SYNTHESIS OF 2,5-DIMETHOXYBENZALDEHYDE

HTML by Rhodium

2-HYDROXY-5-METHOXYBENZALDEHYDE BY THE FORMYLATION OF 4-METHOXYPHENOL

Formylation of 4-Methoxyphenol (4-hydroxyanisole, hydroquinone monomethyl ether) yields 2-Hydroxy-5-Methoxybenzaldehyde (5-Methoxysalicylaldehyde). The most promising procedures include Reimer-Tiemann formylation ($CHCl_3$/KOH) and Mg-mediated phenol ortho-formylation with paraformaldehyde. A few variations on this theme is presented below.

REIMER-TIEMANN FORMYLATION OF 4-METHOXYPHENOL[5]

It is known that 2-hydroxy-5-methoxybenzaldehyde is formed by reacting hydroquinone monomethyl ether with chloroform in the presence of sodium hydroxide[6]. However, in this process, it is necessary to purify the reaction mixture after completion of the reaction by steam distillation and treatment with sodium bisulphite. The end product is obtained in a low yield. By using a relatively large amount of sodium hydroxide, the reaction proceeds at a high rate and the end product precipitates from the reaction mixture in the form of a sodium salt so that the end product can be purified by filtration and washing, and the end product is obtained in a purity of 98.5% (GC) rendering steam distillation and treatment with bisulphite unnecessary.

From a theoretical point of view, it would appear that chloroform could be used in an equimolar amount to the starting phenol, but this lowers the yield; accordingly, it is preferable to use 1.5-2 molar equivalents of chloroform; even larger amounts does not increase the yield further. A too high concentration of sodium hydroxide in the reaction mixture causes decomposition of the end product, while a too low concentration results in too low a rate of formylation and causes dissolution of the sodium salt of 2-hydroxy-5-methoxybenzaldehyde in the aqueous reaction medium, making workup difficult. Thus, in order to obtain a purified end product in 48-53% yield, it's necessary to use 300-450 g NaOH dissolved in 480-720 mL water per 100 g of hydroquinone monomethyl ether. It is advantageous to add the hydroquinone monomethyl ether as a solution in a portion of the aqueous sodium hydroxide solution and then add the remainder of the solution dropwise.

If KOH or LiOH are used in place of NaOH in the process, the end product is obtained in a low yield of at the most 14% in the case of KOH, and with LiOH substantially no product is obtained. The duration of the reaction is not critical, and the reaction is merely carried out at 50-60°C (above this range polymeric tars will form as byproducts, lowering the yield) until reaction completion is obtained. Usually about 1 hour is sufficient.

EXPERIMENTAL[5]

200g of hydroquinone monomethyl ether were dissolved in a solution of 190 g of sodium hydroxide in 550 ml of water and the resulting solution was heated to 50°C on a water bath. To the solution maintained at 50-60°C, there were added dropwise 420 g of chloroform and a solution of 560 g of sodium hydroxide in 500 ml of water from two separate dropping funnels and, thereafter, the reaction mixture was heated for 1 hour at a temperature of 50-60°C and atmospheric pressure. After cooling, the precipitated sodium salt of 2-hydroxy-5-methoxybenzaldehyde was recovered by filtration and washed with 100 ml of ethanol.The sodium salt thus obtained was dissolved in 800 ml of water, slightly acidified with dilute sulphuric acid (1200 mL of 3N dilute sulphuric acid were added at room temperature and atmospheric pressure) and then extracted with 200 ml of toluene. The extract was dried with calcium chloride, distilled to eliminate toluene and then distilled under reduced pressure to obtain 132 g of 2-hydroxy-5 methoxybenzaldehyde having a boiling point of 110°C/5mmHg.

FORMYLATION WITH PARAFORMALDEHYDE/MAGNESIUM METHOXIDE

Written by **DTT**, Russian Translation by **Dioulasso**

This formylation method can be a superior alternative to the much discussed Reimer-Tiemann formylation (a selective ortho-formylation of phenols).

EXPERIMENTAL

A 2000 mL RBF equipped with a reflux conenser, a mechanical stirrer, and an addition funnel is charged with 32g of magnesium followed by 200ml dry Methanol. It is possible to ad more MeOH so Mg dissolves faster. The reaction is vigorus. Sometimes the flask has to be cooled to prevent the condenser from spitting around. When the mixture is beginnig to get thick, 250g of 4-methoxyphenol in 300-500ml of hot toluene is added in a slow stream from the addition funnel. The mixture is heated up with good stirring. (Watch out - the precipitated phenolate can stick to the bottom).

When all the magnesium has dissolved, the MeOH is evaporated (it is also possible not to evaporate all[I]). A suspension of 180g of Paraformaldehyde[II] in Toulene is added in small portions every 10 minutes (exotermic!), with good stirring of the thick mixture. This takes about an hour. The mixture turns yellow and gets less thick. The mixture is than stirred for another 30 min and acidified with dilute Sulfuric Acid[III]. The toluene layer is separated and the toluene is driven off. The rest is 2-Hydroxy-5-Methoxy-Benzaldehyde.

The thus obtained product is not contaminated with 4-methoxyphenol, but containes the dimer as an inpurity. It may be cleaned via the bisulphite adduct or it can be distilled under reduced pressure. Yield is around 80%. The aldehyde may stain the skin yellow.

NOTES:

A. IMHO it is not necesseary...Once I have tried not to evaporate all of it and all seemed to work fine.
B. Dry paraformaldehyde was used.
C. In the patent the acidified mixture is stirred for 5h. I'm not sure about that half an hour figure - just act by the situation. You can see the decomposition of phenolate visually as it dissolves in toluene. One has to scratch it diligently off the flask's wall, though.

Some final notes by Dioulasso:

- It might be necesseary to efficently stir the acidified mixture in order to achive full conversion of the phenolate. Swim experienced a lot of tar like residue after steam distilling his Reimer-Tiemann product. Is it possible that unconverted phenolate was extracted from the not fully acidified reaction mixture, and partially that was the residue left behind? This would explain his low yields (less than 50%)...
- For smaller batches, it might be advantageous to initiate the $Mg(MeO)_2$ formation with small crystals of Iodine.

PREPARATION OF MAGNESIUM METHOXIDE

Below follows some a rticles describing the practical preparation of magnesium methoxide from Mg and MeOH.
The trick to get it to start working is no surprise: A crystal of elemental iodine as catalyst - and heat (60°C).

J. Med. Chem., 36(6), 758-764 (1993)
[The] magnesium methoxide was generated by refluxing a solution of magnesium (1 g) in 20 mL of MeOH containing 10 mg of iodine.

Tet. Lett., 37(29), 5159-5160 (1996)
In the presence of iodine and hexane, alcohols readily react with magnesium to produce corresponding magnesium alkoxides By the simplified method used in this paper, the preparation of magnesium alkoxides was carried out in the absence of hexane or any other saturated hydrocarbons.*

Magnesium alkoxides are prepared by heating 2.43 (100 mmol) of magnesium powder, (2 mmol) of iodine, 0.2 mol of alcohol at 60°C until the iodine color disappeared. The rest of the alcohol (MeOH 1.4 mol; EtOH 0.7-1.1 mol; *n*-PrOH/*n*-BuOH 0.4-0.6 mol) was then added and the mixture was refluxed until all magnesium powder was digested. The resulting magnesium alkoxides in alcohol can be used directly *[...]*

***** *Idemitsu Kosan Co. Ltd.,* **Japan Pat. JP58041832** (1983) - Chem. Abstr. 99, 104778v (1983)

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MAGNESIUM-MEDIATED ORTHO-FORMYLATION OF PHENOLS[1]

2-OH-5-MeO-benzaldehyde from 4-MeO-phenol, $Mg(OMe)_2$, and paraformaldehyde in MeOH/toluene. **Yield:** 97%
The procedures are described for (nonyl)Phenol, simply use an equimolar amount of 4-Methoxyphenol instead.

EXPERIMENTAL

Phenol (37.6 g, 0.4 mol) was added to magnesium methoxide (259 g of 8% (w/w) solution in methanol; 20.7 g, 0.24 mol) and the mixture was heated to reflux. Approximately half of the methanol was distilled off and toluene (300 g) was added to the residue. The azeotropic mixture of toluene and and methanol was removed by fractional distillation, until the temperature of the reaction rose to 95°C. A slurry of paraformaldehyde powder (43.2 g, 1.44 mol) in toluene (75 g) was added in small portions over 1 h to the reaction mixture at 95°C with concurrent removal of the volatile materials by didtillation. Stirring was continued at 95°C for 1 h, after which the mixture was cooled to 25°C and added slowly to 10% sulfuric acid (450 g), The resulting mixture was stirred at 30-40°C, after which the aqueous layer was separated and extracted with toluene (2x100 g). The combined organic layers and extracts were washed with 10% sulfuric acid (50 g) and water (50 g) and evaporated under reduced pressure to give the aldehyde as a pale yellow oil (48.35 g, 84% w/w by GC and ^{1}H-NMR comparisn against a reference standard and against a commercial sample of known purity; 83% yield).

In similar reactions they used the following conditions:

Magnesium raspings (7.3 g, 0.3 mol), methanol (112 g), toluene (48.5 g) and magnesium methoxide (1.6 g of 8% w/w solution in methanol; 1.5 mmol) were heated under reflux for 2 h untile the magnesium had dissolved and hydrogen evolution had ceased. 4-Nonylphenol (112 g, 0.5 mol) was added to the mixture [...]

CONVENIENT METHOD FOR THE ORTHO-FORMYLATION OF PHENOLS[2]

2-Hydroxy-5-Methoxybenzaldehyde from 4-Methoxyphenol, $MgCl_2$, Et_3N, and paraformaldehyde in MeCN.
Yield: 97% **Reaction time:** 2 h

Phenolic derivs. are formylated selectively ortho to the hydroxy group by paraformaldehyde with magnesium dichloride-triethylamine as base. With alkyl-substituted phenols, e.g., 2-, 3-, 4-Methylphenols, excellent yields of the corresponding salicylaldehyde derivs. were obtained. Similar results were obtained with 2-, 3-, and 4-chloro-substituted phenols and with 3-and 4-methoxyphenol, while 2-methoxyphenol was unreactive. A good yield of Methyl 3-formyl-4-hydroxybenzoate was obtained by this method as well, but generally phenols with electron-attracting groups reacted sluggishly; the long reaction times required caused the formation of byproducts, particularly MOM-derivs. of the phenols.

EXPERIMENTAL[2]

Dry (P_2O_5) paraformaldehyde (135 mmol) was added to a mixture of the phenolic derivative (20 mmol), commercially available anhydrous magnesium dichloride (30 mmol) and dry (Na) triethylamine (75 mmol) in acetonitrile (100 mL; distilled over CaH_2), and the mixture was heated under reflux for the reaction time recorded. The mixture was cooled to room temperature after which 5% aq. HCl was added and the product extracted with ether. The dried ($MgSO_4$) extract was evaporated and the residue purified by flash chromatography on silica gel.

2,5-DIMETHOXYBENZALDEHYDE BY DIRECT METHYLATION OF THE CRUDE PRODUCT FROM THE ORTHO-FORMYLATION OF 4-METHOXYPHENOL[8]

2,5-dimethoxybenzaldehyde finds use in the preparation of photographic developers, textile dyes; and as an electroplating bath additive. Numerous methods for its preparation have been reported, the two most common being Gattermann formylation of 1,4-dimethoxybenzene (GB1069409), and alkylation of 2-hydroxy-5-methoxy benzaldehyde with dimethyl sulfate U.S. Pat. 3,867,458. The first of these methods suffers from the need to use highly toxic and volatile hydrogen cyanide under acidic conditions. The second uses no toxic gases, but the 2-hydroxy-5-methoxybenzaldehyde must be purified before the final alkylation step. This invention allows for a synthesis of 2,5-dimethoxybenzaldehyde that avoids the use of highly toxic cyanides while simultaneously eliminating the need for a time-consuming distillation step.

A common method for preparing the 2-hydroxy-5-methoxy benzaldehyde comprises reacting a magnesium salt of 4-methoxyphenol (Mg^{2+} supplied as either $Mg(MeO)_2$[9] or $MgCl_2$[2]) with paraformaldehyde [a source of anhydrous formaldehyde] followed by acidic quench and workup/purification (**Reaction I**).

Typically, distillation or chromatography of the 2-hydroxy-5-methoxy-benzaldehyde product has been required in order to achieve a good yield in the alkylation step. A recent article[2] claims a 97% for the subject compound, which indicates few by-products. However, repetition of that disclosure (**Example 1a**) indicates the presence of several impurities that lower the assay and the yield, necessitating purification prior to alkylation (*cf.* **Examples 1b** and **1c**).

We have discovered that unpurified, or crude, reaction product obtained from the formation of the 2-hydroxy-5-methoxybenzaldehyde, can be treated *in situ* with an alkali hydroxide to generate substantially pure metal salts of 2-hydroxy-5-methoxy-benzaldehyde [**Reaction II**], which can be separated by filtration, and which are suitable for

alkylation with dimethylsulfate to thereby produce 2,5-dimethoxybenzaldehyde.

Example 1a:
Preparation 2-Hydroxy-5-Methoxybenzaldehyde from 4-Methoxyphenol
A mixture of 600 g of acetonitrile, 186.2 g of 4-methoxyphenol (1.5 moles) and 214 g (2.25 moles) of anhydrous magnesium chloride was warmed to 45°C. and 227.4 g (2.25 moles) of triethylamine was added dropwise at that temperature. Paraformaldehyde (150 g, 4.75 moles) was then added and the reaction was heated to reflux. Methanol was removed over 3 hours by distillation, using a 10-inch column packed with Penn-State packing. The weight of the methanol removed (vapor temperature 60-65°C.) was 130g. The solution was cooled to 60°C. and added to 900 mL of water. The solution was acidified with 240 mL of conc. HCl and extracted with 150 g of ethyl acetate. The ethyl acetate solution was washed once with 300 mL of tap water, clarified through diatomaceous earth, and stripped on a rotary evaporator at 10 mm pressure and 85°C. bath temperature. The weight of the product was 206.5 g, the liquid chromatograph area percent was 86%, and liquid chromatograph weight percent was 82%. The overall assay yield was 74%.

Example 1b:
Methylation of crude 2-Hydroxy-5-Methoxybenzaldehyde
The above crude oil (6.1 g, 81% assay, 0.33 moles), 25 mL of acetone, 6.8 g of potassium carbonate, and 5 g of dimethylsulfate was refluxed for 3 hours and drowned into 200 mL of water. The dark oil solidified overnight, and the product was collected by filtration and dried to yield 5.6 g of black solid (77% yield, 83% purity).

Example 1c:
Methylation of Distilled 2-Hydroxy-5-Methoxybenzaldehyde
The oil from **Example 1a** was distilled at 10 mmHg through a 6" Vigreaux column. A light yellow fraction boiling at 124-129°C was collected. The liquid chromatograph area percentage was 95% and the liquid chromatographic weight percentage was 90%. The overall assay yield based on the starting 4-methoxyphenol was 70%. The distilled oil was then converted to 2,5-dimethoxybenzaldehyde via the procedure in **Example 1b**. An 82% yield of light yellow crystals was obtained.

Example 2:
Isolation of the Potassium Salt of 2-Hydroxy-5-Methoxybenzaldehyde
The black oil from **Example 1a** (202 g, 82% assay, 1.1 moles) was dissolved in 900 g of acetone and the solution was cooled to 0-5°C and treated dropwise with 136 g of 45% potassium hydroxide solution, holding the temperature below 5°C. The resulting slurry of bright yellow solid was stirred 30 min and filtered. The product cake was washed with 750 g of cold acetone, and dried at room temperature in a nitrogen-purged oven. A total of 210 g of bright yellow product having a weight% assay of 91%, was obtained. The overall yield based on 4-methoxyphenol was 67%.

Example 4
Isolation of the Sodium Salt of 2-Hydroxy-5-Methoxybenzaldehyde
The black oil from **Example 1a** (45.9 g, 82% assay, 0.25 moles moles) was dissolved in 100 g of ethyl acetate and the solution was cooled to 0-5°C. and treated dropwise with 20 g of 50% sodium hydroxide solution, holding the temperature below 5°C. The resulting slurry of bright yellow solid was stirred 1 hour and filtered. The product cake was washed with 75 g of cold ethyl acetate, and dried at room temperature in a nitrogen-purged oven. A total of 39.1 g of bright yellow product, weight percent assay by HPLC of 72% (area % was 98.4) was obtained. The overall yield based on 4-methoxyphenol was 48%.

Example 5
Alkylation of the Potassium Salt in Acetone
A slurry of 21.7 g of the potassium salt (90 wt % assay, 0.103 moles), 100 mL of acetone, and 15 g (0.119 moles) of dimethyl sulfate was warmed to 35-40°C. and held at that temperature for 2 hours at which point an analysis by TLC indicated that the reaction was complete. The resulting slurry was drowned into 300 mL of water and the resulting light yellow crystals were filtered off, washed with water, and air-dried. The weight of product was 15.1 g (**88.3% yield**).

Example 7
Alkylation of the Potassium Salt in Isopropyl Alcohol
A slurry of 19.0 g of potassium salt (90 wt% assay, 0.09 moles), 65 g of isopropyl alcohol, 0.1 g of tetrabutylammonium bromide, and 13.9 g (0.11 moles) of dimethyl sulfate was warmed to 35-40°C. and held for 30 minute at which time an analysis by TLC indicated that the reaction was complete. The resulting slurry was treated with 65 g of water and the product slurry was cooled to 20°C. The product was collected by filtration and washed with 50% aqueous isopropyl alcohol, and dried. The product weight was 10.9 g (**70% yield**).

Example 8
Alkylation of the Sodium Salt in Acetone
A slurry of 7.87 g of sodium salt (73 wt% assay, 0.033 moles), 25 mL of acetone, and 5 g (0.04 moles) of dimethyl sulfate was refluxed for 3 hours at which time an analysis by TLC indicated that the reaction was complete. The resulting slurry was drowned into 200 mL of water and the resulting light yellow crystals were filtered off, washed with water, and air-dried. The weight of product was 5.1 g (**88.3% yield**).

2,5-DIHYDROXYBENZALDEHYDE (GENTISANALDEHYDE)

FROM 3-HYDROXYBENZALDEHYDE

Neubauer and Flatow[3] prepared 2,5-dihydroxybenzaldehyde by the oxidation of salicylaldehyde but the present method with *m*-hydroxybenzaldehyde as initial material gives an improved yield of a less crude product.

Gentisinaldehyde could not be obtained from 2-nitro-5-hydroxybenzaldehyde by reduction, diazotisation and decomposition of the azo-compounds. The latter could however be obtained in 30% yield.

EXPERIMENTAL[4]

A solution of *m*-hydroxybenzaldehyde (61 g) and NaOH (25 gr) in water (400 mL), while being vigorously stirred and kept at 30-35°C, is treated simultaneously from separate dropping funnels with aqueous solutions of potassium persulphate (150 gr in 1500 mL) and NaOH (200 mL, 40%), the additions being made during 90 min. at such rates that the mixture is always alkaline. After 36 hours of standing, the deep brown solution is rendered faintly acidic (Congo Red paper), and unchanged *m*-hydroxybenzaldehyde (31 g) is extracted with ether. The solution is then strongly acidified (350 mL of conc HCl) and heated slowly to 70°C, the dark brown amorphous precipitate which forms gradually, being filtered off (this substance, which chars above 330°C, is almost insoluble in all organic solvents, but readily soluble in aq. Na_2CO_3 - it contains the aldehyde group as shown by the formation of the p-nitrophenylhydrazone, and invariably constitutes about 40% of the yield). The 2,5-dihydroxybenzaldehyde is extracted from the filtrate by ether, ether removed by evaporation, and the residue extracted by benzene. Yield 13g, mp 89-92°C. This substance crystallises from benzene in bright yellow needles, but they still contain solvent. They rapidly effloresce at room temperature, leaving yellow needles, mp. 98-99°C.

2-ALKOXY-5-METHOXYBENZALDEHYDES FROM 2-HYDROXY-5-METHOXYBENZALDEHYDE[7]

A process for preparing 2-methoxy- and 2-ethoxy-5-methoxybenzaldehyde by alkylating 2-hydroxy-5-methoxybenzaldehyde with dimethyl- or diethyl sulfate in the pressence of potassium carbonate.

EXPERIMENTAL

Example 1

50 g of 2-hydroxy-5-methoxybenzaldehyde, 68 g of potassium carbonate and 50 g of dimethyl sulfate were refluxed in 250 mL of acetone for about 3 hours under stirring. After the reaction, the reaction mixture was filtered and the acetone was distilled off from the filtrate and then the residue was poured into 300 mL of water. The precipitated crystals were collected by filtration and dried whereby 45 g of 2,5-dimethoxybenzaldehyde having a melting point of 48°C were obtained (Yield: 82.5%).

Example 2

On standing the mixture of 2-hydroxy-5-methoxybenzaldehyde, potassium carbonate and dimethyl sulfate as in **Example 1** at room temperatures the reaction was completed in 7 days. This was confirmed by gas chromatography. By treating the reaction mixture as described in Example 1, 44.5 g of 2,5-dimethoxybenzaldehyde having a melting point of 47°C were obtained (Yield: 81.5%).

Example 4

By repeating the procedures described in **Example 1** except that 31 g of diethyl sulfate were used instead of 50 g of dimethyl sulfate, 53 g of 2-ethoxy-5-methoxybenzaldehyde having a melting point of 47-48°C were obtained (Yield: 97.5%).

2-HYDROXY-5-METHOXYBENZALDEHYDE TO 2,5-DIMETHOXYBENZALDEHYDE

Written by Antoncho

4,7 g of crude dark-brown 2-hydroxy-5-MeO-benzaldehyde obtained by Reimer-Tiemann formylation (steam-distilled) was placed into a 150ml three-necked RBF. There was added 25mls dioxane (undried, but kept over $FeSO_4$ to remove peroxides), 5g freshly fused potassium carbonate, 1ml MeOH (**Note 1**) and, at last, 2mls (4,6g = 25% molar xcess) methyl iodide. The central neck of the flask was fitted w/a condenser, one of the side-necks - w/a thermometer, and the 3rd one was plugged to bee later used for various tests and additions. The apparatus was flushed w/butane and all was brought to a very gentle reflux on a waterbath.

The temp, measured inside the boiling liquid, at first was ~77°C, increased to 85°C in ~30mins, and went up to 92°C over the next 3 hours. Boiling was cont'd overnight (**Note 2**)

An aliquot of the liquid was taken w/a syringe, acidified, evaporated under draught to remove carcinogenic dioxane and smelled. The specific smell of unreacted starting material was apparent, mixed w/a somewhat similar, but sweet, aroma of p-diMeO-benzene (**Note 3**).

So 0,7mls of MeI were added and reflux recommenced. After 4 hrs (internal temp 92°C) another test was taken which again indicated the presence of the starting material. Another 0.7 mls MeI were added and refluxed for several more hours; the third test revealed the completion of the rxn.

The rxn was flooded with 60 ml of 20% KOH, saturated w/NaCl and xtracted w/ 30+15 mls of IPA. Alcohol was separated, some 10g of Na_2SO_4 were added in a faint attempt of drying, followed by 90mls of saturated aq. metabisulfite. The mixtr was subjected to vigorous mech stirring for 7 min and the precipitate (which ended up in the alcohol layer) was filtered, washed twice with a lil IPA to almost completely remove yellow coloration (**Note 4**), pressed between filter paper and somewhat dried under draught. Still containing some IPA, it weighed 8.7g.

Thus obtained adduct was thrown into 50mls of pre-chilled in the freezer 20% KOH, stirred and left for 30 mins in warm water (**Note 5**). Precipitated aldehyde was filtered, washed with water 3 times, pressed between filters as dry as possible, chopped on a plate and left to air-dry. Still containing a little water, it was off-white, but still pretty, vanillin-like powder without any noticeable smell and weighed 3.6g (**Note 6**). After drying it was 2.7g.

NOTES:

1. Dioxane was chosen for the following reasons:
   - **a.** a much higher bp as compared to acetone
   - **b.** unreactivity towards the carbonyl group, which is a possible disadvantage of using acetone
   - **c.** ability to dissolve both MeI and, to some xtent, alkali.

   The rationale beehind addind MeOH was the following: K_2CO_3 reacts with it to form $KHCO_3$ and $KOCH_3$. The latter, being more soluble than K_2CO_3, was supposed to act as sort of a PTC. Unfortunately, it later turned out that SWiHKAL's MeOH was VERY wet (not to mention water in dioxane), so the effectiveness of this additive remains to bee researched. In any case, the two-fold amt of MeI that was required for the rxn, warrants further investigation. Probably, unhydrous conditions would bee better. Maybee, methanol shouldn't bee added at all - to minimize hydro/methanolysis of MeI, which is the major side rxn.
2. Probably, there is no need to reflux the mixture more than 30-60 min after the internal temp reached maximum. SWiHKAL just wanted to bee sure.
3. p-MeO-phenol is a major impurity contained in the hydroxyaldehyde isolated by steam-distillation from a RT formylation. It's hard to estimate, but there is quite a bit of it in there, probably not less than 20%.
4. This intensely colored yellow impurity is, probably, benzoquinone which survives all the transformations since its usage in methylation of hydroquinone. The next time SWiHKAL does that, he'll first try to remove it with bisulfite from the crude p-MeO-phenol.
5. SWiHKAL wanted to make sure all adduct decomposed. Since the appearance of the substance virtually doen't change, several tests were needed to confirm that. However, decomposition of the adduct seems to proceed fast even w/cold KOH.
6. The mp was measured and found to bee circa 45°C, whereas the lit value is 51°C. Could anyone suggest to what kind of (im)purity that corresponds?

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