[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, UNIVERSITY OF CHICAGO]

Reactions of Hindered Phenols. I. Reactions of 4,4′-Dihydroxy-3,5,3′,5′,-tetra-*tert*-butyl Diphenylmethane*

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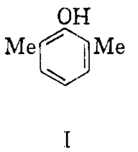
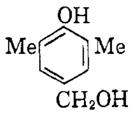
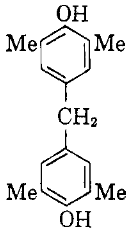
It was found that the base-catalyzed condensation of formaldehyde with 2,6-di-*tert*-butyl phenol gives products VI and V depending on the alcohol used as a solvent. Compound V, when treated with bromine (in various media), undergoes unusual transformations which are here elucidated. The oxidations by ferricyanide of XVI and V are described. The latter compound gives a free radical; one canonical form of this resonance hybrid is indicated by XV. An explanation is offered which accounts for the color of XIII in solution (*i.e.* formation of a stable anion XII).

In connection with an investigation of steric effects on the behavior of free radicals, some chemical transformations of highly hindered phenols have been investigated. The first paper on this subject deals with certain chemical reactions of 4,4′-dihydroxy-3,5,3′,5′-tetra(*tert*-butyl)diphenylmethane. The second paper deals with the oxidation products.

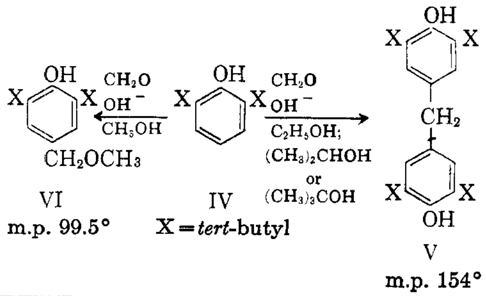
It was claimed by Bamberger[2a] that, in the presence of alkali, I reacts with formaldehyde at room temperature to give II. About 30 years later this observation was disputed by Granger.[2b] The latter investigator claimed that, under a variety of experimental conditions, I condenses with formaldehyde to give exclusively III. The authors, however, found no difficulties in preparing II by the Bamberger procedure, nor in preparing III by the procedure used by Auwers.[2c]


I

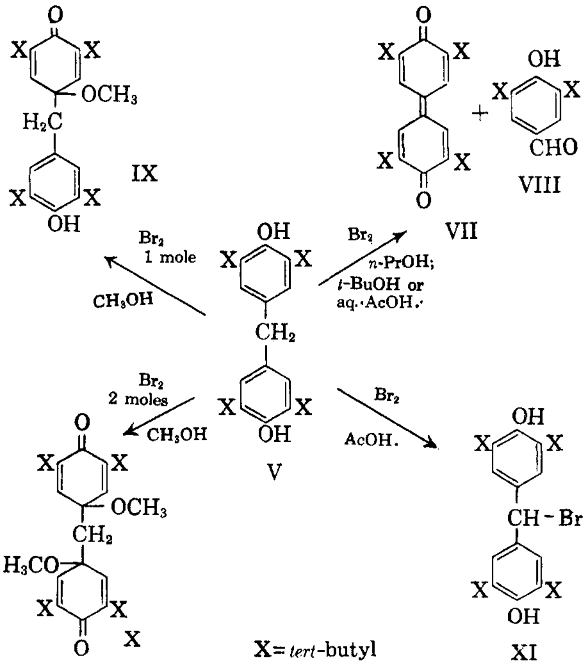

II


III

The base-catalyzed condensation of formaldehyde with IV is here carefully examined and is shown to give two different products depending upon the alcohol used as a solvent.



On the basis of analyses, as well as determination of the molecular weight and the ultraviolet[3] (λ_{max} 276, 282 mμ; ϵ_{max} 4100 and 4050, respectively) and infrared spectra[4] (hindered OH group, 3640 cm.$^{-1}$), structure V was assigned to the compound melting at 154°. The formation of VI in methanol and not in other alcohols (ethanol, 2-propanol, *t*-butyl alcohol) may be attributed to the higher acidity of methanol.[5] In the literature there is no detailed description of the preparation of V, although this substance was used by Coppinger,[6] in the preparation of XV. It should be emphasized that oxygen must be rigidly excluded in all the base-catalyzed reactions of IV, otherwise there is a rapid condensation of IV to 3,5,3′,5′-tetra-*tert*-butyldiphenoquinone VII. This subject will be discussed in greater detail in the next paper.



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[*] This paper is a contribution in honor of Lyndon F. Small, former Editor of the Journal.

[1] The authors are deeply indebted to Dr. N. C. Yang for many helpful discussions of the spectroscopic data here recorded.

[2] (*a*) E. Bamberger, *Ber.*, **36**, 2036 (1903); (*b*) F. S. Granger, *Ind. Eng. Chem.*, **24**, 442 (1932); (c) K. Auwers, *Ber.*, 40, 2524(1907).

[3] H. Hart and E. A. Haglund, *J. Org. Chem.*, **15**, 396 (1950); N. D. Coggeshall and A. S. Glessner, *J. Am. Chem. Soc.*, **71**, 3150 (1949).

[4] W. C. Sears and L. J. Kitchen. *J. Am. Chem. Soc.*, **71**, 4110 (1949); N. D. Coggeshall, *J. Am. Chem. Soc.* **69**, 1620 (1947).

[5] J. Hine and M. Hine, *J. Am. Chem. Soc.*, **74**, 5266 (1952).

[6] G. M.Coppinger, *J. Am. Chem. Soc.*, **79**, 501 (1957).

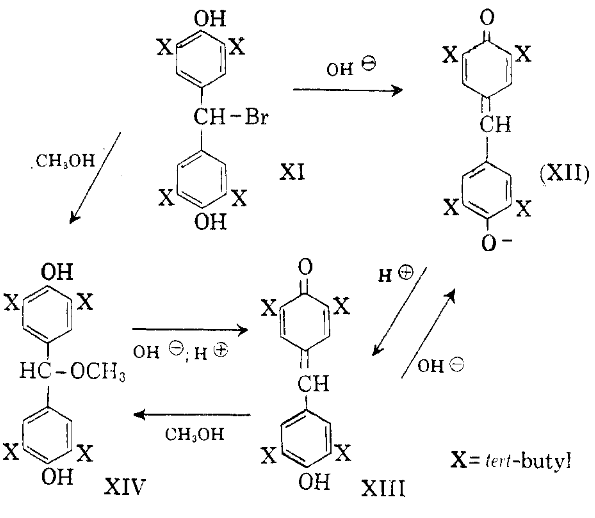
Compound V undergoes many interesting reactions. Bromination in dilute acetic acid, isopropyl alcohol or *tert*-butyl alcohol gives VII (3,5,3′,5′-tetra-*tert*-butyldiphenoquinone) and VIII (4-hydroxy-3,5-di-*tert*-butylbenzaldehyde). Both these compounds were identified by comparison with authentic samples.[7,8] But when the bromination of V was carried out in absolute methanol, other products were obtained. When one mole of bromine was used compound IX was the predominant product, whereas when two moles of bromine were used and the reaction mixture was allowed to stand for about 1.5 hr., compound X was formed.

Structure IX is assigned to the compound on the basis of (*a*) analyses and (*b*) determinations of the ultraviolet and infrared spectra. The ultraviolet spectrum shows absorption due to the dienone[8] ($\lambda_{max}^{iso\text{-}octane}$ 229 mμ; ϵ_{max}16,000) and the phenolic functions ($\lambda_{max}^{iso\text{-}octane}$ 271 mμ; ϵ_{max} 2700). The infrared spectrum (OH stretching frequency at 3640 cm.$^{-1}$; a twin band at 1665 and 1646 cm.$^{-1}$ due to the dienone structure, and a single band at 1070 cm.$^{-1}$ due to the ether linkage) supports the above conclusion.[9]

The structure of compound X is based on considerations similar to those cited above ($\lambda_{max}^{iso\text{-}octane}$ 239 mμ; ϵ_{max} 22,600. No OH bands occur in the infrared spectrum; there is a twin band at 1665 and 1645 cm.$^{-1}$, characteristic of the dienone grouping, and a single ether band at 1070 cm.$^{-1}$). Both compounds IX and X are quite stable in ethanolic alkali even in the presence of oxygen.

An entirely different reaction takes place when V is treated with bromine in glacial acetic acid. Here a good yield of the monobromo compound XI is obtained. The structure XI is assigned to this compound on the basis of (*a*) analyses, (*b*) determination of the infrared spectrum (OH stretching at 3620 cm.$^{-1}$ and no carbonyl bands), and (*c*) determination of the ultraviolet spectrum in iso-octane (λ_{max} 257 mμ; ϵ_{max} 11,000).

Compound XI is quite stable when dry. In hydroxylic solvents it reacts immediately with aqueous silver nitrate to give silver bromide. Solutions of XI in organic solvents give an intense purple upon addition of alkali, due to the formation of the anion XII. Dehydrobromination of XI in ethanolic alkali and subsequent neutralization give XIII. The structure of XIII was deduced from: (*a*) analyses and (*b*) determination of the infrared spectrum [OH stretching at 3620 cm.$^{-1}$, and four intense absorption bands in the carbonyl region (1500–1610 cm.$^{-1}$)].



Compound XIII, dissolved in ethanol, has a weak absorption band at 575 mμ, indicating that there is little ionization (Fig. 1). Upon addition of alkali an intensely purple solution is obtained. At the same time there is a tremendous increase in the intensity of the absorption (λ_{max} 575 mμ; ϵ_{max} 220,000), and the compound is transformed into the anion XII. The very deep color of this anion is probably associated with resonance stabilization.

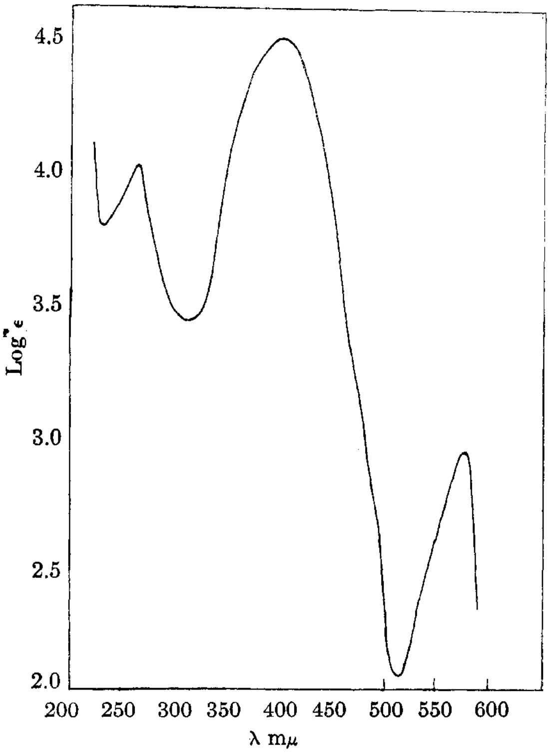


Fig. 1. (XIII) Solvent—Absolute Ethanol

Compound XIII, dissolved in methanol, is transformed by acid into XIV,[6] the product formed by heating XI in methanol. The structure assigned

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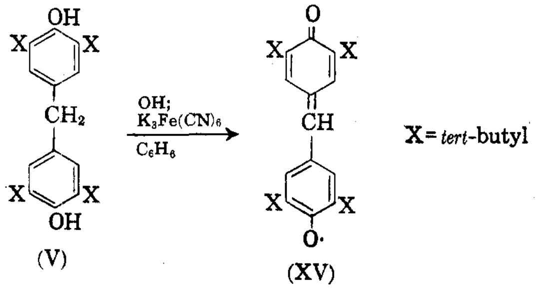
[7] H. Hart and F. A. Cassis, *J. Am. Chem. Soc.*, **73**, 3179 (1951); G. R. Yohe *et. al.*, *J. Org. Chem.*, 21, 1289 (1956).

[8] G. M. Coppinger and Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953).

[9] Note that the compound IX shows a hypsochromic shift when compared with other dienone structures which absorb around 234–240 mμ; the chemical and infrared evidence, however, leaves no doubt about the structure of this compound.

to XIV was substantiated by: (*a*) analyses; (*b*) determination of the infrared (OH stretching at 3640 cm.$^{-1}$ and ether linkage at 1075 cm.$^{-1}$); and (*c*) determination of the ultraviolet spectrum (phenolic absorption bands at λ_{max} 273 and 281 mμ; ϵ_{max} 3400 and 3300, respectively). Compound XIV when treated with alkali reacts as does XI; it gives first XII, which, when acidified, gives XIII.

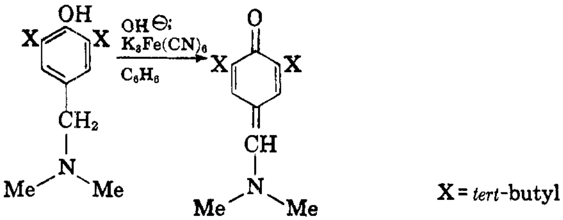
Many papers dealing with one-electron oxidations of hindered phenols have recently appeared.[6,10] Coppinger,[6] in an excellent communication, reports that an ethereal solution of V is readily oxidized by lead dioxide to the free radical XV. This free radical was here obtained by the ferricyanide oxidation of V dissolved in benzene. It crystallizes from ethanol in deep blue needles. Its visible spectrum (iso-octane solution) shows an intense absorption band at λ_{max} 423 mμ; ϵ_{max} 180,000; its infrared spectrum shows a strong band which has been attributed to the oxygen radical[11] in the carbonyl region at 1570 cm.$^{-1}$ Electron magnetic resonance studies of the free radical XV gave "g" = 2.006 ± 0.0005, indicating an unpaired electron.[12]



(V) (XV)

It is of interest that a benzene solution of XV is quite stable toward oxygen, whereas other free radicals formed from hindered phenols react with oxygen.[10] Solutions of XV in hydroxylic solvents tend to decompose when allowed to stand in air in the presence of alkali. The products formed when XV decomposes will be discussed in the next paper.

Compound IV undergoes the Mannich reaction and with dimethylamine gives 2,6-di-*tert*-butyl-4-(*N*,*N*-dimethylaminomethyl)phenol XVI. Oxidation of XVI with potassium ferricyanide gives the methylenequinone XVII, the absorption at λ_{max} 372 mμ; ϵ_{max}31,000 may be attributed to the conjugated system containing the dimethylamino and the carbonyl groups.[13] The infrared spectrum (KBr disk) shows a medium band at 1665 cm.$^{-1}$ (C=O), and two strong bands at 1605 and 1535 cm.$^{-1}$ The methylenequinone hydrolyzes very readily to give 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde VIII.



XVI XVII

EXPERIMENTAL

4-Hydroxy-3,5-di-tert-butylbenzyl methyl ether (VI). 2,6-Di-*tert*-butylphenol (5.2 g.), 36% formaldehyde (5 ml.) and absolute methanol (50 ml.) were dissolved in a three-necked flask and a solution of potassium hydroxide (2 g. in 2 ml. water) was added under an atmosphere of nitrogen. The solution was refluxed for 30 min. under a current of nitrogen. After cooling, the pale yellow crystalline product was collected (5.5 g., 82%) on a filter, and crystallized several times from methanol. Colorless plates were thus obtained which melted at 99.5°.

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.8; H, 10.4. Found: C, 76.9; H, 10.4.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyldiphenylmethane (V). 2,6-Di-*tert*-butylphenol (20.6 g.) and 36% formaldehyde (15 ml.) were dissolved in absolute ethanol (50 ml.) and nitrogen gas (Linde) was bubbled in throughout the reaction. A solution of sodium hydroxide (8 g. in 15 ml. water) was gradually added and the solution gently heated for 10–15 min. A vigorous reaction took place and a crystalline mass (20 g., 90%) separated from the mixture. Crystallization of this material from ethanol (100 ml.) gave shining colorless plates which melted at 154°.

Anal. Calcd. for $C_{29}H_{44}O_2$: C, 82.0; H, 10.4; mol. wt. 426. Found: C, 81.9; H, 10.3; mol. wt. 416.

2,6,3',5'-Tetra-tert-butyl-4'-hydroxyphenyl-4,1'-methylene-4-methoxy-2,5-cyclohexadiene-1-one (IX). Compound V (1.06 g.) was dissolved in methanol (20 ml.) and bromine (0.16 ml.) in methanol (6 ml.) was added. The solution was flushed with nitrogen and left at room temperature for 20 min. The crystalline material which separated was collected on a filter. The material (0.8 g.) when crystallized from methanol gave colorless plates of IX which melted at 122–123°.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.3; H, 10.2. Found: C, 79.4; H, 10.4.

2,6,3',5'-Tetra-tert-butyl-4,1'-dimethoxy-4,1'-methylene-2,5,-2',5'-bis cyclohexadiene-1,4'-one (X). Compound V (1.06 g.) was dissolved in absolute methanol (20 ml.) and bromine (0.32 ml. in 5 ml. methanol) was added. The flask was flushed with nitrogen, then stoppered and left at room temperature for 1.5 hr. On scratching the sides of the flask, a crystalline precipitate (0.8 g.) separated. On crystallization from methanol (three times) colorless plates were obtained which melted at 126–127°.

Anal. Calcd. for $C_{31}H_{48}O_4$: C, 76.9; H, 9.9. Found: C, 77.4; H, 10.0.

Oxidation of 4,4'-dihydroxy-3,5,3'5',-tetra-tert-butyl diphenylmethane with bromine. Bromine (0.2 ml.) was added to a solution of the diphenylmethane V (1 g.) in *n*-propyl alcohol (20 ml.). The mixture was allowed to stand at room temperature (22°) for 20 min. The crystalline precipitate which separated was collected on a filter. The material upon crystallization from ethanol melted at 245–246°. The ultraviolet, visible, and infrared spectra of the compound were shown to be identical with an authentic sample of 3,5,3',5' tetra-*tert*-butyldiphenoquinone.

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(10) C. D. Cook and coworkers, *J. Am. Chem. Soc.*, **78**, 3797 (1956) and earlier papers; E. Müller and coworkers, *Ber.*, **89**, 1738 (1956) and earlier papers.

(11) E. Müller and K. Ley, *Ber.*, **87**, 922 (1954); **88**, 601 (1955).

(12) We are grateful to Professor C. A. Hutchison, Jr. for these measurements.

(13) A. Burawoy, *J. Chem. Soc.*, 1177 (1939).

The filtrate after removal of the quinone gave, on concentration, shining white flakes (0.2 g.) melting at 185° and identical in all respects with 4-hydroxy-3,5-di-*tert*-butylbenzaldehyde.

Similarly, when the bromination was carried out in *tert*-butyl alcohol, or in aqueous acetic acid, the diphenoquinone and the aldehyde were found to be the reaction products.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyldiphenylbromomethane (XI). To a solution of the diphenylmethane V (1.06 g., 0.0025 mole) in glacial acetic acid (25 ml.), bromine (0.2 ml., 0.0036 mole) in glacial acetic acid (2 ml.) was gradually added. The solution was left at room temperature for about 2 hr. The colorless silky needles which separated were collected on a filter stick (nitrogen atmosphere is absolutely necessary) and quickly transferred to a desiccator and dried at reduced pressure. The yield of the bromo compound XI was (1 g., 80%). In the presence of a solvent, the bromo compound readily changes to a yellow product. A small sample of the material when crystallized from acetic acid, and dried at 60°/0.1 mm. melted at 159–160°.

Anal. Calcd. for $C_{29}H_{43}O_2Br$: C, 69.3; H, 8.5; Br, 15.9; Found: C, 69.2; H, 8.1; Br, 15.6.

2,6,3',5'-Tetra-tert-butyl-4'-hydroxyphenyl-4-methylene-2,5-cyclohexadiene-1-one (XIII). To a solution of the bromo compound XI (60 mg.) in ethanol (5 ml.), 5% sodium hydroxide (0.2 ml.) was added. A slow current of nitrogen was passed through the solution. The solution immediately changed to a deep purple. After 20 min. the reaction mixture was poured into crushed ice, neutralized with acetic acid, and extracted with ether. From the ether extract was obtained 45 mg. of a yellow solid which melted at 150–152°. The material was readily soluble in ether, petroleum ether, and benzene. Two crystallizations of the material from aqueous ethanol gave bright yellow needles which melted at 158–159°.

Anal. Calcd. for $C_{29}H_{42}O_2$: C, 82.5; H, 9.9. Found: C, 82.4; H, 9.9.

4,4'-Dihydroxy-3,5,3',5'-tetra-tert-butyldiphenylmethoxymethane (XIV). (*a*) *From the bromo compound* (*XI*). The compound XI (0.2 g.) was refluxed with absolute methanol (10 ml.) for about 10 min. and anhydrous sodium acetate (50 mg.) was added to the solution. It was heated about 5 min. longer and the mixture was filtered when hot. Upon cooling the filtrate a product separated. Upon two crystallizations from methanol, colorless plates of XIV were obtained which melted at 160–161°.

Anal. Calcd. for $C_{30}H_{46}O_3$: C, 79.3; H, 10.1. Found: C, 79.3; H, 10.1.

(*b*) *From the methylenequinone* (XIII): The methylenequinone XIII (50 mg.) was added to methanol (2 ml.) containing a trace of hydrochloric acid, and the whole was heated for about 10 min. and filtered when hot. From the filtrate colorless plates identical with XIV were obtained which melted at 160°. This product was identical with XIV; prepared from the bromo compound (XI).

2,6,3',5'-Tetra-tert-butyl-4'-phenoxy-4-methylene-2,5-cyclohexadiene-1-one radical (XV). A solution of 3,5,3',5'-tetra-*tert*-butyl-4,4'-dihydroxydiphenylmethane V (1.41 g; 0.0033 mole) in benzene (15 ml.) was added within 30 min. to a well-stirred mixture of potassium ferricyanide (3.94 g; 0.012 mole), potassium hydroxide (0.6 g.), water (15 ml.), and benzene (80 ml.). All of the operations were performed in an atmosphere of nitrogen. The reddish yellow mixture was stirred for about one hr. The benzene layer was washed thoroughly with water, dried over sodium sulfate, and the benzene was removed at reduced pressure. The dark blue crystalline powder (1.3 g.) thus obtained melted at 150–151°. It is very soluble in petroleum ether, benzene, and cyclohexane. When crystallized rapidly from absolute ethanol deep blue needles are obtained which melt at 157.5°. The solutions of the free radical in methanol or ethanol decompose upon standing.

Anal. Calcd. for $C_{29}H_{41}O_2$: C, 82.6; H, 9.7. Found: C, 82.6; H, 9.8.

The absorption spectrum (iso-octane) showed λ_{max} 280, 289, 400, and 423 mμ; $\epsilon_{max} \times 10^{-3}$ 9.39, 9.4, 24.3 and 180.0 respectively.

2,6-Di-tert-butyl-4-(N,N-dimethylaminomethyl)phenol (XVI). A mixture of 2,6-di-*tert*-butylphenol (4.1 g.) in ethanol (50 ml.), formaldehyde (36%; 2 ml.), and dimethylamine (25%; 5 ml.) was stirred for 1 hr. The whole was then refluxed for 1 hr. on the water bath, and evaporated to dryness at reduced pressure. The crude product (4.2 g.) was crystallized twice from ethanol. Large colorless plates were thus obtained which melted at 91.5°. The compound has a very pleasant odor.

Anal. Calcd. for $C_{17}H_{29}ON$: C, 77.5; H, 11.1. Found: C, 77.7; H, 10.9.

2,6-Ditert-butyl-4(N,N-dimethylaminomethylene)-2,5-cyclohexadiene-1-one (XVII). A mixture consisting of potassium ferricyanide (6 g.), potassium hydroxide (1 g.), water (25 ml.), and benzene (50 ml.), was stirred in an oxygen-free atmosphere and a solution of compound XVI (1.3 g.) dissolved in benzene (50 ml.) was added during the course of 30 min. The solution was stirred for 1 hr longer and the red-colored benzene layer separated and washed with water. The benzene solution was dried with sodium sulfate and the benzene removed at reduced pressure. The solid thus obtained appeared to be a mixture of two colored products, yellow and red, in which the yellow product predominated. It was washed with hot ligroin (30–60°). The greenish yellow residue (1 g.) which remained was crystallized twice from *n*-hexane. Bright yellow needles which melted at 158–159° were thus obtained.

Anal. Calcd. for $C_{17}H_{27}ON$: C, 78.1; H, 10.4. Found: C, 78.5; H, 10.5.

The absorption spectrum showed $\lambda_{max}^{iso\text{-}octane}$ 268, 372 mμ ϵ_{max} 6300 and 31,000 respectively and an inflexion at 225 mμ having ϵ, 4200.

The petroleum ether washings gave on concentration, red-brown crystals (0.15 g.) m.p. 242–243°. This material was shown to be 3,5,3',5'-tetra-*tert*-butyldiphenoquinone.

The compound XVII (100 mg.) was dissolved in ethanol (20 ml.) and a solution of 2,4-dinitrophenylhydrazine added to it. The yellow-orange precipitate was collected on a filter and crystallized from ethanol. Shining orange-red plates which melted at 236–238° were thus obtained. The material did not depress the melting point of the 2,4-dinitrophenylhydrazone prepared from an authentic sample of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde.

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