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# The Synthesis of 2,3-Dimethoxy-5-methylbenzoquinone

Akira KASAHARA, Taeko IZUMI, and Hiroshi NAKAMURA

*Department of Applied Chemistry, Faculty of Engineering*

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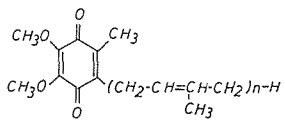
**Abstract**

2,3-Dimethoxy-5-methylbenzoquinone (**2**), the key intermediate of the synthesis of coenzyme Q, was synthesized from 2-hydroxy-5-methylbenzaldehyde or 2-hydroxy-5-methylacetophenone *via* the intermediate 2,3-dimethoxy-5-methylphenol (**3**), the oxidation of **3** to **2** being effected by potassium dichromate.

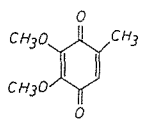
The oxidation of 2-bromo-3,4,5-trimethoxytoluene with $H_2O_2$-acetic acid led to the formation of 6-bromo-2.3-dimethoxy-5-methylbenzoquinone (**4**).

## Introduction

Coenzyme $Q_n$ (n= 1～10) (**1**),[1] the isoprenoid 2,3-dimethoxy-5-methylbenzoquinone, was first discovered in rat liver and heart muscle as coenzyme $Q_{10}$ in 1958 by Morton.[2] A subsequent research for other examples of this new class of isoprenoid benzoquinones revealed their wide-spread distribution in many kinds of animal tissue and bacteria.



(1)



(2)

Fig. 1

Coenzyme Q has been synthesized by the reaction of 2,3-dimethoxy-5-methylhydroquinone with polyprenyl alcohol, followed by the oxidation of the condensation product.[3,4] Moreover, the reactions of 2,3-dimethoxy-5-methylbenzoquinone (**2**)[5] or 6-bromo-2,3-dimethoxy-5-methylhydroquinone[5a,6] with 1,1-dimethyl-$\pi$-allylnickel (II) bromide led to the formation of **1**.

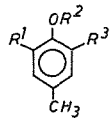
The quinone **2**: the key intermediate of the synthesis of coenzyme Q: was first prepared by Raistrick *et al.*[7] in the course of structural determination of fumigatin, a fungus metabolite, and thereafter several investigators have studied the synthesis of **2** from vanillin[8-12] and gallic acid.[12-15] In this report, we wish to describe a new method for the preparation of **2** *via* the intermediate 2,3-dimethoxy-5-methylphenol (**3**). Furthermore, a synthesis of 6-bromo-2,3-dimethoxy-5-methylbenzoquinone (**4**): the another key intermediate of the synthesis of **1**: will be described.

## Results and Discussion

It has previously been reported that the dry distillation of 3-hydroxy-4,5-dimethoxyphenylacetic acid (iridinic acid) led to the formation of **3**, and Tomita and Watanabe[17] also synthesized **3** from 2-methoxy-4-methylphenol in four steps. 2-Hydroxy-5-methylbenzaldehyde (**5**),[18] obtainable by the Reimer-Tiemann reaction of *p*-cresol, and bromine in acetic acid afforded 3-bromo-2-hydroxy-5-methylbenzaldehyde (**6**) in a good yield.[19] The reaction of **6** with cupric sulfate in aqueous sodium hydroxide solution gave 2,3-dihydroxy-5-methylbenzaldehde (**7**), which can be methylated with dimethyl sulfate to 2,3-dimethoxy-5-methylbenzaldehyde (**8**), in a moderate yield. Byck and Dawson[20] had previously reported the synthesis of **8** from vanillin in three steps. The Baeyer-Villiger oxidation of **8** with perbenzoic acid, and following hydrolysis of the product with aqueous sodium hydroxide solution led to the formation of **3** in a moderate yield, Moreover, the Baeyer-Villiger oxidation of **8** with peracetic acid afforded **2**, without the formation of **3**.

On the other hand, the bromination of 2-hydroxy-5-methylacetophenone (**9**) in acetic acid gave 3-bromo-2-hydroxy-5-methylacetophenone (**10**) in a quautitative yield. The reaction of **10** with cupric sulfate in aqueous sodium hydroxide solution afforded 2,3-dihydroxy-5-methylacetophenone (**11**) and a successive methylation of **11** with dimethyl sulfate led to the formation of 2,3-dimethoxy-5-methylacetophenone (**12**). The Baeyer-Villiger oxidation of **12** with peracetic acid and following hydrolysis of the product afforded **3**.

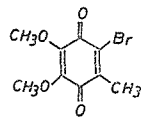
Finally, the **3** compound was oxidized with potassium dichromate and hydrochloric acid or with ferric chloride to afford the desired quinone **2** in a moderate yield: this quinone was identical in all respects with an authentic sample.



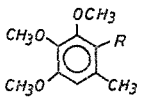
3: $R^1$ = OH, $R^2$ = $CH_3$, $R^3$ = $OCH_3$
5: $R^1$ = CHO, $R^2$ = H, $R^3$ = H
6: $R^1$ = CHO, $R^2$ = H, $R^3$ = Br
7: $R^1$ = CHO, $R^2$ = H, $R^3$ = OH
8: $R^1$ = CHO, $R^2$ = $CH_3$, $R^3$ = $OCH_3$
9: $R^1$ = $COCH_3$, $R^2$ = H, $R^3$ = H
10: $R^1$ = $COCH_3$, $R^2$ = H, $R^3$ = Br
11: $R^1$ = $COCH_3$, $R^2$ = H, $R^3$ = OH
12: $R^1$ = $COCH_3$, $R^2$ = $CH_3$, $R^3$ = $OCH_3$

Fig. 2

***Synthesis of 4.*** Sato *et al.*[6] had previously reported that the quinone 4 was prepared by the bromination of **2** in carbon tetrachloride. Herein, we wish to report a more convenient method for the synthesis of 4 from gallic acid. 3,4,5-trimethoxytoluene (**13**), prepared from gallic acid in four steps, and cupric bromide in methanol afforded 2-bromo-3,4,5-trimethoxytoluene (**14**) in 70% yield. An oxidation of **14** with hydrogen peroxide in acetic acid resulted in the formation of the quinone 4 in 38.5% yield.



(4)



13: R = H
14: R = Br

Fig. 3

## Experimental

*Materials and analysis.* All the melting points and boiling points are uncorrected. The 2-hydroxy-5-methylbenzaldehyde (**5**) was prepared by the Reimer-Tiemann reaction of *p*-cresol,[18] and the 2-hydroxy-5-methylacetophenone (**10**) was also synthesized by the Fries reaction of 4-methylphenyl acetate.[21] The 3,4,5-trimethoxytoluene (**13**) was prepared from gallic acid in four steps, according to the method described by Sugihara et al.[15]

The IR spectra were measured with a Hitachi model 215 grating spectrometer. The NMR spectra were taken in $CDCl_3$ with TMS as the standard and were recorded with a Hitachi R-22 spectrometer at 90 MHz. The mass spectra were obtained with a Hitachi RMU-6M mass spectrometer, using a direct inlet and an ionization energy of 70 eV.

*3-Bromo-2-hydroxy-5-methylbenzaldehyde* (**6**). In the presence of anhydrous sodium acetate (8.2 g, 100 mmol), bromine (16.0 g, 100 mmol) was added to

a solution of **5** (13.6 g, 100 mmol) in 100 ml of acetic acid. After stirring for 2 h at room temperature, the reaction mixture was added to 500 ml of water. The resultant precipitate was removed by filtration and was recrystallized from a mixture of benzene and hexane; to yield a product (18.7 g, 87% yield) mp 64～65 °C (lit.[19] mp 65 °C).

*2,3-Dihydroxy-5-methylbenzaldehyde* (**7**). The compound **6** (21.5 g, 100 mmol), hydrated cupric sulfate (25 g, 100 mmol), and 4 N sodium hyroxide (760 ml) were refluxed (105 °C) for 6.5 h with continuous stirring under a nitrogen atomosphere. After cooling to 50～60 °C, the mixture was filtered under suction and the residue was washed with hot water (3 ×100 ml). The alkaline solution was cooled to 10 °C and acidified to pH 3～4, by the dropwise addition of concentrated hydrochloric acid. During this addition the mixture was stirred continuously and the temperature maintained below 10 °C. The resulting mixture was extracted with ether. After being dried over anhydrous $MgSO_4$, the ether was removed to leave a dark gray product (4.2～6.3 g, 30～45%). Recrystallization from ethanol-$H_2O$ gave a pure product, mp 104～105 °C. IR: 3200 (OH), 2780 and 1660 (CHO), 1600, 1580, and 850 $cm^{-1}$ (aromatic ring). NMR: $\delta$ 2.31 (*s*, 3H, $CH_3$), 7.02 (*m*, 1H, aromatic H), 7.10 (*m*, 1H, aromatic H), 9.94 (*br s*, 2H, OH), and 10.98 *ppm* (*s*, 1H, CHO). MS: *m/e* 152 ($M^+$).
Found: C, 62.98; H, 5.21%. Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30%; mol wt, 152.

*2,3-Dimethony-5-methylbenzaldehyde* (**8**). The compound **7** (46.2 g, 330 mmol) was dissolved in a solution of potassium hydroxide (80 g) in water (175 ml), and a 100 ml of dimethyl sulfate was added dropwise under cooling. The solution was then refluxed for 3 h, cooled, diluted, and extracted with ether. The ether extracts were washed successively with 10% NaOH, 5% HCl, and water, and dried over anhydous $MgSO_4$. Evaporation of this ethereal solution left an oily product, which was purified by distillation yielding 44.8～51.0 g of a colorless oil, bp 103～105 °C/2 mm Hg, (76～85%). IR: 1710 (CHO), 1600, 1580, and 845 $cm^{-1}$ (aromatic ring). NMR: $\delta$ 2.34 (*s*, 3H, $CH_3$), 3.93 (*s*, 3H, $OCH_3$), 3.96 (*s*, 3H, $OCH_3$), 7.27 (*m*, 1H, aromatic H), 7.66 (*m*, 1H, aromatic H), and 10.30 *ppm* (*s*, 1H, CHO). MS: *m/e* 180 ($M^+$).
Found: C, 66.48; H, 6.63%. Calcd for $C_{10}H_{12}O_3$; C, 66.65; H, 6.71%; mol wt, 180.

*Baeyer-Villiger reaction of* **8** *with perbenzoic acid.* A chloroform (120 ml) solution containing 24 mmol of perbenzoic acid was added to a solution of the benzaldehyde **8** (3.6 g, 20 mmol) in chloroform (15 ml) at 0～5 °C. After stirring for 24 h in the dark at room temperature, the reaction mixture was then washed with aqueous sodium hydrogencarbonate, followed by a water wash. The chloroform solution was dried over anhydrous $MgSO_4$, and the solvent distilled.

The resulting residue was treated with 10% sodium hydroxide (50 ml) under reflux for 2.5 h. The aqueous alkali layer, after extractions with ether to remove non-hydrolyzed materials, was acidified with hydrochloric acid and extracted with ether. The ethereal extract was then dried and distilled to afford phenol **3** (1.56～1.63 g, 46～48%) ; bp 145～148 °C/1 mmHg, mp 55～57°C (benzene-hexane), (lit.[16] mp 57°C). IR: 3300, 1210 (OH), 1600, 1580, and 860 $cm^{-1}$ (aromatic ring). MMR: $\delta$ 2.31 (*s*, 3H, $CH_3$), 3.90 (*s*, 3H, $OCH_3$), 3.94 (*s*, 3H, $OCH_3$), 7.10 (*m*, 1H, aromatic H), 7.22 (*m*, 1H, aromatic H), and 9.88 *ppm* (*s*, 1H, OH). MS: *m/e* 168. Found: C, 64.41; H, 7.32%. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19%; mol wt, 168.

*Baeyer-Villiger oxidation of* **8** *with peracetic acid.* To 25 ml of an acetic acid solution of 0.9 M of peracetic acid, the benzaldehyde **8** (1.80 g, 10 mmol) and 1 ml of concentrated sulfuric acid were successively added at 0～5 °C. After the solution is allowed to stir for 30 h at room temperature, an aqueous 2% sodium hydroxide solution was added and the mixture was extracted with ether. The ethereal extract was dried over anhydrous $MgSO_4$ and concentrated to afford crude quinone **2**, which was then recrystallized from ethanol: mp 56～58°C (lit. mp 59°C,[7,8,15] 56～58°C,[22] 58～59°C,[12,13] 59～60°C,[10,14]). IR: 1670, 1655, 1640, 1605 cm.$^{-1}$ NMR: $\delta$ 2.02 (*d*, 3H, $CH_3$), 4.01 (*s*, 3H, $OCH_3$), 4.03 (*s*, 3H, $OCH_3$), and 6.58 *ppm* (*q*, 1H, C-H). MS: *m/e* 182 ($M^+$).
Found: C, 59.41; H, 5.46%. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53%; mol wt, 182.

*3-Bromo-2-hydroxy-5-methylacetophenone* (**10**). The reaction ef 2-hydroxy-5-methylacetophenone (**9**) (30 g, 200 mmol) with bromine (32 g, 200 mmol) in acetic acid (150 ml) in the presence of anhydrous sodium acetate (16 g, 200 mmol) afforded acetophenone **10** (yield 95%), mp 87～88°C, (lit.[23] mp 88°C).

*2,3-Dihydroxy-5-methylacetophenone* (**11**). The acetophenone **10** (22.9 g, 100 mmol), hydrated cupric sulfate (24.9 g, 100 mmol), and 4 N aqueous sodium hydroxide solution (760 ml) were refluxed (106°C) for 8 h with continuous stirring under nitrogen. As a result of a procedure similar to that used for the isolation of **7**, an ether extract was recrystallized from ethanol-$H_2O$ to afford the acetophenone **11** (13.7～15.6 g, 41～47%), mp 85～86°C. IR: 3100 (OH), 1640 (C=O), 1600, 1580, and 860 $cm^{-1}$ (aromatic ring). NMR: $\delta$ 2·28 (*s*, 3H, $CH_3$), 2.61 (*s*, 3H, $COCH_3$), 7.48 (*d*, 1H, aromatic H), 7.56 (*d*, 1H, aromatic H), and 9.89 (*s*, 1H, OH). MS: *m/e* 166 ($M^+$).
Found: C, 65.18; H, 6.21%. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%; mol wt, 166.

*2,3-Dimethoxy-5-methylacetophenone* (**12**). The acetophenone **11** (16.6 g, 100 mmol) in aqueous potassium hydroxide solution (KOH 24.4 g+$H_2O$ 60 ml) was heated under reflux with dimethyl sulfate (32 g, 250 mmol) for 3 h. After

an addition of water (300 ml), the mixture was extracted with ether. The ether extract was dried over anhydrous $MgSO_4$ and the solvent was distilled off. The residue was distilled in vacuo, bp 111～114 °C/3 mmHg, to afford **12** (14.5 g, 74%). IR: 1685 (C=O), 1600, 1580, and 865 $cm^{-1}$ (aromatic ring). NMR: $\delta$ 2.30 (*s*, 3H, $CH_3$), 2.61 (*s*, 3H, $COCH_3$), 3.92 (*s*, 6H, $OCH_3$), 6.99 (*d*, 1H, aromatic H), and 7.12 *ppm* (*d*, 1H, aromatic H). MS: *m/e* 194 ($M^+$). Found: C, 68.15; H, 7.14%. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27%; mol wt, 194.

*Baeyer-Villiger oxidation of* **12** *with peracetic acid.* To 20 ml of 0.9 M peracetic acid solution in acetic acid, the acetophenone **12** (1.94 g, 10 mml) and 1 ml of concentrated sulfuric acid were added successively at 0～5 °C. The reaction mixture was stirred for 30 h at room temperature in a dark and, after an addition of water (300 ml), was then extracted with ether. The ethereal extract was washed with 5% aqueous sodium hydrogencarbonate solution, followed by water wash, dried over anhydrous $MgSO_4$ and concentrated. The resulting residue was treated with 10% aqueous sodium hydroxide solution (50 ml) under reflux for 3 h. The aqueous alkali layer, after extraction with ether to remove non-hydrolyzed materials, was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was then washed with water, dried over anhydrous $MgSO_4$ and concentrated to afford crude phenol **3** (0.38 g, 22%): bp 140～142 °C/1 mmHg, mp 55～57 °C.

*Oxidation of phenol* **3** *to quinone* **2**. (a). To a solution of **3** (0.84 g, 5 mmol) in 5% aqueous sodium hydroxide solution (5 ml), were added a solution of potassium bichromate (0.735 g, 10 mmol) in water (50 ml) and the 1 N hydrochloric acid (20 ml). The mixture was stirred for 2 h before it was extracted with ether. The extracts were dried and freed of any solvent to afford quinone **2** (0.68 g, 75%); mp and mixed mp 57-58 °C.

(b). To the mixture of **3** (0.84 g), 3% aqueous hydrochloric acid (25 ml), and benzene (100 ml), hydrated ferric chloride (8.1 g) in water (10 ml) was added and the mixture was shaken for 4 h. The benzene layer was separated, dried over anhydrous magnesium sulfate and distilled to dryness *in vacuo*, leaving quinone **2** (0.36 g, 40%); mp 57-58 °C.

*2-Bromo-3,4,5-trimethoxytoluene* (**14**). A solution of **13** (18.2 g, 100 mol) and cupric bromide (44.6 g, 200 mmol) in methanol (100 ml) was boiled under reflux for 24 h. Methanol was removed by distillation and, after an addition of water (200 ml), the resulting mixture was extracted with ether. The ethereal extract was dried over anhydrous magnesium sulfate and concentrated to afford **14** (18.2 g, 70%), bp 107-110 °C/2 mmHg. IR: 1600, 1580, and 1480 $cm^{-1}$. NMR: $\delta$ 2.32 (*s*, 3H, $CH_3$), 3.84, 3.89, and 3.92 (each *s*, 3H, $-OCH_3$), and 6,65 ppm (*s*, 1H, aromatic H). MS: *m/e* 261 ($M^+$). Found: C, 45.83; H,

4.81%. Calcd for $C_{10}H_{13}BrO_3$: C, 45.97; H, 4.98%; mol wt, 261.

*5-Bromo-2,3-dimethoxy-6-methylbenzoquinone* (4). To a solution of **14** (4.30 g, 165 mmol) in 15 ml of acetic acid, 6 ml of 30% hydrogen peroxide and 2 drops of 10% sulfuric acid were added successively, and the mixture was stirred in a dark for 40 h at room temperature. After an addition of water (200 ml), the resulting mixture was extracted with ether. The ethereal extract was washed with water, 5% aqueous sodium hydrogencarbonate, and water, dried over anhydrous $MgSO_4$ and concentrated to afford crude quinone **4** (1.65 g, 38.3%), which was purified by column chromatography (benzene-silica gel), mp 72~74°C (lit.[6] mp 73~74°C). IR: 1660, 1650, 1620, 1600, and 1280 $cm^{-1}$. NMR: $\delta$ 2.20(*s*, 3H, $CH_3$), 4.04 (*s*, 3H, $OCH_3$), and 4.07 *ppm* (*s*, 3H, $OCH_3$). Found: C, 41.25; H, 3.68%. Calcd for $C_9H_9O_4Br$: C, 41.41; H, 3.47%.

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# 2,3-ジメトキシ-5-メチルベンゾキノンの合成

笠原　晃・泉　多恵子・中村　博

工学部　応用化学科

補酵素Q合成の重要な中間体である2,3-ジメトキシ-5-メチルベンゾキノン（2）は，2-ヒドロキシ-5-メチルベンツアルデヒド又は2-ヒドロキシ-5-メチルアセトフェノンを出発原料とし，2,3ジメトキシ-5-メチルフェノール（3）をへて合成した。3より2への反応は，3の重クロム酸カリウム酸化により行った。

一方，2-ブロム-3,4,5-トリメトキシトルエンの過酸化水素—酢酸による酸化は，補酵素Q合成のもう一つの中間体である6-ブロム-2,3-ジメトキシ-5-メチルベンゾキノン（4）を生じた。