[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF VERMONT]

Oxidation of Hindered Phenols. II. The 2,4,6-Tri-*t*-butylphenoxy Radical

BY CLINTON D. COOK AND ROBERT C. WOODWORTH

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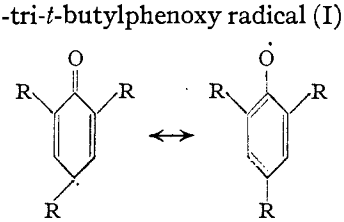
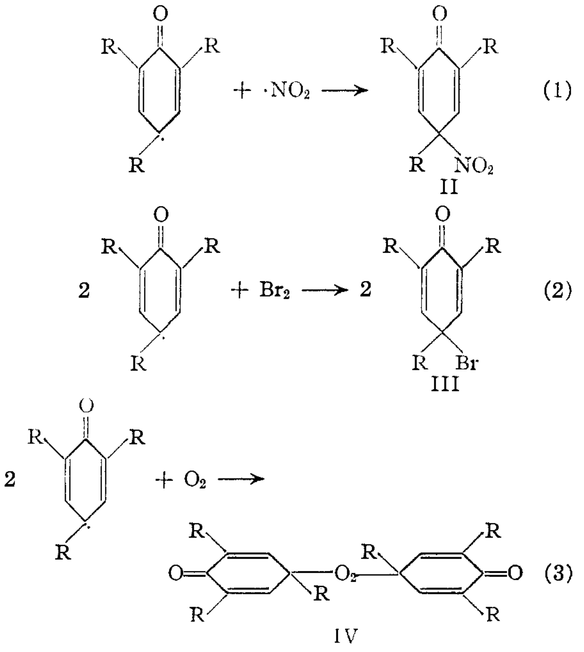
Evidence is presented for the formation of the 2,4,6-tri-*t*-butylphenoxy radical upon the oxidation of 2,4,6-tri-*t*-butylphenol and upon the dissociation of certain 4-substituted 2,5-cyclohexadienones. The reactions of this radical with nitrogen dioxide, bromine and oxygen are discussed and evidence cited for the structures of the products.

It was recently noted[1] that the oxidation of 2,4,6-tri-*t*-butylphenol in solution leads to an intense cobalt blue which was attributed to the formation of the 2,4,6-tri-*t*-butylphenoxy radical (I). Further study has shown that this is undoubtedly the case. When a solution of 2,4,6-tri-*t*-butylphenol was treated with lead dioxide or, preferably, alkaline ferricyanide, an intense blue solution of I was formed. The course of this reaction was easily followed since I reacted rapidly with acidic solutions of sodium iodide to form iodine and regenerate the parent phenol. The iodine was then determined by conventional means. As the radical reacted rapidly with oxygen, it was necessary to run and sample the reaction under an atmosphere of nitrogen. With the apparatus described under Experimental, 99–100% yields of the radical I were easily obtained when alkaline ferricyanide was used as the oxidizing agent.



I, R = *t*-butyl

The radical reacted with nitrogen dioxide, bromine and oxygen as shown below



R = *t*-butyl

The known affinity of these reagents for free radicals and the stoichiometry of reactions 2 and 3 provides very strong evidence that we are indeed dealing with a free radical.

The products of these reactions are all light yellow, rather unstable compounds having ultraviolet spectra markedly similar to that of *p*-benzoquinone. This and the similarity of extinction coefficients (Table I) support the proposed 2,5-cyclohexadienone structures. In this respect, it is particularly significant that the bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide has a molar extinction coefficient approximately twice that of the other compounds. Hindered phenols have a minimum absorption in the region from 240–260 mμ where these compounds show maxima.[4]

TABLE I

Compound	λ_{max} mμ	$\epsilon \times 10^{-3}$	Solvent
2,4,6-Tri-*t*-butyl-4-nitro-2,5-cyclohexadienone (II)	241	10.6	Cyclohexane
2,4,6-Tri-*t*-butyl-4-bromo-2,5-cyclohexadienone (III)	251	13.1	Cyclohexane
Bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide (IV)	242	25.8	Cyclohexane
2,5-Di-*t*-butyl-4-methyl-4-bromo-2,5-cyclohexadienone[2]	248	14	Isoöctane
p-Benzoquinone[3]	242	17.9	Cyclohexane

The infrared spectra of the peroxide showed a doublet at about 6 μ and a band at about 11.4 μ which Campbell and Coppinger[5] associate with a carbonyl group conjugated with carbon–carbon unsaturation and with a peroxide linkage, respectively. No absorption occurred in the region of 2.7–2.8 μ which has been related to the hindered phenolic hydroxyl group.[6]

The cyclohexadienones produced were all thermally unstable. The nitro compound II decomposed rapidly around 90° to evolve nitric oxide, the bromo compound III slowly decomposed at about the same temperature to yield bromine and the peroxide IV underwent a unique decomposition at its melting point (148–149°) to evolve *one* mole of isobutylene per mole of peroxide. These decompositions are being studied further.

It seems likely that the decomposition of II and III proceed first through dissociation to the phenoxy radical (I); *i.e.*, essentially through the reverse

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[1] C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953).

[2] G. M. Coppinger and T. W. Campbell, THIS JOURNAL, **75**, 734 (1953).

[3] E. A. Braude, *J. Chem. Soc.*, 490 (1945).

[4] N. D. Coggeshall and E. M. Lang, THIS JOURNAL, **70**, 3283 (1948).

[5] T. W. Campbell and G. M. Coppinger, *ibid.*, **74**, 1496 (1952).

[6] W. C. Sears and L. J. Kitchen, *ibid.*, **71**, 4110 (1949).

of reactions 1 and 2. Thus warm solutions of the bromo compound III in petroleum ether slowly took on a greenish coloration suggestive of a mixture of the radical I and bromine. This color faded when bromine vapors were admitted to the flask. The same coloration appeared near the end-point when the radical was titrated with bromine (see Experimental).

Both II and III reacted with neutral, alcoholic sodium iodide to yield iodine and the radical I and with acidic, alcoholic sodium iodide to regenerate the parent phenol and iodine. With the bromo compound, this latter reaction was found to be essentially quantitative.

When the bromo compound III in petroleum ether was shaken with mercury, the blue color characteristic of the radical I rapidly developed.

The facile dissociation of these cyclohexadienones is not surprising since it permits the formation of the benzenoid structure. It provides a ready explanation for the fact that Goldhalm[7] found that 2,4,4,6-tetrabromo-4-methyl-2,5-cyclohexadienone would effect the side chain bromination of toluene and ethylbenzene.

In acetic acid, 2,4,6-tri-*t*-butylphenol reacted readily with nitric acid and with bromine to yield II and III, respectively. Coppinger and Campbell[2] have prepared 2,6-di-*t*-butyl-4-methyl-2,5-cyclohexadienone by brominating the corresponding phenol under the same conditions. Albert, Forman and Sears[8] have briefly reported the formation of 4-nitrocyclohexadienones upon the nitration of hindered phenols. Unfortunately, no detailed publication of these results has yet appeared.

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Experimental

Preparation of 2,4,6-Tri-*t*-butylphenol.—This phenol was prepared by a modification of the method of Stillson, Sawyer and Hunt.[9] Phenol was alkylated with isobutylene using sulfuric acid as a catalyst. The reaction was run in a tube approximately 4 cm. in diameter and 35 cm. long and equipped with a reflux condenser and a sealed stirrer. The stirrer extended to the bottom of the tube and the isobutylene was admitted through a jacket surrounding the stirrer shaft. In a typical run 94 g. (1 mole) of phenol was dissolved in 45 ml. of benzene, 5 ml. of concentrated sulfuric acid added and isobutylene passed through the mixture which was maintained at 50–60°. When the weight gain was approximately 168 g. (3 moles of isobutylene), sufficient benzene was added to dissolve the crystalline 2,4,6-tri-*t*-butylphenol which had precipitated, and the mixture extracted with water and then with dilute base. The benzene was distilled until the pot temperature reached 120°, 200 ml. of ethanol added and the mixture allowed to crystallize. A second and third crop of material were collected from the ethanol; yield 190 g. (72%). After a second recrystallization from ethanol the white crystals melted at 131–132°; reported 130–131°.[9]

Oxidation of 2,4,6-Tri-*t*-butylphenol.—Oxidation of the phenol in benzene solution with alkaline ferricyanide was carried out with mechanical stirring in a one-liter flask. A sampling tube extending into the benzene layer was attached to a self leveling buret. This was so arranged that oxygen-free nitrogen[10] slowly passed through the solution during the oxidation. To sample the reaction, stirring was stopped, the layers were allowed to separate and the buret then filled by reversing the flow of nitrogen. When the buret was filled, the nitrogen flow was again reversed causing the buret to drain to its calibrated volume. The sample (15.93 ml.) was run into a hot solution of 1.6 g. of sodium iodide in 25 ml. of isopropyl alcohol and 10 ml. of glacial acetic acid. Small periodic additions of sodium carbonate provided a carbon dioxide blanket during this analysis. After approximately a minute, 50 ml. of water was added to the mixture and the free iodine titrated with thiosulfate to a colorless end-point. Extraction of such a reaction mixture with benzene and evaporation to dryness gave a white residue, recrystallized from ethanol to give white needles, m.p. 130–131°. A mixture melting point with 2,4,6-tri-*t*-butylphenol gave m.p. 130–132°.

During a typical oxidation, 39.4 g. (0.12 mole) of potassium ferricyanide and 6 g. of potassium hydroxide in 150 ml. of water and 800 ml. of benzene were stirred for 1.5 hours while flushing with nitrogen; then 12.5 g. (0.048 mole) of 2,4,6-tri-*t*-butylphenol was added and the mixture stirred at room temperature for two hours. (With the relatively slow stirring provided by a cone drive stirrer, maximum yields were attained after one to two hours.)

2,4,6-Tri-*t*-butyl-4-bromo-2,5-cyclohexadienone (III). **Method A. Reaction of the Radical with Bromine.**—A benzene solution (162 ml.) containing 2.26 g. (0.0087 mole) of the radical I was slowly titrated under a nitrogen atmosphere with a solution of bromine in carbon tetrachloride. Near the equivalence point the reaction between the radical and the bromine was obviously rather slow. The titer corresponded to 0.005 mole of bromine or a ratio of approximately one mole of bromine to two moles of the radical. The high value may be attributed to the slowness of the reaction near the end-point and a consequent passing of the end-point. The resulting greenish yellow solution was evaporated to dryness and the yellow crystalline residue recrystallized once from dioxane–water and twice from petroleum ether. One gram of blunt yellow needles, m.p. 80.5–81.5°, resulted.

Anal. Calcd. for $C_{18}H_{29}OBr$: C, 63.34; H, 8.56. Found: C, 63.57; H, 8.66.

Method B. Reaction of Bromine with 2,4,6-Tri-*t*-butylphenol.—A suspension of 2.4 g. (0.09 mole) of the phenol in a mixture of 24 ml. of glacial acetic acid and 3 ml. of water was treated with 0.46 ml. (0.09 mole) of bromine. The solution was vigorously shaken while cooling under the tap. A mass of yellow crystals (m.p. 76–80°) rapidly formed. After recrystallization from petroleum ether approximately 1.5 g. of material, m.p. 80.5–81.5°, was obtained. A mixture melting point with the material prepared by method A gave m.p. 80–81.5°.

Reactions of 2,4,6-Tri-*t*-butyl-4-bromo-2,5-cyclohexadienone.—This compound was found to react with acidified solutions of sodium iodide under the same conditions as did the radical. The addition of 10 ml. of benzene to provide an organic phase was, however, necessary. When 0.151 g. (4.44 mmoles) of the compound was so treated 4.32 mmoles of iodine was formed. The benzene layer was evaporated to dryness and the residue recrystallized from ethanol; m.p. 130–132°, mixture m.p. with 2,4,6-tri-*t*-butylphenol, 130–132°.

When the bromocyclohexadienone was added to a solution of sodium iodide in isopropyl alcohol a greenish-brown solution was found suggestive of a mixture of iodine and the radical. Upon the addition of benzene and aqueous thiosulfate the brilliant blue color characteristic of the radical immediately appeared in the benzene layer.

Solutions of the bromo compound in petroleum ether took on a definite green color at the boiling point (60°). This color rapidly faded on admission of bromine vapors. Upon standing at room temperature for a few days, the solid became streaked with green. When methanol, ethanol or acetic acid was used as a recrystallization solvent, the bromo compound apparently reacted with the solvent.[11]

2,4,6-Tri-*t*-butyl-4-nitro-2,5-cyclohexadienone. (II). **Method A. Reaction of Nitrogen Dioxide with the Radical.**—When nitrogen dioxide was bubbled through 6.56 g. (0.025 mole) of the radical in 160 ml. of benzene, the blue color rapidly disappeared. Evaporation of the solvent at room

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[7] H. Goldhalm, *Osterr. Chem. Z.*, **44**, 244 (1941); *C. A.*, **37**, 3745^{2} (1943).

[8] H. E. Albert, L. E. Forman and W. C. Sears, Abstracts 118th Meeting A.C.S., 5-L (1950).

[9] G. H. Stillson, D. W. Sawyer and C. K. Hunt, THIS JOURNAL, **67**, 303 (1945).

[10] L. Meites and T. Meites, *Anal. Chem.*, **20**, 984 (1948).

[11] *Cf.* reference 2.

temperature gave a mass of yellow, rather unstable crystals. Cautious recrystallization from ethanol gave approximately 5 g. of blunt yellow needles, m.p. 83.5–84.0°.

Anal. Calcd. for $C_{18}H_{29}O_3N$: C, 70.33; H, 9.5. Found: C, 70.36; H, 9.63.

Method B.[12] **Reaction of Nitric Acid with 2,4,6-Tri-*t*-butylphenol.**—Concentrated nitric acid (2 ml., 0.05 mole) was added to 3.93 g. (0.015 mole) of 2,4,6-tri-*t*-butylphenol dissolved in 20 ml. of glacial acetic acid. The solution was shaken under the tap and a voluminous precipitate rapidly formed. Upon filtration 3.5 g. (90%) of the nitro compound (m.p. 76–80°) was obtained. Two recrystallizations from ethanol raised the melting point to 83.5–84°. A mixture melting point with material produced by method A was 83.5–84.5°.

Regeneration of the radical and of the parent phenol upon treatment with neutral or acidic, alcoholic sodium iodide occurred exactly as described under the bromo compound.

Bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one). Peroxide (IV).—Upon exposure to the air, solutions of the radical rapidly turned from blue to greenish yellow. Evaporation of the solvent (usually benzene) at room temperature gave yellow crystals which, upon cautious recrystallization from ethanol, melted at 148–149° dec.

A more convenient method of preparing the peroxide consisted of oxidizing the phenol in the presence of air. In a typical run a solution of 20 g. (0.076 mole) of the phenol in 250 ml. of benzene was vigorously stirred for two days with a solution of 75 g. (0.23 mole) of potassium ferricyanide and 25 g. of potassium hydroxide in 250 ml. of water. (When air was bubbled through the reaction mixture the reaction time was reduced to a few hours.) The yellow benzene layer was separated, washed with water and evaporated to dryness under an air stream at room temperature. The yellow residue was taken up in hot ethanol, filtered and quickly cooled; yield 17 g. (81%), m.p. 146–147°; after a second recrystallization m.p. 148–149°. The hot ethanolic solutions darkened rapidly and to obtain a pure product it was necessary to perform the recrystallizations rapidly.

Anal. Calcd. for $C_{36}H_{58}O_4$: C, 77.93; H, 10.54; mol. wt., 554.8. Found: C, 77.91; H, 10.65; mol. wt. (f.p., benzene), 555, 560.

Upon heating above the melting point, the peroxide decomposed to evolve isobutylene; one mole of peroxide yielding one mole of isobutylene. Thus 2.362 g. (0.00425 mole) of peroxide gave 103 ml. of gas (25°, 760 mm. or 0.0042 mole).

A detailed study of this decomposition will be reported in the near future.

The oxygen uptake of the radical was measured by oxidizing the phenol with alkaline ferricyanide in an oxygen atmosphere and measuring the oxygen absorption. Thus, 1.967 g. (0.0075 mole) of the phenol in 75 ml. of benzene and 6.35 g. (0.019 mole) of potassium ferricyanide and 1.0 g. of potassium hydroxide in 24 ml. of water were placed in a 200-ml. round-bottom flask which was attached to a 100-ml. gas buret. The flask was agitated in a mechanical shaker for 82 hours. A blank, which contained the end-point proportions of potassium ferricyanide and potassium ferrocyanide, but which excluded the peroxide, was also run. Both solutions were flushed with nitrogen prior to the run. The oxygen absorption due to the radical was 87.2 ml. at 26° and 760 mm. or 0.0036 mole. This indicates a reaction ratio of two moles of radical per mole of oxygen.

Spectra.—The ultraviolet spectra were measured in cyclohexane at concentrations of 2×10^{-4} to 5×10^{-5} mole/l. Over this range Beer's law was obeyed. The infrared spectrum of the peroxide was taken in carbon disulfide.

BURLINGTON, VERMONT

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[12] University of Vermont Bachelor's Thesis, 1953, by Miss Barbara A. Johnson.

[CONTRIBUTION FROM THE MOLTENO INSTITUTE, UNIVERSITY OF CAMBRIDGE]

On the Configuration of the So-called Dihydroxymaleic Acid

BY E. F. HARTREE

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Previous studies on aqueous solutions of "dihydroxymaleic" acid have indicated a *trans* configuration. Treatment of the acid with methanolic and ethanolic HCl gives 3 types of ester which are identified as *cis*, *trans* and keto forms. The ester produced by treatment with diazomethane in ethereal solution has the *trans* structure; hence the free acid appears to be dihydroxyfumaric acid. Further evidence for the proposed structures is obtained from the effect of boric acid on the spontaneous decomposition of the acid and its esters in aqueous solution.

Although "dihydroxymaleic" acid was prepared as long ago as 1874[1] and later studied extensively by Fenton,[2–6] no satisfactory proof of its configuration has yet been given. However, the importance which this acid is now assuming in biochemistry calls for a solution of this problem, *i.e.*, whether it is dihydroxymaleic or dihydroxyfumaric acid. The evidence to be brought forward in this and in the following paper supports the view that it is dihydroxyfumaric acid (DF).

It has been shown that many plants contain a "DF-oxidase"[7] and, by fractionating horse-radish root extracts Theorell and Swedin[8] were able to demonstrate a proportionality between peroxidase and DF-oxidase activities. Although the latter activity, unlike the former, was insensitive to cyanide, it was suggested that the two enzymes are identical.

In the field of photosynthesis Locke,[9] and also Hough and Jones,[10] suggested that DF was the precursor of glycol aldehyde in the synthesis of hexoses. Calvin, in a study of photosynthesis in presence of $C^{14}O_2$, showed that 6-C units were built up from pairs of 3-phosphoglyceric acid molecules. He postulates DF as an intermediate in the biosynthesis of this acid.[11] It is of interest that sunlight catalyzes the formation of DF from tartaric acid in presence of ferrous tartrate and air.[3]

Previous Work on the Structure of Dihydroxyfumaric Acid.—Fenton[4] originally proposed the *cis* configuration for DF because the instability of its aniline salts is more reminiscent of those of

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[1] E. Bourgoin, *Compt. rend.*, **79**, 1053 (1874).

[2] H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894).

[3] H. J. H. Fenton, *Brit. Assoc. Advance. Sci. Rep.*, 663 (1895).

[4] H. J. H. Fenton, *J. Chem. Soc.*, **69**, 546 (1896).

[5] H. J. H. Fenton, *ibid.*, **73**, 78 (1898).

[6] H. J. H. Fenton and W. A. R. Wilks, *ibid.*, **101**, 1570 (1912).

[7] G. A. Snow and S. S. Zilva, *Biochem. J.* (*London*), **32**, 1932 (1938); I. Banga and A. Szent-Györgyi, *Hoppe-Seyler's Z. physiol. Chem.*, **255**, 58 and 256 (1938); I. Banga and E. Phillipot, *ibid.*, **258**, 147 (1939).

[8] H. Theorell and B. Swedin, *Nature*, **145**, 71 (1940).

[9] A. Locke, THIS JOURNAL, **46**, 1246 (1924).

[10] L. Hough and J. K. N. Jones, *Nature*, **167**, 180 (1951).

[11] M. Calvin, *J. Chem. Educ.*, **26**, 639 (1949).