of the p-CH_3SO_2 group on the acid dissociation constants of benzoic acid, phenol, and the anilinium ion, Bordwell and Copper[13] have likewise observed evidence indicating appreciable conjugative effects for the p-sulfone group even in the ground state. Therefore, the inability of V to undergo an Ar_1-3 assisted solvolysis can be rationalized by considerable charge delocalization in the phenoxide moiety.

Experimental[14]

Chloromethyl Cyclohexyl Sulfide (I).—Cyclohexylmercaptan was treated with paraformaldehyde and anhydrous hydrogen chloride according to the method of Walter, Goodson, and Fosbinder[5] to give I as a colorless, foul-smelling liquid, b.p. 99–102° (14 mm.).

Chloromethyl Cyclohexyl Sulfone (II).—To a stirred solution of 34.5 g. (0.20 mole) of *m*-chloroperbenzoic acid in 400 ml. of chloroform cooled to −5 to −10° was added dropwise over 15 min. 16.5 g. (0.10 mole) of chloromethyl cyclohexyl sulfide. When the addition was completed, the contents were allowed to warm to room temperature and kept overnight in this condition. The insoluble *m*-chlorobenzoic acid was removed by filtration and washed with chloroform. The combined filtrate and washings were shaken with 10% sodium carbonate solution, dried, filtered, and evaporated to give 19.0 g. (97.0%) of a colorless oil which crystallized on scratching, m.p. 35–39°. Pure II was obtained as shiny white plates from ether–hexane; m.p. 51°, ν^{Nujol} 1300 and 1135 cm.$^{-1}$ (SO_2).

Anal. Calcd. for $C_7H_{13}ClO_2S$: C, 42.74; H, 6.66; S, 16.30; Cl, 18.03. Found: C, 43.01; H, 6.90; S, 16.38; Cl, 17.93.

Methylenecyclohexane—A mixture of 5.9 g. (0.03 mole) of II and 50 ml. of 25% aqueous sodium hydroxide solution was refluxed with stirring for 24 hr. The flask was cooled and the liberated oil was extracted with ether and the combined ethereal layers were washed with water and dried. The dried ethereal solution was carefully distilled at atmospheric pressure through a 2-ft. Vigreux column to remove the major portion of the ether. The residual colorless liquid was subsequently carefully distilled through a 1-ft. Vigreux column to give 2.3 g. (80%) of methylenecyclohexane, b.p. 97–99°.

Chloromethyl *n*-Hexyl Sulfide (III).—1-Hexanethiol (Eastman White Label) was treated with paraformaldehyde and anhydrous hydrogen chloride according to the method of Walter, Goodson, and Fosbinder[5] to give III as a colorless, foul-smelling liquid, b.p. 90–93° (13 mm.).

Chloromethyl *n*-Hexyl Sulfone (IV).—A 0.10-mole sample (16.7 g.) of II was oxidized as described above for II to give 19.2 g. (97.0%) of white solid, m.p. 47–50°. Pure IV was obtained as a white solid from ether–hexane; m.p. 50.5–51.5°, ν^{Nujol} 1300 and 1135 cm.$^{-1}$ (SO_2).

Anal. Calcd. for $C_7H_{15}ClO_2S$: C, 42.31; H, 7.61; S, 16.14. Found: C, 42.36; H, 7.72; S, 16.60.

Hexene-1.—A mixture of 9.9 g. (0.05 mole) of IV and 75 ml. of 25% aqueous sodium hydroxide solution was refluxed overnight with stirring. The resulting heptene-1 was isolated as described above for methylenecyclohexane to give 3.8 g. (77.6%) of colorless liquid, b.p. 88–92°.

(13) F. G. Bordwell and G. D. Cooper, *J. Am. Chem. Soc.*, **74**, 1058 (1952).

(14) Melting points and boiling points are uncorrected. An F and M Model 500 gas chromatograph equipped with a 20% Carbowax-packed column (0.25 in. × 4 ft.) was employed for the v.p.c. analyses. The author is indebted to the Physical and Analytical Chemistry Department of The Upjohn Co. for the microanalytical and spectral determinations.

[CONTRIBUTION FROM SHELL DEVELOPMENT CO., EMERYVILLE, CALIF.]

Inhibition Reactions of Hindered Phenols[1]

BY G. M. COPPINGER

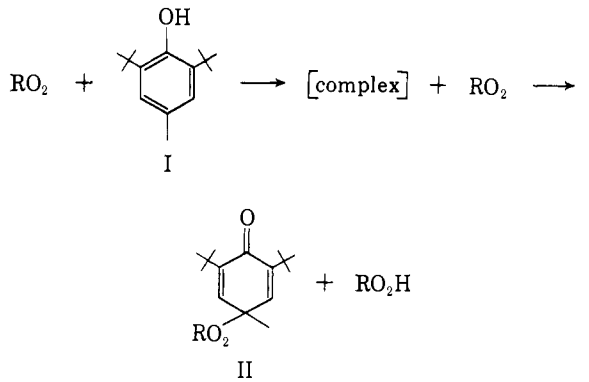
RECEIVED JUNE 1, 1964

The principal alternative descriptions of oxidative chain inhibition by hindered phenols have been examined with reference to products found in model peroxy radical hindered phenol systems. An alternative description involving a charge-transfer complex between peroxy radical and phenol is presented.

Introduction

There has existed for some time two general and different views of the course of the inhibition reactions of hindered phenols in oxidizing substrates.

Hammond and Boozer[2] found that the rate of inhibition of oxidation in which the propagating species was a peroxy radical was first order in peroxy radical and half order in inhibitor. They concluded from this that the transition state of the rate-determining step involves two peroxy radicals and one molecule of phenol. They suggested that there must be a complex formed between a peroxy radical and the phenol as the rate-determining step.



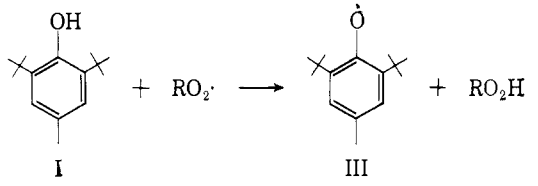
Both Ingold[3a] and Shelton[3b] have observed that when the hydroxyl hydrogen is replaced by deuterium a kinetic isotope effect is observed in the rate of inhibition. The ratio k_H/k_D is somewhere between 6 and 10 at room temperature. From this both Ingold[3a] and Shelton[3b] have concluded that the rate-determining step is abstraction of a hydrogen atom from the phenol hydroxyl group by a peroxy radical with formation of a phenoxyl free radical, which subsequently reacts with a second peroxy radical. In all investigations of this problem in which the propagating species is a peroxy radical, the products observed from the inhibitor were peroxycyclohexadienones of the type II.[2-4] It seems to us that it might be possible to distinguish between these two descriptions by examination of the reactivity of phenoxy free radicals under conditions which parallel, as closely as experimental

(1) This work was presented before the 147th National Meeting of the American Chemical Society, Philadelphia Pa., April, 1964.

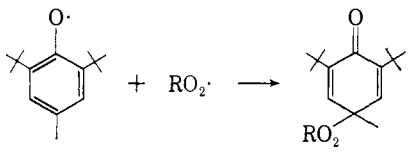
(2) G. S. Hammond, C. E. Boozer, *et al. J. Am. Chem. Soc.*, **77**, 3233, 3238 (1955).

(3) (a) K. U. Ingold and J. A. Howard, *Can. J. Chem.*, **40**, 1851 (1962); (b) J. R. Shelton and D. W. Vincent, *J. Am. Chem. Soc.*, **85**, 2433 (1963).

(4) T. W. Campbell and G. M. Coppinger, *ibid.*, **74**, 1469 (1952); A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 3211 (1953).



I III

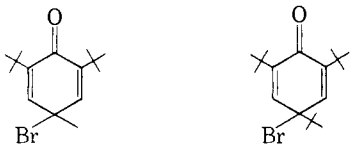


III II

limitations permitted, the reaction systems in which these previous kinetic measurements were made. It was not possible to generate, simultaneously, peroxy radicals and phenoxy radicals, and oxygen was chosen as an acceptable model for a peroxy radical.

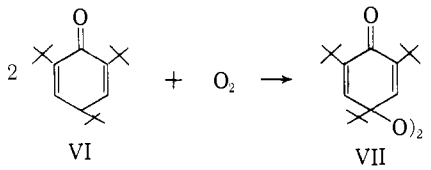
Results and Discussion

The two phenols, 2,6-di-*t*-butyl-4-methylphenol and 2,4,6-tri-*t*-butylphenol, were chosen as models for this examination. The phenoxy radicals were prepared from the corresponding bromocyclohexadienones[5] in

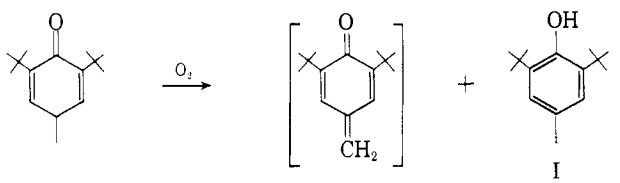


IV V

three solvents—methanol, ethyl ether, and isooctane—through which oxygen was bubbled. The products observed and reaction paths can be formulated



VI VII

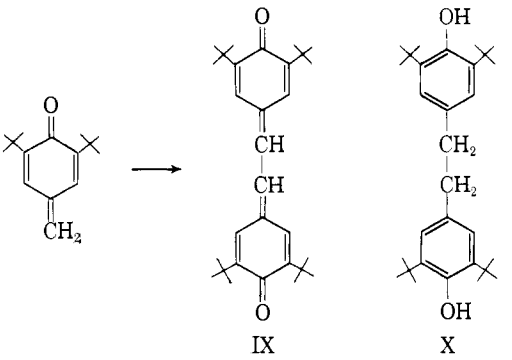


VIII I

No oxygen is consumed in the second reaction. The quinone methide is rapidly converted to two products in a subsequent step.[6]

In all previous kinetic examinations the products obtained from these two phenols and peroxy radicals have been peroxycyclohexadienones. The dimeric products IX and X have not been observed. This rather striking difference in products does not support a general mechanism for inhibition which incorporates phenoxy free radical as an intermediate.

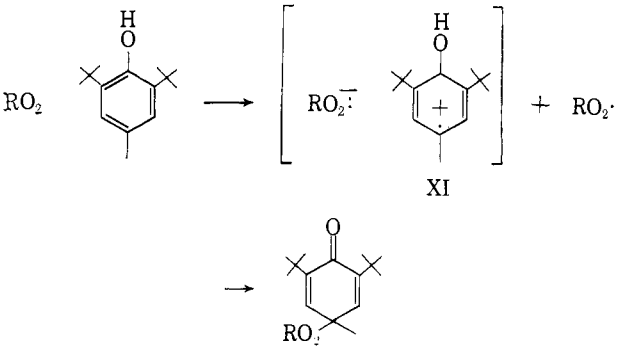
The validity of oxygen as a model for peroxy free radicals is supported by the observation that the



IX X

peroxy radical from 2,4,6-tri-*t*-butylphenol can coexist with the tri-*t*-butylphenoxyl radical in the presence of oxygen (Fig. 1). When tri-*t*-butylphenoxyl in isooctane is exposed to air the electron spin resonance spectra reveals the formation of a second free radical, the corresponding peroxy radical which decays at a rate comparable to that of the tri-*t*-butylphenoxyl. Since the final product is the symmetrical peroxide, these observations indicate that peroxy radical formation and peroxy radical reaction occur at comparable rates.[7]

The kinetic isotope effects and the termolecular kinetics can both be accommodated in a single mechanism if the initial complex suggested by Hammond is, in fact, a charge-transfer complex. Hyperconjugation[8] within the charge-transfer complex could account quite adequately for the kinetic isotope effect. The



XI

isotope effect is the result of the relative contributions by hyperconjugation of hydrogen and deuterium to stabilization of the charge-transfer complex.

The reaction of the quinone methide VIII with itself is quite unusual.[6] It proceeds through intermediates which are free radicals. The quinone methide may be prepared by a variety of methods so that its existence is well established. The dimerization occurs quite rapidly at room temperature. The e.s.r. spectrum of the intermediate phenoxy radical is displayed in Fig. 2. It consists of an equal concentration of two free radical species with the partial structures XII and XIII, the first giving rise to a hyperfine pattern of two triplets and the second a pattern of three triplets. The separation of the complex spectra into its component parts is shown in Fig. 3. This is not a photochemical reaction, nor is it catalyzed by acids or bases. It seems pos-

(5) C. D. Cook, N. G. Nash, and H. R. Flannagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955).

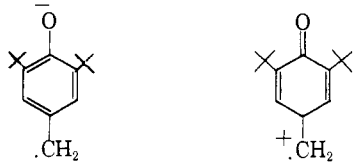
(6) R. H. Bauer and G. M. Coppinger, *Tetrahedron*, **19**, 1201 (1963); L. H. Filar and S. Winstein, *Tetrahedron Letters*, **25**, 9 (1960).

(7) A referee has correctly pointed out an objection to the validity of this model. The rate of reaction of the peroxy radical from tri-*t*-butylphenol may be slower than other peroxy radicals (for example, *t*-butylperoxy) and this would permit the coexistence of phenoxy and peroxy radicals from tri-*t*-butylphenol.

(8) P. B. D. de la Mare, "Conference on Hyperconjugation," Pergamon Press, New York, N. Y., 1959, p. 136.

XII XIII

sible that the reaction is initiated by a prior charge-transfer complex in which the simplest canonical structures can be represented by



XIV

This implies that the electrons are sufficiently uncoupled to permit subsequent free-radical dimerization followed by a disproportion reaction to get the hydrogens properly sorted among the two dimeric products. It is unusual

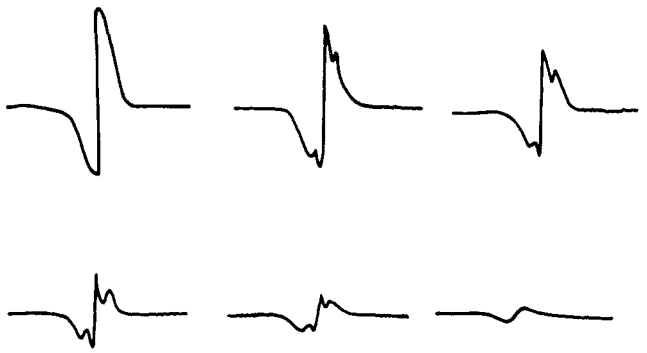
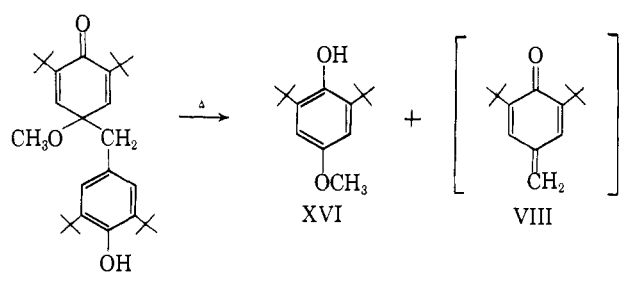


Fig. 1.—Reaction of tri-*t*-butylphenoxyl with oxygen; 10^{-3} *M* isooctane solution, 10-min. intervals.

to consider charge-transfer complexes in which a molecule can serve simultaneously as the donor and the acceptor, but it may well be that the tendency for quinone methides to achieve the aromatic sextet configuration[9] is sufficient driving force for the transfer complex.

This interesting reaction has been observed in a somewhat different system. The complex phenol XV[10] when heated in isooctane above 50° undergoes carbon–carbon cleavage. Whether the initial cleavage reaction is free radical is not known; it is not subject to acid catalysis. The reaction, when followed in the cavity of an e.s.r. spectrometer, displays the same hyperfine



XV XVI VIII

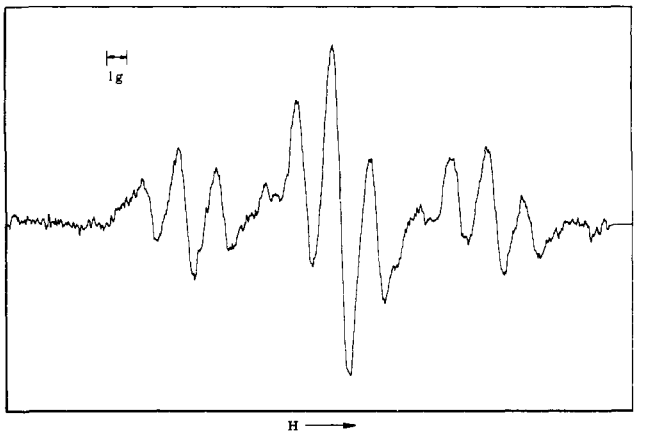


Fig. 2.—3,5-Di-*t*-butyl-*p*-quinone methide in isooctane solution; first derivative, e.p.r. spectrum.

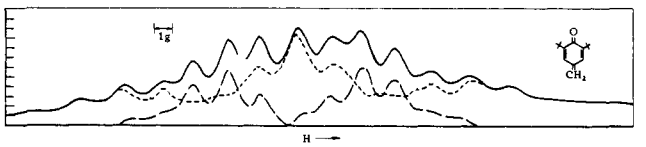


Fig. 3.—3,5-Di-*t*-butyl-*p*-quinone methide in isooctane solution; absorption e.p.r. spectrum.

spectrum as that shown in Fig. 2, indicating the intermediate presence of the quinone methide VIII.

Experimental

4-Bromo-4-methyl-2,6-di-*t*-butylcyclohexa-2,5-dienone.—A solution of 20 g. of 4-methyl-2,6-di-*t*-butylphenol in 90% aqueous acetic acid was treated with 15 g. of bromine at 0°. The bromo compound spontaneously crystallized from solution. The product was recrystallized from petroleum ether in 68% yield, m.p. 92–93° (lit.[11] 91–92°).

4-Bromo-2,4,6-tri-*t*-butylcyclohexa-2,5-dienone.—The procedure outlined above was repeated using 2,4,6-tri-*t*-butylphenol. Upon recrystallization, the yield was 53%, m.p. 82° (lit.[5] 80–81.5°).

Preparation and Reaction of Phenoxyl Radicals.—The phenoxyl radicals were prepared by dissolving the corresponding bromo compounds in a solvent—methanol or diethyl ether or isooctane—and mixing with an excess of metallic mercury. Air or oxygen was sparged through the solutions simultaneously. The bromine was stripped off as mercuric bromide. All the products remained in solution. The blue color of the phenoxyl was discharged very rapidly.

Products of Reaction of Phenoxyl Radicals with Oxygen. 4-Bromo-4-methyl-2,6-di-*t*-butylcyclohexa-2,5-dienone.—The products isolated were 4-methyl-2,6-di-*t*-butylphenol, 3,3′,5,5′-tetra-*t*-butylstilbene-4,4′-quinone, and 1,2-bis(3,5-di-*t*-butyl-4-hydroxyphenyl)ethane. The detailed separation is described in ref. 6. No peroxidic products were observed.

4-Bromo-2,4,6-tri-*t*-butylcyclohexa-2,5-dienone.—The mercury and mercuric bromide was removed by filtration. Upon removal of the solvent, a single product was obtained, m.p. 142–145° dec., recrystallized from methanol, m.p. 147–148° (lit.[11] 148–149°). This product was the symmetrical peroxide VII. The peroxide was recovered in all experiments in yields above 90%.

3,5-Di-*t*-butyl-4-hydroxyphenylmethyl-4-methoxy-2,6-di-*t*-butyl-cyclohexa-3,5-dienone was prepared by bromination of the parent phenol in methanol after the method of Kharasch.[10] When the compound was heated in isooctane above 50°, an orange color developed. After 30 min., the solution was cooled; orange crystals separated from the solution. This compound was 3,3′,5,5′-tetra-*t*-butylstilbene-4,4′-quinone, m.p. 316° (lit.[6] 316°), yield 9%. The remaining was chromatographed on alumina with separation of the products: 4-methyl-2,6-di-*t*-butylphenol, yield 12%, m.p. 69° (lit.[6] 69°); 4-methoxy-2,6-

(9) R. H. Bauer and G. M. Coppinger, *J. Phys. Chem.*, **67**, 2846 (1963).
(10) M. J. Kharasch and B. S. Joshe, *J. Org. Chem.*, **22**, 1435 (1957).
(11) C. D. Cook, D. A. Kuhn, and P. Fianu, *J. Am. Chem. Soc.* **78**, 2002 (1956).

di-*t*-butylphenol, yield 36%, m.p. 105° (lit.[11] 103.5–104.5°); 1,2-bis(3,5-di-*t*-butyl-4-hydroxyphenyl)ethane, yield 6%, m.p. 171–172° (lit.[5] 169–170°).

E.s.r. Measurements.—The spectra of the phenoxy radicals were obtained in solution with a Varian V-4500 spectrometer utilizing 100 kc. modulation.

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, BETHESDA 14, MD.]

The Chemistry of 9-Hydroxy-α-tocopherone, a Quinone Hemiacetal[1]

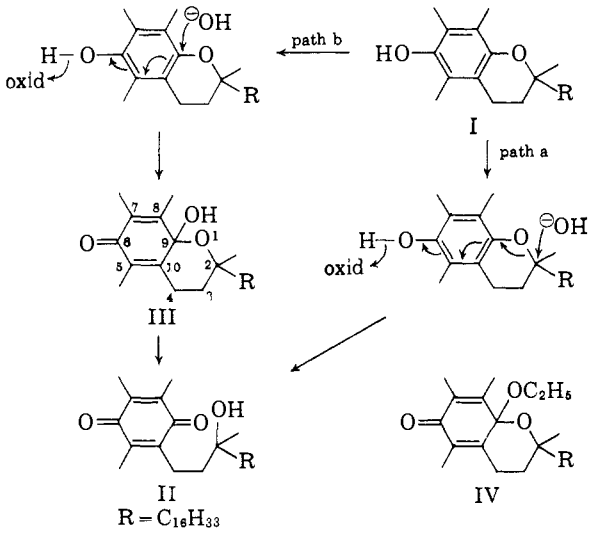
BY WALTER DÜRCKHEIMER[2] AND LOUIS A. COHEN

RECEIVED FEBRUARY 5, 1964

Oxidation of α-tocopherol with N-bromosuccinimide or with tetrachloro-*o*-quinone in aqueous acetonitrile leads to the formation of 9-hydroxy-α-tocopherone (III), the cyclic hemiacetal tautomer of tocopherylquinone. At pH' 5.5, the dienone has a half-life time of 44 min.; in petroleum ether, the half-life time is extended to 3–4 hr. The compound is converted into the quinone by acid or alkali and is readily reduced to tocopherol by a variety of agents. The oxidation–reduction potential of α-tocopherol, measured for the first time under reversible conditions, was found to be +720 mv. Oxidation of α-tocopherol in the presence of acetate ion leads to an analogous, highly labile acetoxydienone. The energetics of chromanols and quinones in oxidative phosphorylation are discussed in light of the new data.

Recent years have witnessed a number of efforts to elucidate the mechanisms by which the energy generated in a biological oxidation process may be conserved through the formation of covalent bonds, particularly and ultimately by the conversion of ADP to ATP.[3] The demonstration that chromanols (such as α-tocopherol) and quinones (such as ubiquinone) occur extensively in mitochondrial aggregates,[4] a site of such oxidative phosphorylation, has prompted various proposals regarding the metabolic role of these materials and the manner in which they may serve in electron transport and energy conservation.[3]

The design of a chemical approach to the problem has been hampered, in part, by limitations in the present-day understanding of oxidation mechanisms, particularly with respect to complex phenolic systems. For example, the oxidation of a chromanol (I; or of a hydroquinone monoether, in general) to the corresponding quinone II requires the introduction of an additional oxygen atom; two pathways may be considered which differ in the final disposition of the chroman oxygen atom.[5] The identification of IV as an oxidation product of α-tocopherol in ethanol[6] supports path b and encourages consideration of III as an intermediate in the oxidation of I in the presence of water.[7] It is with the preparation, isolation, and properties of III that the present paper is principally concerned.



The reaction of α-tocopherol with a variety of oxidants (Ag^{+1},[8a] Fe^{+3},[8a] Au^{+3},[8b] Ce^{+4},[8c] Pb^{+4} [8d]) in aqueous media leads ultimately to the quinone, as may be observed by a rapid shift in the ultraviolet spectrum from 292 to 265 mμ. With *neutral, organic* oxidants, such as tetrachloro-*o*-quinone (TClQ) or N-bromosuccinimide (NBS), however, a labile intermediate with a spectral peak at 242 mμ may be detected. We conclude, from the evidence set forth below, that the intermediate is 9-hydroxy-α-tocopherone (III).[9,10] In the presence of stoichiometric quantities of oxidant, the peak at 242 mμ reaches a maximum value in 1–2 min. The rate at which the intermediate is converted

(1) Paper I of a series "Oxidation Mechanisms in Biochemical Processes." A preliminary account of this work has been published: *Biochem. Biophys. Res. Commun.*, **9**, 262 (1962).

(2) Associate in the Visiting Program of the USPHS, 1961–1962.

(3) For recent comprehensive and critical reviews, see (a) Ciba Foundation Symposium, "Quinones in Electron Transport," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1960; (b) E. Racker, "Advances in Enzymology," Vol. 23, F. F. Nord, Ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 323; (c) E. C. Slater, *Rev. Pure Appl. Chem.*, **8**, 221 (1958); (d) E. C. Slater, *Proc. Intern. Congr. Biochem., 4th, Vienna*, **9**, 316 (1958); (e) P. D. Boyer, "The Enzymes," Vol. III, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1960, p. 353.

(4) D. M. Ziegler, *Am. J. Clin. Nutr.*, **9** (Part II), 43 (1961); F. L. Crane, *Biochemistry*, **1**, 510 (1962).

(5) The duality of pathways has been studied by O^{18} tracer techniques: (a) A. Lapidot and D. Samuel, *Biochem. Biophys. Acta*, **65**, 164 (1962); (b) E. Adler, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962); (c) P. Schudel, H. Mayer, J. Metzger, R. Rüegg, and O. Isler, *Helv. Chim. Acta*, **46**, 333 (1963). For studies based on product identification, see paper II of this series (W. Dürckheimer and L. A. Cohen, *J. Am. Chem. Soc.*, in press.

(6) (a) C. Martius and H. Eilingsfeld, *Ann.*, **607**, 159 (1957); (b) P. D. Boyer, *J. Am. Chem. Soc.*, **73**, 733 (1951).

(7) The existence of III as an oxidation intermediate has been considered previously. See W. H. Harrison, J. E. Gander, E. R. Blakley, and P. D. Boyer, *Biochim. Biophys. Acta*, **21**, 150 (1956).

(8) (a) W. John, E. Dietzel, and W. Emte, *Z. physiol. Chem.*, **257**, 173 (1939); (b) P. Karrer and A. Geiger, *Helv. Chim. Acta*, **23**, 455 (1940); (c) M. Kofler, *Verhandl. Schweiz. Naturforsch. Ges.*, 239 (1941); (d) A. Issidorides, *J. Am. Chem. Soc.*, **73**, 5146 (1951).

(9) The parent compound, α-tocopherone, would then be the dienone tautomer of α-tocopherol. Although the 9-hydroxyl function may be *cis* or *trans* to the phytyl side chain, no information has been obtained on the geometrical homogeneity or lack of it in preparations of III.

(10) Although III is almost certainly an intermediate in oxidation reactions effected by inorganic cations, its presence is difficult to demonstrate since such cations generally mask the 242 mμ peak of the dienone and become either unreactive or insoluble in the pH range in which III has optimal stability.