Reaction of Some Hindered Phenoxy Radicals with Ethyl 3-(*p*-Hydroxyphenyl)-propionate, 3-(*p*-Hydroxyphenyl)propionic Acid, and Oxygen

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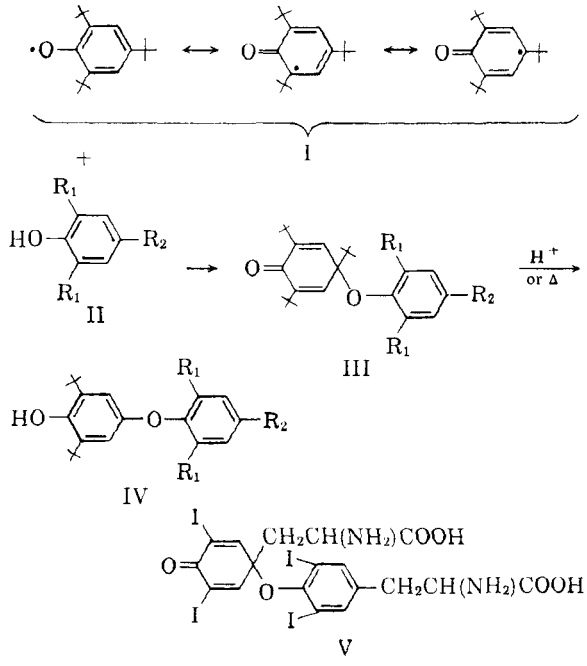
Various 2,6-di-*t*-butylphenoxy radicals having an electron-withdrawing group in position *para* to the oxygen function (VI) react with ethyl 3-(*p*-hydroxyphenyl)propionate and with 3-(*p*-hydroxyphenyl)propionic acid to form diphenyl ethers (VIII), probably *via* unstable *o*-quinol ethers (VII). The same free radicals react with oxygen to form various reaction products which apparently arise from unstable peroxide intermediates (Xa or Xb and XIa or XIb).

In a previous study[1] on nonenzymic model reactions for the formation of thyroxine *in vivo* the synthesis of several quinol ethers of type III and the conversion of some of them to the corresponding analogs of thyroxine (IV) has been described.

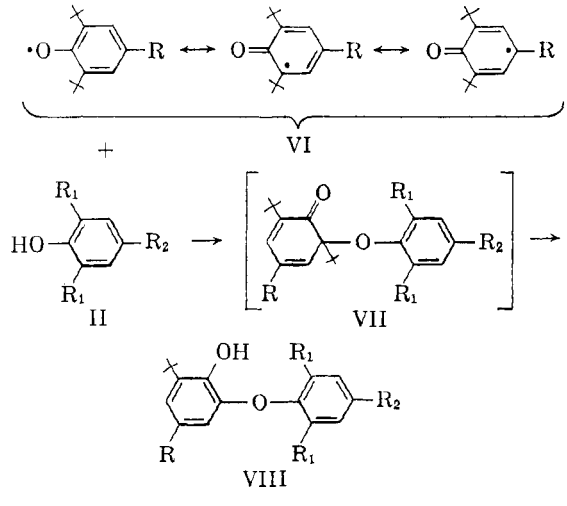


R_1 = H or Br or I
R_2 = $CH_2COOC_2H_5$ or $(CH_2)_2COOC_2H_5$ or $(CH_2)_2COOH$
+ = $C(CH_3)_3$

The quinol ethers III are analogs of the hypothetical quinol ether V which has been postulated as an intermediate in the biosynthesis of thyroxine.[2,3]

The free radical I has an electron-donating *t*-butyl group in the position *para* to the oxygen function. The present investigation was undertaken to determine whether similar free radicals, in which this group is replaced with an electron-withdrawing one (VI), would react with ethyl 3-(*p*-hydroxyphenyl)propionate [II; R_1=H; R_2=$(CH_2)_2COOC_2H_5$] and with 3-(*p*-hydroxyphenyl)-propionic acid [II; R_1=H; R_2=$(CH_2)_2COOH$] in the same manner as the free radical I. A related problem, the reaction of some of the free radicals VI with oxygen was also investigated.

The reaction of the free radicals VI with ethyl 3-(*p*-hydroxyphenyl)propionate or with 3-(*p*-hydroxyphenyl)propionic acid (phloretic acid) did not lead to *p*-quinol ethers of type III. The diphenyl ethers VIII were formed instead, apparently *via* the unstable *o*-quinol ethers VII.



+ = $C(CH_3)_3$ R = $COCH_3$ or $COOC_2H_5$ or CN
R_1 = H R_2 = $(CH_2)_2COOC_2H_5$ or $(CH_2)_2COOH$

The free radical VI (R=$COCH_3$) was prepared by oxidation of 3,5-di-*t*-butyl-4-hydroxyacetophenone with potassium ferricyanide. This phenol was obtained in 71% yield from 2,6-di-*t*-butylphenol in a modified Friedel–Crafts reaction in which trifluoroacetic anhydride is used as the catalyst.[4,5] The oxidation of the phenol to the free radical proceeds rapidly. The color of the free radical in organic solvents varies from green

(1) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1960).

(2) T. B. Johnson and L. B. Tewkesbury, Jr., *Proc. Natl. Acad. Sci. U.S.*, **28**, 73 (1942).

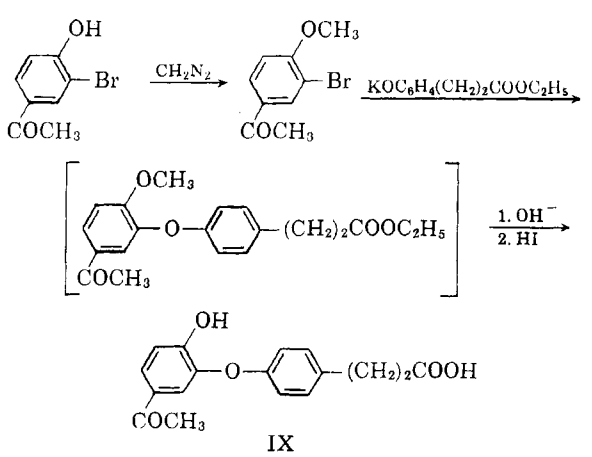
(3) C. R. Harington, *J. Chem. Soc.*, 193 (1944).

(4) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *ibid.*, 718 (1951).

(5) E. J. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, *ibid.*, 2006 (1954).

to bluish green depending on the solvent. It was never found to be blue.[6] Solutions of the free radical in inert organic solvents are relatively stable if oxygen is rigorously excluded. The absorbancy at 704 mμ (λ_{max}) does not follow Lambert–Beer's law. The molar extinction coefficient increases with increasing dilution. The simplest explanation for this is that in solution the free radical is in equilibrium with its dimer,[7] and that with increasing concentration this equilibrium is shifted towards the dimer.

When the ethyl ester of phloretic acid [II; $R_1=H$; $R_2=(CH_2)_2COOC_2H_5$] was added to a solution of VI ($R=COCH_3$) the free radical color disappeared. The major reaction product was a viscous liquid which gave a crystalline 2,4-dinitrophenylhydrazone, $C_{29}H_{32}N_4O_8$. Alkaline hydrolysis gave a crystalline acid, $C_{21}H_{24}O_5$, which was characterized as its semicarbazone, $C_{22}H_{27}N_3O_5$. The same acid was obtained by treating the free radical VI ($R=COCH_3$) with phloretic acid. Esterification of the acid with ethanol gave an oily ester whose infrared spectrum is identical with the one of the viscous liquid mentioned above. The infrared and ultraviolet spectra of the acid show clearly that it is not a quinol ether. Elemental analysis of the acid and of its derivatives show further that it contains only one *t*-butyl group. The structure VIII [$R=COCH_3$; $R_1=H$; $R_2=(CH_2)_2COOH$] must therefore be assigned to the acid and structure VIII [$R=COCH_3$; $R_1=H$; $R_2=(CH_2)_2COOC_2H_5$] to the oily ester. These structures are fully supported by the infrared spectra. De-*t*-butylation of the acid with aluminum chloride gave a crystalline acid (IX). The ultraviolet spectra of both acids are shown in Fig. 1. The structure of IX was proved by its synthesis from 3-bromo-4-hydroxyacetophenone:



IX

As already observed by others,[6] the free radical VI ($R=COCH_3$) absorbs oxygen much slower than the 2,4,6-tri-*t*-butylphenoxy radical [VI; $R=C(CH_3)_3$]. When oxygen was bubbled through a solution of VI ($R=COCH_3$) for several hours the solution turned from green to orange. Chromatography of the reaction product on a column of silica gel yielded three crystalline substances, one of which was not further investigated since it was obtained in very small yield. The major reaction product was 2,6-di-*t*-butylbenzoquinone (XII).[8]

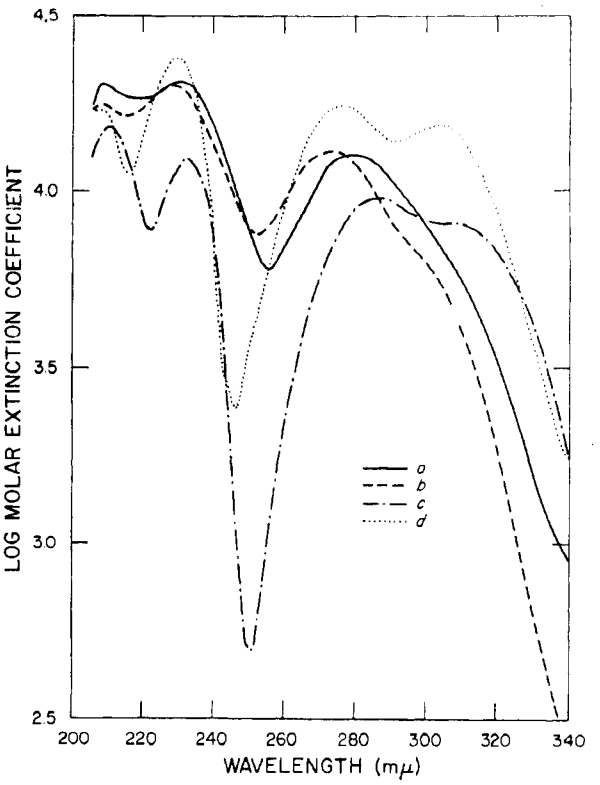


Fig. 1.—Ultraviolet spectra in ethanol of a, VIII [R = $COCH_3$; R_1 = H; R_2 = $(CH_2)_2COOH$]; b, IX; c, XIII (R = $COCH_3$; R_1 = H); d, acetovanillone (3-methoxy-4-hydroxyacetophenone).

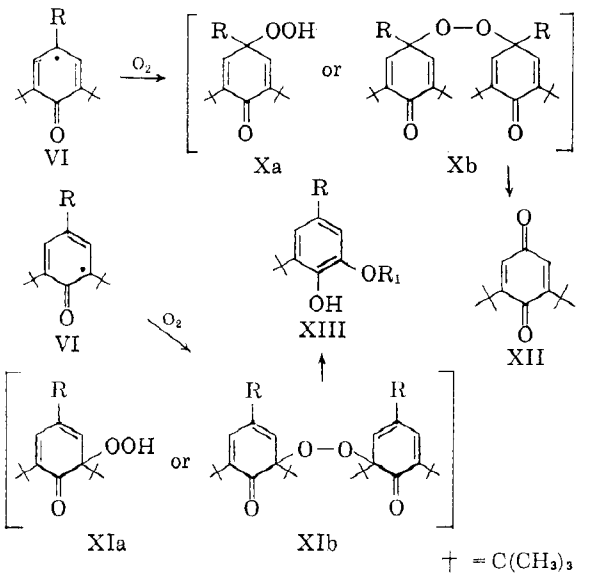
A third substance was obtained in the form of colorless crystals, $C_{12}H_{16}O_3$. Its catechol structure was proved in various ways. It gave a color reaction with ferric chloride and sodium carbonate that is characteristic for catechols.[9] The ultraviolet spectrum (Fig. 1) which resembles the one of acetovanillone (3-methoxy-4-hydroxyacetophenone) shows a bathochromic shift upon addition of boric acid and sodium acetate. This also is typical for *ortho*-diphenols.[10] The most conclusive evidence for the catechol structure was provided by the fact that the substance is a substrate for catechol O-methyl transferase.[11] This enzyme, in the presence of S-adenosylmethionine, converted the substance to a methyl ether which was chromato-

(6) C. D. Cook and N. D. Gilmour, *J. Org. Chem.*, **25**, 1429 (1960).
(7) *Cf.* ref. 1, footnote 8.
(8) (a) C. F. H. Allen and D. M. Burness, U.S. Patent 2,657,222 (1953); (b) E. Müller and K. Ley, *Chem. Ber.*, **88**, 601 (1955); (c) K. Ley and E. Müller, *ibid.*, **89**, 1402 (1956); (d) G. R. Yohe, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, G. H. Lee, and E. C. Smith, *J. Org. Chem.*, **21**, 1289 (1956).
(9) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. III, Elsevier Publishing Co., Amsterdam, The Netherlands, 1954, p. 465.
(10) L. Jurd, *Arch. Biochem. Biophys.*, **68**, 376 (1956).
(11) J. Axelrod and R. Tomchick, *J. Biol. Chem.*, **233**, 702 (1958).

graphically identical with the monomethyl ether obtained on treatment of the catechol with diazomethane. The fact that one of the phenolic groups could not be methylated shows that it is hindered. The monomethyl ether gave a negative ferric chloride test but a positive ferric chloride–ferricyanide test[12] as is to be expected from a hindered phenol. It gave a negative test with diazotized N^1,N^1-diethylsulfanilamide (modified Pauly test),[13] while the catechol gave a positive one. This shows that in the ether all *ortho* and *para* positions are substituted. Two doublets with a spin coupling of 2 c.p.s. in the aromatic region of the proton n.m.r. spectrum of the catechol show that the molecule has two aromatic hydrogens which are *meta* to each other.[14] The ether gave a crystalline 2,4-dinitrophenylhydrazone, $C_{19}H_{22}N_4O_6$.

All these data show that the catechol has the structure XIII ($R=COCH_3$; $R_1=H$) and the monomethyl ether the structure XIII ($R=COCH_3$; $R_1=CH_3$).

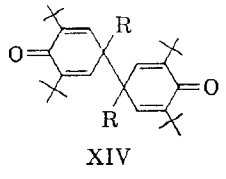
The two major products obtained in the reaction of the free radical VI ($R=COCH_3$) with oxygen, the quinone XII and the catechol XIII ($R=COCH_3$ $R_1=H$), are apparently formed *via* unstable peroxides (Xa or Xb, XIa or XIb; $R=COCH_3$) which could not be isolated.



The hydroperoxides Xa and XIa ($R=COCH_3$) seem to be more likely intermediates[15] than the peroxides Xb and XIb ($R=COCH_3$) since the peroxide Xb [$R=C(CH_3)_3$] has been shown to be relatively stable.[16,17]

The fact that the catechol is a substrate for catechol O-methyltransferase is of interest inasmuch as it shows that the bulky *t*-butyl group does not prevent this substrate from attaching itself onto the surface of the enzyme. All previous transmethylations have been carried out with unhindered catechols.

The free radical VI ($R=COOC_2H_5$) was prepared by oxidation of its parent phenol with potassium ferricyanide. When the oxidation was carried out in the presence of methanol, a dimer of VI was obtained. Both the free radical and its dimer have recently been described by Müller, *et al.*[18] These authors were unable to prepare the parent phenol according to the method of Cohen.[19] In our laboratory a slight modification of Cohen's method was used which gave the desired phenol in 70–80% yield. In various organic solvents the dimer dissociates into free radicals as evidenced by the green color of the solutions. In view of this instability of the dimer, it was not possible to ascertain its structure. The infrared spectrum of the solid dimer seems, however, to exclude the quinol ether structure proposed by Müller, *et al.*[18] An inspection of the infrared spectra (Nujol and KBr) of a large number of aromatic quinol ethers revealed that they all show very pronounced ether bands at 980–990 cm.$^{-1}$ and at 1235–1250 cm.$^{-1}$. These very typical, prominent bands[20] are absent from the spectrum of the dimer, which shows only a shoulder at about 1245 cm.$^{-1}$ and no band at all between 970 and 1000 cm.$^{-1}$. The spectrum has no hydroxyl bands, but typical dienone bands at 1641 and 1660 cm.$^{-1}$. The ester groups seem to be nonconjugated since the C=O stretching vibration is at 1737 cm.$^{-1}$.[21] Structure XIV is consistent with these data but there is no direct proof for it



XIV

+ = $C(CH_3)_3$
R = $COOC_2H_5$

at present. The free radical VI ($R=COOC_2H_5$) reacted with the ethyl ester of phloretic acid [II; $R_1=H$; $R_2=(CH_2)_2COOC_2H_5$] to form a crystalline product, $C_{24}H_{30}O_6$, in good yield. The infrared spectrum of this substance shows nonconjugated aliphatic ester and aromatic ester bands but no

(12) G. M. Barton, R. S. Evans, and J. A. F. Gardner, *Nature*, **170**, 249 (1952).

(13) T. Matsuura and H. J. Cahnmann, *J. Am. Chem. Soc.*, **81**, 871 (1959).

(14) *Cf.* L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry," Pergamon Press, New York, 1959, p. 85.

(15) *Cf.* H. R. Gersmann and A. F. Bickel, *J. Chem. Soc.*, 2711 (1959).

(16) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

(17) E. Müller and K. Ley, *Chem. Ber.*, **87**, 922 (1954).

(18) E. Müller, A. Rieker, R. Mayer, and K. Scheffler, *Ann.*, **645**, 36 (1961).

(19) L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).

(20) E. Müller, K. Ley, and G. Schlechte, *Chem. Ber.*, **90**, 2660 (1957).

(21) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, New York, 1958, p. 179.

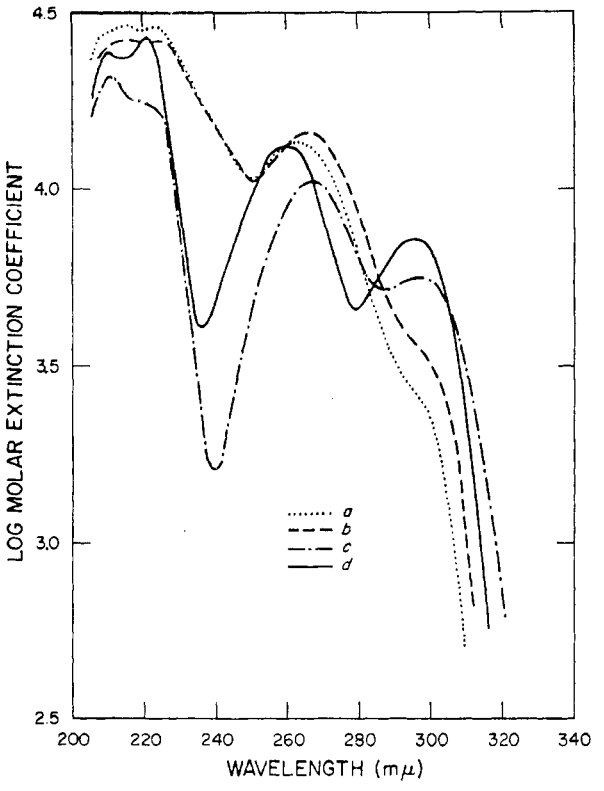


Fig. 2.—Ultraviolet spectra in ethanol of a, VIII [R = COOH; R_1 = H; R_2 = $(CH_2)_2COOH$]; b, VIII [R = $COOC_2H_5$; R_1 = H; R_2 = $(CH_2)_2$ $COOC_2H_5$]; c, XIII (R = $COOC_2H_5$; R_1 = H); d, protocatechuic acid (3,4-dihydroxybenzoic acid).

dienone bands. The ultraviolet spectrum (Fig. 2) shows a similarity with the spectrum of protocatechuic acid (3,4-dihydroxybenzoic acid). This suggests a similar structure. The presence of a hindered phenol is indicated by a positive ferric chloride–ferricyanide test[12] and a negative color test with ferric chloride.

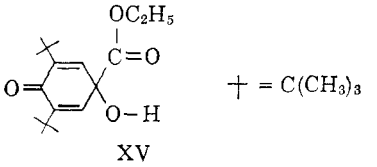
Alkaline hydrolysis gave a crystalline dicarboxylic acid, $C_{20}H_{22}O_6$. The ultraviolet (Fig. 2) and infrared spectra have similar characteristics as the spectra of the diethyl ester and of the dimethyl ester, $C_{22}H_{26}O_6$, which was obtained by treatment of the acid with diazomethane.

On the basis of these data the acid must be formulated as VIII [R = COOH; R_1 = H; R_2 = $(CH_2)_2COOH$], and the esters as the corresponding dimethyl and diethyl esters. These structures were fully confirmed by the proton n.m.r. spectrum of the dimethyl ester. Two doublets with a spin coupling of 2 c.p.s. indicate the presence of two hydrogens *meta* to each other and two other doublets with a spin coupling of 8 c.p.s. the presence of two chemically equivalent pairs of hydrogens *ortho* to each other.[14]

The free radical VI(R = $COOC_2H_5$) reacted with phloretic acid to form the diphenyl ether VIII [R = $COOC_2H_5$; R_1 = H; R_2 = $(CH_2)_2COOH$] which upon alkaline hydrolysis yielded the above-mentioned dicarboxylic acid, $C_{20}H_{22}O_6$.

A solution of the free radical VI (R = $COOC_2H_5$) reacted slowly with oxygen. The color of the solution gradually changed from green to yellow. The major reaction product was a viscous liquid, $C_{17}H_{26}O_4$, whose infrared spectrum indicates a dienone structure and the presence of a hydroxyl and an ester group. Aromatic bands are absent. The location of the ester C=O stretching band at 1733 cm.$^{-1}$ (CCl_4) and 1734 cm.$^{-1}$ (Halocarbon Oil) shows that the ester is nonconjugated and hydrogen-bonded.[21,22] The infrared data and the wave length of maximal absorption in the ultraviolet region (248 mμ)[16] indicate a 2,5-dienone structure. The dienone XV is the only structure which is consistent with both the spectral data and the empirical formula. Hydrogen-bonding occurs between the ester carbonyl and the phenolic hydroxyl.[22] This compound is apparently formed *via* an unstable peroxide (Xa or Xb; R = $COOC_2H_5$).

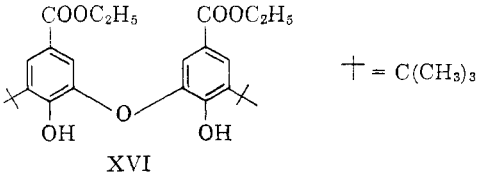
VI (R = $COOC_2H_5$) → [Xa or Xb; R = $COOC_2H_5$] →



XV

The reaction of the free radical VI (R = $COOC_2H_5$) with oxygen led also to a number of other compounds some of which were isolated in pure form. The yields were poor and erratic. One of these substances, obtained as colorless crystals, $C_{13}H_{18}O_4$, was shown to be a catechol by some of the previously mentioned catechol reactions. On the basis of its infrared spectrum and of the great similarity of its ultraviolet spectrum with the one of protocatechuic acid (Fig. 2) it must be assigned structure XIII (R = $COOC_2H_5$; R_1 = H).

The infrared spectrum of another colorless crystalline substance, $C_{26}H_{34}O_7$, shows hydroxyl and aromatic ester bands but no dienone bands. The ultraviolet spectrum is similar to the one of protocatechuic acid and of the catechol XIII (R = $COOC_2H_5$; R_1 = H). On the basis of these data structure XVI has been tentatively assigned to this compound. There was not enough substance available for additional confirmatory tests.



XVI

This substance as well as the catechol XIII (R = $COOC_2H_5$; R_1 = H) were probably formed *via*

(22) S. Searles, M. Tamres, and G. M. Barrow, *J. Am. Chem. Soc.*, **75**, 71 (1953).

an unstable peroxide (XIa or XIb; R = $COOC_2H_5$).

The free radical VI (R = CN) and its dimer were prepared according to Müller, *et al.*[23] These authors have described various properties and reactions of the radical, including its reaction with oxygen. The present investigation has therefore been confined to a study of its reaction with phloretic acid and its ethyl ester.

The reaction of VI (R = CN) with the ethyl ester of phloretic acid gave an oily substance, $C_{22}H_{25}NO_4$, in good yield. The infrared spectrum of this substance indicates the presence of hydroxyl, nitrile, and aliphatic ester groups and the absence of a dienone structure. Hydrolysis of the nitrile and ester groups led to the previousy described dicarboxylic acid VIII [R = COOH; R_1 = H; R_2 = $(CH_2)_2COOH$]. The substance has therefore structure VIII [R = CN; R_1 = H; $R_2 = (CH_2)_2COOC_2H_5$]. Reaction of the free radical with phloretic acid gave a crystalline acid, $C_{20}H_{21}NO_4$, whose structure [VIII; R = CN; R_1 = H; $R_2 = (CH_2)_2COOH$] was confirmed by spectral analysis and by hydrolysis which converted it to the above-mentioned dicarboxylic acid.

Experimental[24]

4-Hydroxy-3,5-di-*t*-butylacetophenone.—A solution of 41.1 g. (0.2 mole) of 2,6-di-*t*-butylphenol in 18 ml. (0.3 mole) of glacial acetic acid was added dropwise with stirring and some cooling, to keep the temperature of the reaction mixture below 25°, to 63.0 g. (0.3 mole) of freshly redistilled trifluoroacetic anhydride. The dark brown reaction mixture was permitted to stand overnight and was then diluted with chloroform and neutralized with a saturated aqueous solution of sodium bicarbonate. The chloroform layer was washed with water, then dried over sodium sulfate. Evaporation of the solvent and drying of the residue *in vacuo* over potassium hydroxide gave 50.8 g. of reddish brown, slightly sticky crystals. One recrystallization from carbon tetrachloride yielded 38.7 g. (78%) of slightly colored crystals, m.p. 150° (Kofler stage). Before filtration the crystalline mass was cooled at −20°. Also the washing of the crystals was done with precooled carbon tetrachloride. After two more recrystallizations white crystals, m.p. 150–151° (Kofler stage), were obtained (71% yield).

2,6-Di-*t*-butyl-4-acetylphenoxyl (VI; R = $COCH_3$). Preparation of a 5 × 10^{-2} *M* Solution.—A solution of 1.24 g. (5 mmoles) of 4-hydroxy-3,5-di-*t*-butylacetophenone in 100 ml. of benzene[25] was saturated with oxygen-free nitrogen.[26] Then 25 ml. of an aqueous solution containing 20% potassium ferricyanide and 11% potassium hydroxide was added and stirring was started. The benzene layer turned green immediately. Iodimetric titration of aliquots showed that the yield of the free radical or its dimer was over 90% of the theory after a few minutes and 97–100% after 1 hr.

When more dilute solutions of 3,5-di-*t*-butylacetophenone were oxidized, the yield of the free radical was lower. Thus, in the preparation of a 5 × 10^{-3} *M* solution, the yield of free radical after 1 hr. was 94%, in the preparation of a 5 × 10^{-4} *M* solution 88%. Solutions of the free radical in benzene have an absorption maximum at 704 mμ; $\epsilon_{max}^{benzene}$ (extrapolated to solutions containing 100% free radical or its dimer): 35.6 (5 × 10^{-2} *M* solution); 107 (5 × 10^{-3} *M* solution); 310 (5 × 10^{-4} *M* solution). When a 5 × 10^{-3} *M* solution was permitted to stand 24 hr. under oxygen-free nitrogen, the absorbancy at 704 mμ decreased 13%. Without exclusion of oxygen the 704-mμ peak disappeared completely within the same period of time, and the visible region of the spectrum showed then peaks at 404 and 426 mμ.

Reaction of 2,6-Di-*t*-butyl-4-acetylphenoxyl with Ethyl 3-(*p*-Hydroxyphenyl)propionate.—A solution of 1.24 g. (5 mmoles) of 4-hydroxy-3,5-di-*t*-butylacetophenone in 50 ml. of benzene was stirred with 40 ml. of an aqueous solution containing 9% potassium ferricyanide and 5% potassium hydroxide. After 40 min. the aqueous layer was removed and the benzene layer washed with water. Then 12.5 ml. of a 0.2 *M* solution of ethyl 3-(*p*-hydroxyphenyl)-propionate[27] in benzene was added. The solution turned pale orange. It was again stirred for 1 hr. with 40 ml. of alkaline potassium ferricyanide solution. After removal of the aqueous layer and washing of the benzene layer with water, 6.25 ml. of an 0.2 *M* solution of ethyl 3-(*p*-hydroxyphenyl)propionate in benzene was added. The treatment with alkaline ferricyanide and the ethyl ester of phloretic acid (5.0 ml. of a 2 *M* solution) was repeated. In the three additions a total amount of 4.75 mmoles of phloretic ester was used. The orange solution was evaporated *in vacuo* to give a reddish orange liquid which was dissolved in petroleum ether and chromatographed on a column of 40 g. of silica gel.

Elution with benzene–petroleum ether (1:4) yielded 18 mg. of orange crystals which were not further investigated.

Elution with benzene gave 0.28 g. of 4-hydroxy-3,5-di-*t*-butylacetophenone, m.p. 148–150°, identified through its infrared spectrum and mixed m.p. Elution with benzene–ether (9:1) yielded 1.08 g. (59%) of crude ethyl 3-[4-(2-hydroxy-3-*t*-butyl-5-acetylphenoxy)phenyl]propionate [VIII; R = $COCH_3$; R_1 = H; $R_2 = (CH_2)_2COOC_2H_5$] which was freed from a small amount of impurities by rechromatography.

This ester gave a 2,4-dinitrophenylhydrazone which was recrystallized from ethyl acetate–ethanol; orange-red plates, m.p. 167–168°.

Anal. Calcd. for $C_{29}H_{32}N_4O_8$: C, 61.69; H, 5.71; N, 9.92. Found: C, 61.55; H, 5.83; N, 10.27.

3-[4-(2-Hydroxy-3-*t*-butyl-5-acetylphenoxy)phenyl]propionic Acid [VIII; R = $COCH_3$; R_1 = H; $R_2 = (CH_2)_2COOH$].—A solution of 0.23 g. of the crude ester mentioned in the preceding paragraph in 10 ml. of ethanol and 2 ml. of 1 *N* sodium hydroxide was heated on a water bath for 1 hr. Most of the organic solvent was evaporated and the residue acidified. The precipitate formed was collected by filtration, dried, and dissolved in a small amount of hot benzene. On cooling, this solution deposited 0.11 g. of straw-colored crystals which after two recrystallizations from benzene gave colorless plates, m.p. 174–175°; λ_{max}^{EtOH} 209 mμ (log ε 4.31), 232 mμ (4.31), 280 mμ (4.11).

Infrared bands (Nujol) at 3430 and 3360 (hydroxyl), 1716 (carboxyl), 1692 (bonded carboxyl), 1671 (aryl ketone), 1597 (aromatic double bond), 902 (single aromatic hydrogen), and 857 $cm.^{-1}$ (two adjacent aromatic hydrogens); no dienone bands.

Anal. Calcd. for $C_{21}H_{24}O_5$: C, 70.76; H, 6.79. Found: C, 70.60; H, 7.01.

A solution in ethanol produced no color with ferric chloride but gave a blue color with ferric chloride–ferricyanide reagent.[12]

(23) E. Müller, A. Rieker, K. Ley, R. Mayer, and K. Scheffler, *Chem. Ber.*, **92**, 2278 (1959).

(24) The microanalyses were made by Mr. J. Goda and his associates of the Faculty of Science, Osaka City University, and by Mr. H. McCann and his associates of the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health. Unless specified otherwise, melting points were determined in capillary tubes and are uncorrected. Free radical solutions were prepared in a previously described reaction flask (*cf.* ref. 1, footnote 27) under rigorous exclusion of oxygen.

(25) Redistilled over sodium and benzophenone according to E. Müller, K. Ley, and W. Kiedaisch, *Chem. Ber.*, **87**, 1605 (1954).

(26) L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

(27) *Cf.* ref. 1, footnote 31.

The acid gave a semicarbazone which was recrystallized from ethanol; m.p. 225° dec.

When a solution of the acid in ethanol was treated with dry hydrogen chloride, an ethyl ester was obtained whose infrared spectrum is identical with the one of the above-mentioned ester VIII [R = $COCH_3$; R_1 = H; R_2 = $(CH_2)_2$-$COOC_2H_5$]. The ester was converted to its semicarbazone which did not crystallize and was therefore treated with 2,4-dinitrophenylhydrazine. The 2,4-dinitrophenylhydrazone formed was identical with the one described above (mixed melting point and infrared spectrum).

Anal. Calcd. for $C_{22}H_{27}N_3O_5$: C, 63.90; H, 6.58; N, 10.16. Found: C, 63.89; H, 6.74; N, 10.16.

Reaction of 2,6-Di-*t*-butyl-4-acetylphenoxyl with 3-(*p*-Hydroxyphenyl)propionic Acid (Phloretic Acid).—A solution of 2.48 g. (10 mmoles) of 4-hydroxy-3,5-di-*t*-butylacetophenone in 100 ml. of benzene was stirred with a solution of 18 g. of potassium ferricyanide and 10 g. of potassium hydroxide in 100 ml. of water. After 1.25 hr. the aqueous layer was removed and the benzene layer washed with water. A solution of 0.83 g. (5 mmoles) of phloretic acid[28] in 10 ml. of ethyl acetate was then added. The solution turned immediately from green to brown. After a few minutes it was dried over sodium sulfate and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on a column of 40 g. of silica gel. Elution with benzene yielded 0.10 g. of a reddish orange solid which was not further investigated. Further elution with benzene gave 1.16 g. of orange crystals which, upon recrystallization from methanol, gave yellowish crystals of 4-hydroxy-3,5-di-*t*-butylacetophenone, m.p. 148–151°, identified through its infrared spectrum and mixed melting point.

Elution with ether–benzene (1:9) gave 2.0 g. of a brown viscous liquid. When a solution of this liquid in benzene was allowed to stand at 2°, 0.59 g. (33%) of crystals separated from the solution. Upon two recrystallizations from aqueous ethanol, colorless plates, m.p. 174–175°, were obtained. They were identical with the 3-[4-(2-hydroxy-3-*t*-butyl-5-acetylphenoxy)phenyl]propionic acid [VIII: R = $COCH_3$; R_1 = H; R_2 = $(CH_2)_2COOH$] described above (mixed melting point and infrared spectrum).

4-Hydroxy-3-bromoacetophenone.—A solution of 2.72 g. (20 mmoles) of *p*-hydroxyacetophenone in a mixture of 50 ml. of concentrated hydrochloric acid and 50 ml. of water was heated to 50–60° and 1.02 ml. (40 g.-atoms) of bromine dissolved in 20 ml. of a 20% (w./v.) aqueous potassium bromide solution was added at once with vigorous stirring. The white precipitate formed was collected and treated with a large volume of boiling water. The insoluble material consisting mainly of 4-hydroxy-3,5-dibromoacetophenone was removed by filtration. On cooling, the filtrate deposited colorless needles (3.0 g.; 70%) of the hydrate of 4-hydroxy-3-bromoacetophenone, m.p. 97–99° (lit.,[29] m.p. 95–100°). Recrystallization from benzene gave fine needles of the anhydrous compound, m.p. 119–121° (lit.,[30] m.p. 112°).

4-Methoxy-3-bromoacetophenone.—A solution of 9.9 g. (46 mmoles) of 4-hydroxy-3-bromoacetophenone in 100 ml. of ether was allowed to stand with an excess of an ethereal solution of diazomethane for 3 hr. The solution was then evaporated and the residue recrystallized from ether–petroleum ether; colorless needles, m.p. 87–88° (8.6 g.; 82%).

Anal. Calcd. for $C_9H_9BrO_2$: C, 47.18; H, 3.97. Found: C, 47.49; H, 4.33.

3-[4-(2-Hydroxy-5-acetylphenoxy)phenyl]propionic Acid (IX). A. From 3-[4-(2-Hydroxy-3-*t*-butyl-5-acetylphenoxy)-phenyl]propionic Acid.—To a solution of 0.25 g. (0.71 mmole) of the acid VIII [R = $COCH_3$; R_1 = H; R_2 = $(CH_2)_2$-COOH] in 10 ml. of hot benzene was added 1 g. of powdered anhydrous aluminum chloride. The mixture was evaporated and the residue heated on a boiling water bath for 2 hr. The reaction mixture was then decomposed with ice water and extracted with ether. The ether layer was washed with water and dried over sodium sulfate. The ether was evaporated and the residue dissolved in a small amount of hot benzene. On cooling, crystals, m.p. 146–148° (0.10 g.; 47%), formed. Two recrystallizations from hot water gave fine colorless needles, m.p. 149–150°; λ_{max}^{EtOH} 209 mμ (log ε 4.25), 229 mμ (4.31), 275 mμ (4.11).

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.35. Found: C, 68.11; H, 5.52.

B. From 4-Methoxy-3-bromoacetophenone.—A solution of 1.94 g. (10 mmoles) of ethyl 3-(*p*-hydroxyphenyl)propionate in 20 ml. of anhydrous benzene was refluxed with 0.39 g. (10 g.-atoms) of potassium for several hours until the metal was completely dissolved. Then 1.83 g. (8 mmoles) of 4-methoxy-3-bromoacetophenone and 30 mg. of active copper powder[31] were added. The mixture was evaporated and the residue heated at 200–210° for 2.5 hr. After cooling, the reaction mixture was shaken with a mixture of ether and water. Insoluble material was removed by filtration and the ether layer washed with water, dried over sodium sulfate, and evaporated. A solution of the reddish brown residue in a mixture of 15 ml. of 1 *N* potassium hydroxide and 30 ml. of ethanol was refluxed for 2 hr. The mixture was evaporated *in vacuo* and the residue diluted with water and then extracted with ether. The aqueous layer was acidified and extracted with ether. This ether extract was dried and evaporated. A solution of the reddish brown residue in benzene was chromatographed on a column of 30 g. of silica gel. Elution with benzene–ether (9:1) gave 1.16 g. of a viscous liquid which did not crystallize. It was dissolved in 8 ml. of glacial acetic acid and 8 ml. of constant-boiling hydroiodic acid. This solution was refluxed for 3 hr. in the presence of a small amount of red phosphorus. The reaction mixture was diluted with water and extracted with ether. The ether layer was washed with water, with a solution of sodium thiosulfate, and again with water, then dried over sodium sulfate and evaporated. Crystallization of the residue (0.88 g.) from water gave 0.25 g. (10%) of needles which, after recrystallization from water, melted at 147–149°. The substance was identical with the one obtained in procedure A (mixed melting point and infrared spectrum).

Reaction of 2,6-Di-*t*-butyl-4-acetylphenoxyl with Oxygen.—A solution of 1.24 g. (5 mmoles) of 4-hydroxy-3,5-di-*t*-butylacetophenone in 50 ml. of benzene was stirred with a solution of 9 g. of potassium ferricyanide and 5 g. of potassium hydroxide in 50 ml. of water. After 30 min. the aqueous layer was removed and the benzene layer washed with water. Then oxygen was bubbled through the benzene layer until the greenish color had completely disappeared (6 hr.). The pale brown solution was evaporated *in vacuo* and a solution of the residue in benzene–petroleum ether (1:1) chromatographed on a column of 20 g. of silica gel.

Elution with the same solvent yielded 0.27 g. (25%) of 2,6-di-*t*-butylbenzophenone as orange crystals. Recrystallization from methanol gave orange needles, m.p. and mixed m.p. 67–68° (lit.,[8] m.p. 67–68°).

Elution with benzene–ether (49:1) gave 0.25 g. of a liquid which on standing deposited 10 mg. of yellow prisms, m.p. 140° dec. This substance could not be obtained in all runs and was not further investigated; λ_{max}^{EtOH} 213, 252, 315 mμ. Infrared spectrum (Nujol): 3320 (weak), 1680, 1645 (weak), 1590 cm.$^{-1}$ (weak).

Elution with benzene–ether (9:1) and with ether gave 0.52 g. of a brownish orange liquid. Its solution in benzene,

(28) H. J. Cahnmann and T. Matsuura, *J. Am. Chem. Soc.*, **82**, 2050 (1960).

(29) R. P. Edkins and W. H. Linnell, *Quart. J. Pharm. Pharmacol.*, **9**, 75 (1936).

(30) F. C. Chen and T. H. Tsai, *J. Taiwan Pharm. Assoc.*, **4**, 42 (1952).

(31) R. Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, 1943, p. 445.

on standing at 2°, deposited 123 mg. (12%) of almost colorless crystals of 3,4-dihydroxy-5-*t*-butylacetophenone (XIII; R=$COCH_3$; R_1=H). Recrystallization from benzene gave colorless leaflets, m.p. 180.5–181.5°; λ_{max}^{EtOH} 211 mμ (log ε 4.19), 233 mμ (4.10), 286 mμ (3.98), 306 mμ (3.91); $\lambda_{max}^{EtOH-H_3BO_3-CH_3COONa}$ 245 mμ (log ε 4.20), 302 mμ (3.88), 334 mμ (4.08).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.20, H, 7.80.

The substance gave a 2,4-dinitrophenylhydrazone. Ferric chloride produced with an alcoholic solution of the catechol a dark green color which turned dark red on addition of sodium carbonate.

Catechol O-Methyltransferase Test.—An adult male rat was exsanguinated. The liver was removed and chilled on ice, then homogenized with 2 vol. of ice-cold isotonic potassium chloride solution (1.15%). The mixture was centrifuged at 0–5° for 45 min. (78,000 × g.). The clear supernatant was used for the test (enzyme solution). A solution of 2 μmoles of 3,4-dihydroxy-5-*t*-butylacetophenone in 0.25 ml. of propylene glycol was incubated for 2 hr. at 37° with 0.5 ml. of 0.5 *M* phosphate buffer (pH 7.9), 0.1 ml. of 0.5 *M* magnesium chloride, 2.4 μmoles of adenosylmethionine, and 1 ml. of enzyme solution.

After the incubation the mixture was extracted three times with about 3 vol. of ether. The layers were separated by centrifugation. The combined ether extracts were washed two times with about 2 vol. of water, dried over sodium sulfate, and evaporated *in vacuo*. An aliquot of the residue was chromatographed on a thin layer of silica gel with methanol–chloroform (1:99). The chromatogram was sprayed with ferric chloride–ferricyanide reagent,[12] which revealed a spot (R_f 0.01) corresponding to the catechol and another spot (R_f 0.38) corresponding to its monomethyl ether, 4-hydroxy-3-methoxyacetophenone (below). When in the catechol O-methyltransferase test the addition of adenosylmethionine was omitted or an enzyme solution was used which had been inactivated by heating, the monomethyl ether spot was absent.

The catechol spots turned brown on spraying with a solution of diazotized N^1,N^1-diethylsulfanilamide,[13] but the location of the catechol monomethyl ether could not be revealed by this reagent.

2,4-Dinitrophenylhydrazone of 4-Hydroxy-3-methoxyacetophenone.—An ethereal solution of 20 mg. of the catechol XIII (R=$COCH_3$; R_1=H) was mixed with an excess of diazomethane in ether and the mixture was permitted to stand overnight. Evaporation of the ether gave a viscous residue of crude monomethyl ether which gave no color with ferric chloride solution, but did give a blue color with ferric chloride–ferricyanide reagent.[12]

The methyl ether gave a 2,4-dinitrophenylhydrazone which was recrystallized from ethyl acetate–ethanol; vermillion needles, m.p. 189–190°.

Anal. Calcd. for $C_{19}H_{22}N_4O_6$: C, 56.72; H, 5.51; N, 13.92. Found: C, 56.92; H, 5.90; N, 13.82.

Ethyl 4-Hydroxy-3,5-di-*t*-butylbenzoate.—A solution of 12.42 g. (54 mmoles) of 4-hydroxy-3,5-di-*t*-butylbenzonitrile[19] in 200 ml. of absolute ethanol was cooled in an ice bath and saturated with dry hydrogen chloride. The mixture was permitted to stand overnight at room temperature, then evaporated *in vacuo*. The residue was shaken with a mixture of 100 ml. of ether and 200 ml. of water. The ether layer was washed with water and the combined aqueous layers were heated on a water bath for 1.5 hr. After cooling, the mixture was extracted with ether. The ether extract was washed with water, then with a solution of sodium bicarbonate, and again with water. It was then dried over sodium sulfate. The crystalline residue obtained after evaporation of the solvent was recrystallized from aqueous ethanol; colorless needles, m.p. 106–108° (lit.,[19] m.p. 108–109°). The yields varied from 67 to 82% in various runs.

2,6-Di-*t*-butyl-4-ethoxycarbonylphenoxyl (VI; R=$COOC_2H_5$).—A solution of 150 mg. (0.54 mmole) of ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate in 10 ml. of benzene was stirred with a solution of 0.90 g. of potassium ferricyanide and 0.55 g. of potassium hydroxide in 5 ml. of water. After 30 min. the aqueous layer was removed and the green benzene layer washed with water. Iodimetric titration showed that the yield of the free radical or its dimer was 97%. After the titration, the benzene layer was dried and evaporated. The crystalline residue was ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate (melting point and mixed melting point).

Dimer of 2,6-Di-*t*-butyl-4-ethoxycarbonylphenoxyl.—To a solution of 278 mg. (1 mmole) of ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate in 5 ml. of methanol was added 0.6 g. of sodium hydroxide and the mixture was diluted with 90 ml. of water. A solution of 1 g. of potassium ferricyanide in 10 ml. of water was then added with stirring. The yellow precipitate formed was collected by filtration, washed with water, and dried; m.p. 96–97° (green melt); yield 246 mg. (89%).

Anal. Calcd. for $C_{34}H_{50}O_6$: C, 73.61; H, 9.09. Found: C, 73.62; H, 9.27.

Solutions of the dimer in various organic solvents are green (dissociation); $\lambda_{max}^{benzene}$ 410 mμ (log ε 2.71), 425 mμ (2.81), 720 mμ (2.65).

Addition of 6 ml. of glacial acetic acid to a suspension of 100 mg. (0.18 mmole) of the dimer in a saturated aqueous solution of 1 g. of potassium iodide caused the liberation of iodine. Titration with sodium thiosulfate showed that the amount of iodine corresponded to 96% of the theory. After the titration water was added which caused the formation of a precipitate (100 mg.), which was then crystallized from aqueous methanol. Colorless needles of ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate (melting point and mixed melting point) were thus obtained.

Reaction of 2,6-Di-*t*-butyl-4-ethoxycarbonylphenoxyl with Ethyl 3-(*p*-Hydroxyphenyl)propionate.—A solution of the free radical was prepared from 3.45 g. (12.4 mmoles) of ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate as described above. After stirring for 15 min. the aqueous layer was removed and the benzene layer washed with water. Then a solution of 1.20 g. (6.2 mmoles) of ethyl 3-(*p*-hydroxyphenyl)propionate[27] in 40 ml. of benzene was added. The mixture was stirred for 2 hr., then dried over sodium sulfate, and evaporated *in vacuo*. A solution of the pale brown residue in petroleum ether was chromatographed on a column of 80 g. of silica gel.

Elution with benzene yielded 1.81 g. of a crystalline mass which on recrystallization from methanol gave ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate (melting point and mixed melting point). Elution with benzene–ether (5:1) yielded 2.69 g. (93%) of crude ethyl 3-[4-(2-hydroxy-3-*t*-butyl-5-ethoxycarbonylphenoxy)phenyl]propionate [VIII; R=$CO-OC_2H_5$; R_1=H; R_2=$(CH_2)_2COOC_2H_5$] as a brownish yellow liquid. The bulk of it distilled at a bath temperature of 220–240° and a pressure of 0.1 mm. The distillate crystallized on addition of petroleum ether. Two recrystallizations from petroleum ether gave colorless needles, m.p. 67–68°; λ_{max}^{EtOH} 216 mμ (log ε 4.42), 227 mμ (4.42), 267 mμ (4.16), 298 mμ (3.55). Infrared bands (Nujol) at 3270 (hydroxyl), 1737 (nonconjugated ester), 1688 (aromatic ester), 1600 and 1507 $cm.^{-1}$ (aromatic double bond).

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.72; H, 7.34.

Reaction of 2,6-Di-*t*-butyl-4-ethoxycarbonylphenoxyl with 3-(*p*-Hydroxyphenyl)propionic Acid (Phloretic Acid).—A solution of the free radical was prepared from 2.78 g. (10 mmoles) of ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate as described in the preceding paragraph. To the washed benzene layer a solution of 0.83 g. (5 mmoles) of phloretic acid[28] in 50 ml. of ethyl acetate was added and the mixture stirred for 20 min. The solution that had become brownish yellow was dried over sodium sulfate and evaporated *in vacuo*. A solution of the residue in benzene was chromatographed on a column of 90 g. of silica gel. Elution with benzene–

ether (99:1) gave 1.59 g. of crude ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate which, after one recrystallization from methanol, gave colorless needles; m.p. and mixed m.p. 103–106°.

Elution with benzene–ether (9:1) yielded 1.16 g. (48%) of crude 3-[4-(2-hydroxy-3-*t*-butyl-5-ethoxycarbonylphenoxy)-phenyl]propionic acid [VIII; R = $COOC_2H_5$; R_1 = H; R_2 = $(CH_2)_2COOH$] as a liquid which did not crystallize. It gave no color with ferric chloride solution but produced a blue color with ferric chloride–ferricyanide reagent.[12]

3-[4-(2-Hydroxy-3-*t*-butyl-5-carboxyphenoxy)phenyl]propionic Acid [VIII; R = COOH; R_1 = H; R_2 = $(CH_2)_2$-COOH]. A. From 3-[4-(2-Hydroxy-3-*t*-butyl-5-ethoxycarbonylphenoxy)phenyl]propionic Acid.—A solution of about 0.5 g. of the crude liquid ester described in the preceding paragraph in 10 ml. of a 10% alcoholic solution of potassium hydroxide was refluxed for 30 min. The residue obtained after evaporation of the solvent *in vacuo* was diluted with 10 ml. of water and the solution acidified. Extraction with ether, drying of the ether extract over sodium sulfate and evaporation of the ether gave a residue which was dissolved in a few milliliters of hot benzene. This solution deposited 0.19 g. of crystals which, after recrystallization from methanol–benzene, gave colorless prisms m.p. 228.5–230°; λ_{max}^{EtOH} 216 mμ (log ε 4.45), 224 mμ (4.45), 264 mμ (4.14), 298 mμ (3.39).

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19. Found: 66.93; H, 6.18.

B. From Ethyl 3-[4-(2-Hydroxy-3-*t*-butyl-5-ethoxycarbonylphenoxy)phenyl]propionate.—A solution of 400 mg. (0.87 mmole) of the diester in a mixture of 5 ml. of 1 *N* potassium hydroxide and 3 ml. of ethanol was heated for 2.5 hr. on a water bath. The hydrolysate was diluted with water and neutralized (phenolphthalein) with 0.1 *N* sulfuric acid (30.48 ml.); saponification equivalent: 205 (calcd. 207). Acidification (Congo red) produced a white precipitate which was collected, washed with water, and dried. Recrystallization from methanol–benzene gave colorless prisms, m.p. 228.5–230°, which were identical with those obtained in procedures A, C, and D (mixed melting point and infrared spectrum).

C. From Ethyl 3-[4-(2-Hydroxy-3-*t*-butyl-5-cyanophenoxy)phenyl]propionate.—A solution of 692 mg. of the ester (*cf.* below) in 20 ml. of ethanol was saturated with dry hydrogen chloride under ice-cooling. The mixture was allowed to stand overnight and was then evaporated *in vacuo*. The residue was shaken with a mixture of ether and water. The ether layer was washed with water and the combined aqueous layers were heated for 1 hr. on a water bath. After extraction with ether, drying of the ether extract, and evaporation, a residue was obtained which was dissolved in a solution of 1 g. of potassium hydroxide in 1 ml. of water and 2 ml. of ethanol. After refluxing for 30 min., evaporation of the solvent, and acidification, 382 mg. of a precipitate was obtained which, after recrystallization from methanol–benzene–petroleum ether, gave colorless prisms, m.p. 228–230°, identical with those obtained in procedures A, B, and D (mixed melting point and infrared spectrum).

D. From 3-[4-(2-Hydroxy-3-*t*-butyl-5-cyanophenoxy)-phenyl]propionic Acid.—The acid (50 mg.) was hydrolyzed as described for the ester in procedure C. The product (41 mg.; m.p. 228–230°) was identical with the dicarboxylic acid obtained in procedures A, B, and C (mixed melting point and infrared spectrum).

Methyl 3-[4-(2-Hydroxy-3-*t*-butyl-5-methoxycarbonylphenoxy)phenyl]propionate [VIII; R = $COOCH_3$; R_1 = H; R_2 = $(CH_2)_2COOCH_3$].—An ethereal solution of 100 mg. of the diacid described in the preceding paragraph was treated with an excess of diazomethane in ether. The mixture was permitted to stand overnight and was then evaporated. The residue was recrystallized from ether–petroleum ether; 95 mg. of colorless elongated prisms, m.p. 98–99°; λ_{max}^{EtOH} 220 mμ (log ε 4.37), 268 mμ (4.12), 296 mμ (3.41).

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.61; H, 6.76.

Reaction of 2,6-Di-*t*-butyl-4-ethoxycarbonylphenoxyl with Oxygen.—A solution of 2.0 g. (7.2 mmoles) of ethyl 4-hydroxy-3,5-di-*t*-butylbenzoate in 50 ml. of benzene was stirred with a solution of 13.5 g. of potassium ferricyanide and 7.5 g. of potassium hydroxide in 75 ml. of water. After 5 min. the benzene layer was washed with water and then oxygen was bubbled through it for 3.5 hr., after which time the solution had become yellow. The residue obtained after evaporation of the solvent *in vacuo* was dissolved in benzene and chromatographed on a column of 50 g. of silica gel.

Elution with benzene yielded 1.58 g. of crude 4-hydroxy-4-ethoxycarbonyl-2,6-di-*t*-butyl-2,5-cyclohexadien-1-one (XV) as a greenish yellow, viscous liquid which did not crystallize, even after rechromatography and distillation at 0.1 mm. (bath temperature 90–120°).

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.51; H, 8.99.

From the residue of the distillation of the crude ester a few milligrams of crystals, m.p. 178–179°, separated which were not further investigated. Infrared spectrum (Nujol): 1790, 1720, 1670, 1640, 1600 cm.$^{-1}$; no hydroxyl bands.

When the column used for the rechromatography of the crude ester was eluted with benzene–ether (9:1), 0.28 g. of a liquid was obtained whose solution in petroleum ether deposited a few milligrams of crystals. After recrystallization from benzene, they gave colorless prisms, m.p. 236–238°, which are supposed to be bis(2-hydroxy-3-*t*-butyl-5-ethoxycarbonylphenyl) ether (XVI); λ_{max}^{EtOH} 212 mμ (log ε 4.44), 226 mμ (4.46), 263 mμ (4.35), shoulder at 296 mμ (3.79). Infrared bands (Nujol) at 3280 (hydroxyl), 1690 (aromatic ester), 1600 and 1580 cm.$^{-1}$ (aromatic double bond).

Anal. Calcd. for $C_{26}H_{34}O_7$: C, 68.10; H, 7.47. Found: C, 68.21; H, 7.57.

When the above-mentioned silica gel column from which 1.58 g. of a viscous liquid had been eluted, was further eluted with benzene–ether (9:1), 0.42 g. of a viscous brown liquid was obtained. Its solution in petroleum ether deposited 20 mg. of crystals of ethyl 3,4-dihydroxy-5-*t*-butylbenzoate (XIII; R = $COOC_2H_5$; R_1 = H). On recrystallization from benzene they gave colorless prisms, m.p. 136.5–138°; λ_{max}^{EtOH} 212 mμ (log ε 4.34), shoulder at 222 mμ (4.24), 268 mμ (4.02), 298 mμ (3.75); $\lambda_{max}^{EtOH-H_3BO_3-CH_3COONa}$ 234 mμ (4.34), 284 mμ (4.06), 310 mμ (4.14).

Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.74; H, 7.61.

An alcoholic solution produced with ferric chloride a dark green color which turned dark red on addition of sodium carbonate.

In one run, the benzene–ether eluate of the silica gel column did not yield this catechol, but instead 0.10 g. of fine crystals which did not melt at 320°. They were not identified; λ_{max}^{EtOH} 252, 300, 332 mμ. Infrared bands (Nujol) at 3200, 1705, and 1600 cm.$^{-1}$.

Anal. Found: C, 69.38, 69.11; H, 6.08, 5.81.

Reaction of 2,6-Di-*t*-butyl-4-cyanophenoxyl (VI; R = CN) with Ethyl 3-(*p*-Hydroxyphenyl)propionate.—A solution of 2.30 g. (10 mmoles) of 4-hydroxy-3,5-di-*t*-butylbenzonitrile[19] in 100 ml. of benzene was stirred for 6 min. with a solution of 9.0 g. of potassium ferricyanide and 5.0 g. of potassium hydroxide in 50 ml. of water. After removal of the water layer and washing of the green benzene layer with water, 1.03 g. (5.3 mmoles) of ethyl 3-(*p*-hydroxyphenyl)propionate[27] was added. The mixture was stirred for 10 min. and then dried over sodium sulfate and evaporated *in vacuo*. A solution of the residue in petroleum ether was chromatographed on a column of 90 g. of silica gel.

Elution with benzene–ether (10:1) yielded 1.40 g. (72%) of crude ethyl 3-[4-(2-hydroxy-3-*t*-butyl-5-cyanophenoxy)-phenyl]propionate [VIII; R = CN; R_1 = H; R_2 = $(CH_2)_2$-$COOC_2H_5$] as a reddish brown liquid, which on distillation

at 0.1 mm. (bath temperature 250°) gave a yellow liquid. The infrared spectra before and after the distillation were identical; λ_{max}^{EtOH} 220 mμ (log ε 4.47), 256 mμ (4.12), inflection at 2.93 mμ (3.40).

Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.94; H, 7.13; N, 4.00.

Conversion to the corresponding dicarboxylic acid [VIII; R = COOH; R_1 = H; R_2 = $(CH_2)_2$COOH].—*Cf.* above.

Reaction of 2,6-Di-*t*-butyl-4-cyanophenoxyl with 3-(*p*-Hydroxyphenyl)propionic Acid (Phloretic Acid).—In this reaction the free radical was prepared *in situ* by dissociation of its dimer. To a solution of 200 mg. (1.22 mmoles) of phloretic acid[28] in 10 ml. of ethyl acetate 0.56 mg. (1.2 mmoles) of the dimer[32] of the free radical was added in small portions with stirring. The solvent was then evaporated *in vacuo* and a solution of the crystalline residue in benzene chromatographed on a column of 30 g. of silica gel. Elution with benzene gave 4-hydroxy-3,5-di-*t*-butylbenzonitrile.[19] Elution with ether yielded a liquid which crystallized on treatment with petroleum ether. Recrystallization from benzene–petroleum ether gave 0.20 g. (42%) of 3-[4-(2-hydroxy-3-*t*-butyl-5-cyanophenoxy)phenylpropionic acid [VIII; R = CN; R_1 = H; R_2 = $(CH_2)_2$COOH] as colorless plates, m.p. 151–153°; λ_{max}^{EtOH} 220 mμ (log ε 4.51), 256 mμ (4.17), inflection at 294 mμ (3.36). Infrared bands (Nujol) at 3435 (hydroxyl), 2225 (nitrile), 1716 (carboxyl) 1602, 1587, and 1509 cm.$^{-1}$ (aromatic double bond).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 71.11; H, 6.55; N, 4.06.

Conversion to the Corresponding Dicarboxylic Acid [VIII; R = COOH; R_1 = H; R_2 = $(CH_2)_2$COOH].—*Cf.* above.

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The Synthesis of C-18 Functionalized Steroid Hormone Analogs. II. Preparation and Some Reactions of 18-Chloro Steroids[1a]

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A number of 20-methylamino steroids have been prepared by reductive amination of the corresponding 20-keto steroids. Irradiation of the *N*-chloro derivatives of these amines in trifluoroacetic acid produced 18-chloro-20-methylamino steroids which were isolated as their trifluoroacetate salts. Treatment of the salts with base caused ring closure to conanines. However, when an 11-keto function was present, alkali treatment resulted in formation of 12,18-cyclo steroids in addition to 11-ketoconanines. The interconvertibility of 11-keto-12,18-cyclo steroids and 11-ketoconanines was demonstrated by conversion of 3β-hydroxy-20α-methylamino-12,18-cyclo-5α-pregnane-11-one (XVIII) into 3β-hydroxyconanine-11-one (XVIIb) and transformation of the latter compound into 3β-hydroxy-12,18-cyclo-5α-pregn-20-ene-11-one (XXII).

The presence of a 13-aldehyde group in aldosterone has focused attention on methods for preparing 18-functionalized steroids. The solution to this problem was originally approached by methods involving total synthesis, by partial syntheses from *Holarrhena* alkaloids and by way of 13,17-seco steroids.[2]

A fundamentally different type of synthetic route was made available when methods were found for the direct introduction of substituents at the C-18 methyl group of intact steroids. Functionalization by means of the Hofmann–Loeffler–Freytag reaction with formation of a carbon–nitrogen bond at C-18 was the first method reported.[3,4] Other methods for direct attack on the angular methyl group followed in rapid succession: thermal decomposition of a 21-diazo-20-ketone to form an 18,21-cyclo steroid,[5] irradiation of 20-keto steroids to form 18,20-cyclo-20-ols,[6] lead tetraacetate treatment of 20-hydroxy steroids to yield 18,20-epoxides[7] or, with iodine added, to form 18-iodo-18,20-epoxides,[8] photochemical rearrangement of 11β- or 20-nitrite esters to 18-oximes,[9]

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