One-Electron Oxidation of a Naphthoquinol Monoacetate

Leon Hageman and Edward McNelis*

Department of Chemistry, New York University, New York, New York 10003

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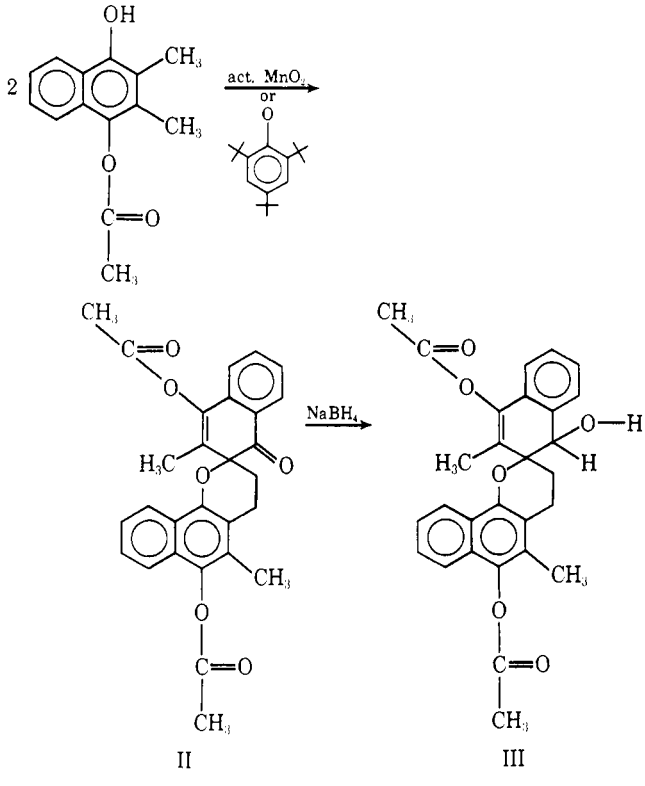
The oxidations of quinol monoesters have elicited interest owing to their possible relationship to oxidative phosphorylation, wherein the oxidative process generates a labile phosphoryl or acyl group suitable for anhydride formation. Several model reactions, wherein a quinol monoester was oxidized to an intermediate that contained the active precursor, were carried out with oxidants such as bromine,[1] periodic acid,[2] or high-potential quinones[3] such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in polar solvents. The mode of such oxidations were either clearly two-electron oxidations or one-electron oxidations followed by a heterolytic cleavage. We have sought to determine the products of a quinol monoacetate oxidation by mild one-electron oxidants.

The quinol ester, 2,3-dimethyl-1,4-naphthalenediol monoacetate (I), is a model for the Vitamin K series. It was stirred overnight in methylene chloride over activated manganese dioxide at room temperature. The yellow, glassy residue of this reaction was chromatographed on silica gel several times. The major component, whose crude yield was 70%, was assigned the structure II, 3,4-dihydro-3′,5-dimethyl-4′,6-dihydroxyspiro[2*H*-naphtho[1,2-*b*]pyran-2,2′-naphthalen-1′-one] diacetate, mp 148–150°. The infrared spectrum of II had carbonyl peaks at 1745 and 1690 cm^{-1}. The latter band was lacking in the reduction product III, which possessed a hydroxyl band at 3400 cm^{-1}. Whereas II did not volatilize in the mass spectrum, compound III (mp 184–185.5°) did do so to display a parent peak at 458, a molecular weight corresponding to oxidative dimerization. The same product II was obtained by the oxidation of I with the stable free radical, 2,4,6-tri-*tert*-butylphenoxyl.

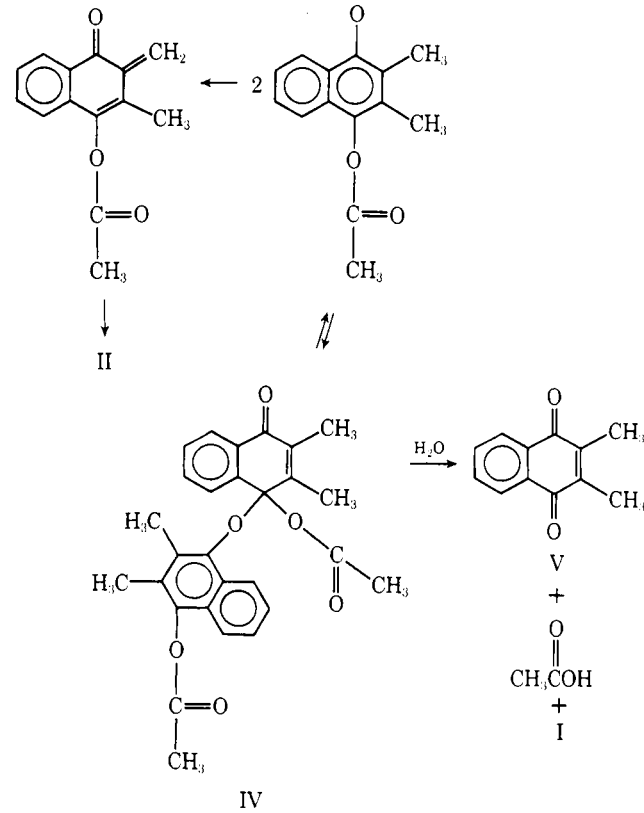


II III

In the nuclear magnetic resonance spectrum of II there are four methyl singlets at 2.48, 2.41, 2.18, and 1.98 ppm. In III the values for the methyl groups are 2.48, 2.34, 2.18, and 1.66 ppm. Since the 2.48 and 2.18 peaks did not shift, they are in an environment unaffected by the reduction. Hence, the former may be assigned to the methyl of the ester C-6 of the naphtho[1,2-*b*]pyran ring of II and the latter assigned to the methyl at the C-5 of that ring system. The values for the other ester methyl and vinyl methyl of the naphthalen-1′-one ring of II are then 2.41 and 1.98 ppm, respectively. Multiplets at 2.7 and 2.8 ppm can be assigned to the four pyran protons. In the aromatic region of both II and III there is a multiplet (1 H) at about 8.22 ppm which is reported to be characteristic of the C-10 hydrogen of such naphthopyran structures.[4] Since the neighboring unresolved doublet at 7.94 ppm (1 H) of II does not appear in the NMR of III, it can be assigned to the 8′ H in the naphthalen-1′-one system. A neighboring multiplet at 7.62 ppm (2 H) is assignable to the hydrogens at C-7 and C-5′, peri to the ester groups. The remaining four hydrogens can be assigned to the 7.16–7.53-ppm multiplet.

The structures II and III agree with the proposed mode of coupling for an *o*-quinone methide intermediate with carbon to carbon rather than oxygen to carbon coupling. Such couplings are common to related oxidations such as those of tocopherols,[5] 2,4-di-*tert*-butyl-6-methylphenol, and 4-substituted 2,6-dimethylphenols.[6] Although oxidations of these classes of compounds lead to trimers as well as dimers, we have no evidence for trimer formation in these oxidations of I.

In both oxidation reactions 2,3-dimethyl-1,4-naphthoquinone (V) was formed in 10–25% yields. This would be the expected product if coupling had proceeded to an active acetate species IV, which reacted subsequently with a nucleophile. Such a species could have formed, but in the nonpolar solvents and in the absence of any nucleophile save for the water of oxidation in the MnO_2 reaction it would have reverted to radicals which can also disproportionate to the *o*-quinone methide.



IV

With the knowledge of the behavior of I with mild one-electron oxidants we proceeded to the study of the oxidation of I with its parent quinone V. If this compound served as an oxidant, a reaction more akin to a biochemical event would be at hand. Such an oxidation would proceed through charge-transfer complexes to radicals, whose products would be either IV or another active acetate. When I and V were mixed in benzene or benzene–methanol, only starting materials were recovered. Evaporation of the benzene solution did afford a highly colored quinhydrone. Similar results were obtained with the duroquinone and 2,3-dimethyl-5,6-dimethoxy-1,4-benzoquinone and their respective hydroquinone monoacetates. Although addition of catalytic quantities of *p*-toluenesulfonic acid had no effect on these combinations, the presence of at least 1 mol of base leads to products currently under examination. These latter reaction are complicated by the base reactions of V[7] or duroquinone[8] to afford products formed by the Diels–Alder addition of *o*-quinone methides to quinones.

The high-potential quinone DDQ did react with I at room temperature in benzene to give a 1:1 adduct. This adduct formed principally II and reduced DDQ when it was treated with hot methanol or benzene solutions of 2,6-xylenol, mesidine, pyridine, or acetic acid.

Experimental Section

Materials were reagent grade and were purchased from the Aldrich Chemical Co. and the J. T. Baker Chemical Co. Elemental analyses were determined by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined on a Thomas-Hoover Unimelt apparatus, whose thermometer was checked periodically with melting point standards supplied by A. H. Thomas Co., Philadelphia, Pa. The following instruments were used: infrared, Perkin-Elmer Model 137; nuclear magnetic resonance, Varian Associates Model A-60; mass spectra, Varian Associates Model M-66. Thin layer chromatography was performed on precoated silica gel plates with uv indicator supplied by the Woelm Co.

2,3-Dimethyl-1,4-naphthalenediol Monocetate (I). A modified procedure of Wieland and Aguila was used.[9] To a stirred solution of 2.3 g of 2,3-dimethyl-1,4-naphthohydroquinone in 10 ml of pyridine was added a solution of 1.4 g of acetyl chloride in 10 ml of chloroform over a 15-min period. After being stirred for an additional 1 hr, the liquid was transferred to a separatory funnel. The solution was washed three times with 50-ml portions of 7% HCl. After being washed with water and dried over $MgSO_4$, the chloroform solution was evaporated to a brown solid, which was chromatographed on a silica gel column with chloroform as eluent. The middle fractions contained the monoester, which was recrystallized three times from hexane–benzene to give 0.487 g of white crystals: mp 152–153° (lit. mp 153–154°); mass spectrum (70 eV) *m/e* (rel intensity) 230 (7) and 187 (100); NMR (CCl_4) δ 7.83 (m, 1), 7.44 (m, 1), 7.26 (m, 2), 5.52 (m, 1), 2.50 (s, 3), 2.06 (s, 3), and 1.64 ppm (s, 3); ir (Nujol) 3450 (s), 1730 (s), 1600 (m), 1570 (w), 1490 (w), 1275–1200 (tr, vs), 1175 (m), 1090 (m), 1060 (s), 1020 (m), 975 (m), 910 (m), 860 (m), 810 (m), 770 cm^{-1} (s).

Oxidation of I with Activated Manganese Dioxide. A solution of 2.30 g of I in 175 ml of methylene chloride was stirred for 3 days at room temperature with 1.305 g of activated manganese dioxide (Beacon-Winthrop). The brown mixture was filtered twice and the solvent was evaporated. The yellow glassy residue weighed 2.39 g and was chromatographed on a silica gel column with chloroform as the initial solvent. A second 50-ml fraction containing 1.81 g was chromatographed further on a dry silica gel column with benzene–chloroform mixtures as eluents. The center fraction of 1.06 g was chromatographed on a preparative TLC plate. The midband of the plate was extracted and recrystallized from hexane–benzene, mp 148–150°. This material (II) could neither be sublimed nor volatilized in the mass spectrum: NMR ($CDCl_3$) δ 8.22 (m, 1), 7.94 (d, 1, J = 8), 7.62 (m, 2), 7.16–7.53 (m, 4), 2.70 (m, 2), 2.48 (s, 3), 2.41 (s, 3), (m, 2), 2.18 (s, 3), and 1.98 ppm (s, 3); ir (Nujol) 1745 (s), 1690 (s), 1660 (w), 1630 (w), 1590 (s), 1570 (m), 1350 (s), 1300 (m), 1260 (m), 1160–1200 (vs), 1120 (s), 1060 (s), 1030 (m), 1000 (m), 960 (m), 940 (m), 890 (s), 870 (m), and 760 cm^{-1} (s).

Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 74.65; H, 5.45.

Oxidation of I with 2,4,6-Tri-*tert*-butylphenoxyl. A 0.100-g sample of I was placed in an erlenmeyer flask equipped with magnetic stirrer and connected with an addition funnel and a sintered glass addition funnel upon which was mounted a third addition funnel. All funnels had side arms so that the entire system could be maintained under a slightly positive nitrogen pressure after evacuation of air. In the first funnel was 5 ml of benzene which was added to dissolve the monoester I. In the sintered glass funnel was a bed of 2.0 g of $NaBiO_3$, to which was added a solution of 2.0 g of 2,4,6-tri-*tert*-butylphenol in benzene. As the dark blue radical solution was added dropwise to the stirred monoester solution, the color was discharged. When the blue color persisted, addition was stopped and the mixture was stirred for an additional 90 min. The solvent was removed in vacuo with occasional warming on a steam bath. The residue of 0.32 g was washed with hexane. The hexane-soluble material weighed 0.196 g and was identified as 2,4,6-tri-*tert*-butylphenol by infrared spectra. The hexane-insoluble material (0.087 g) possessed the same ir spectrum as the product of the MnO_2 oxidation of I.

Reduction of Oxidation Product of I. Sodium borohydride was added in small portions to a solution of 0.100 g of compound II in 20 ml of methanol. (Compound II is stable in refluxing methanol.) The mixture was poured into a separatory funnel containing 125 ml of 2% HCl and was extracted with ether. Evaporation of the ether after a water wash and drying with $MgSO_4$ afforded 0.088 g of an off-white solid. Crystallization from hexane–benzene gave a white powder: mp 184–185.5°; mass spectrum (70 eV) *m/e* (rel intensity) 457 (5), 415 (10), 355 (10), 229 (20), 200 (15), 187 (100), and 171 (75); NMR ($CDCl_3$) δ 8.24 (m, 1), 7.64 (m, 2), 7.26–7.52 (m, 4), 7.12 (m, 1), 5.40 (d, 1, J = 3 Hz), 2.64–2.84 (m, 2), 2.56 (d, 1, J = 3 Hz), 2.48 (s, 3), 2.34 (s, 3), 2.18 (s, 3) 2.00 (m, 2), and 1.6 ppm (s, 3), ir (Nujol) 3300–3500 (tr, m), 1745 (s), 1600 (w), 1570 (w), 1160–1220 (tr, s), 1100 (m), 1050 (s), 1000 (m), 890 (m), and 760 cm^{-1} (s).

Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.71. Found: C, 73.35; H, 5.87.

Reaction of DDQ with I. To a solution of 0.100 g of I in 12 ml of benzene was added a solution of 0.100 g of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 8 ml of benzene. The mixture stood overnight. The precipitate was filtered and washed with benzene and methylene chloride. It weighed 0.191 g. It had no definite melting range and did not give a mass spectrum. No NMR spectrum was obtained owing to insolubility in CCl_4, $CDCl_3$, and C_6H_6 and decomposition in polar solvents such as CD_3COCD_3. The infrared spectrum (Nujol) was as follows: 3100–3300 (tr, m), 2240 (m), 1740 (s), 1660 (s), 1600 (m), 1550 (m), 1330 (m), 1280 (m), 1240 (s), 1200 (s), 1070 (w), 1030 (m), 990 (m), 960 (s), 890–920 (tr, s), 860 (s), 770 (s), 750 (s), and 715 cm^{-1} (s).

Anal. Calcd for $C_{22}H_{14}Cl_2N_2O_5$: C, 57.78; H, 3.09; N, 6.15. Found: C, 56.46; H, 3.17; N, 6.03.

A solution of 0.100 g of this adduct in 10 ml of methanol was heated on a steam bath for 25 min. After evaporation of the methanol, the residue was treated with benzene. The insoluble material weighed 0.031 g and displayed an ir spectrum identical with that of 2,3-dichloro-5,6-dicyano-1,4-hydroquinone. The benzene filtrate was evaporated to 0.050 g of a residue whose ir spectrum was almost identical with that of II. Similar products were obtained when benzene solutions of 2,6-xylenol, mesidine, pyridine, or acetic acid were used to treat the adduct.

Registry No.—I, 25181-86-6; II, 56292-32-1; III, 56292-33-2; V, 2197-57-1; 2,3-dimethyl-1,4-naphthohydroquinone, 38262-43-0; acetyl chloride, 75-36-5; manganese dioxide, 1313-13-9; 2,4,6-tri-*tert*-butylphenoxyl, 2525-39-5; DDQ, 84-58-2.

References and Notes

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