mole), zinc cyanide (29.4 g, 0.25 mole) and carbon tetrachloride (60 ml) under anhydrous conditions contained in a three necked R.B. flask (1 litre capacity), fitted with a stirrer, a reflux condenser, an inlet tube and a thermometer. The passage of hydrogen chloride gas is continued for 2-3 hr till the zinc cyanide is decomposed (all the operations must be done in an efficient fume cupboard). The flask is now immersed in ice-bath, the inlet tube for the supply of hydrogen chloride removed and finely powdered aluminium chloride (47.8 g, 0.36 mole) is added to the mixture with vigorous stirring. The reaction is exothermic; the mixture attains a temperature of 70° at the end of an hour. It is stirred for 2 hr more at $68-70^\circ$. The cooled mixture is poured cautiously with stirring into crushed ice (about 400 g) to which has been added concentrated hydrochloric acid (20 ml). It is allowed to stand overnight and refluxed for 2.5 hr. The total mixture is steam-distilled. The first 120-130 ml of the distillate is kept separately for recovery of the solvent; the subsequent portion is collected as long as oily drops are observed (3.5- 4 hr). The steam distillate is extracted with benzene (2×150 ml). The solvent is removed on steam bath and the residual oily product distilled. The fraction boiling at $118-121^\circ/16$ mm is collected (lit.²⁰ b.p. $118-21^\circ/16$ mm). Yield 20.4 g (81%).

2.20 2,3,4-TRIHydroxybenzaldehyde (PYROGALLOL ALDEHYDE)

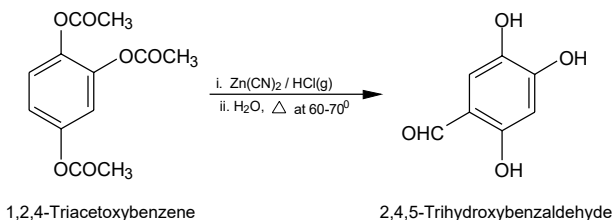


Pyrogallol (20 g, 0.16 mole) is dissolved in dry ether (200 ml) zinc cyanide (40 g, 0.34 mole) and powdered anhydrous aluminium chloride (5 g, 0.037 mole) is added at 0° . Dry hydrogen chloride gas is passed through the mixture under anhydrous conditions (0°). The separated oily aldimine hydrochloride solidifies after leaving the reaction mixture in ice-chest. The reaction mixture is allowed to stand for 2 days at room temperature. The clear ether solution is decanted and the aldimine

distilled and the residual product is crystallised from petroleum ether as colourless prisms. Yield 0.74 g (62.7%). M.p. 73-74° (lit.²³ m.p. 74°).

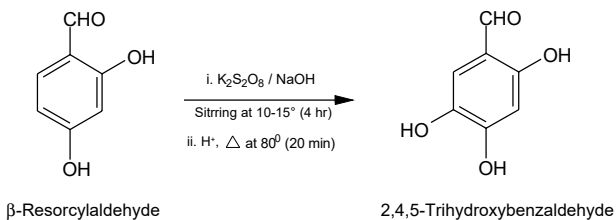
2.23 2,4,5-TRIHIDROXYBENZALDEHYDE

Method (i)



A current of dry hydrogen chloride gas is passed through a cooled solution (0°) of 1,2,4-triacetoxybenzene (1.21) (10 g, 0.04 mole) in dry ether (100 ml) containing zinc cyanide (14 g, 0.12 mole) under anhydrous conditions. After 5 hr, the current of hydrogen chloride gas is stopped and the reaction mixture left for 2-3 hr at 0°. The clear ether solution is decanted and the remaining oily product washed with ether (2 × 25 ml). It is dissolved in water (40 ml) and the solution heated at 60-70° for 15 min. The cooled solution is extracted with ethyl acetate (5 × 25 ml). The combined extract is dried (sodium sulphate) and distilled. The residual product is crystallised from water containing a little dilute hydrochloric acid as pink plates. Yield 4.0 g (65.6%). M.p. 221-22° (lit.²⁴ m.p. 223°).

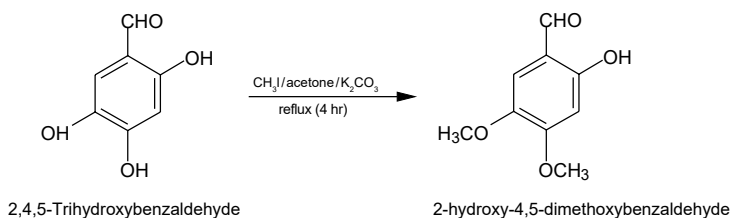
Method (ii)



A solution of potassium persulphate (27.2 g, 0.1 mole in 500 ml water) is added dropwise to a cooled solution (5-10°) of β -resorcyraldehyde (2.5) (13.8 g, 0.1 mole) in aqueous sodium hydroxide (10%, 200 ml). The mixture is stirred for 4 hr at 10-15° and allowed to stand for 24 hr at room temperature. The mixture is cooled and acidified to congo red with dilute hydrochloric acid. The unreacted aldehyde is removed by ether extraction

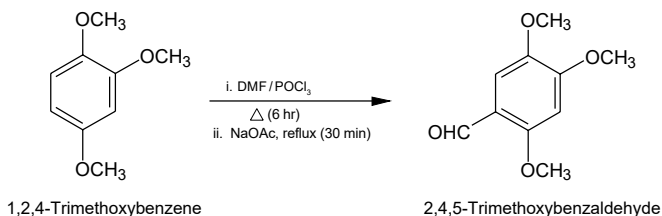
(3 × 100 ml) and the remaining solution is heated for 20 min at 80° with concentrated hydrochloric acid (175 ml) and sodium sulphate (10 g). The cooled solution is extracted with ether (5 × 100 ml). The extract is dried (sodium sulphate) and distilled. The 2,4,5-trihydroxybenzaldehyde is crystallised from water as light pink plates. Yield 1.2 g (7.8%). M.p. 220°.

2.24 2-HYDROXY-4,5-DIMETHOXYBENZALDEHYDE



A solution of 2,4,5-trihydroxybenzaldehyde (2.23) (1g, 0.0065 mole) in dry acetone (50 ml) containing ignited potassium carbonate (3 g) and methyl iodide (1.5 ml, 3.42 g, 0.024 mole) is refluxed for 4 hr till the starting compound disappeared (TLC on silica gel plates; benzene-ethyl acetate, 47:3). The acetone is filtered, inorganic residue washed with hot acetone (20 ml). The combined acetone solution is distilled. The residual product is crystallised from alcohol as cream coloured needles. Yield 0.6 g (50.8%). M.p. 104-5° (lit.²⁵ m.p. 105°).

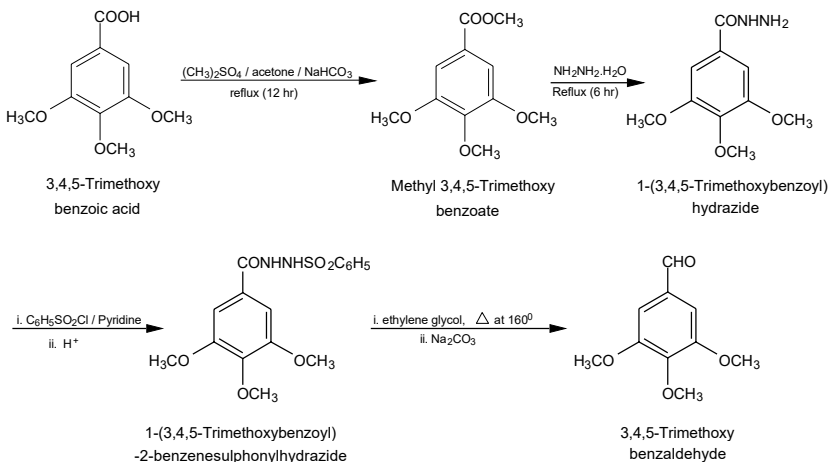
2.25 2,4,5-TRIMETHOXYBENZALDEHYDE (ASARLALDEHYDE)



A mixture of 1,2,4-trimethoxybenzene (1.22) (15 g, 0.09 mole) dimethylformamide (10.5 g, 11.12 ml, 0.14 mole) and freshly distilled phosphorous oxychloride (15 ml, 24.7 g, 0.165 mole) is heated on a boiling water bath for 6 hr under anhydrous conditions. A saturated solution of sodium acetate (50 ml) is then added and the mixture refluxed for 30 min. The solution is cooled and the separated product is filtered and washed

with cold water. It is crystallised from boiling water as colourless slender needles. Yield 10.5 g (60%). M.p. 113-114° (lit.^{26,27} m.p. 115°).

2.26 3,4,5-TRIMETHOXYBENZALDEHYDE (TRI-O-METHYLGALLALDEHYDE)



Step (i) Methyl 3,4,5-trimethoxybenzoate (See 3.28)

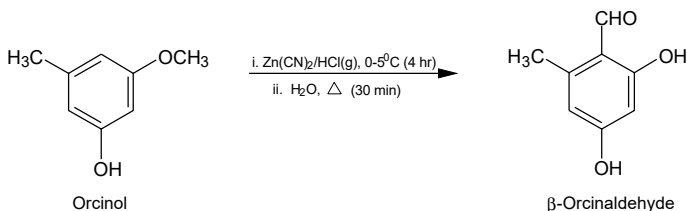
Step (ii) 1-(3,4,5-Trimethoxybenzoyl) hydrazide

A mixture of methyl 3,4,5-trimethoxybenzoate (44 g, 0.19 mole) and hydrazine hydrate (14 ml, excess) is refluxed for 6 hr. Excess hydrazine is removed under reduced pressure. The residue is treated with water and the separated product is filtered and washed with water. It is crystallised from alcohol as colourless shining needles. Yield 42 g (95.5%). M.p. 159-60° (lit.²⁰ m.p. 159-60°).

Step (iii) 1-(3,4,5-Trimethoxybenzoyl)-2-benzene sulphonylhydrazide

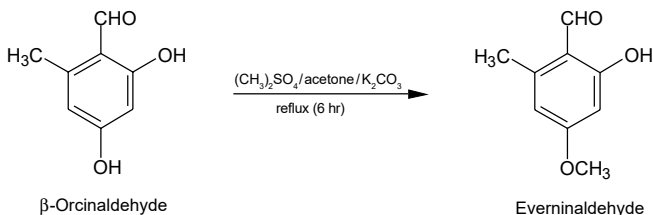
The above hydrazide (41 g, 0.18 mole) is dissolved in pyridine (50 ml) and treated with benzene sulphonyl chloride (34.5 g, 0.18 mole) with stirring. The mixture is stirred for 2 hr. It is poured over a mixture of ice and hydrochloric acid (the overall mixture should be acidic). The separated product is filtered and washed with water. It is crystallised from alcohol as creamish coloured plates. Yield 56 g (81.2%). M.p. 243-44°. (lit.²⁸ m.p. 243-44°).

2.28 2,4-DIHYDROXY-6-METHYLBENZALDEHYDE (β -ORCINALDEHYDE)



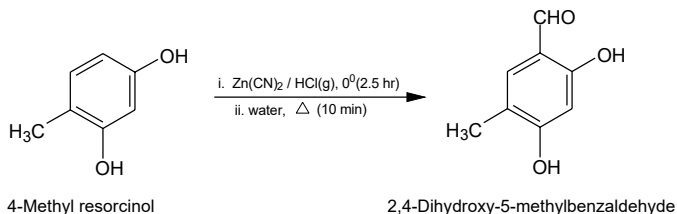
A solution of orcinol (6 g, 0.048 mole) in dry ether (100 ml) containing zinc cyanide (15 g, 0.13 mole) is saturated with dry hydrogen chloride gas at 0-5° for 4 hr under anhydrous conditions; the mixture is stirred gently during saturation. The oily aldimine hydrochloride is obtained first as a thick oil; it slowly solidifies after about 1 hr. The mixture is left in an ice chest for 2 days. The ether solution is decanted and the solid product washed with dry ether (2 × 30 ml). It is dissolved in water (100 ml) and heated on a water bath for 30 min. The resulting solution is cooled and the separated product is filtered and washed with water. It is crystallised from alcohol as colourless needles. Yield 3.5 g (47.6%). M.p. 182-83° (lit.^{24,30} m.p. 180°).

2.29 2-HYDROXY-4-METHOXY-6-METHYLBENZALDEHYDE (EVERNINALDEHYDE)



A solution of β -orcinaldehyde (2.28) (1.52 g, 0.01 mole) in anhydrous acetone (50 ml) is refluxed with dimethyl sulphate (1.0 ml, 1.3 g, 0.11 mole) and anhydrous potassium carbonate (3 g) for 6 hr under anhydrous conditions. The acetone solution is filtered and inorganic residue washed with more acetone (15 ml). The combined acetone solution is distilled and the residue macerated with ice-water. The separated product is filtered and washed with water. It is crystallised from methanol as colourless needles. Yield 1.4 g (84.3%). M.p. 63-64° (lit.³¹ m.p. 65°).

2.30 2,4-DIHYDROXY-5-METHYLBENZALDEHYDE



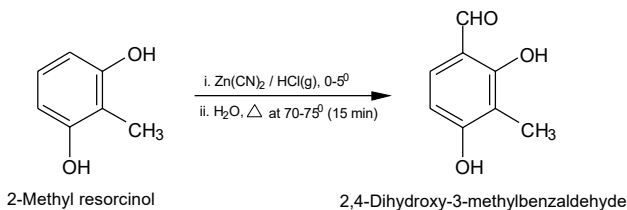
A rapid stream of dry hydrogen chloride gas is passed through a solution of 4-methyl resorcinol (1.18) (6 g, 0.048 mole) in dry ether (75 ml) containing dry zinc cyanide (12 g, 0.10 mole) at 0° for 2.5 hr. The mixture is allowed to stand overnight. The clear ether solution is decanted and the oily residue washed with dry ether (25 ml). The remaining oily product is dissolved in water (50 ml) and heated on a boiling water bath for 10 min. The solution is cooled and the separated product is filtered. It is crystallised from chloroform as colourless shining needles. Yield 4.5 g (61.2%). M.p. $144-45^\circ$ (lit.³² m.p. $146-47^\circ$).

2.31 2,4-DIHYDROXY-3-METHYLBENZALDEHYDE

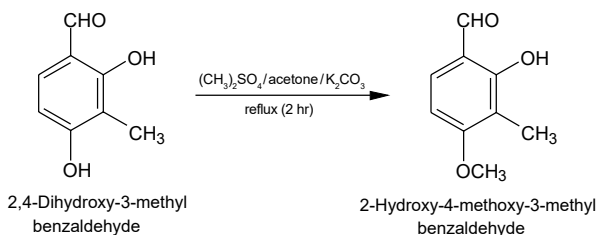
Method (i)



To a stirred solution of 2-methyl resorcinol (14 g, 0.11 mole) in dimethyl formamide (10 ml, 9.44 g, 0.13 mole) is added phosphorus oxychloride (10 ml, 16.45 g, 0.11 mole) in small portions. The mixture is heated on a water bath for 3 hr under anhydrous conditions. It is cooled, water (50 ml) added and the mixture is extracted with ether. The ether extract is washed with water, dried (magnesium sulphate) and distilled. The residual product is crystallised from methanol as colourless needles. Yield 10.5 g (61.2%). M.p. $145-46^\circ$ (lit.^{33,34} m.p. $145-46^\circ$).

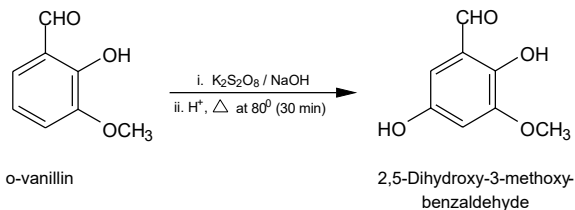
Method (ii)

A rapid stream of dry hydrogen chloride gas is passed for 5-6 hr through a cooled solution ($0-5^\circ$) of 2-methyl resorcinol (1.17) (5 g, 0.04 mole) in dry ether (100 ml) containing anhydrous zinc cyanide (7.5 g, 0.064 mole) until the imine hydrochloride formed as a thick oil solidifies. The mixture is left for 24 hr in an ice chest. The ether is decanted and the residual product washed with dry ether (2×20 ml). It is dissolved in water (70 ml) and heated on a water-bath ($70-75^\circ$) for 15 min. The solution is cooled and separated product filtered. It is crystallised from methanol as colourless needles. Yield 3.8 g (61.99%). M.p. $146-47^\circ$.

2.32 2-HYDROXY-4-METHOXY-3-METHYLBENZALDEHYDE

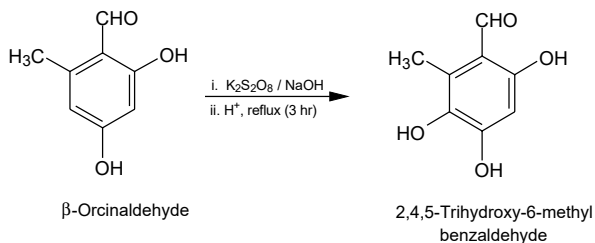
A solution of 2,4-dihydroxy-3-methyl benzaldehyde (2.31) (1 g, 0.0065 mole) in dry acetone (50 ml) is refluxed for 2 hr with dimethyl sulphate (0.66 ml, 0.88 g, 0.007 mole) in presence of anhydrous potassium carbonate (2 g). The mixture is filtered and the inorganic salts washed with hot acetone (20 ml). The combined acetone solution is distilled and the residue treated with ice-water. The separated product is filtered. It is crystallised from benzene-petroleum ether as colourless needles. Yield 0.84 g (77.1%). M.p. $66-67^\circ$ (lit.³⁵ m.p. $66-67^\circ$).

2.33 2,5-DIHYDROXY-3-METHOXYBENZALDEHYDE

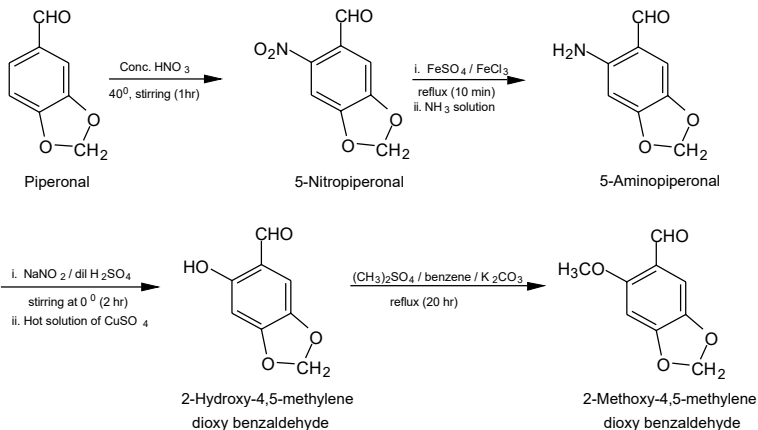


A solution of potassium persulphate (36 g, 0.133 mole) in water (720 ml) is added dropwise during 3-4 hr at 10-15° to a stirred solution of o-vanillin (20 g, 0.13 mole) in water (160 ml) containing sodium hydroxide (32 g). The mixture is stirred for 1 hr more and allowed to stand for 24 hr at room temperature. The reaction mixture is cooled and acidified to congo red with hydrochloric acid. The separated unchanged o-vanillin is filtered and the solution extracted with ether (2 × 100 ml) to remove the starting material completely. The solution is heated at 80° for 30 min with concentrated hydrochloric acid (250 ml) and sodium sulphite (10 g). The solution is cooled and extracted with ether (5 × 100 ml). The ether extracted is dried (sodium sulphate) and distilled. The crude aldehyde thus obtained is crystallized from benzene as pale yellow needles. Yield 7 g (31.6%). M.p. 144° (lit.³⁶ m.p. 144°).

2.34 2,4,5-TRIHYDROXY-6-METHYLBENZALDEHYDE



To a stirred and cooled solution (10-15°) of β-orcinaldehyde (2.28) (10g, 0.066 mole) in potassium hydroxide (150 ml, 12%) is added dropwise during 4 hr a saturated solution of potassium persulphate (18 g, 0.067 mole in 300 ml water). The solution is stirred for 1 hr more and allowed to stand overnight at room temperature. It is cooled and acidified to congo red with hydrochloric acid. The solution is extracted with ether (3 × 100 ml) to remove the unreacted aldehyde. The aqueous solution is refluxed under a



separated product is filtered, washed with cold water and then with sodium bicarbonate solution (to remove excess of nitric acid) and finally with cold water. It is crystallised from ethanol as pale yellow needles. Yield 30 g (46.2%). M.p. $97-98^\circ$ (lit.⁴¹ m.p. $97-98^\circ$).

Step (ii) 6-Aminopiperonal

To a boiling solution of ferrous sulphate (100 g in 500 ml water) containing little ferric chloride (1.5 g) is added with stirring during 10 min, a solution of 6-nitropiperonal (10 g, 0.05 mole) in alcohol (500 ml, 50%). After the addition the reaction mixture is refluxed for 10 min and then a strong solution of ammonia (150 ml of 50% liquor ammonia) is added in lots of 10 ml with vigorous stirring. The solution is filtered and the residual product washed with boiling water (250 ml). The combined filtrate and washings on cooling gave a solid product. It is filtered and crystallised from hot water as bright yellow needles. Yield 6.3 g (74.5%). M.p. $107-108^\circ$ (lit.⁴² m.p. $107-108^\circ$).

Step (iii) 2-Hydroxy-4,5-methylenedioxybenzaldehyde

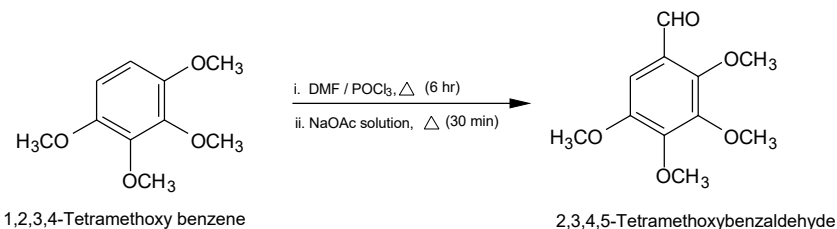
6-Aminopiperonal (10 g, 0.06 mole) is suspended in water (300 ml), cooled to 0° and dilute sulphuric acid (10 ml concentrated sulphuric acid in 60 ml water) is added dropwise with shaking. The mixture is stirred and cooled (0°). It is treated with a solution of sodium nitrite (5 g, 0.72 mole in 50 ml water) added dropwise during 30 min. The mixture is stirred for 2 hr at 0° and the reaction mixture is left overnight at room temperature. It is diluted with an equal volume of water and then added slowly to a hot solution of

copper sulphate (150 g in 150 ml water). The solution is steam distilled (10 hr). The collected distillate (approx. 4.5 litres) is extracted with ether (4 × 250 ml). The ether extract is concentrated and extracted with sodium hydroxide solution (10%, 3 × 100 ml). The combined clear alkaline extract is acidified and the separated product filtered. It is crystallised from dilute alcohol as colourless needles. Yield 2.5 g (24.9%). M.p. 125-26° (lit.⁴² m.p. 125-26°).

Step (iv) 2-Methoxy-4,5-methylenedioxybenzaldehyde

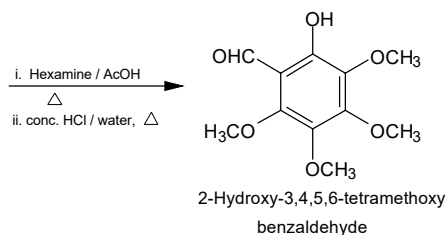
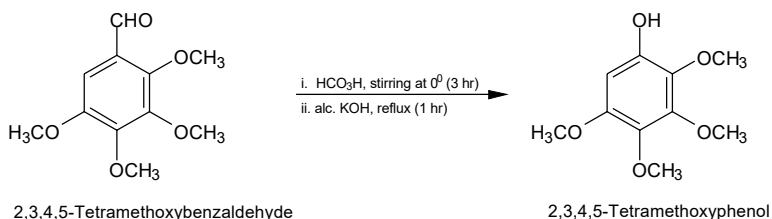
A mixture of the above 2-hydroxy-4,5-methylenedioxybenzaldehyde (6 g, 0.036 mole) in dry benzene (100 ml) containing anhydrous potassium carbonate (20 g) and dimethyl sulphate (9 ml, 12 g, 0.095 mole) is refluxed for 20 hr. The mixture is filtered and the inorganic salts washed with hot benzene (2 × 25 ml). The combined benzene solution is concentrated in vacuo and the residue treated with cold water. The separated product is filtered. It is crystallised from hot water as colourless needles. Yield 4.5 g (69.2%). M.p. 112° (lit.⁴² m.p. 112°).

2.38 2,3,4,5- TETRAMETHOXYBENZALDEHYDE⁴³



1,2,3,4-Tetramethoxybenzene (1.36) (5 g, 0.025 mole) is dissolved in dry dimethyl formamide (5 g, 5.3 ml, 0.068 mole) and treated with phosphorous oxychloride (5 ml, 8.2 g, 0.054 mole). The mixture is heated for 6 hr in a boiling water bath under anhydrous conditions. Saturated sodium acetate solution (20 ml) is then added and the reaction mixture heated for 30 min more. It is cooled, diluted with water (100 ml) and extracted with ether (3 × 100 ml). The combined ether extract is washed with water, dried (magnesium sulphate) and distilled. 2,3,4,5-Tetramethoxybenzene is obtained as an oil. Yield 4g (70.2%).

2.39 2-HYDROXY-3,4,5,6-TETRAMETHOXYBENZALDEHYDE



Step (i) 2,3,4,5-Tetramethoxyphenol⁴³

2,3,4,5-Tetramethoxybenzaldehyde (2.38) (5 g, 0.022 mole) is dissolved in dry chloroform (50 ml) and treated dropwise with performic acid (1.36) (25 ml) with constant stirring; the temperature of the reaction mixture is maintained at 0°. The reaction mixture is stirred for 3 hr and treated with sodium bisulphite (1 g). Performic acid is removed in vacuo and the residue rendered alkaline with alcoholic potassium hydroxide (10%). The solution is refluxed for 1 hr with potassium hydroxide solution (50 ml, 10%). The alcohol is removed in vacuo and the residue acidified with hydrochloric acid. The reaction mixture is extracted with ether, ether extract dried (sodium sulphate). The ether is distilled and 2,3,4,5-tetramethoxyphenol is obtained as an oil. Yield 2 g (42.3%).

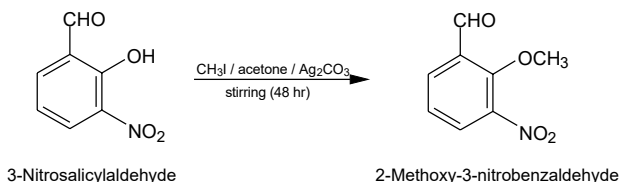
The above phenol (1 g, 0.0047 mole) is refluxed for 4 hr in dry acetone (50 ml) dimethyl sulphate (1 ml, 1.3 g, 0.01 mole) in the presence of anhydrous potassium carbonate (5 g). The reaction mixture is worked up in the usual way. 1,2,3,4,5-Pentamethoxybenzene is crystallised from petroleum ether as colourless needles. Yield 1 g (94.3%). M.p. 58-59° (lit.⁴⁴, m.p. 58-59°).

Step (ii) 2-Hydroxy-3,4,5,6-tetramethoxybenzaldehyde⁴³

A mixture of the above 2,3,4,5-tetramethoxyphenol (2 g, 0.009 mole), glacial acetic acid (20 ml) and hexamine (6 g) is heated in a boiling water bath under anhydrous conditions. Concentrated hydrochloric acid (10 ml)

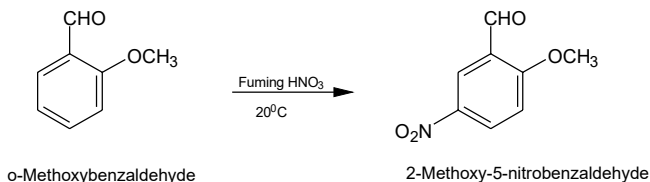
and water (20 ml) is then added to the reaction mixture and heating continued for 30 min more. The reaction mixture is cooled, diluted with water and extracted with ether. The ether solution is washed with water, dried (sodium sulphate) and distilled. 2-Hydroxy-3,4,5,6-tetramethoxybenzaldehyde is obtained as an oil. Yield 0.5 g (22.4%) (lit.⁴⁴ oil).

2.40 2-METHOXY-3-NITROBENZALDEHYDE



To a solution of 3-nitrosalicylaldehyde (2.42) (2.2 g, 0.013 mole) in pure dry acetone (70 ml) is added air-dried silver carbonate (5.4 g) and methyl iodide (2.5 ml, 5.7 g, 0.04 mole). The mixture is stirred for 48 hr, allowed to stand for 6 days at room temperature and filtered. The filtrate is concentrated in vacuo. The solid product is taken up in ether, the ethereal solution washed with sodium hydroxide solution (5%), water and then distilled. The residual product is crystallised from alcohol as almost colourless needles with a yellow tinge. Yield 2 g (84%). M.p. 97-99° (lit.⁴⁵ m.p. 102°).

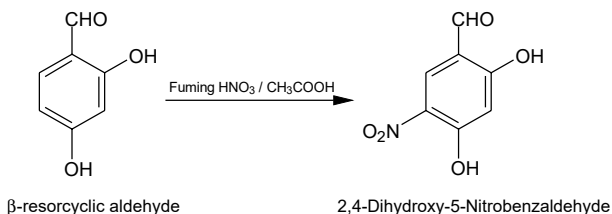
2.41 2-METHOXY-5-NITROBENZALDEHYDE



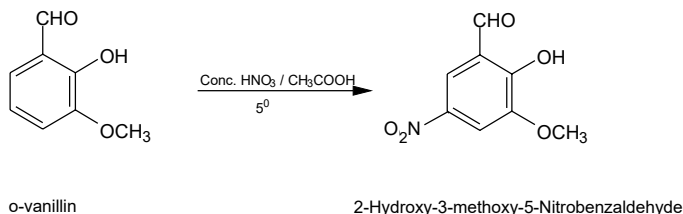
o-Methoxybenzaldehyde (2.1) (5 ml, 5.6 g, 0.04 mole) is slowly added to cold fuming nitric acid (25 ml, d, 1.5) at such a rate that temperature did not rise above 20° during the addition. The deep yellow solution is allowed to stand at 20° for 15-20 min and poured into ice-water (200 ml). The separated product is filtered and washed with cold water. It is crystallised from large volume of water as nearly colourless slender long needles. Yield 4 g (53.7%). M.p. 86-88° (lit.⁴⁶ m.p. 89-90°).

Step (ii) 3,5-Dinitrosalicylaldehyde

The mixture of 3- and 5- nitrosalicylaldehydes obtained above (3.3 g, 0.02 mole) is cautiously added to an ice-cold mixture of concentrated sulphuric acid (4 ml) and fuming nitric acid (2 ml, d, 1.5). The mixture is allowed to stand for 30 min with occasional shaking. It is poured into cold water and the separated yellow product filtered and washed with water. It is crystallised twice from benzene as lemon yellow prisms. Yield 1.6 g (38.2%). M.p. 60-61° (lit.⁵⁰ m.p. 62-63°).

2.43 2,4-DIHYDROXY-5-NITROBENZALDEHYDE (5-NITRORESORCYLIC ALDEHYDE)

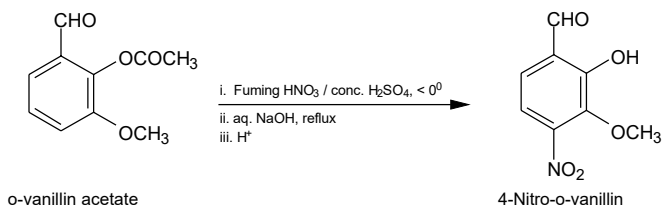
A cold solution of β -resorcylic aldehyde (2.5) (5 g, 0.036 mole) in glacial acetic acid (10 ml) is added to cold solution of fuming nitric acid (2.1 ml, d, 1.5) in glacial acetic acid (5 ml). As soon as the reaction subsided, the reaction mixture is heated for 10-15 min in a boiling water bath and then poured into water (30 ml). The separated product is filtered and washed with water. It is crystallised from benzene as brownish yellow prisms. Yield 3 g (45.2%). M.p. 148-49° (lit.⁵¹ m.p. 148-49°).

2.44 2-HYDROXY-3-METHOXY-5-NITROBENZALDEHYDE (5-NITRO-o-VANILLIN)

Concentrated nitric acid (1.5 ml, d, 1.5) is added dropwise with stirring to a cooled (5°) solution of o -vanillin (3 g, 0.002 mole) in glacial acetic acid (1.2 ml). The reaction mixture is allowed to stand for 30 min

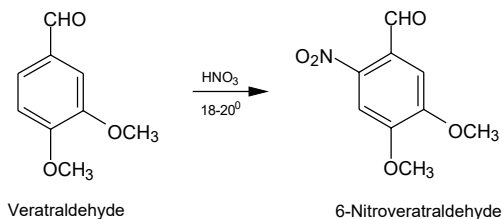
and then poured into water. The separated product is filtered and washed with water. It is crystallised from acetic acid as yellow needles. Yield 3 g (77.3%). M.p. 140-142° (lit.⁵² m.p. 142°).

2.45 2-HYDROXY-3-METHOXY-4-NITROBENZALDEHYDE (4-NITRO-*o*-VANILLIN)



To a previously cooled mixture (-6°) of fuming nitric acid (10 ml, d, 1.52) and concentrated sulphuric acid (2 ml), *o*-Vanillin acetate (3 g, 0.015 mole) is added in small lots with brisk stirring. During the reaction and subsequent 15 min, the reaction mixture is kept stirred ($< 0^\circ$). It is poured into crushed ice and the separated viscous oil taken up in benzene. The benzene extract is washed with ice-cold water (3×100 ml), cold aqueous sodium bicarbonate (5 g) and again with water. The deep red bicarbonate solution on acidification gave the 5-nitro isomer (0.2 g), m.p. 140-42° (after crystallisation from acetic acid). The remaining benzene solution is distilled and the residual oily product is refluxed with aqueous sodium hydroxide (20 ml, 2%) for 10-15 min. The clear solution is cooled and acidified. The separated product is filtered and washed with water. It is crystallised from acetic acid as yellow needles of 4-nitro-*o*-vanillin. Yield 0.8 g (26.3%). M.p. 92-93°. (lit.⁵² m.p. 92-93°).

2.46 3,4-DIMETHOXY-6-NITROBENZALDEHYDE (6-NITROVERATRALDEHYDE)



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