Notes

An Oxidative Degradation Approach to *p*-Quinones

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A large number of natural products containing the quinone functionality have shown useful chemotherapeutic activity.[1,2] As a result of the utility of these compounds, intense synthetic efforts have been directed toward the development of methods which would permit construction of quinones and on the regioselective introduction of functionality into quinones.[3]

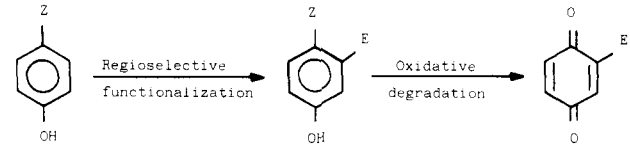
We have chosen to examine benzene and naphthalene ring systems substituted by functionality which would first serve as directing group for the regioselective introduction (specifically via metalation chemistry) of additional functionality and then be removed under oxidizing conditions to give a *p*-quinone group. The overall reaction sequence is illustrated in Scheme I.

Apparently none of the most commonly employed quinone precursors[4] appear to meet our demands. Consequently we turned our attention to the study of the oxidative degradation of *p*-hydroxybenzaldehydes and *p*-hydroxybenzoic acids[5] on the expectation that easily available derivatives of them (acetals, oxazolines, etc.) might be suitable substrates for our metalation[6] purposes.

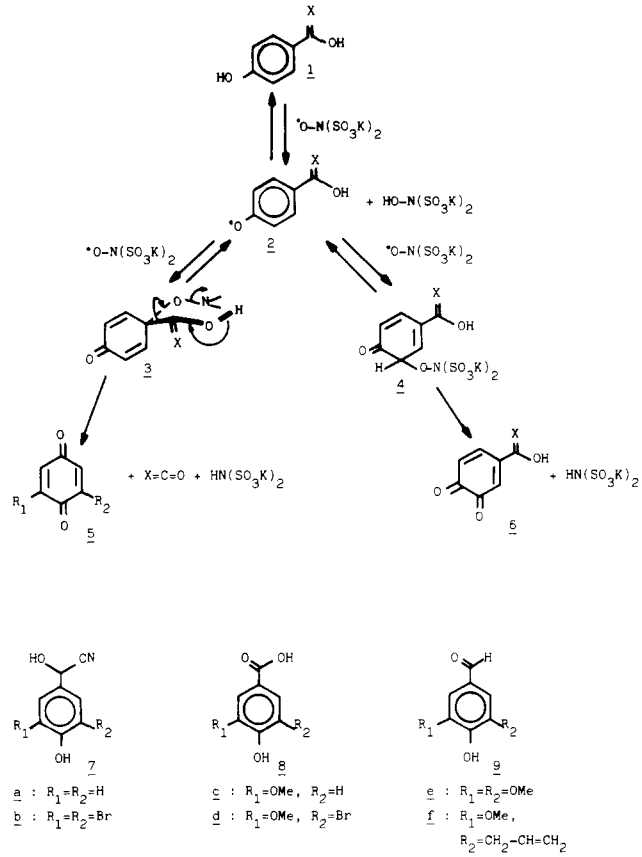
We would like now to report our first observations regarding the second objective of our plan, namely, the oxidative degradation approach to *p*-quinones, which originates on some interesting data reported back in the mid-century.

In particular, the present oxidative degradation approach to quinones has emerged from the rationalization of a series of unconnected reports related to the abnormal Fremy's salt[7] (F.S.) oxidation of some para-substituted phenols. Thus, on the one hand, Scandinavian workers[8] reported late in 1961 that *p*-hydroxy substituted benzyl alcohols underwent oxidative degradation by F.S. providing the corresponding 1,4-benzoquinones. On the other hand,

Scheme I



Scheme II



Teuber et al. in their pioneering studies with F.S. showed that *p*-hydroxybenzoic acid[9] was oxidized to 1,4-benzoquinone in low yield (ca. 5%), while syringic acid **8e**[10] gave 2,6-dimethoxy-1,4-benzoquinone on 98% yield. Interestingly, the action of reagents such as DDQ,[11] silver oxide,[12] potassium ferricyanide,[13,14] PbO_2,[14] or phenoxy radicals[13] on these type of substrates leads to dimers (diphenoquinones) or to side chain oxidation.[15]

Mechanistically the above results (F.S. oxidation) can be interpreted as ocurring through the well-known path-

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(5) This work has been presented in part at the 11th Reunión Bienal del Grupo de Química Orgánica de la RSEQ, Valladolid, Spain, Sept. 1985.
(6) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(7) Fremy's salt oxidation of para-substituted phenols generally provides the corresponding *p*-quinone system. There are, however, several exceptions; see the test and: Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229
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(10) Teuber, H. J.; Rau, W. *Chem. Ber.* **1953**, *86*, 1036. The $Pb(OAc)_4$ degradative oxidation of syringic acid **8e** to **4c** has also been published: Wesseley, F.; Kotlan, J. *Monatsh. Chem.* **1953**, 291.
(11) Becker, H. D.; Adler, E. *Acta Chem. Scand.* **1961**, *15*, 218.
(12) Pearl, I. A. *J. Org. Chem.* **1947**, *12*, 85.
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(15) To our knowledge only the PbO_2-mediated degradative oxidation of *p*-hydroxybenzaldehydes (but not benzoic acids) leads to the *p*-benzoquinone system. See ref 13 for the required conditions.

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Table I. Fremys's Salt Oxidative Degradation of Phenolic Substrates 7–10

entry	phenolic substrate (mmol)	reaction time	product (yield)
1	**7a** (1.34)[a]	18 h	**9a** (90%)[d]
2	**7b** (0.65)[a]	18 h	**9b** (60%)[d]
3	**7c** (1.67)[a]	45 min	**4c** (95%)
4	**7c** (20.1)[a]	75 min	**4c** (62%)
5	**7d** (1.16)[a]	60 min	**4d** (94%)
6	**7e** (1.00)[a]	15 min	**4e** (85%)
7	**8a** (3.62)	14 h	**4a** (5%)
8	**8b** (1.68)	14 h	**4b** (66%)
9	**8c** (2.97)	14 h	**4c** (76%)
10	**8c** (29.7)	16 h	**4c** (44%)
11	**8d** (2.02)	14 h	**4d** (95%)
12	**8d** (6.06)	14 h	**4d** (90%)
13	**8e** (2.52)	1 h	**4e** (95%)
14	**9b** (1.07)	10 h	**9b** (73%)[b]
15	**9c** (3.28)	16 h	**9c** (36%)[b]
16	**9d** (2.16)	10 h	**9d** (70%)[b]
17	**9e** (2.75)	2 h	**4e** (85%)
18	**9f** (1.56)	72 h	80:20[c] **4f**/**9f** (95%)
19	**9f** (4.68)	72 h	60:40[c] **4f**/**9f** (90%)
20	**10a** (0.9)	10 h	**11a** (85%)
21	**10b** (0.9)	9 h	**11b** (84%)

[a] Crude cyanohydrins employed usually contained small amounts (ca. 5%) of the aldehyde precursor. [b] Recovered starting material. [c] Determined by ^{1}H NMR. [d] Recovered aldehyde. Only traces of quinone detected by ^{1}H NMR.

way[16] for the F.S. oxidation of phenols (**1** → **2** → **3**), followed, in a late stage, by a chair-like transition state fragmentation (**3** → **5**) of the type shown[17] (Scheme II). Furthermore, this route apparently competes favorably with the alternative ortho coupling (**1** → **2** → **4**), which would eventually lead to nondegraded *p*-quinones **6**.

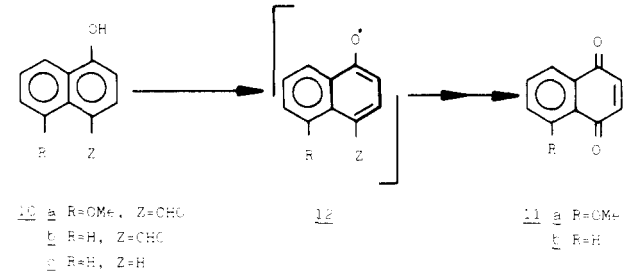
Thus, *p*-hydroxybenzyl alcohols, *p*-hydroxybenzoic acids **8**, p-hydroxybenzaldehydes **9** (via their cyanohydrins or hydrates) and related substances would also undergo F. S.-promoted oxidative degradation to give the corresponding 1,4-benzoquinones. A requirement[18] for these reactions to take place at a reasonable rate is that the substrate's redox potential should be lower than that of F.S.[19]

We first submitted cyanohydrins **7** to F.S. oxidation in a buffered[20] two-phase system (see Experimental Section). As expected the corresponding 1,4-benzoquinones **4** were obtained in good yields, except for **7a** and **7b** (Table I), which hydrolized back to the benzaldehyde stage at a higher rate than their oxidative degradation.

When the above reactions were scaled-up, somewhat lower yields were obtained (see entries 4, 10, 12, and 19.

p-Hydroxybenzoic acids **8** also underwent oxidative degradation by F.S. to 1,4-benzoquinones **4** in good yields (Table I). The rate of these oxidations were significantly lower than that of cyanohydrins **7** and were highly dependent on the number and type of substituents on the aromatic ring, as predicted by substituent effects on the redox potentials of phenols.[21]

Scheme III



p-Hydroxybenzaldehydes **9** that have appropriate redox potentials should also undergo oxidative degradation by F.S.[18] Hydration of the aldehyde residue could occur easily at the intermediate cyclohexadienone stage, thus providing the required functionality for the final fragmentation.

As shown in Table I our expectations proved correct. Thus, while *p*-hydroxybenzaldehyde (**9a**), vanillin (**9c**), and 5-bromovanillin (**9d**) were found to be almost unreactive (see entries 14–16), syringaldehyde (**9e**) and 5-allylvanillin (**9f**)[22] were converted into the corresponding benzoquinones **4e** and **4f**.

Further examples were tried in the naphthaldehyde series.[23] There is a powerful peri effect[24] operating for the Fremy's salt oxidation of 1-naphthols, so increasing amounts of 1,2-naphthoquinones are produced as a function of the steric hindrance of the substituent at C-5.

To our delight when naphthaldehyde (**10a**) (prepared according to Rapoport[25]) was treated as usual with F.S., juglone methyl ether (**11a**)[25] was obtained in 85% yield together with an unidentified minor byproduct (5%). Under the same conditions naphthaldehyde derivative **10b** gave 1,4-naphthoquinone (**11b**) (83% yield) (Scheme III).

We feel the later results are best explained by assuming that electron density at C-4 on the intermediate **12** (Z = CHO) is higher than at the alternative coupling site C-2, thus overwhelming steric factors which tend to inhibit coupling at C-4. Conversely, since electron densities at C-4 and C-2 in **12** (Z = H) should be much closer in value, the competition between equilibria leading to C-4 and C-2 coupled intermediates is mainly governed by steric factors. Obviously this speculative reasoning needs further theoretical as well as experimental support.

Apart from the mechanistic speculation, the direct or indirect oxidative degradation of *p*-hydroxybenzaldehydes and naphthaldehydes promoted by F.S. appears as a good alternative to the classic approach for the preparation of quinones from aromatic aldehydes, i.e., Dakin oxidation[26] followed by further oxidation of the resulting hydroquinones.[4]

In summary, *p*-hydroxybenzaldehydes, naphthaldehydes, and benzoic acids are highly promising *p*-quinone precursors. Presumably suitable derivatives of these type of compounds may be useful substrates for regioselective metalation and subsequent functionalization.

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(18) It has been stated that: "... *p*-hydroxybenzaldehydes, benzoic acids, (benzyloxy)phenols and nitrophenols are not attacked by Fremy's salt. Phenols and α-naphthols substituted at C-4 normally give orthoquinones....". See ref 4, page 30.

(19) The redox potential of Fremy's salt = 0.24 v. at pH 10 vs. SCE. P. N.; Balasubramanian, E. S. Gould, *Inorg. Chem.* **1983**, *22*, 1100 and references therein.

(20) Several buffer solutions were tried (pH 10, 7, and 6). The best results were found when working at pH 6.

(21) Fieser, L. S. J. *Am. Chem. Soc.* **1930**, *52*, 5204.

(22) Claisen, L.; Eisleb, O. *Ann.* **1913**, *401*, 112.

(23) To the best of our knowledge only one related precedent has been reported. See: Correa, J.; Romo, J. *Tetrahedron* **1966**, *22*, 685.

(24) Ishii, H.; Kanaoka, T.; Asaka, T.; Harada, Y.; Ikeda, N. *Tetrahedron*, **1976**, *32*, 2693 (1976). For some other examples where the peri effect operates, see: Achari, B.; Bandyopadhyay, S.; Basu, K.; Pakrashi, S. C. *Tetrahedron* **1985**, *41*, 107. Remers, W A.; Weiss, M. J. *J. Am. Chem. Soc.* **1966**, *88*, 804. Roth, R. H.; Remers, W. A.; Weiss, M. J. *J. Org. Chem.* **1966**, *31*, 1012. Eisenhuth, W.; Schmid, H. *Helv. Chim. Acta* **1958**, *41*, 2021.

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Further work along these lines is in progress.

Experimental Section

Melting points are uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrometer with KBr pellets unless otherwise stated. Proton NMR were obtained with a Varian CFT-80 apparatus with $CDCl_3$ as solvent and Me_4Si as internal standard. Mass spectra were recorded with a Kratos MS-25 or a Hewlett-Packard 5985 B instrument at a 70-eV ionizing energy.

All commercial phenols were directly used without purification. Cyanohydrins **7** were prepared according to the literature methods.[27] Allylvanillin (**9f**) was prepared as previously described.[22]

Sodium phosphate buffers (0.2 M, pH 6, 7, or 10) were prepared by the literature methods.[28]

General Procedure for Fremy's Salt Promoted Degradative Oxidation of 7–10. Fremy's salt was dissolved in 0.2 M sodium phosphate buffer (pH 6) to give a 0.3 M solution. This was then added to a 0.1 M solution of the phenolic substrate in either $CHCl_3$ or Et_2O. The resulting two-phase mixture was then vigorously stirred until the starting material disappeared (TLC). The organic phase was separated and the aqueous solution extracted, at least three times, with $CHCl_3$. The combined extracts were then washed with H_2O and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure usually led to a solid residue which crystallized as indicated.

4b: mp 128–129 °C (EtOH) (lit.[29] mp 130–131 °C); IR 1690, 1660 cm^{-1}; ^1H NMR 7.32 (s) ppm.

4c: mp 138–139 °C (H_2O) (lit.[30] mp 138–139 °C); IR 1675, 1650 cm^{-1}; ^1H NMR 3.85 (s, 3 H), 5.95 (s, 1 H), 6.72 (s, 2 H) ppm.

4d: mp 162–163 °C (lit.[31] mp 161–162 °C); IR 1680, 1640 cm^{-1}; ^1H NMR 3.85 (s, 3 H), 5.95 (d, 1 H, J = 2 Hz), 7.19 (d, 1 H, J = 2 Hz).

4e: mp 252–254 °C (C_6H_6) (lit.[32] mp 249 °C); IR 1690, 1640 cm^{-1}; ^1H NMR 3.82 (s, 6 H), 5.85 (s, 2 H).

4f: mp 80–82 °C (hexane) (lit.[33]); IR 3050, 1675, 1645 cm^{-1}; ^1H NMR 3.19 (dd, 2 H, J = 6.5, 1.2 Hz), 3.82 s, 3 H), 5.04–6.1 (m, 3 H), 5.88 (d, 1 H, J = 2.3 Hz), 6.50 (m, 1 H) ppm; MS, m/e (relative intensity) 178 (M^+, 21), 163 (46), 150 (11), 135 (24), 107 (29), 94 (85), 69 (100).

11a: mp. 182–183 °C (sublimed) (lit.[34] mp 184–186 °C); IR 1665, 1655 cm^{-1}; ^1H NMR 4.00 (s, 3 H), 6.86 (s, 2 H), 7.24–7.74 (m, 3 H) ppm; MS, m/e relative intensity 188 (M^+, 100), 159 (21).

11b: mp 128–130 °C (sublimed) (lit.[35] mp 128 °C); IR 1660 cm^{-1}; ^1H NMR 6.97 (s, 2 H), 8.15–7.69 (m, 4 H) ppm.

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Registry No. **5a**, 106-51-4; **5b**, 19643-45-9; **5c**, 2880-58-2; **5d**, 23030-47-9; **5e**, 530-55-2; **5f**, 31788-37-1; **7a**, 13093-65-7; **7b**, 104266-79-7; **7c**, 33630-46-5; **7d**, 54246-09-2; **7e**, 102742-10-9; **8a**, 99-96-7; **8b**, 3337-62-0; **8c**, 121-34-6; **8d**, 6324-52-3; **8e**, 530-57-4; **9a**, 123-08-0; **9b**, 2973-77-5; **9e**, 134-96-3; **9f**, 20240-58-8; **10a**, 69833-14-3; **10b**, 7770-45-8; **11a**, 4923-61-9; **11b**, 130-15-4; $(KSO_3)_2NO$, 14293-70-0.

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2,2,2-Triphenyl-4,5-(2′,2″-biphenylene)-1,3,2-dioxaphospholane: An Effective Reagent for Converting Diols, Amino Alcohols, and Especially Mercapto Alcohols to the Corresponding Heterocycles

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The successful application of diethoxytriphenylphosphorane [$Ph_3P(OEt)_2$; DTPP] for cyclodehydration[1,2] and oxidative cleavage[3] of diols to cyclic ethers and ketones, respectively, prompted an investigation to determine the efficiency with which DTPP would effect cyclodehydration of α,ω-mercapto alcohols to cyclic sulfides.[4] We subsequently established that in cases where the rates of DTPP-promoted chain closure of mercapto alcohols to cyclic sulfides are low, the rates of competitive S-ethylations affording the ethyl thio alcohols dominate the course of the reaction.[4]

Our choice of 2,2,2-triphenyl-4,5-(2′,2″-biphenylene)-1,3,2-dioxaphospholene (TDP)[5] as a cyclodehydrating reagent especially for α,ω-mercapto alcohols reflects an attempt to eliminate competitive S-alkylations, a process which impedes the desired ring closure reaction using DTPP. With TDP, the competitive side reaction involving thiolate displacement of triphenylphosphine oxide (TPPO) would require thiolate attack on an sp^2 carbon which should be energetically prohibitive.

TDP, arising from the equivalent of a concerted [4 + 2] cycloaddition of phenanthrenequinone and triphenylphosphine (70 °C),[6] is hydrolytically labile but otherwise quite stable in dry toluene solvent. The ^{13}C and ^{31}P (δ −16.8 in toluene) NMR parameters[7] are consistent with the expected structure and the ^{31}P NMR shift corroborates that previously reported by Ramirez et al. (δ −15.6).[5a]

TDP is best prepared and used under an argon or nitrogen atmosphere since exposure to oxygen slowly leads to formation of TPPO and phenanthrenequinone 1.[9] Presumably, a retro [4 + 2] collapse of TDP, followed by slow oxidation of triphenylphosphine with molecular oxygen adequately accounts for this observation. One further note may be useful. 1,2-Dihydroquinone **2** is immediately

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(7) The ^{13}P NMR shift for TDP is solvent and phase dependent: ^{31}P δ −16.45 in benzene-d_6, δ −16.05 in $CDCl_3$, and δ −1.5 in the solid state.[8]

(8) Dennis, L. W.; Bartuska, V. J.; Maciel, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 230–235.

(9) (a) We have determined using ^{13}C and ^{31}P NMR that TDP slowly reacts with molecular oxygen (40 °C, 80 h) to afford triphenylphosphine oxide and phenanthrenequinone. (b) Buckler has also shown that triphenylphosphine reacts slowly with molecular oxygen affording TPPO in benzene solvent. See: Buckler, S. A. *J. Am. Chem. Soc.* **1962**, *84*, 3093.

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