parison of their peak areas with those found before illumination. Necessary corrections for differences in the quantities chromatographed were made from the peak areas of the chlorobenzene. The data obtained from these studies are shown in Table II.

Registry No.—I, 2001-50-5; VI and VII, 7430-63-9; IV and V, 7430-64-0; VIII and IX, 7430-65-1.

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Phenoxy Radical Intermediates. II.[1a] The Oxidative Detoxification of Phenols in Incense Cedar Heartwood

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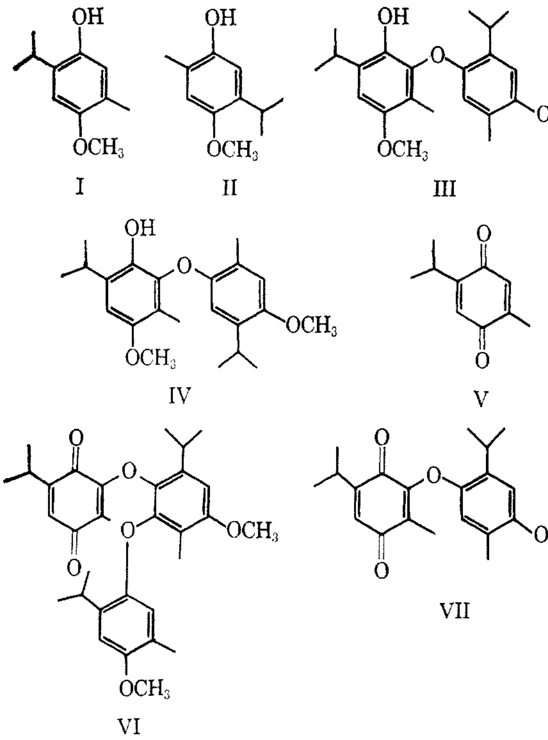
The fungicidal phenols, *p*-methoxythymol (I) and *p*-methoxycarvacrol (II), are converted to stable radical species upon oxidation. Their naturally occuring detoxification products, libocedrol (III) and heyderiol (IV), form unusually stable radical species upon further oxidation. Hyperfine coupling constants are assigned to all phenoxyls. Their role in the detoxification mechanism is discussed, as well as their individual properties.

The decay-resistant properties of incense cedar (*Libocedrus decurrens*, Torrey) have been attributed to the presence of the fungicidal phenols, *p*-methoxythymol (I) and *p*-methoxycarvacrol (II).[2] Decrease of decay resistance with aging of the wood is concommitant with the decrease in concentration of I and II, and the increase in the concentration of the diaryl ethers, libocedrol (III) and heyderiol (IV), as well as the increase of thymoquinone (V), 3-libocedrothymoquinone (VI), and libodedroquinone (VII) (Chart I).

CHART I



It has been proposed[2,3a] that phenols I and II were oxidized to phenoxy radical intermediates (Ia and IIa), which then undergo a variety of coupling reactions to yield dimeric and trimeric products.[3b] We now wish to report the isolation and characterization of these intermediates, by means of electron spin resonance (esr) spectroscopy.

Results

Esr Spectra in Benzene.—When dilute (10^{-3} *M*) solutions of I and II in benzene are oxidized with PbO_2, low concentrations of radical species Ia and IIa were obtained. An analysis of the esr spectra (Figures 1–3), aided by a computer program designed to plot synthetic spectra,[4] established the following hyperfine coupling constants for the species (Table I). The radicals appeared to be stable for many hours in deoxygenated solutions under nitrogen.

TABLE I

COUPLING CONSTANTS[a] IN BENZENE

Radical	$H_{\text{isopropyl}}$	H_{CH_3}	H_{ring}	H_{OCH_3}
Ia	3.20(1)	1.60(3)	0.80(1)[b]	1.60(3)
IIa	1.53(1)	7.65(3)	1.53(2)[c]	1.53(3)
IIIa	2.80(1)	1.40(3)	. . .	1.40(3)
IVa	2.80(1)	1.40(3)	. . .	1.40(3)

[a] In gauss. Numbers in parenthesis indicate number of protons. [b] *ortho* ring proton. [c] *ortho* and *meta* ring protons.

The oxidation of libocedrol (III) and heyderiol (IV) under identical conditions produced strong esr signals, indicating a high concentration of radical species IIIa and IVa. As might be anticipated from their structures, the spectra of IIIa and IVa were identical. The coupling constants (Table I) reflect their similarity to Ia, differing notably in the absence of any interac-

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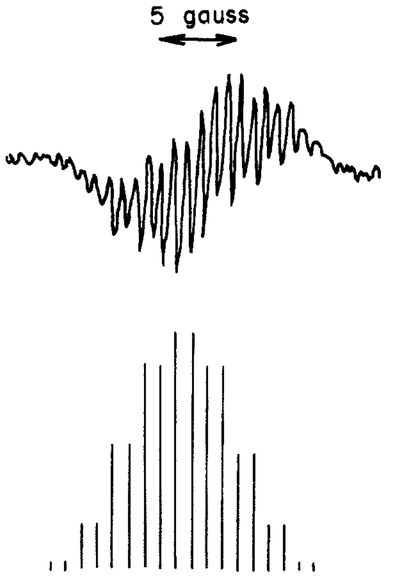
(1) (a) Part I of this series: C. Steelink, *J. Am. Chem. Soc.*, **87**, 2056 (1965). (b) To whom requests for reprints should be sent.

(2) (a) A. B. Anderson, T. C. Scheffer, and C. G. Duncan, *Holzforschung*, **17**, 1 (1963); (b) *Chem. Ind.* (London), 1289 (1962).

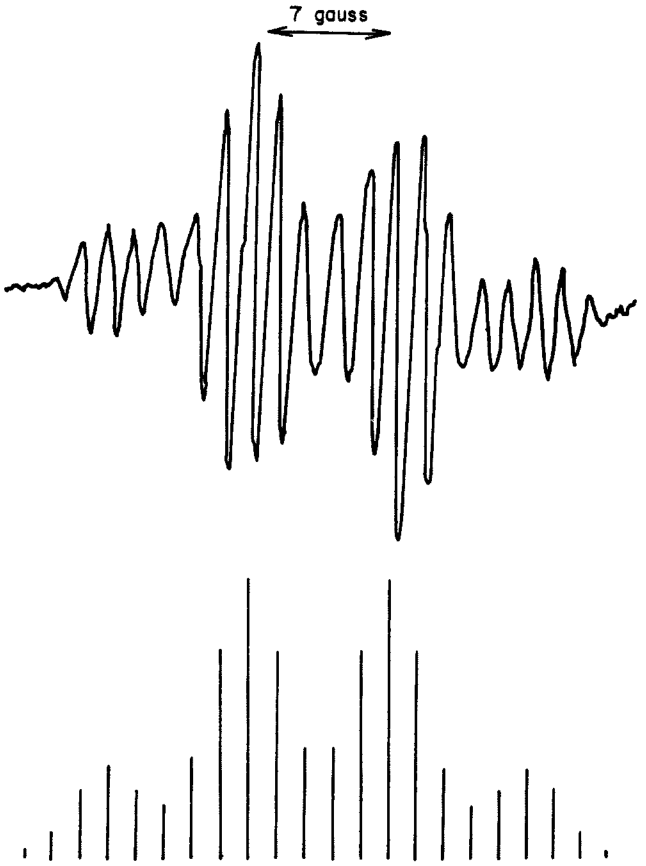
(3) (a) E. Zavarin, *J. Org. Chem.*, **23**, 1198 (1958). (b) Theoretically, four products are possible for the dimerization of Ia and IIa. However, only III and IV were isolated by Zavarin.[5a]

(4) We are indebted to Professor John Harriman of the Department of Chemistry, University of Wisconsin, and Professor Leslie Forster of the Department of Chemistry, University of Arizona, for writing this program.



Ia

Figure 1.—First-derivative esr spectrum in benzene of *p*-methoxythymoxy radical (Ia). The reconstructed spectrum is under the experimental spectrum. The center of lines is at approximately $g = 2$.

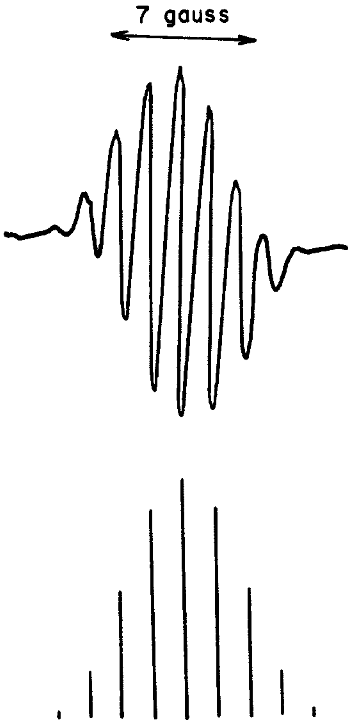


IIa

Figure 2.—First-derivative esr spectrum in benzene of *p*-methoxycarvacroxy radical (IIa). The reconstructed spectrum is under the experimental spectrum. The center of lines is at approximately $g = 2$.

tion with an *ortho* ring proton. In IIIa and IVa, no evidence for hyperfine splitting from *meta* ring protons was found.

Effect of Solvent.—The lack of spectral evidence for one of the ring protons prompted us to reinvestigate two of the phenols in a more polar solvent. Oxidation of II and III in dichloromethane gave very complex esr spectra. These were finally resolved, although the spectrum for IIa was somewhat obscured by background noise. Coupling constants were assigned, as shown in Table II. In dichloromethane, the *meta* proton in libocedrol (IIIa) showed a weak interaction, which was obscured in benzene. For the carvacrol radical (IIa), the polar solvent appeared to decrease one ring proton coupling constant and to increase the other.



IIIa

Figure 3.—First-derivative esr spectrum in benzene of libocedroxy radical (IIIa). The reconstructed spectrum is under the experimental spectrum. The center of lines is at approximately $g = 2$.

TABLE II

COUPLING CONSTANTS IN DICHLOROMETHANE[a]

Radical	$H_{\text{isopropyl}}$	H_{CH_3}	H_{ring}	H_{OCH_3}
IIa	1.53(1)	7.65(3)	0.7 (1) 2.2 (1)	1.53(3)
IIIa	2.80(1)	1.40(3)	0.30(1)	1.40(3)

[a] See footnote *a* of Table I.

Dilution Experiments.—Numerous authors have suggested that phenoxy radicals are in equilibrium with quinol ether dimers.[5] Becker[5a] recently characterized such a system (VIII ⇌ IX); Mauser and Nickel[5b] derived equilibrium constants for the radical–dimer species. Zavarin[3a] proposed that oxidized libocedrol (IIIa) was such an equilibrium mixture, based on his interpretation of spectral evidence.

When libocedrol was oxidized with PbO_2 under nitrogen (or with aqueous alkaline potassium ferricyanide), and the organic layer was separated, dried, and evaporated to dryness, a yellow oil was formed. The

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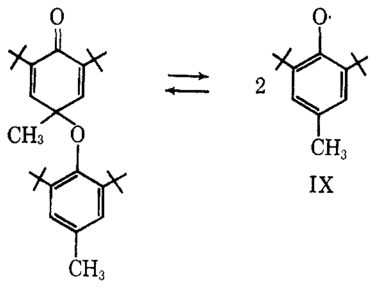
(5) (a) H.-D. Becker, *J. Org. Chem.*, **30**, 982 (1965); (b) H. Mauser and B. Nickel, *Angew. Chem., Intern. Ed. Engl.*, **4**, 354 (1965); (c) K. Dimroth and A. Berndt, *Angew. Chem.*, **76**, 434 (1964).



VIII

IX

oil exhibited bands in the infrared at 1660 and 1640 cm^{-1}, with a small shoulder at 1690 cm^{-1}, where none of these bands had existed in the original III. *p*-Methoxycarvacrol (II), under the same conditions, also yielded an oil with the same spectral bands. These bands are characteristic of quinol ethers of the type VIII.[5–7] An alternate structure, of the 6,6-diaryloxy-2,4-cyclohexadienone type, is also possible; for this type of dimer, one would expect a band at 1680–1690 cm^{-1} in the infrared.[7] The evidence for the dimer of libocedrol would favor the 2,5-cyclohexadienone structure (such as VIII) mixed with some of the 2,4-cyclohexadienone compound.

The oil from III exhibited a weak esr signal, identical with that signal of IIIa in solution. Stepwise addition of benzene to the oil in a quartz cell in the esr cavity increased the esr signal fiftyfold at sixfold dilution. Removal of solvent decreased the signal. The same dilution behavior was shown by the carvacrol radical–dimer system (IIa), although the signal intensities were much lower than those of IIIa.

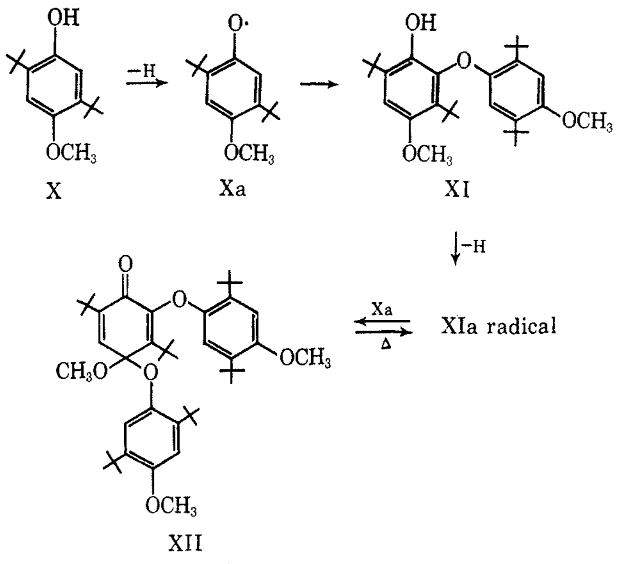
Discussion

These results establish the identities of the intermediate radical species which were proposed some years ago by Zavarin[3a] to explain the presence of a number of oxidation products in incense cedar heartwood. They also supplement the work of Mueller[6] and Hewgill,[7] both of whom oxidized X to dimeric and trimeric aryl ethers XI and XII which are closely related to the compounds under discussion here (Scheme I). Mueller[6] obtained esr spectra for Xa and XIa, although he could not resolve the complex spectrum of Xa.

Properties of Phenoxy Radicals.—The monomeric radicals Ia and IIa are remarkably stable in dilute benzene solutions. Normally, an unsubstituted position *ortho* to the hydroxyl function prevents the formation of long-lived radicals; instead, C–C coupling occurs rapidly in that position.[1,6,7] However, the presence of the *meta* methyl group in Ia or the *meta* isopropyl group in IIa apparently hinders the coupling reaction effectively. The resulting phenoxyls give esr signals of the same order of magnitude and lifetime as those observed for the *t*-butyl analogs (Xa).[6] The low value of the *meta* methyl proton hfsc (1.60 gauss) in Ia compared with the *ortho* methyl proton hfsc (7.65 gauss) in IIa is consistent with observations of Becconsall.[8]

The equivalence of the ring proton coupling constants in benzene with those of the alkyl and alkoxy protons in IIa may be fortuitous. A change in solvent from benzene to dichloromethane causes small changes in the electron density at ring proton, with a resulting complicated pattern in the esr spectrum. The change at the *meta* ring proton is in the opposite direction from the *ortho* ring proton. However, the over-all spin density distribution does not seem to be materially affected by solvent polarity[9,10] as Tables I and II indicate. In our own experience with related systems,[11] we find very similar hyperfine splitting patterns for radicals generated in such different solvents as water and benzene.

Scheme I



X

Xa

XI

XII

Libocedrol (III) and heyderiol (IV) form exceptionally stable phenoxyls in high concentration. Benzene solutions of the radicals still show strong esr signals after 24-hr exposure to air. The solid dimer, made by removal of solvent from the radical solution, appears to be only slightly changed after 24-hr exposure to air. In this respect, IIIa and IVa approach the stabilities of 2,4,6-tri-*t*-butylphenoxyls.[5b] This is undoubtedly due to the bulky isopropyl and thymoxy groups on positions 2 and 6 in IIIa, which prevent coupling at those positions. Resonance delocalization of the unpaired electron through the diaryl ether linkage does not appear to be a contributing factor in this stability, as evidenced by the lack of hyperfine structure in the esr spectrum from the aryloxy substituent. This has also been observed in other diaryl ether radical systems.[12]

Libocedrol radical (like Ia) exhibits changes in the esr hyperfine structure with change of solvent. In this case, the *meta* ring proton appears in the more polar solvent, as contrasted to its absence in benzene.

Role of Radical Intermediates in Detoxification Reactions.—A reaction sequence for *p*-methoxythymol (I) analogous to Scheme I now seems credible. In nonhydroxylic solvents, each of the radial species is in equilibrium with a quinol ether dimer. Depending on their relative stabilities, the radical species may (a)

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(6) E. Mueller, H. Kaufmann, and A. Rieker, *Ann.*, **671**, 61 (1964).

(7) F. R. Hewgill, B. R. Kennedy, and D. Kilpin, *J. Chem. Soc.*, 2904 (1965).

(8) J. Becconsall, S. Clough, and G. Scott, *Trans. Faraday Soc.*, **56**, 459 (1960).

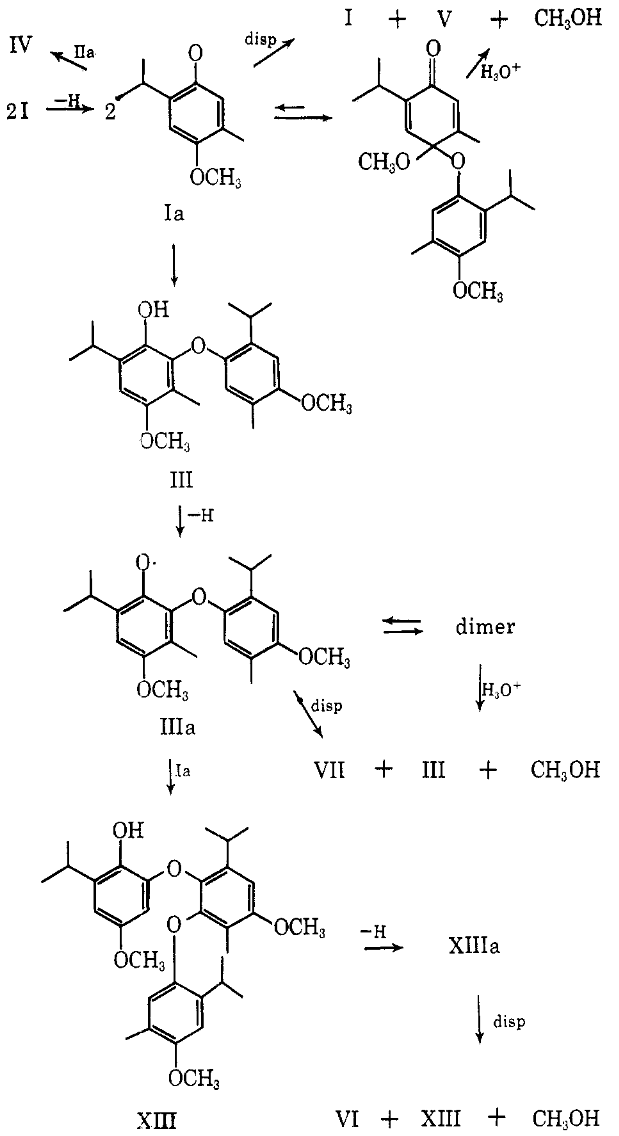
(9) E. W. Stone and A. H. Maki, *J. Am. Chem. Soc.*, **87**, 454 (1965).

(10) C. Cook and B. Norcross, *ibid.*, **81**, 1176 (1959).

(11) C. Steelink, Advances in Chemistry Series 59, American Chemical Society, Washington, D. C., 1966, p 51.

(12) D. A. Bolon, *J. Am. Chem. Soc.*, **88**, 3148 (1966).

SCHEME II



disp = disproportionation or scavenging of hydroperoxy radicals

couple to form diphenyl aryl ethers, (b) disproportionate into quinones and phenols, and (c) scavenge less stable radicals such as hydroperoxides and transient phenoxyls to form complexes which decompose into quinones. The quinol ether dimers, in the presence of aqueous acid, would also decompose to quinones and phenols. For the very stable phenoxy radicals such as IIIa, disproportionation would appear to be a favored course of reaction.[5a,13] The same reaction products, however, could be obtained by the scavenging of oxygen radical species in solution, with subsequent hydrolysis. The first-order kinetics of decay of some phenoxy radicals would favor the latter assumption.[1,5b]

To account for the variety of quinones and dimeric and trimeric products found in aged incense cedar heartwood, Zavarin[3a] and Mueller[6] proposed the existence of stable phenoxy precursors. The present work confirms the nature and stability of these phenoxy radicals *in vitro;* their central role in the detoxification reactions is outlined in Scheme II. Thus, the less stable radicals such as Ia would yield chiefly coupling products. These coupling products (III), on further oxidation, would give very stable phenoxyls, which would slowly decompose to a variety of quinones and phenols, such as I, III, V, and VII. In the presence of *p*-methoxythymol (I), which co-occurs with III in incense cedar, the stable libocedroxy radical (IIIa) could readily dehydrogenate I and then form the trimer, XIII. The dimer of IIIa could also disproportionate to trimer radical XIIIa and Ia, a phenomenon observed by Mueller[6] in related systems.

Experimental Section

Phenols.—Samples of *p*-methoxythymol, heyderiol, libocedrol, and *p*-methoxycarvacrol were kindly provided by Dr. A. B. Anderson, Forest Products Laboratory, University of California. Only small quantities of the first two phenols were available; for this reason, dilution and oxidation experiments to produce the dimers were not carried out with these compounds.

Esr Spectra.—An X-band esr spectrometer equipped with a microwave circulator and a TE-102 cavity was used to determine the spectra, as previously described.[14] Benzene solutions of the phenols (10^{-3} *M*)[15] were placed in one arm of a specially designed quartz cell; the other arm contained PbO_2. The contents of the cell were degassed by repeated freezing and thawing under vacuum. Then the reactants were mixed and the cell assembly was immediately placed in the esr spectrometer cavity.

Infrared Spectra.—All infrared spectra were measured on thin films with an Infracord spectrometer. Carbon tetrachloride solutions of libocedrol (and carvacrol) were stirred under nitrogen with PbO_2 for 10 min to 1 hr and filtered. The filtrate was evaporated until an oil or glass remained. This was transferred to an infrared microcell. In other experiments, dichloromethane solutions of the phenols were shaken with aqueous, alkaline ferricyanide for 10 min. The green organic later was separated from the mixture, dried over sodium sulfate, and evaporated to a yellow oil. Portions of these same oils were also placed in esr quartz cells for dilution experiments. The height of the esr signal was taken as a relative measure of the concentration of the radical species.

Registry No.—Ia, 7732-52-7; IIa, 7732-53-8; IIIa, 7771-29-1; IVa, 7732-51-6.

Acknowledgments.—We are indebted to Dr. Arthur B. Anderson of the Forest Products Laboratory, University of California, for providing us with authentic samples of phenols from incense cedar. This work was supported by a U. S. Forest Service Grant (No. 1) and a National Science Foundation Institutional Grant at the University of Arizona, as well as a National Institutes of Health grant (GM 12394) at the Institute for Enzyme Research.

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[13] A. L. Buchachenko, "Stable Radicals," Consultants Bureau, New York, N. Y., 1965, Chapter 3.

[14] C. Steelink and R. E. Hansen, *Tetrahedron Letters*, 105 (1966).

[15] Dichloromethane solutions of the phenols produced radicals whose half-lives were somewhat shorter than in benzene solutions.