New Synthesis of 2,3-Dimethoxy-5-methyl-1,4-benzoquinone and Hexahydrocoenzyme Q_4 Chromanol

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A new efficient synthesis of 2,3-dimethoxy-5-methyl-1,4-benzoquinone ("coenzyme Q_0") from vanillin is reported. The conversion of this quinone to hexahydrocoenzyme Q_4 chromanol by a simple method is also described.

THE nuclear component of the coenzyme Q series (*10*), 5-methyl-2,3-dimethoxy-1,4-benzoquinone (VI, "coenzyme Q_0"), an important intermediate for the synthesis of these coenzyme analogs, was first synthesized in 7% yield from 2-methoxy-4-methylphenol (creosol) by Anslow, Ashley, and Raistrick (*1*) and more recently by Shimizu and Koshi (*5*) in 47% yield over ten steps from vanillin. Another synthesis from methyl trimethylgallate was reported, but no details were provided (*2*). The authors report here a new, improved five-step synthesis of this quinone from vanillin in 57% yield and a simple conversion of VI into hexahydrocoenzyme Q_4 chromanol (VII).

2-Nitro-3,4-dimethoxybenzaldehyde (III) prepared in two steps from vanillin acetate according to Pschorr and Sumuleanu (*4*) and MacDonald (*3*) was hydrogenated over 5% palladium-on-carbon in methanolic hydrogen chloride to produce 96% of 2,3-dimethoxy-6-methylaniline hydrochloride (IV). This amine, with both ortho positions blocked, was cleanly oxidized with potassium nitrosodisulfonate (*8*) in neutral aqueous phosphate buffer at room temperature giving the probable intermediate (V) (*9*), which on acidification with acetic acid yielded 95% of the para-quinone (VI).

The original synthesis employed the isomeric amine, 2,3-dimethoxy-5-methylaniline (VIII), which has an unsubstituted position ortho to the amine function. The authors found that oxidation of this amine with potassium nitrosodisulfonate gave, due to attendant ortho-quinone formation, a tarry mixture of products from which the para-quinone could be isolated in only 18% yield. Chromic acid oxidation of VIII as originally reported by Anslow, Ashley, and Raistrick (*1*) also proceeded poorly, providing crude VI in 30% yield.

Conversion of VI to hexahydrocoenzyme Q_4 chromanol (VII) (*6*) was accomplished in 82% yield by reduction with zinc in 98% formic acid followed by condensation of the resulting hydroquinone with phytol in the same solvent under reflux.

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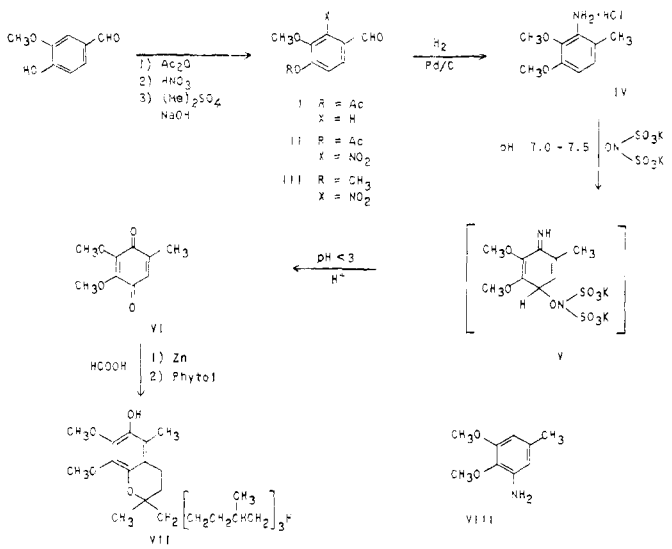

EXPERIMENTAL

2-Nitrovanillin Acetate (II). The nitration of vanillin acetate (*7*) by fuming nitric acid according to Pschorr and Sumuleanu (*4*) produced 75% of 2-nitrovanillin acetate, m.p. 83–85° C. (lit. m.p. 85–87° C.).

2-Nitro-3,4-dimethoxybenzaldehyde (III). The action of dimethylsulfate in aqueous alkali on II according to the procedure of MacDonald (*3*) formed 87% of 2-nitro-3,4-dimethoxybenzaldehyde, m.p. 60–63° C. (lit. m.p. 62–63° C.).

2,3-Dimethoxy-6-methylaniline Hydrochloride (IV). A solution of 2-nitro-3,4-dimethoxybenzaldehyde (21.1 grams, 0.1 mole) in methanol (320 ml.) and methanolic hydrogen chloride (82 ml., 1.7*N*, 0.14 mole) was hydrogenated over 5% palladium on charcoal (5 grams) under 3 atm. of hydrogen pressure. The exothermic reaction absorbed the theoretical amount of hydrogen (5 molar equivalents) within 1 hour. The catalyst was removed and the solvent evaporated in vacuo. The crystalline residue was flushed twice with ether (100 ml.) and filtered to yield 19.2 grams (95%, dried in vacuo at 50° C.) of 2,3-dimethoxy-6-methylaniline

hydrochloride, m.p. 235° C. with decomposition. Anal. Calcd. for $C_9H_{14}ClNO_2$ (203.6): C, 53.09; H, 6.93; Cl, 17.41; N, 6.88. Found: C, 53.29; H, 6.79; Cl, 17.71; N, 6.87.

2,3-Dimethoxy-5-methyl-1,4-benzoquinone (VI). A solution of potassium nitrosodisulfonate (6.0 grams, 0.022 mole) and disodium hydrogen phosphate (2.84 grams, 0.02 mole) in water (100 ml.) was mixed at 25° C. with a solution of 2,3-dimethoxy-6-methylaniline hydrochloride (2.03 grams, 0.01 mole) in water (20 ml.). After one-half hour the mixture was acidified with glacial acetic acid (4.0 ml.), stirred for an additional one-half hour, and extracted with methylene chloride. The dried ($MgSO_4$) extracts were evaporated in vacuo to an orange oil residue which rapidly crystallized. The yield of 2,3-dimethoxy-5-methyl-1,4-benzoquinone was 1.74 grams (95%), m.p. 55–57° C. A small sample was sublimed at 45° C. at 1 mm. giving the quinone with m.p. 59° C., λ_{max}^{MeOH} 264 mμ (ε 13,400), $\nu_{max}^{CCl_4}$ 1660, 1605, 1450, 1320, 1280, 1220, 1140, 1085, 885 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{10}O_4$ (182.2): C, 59.33; H, 5.53. Found: C, 59.49; H, 5.52.

Dimethoxy-5-methyl-1,4-benzoquinone was also prepared by the method of Anslow, Ashley, and Raistrick (*1*) in 7.3% over-all yield from 2-methoxy-4-methylphenol. Recrystallization from hexane gave a product, m.p. 55–57° C., exhibiting infrared and ultraviolet spectra identical to those of the quinone prepared above.

Oxidation of 0.01 mole 2,3-dimethoxy-5-methylaniline (VIII) with 0.022 mole potassium nitrosodisulfonate was carried out under the same conditions as those described above. The product obtained on acidification of the reaction mixture with acetic acid followed by methylene chloride extraction was a dark oil which could not be crystallized. Exhaustive extraction of this oil with hot hexane left a black tarry insoluble residue. Evaporation of the hexane extracts to dryness produced 0.327 grams (18%) of VI, m.p. 51–55° C. The infrared spectrum was identical with that of authentic 2,3-dimethoxy-5-methyl-1,4-benzoquinone.

Hexahydrocoenzyme Q_1 Chromanol (VII). A mixture of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (5.0 grams, 0.0275 mole), 98% formic acid (50 ml.), and zinc dust (0.2 grams) under nitrogen was stirred and heated to 85° C. at which point an exothermic reaction began. Heating was discontinued and external cooling applied as necessary to keep the temperature below 90° while additional zinc dust (4.8 grams) was added in small portions over a period of 15 minutes. Phytol (natural, redistilled, 16.2 grams, 0.0544 mole) was added and the mixture heated under reflux for 3 hours. The mixture was cooled to room temperature, diluted with methylene chloride (200 ml.), and filtered. The filtrate was washed twice with water (150 ml.), once with saturated aqueous sodium bicarbonate (200 ml.), dried ($MgSO_4$), and concentrated in vacuo to a viscous oil. This oil was dissolved in iso-octane (100 ml.) and chromatographed on a column of Florisil (300 grams). The column was first eluted with iso-octane (2.5 liters), and then the product was removed with 4 to 1 ethyl ether–iso-octane (3.0 liters). The ether-containing fractions were evaporated in vacuo to 13.0 grams of a viscous oil. Residual formate esters were saponified by treatment of a solution of this oil in anhydrous methanol (225 ml.) under nitrogen with a methanolic solution of sodium methoxide (6 ml. of 1.2*N*). After 5 minutes, glacial acetic acid (1.0 ml.) was added, the volatile components were evaporated in vacuo, and the oily residue was dissolved in iso-octane (200 ml.). This solution was washed twice with water (100 ml.), dried ($MgSO_4$), and concentrated in vacuo until it reached constant weight (12.75 grams) and was thoroughly degassed. Final purification was effected by short path distillation in a Hickman still, b.p. 155–160° C. at 10^{-2} mm. A viscous oil (10.42 grams, 82%), exhibiting infrared, ultraviolet, and NMR spectra identical with those of authentic hexahydrocoenzyme Q_1 chromanol (*6*), was obtained.

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