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THE CHEMISTRY OF STABLE PHENOXY RADICALS

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I. INTRODUCTION

The chemistry of hindered phenols, *i.e.*, phenols carrying bulky *ortho* substituents, has been investigated intensively during the last 15 years primarily for two reasons: (1) many of these phenols form relatively stable free radicals; (2) both these phenols and their phenoxy radicals are important in the autoxidation inhibition of organic substances. In recent years, esr studies have shed light on the detailed structure of phenoxy radicals and on their role as intermediates in radical reactions. The purpose of this review is to summarize the chemistry of stable phenoxy radicals. Phenoxy radicals are defined as monovalent oxygen radical species (which can be formed formally from phenols by homolysis of the O–H bond); delocalization of the unpaired electron over the aromatic ring and many side-chain substituents has been proved (16, 205, 232). For a phenoxy radical to exist as a more than transient intermediate, it is necessary that the *ortho* and *para* positions of the phenol be blocked by groups which give increased steric protection or resonance stabilization.

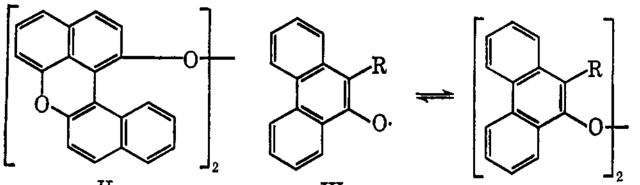
A useful definition of the description "stable" as applied to radicals has been suggested by Kosower (174): it means survival of the species for a sufficient time so that it can be used in another experiment. The terms "sufficient time" and "experiment" depend, of course, on the particular experimental conditions and techniques employed. The definition is here applied in a broad sense, so that the chemistry of such phenoxy radicals as 2,6-di-*t*-butyl-4-methyl and 2,6-di-*t*-butylphenoxy is included, although these two radicals are far less stable than 2,4,6-tri-*t*-butylphenoxy (I) which has served as an experimental standard for stable phenoxy radicals. It will be shown in this review that phenoxy radicals undergo many of the reactions of both oxygen and carbon radicals, such as dimerizations and association, hydrogen abstraction, addition, isomerization, and disproportionation. In a large number of these cases, the reaction of the C-radical form will occur exclusively, favored by 2,6 disubstitution.

The terms phenoxy and phenoxyl have been used interchangeably in the literature. *Chemical Abstracts* prefers phenoxy and this term will be used throughout this review.

Letter abbreviations for chemical compounds have been used sparingly, because different workers use different letters for the same compound. An attempt has been made to hold the Roman numerals to a minimum. When a Roman numeral designates a radical, *e.g.*, 2,4,6-tri-*t*-butylphenoxy is I, I·H refers to the corresponding phenol, *i.e.*, 2,4,6-tri-*t*-butylphenol.

II. HISTORICAL PERSPECTIVE AND SCOPE OF REVIEW

Univalent radicals, with the unpaired electron on the oxygen atom, were introduced shortly after Gomberg's discovery and postulate of the triphenylmethyl radical (123). The term phenoxy radical (Aroxyle) was coined by Pummerer (258). It rationalized conveniently the products of oxidative coupling of certain naphthols and phenanthrols which were formulated as diaryl peroxides II and III (119–122, 256, 260–263). The equilibrium (Eq 1) presumably was supported by molecular weight determination, nonadherence to Beer's law, and chemical reactions thought to be typical of peroxides. Dissociation values of up to 62% were claimed (see section V.D for a correct interpretation of these observations).

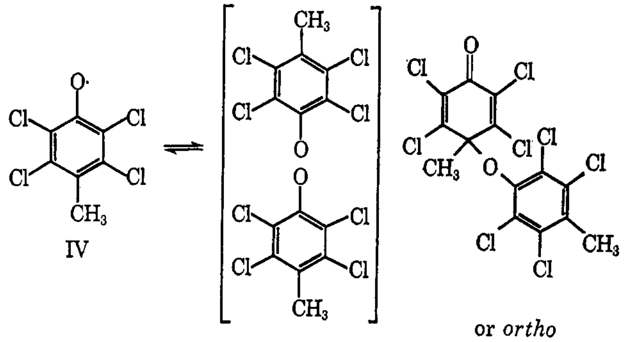


II III

(Eq 1)

Certain observations by Hunter and his co-workers anticipated some of the present-day chemistry of phenoxy radicals. It was noted, for example, that silver salts of halogenated phenols (2,4,6-tribromo, -chloro, and -iodo) reacted with dry ethyl iodide with the transient formation of a deep blue color (see, however, section V.B.3). In many instances the thermal decomposition of these salts gave polymers. Reaction of 2,4,4,6-tetrabromocyclohexadienone with mercury or light also led to polymerization. Oxidations of the halogenated phenols and 2,6-dimethoxy-3,4,5-tribromophenol with several oxidizing agents (chromic oxide, lead dioxide, potassium permanganate, or alkaline $K_3Fe(CN)_6$) gave substitution and coupling products that are best explained by assuming the formation of radical intermediates (151–154).

In 1919, Pummerer proposed that Zincke's (338) methylenequinone was actually a phenoxy radical (IV) in equilibrium with its dimer. Several product studies supported the formulation of IV as a phenoxy radical (section V.B.3). A quinol ether structure for the dimer was suggested (257, 262).



IV

As part of the basis for the apparent oxidation potential scale, Conant suggested reversible removal of a hydrogen atom from a phenolic hydroxyl group. This suggestion received support from measurements of critical oxidation potentials and from recent molecular orbital calculations. In the autoxidation inhibition action of phenols, the first step was considered to be hydrogen abstraction to give a phenoxy radical (32, 57, 102, 155).

Recent activity in this field commenced about 14 years ago with the independent discovery by Cook and Müller and co-workers of the stable radical 2,4,6-tri-

t-butylphenoxy (I) (59, 68, 211, 214). In this review the emphasis has been placed on these more recent results. Much of the experimental work prior to 1952, where the existence of stable phenoxy radicals has not been proved, is not included (although radical intermediates are probably involved in many instances).

Most of the chemistry of phenol, cresols, etc. has been excluded. Recent review articles summarize all aspects of phenol oxidation (242, 297, 303). The role of phenols and phenoxy radicals in autoxidation inhibition has been the subject of an excellent review by Ingold (157). Only more recent, pertinent data will therefore be mentioned. Semiquinones, which are closely related to phenoxy radicals but have a unique structural feature in that they are radical anions, will be mentioned only briefly. The chemistry of semiquinones has been the subject of an earlier review paper (202; for recent references *cf.* 58, 208, 313). Stable radicals based on polynuclear phenols (such as naphthols etc.) will be discussed.

Electron spin resonance spectroscopy has contributed more than any other tool to the structural analysis of phenoxys and to the characterization of many new radicals. The results from esr work will be introduced where pertinent, but a detailed discussion of the many spectra that have been published is considered beyond the scope of this review. Excellent summaries of the esr method (232, 325) and its application to phenoxy radicals have appeared (44, 205).

The literature has been reviewed through September 1966; a number of later references are included.

III. GENERATION OF PHENOXY RADICALS

A. METHODS OF PREPARATIVE VALUE

1. Introduction

The most widely used methods for the generation of phenoxy radicals from phenols in high yields consist of the use of inorganic oxidizing agents capable of undergoing one-electron reduction, such as PbO_2, Ag_2O, MnO_2, HgO, $K_3Fe(CN)_6$, and others (242). These reactions proceed usually in a heterogeneous system (solution of the phenol in an inert solvent; suspension or aqueous phase of the oxidizing agent) and are carried out at room temperature under nitrogen. However, the use of the latter is only necessary when maximum yields of the radical are desired. Solutions of phenoxy radicals are often stable over periods of hours or even days in the presence of limited amounts of air, although the radical concentration will not remain constant. Phenoxy solutions in organic solvents are characterized by their brilliant colors. In certain cases removal of the organic solvent permits the isolation of phenoxys in the solid state. Chemical reactivity, magnetic susceptibility measurements, and spectral data (infrared, ultraviolet–visible, nmr, and esr) have established the nature of the radical species generated (sections IV, V, VI).

2. Alkaline Potassium Ferricyanide

This reagent was first used to generate I (59, 214) and is generally useful when high yields of phenoxy radicals are desired. Phenol oxidation reactions with this reagent have been reviewed (318). Mechanistic details of the oxidation process are not well understood. The complexity of the reaction was pointed up by a kinetic study of cresol oxidation (138). The requirement of a large excess of oxidizing agent to approach quantitative yields of phenoxy radical is in agreement with a reversible one-electron-transfer reaction. The high rate of the reaction indicates that the redox potential of the reagent (0.49 v) is well above that of most phenols. The behavior of 2,6-di-*t*-butyl-4-cyanophenoxy (V) suggests that its potential is similar to that of the oxidizing agent in an alkaline medium (see section V.A.5).

3. Lead Dioxide

Oxidations of hindered phenols with lead dioxide approach quantitative yields of phenoxy radicals only when the sample of lead dioxide is high in active oxygen and when the solutions are dilute in the phenol (<0.04 *M*) (214). With certain samples of lead dioxide, conversion to I, for example, was only 57%; 43% of I·H remained. Yields of I consistently are highest in pure benzene and lower in cyclohexane, petroleum ether, and ether. This suggests reaction between phenoxy radical and the solvent (*cf.* section VI.E).

The results of Blanchard with silver oxide (see below) and the dependence of the yield of phenoxy on the activity of the reagent suggest the possibility that some oxygen used in the formation of cyclohexadienone peroxides (section VI.N.1) comes from the oxide.

4. Silver Oxide and Mercuric Oxide

It was shown by Blanchard (28) that the oxidation of I·H to bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadien-4-on-1-yl) peroxide (section VI.N) *via* I with silver oxide required the partial utilization of the oxygen from the oxide, since 90–100% yields of peroxide were obtained while only 60–70% of the theoretical amount of oxygen was absorbed. To prepare high yields of phenoxy radicals, freshly prepared samples of silver oxide should be used; alkaline potassium ferricyanide or lead dioxide appear to be superior reagents for this purpose (333). Mercuric oxide was also effective (33).

5. Manganese Compounds

Highly active manganese dioxide has been used to prepare high yields (18) of phenoxy radicals. This procedure appears to be especially convenient for the preparation of quinol ethers (section VI.L.2) in high yields. The products from the oxidation of mesitol have been formulated as forming *via* phenoxy radicals (200).

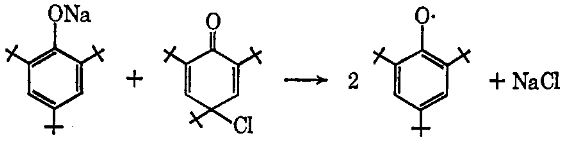
Alkaline potassium permanganate was used to prepare 2,4,6-triphenylphenoxy (VI) and its dimer from VI·H; VI was stable to permanganate (89).

6. *Reaction of 4-Halo-2,5-cyclohexadienones with Metals*

The title compounds (section VI.B) when shaken with a metal (Hg, Ag, Cu, Zn, Na–K) in an inert solvent under a nitrogen atmosphere can give nearly quantitative yields of phenoxy radicals. The method is convenient, for the metal halide which forms as a result of the reducing action of the metal is readily removed by filtration (65, 68, 214). However, this reaction (Eq 2) is not equally suitable for all phenoxy radicals. Although 2,6-di-*t*-butyl-4-phenylphenoxy (VII) is formed as shown in Eq 2 from 4-bromo-4-phenyl-2,6-di-*t*-butylcyclohexa-2,5-dienone (VIII), it reacts further to give 2-bromo-6-*t*-butyl-4-phenylphenol and isobutylene (235); 2-chloro-4-cyano-2,6-di-*t*-butylcyclohexa-2,4-dienone on heating gave isobutylene and 2-chloro-4-cyano-6-*t*-butylphenol (216). The reaction of sodium 2,4,6-tri-*t*-butylphenoxide with Br_2 (or I_2) or VIII (4-bromo-4-*t*-butyl) yields I (quinol ethers are formed in the case of less hindered phenoxides; section VI.L.2) (214, 215). This reaction very probably involves electron transfer between the phenoxide ion and the oxonium ion, since a displacement of chloride by 2,4,6-tri-*t*-butylphenoxide is sterically prohibitive.

VIII
R = Br, Cl
I

(Eq 2)

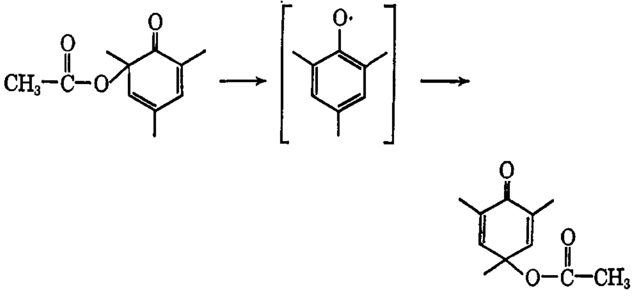


Compounds VIII undergo photo- and thermal reactions to generate phenoxys. Irradiation of 4-bromo-4-cyano-2,6-di-*t*-butyl-2,5-cyclohexadienone gave V by C–Br homolysis (216). On heating from room temperature to 120°, VIII (R = Cl) did not exhibit the esr signal of I; however, VIII (R = Br) showed a weak signal for I at 80° which became very intense at 100° and then gradually decreased (40).

B. OTHER METHODS

1. *Lead Tetraacetate*

The extensive work with this reagent in the oxidation of phenols, primarily by Wessely and his co-workers (51, 327–331) has been summarized (75). The oxidation has been interpreted as a radical reaction; this is supported by esr studies (30). From I·H and 2,6-di-*t*-butyl-4-methylphenol (IX·H) the compounds 4-*t*-butyl- and 4-methyl-4-acetoxy-2,6-di-*t*-butyl-2,5-cyclohexadienone were isolated (see section VI.O). For less hindered phenols the radical mechanism is in doubt, however. An oxonium ion mechanism is favored (75). The quinol acetates can rearrange thermally, and an intermediate trimethylphenoxy radical has been postulated in this rearrangement (340).



The polymerization of sodium 2,6-dimethyl-4-bromophenoxide is catalyzed by lead tetraacetate (as well as $\mathrm{Fe(CN)_6}^{-3}$ or iodine–benzoyl peroxide). It was suggested that the anion is oxidized to the phenoxy radical which attacks another anion in a fast step with displacement of bromide ion and formation of a phenoxy radical (304).

2. *Iron Salts*

The reagents ferric stearate (203), anhydrous ferric chloride (37, 280), ferrous or ferric ion in aqueous potassium persulfate (5), and ferrous sulfate–hydrogen peroxide (74) have been used for the oxidation of unhindered phenols. Ferric chloride has been used extensively in the oxidation of polyhydroxyphenols (297).

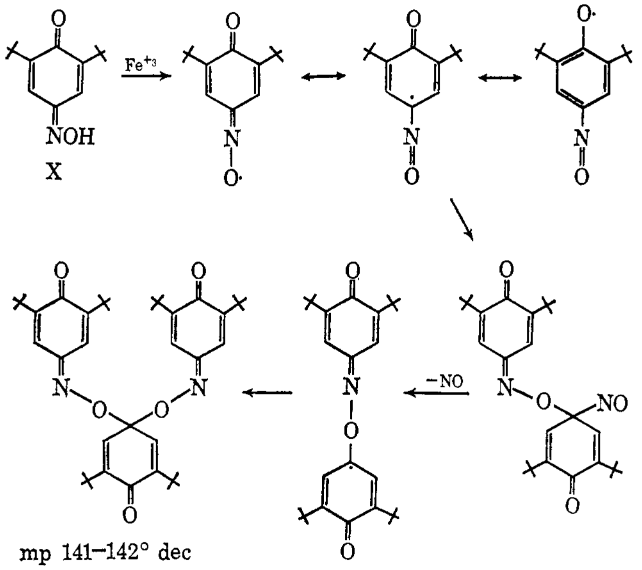
An interesting sequence has been postulated by Kharash and Joshi (169) to account for the product on treatment of the monoxime of 2,6-di-*t*-butylbenzoquinone (X) with ferric ion (see Scheme I).

3. *Silver Salts*

Fifty years ago characteristic colors and polymers were reported when the silver salt of triiodophenol was decomposed in the presence of ethyl iodide (154, 334). However, the brilliant blue color observed in a similar reaction, treatment of silver 2,4,6-tribromophenoxide in benzene with iodide (63), was not associated with an esr signal (223) and therefore cannot be attributed to a phenoxy radical.

Oxidations of cresols, xylenols, and mesitol with silver oxide and silver persulfate have been reported (6, 183, 255).

Scheme I



4. Copper Salts

Copper salts of carboxylic acids oxidize phenols in a manner characteristic of single-electron oxidizing agents to produce products coupled at vacant *ortho* and *para* positions. Many new dimers and their nmr spectra have been reported (164). A large number of oxidations have been carried out with Cu–amine catalysts and oxygen. Brackman and Havinga (38) have studied the oxidation of several phenols and naphthols and obtained dimeric products consistent with radical coupling.

The oxidative coupling of 2,6-disubstituted phenols has been studied extensively with the cupric ion–pyridine system (96, 104, 135, 136, 247). The reaction products are polyphenyl ethers *via* C–O coupling or diphenoquinones *via* C–C coupling. A complex of the phenoxy radical with the catalyst was suggested. Oxidation of I·H with $pyCuClOCH_3$ gave I (104). Esr spectroscopy has demonstrated that oxidation of I·H with the system cuprous chloride–pyridine saturated with oxygen gives I. The main oxidation product is X. When the system was not saturated with oxygen, only a low conversion to I was realized. It is postulated that the catalyst complex which contains 1 mole of oxygen reacts with I·H to give 2,4,6-tri-*t*-butylphenoxide. This reduces the complex and forms I (124).

5. Other Metal Salts

The generation of stable phenoxy radicals with cobalt(III), vanadium(V), and manganese(III) has not been reported. The results obtained with these reagents have been summarized by Criegee (75). Another reagent with a high redox potential, cerium(IV), has been used successfully to produce stable phenoxy radicals which were detected by esr (305).

6. Organic Oxidizing Agents

Several enzymatic systems have been used to oxidize phenols to dimeric coupling products. The reaction has been applied to phenols such as 2,6-dimethyl- and 2,6-dimethoxy-, but not specifically to phenols capable of forming stable phenoxy radicals. It seems clear, of course, that nature is capable of generating long-lived radicals. Many of these radicals may well be formed by enzymatic processes (*cf.* section IX). The results have been summarized in several reviews (137, 297).

Quinones of high oxidation potential can be used successfully as oxidizing agents. An excess of diphenoquinone (oxidation potential 0.95 v) generated 2,6-di-*t*-butyl-4-methoxyphenoxy (XI) from XI·H, although the presence of the radical was inferred only from the color of the solution; I was not generated under these conditions (64). Tetrachloro-1,2-benzoquinone (0.872 v) has been applied to the oxidation of pyrogallols and catechols (242, 297), and quinones such as 3,3′,5,5′-tetrachlorodipheno- (1.0 v) and 2,3-dichloro-5,6-dicyano- (1.0 v) should be even more efficient. The latter reagent was studied with several 2,4,6-trisubstituted phenols and the products were best rationalized by assuming phenoxy radicals as intermediates in the reaction (19) (sections V.A and VI.L.2). The use of *p*-benzoquinone has been reported (section V.A.7).

The formation of phenoxy radicals by the reaction of phenols with peroxides and hydroperoxides is discussed in section VI.O, and the reaction which involves an exchange between a phenol and a phenoxy radical to generate a new phenoxy radical is discussed in section VI.L.1.

7. Dissociation

The formation of phenoxy radicals during thermal dissociation of phenoxy dimers, quinol ethers, and peroxides is treated in sections IV.A, VI.L.2, and VI.N, respectively.

8. Photolysis

The photolysis of 2,4,6-tri-*t*-butyl-4-methoxy-2,5-cyclohexadienone or of bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadien-4-on-1-yl) peroxide gave I·H as one of the products (193). This strongly suggests I as an intermediate.

Both transient and stable phenoxy radicals have been generated by flash photolysis and the spectra analyzed by visible, ultraviolet, and esr spectroscopy. Conversions of 1–2% were realized (4, 128, 177, 178, 312).

9. Electrochemical Methods

Years ago it was suggested that the first step in the anodic oxidation of phenols was the formation of a phenoxy radical (101). Subsequent attempts to measure oxidation potentials of phenols were made by Conant (57), Fieser (102), and others; brief summaries of these methods have been given by Penketh (252). A chief obstacle is the choice of a suitable electrode, since mercury electrodes are readily oxidized to mercury phenolates (252, 311) and platinum electrodes can be poisoned. However, the latter were used successfully in the oxidation of vanillate anion to dehydrodivanillin in acetonitrile by a one-electron transfer (321). Voltametric studies by the same authors on IX·H led them to propose a two-electron reaction. The proposal of a phenoxy radical intermediate was supported by measurements of half-wave potentials on a microplatinum (one-electron transfer) electrode (105). The oxidation potentials of many phenols, as measured on a wax-coated graphite electrode, showed some relationship to the antioxidant efficiency (252).

The half-wave potentials of 29 polysubstituted phenylphenols and four phenanthrols were determined on a rotating graphite electrode against an aqueous silver chloride electrode in aqueous acetonitrile and tetramethylammonium hydroxide–tetramethylammonium chloride as buffer (311). Comparisons with I showed it to have the lowest potential. The values, in millivolts, are given in Table I; $E_{1/2}'$ refers to the values for the formation of the radical (step 1, Eq 3). In aqueous acetic acid containing sodium acetate the phenoxy radicals were oxidized further to cations which reacted with the acetate anion to form quinol acetates (these were isolated in high yields). The values $E_{1/2}{}^{1+2}$ (Table I) are measures of the steps 1 + 2 (Eq 3) since it was concluded that the slopes of

$$\mathrm{ArOH} \underset{\substack{+e^{\ominus},+H^{\ominus}\\ \text{step 1}}}{\overset{-H^{\oplus},-e^{\ominus}}{\rightleftharpoons}} \mathrm{ArO}\cdot \underset{\substack{+e^{\oplus}\\ \text{step 2}}}{\overset{-e^{\ominus}}{\rightleftharpoons}} \mathrm{ArO}^{\oplus} \rightleftharpoons \text{quinol acetates} \quad \text{(Eq 3)}$$

the curves obtained were consistent with two single electron transfers (*i.e.*, the phenoxy radical is an intermediate in acid solution) rather than a two-electron oxidation. The reversibility of the reaction was confirmed by the cathodic reduction of the quinol acetate of VI·H.

TABLE I

OXIDATION POTENTIALS[a] OF POLYPHENYLPHENOLS (311)

	$E_{1/2}'$	$E_{1/2}{}^{1+2}$	E_f (90)
2,4,6-Triphenyl-3,5-dicyano	+723	+1061	...
2,6-Diphenyl-4-cyano	+549	+952	...
2,6-Diphenyl-4-*p*-bromophenyl-3-cyano	+452	+931	...
2,3,4,5,6-Pentaphenyl	+366	+930	...
2,4,6-Triphenyl-3-cyano	+433	+926	...
2,4,6-Tri-*p*-bromophenyl	+406	+875	...
3-Chloro-2,4,6-triphenyl	+347	+858	...
2,3,4,6-Tetraphenyl	+238	+854	...
2,6-Diphenyl-4-*p*-cyanophenyl	+294	+845	...
2,6-Diphenyl-4-sulfonylphenyl	+227	+803	...
4-Phenyl-2,6-bis-*p*-bromophenyl	+257	+794	...
2,4,6-Triphenyl	+211	+786	+327
2,6-Diphenyl-4-*p*-bromophenyl	+236	+784	+346
4-Fluoro-2,6-diphenyl	+164	+757	...
2,4,6-Tri-*p*-phenoxyphenyl	+179	+747	...
2,6-Diphenyl-4-*p*-methoxyphenyl	+167	+710	+274
4-Phenyl-2,6-bis-*p*-methoxyphenyl	+156	+692	+265
2,4,6-Tri-*p*-methoxyphenyl	+124	+671	+244
2,6-Di-*t*-butyl-4-phenyl	−14	...	...
2,4,6-Tri-*t*-butyl	−59	...	+72

[a] Values in millivolts.

The relative magnitude of oxidation potentials was confirmed further by potentiometric titration of several lithium phenolates with gold(III) chloride (90) in anhydrous acetonitrile at a platinum electrode. Although higher, the E_f values obtained rate the phenols studied in the same relative order as did the polarographic half-wave potentials ($E_{1/2}'$). The potentials reported in Table I are not readily related to those of aqueous systems because of difficulties in assessing the importance of solvation and diffusion.

The redox potentials of four 4-R-2,6-di-*t*-butylphenoxy radicals were measured directly with a sintered boron carbide electrode in acetate-buffered ethanol (197) (R = CO_2CH_3, $CO_2C_2H_5$, *t*-butyl (I), C_6H_5 (VII)). The former two compounds were used as their dimers; the latter two were prepared by electrolytic oxidation of the corresponding phenols, and the reaction was followed spectroscopically at the maximum of the long wavelength absorption (*cf.* section IV.B).

10. Hypohalide Oxidation

Oxidation of phenoxides with hypobromite can be used to generate phenoxy radicals. Two moles of V·H reacted with hypobromite to form V which was isolated as the dimer (216).

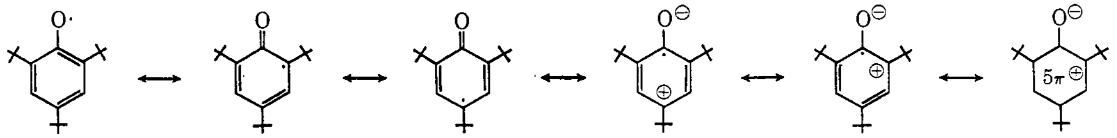
11. Potassium Nitrosodisulfonate

The oxidation of 2,4,6-trialkylphenols with this reagent has been summarized (189). In the case of mesitol and IX·H, the products are best explained by postulating phenoxy radicals as intermediates (*cf.* section VII.D). Phenols such as 2,4-di-*t*-butyl-6-acetonyl- and 2,6-di-*t*-butyl-4-phenyl- are oxidized to *o*-quinones by loss of one *o*-*t*-butyl group (189, ref 4 in 208).

12. Diphenylpicrylhydrazyl (DPPH)

The rate of the bimolecular reaction of hindered phenols with diphenylpicrylhydrazyl in carbon tetrachloride was determined (199). For I·H, *k* (l. mole^{-1} min^{-1}) = 22 (19.2°); for IX·H, *k* = 31 (18.3°); and for 2,6-di-*t*-butyl-4-ethylphenol, *k* = 32 (17.0°). These findings suggested that inductive effects were

SCHEME II



more important than steric effects, since $k = 83$ for 4-*t*-butylphenol, but 2,4-di-*t*-butylphenol was considerably faster ($k = 520$), although a steric argument can be made by comparison of the latter with I·H. A rough correlation with σ^-- or σ^+-substituent constants was found (142); the rate-determining step is the H abstraction by DPPH to generate a phenoxy radical. The rate and equilibrium constants for the reaction of BIPH (*cf.* section V.A.7) with DPPH were found to be 12.6 l. mole^{-1} min^{-1} and 38.4 (at equimolar concentrations), respectively (10). Deuterium isotope effects of 1.95 for IX·H (26) and 8.1 for 2,6-di-*t*-butylphenol (27) have been reported.

13. Others

The formation of I was reported from the reaction of I·H with benzenediazonium chloride (208, p 144). An esr signal for I was observed when 2,4,6-tri-*t*-butylmagnesium bromide was treated with oxygen or quinones (232).

14. Phenoxy Radicals Containing Isotopes

The synthesis of hindered phenols and the corresponding phenoxy radicals which contain various isotopes has been described in several papers (86, 87, 231, 273, 277, 279, 281).

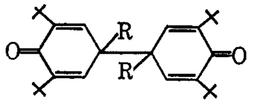
IV. STRUCTURE

That paramagnetic substances were indeed formed under conditions such as reported in section III was proved first by the Gouy method, which also showed that I was essentially monomeric (210). The stability of the radicals, for example, I, and their reactivity with reagents such as oxygen, bromine, and nitrogen dioxide suggested the importance of resonance (delocalization) and steric factors. Detailed structural information has come from spectral methods; the Gouy method is useful for the quantitative determination of radical content and has given evidence for the radical monomer–dimer equilibrium (see below). The use of reducing agents such as potassium iodide for the estimation of radical content is unreliable, since most radical dimers and quinol ethers will react as monomeric radicals after dissociation.

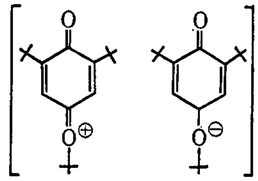
A. INFRARED SPECTRA

Infrared spectra of phenoxy radicals show a broad strong band in the 1600-cm^{-1} region and in many cases a weak to medium band in the 1500-cm^{-1} region. The 1600-cm^{-1} band resembles a weak carbonyl absorption which makes its contributions to the canonical forms (illustrated for I in Scheme II) (210). Structures involving charge separation have been invoked to explain the 1500-cm^{-1} band. The intensity of this band diminishes with increasing dilution in nonpolar solvents, suggesting the possibility of monomer–dimer equilibria. There is other evidence which supports such an equilibrium. In certain instances, attempts to isolate the highly colored phenoxy radicals in the solid state have been successful. In other cases, dimeric, diamagnetic solids of much weaker or no color have been isolated when the solvent was removed. When dissolved, these dimers give the characteristic radical colors, the solutions are paramagnetic, and the chemical behavior is that of the radical.

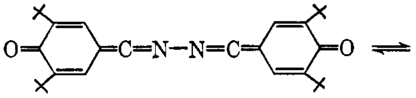
The radical 2,6-di-*t*-butyl-4-*t*-butoxyphenoxy (XII), reported to exist about 95% as the monomer in solution, forms a white diamagnetic solid (222). Infrared bands at 1656 and 1635 cm^{-1} support a cyclohexadienone structure (XII absorbs at 1570 cm^{-1}). Structure XIIIa (R = *t*-butoxy) was rejected (in view of the bulk of the R groups), and a charge-transfer structure XIIIb was proposed. Structure XIIIa was advanced for R = methoxy (212) to explain the low (27%) radical content in the solid state; XIIIa (R = methoxy) has not been isolated. Esr data for XI and XII support participation of charge-transfer structures (217, 273, 290). For the crystalline dimer formed from V the equilibrium in Eq 4 was proposed, but no real evidence exists for the rather unreasonable species Vb (216). This dimer showed no nitrile bands in the infrared but structure Va alone was thought unlikely since careful reduction produced no evidence for hy-



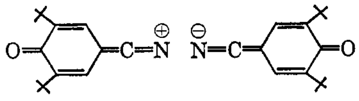
XIIIa



XIIIb



Va

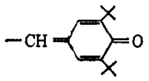


(Eq 4)

Vb

TABLE II

2,6-DI-t-BUTYL-4-R-PHENOXY RADICALS

R	λ_{max}, mμ	ϵ^a	Ref
t-C_4H_9	625	410 (benzene)	67
sec-C_4H_9	630	. . .	67
Cyclohexyl	630	450 (cyclohexane)	67
C_6H_5	347, 488	2,780	3, 29, 197
p-MeC_6H_4	506, 580	. . .	29
o-MeC_6H_4	479, 495	. . .	29
p-$MeOC_6H_4$	530, 573	. . .	29
1-Naphthyl	604	. . .	29
$-CHMe_2$	310, 386, 408, 630	404 (benzene)	67, 149
$-C(OMe)Me_2$	637	. . .	66
$-CH(OMe)C_6H_5$	310, 388, 408, 625	430 (cyclohexane)	149
$-CH(C_6H_5)_2$	314, 390, 413, 630	500 (cyclohexane)	149
$-CHC_6H_5(OCH_2C_6H_5)$	388, 410, 630	240 (cyclohexane)	149
MeO	535	. . .	217
EtO	530	. . .	217
t-C_4H_9O	538	. . .	254
$-COMe$	704	310 (5×10^{-4} in benzene)	196
BIP ($cf.$ section V.A.7)	312, 325, 454, 625, 770 (sh)		10
	407, 431, 772.5	1,889	
	420	200,000	9, 10
	423	180,000 (isooctane)	71, 167
PhO	533	150	33
$-N(p$-$C_6H_4NMe_2)_2$	650	6,000	245
$-CO_2Et$	410, 425, 720	447	196

^{a} Refers to longest wavelength listed.

drazine derivatives. Structure XIIIa or quinol ether structures have been assigned to R = 4-CO_2R, 4-OCOR, 4-$POPh_2$, 4-$PSPh_2$ (196, 206, 219, 230, 234), and 2-t-butoxy- and 2-phenyl-4,6-di-t-butylphenoxy; in many instances, these assignments are not definitive, although quinol ether bands (section VI.L.2) appear to be quite characteristic and useful for diagnostic purposes (196).

Dehydrogenation of IX·H with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (19) gave a colorless dimer which showed quinol ether bands at 1652 and 1635 cm^{-1} which disappeared within 1 week even in the solid state. This and other evidence (section VI.L.2) established that the dimer is the quinol ether which was partially dissociated into the phenoxy radical IX. A 1668–1653-cm^{-1} doublet for the dimer of VI (VI is largely associated; on cooling dilute solutions turn colorless, but heating regenerates the radical color) favored a quinol ether structure or XIIIa (R = C_6H_5). Dimroth at one time preferred a charge-transfer structure (84) but later (85) proved the quinol ether structure by an infrared study of the carbonyl and ether band shifts in the dimer substituted with ^{18}O.

B. ULTRAVIOLET AND VISIBLE SPECTRA

The strikingly different (from those of the corresponding phenols) spectra of phenoxy radicals show several maxima in the ultraviolet and visible regions. The long wavelength band, usually the weakest in intensity, is found in the visible region; the short wavelength band is found at about 300 mμ. The appearance of these bands and the brilliant colors of most phenoxy radicals lend further support to structures which include the conjugated keto forms as well as charge separation.

Tables II and III list the absorption maxima of several phenoxy radicals; in most instances, only the longest wavelength band has been given.

Further evidence for the monomer–dimer equilibrium has been obtained from a study of these bands. For example, the absorbancy at 704 mμ for 2,6-di-t-butyl-4-acetylphenoxy (196) does not follow Beer's law, and the molar extinction coefficient increases with increasing dilution; obviously, an increase in concentration favors dimer formation. At the 704 mμ maximum in benzene ϵ values of 35.6 (5×10^{-2} M, concentration extrapolated to 100% radical content), 107 (5×10^{-3} M), and 310 (5×10^{-4} M) were reported.

The disproportionation of phenoxy radicals has been followed in the visible region (section VIII). The

TABLE III

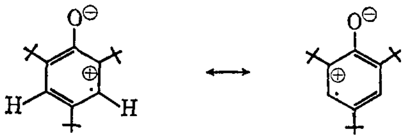
MISCELLANEOUS PHENOXY RADICALS

Structure	λ_{max}, mμ	ϵ	Ref
2,4,6-Triphenyl (VI)	535	. . .	89
Syrinoxyl	413, 458, 650, 850	. . .	306
2,6-Dimethoxy-4-R (R = H, CH_3, C_2H_5)	420, 450, 470, 750	. . .	305
2,4-Diphenyl-6-(2,4,6-triphenylphenoxy)phenyl	585		89
2,4,6-Tri-p-phenoxyphenyl	585	4100	89
II-monomer	518	4300	280

spectra of the phenoxy radicals obtained upon flash photolysis have been examined in the 600–300-mμ region (198), and second-order rate constants of dimerization (10^7–10^8 l./mole sec) were estimated from these spectra. Rieker (270) has reported that a linear relationship exists between the long wavelength absorption (~600 mμ) and the $a_{\mathrm{H},meta}$ coupling constants which result from esr measurements.

C. ESR SPECTRA

g values for phenoxy radicals have been determined by several workers, with values for I ranging from 1.99 to 2.0052 (210, 326). This indicates a very high radical content (the value for the completely free electron is 2.0023). The importance of an accurate determination of *g* values has been emphasized (232). A study of hyperfine splitting constants has yielded detailed information about radical structures. The significant results and conclusions from this work have been summarized (16, 17, 207, 232, 273, 292). All atoms, the oxygen as well as the six carbon atoms in the ring, show a spin density for the unpaired electron. For I a 1:2:1 triplet is observed (231), explained by the contribution of Ia and Ib to the resonance stabilization. This view is supported by the observation of a 1:1 doublet when one of the *m*-hydrogens is replaced by deuterium, and only a singlet spectrum is present when both *meta* positions are occupied by deuterium. The participation of resonance structures in the ground state which had the unpaired electron in the *ortho* and *para* positions had been inferred already from the chemical reactivity and was substantiated further by the esr examination of 2,4,6-tri(diphenylmethyl)-phenoxy (231). Its 15-line spectrum was explained best by hyperconjugation involving the substituents. Also, the high-resolution hyperfine splitting pattern of I shows the direct participation of the *t*-butyl groups (134, 292). A direct proof of a spin density of the unpaired electron on the oxygen atom and on carbon 1 was obtained from the esr spectra of (1-^{13}C)-2,4,6-tri-*t*-butylphenoxy (279) and (^{17}O)-2,4,6-tri-*t*-butylphenoxy (277). The per cent 2s character (205) of the electron at each position was calculated to be 1.25 for the oxygen atom and 1.75, 1.80, 1.79, and 3.31 for C-1 to C-4, respectively. The statistical weight distributions were 36% for the oxygen and 4.5, 12.5, 5.0, and 25.0% for C-1 to C-4, respectively. The esr spectrum of (^{17}O)-VI (86) also indicates a high spin density on oxygen. Coupling constants for (^{17}O)-I ($a_{^{17}\mathrm{O}} = 10.23$, $a_{\mathrm{H},meta} = 1.8$ gauss) and (^{17}O)-VI ($a_{^{17}\mathrm{O}} = 9.7$, $a_{\mathrm{H},meta} = 1.8$ gauss) are of similar magnitude and suggest a comparable distribution of the unpaired electron in the two phenoxys (276). Thus, the data support a formulation of phenoxy radicals as $5\pi^+$ systems, *i.e.*, the positive charge and the unpaired electron can reside on each carbon atom of the ring, and oxygen radicals.



Ia Ib

Examination of the esr spectra for numerous R groups in the system 4-R-2,6-di-*t*-butylphenoxy has proved side-chain and heteroatom participation in the ground-state stabilization and has given information on reaction intermediates (sections V, VI, X). The prodigious and prolific efforts of Müller and his students have demonstrated the skillful use of the aryloxy system as an aid in proving the existence of several hetero radicals, namely phosphorus, arsenic, tin, sulfur, selenium, and nitrogen; *cf.* section V.6–8. This was accomplished by the synthesis of 2,6-di-*t*-butylphenols with the appropriate hetero group in the 4 position and the analysis of the esr spectra of the corresponding phenoxy radicals. Reference 205 contains a lucid discussion of these results.

The technique of electron nuclear double resonance provides increased resolution of spectra and more accurate hyperfine splitting and should be especially useful in the elucidation of additional structural details and determination of reaction intermediates (156).

V. CLASSES OF PHENOXY RADICALS

A. 2,6-DI-*t*-BUTYL-4-R-PHENOXY RADICALS

In this section representative examples of phenoxy radicals are compiled in tabular form, but not all phenoxy radicals that have ever been reported are listed. Tables IV–XIII list examples of 4-R-2,6-di-*t*-butylphenoxy radicals. References given refer to the preparation and, where available, to the esr spectra.

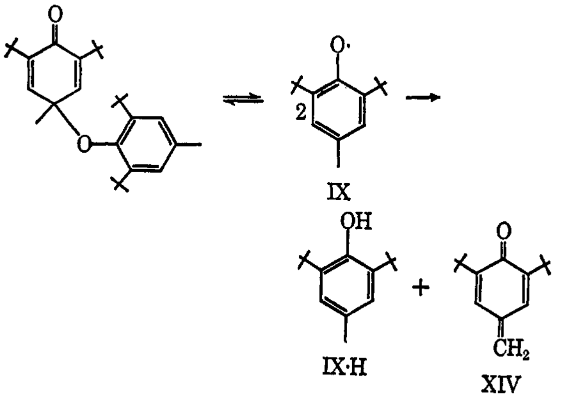
1. 4-Alkyl and 4-Aralkyl (Table IV)

Radical stability increases when methyl is replaced by larger alkyl groups. Radical IX was discussed in some detail by Becker (19) who isolated it as the dimer in the solid state. This dimer gave an esr signal in the solid state; its infrared spectrum was consistent with a quinol ether structure. These data indicated partial dissociation even in the solid state ac-

TABLE IV
4-ALKYL- AND 4-ARALKYLPHENOXY RADICALS

4-R substituent	Ref	4-R substituent	Ref
Methyl (IX)	16, 19	$CHPh_2$	144, 223, 290
Ethyl	16	CPh_3	224
Isopropyl	149, 223	$CH(OCH_3)Ph$	149
sec-Butyl	67	$CH(OCH_2Ph)Ph$	149
t-Butyl (I)	59, 68, 134,	CH_2Ph	17, 292
	211, 214	CPh_2CH_3	292
Cyclohexyl	67, 292	$CPh(CH_3)_2$	146, 292

cording to Eq 5. Irreversible disproportionation of IX to IX·H and XIV occurred as was proved by infrared and ultraviolet spectra (15, 19). The latter were in complete accord with the results of the debromination of 4-bromo-2,6-di-*t*-butyl-4-methyl-2,5-cyclohexadien-1-one. In ether or isooctane the maximum at 285 mμ for XIV was reached within a few minutes after the dimer had been dissolved.



(Eq 5)

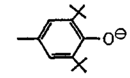
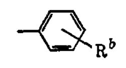
All phenoxy radicals which have α-H's on the carbon atom in the 4 position disproportionate to the parent phenol and a quinone methide. This reaction is discussed further in section VIII. A slower oxidation reaction which converts the α-methylene group to a carbonyl group takes place in the presence of oxidizing agent; this has been shown by esr (16, 141).

The properties and reactions of I have been investigated more extensively than those of any other phenoxy radical. It has been isolated as a deep blue solid, mp 95–98°, which has a half-life of 7 days at 25° under nitrogen in a sealed ampoule. Its esr spectrum has been studied thoroughly, notably by the use of isotopes D, ^{17}O, 1-^{13}C (see section IV.C). While I exists as a completely monomeric radical in both the solid state and in solution, increased tendency toward dimerization occurs when the size of the 4-alkyl group decreases (IX above), although electronic effects of 4 substituents larger than methyl may still result in more stable dimers (*cf.* section X).

2. 4-Aryl and 4-Substituted Aryl (Table V)

TABLE V

4-ARYL AND 4-SUBSTITUTED ARYLPHENOXY RADICALS

4-R substituent	Ref
Phenyl	29, 63, 235, 276
	100[a]
	29, 276
1-Naphthyl	29, 276

[a] *Cf.* section V.A.3. [b] R = *o*-deuterio, *o*-methyl, *o*-methoxy, *m*-deuterio, *p*-methyl, *p*-methoxy, *p*-deuterio, *p*-phenyl, *p*-methyl, *p*-methoxy, *p*-*t*-butyl, *p*-bromo, and several polysubstituted 4-phenyl groups.

The radical 2,6-di-*t*-butyl-4-phenylphenoxy (VII) has been discussed in detail (63, 235, 276). This radical and most of the substituted phenyl radicals have a reddish purple color; VII has been isolated as a crystalline solid, mp 68–71°; it is monomeric in solution (235). The esr spectra of these phenoxys have been studied in detail and clearly show the participation of the phenyl ring in ground-state stabilization (276).

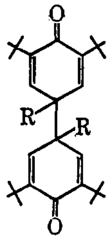
3. 4-H, -Cl, -Br, -I (Table VI)

TABLE VI

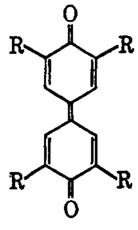
4-CHLORO-, 4-BROMO-, AND 4-IODOPHENOXY RADICALS

4-R substituent	Ref	4-R substituent	Ref
H (XVI)	28, 100, 181, 249	Br	181, 249
Cl	181	I	181, 230

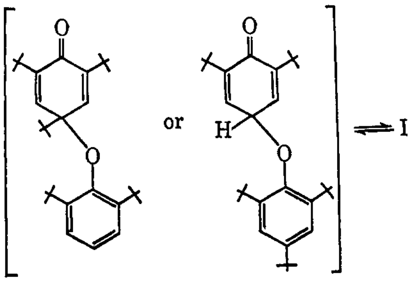
The esr spectrum of the 2,6-di-*t*-butylphenoxy radical was observed upon ultraviolet irradiation of the corresponding phenol in the presence of di-*t*-butyl peroxide (249). The spectrum consists of a weak doublet of triplets. Hydrogen abstraction by the *t*-butoxy radical from the phenol was postulated (see also section VI.O.3). Under similar conditions or on lead dioxide oxidation, no esr signal for 4-bromo-2,6-di-*t*-butylphenoxy was observed. The end product of oxidation of 2,6-di-*t*-butylphenol (XVI·H) with I is XV (R = *t*-butyl), which is formed *via* the dimer XIIIa (R = H); this dimer is isolable (168, 181). When XVI·H was oxidized with 2 moles of I, evidence for a readily dissociable quinol ether was obtained (181). A few minutes after completion of the reaction, the solution becomes deep blue again, due to the formation of I. The decay of this unstable product was followed by esr; the half-life of XVI was estimated as 10^{-6} sec.



XIIIa

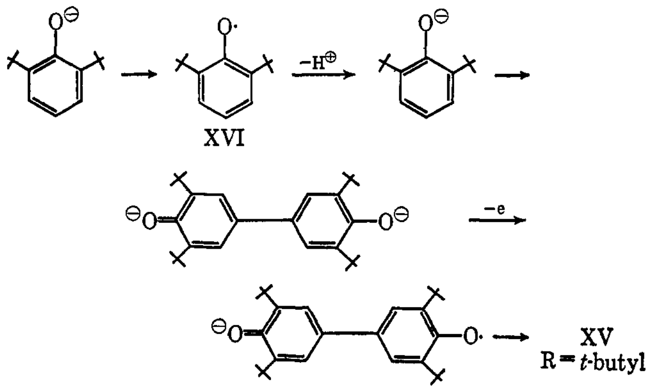


XV

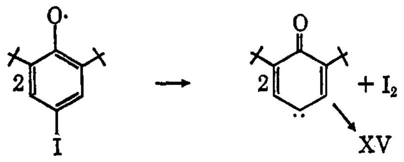


An esr study of the oxygen oxidation of XVI·H in alcoholic potassium hydroxide led to the postulate of the sequence shown in Scheme III (100); see also section VII.

SCHEME III

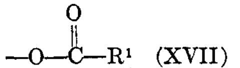
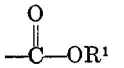
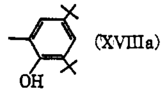


The 4-Cl and 4-Br radicals undergo rapid coupling to structures XIIIa (R = Cl and Br) which readily oxidize further to XV (R = t-butyl). For the chloro compound, this requires silver; for the bromo compound, bromine is already lost slowly at room temperature. The dimer from the 4-I radical loses iodine spontaneously to form the diphenoquinone; *cf.* section VII.C. Another possible mechanism for this reaction was proposed (181); it involves the coupling of two carbenes to give the diphenoquinone. No direct evidence exists for this path (see also ref 61).



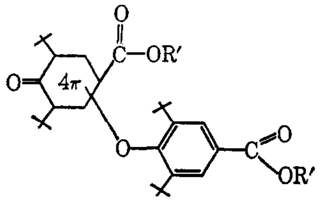
4. *4-Aryl Esters and 4-Benzoates* (*Table VII*)

TABLE VII
4-ARYL ESTERS AND 4-BENZOATES

4-R substituent	Ref
 $-O-C(=O)-R^1$ (XVII) R^1 = methyl, t-butyl, and phenyl	230, 273
 $-C(=O)-OR^1$ (XVIII) R^1 = methyl, ethyl, n-propyl, isopropyl, t-butyl, cyclohexyl, phenyl, diphenylmethyl, and  (XVIIIa)	196, 230

Phenoxy radicals of class XVII form noncolored solutions; characteristic radical colors are obtained on heating. From these solutions yellow solids can be isolated under nitrogen; these are dimers. In solution, they act as monomers. Esr spectra indicate that the 4 substituent is involved in the stabilization (230).

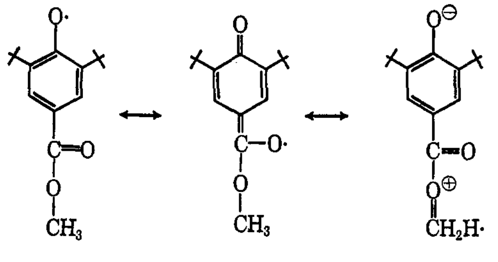
Radicals of class XVIII are very oxygen sensitive in solution and are largely unstable even under nitrogen. They can be isolated as diamagnetic, yellow solids, which preferably are obtained by carrying out the oxidation in aqueous methanol. Structure XVIII



XVIII dimer

has been proposed for these dimers (217, 230) (see also section VI.L.3).

The esr spectra of radicals which contain no α-hydrogen in the R^1 group show no hyperfine splitting. By contrast, the esr spectrum for XVIII (R^1 = methyl) suggests contributions of the resonance structures.

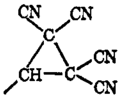
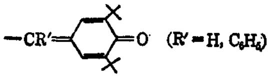


Oxidation of XVIIIa·H has given esr evidence for short-lived radicals which appear to be formed by oxidation at both hydroxyl groups. The 4-COOH, -COCl, $-CONH_2$, and $-CONR_2$ derivatives also give rise to phenoxy radicals as shown by esr (230).

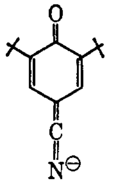
5. *4-C Substituent* (*Part of a Functional Group*)

Table VIII presents a number of representative radicals containing functional groups attached in the 4 position through carbon, such as hydroxy, alkoxy, carbonyl, cyano, etc. When V·H is oxidized with

TABLE VIII

4-R substituent	Ref
CN (V)	216
CHO (XIX)	16, 217
CH_2OH	16, 223
CH_2OR'	16, 223
CH_2NR_2'	16
CH=CHR' (R' = CN, CHO, CO_2-alkyl)	227, 238
CH=NR' (R' = C_6H_5, 1-naphthyl, *o*- and *p*-methylphenyl, *p*-nitrophenyl)	48
CH=NOR''	44, 225, 292
COR' (R' = CH_3, C_6H_5)	63, 223
CH=C(CN)R' (R = CO_2Et, CN, C_6H_5)	227
	205
	9, 16, 24, 217, 332

alkaline $K_3Fe(CN)_6$ (alkali solubility is explained by contribution from structure Vc), an equilibrium is established which can be displaced to the dimer of V (mp 111°) by addition of aqueous methanol.



Vc

In addition to the chemical evidence for the participation of the nitrile group in the stabilization of V, the nine-line esr spectrum supports the formulation of this phenoxy radical as a resonance hybrid with contributions from O, C, and N radical forms. In solution V exists to the extent of 50–60% (by titration) but is isolated as a solid dimer (216). Oxidation of 2,6-di-*t*-butyl-4-formylphenol (XIX·H) gives the phenoxy radical XIX, the same species which is observed as a secondary oxidation product of IX·H (16, 217).

The chemistry of radicals where an olefinic double bond has been inserted between the aromatic ring and the functional group is discussed further in section VII.E. A 12-line esr spectrum proved the participation of an allylic radical form in the stabilization. The introduction of a cyclopropyl group into the 4 position gave a radical species which gave no evidence for sp^2 hybridization with the cyclic group; only an interaction with the α-hydrogen was shown by esr. The esr spectra of several radicals in this group have been discussed by Becconsall, Clough, and Scott (16). Those phenols which carry a 4-α-methylene group give rise to the corresponding primary radical immediately; this is subsequently oxidized to a secondary radical which has an α-carbonyl group. Thus, the transformations $CH_2OH \rightarrow COOH$, $CH_2OCH_3 \rightarrow COOCH_3$, and $CH_2NR_2 \rightarrow CONR_2$ have been demonstrated. No phenoxy radical spectrum was observed for 2,6-di-*t*-butyl-4-bromomethyl- and 4-nitromethylphenol under oxidizing conditions (249).

Coupling of the unpaired electron with the nitrogen is observed for the Schiff bases; these radicals were said to be stable in the solid state for 6 months (48). For the 4-benzoyl and the 4-acetyl radicals, 1:2:1 triplets have been reported, which indicates lack of participation of the side chain in the stabilization. Additional examples of radicals which would fall in this group are given by Buchachenko (44), Pannell (249), and Scheffler (292).

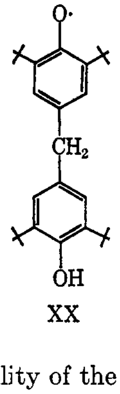
One of the most stable phenoxy radicals is galvinoxyl (9, 11, 71, 167) formed upon oxidation of 4,4′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenylmethane. This radical can be obtained as a blue crystalline solid, mp 153.2–153.6°, of 100% radical content, as well as in solution. Its spectral properties are listed in Table II. This compound is said to be stable in the solid state for more than 3 months. It is unreactive in isooctane and benzene but decomposes in methanol or ethanol (see below). The rate of decay of a 0.62 × 10^{-3} M benzene solution under nitrogen at 62.5° has been determined as 4 × 10^{-8} sec^{-1} (this is a half-life of about 200 days). Coppinger (71) reported galvinoxyl to be unreactive toward oxygen, but Greene and Adam (126) showed that the inhibition was due to hydrogalvinoxyl which is difficult to remove as an impurity. Galvinoxyl consumes oxygen; two of the products formed in this reaction are X and XIX·H. Addition of trihydrogalvinoxyl (*i.e.*, 4,4′-dihydroxy-3,3′5,5′-tetra-*t*-butyldiphenylmethane) to galvinoxyl produces an inhibition. Oxidation of the former by the latter leads to hydrogalvinoxyl. An ethanolic sodium hydroxide solution of galvinoxyl forms the anion in the presence or absence of oxygen, as determined by visible absorption spectra (168).

Since galvinoxyl is a quinone methide, it undergoes acid-catalyzed addition of methanol to the expected bisphenol. The formation of XV in this reaction is more surprising (71).

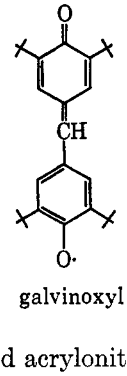
Galvinoxyl is unreactive toward triethyltin hydride (244), substituted stilbenes (127), and acyclic acyl peroxides (127).

A number of workers (9, 127, 176, 184) have used galvinoxyl as an efficient scavenger of C and O radicals.

The esr-spectrum of galvinoxyl has been examined by several workers. An initial nine-line spectrum is assigned to the phenoxy radical XX, while the final symmetrical ten-line spectrum indicates the equivalence of the four ring hydrogens in galvinoxyl.



XX



galvinoxyl

The stability of the substituted acrylonitrile radicals (R = CH=CH(R′)CN) varies with the nature of the R′ substituent; R′ = phenyl was more stable than the other two (Table VIII). A 1.15 × 10^{-3} M solution of the R′ = phenyl species had a half-life of about 14 days; the radical was isolable as a dark green solid (227). Participation of both the phenyl (R′) and cyano group in the resonance stabilization was shown by esr. In general, these three radicals were more stable than those based on cinnamic esters (section VII.E).

6. *Functional Groups Attached in the 4-Position through Group VI Elements (O, S, Se)*

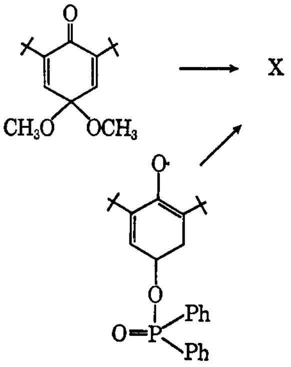
a. Oxygen (Table IX; *cf.* Table VII)

TABLE IX

4-R substituent	Ref
O—SO_2R' (R' = alkyl, aryl)	273
$OPOR''_2$ (R'' = alkyl, aryl, alkoxy, aryloxy)	273
O-Methyl (XI)	212, 217, 290
O-Ethyl	64, 217
O-Isopropyl	217
O-*t*-Butyl	222, 254, 273
Hydroxy	249
O-Phenyl	33, 292
O-Pentachlorophenyl	273

The change in the esr spectrum for the O-alkyl radicals from a three-line spectrum for O-*t*-butyl, a four-line spectrum for O-isopropyl, and a seven-line spectrum for O-ethyl to a nine-line spectrum for O-methyl shows clearly the importance of hyperconjugative participation of the hydrogens on the α-carbon of the alkyl group attached to oxygen. No transfer of the electron across the diaryl ether linkage occurs; only a triplet is observed (33, 292), while the R = $OPOPh_2$ substituent shows participation of phosphorus across oxygen (two triplets).

In contrast to lead dioxide or alkaline $K_3Fe(CN)_6$, DDQ in methanol does not oxidize XI·H to XI but rather forms an intermediate dimethyl ketal which readily hydrolyzes to X (19), which also results when the phosphorus compound is further oxidized by prolonged contact with alkaline $K_3Fe(CN)_6$ (273).

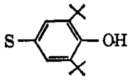
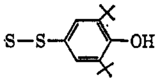
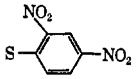


The esr spectrum of 2,6-di-*t*-butyl-4-hydroxyphenoxy (a doublet of triplets; only five lines observed due to partial overlap) was formed on ultraviolet irradiation of di-*t*-butyl peroxide and 2,6-di-*t*-butylhydroquinone at −15° (249).

b. Sulfur (Table X)

Although sulfur-containing phenols and polyphenols are widely used as antioxidants, few detailed examinations of the oxidation chemistry of such phenols have been reported. Müller and co-workers (239, 310) have prepared a large number of S-containing 2,6-di-*t*-butylphenols (XXI·H) and have studied many of the phenoxy radicals obtained on oxidation. In contrast to most hindered phenols, but analogous to V·H, XXIe–h·H are soluble in 2 *N* sodium hydroxide; this is explained by d-shell participation of sulfur.

TABLE X

4-R substituent	Compd no.	Ref
S-CH_3	XXIa	239 (XXIa–h)
S-*t*-butyl	XXIb	
S-C_6H_5	XXIc	
S-$COCH_3$	XXId	
$SOCH_3$	XXIe	
SOC_6H_5	XXIf	
SO_2CH_3	XXIg	
$SO_2C_6H_5$	XXIh	
	LIX	239
	LIX	239
		292
S-$CH_2CH_2C_6H_5$		310
S-CH=CHC_6H_5		293, 310
S-CH=CHCH=$CHOCH_3$		310
SOCH=CHC_6H_5		310
SO_2CH=CHC_6H_5		310
S-$PO(OC_6H_5)_2$		293

The phenoxy radicals XXIa–d are stable for several days, others only for a few hours. Yellow diamagnetic compounds have been isolated from the oxidation mixtures. The structure of these products is uncertain; upon addition of solvent, paramagnetic colored solutions are obtained again. These experimental observations indicate the existence of the equilibrium

$$\text{dimer (diamagnetic)} \overset{K}{\rightleftharpoons} \text{2 monomer (paramagnetic)}$$

and this has been proved by the quantitative evaluation of the esr spectrum of XXIa in benzene using diphenylpicrylhydrazyl as a standard (292). The equilibrium was temperature and concentration dependent; *K* increased with increasing temperature. The dissociation energy was calculated to be 9.85 kcal/mole; the degree of dissociation decreased sharply for concentrations exceeding 10^{-3} *M*. The radical appeared to decompose above 80°.

Somewhat surprisingly, the esr spectrum of XXIc showed only a triplet, a finding not consistent with participation of the phenyl group in the mesomerism. The same is true for the 4-dimethylaminophenyl group attached to sulfur. Sulfur d-shell participation clearly is proved, however, by the nine-component esr spectrum of XXIa. Resonance participation is also observed for the vinyl-containing side chains. In addition, a g factor greater than that found for I favors some localization of the unpaired electron on the S atom. The characteristic doublet of triplets observed in the esr spectra of phosphorus containing radicals (section V.A.7.b) is preserved in the radical with the 4-S-P-(=O)(OC_6H_5)$_2$ substituent (as well as in the oxygen analog), certainly strong experimental support for participation of S and O radicals in the mesomeric stabilization (205, 273).

c. Selenium (Table XI)

TABLE XI

4-R substituent	Ref
Se–CN	240
Se–CH_3	240
Se–isopropyl	240
Se–*t*-butyl	240
Se–C_6H_5	240

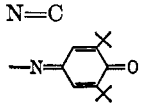
In contrast to oxygen and sulfur whose magnetic isotopes (^{17}O, ^{33}S) exists in such low concentrations in the natural isotope mixture that a direct proof of the participation of such heteroatoms in the resonance stabilization is not possible, ^{77}Se is present to about 7.6% in the natural mixture. The esr spectra of Se-containing radicals should therefore show resonance participation of a Se–R^1 group directly. This was proved for R^1 = isopropyl and *t*-butyl.

The Se-containing phenoxy radicals formed red solutions which were unstable in air or nitrogen. Maximum radical content was only about 10%. As with S substituents the monomer $\rightleftharpoons$ dimer equilibrium was far to the right.

7. *Functional Groups Attached in the 4 Position through Group V Elements (N, P, As)*

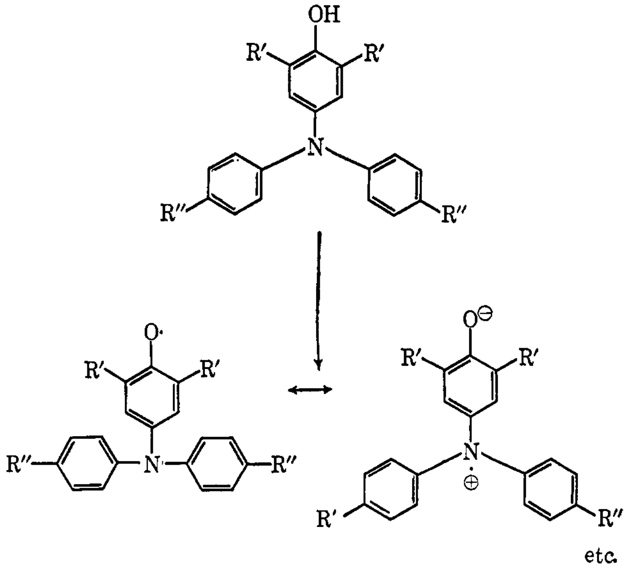
a. Nitrogen (Table XII)

TABLE XII

4-R substituent	Ref
NH_2	44
$N(CH_3)_2$	271
$N(C_6H_5)_2$ (XXII)	205
NO	44
NO_2	278
N=C	278
 (BIP)	10, 73

Esr data for all substituents have been reported. The change with temperature of the spectrum of R = NH_2 indicated interaction of the unpaired electron with the N nucleus (44). Hyperconjugative participation of the side chain was observed for R = $N(CH_3)_2$, but for R = $N(C_6H_5)_2$ a 1:2:1 triplet did not support any interaction with the N nucleus (205).

The effect of substituents R″ in the R group of XXII (R = NPh_2) suggested the participation of polar structures, however. One of the resonance structures written by Müller to account for the stability and color of phenoxy radicals is a zwitterion type with a positive charge on one of the ring C atoms (217). It was reasoned that a greater participation of polar structures was to be expected for *p*-hydroxytriarylamines since the central N atom might show tendencies toward quaternization (245).

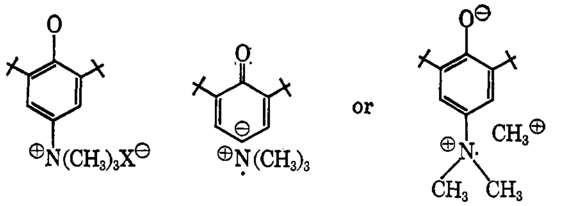


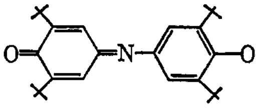
XXIIa, R″ = NMe_2; R′ = H
b, R″ = NMe_2; R′ = *t*-Bu
c, R″ = H; R′ = *t*-Bu
d, R″ = OMe; R′ = *t*-Bu

Lead dioxide or silver oxide oxidation of XXIIa·H in benzene gave a blue radical which was stable only for a few minutes. In the more polar nitrobenzene, the radical was green and somewhat more stable. These results not only support a stabilization by polar structures, but also indicate the pronounced stabilizing effect of a 4-NPh_2 group in the absence of 2,6-di-*t*-butyl substitution.

The stable brown radical XXIIb was conveniently prepared from the corresponding phenol by oxidation with *p*-benzoquinone in acetone; XXIIb precipitated and was isolated in 80% yield (mp 194–196° dec). A strong esr triplet was reported due to the splitting of the ^{14}N nucleus. This means that the proton coupling constants of the phenyl nuclei must be very small. However, an increase in the a_N interaction constant (to 4.17 for XXIIb) (278) and dipole moment measurements (XXIIb·H, μ = 2.9 D.; XIIb, μ = 8.7 D.) (245) support a dipolar structure with the positive charge on nitrogen. Shifts in visible absorption maxima also point toward participation of polar structures in the stabilization (λ_{max} 650 mμ (ϵ 6000) in heptane, 680 (8300) in acetone, and 690 (14,100) in methanol). In air, solid XXIIb decomposed slowly; the radical content of a benzene solution was unchanged after 3 hr of contact with oxygen (*cf.* section VI.N); XXIIc and d were stable for weeks in solution but have not been isolated in the solid state.

Quaternary ammonium radical salts (X = I, CH_3SO_4, ClO_4) show only a 1:2:1 triplet (two equivalent *m*-hydrogens) and no evidence for "no-bond resonance structures" involving nitrogen (278). BIP, a radical prepared by Coppinger (73), is more stable than galvinoxyl to which it is closely related. The solid radical melts at 155–156°; it is described as inert toward oxygen. A sample of the radical has remained unchanged in air for 3 years. The esr spectrum indicates equivalence of the four *meta* protons (44, 73).



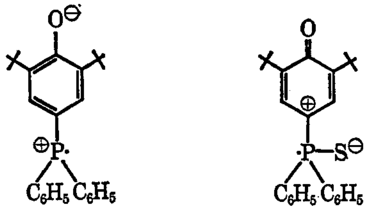


BIP

Competitive scavenging experiments showed 2,3′,5′,6-tetra-*t*-butylindophenoxy (BIP, 10) to have efficiencies toward cyanoisopropyl and *t*-butoxy radicals comparable to those of galvinoxyl.

b. Phosphorus (Table XIII)

Evidence for an unpaired electron on phosphorus has been reported by Ramirez (264, 265), and phosphorus-containing phenoxy radicals were prepared with the objective of showing the participation of phosphorus in the resonance stabilization (206). Radical XXIIIa is extremely unstable in air; it is oxidized to XXIIIb, which then undergoes decomposition. All phosphorus-containing phenoxy radicals give a doublet of triplets, an observation compatible with interaction of the odd electron with the P^{31} nucleus, which can be represented by resonance structures such as



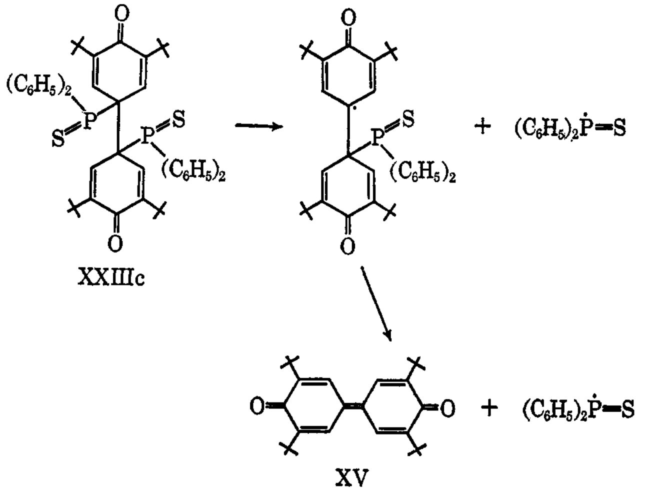
A measure of the probability of finding the unpaired electron on phosphorus is given (*i.e.*, for the 3s component of the wave function which describes this electron) by the coupling constants a_P (which changed from 6.8 to 16.8 gauss for XXIIIa–e) and the parallel increase in $a_{H,meta}$ (1.6–2.35 gauss). The positive charge on phosphorus therefore leads to an increase in electron density toward it and away from the oxygen radical form.

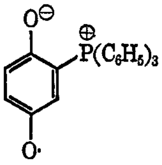
TABLE XIII

4-R substituent	Compd no.	Ref
$P(C_6H_5)_2$	XXIIIa	206
$P{=}O(C_6H_5)_2$	XXIIIb	206
$P{=}S(C_6H_5)_2$	XXIIIc	206
$P^{\oplus}(C_6H_5)_2CH_2OHCl^{\ominus}$	XXIIId	206
$P^{\oplus}(C_6H_5)_2C_2H_5BF_4^{\ominus}$	XXIIIe	206

The instability of these radicals did not permit their isolation as solids. A yellow diamagnetic dimer of XXIIIc was oxidized to XV (R = *t*-butyl) in ethanol. When the dimer was warmed gradually from frozen benzene and the change followed by esr, an intermediate triplet suggested loss of $(C_6H_5)_2\dot{P}{=}S$ and formation of a new phenoxy radical (Scheme IV). The esr spectra of phenoxy radicals with phosphobetaine structure have been discussed by Lucken (187, 188, 207).

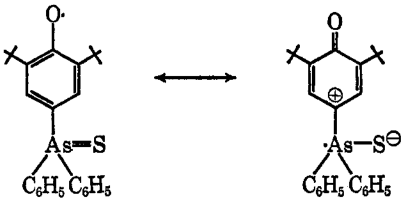
SCHEME IV





c. Arsenic

Mesomerism involving arsenic radicals was shown by an esr examination of an appropriately substituted radical, which was green colored and relatively unstable. The coupling constants are $a_{As} = 14.4 \pm 0.5$ and $a_H = 2.0 \pm 0.1$ gauss (205, p 241).



8. *Functional Groups Attached in the 4 Position though Group IV Elements (Si, Sn)*

The radical 2,4,6-trimethylsilylphenoxy was found to have a half-life of 2600 min and to be relatively stable to oxygen. Its esr and infrared spectra were discussed (171).

The tin-containing radical 2,6-di-*t*-butyl-4-triphenylstannylphenoxy was prepared by PbO_2 oxidation of the phenol; a green, unstable color was observed. The esr spectrum showed interaction of the unpaired electron with ^{117}Sn and ^{119}Sn (205, 309). A π–σ mechanism seems a plausible explanation since Sn has no electron pair available for bonding.

B. PHENOXY RADICALS WITHOUT 2,6-DI-*t*-BUTYL SUBSTITUTION

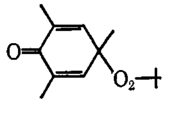
In Tables XIV–XVII phenoxy radicals are compiled which are not characterized by 2,6-di-*t*-butyl substitution. For example, polyalkyl-, polyphenyl-, polyhalo-, and *o*-alkoxy-substituted radicals will be discussed.

1. *Polyalkylphenoxy Radicals (Table XIV)*

TABLE XIV

Substituents	Compd no.	Ref
2,4,6-Tri-*t*-amyl	XXIVa	69
2,6-Di-*t*-amyl-4-methyl	XXIVb	253
2-Methyl-4-formyl-6-*t*-butyl	XXIVc	16
2,4-Di-*t*-butyl-6-methyl	XXIVd	16
2,6-Dimethyl-4-*t*-butyl	XXIVe	16
2,4-Di-*t*-butyl-5,6-dimethyl	XXIVf	16

The 2,4,6-tri-*t*-amylphenoxy radicals was found to be less stable than I (69). Oxidation of 2,6-di-*t*-amyl-4-methylphenol with lead dioxide reportedly leads to the 4-hydroxy-3,5-di-*t*-amyl-4-benzyl radical (253) (see section VII.D). Phenoxy radicals XXIVc–e were quite unstable, as indicated by their short-lived esr signals; however, the signal from XXIVf was both intense and stable, suggesting increased stability due to increased steric crowding (16). A number of other mono-*t*-butyl-, methyl-, and ethyl-substituted phenols described by Becconsall, Clough, and Scott (16) did not give primary radicals; instead the spectra observed were those of oxidized radicals. For example, in the oxidation of 2-*t*-butyl-4-ethyl-6-methylphenol the esr spectrum observed is ascribed to 2-*t*-butyl-4-acetyl-6-methylphenoxy. The radical 2,6-dimethyl-4-formylphenoxy was observed upon oxidation of mesitol. In the oxidation of mesitol with *t*-butyl hydroperoxide the cyclohexadienone peroxide formed could arise by a mechanism involving 2,4,6-trimethylphenoxy (25, 50) (*cf.* section VI.O.2). Primary phenoxy radicals of low stability can be trapped as quinol ethers (*cf.* section VI.L.3).

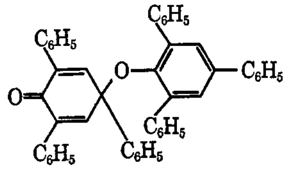


2. *o-Phenyl- and Polyphenylphenoxy Radicals (Table XV)*

TABLE XV

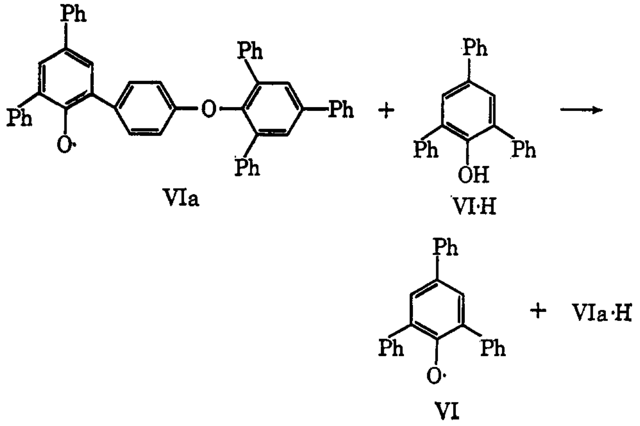
Substituents	Ref
2,4,6-Triphenyl (VI)	88, 91
2,3,4,6-Tetraphenyl	95
Pentaphenyl	311
2,4-Diphenyl-6-*t*-butyl	311, 333
2,6-Diphenyl-4-*t*-butyl	311, 333
2-Phenyl-4,6-di-*t*-butyl (XL)	234, 333
3-Hydroxy-2,4,6-triphenyl	84
2-Benzoyl-4-*t*-butyl-6-phenyl	216, 333

A number of additional radicals of this class have been listed in Table I (section III.B.9). Infrared, esr, and electrochemical results have been discussed already for VI. The chemistry of this radical has been investigated principally by Dimroth and his school (84, 88, 89, 91). The dimers of these phenoxy radicals have been formulated as quinol ethers.

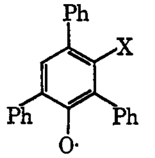


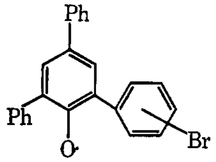
The proof for this structural assignment was mentioned in section IV.A. In the presence of alkaline $K_3Fe(CN)_6$, VI was a catalyst for the dehydrogenation of 4-H-4-alkylpyrans (93); this provided further evidence for the ability of VI to act as a hydrogen abstractor.

When solutions of VI were heated, a gradual shift in the absorption maximum from 535 to 585 mμ was observed, and the solution finally turned blue. To this blue substance was assigned structure VIa and a mobile equilibrium between VIa and VI was noted. Sodium–pyridine reduction of VIa gave VI·H and triphenylbenzene. Similar behavior was noted for another blue radical, 2,4,6-tri(4-phenoxyphenyl)phenoxy. The brominated and chlorinated radicals, VI-Br and VI-Cl, respectively, show an even greater tendency



toward dimerization than VI, while the radical VIb, which contains bromine in the side chain, behaves more like VI. One would have anticipated that increased crowding in VI-Br and VI-Cl would favor the monomer. The structures of these dimers have not been proved; they are perhaps not simple quinol ethers.

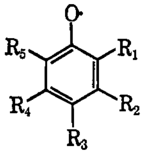

VI-Br (X = Br)
VI-Cl (X = Cl)

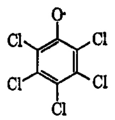

VIb

Radical XL exists in a monomer–dimer equilibrium (a 20% solution in benzene gives a 13% monomer content by the Gouy method). It is a strong oxidizing agent and oxidizes XVI·H to XV and IX·H to LVI in high yield. The esr spectrum of XL showed only a broad line, in contrast to the 13-line spectrum of VII.

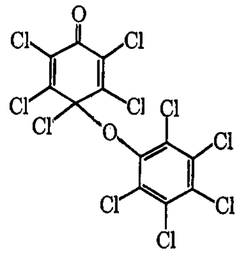
3. *Polyhalophenoxy Radicals (Table XVI)*

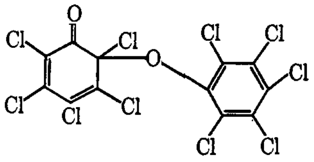
Table XVI



Compd	R_1	R_2	R_3	R_4	R_5	Isolable as dimer	Ref
XXVa	Cl	H	Cl	H	Cl	−	229
XXVb	Cl	H	Cl	H	I	−	229
XXVc	Cl	Cl	Cl	H	Cl	+	229
XXVd	Br	Br	Br	H	Br	−	229
XXVe	Cl	Cl	Cl	Cl	Cl	+	229, 267
XXVf	Br	Br	Br	Br	Br	−	229
XXVg	Cl	Br	Cl	Br	Cl	−	229
XXVh	Cl	CH_3	Cl	CH_3	Cl	+	229
IV	Cl	Cl	CH_3	Cl	Cl	+	229
XXVi	Cl	Cl		Cl	Cl	+	229

The action of lead dioxide or fuming nitric acid (at −25°) on polyhalophenols gives rise to paramagnetic compounds which have been characterized by examination of their esr spectra (229). This group of phenoxy radicals very readily undergoes dimer formation and many of the dimers have been isolated. In solution the dimers react as monomeric phenoxy radicals, although monomer concentration is generally less than 1%. They are relatively (compared to I) unreactive toward oxygen. Their stability must be due to mesomeric contributions of halogen. Radical XXVe and its dimer have been extensively investigated (229, 267). The dimers have a 4,4-quinol ether structure, supported by infrared absorption (1705 cm^{-1}). The dimer of XXVe is also obtained by direct oxidation of the phenol at 0° with fuming nitric acid. It can be oxidized further to chloranil in 80% yield (55). The 2,2 isomer has been reported (80) from the reaction of 2,2,3,4,5,6-hexachloro-3,5-cyclohexadienone and sodium pentachlorophenoxide; however, the properties of this compound appear identical with the 4,4 isomer (81).



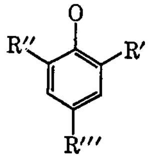


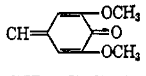
Reactions of halogenated phenols which in some cases appear to involve phenoxy radicals were reported years ago by Hunter and his co-workers (151–154). The unreliability of attributing color formation to radical generation was pointed out dramatically by Müller (223), who showed that the brilliant blue color observed upon oxidation of silver 2,4,6-tribromophenoxide (63) was not associated with an esr signal.

The polymeric ethers formed an oxidation of XXVa·H with benzoyl peroxide (*cf.* section VI.O.1) most probably arise *via* the corresponding phenoxy radicals; polyethers also are formed on lead dioxide oxidation of 2,4,6-tribromophenol, XXVa·H, and XXVf·H (79, 82, 139).

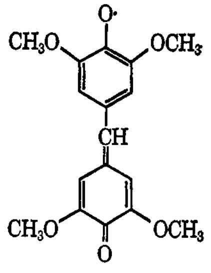
4. *o-Alkoxyphenoxy Radicals (Table XVII)*

Table XVII



Compd	R′	R″	R‴	Ref
XXVIa	CH_3O	CH_3O	CHO	305
XXVIb	CH_3O	CH_3O	$COCH_3$	305
XXVIc	CH_3O	CH_3O	COC_2H_5	305
XXVId	CH_3O	CH_3O		306
XXVIe	CH_3O	CH_3O	$CH{=}C(CN)_2$	209
XXVIf	CH_3O	*t*-Butyl	*t*-Butyl	7
XXVIg	*t*-Butoxy	*t*-Butyl	*t*-Butyl	207, 219

Stable phenoxy radicals were generated at room temperature from a number of 2,6-dimethoxyphenols (305) and were detected by their color (green) and their visible and esr spectra. The latter clearly showed the involvement of methoxy protons and the conjugate group in the 4 position. Guaiacol derivatives did not form stable radicals. These observations are important in lignin chemistry since these phenols may serve as model compounds of the lignin structure. As a result of further work on such model systems, a stable purple solid free radical, syrinoxyl (XXVId), was obtained from the oxidation of 4,4′-methylenebis-2,6-dimethoxyphenol (306). This material melted at 250° (sintered at 190°). It showed the characteristic phenoxy radical absorption at 6.45 μ and visible bands at 413, 458, 650, and 850 mμ. The structure of XXVId was supported by a detailed esr analysis, which surprisingly suggested an asymmetry which makes the 2 and 6 positions nonequivalent, although interaction of the unpaired electron with the methide hydrogen atom was shown. When exposed to the air for 1 week, the radical content of XXVId decreased to one-fifth its original value.



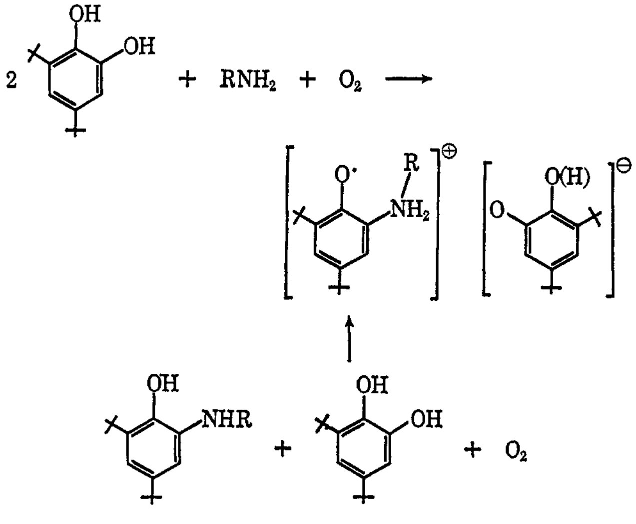
XXVId

The stability of XXVId makes it clear than 2,6-dimethoxyphenols which are substituted with a conjugated system in the 4 position form remarkably stable radicals. Radical XXVIg exists as a diamagnetic solid; *ortho*- and *para*-coupled quinol ethers or charge-transfer structures were suggested. A 5.5% benzene solution showed a 2% radical concentration.

5. Radical Salts

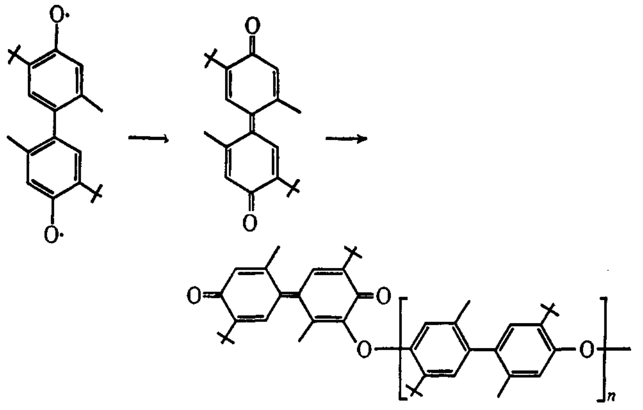
Radicals salts stable toward oxygen and moisture were prepared by the reaction of 4,6-di-*t*-butylcatechol with certain aliphatic amines (R = *t*-butyl, cyclohexyl, N-methylcyclohexyl) and oxygen or by interaction of equimolar amounts of 4,6-di-*t*-butylcatechol and 4,6-di-*t*-butyl-2-alkylaminophenol and oxygen (Scheme V). The radical character of the crystalline products was proved by esr; these materials were polymerization inhibitors (179). The structure of these salts was not elucidated.

SCHEME V

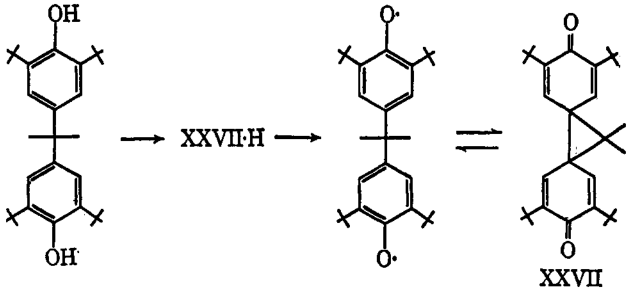


C. BIRADICALS OF OXYGEN

Bourdon and Calvin reported the preparation of an oxygen diradical (36). The product slowly polymerized and a series of polymers were characterized by their ultraviolet spectra. For maximum stability these authors suggested the introduction of two additional *o*-*t*-butyl groups into the diradical. Chlorine as a substituent failed to give any evidence for oxidation to a diradical.

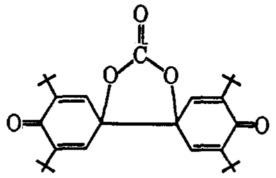


Esr signals attributable to biradicals ($g \cong 4$) were not observed for XXVII or XXVIII. The latter was prepared from the potassium ferricyanide oxidation of 2,6-di-*t*-butylhydroquinone in the presence of phosgene and exists as the dispiran (274). XXVII, a red solid (characterized by its infrared spectrum), is derived from the oxidation of 2,2-bis(3,5-di-*t*-butyl-4-hydroxyphenyl)propane (XXVII·2H) whose oxidation yields the monophenoxy radical (XXVII·H) initially. Further oxidation is accompanied by a loss of intensity of the esr spectrum, interpreted in terms of the equilibrium XXVII·2H + XXVII $\rightleftharpoons$ 2XXVII·H. Although the biradical form of XXVII could not be observed directly, the equilibrium biradical $\rightleftharpoons$ dis-

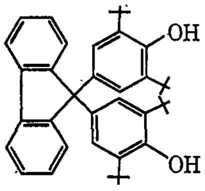


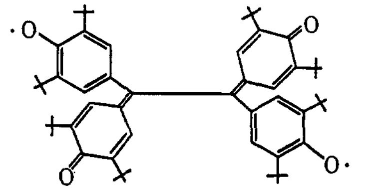
XXVII

piran was inferred from the rapid reaction of XXVII with oxygen and from line broadening in the nmr (53).

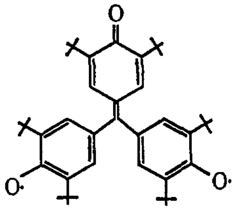

XXVIII

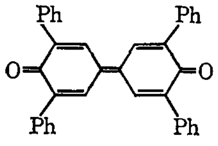
When the bridging group was modified, as in XXIX, internal bond formation was made more difficult (54) and oxidation yielded a triplet species when observed at *ca.* −180° by esr. Rapid interconversion of this species and the corresponding dispiran was noted when the sample was heated. Oxidation of XXIX at room temperature with alkaline potassium ferricyanide gave a dark oil, and the infrared spectrum of the latter supported a triplet ⇌ dispiran equilibrium. Bisgalvinoxyl (XXX) was obtained as a dark crystalline solid by oxidation of the corresponding bisphenol (52). The esr spectra of XXX in a solid matrix (77°K) as well as in solution at room temperature are consistent with a triplet electronic state.

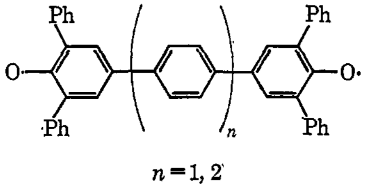

XXIX


XXX

For the stable biradical XXXI (mp 280°), obtained by oxidation of the bisphenol, a triplet was postulated in agreement with MO calculations and paramagnetic susceptibility measurements (165, 335). The unusual carbonyl absorption (about 1600 cm^{-1}), which is in agreement with that assigned to the keto form of phenoxy radicals (see section IV.A), of tetra-*t*-butylstilbenequinone led to the postulate of a low-lying diradical state (31). This compound showed high reactivity and was copolymerized with styrene.


XXXI


XV


$n = 1, 2$

While tetraphenyldiphenoquinone XV (R = Ph) gave only a weak esr signal, strong signals were obtained for polyphenylphenoxy radicals. Polyphenylphenols without *o*-phenyl substituents gave no evidence for radical formation (92).

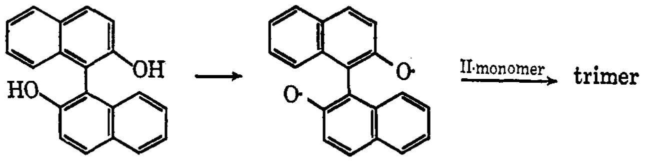
The coupling of biradicals is an important step in ring formation in natural product synthesis (section IX).

D. POLYNUCLEAR ARYLOXY RADICALS

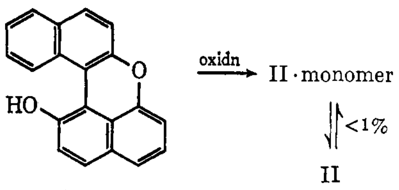
Oxidation of α- and β-naphthol with various reagents (peroxy radicals, lead dioxide, silver oxide) is accompanied by esr signals (44, 269). These signals were reported to show that the α-naphthoxy radical was more stable than the β-naphthoxy radical, although it is not entirely certain that the spectra were due to the monomeric radicals (171, 280, 312). Substitution increased radical stability; 1-triphenylmethyl- and 1,6-di-*t*-butyl-β-naphthoxy had half-lives of about 40 hr at 20° in benzene solution (44, 266). However, dehydrogenation of 3,3′-bis(1,6-di-*t*-butyl-β-naphthol) gives rise to the same esr spectrum as 1,6-di-*t*-butyl-β-naphthol, so that the latter evidently does not exist as a monomeric radical. Oxidation of 1,3,4-trichloro-β-naphthol with lead dioxide gave a fairly stable triplet of triplets in the esr. The radical was isolable as a diamagnetic dimeric solid (280).

Oxidation of naphthols with stable radicals such as I leads to quinol ethers (*cf.* section VI.L.2).

Although several coupling products are possible for the β-naphthoxy radical, 1,1′-dinaphthol (XXXII·2H) is the major product when β-naphthol is oxidized with ferric chloride (280). Depending on the oxidizing agent XXXII·2H can be oxidized to a number of different products. The monomeric radical, II·monomer, which is formed when II is dissolved in benzene or chloroform with formation of a reddish purple color, is stable for several hours. There is no direct proof by esr measurement for XXXII (280); it forms a bisquinol ether with I rapidly. The O–O coupling postulated for the dimer II, although disproved, has recently been reiterated (170). In the crystalline state, the degree of dissociation is low; this is also the case for "Gold-

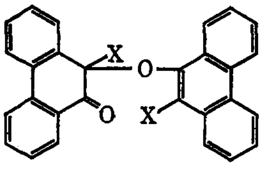


XXXII·2H XXXII



II·H(monomer)

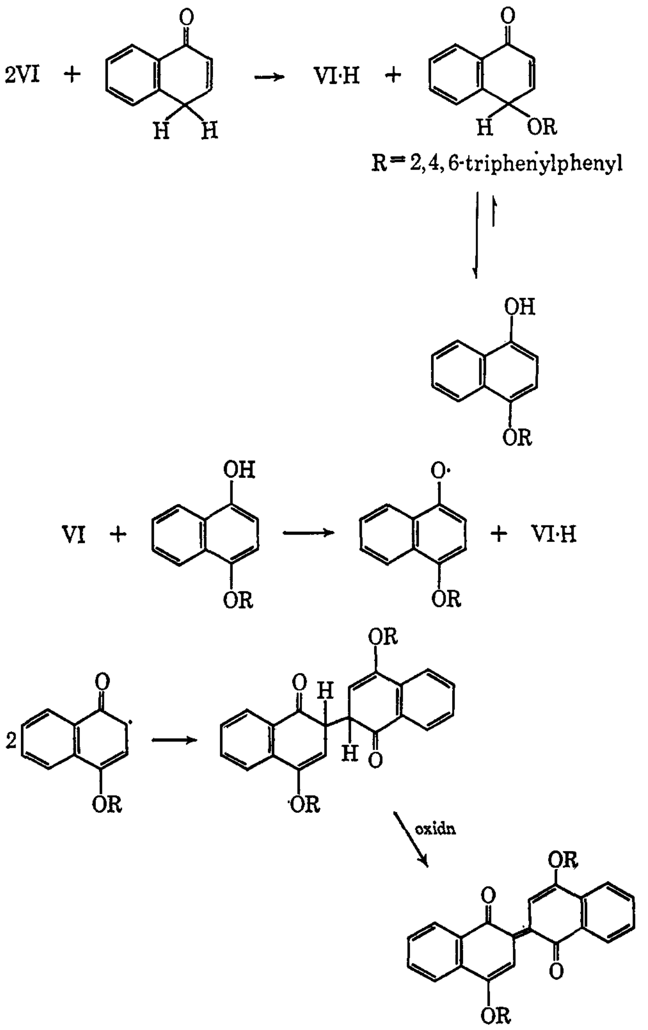
schmidt's radical" (III) derived from substituted phenanthrols, which in solution is dissociated to a very small extent, since no esr signal has been observed (237). Lack of dissociation in the dark and appearance of paramagnetism only on irradiation cast additional doubt upon any appreciable existence of III as a radical monomer (76). The structure of III is not that of a peroxide but is a quinol ether IIIa, an assignment supported by infrared absorption at about 1690^{-1} cm (237).



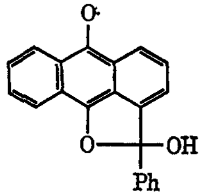
IIIa

Oxidation of α-naphthol with VI and further oxidation of the intermediate 1,4-naphthohydroquinone monotriphenylphenyl ether with added VI gave a bisnaphthoquinone derivative. For its formation the series of reactions in Scheme VI was suggested (89).

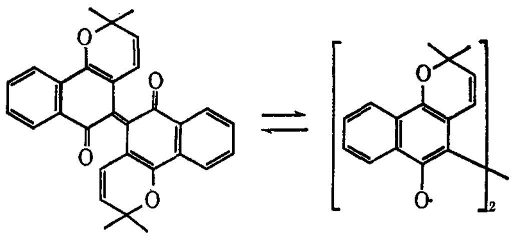
SCHEME VI

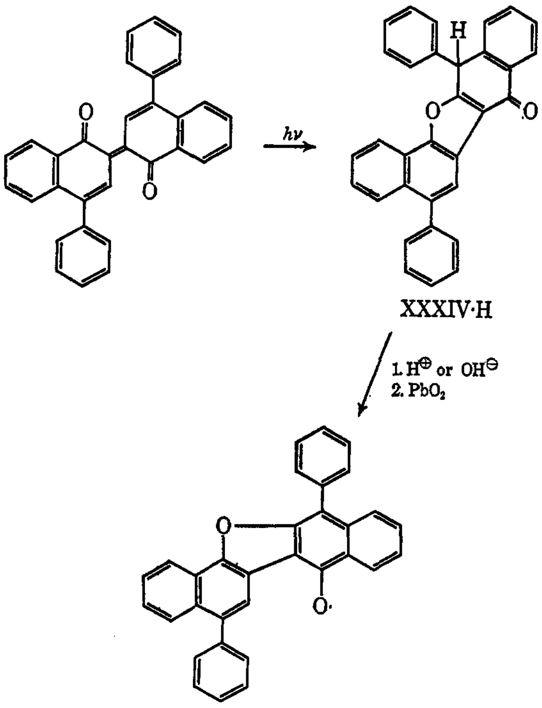


Another alleged example of an aryloxy radical species (XXXIII) reportedly is formed by electrolytic oxidation (294). Related examples of aryloxy radicals have been confirmed by esr measurements. A compound (289) isolated from teak gave a weak esr signal in the solid state, but not in solution. This and other evidence was interpreted in terms of the equilibrium shown. The green-black radical XXXIV was formed from the oxidation of the dienone–phenol rearrangement product of XXXIV·H (295); it was 15% in the radical form in the solid state and stable to oxygen. In solution it was found to be monomeric in the 10^{-6} to the 5×10^{-4} mole/l. range. Its degree of dissociation places it between I and VI. Comparison of XXXIV with α,α-diphenylpicrylhydrazyl in their efficiency to trap radicals formed from organic solvents by cobalt-60 α-radiolysis showed the former to be slightly more efficient (295).



XXXIII





Additional examples of polynuclear coupling products which can arise *via* phenoxy radicals are given by Scott (297).

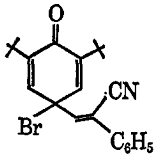
VI. REACTIONS OF PHENOXY RADICALS

A. REDUCING AGENTS

Phenoxy radicals are reduced to the corresponding phenols in high yield by a variety of reagents. Among these are iodide ion, catalytic hydrogenation over suitable catalysts (such as Pt and Pd), hydroquinone, hydrazobenzene (210, 211, 213, 214), and metals, metal hydrides, and organometallic compounds (section VI.K). Iodide ion also reduces phenoxy radicals dimers and quinol ethers to the respective phenols.

B. HALOGENS, PHENYLIODONIUM DICHLORIDE AND DIPHENYLIODONIUM CHLORIDE

The reaction (68) of phenoxy radicals with bromine or chlorine yields the derivatives of type VIII which are useful for the generation of phenoxy radicals by the action of metals (section III.A.6). These compounds are crystalline solids. They react with base or alcoholic base to form quinols or quinol ethers, respectively (214). The triply allylic bromide XXXV gives the methyl ether simply on treatment with methanol (227).

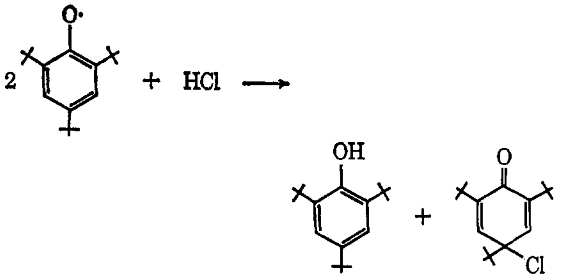


XXXV

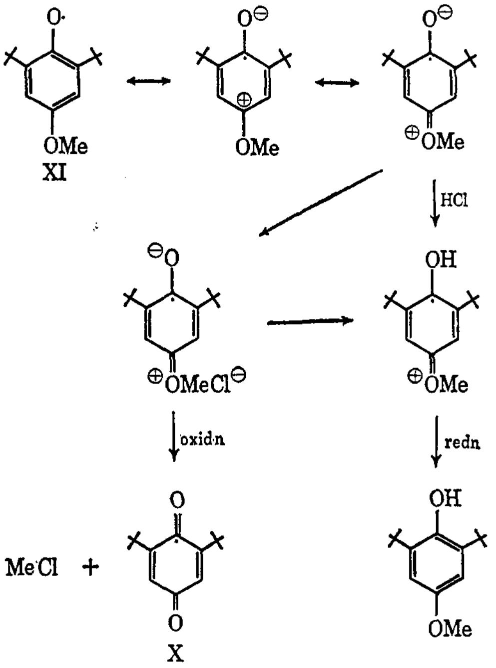
Compound VIII (R = Cl) is also formed by the reaction of 2 moles of I with phenyliodonium dichloride (214). The other product of the reaction is iodobenzene. Phenyl radicals generated from diphenyliodonium ion apparently are capable of displacing *t*-butyl groups from phenoxy radicals. It was reported (23), for example, that I formed both VII·H and 2,4-di-*t*-butyl-6-phenylphenol (XL·H) as well as isobutylene. The products are readily explained by assuming 2,2- and 4,4-disubstituted cyclohexadienones as intermediates. From the attack of phenyl radicals on VII 2,4-diphenyl-6-*t*-butylphenol and 2,6-di-*t*-butyl-4-phenylphenyl phenyl ether were identified tentatively. In the reactions of phenoxy radicals with Grignard reagents where phenyl radicals also intervene, no such substitutions have been reported (*cf.* section VI.K).

C. ACIDS

The reactions of several phenoxy radicals with both inorganic and organic acids have been reported, but in many cases products have not been fully characterized and mechanisms are speculative. Concentrated hydrochloric acid reacts with I yielding both I·H and VIII (in a ratio of 3:1). The disproportionation to phenol and a cyclohexadienone derivative appears to be a general reaction (Eq 6). A concerted displacement mechanism has been suggested, based on attack of Cl^- on the quinol ether dimer of I (333). Loss of the methyl group occurs with XI to give approximately equal amounts of XI·H and X; the mechanism below has been suggested (215).

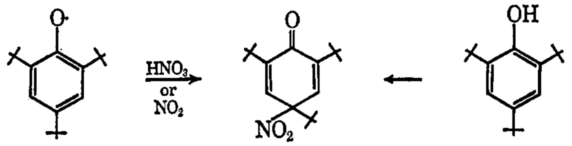


(Eq 6)

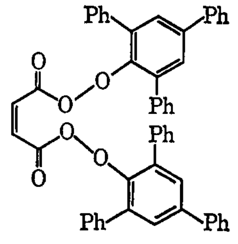


The reaction with acids is reversible in a sense; *i.e.*, treatment of VIII with sodium 2,4,6-tri-*t*-butylphenoxide results in the blue color of I and sodium bromide (182). Two modes of reaction with hydrochloric acid are reported for VI. An intermediate hypochlorite is not isolated but goes to chlorinated products on standing, or reverts to the radical on treatment with base (89). Two moles of VI react according to Eq 6, a reaction which is likewise reversible by base. Perchloric (70%) or sulfuric acids lead to a deep blue coloration which was unstable. This was thought to be due to protonated VI. Evidence for this cation radical was obtained from esr spectra obtained on flash photolysis of VI·H in aqueous ethanol containing 50% perchloric or sulfuric acid. In the absence of acid the spectrum was that of the phenoxy radical VI (177). It was concluded that phenoxy radicals are very weak bases and only at very high acid concentration are spectra observed which are attributable to cation radicals.

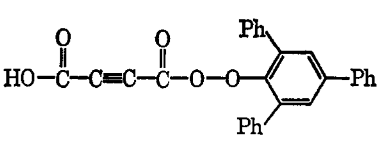
The reaction of I with nitric acid forms the nitration product VIII (R = NO_2) identical with the product of nitration of I·H with nitric acid or nitrogen dioxide (68, 180, 339).



Reaction of I with acetic acid (182) has been reported, but the products have not been characterized. Dimroth (88, 89) has also reported the reaction of VI with a series of organic acids. The products are formulated as peresters. These results should be contrasted with the general statement of Müller, that phenoxy radicals have been found to be unreactive toward carboxylic acids (226). However, the conditions employed by Dimroth appear to be somewhat more vigorous than those commonly employed in phenoxy radical reactions involving hydrogen abstraction. Thus, VI reacts with maleic acid in boiling carbon tetrachloride to give VI·H and XXXVI. Various degradation reactions are cited to support this structure. An alternate quinol ether structure for XXXVI appears to be ruled out since no infrared absorption is found in the 1580–1670-cm^{-1} region. Acetylenedicarboxylic acid reacts on only one hydrogen to give XXXVII. This reaction of VI is said to take place with other acids which have pK_a values greater than 3.5. Structures XXXVI and XXXVII appear to be in need of further substantiation.

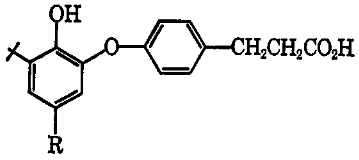


XXXVI



XXXVII

Reactions with phloretic acid (3-(*p*-hydroxyphenyl)-propionic acid) proceed exclusively at the phenolic hydroxyl of the acid to give diphenyl ethers *via* quinol ether formation and loss of isobutylene (section VI.L.5).

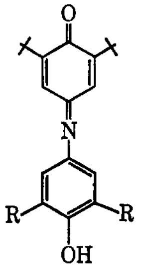


R = CN, $COCH_3$, $CO_2C_2H_5$

D. BASE AND AMINES

Phenoxy radicals generally are unreactive toward hydroxide ion but only a few observations have been reported. The fact that I can be generated from VIII (R = Cl) and I·H by the action of sodium hydroxide indicates that phenoxy radicals are not reactive toward base (213; see also 88). Radical XXIIb does not react with aqueous base (245). Alkali accelerates the decomposition of VI in methanol (88).

The reaction of I with *m*-chloraniline occurred readily at room temperature in carbon tetrachloride. The reaction was second order, with a bimolecular rate constant = 4.0 l. $mole^{-1}$ min^{-1} (198). Products of this reaction were not characterized. Reaction of I with *p*-phenylenediamine (250) showed a mole ratio of 3.11 ± 0.17 which indicated secondary reactions after the initial abstraction reaction to produce I·H. Treatment of a benzene solution of I with *p*-aminophenol was reported to give a mixture of I·H, unreacted *p*-aminophenol, and indophenols (XXXVIII) (246).



XXXVIII
R = H, or *t*-butyl

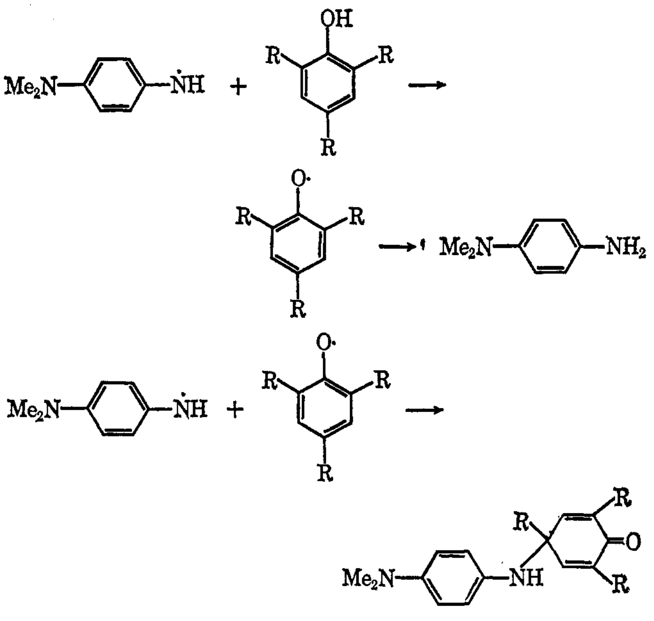
Würster's blue was generated from the action of VI on tetramethyl-*p*-phenylenediamine (88). Disproportionation of VII was observed with piperidine, but not pyridine (333). The dimer of XXVe oxidizes aniline, diphenylamine, and benzylamine to highly colored solutions (267).

Alkali-stable quinamines were formed by the action of Würster's red (derived from *p*-dimethylaminoaniline) on I·H and mesitol. Evidence was presented that the Würster salt oxidized the phenols to the phenoxy radical which then coupled (150) (Scheme VII).

E. HYDROCARBONS, OLEFINS, AND DIENES

Generally, phenoxy radicals are prepared in hydrocarbon solvents, and they are quite stable in solutions of such solvents. However, reaction with solvent is suggested by variations in yield of phenoxy radicals in

SCHEME VII



R = methyl or *t*-butyl

different solvents. For example, the lead dioxide oxidation of I · H gives the highest yield of I in benzene, a lower yield in cyclohexane or petroleum ether. The slow decrease in radical content even when air and moisture are rigorously excluded is further evidence of radical decomposition due to disproportionation which may involve the solvent. The products of disproportionation of many phenoxy radicals have been identified (*cf.* section VIII).

The rates of reaction of I with *n*-decane, isodecane, toluene, ethylbenzene, and cumene were reported (243) over a temperature range of 70–150°. The reaction was first order in phenoxy radical, and the rate was fastest in ethylbenzene and slowest in isodecane. The sequence

$$\mathrm{I} + \mathrm{RH} \xrightarrow{k_1} \mathrm{I{\cdot}H} + \mathrm{R}\cdot$$

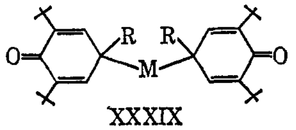
$$\mathrm{I} + \mathrm{R}\cdot \xrightarrow{k_2} \mathrm{I{\cdot}R}$$

was postulated, with k_1 being highly endothermic. Activation energies ranged from 27.5 kcal/mole (*n*-decane) to 16.5 kcal/mole for the weakest C–H bond (in cumene). Products were not characterized, and the reaction is evidently more complex than the sequence suggests (section VI.O.3). It would appear that the data actually reflect rates of disproportionation of I in various solvents (*cf.* section VIII).

The reaction of halogen-containing phenoxy radicals such as pentachlorophenoxy (XXVe) with hydrocarbons has been reported to yield crystalline products (267). The dimer of XXVe, which yields the monomer on heating, reacts with hydrocarbons such as hexane, cyclohexane, and 1-octene to give pentachlorophenol (XXVe · H) and yellow oils. Triphenylmethane reacts to yield XXVe · H and the aryl ether ArOR (R = Ph_3C).

These ethers are formed also when XXVe · H, toluene, or triphenylmethane and lead dioxide are heated. The mechanistic sequence postulated involves phenoxy radical attack on the solvent in the second step; the reaction terminates by a radical-coupling step. The ethers ArOR (ArO = XXVh, R = Ph_3C, $PhCH_2$; ArO = IV, R = $PhCH_2$) have been prepared and isolated. Compounds of this type have not been isolated from similar reactions with I, V, and XVIII (229, 233). However, an ether is formed from VI and triphenylmethane (ArO = VI, R = Ph_3C), whereas hydrogen abstraction from cyclohexene gave VI · H and 2,2′-bicyclohexene (89). Radical IV was found to be unreactive toward styrene, cyclohexene, and dimethylfulvene (262). The dienes 2,3-dimethylbutadiene and cyclopentadiene and anthrahydroquinone dimethyl ether react by 1,4 addition to products formulated as 1,4 diethers (262).

The 2:1 additive dimerization products (XXXIX) prepared by the reaction of I or VII with certain olefins are predominantly those of *para* substitution (although there was evidence for *ortho* substitution in some cases) (Table XVIII) (133). When heated these compounds decompose with loss of isobutylene. The yields appear to be governed to some extent by the electron density in the *para* position of the radical. The reaction of VI with butadiene proceeds by hydrogen abstraction to VI · H and unidentified higher hydrocarbons (89).

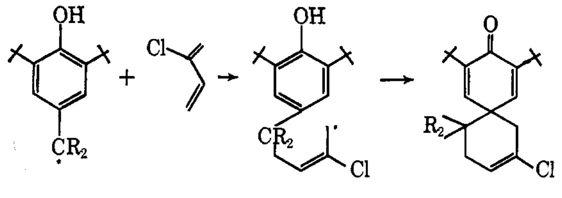


XXXIX

TABLE XVIII

R	M	% yield
t-Butyl	$-CH_2CH{=}CHCH_2-$	61
Ph	$-CH_2CH{=}CHCH_2-$	2
t-Butyl	$-CH_2CH{=}C(Cl)CH_2-$	79
Ph	$-CH_2CH{=}C(Cl)CH_2-$	8
t-Butyl	$-CH_2CHCN-$	1
t-Butyl	$-CH_2CHCl-$	11
t-Butyl		~100

Under oxidizing condition IX · H and 2,6-di-*t*-butyl-4-isopropylphenol added chloroprene to form spiro compounds in high yield (132). The reaction was formulated as an addition of chloroprene to the intermediate 3,5-di-*t*-butyl-4-hydroxybenzyl radical (Eq 7). However, 1,2 addition to a quinone methide is a plausible alternate route, in view of the lack of definite evidence for the benzyl radical and the proof for the participation of the quinone methide in related oxidations (*cf.* sections VII.D and VIII).



(Eq 7)

R = H, CH$_3$

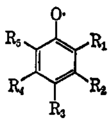
From cycloheptatriene I abstracts hydrogen to form the tropyl radical, which dimerizes to ditropyl. Tropone and several phenolic oxidation products were also formed (248).

The polymerization of styrene and acrylic esters is inhibited by I (214).

F. DIAZOMETHANE

Thermal or photochemical reaction of several phenoxy radicals with diazomethane gives crystalline, high-melting condensation products, (ArO)$_2$CH$_2$ (213, 228), in low yields. The structures of these products have not been firmly established. Table XIX summarizes the substituents investigated. Products derived from chlorinated phenoxys appear to have the structure of a methylene ether. The product derived from V showed no nitrile bands in the infrared and, based on nmr, is not a simple methylene bridged product. On heating to 80°, the product from I gave isobutylene and the color characteristic of I. This product showed a typical quinone doublet in the infrared.

TABLE XIX



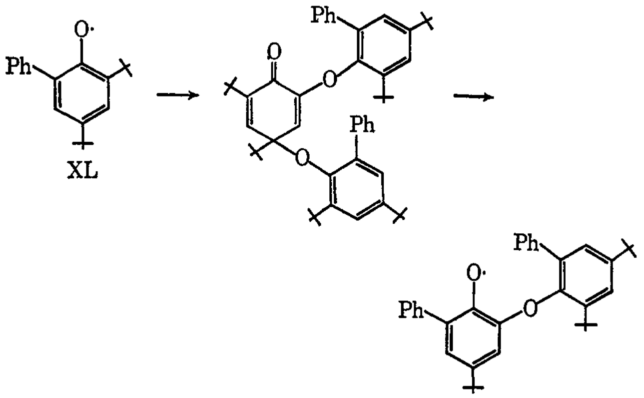
Compd	R$_1$	R$_2$	R$_3$	R$_4$	R$_5$
XXVe	Cl	Cl	Cl	Cl	Cl
XXVh	Cl	Me	Cl	Me	Cl
V	*t*-Butyl	H	CN	H	*t*-Butyl
I	*t*-Butyl	H	*t*-Butyl	H	*t*-Butyl

G. ALCOHOLS

Phenoxy radicals are often decomposed to unknown products by reactive solvents such as alcohols, although oxidation of alcohols to aldehydes has been shown for several phenoxy radicals. Thus, XL (216) forms benzaldehyde and acetaldehyde from benzyl alcohol and ethanol, respectively. However, reactions with phenoxy radicals can be carried out in alcoholic solvents.

In methanol, XL reacts to form a trimer (minus one *t*-butyl group) which dissociates to a stable phenoxy radical. In ethanol, unidentified products were formed, but in *t*-butyl alcohol no reaction was observed (234).

It has been possible to oxidize 2,6-di-*t*-butyl-4-formylphenol (XIX·H) with I in methanol to XVIII (Table VII), although the reaction apparently is not of preparative value (230, footnote 6c).

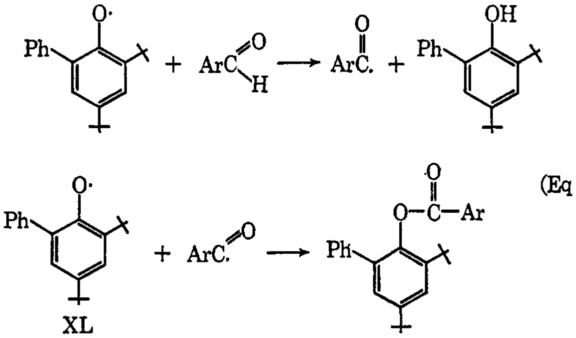


XL

XLa

H. ALDEHYDES AND KETONES

When an excess of phenoxy radicals is employed in the oxidation of alcohols, further reaction takes place with the aldehyde that is formed (216). The major products are esters (Eq 8); the reaction is formulated as another example of a radical coupling reaction and requires 2 moles of phenoxy radical. The reaction was slowest for *p*-nitrobenzaldehyde which would be in agreement with a rate-controlling attack of the electrophilic radical on the aldehyde.



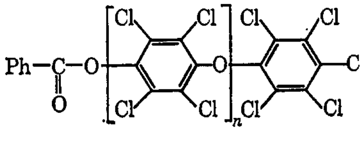
XL

(Eq 8)

Ar = phenyl, *p*-biphenyl, *p*-nitrophenyl

A second product isolated from the reaction of XL with benzaldehyde was 2-hydroxy-3-phenyl-5-*t*-butylbenzophenone, probably formed by loss of isobutylene from the intermediate quinol ketone.

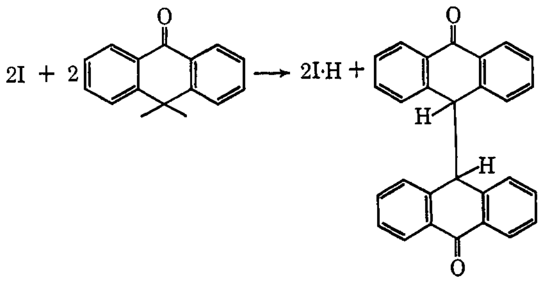
Reaction of benzaldehyde with XXVe yielded a polymeric benzoic acid ester (molecular weight 800–1100) (*cf.* section VI.K), softening point 94–115°. A possible route to this material is the loss of chlorine radicals from the intermediate quinol ether to give an



$n \cong 2$

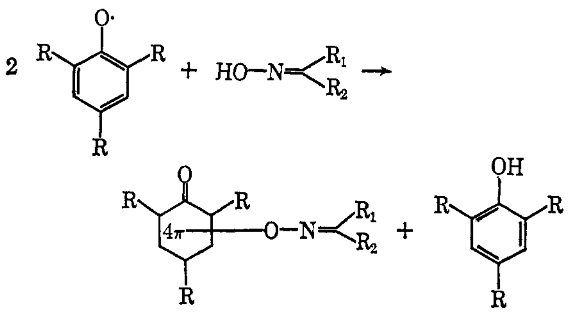
intermediate phenoxy radical which couples with the benzoyl radical or reacts further with XXVe.

Hydrogen abstraction from anthrone by I led to an 80% yield of dihydrodianthrone. No quinol ether was formed and further oxidation to dianthrone was not observed (181). Reaction with V likewise stops at the dihydrodianthrone stage (216).



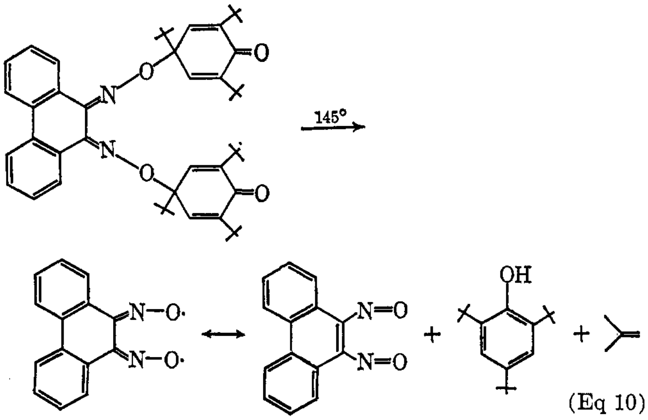
I. OXIMES

Mono- and dioximes of aldehydes and ketones react at 40–60° stoichiometrically according to the over-all Eq 9 (226). The crystalline products are formulated as oxime-O-quinol ethers and are isolated in high yields (ref 226 lists 16 products). Most of these reactions have been reported with I; VI reacts with fluorenone oxime and examples have been reported with V, VII, XVIII, 4-CH=CPh(CN)-2,6-di-*t*-butylphenoxy, XXV, XVII, and XVI, (226, 229, 230). Radical XL which does not form quinol or thioquinol ethers reacts with oximes (234).

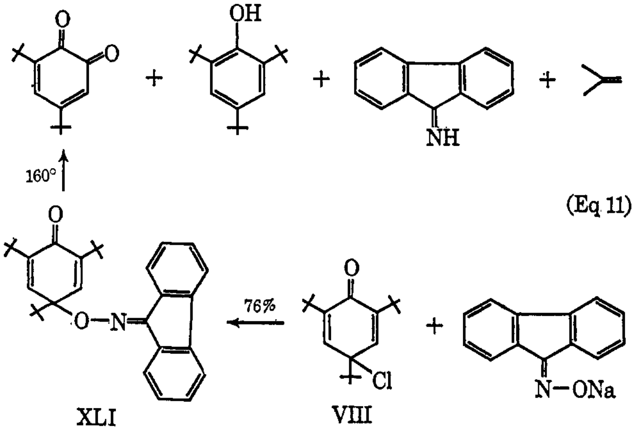


(Eq 9)

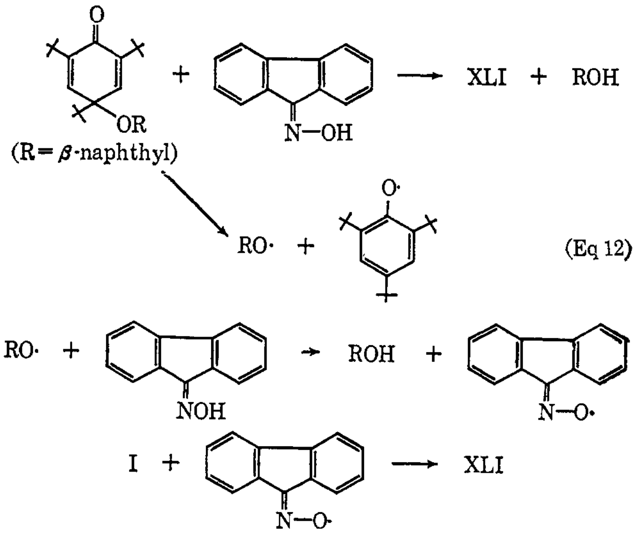
In solution many of these quinol ethers are weakly dissociated and the esr spectra of these solutions correspond to those of the phenoxy radical. The degree of dissociation on thermal decomposition is, however, quite low (0–0.25%). Products of the thermal cleavage of these quinol ethers can arise from both C–O and O–N scission. C–O scission is favored in Eq 10 because the resulting radicals are resonance stabilized. The products from XLI are best formulated *via* O–N cleavage followed by β fission of the resulting alkoxy radical. The products also imply the existence of XLI as an *ortho*-substituted quinol ether, or a rearrangement from the *para* isomer prior to cleavage. Although the position of substitution in these oxime-O-quinol ethers was left open, a doublet at 1640–80 cm^{-1} in the infrared, the independent synthesis of XLI from VIII (R = Cl) and sodium fluorenone oxime (Eq 11), and the transetherification with quinol ethers of proved *para* structure at 60–80° favor 4,4 disubstitution (226). This latter reaction (Eq 12) has been formulated as a radical reaction. The reaction of a compound containing both a phenolic and an oxime hydroxyl group (XLII) proceeds initially at the latter. Treatment of the resulting intermediate (XLIII·H) with alkaline $K_3Fe(CN)_6$ or I, or initial treatment of XLII with 3 equiv of I, gives a



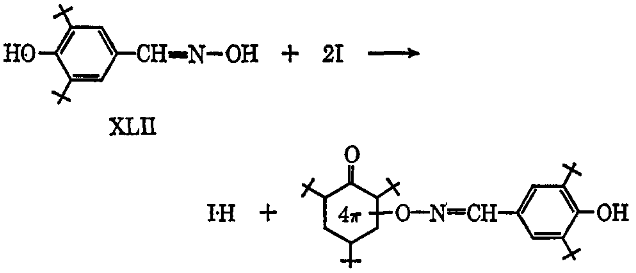
(Eq 10)



(Eq 11)



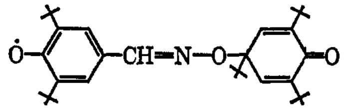
(Eq 12)



XLII

XLIII·H

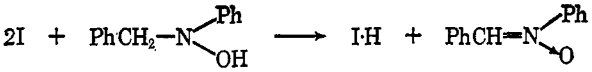
deep purple solution; esr showed the presence of the radical XLIII (225), which is less reactive toward O_2 than I and is more stable in solution than in the solid state. (The esr spectrum has been interpreted in terms of a delocalization of the unpaired electron over the conjugated system including nitrogen.)



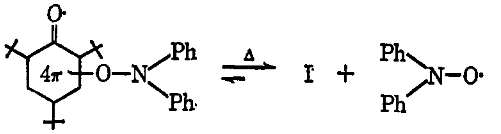
XLIII

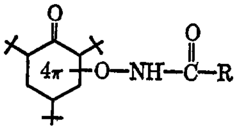
J. HYDROXYLAMINES, HYDROXAMIC ACIDS, AND *aci*-NITRO COMPOUNDS

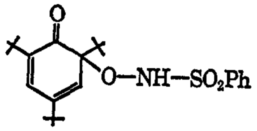
Oxidation of β-phenylhydroxylamine with I was complex; a small amount of nitrosobenzene was isolated. Radical I is also an efficient oxidizing agent for the conversion of N-benzyl-N-phenylhydroxylamine to a nitrone. The presumed intermediate quinol ether was not isolated. The reaction is reported to be quantitative. A hydroxylamine which has no α hydrogens gives the expected quinol ether. The dissociation into radicals of a 10^{-2} *M* benzene solution of this product at 20° is *ca.* 1%, and the existence of both I and the diphenylnitroxide radical was shown by esr (226). The products from the oxidation of hydroxamic or sulfonylhydroxamic acid and *aci*-phenylnitromethane with I were formulated as quinol ethers (226).

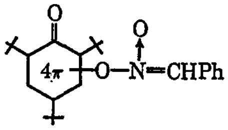


$$2\mathrm{I} + \mathrm{PhCH_2{-}N}\begin{smallmatrix}\mathrm{Ph}\\ \mathrm{OH}\end{smallmatrix} \longrightarrow \mathrm{I{\cdot}H} + \mathrm{PhCH{=}N}\begin{smallmatrix}\mathrm{Ph}\\ \rightarrow\mathrm{O}\end{smallmatrix}$$







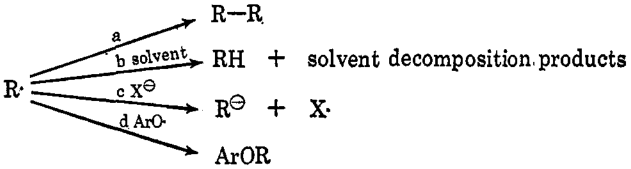


K. ORGANOMETALLICS AND METALS

Triphenylmethylsodium and phenyllithium react with I to form the phenoxide ion. This general reaction is another example of electron transfer and was studied in more detail for Grignard reagents. The over-all reaction Scheme VIII was postulated (214, 275).

SCHEME VIII

$$\mathrm{ArO\cdot} + \mathrm{RMgX} \longrightarrow \mathrm{ArO^{\ominus}} + \mathrm{MgX^{\oplus}} + \mathrm{R\cdot}$$



The fate of the radical R· would depend on many factors. Relatively stable R· yields mainly R–R (path a). Thus, benzylmagnesium bromide reacts with V (most reactions have been reported with this phenoxy radical) to give 75% bibenzyl. Reactive radicals such as $CH_3\cdot$ and $C_6H_5\cdot$ show primarily attack on solvent, path b. Path c is observed for an ArO·/Mg ratio of 1:1; under such conditions 8% I_2 and 1% MeI are formed from methylmagnesium iodide in anisole.

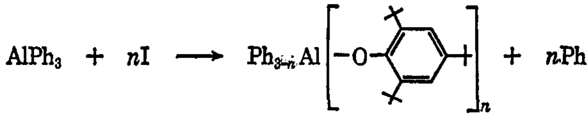
A direct attack of phenoxy radical on hydrocarbon solvent was not observed (see, however, section VI.E).

Phenoxy radicals containing halogen also show reactivity toward metal organic compounds. Diphenylmagnesium (in benzene–ether) reacts instantly with XXVe (dimer) to give some benzene, 3% biphenyl, 21% pentachlorophenol, and 66% of a polymer which contains about three phenyl groups and ten chlorophenoxy groups. The dimer presumably reacts to generate radicals in an equilibrium step; these then attack the organometallic compound to generate phenyl radicals (153, 229).

$$\mathrm{XXVe\ (dimer)} \rightleftharpoons 2(\mathrm{monomer})$$

$$2\mathrm{XXXe} + \mathrm{Ph_2Mg} \rightarrow 2\mathrm{Ph\cdot} + \mathrm{Mg} + 2\mathrm{XXVe^{\ominus}}$$

Triphenylaluminum reacts with I in a mole ratio of 1:1 and 1:2 in toluene. An intermediate complex was postulated to explain the products.

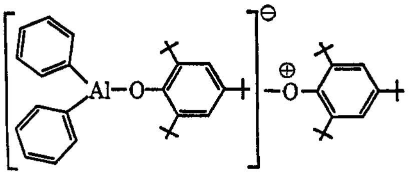


$n = 1$ or 2

$$2\mathrm{Ph\cdot} \longrightarrow \text{biphenyl}$$

$$\mathrm{Ph\cdot} + \text{solvent} \longrightarrow \text{benzene} + \text{decomposition products}$$

When the mole ratio 1:2 was exceeded slightly, *i.e.*, 1:2.01, a new complex radical was obtained. On the basis of its esr spectrum, an aluminum radical was present and structure AL was suggested for it (241).



AL

Reactions of phenoxy radicals with alkali metals lead to phenolates; VI reacts with mercury (89). The colorless dimer of VI is reduced to VI·H by triethyltin hydride at 20° in cyclohexane (244).

L. PHENOLS

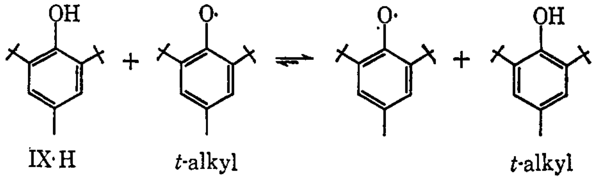
Phenoxy radicals undergo a variety of reactions with phenols; products depend on conditions and structural features.

1. *Formation of New Stable Phenoxy Radicals*

The position of the equilibrium which is formed when phenoxy radicals react with phenols which in turn are capable of forming stable radicals is determined by structural features, concentration, and solvent (60, 64, 88, 212, 222). A rough but significant correlation exists between Hammett σ values and Fieser's critical oxidation potentials (60). The slope of such a correlation suggests a wide range of oxidation potentials. The advantage of these systems over inorganic oxidizing agents is a neutral, nonaqueous medium. Few quantitative data exist, however. If a small amount of XII·H is added to a solution of I the red color of XII appears immediately. On addition of I·H to this solution, the color changes to purple and, if enough I·H is added, returns completely to blue (60). The equilibrium constant for the forward reaction was determined spectrophotometrically; at 25° it was 51.7 ± 4.1. For the equilibrium between I and XI·H the constant was approximately 210.

It was already pointed out (section V.A.5) that V forms an equilibrium with alkaline potassium ferricyanide which can only be shifted to the phenoxy radical dimer by the addition of methanol. This and other qualitative observations are in agreement with the expectation that electron-withdrawing groups increase the oxidizing power of the radical, and correspondingly electron-releasing groups in the phenols increase the ease with which they are oxidized. Most 2,6-di-*t*-butyl-4-R-phenols are oxidized irreversibly by V. Only VI (and presumably other polyphenylphenoxy radicals) forms a reversible equilibrium which is approachable from both sides (216). In a series of *o*-phenyl-substituted phenoxy radicals pentaphenylphenoxy is the strongest, while 2,6-diphenyl-4-methoxyphenoxy is the weakest oxidizing agent (84). Introduction of electron-releasing substituents into the phenyl rings reduces the oxidizing power of the phenoxy radical; VI is a stronger oxidizing agent than 2,6-di-*p*-methoxyphenyl-4-phenylphenoxy. Both of these radicals oxidize I·H, as does 2,6-diphenyl-4-methoxyphenoxy. Similar oxidation potentials are reported for I and 2,6-di-*t*-butyl-4-triphenylmethylphenoxy (224); *cf.* Tables I and XXX.

In his studies of the reaction of *t*-butoxy radicals with phenols (*cf.* section VI.O.3) Ingold showed the effect of the 4 substituent on the position of the equilibrium (159). When the decomposition of the peroxide was carried out in the presence of two phenols (one of which was IX·H), the equilibrium was far to the right owing to consumption of IX by dimerization whereas the radicals carrying a 4-*t*-alkyl substituent were relatively unreactive toward one another and toward *t*-butoxy radicals.



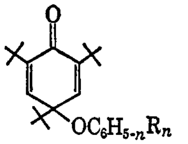
The intermolecular hydrogen transfer between I and I·H has been measured by line broadening in the nmr (175). A second-order rate constant (K = 300 l. mole^{-1} sec^{-1}) and an activation energy of 1 ± 0.5 kcal/mole was found. The low activation energy supports a polar transition state (see section X for further discussion of this point). A rate constant of similar magnitude (200 l. mole^{-1} sec^{-1}) was obtained for the reaction of BIP·H with galvinoxyl (10).

When these rates are compared to the rates of quinol ether formation, *i.e.*, I plus unhindered phenols (Table XXIII), polar factors appear to outweigh steric factors. The electron release of the 4-*t*-butyl group in 4-*t*-butylphenol (which seems to be responsible for the rate acceleration relative to hydrogen) would be expected to be offset by the effect of 2,6-di-*t*-butyl substitution (I), yet I reacts with I·H about three times faster than with 4-*t*-butylphenol.

2. *Formation of Mixed Quinol Ethers*

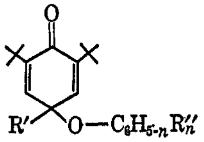
Phenoxy radicals such as I react with phenols and naphthols to give quinol ethers (18, 49, 195, 218, 220, 233). The over-all reaction is represented by the equation: $2ArO\cdot + Ar'OH \rightleftharpoons ArOH + ArOAr'O$. The products (Tables XX–XXII) generally are crystalline, dissociate into radicals on heating, and possess the 4,4-cyclohexadienone structure as shown by infrared (cyclohexadienone doublet at about 1635–50 and 1660–80, ether bands at 1235–50 and 980–90 cm^{-1}) and ultraviolet (λ_{max} 230–240 mμ (log ϵ ~4.3), several inflections between 270 and 350 mμ) spectra. Two moles of hindered phenoxy radical are required to form 1 mole

TABLE XX
QUINOL ETHERS



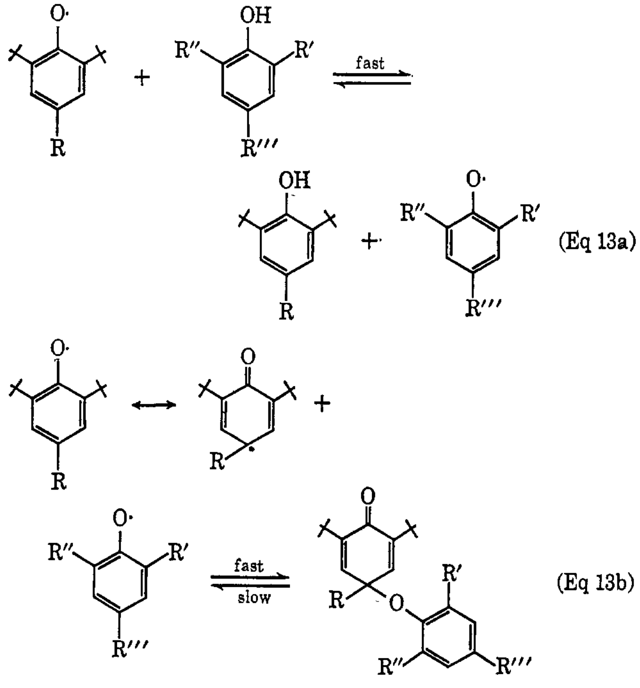
R	Mp, °C	Ref
H	Oil	18
2-Methyl	...	
4-Methyl	112–113	233
3,5-Dimethyl	...	77
2,3,6-Trimethyl	...	245a
3-*t*-Butyl	...	77
4-*t*-Butyl	91–92	77, 220
2,4-Di-*t*-butyl	109–120 dec	220
2,6-Di-*t*-butyl	...	181
3,5-Di-*t*-butyl	134–136.5	233
4,6-Di-*t*-butyl-3-methyl	139–141	233
2,5-Di-*t*-butyl-4-methoxy	145–150 dec	220
4-Methoxy	77–78	18, 77
3-Hydroxy	120–130 dec	220
3,5-Dihydroxy	130–140	220
4-Phenyl	...	77
4-Phenoxy	Oil	18
3-Carboethoxy	...	77
3-Carbomethoxy	...	77
4-Benzoyloxy	132–133	18
4-Benzyloxy	104–105	18
4-SC_6H_5	112–113	18
4-$CH_2COOC_2H_5$	65–67	49
4-$(CH_2)_2COOC_2H_5$	32.5–33.5	49
4-$(CH_2)_2COOH$	111–113	49
4-$CH_2CH(NH_2)COOC_2H_5$	42–43	195
4-$CH_2CH(NHCOCH_3)COOH$	144–144.5	195
4-$CH_2CH(NHCOCH_3)COOCH_3$	Oil	195
2,4,6-Trichloro	127–129	18
2,3,4,6-Tetrachloro	117–118	233
Pentachloro	145–146; 157–158	18, 233
2,4-Dichloro-3,5-dimethyl	108–110	233
2,4,6-Trichloro-dimethyl	150–152	233
Tetrachloro-4-methyl	145–146.5	233
2,4-Dichloro-6-iodo	111–113	233
4-Bromo	...	77
2,4,6-Tribromo	124–125	220
Pentabromo	137–138	233
3,5-Dibromotrichloro	146	233
2,6-Br_2-4-$CH_2COOC_2H_5$	89.5–90.5	49
2,6-Br_2-4-$(CH_2)_2COOC_2H_5$	103–104	49
2,6-Br_2-4-$(CH_2)_2COOH$	119 dec	49
2,6-I_2-4-$CH_2COOC_2H_5$	89–90 dec	49
2,6-I_2-4-$(CH_2)_2COOC_2H_5$	97 dec	49
2,6-I_2-4-$(CH_2)_2COOH$	114 dec	19
3- and 4-CN	...	77
2-, 3-, 4-nitro	...	46
2,4,6-Trinitro	...	46
$C_6H_{5-n}R_n$		
2-Naphthyl	75–76	220
2-Naphthyl-1,3,4-trichloro	132–133.5	280
2-Naphthyl-6-triphenylmethyl	160–161 dec	280

TABLE XXI
QUINOL ETHERS



R′	R″	Mp, °C	Ref
Phenyl	2-Naphthyl	100–101	235
Phenyl	Pentachloro	115	233
t-Butoxy	2,5-Di-*t*-butyl-4-methoxy	97–98 dec	209, 220
t-Butoxy	2-Naphthyl	91–92.5	220
Triphenyl-methyl	Pentachloro	110–160 dec	233
Benzoyloxy	Pentachloro	133–134	233
SCN	Pentachloro	Dec	233
Chloro	Pentachloro	158–159	233
Bromo	Pentachloro	137–140	233
CO_2Me	2-Naphthyl	117–119 dec	230
CO_2Et	2-Naphthyl	116–117	230

of quinol ether and 1 mole of hindered phenol. Separation problems inherent in this procedure are avoided by the elegant use of lead dioxide or manganese oxide (18, 233) which efficiently reoxidizes ArOH and thus can give a high over-all yield of quinol ether from oxidation of equimolar amounts of the two phenols. Highly active manganese dioxide is required for this oxidation.



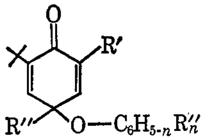
(Eq 13a)

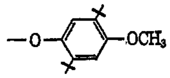
(Eq 13b)

XLIVa

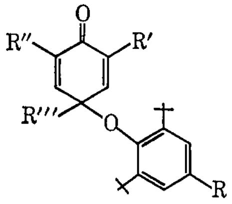
These equilibrium steps are involved in reactions 13a and b. For sterically hindered radicals which have a high degree of carbon radical character (231), the equilibrium in Eq 13b is far to the right, and rapid coupling leads only to products of type XLIVa (Eq 13b) and no XLIVb is formed; *i.e.*, the less hindered phenol reacts in the oxygen radical form. Evidence for the reversibility of Eq 13a comes from the observation (233) that XXVe and I·H, cooxidation of XXVe·H and I·H, and I and XXVe·H all yield 2,4,6-tri-*t*-butyl-

TABLE XXII
QUINOL ETHERS



R′	R″	R‴	Mp, °C	Ref
t-Butoxy	*t*-Butyl	2,5-Di-*t*-butyl-4-methoxy	100–102 dec	220
Phenyl	*t*-Butyl	Pentachloro	119.5–120	233
Phenyl	*t*-Butyl	2,4,6-Triphenyl	128–130	233
	Methoxy	2,5-Di-*t*-butyl-4-methoxy	182–183	209

4-pentachlorophenoxy-2,5-cyclohexadien-1-one. In general, mixed quinol ether formation is favored when R is electron releasing and R′, R″, and R‴ have low steric requirements.



XLIVb

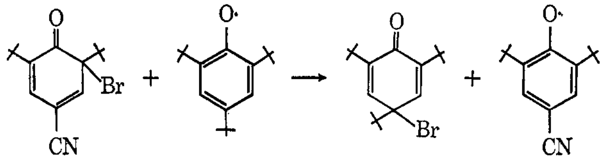
Kinetic studies are in full accord with the scheme given in Eq 13a and 13b and show that I is a highly selective radical (46, 77). The second-order rate constants varied over a range of 10^4 (Table XXIII), and a k_H/k_D ratio of 7.5 (for the reaction of I with 4-phenylphenol) proved that Eq 13a was the rate-controlling step.

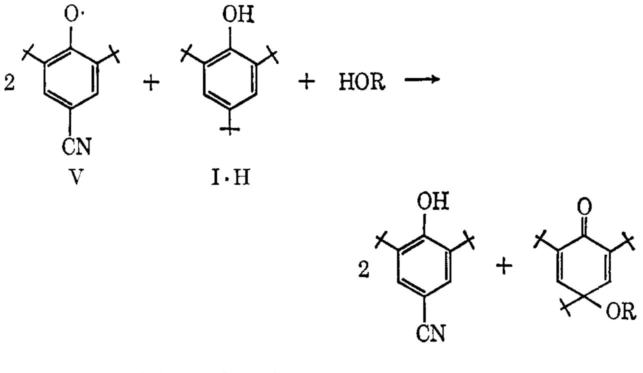
TABLE XXIII
RATE CONSTANTS FOR THE REACTION OF 2,4,6-TRI-*t*-BUTYLPHENOXY (I) WITH UNHINDERED PHENOLS at 24 ± 0.5° IN BENZENE (46, 77)

Phenol	K, l. mole^{-1} sec^{-1}
4-Methoxy	6060 ± 235
4-Phenyl	251 ± 20
4-*t*-Butyl	92.5 ± 6.5
4-Bromo	8.70 ± 0.6
4-Carbomethoxy	.419 ± 0.018
4-Cyano	.153 ± 0.010
Hydrogen	6.17 ± 0.47
3-*t*-Butyl	20.8 ± 1.9
3,5-Dimethyl	30.7 ± 2.4
3-Carboethoxy	1.19 ± 0.08
3-Cyano	0.163 ± 0.009
o-, *m*-, *p*-Nitro	<0.1

Also, an excess of I·H added to the reaction had no effect on the rate. Rates were fastest for electron-releasing substituents in the 4 position of the unhindered phenol, but neither σ nor σ^+ substituent constants gave satisfactory correlations. The activation energies were below 10 kcal/mole (77); for the three isomeric nitrophenols and 2,4,6-trinitrophenol in more concentrated solutions these values varied from 10.2 to 13.2 kcal/mole (46).

The tendency toward quinol ether formation varies considerably with the nature of the 4 substituent in 2,6-di-*t*-butylphenoxy radicals. Although V oxidizes most other 2,6-di-*t*-butyl-4-R-phenols to the radicals, Müller, Rieker, and Schick (233) showed a ready exchange between an *o*-quinonoid derivative of V and I, a reaction which indicates a greater tendency for I to exist in a 4-keto form. Furthermore, these authors carried out the interesting competition experiments summarized in the equation below. The oxidation of I·H by V is faster than the reaction of V with oximes or phenols, although V, when allowed to react alone with oximes (226) or polyhalophenols (233) forms quinol ethers. In the competition experiment, however, only quinol ether derivatives of I were isolated. These experiments again emphasize the importance of the polar factors in the hydrogen-abstraction step. Rate studies similar to those of Da Rooge and Mahoney (77), but using a series of 4-R-2,6-di-*t*-butylphenoxy radicals, would help to elucidate these factors further (electron-releasing as well as electron-withdrawing R groups should be examined).

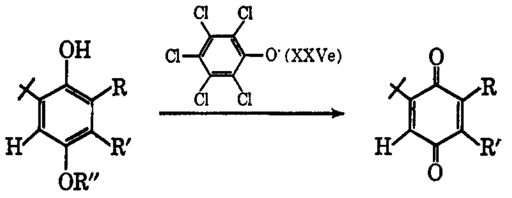


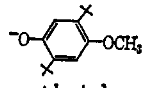


R = 2,4,6-trichlorophenyl, 2,4,6-tribromophenyl, $-N{=}CPh_2$

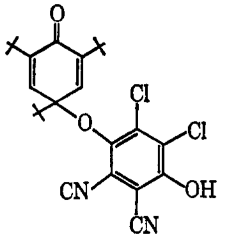
Quinol ethers dissociate on heating and give characteristic radical colors. These observations have been confirmed by esr (40); for example, XLIVa (R = *t*-butyl) gives an esr signal for I on heating, and exchange reactions with other phenols (18) or oximes (230) take place. Reduction of quinol ethers results in formation of the parent phenols (222).

In many cases attempts to isolate quinol ethers, or further reaction of quinol ethers with appropriate reagents, lead to hydroxydiphenyl ether derivatives (section VI.L.5). The oxidation of certain hydroquinone derivatives with XXVe or I results in the formation of substituted benzoquinones, presumably *via* quinol ethers which could not be isolated (233).

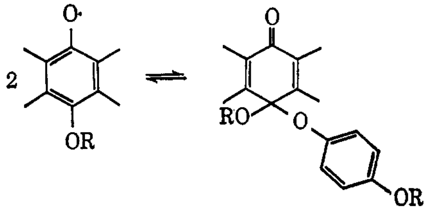


	Example 1	Example 2
R	*t*-butyl	
R′	H	*t*-butyl
R″	*t*-butyl and $SO_2C_6H_5$	methyl

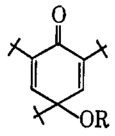
It was found, however, that interaction of I·H with DDQ in methanol gave the monoquinol ether of the corresponding hydroquinone in up to 82% yield (19).



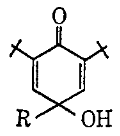
Quinol ketals are formed from phenols which have an alkoxy group in the 4 position. An additional example to those given in Tables XX–XXII and in section V.A.6 is the product of alkaline potassium ferricyanide oxidation of 2,3,5,6-tetramethyl-4-methoxyphenol (191).



Aliphatic quinol ethers (as well as the "parent" quinol) are also known (212, 214, 276); *cf.* section VI.O.2.



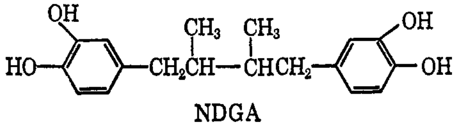
R = aliphatic



R = alkyl, aryl

So-called simple quinol ethers, formed by coupling of two identical phenoxy radicals which arise from oxidation with a different phenoxy radical, are discussed in section VI.L.3. In addition, the dimers of many phenoxy radicals, prepared by a variety of oxidation procedures, often possess the quinol ether structure (*cf.* sections IV.A and V.A).

The expected stoichiometry has not been found in all cases. The mole ratio for the reaction of I with 2,6-di-*t*-butyl-4-dimethylaminomethylphenol was about 4, for hydroquinone it was 2.7, and for NDGA it varied between 3 and 5 (250).

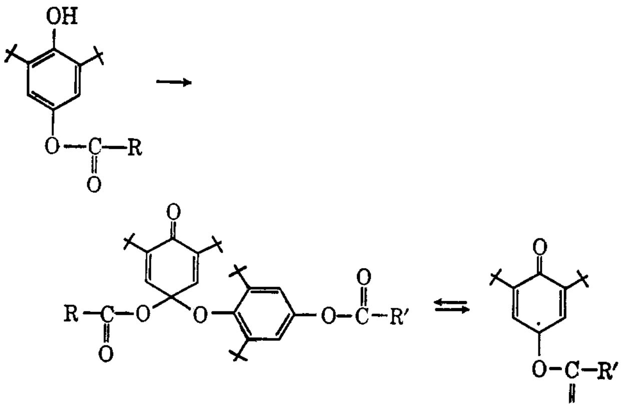


NDGA

3. *Formation of Simple Quinol Ethers*

Certain phenols when oxidized with phenoxy radical form simple quinol ethers by intermolecular reaction and do not couple with the oxidizing agent. An example of such a reaction already mentioned is the oxidation of phenanthrols with I to prepare Goldschmidt's peroxides; these have the structure of simple quinol ethers (section V.D) (119, 122, 237).

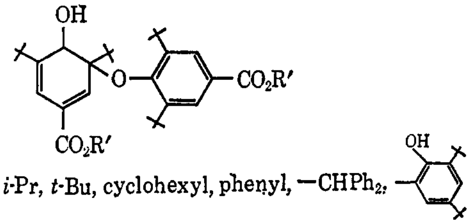
When hindered phenols carrying an ester group in the *para* position are oxidized with I, quinol acetals are formed. These are diamagnetic dimers and show a characteristic doublet at 1667–1640 cm^{-1}. The dissociation has been shown to be only about 0.3% at 20° by esr measurements, but the quinol acetals react as phenoxy radicals (230). When *p*-hydroxybenzoates are oxidized (Table VII), quinol ethers are formed; a



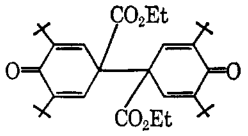
R = Me, *t*-Bu, Ph

single band at 1667 cm^{-1} favors *ortho* coupling for most products.

These compounds also dissociate readily in various

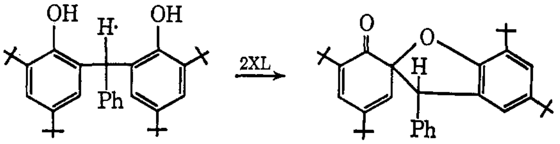

R′ = Me, Et, n-Pr, i-Pr, t-Bu, cyclohexyl, phenyl, —$CHPh_2$,

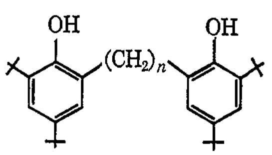
solvents as shown by the green color and by esr spectra, which are identical with those obtained during the oxidation and indicate a degree of dissociation up to 62%. Closer examination of the infrared spectra has shown that in at least one case (R′ = Et) the quinol ether structure of the solid dimer is probably incorrect and that a dimer structure (XIIIa) resulting from *para–para* coupling is more reasonable (section IV.A). This is suggested by the absence of prominent ether bands at 985 and 1240 cm^{-1} and the presence of a dienone doublet at 1641 and 1660 cm^{-1} (196).

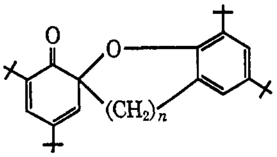

XIIIa (R = CO_2Et)

4. Formation of Spiro Compounds. Internal Quinol Ethers from Certain Bisphenols

Oxidation of some bisphenols with phenoxy radicals (such as I or XL) proceeds with intramolecular ring closure (234). The internal quinol ethers which are formed are thermally stable and do not decompose into radicals. The size of the heterocyclic ring depends on the number of carbon atoms in the bridge connecting the two phenol moieties. The oxidation of XLVa (n = 0) with I proceeds, with intermediate formation of a purple color, to a pale yellow product, which was assigned the structure of an internal quinol ether XLVb (n = 0) primarily on the basis of nmr spectra. Another route to XLVb (n = 0) was the oxidation of 2-iodo-4,6-di-*t*-butylphenol (221). The esr signal observed in this reaction was assigned to 2-iodo-4,6-di-*t*-butylphenoxy; this signal disappeared much more rapidly than the red-purple color of the solution. The four-membered oxetane ring (XLVb, n = 0) was cleaved by triphenylphosphine to 1,3,6,8-tetra-*t*-butyldibenzofuran; the five-membered dihydrofuran ring (XLVb, n = 1) did not react with this reagent. XLVb was not observed in the peroxy radical oxidation of 2,4-di-*t*-butylphenol (145).

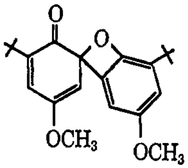


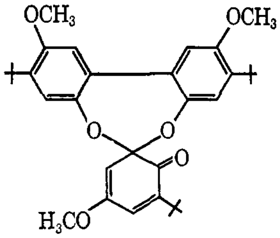

XLVa


XLVb

Other compounds which have been oxidized to internal quinol ethers are XLVa (n = 2), bisphenols where one or more bridge hydrogens have been replaced by methyl or phenyl, and 2,2′-methylenebis-3-methyl-4,6-di-*t*-butylphenol. These spiro compounds can also be prepared from monophenols that have a substituent in the *ortho* position which can undergo a hydrogen-abstraction reaction. Oxidation of 2-methyl-4,6-di-*t*-butylphenol gave XLVb (n = 2), identical with the product obtained from the oxidation with silver oxide (203). This reaction may proceed by Barton's (13) transfer mechanism *via* XLVa (n = 2).

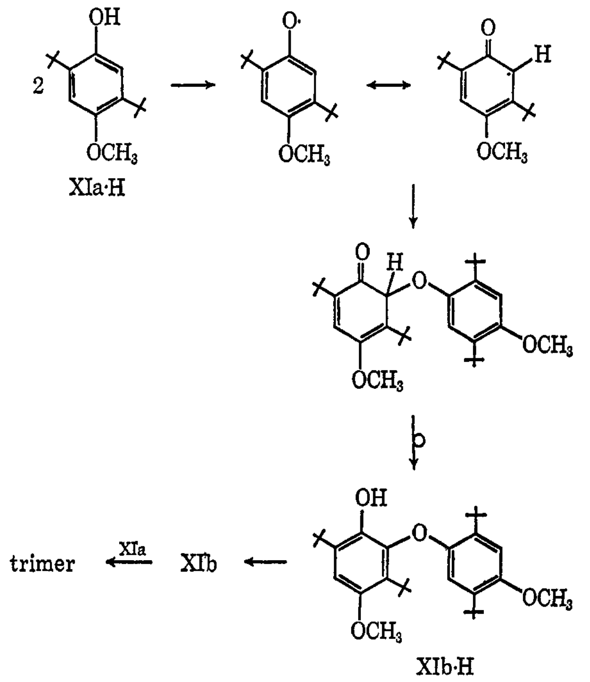
Less hindered phenols can also yield spiro compounds. Thus, oxidation of 2-*t*-butyl-4-methoxyphenol (7) gives a dimer which is probably (209) the spiro compound XLVI. Hewgill (140) has recently investigated the oxidation of 2- and 3-*t*-butyl-4-methoxyphenol as well as their cooxidation. From this latter reaction a spiroketal was one of the products. Additional examples of formation of spiro compounds can be found in the chemistry of natural products.


XLVI

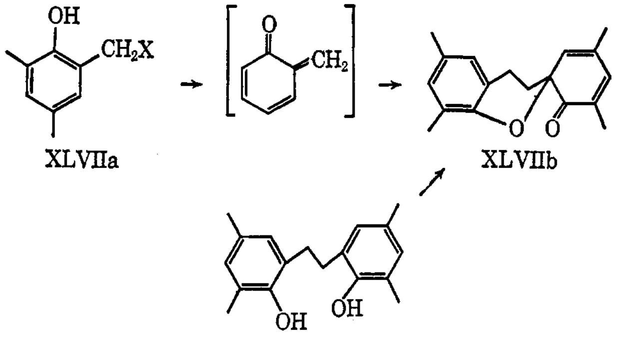


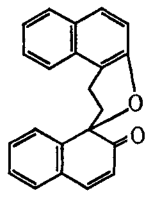
When an additional blocking group was introduced, as in 2,5-di-*t*-butyl-4-methoxyphenol (XIa·H), spiro compounds are no longer formed upon oxidation (XI·H forms the stable radical) (209). Instead, the oxidation of XIa·H in methanol with alkaline K_3Fe-

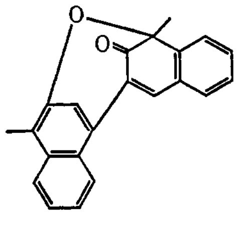
Scheme IX



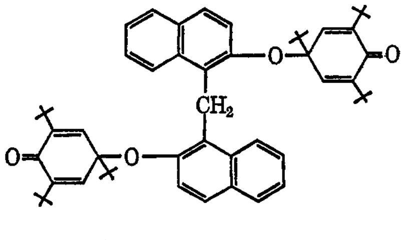
(CN)$_6$ yields a trimer (*cf.* Table XXII for the structure of the trimer) which can be reduced to XIa·H and XIb·H, an *o*-hydroxydiphenyl ether (*cf.* section VI.L.5). These two compounds can be cooxidized to re-form the trimer. An esr signal for XIb was observed when the trimer was heated in benzene. Lead dioxide oxidation of XIa·H in benzene gave an esr spectrum tentatively assigned to XIa, and a reasonable route to the trimer involves this phenoxy radical (209) (Scheme IX). In connection with attempts to prepare quinone methides (section VIII), XLVIIb was obtained from XLVIIa (114). Similar structures have also been written for naphthol oxidation products (257, 263). Although one might expect that these spiro compounds could form biradicals in view of the twisting of the rings with respect to one another, there is no evidence to support this hypothesis.





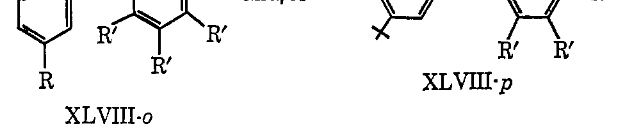


Oxidation of 1,1′-methylenebis-β-naphthol with alkaline K$_3$Fe(CN)$_6$ yields the expected spiroquinol ether, whereas oxidation with I yields a bisquinol ether (280).



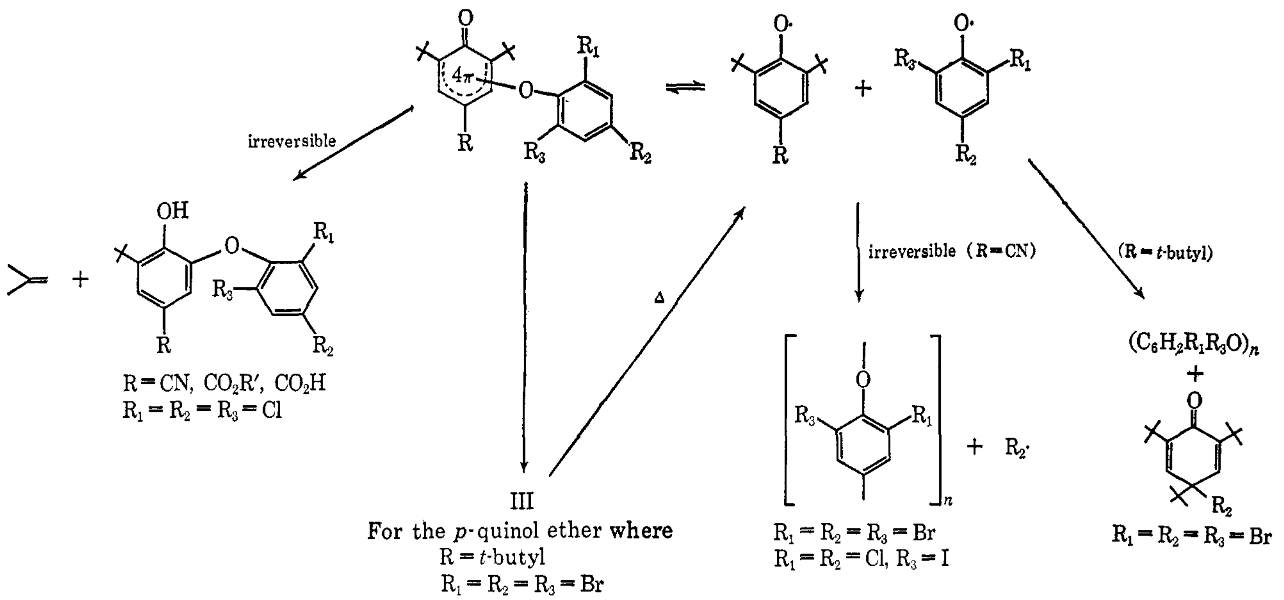
5. *Hydroxyphenyl Phenyl Ether Formation*

In certain cases attempts to prepare quinol ethers led to the isolation of *o*- or *p*-hydroxyphenyl phenyl ethers, XLVIII (*o*- or *p*-) (49, 196, 230). These compounds can also arise from cleavage of quinol ethers (4,4 or 2,2 disubstituted). Compounds of class XLVIII have been isolated from the general reaction of 2,6-di-*t*-butyl-4-R-phenoxy radicals with phenols or thiols, and a more detailed study (272) has delineated many of the structural factors that favor *o*-hydroxyphenyl phenyl ether formation. In the reaction of 2,6-di-*t*-butyl-4-R-phenoxy radicals with less hindered phenols, *o*-hydroxyphenyl phenyl ethers are favored products for electron-withdrawing R groups such as ester, carboxyl, cyano, acyl, and benzoyl. The less hindered phenols (or thiophenols) used contain halogen, cyano, ester, phenyl, or methyl groups (R′). The products are high-melting crystalline solids and generally are formed in 70–80% yields. The expected intermediate *o*-quinol ethers are not isolable; they are, however, reaction intermediates (see below). Reference 272 lists 19 *o*-hydroxyphenyl phenyl ethers which were prepared by the methods applicable to quinol ether synthesis (section VI.L.2).



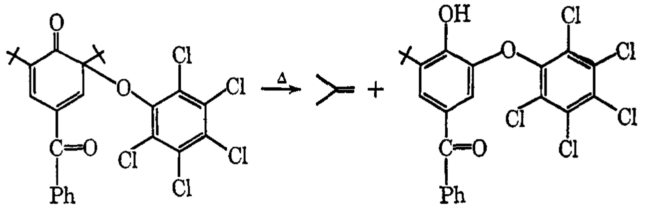
The effect of the R group in the phenoxy radical is shown by the fact that 2,4,6-tribromophenol or 2,4-dichloro-6-iodophenol forms stable *p*-quinol ethers with

SCHEME X



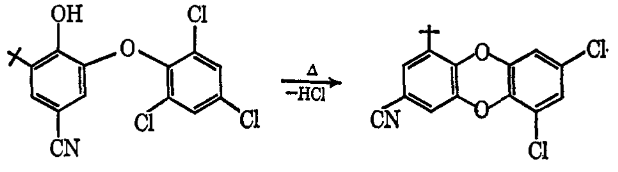
I (section VI.L.2, Table XX), whereas reaction with 2,6-di-*t*-butyl-4-cyanophenoxy (V) leads to polymer formation by loss of halogen (Scheme X); only a 6% yield of the *o*-hydroxyphenyl phenyl ether was isolated in this case (153, 229). The choice as to polymer or *o*-hydroxyphenyl phenyl ether formation corresponds to the stability (229) of the halogenated phenoxy radicals; *i.e.*, trichloro and higher halogenated phenoxy radicals favor the latter products.

The presence of *o*-quinol ethers as intermediates in these preparations is shown by the identification of isobutylene and the isolation of XLIX in 94% yield.



XLIX

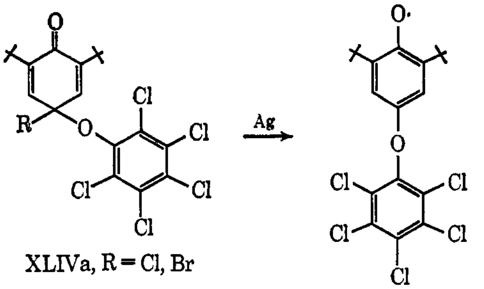
An infrared doublet at 1683–1656 cm^{-1}, however, may favor a *p*-quinol ether structure, and radical rearrangement prior to loss of isobutylene, for which there is considerable evidence, cannot be ruled out (section VI.N and O); on the other hand, the *o*-quinol ether structure may reasonably be expected to show a singlet. The assignment of an *o*-hydroxyphenyl phenyl ether structure is supported by independent synthesis (sodium trichlorophenolate and 2-bromo-4-cyano-2,6-di-*t*-butylcyclohexadienone react with loss of isobutylene to give 2-hydroxy-3-*t*-butyl-5-cyanophenyl-2,4,6-trichlorophenyl ether which, when heated, loses HCl to form L) and spectral analysis. The infrared hydroxyl band has been shifted to a lower frequency (3290 cm^{-1}) and broadened (hydrogen bonding) and ultraviolet spectra are consistent with model compounds. The esr spectra indicate two equivalent *meta* protons ($a_{H,meta}$ = 1.6–1.9).



L

Similar products have been obtained in connection with the synthesis of model compounds related to thyroxine (49, 196). The structural assignments cannot be considered final in all cases, however. Thus, *o*-hydroxyphenyl phenyl ethers were formed from the reaction of 2,6-di-*t*-butyl-4-R-phenoxy (R = acetyl, carbethoxy, cyano) with 3-(*p*-hydroxyphenyl)ethyl propionate or 3-(*p*-hydroxyphenyl)propionic acid. The structure was supported by ultraviolet spectra and an infrared band at about 3300 cm^{-1}. The products from the interaction of I with several tyrosine and dibromotyrosine derivatives were formulated as thyroxine analogs (*p*-hydroxyphenyl phenyl ethers) (195). It has been suggested (ref 233, footnote on p 49) that these compounds may be the *ortho* isomer. However, these products possess infrared absorption at 3400–3600 cm^{-1} while all those ethers for which the *o*-hydroxyphenyl phenyl ether structure has been established (196, 272) show absorption at 3200–3300 cm^{-1}. The absorption at higher frequency is more consistent with 2,6-di-*t*-butyl substitution.

Quinol ethers XLIVa (R = Cl, Br) can be cleaved to phenoxy radicals which are readily reduced to *p*-hydroxyphenyl phenyl ethers. This transformation can be achieved simply by shaking with silver powder

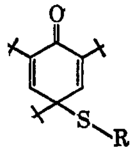


XLIVa, R = Cl, Br

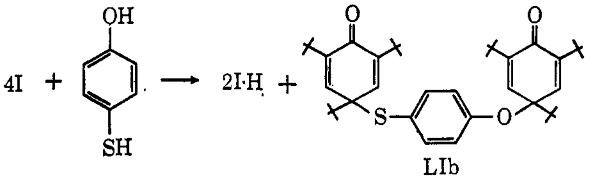
in benzene under nitrogen (233). Proof of structure comes from the esr spectrum of XLVIII-*p* (R′ = Cl), which shows two equivalent *m*-hydrogens, infrared spectrum, and independent synthesis (*i.e.*, 2,6-di-*t*-butylphenol and XXVe give XLVIII in 37% yield (233)); the phenoxy radical was also generated by addition of I·H to the quinone ketal prepared by MnO_2 oxidation of 2,6-di-*t*-butyl-4-bromophenol and XXVe·H (18).

M. SULFUR COMPOUNDS

The reactions of phenoxy radicals with thiols lead to sulfur analogs of quinol ethers or, in many cases, to disulfides. Oxidation of thiophenol, thionaphthol, or 4-hydroxythiophenol with I yields the thioquinol ethers LIa and LIb (236); LIb dissociates on heating. The radicals V, XVII, XVIII, and XL yield only β-naphthyl disulfide and diphenyl disulfide (216, 230, 234). Halogenated phenoxy radicals (Table XVI) have been reported to react with thiols to form crystalline products; no details have been published (229). Presumably, these compounds are thioquinol ethers.



LIa, R = Ph



LIb

The oxidation of 2,4,6-tri-*t*-butylthiophenol was not accompanied by an esr signal for the expected radical. The coupling product di-2,4,6-tri-*t*-butylphenyl disulfide was isolated (282). However, ultraviolet irradiation of the thiophenol gave the thiophenoxy radical which had a half-life of about 30 min at room temperature in solution (284). The absence of any hyperfine splitting in the esr spectrum suggested that the unpaired electron is localized largely on sulfur. Incorporation of ^{33}S into the molecule lead to hyperfine splitting, which proved the existence of an S radical. When heated in benzene at 80° in the presence of dibenzoyl peroxide, relatively large stationary concentrations of the radical are available from the thiophenol (283).

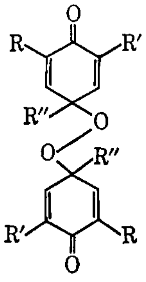
Low (185) showed that several hindered phenols and galvinoxyl acted as inhibitors in the free-radical addition of thiols to olefins. One mode of their action was the scavenging of chain-propagating radicals resulting from the addition of thiyl radicals to the olefin.

$$\mathrm{R{-}S{-}\dot{C}H_2{-}CH{-}R} + \mathrm{ArO}\cdot \rightarrow \text{stable product}$$

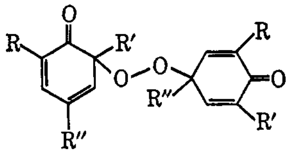
N. OXYGEN COMPOUNDS

1. *Oxygen*

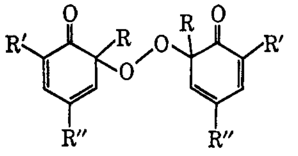
Most "stable" phenoxy radicals react with oxygen, a diradical, to form peroxides for which at least three isomeric structures are possible, depending on the position of coupling. These compounds are crystalline solids which melt with decomposition; they are listed in Table XXIV. Structural assignments have been made on the basis of infrared, ultraviolet, and nmr data. However, for a considerable number of these compounds these data have not been obtained and their structures remain in doubt; LII-*pp*, which is the product of reaction at the least hindered position would be expected to be the predominant isomer. For LII (R = R′ = R″ = *t*-butyl) it was shown by 100-Mc nmr spectroscopy and thin layer chromatography that LII-*op* and LII-*oo* were present as minor constituents (145). The formation of these peroxides probably proceeds *via* an intermediate peroxy radical. Evidence from esr spectra has indicated that I and the peroxy radical derived from it by reaction with oxygen can coexist and may react at comparable rates (72). It is interesting, however, that so far it has not been possible to obtain a "mixed peroxide" from a competition reaction between two different phenoxy radicals. Reaction of I and XI with oxygen gave both I_2O_2 and XI_2O_2 but no $I\cdot O_2\cdot XI$ (3). Obviously, these reactions require further study.



LII-*pp*



LII-*op*



LII-*oo*

TABLE XXIV
BISCYCLOHEXADIENONE PEROXIDES

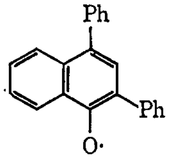
R = R′	R″	Predominant structure, LII[a]	Ref
t-Bu	*i*-Pr	*pp*	66
t-Bu	*t*-Bu	*pp*	68, 214
t-Bu	OMe	*pp*	64, 212
t-Bu	*t*-BuO	*pp*	64, 202
t-Bu	$CMe_2(OMe)$	ND	66
t-Bu	*t*-Am	ND	70
t-Bu	*t*-AmO	ND	64
t-Bu	O-COMe	*pp* or *op*	230
t-Bu	$CHPh_2$	*oo*	223
t-Bu	CHPh(OCOPh)	ND	223
t-Bu	COPh	*oo*	63, 196, 223
t-Bu	CPh_3	ND	63
t-Bu	CN	*op* or *oo*	216
t-Bu	COMe	D	196
t-Bu	CO_2Et	D	196
t-Bu	1-Naphthyl	*pp*	29
t-Bu	*p*-MeC_6H_4	*pp*	29
t-Bu	Cumyl	*oo*	40
R = *t*-Bu, R′ = Ph	*t*-Bu	*pp*	234

[a] ND, not determined; D, only decomposition products isolated.

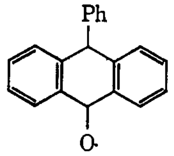
Only semiquantitative estimates of the reaction rates of phenoxy radicals with oxygen are available. These lead to the following series of decreasing reactivity for several *t*-butylphenoxy radicals (63, 68, 196, 230, 234, 235): I (0.5 hr) > XL > XVIII > XVII > VII (8 hr) > 4-Ph_3C > 4-PhC(=O)– > V. The reported lack of reactivity of VI with oxygen (89) is questionable; decomposition has been shown (234). Galvinoxyl, once thought to be unreactive toward oxygen (71), consumes oxygen. The reported inhibition was shown to be due to hydrogalvinoxyl which is difficult to remove as an impurity (127). Radical XLa is reported to be much less reactive toward oxygen than I (234). An attempt to prepare LII (R = R′ = *t*-butyl; R″ = H) by the oxidation of XVI·H with oxygen in the presence of silver oxide or alkaline potassium ferricyanide was unsuccessful (28). This is somewhat surprising since one might expect XVI to be an efficient scavenger for oxygen. It appears that this radical undergoes an oxidative coupling reaction readily or perhaps XVI·H is an efficient scavenger for the radical, since the only product was 3,3′,5,5′-tetra-*t*-butyldiphenoquinone (XV, R = *t*-butyl). This lack of reactivity of XVI with oxygen was explained by Russell and Bridger (287) in terms of the high energy content of the probable polar transition state. The decrease in rate observed for many radicals relative to I (see above) may be due to increased resonance stabilization of radicals such as VI and VII and a lower tendency for radicals carrying electron-withdrawing substituents to react in the keto form. Since the latter is closely related to the $5\pi^+$-resonance form which is an electron acceptor (*cf.* section X), greater tendency to exist in this form would lead to slower reaction since the polar transition state would be of higher energy, in agreement with Russell's explanation.

The importance of resonance stabilization is illustrated in the series VI, LIII, LIV; LIII yields a crystalline peroxide slowly, while LIV reacts instantaneously; both react at the position *para* to oxygen (84).

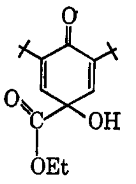
From the phenoxy radicals XVIII (R′ = Et) and 2,6-di-*t*-butyl-4-acetyl only decomposition products, presumably formed *via* intermediate peroxides or hydroperoxides, were isolated (196). The former gives the products LVa–c; the latter yields X and 2-*t*-butyl-4-acetylcatechol.



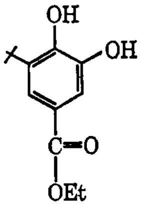
LIII



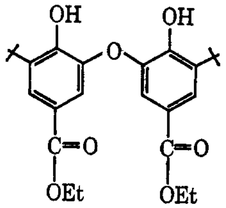
LIV



LVa



LVb



LVc

The reaction of I with oxygen has been proposed as an analytical method for the determination of small amounts of dissolved oxygen in organic solvents (250).

2. Thermal Decomposition of Biscyclohexadienone Peroxides

Peroxides LII decompose thermally and the pathway of homolytic decomposition depends on the nature of the group R″; *i.e.*, for LII-*pp*, R″ = *t*-butyl, the expected O–O homolysis is observed. The products formed were isobutane, isobutylene, X, and XII·H (62, 69, 222, 254). That the latter compound was formed *via* its phenoxy radical was confirmed by esr (62, 254). No signal for I was observed, but it has recently been reported (273) that I·H appeared as a minor product which does suggest the possibility of a C–O homolysis. The decomposition of this peroxide also initiated vinyl polymerization (69). These data make a proposed ionic mechanism (222) for its decomposition unlikely. For LII-*pp* (R″ = Ph, OMe, *t*-butoxy) (2, 62), remarkably, C–O homolysis has been demonstrated. Phenoxy radical esr spectra were observed on heating benzene solutions of the peroxides above 60°. These radicals could only be formed by direct C–O homolysis. Increased resonance stabilization of these phenoxy radicals over I may account in part for this unexpected change in the direction of cleavage. Product isolation studies on LII (R″ = Ph) as well as the polymerization inhibiting action of these peroxides further supported the fundamentally different mode of their decomposition. Interestingly, the esr spectrum of the decomposition of LII (R″ = Ph) gave no evidence of a peroxy radical in contrast to the observation of Coppinger (who showed the presence of I-$O_2\cdot$ in the formation of LII (R″ = *t*-butyl) from I; *cf.* section VI.N.1) although a resonance-stabilized peroxy radical would be an attractive intermediate to explain the formation of a stable isomer of LII-*pp* (R″ = Ph) (2). Crude kinetic measurements gave a value of about 30 kcal/mole for the C–O bond dissociation energy in LII-*pp* (R″ = Ph), *i.e.*, a value comparable to a normal O–O bond.

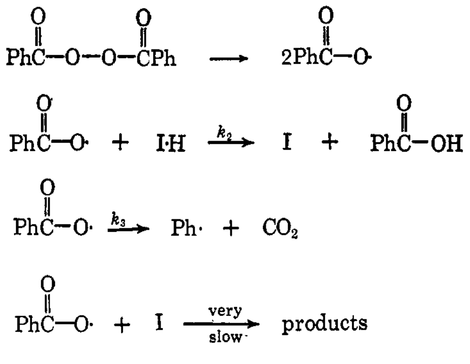
C–O scission has also been observed for peroxides where the formation of a stable phenoxy radical would provide a more ready rationale for the direction of cleavage. Thus, the thermal decomposition of 2,6-di-*t*-butyl-4-*t*-butylperoxy-4-methyl-2,5-cyclohexadien-1-one gave an esr signal for IX (see also section VI.O) (320). Oxidation of such cyclohexadienone peroxides with other peroxides also leads to the phenoxy radical (41). The oxygen oxidation of IX·H at 100° has been reported to yield LVII·2H and LVI (341).

The finding of an interconversion between the *p*-cyclohexadienone peroxides (VIIId) and the *ortho* isomers (25, 26, 118) suggests that C–O homolysis can take place quite readily in these systems.

O. PEROXY AND ALKOXY RADICALS

1. *Reaction with Acyl Peroxides*

Although relatively unhindered phenols such as 2,6-dimethylphenol react with peroxides and peroxy radicals readily (14, 74, 328), the hindered phenols I·H and IX·H react only at elevated temperature with benzoyl peroxide at an appreciable rate and I was shown to be an inefficient scavenger for benzoyloxy radicals (60, 324). When a benzene solution of I·H and benzoyl peroxide was refluxed, the blue color of I appeared immediately; it slowly faded over 24 hr, indicating slow secondary reactions. Isolated products were benzoic acid and biphenyl; the use of chloroform yielded benzoic acid and hexachloroethane. A k_3/k_2 ratio of 0.13 (80°) and 0.06 (70°) was in agreement with rapid formation of I and its slow disappearance.



$$\mathrm{Ph\overset{\overset{O}{\|}}{C}{-}O{-}O{-}\overset{\overset{O}{\|}}{C}Ph} \longrightarrow \mathrm{2Ph\overset{\overset{O}{\|}}{C}{-}O\cdot}$$

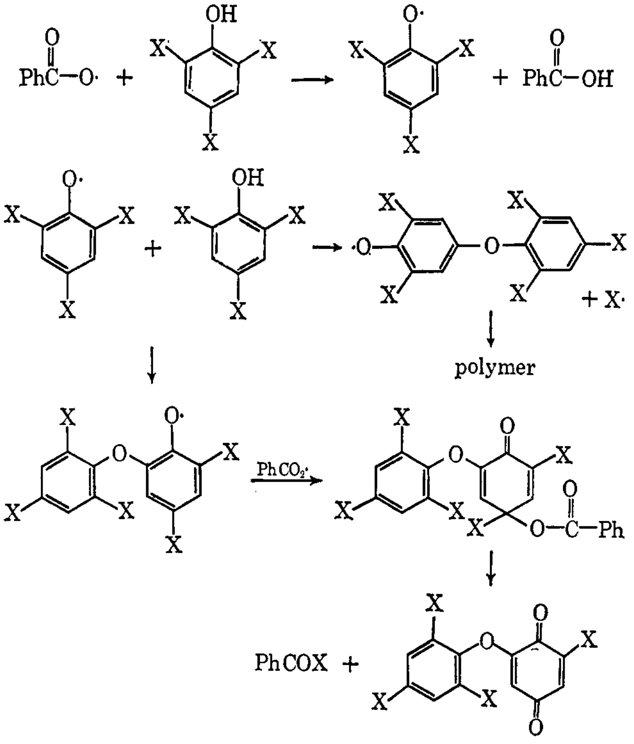
$$\mathrm{Ph\overset{\overset{O}{\|}}{C}{-}O\cdot} + \mathrm{I{\cdot}H} \xrightarrow{k_2} \mathrm{I} + \mathrm{Ph\overset{\overset{O}{\|}}{C}{-}OH}$$

$$\mathrm{Ph\overset{\overset{O}{\|}}{C}{-}O\cdot} \xrightarrow{k_3} \mathrm{Ph\cdot} + \mathrm{CO_2}$$

$$\mathrm{Ph\overset{\overset{O}{\|}}{C}{-}O\cdot} + \mathrm{I} \xrightarrow[\text{slow}]{\text{very}} \text{products}$$

For phenols containing electron-withdrawing groups (X = Br, Cl), a similar sequence has been proposed to explain the formation of phenyl ethers, polymers, and cyclohexadienones (162) (Scheme XI). This would be consistent with the reactivity reported for I and related radicals. The oxidation of IX·H with benzoyl peroxide yielded LVII·2H and LVI (*cf.* section VII.D).

SCHEME XI



Although considerable evidence has been obtained thus to support radical intermediates in these reactions, Walling (324), on the basis of his data with less hindered and nonhindered phenols, favored a bimolecular, four-center ionic mechanism. This mechanism has received some support from O^{18} tracer studies (83).

The formation of a coupling product such as 4-acetoxy-4-*t*-butyl-2,6-di-*t*-butyl-2,5-cyclohexadienone from lead tetracetate and I·H (*cf.* section III.B.1) suggests that acetoxy radicals can abstract hydrogens from the hindered phenol and couple with the resulting phenoxy radical.

Methyl radicals generated from the thermal decomposition of acetyl peroxide abstract the hydrogen from the phenolic hydroxyl group of I·H; this reaction has a large tritium isotope effect. Furthermore, methyl radicals reacted with this phenolic hydroxyl hydrogen about 100 times faster than with a C–H bond in *n*-heptane and about 30 times faster than with the hydroxyl hydrogen of *t*-butyl alcohol (299); *cf.* section VI.O.3.

2. *Reaction of Hindered Phenols and Phenoxy Radicals with Hydroperoxides and Peroxy Radicals*

In his review (157) on the inhibition of autoxidation of organic substances, Ingold thoroughly discussed the nature of the chain-breaking step which involves the inhibitor (reaction A, illustrated for I·H). Three other reactions (B, C, D) have to be considered in this connection.

$$RO_2\cdot + I{\cdot}H \longrightarrow I\cdot + RO_2H \quad (A)$$

$$I\cdot + RO_2H \longrightarrow I{\cdot}H + RO_2\cdot \quad (B)$$

$$I\cdot + RO_2\cdot \longrightarrow RO_2I \quad (C)$$

$$I{\cdot}H + RO_2H \xrightarrow{\text{slow}} \text{products} \quad (D)$$

Of these, the molecular reaction between a hindered phenol and a hydroperoxide has been reported once; this reaction would not be expected to compete at all with A, B, and C (see below).

Much of the earlier work was concerned with the mechanism of steps A and C since the expected deuterium isotope effect was nil (35); this was inconsistent with a rate-controlling hydrogen abstraction in reaction A. However, since 1961, Ingold and others have shown definite and sometimes large isotope effects (Table XXV) and thus, it appears that reaction A is a rate-controlling hydrogen abstraction step, where $RO_2\cdot$ is derived from the oxidizing substrate. The failure to detect any appreciable isotope effect in the previous work can be attributed to rapid exchange of deuterium between the deuterated phenol and hydroxyl-containing impurities or products in the substrate. A kinetic study of the inhibited autoxidation of 9,10-dihydroanthracene was also in agreement with step A (190).

TABLE XXV
DEUTERIUM ISOTOPE EFFECTS IN INHIBITED AUTOXIDATIONS (REACTION A)

Substrate	Initiator	Temp, °C	Inhibitor	Isotope effect k_H/k_D	Ref
Styrene	AIBN	65	IX·H	~10.6	160
Cumene	AIBN	65	IX·H	≥4.2	161
cis-1,4-Polyisoprene	...	60	IX·H	1.76	298
Styrene	AIBN	65	XVI·H	10.5	146
Tetralin	AIBN	65	IX·H	~10	147
Tetralin	AIBN	65	I·H	10.0	117

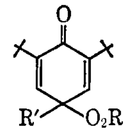
The rates of reaction A were measured for a series of substituents in both hindered and unhindered phenols in styrene (146) and in tetralin (148). Table XXVI compares the rates in the two substrates. In both substrates the data correlated with σ^+ substituent constants and, Hammett ρ values of -1.36 (tetralin) and -1.12 (styrene) were calculated. The reaction showed a moderate steric effect; for example, 2,6-dimethylphenol reacted about 3.5 times faster than XVI·H, but polar effects were more pronounced (Table XXVI). The results were discussed in terms of a transition state with three contributing resonance structures; in view of the polar effects observed VIIIb appears to be the largest contributor, although the magnitude of the ρ values indicates only a moderate degree of charge separation (*cf.* section X). Polar effects in the attacking peroxy radical were also found (148); for three ring-substituted styrenes, the inhibited (with IX·H) autoxidation rate decreased along the series 3-Cl > H > 4-MeO.

TABLE XXVI
RATES FOR REACTION A FOR 2,6-DI-*t*-BUTYL-4-R′-PHENOLS AT 65°

R′	Rate, l. mole⁻¹ sec⁻¹ Tetralin	Styrene
MeO (XI·H)	89	78
Me (IX·H)	24	17
t-Bu (I·H)	28	16
H (XVI·H)	7.7	4.9
Cl	8.5	6.8
CN (V·H)	1.6	1.7
NO₂	0.6	1.0

$$\underset{\text{VIIIa}}{R'C_6H_4OH{\cdot}O_2R} \leftrightarrow \underset{\text{VIIIb}}{R'C_6H_4O\overset{\oplus}{H}{:}\overset{\ominus}{O_2}R} \leftrightarrow \underset{\text{VIIIc}}{R'C_6H_4O{\cdot}HO_2R}$$

Reaction A is generally followed by reaction C; *i.e.*, products of type VIIId are isolated (see below), but it was not until 1966 that Horswill and Ingold (144) isolated for the first time a compound of structure VIIId under conditions of inhibited oxidation in which the R group was derived from the oxidizing hydrocarbon. The product (R = α-tetralyl) was isolated in 86 ± 10% yield from the inhibited (with IX·H) autoxidation of tetralin at 40°; this supports well the assumption made on a kinetic basis (35) that 2 moles of peroxy radicals react per mole of phenolic inhibitor. In the absence of tetralin, the yield of VIIId (R = $Me_2(CN)C$), derived from the decomposition of the initiator (AIBN) was only 60–70% which suggested that IX·H and IX were relatively inefficient traps for the $Me_2(CN)CO_2\cdot$ radicals. [Previous studies generally had led to high yields of cyclohexadienone peroxides (VIIId) from the metal-catalyzed reaction of various hydroperoxides with several hindered phenols (25). Presumably, the peroxy radical is generated and steps A and C follow. Or the mechanistic path to VIIId may involve transfer of the peroxy ligand to the phenoxy radical, similar to that proposed by Kochi (173).] Accurate determination of the stoichiometry has further solidified steps A and C as the reaction sequence. For a number of hindered phenols the stoichiometry with cumyl peroxy radicals was measured by an induction-period method (143); pertinent findings are summarized in Table XXVII.



VIIId

TABLE XXVII

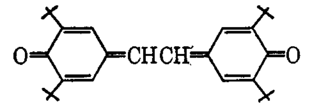
n FACTORS[a,b]

Phenol	n	Phenol	n
XVI·H	2.0	XLVa·H	2.8
IX·H	2.0	2,6-Di-*t*-Bu-4-Cl	1.0
I·H	1.8	2-Me-6-*t*-Bu-4-H	1.9
XI·H	2.1	2-Me-6-*t*-Bu-4-Me	2.0
V·H	2.2	2-Me-4,6-di-*t*-Bu	1.5

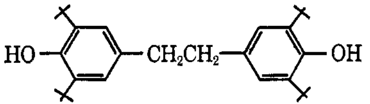
[a] n = moles of cumyl peroxy radical per mole of phenol.
[b] In a recent publication, by J. C. W. Chien, *J. Phys. Chem.*, **71**, 2247 (1967), has reported n factors as large as 11 for the oxidation of squalane inhibited by I·H, IX·H, and XVI·H. A possible explanation for these findings is the reaction of a Boozer–Hammond complex (35) with phenoxy radical to regenerate 2 moles of inhibitor.

For I·H, the n value lower than 2.0 may be due to formation of LII; for 2,6-di-*t*-butyl-4-chlorophenol, it may be the result of phenoxy radical coupling to XIII (R = Cl).

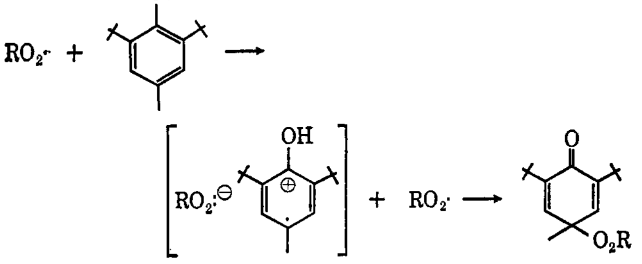
Not all peroxy radicals oxidize IX·H to a cyclohexadienone peroxide. Tritylperoxy radicals form mainly LVI from IX·H (25); *t*-butylperoxy radicals oxidize XVI·H to X and XV (144). The decomposition of 4-bromo-4-methyl-2,6-di-*t*-butylcyclohexadienone with mercury in the presence of oxygen gave no LII (R″ = methyl) but instead yielded LVII·2H and LVI *via* XIV, whereas under the same conditions 4-bromo-2,4,6-tri-*t*-butylcyclohexadienone yielded LII (R″ = *t*-butyl); *cf.* section VI.N.1 (72). The former reaction consumed no oxygen. Although esr data indicated that I and its peroxy radical, $IO_2\cdot$, could coexist, no peroxidic products derived from IX were observed; this suggests that the rate of disproportionation of IX is considerably faster than the rate of reaction with oxygen and that oxygen and peroxy radicals do not react at comparable rates with IX. However, Coppinger (72) has used this finding as support for the proposal of a modified Boozer–Hammond complex (35), which accomodates both the isotope effects (see above) and the termolecular kinetics (2 moles of peroxy radical per mole of phenol), with hyperconjugation within the charge-transfer complex accounting for the isotope effect. The recent results of Becker (19; *cf.* section V.A.1) should make it possible to test this proposal more directly by studying the products from the reactions of the dimer of IX with hydroperoxides as well as peroxy radicals.



LVI



LVII·2H



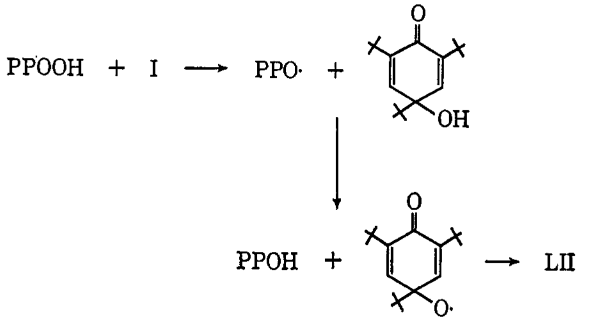
Quantum mechanical studies of oxidation potentials and antioxidant action of phenols favor electron transfer as the rate-determining step with resonance stabilization of the charge-transfer transition state (115). Ingold has concluded that the very large deuterium isotope effects do not allow for a rate-controlling electron transfer, but that σ^+ correlation of substituents shows that charge transfer is important in the transition state (146).

Reaction B (the reverse of A) has been reported by several workers and can occur together with step C. The reaction of 2 moles of I with trityl hydroperoxide gave a 70% yield of VIIId (R = trityl; R′ = *t*-butyl) and 95% I·H (226), which suggests comparable rates for steps B and C. With hydrogen peroxide, I did not form a hydroperoxide. Instead, LII (R″ = *t*-butyl) was isolated. Since 4 equiv of I was required, this reaction conceivably involves hydrogen abstraction by I from the intermediate hydroperoxide (226). The reaction of I with *t*-butyl hydroperoxide gave bimolecular rate constants of 30 (0°) and 90 (20°) l. mole^{-1} min^{-1} (198); extrapolation to 57° gave a value of 430 l. mole^{-1} min^{-1} (316).

The importance of step B in autoxidation reactions has been determined by studying the effect of added hydroperoxide on the inhibited rate. The effects observed depend on the structure of the oxidizing hydrocarbon, the added hydroperoxide, and the type of phenol (147, 190, 316). The oxidation of tetralin inhibited by I·H, for example, was not affected by added tetralin hydroperoxide which shows that reaction B is nil in this system (117). Added tetralin hydroperoxide also had little or no effect when the inhibitors were IX·H and 4-methoxyphenol, but in this system (147) and in cumene oxidation (315) addition of hydroperoxide increased the inhibited rate when the inhibitor was phenol. From the kinetic study of the inhibited autoxidation of tetralin, B:C ratios were calculated; this ratio decreased along the series phenol, 2,6-dimethylphenol, 2-methyl-6-*t*-butylphenol, and XVI·H by a factor of about 5000; *i.e.* for XVI step C > B (the products from the oxidation of XVI·H with peroxy radicals are chiefly X and XV (144)), while in the other cases the B:C ratio is greater than 1. The steric effect of the hydroperoxide was demonstrated by comparing the B:C ratio for tetralin, *t*-butyl, cumyl, and trityl hydroperoxide in the presence of V·H. The ratio decreased from 4.9, 1.3, 1.5, to 0.2, respectively (148).

Only one reference to the reaction of a hydroperoxide with a hindered phenol in the absence of an initiator was found (116). Tetralin hydroperoxide and IX·H when heated for 50 hr at 80° gave LVII in about 25% yield. This reaction probably involves alkoxy radical attack (*cf.* next section) on the phenol.

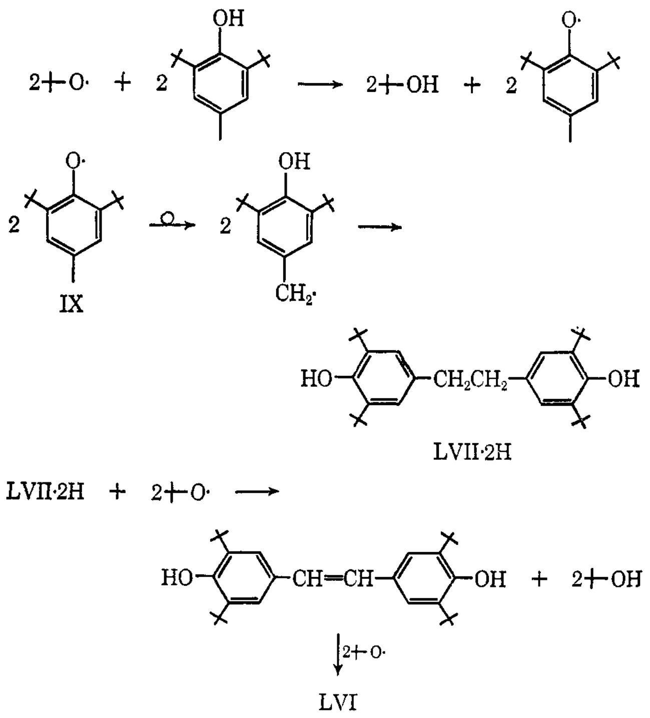
In the inhibition of polypropylene oxidation with I·H, VI·H, and XX·H, the formation of LII (R″ = *t*-butyl) was suggested to occur by a sequence *via* alkoxy radicals, formed by reaction of polypropylene hydroperoxide (PPOOH) with the phenoxy radical, although the direct reaction of oxygen with I was not disproved (302).

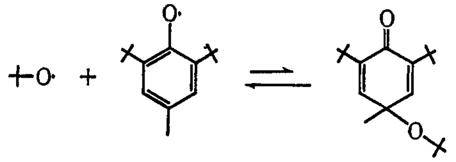


3. *Reaction of Hindered Phenols and Phenoxy Radicals with Alkoxy Radicals*

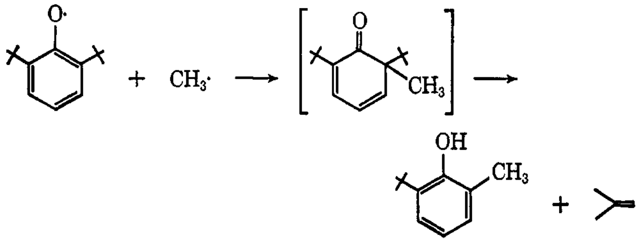
The relative rates of hydrogen abstraction from a series of substituted phenols (including several hindered phenols such as I·H) by *t*-butoxy were correlated with σ^+-substituent constants (159). The *t*-butoxy radicals were obtained from di-*t*-butyl peroxide, and for IX·H the sequence in Scheme XII was postulated (*cf.* section VII.D). A deuterium isotope effect of 6.4 ($k_{\mathrm{IX \cdot H}}/k_{\mathrm{IX \cdot D}}$) was found for the reaction. A cyclohexadienone product (VIIIe) was not present. The equilibrium which lies to the right with peroxy radicals appears to favor the dissociated radicals at 122°. The presence of the phenoxy radicals during the reaction was shown by esr. In the reaction with I·H esr indicated that at least 20% I was present shortly after completion of the run (16 hr at 122°). The occurrence of radical displacements during these reactions was shown by the formation of isobutylene (not formed in the absence of phenols containing *t*-butyl groups), substitution of *t*-butyl by methyl, the formation of α-methylstyrene in the reaction with 2,6-di-*t*-butyl-4-cumylphenol, and the formation of small amounts of 2,6-di-*t*-butyl-4-trichloromethylphenol in all cases of 4 substituents that were studied. The latter probably arises by attack of trichloromethyl radicals on the phenoxy radicals (the reactions were carried out in carbon tetrachloride). Yields of methane, chloroform, methyl chloride, and hexachloroethane in these reactions were very low.

SCHEME XII





VIIIe



The relative rates of hydrogen abstraction were determined by measurement of the *t*-butyl alcohol/acetone ratio, and log plots of this ratio *vs.* σ^+ constants were linear. This ratio as well as the rate of reaction were lower for 2,6-di-*t*-butyl-4-R-phenols than for simple phenols. Probably, two *o*-*t*-butyl groups prevent a close approach of the alkoxy radical to the phenolic hydrogen with a consequent increase in the activation energy.

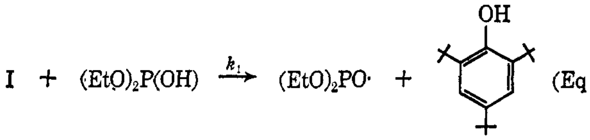
For the radicals galvinoxyl and BIP, the equilibrium between the *t*-butoxy radical and the phenoxy radical is far to the right and the coupling products (aliphatic quinol ethers) have been isolated (9, 10). The aliphatic quinol ether 4-methoxy-2,4,6-tri-*t*-butyl-2,5-cyclohexadienone is also quite stable and does not decompose (to XI·H) below 200° (212). However, during heating esr has given evidence for both XI and I (40). The position of the above equilibrium in products of this type appears to be influenced by both steric factors and relative stabilities of the two radicals.

P. MISCELLANEOUS COMPOUNDS

1. *Diethyl Phosphite*

The reaction of I with diethyl phosphite is another example of the hydrogen-abstracting ability of phenoxy radicals, followed by a coupling step (47). The rate was followed by esr, and the rate of the hydrogen-abstraction step was determined. Dissociation of a diethyl phosphite dimer was postulated as the first step (Eq 14).

$$2(EtO)_2P(O)H \rightleftharpoons [(EtO)_2P(O)H]_2$$

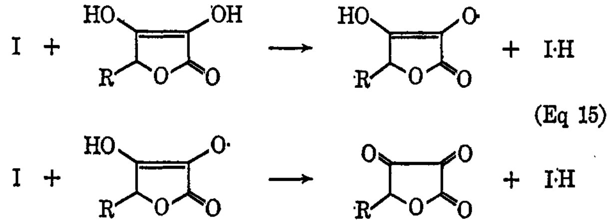


(Eq 14)

$$I + (EtO)_2PO\cdot \longrightarrow \text{stable products}$$

2. *Ascorbic Acid and Maleic Anhydride*

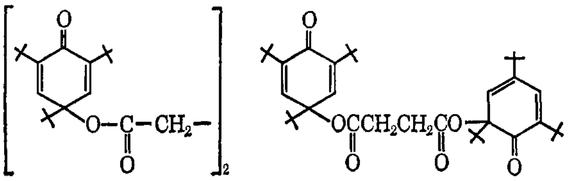
The reaction of this lactone with I has been mentioned (213) and a stoichiometry of 2:1 (I: ascorbic acid) suggested two hydrogen-abstraction steps involving I (250) (Eq 15).



(Eq 15)

R = –CHOHCH$_2$OH

From the reaction of I with maleic anhydride several products were reported; the major one was an unidentified anhydride or lactone, $C_{26}H_{38}O_6$ (133). Two dimeric products (structural assignments based on infrared and ultraviolet data) and VIII (R = OH) were characterized.



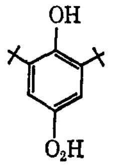
VII. RADICAL DIMERIZATION

Phenoxy radical dimerizations, some of which are reversible, can be placed into six classes.

A. OXYGEN–OXYGEN DIMERIZATION

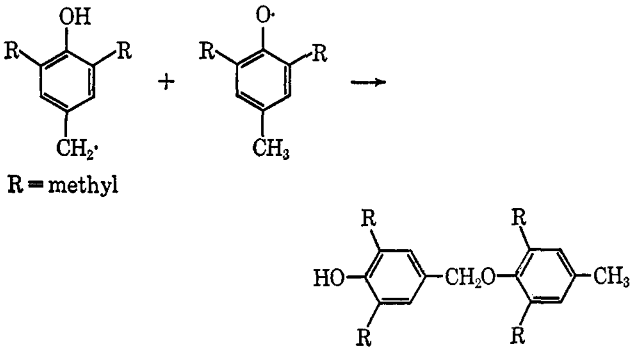
No *bona fide* members of this class of head-to-head dimers exist. The evidence against such structures which have been postulated repeatedly has been cited already in section V.D. Another recent example was claimed to be the hydrogen peroxide oxidation product of tyrosine in hydrochloric acid (78). However, no aryl peroxide was actually present (172). All alleged compounds in this class properly belong in class B or C.

It is pertinent in this connection that attempts to isolate simple aromatic hydroperoxides, ROOH (where R is a substituted benzene ring), by the oxidation of Grignard reagents have been unsuccessful (323). Apparently, the high resonance energy of phenoxy radicals makes the O–O bond dissociation energy of such hydroperoxides very low and only decomposition products can be isolated. However, based on an esr study of the oxidation of XVI·H with oxygen, a side reaction possibly involving the hydroperoxide was proposed to explain the changes observed in the spectra (100).

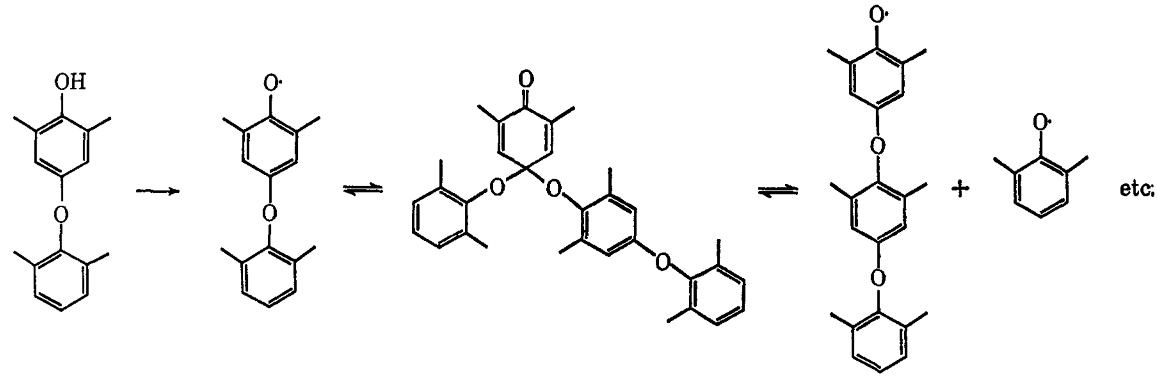


B. CARBON–OXYGEN DIMERIZATION

C–O coupling usually leads to quinol ethers (section VI.L.3). From the oxidation of mesitol with potassium nitrosodisulfonate (section III.B.11), Magnusson isolated a benzyl ether which was thought to arise through a benzyl–phenoxy radical coupling. The corresponding ether was not formed on oxidation of IX·H. The formation of this benzyl ether apparently does not take place *via* the plausible route of addition to a quinone methide, since 2,6-dimethylquinone methide did not react with mesitol (189). However, since this benzyl ether is formed in the presence of 2 moles of oxidizing agent per mole of mesitol and is isolated in only low yield, addition of the phenoxy radical to the quinone methide is an alternate possibility (*cf.* section VII.D).



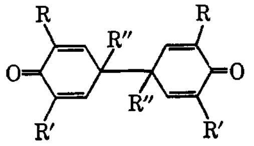
It has already been mentioned that the oxidative coupling of certain 2,6-disubstituted phenols yields polyphenyl ethers (section III.B.4). The reaction involves C–O coupling of phenoxy radicals (70, 135), but the increase in the degree of polymerization toward the end of the reaction is inconsistent with the addition of monomeric phenoxy radicals to the growing polymer chain. By a study of the model compound, xylenol dimer, a mechanism consistent with quinol ether equilibration was proposed (70). Since it was found that oxidation of this dimer gave monomer–tetramer (and probably higher homologs), two phenoxy radicals could combine to form a quinol ether capable of dissociation to form new phenoxy radicals (Eq 16).



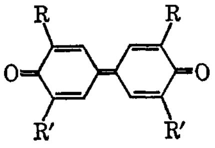
(Eq 16)

C. CARBON–CARBON DIMERIZATION

This may proceed with or without loss of R to give XIII or XV. The formation of such dimers has been reported for a large number of phenols including those which do not form stable phenoxy radicals (13, 28, 51, 74, 135, 168, 182, 183, 259, 336). Structure XIII

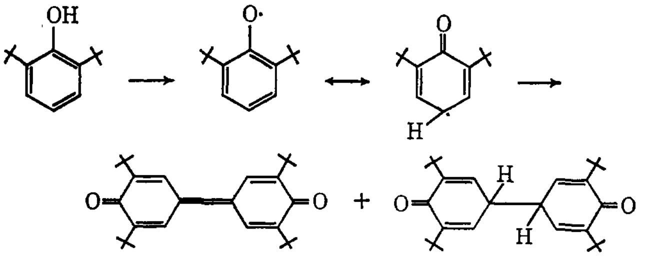


XIII



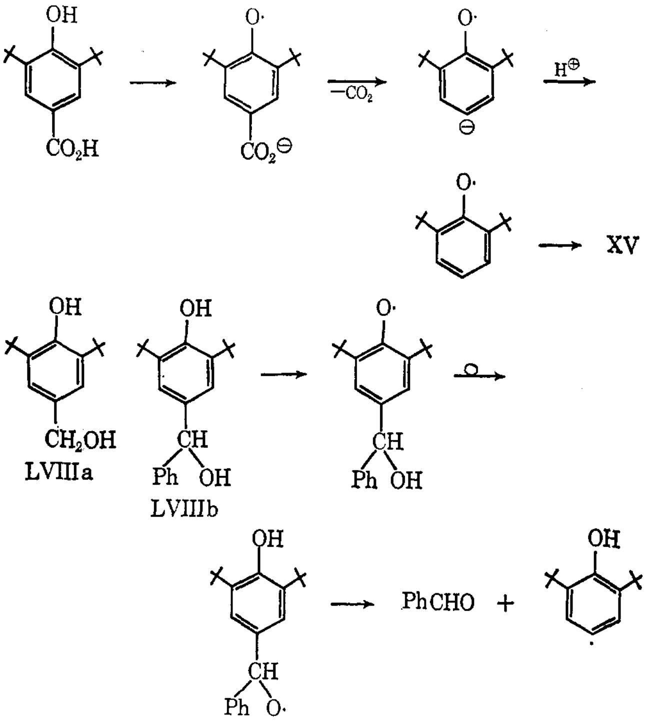
XV

has been proposed for several phenoxy radical dimers (section IV.A) although some of these are undoubtedly quinol ethers. These dimers are formed under a variety of oxidizing conditions, and some examples have already been mentioned. Silver oxide oxidation of XVI·H gave both XIII (R″ = H) and XV (R = R′ = *t*-butyl). When the oxidation was carried out with base and oxygen, XV was the sole product (337);

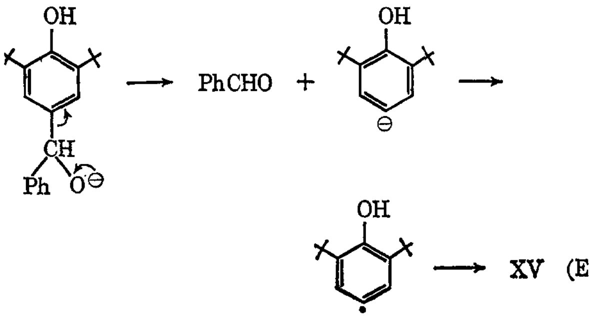


with alkaline $K_3Fe(CN)_6$ in benzene XIII was isolated. It isomerized rapidly to 4,4′-dihydroxytetra-*t*-butylbiphenyl when contacted with a polar reagent such as methanol. The final product of oxidative decarboxylation of 3,5-di-*t*-butyl-4-hydroxybenzoic acid (or XIX·H) is also XV (61); this diphenoquinone likewise arises from the alkaline $K_3Fe(CN)_6$ oxidation of LVIIIa and LVIIIb. A high yield of benzaldehyde is obtained from LVIIIb and the mechanism in Scheme XIII has been suggested (223).

SCHEME XIII

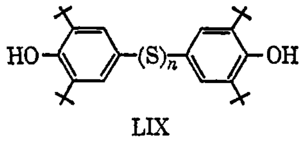


An alternate possibility might be Eq 17 especially



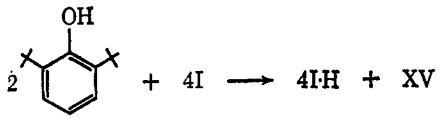
(Eq 17)

since oxidation with I leads to the quinone methide (*cf.* section VIII). The coupling of the 4-halo-2,6-di-*t*-butylphenoxy radicals was mentioned already (section V.A.3); the 4-nitro radical also yields XV. A plausible intermediate in this oxidation is XIII (R″ = NO_2), but this has not been isolated (8). Lead dioxide oxidation of the mono- and disulfide (LIX) proceeds in both cases with loss of sulfur to XV (239), and a series of phenoxy radicals which have selenium attached in the 4 position (section V.A.6.c) also gives the diphenoquinone (240).

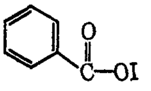


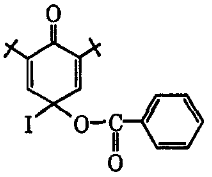
LIX
$n = 1, 2$

When phenoxy radicals are used as oxidizing agents, the products are in many cases those observed with other oxidizing agents. Oxidation of XVI·H with I yields XV according to the over-all Eq 18 (181). There is evidence that the formation of an unstable quinol ether takes place in this reaction (section V.A.3). Oxidation of 4-iodo-2,6-di-*t*-butylphenol with XVII (4-OOCPH) gave benzoic acid as well as XV (230). Two iodine-containing intermediates, benzoyl hypoiodite and 4-iodo-4-benzoyloxy-2,6-di-*t*-butylcyclohexadien-1-one, were postulated. The latter, as well as XIII (R = I), is said to lead to XV. The former generates benzoic acid by reaction with XVII·H which has been formed in the original oxidation.



(Eq 18)

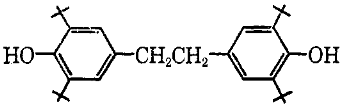




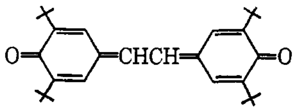
When not prevented by the nature of the substituents in the phenols to be oxidized, the reaction with stable phenoxy radicals leads, as expected, to quinol ethers.

D. CARBON–CARBON DIMERIZATIONS INVOLVING A "FORMAL RADICAL REARRANGEMENT"

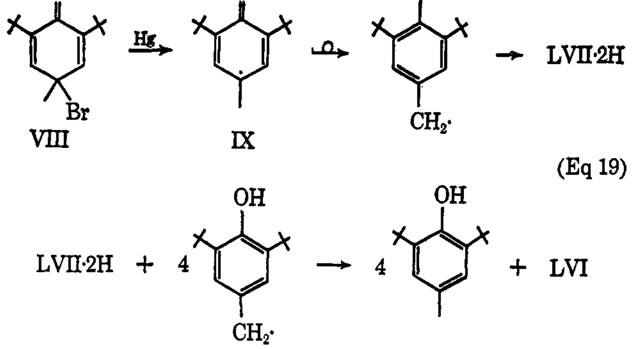
The oxidation of 2,6-di-*t*-butyl-4-methylphenol (IX·H) has been the subject of considerable experimentation and controversy. Two principal products, the bibenzyl (LVII·2H) and the stilbenequinone (LVI), are formed. To explain these products the direct oxidation of the phenol to the 4-hydroxy-3,5-di-*t*-butylbenzyl radical was first suggested by Waters (203). Radical IX, when generated by the treatment of VIII (R = Br) with mercury, yielded IX·H and the stilbenequinone LVI (65) (Eq 19), and the stoichiometry of the reaction suggested the possibility that the bibenzyl LVII·2H was oxidized by the benzyl radical. Evidence has been presented, however, which showed that the disproportionation of IX to the parent phenol and the two dimeric compounds is not an exception to the more general path of second-order disproportionation (15); *cf.* section VIII. The products IX·H, LVII·2H, and LVI were obtained in the ratio of 4:1:1 and the quinone methide XIV was shown to be an intermediate in this reaction by ultraviolet spectroscopy (*cf.* section V.A.1).



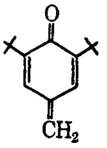
LVII·2H



LVI

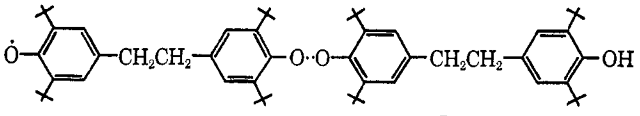


(Eq 19)

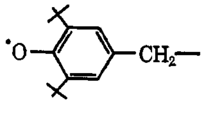


XIV

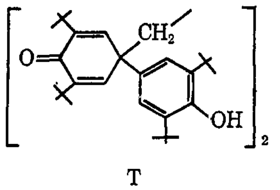
The formation of LVI and LVII·2H *via* the quinone methide involves intermediate free radicals; the exact nature of these has not been elucidated by esr (15, 72, 186). It seems plausible, however, that the dimeric products arise *via* the biradical LVII (186). A partial structure (XIV-P) has been postulated (72, 186); its esr spectrum is very similar to that reported for LVII·H (44). Coupling of LVII with 2 moles of XVI has been invoked to explain the tetranuclear structure T (245a).



LVII LVII·H

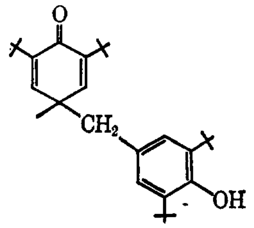


XIV-P



T

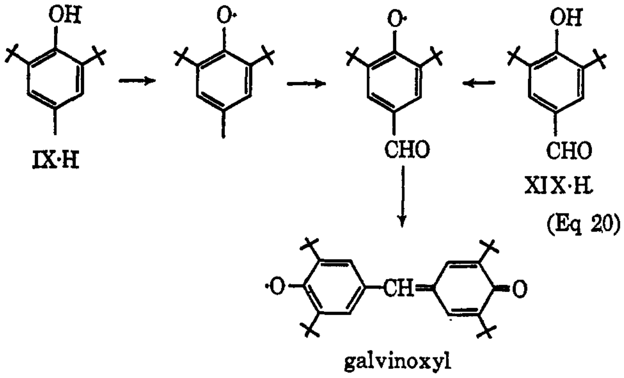
Bennett's data (*cf.* section VIII) support a phenoxy-to-benzyl radical rearrangement, but second-order kinetics have also been reported (178). Magnusson (189) also provided further evidence for the rearrangement from products studies. The formation of 2,6-di-*t*-butyl-4-(3,5-di-*t*-butyl-4-hydroxybenzyl)-4-methyl-2,5-cyclohexadienone is cited as support for the isomerization. This product had not been observed previously; experimental details have not been published.



Unlike the quinol ether dimer (19), this isomer presumably is more stable due to lack of steric crowding; it could arise, perhaps by addition of the keto-radical form to the quinone methide.

On the basis of the chemical evidence available, it must be concluded that the presence of the 3,5-di-*t*-butyl-4-hydroxybenzyl radical has not been proved. Esr studies, though also ambiguous, do not favor it either (see below).

The oxidation of IX·H has been studied extensively by esr. An initial quartet of triplets (1:3:3:1) is converted after 10 min into a 1:2:1 triplet. The same triplet is observed in the oxidation of XIX·H. Eq 20 summarizes an interpretation of these observations. After several days, the esr spectrum of galvinoxyl is observed (16, 223). These workers saw no evidence for an isomeric benzyl radical. A dimeric complex, rather than a benzyl radical coupling was proposed to explain the formation of the bibenzyl LVII·2H and its oxidation products (17). Different interaction constants (in gauss) have been reported, however, for the triplet, *i.e.*, $a_{\mathrm{H},meta} = 1.8$ for IX (16, 45, 223), but $a_{\mathrm{H},meta} = 1.8$ (16) and 2.5 (45) for XIX. Moreover, this triplet has been assigned to the 3,5-di-*t*-butyl-4-hydroxy- and the 3,5-di-*t*-amyl-4-hydroxy-1-benzyl radicals. No evidence for the benzyl radical was obtained when the oxidation of 2,6-di-*t*-amyl-4-methylphenol was carried out with peroxides, but lead dioxide oxidation reportedly gave the esr spectrum consistent with this radical (253). The formation of the benzyl radical was claimed to be confirmed by an examination of the changes in both esr and infrared spectra when deuterated IX·H (deuterium in the 4-methyl group) was used (42). However, the finding that the product LVII·2H contains deuterium in the hydroxyl groups is not a compelling argument for the existence of the benzyl radical, since a head-to-tail dimer (67) or disproportionation *via* the quinone methide (15) would provide a ready mode of exchange. Moreover, the esr spectrum of the benzyl radical would be expected to show splitting due to interaction of the electron with the *o*-hydrogens as well as with hydroxyl hydrogen (*cf.* ref 227).

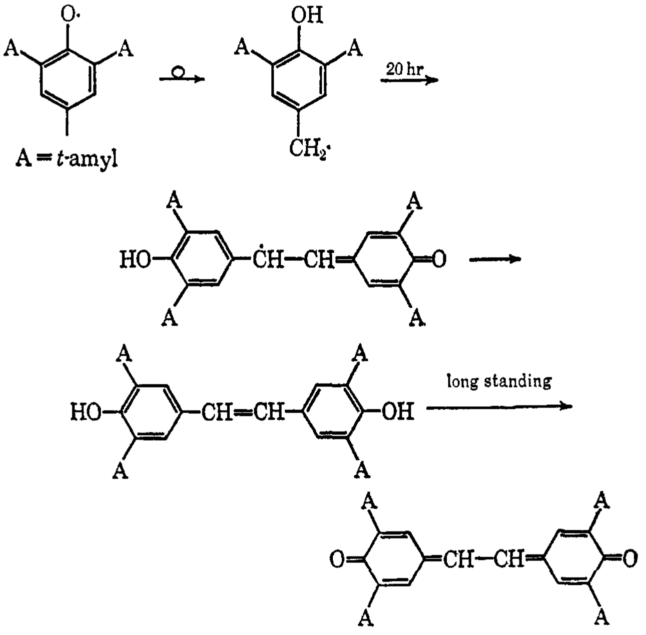


IX·H

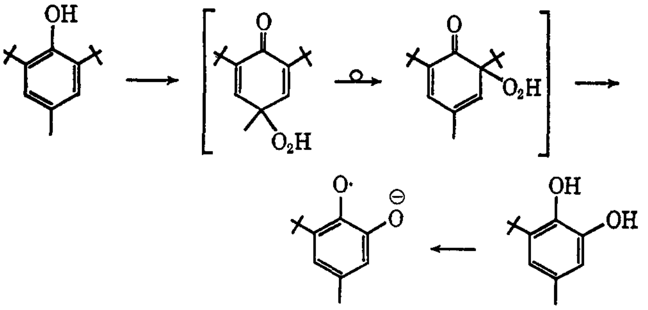
XIX·H

(Eq 20)

galvinoxyl



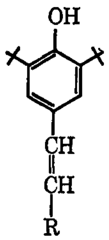
Base-catalyzed oxidation of IX·H leads to an entirely different product, namely, an *o*-semiquinone; the same product is formed on oxidation of 4-methyl-6-*t*-butylcatechol (58, 208); β cleavage of an intermediate hydroperoxide is a plausible pathway in this reaction (58).



Esr evidence for a phenoxy-to-benzyl radical rearrangement in 4-hydroxyphenylethylene derivatives has been published (*cf.* section VII.E).

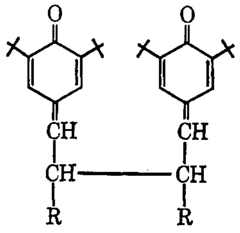
E. COUPLING OF 4-HYDROXYPHENYLETHYLENE DERIVATIVES

The coupling products obtained on oxidation of model compounds related to coniferyl alcohol (*cf.* section IX) depend on the nature of the R group (227, 238). For LXa–c·H the coupled products were quinone methides



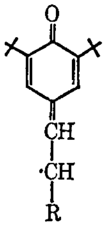
LX·Ha, R = CO_2Me
b, R = CO_2Et
c, R = CO_2*i*-Pr
d, R = CN
e, R = CHO

LX-Q; analysis of the esr spectra obtained during the dehydrogenation indicated the participation of the



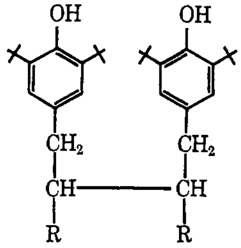
LX-Q

allyl radical LX and coupling of this radical could lead to the observed products.



LX

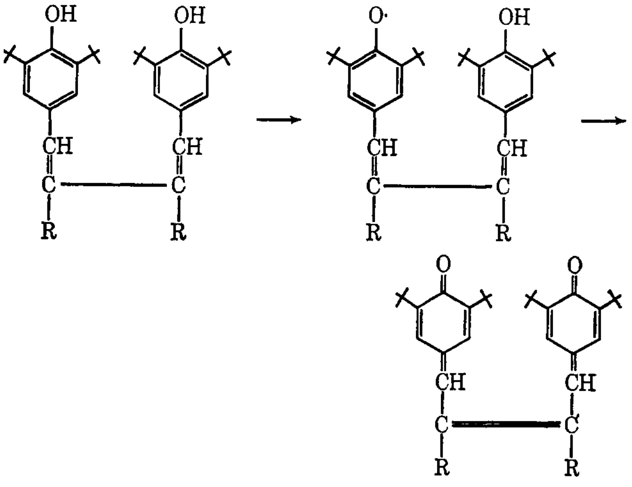
Reduction of LX-Q gave the expected bisphenols (LX·2H). When LX·2H was reoxidized and the



LX·2H

reaction followed by esr, the spectrum was consistent with a monophenoxy-to-monobenzyl radical rearrangement as pathway to LX-Q. Only the signal for the benzyl radical was observed (a six-line spectrum).

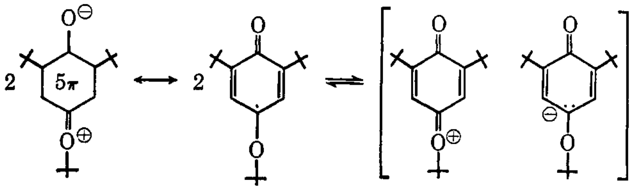
Dehydrogenation of LXd,e·H gave dimers which were identified as the tetra-*t*-butyl homologs of isoxanthocillin by comparison of the ultraviolet spectra; these were further oxidized *via* a monophenoxy radical to a bisquinone methide (130). The observed differences with respect to the R group may be explained by the greater activation effect of the formyl and cyano groups on the α-methyl hydrogen of LX-Q. This leads to a 1–7 proton shift which is facilitated by the aromatization.



R = CN, CHO

F. CHARGE-TRANSFER COMPLEXES

In a number of cases charge-transfer complexes have been proposed for phenoxy radical dimer on the basis of steric, spectral, or chemical evidence (213, 217, 222). Two such structures are Vb and XIIIb. Radical XII was isolated as a colorless dimeric, diamagnetic solid which even in nonpolar solvents dissociates to the highly colored monomeric paramagnetic species. The structure proposed for the dimer of XI, XIIIa, was thought to be unlikely for XII, since the greater bulk of the *t*-butoxy groups would be expected to destabilize the dimer XIIIa (R = *t*-butoxy) with respect to the dimer XIIIa (R = methoxy). Since the reverse is true and since the dimer of XII is colorless, complete electron transfer was suggested (Eq 21). This means that



XII

(Eq 21)

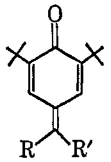
XII can act as both electron donor and acceptor. Infrared bands at 1655 and 1635 cm^{-1} were in agreement with a conjugated cyclohexadienone system, but the quinol ether structure which has been proposed for the dimer of 2,4-di-*t*-butyl-6-*t*-butoxyphenoxy (which dissociates only feebly in solution) was deemed unlikely on steric grounds.

A charge-transfer structure was proposed at one time for the dimer of VI, but was disproved later by a more detailed study of the infrared spectrum using ^{18}O (*cf.* section IV.A). The finding that V and XII, for instance, form dimers while I does not may lend some validity to these complexes, but there appears to be no real proof of their structure. One might expect that a complex would be formed even more readily between a phenoxy radical which had an electron-releasing substituent and one which had an electron-attracting substituent in the 4 position, but such dimers have never been reported. The behavior of these dimers in solvents of different polarity should also be examined.

VIII. Quinone Methides and Radical Disproportionation

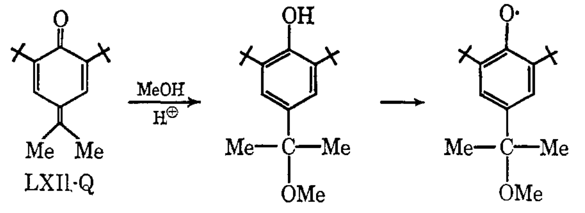
Hindered phenols which carry a 4 substituent bearing on α hydrogen can be oxidized to phenoxy radicals of transient existence or moderate stability. These phenoxy radicals disproportionate to starting phenols and quinone methides, LXI-Q, which often can be isolated in 70–90% yield (66, 223, 234). The esr spectra of several phenoxy radicals which give rise to quinone methides have been studied (16, 223, 234) and Table XXVIII lists several examples of 2,6-di-*t*-butylquinone methides. Quinone methides add nucleophiles such as alcohols, amines (43, 103, 319), and phosphorus compounds (317). The acid-catalyzed addition of alcohols gives phenols which contain an ether group; these form stable phenoxy radicals in most cases. For LXIs-Q the phenol derived from addition of methanol is not isolated, but decomposes to methyl benzoate and LXIp·H (Eq 22).

Table XXVIII
Quinone Methides (LXI-Q)



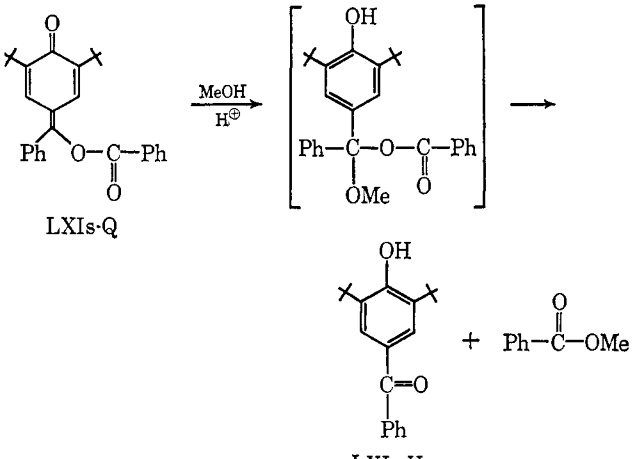
Compd	R	R′	λ_{max}, mμ	ε	Ref
XIV	H	H	285	27,000	103
LXIa-Q	H	Me			67
b	H	Et			99
c	H	*i*-Pr			99
d	H	Bu			99
e	H	Ph			223
f[a]	H	OH			223
g	H	OMe			223
h	H	CH_2OH			99
i	H	CO_2H			99
j	H	CN			99
k	H	N-Piperidyl			99
l	Me	Me	317	30,000	149
m	Me	Et			66
n	Me	Ph			223
o	Ph	Ph	368	30,000	149
p[b]	Ph	OH			223
q	Ph	OMe	350	30,000	149
r	Ph	OCH_2Ph	352	25,000	149
s	Ph	OCOPh			223
t	$-(CH_2)_5-$	. . .			67

[a] Tautomeric with XIX·H. [b] Tautomeric with 4-benzoyl-2,6-di-*t*-butylphenol.



LXII-Q

(Eq 22)

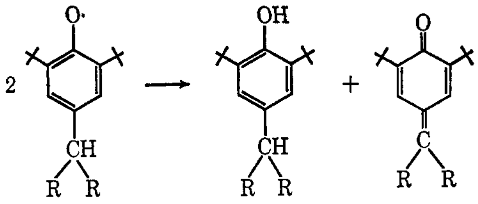


LXIs-Q

LXIp·H

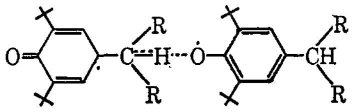
The disproportionation of phenoxy radicals whose 4 substituent bears an α-hydrogen has been studied quantitatively by several workers. Bennett (21) preferred alkaline potassium ferricyanide over lead dioxide in his esr study of the problem, since the former is said to avoid the formation of secondary radicals; the formation of such secondary radicals with lead dioxide has definitely been shown (16). First-order decay constants (about 10^{-2} sec^{-1}) were reported for the solvent dependent decomposition of I, IX, and 4-ethyl-2,6-di-*t*-butylphenoxy for 0.1–5% solutions. In methylcyclohexanone an activation energy of 11.4 kcal/mole and a frequency factor of 3.1×10^6 sec^{-1} were calculated; the latter value is quite low for a unimolecular process. The data were interpreted as being consistent with a phenoxy to *p*-hydroxybenzyl radical rearrangement (*cf.* section VII.D).

The rate of disproportionation of 2,6-di-*t*-butyl-4-isopropylphenoxy (LXII) was followed spectrophotometrically at 625 mμ and gave good second-order kinetics in agreement with Eq 23 (67). For the 4-isopropyl-, 4-*sec*-butyl-, and 4-cyclohexylphenoxy radicals, the enthalpies of activation showed regular dependence on the dielectric constant of the solvent. Thus, in the series cyclohexane, benzene, chlorobenzene, anisole,


LXII

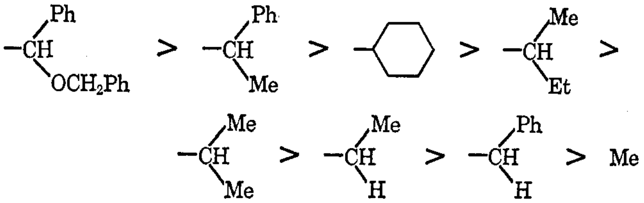
(Eq 23)

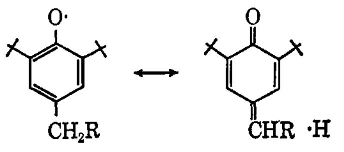
and benzonitrile the enthalpies of activation for the disproportionation of LXII increase from 4.91 ± 0.16 to 7.57 ± 0.17. The rates are found to be relatively insensitive to solvent effects, however, 3.82 ± 0.09 (cyclohexane) to 5.64 ± 0.07 l. mole^{-1} sec^{-1} (benzonitrile) at 25°, but an isokinetic relationship has been demonstrated. A head-to-tail model was suggested for the transition state (67).



Although the values reported for the second-order reaction of LXII by different authors at the same concentration (0.01 *M*) are in good agreement, 3.82 (67) and 4.2 l. mole^{-1} sec^{-1} (149), increased dilution leads to rate acceleration and results which are not compatible with Eq 23. At a 10^{-4} *M* concentration a new product is observed by the appearance of strong band at 235 mμ; a α-methyl-*p*-hydroxystyrene derivative has been suggested (149). These authors followed the reactions of LXIo, l, r, and q by the disappearances of several phenoxy radical peaks as well as the appearance of quinone methide absorptions. For LXIo four radical bands decreased and two quinone methide bands increased with equal speed, and three isosbestic points were found. These results were in agreement with Eq 23. However, for LXIq a first-order rate constant (3 × 10^{-4} sec^{-1}) was found. Only for LXIo and LXIr were second-order kinetics observed over a 100-fold range in concentration. It can be concluded that while Eq 23 is a possible route, it is not the only pathway of disproportionation.

Based on ultraviolet (67) and esr data (223) radical stability decreased along the following series of 4 substituents.

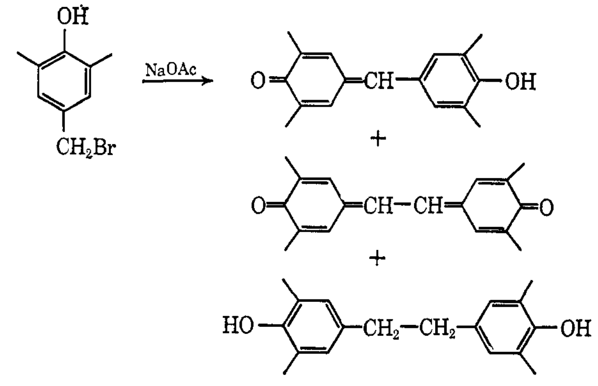




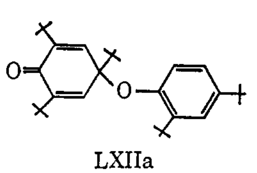
Esr data showed the participation of the 4 substituent in ground-state stabilization. Reactions of these phenoxy radicals with oximes or phenols do not occur; apparently the disproportionation is too fast. However, some rates of quinol ether formation (for example, I plus several phenols; *cf.* Table XXIII) are considerably faster than the rates of disproportionation reported here, and therefore it would appear that disproportionation could be suppressed by a favorable choice of conditions (use of an excess of phenol which carries an electron releasing substituent such as *p*-methoxy). The products of oxidation of these phenols (LXI·H) depend on the oxidizing agent. Oxidation with I of LXI·Hf, g, and p gives the corresponding quinone methides while alkaline potassium ferricyanide yields coupling products (section VII·C).

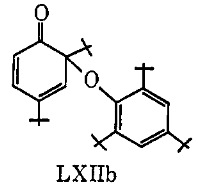
The role of the quinone methide XIV in the oxidation of IX·H and the dimerization has been discussed by several workers (15, 103) and is described in further detail in section VII.D. A 10^{-2} *M* isooctane solution of this compound is quite stable, only 2% having reacted in 72 hr (103).

Attempts to isolate quinone methides go back more than 60 years (114). Efforts based on 2,6-dimethyl-4-bromomethylphenol produced only dimers, among them the methyl analog of hydrogalvinoxyl, presumably formed by an oxidative dealkylation (114).



Stable phenoxy radicals such as I also disproportionate, but the details and the products of these reactions are not well understood. One of the products is usually the parent phenol. From the decomposition of I at 80° isobutylene and two higher molecular weight products result in addition to I·H. One of these products has been characterized as the dimer (minus 1 mole of isobutylene) and structure LXIIIa was assigned to it (65, 214). Apparently the same product is obtained in low yield from the reaction of I with maleic anhydride


LXIIa

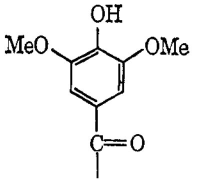

LXIIb

(*cf.* section VI.P.2). The absence of a 244-mμ band (characteristic of cross-conjugated cyclohexadienone) and the presence of bands at 277 and 287 mμ led to the alternate structural proposal, LXIIb (133). The position from which *t*-butyl is lost remains uncertain; LXIIb would appear to be less likely than LXIIa on steric grounds.

IX. PHENOXY RADICALS IN NATURAL PRODUCTS

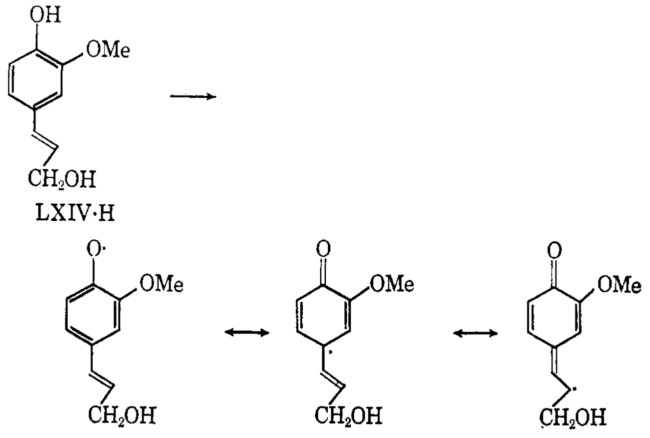
From the results of many investigators, it has become clear that radicals of the phenoxy type and those closely related to them are present in nature in a wide range of stabilities, from species of transient existence to those which are stable for years. Of prime importance has been the oxidative coupling of phenolic compounds in the synthesis of alkaloids and numerous other plant and fungal products. A definitive summary of this work has been written (297). It was shown by Barton and Cohen (12) that application of the principles or *ortho* and *para* C–C and C–O oxidative coupling accounts for the structural features found in many classes of alkaloids. The coupling products obtained by the action of enzyme systems, such as horseradish peroxidase–hydrogen peroxide are the same in many cases as those obtained by the action of one-electron oxidizing agents. An enzyme isolated from wood rotting fungi did not require the use of added hydrogen peroxide; this material oxidized 2,6-dimethyl- and 2,6-dimethoxyphenol to XV (R = CH_3 and OCH_3) (34). The formation of this product certainly suggests a radical coupling step (*para* C–C) followed by oxidation. The role of oxygenases and the possible occurrence of phenoxy radicals has been discussed by Hayaishi (137). No results have been reported with more highly substituted and hindered phenols. Additional examples of enzymes which do not require added hydrogen peroxide are given by Scott (297).

The importance of phenoxy radicals in the biosynthesis of lignin from phenols and sugars had been suggested by the work of Freudenberg (106–109, 111, 112) and his co-workers. Evidence has been presented in recent years for the existence of stable species in lignin. Esr signals were observed for both native and oxidized lignins (268, 307). These species may be stabilized indefinitely in the solid lignin matrix. The α-carbonyl syringyl moiety (LXIII) appears to be an inherent part of lignin structures (110, 192) and recent work on model systems based on LXIII has tended to confirm the high stability of radicals derived from it (305, 306); *cf.* section V.B.4.



LXIII

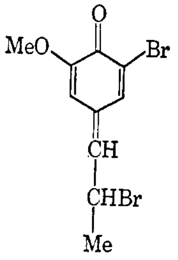
Freudenberg's work (108) led to the postulate of coniferyl alcohol (LXIV·H) as a lignin building block, which could readily undergo coupling reactions through mesomeric radicals such as LXIVa and b. Experiments with model compounds have lent support to this view (297); *cf.* section VII.E. In studies of models related to lignin, the polymerization of the quinone methide LXV was found to be base catalyzed, but was not initiated through I (113).



LXIV·H

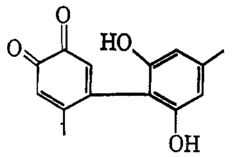
LXIVa

LXIVb

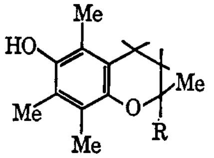


LXV

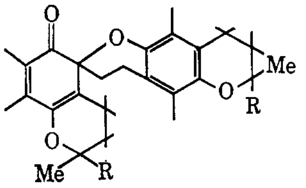
Solid soil humic acid and its solutions exhibit paramagnetism and it was shown that the radicals were an integral part of the molecular structure and not impurities or trapped species. Several groups were suggested as possible radical sources; one is shown (308).



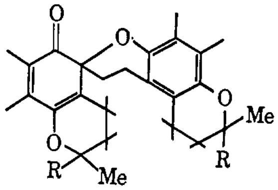
Extensive studies have been carried out on tocopherols and related model compounds (301). Oxidation of *dl*-α-tocopherol (LXVI-A) and a model, 6-hydroxy-2,2,5,7,8-pentamethylchroman (LXIV-B), with alkaline potassium ferricyanide gave dimers which were internal quinol ethers (see section VI.L.4). Structures A′ and B′ and A″ and B″ were favored over the



LXVI-A, R = $C_{16}H_{33}$ (tocopherol)
LXVI-B, R = CH_3

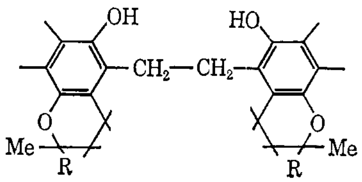


A′
B′

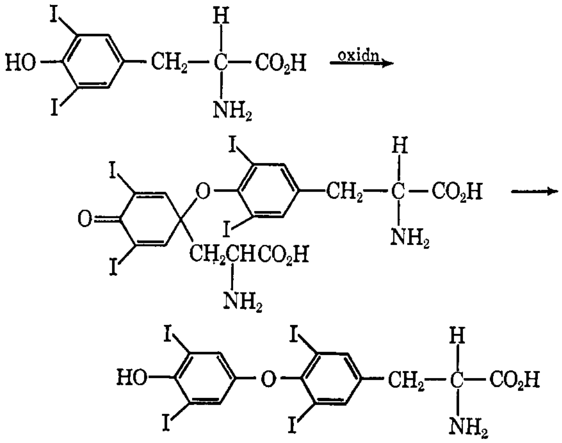


A″
B″

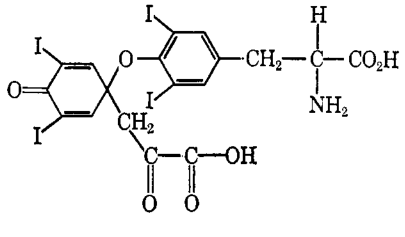
two additional isomers, with A″ and B″ the most likely. The product A″ was also obtained when LXVI-A was oxidized with I (94). A coupling through the methylene group was observed when LXVI-A,B were treated with azobisisobutyronitrile (300).



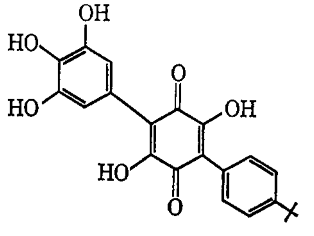
Investigations of the biosynthesis of thyroxine have led to the synthesis of numerous model systems and their precursors. A free radical coupling of the 2 moles of 3,5-diiodotyrosine (DIT) to form thyroxine under oxidizing conditions was originally proposed over 20 years ago (131, 163). The dimerization involved the intermediate formation of a quinol ether (Eq 24). The synthesis of several model systems, for example, the reaction of I with a number of substituted phenols (*cf.* section VI.L) to form quinol ethers and the elimination of the alkyl group on treatment with acid or heat, lent strong support to such a route (49, 196). The close analogy of the formation of thyroxine to other oxidative dealkylations involving phenols has been pointed out (200). While 2 moles of DIT give only a low yield of thyroxine, the reaction of DIT with 4-hydroxy-3,5-diiodophenylpyruvic acid (DIHPPA) in the presence of oxygen yields thyroxine rapidly and in good yield (194, 201). The oxygen oxidation of DIHPPA was followed by esr, and at pH 6.5–9 the observed signal was tentatively attributed to the phenoxy radical (194). This makes it very likely that the intermediate quinol ether is produced *via* formation of this radical which reacts with the phenoxy radical derived from DIT, a product expected on the basis of relative stability. The fate of the alkyl group which cleaves when thyroxine is formed has not been determined.



(Eq 24)



Polyporic acid was reported to be an antioxidant; a number of modified compounds were synthesized. Of these, LXVII was said to be an outstanding antioxidant (22); its function probably involves an intermediate phenoxy radical.



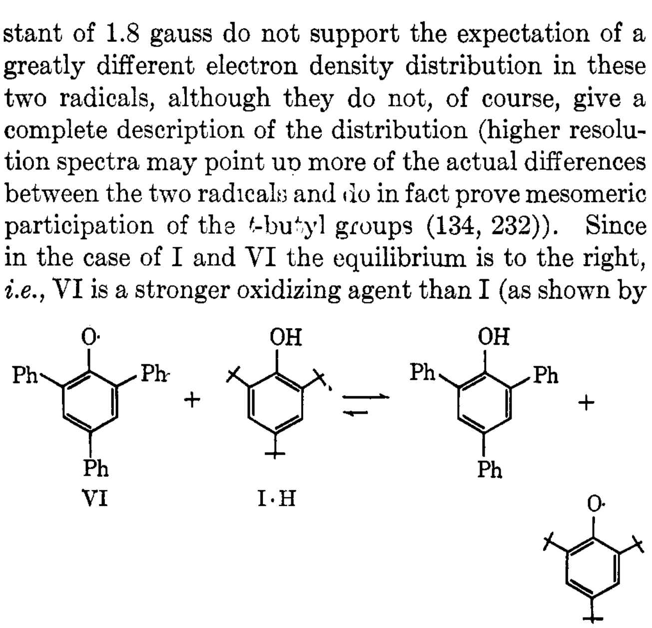
LXVII

X. DISCUSSION

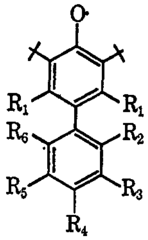
It is instructive, first of all, to consider the reactions that have been discussed by comparison to other radical species. For alkoxy radicals, for example, Gray and Williams (125; also *cf.* ref 314) list eight modes of reaction: (1) association (dimerization), (2) hydrogen abstraction, (3) addition, (4) rearrangement, (5) decomposition by C–H bond fission, (6) decomposition by C–C bond fission, (7) disproportionation, (8) decomposition by radical attack. These reactions are shown also by carbon radicals and there is an abundance of examples to show that phenoxy radicals react as oxygen or carbon radicals. For example, association and dimerization are illustrated by the formation of phenoxy dimers (section VII), formation of quinol ethers (section VI.L) and aryl benzyl ethers (section VI.E), and reaction with peroxy radicals (section VI.O) and nitric oxide. Hydrogen abstraction takes place with phenols, thiols, aldehydes, oximes, etc., and there are examples with hydrocarbons and olefins. Addition occurs to olefins and dienes (section VI.E) and internal addition forms spiro compounds (section VI.L.4). There is evidence for rearrangement in hydroxyphenylethylene derivatives and possibly IX. Examples of decomposition by C–H and C–C bond fission may be known but are not thoroughly substantiated (section VII.C). Disproportionation is thoroughly substantiated (section VIII) and experimental evidence suggests that decomposition by radical attack is possible (23, 159). Some of these reactions will be discussed in more detail below.

In spite of these broad similarities, it is clear that the phenoxy radicals considered here not only differ from other oxygen and carbon radicals, but also differ from "unstable" phenoxy radicals, *i.e.*, those derived from phenol, cresols, xylenols, etc. The reason for this is to be found in the increased amount of substitution, and it is obvious that certain minimum steric and mesomeric requirements must be met to have a phenoxy radical that fits the definition of stable as mentioned in the Introduction. To what extent these substituents influence the relative stability of phenoxys (within the class of stable phenoxy radicals) has been the subject of much of the physical and chemical experimentation in this field.

Relative stability conceivably could be measured by a number of different criteria, for example, relative oxidizing power ($ArO\cdot + e \rightarrow ArO^-$), rate of reaction with oxygen, or radical content in the solid state. The first two are more properly measures of relative reactivity. Esr spectroscopy gives detailed information about the ground state and therefore offers the best approach to relative radical stabilities. The esr spectra for the unsubstituted phenoxy radical and those having one or two small substituents were determined by a flow technique, and the lifetime of these radicals was found to be about 10^{-2}–10^{-6} sec (44, 312). Reference has already been made to the detailed examination of I (section IV.C) and the fact that a finite electron density on oxygen and all ring carbon atoms has been proved. The stability of I and its existence as a monomeric radical thus appears to be the result of electron delocalization and steric factors (276); *i.e.*, the bulky *t*-butyl groups prevent rapid dimerization or other modes of decomposition. In view of the increased stability of I over other trialkylphenoxys, such as 2,4,6-trimethyl or IX (as measured by intensity and duration of the esr signals (16), one is inclined to attribute the stability of I entirely to steric factors. The replacement of *t*-butyl groups by phenyl groups to form the stable radical VI appears then to be primarily a case of replacing bulky groups with groups which, although they have a lower steric requirement, offer increased opportunity for electron delocalization. As already mentioned (section IV.C), however, the $a_{^{17}O}$ interaction constant for I (10.23 gauss) and VI (9.7 gauss) as well as the comparable $a_{H,meta}$ coupling constant of 1.8 gauss do not support the expectation of a greatly different electron density distribution in these two radicals, although they do not, of course, give a complete description of the distribution (higher resolution spectra may point up more of the actual differences between the two radicals and do in fact prove mesomeric participation of the *t*-butyl groups (134, 232)). Since in the case of I and VI the equilibrium is to the right, *i.e.*, VI is a stronger oxidizing agent than I (as shown by oxidation potential measurements; Table I), ground-state considerations give only an incomplete description of radical reactivity. Rieker and Scheffler (276) have made a more detailed inquiry into the question of mesomeric participation of the phenyl ring by the esr study of a series of 2,6-di-*t*-butyl-4-substituted phenylphenoxy radicals; *i.e.*, the steric factor around the oxygen was identical with that of I (see section V.A.2, Table V for a list of the substituents investigated). Coupling constants were determined for R_1–R_6 (see formula VII); they were not affected greatly by the nature of the substituent nor its position (no pronounced effect was noted for methyl or methoxy at R_2 and R_6). The results generally indicate the stabilizing effect of 4-*t*-butyl or substituted phenyl to be of the same order of magnitude (Rieker and Scheffler use stability as described by the equilibrium $ArO\cdot + e \rightleftharpoons ArO^-$); this is also suggested by the oxidation potentials of comparable magnitude (Table I) and the mobile equilibrium between I and VII.



VI I·H



VII

(R_1–R_6 = substituted phenyl)

Electron-withdrawing substituents in the 4 position of 2,6-di-*t*-butyl-substituted phenoxy radicals lead to a stronger interaction of the unpaired electron with the *meta* ring protons, as is indicated by larger $a_{H,meta}$ coupling constants (a selected group of such constants is listed in Table XXIX). No linear relationship exists

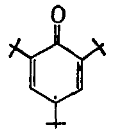
TABLE XXIX

$a_{H,meta}$ COUPLING PARAMETERS (GAUSS) FOR 2,6-DI-*t*-BUTYL-4-R-PHENOXY RADICALS

R	$a_{H,meta}$	σ^a	σ^{+b}	Ref
NMe_2	<0.15	−0.60	−1.7	271
NH_2	0.5	−0.66	−1.4	44
NC	0.88			278
OMe, $OCMe_3$	1.0	−0.268	−0.778	217
N^+Me_3	1.1	+0.86	+0.408	278
SMe	1.4	−0.047	−0.604	239, 292
OC_6Cl_5	1.4			273
$OPOPh_2$	1.55			273
$SeMe_3C$	1.57			240
PPh_2	1.6			206
Naphthyl	1.6			44, 276
Phenyl	1.68	+0.009	−0.179	276
CH=NOMe	1.7			292
OCOMe	1.75			273, 230
S-2,4-Dinitrophenyl	1.75			292
Me	1.8	−0.17	−0.311	16, 19
CMe_3	1.8	−0.197	−0.256	16, 217
CHO	1.8			16, 217
$SnPh_3$	1.82			205, 309
SCOMe	1.9			44, 239
SOMe	2.0			239
$POPh_2$	2.0			206
$PSPh_2$	2.0			206
$AsSPh_2$	2.0			205
NO_2	2.14	+1.27	+0.790	278
$P^+Ph_2CH_2OH$	2.15			206
CN	2.2	+1.00	+0.659	217
CO_2Et	2.2	+0.68	+0.482	230
COMe	2.3	+0.87		16, 217
P^+Ph_2Et	2.35			206

[a] These values are taken from J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p 72. [b] H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80,** 4980 (1958).

between these values and either σ or σ^+ values, although larger $a_{H,meta}$ values parallel to some extent increasing substituent constants. But no obvious relationship exists between these values and either radical stability (as measured by intensity and duration of the esr signal) or radical reactivity (as measured, for example, by rate of reaction with oxygen). Nor is the degree of side-chain interaction with the unpaired electron as determined by esr a measure of relative stability. Thus, the spectra of radicals XVIII (4-COOR′) show participation of the R group in the mesomeric distribution of the electron density; but these radicals are very unstable and are isolable as stable dimers only. Nevertheless, it has often been implied that increased delocalization of the unpaired electron leads to increased stability of the radical, but it has also been pointed out (44) that there is not necessarily a direct relationship between spin density and electron charge density. Müller (231) has also emphasized that the assignment of a statistical weight of 25% to the spin density of carbon 4 in the ground state of I (and other 2,6-di-*t*-butyl-4-R-phenoxys) is not synonymous to a participation of the keto resonance form to the extent of 25% in ground-state stabilization, and is even less likely to reflect the transition state.



The keto resonance forms must be important contributors to the transition state, since so many of the products of phenoxy radical reactions are the result of reaction at the 4 position. The reason for this appears to be primarily steric. Radicals with smaller 2,6 substituents (for example, XXV) show a greater tendency to react in the oxygen radical form (hydrocarbons, section VI.E; diazomethane, section VI.F). Steric considerations of the oxygen radical form (and 2,6 disubstitution) show that bulkier groups increase radical stability (*t*-butyl > methoxy > methyl), but electronic effects of 4 substituents can be important alone (for example, XXIIa is stable for a few minutes; section V.A.7) or contribute to the increased stability of radicals such as XXVIa–c (Table XVII) which carry smaller 2,6 substituents.

Steric factors in the 4 position primarily account for the fact that I is monomeric both in the solid state and in solution and reacts readily with small radicals such as oxygen and phenoxy. Replacement of 4-*t*-butyl by phenyl, as in VII, gives a radical which is likewise monomeric in the solid state and solution, but which reacts with oxygen $^1/_{16}$th as fast as I, but XL (2-phenyl-4,6-di-*t*-butyl) cannot be isolated as a monomeric radical and exists only 13% dissociated in solution; it does, however, react faster with oxygen than VII. Other radicals which exist partly or completely as monomeric solids are galvinoxyl, 2,6-di-*t*-butyl-4-CH=N-OR-phenoxys, IX, and XI, while V, XXI, XVII, XVIII, and XXV are isolable as solid dimers only. Radicals in the latter group contain one or more electron-withdrawing groups, but XII cannot be rationalized on this basis. In solution, decreasing steric effects and electron-withdrawing groups in the 4 position appear to be responsible for the increasing tendency toward dimer formation along the series: I → IX → XVII → XVIII → V → VI → XXV. Although phenoxy radicals with electron-withdrawing groups have a much greater tendency to react with hydrocarbons and do so in the oxygen radical form (section VI.E) and show a lower tendency toward quinol ether formation (section VI.L.3) than I, they do show a greater tendency toward formation of dimers, which appear to exist mostly as simple quinol ethers or as structure XIII; therefore, their formation must involve the keto form. Nevertheless, it is difficult to predict how important a steric factor might be. Several 4-*t*-alkyl-2,6-di-*t*-butylphenols as well as phenols with others 4 substituents gave excellent σ^+-substituent correlations when employed as inhibitors in the autoxidation of styrene (146; *cf.* section VI.O.2), and it can be concluded, therefore, that 4-*t*-alkyl groups in the initially formed phenoxy radical offered no special steric effect toward the attack of the styryl peroxy radical.

It should be remembered that all phenoxy radicals are readily reduced to the parent phenols, so that the reactivity of these radicals depends both on steric and electronic demands of the substituent as well as those of the other reactant.

Examination of some additional oxidation potential values, Table XXX (311) (*cf.* Table I and section VI.L.1), further illustrates steric and electronic effects.

TABLE XXX

OXIDATION POTENTIALS OF HINDERED PHENOLS (311)

Substituents	$E_{1/2}'$, v
4-Phenyl-2,6-dicyano	>+800
4,6-Diphenyl-2-cyano	+593
2,6-Diphenyl-4-cyano	+549
2,4,6-Triphenyl(VI·H)	+211
4-*t*-Butyl-2,6-diphenyl	+120
6-*t*-Butyl-2,4-diphenyl	+112
4,6-Di-*t*-butyl-2-phenyl (XL·H)	+76
2,6-Di-*t*-butyl-4-phenyl (VII·H)	−14
2,4,6-Tri-*t*-butyl (I·H)	−59

The 4-phenyl-2,6-dicyanophenoxy radical should be capable of oxidizing all other phenols in this table. This compound contains the strongest electron-withdrawing group and the least hindrance in the 2,6 position. Comparison of XL·H with VII·H and 4-*t*-butyl-2,6-diphenyl- with 6-*t*-butyl-2,4-diphenylphenol shows the effect of the *o*-*t*-butyl group which, in addition to its electron-releasing power (relative to phenyl and cyano), exerts a steric effect which contributes to the lowering of the oxidation potential.

Polynuclear phenoxy radicals derived from naphthols such as II and 1,3,4-trichloronaphthoxy (280) exist as dimeric solids which show only a low degree of dissociation in solution. A 2-*t*-butyl group is not sufficient to lend any stability to the radical derived from β-naphthol (280). However, increased resonance combined with some shielding seems to play a role in the much higher stability of XXXIV (section V.D).

C–H bond cleavage is suggested by the finding that the esr spectra of phenoxy radicals which have α-H's on the 4-C substituent are changed on further oxidation to those of phenoxy radicals which carry α-carbonyl groups. Moreover, the α-carbonylphenols were isolated in low yields from the respective α-methylenephenols during the inhibited autoxidation of cumene (141). This side-chain oxidation could occur conceivably by α-hydrogen abstraction by an oxidizing species or it may involve the quinone methide. An esr study of the oxidative decarboxylation of 3,5-di-*t*-butyl-4-hydroxybenzoic acid (Scheme XIII, section VII.C) may show the sequence of the proposed steps; *i.e.*, is carbon dioxide lost from the anion or the anion radical.

The reactions of phenoxy radicals with carbon radicals are quite varied. The formation of 2-methyl-6-*t*-butylphenol during the oxidation of XVI·H by *t*-butoxy radicals (section VI.O.3) is explained plausibly by attack of methyl radicals on XVI (159). Phenyl radicals apparently are capable of displacing the *t*-butyl groups (section VI.B), although such a product was not reported from the reaction of phenylmagnesium bromide with phenoxy radicals (section VI.K). Galvinoxyl can react with carbon radicals in a terminating coupling step (9, 10); the stable products have been characterized.

The formation of a phenoxy radical from a phenol is a hydrogen abstraction and many of the reactions of phenoxy radicals are hydrogen abstractions re-forming the phenol. This removal or return of hydrogen can take place formally *via* three pathways. (1) The first is a rate-determining hydrogen abstraction.

$$\text{—X—H} + \text{R}\cdot \rightarrow \text{R—H} + \text{—X}\cdot$$

This reaction was originally postulated by Haber and Willstätter (129) and has since been used as a basis of interpretation of many kinetic studies. This view has been attacked sweepingly by Kenner, who favors the primary importance of electron transfer in numerous oxidation reactions (see below).

(2) The second pathway is electron transfer, followed by proton transfer in the second step (166).

$$\begin{array}{r}\text{—X—H} + \text{R}\cdot \rightarrow [\text{—X—H}\cdot\text{R}] \leftrightarrow [\text{X}^{\oplus}\cdot\text{H}:\text{R}^{\ominus}] \leftrightarrow [\text{X}\cdot\text{H}:\text{R}] \\ \downarrow \quad \\ \text{R—H} + \text{—X}\cdot\end{array}$$

In phenoxy radical chemistry (R· = phenoxy radical), this would then be followed by a fast third step, radical combination to RX (and RH and RX are the two observed products). Alternately, proton transfer could precede electron transfer.

(3) The third possibility, ionic hydrogen abstraction, has been discussed by Dimroth for phenoxy radicals (84). Presumably, the first step is a complete electron transfer (251).

$$2\text{R}^{\oplus} \rightleftharpoons \text{R}^{\oplus}\text{R}^{\ominus}$$

$$\text{(a)} \quad \text{—X—H} + \text{R}^{\oplus}\text{R}^{\ominus} \rightarrow \text{X}^{\ominus} + \text{RH} + \text{R}^{\oplus} \rightarrow \text{RH} + \text{RX}\ (\text{H}^{\oplus}\ \text{transfer})$$

$$\text{(b)} \quad \text{—X—H} + \text{R}^{\ominus}\text{R}^{\oplus} \rightarrow \text{X}^{\oplus} + \text{RH} + \text{R}^{\ominus} \rightarrow \text{RH} + \text{RX}\ (\text{H}^{\ominus}\ \text{transfer})$$

The controversy of rate-determining hydrogen abstraction *vs.* rate-determining electron transfer has been quite lively, but the question is not likely to be settled in favor of either one alone, since there is abundant evidence for both; although, when some individual reactions are considered, the available results may support one of the two paths very strongly. The finding of significant deuterium isotope effects in both the formation (*i.e.*, IX·H + peroxy radicals, section VI.O.2) and reactions of phenoxy radicals (*i.e.*, I + unhindered phenol to give I·H and quinol ethers, section VI.L.3) argues strongly for a rate-determining hydrogen transfer. However, electronic factors also make their contribution since sometimes excellent correlations have been observed with substituent constants. Polar effects are well recognized in radical reactions (285, 322) and the picture that emerges is based on the suggestions of Russell (286). Ingold (148, 159) has discussed his results in detail in terms of this picture which regards electron transfer as a stabilizing factor in a rate-controlling hydrogen transfer Three contributing structures to the transition state can be considered (VIIIa–c, section VI.O.2). Polar effects will be most important in VIIIb, least in VIIIc (the use of the numeral does not imply a 4,4-cyclohexadienone structure in this instance). Structure VIIIc would be important when there is considerable bond breaking in the transition state and the resulting radical is stabilized by resonance (such as a phenoxy radical). The results correlated with σ^+-substituent constants for both peroxy and alkoxy radical attack, but the rates for reaction of 2,6-di-*t*-butyl-4-R′-phenols were slower than for nonhindered phenols. Structure VIIIa would be expected to make an increased contribution if there is little O–H bond lengthening or breaking in the transition state. The reason for this is not lack of coplanarity (26) in the ground state; for this there is no evidence from infrared, ultraviolet, or nmr spectra (56, 158). It would appear that two *o*-*t*-butyl groups do not permit the attacking radical to approach the phenolic hydrogen as closely as is possible for unhindered phenols. This could account for an increased activation energy and a decreased reaction rate.

$$R'C_6H_4OH + X\cdot \rightarrow$$

$$\underset{\text{VIIIa}}{[R'C_6H_4O{:}H\cdot X]} \leftrightarrow \underset{\text{VIIIb}}{[R'C_6H_4O^{\oplus}\cdot H{:}X^{\ominus}]} \leftrightarrow \underset{\text{VIIIc}}{[R'C_6H_4O\cdot H{:}X]} \rightarrow$$

$$R'C_6H_4O\cdot + HX$$

Although such evidence supports the formation of phenoxy radicals by a rate-determining hydrogen abstraction, there are reactions which appear to be governed by electron transfer. Kinetic studies of the alkaline potassium ferricyanide oxidation, though these have not been carried out specifically with hindered phenols, are in favor of an electron transfer preceded by a fast proton transfer (*cf.* section III.A.2). Oxidation of several phenols with oxygen in basic solution to cyclohexadienone 4-hydroperoxides was found to be catalyzed by aromatic nitro compounds. An electron donor–acceptor complex was proposed which led to a partial radical character of the phenoxide ion; this permitted rapid reaction with oxygen (118). However, the extent of electron transfer in the system IX·H–*m*-dinitrobenzene–sodium ethoxide was only 0.5%, as determined by esr (228); but under certain conditions, phenoxy radicals do intervene in oxidations of phenols in the presence of base (1, 58); *cf.* section VII.D.

In the reaction of phenoxy radicals, there appears to be no correlation between acidity of the hydrogen and the ease of its removal. Thus, we have seen that phenoxy radicals react smoothly with phenols, naphthols, thiophenols, oximes, hydroxylamines, etc., but not with enols, alcohols, and carboxylic acids under comparable conditions. These considerations led Müller (226) to propose an electron-transfer step rather than hydrogen abstraction, as the mechanistically dominating feature of the reaction. Since considerable evidence exists that $5\pi^+$ structures contribute to the stabilization of phenoxy radicals, the latter seem especially set up for electron transfer, which would lead to the stable phenolate anion

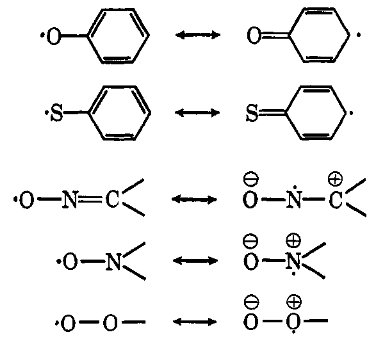
$$5\pi^{\oplus} + e \rightarrow 6\pi$$

or

$$5\pi\cdot^{\oplus} - O^{\ominus} + e \rightarrow 6\pi - O^{\ominus}$$

One attractive feature of the scheme is that it encompasses reactions of phenoxy radicals with anions which cannot involve hydrogen abstraction. This includes I^-, H^-, SCN^-, alcoholates, phenolates, enolates, oxime salts, and organometallics, but not carboxylates, acetylides, and nonreducing inorganic salts (20, 210). The case of reaction of OH and SH groups attached to aromatic rings, N, or O atoms points to special stabilization of the radical Y–X·, where Y ≡ N, O, or aromatic, *i.e.*

$$R\cdot + H{-}X{-}Y{-} \longrightarrow RH + \cdot X{-}Y{-}$$



The reaction with species such as sodium, iodide, or SCN^- may be governed by factors such as polarizibility in the attacking nucleophile (I^- and SCN^- react; OH^- and carboxylate ion do not react), or by the α effect (97), *i.e.*, the presence of an unshared pair of electrons on the atom adjacent to the nucleophilic atom. The latter may explain the reactivity of oximes, hydroxylamines, and hydroperoxides, and the lack of reactivity of alcohols. However, not enough is known about relative rates, solvent effects, etc. to permit an accurate assessment of the importance of these two factors.

Molecular orbital calculations generally have supported a rate-determining electron-transfer mechanism even in cases where hydrogen abstraction is possible (115, 204).

XI. USES

The wide range of oxidation potentials encompassed by phenoxy radicals depending on the substituents suggests their increased use as selective oxidizing agents in a homogeneous medium; moreover, the existence of many radicals as solid dimers (monomer in solution), "canned phenoxy radicals," increases their availability and usefulness (230).

The property of phenoxy radicals to scavenge other radicals has been referred to repeatedly, and hundreds of hindered phenols are described as antioxidants in the patent literature, and function presumably *via* the corresponding phenoxy radicals (296). The reaction with oxygen has been proposed as an analytical method (section VI.N.1).

Phenoxy radicals can also be useful as polymerization inhibitors (39, 98, 214).

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