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Electronic Control of Steric Hindrance in Hindered Phenols[1]

LOUIS A. COHEN

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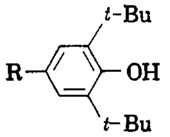
2,6-Di-*tert*-butylphenols with electronegative substituents in the *para* position have been prepared and found to be readily soluble in aqueous alkali. The phenomenon has been explained in terms of facilitation of charge dispersion. The preparation of the corresponding highly hindered anisoles is described.

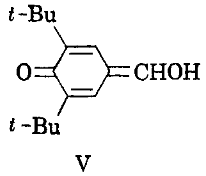
The chemistry of the highly hindered 2,6-di-*tert*-butylphenols has been the subject of a number of investigations in recent years.[2] The noteworthy properties of these compounds include (*a*) the stability of the phenoxy radicals,[2c,e,g] (*b*) the ease of formation and the stability of the corresponding cyclohexadienones,[2b,d,f,h] and (*c*) the failure to exhibit normal phenolic properties.[2a,h]

During the course of synthetic work on some amino acid analogs, 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (I) was prepared[2b] and was found to be readily soluble in dilute, aqueous alkali.[3] The observation of this one exception to the general behavior of 2,6-di-*tert*-butylphenols prompted an investigation of the phenomenon, a portion of that investigation being the subject of the present report.



I, R = CHO
II, R = CH_3
III, R = CN
IV, R = $CO_2C_2H_5$

Two explanations for the behavior of the aldehyde were considered: (1) Solubility in alkali was due to the enolic form V, the result of a facile tautomerism or (2) the inductive and/or resonant properties of the carboxaldehyde function greatly increased the acidity of the phenol. That tautomerism does not offer a rigorous explanation was demonstrable by the following observations: (1) III and IV were also soluble in dilute alkali and could be recovered upon acidification of the alkaline solutions. (2) A comparison of the infrared absorption bands of the phenols and of their sodium salts (Table I) suggests that a somewhat greater fraction of the negative charge may reside on the *para* substituent in the hindered than in the unhindered phenols.[3a] The same conclusion may be drawn from a comparison of the ultraviolet spectra in neutral and alkaline media (Table II), particularly for compounds I and IV. By treatment of the sodium salts of II, III and IV with methyl iodide, the corresponding anisoles, VIII, IX, and X were obtained. Attempts to make VII by the same procedure led only to the isolation of the diphenoquinone VI.

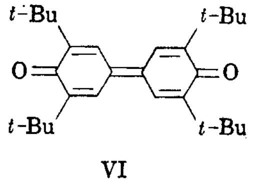


V

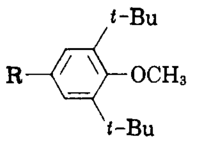
TABLE I

EFFECT OF ALKALI ON INFRARED SPECTRA

	Phenol	Sodium Phenoxide	Di-*tert*-butyl Phenol	Sodium di-*tert*-butyl Phenoxide
p-Formyl	5.92 μ	6.10 μ	5.93 μ	6.16 μ
p-Carbethoxy	5.85	5.95	5.86	6.05
p-Cyano	4.50	4.50	4.51	4.57



VI



VII, R = CHO
VIII, R = CH_3
IX, R = CN
X, R = $CO_2C_2H_5$

I, III, and IV, as well as II, failed to react with diazomethane or with sodium in boiling ligroin, confirming the assumption that the stereochemistry at the phenol has not been modified by a *para* substituent.

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

[2] For example, *Cf.* (a) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945). (b) T. W. Campbell and G. M. Coppinger, *J. Am. Chem. Soc.*, **74**, 1469 (1952). (c) G. M. Coppinger and T. W. Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953). (d) C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953). (e) C. D. Cook, N. G. Nash, and H. R. Flanagan, *J. Am. Chem. Soc.*, **77**, 1783 (1955). (f) C. D. Cook and B. E. Norcross, *J. Am. Chem. Soc.*, **78**, 3797 (1956). (g) E. Müller, K. Ley, and W. Schmidhuber, *Chem. Ber.*, **89**, 1738 (1956) and earlier papers. (h) T. Fujisaki, *J. Chem. Soc., Japan*, **77**, 733 (1956) and earlier papers.

[3] The same observation has been reported recently from another laboratory: G. R. Yohe, J. E. Dunbar, R. L. Pedrotti, F. M. Scheidt, F. G. H. Lee, and E. C. Smith, *J. Org. Chem.*, **21**, 1289 (1956).

[3a] R. N. Jones and C. Sandorfy, *Chemical Applications of Spectroscopy*, W. West, editor, Interscience Press, Inc., New York, N. Y., 1956, p. 481.

TABLE II

EFFECT OF ALKALI ON ULTRAVIOLET SPECTRA

	Phenol			Di-*tert*-butylphenol		
	Neutral	Alkali[a]	Δλ	Neutral	Alkali[a]	Δλ
p-Formyl	284 mμ (4.2)[b]	330 mμ (3.9)	46	287 mμ (4.1)	370 mμ (4.5)	83
p-Carbethoxy	255 (4.3)	300 (4.4)	45	262 (4.2)	330 (4.5)	68
p-Cyano	247 (4.3)	280 (4.3)	33	252 (4.2)	287 (4.5)	35

[a] Sodium ethoxide solution was added to the ethanol solutions to make a final concentration of 0.01M. [b] Figures in parentheses are log ϵ_{max}.

The dissociation constants of I, III, and IV (Table III) show the same order of activation by the *para* substituent as do the nonalkylated phenols. However, the acidity is substantially lower.

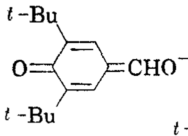
If we regard the ability of a phenolate anion to become solvated and to disperse its negative charge through the solvent sphere as a prerequisite to acidic behavior and alkali solubility, it is evident that II cannot meet these requirements. This phenomenon has been termed "steric hindrance to solvation." [4] However, if the negative charge has an opportunity to become dispersed *via* resonance between the phenolate anion and a strong *para* electron-sink, as in I, III, and IV and the corresponding structures Ia, IIIa, and IVa, the ease of anion formation should be greatly increased. Either a much smaller solvent sphere is necessary at the phenolic oxygen for charge dispersion or no solvent participation at all.

TABLE III

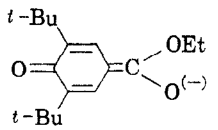
DISSOCIATION CONSTANTS OF PHENOLS

	Phenol pK_a	Di-*tert*-butyl Phenol[a] pK_a
p-Formyl	8.81[b]	11.3
p-Cyano	9.10[b]	11.4
p-Carbethoxy	9.61[b]	11.8
p-Bromo	10.50	[c]

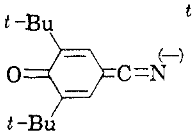
[a] Dissociation constants were measured in 50% ethanol by the procedure of T. V. Parke and W. W. Davis, *Anal. Chem.*, 26, 642 (1954). [b] These values were obtained by adding 1.15 units (to correct for the solvent difference) to the values measured in water as recorded in E. A. Braude and E. C. Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press Inc., New York, 1955, p. 589. [c] The acidity was too weak to measure in this system.



Ia



IVa



IIIa

On the basis of models, the impairment of resonance should be greater in the methyl ethers than in the phenols.[4a] No significant differences were found in the ultraviolet absorption spectra of the anisoles and of corresponding unhindered compounds (Table IV). However, the 6.25-μ aromatic band in the infrared was markedly reduced in intensity by the bulky *ortho* substituents.

TABLE IV

ULTRAVIOLET SPECTRA OF ANISOLES

	Anisole	Di-*tert*-butyl anisole
p-Methyl	275 mμ (3.2)	275 (3.0)
p-Formyl	277 (4.2)	
p-Carbethoxy	254 (4.3)	250 (4.0)
p-Cyano	255 (4.3)	243 (4.2)

EXPERIMENTAL[5]

3,5-Di-tert-butyl-4-hydroxybenzaldehyde (I). For large-scale preparation, the use of aqueous acetic acid as solvent was found preferable to tertiary butyl alcohol. The method of Coppinger and Campbell[2(c)] was adapted to a larger scale.

A solution of 80 g. (0.36 mole) of 2,6-di-*tert*-butyl-4-methylphenol (II) (commercial grade) in 800 ml. of glacial acetic acid was diluted with 200 ml. of water. Two equivalents of bromine (37 ml.) was added dropwise with mechanical stirring over a period of 2 hr. Toward the end of the addition the product began to separate. Stirring was continued for 1 hr. and the suspension diluted with 500 ml. of ice water. After the mixture had been chilled for several hours at 0°, it was filtered, and the pale yellow product was washed with 50% acetic acid and with water and dried *in vacuo*. In several preparations, yields of 77–85% were obtained, the aldehyde melting at 178–181° (lit.[2(c)] 189–190°). For purification, the compound was recrystallized from ligroin; however, the crude product was satisfactory for further work in most instances.

3,5-Di-tert-butyl-4-hydroxybenzaldoxime. The oxime was prepared from crude aldehyde by the usual procedure, using a 0.1 mole scale. A colorless oil was obtained which was dis-

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(4) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954). N. D. Coggeshall and A. S. Glessner, Jr., *J. Am. Chem. Soc.*, **72**, 2275 (1950). E. E. Betts and L. R. C. Barclay, *Can. J. Chem.*, **33**, 1768 (1955). The low acidity observed by Betts and Barclay for 2,4,6-tri-*tert*-butylbenzoic acid may be due to steric hindrance to solvation of the carboxylate anion.

(4a) P. Rumpf and H. Lumbroso, *Bull. soc. chim. France*, 283 (1950); K. B. Everard and L. F. Sutton, *J. Chem. Soc.*, 2312 (1949); M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1956, p. 511.

(5) All melting points were taken on a Kofler block and are corrected. Infrared spectra were measured in chloroform solution; spectra of sodium phenolates were run on Nujol mulls. Ultraviolet spectra were run in absolute ethanol. Unless otherwise specified, petroleum ether refers to the 30–40° fraction.

solved in 100 ml. of ligroin (90–100°) and concentrated. The residual syrup deposited 16 g. of thin plates from petroleum ether, m.p. 120–125°. Evaporation of the mother liquor yielded an additional 6 g. The oxime appeared to be solvated whether recrystallized from petroleum ether or dilute alcohol. The combined fractions separated as thin plates from dilute alcohol. After the total product had been dried at 100°/1 mm. for 12 hr. it weighed 20 g. (80%), m.p. 138–139°.

Anal. Calcd. for $C_{15}H_{23}O_2N$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.39; H, 9.50; N, 5.51.

3,5-Di-tert-butyl-4-hydroxybenzonitrile (III). A solution of 24.9 g. (0.1 mole) of the oxime in 50 ml. of acetic anhydride was heated on a steam bath for 2 hr. The solution was poured into one l. of normal sodium bicarbonate and stirred until hydrolysis of the acetic anhydride was complete. The solid residue was extracted with 2 × 150 ml. of methylene chloride, and the extract was washed with sodium bicarbonate, dried, and concentrated to a yellow solid. The material was best purified by extracting an ether solution with cold normal sodium hydroxide and precipitating with 3*N* hydrochloric acid. The product separated as colorless granules which were dried and recrystallized from petroleum ether as needles, m.p. 147°; 18 g. (78%).

Nitrile absorption in the infrared occurred at 4.51 μ. In the ultraviolet, the nitrile absorbed at 252 mμ (log ϵ_{max} 4.18). When sodium ethoxide solution was added to make the final concentration 0.01 molar in base, the spectrum shifted to 232 mμ (log ϵ_{max} 3.82) and 287 mμ (log ϵ_{max} 4.46).

Anal. Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.95; H, 9.05; N, 6.27.

Ethyl 3,5-di-tert-butyl-4-hydroxybenzoate (IV). A solution of 23.1 g. (0.1 mole) of the nitrile (III) in 200 ml. of ethanol was saturated with hydrogen chloride at 0° and stored at 25° for 2 days. The red-violet solution was concentrated to a crystalline residue of the iminoether hydrochloride (m.p. 260°). The material was extracted with 3 × 100 ml. of ether and the almost colorless residue was dissolved in 100 ml. of 50% ethanol. After addition of 100 ml. of normal sodium bicarbonate, the mixture was heated on steam for 1 hr. and concentrated to a small volume. The oily ester was extracted with 2 × 150 ml. of methylene chloride and the extract was dried and concentrated to a colorless sirup. The product separated from petroleum ether as granules, m.p. 107–108°, 21 g. (75%). It was recrystallized from dilute alcohol as plates, m.p. 108–109°.

Ester absorption in the infrared occurred at 5.86 μ. In the ultraviolet, IV absorbed at 262 mμ (log ϵ_{max} 4.15); in 0.01*M* sodium ethoxide, the spectrum shifted to 240 mμ (log ϵ_{max} 3.96) and 330 mμ (log ϵ_{max} 4.47).

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.21; H, 9.19.

A sample of the ester was saponified by heating with 0.1*N* sodium hydroxide to form 3,5-di-*tert*-butyl-4-hydroxybenzoic acid, m.p. 216–217° (lit.[8] 217–218°).

Alkali solubility test. One-tenth gram samples of I, III, and IV were dissolved in several drops of ethanol and diluted with 20 ml. of normal sodium hydroxide. Solution was complete in each case. After acidification, the phenols could be recovered.

2,6-Di-tert-butyl-4-bromophenol, was prepared by the bromination of commercial 2,6-di-*tert*-butylphenol in carbon tetrachloride solution. Contrary to the experience of Hart and Cassis,[6] bromination proceeded rapidly to give an excellent yield of the bromophenol.

2,6-Di-tert-butyl-4-methylanisole (VIII). *Method A.* The sodium salt of II was prepared in liquid ammonia according to the published procedure[2(a)] using 2.2 g. (0.01 mole) of the cresol. Without isolating the salt, the ammonia was evaporated and replaced with 50 ml. of toluene. After concentration to dryness to remove residual ammonia, 50 ml. of toluene was added and the suspension transferred to a pressure bottle. Ten ml. of methyl iodide was added, the air was replaced by nitrogen, the bottle was sealed and the mixture was heated by steam for 18 hr. It was then cooled and concentrated. The residue was extracted with 2 × 50 ml. of petroleum ether and the extract was concentrated to a pale green oil weighing 1.7 g. Purification could not be achieved by fractional distillation, VIII and II distilling at about the same temperature. The oil was transferred to a column of 25 g. of basic alumina and eluted with petroleum ether. Progress of the elution could be followed by using the phosphomolybdic acid test for phenols on the dried fractions.[2(a)] The methyl ether was the first material to separate from the column, 1.4 g. (60%) of colorless oil being obtained.

The infrared spectrum showed only a weak aromatic band at 6.25 μ. In the ultraviolet, VIII absorbed at 275 mμ.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.97; H, 11.33.

Method B: To a solution of 2.2 g. (0.01 mole) of II in 25 ml. of methanol was added 10 ml. of molar sodium methoxide and the mixture was concentrated to dryness under reduced pressure. Fifty ml. of toluene was added, the mixture concentrated to dryness and the process repeated. The residual material, which had begun to darken, was transferred to a pressure bottle as described above. From this point, Method A was followed and a 10% yield of the anisole was obtained after chromatography.

Attempted preparation of 3,5-di-tert-butyl-4-methoxybenzaldehyde (VII). When Method A was used to prepare the sodium salt of I (purified), the products obtained from the alkylation were 3,5-di-*tert*-butyl-4-hydroxybenzyl alcohol (m.p. 137–138°)[2(c)] and the corresponding methyl benzyl ether (m.p. 102–103°).[2(h)] Apparently, sodium in liquid ammonia preferentially reduced the aldehyde and formed the sodium salt of the newly-formed primary hydroxyl.

Using Method B, a dark red oil was obtained. The only nonphenolic material which could be isolated by chromatography was VI, m.p. 245–246°.[2(h)] Presumably, the diphenoquinone was formed *via* a free-radical dimerization.

3,5-Di-tert-butyl-4-methoxybenzonitrile (IX). The methyl ether was prepared from III using method B. After chromatographic purification, a 65% yield of colorless plates was obtained, m.p. 73–75°. The melting point was unchanged by recrystallization from cold petroleum ether. The infrared spectrum showed a nitrile band at 4.51 μ and a weak aromatic band at 6.29 μ. In the ultraviolet, the compound absorbed at 243 mμ (log ϵ_{max} 4.18).

Anal. Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.35; H, 9.64; N, 5.75.

Ethyl 3,5-di-tert-butyl-4-methoxybenzoate (X). The methyl ether was prepared from IV by method B. A 58% yield of colorless oil was obtained after chromatography. The infrared spectrum showed an ester band at 5.83 μ and a weak aromatic band at 6.25 μ. Absorption in the ultraviolet occurred at 250 mμ (log ϵ_{max} 3.98).

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.82; H, 9.89.

Sodium salts of I, III, and IV and of the corresponding nonalkylated phenols were obtained by Method B but were dried *in vacuo* after two concentrations with toluene.[7] The residues were triturated several times with ether, the solvent was decanted, and the sodium salts again dried *in vacuo.* The compounds were stored under nitrogen at 0°.

Acknowledgment. The author thanks Dr. William C. Alford and his associates, all of this institute, for carrying out the microanalyses, and Wm. M. Jones for measuring the infrared and ultraviolet spectra.

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[6] H. Hart and F. A. Cassis, Jr., *J. Am. Chem. Soc.,* **73,** 3179 (1951).

[7] Rigorous drying was necessary to free the phenolates completely from solvent.