Oxidation of Alkoxyphenols. Part XIX.† Base-induced Coupling of Halogenophenols [1]

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6-Bromo-4-t-butyl-*o*-cresol reacts with alkali to give a trimeric spiro-acetal (IV), and 2-bromo-4,6-di-t-butylphenol gives a dimeric benzoxet (VIII). 2-Bromo-4-methoxy-5-t-butylphenol gives some of the corresponding spiro-acetal (XII) but is partly demethylated. These reactions can be explained by an electron transfer from the phenoxide anion to the keto-tautomer of the phenol, and loss of bromide from the resulting radical-anion. A chain reaction ensues involving debromination of an intermediate bisbromocyclohexadienone to a dipheno-2,2′-quinone [bi(cyclohexa-2,5-dien-1-ylidene)-2,2′-quinone]. Evidence is presented in support of these proposals.

THE formation of oxidative coupling products from phenols has been so extensively studied that it needs no specific reference. However, from time to time there have been records of the isolation of similar products from reactions of phenols which would not normally be thought of as oxidations. Thus, Hunter and his colleagues [2] found that silver or sodium 2,4,6-trihalogenophenoxides were converted by trace amounts of iodine or alkyl iodides into polymeric ' dihalophenylene oxides ', and suggested that a dihalogenophenoxyl biradical, formed by loss of a halogen atom from a trihalogenophenoxyl radical, was involved. Subsequently, Dewar and James [3] proposed that the polymer building

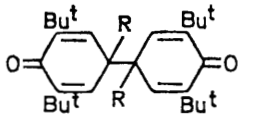
† Part XVIII, F. R. Hewgill and S. L. Lee, *J. Chem. Soc.* (*C*), 1969, 2080.

[1] A preliminary account of this work appeared in *Chem. Comm.*, 1968, 524.

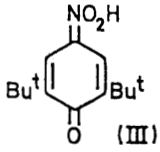
[2] H. A. Torrey and W. H. Hunter, *J. Amer. Chem. Soc.*, 1911, **33**, 194; W. H. Hunter and R. B. Whitney, *ibid.*, 1932, **54**, 1167; and intervening papers by W. H. Hunter *et al.* (*ibid.*).

[3] M. J. S. Dewar and A. N. James, *J. Chem. Soc.*, 1958, 917.

step was insertion by the trihalogenophenoxyl radical into the trihalogenophenol. Müller and his colleagues,[4] however, have since reported that the deep blue colour of the reaction mixture is not associated with an e.s.r. signal. Another reaction that appears to belong to the same category is that of 2,4-dihalogeno-1-naphthols with base or copper, first mentioned by Zincke[5] and examined further by Willstätter and Schuler.[6] The blue products could not be purified sufficiently for definite structural assignment, but on the basis of their reduction to 1,1′-dihydroxy-2,2′-binaphthyls were accorded 2,2′-binaphthyl-1,1′-quinone structures. Their formation was thought to involve dehydrohalogenation of the keto-tautomer of the naphthol, and dimerisation of the resulting carbene, but no evidence was obtained for either of these intermediates. On repeating these reactions with 2,4-dibromo-1-naphthol we were also unable to obtain



(I) R = I
(II) R = [NO_2H]•

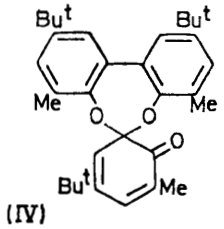


(III)

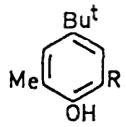
pure material, as the crude product was rather unstable. T.l.c. indicated that more than one product was produced. Müller[7] has also described a reaction which involves more than simple coupling. In this, molecular equivalents of 4-benzoyloxy-2,6-di-t-butylphenoxyl and 4-iodo-2,6-di-t-butylphenol react to give nearly 2 mol of 3,3′,5,5′-tetra-t-butyldipheno-4,4′-quinone by way of the C–C coupled dimer (I). Closely related is the thermal decomposition of 4-nitro-2,6-di-t-butylphenol described by Barnes and Hickinbottom,[8] which leads to the same diphenoquinone. The proposed intermediate (II) is thought to be formed by dimerisation of the keto-tautomer (III).

Our interest in such reactions is connected with the formation of the spiro-ketal trimer (IV) from the bromo-cresol (V). The formation of (IV) upon oxidation of the cresol (VI) and its significance as a variant of the usual oxidation pattern of 4-alkylphenols have been briefly discussed in a preliminary communication,[9] and subsequently the same trimer was described by Karpov and Khidekel[10] as the major product of the copper-amine-catalysed oxidation of the cresol (VI). In view of the importance of the trimer in what follows, details of the proof of its structure are given in the Experimental section.

When preparing 2-bromo-6-methyl-4-t-butylanisole by the reaction of dimethyl sulphate with the bromo-cresol (V) in acetone in the presence of solid potassium hydroxide, we noticed an intense blue colour near the surface of the hydroxide. This faded to yellow, and in addition to the anisole a 30% yield of the trimer (IV) was obtained. In the absence of dimethyl sulphate the yield of trimer was quantitative. We naturally tried the reaction with other halogenated phenols, and of those

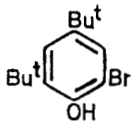


(IV)

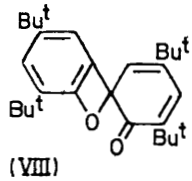


(V) R = Br
(VI) R = H
(X) R = OMe

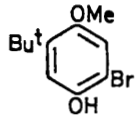
examined 6-iodo-4-t-butyl-*o*-cresol gave the trimer (IV), though the reaction was incomplete, while the chloro-analogue did not react at all, even when heated. 2-Bromo-4,6-di-t-butylphenol (VII) and 2-iodo-4,6-di-t-butylphenol gave a similar reaction, the product, again formed quantitatively from the bromo-compound, being the benzoxet (VIII), previously described by Müller and his co-workers.[11] Dimethylformamide, dimethyl sulphoxide, and acetone proved to be the best solvents for these reactions. Although 4-methoxy-3-t-butyl-



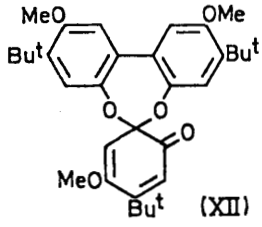
(VII)



(VIII)



(IX)



(XII)

phenol is easily oxidised to the trimeric spiro-ketal (XII),[12] reaction of the bromo-phenol (IX) with potassium hydroxide in dimethylformamide gave an unidentified mixture, the initial blue colour becoming pink as the reaction proceded. By passing a solution of the bromophenol in light petroleum through a column of slightly alkaline alumina, a small quantity of the spiro-ketal (XII) was obtained. No reaction was observed with 2,4,6-tribromophenol, 2-bromo-4-t-butylphenol, 4-bromo-2-t-butylphenol, 4-bromo-2-methoxy-6-t-butylphenol, or 4-chloroguaiacol.

[4] E. Müller, R. Mayer, U. Heilmann, and K. Scheffler, *Annalen*, 1961, **645**, 66.
[5] T. Zincke, *Ber.*, 1888, **21**, 1027.
[6] R. Willstätter and L. Schuler, *Ber.*, 1928, **61**, 362.
[7] E. Müller, A. Rieker, R. Mayer, and K. Scheffler, *Annalen*, 1961, **645**, 36.
[8] T. J. Barnes and W. J. Hickinbottom, *J. Chem. Soc.*, 1961, 953.
[9] D. F. Bowman and F. R. Hewgill, *Chem. Comm.*, 1967, 471.
[10] V. V. Karpov and M. L. Khidekel, *Zhur. org. Khim.*, 1968, **4**, 861.
[11] E. Müller, R. Mayer, A. Rieker, and K. Scheffler, *Annalen*, 1961, **645**, 25.
[12] F.R. Hewgill, *J. Chem. Soc.*, 1962, 4 987.

The effect of varying the reaction conditions for the bromocresol (V) is shown in Table 1, and it will be seen that: (*a*) alkali in excess of 1 mol prevents reaction, (*b*) the exclusion of light and oxygen has no effect, (*c*) the reaction cannot be started or sustained at −80°, and (*d*) oxidation of phenols, and then only in cases where the rates of oxidation are presumed to be nearly identical, or when one of the components forms a very stable radical which can be present in reasonably high concentration throughout the reaction.

TABLE

Reactions of 6-bromo-4-t-butyl-*o*-cresol (V) with alkali in various media

Base	Medium	Time	Temperature	Products (yield)
KOH	Dimethylformamide	30 min	20°	(IV) (>95%), KBr (94%)
KOH or NaOH	Acetone	30 min	20°	(IV) (>95%)
NaOH	Deoxygenated DMF	1 h	20°	(IV) (>95%)
NaOH	Acetone (dark)	30 min	20°	(IV) (90%)
NaOH	Acetone	4 h	−80°	No reaction
NaOH (1·0 mol)	Acetone–water (9 : 1)	5 min	20°	(IV) (70%), (XXIII) (10%)
NaOH (1·5 mol) *	Acetone–water (9 : 1)	2 h	Reflux	No reaction
NaOMe (1·0 mol)	MeOH	5 min	20°	(IV) (40%), (XXIII) (20%), (X) (20%)
NaOMe (1·5 mol)	MeOH	2 h	Reflux	No reaction
Na	Benzene	2 d	20°	(IV) (30%), (XXIII) (40%)
$NaNH_2$	Liquid NH_3	1 h	−30°	(IV) (40%), (XXIII) (30%)
NaOH	Light petroleum	3 h	20°	No reaction

* The cresol was first dissolved in aqueous alkali.

in protic solvents some reduction to the dihydroxybiphenyl (XXIII) occurs. We also found that traces of easily oxidised amines or phenols inhibit the reaction (*i.e.* delay the formation of the blue material). This indicates that a chain reaction is involved.

In considering likely mechanisms, the fact that the trimer (IV) and the benzoxet (VIII) are precisely the products of one-electron oxidation of the cresol (VI) and 2,4-di-t-butylphenol [11] respectively cannot, we feel, be overestimated as evidence for the intermediacy of phenoxyl radicals. If an ionic mechanism were involved one might expect to obtain cross-coupled products by treating a mixture of the bromocresol (V) and the bromophenol (VII) with alkali. In fact only the trimer (IV), the benzoxet (VIII), and some 2,2′-dihydroxy-3,5,3′,5′-tetra-t-butylbiphenyl were formed. This is in accord with other reactions involving phenoxyl radicals where, for example, cross-coupled products arising by intermolecular radical coupling are rarely observed in the

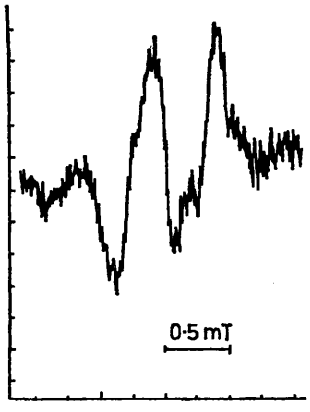


FIGURE 1 E.s.r. signal from the reaction of (V) with potassium hydroxide in dimethylformamide

[13] T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 1964, 213.

Immediate e.s.r. examination of the blue solution produced by adding solid alkali to the bromophenols (V) and (VII) in dimethylformamide gave the weak signals shown in Figures 1 and 2, which, although ill-defined, are not incompatible with the spectra expected for the corresponding bromophenoxyl radicals. An unanalysable signal was obtained in this way from phenol (IX). Though a number of flow systems were tried, we were unable to obtain stronger signals. Nor were we able to obtain e.s.r. spectra by flowing the bromophenols against ferricyanide or ceric sulphate. Under these conditions [13] phenol (VI) with ceric sulphate gave a quintet with $a_{H\text{-}CH_3} = a_{H\text{-}ortho} = 0{\cdot}60$ mT. When reacting solutions of the bromocresol (V) were added to solutions of 2,4,6-tri-t-butylphenol, the strong triplet, characteristic of 2,4,6-tri-t-butylphenoxyl was produced. This undoubtedly indicates the presence of an intermediate of higher oxidation potential than 2,4,6-tri-t-butylphenol. Similarly, when a judicious quantity of water was added to the reacting bromocresol (V) in dimethylformamide, the blue colour became orange and

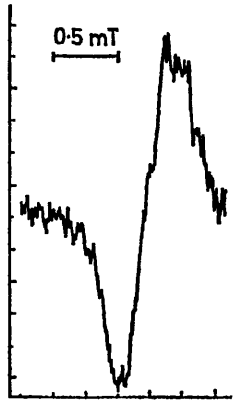
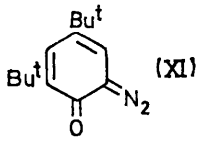


FIGURE 2 E.s.r. signal from the reaction of (VII) with potassium hydroxide in dimethylformamide

the spectrum of 3-methyl-5-t-butylbenzo-1,2-semiquinone [14] was observed. Too much water produced a mixture of quartet splittings which we have not been able to assign. Although the direct e.s.r. evidence is not strong enough for unambiguous identification of the radicals, we feel there is little doubt that phenoxyl radicals are involved, and we now consider ways in which they may be produced.

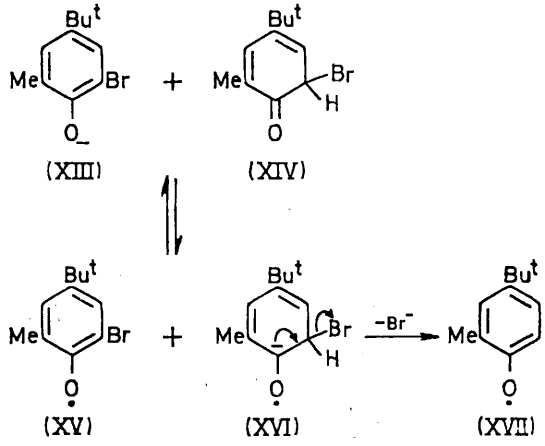
The intermediacy of a carbene, as proposed for the analogous bromonaphthol reaction,[6] may not be likely in that carbenes rarely dimerise.[15] On the other hand, a carbene, if produced, could conceivably abstract hydrogen from a phenol molecule and thus give rise to two phenoxyl radicals. The same could be said of a benzyne intermediate. The obvious objection to such intermediates is that very low concentrations of base will start the reaction. For instance, the addition of an aqueous solution containing as little as 30 μg of potassium hydroxide will produce a blue colour in 10 ml of 0·01M-(V) in acetone. If a benzyne intermediate is involved, the anisole (X) should react with equal ease, however, no reaction at all took place when alkali was added to (X). The intermediacy of a carbene was deemed less likely when the addition of cyclohexene, maleic acid, or maleic anhydride had no effect on the reaction of the bromocresol (V) with alkali. Nevertheless, as it is not certain that these carbene traps would be more reactive than a phenol molecule, we prepared a carbene precursor, the diazo-oxide (XI), by the method of Anderson and Roedel.[16] When heated in dipolar solvents, with or without the bromophenol (VII), the diazo-oxide gave only a blue gum containing nitrogen. Although this product could not be purified, chromatography showed that it did not contain the diphenoquinone or derived benzoxet (VIII). It may well be an azo-compound, as dyes of this type have been produced by decomposition of the diazo-oxide from 3-amino-4-hydroxybenzenesulphonic acid.[17] Under photolytic conditions extensive degradation of (XI) occurred and again no benzoxet was formed. We therefore conclude that carbenes are probably not involved, although no unequivocal way of conducting the decisive experiment, *i.e.* generating (XI) in the presence of the basified bromophenol (VII), could be devised.



(XI)

The observation that the reaction does not occur if alkali in excess of one mol is present implies that both the anion and the phenol are involved. In fact, reaction can be induced in a solution of the sodium phenoxide by addition of the phenol. We can therefore exclude on this ground alone a simple homolysis of the carbon–bromine bond, although the mesomerism of the phenoxide anion should make the charge distribution about this bond fairly symmetrical and conducive to its homolysis.

The presence of bulky *ortho*-substituents greatly increases the stability of keto-tautomers of phenols, and alkaline conditions favour their formation.[18] The phenoxide (XIII) formed by ionisation of the cresol (V), and especially that from phenol (VII), might thus be expected to have considerable carbanion character and form a keto-tautomer. On this basis the formation of phenoxyl radicals could occur as in Scheme 1. Such a



(XIII) (XIV) (XV) (XVI) (XVII)

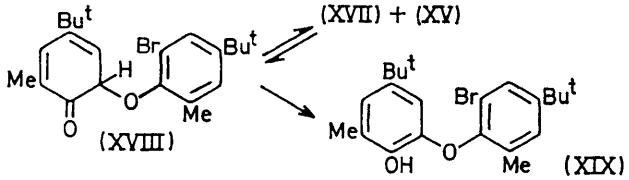
SCHEME 1

transfer of a π-electron to an unsaturated system has been demonstrated for nitrobenzenes and other compounds by Russell and Janzen.[19] It is, of course, apparent that the electron transfer could not operate in an excess of base, as here the keto-tautomer (XIV) would be completely converted into the phenoxide anion (XIII). In this connection it is worth noting that Battiste and his co-workers [20] have recently found the same limitation in the formation of a radical-anion from a tetrazine by electron transfer. Loss of bromide from the radical anion (XVI) finds analogy in the loss of α-bromine during the reduction of α-bromo-ketones by dissolving metals,[21] and is apparently too rapid for satisfactory identification of the radical anion by e.s.r. spectrometry. This loss of bromide must provide the driving force of the reaction, otherwise phenols without a good leaving group could so couple.

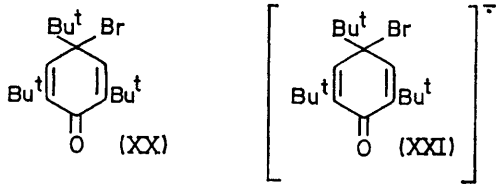
A distinctly less attractive alternative to Scheme 1 is nucleophilic attack by phenoxide on the bromo-ketone (XIV) to produce the ether (XIX). Although the re-

[14] C. Trapp, C. A. Tyson, and G. Giacometti, *J. Amer. Chem. Soc.*, 1968, **90**, 1394.
[15] T. L. Gilchrist and C. W. Rees, 'Carbenes, Nitrenes and Arynes,' Nelson, London, 1969, p. 82.
[16] L. C. Anderson and M. J. Roedel, *J. Amer. Chem. Soc.*, 1945, **67**, 955.
[17] O. Süs, *Annalen*, 1944, **556**, 65.
[18] V. V. Ershov and G. A. Nikiforov, *Russ. Chem. Rev.*, 1966, **35**, 817.
[19] G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, 1967, **89**, 300. See also earlier papers by Russell.
[20] H. Malkus, M. A. Battiste, and R. M. White, *Chem. Comm.*, 1970, 479.
[21] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 56.

action of 2,4,6-trialkyl-4-bromocyclohexadienones with phenoxides is a standard route to such ethers, (XIV) is not truly analogous, in that it has a proton at C-2 that could be removed by an attacking nucleophile, with the regeneration of the anion (XIII). An equally strong objection is the rather hindered nature of the phenoxide nucleophiles derived from (V) and (VII). Though we have found that highly reactive nucleophiles such as azide and cyanide inhibit the reaction, it is not possible to say whether this occurs during initiation or propagation. Nor has it been possible to obtain products from the reactions of (V) with hydroxylamine or borohydride. It should be noted that the presence of a mono- or di-bromocyclohexadienone as a contaminant of the original phenol is ruled out by our finding that the reaction works just as well with a sample of bromocresol (V) that has been treated with zinc in boiling acetic acid.



If radicals (XV) and (XVII) couple before diffusion from the solvent cage, the ether (XIX) is a likely product from Scheme 1 also, and no such products were detected by t.l.c. This is of little consequence in the case of the bromocresol (V) as ethers of type (XIX) have been shown to be intermediate in one route to trimers of type (IV).[22] In the case of the di-t-butylphenol (VII) one is more justified in assuming that dissociation of the keto-tautomer corresponding to (XVIII) competes effectively with enolisation.



An interesting comparison is the reaction of sodium 2,4,6-tri-t-butylphenoxide with the bromo-dienone (XX) which results in immediate and almost quantitative production of 2,4,6-tri-t-butylphenoxyl.[23] We have repeated these experiments using aqueous alkali in dimethylformamide with a similar result. The same reaction occurs in the 2,4,6-triphenylphenoxyl series.[24] With less hindered phenols the normal product of such reactions is an aryloxycyclohexadienone dimer,[25] but in the tri-t-butyl compound steric hindrance is such that the dimer has never been prepared. Although the exact mechanism has not been established, Altwicker[26] points out that nucleophilic displacement of bromide by 2,4,6-tri-t-butylphenoxide is sterically prohibitive, and suggests that electron transfer between phenoxonium and phenoxide ions is responsible. In agreement with this interpretation we find that (*a*) addition of such reactive nucleophiles as azide has no effect on the reaction, and (*b*) 2,4,6-tri-t-butylphenol reacts with sodium hypobromite to give the same result.

Support for a radical-anion intermediate in the bromocresol reaction is provided by the recent work of Pokhodenko and Kalibabchuk[27] who conclude that the radical-anion (XXI) is formed during the reaction of (XX) with potassium, potassium hydroxide, and methyl *p*-nitrophenylbenzoate. Loss of bromide then leads to the phenoxy radical. In contrast to our previous report[1] we have confirmed that (XX) alone does react with base, but very much more slowly than when 2,4,6-tri-t-butylphenol is present.

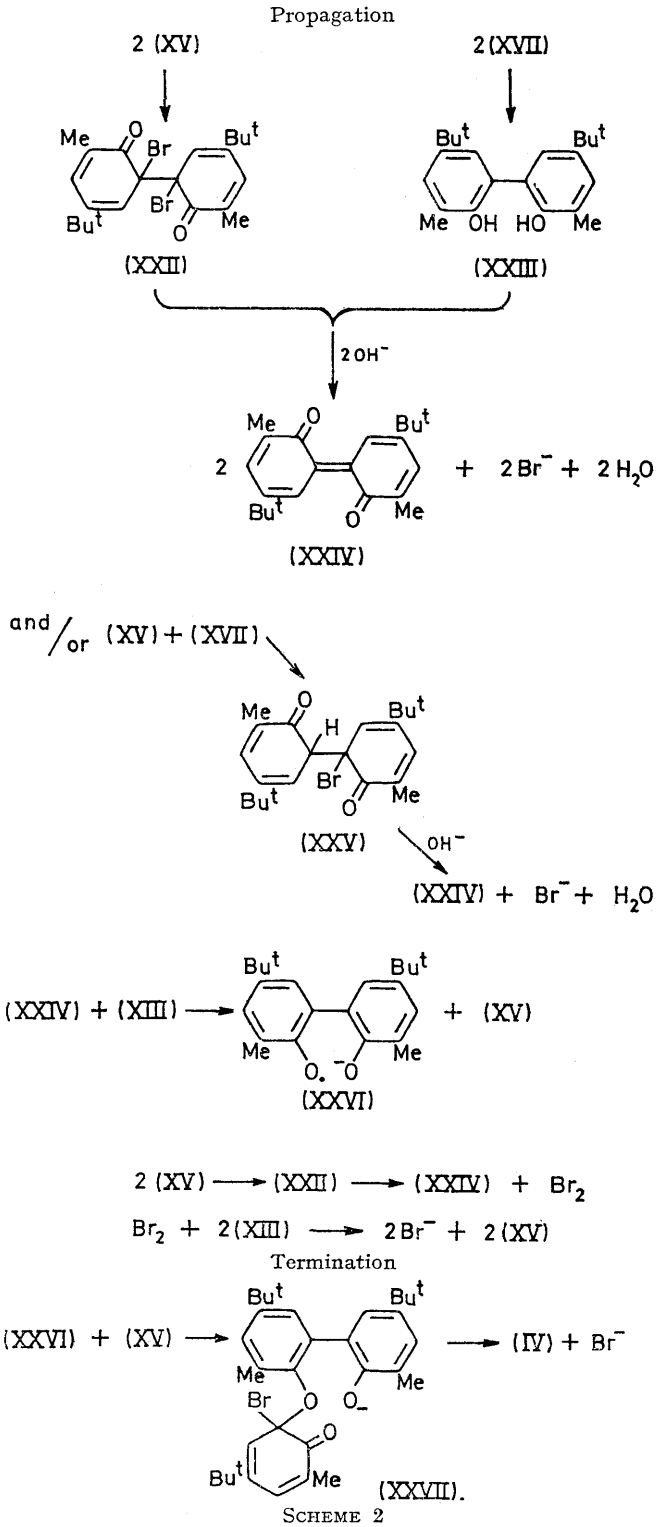
Considering now the propagation and termination steps in the bromocresol reaction, bromine or bromine radicals appeared the most likely species for radical transfer, and the deep blue colour of the solution suggested the presence of a dipheno-2,2′-quinone.[28] Scheme 2 involving these intermediates, fits the observed stoicheiometry. A similar mechanism may be written for the formation of the benzoxet (VIII). The following evidence supports Scheme 2.

The first step, involving coupling of phenoxyl radicals at brominated carbon positions has analogy in the low-temperature oxidation of 4-bromo-2,6-di-t-butylphenol, giving compound (I; R = Br).[29-31] Moreover, both the bromocresol (V) and the iodocresol give the trimer (IV) on oxidation with silver oxide. The alternative, carbon–oxygen coupling at the alkylated *ortho*- or *para*-carbons, leads only to easily dissociable aryloxycyclohexadienones, and, while it may occur, is thus completely reversible, not influencing the final products but perhaps being responsible for such e.s.r. spectra as were obtained.

Elimination of bromine from (XXII) is entirely paralleled by the spontaneous evolution of bromine from the bisbromocyclohexadienone (I; R = Br) at room temperature, the product being the dipheno-4,4′-quinone.[29,31] This elimination has been shown to be much more rapid in the presence of mercury.[30] When mercury was included in the bromocresol reaction mixture considerable reduction occurred, and 30% of the 2,2′-dihydroxybiphenyl (XXIII) was isolated as well as the trimer (IV). This corresponds to a partial interruption of the propagation sequence at this point in agreement with the proposed presence of (XXII). The failure of the bromocresol reaction to begin or continue at low temperatures

[22] F. R. Hewgill and D. G. Hewitt, *Tetrahedron Letters*, 1965, 3737.
[23] E. Müller, K. Ley, and W. Kiedaisch, *Chem. Ber.*, 1955, **88**, 1819.
[24] K. Dimroth, F. Kalk, R. Sell, and K. Schlömer, *Annalen*, 1959, **624**, 51.
[25] H. Musso in 'Oxidative Coupling of Phenols,' eds. W. I. Taylor and A. R. Battersby, Arnold, London, 1967, p. 59.
[26] E. R. Altwicker, *Chem. Rev.*, 1967, **67**, 478.
[27] V. D. Pokhodenko and N. N. Kalibabchuk, *Zhur. org. Khim.*, 1969, **5**, 1794.
[28] F. R. Hewgill and D. G. Hewitt, *J. Chem. Soc.* (*C*), 1967, 723.
[29] K. Ley, E. Müller, R. Mayer, and K. Scheffler, *Chem. Ber.*, 1958, **91**, 2670.
[30] C. D. Cook and N. D. Gilmour, *J. Org. Chem.*, 1960, **25**, 1429.
[31] H.-D. Becker, *J. Org. Chem.*, 1965, **30**, 982.

may well be due to increased stability of (XXII) under these conditions. Debromination of *vic*-dibromides with iodide is a well-known reaction,[32] and partial support for the presence of such compounds was obtained by the immediate intensification of the blue colour when a solution of sodium iodide in acetone was added to a reacting solution of the bromophenol (VII) in the same solvent. However, we were unable to observe this effect with the bromocresol (V).



SCHEME 2

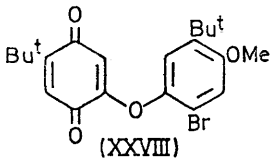
Oxidation of the anion (XIII) by the quinone (XXIV) is again interpreted as electron transfer. The quinone (XXIV) may be prepared in solution by oxidation of the bisphenol (XXIII) with silver oxide, and would be expected to have a high oxidation potential.[33] The oxidation of the phenoxide ion (XIII) directly by this quinone would obviously give equivocal results, but 4-methoxy-2-t-butylphenol was oxidised to the corresponding biphenol. A similar oxidation by a dipheno-4,4′-quinone has recently been reported by Bacon and Stewart.[34] The addition of bromine to a solution of the phenoxide (XIII) in an excess of alkali produces the blue colour of the diphenoquinone (XXIV), which indicates that bromine can in fact be regarded as a chain carrier; a supposition that appears to be required by the high yield of the spiro-acetal (XII) obtained.

Although there are numerous examples of the oxidation of phenols to quinones by halogens,[35] in only a few cases have coupled products been obtained.[36] In an attempt to show that one-electron oxidation is possible we have examined the reaction of selected phenols with iodine in alkaline conditions. An aqueous alkaline solution of the cresol (VI) reacted with ethereal iodine to give a high yield of the iodocresol, and no e.s.r. signal was detected when the alkaline cresol solution was flowed against the tri-iodide ion. By contrast, alkaline 4-methoxy-3-t-butylphenol gave the corresponding spiro-acetal trimer (XII) in 30% yield when treated with ethereal iodine, and the e.s.r. spectrum of its phenoxyl radical was observed with tri-iodide as the oxidant. Müller has found that nuclear iodination of phenols is rapid in alkylamine solvents,[37] but in diethylamine 4-methoxy-3-t-butylphenol again gave coupled products: the spiro-acetal (XII), 2,2′-dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl, and 8-methoxy-3,7-di-t-butyldibenzofuran-1,4-quinone.

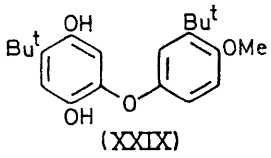
We have also examined the behaviour of 2-bromo-4-methoxy-5-t-butylphenol (IX). With ethereal iodine an alkaline solution of this phenol gave the spiro-acetal trimer (XII) and 4,4′-di-t-butyl-2-2′,5,5′-dibenzoquinone (XXXI). No e.s.r. signal was observed when the phenol was oxidised with tri-iodide under flow conditions, but a long-lived signal appeared when the flow was stopped, consisting of two overlapping doublets of doublets. These were later shown to be identical with the spectra of the semiquinones produced by reduction of 2-bromo-5-t-butylbenzo-1,4-quinone (a_H = 0·142 and 0·292 mT) and (XXVIII) (a_H = 0·145 and 0·282 mT).

[32] J. Hine and W. H. Brader, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 361.
[33] L. Horner and E. Geyer, *Chem. Ber.*, 1965, **98**, 2016.
[34] R. G. R. Bacon and O. J. Stewart, *Chem. Comm.*, 1967, 977.
[35] J. Cason, 'Organic Reactions,' Wiley, London, 1948, vol. IV, p. 305.
[36] Ref. 25, Table 1-1.
[37] E. Müller, R. Mayer, B. Narr, A. Rieker, and K. Scheffler, *Annalen*, 1961, **645**, 25.

The bromosemiquinone spectrum was centred at 0·075 mT lower field than that of (XXVIII), corresponding to an increase in *g*-value for the bromosemiquinone of 0·00045, which is consistent with *g*-values for similar semiquinones.[38] When the oxidation potential was



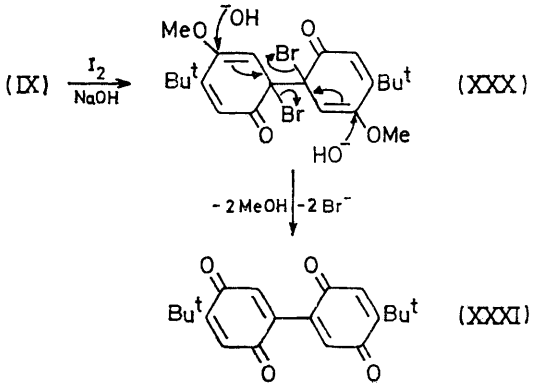
(XXVIII)



(XXIX)

lowered by the addition of 4 mol of iodide to the iodine, the phenoxyquinone (XXVIII) was formed in sufficient yield to be isolated. The n.m.r. and i.r. spectra are in accord with this structure. Reduction gave the unstable hydroquinone, and catalytic reduction in alkali gave the debrominated product (XXIX), identical with an authentic sample.

These experiments show that aryloxyl radicals and coupled products are formed in the oxidation of phenoxides by halogens. Although the demethylation observed with the bromomethoxyphenol (IX) can be explained by the formation of a phenoxonium ion,[39] the formation of the dibenzoquinone (XXXI) clearly involves prior C–C coupling to the bis-dienone (XXX), which in alkaline solution is more likely to be demethylated by nucleophilic attack as shown in Scheme 3. This,

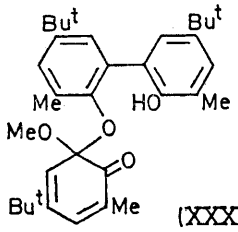


(IX) (XXX) (XXXI)

SCHEME 3

and the variety of products isolated from the phenol provide sufficient explanation for the low yield of the spiro-acetal (XII) in the reaction with alkali alone.

The Table shows that the reaction of the bromocresol (V) with sodium methoxide in methanol gives a considerable quantity of the guaiacol (X). As the corresponding reaction of the bromophenol (VII) gave only the benzoxet (VIII) and its reduction product, the dihydroxybiphenyl, we conclude that formation of the guaiacol (X) is initiated by nucleophilic attack of methoxide on the bromocyclohexadienone (XXVII), giving the acetal (XXXII). Such reactions have ample precedent.[40] The bromophenol (VII) is too hindered to form a cyclohexadienone of this type.[41] Formation of the acetal (XXXII) does not interfere with the propagation steps of Scheme 2, and by analogy with other compounds of this type homolysis to radicals should be easy,[42] leading by reduction to the guaiacol (X) and the bisphenol (XXIII). Formation of 3-methyl-5-t-butylbenzo-1,2-semiquinone might well be the result of a similar attack by hydroxide on (XXVII), and its detection cannot therefore be claimed as evidence for the presence of the keto-tautomer (XIV), as we were unable to detect the similar semiquinone in the reaction of the bromophenol (VII). The general occurrence of some reduction to bisphenols in these reactions in protic solvents suggests disproportionation of the intermediate dipheno-2,2′-quinone; a reaction to which similar quinones are known to be prone.[28]



(XXXIII)

The observed inhibition of the bromocresol (V) and bromophenol (VII) reactions by iodide ion may be the result of the exchange reaction with bromine, giving iodine, which in the presence of a large excess of iodide may be unable to oxidise the phenoxide ion (XIII). A similar concentration of bromide does not have an inhibiting effect. This may explain the incomplete reaction of the iodo-compounds. We can only suggest that the failure of the chloro-analogue of (V) to react may be the result of insufficiently rapid elimination of chloride from the radical-anion corresponding to (XVI).

It seems likely that the reaction of 2,4-dibromo-1-naphthol also involves formation and debromination of a radical-anion as in Scheme 1, for we find that here again the reaction does not occur in an excess of alkali. This reaction is considerably faster than that of the bromocresol (V), and we could not detect radical intermediates by e.s.r. spectroscopy. Nor were we able to detect radical intermediates in the copper-catalysed reactions. As both metallic copper and copper(II) salts were effective, we conclude that a redox system is operating.

The spiro-acetal (IV) is particularly resistant to acid hydrolysis, and it is of considerable interest that this compound was formed in 25% yield in the nitration of cresol (VI). Other cases of coupling to bisphenols during the nitration of heavily substituted, phenols *e.g.* 5-methyl-2,4-di-t-butylphenol, have been reported by

[38] M. Adams, M. S. Blois, and R. H. Sands, *J. Chem. Phys.*, 1958, **28**, 774.
[39] C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc.* (*C*), 1968, 2770.
[40] G. M. Coppinger and T. W. Campbell, *J. Amer. Chem. Soc.*, 1953, **75**, 734.
[41] D. F. Bowman and F. R. Hewgill, *J. Chem. Soc.* (*C*), 1966, 2274.
[42] C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc.*, 1968, 1443.

Albert.[43] It therefore seemed feasible that 2-methyl-6-nitro-4-t-butylphenol might undergo a similar reaction to that of 4-nitro-2,6-di-t-butylphenol. However, when heated under the same conditions, although decomposition occurred, none of the spiro-acetal (IV) could be detected by t.l.c.

In conclusion, the formation of radicals from phenols by a process such as that of Scheme 1 appears to depend both on the stability of the keto-tautomer, and on the presence of a suitable leaving group. It is therefore unlikely to be of frequent occurrence. However, such a combination of circumstances could contribute to the autoxidation of hindered phenols in dilute alkaline solution, where instead of halogen as in (XIV) a hydroperoxy-group is present.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage. N.m.r. spectra were obtained with a Varian A60 spectrometer at 60 MHz, and i.r. spectra with a Perkin-Elmer 137G instrument. E.s.r. spectra were obtained with a Varian V-4500-10A spectrometer: the flow system used was that described by Dixon and Norman.[44] Light petroleum had b.p. 56—60°. Extracts were dried with sodium sulphate. 4-t-Butyl-*o*-cresol, b.p. 90—92°/0·8 mmHg, was prepared by the method of Chitchibabin.[45] The yield was increased to 90% by extracting the cresol from there action mixture with 5% aqueous sodium hydroxide. 2-Bromo-4,6-di-t-butylphenol had m.p. 57—58° (lit.,[46] 55·5°).

Oxidation of 4-*t-Butyl*-o-*cresol*.—The cresol (VI) (4·2 g) in ether (150 ml.) was shaken with an excess of silver oxide for 3 hr. The solution was filtered and evaporated to give 3′,4,8-trimethyl-2,5′,10-tri-t-butyldibenzo[1,3][*d*,*f*]dioxepin-6-spirocyclohexa-3′,5′-dien-2′-one (IV) (1·8 g) as yellow prisms, m.p. 238—240° (lit.,[10] 228—229°) (from light petroleum) (Found: C, 81·9; H, 8·6. Calc. for $C_{33}H_{42}O_3$, C, 81·4; H, 8·7%). Hydrogenation in ethanol over palladium–charcoal gave 2-hydroxy-2′-(2-hydroxy-3-methyl-5-t-butylphenoxy)-3,3′-dimethyl-5,5′-di-t-butylbiphenyl as cubes, m.p. 149—151° (lit.,[10] 144—145°) (from light petroleum) (Found: C, 81·3; H, 9·0. Calc. for $C_{33}H_{44}O_3$, C, 81·1; H, 9·1%). With dimethyl sulphate and potassium hydroxide in refluxing aqueous acetone during 16 h, the *dimethyl ether* was obtained as cubes, m.p. 122—123° (from light petroleum) (Found: C, 81·5; H, 9·7. $C_{35}H_{48}O_3$ requires C, 81·4; H, 9·4%), τ (CCl_4) 2·67, 2·77, 3·03, 3·15, 3·37, 3·68 (doublets, J 2·4 Hz, 6 ArH), 6·62 (2 OMe), 7·75, 7·83 (3 Me) and 8·60, 8·83, and 8·96 (3 Bu^t).

Hydrolysis of the Spiro-acetal (IV).—The spiro-acetal (IV) (3 g) in methanol (180 ml), water (2 ml), and perchloric acid (1 ml of 70%) was heated under reflux for 36 h. Most of the methanol was distilled off; the residue was poured into water and extracted with ether. The extract was washed with water and dried, and the residue, after removal of the ether, was chromatographed on alumina. Benzene–light petroleum eluted 2,2′-*dihydroxy*-3,3′-*dimethyl*-5,5′-*di*-t-*butyl*-*biphenyl* (XXIII) (1·8 g), as plates (changing to needles at 70°), m.p. 115—116° (from aqueous methanol or light petroleum) (Found: C, 80·8; H, 9·3. $C_{22}H_{30}O_2$ requires C, 80·9; H, 9·3%), $\nu_{max.}$ (CS_2) 3545 cm^{-1}; τ (CCl_4) 2·88, 3·01 (doublets, J 2·8 Hz, 4 ArH), 5·0 (OH), 7·73 (Me) and 8·70 (Bu^t). More polar solvents eluted only noncrystalline material. The spiro-acetal proved resistant to hydrolysis by weaker acids.

The same dimer (XXIII) was obtained in 20% yield by oxidation of cresol (VI) with ferricyanide, and in 60% yield by oxidation with ceric sulphate.

Synthesis of the Dihydroxybiphenyl (XXIII).—4-t-Butyl-*o*-cresol (VI) (20 g) was nitrated by the method of Albert.[43] The crude product was triturated with ether–light petroleum (1 : 1) and filtered. Crystallisation of the residue gave the spiro-ketal (IV) (5 g), m.p. and mixed m.p. 238—240°. The filtrate was chromatographed on alumina, light petroleum eluting 6-nitro-4-t-butyl-*o*-cresol, m.p. 39—40° (lit.,[43] 39—40°).

The nitrocresol was methylated with dimethyl sulphate and potassium carbonate in refluxing acetone during 24 h. Chromatography on alumina and elution with light petroleum gave 2-*methyl*-6-*nitro*-4-*t*-*butylanisole* (13 g) as prisms, m.p. 53—54° (from methanol) (Found: C, 64·3; H, 7·6; N, 6·4. $C_{12}H_{17}NO_3$ requires C, 64·5; H, 7·7; N, 6·3%).

Catalytic reduction of the nitroanisole in methanol over palladium–charcoal gave 3-*methyl*-5-*t*-*butyl*-o-*anisidine* (10 g), b.p. 100°/0·8 mm (Found: C, 74·3; H, 9·9; N, 7·5. $C_{12}H_{19}NO$ requires C, 74·6; H, 9·9; N, 7·3%).

The amine (2·4 g) in acetic acid (40 ml) and water (20 ml) was diazotised at 0° with sodium nitrite (3 g) in water (20 ml). Potassium iodide (5 g) in water (25 ml) was added slowly with stirring. After 3 h the mixture was poured into 5% aqueous sodium bisulphite and extracted with ether. The residue obtained on removal of the dried solvent was chromatographed on alumina, benzene–light petroleum eluting 2-*iodo*-6-*methyl*-4-*t*-*butylanisole* (2·5 g), as prisms, m.p. 62—63° (from aqueous methanol) (Found: C, 46·9; H, 5·3; I, 40·7. $C_{12}H_{17}IO$ requires C, 47·4; H, 5·6; I, 41·7%), τ (CCl_4) 2·52, 2·96 (doublets, J 2·5 Hz, 2 ArH), 6·30 (OMe), 7·70 (Me), and 8·72 (Bu^t).

The iodoanisole (2 g) was heated with copper powder (2·5 g) at 180° for 20 min. The cooled mixture was extracted with boiling ethanol, the filtered extract evaporated, and the residue chromatographed on alumina. Elution with light petroleum and crystallisation from aqueous methanol gave 2,2′-*dimethoxy*-3,3′-*dimethyl*-5,5′-*di*-t-*butyl*-*biphenyl* as prisms, m.p. 39—40° (Found: C, 81·1; H, 9·9. $C_{24}H_{32}O_2$ requires C, 81·3; H, 9·7%).

The dimethoxybiphenyl (0·5 g) in acetic acid (20 ml) containing hydrobromic acid (5 ml of 45%) was heated under reflux for 4 h. The solution was poured into water and extracted with ether. The extract was washed with water, aqueous sodium hydrogen carbonate, and water, dried, and after removal of the solvent, chromatographed on alumina, giving the dihydroxybiphenyl (XXIII) (0·3 g), m.p. and mixed m.p. 115—116°.

Attempted Condensation of 2-*Hydroxy*-2′-*methoxy*-3,3′-*dimethyl*-5,5′-*di*-t-*butylbiphenyl with* 2-*Iodo*-6-*methyl*-4-*t*-*butylanisole*.—The *hydroxybiphenyl* (3·6 g) [prisms, m.p. 85—87° (from aqueous methanol) (Found: C, 80·7; H, 9·5. $C_{23}H_{32}O_2$ requires C, 81·1; H, 9·5%)] was prepared by methylation of the dihydroxybiphenyl (XXIII) (4 g) with an excess of diazomethane. When heated for 72 h under nitrogen in *s*-collidine with 2-iodo-6-methyl-4-t-butylanisole and cuprous oxide the only identifiable product was 2-methyl-4-t-butylanisole. Reduction also occurred on attempts to condense the iodoanisole with the sodium salt of the hydroxybiphenyl in dimethylformamide, or with the di-

[43] H. E. Albert, *J. Amer. Chem. Soc.*, 1954, **76**, 4983.
[44] W. T. Dixon and R. O. C. Norman, *J. Chem. Soc.*, 1963, 3119.
[45] A. E. Chitchibabin, *Bull. Soc. chim. France*, 1935, **2**, 496.

hydroxybiphenyl (XXIII) or its disodium salt. Reactions with the bromoanisole were no more successful.

By comparison, the cuprous oxide-catalysed reaction between 2-hydroxy-2′,5,5′-trimethoxy-3,3′-dimethylbiphenyl (0·4 g) and 2,5-dimethoxy-3-iodotoluene (0·4 g) gave 2,5,5′-trimethoxy-2′-(2,5-dimethoxy-3-methylphenoxy)-3,3′-dimethylbiphenyl (0·3 g), m.p. and mixed m.p. 121—122°.

Reductive Cleavage of 2-Methoxy-2′-(2-methoxy-3-methyl-5-t-butylphenoxy)-3,3′-dimethyl-5,5′-di-t-butylbiphenyl.—The dimethyl ether (0·4 g) in dry ether (30 ml) was stirred with refluxing, redistilled liquid ammonia (120 ml) whilst sodium (1·4 g) was added during 30 min; the mixture was then stirred for a further 1 h. The ammonia was allowed to evaporate overnight; ether was added to the residue followed by an excess of ice-water. Hydrochloric acid was then added dropwise with stirring. The ether layer was washed with water, dried, and evaporated, leaving a colourless gum, which was taken up in light petroleum and extracted with Claisen's alkali. The acidified extract was shaken with ether, and the ether solution was dried and evaporated to give *3-methyl-5-t-butylguaiacol* (90 mg) as prisms, m.p. 81—83° (from light petroleum) (Found: C, 73·9; H, 9·3. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%), $\nu_{max.}$ (CS_2) 3535 cm^{-1}; τ (CCl_4) 3·26, 3·39 (doublets, J 3 Hz, 2 ArH), 4·18 (OH), 6·29 (OMe), 7·75 (Me), and 8·75 (Bu^t). Evaporation of the light petroleum extract gave a gum which could not be purified.

3-Methyl-5-t-butylguaiacol.— 3-Methyl-5-t-butylanisidine (4·4 g) was diazotised in sulphuric acid, and the cold solution was introduced portionwise below the surface of a stirred solution of sodium sulphate (40 g) in sulphuric acid (40 ml) and water (100 ml) at 60°. When evolution of nitrogen had ceased the mixture was cooled, and extracted with ether. The residue after evaporation of the ether was chromatographed on alumina. Elution with benzene–light petroleum gave an azo-compound and then the guaiacol (3 g), m.p. and mixed m.p. 81—83°.

2-Bromo-6-methyl-4-t-butylanisole.—Bromination of 4-t-butyl-*o*-cresol (VI) in carbon tetrachloride gave 6-bromo-4-t-butyl-*o*-cresol (V), m.p. 47—49°, as thick plates from light petroleum (Found: C, 54·3; H, 6·6; Br, 33·1. Calc. for $C_{11}H_{15}BrO$: C, 54·3; H, 6·2; Br, 32·9%) (lit.,[46] b.p. 96°/3 mm), $\nu_{max.}$ ($CHCl_3$) 3580 cm^{-1}; τ (CCl_4) 2·82, 3·02 (doublets, J 2·7 Hz, 2 ArH), 4·7 (OH), 7·75 (Me), and 8·75 (Bu^t). The bromocresol (V) (4·8 g), dimethyl sulphate (2·5 ml), and potassium hydroxide (0·5 g) were heated in refluxing acetone (100 ml). The initial intense blue colour faded after 30 min to yellow. The mixture was poured into 5% ammonia solution, extracted with ether, and washed with water. Addition of light petroleum to the residue after evaporation of the ether produced crystals of the spiro-ketal (IV) (0·9 g), m.p. and mixed m.p. 238—240°. Distillation of the mother liquor gave *2-bromo-6-methyl-4-t-butylanisole* (2·9 g), b.p. 93°/0·5 mm, as cubes, m.p. 32—33° (from light petroleum) (Found: C, 56·2; H, 6·8; Br, 31·3. $C_{12}H_{17}BrO$ requires C, 56·0; H, 6·7; Br, 31·1%).

6-Iodo-4-t-butyl-o-cresol.—Iodine (20·4 g) and sodium iodide (20 g) in water were added dropwise during 1 h to a stirred solution of 4-t-butyl-*o*-cresol (13·1 g) in diethylamine (80 ml) and ethanol (40 ml) at 0°. The solution was poured into water and extracted with ether. The extract was washed repeatedly with aqueous sulphuric acid (5%) and water, dried, and evaporated, leaving *6-iodo-4-t-butyl-o-cresol* (22 g) as prisms, m.p. 82—83° (from methanol) (Found: C, 45·1; H, 5·5; I, 43·5. $C_{11}H_{15}IO$ requires C, 45·5; H, 5·2; I, 43·7%), τ (CCl_4) 2·62, 2·96 (doublets, J 2·7 Hz, 2 ArH) 4·98 (OH), 7·72 (Me), and 8·74 (Bu^t).

2-Bromo-4-methoxy-5-t-butylphenol (IX).— 2-Bromo-4-methoxyphenol (102 g) and orthophosphoric acid (120 ml; 100%) were stirred vigorously at 70° while t-butyl alcohol (60 ml) was added during 2 h. Stirring was continued at 60° for 3 h after which the lower, acid layer was separated, diluted with water and extracted with light petroleum (300 ml). The combined organic layers were washed with water and extracted with 3% aqueous sodium hydroxide (20 × 100 ml). Fractions 1—6 contained unchanged 2-bromo-4-methoxyphenol. Fractions 7—12 were acidified and the oil distilled at 130°/3 mmHg to give *2-bromo-4-methoxy-5-t-butylphenol* (IX) (35 g), as large plates, m.p. 62—63° (from light petroleum) (Found: C, 51·0; H, 5·9; Br, 30·9. $C_{11}H_{15}BrO_2$ requires C, 51·0; H, 5·8; Br, 30·8%), τ (CCl_4) 3·11, 3·17 (2 ArH), 5·12 (OH), 6·22 (OMe), and 8·67 (Bu^t). Fractions 12—20 gave impure 2-bromo-4-methoxy-6-t-butylphenol (15 g) which had an i.r. identical with that of an authentic sample. Evaporation of the residual light petroleum solution gave 2,5-di-t-butyl-1,4-benzoquinone, m.p. and mixed m.p. 152—153°.

Reaction of 6-Bromo-4-t-butyl-o-cresol (V) *with Alkali.*—(a) The bromocresol (0·01 mol) in dimethylformamide or acetone (80 ml) was shaken with an excess of solid potassium or sodium hydroxide for 30 min, by which time the blue colour had become yellow. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, and the dried solvent was removed. Crystallisation of the residue from light petroleum gave the spiro-acetal (IV), m.p. and mixed m.p. 238—240°, i.r. and n.m.r. spectra identical with those of an authentic sample, in yields consistently higher than 95%. No phenolic material other than unchanged (V) could be detected by t.l.c.

(b) *In the absence of oxygen.* Redistilled dimethylformamide was distilled again under nitrogen onto solid sodium hydroxide (0·02 mol) and the mixture was deoxygenated by alternate freezing and thawing under a low pressure of nitrogen. The redistilled and degassed bromocresol (0·01 mol) was introduced in a sealed ampoule without exposure to the atmosphere, the ampoule was broken, and the mixture was shaken for 1 h. The spiro-acetal (IV) was obtained in quantitative yield.

(c) *At low temperature.* The bromocresol (0·01 mol) was stirred with solid sodium hydroxide (0·02 mol) in acetone at −80°. After 4 h only unchanged bromocresol could be recovered. When a reacting mixture of the bromocresol and sodium hydroxide in acetone was cooled to −80° the blue colour persisted, and portion of the bromocresol was recovered after 3 h.

(d) *With aqueous sodium hydroxide.* The bromocresol (0·01 mol) in acetone (90 ml) was added to sodium hydroxide (0·01 mol) in water (9 ml) and the mixture was shaken for 5 min, then separated into alkali-soluble and insoluble fractions with Claisen's alkali. Crystallisation of the latter from light petroleum gave the spiro-acetal (70%). The former was chromatographed on alumina. Light petroleum eluted the bromocresol (10%) and 2,2′-dihydroxy-3,3′-dimethyl-5,5′-di-t-butylbiphenyl (XXIII) (10%), m.p. and mixed m.p. 115—116°. More polar solvents eluted only amorphous material.

When the experiment was repeated with aqueous sodium

[46] U.S.P. 2,221,808, 1935 (*Chem. Abs.*, 1941, **35**, 1936).

hydroxide (0·015 mol), no blue colour was observed and the unchanged bromocresol was recovered after 2 h. A similar result was obtained with 2,4-dibromo-1-naphthol. In both cases the phenol was first dissolved in aqueous alkali.

The bromocresol (0·01 mole) in acetone was treated with sodium hydroxide (0·01 mol) in water (9 ml). As soon as the blue colour appeared, additional sodium hydroxide solution (0·01 mol) was added. The blue colour faded and the bromocresol was recovered in 70% yield.

When the bromocresol was dissolved in a slight excess of aqueous sodium hydroxide and diluted to five times the volume with dimethylformamide, addition of more bromocresol, or of bromine, produced the blue colour.

(e) *With sodium methoxide in methanol.* Sodium (0·23 g, 0·01 mol) was dissolved in dry methanol (40 ml) and the bromocresol (0·01 mol) in methanol (40 ml) was added. The immediate blue colour faded during 3 min. to pale orange. The mixture was poured into water and extracted with benzene–light petroleum. Separation with Claisen's alkali gave the spiro-acetal (IV) (40%) from the alkali-insoluble fraction. Chromatography of the residue from the alkali-soluble fraction on alumina, and elution with light petroleum gave the bromocresol (10%), and 6-*methyl*-4-*t*-*butylguaiacol* (X) (20%), b.p. 75—77°/0·05 mmHg (Found: C, 74·0; H, 9·3. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%), τ 3·38 (2 ArH), 4·60 (OH), 6·18 (OMe), 7·79 (Me), and 8·74 (Bu^t); the *benzoate* formed prisms, m.p. 79—81° (from light petroleum) (Found: C, 76·3; H, 7·2. $C_{19}H_{22}O_3$ requires C, 76·5; H, 7·4%). Further elution with light petroleum gave the dihydroxybiphenyl (XXIII) (20%) m.p. and mixed m.p. 115—116°.

When the bromocresol (0·01 mol) was added to sodium methoxide (0·015 mol) in methanol and heated under reflux, no blue colour was observed during 2 h. Acidification gave the unchanged bromocresol.

(f) *With sodium in benzene.* The bromocresol (0·01 mol) in dry benzene (70 ml) was shaken overnight with sodium (0·01 mol) giving a flocculent precipitate. A blue colour developed, fading during one day to yellow. The suspension was poured into methanol (5 ml) and the solution was washed with hydrochloric acid (1%) and water. The organic layer was diluted with light petroleum and separated with Claisen's alkali. Work-up as described in (d) gave the spiro-acetal (IV) (30%), the dihydroxybiphenyl (XXIII) (48%), and unchanged bromocresol (20%).

(g) *With sodamide in liquid ammonia.* Sodium (0·46 g, 0·02 mol) and ferric nitrate (0·1 g) were stirred in liquid ammonia (170 ml) for 30 min. The bromocresol (0·01 mol) in dry ether (30 ml) was added portionwise, the mixture being stirred for 1 h. After the addition of an excess of solid ammonium chloride the ammonia was allowed to evaporate overnight. The grey suspension was treated with water and extracted with ether. The extract was washed with hydrochloric acid (2%) and water, dried, and evaporated. Work-up of the residue as in (d) gave the spiro-acetal (IV) (40%), and the dihydroxybiphenyl (XXIII) (30%), as well as amorphous material. Ether extraction of the basified acid-washings gave a brown tar (80 mg).

2-Bromo-6-methyl-4-t-butylanisole did not react under these conditions.

(i) *In the presence of mercury.* The bromocresol (5·1 g), potassium hydroxide (1·4 g), and mercury (11 g) were shaken in dimethylformamide for 1 h. Work-up as in (d) gave the spiro-acetal (IV) (1·6 g), the dihydroxybiphenyl (XXIII), 1·0 g), and unchanged bromocresol (0·6 g).

(j) *In the presence of inhibitors.* Addition of the following compounds (0·05 mol) to the bromocresol (1 mol) in acetone delayed the formation of the blue colour by more than 5 min. when the mixture was shaken with aqueous sodium hydroxide: *o*-phenylenediamine, aniline, hydroquinone, 2-t-butylphenol, 4-t-butylphenol, 4-methoxy-2-t-butylphenol, 4-methoxy-3-t-butylphenol, 2,4,6-tri-t-butylphenol, 2-bromophenol, 4-bromophenol, 4-chloroguaiacol, sodium azide, and sodium cyanide. No reaction was observed during 16 h when sodium iodide (2 mol) was present.

With *o*-phenylenediamine at 0·005, 0·01, 0·02, and 0·04 mol. the inhibition times were 1·1, 2·5, 5·2, and 8·7 min respectively.

Compounds which showed no inhibition included *NN*-dimethylaniline, 2-bromo-4,6-di-t-butylphenol, 2,4,6-tribromophenol, 4-bromo-2,4,6-tri-t-butylcyclohexa-2,5-dienone, maleic anhydride, maleic acid, chloroform, cyclohexene, ethanol, and ethylenediaminetetra-acetic acid.

6-*Methyl*-4-*t*-*butylguaiacol* (X).—The mixture of 4- and 5-t-butylguaiacol (42 g) obtained by butylation of guaiacol,[47] in aqueous dimethylamine (120 g of 30%) was treated dropwise at 20° with aqueous formaldehyde (24 g of 40%) during 1 h. The mixture was stirred at 80° for a further 3 h, after which it was cooled and extracted with light petroleum. Extraction of the light petroleum solution with aqueous hydrochloric acid (10%) gave, on neutralisation, an oil which was extracted with light petroleum. The residue obtained from this extract crystallised from aqueous methanol or light petroleum giving 6-*dimethylaminomethyl*-4-*t*-*butylguaiacol* (31 g) as prisms, m.p. 61—62° (Found: C, 70·8; H, 9·8; N, 5·8. $C_{14}H_{23}NO_2$ requires C, 70·8; H, 9·8; N, 5·9%), τ (CCl_4) 3·27, 3·51 (doublets, *J* 2·7 Hz, 2 ArH), 5·30 (OH), 6·20 (OMe), 6·46 (CH_2), 7·68 (2NMe), and 8·73 (Bu^t). 5-t-Butylguaiacol (18 g) was recovered from the acid-insoluble fraction.

The aminoguaiacol (3 g) was stirred with an excess of iodomethane in dry ether. Evaporation *in vacuo* gave the methiodide salt which was added to a suspension of lithium aluminium hydride (1 g) in tetrahydrofuran (60 ml), and the mixture was heated under reflux for 16 h. The cooled solution was diluted with ice, acidified, and extracted with chloroform. Evaporation of the extract gave 3-methyl-5-t-butylcatechol (1·7 g), m.p. 120—121° (from carbon tetrachloride–light petroleum) (lit.,[48] 114—115°).

The aminoguaiacol (20 g) in ethanol (100 ml) was hydrogenolysed over Raney nickel at 160°/100 atm. during 2 h. The product was taken up in ether, washed with aqueous hydrochloric acid (10%), and water, and then dried. Distillation gave 6-methyl-4-t-butylguaiacol (11 g). The benzoate had m.p. and mixed m.p. 79—81°.

Reaction of 6-*Chloro- and* 6-*Iodo*-4-*t*-*butyl*-o-*cresol with Alkali.*—The chloro-compound [46] did not react with alkali in acetone or dimethylformamide either in the cold or when heated. The iodo-compound (0·01 mol) when shaken with solid potassium hydroxide in acetone for 30 min gave the spiro-acetal (IV) (38 mg), m.p. and mixed m.p. 238—240°. A similar yield was obtained with dimethylformamide. In both cases the solution became blue.

Reaction of 2-*Bromo- and* 2-*Iodo*-4,6-*di*-*t*-*butylphenol with Alkali.*—When shaken in acetone or dimethylformamide with solid potassium hydroxide the bromo-compound gave 3′,4,5′,6-tetra-t-butylbenzoxet-2-spirocyclohexa-3′,5′-dien-

[47] R. H. Rosenwald, *J. Amer. Chem. Soc.*, 1952, **74**, 4602.
[48] E. Müller, F. Guenter, and A. Rieker, *Naturforsch.*, 1963, **18b**, 1002.

2′-one (VIII) in >90% yield, m.p. alone and when mixed with an authentic sample [37] 151—152°, and with identical n.m.r. and i.r. spectra. Lower yields of the same compound were obtained from the iodophenol. In both cases the solution became purplish blue and faded to yellow.

The bromophenol (VII) (2·8 g) in acetone (60 ml) was cooled in an ice–salt bath, and potassium hydroxide (0·56 g) in water (5 ml) was added. As soon as reaction commenced, sodium iodide (3·0 g) in acetone (25 ml), similarly cooled, was added in one portion. The enhanced blue colour faded rapidly to yellow. The bromophenol (VII) was recovered from the reaction mixture in 80% yield.

Reaction of a Mixture of Bromophenols (V) *and* (VII) *with Alkali*.—The bromophenols (V) and (VII) (0·01 mol of each) were shaken with solid potassium hydroxide (0·03 mol) in dimethylformamide for 2 h. The mixture was diluted with water and extracted with light petroleum. The extract was separated into nonphenolic and phenolic fractions with Claisen's alkali. Crystallisation of the former from light petroleum gave the spiro-acetal (IV) [70% based on (V)], m.p. and mixed m.p. 238—240°. The evaporated mother liquors were chromatographed on alumina. Light petroleum eluted the benzoxet (VIII) [30% based on (VII)], m.p. and mixed m.p. 151—152°. Chromatography of the phenolic fraction on alumina and elution with light petroleum gave 2,2′-dihydroxy-3,3′,5,5′-tetra-t-butylbiphenyl [30% based on (VII)], m.p. 193—194° (lit.,[37] 194·5—195·5°). Further elution with light petroleum gave a mixture of the bromophenols (V) and (VII).

Reaction of 2-Bromo-4-methoxy-5-t-butylphenol (IX) *with Alkali*.—(a) *In dimethylformamide*. When the bromophenol (IX) in dimethylformamide was treated with solid potassium hydroxide the colour became blue, then pink with a blue fluorescence. Dilution with water, acidification, and extraction with ether gave a brown gum on evaporation of the extract. Chromatography on alumina did not result in crystalline products.

(b) *On alumina*. A solution of the bromophenol (400 mg) in light petroleum (10 ml) was adsorbed on alkaline alumina (20 g; Spence, Type H), becoming blue, then pink. Elution with benzene–light petroleum (1 : 3) gave the spiro-acetal (XII) (24 mg), m.p. and mixed m.p.[12] 208—210°. No other crystalline products were obtained.

(c) *In ether*. The bromophenol (2·5 g) in ether (100 ml) was shaken with aqueous sodium hydroxide (100 ml of 0·4%) for 5 min. The initial intense blue colour faded rapidly to brown. The dried ether solution was chromatographed on neutral alumina. Elution with light petroleum gave the unchanged bromophenol (90%). More polar solvents eluted brown amorphous material with $\nu_{max.}$ (CS_2) 1680 and 1640 cm^{-1}.

Preparation and Decomposition of 1-Diazo-3,5-di-t-butylbenzene-2-oxide (XI).—2,4-Di-t-butylphenol (8·4 g) in benzene (40 ml) was stirred at 10° while nitric acid (20 ml of 35%) was added during 1 h. The benzene layer was separated, washed with water, dried, and evaporated. The residue, in light petroleum, was filtered through alumina to give *2-nitro-4,6-di-t-butylphenol* (6·3 g) as yellow cubes, m.p. 59—60° (from methanol) (Found: C, 67·3; H, 8·6; N, 5·8. $C_{14}H_{21}NO_3$ requires C, 66·9; H, 8·4; N, 5·6%), τ (CCl_4) 2·05, 2·38 (doublets, J 2·5 Hz, 2 ArH), 8·55 and 8·67 (2 Bu^t).

The nitrophenol (5·7 g) in ethanol was hydrogenated over palladium–charcoal. The mixture was poured into ethanol containing hydrogen chloride, and the solution was filtered and evaporated to dryness. The amine hydrochloride was stored over phosphorus pentoxide. The *acetate* was obtained as needles, m.p. 146—148° (from light petroleum) (Found: C, 72·8; H, 9·7; N, 5·2. $C_{16}H_{25}NO_2$ requires C, 73·0; H, 9·6; N, 5·3%).

The amine hydrochloride (4·2 g) in dry chloroform (120 ml) containing hydrogen chloride was cooled to −10° and stirred vigorously during the addition of iso-pentyl nitrite (5 ml). The solution was filtered in subdued light into light petroleum (400 ml) and then set aside for 30 min. The white precipitate was dissolved in ice–water, extracted with carbon tetrachloride, and the yellow extract was evaporated with a stream of air. The orange gum (2·2 g) darkened rapidly at room temperature or when exposed to light.

The diazo-oxide (0·2 g) and the bromophenol (VII) were irradiated in a Hanovia Photochemical Reactor with a medium-pressure arc tube (125 watts) under nitrogen. After 30 min. the solution was evaporated. The benzoxet (VIII) could not be detected by t.l.c.

When the diazo-oxide (0·2 g) was heated in light petroleum or dimethylformamide to 70° with or without the bromophenol (VII), no benzoxet could be detected. The product was a deep-blue gum which could not be purified, and which gave a positive test for nitrogen.

Reaction of 3,3′-Dimethyl-5,5′-di-t-butylbi(cyclohexa-2,5-dien-1-ylidene)-2,2′-quinone (XXIV) *with 4-Methoxy-2-t-butylphenol*.—A filtered solution of the blue 2,2′-diphenoquinone (XXIV) [prepared by shaking the bisphenol (XXIII) (0·42 g) with silver oxide in dimethylformamide] was added to 4-methoxy-2-t-butylphenol (0·11 g) in dimethylformamide. The solution was poured into water and extracted with light petroleum. 2,2′-Dihydroxy-3,3′-dimethyl-5,5′-di-t-butylbiphenyl (XXIII) and 2,2′-dihydroxy-5,5′-dimethoxy-3,3′-di-t-butylbiphenyl were detected in this extract by t.l.c.

Reaction of 4-Bromo-2,4,6-tri-t-butylcyclohexa-2,5-dienone (XX) *and 2,4,6-Tri-t-butylphenol with Alkali*.—The bromocyclohexadienone (0·34 g) and 2,4,6-tri-t-butylphenol (0·26 g) in dimethylformamide (5 ml) were shaken with sodium hydroxide (0·06 g) in water (3 ml) for 2 min under nitrogen. The blue solution was poured into benzene (20 ml), and the mixture was washed with water and dried. A portion of this solution was deoxygenated by alternate freezing and thawing *in vacuo*. The e.s.r. spectrum had $a_{H\text{-}meta}$ 0·170 mT and $a_{H\text{-}Bu^t}$ 0·033 mT. Sodium azide did not inhibit this reaction.

Under these conditions no signal was observed for the phenol or bromocyclohexadienone alone. When the latter was treated with solid potassium hydroxide in dimethylformamide under nitrogen the blue colour of the 2,4,6-tri-t-butylphenoxyl radical appeared after 5—10 min, and its presence was confirmed by e.s.r.

Addition of bromine in aqueous sodium hydroxide to a solution of 2,4,6-tri-t-butylphenol in dimethylformamide gave an immediate blue colour. No blue colour was observed unless alkali was present.

Reaction of 4-Butyl-o-cresol (VI) *with Iodine*.—The cresol (9·8 g) and sodium hydroxide (3·0 g) in water (100 ml) were shaken vigorously with iodine (17 g) in ether (160 ml) for 5 min. The initial green colour faded to light yellow. The ether layer was separated, washed with aqueous sodium hydroxide (2%), sodium thiosulphate (5%) and water, and then dried and evaporated. The residue (14·1 g) crystallised from methanol to give 6-iodo-4-t-butyl-*o*-cresol as prisms, m.p. and mixed m.p. 82—83°. Acidification of the alkaline washings gave 4-t-butyl-*o*-cresol (0·9 g).

Reaction of 4-Methoxy-3-t-butylphenol with Iodine.—(a) *In ether.* The phenol (3·0 g) and sodium hydroxide (0·9 g) in water (150 ml) were shaken vigorously with iodine (4·3 g) in ether (50 ml). The initial deep blue colour faded during 5 min to pale brown. The ether layer was washed with aqueous sodium hydroxide (5%) and water, dried, and evaporated. Chromatography of the residue on alumina and elution with benzene–light petroleum (1 : 1) gave the spiro-acetal (XII) (0·9 g), m.p. and mixed m.p. 209—210°. More polar solvents eluted only noncrystalline material. Acidification of the alkaline washings gave 4-methoxy-3-t-butylphenol (0·2 g).

(b) *In dimethylamine.* The phenol (7·7 g) in dimethylamine (35 ml) and ethanol (20 ml) at 0° was treated dropwise with a solution of iodine (9·8 g) and sodium iodide (10·0 g) in water (30 ml) during 40 min. After being stirred for 3 h the brown solution was poured into water and extracted with ether. Removal of the washed (10% hydrochloric acid) and dried solvent left a residue which crystallised from ether–light petroleum to give 2,2′-dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl (3·1 g) m.p. alone and when mixed with an authentic sample [12] 169—170°. The mother liquors were adsorbed on alumina. Benzene–light petroleum (1 : 4) eluted the spiro-acetal (XII) (0·41 g). Further elution with the same solvent gave 8-methoxy-3,7-di-t-butyldibenzofuran-1,4-quinone (0·22 g), m.p. and mixed m.p. 190—192°.[28] More polar solvents eluted yellow noncrystalline material.

Reaction of 2-Bromo-4-methoxy-5-t-butylphenol (IX) *with Iodine.*—(a) *In ether.* The bromophenol (5·2 g) in acetone (20 ml) was added to sodium hydroxide (0·9 g) in water (120 ml) and the mixture was shaken while iodine (5·0 g) in ether (100 ml) was added portionwise during 5 min. The blue colour at each addition faded rapidly to light brown. The ether layer was separated, washed with aqueous sodium thiosulphate (5%) and water, dried, and evaporated. The residue was extracted with ethanol leaving yellow crystals, of 4,4′-di-t-butyl-2,2′,5,5′-dibenzoquinone (XXXI) (0·61 g), m.p. and mixed m.p. 195—196°.[28] The evaporated ethanol extracts were chromatographed on alumina. Benzene–light petroleum eluted the spiro-acetal (XII) (93 mg), and a dark red gum which had $\nu_{max.}$ (CS_2) 1680, 1645, and 1640 cm^{-1}. A similar gum was produced from 2-bromo-5-t-butyl-1,4-benzoquinone with alkali.

(b) *With iodine in sodium iodide.* The same quantities of the bromophenol and alkali were shaken with iodine (4·9 g) and sodium iodide (11 g) in water (100 ml). The brown mixture was extracted with ether, and the extract was washed with aqueous sodium thiosulphate (5%) and water, and then dried and evaporated. Chromatography of the residue on alumina and elution with benzene–light petroleum (1 : 4) gave the spiro-acetal (XII) (22 mg). Further elution with benzene–light petroleum (1 : 2) gave 2-(*2-bromo-4-methoxy-5-t-butylphenoxy*)-*5-t-butyl*-1,4-*benzoquinone* (XXVIII) (0·21 g) as yellow needles, m.p. 146—148° (from light petroleum) (Found: C, 59·6; H, 6·1; Br, 10·9. $C_{21}H_{25}BrO_4$ requires C, 59·9; H, 6·0; Br, 10·9%), τ (CCl_4) 2·97, 3·01 (2 ArH), 3·50, 4·62 (2 vinylic H), 6·10 (OMe), 8·64 and 8·69 (2 Bu^t); $\nu_{max.}$ (CS_2) 1685 and 1655 cm^{-1}.

Catalytic reduction of the compound in ethanol gave the *hydroquinone*, τ (CCl_4) 2·98, 3·04, 3·15, 4·12 (4 ArH), 6·13 (OMe), 8·63 and 8·68 (2 Bu^t), which reverted to the quinone during recrystallisation. Catalytic hydrogenolysis in ethanol and sodium hydroxide (4 mol) during 8 h gave 2-(4-methoxy-3-t-butylphenoxy)-5-t-butylhydroquinone (XXIX) (80%), m.p. and mixed m.p. [49] 137—139°.

Reaction of the Bromophenols (V) *and* (IX) *with Metals.*—Solutions of the bromocresol (V) in dimethylformamide became blue and then yellow, and gave the spiro-acetal (IV) in good yield when treated with the following: copper, cuprous oxide, cupric oxide, copper sulphate, bis(acetylacetonato)copper(II), and silver acetate. No change was observed with iron, zinc, or mercury.

With bis(acetylacetonato)copper(II) in acetone the bromophenol (IX) gave the pink solution obtained with sodium hydroxide. When the bromophenol (IX) (450 mg) was stirred in acetone containing bis(acetylacetonato)copper(II) and anhydrous sodium acetate, the spiro-acetal (XII) (240 mg) was obtained. Sodium acetate alone gave the pink solution.

Thermal Decomposition of 6-Nitro-4-t-butyl-o-cresol.—The nitro-compound (1 g) was heated in a stream of nitrogen in n-dodecane for 4 h at 215°. The dodecane was removed under reduced pressure leaving a pale brown oil. T.l.c. showed some decomposition but no spiro-acetal.

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