3.96 (s, 3 H), 3.13 (dd, 1 H, J = 8.0 Hz, J = 6.0 Hz), 2.57 (dd, 1 H, J = 8.0 Hz, J = 8.0 Hz), 1.97 (t, 3 H, J = 2.0 Hz), 1.30 (t, 3 H, J = 7.0 Hz); IR (film) 2980 (m), 1800 (s), 1765 (s), 1690 (s), 1445 (m), 1380 (m), 1255 (s), 1220 (s), 1105 (m), 1045 (m), 740 (m) cm^{-1}; MS, m/z (relative intensity) 270.1 (M^+ - 45, 1.3) 139.1 (43.1), 125.1 (33.0), 111.1 (1.8), 97.1 (100); high-resolution mass spectrum, m/z 270.0611, calcd for $C_{11}H_{12}NO_7$ m/z 270.0613.

Pyrrolidinone 40. With the general FVT procedure at 35 V, 89.1 mg of compound **38** gave 55.1 mg of the crude product **40**. This crude product was chromatographed on silica gel (1:3 hexanes-ethyl acetate) to afford 22.1 mg of pure **40** (32.6%): TLC (1:3 hexanes-ethyl acetate) R_f 0.22; ^1H NMR ($CDCl_3$, NT-300) δ 6.49 (d, 1 H, J = 1.0 Hz), 5.92 (d, 1 H, J = 1.0 Hz), 5.11 (td, 1 H, J = 6.0 Hz, J = 1.0 Hz), 4.96 (d, 1 H, J = 3.0 Hz), 4.48 (d, 1 H, J = 18.0 Hz), 4.27-4.15 (m, 2 H), 3.60 (d, 1 H, 3.60 (d, 1 H, J = 18.0 Hz), 2.97-2.78 (7, 2 H), 1.29 (t, 3 H, J = 7.2 Hz); IR (CH_2Cl_2) 2940 (m), 1775 (s), 1745 (s), 1715 (s), 1430 (m), 1410 (m), 1380 (m), 1220 (s), 1130 (m), 1045 (m) cm^{-1}; MS, m/z (relative intensity) 239.1 (M^+, 8.3), 197.1 (25.0), 167.1 (10.1), 166.0 (100), 138.1 (14.1); high-resolution mass spectrum, m/z 239.0793, calcd for $C_{11}H_{13}NO_5$ m/z 239.0794.

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Effects of Halogen Substitution on Reactions of *o*-Quinol Acetates with Isopropylmagnesium Bromide and Diisopropylmagnesium. Competition between Unimolecular Decomposition and Bimolecular Reactions of Radical Anions

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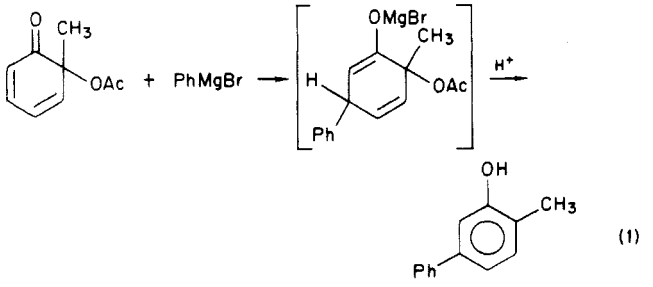
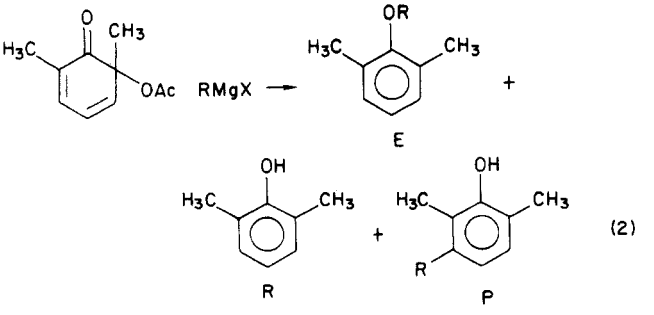
When a single methyl substituent at C-2 or C-4 of an *o*-quinol acetate (1) is replaced by a halogen atom, a greatly decreased yield of the corresponding 3-isopropylphenol is obtained from reaction of 1 with isopropylmagnesium bromide. Replacement of a second methyl group by halogen results in a marked *increase* in the yield of the 3-isopropylphenol. Essentially identical product distributions are obtained from reactions of halogenated *o*-quinol acetates with concentrated and dilute Grignard solutions and with diisopropylmagnesium, in contrast to reactions with halogen-free *o*-quinol acetates. Reactions with hexadeuterioisopropylmagnesium bromide gave reduction products bearing increasing percentages of deuterium at C-3 as the number of bromines on the rings of the ω-quinol acetates increased. These data are consistent with reactions of halogenated *o*-quinol acetates, in contrast to those of halogen-free analogues, proceeding solely by SET processes. The reactions of halogen-stabilized radical anions with isopropyl radicals compete with decomposition of the radical anions to phenoxy radicals.

Three decades ago, F. Wessely and his co-workers at the University of Vienna reported that alkyl or aryl groups can be introduced at positions meta to the hydroxy groups of phenols by reacting *o*-quinol acetates (6-acetoxy-2,4-cyclohexa-2,4-dien-1-ones) with Grignard reagents (e.g., eq. 1).[1]



(1)

Our research group later demonstrated that the synthetic utility of this process is largely limited to the introduction of aryl or primary alkyl groups. The reactions of *o*-quinol acetates with secondary or tertiary Grignard reagents,[2] or with benzylic Grignards,[2,3] yielded alkyl aryl ethers E and reduction products (the parent phenols R) as the principal products. *m*-Alkylphenols P were obtained in significant yields when secondary alkyl Grignards were employed but were only trace products from reactions of *o*-quinol acetates with tertiary or benzylic Grignards. Products resulting from 1,2-addition to the carbonyl groups were obtained in significant yields from reactions with



(2)

(1) (a) Wessely, F.; Holzer, L.; Vilcsek, H. *Monatsh. Chem.* **1952**, *83*, 1253. (b) Wessely, F.; Kotlan, J. *Ibid.* **1953**, *84*, 124. (c) Wessely, F.; Holzer, L.; Langer, F.; Schinzel, E.; Vilcsek, H. *Ibid.* **1955**, *86*, 831. (d) Wessely, F.; Zbiral, E. *Justus Liebigs Ann. Chem.* **1957**, *605*, 98. (e) Wessely, F.; Leitich, J. *Monatsh. Chem.* **1961**, *92*, 1004.

(2) (a) Miller, B. *J. Am. Chem. Soc.* **1973**, *95*, 8458; (b) *J. Org. Chem.* **1977**, *42*, 1402.

(3) Miller, B. *J. Org. Chem.* **1977**, *42*, 1408.

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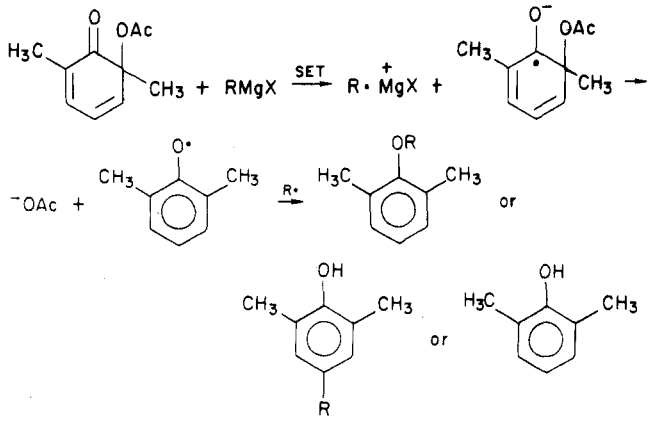
Scheme I



primary Grignards but were very minor products from reactions with more substituted Grignards. Finally, when the C-4 positions of the *o*-quinol acetates were unsubstituted, small yields were obtained of phenols substituted at the para positions with alkyl or benzyl groups from the Grignard reagents.[2,3]

On the basis of reactions of Grignard reagents with *o*-quinol acetates bearing only alkyl substituents on the rings, we have proposed[2-4] that *m*-alkylphenols P, as well as products of 1,2-addition, are formed by typical polar additions of the Grignard reagents to the unsaturated carbonyl systems. The ethers and reduction products E and R in contrast, appear to be formed by processes involving single-electron transfer (SET) as the initial steps. The radical anions resulting from SET can lose acetate anions to yield phenoxy radicals, which may combine with alkyl radicals to form alkyl aryl ethers and para-substituted phenols (when substitutions at the para position are possible) as well as form reduction products by disproportionation with alkyl radicals. This mechanism is outlined in Scheme I.

Several lines of evidence support the dual polar and SET mechanisms outlined above. First, products of conjugate and direct addition to the unsaturated carbonyl system predominate in reactions with primary alkyl and aryl Grignards, which have relatively high oxidation potentials, while ethers E and reduction products R predominate in reactions with Grignards with lower oxidation potentials.[2] In reactions with benzylic Grignards, yields of *m*-benzylphenols increase with increases in the Hammett σ values of substituents on the benzyl groups.[3] In contrast, the ratios of yields of *p*-benzylphenols to aryl benzyl ethers are essentially independent of the nature of the substituents.[3] Reactions with dialkylmagnesium reagents, which should be better electron donors than the corresponding Grignard reagents, yield much higher proportions of E and R, and much lower proportions of P, than do reactions with the Grignards.[4] However, the relative yields of the three major products are strongly dependent on the concentrations of the Grignard reagents. Very dilute Grignard solutions yield much higher proportions of E and R than do more concentrated solutions. It has been suggested that this phenomenon can be explained by the relatively high proportion of dialkylmagnesiums present (from the Schlenk equilibrium) in dilute Grignard solutions.[4] However, it is also possible that monomeric Grignards are intrinsically better electron donors than the more associated forms found in concentrated solutions.[5]

While the effects of variations in structures of Grignard reagents on their reactions with *o*-quinol acetates appear to be reasonably well understood, little information is available about the effects of substituents on the *o*-quinol acetates (other than fairly obvious steric effects of the alkyl substituents employed in previous studies). This paper reports the results of an investigation of the effects of halogen substitution on reactions of *o*-quinol acetates with isopropylmagnesium bromide.[6]

Methods and Results

A series of 2- and 4-halo-6-acetoxy-6-methylcyclohexa-2,4-dien-1-ones (**1a–f**) was prepared by reaction of the corresponding phenols with lead tetraacetate.[7,8] In addition, the 2,4,6-trimethyl-3,5-dibromo derivative **1g** was prepared. One compound missing from the series is 2-chloro-4,6-dimethylcyclohexa-2,4-dien-1-one, which could neither be crystallized nor obtained pure by column chromatography.

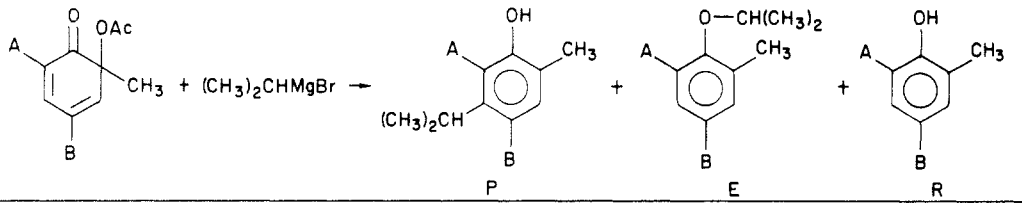
Each *o*-quinol acetate (in ether solution) was added to stirred solutions containing 10–15 mol equiv of isopropylmagnesium bromide, prepared from magnesium of better than 99.999% purity. The Grignard solutions were 0.55 M before addition of the *o*-quinol acetate solutions, which were $^1/_{10}$ the volume of the Grignard solutions. Thus, the concentrations of the Grignards in the reaction mixtures were ca. 0.5 M.[9] Each reaction was then repeated employing a different preparation of the Grignard solution.

All reactions were quite clean, yielding only three significant products in each case. These products were isolated by GLPC and identified as isopropyl aryl ethers E, parent phenols R of the *o*-quinol acetates, and *m*-isopropylphenols P. Only one of the two possible *m*-isopropylphenols was obtained (in each case) from reactions with **1d–f**. The product from reaction with **1d** was readily identified as 2-bromo-3-isopropyl-4,6-dimethylphenol—the product of 1,4-addition at C-3 rather than 1,6-addition at C-5—since the low-field hydrogen absorptions at δ 7.1 which is present in the spectrum of 2-bromo-4,6-dimethylphenol (and of its isopropyl ether) was missing in the spectrum of the product. The spectra of the *m*-alkylphenols from the 2,4-dihalogenated *o*-quinol acetates **1e** and **1f**, in contrast, although indicative of attack at C-3, were not unambiguous. Irradiation of the methyl peaks in the spectra of the *m*-alkylphenols from reactions with **1e** and **1f**, however, resulted in constriction of the aromatic protons from broad and jagged signals to very sharp singlets, indicating that the aromatic protons were ortho to the methyl groups. Similar irradiation of the parent phenols resulted, as expected, in sharpening of the high-field aromatic peaks but had little effects on the low-field peaks, confirming that only hydrogens ortho to the methyls were affected by irradiation of the methyl groups.

The yields of products obtained from reactions of isopropylmagnesium bromide with **1a–g** are summarized in Table I. It will be seen that yields of the reduction products R increase consistently with increasing halogen substitution or with replacement of chlorine by bromine. Yields of E appear to be relatively unaffected by monohalogen substitution but drop very sharply on dihalogen substitution, while yields of P drop on monohalogen substitution but (except for the 3,5-dibromo derivative, which yields no P) rise again on dihalogen substitution to percentages close to those obtained from the halogen-free *o*-quinol acetate **1a**!

(4) (a) Miller, B.; Matjeka, E. R.; Haggerty, J. G. *Tetrahedron Lett.* **1977**, 323; (b) *J. Org. Chem.* **1984**, *49*, 3121.
(5) E.g.: Walker, F.; Ashby, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 3945.
(6) A preliminary report of this work has been published: Miller, B.; Haggerty, J. G. *J. Chem. Soc., Chem. Commun.* **1984**, 1617.
(7) Budzikiewicz, H.; Schmidt, G.; Stockhammer, P.; Wessely, F. *Monatsh. Chem.* **1959**, *90*, 609.
(8) Metlesics, W.; Schinzel, E.; Vilcsek, H.; Wessely, F. *Monatsh. Chem.* **1957**, *88*, 1069.
(9) Solutions of **1f** were slightly more dilute. See Experimental Section.

Table I. Reactions of *o*-Quinol Acetates with 0.5 M Isopropylmagnesium Bromide



o-quinol acetate	reaction products (mol %) P	E	R	mol % E/mol % R
1a, A = B = CH_3[a]	23.5 ± 0.6	40.7 ± 0.4	34.4 ± 0.5	1.18
1b, A = CH_3; B = Cl	12.5 ± 1.0	43.5 ± 0.7	43.9 ± 0.9	0.99
1c, A = CH_3; B = Br	10.2 ± 0.2	42.1 ± 1.1	47.9 ± 0.8	0.88
1d, A = Br; B = CH_3	14.8 ± 1.1	32.2 ± 0.3	53.1 ± 1.0	0.61
1e, A = B = Cl	25.8 ± 0.8	11.1 ± 0.4	63.5 ± 0.5	0.18
1f, A = B = Br	19.9 ± 0.8	8.0 ± 0.1	72.3 ± 0.4	0.11
1g, A = B = CH_3[b,c]	0	27.7 ± 3.6	72.4 ± 3.7	0.38

[a] Data from ref 4b. [b] *o*-Quinol Acetate **1g** and its products are substituted with bromine atoms at C-3 and C-5. [c] Grignard concentration was ca. 0.46 M.

Table II. Reactions of *o*-Quinol Acetates with Diisopropylmagnesium and Dilute (0.05 M) Isopropylmagnesium Bromide Solutions

o-quinol acetate	reagent	reaction products (mol %) P	E	R	mol % E/ mol % R	mol % P/ mol % E
1a	$[(CH_3)_2CH]_2Mg$[a,b]	2.18 ± 1.1	49.5 ± 1	49.4 ± 1	1.0	0.044
	$(CH_3)_2CHMgBr$[b]	6.1	54.0	38.8	1.39	0.11
1b	$[(CH_3)_2CH]_2Mg$[a]	10.5	41.5	48.1	0.86	0.25
	$(CH_3)_2CHMgBr$	13.0	43.1	44.0	0.98	0.30
1c	$[(CH_3)_2CH]_2Mg$[a]	9.1	37.3	53.6	0.70	0.24
	$(CH_3)_2CHMgBr$	12.1	39.9	48.0	0.83	0.30
1f	$[(CH_3)_2CH]_2Mg$[a]	16.3	6.3	77.4	0.08	2.6
	$(CH_3)_2CHMgBr$	19.8	8.3	71.9	0.12	2.4

[a] Solvent was diethyl ether–dioxane (70:30 v/v). [b] Data from ref 4b.

Table III. Reactions of *o*-Quinol Acetates with 0.5 M 1,1,1,3,3,3-Hexadeuterioisopropylmagnesium Bromide

o-quinol acetate	reaction products (mol %) P	E	R	mol % E/mol %R	mol % P/mol % E	% D at C-3 of R
1a	25.2	55.5	19.3	2.9	0.45	1 ± 3
1c	22.4	49.7	28.5	1.7	0.45	(13 ± 4)[a]
1f	34.4	20.4	43.3	0.47	1.7	22 ± 2

[a] The value reported is twice the measured value, 6.5 ± 2%, of total hydrogen at C-3 and C-5.

The reactions of several of the *o*-quinol acetates (**1b**, **1c**, and **1f**) were repeated employing a much more dilute (0.05 M) Grignard solution. In contrast to the previously reported reactions of *o*-quinol acetate **1a**,[4] reactions with the dilute Grignard solution gave product distributions which, in all three cases, were almost identical with those obtained from the concentrated solution (Table II). Similarly, the massive decrease in yield of P which resulted from reaction of **1a** with diisopropylmagnesium rather than the Grignard reagent was not paralleled in reactions with **1b**, **1c**, or **1f**. The results obtained with diisopropylmagnesium are not directly comparable to those from reaction with the Grignard, since reactions with the dialkylmagnesium were carried out in 70:30 diethyl ether–dioxane solutions rather than in pure diethyl ether. Nonetheless, inspection of Table II shows that use of diisopropylmagnesium in place of the Grignard causes only slight changes in the reaction products. The yields of R are slightly increased, as has been previously observed for reaction with **1a**,[4] but the P/E ratios from reaction with isopropylmagnesium bromide and diisopropylmagnesium are quite similar.

To help elucidate the mechanisms of reactions leading to E, R, and P, *o*-quinol acetates **1a**, **1c**, and **1f**, containing zero, one, and two bromine atoms, respectively, were reacted with solutions of 1,1,1,3,3,3-hexadeuterioisopropylmagnesium bromide (Table III). In all three cases the yields of reduction product R decreased, as would be expected of a process involving hydrogen transfer. Interestingly, however, the yield of the *m*-isopropylphenol P from **1a** was essentially unchanged from that obtained from reaction with the undeuterated Grignard, while the yields of P from reactions witth **1d** and **1g** were appreciably increased.

The deuterium content at C-3 of the reduction product R from each reaction was determined from its ^1H NMR spectrum. Whereas the product from **1a** incorporated no deuterium, within experimental error, the reduction products from **1c** and **1f** showed significantly lower aromatic proton content than did the phenols from which **1c** and **1f** were initially prepared. In the 2,4-dibromo-6-methylphenol from **1f** the deterium content was clearly located at C-3. The protons at C-3 and C-5 in 4-bromo-2,6-dimethylphenol cannot be distinguished, but, by analogy with the reaction of **1f**, it is postulated that deuterium incorporation takes place only at C-3 of **1c**. The percentage of deuterium incorporation at that position, therefore, is considered to be twice the measured percent deuterium incorporation at C-3 and C-5.

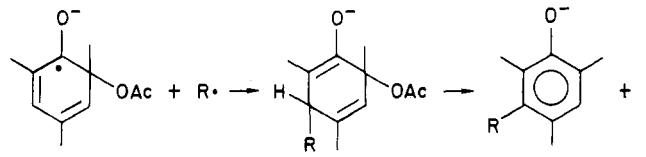
Discussion

The results outlined in Tables I–III provide appreciable information about the mechanisms of the reactions of isopropylmagnesium bromide with *o*-quinol acetates.

The fact that changing by a factor of 10 the Grignard concentrations employed in reactions with halogenated *o*-quinol acetates or substituting diisopropylmagnesium for the Grignard causes little change in the product ratios contrasts sharply with the results of similar changes in

reactions with the halogen-free *o*-quinol acetate **1a**. The marked decrease in the yield of P from the latter reaction resulting from dilution of the Grignard reagent, and the even more marked decrease resulting from substitution of diisopropylmagnesium for the Grignard was explained on the grounds that formation of P resulted largely from a polar addition process, whereas formation of E and R resulted principally from SET.[4] The absence of similar effects from reactions with halogenated *o*-quinol acetates suggests that only SET processes occur with these substrates. (The alternative possibility that only polar processes occur does not provide a mechanism to account for formation of aryl isopropyl ethers.)

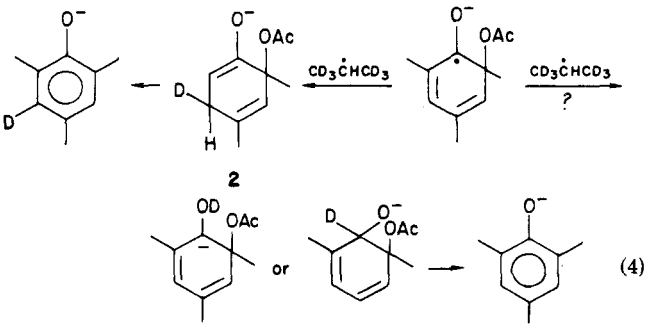
Since *m*-alkylphenols are formed from reactions of Grignard or magnesium reagents with halogenated *o*-quinol acetates, there must be a mechanism for their formation other than by a polar conjugate-addition process. Combination of the radical anion and isopropyl radicals initially formed by SET (eq 3) provides such a path. The possibility of mechanisms of this type has been previously proposed,[2b] but no evidence for their existence was obtained in reactions of halogen-free *o*-quinol acetates.



(3)

The hypothesis that *m*-isopropylphenols P can be formed by reactions of isopropyl radicals with radical anions is supported by the fact that reactions of **1c** and **1f** with the deuterated Grignard reagent result in appreciably increased yields of P compared to reactions with the undeuterated Grignard, whereas reaction with **1a** gives an essentially unchanged yield of P (Table III). The latter observation is consistent with the hypothesis that formation of P from **1a** occurs via a process (polar conjugate addition) which is independent of the SET processes leading to E and R and is thus unaffected by deuterium substitution (except for secondary isotope effects). In contrast, the rates of formation of P from **1c** and **1f** are strongly affected by deuterium substitution on the Grignard, and formation of P must therefore follow electron transfer.

In earlier work little evidence was obtained about the mechanisms by which Grignard reagents or dialkylmagnesiums reduce *o*-quinol acetates to their parent phenols. One reasonable path is by disproportionation between isopropyl radicals and phenoxy radicals, but an alternative possibility is disproportionation between isopropyl radicals and radical anions. In principle reactions of isopropyl radicals with the radical anions might proceed by transfer of hydrogen to oxygen atoms, to carbonyl carbons, or to C-3 or C-5 of the *o*-quinol acetate rings (eq 4). The first two possibilities seem unlikely, since they would result in formation of anions of comparatively high energy. Since loss of acetic acid to yield phenols would eliminate any deuterium acquired in those processes, no direct evidence exists to confirm or deny their existence. However, reaction with the deuterium-labeled Grignard shows that hydrogen transfer to C-3 of **1f** does occur and that a minimum of 25% (and possibly much more) of R from that reaction is formed in this manner. Unfortunately, it is impossible to estimate the actual yield of R formed by this process, since loss of deuterated acetic acid from the intermediate anion **2** may reduce the deuterium content of the phenolic product. The relative amounts of hydrogen and deuterium lost from C-3 would probably depend on whether the deuterium were cis or trans to the acetoxy group in **2** and, unless loss of acetic acid were entirely stereospecific, on the deuterium isotope effect for loss of acetic acid, and neither the isotope effect nor the geometry of **2** is known. Nonetheless, the fact that an appreciable amount of deuterium is retained at C-3 in the reduction product from **1f** suggests that the absence of any deuterium at C-5 in that molecule is not the result of complete loss of any deuterium introduced at that position but results from the lack of any transfer of deuterium there. The absence of any reaction at C-5 may be due to steric effects, or to an intrinsic preference for hydrogen transfer to the interior of the radical chain.



Because of the possible loss of deuterium from intermediates in formation of R, it cannot conclusively be stated that the percentage of R formed via disproportionation of radical anions increases with increasing numbers of bromine atoms. However, that appears to be the simplest interpretation of the data.

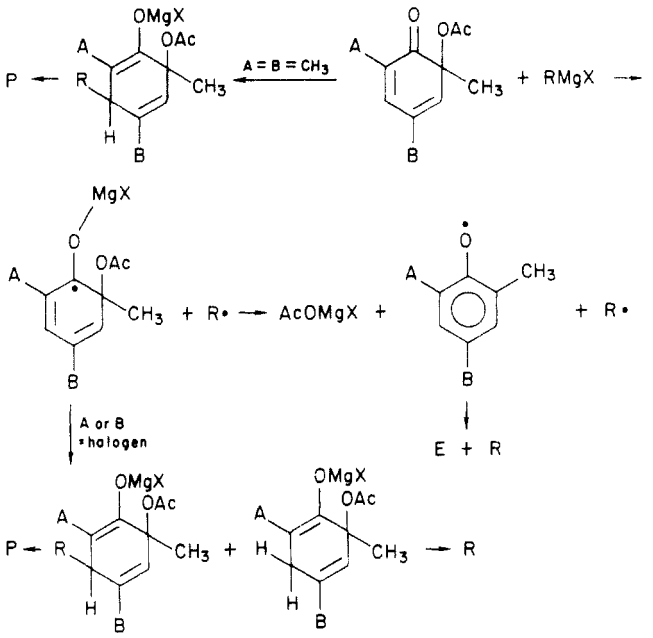
The rates of decomposition of the radical anions from *o*-quinol acetates should be directly related to the degree of halogen substitution. Each replacement of a methyl group by an electronegative halogen atom should decrease the rate of loss of acetate anion and thus increase the lifetime of the radical anion. The longer the lifetime of the radical anion, the greater is the opportunity provided for an isopropyl radical to react with the radical anion, rather than with the phenoxy radical formed from the radical anion. The percentages of deuterium incorporation shown in Table III are consistent with this picture.

On the basis of the mechanisms outlined above, we can account for perhaps the most surprising results of our work—the observation that yields of *m*-isopropylphenols decrease markedly on substitution of a halogen atom for a methyl group but then increase just as markedly on substitution of a second halogen for another methyl group. Substitution of a single halogen atom for a methyl group of an *o*-quinol acetate eliminates the polar addition process and thus results in the observed sharp reduction in the yields of P. The radical anions resulting from SET to monohalo-*o*-quinol acetates lose acetate anions relatively rapidly, thereby forming phenoxy radicals which are not intermediates in the formation of P. Substitution of a second halogen atom results in formation of a longer lived radical anion and thus allows a greater opportunity for formation of P via the SET process.

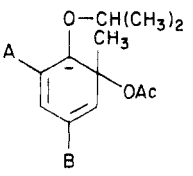
The results of substitution with chlorine and bromine are basically similar. However, the larger size of the bromine atom favors hydrogen transfer (disproportionation) rather than radical combination at C-3. Thus, substitution with bromine rather than chlorine results in formation of higher yields of R in proportion to P.

Finally, formation of aryl isopropyl ethers E seems likely to proceed entirely by combination of isopropyl and phenoxy radicals, since formation of an isopropoxy group

Scheme II



at the radical anion stage would form a high energy anion (3) rather than an enolate anion. It follows that the less



3

stable the radical anion, the higher the expected ratio of E to R. Indeed, this turns out to be the case (Table I).

The proposed mechanisms (Scheme II) for the reactions of *o*-quinol acetates with Grignard reagents thus account for the ways in which the product distributions vary with halogen substitution. As previously suggested, *o*-quinol acetates having only alkyl substituents on the ring form P by a polar addition mechanism, simultaneously undergoing a competing SET process. The radical anion resulting from SET is short-lived and rapidly decomposes to form phenoxy radicals, which react with isopropyl radicals to form E and R. Halogen-substituted *o*-quinol acetates react solely by initial SET. These processes form longer lived radical anions, in which loss of acetate anions to form phenoxy radicals compete with reactions with isopropyl radicals, yielding P and R.

Experimental Section

General. Purifications of solvents and preparations of solutions of isopropylmagnesium bromide and diisopropylmagnesium were carried out as previously described.[4b] GLPC and spectroscopic data were collected as previously described.

4-Chloro-2,6-dimethylphenol,[10a] 4-bromo-2,6-dimethylphenol,[10a] 2-bromo-4,6-dimethylphenol,[10b] 2,4-dibromo-6-methylphenol,[11] and 2,4-dichloro-6-methylphenol[12] were prepared as described in the literature.

3,5-Dibromo-2,4,6-trimethylphenol was prepared by slowly adding 24.0 g (0.15 mol) of bromine to a stirred solution of 2,4,6-trimethylanisole (10.7 g, 0.071 mol) in 200 mL of glacial acetic acid which was shielded from light. The reaction mixture was stirred for 1 h, ca. 1 L of water was added, and the mixture wa extracted several times with methylene chloride. The combined organic layers were washed with 0.1% sodium bisulfite and with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated to give a brown solid, which was recrystallized three times from ethanol to yield 10.21 g (0.032 mol, 45%) of 3,5-dibromo-2,4,6-trimethylphenyl methyl ether as white crystals, mp 75–77 °C. That product was refluxed for 60 h in a solution of 20.8 mL of 48% hydrobromic acid in 25 mL of acetic acid. The solution was cooled to room temperature, and the black solid which precipitated was recrystallized from mixed hexanes to yield 3,5-dibromo-2,4,6-trimethylphenol as pale yellow needles, mp 156–157.5 °C (reported, mp 158–159 °C[13]).

Preparation of *o*-Quinol Acetates. *o*-Quinol acetates **1b–g** were synthesized by reaction of the appropriate phenols with pastes of lead tetraacetate in either chloroform[7] or acetic acid[8] and recrystallized (if crystalline) from hexane, in some cases after chromatography on activity III alumina, eluting with mixed hexanes.

Prepared by reaction in chloroform were the following:

6-Acetoxy-4-chloro-2,6-dimethylcyclohexa-2,4-dien-1-one (1b): mp 82–84 °C; 49% yield. Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17. Found: C, 55.94; H, 5.13. ^{1}H NMR δ 1.33 (s, 3 H), 1.95 (d, J = 1 Hz, 3 H), 2.02 (s, 3 H), 6.05 (d, J = 2 Hz, 1 H), 6.70 (m, 1 H); IR 1745, 1680, 1639 cm^{-1}.

6-Acetoxy-4-bromo-2,6-dimethylcyclohexa-2,4-dien-1-one (1c): mp 77–78.5 °C; 50% yield. Anal. Calcd for $C_{10}H_{11}BrO_3$: C, 46.35; H, 4.28. Found: C, 46.60, H, 4.30. IR 1745, 1678, 1640 cm^{-1}; ^{1}H NMR δ 1.34 (s, 3 H), 1.93 (d, J = 1 Hz, 3 H), 2.00 (s, 3 H), 6.30 (d, J = 1 Hz, 1 H), 6.78 (m, 1 H).

6-Acetoxy-3,5-dibromo-2,4,6-trimethylcyclohexa-2,4-dien-1-one (1g): mp 86–88 °C; 38% yield. Anal. Calcd for $C_{11}H_{12}Br_2O_3$: C, 37.53; H, 3.44; Br, 45.40. Found: C, 37.45; H, 3.88; Br, 46.13. IR 1745, 1675, 1640 cm^{-1}; ^{1}H NMR δ 1.40 (s, 3 H), 2.06 (s, 6 H), 2.34 (s, 3 H).

Prepared by reaction in acetic acid were the following:

6-Acetoxy-2,4-dichloro-6-methylcyclohexa-2,4-dien-1-one (1e): mp 87–88.5 °C; 41% yield. Anal. Calcd for $C_9H_8O_3Cl_2$: C, 45.99; H, 3.43. Found: C, 46.37; H, 3.28. ^{1}H NMR δ 1.41 (s, 3 H), 2.04 (s, 3 H), 6.14 (d, J = 2 Hz, 1 H), 7.07 (d, J = 2 Hz, 1 H).

6-Acetoxy-2-bromo-4,6-dimethylcyclohexa-2,4-dien-1-one[14] (1d): yellow oil; 31% yield; IR 1742, 1680, 1640 cm^{-1}; ^{1}H NMR δ 1.35 (s, 3 H), 1.95 (d, J = 2 Hz, 3 H), 2.00 (s, 3 H), 5.92 (m, 1 H), 7.26 (d, J = 1.5 Hz, 1 H).

6-Acetoxy-2,4-dibromo-6-methylcyclohexa-2,4-dien-1-one (1f): mp 92–93 °C (reported, mp 98 °C); ^{1}H NMR δ 1.41 (s, 3 H), 2.05 (s, 3 H), 6.37 (d, J = 2 Hz, 1 H), 7.41 (d, J = 2 Hz, 1 H).

Reactions of *o*-Quinol Acetates with 0.5 M Isopropylmagnesium Bromide. In each reaction, a 0.3–0.5 mmol sample of the *o*-quinol acetate dissolved in 1 mL of anhydrous ether (2 mL in the case of *o*-quinol acetate **1f**) was added as rapidly as possible to 10 mL of 0.55 M isopropylmagnesium bromide (freshly prepared and standardized) which was kept under an atmosphere of prepurified nitrogen. The reaction mixture was stirred for 18 h. A solution of 0.1 M hydrochloric acid was added, and the mixture was extracted with four 10-mL samples of methylene chloride. The combined organic layers were washed with water, dried over magnesium sulfate, and filtered, and the solvent was evaporated under vacuum.

The reaction mixtures were analyzed by GLPC using a $^1/_4$ in. × 6 ft column packed with 5% DEGS on Chromosorb W. The products were isolated employing a $^3/_8$ in. × 6 ft column with the same packing.

Reaction with 1b gave three products with retention times at 150 °C of 1.5 (identified as 4-chloro-2,6-dimethylphenyl isopropyl ether by comparison with an authentic sample), 8.6 (4-chloro-2,6-dimethylphenol),[10a] and 15.5 min (4-chloro-2,6-dimethyl-3-isopropylphenol).

Reaction with 1c gave products with retention times at 180 °C of 1.4 (4-bromo-2,6-dimethylphenol),[10a] 6 (4-bromo-2,6-dimethylphenyl isopropyl ether), and 10.3 min (4-bromo-2,6-dimethylphenol).

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Reaction with 1d gave products with retention times at 180 °C of 2.0 (2-bromo-4,6-dimethylphenyl isopropyl ether), 2.7 (2-bromo-4,6-dimethylphenol),[10b] and 4.8 min (2-bromo-4,6-dimethyl-3-isopropylphenol).

Reaction with 1e gave components with retention times at 180 °C of 1.8 (2,4-dichloro-6-methylphenyl isopropyl ether), 3.6 (2,4-dichloro-6-methylphenol),[12] and 5.0 min (2,4-dichloro-3-isopropyl-6-methylphenol).

Reaction with 1f gave products with retention times at 180 °C of 4.8 (2,4-dibromo-6-methylphenyl isopropyl ether), 8.7 (2,4-dibromo-6-methylphenol),[11] and 11.5 min (2,4-dibromo-3-isopropyl-6-methylphenol).

Reaction with 1g gave products with retention times at 200 °C of 3.1 (3,5-dibromo-2,4,6-trimethylphenyl isopropyl ether), and 17.0 min (3,5-dibromo-2,4,6-trimethylphenol).

Properties of *m*-Isopropylphenols. 4-Chloro-2,6-dimethyl-3-isopropylphenol was obtained as a pale yellow oil. Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.50; H, 7.61. Found: C, 66.71; H, 7.59. ^1H NMR δ 1.36 (d, J = 8 Hz, 6 H), 2.15 (br s, 3 H), 2.23 (s, 3 H), 3.75 (m, 1 H), 6.92 (br s, 1 H).

4-Bromo-2,6-dimethyl-3-isopropylphenol was obtained as a yellow oil. Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22; Br, 32.86. Found: C, 54.51; H, 6.29; Br, 32.58. ^1H NMR δ 1.37 (d, J = 8 Hz, 6 H), 2.09 (s, 3 H), 2.23 (s, 3 H), 3.65 (sept, 1 H), 4.50 (br s, 1 H), 7.06 (s, 1 H).

2-Bromo-4,6-dimethyl-3-isopropylphenol. Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.31; H, 6.50. ^1H NMR δ 1.33 (d, J = 8 Hz, 6 H), 2.16 (s, 3 H), 2.27 (s, 3 H), 4.58 (sept, J = 8 Hz, 1 H), 5.60 (br s, 1 H), 6.74 (s, 1 H).

2,4-Dichloro-3-isopropyl-6-methylphenol was a pale yellow oil. Anal. Calcd for $C_{10}H_{12}OCl_2$: C, 54.82; H, 5.52. Found: C, 54.81; H, 5.71. ^1H NMR δ 1.37 (d, J = 8 Hz, 6 H), 2.19 (s, 3 H), 3.78 (sept, 1 H), 5.83 (br s, 1 H), 7.05 (br s, 1 H).

2,4-Dibromo-3-isopropyl-6-methylphenol was obtained as a yellow oil. Anal. Calcd for $C_{10}H_{12}OBr_2$: C, 38.99; H, 3.93. Found: C, 39.09; H, 3.81. ^1H NMR δ 1.41 (d, J = 8 Hz, 6 H), 2.22 (s, 3 H), 3.80 (m, 1 H), 5.75 (br s, 1 H), 7.26 (br s, 1 H).

Synthesis of Aryl Isopropyl Ethers. In a typical reaction, 0.02 mol of the phenol was added to a solution of potassium *tert*-butoxide (2.4 g, 0.021 mol) in 20 mL of Me_2SO. The resulting solution was stirred at room temperature for 1 h, and a solution of 2-bromopropane (2.7 g, 0.022 mol) in 10 mL of Me_2SO was added slowly. After 1 h the solution was diluted with 100 mL of water and extracted twice with mixed hexanes. The combined organic layers were washed with water and extracted with Claisen's alkali, until the alkaline layer was colorless. The organic layer was washed with water, dried over magnesium sulfate, and filtered and the solvent evaporated under vacuum to give the nearly pure ether, which was chromatographed on activity III alumina, eluting with mixed hexanes.

4-Chloro-2,6-dimethylphenyl isopropyl ether (28% yield) was a colorless oil. Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.50; H, 7.61. Found: C, 66.28; H, 7.51. ^1H NMR δ 1.23 (d, J = 7 Hz, 6 H), 2.21 (d, J = 1 Hz, 6 H), 4.13 (m, J = 7 Hz), 6.95 (m, 2 H).

4-Bromo-2,6-dimethylphenyl isopropyl ether (31% yield) was a colorless oil. Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.18; H, 5.84. ^1H NMR δ 1.25 (d, J = 8 Hz, 6 H), 2.20 (s, 6 H), 4.10 (sept, J = 8 Hz, 1 H), 7.07 (br s, 2 H).

2-Bromo-4,6-dimethylphenyl isopropyl ether (22% yield) was a pale yellow oil. Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.39; H, 5.96. ^1H NMR δ 1.26 (d, J = 8 Hz, 6 H), 2.20 (s, 3 H), 4.42 (sept, J = 8 Hz), 6.84 (m, 1 H), 7.13 (m, 1 H).

2,4-Dichloro-6-methylphenyl isopropyl ether was a pale yellow oil. Anal. Calcd for $C_{10}H_{12}OCl_2$: C, 54.82; H, 5.52. Found: C, 54.79; H, 5.27. ^1H NMR δ 1.22 (d, J = 8 Hz, 6 H), 2.15 (s, 3 H), 4.37 (sept, J = 8 Hz, 1 H), 6.95 (d, J = 2 Hz, 1 H), 7.13 (d, J = 2 Hz, 1 H).

2,4-Dibromo-6-methylphenyl isopropyl ether was a yellow oil. Anal. Calcd for $C_{10}H_{12}OBr_2$: C, 38.99; H, 3.93. Found: C, 39.20; H, 3.98. ^1H NMR δ 1.20 (d, J = 7.5 Hz, 6 H), 2.14 (s, 3 H), 4.07 (sept, J = 7.5 Hz, 1 H), 7.05 (m, 2 H).

3,5-Dibromo-2,4,6-trimethylphenyl isopropyl ether was a yellow oil. Anal. Calcd for $C_{12}H_{16}OBr_2$: C, 42.89; H, 4.80. Found: C, 42.97; H, 5.01. ^1H NMR δ 1.39 (d, J = 8 Hz, 6 H), 2.41 (s, 6 H), 2.71 (s, 3 H), 4.16 (m, J = 8 Hz, 1 H).

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Metalation-Induced Double Migration of Phosphorus from O→C. Convenient Preparation of Bis(2-hydroxyaryl)phosphinic Acids

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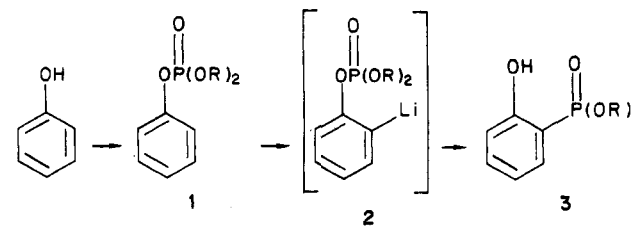
Treatment of diaryl ethyl phosphates **8** with lithium diisopropylamide in tetrahydrofuran yields ethyl bis(2-hydroxyaryl)phosphinates **9**. The reaction involves the double migration of phosphorus from O→C and is probably intramolecular. These phosphinate esters **9** on treatment with trimethylsilyl chloride and sodium iodide in acetonitrile undergo transesterification to give trimethylsilyl esters that yield the corresponding phosphinic acids **15** on treatment with water.

Treatment of dialkyl aryl phosphates **1** with lithium diisopropylamide results in a rearrangement that involves the fission of an oxygen–phosphorus bond and formation of a carbon–phosphorus bond, yielding dialkyl (2-hydroxyaryl)phosphonates **3**.[1-4] Since **1** can be easily obtained from phenols, the net result of the sequence of reactions shown in Scheme I is the introduction of a dialkyl phosphonyl group $-P(=O)(OR)_2$ group ortho to the phenolic OH group. We are interested in exploring the synthetic potential of this rearrangement and have previously shown[5] that (a) the above sequence of reactions can be

Scheme I



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