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The Synthesis of 2,3-Dimethoxy-5-methyl-*p*-benzoquinone

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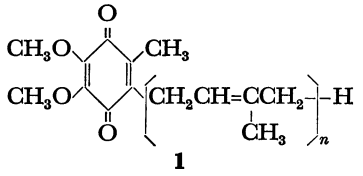
2,3-Dimethoxy-5-methylbenzoquinone, the key intermediate of the synthesis of coenzyme Q, was synthesized *via* two new routes. The methylation of 5-nitrovanillin gave 5-nitroveratraldehyde, which was then catalytically reduced to afford 5-aminohomoveratrol. The oxidation of 5-aminohomoveratrol gave 2,3-dimethoxy-5-methylbenzoquinone. 2,3,4-Trimethoxyphenol was obtained by the decarboxylation of 3,4,5-trimethoxysalicylic acid. This was converted *via* Mannich reaction to 2,3,4-trimethoxy-6-methylphenol, which was then easily oxidized to 2,3-dimethoxy-5-methylbenzoquinone.

Coenzyme Q_n (n=1—12) (**1**),[1] the 2,3-dimethoxy-5-methylbenzoquinone containing the unsaturated isoprenoid substituent in the 6-position, was first discovered in rat liver and heart muscle as coenzyme Q_{10} in 1958 by Morton *et al.*,[2] who used the designation "ubiquinone (50)."



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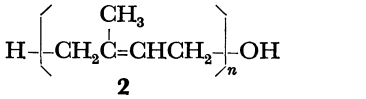
A subsequent search for other examples of this new class of isoprenoid benzoquinones revealed their widespread distribution in many kinds of animal tissue and bacteria.

Coenzyme Q has also been synthesized by the condensation of 2,3-dimethoxy-5-methylhydroquinone with polyprenyl alcohol (**2** or **3**), followed by the oxidation of the condensation product[3,4].



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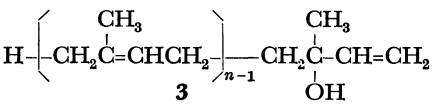

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Several investigators have studied the synthesis of 2,3-dimethoxy-5-methylbenzoquinone (**4**) from vanillin[5–9] and gallic acid.[10–12] The present paper will describe convenient methods for the preparation of **4**.

From 5-Nitrovanillin. Anslow *et al.*[5] synthesized **4** from vanillin in five steps. If the reduction of both formyl and nitro groups of nitrovanillin is achieved in the same stage, all the reaction steps are much shortened.

Anhydrous potassium salt of 5-nitrovanillin (**5**),[13]

1) For a review, see a) R. A. Morton, *Nature*, **182**, 1764 (1958); b) K. Folkers, C. H. Shunk, B. O. Linn, N. R. Trenner, D. E. Wolf, C. H. Hoffman, and A. C. Page, "Ciba Foundation Symposium on Quinones in Electron Transport," Churchill, London (1961), p. 100; c) K. Sato, T. Matsuura, and S. Inoue, *Yuki Gosei Kagaku Kyokai Shi*, **27**, 138 (1969).

2) G. N. Festenstein, F. W. Heaton, J. S. Lowe, and R. A. Morton, *Biochem. J.*, **59**, 558 (1955); J. C. Cain and R. A. Morton, *ibid.*, **60**, 274 (1955); F. W. Heaton, J. S. Lowe, and R. A. Morton, *J. Chem. Soc.*, **1956**, 4094.

3) U. Gloor, O. Isler, R. A. Morton, R. Ruegg, and O. Wiss, *Helv. Chim. Acta*, **41**, 2357 (1958).

4) C. H. Shunk, B. O. Linn, E. L. Wong, P. E. Wittreich, F. M. Robinson, and K. Folkers, *J. Amer. Chem. Soc.*, **80**, 4753 (1958).

5) W. K. Anslow, J. N. Ashley, and H. Raistrick, *J. Chem. Soc.*, **1938**, 439.

6) M. Shimizu and K. Koshi, *Chem. Pharm. Bull.* (Tokyo), **11**, 404 (1963).

7) M. Matsui and Y. Mori, Jap. 1963—17322, 17323, 21362, 22574 (1963).

8) L. Bláha and J. Weichet, *Coll. Czech. Chem. Commun.*, **30**, 2068 (1965).

9) L. M. Weinstock, R. Tull, B. Handelsmen, and E. F. Schoenewaldt, *J. Chem. Eng. Data*, **12**, 154 (1967).

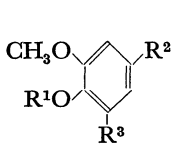
10) O. Isler, R. Ruegg, A. Rangemann, P. Schundel, G. Ryser, and J. Wursch, "Ciba Foundation Symposium on Quinones in Electron Transport" (*cf.* Ref. 1b), p. 82.

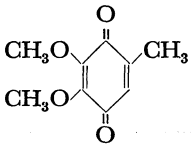
11) F. Hoffmann-La Roche Co., Brit. 889704 (1962); *Chem. Abstr.*, **57**, 4596 (1962).

12) E. A. Obol'nikova, O. I. Volkova, and G. I. Samokhvalov, *Zh. Obshch. Khim.*, **38**, 459 (1968).

13) K. H. Slotta and G. Szyszka, *Ber.*, **68**, 184 (1935).

obtainable from vanillin, and dimethyl sulfate in refluxing xylene afforded 5-nitroveratraldehyde (**6**) in a moderate yield. 5-Nitrocreosol has been reported to be easily methylated to 5-nitrohomoveratrol.[5] The presence of a formyl substituent in **5**, on the contrary, seems to diminish the reactivity of the O-methylation.





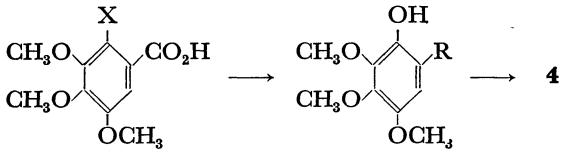
4

5, $R^1=H$, $R^2=CHO$, $R^3=NO_2$
6, $R^1=CH_3$, $R^2=CHO$, $R^3=NO_2$
7, $R^1=CH_3$, $R^2=CH_2OH$, $R^3=NH_2$
8, $R^1=CH_3$, $R^2=CH_3$, $R^3=NH_2$

The catalytic hydrogenation of **6** then gave 5-amino-3,4-dimethoxybenzyl alcohol (**7**), which could not be further reduced under the same reaction conditions because of the poisonous effects of the amino group on the catalyst. Therefore, the alcohol (**7**) was hydrogenated over palladium/charcoal in the form of its hydrochloride to afford **8**, which has been transformed to the quinone (**4**) by Anslow *et al.*[5]

From 3,4,5-Trimethoxysalicylic Acid. In 1956 Mayer and Fikentscher[14] found that 2-bromo-3,4,5-trimethoxybenzoic acid (**9**) underwent a relatively facile hydrolysis with the aid of cupric ions in an aqueous alkaline medium to give 3,4,5-trimethoxysalicylic acid (**10**). This acid (**10**) was then decarboxylated by heating in *N,N*-dimethylaniline to afford 2,3,4-trimethoxyphenol (**11**).

The transformation of **11** to 6-methyl-2,3,4-trimethoxyphenol (**13**) was successfully achieved by means of the Mannich reaction. When the phenol (**11**) was treated with dimethylamine and formaldehyde, the Mannich base, 6-(*N,N*-dimethylamino)methyl-2,3,4-trimethoxyphenol (**12a**), was obtained in a quantitative yield. The structure of this compound was apparent from its PMR spectrum, which had a singlet for the aminomethylene at δ 3.42, and another singlet at δ 2.26 for the aminomethyl groups, in the ratio of 1 : 3. The phenolic proton peak appeared far downfield at δ 8.90 because of hydrogen bonding with the amino-nitrogen. That the dimethylaminomethyl group was introduced at the *ortho* position to the hydroxy was also confirmed by the infrared spectrum, in which the O–H stretching absorption band was broadened and shifted to *ca.* 3000 cm^{-1} as a result of the chelation with the nitrogen atom. This Mannich base was then



9, X=Br
10, X=OH

11, R=H
12a, $R=CH_2N(CH_3)_2$
b, $R=CH_2SCN(CH_3)_2$ (S)
13, $R=CH_3$

subjected to hydrogenolysis in the presence of copper chromite to give **13** in a moderate yield.

On the other hand, recently Byck and Dawson[15] used a modified Mannich reaction in preparing 6-methylcatechol derivatives, where the methyl group was derived by the hydrogenolysis of the *N,N*-dimethyldithiocarbamoylmethyl group. When this procedure was applied to the present study, 6-(*N,N*-dimethyldithiocarbamoyl)methyl-2,3,4-trimethoxyphenol (**12b**), which had been obtained from **11**, gave **13** upon hydrogenolysis with Raney nickel W-7.

Finally, the phenol (**13**) was oxidized with potassium bichromate and hydrochloric acid to afford the desired quinone (**4**) quantitatively; this quinone was identica in all respects with an authentic material.

The former method of the synthesis of **4** has shorter reaction steps, but suffers from a low overall yield. On the other hand, the latter one consists of easily practicable reactions and **4** is obtained in a moderate overall yield.

Experimental

All the melting points and boiling points are uncorrected. The infrared (IR) spectra were recorded on a Hitachi EPI-S2 spectrophotometer as neat liquids or KBr pellets. The PMR spectra were obtained on a JEOL Model C-60 spectrometer in a carbon tetrachloride solution, with tetramethylsilane as the internal standard.

5-Nitroveratraldehyde (6). 5-Nitrovanillin (**5**)[13] was heated with an equivalent of 1N potassium hydroxide, and the resultant clear solution was allowed to cool. The precipitated material was collected and then dried at 110°C under reduced pressure. A mixture of well-dried 5-nitrovanillin potassium salt (6 g, 25.5 mmol), dimethyl sulfate (3.6 m*l*, 38.3 mmol), and xylene (60 m*l*) was stirred at 125°C for 8 hr. After the reaction mixture had then been cooled to room temperature, an aqueous 5% potassium hydroxide solution was added and the mixture was filtered. The ethereal extract of the filtrate was dried over anhydrous sodium sulfate and concentrated to afford crude 5-nitroveratraldehyde, which was then recrystallized from aqueous ethanol; mp 88—89°C (lit, mp 90—91°C).[13] Yield, 3.1 g (57%).

5-Amino-3,4-dimethoxybenzyl Alcohol (7). 5-Nitroveratraldehyde (**6**) (8 g, 37.8 mmol) was reduced in ethanol (45 m*l*) in the presence of 5% Pd/C (2 g) under a pressure of 100 atm of hydrogen at room temperature. The catalyst was then removed by filtration, and the solvent was distilled off. The distillation of the residual oil gave a pale brown liquid, bp 135°C/0.4 mmHg, which, on standing, gradually crystallized to colorless crystals. Yield, 4.35 g (63%); mp 64—65°C (from benzene—ligroin). IR: 3500, 3400, 1630, 1600, 1510, 1140, 1060, 840 cm^{-1}.

Found: C, 58.74; H, 7.51%. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15%.

5-Aminohomoveratrol (8). A solution of 5-amino-3,4-dimethoxybenzyl alcohol (**7**) (28 g, 0.153 mol) in methanol (250 m*l*) and concentrated hydrochloric acid (16 m*l*) was shaken with 5% Pd/C (8 g) under an atomospheric pressure of hydrogen. When the absorption of hydrogen ceased, a second crop of the catalyst (3 g) was added, after which the mixture was shaken further until hydrogen was no more absorbed. After the catalyst and solvent had then been removed, the

14) W. Mayer and R. Fikentscher, *Chem. Ber*, **89**, 511 (1956).

15) J. S. Byck and C. R. Dawson, *J. Org. Chem.*, **33**, 2451 (1968).

residue was dissolved in dilute aqueous potassium hydroxide (200 ml) and extracted with ether. The ethereal extract was dried over potassium hydroxide; the subsequent evaporation of the solvent and distillation afforded **8**; bp 90—95°C/0.3 mmHg. *Yield*, 8.2 g (32%). *N*-Acetyl derivative, mp 89°C (lit, mp 89°C).[16]

2,3,4-Trimethoxyphenol (11). 3,4,5-Trimethoxysalicylic acid (**10**)[14] monohydrate (20 g) was dissolved in dimethylaniline (60 ml) and heated under reflux with vigorous stirring. After the evolution of carbon dioxide had ceased, and aqueous sodium hydroxide solution was added to the reaction mixture and dimethylaniline was separated from the aqueous layer. The aqueous alkaline layer, after several extractions with ether, was carefully acidified with hydrochloric acid and extracted with ether. The ethereal extract was then dried and distilled to afford **11** (6.0 g, 46%); bp 141°C/15 mmHg; mp 40—40.5°C (methylene chloride). IR: 3400, 1480, 1090 cm^{-1}. PMR: δ 3,67. 3.78, 3.81 (CH_3O), 5.65 (OH), and 6.45 ppm (aromatic H).

Found: C, 58.88; H, 6.73%. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57%.

6-(N,N-Dimethylamino)methyl-2,3,4-trimethoxyphenol (12a). To a solution of **11** (5.08 g, 27.6 mmol) in ethanol (20 ml), cooled in an ice-water bath, we added 40% aq. dimethylamine (3.26 g, 29 mmol) and then, drop by drop, 37% formalin (2.32 g, 28.6 mmol). The mixture was allowed to stand overnight and then heated under a gentle reflux for 2 hr. The solvents were evaporated under reduced pressure, leaving an oily material (6.2 g, 93% yield) which was shown not to contain any detectable contaminants *via* PMR spectroscopy and thin-layer chromatography on silica gel; n_D^{20} 1.5287. IR: 3000 (broad), 1480, 1127, and 1087 cm^{-1}. PMR: δ 2.26 (NCH_3), 3.42 (CH_2), 3.62, 3.68, 3.73 (OCH_3), 6.00 (aromatic H), and 8.90 ppm (OH).

Found: C, 59.31; H, 7.97%. Calcd for $C_{12}H_{19}O_4N$: C, 59.73; H, 7.94%.

6-(N,N-Dimethyldithiocarbamoyl)methyl-2,3,4-trimethoxyphenol (12b). To a solution of **11** (3.68 g, 20 mmol) in ethanol (20 ml), were added carbon disulfide (1.68 g, 22.1 mmol), 37% formalin (1.68 g, 20.7 mmol), and 40% aq. dimethylamine (2.36 g, 21.0 mmol), successively in this order. After being allowed to stand overnight, the mixture was heated under reflux for 2 hr and then concentrated *in vacuo* to give a crystalline mass which was subsequently purified by column chromatography on silica gel; 4.75 g (75%); mp 86.5—87°C (MeOH). IR: 3350 (OH), 1495, 1468, and 1075 cm^{-1}. PMR: δ 3.45 (NCH_3), 3.77, 3.80, 3.92 (OCH_3), 4.47 (CH_2), 5.53 (OH), and 6.73 (aromatic H).

Found: C, 49.01; H, 6.12%. Calcd for $C_{13}H_{19}O_4NS_2$: C, 49.18; H, 6.03%.

6-Methyl-2,3,4-trimethoxyphenol (13). *(a)* A solution of 6.2 g of the Mannich base (**12a**) in 200 ml of dry dioxane was put into an autoclave and hydrogenated at 160°C for 4 hr in the presence of Cu-CrO (6.0 g), with an initial hydrogen pressure of 140 kg/cm^2. The filtreed solution was then concentrated *in vacuo*. The residual oil was dissolved in 3N HCl (26 ml), saturated with sodium sulfate, and extracted three times with ether. The extract was dried over calcium chloride and distilled to afford **13** (2.5 g, 45.6%); bp 96—97°C/0.35 mmHg; mp 25.6—26.7°C. IR: 3440 (OH), 1470, 1123, and 1080 cm^{-1}. PMR: δ 2.13 (CH_3), 3.72, 3.77, 3.87 (CH_3O), and 6.32 ppm (aromatic H).

Found: C, 60.45; H, 7.44%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

(b) A solution of **12b** (obtained from 3.68 g of **11**) in dry dioxane (120 ml) was refluxed for 16 hr with Raney nickel W-7, prepared from 36.8 g of a nickel aluminum alloy. The filtered solution was diluted with ether (100 ml) and acidified with dilute hydrochloric acid. Two layers were separated, and the aqueous layer was extracted with ether. The combined organic layer was dried over magnesium sulfate and distilled to give **13** (1,5 g. 38% based on the phenol **11**); bp 140°C/14 mmHg. The IR and PMR spectra and the retention time on glpc were all identical with those of the sample of (*a*).

2,3-Dimethoxy-5-methylbenzoquinone (4). *(a)* Aminohomoveratrol (**8**) was oxidized with sodium bichromate in dilute sulfuric acid, essentially according to the method of Anslow. The quinone (**4**) was thus obtained in 29% yield; mp 58—59°C (lit, mp 59°C).[5]

(b) To a solution of **13** (0.198 g, 1 mmol) in 5% sodium hydroxide (1 ml), were added a solution of potassium bichromate (0.147 g, 2 mmol) in water (10 ml) and then 1N hydrochloric acid (4 ml). The mixture was stirred for several minutes before it was extracted with ether. The extracts were dried and freed of any solvent to afford **4** (0.18 g, quantitative yield); mp and mixed mp 57—58°C.

The authors wish to express their gratitude to Mr. Takehiko Goshi for his capable technical assistance in these experiments.

16) L. Bláha and J. Weichet, Czech. 110938 (1964); *Chem. Abstr.*, **62**, 1601 (1965).