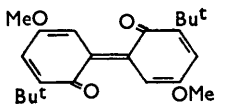
968. *Oxidation of Alkoxy-phenols. Part I. 4-Methoxy-3-t-butylphenol.*

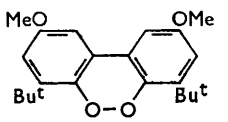
By F. R. Hewgill.

An unstable, blue oxidation product of 4-methoxy-3-t-butylphenol has been isolated and shown to rearrange to the spiro-acetal (III) which contains three units of the original phenol. This illustrates a new type of oxidative coupling of phenols. Acid-hydrolysis products of this acetal have been isolated and their structures proved.

In an attempt to assess the possible toxicity of phenolic antioxidants for use in food, some results of which have been presented elsewhere,[1] their oxidation products became important because, in preventing autoxidation a phenol is itself oxidized, generally to a variety of products, which may therefore be ingested. Kinetic evidence [2] suggests that autoxidation is generally inhibited by reaction of the phenol with peroxy-radicals; this gives phenoxy-radicals [3] which then dimerise or react with a peroxy-radical to produce a peroxycyclohexadienone. The course of oxidative coupling of phenols may be determined by the use of oxidants which abstract electrons singly, and compounds of a variety of types can be so produced,[4] many themselves inhibitors of autoxidation.[5]

Two of the more extensively used antioxidants for addition to fat are 2,6-di-t-butyl-*p*-cresol, and a mixture of 4-methoxy-2- and -3-t-butylphenol (known as BHA). Oxidation of the first compound, a hindered phenol, has been thoroughly investigated (cf. ref. 3). Less is known about the oxidation products of the BHA isomers. Rosenwald and Chenicek [6] reported the isolation of 2,2′-dihydroxy-5,5′-dimethoxy-3,3′-di-t-butylbiphenyl from treated lard and prepared the biphenyl by alkaline ferricyanide oxidation of 4-methoxy-2-t-butylphenol. This biphenyl was also prepared by Baltes and Volbert [7] and is the reduction product of a blue oxidation product which the latter authors consider to be a mesomeric form of the quinone (I). This was in equilibrium with a colourless

(I) 

(II) 

isomer to which they assigned structure (II). Neither set of authors provided chemical proof for the structures of the oxidation products. The present paper is concerned with an oxidation product of the isomer, 4-methoxy-3-t-butylphenol.

Addition of aqueous ferricyanide to an alkaline solution of 4-methoxy-3-t-butylphenol gave a blue precipitate quantitatively, with the consumption of two equivalents of ferricyanide. No method for the purification of this compound could be found as solutions in aprotic solvents rapidly afforded a yellow isomer, considered to be the spiroacetal (III). The same acetal was obtained by shaking ethereal solutions of the phenol with silver oxide or lead dioxide, the initial deep blue colour being allowed to fade. Molecular-weight determination, and the nitrogen content of an oxime, indicated that the new molecule

[1] Johnson *et al.*, *J. Amer. Oil Chemists' Soc.*, 1958, **35**, 496; *Austral. J. Exp. Biol. Med. Sci.*, 1959, **37**, 295, 533; 1961, **39**, 353.

[2] For critical summary see Walling, " Free Radicals in Solution," John Wiley and Sons, Inc., New York, 1957, p. 430.

[3] Dugan in " Encyclopedia of Chemical Technology," ed. Kirk and Othmer, 1st Suppl., Interscience Publ., Inc., New York, 1957, p. 77.

[4] For reviews see Barton and Cohen, and Erdtman and Wachtmeister, in " Festschrift A. Stoll," Birkhauser, Basle, 1957, pp. 117, 144.

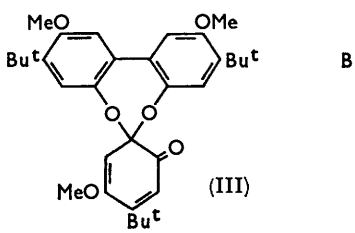
[5] Dunn, Waters, and Roitt, *J.*, 1954, 580.

[6] Rosenwald and Chenicek, *J. Amer. Oil Chemists' Soc.*, 1951, **28**, 185.

[7] Baltes, *Fette und Seifen*, 1954, **56**, 984; Baltes and Volbert, *ibid.*, 1955, **57**, 660.

involved three molecules of the original phenol. The infrared carbonyl absorption was compatible with that of an αβ-unsaturated ketone, and both infrared and nuclear magnetic resonance spectra indicated the absence of hydroxyl groups. The latter spectrum, measured in carbon tetrachloride with tetramethylsilane as internal reference, at 40 Mc./sec., indicated the presence of two vinylic protons (τ 4·16, 4·82), four equivalent aromatic protons (τ 3·18), two similar methoxyl groups (τ 6·14) and another in a different environment (τ 6·40), and two similar t-butyl groups (τ 8·62) with a shoulder (τ 8·67) indicating another in a different environment.

As expected of such a group, the acetal is readily hydrolysed by acid, and the main evidence of structure rests on the acid-hydrolysis products. In warm acetic acid the acetal afforded a mixture from which 2,2′-dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl (IV), the quinone (VI) and a 5-methoxy-4-t-butylcatechol monoacetate (VII) were separated by chromatography. Formation of these products can be explained by a mechanism based on that of acid hydrolysis of acetals.[8] Protonation of one of the acetal-oxygen atoms and fission of the bond joining this to the spiro-atom leads to a carbonium ion, which on reaction with acetate could give an acetoxycyclohexadienone. Protonation of the carbonyl-oxygen atom and abstraction of CH_3^+ by acetate could then give the *p*-quinone (VI) and the catechol monoacetate (VII). Though methyl acetate was not



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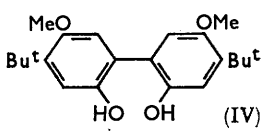

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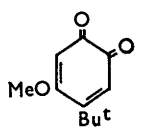

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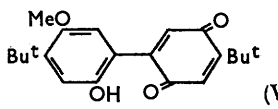

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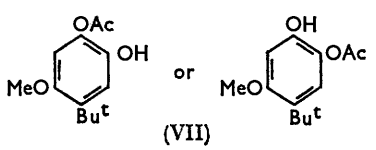

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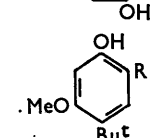

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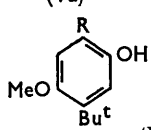


(IX)

R = N:N·C$_6$H$_3$(NO$_2$)$_2$

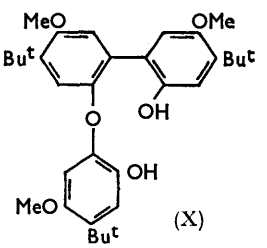
isolated as such, a volatile material was obtained which after hydrolysis and oxidation gave a positive test for formaldehyde. On the other hand, protonation of the diphenyl ether-oxygen of the acetoxycyclohexadienone could lead to the dihydroxybiphenyl (IV). The remaining fragment would be expected to decompose to the quinone (V). Though this compound was not isolated, addition of the acetal to 2,4-dinitrophenylhydrazine in acetic acid gave a mixture of the 2,4-dinitrophenylazophenols (VIII) and (IX) in the proportion 17 : 25. These were distinguished by formation of the latter on coupling of diazotised 2,4-dinitroaniline with 4-methoxy-3-t-butylphenol. As the quinone (V) itself gave these arylazophenols (VIII) and (IX) in the proportion 10 : 1 under the same conditions, the preponderant nucleophilic attack in the reaction of the acetal with 2,4-dinitrophenylhydrazine is at the spiro-atom. The same hydrolysis products were obtained by treating the blue oxidation product with acetic acid. When the reaction was stopped by water before completion, the acetal was also isolated, which suggests conversion into the latter before hydrolysis.

The structures of the hydrolysis products were proved as follows. 2,5,2′,5′-Tetramethoxy-4,4′-di-t-butylbiphenyl was synthesized from 1,4-dimethoxy-2-nitro-5-t-butyl

[8] Bunnett in Weissberger's "Technique of Organic Chemistry, Vol. VIII. Rates and Mechanisms of Reactions," Pt. I, 2nd edn. Interscience Publ., Inc., New York, 1961, p. 231.

benzene by reduction, diazotization, conversion into the iodide, and Ullmann condensation, and was identical with the tetramethyl ether derived from the dihydroxybiphenyl (IV). Both compound (IV) and the reduction product of the quinone (VI) gave 2,5,2′,5′-tetra-acetoxy-4,4′-di-t-butylbiphenyl on demethylation followed by acetylation. Dealkylation of the dihydroxybiphenyl (IV), followed by acetylation, gave 2,8-diacetoxydibenzofuran. The quinone (V) was prepared from 4-methoxy-3-t-butylphenol by oxidation with Fremy's salt; after reduction, acetylation gave a diacetate identical with that derived from the catechol monoacetate (VII). Demethylation of the monoacetate (VII), followed by acetylation, gave the known [9] 2,4,5-triacetoxy-1-t-butylbenzene. Ultraviolet and the hydroxyl regions of the infrared spectra of the dihydroxybiphenyl (IV), the trihydroxy-biphenyl derived from the quinone (VI), and 2,2′-dihydroxy-5,5′-dimethoxybiphenyl were all similar: the infrared spectra indicated that all were largely intramolecularly hydrogen-bonded (bands at 3554, 3556, and 3558 cm.$^{-1}$, respectively). Comparison with the frequency 3563 cm.$^{-1}$ reported by Keussler and Rossmy [10] for intramolecularly bonded 2-hydroxybiphenyl suggests that the hydroxylic-hydrogen atoms in the above compounds are bonded to the π-electrons of the opposite rings. The substantially lower frequency (3346 cm.$^{-1}$) for the quinone (VI) is in agreement with bonding to the adjacent quinone-carbonyl group.

Reduction of the acetal (III), either catalytically with palladium–carbon or with lithium aluminium hydride, gave amorphous material which consisted in part (~10%) of the dihydroxybiphenyl (IV). The bulk of the material, though amorphous, is considered to be the phenoxybiphenyl (X). Its nuclear magnetic resonance spectrum (conditions as above) indicated four similar (τ 3·26), and two dissimilar aromatic protons



(X)

(τ 3·40, 3·61), two hydroxyl protons (τ 4·03), three methoxyl groups (τ 6·19, 6·25, 6·35), and three t-butyl groups (τ 8·70). While the main resonances are in agreement with structure (X), the presence of two shoulders (τ 6·12 and 8·57) indicates some impurity. The ultraviolet spectrum was similar to those discussed above, and bonded-hydroxyl absorption in the infrared region at 3565 cm.$^{-1}$ was again similar to that of 2-hydroxy-biphenyl. Oxidation with silver oxide in ether produced a deep blue solution from which the acetal (III) was isolated in good yield. Demethylation of the reduction product gave 2,5,2′,5′-tetra-acetoxy-4,4′-di-t-butylbiphenyl, and dealkylation gave 2,8-diacetoxydibenzofuran, though both in poor yield. These results are also in agreement with structure (X).

The transformation of the blue oxidation product into the acetal has been examined kinetically. The reaction in cyclohexane in the dark follows second-order kinetics with an activation energy of 10 kcal./mole. The intractable nature of the by-products formed in more concentrated solution suggests that they are polymeric, and that under these conditions polymerisation competes with intramolecular rearrangement. No method could be found for accomplishing the reverse reaction yellow ⟶ blue.

Though several reaction schemes involving the reduction of two equivalents of ferricyanide can be written to account for the formation of the acetal in the original oxidation of the phenol, it is not possible to decide between these on present evidence. Indifferent yields of the dihydroxybiphenyl (IV), the more orthodox product of phenoxy-radical pairing, were obtained by oxidizing 4-methoxy-3-t-butylphenol in aqueous-alcoholic alkali with ferricyanide. Elucidation of the structure of the blue oxidation product must await further experimental evidence. Electron spin resonance measurements exclude a free-radical structure. Similar blue and yellow oxidation products of phenols having a hydrogen atom α to the phenolic hydroxyl group are being investigated in this laboratory.

[9] Flaig, Ploetz, and Biergans, *Annalen*, 1956, **597**, 205.
[10] Keussler and Rossmy, *Z. Electrochem.*, 1956, **60**, 136.

Experimental

Ultraviolet spectra were determined on a Hilger "Uvispek" spectrophotometer or a Unicam S.P. 700 recording spectrophotometer. Where the prism is mentioned, infrared spectra were determined on a Grubb-Parsons single-beam spectrophotometer with water-vapour calibration, otherwise on a Perkin-Elmer "Infracord" instrument. Nuclear magnetic resonance spectra were determined with a high-resolution Perkin-Elmer instrument. M. p.s were determined on a Kofler block. Light petroleum had b. p. 55—60° unless otherwise stated.

Oxidation of 4-Methoxy-3-t-butylphenol.—(*a*) *In aqueous alkaline solution by ferricyanide.* To 4-methoxy-3-t-butylphenol (0·9 g.) in 10% aqueous sodium hydroxide (90 ml.), under nitrogen, potassium ferricyanide (3·3 g.) in water (50 ml.) was added during 10 min. with stirring. The immediate blue coloration was almost instantly followed by formation of a blue precipitate. This was filtered off, washed several times with water, and dried in the dark, *in vacuo*, over phosphoric oxide. This *product* (0·9 g.) could not be recrystallised without decomposition, and when heated in an evacuated tube gradually decomposed with loss of colour, becoming molten at 120—125° (Found: C, 73·6; H, 7·9. $C_{33}H_{42}O_6$ requires C, 74·1; H, 7·9%); it had $\lambda_{max.}$ (in cyclohexane) 220, 260 (infl), 302, 330 (infl), and 617 mμ (log ε 4·50, 4·05, 3·96, 3·30, and 3·83). The broad maximum at 617 mμ moved to 650 mμ in pyridine, and to 633 mμ in 1 : 1 pyridine–cyclohexane.

Potentiometric titration of a 0·05M-solution of the phenol in aqueous 0·1M-sodium hydroxide with aqueous 0·05M-potassium ferricyanide showed reduction of 1·9 equiv. A rapid decrease of the initial voltage after each addition of reagent was responsible for some lack of precision.

(*b*) *By silver oxide.* A solution of the phenol (2·5 g.) in ether (100 ml.) was shaken with silver oxide (4 g.) in the presence of a few drops of aqueous sodium hydroxide. After several hours the deep blue colour of the solution became green, then yellow. Filtration followed by removal of the dried ($MgSO_4$) ether left a yellow gum which later crystallised. Recrystallisation from cyclohexane–light petroleum gave the acetal, *2,5′,10-trimethoxy-3,4′,9-tri-t-butyldibenzo*[d,f]-*dioxepin-6-spiro-2′-cyclohexa-3′,5′-dienone* (III), as lemon-yellow prisms, m. p. 209—210° [Found: C, 74·3; H, 7·9%; *M* (by f. p. depression of cyclohexane), 495. $C_{33}H_{42}O_6$ requires C, 74·1; H, 7·9%; *M*, 535], $\lambda_{max.}$ (in cyclohexane) 219, 258, 305, 331 (infl) mμ (log ε 4·63, 4·23, 4·12, and 3·38), $\nu_{max.}$ (in CCl_4, CaF_2 prism) 1688 cm.$^{-1}$ (αβ-unsaturated ketone). Originally, yellow crystals, m. p. 133—136°, were obtained. On further recrystallisation they yielded the material, m. p. 209—210°, which was obtained in all subsequent oxidations. The two forms are presumably polymorphs.

When heated for 4 hr. at 100° with hydroxylamine hydrochloride in pyridine, the acetal gave an *oxime* as needles (from ethanol), m. p. 195—196°, exhibiting a change of crystalline form at 180° to blades (Found: N, 2·8. $C_{33}H_{43}NO_6$ requires N, 2·6%).

(*c*) *By alkaline ferricyanide in the presence of benzene.* The quantities of reagents were those described under (*a*). Benzene (50 ml.) was added to the alkaline solution before addition of the ferricyanide. An intense blue colour was produced at each addition of ferricyanide but faded almost immediately. At the end of the reaction the layers were separated, the aqueous layer was extracted with benzene, and the combined benzene extracts were washed with water and dried ($MgSO_4$). Removal of the benzene and recrystallisation of the residue gave the acetal (420 mg.), m. p. 209—210°. Extraction of the acidified aqueous layer gave no phenolic material.

Conversion of the Blue Oxidation Product into the Acetal.—The colour of solutions (*e.g.*, 0·1M) of the blue oxidation product in hydrocarbon solvents, ether, or ethanol rapidly changed from blue to brownish-yellow. Removal of the solvent and recrystallisation from cyclohexane–light petroleum gave the acetal in ~60% yield. Chromatography of the mother-liquors on alumina, and elution with solvents (*e.g.*, light petroleum, methanol) gave amorphous material, but not in clearly defined fractions. Infrared spectra showed this material to be similar to the amorphous reduction product (described below) of the acetal. It was insoluble in aqueous alkali. However, in the dark, in very dilute solutions (<0·001M) in cyclohexane these by-products were apparently not formed, the blue colour fading more slowly to pale yellow; the ultraviolet spectra of the resulting solutions were identical with that of the acetal.

Kinetics of the Conversion of the Blue Oxidation Product into the Acetal in Cyclohexane in the Dark.—The rate was determined spectrophotometrically by following the decrease in optical density at 6170 Å. Beer's law held for solutions <0·001M. Freshly prepared samples of the

blue oxidation product were used, as a sample two months old lost colour too rapidly to be measured by this method in $1{\cdot}67 \times 10^{-4}$M-solution. All solutions were made up by adding the required volume of cyclohexane to the weighed, blue oxidation product in a light-proof flask, and not by dilution of more concentrated solutions. Solution was almost instantaneous.

Plots of $1/D_{6170}$ against time gave straight lines for solutions of concentration $1{\cdot}33 \times 10^{-4}$M to $8{\cdot}33 \times 10^{-5}$M; reaction of a $1{\cdot}67 \times 10^{-4}$M-solution was followed for seven half-lives without significant departure from linearity (see Table). Second-order kinetics were therefore applied. A slightly faster initial rate was observed but discounted in calculating rate constants.

Rate of loss of colour of a $1{\cdot}67 \times 10^{-4}$M-solution in cyclohexane in the dark at 30°.

Time (min.) from solution ...	8	27	58	90	115	152	189	216	250
$1/D_{6170}$	0·885	1·15	1·42	1·67	1·86	2·13	2·41	2·63	2·86

Variation of ±5% in values of k for different lots of the same sample no doubt arises from the lack of a method for purification of the oxidation product. To minimise the effect of this variation in determining Arrhenius parameters, solutions were divided into two portions as soon as dissolution was complete. One portion was kept at 30·0°, and the other at the temperature being investigated. Values of k obtained in this way for the following pairs of temperatures were: $k_{22\cdot0} = 0{\cdot}469$, $k_{30\cdot0} = 0{\cdot}714$; $k_{35\cdot1} = 1{\cdot}01$, $k_{30} = 0{\cdot}735$; $k_{40\cdot6} = 1{\cdot}41$, $k_{30\cdot0} = 0{\cdot}775$ l. mole^{-1} sec.$^{-1}$. A mean value of $k_{30\cdot0} = 0{\cdot}741$ and correction of values of k at other temperatures by a factor of $k_{30\cdot0}$ (mean)/$k_{30\cdot0}$ (for the temperature concerned) gave $k_{22\cdot0} = 0{\cdot}487$, $k_{35\cdot1} = 1{\cdot}02$, and $k_{40\cdot6} = 1{\cdot}35$. Arrhenius values thus calculated were $E = 10$ kcal. mole^{-1} and $A = 2 \times 10^7$ sec.$^{-1}$.

Addition of ethanol, acetic acid, or 4-methoxy-3-t-butylphenol to the blue solutions in cyclohexane increased the rate of fading, and gave departures from second-order kinetics. Irradiation of the cyclohexane solution in a quartz flask by an ultraviolet lamp gave an approximately linear plot of log D against time, indicating a first-order reaction. In this case the ultraviolet spectrum of the completely faded solution differed markedly from that of the acetal.

Reduction of the Acetal.—(*a*) *By hydrogenation.* The acetal (20·0 mg.) was hydrogenated in cyclohexane over 10% palladium–charcoal. Uptake ceased when 1·02 ml. at 24°/772 mm. (1·13 mol.) had been absorbed, the solution becoming colourless. Evaporation of the filtered solution gave a colourless glass. The product (500 mg.) from a larger-scale hydrogenation was dissolved in a little light petroleum and extracted with five portions of 10% aqueous sodium hydroxide. After washing of the light petroleum solution with water and drying (Na_2SO_4), evaporation gave *2-hydroxy-2′-(2-hydroxy-5-methoxy-4-t-butylphenoxy)-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl* (X) as a glass [Found: C, 73·6; H, 8·5; active H, 0·37%; *M* (f. p. depression of cyclohexane), 546. $C_{33}H_{44}O_6$ requires C, 73·9; H, 8·3%; *M*, 537], $\lambda_{max.}$ (in EtOH) 213, 250 (infl), 299 mμ (log ε 4·65, 3·84, 3·84), $\nu_{max.}$ (in CCl_4, CaF_2 prism) 3565 cm.$^{-1}$ (bonded OH), shoulder at 3600 cm.$^{-1}$ (weak free OH). The compound was very soluble in organic solvents. In alcoholic alkali it exhibited a blue fluorescence in ultraviolet light. Chromatography on alumina failed to reveal heterogeneity. With acetic anhydride–pyridine the product gave a *diacetate* as a glass after sublimation at 220°/0·1 mm. (Found: C, 71·3; H, 7·8. $C_{37}H_{48}O_8$ requires C, 71·6; H, 7·8%), whose infrared spectrum showed no OH absorption but a band at 1760 cm.$^{-1}$ (acetate).

Acidification of the alkaline washings of the hydrogenated solution followed by extraction with chloroform gave a residue (19 mg.) on evaporation of the dried extract. This was chromatographed on Whatman No. 1 paper in 1 : 1 methanol–1% aqueous sodium borate. The air-dried paper was sprayed with 1% aqueous sodium hydroxide and observed in ultraviolet light, giving a blue spot of R_F 0·63, corresponding to 2,2′-dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl (see below). Subsequent spraying with 1% aqueous potassium ferricyanide gave a blue spot in the same position.

Treatment of the crude hydrogenation product (500 mg.) with benzoyl chloride in pyridine gave an oil from which *2,2′-dibenzoyloxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl* (25 mg.) was obtained as tabular crystals, m. p. 173—174°, from light petroleum (Found: C, 76·6; H, 6·7. $C_{36}H_{38}O_6$ requires C, 76·3; H, 6·8%).

(*b*) *With lithium aluminium hydride.* The acetal (200 mg.) in ether was added to lithium aluminium hydride (200 mg.) in ether. After 30 minutes' boiling under reflux the excess of hydride was decomposed with methyl acetate, 10% aqueous sulphuric acid was added, and the

ether separated, washed with water, and dried (Na_2SO_4). Evaporation gave a glass (200 mg.). Washing this with 10% aqueous sodium hydroxide as in (*a*) left a glass (190 mg.), which from its infrared spectrum appeared identical with that obtained by hydrogenation. Acidification of the alkaline washings produced an oil (16 mg.) which contained 2,2′-dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl (identified by paper chromatography).

Oxidation of the Amorphous Reduction Product.—The amorphous reduction product (200 mg.) in ether (20 ml.) was shaken with silver oxide (400 mg.), after addition of 1 drop of aqueous sodium hydroxide, until the solution had changed colour from blue to yellow. Filtration and removal of the ether from the dried ($MgSO_4$) solution gave the acetal (110 mg.), m. p. and mixed m. p. 208—209° (from light petroleum).

Hydrolysis of the Acetal.—(*a*) *With acetic acid.* The acetal (2 g.) was dissolved in acetic acid (50 ml.). When the solution was warmed, the colour passed through deep green to red, which darkened after 30 minutes' boiling. The acid was then removed under reduced pressure, leaving a red gum. This was taken up in light petroleum and, on cooling, crystals were deposited. Recrystallisation from benzene–light petroleum gave a *monoacetate* of 5-*methoxy*-4-*t*-*butylcatechol*, plates (180 mg.), m. p. 136—137° (Found: C, 65·4; H, 7·6%; *M*, 226. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·6%; *M*, 238). The mother-liquors were passed through a short column of alumina and eluted with light petroleum, leaving strongly adsorbed material, probably polyphenolic, later eluted with ethanol–acetic acid 1 : 1 as colourless material of high but indefinite m. p. The light petroleum eluate was rechromatographed on alumina. Elution with light petroleum gave unidentified orange-red crystals (6 mg.), m. p. 190° (from ethanol). Elution with light petroleum–benzene (2 : 1) gave a violet solution from which, after recrystallisation from light petroleum (b. p. <40°), 2-(2-*hydroxy*-5-*methoxy*-4-*t*-*butylphenyl*)-5-*t*-*butyl*-1,4-*benzoquinone* (VI) was obtained as violet needles (140 mg.), m. p. 138—139° (Found: C, 73·6; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·6; H, 7·7%), $\lambda_{max.}$ (in cyclohexane) 219, 243 (infl), 270, 298 mμ (log ε 4·38, 4·19, 3·98, 3·95), $\nu_{max.}$ (in CCl_4, CaF_2 prism) 3610 (weak free OH), 3346 cm.$^{-1}$ (bonded OH). Subsequent recrystallisations of this material from light petroleum gave violet prisms, m. p. 158—159°, mixed m. p. with the violet needles 158—159°. These two forms are therefore polymorphs. Elution with benzene, followed by recrystallisation from the same solvent, gave 2,2′-*dihydroxy*-5,5′-*dimethoxy*-4,4′-*di*-*t*-*butylbiphenyl* (IV) (160 mg.) as prisms, m. p. 169—170° (Found: C, 73·9; H, 8·5. $C_{22}H_{30}O_4$ requires C, 73·7; H, 8·4%), $\lambda_{max.}$ (in EtOH) 210, 222 (infl), 251, 307 mμ (log ε 4·63, 4·47, 4·14, 4·11), $\nu_{max.}$ (in CCl_4, CaF_2 prism) 3554 cm.$^{-1}$ (completely bonded OH).

Similar quantities of the same products were obtained by treatment of the blue oxidation product with acetic acid. To detect the liberated one-carbon unit the blue oxidation product (500 mg.) was boiled under reflux in acetic acid for 10 min. Water was added and 5 ml. of distillate collected. This was boiled under reflux with sodium hydroxide for 20 min. (to hydrolyse methyl acetate), and then distilled. The first 5 ml. of distillate, after oxidation with permanganate, gave a positive test for formaldehyde with chromotropic acid.[11] On the same treatment 4-methoxy-3-t-butylphenol gave a negative test.

(*b*) *With acetic acid in the presence of* 2,4-*dinitrophenylhydrazine.* The acetal (300 mg.) was added to a solution of 2,4-dinitrophenylhydrazine (250 mg.) in acetic acid at 100°. After 30 min. at this temperature the solution was poured into water, and the product filtered off, dried, and chromatographed on alumina. After small quantities of yellow and orange materials had been eluted, elution with benzene–light petroleum (3 : 1) removed a purple band (25 mg.) that gave a crimson solution from which 2-(2,4-*dinitrophenylazo*)-4-*methoxy*-5-*t*-*butylphenol* was obtained as brown plates, m. p. 279—280°, from benzene–light petroleum (Found: C, 54·3; H, 5·2; N, 14·7. $C_{17}H_{18}N_4O_6$ requires C, 54·5; H, 4·9; N, 15·0%). Elution with benzene removed an orange band (17 mg.) from which 2-(2,4-*dinitrophenylazo*)-5-*methoxy*-4-*t*-*butylphenol* was obtained as orange needles, m. p. 300° (from benzene) (Found: C, 54·8; H, 5·2; N, 14·9%). A similar result was obtained on reaction in ethanolic sulphuric acid.

Characterisation of the Hydrolysis Products of the Acetal.—Methods. Demethylation was effected by freshly distilled pyridinium chloride at 220° in 1 hr. After slight cooling, acetic anhydride and pyridine were added and the solution heated under reflux for 30 min. When cool the mixture was poured into water, the acetates crystallising.

Complete dealkylation was effected by boiling 48% hydrobromic acid, with enough acetic

[11] Snell and Snell, " Colorimetric Methods of Analysis," 3rd edn., Vol. III, D. Van Nostrand and Co. Ltd., New York, 1957, p. 45.

acid to bring the material into solution. After 6 hr. solutions were evaporated to dryness *in vacuo* and the products acetylated as above.

These procedures were selected by using 4-methoxy-2- and -3-t-butylphenol as model compounds. Good yields of t-butylquinol and quinol were obtained. A variety of reagents failed to effect debutylation unaccompanied by demethylation.

Monoacetate of 5-Methoxy-4-t-butylcatechol.—Acetylation of this compound with acetic anhydride–pyridine gave the *diacetate*, plates, m. p. 86—87° (from light petroleum) (Found: C, 64·5; H, 7·2. $C_{15}H_{20}O_5$ requires C, 64·3; H, 7·2%). Demethylation of the monoacetate (30 mg.) followed by acetylation gave 2,4,5-triacetoxy-t-butylbenzene (7 mg.), m. p. 119—120°, undepressed on admixture with material, m. p. 119—120°, prepared as described by Flaig, Ploetz, and Biergans.[9]

Reactions of 2-(2-Hydroxy-5-methoxy-4-t-butylphenyl)-5-t-butyl-1,4-benzoquinone (VI).—When treated with 2,4-dinitrophenylhydrazine in ethanolic sulphuric acid the quinone gave a *2,4-dinitrophenylazo-derivative* as red prisms, m. p. 259—260° (from aqueous ethanol) (Found: C, 62·2; H, 5·9; N, 10·6. $C_{27}H_{30}N_4O_7$ requires C, 62·1; H, 5·8; N, 10·7%).

The quinone (47·6 mg.) was hydrogenated (1·01 mol.) in ethanol over 10% palladium–charcoal at 17°/747 mm. The colourless solution, on filtration, removal of solvent, and recrystallisation of the residue from aqueous ethanol, gave *2,2′,5′-trihydroxy-5-methoxy-4,4′-di-t-butylbiphenyl*, associated with one mol. of ethanol, as prisms, m. p. 120—121° (Found: C, 70·7; H, 8·8. $C_{21}H_{28}O_4,C_2H_5{\cdot}OH$ requires C, 70·7; H, 8·8%), $\lambda_{max.}$ (in EtOH) 211, 222 (infl), 250 (infl), 302 mμ (log ε 4·54, 4·45, 4·06, 4·05), $\nu_{max.}$ (in CCl_4, CaF_2 prism) 3609 (free OH), 3556 cm.$^{-1}$ (bonded OH) [*triacetate*, needles, m. p. 174—175°, from aqueous acetic acid (Found: C, 68·9; H, 7·2. $C_{27}H_{34}O_7$ requires C, 68·9; H, 7·3%)].

The trihydroxy-compound with dimethyl sulphate in aqueous acetone containing sodium hydroxide gave *2,5,2′,5′-tetramethoxy-4,4′-di-t-butylbiphenyl* as plates, m. p. 213·5—214·5° (from light petroleum) (Found: C, 74·9; H, 8·9. $C_{24}H_{34}O_4$ requires C, 74·6; H, 8·9%).

Demethylation and subsequent acetylation of the trihydroxy-compound (100 mg.) gave *2,5,2′,5′-tetra-acetoxy-4,4′-di-t-butylbiphenyl* (120 mg.) as prisms, m. p. 215—216° (from aqueous acetic acid) (Found: C, 67·6; H, 6·9. $C_{28}H_{34}O_8$ requires C, 67·4; H, 6·9%).

Reactions of 2,2′-Dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl.—Acetylation of this compound gave the *diacetate* as needles, m. p. 165·5—166·5° (from aqueous acetic acid) (Found: C, 70·7; H, 7·8. $C_{26}H_{34}O_6$ requires C, 70·6; H, 7·7%). Benzoylation gave the dibenzoate, m. p. and mixed m. p. 173—174°, described above. With an excess of diazomethane in ether it gave *2-hydroxy-5,2′,5′-trimethoxy-4,4′-di-t-butylbiphenyl* as needles, m. p. 129—130° (from aqueous methanol) (Found: C, 73·8; H, 8·9. $C_{23}H_{32}O_4$ requires C, 74·2; H, 8·7%). Methylation of either the di- or the tri-methoxy-compound with dimethyl sulphate gave the tetramethyl ether, m. p. and mixed m. p. 213·5—214·5°.

Demethylation and subsequent acetylation of the dihydroxy-compound (150 mg.) gave 2,5,2′,5′-tetra-acetoxy-4,4′-di-t-butylbiphenyl (135 mg.), m. p. and mixed m. p. 215—216°. Dealkylation of the dihydroxy-compound (150 mg.) and subsequent acetylation gave 2,8-diacetoxydibenzofuran (25 mg.), m. p. 152—153°. Schimmelschmidt [12] gives m. p. 154—155° for this compound. Both this compound and 2,5,2′,5′-tetra-acetoxybiphenyl were obtained on similar dealkylation of 2,2′-dihydroxy-5,5′-dimethoxybiphenyl. This last compound, prepared as described by Haynes, Turner, and Waters,[13] had $\lambda_{max.}$ (in EtOH) 212, 222 (infl), 250 (infl), 308, 345 (infl) mμ (log ε 4·50, 4·45, 4·00, 3·95, 3·47), $\nu_{max.}$ (in CCl_4, CaF_2 prism) 3605 (weak free OH), 3558 cm.$^{-1}$ (bonded OH).

Synthesis of 2,5,2′,5′-Tetramethoxy-4,4′-di-t-butylbiphenyl.—1,4-Dimethoxy-2-nitro-5-t-butylbenzene, m. p. 99—100°, was prepared in 86% yield by addition of 35% aqueous nitric acid (50 ml.) to 2,5-dimethoxy-1-t-butylbenzene (10·5 g.) in ice-cold acetic acid (100 ml.). The mixture was poured into water, and the product filtered off and recrystallised from ethanol (Carpenter, Easter, and Wood [14] give m. p. 96—97°). Hydrogenation of the nitro-compound (9 g.) in ethanol over 10% palladium–charcoal was quantitative and afforded *2,5-dimethoxy-4-t-butylaniline* (6·8 g.) as needles, m. p. 84—85° (from light petroleum) (Found: C, 69·0; H, 9·1; N, 6·9. $C_{12}H_{19}NO_2$ requires C, 68·9; H, 9·2; N, 6·7%).

The amine (2·1 g.) in acetic acid (50 ml.) and water (10 ml.) was diazotized at 5° by sodium

[12] Schimmelschmidt, *Annalen*, 1950, **566**, 201.
[13] Hayes, Turner, and Waters, *J.*, 1956, 2829.
[14] Carpenter, Easter, and Wood, *J. Org. Chem.*, 1951, **16**, 616.

nitrite (1 g.) in water. Potassium iodide (2·4 g.) in water was added in one portion, producing a brown precipitate. The mixture was stirred for 90 min. at room temperature, then heated on a steam-bath for 30 min. and finally poured into water where dark crystals were formed overnight. These were filtered off, taken up in ether, and washed with aqueous sodium thiosulphate and then water. Removal of the ether from the dried (Na_2SO_4) solution gave a dark-red crystalline residue. Chromatography on alumina and elution with benzene–light petroleum (1 : 20) gave colourless crystals (1·5 g.). Recrystallisation from light petroleum gave 1-*iodo*-2,5-*dimethoxy*-4-*t*-*butylbenzene* as prisms, m. p. 85—86° (Found: C, 45·0; H, 5·6; I, 40·1. $C_{12}H_{17}IO_2$ requires C, 45·0; H, 5·4; I, 39·6%).

The iodide (0·93 g.) was heated at 260—280° for 20 min. with copper powder (2 g.). Extraction with boiling benzene, evaporation of the extract, and recrystallisation of the residue from light petroleum gave 2,5,2′,5′-tetramethoxy-4,4′-di-t-butylbiphenyl (0·41 g.), m. p. and mixed m. p. 213—214°.

Synthesis of 4-*Methoxy*-5-*t*-*butyl*-1,2-*benzoquinone and Derived Compounds.*—4-Methoxy-3-t-butylphenol (0·9 g.) in acetone (100 ml.) was added to a stirred solution of potassium nitrosodisulphonate (3·75 g.) in 0·04M-aqueous potassium dihydrogen phosphate (200 ml.) at 10°. After 15 min. water (100 ml.) was added, and stirring continued at room temperature for 1½ hr.[15] The solution was extracted with chloroform, the extract washed with water and dried (Na_2SO_4), and the solvent removed under reduced pressure. Recrystallisation of the residue from light petroleum gave 4-*methoxy*-5-*t*-*butyl*-1,2-*benzoquinone* (0·85 g.) as vermilion plates, m. p. 99—100° (Found: C, 68·2; H, 7·3. $C_{11}H_{14}O_3$ requires C, 68·0; H, 7·3%). The quinone imparts a characteristic green colour to the skin. The quinone (200 mg.) was added to a solution of 2,4-dinitrophenylhydrazine (200 mg.) in acetic acid (50 ml.) at 100°. After 30 min. at this temperature the solution was cooled, giving 2-(2,4-dinitrophenylazo)-5-methoxy-4-t-butylphenol (190 mg.), m. p. and mixed m. p. 300°. A further 50 mg. was obtained by chromatography of the evaporated mother-liquors on alumina, together with 2-(2,4-dinitrophenylazo)-4-methoxy-5-t-butylphenol (26 mg.), m. p. and mixed m. p. 279—280°, also obtained by addition of diazotised 2,4-dinitroaniline to an aqueous alkaline solution of 4-methoxy-3-t-butylphenol.

The quinone (400 mg.) with *o*-phenylenediamine (450 mg.) in chloroform in the presence of anhydrous sodium sulphate during 4 days gave 2-*methoxy*-3-*t*-*butylphenazine* (520 mg.), yellow needles, m. p. 88·5—89·5° (from light petroleum) (Found: C, 76·4; H, 7·0; N, 10·5. $C_{17}H_{18}N_2O$ requires C, 76·7; H, 6·8; N, 10·5%).

Hydrogenation of the quinone in ethanol over 10% palladium–charcoal was quantitative and gave 4-*methoxy*-5-*t*-*butylcatechol*, needles, m. p. 88—89° (from light petroleum) (Found: C, 67·4; H, 8·2. $C_{11}H_{16}O_3$ requires C, 67·3; H, 8·2%). Acetylation gave the diacetate described above, m. p. and mixed m. p. 86—87°.

Degradation of 2-*Hydroxy*-2′-(2-*hydroxy*-5-*methoxy*-4-*t*-*butylphenoxy*)-5,5′-*dimethoxy*-4,4′-*di*-*t*-*butylbiphenyl.*—Demethylation of this compound (240 mg.) with pyridinium chloride, followed by acetylation, gave an oil when the product was poured into water. Chromatography on acid-washed alumina and elution with benzene–light petroleum (9 : 1) gave 2,5,2′,5′-tetra-acetoxy-4,4′-di-t-butylbiphenyl (40 mg.), m. p. and mixed m. p. 215—216°.

The phenoxybiphenyl (0·4 g.) was boiled under reflux in acetic and hydrobromic acid for 12 hr. Evaporation under reduced pressure left a tar which was acetylated. Pouring the acetylation mixture into water precipitated another tar. The aqueous layer was decanted and extracted with benzene. The benzene extract yielded 2,8-diacetoxydibenzofuran (10 mg.), m. p. and mixed m. p. 151—152°. Attempted dealkylation of the phenoxybiphenyl with hydrogen iodide in acetic acid gave only tar.

Preparation of 2,2′-*Dihydroxy*-5,5′-*dimethoxy*-4,4′-*di*-*t*-*butylbiphenyl.*—Aqueous M-potassium ferricyanide was added under nitrogen to a solution of 4-methoxy-3-t-butylphenol (1 g.) in ethanol (30 ml.) containing sodium hydroxide (0·5 g.), until a permanent green colour was observed. The precipitate was filtered off and dissolved in water. Acidification, extraction with ether, evaporation of the ether, and recrystallisation of the residue from benzene gave the dihydroxybiphenyl (130 mg.), m. p. and mixed m. p. 169—170°.

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[15] Cf. Teuber and Staiger, *Chem. Ber.*, 1955, **88**, 825.

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Department of Chemistry, University of Western Australia,
Nedlands, Western Australia. [*Received, April 27th*, 1962.]