525. *Oxidation of Alkoxyphenols. Part IV.*[1] *4-Methoxy-2,5-di-t-butylphenol*

By F. R. Hewgill and B. R. Kennedy

Further evidence for the structure of the trimer (IIa) is provided by hydrolysis with toluene-*p*-sulphonic acid, nuclear magnetic resonance spectrometry, and hydrogenolysis.

MÜLLER, Kaufmann, and Rieker[2] have recently described the oxidation of 4-methoxy-2,5-di-t-butylphenol (Ia) to a trimer to which they have assigned structure (IIa). We had also observed the formation of this trimer, and had carried out degradations of the molecule by methods differing from those used by Müller *et al.* As our results provide further evidence for structure (IIa) we report them here.

It was found by Müller *et al.* that ferricyanide oxidation of either phenol (Ia) alone in methanol, or (most significantly) of a mixture of phenol (Ia) and the phenoxy-phenol (IVa) in benzene led to the trimer (IIa). However, only 2,5-di-t-butyl-1,4-benzoquinone (III) resulted from ferricyanide oxidation of phenol (Ia) in benzene. In contrast, we have found that ferricyanide oxidation of phenol (Ia) in light petroleum gave the trimer quantitatively. Hydrogenolysis of the trimer in cyclohexane using palladium–charcoal catalyst gave the phenoxy-phenol (IVa) and phenol (Ia) in the molar ratio 1 : 1.

It has been shown by Matsuura and Cahnmann[3] that quinol ethers of type (V) are split by toluene-*p*-sulphonic acid to diphenyl ethers with loss of isobutene. When trimer (II) in ethyl acetate was treated with toluene-*p*-sulphonic acid the phenoxy-quinone (VIa), phenol (Ia), the phenoxy-phenol (IVa), and quinone (III) were obtained in the molar ratio 12 : 11 : 1 : 0·6. Bearing in mind the volatility of the quinone (III) it will be seen that the products fall into two pairs, each pair containing a quinone and a phenol. The fact that no debutylation occurred eliminates the possibility of the trimer possessing structure (IIc). On the basis of the products isolated, consideration of protonation and cleavage of structures (IIa) and (IIb) provides additional evidence in favour of the former.

Protonation at oxygen (i) in structure (IIa), as in (VII), followed by cleavage of bond "a" as in classical acetal hydrolysis[4] should lead to phenol (Ia) and the carbonium ion (VIII). Carbonium ions of this type have been suggested as intermediates in the oxidative dealkylation of *o*- and *p*-alkoxy-phenols,[5] and intermediate (VIII) would therefore lead to the phenoxy-quinone (VIa). The less likely fission of bond "b" should give the same final products. The minor pair of products can be accounted for by protonation of the carbonyl oxygen as in structure (IX), giving the phenoxy-phenol (IVa), and the quinone (III) *via* the corresponding carbonium ion. The duality of mechanism is analogous to

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[1] Part III. F. R. Hewgill and B. S. Middleton, preceding Paper.

[2] E. Müller, H. Kaufmann, and A. Rieker, *Annalen*, 1964, **671**, 61.

[3] T. Matsuura and H. J. Cahnmann, *J. Amer. Chem. Soc.*, 1960, **82**, 2055.

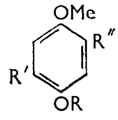
[4] J. M. O'Gorman and H. J. Lucas, *J. Amer. Chem. Soc.*, 1950, **72**, 5489.

[5] E. Adler, I. Falkenhag, and B. Smith, *Acta Chem. Scand.*, 1955, **9**, 319.

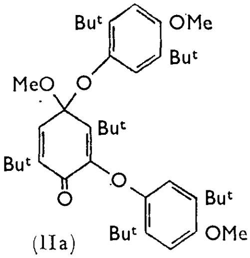
that observed in the hydrolysis of the spiro-acetal[6] from the oxidation of 4-methoxy-3-t-butylphenol. Cleavage of the trimer (IIb) would lead only to 4-methoxy-2,5-di-t-butylphenol (Ia) and 4-methoxy-3,6-di-t-butyl-1,2-benzoquinone.

The nuclear magnetic resonance spectrum of the trimer, measured in carbon tetrachloride, with tetramethylsilane as internal reference at 60 Mc./sec., indicated the presence of three non-equivalent methoxyl groups (τ 6·25, 6·28, 6·72), three equivalent t-butyl groups (τ, 8·58), three non-equivalent t-butyl groups (τ, 8·90, 8·92, 9·10), and five non-equivalent hydrogens (τ 3·18, 3·27, 3·38, 3·77, 4·05). Although the spectrum does not allow a definite assignment of structure at this stage, the resonance at τ 6·72 is consistent with a methoxyl group of an acetal[7] and hence structure (IIa) is indicated.

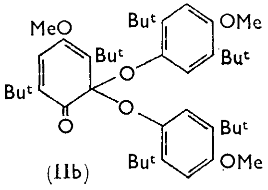
As Müller *et al.* have indicated that evidence for the structure of the phenoxy-phenol (IVa) is to be published, our work on this problem is only briefly reported. The diphenyl ether linkage of the phenoxy-phenol was not cleaved by nitric acid, the only products isolated being compound (VIa) and a compound considered to be 2-(4-methoxy-3-nitro-6-t-butylphenoxy)-3,5-di-t-butyl-1,4-benzoquinone (VIb). This structure is consistent with the nuclear magnetic resonance, infrared, and ultraviolet spectral data, and with the products obtained by the action of nitric acid on the model compounds phenol[2] (Ia) and 1,4-dimethoxy-2,5-di-t-butylbenzene (Ib). As compound (VIb) is inert to nitric acid and piperidine, the nitro-group is considered to be in the 3- and not in the 6-position.



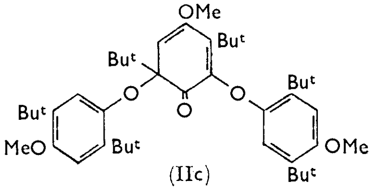
(Ia: $R = H, R' = R'' = Bu^t$)
(Ib: $R = Me, R' = R'' = Bu^t$)
(Ic: $R = Me, R' = Bu^t, R'' = Br$)
(Id: $R = Me, R' = R'' = Br$)



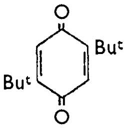
(IIa)



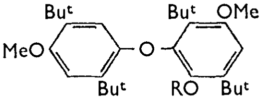
(IIb)



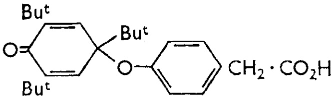
(IIc)



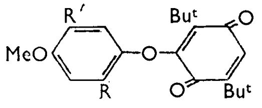
(III)



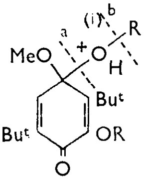
(IVa: $R = H$)
(IVb: $R = Me$)



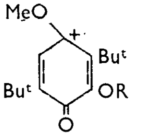
(V)



(VIa: $R = R' = Bu^t$)
(VIb: $R = Bu^t, R' = NO_2$)

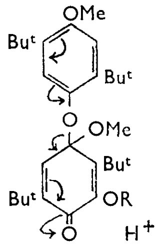


(VII)



(VIII)

[R = 4-methoxy-2,5-di-t-butylphenyl]



(IX)

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[6] F. R. Hewgill, *J.*, 1962, 4987.

[7] Varian Associates, "NMR Spectra Catalog," National Press, U.S.A., pp. 120, 218.

Methylation of compound (IVa) gave 1,4-dimethoxy-2-(4-methoxy-3,5-di-t-butylphenoxy)-3,5-di-t-butylbenzene (IVb). An attempt at synthesis of compound (IVb) by the method of Williamson was unsuccessful owing to inability to prepare the intermediate 2,5-dimethoxy-3,6-di-t-butylbromobenzene. Bromination of compound (Ia) in carbon tetrachloride or acetic acid gave 2,5-di-t-butyl-1,4-benzoquinone (III). 1,4-Dimethoxy-2,5-di-t-butylbenzene was inert to bromine in acetic acid. In the presence of iron powder, bromine in carbon tetrachloride displaced one or both t-butyl groups forming 2,5-dimethoxy-4-t-butylbromobenzene (Ic) and 1,4-dibromo-2,5-dimethoxybenzene (Id). An Ullmann coupling of the former gave 1,5,2′,5′-tetramethoxy-4,4′-di-t-butylbiphenyl. The observation that bromine in acetic acid will oxidatively demethylate the *p*-methoxyphenol (Ia), and yet not react with the *p*-dimethoxy-compound (Ib), suggested a method for interrelation of the phenoxy-phenol (IVa) and the phenoxy-quinone (IVb). When treated with bromine in acetic acid, compound (IVa) was oxidatively demethylated to compound (VIa).

EXPERIMENTAL

Infrared and ultraviolet spectra were determined on Perkin-Elmer 137G and 137UV spectrophotometers. Nuclear magnetic resonance spectra were obtained for carbon tetrachloride solutions, in a Varian A60 instrument operating at 60 Mc./sec. Tetramethylsilane was used as internal reference and peak positions are recorded on the τ scale. Melting points were determined on a Kofler hot-stage apparatus. Light petroleum had b. p. 55—60°.

4-*Methoxy*-4,6-*di*-(4-*methoxy*-2,5-*di*-*t*-*butylphenoxy*)-2,5-*di*-*t*-*butylcyclohexa*-2,5-*dienone* (IIa).—4-Methoxy-2-5-di-t-butylphenol (Ia) (5 g.) in light petroleum (150 ml.) was shaken with potassium ferricyanide (14 g.) and sodium hydroxide (5 g.) in water (400 ml.) for 20 min. After the light petroleum layer had been washed and dried (Na_2SO_4), evaporation, followed by crystallisation from light petroleum, gave the trimer (IIa), yellow prisms, m. p. 189—190° (lit.,[2] 182—183°) [Found: C, 76·4; H, 9·8; O, 13·7%; *M* (by f. p. depression in cyclohexane), 700. Calc. for $C_{45}H_{68}O_6$: C, 76·7; H, 9·7; O, 13·6%; *M*, 705]; $\nu_{max.}$ (in CS_2) 1665 and 1680 cm.$^{-1}$ (C=O of cyclohexadienone).

Hydrogenolysis of Trimer (IIa).—The trimer (IIa) (1·05 g.) was hydrogenolysed in cyclohexane over 10% palladium–charcoal at atmospheric pressure. Evaporation of the filtered solution gave a yellow oil which was chromatographed on alumina. Elution with light petroleum gave prisms (0·70 g.). Crystallisation from light petroleum gave 4-methoxy-2-(4-methoxy-2,5-di-t-butylphenoxy)-3,6-di-t-butylphenol (IVa), m. p. 196—197° (lit.,[2] 190—191°) (Found : C, 76·6; H, 9·7. Calc. for $C_{30}H_{46}O_4$: C, 76·6; H, 9·9%); $\nu_{max.}$ (in CS_2) 3560 cm.$^{-1}$ (bonded OH); τ 8·88, 8·20, 8·62, 8·45 (4 Bu^t) 6·23, 6·20 (2 OMe) 4·93 (hydroxyl) 3·68, 3·58, 3·20 (3 ArH). Elution with chloroform gave an oil (0·35 g.) which crystallised from light petroleum as prisms, m. p. 102—102·5° undepressed on admixture with 4-methoxy-2,5-di-t-butylphenol.

Acid Degradation of Trimer (IIa).—To the trimer (IIa) (1·04 g.) in ethyl acetate (60 ml.) was added 0·09M-toluene-*p*-sulphonic acid in ethyl acetate (1 ml.), and the solution set aside at room temperature for 20 hr. The solvent was evaporated at room temperature and the residue chromatographed on alumina. Elution with light petroleum gave the phenoxyphenol (IVa) (56 mg.). Elution with light petroleum–benzene (9 : 1) gave a dark red crystalline mass (645 mg.). Sublimation of the eluate at 100°/20 mm. afforded yellow needles (15 mg.) of 2,5-di-t-butyl-1,4-benzoquinone (III), m. p. and mixed m. p. 147—148°. Recrystallisation of the sublimation residue from aqueous ethanol gave 2-(4-methoxy-2,5-di-t-butylphenoxy)-3,6-di-t-butyl-1,4-benzoquinone (VIa), m. p. 187·5—188·5° (lit.,[2] 173—175°) (Found: C, 76·8; H, 9·3. Calc. for $C_{29}H_{42}O_4$: C, 76·6; H, 9·3%); $\nu_{max.}$ 1675, 1640 cm.$^{-1}$ (quinone); $\lambda_{max.}$ (in CCl_4) 266, 291 (infl.) mμ (log ε, 4·0, 3·5); τ 8·82, 8·80, 8·63, 8·57 (4 Bu^t) 6·17 (OMe) 3·77, 3·60, 3·20 (2 ArH and 1 vinylic H). Elution with methanol gave crystals (310 mg.). Recrystallisation from aqueous acetic acid gave the phenol (Ia), m. p. and mixed m. p. 102—102·5°.

4-*Methoxy*-6-(4-*methoxy*-2,5-*di*-*t*-*butylphenoxy*)-2,5-*di*-*t*-*butylphenyl Acetate*.—70% Perchloric acid (0·1 ml.) was added to the phenoxy-phenol (IVa) (424 mg.) and acetic anhydride (5 ml.). The mixture after 3 days at room temperature was poured on to iced water and the precipitate chromatographed on alumina. Elution with light petroleum–benzene (4 : 1) and crystallisation from light petroleum then ethanol gave 4-*methoxy*-6-(4-*methoxy*-2,5-*di-t-butylphenoxyl*)-2,5-*di-t-butylphenyl acetate* (110 mg.), prisms, m. p. 170—171·5° (Found: C, 74·9; H, 9·3. $C_{32}H_{48}O_5$ requires C, 75·0; H, 9·4%); $\nu_{max.}$ (in CS_2) 1770 cm.$^{-1}$ (acetate).

1,4-*Dimethoxy*-2-(4-*methoxy*-2,5-*di-t-butylphenoxy*)-3,6-*di-t-butylbenzene*. Dimethyl sulphate (5 ml.) was added to the phenoxy-phenol (IVa) (1·47 g.) and 50% aqueous potassium hydroxide (7 ml.) in dimethyl sulphoxide (70 ml.) and the solution heated on a steam-bath for 3 hr. After cooling and addition of water the mixture was extracted with ether. The extract was washed with dilute ammonia solution, water, and dried (Na_2SO_4), the solvent evaporated and the residue chromatographed on alumina. Elution with and crystallisation from light petroleum gave 1,4-*dimethoxy*-2-(4-*methoxy*-2,5-*di-t-butylphenoxy*)-3,6-*di-t-butylbenzene*, prisms, m. p. 156—158° (Found: C, 76·4; H, 9·8. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%).

Reactions with Nitric Acid.—(*a*) *Phenoxy-phenol* (IVa). 70% Nitric acid (0·5 ml.) was added to phenoxy-phenol (IVa) (367 mg.) in acetic acid (10 ml.). After 10 min. the solution was diluted with water (50 ml.) and the precipitate chromatographed on alumina. Elution with light petroleum–benzene (9 : 1) gave the phenoxy-quinone (VIa) (40 mg.), m. p. and mixed m. p. 187·5—188·5°. Elution with light petroleum–ether (1 : 1) and crystallisation from aqueous ethanol gave 2-(4-*methoxy*-3-*nitro*-6-*t-butylphenoxy*)-3,6-*di-t-butyl*-1,4-*benzoquinone* (VIb) (263 mg.) red-orange prisms, m. p. 183—183·5° (Found: C, 68·0; H, 7·6; N, 3·6. $C_{25}H_{33}NO_6$ requires C, 67·7; H, 7·5; N, 3·2%); $\lambda_{max.}$ (in ethanol) 229, 263 mμ (log ε, 4·26, 4·24); $\nu_{max.}$ (in CCl_4) 1665, 1650 cm.$^{-1}$ (quinone); τ 8·80, 8·63, 8·52 (3 Bu^t) 6·05 (OMe) 3·52, 3·09, 2·90 (2ArH, 1 vinylic H).

(*b*) 1,4-*Dimethoxy*-2,5-*di-t-butylbenzene* (Ib). Compound (Ib) (2 g.) was added slowly with stirring to 90% nitric acid (1 ml.) in acetic acid (3·7 ml.) and acetic anhydride (2 ml.) at 0°. Stirring was continued for 15 min., ice was added, the mixture extracted with ether, and the extract washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and evaporated. Crystallisation of the residue (1·3 g.) from aqueous ethanol gave 2,5-dimethoxy-4-t-butylnitrobenzene, m. p. 99—99·5° undepressed on admixture with a sample prepared by the method of Carpenter, Easter, and Wood.[8]

Brominations.—(*a*) *Phenol* (Ia). Bromine (1·73 g.) in acetic acid (12 ml.) was added to phenol (Ia) (2·5 g.) in acetic acid (40 ml.) over a period of 3 hr. The solution was poured into water and the precipitate crystallised from methanol giving 2,5-di-t-butyl-1,4-benzoquinone m. p. 147—148° (lit.,[9] 152°).

(*b*) *Phenoxy-phenol* (IVa). Similar treatment of phenoxy-phenol (IVa) (388 mg.) gave the phenoxy-quinone (VIa) (276 mg.), m. p. and mixed m. p. 187·5—188·5°.

(*c*) 1,4-*Dimethoxy*-2,5-*di-t-butylbenzene* (Ib). Bromine (9·3 g.) in carbon tetrachloride (55 ml.) was added to compound (Ib) (10 g.) in carbon tetrachloride (100 ml.) in the presence of iron powder (0·4 g.), the mixture heated under reflux for 2 hr., then poured into water. The carbon tetrachloride layer was separated, washed with water, dilute aqueous sodium metabisulphite, dried (Na_2SO_4), and evaporated. Chromatography on alumina, elution with and crystallisation from light petroleum gave 2,5-*dimethoxy*-4-*t-butylbromobenzene* (Ic) as prisms (4·09 g.), m. p. 57—58° (Found: C, 53·0; H, 6·3; Br, 29·9. $C_{12}H_{17}BrO_2$ requires C, 52·8; H, 6·3; Br, 29·9%); τ 8·67 (Bu^t) 6·20 (OMe) 3·05, 3·20 (2ArH). Elution with light petroleum–ether (9 : 1) gave 2,5-dibromo-1,4-dimethoxybenzene (Id), m. p. 146·5—147° (lit.,[10] m. p. 144—145°).

Ullmann Coupling of (Ic).—2,5-Dimethoxy-4-t-butylbromobenzene (Ic) (950 mg.) and copper powder (1·8 g.) were heated at 260—280° for 5 min. then at 300° for 1 min. After cooling, the product was extracted with boiling chloroform (6 × 5 ml.). Evaporation, followed by chromatography on alumina and elution with light petroleum, gave 2,5,2′,5′-tetramethoxy-4,4′-di-t-butylbiphenyl, m. p. 212·5—213° undepressed on admixture with an authentic sample.

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