Oxidation of Alkoxyphenols. Part XV.[1] Autoxidation of 2- and 3-Mono- and 2,5-Di-t-butyl-4-methoxyphenol and Related Compounds

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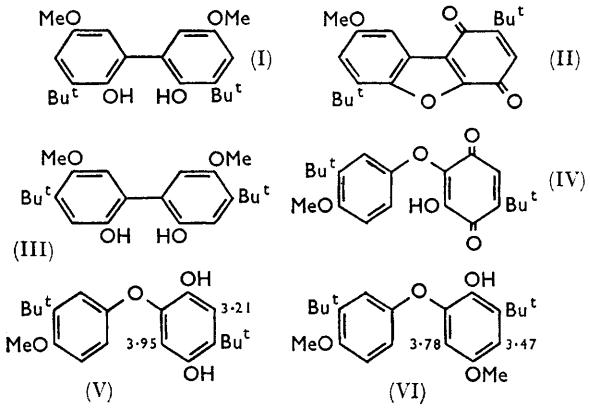
Autoxidation of 4-methoxy-2-t-butylphenol gives the *ortho*-coupled diol, which, in turn, is autoxidised to 8-methoxy-2,6-di-t-butyldibenzofuran-1,4-quinone. Autoxidation of 4-methoxy-3-t-butylphenol also gives some diol, but the major product is 3-hydroxy-2-(4-methoxy-3-t-butylphenoxy)-5-t-butyl-1,4-benzoquinone. Autoxidation of 4-methoxy-2,5-di-t-butylphenol gives a mixture from which 2,5-di-t-butyl-1,4-benzoquinone, its mono-epoxide, and the *cis*- and *trans*-diepoxides were isolated. The reactions of these epoxides with various reducing agents and with hydrogen halides are described, and confirm the assigned structures.

THE BHA (butylated hydroxyanisole) isomers 4-methoxy-2- and 3-t-butylphenol are used extensively as antioxidants in food. 4-Methoxy-2,5-di-t-butylphenol is also used as an antioxidant. Previous papers in this series have described their oxidation by various one-electron abstractors, which in alkaline or neutral solution gave dimers and trimers, and in acid solution, quinones. Our present interest is in their autoxidation in alkaline solution. Solutions of the phenols in a suitable alcohol, containing enough base to give a convenient reaction time, were shaken with oxygen until 1 mol. had been absorbed. The concentration of base was found to affect the rate of reaction but not the nature of the products.

Autoxidation of 4-methoxy-2-t-butylphenol in ethanol gave only one identifiable product, the diol (I). This is presumably formed by the coupling of the aryloxy-radicals derived from the simple phenol, and is also produced when the phenol is oxidised by alkaline ferricyanide.[2] It is relatively insoluble in alcohols, but when autoxidised in t-butyl alcohol the diol (I) gave a small amount of the dibenzofuranquinone (II): the

[1] Part XIV, C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc.* (*C*), 1968, **1443**.
[2] J. Baltes and F. Volbert, *Fet. u. Seifen*, 1955, **57**, 660.

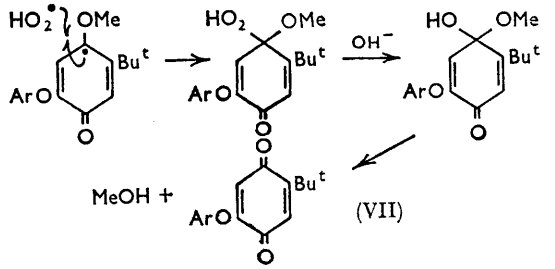
oxidative conversion of (I) into (II) has already been discussed.[3]



Unlike its isomer, 4-methoxy-3-t-butylphenol was not detectably autoxidised in ethanol. In t-butyl alcohol–1,2-dimethoxyethane containing potassium t-butoxide a small amount of the diol (III) was formed, but the major product was the phenoxy-quinone (IV).

Structure (IV), suggested by spectroscopic evidence, by the formation of a mono-acetate, and by reduction to a triol, was confirmed when autoxidation of the hydroquinone (V) under the same conditions gave identical material. The position of the new hydroxy-group between two oxygens is apparent from the chemical shift of the proton *para* to it in the n.m.r. spectrum of the triol. At τ 3·54 this is comparable with that of the ring protons at τ 3·58 in 2,5-di-t-butylhydroquinone, and with the chemical shift (indicated in the formulae) of similarly situated protons in compounds (V) and (VI).[4] It is clearly too low for that of a ring proton between two oxygens, which would be the situation if the new hydroxy-group had entered at the alternative position. The hydroquinone (V) was synthesised unambiguously by the modified[5] Ullmann reaction between 4-methoxy-3-t-butylphenol and 2,5-dibenzyloxy-4-bromo-t-butylbenzene, followed by hydrogenolysis. An attempt to introduce the new oxygen function by Thiele acetylation of the quinone (VII) was unsuccessful.

The orientation of the substituents strongly suggests that the coupling reaction in the formation of the phenoxy-quinone (IV) precedes oxidative demethylation, and there is evidence[6] that this same *ortho*-carbon–oxygen coupling may be involved in the formation of the dibenzo[*d*,*f*][1,3]dioxepin when this phenol is oxidised by ferricyanide. Although there are several possible ways in which oxidative demethylation may occur, one of the most likely is by reaction between a hydrogenperoxy-radical and an aryloxy-radical as in Scheme 1, followed by nucleophilic replacement of hydroperoxide by hydroxide, and loss of methanol. The final hydroxylation must involve attack by a species of higher oxidation state than hydroxide anion, for none of the corresponding hydroxy-hydroquinone was obtained when the quinone (VII) was shaken in alkali under nitrogen. 1,4-Addition of either a hydrogenperoxy-radical, or of the anion, as

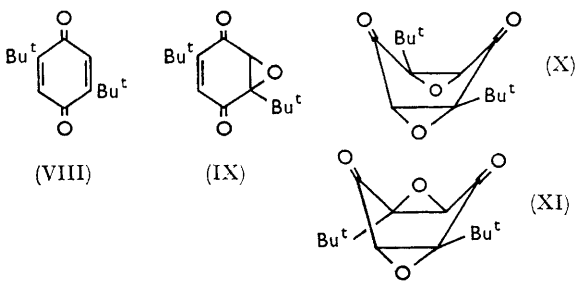


SCHEME 1 (Ar = 4-methoxy-3-t-butylphenoxy)

has recently been discussed by Collier[7] in the oxidation of purpurogalloquinone, could effect this conversion.

No identifiable product could be isolated from autoxidation of the diol (III) and the recovery of much unchanged starting material suggests that some initial product is more rapidly oxidised than the diol.

Autoxidation of 4-methoxy-2,5-di-t-butylphenol in ethanolic alkali followed a different course; no dimeric products being obtained. Uptake of oxygen was rapid, and four products (VIII) (IX), (X), and (XI) were isolated in proportions depending on the precise conditions employed



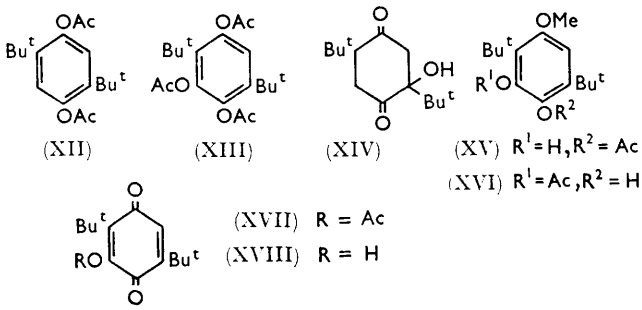
Shortly after the completion of this work the preparation of these epoxides [(IX)—(XI)] by reaction of the quinone (VIII) with alkaline hydrogen peroxide or t-butylhydroperoxide was described by Moore.[8] Although he was able to assign configurations to the diepoxides, he did not succeed in purifying the *cis*-isomer (X). As Moore's structural assignments were made on spectroscopic and analytical data, we present chemical evidence which substantiates them.

Reductive acetylation of the mono-epoxide (IX) gave mainly the diacetate (XII) and triacetate (XIII), and a smaller quantity of the hydroxy-dione (XIV), which was difficult to purify.

The structure of the triacetate (XIII) was proved by synthesis. An obvious route involves Thiele acetylation of the quinone (VIII), but as no reaction occurred

[3] F. R. Hewgill and B. R. Kennedy, *J. Chem. Soc.* (*C*), 1966, 362.
[4] F. R. Hewgill and D. G. Hewitt, *J. Chem. Soc.*, 1965, 3660.
[5] R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1964, 1108.
[6] F. R. Hewgill and D. G. Hewitt, *Tetrahedron Letters*, 1965, 3737.
[7] P. D. Collier, *J. Chem. Soc.* (*C*), 1966, 2255.
[8] H. W. Moore, *J. Org. Chem.*, 1967, **32**, 1996.

even using the most vigorous conditions, the quinone is evidently too hindered. As it has not proved possible to substitute 2,5-dimethoxy-1,4-di-t-butylbenzene electrophilically without debutylation,[9] or 4-methoxy-2,5-di-t-butylphenol without demethylation,[9,10] we employed the



(XII) (XIII) (XIV) (XV) $R^1 = H, R^2 = Ac$ (XVI) $R^1 = Ac, R^2 = H$

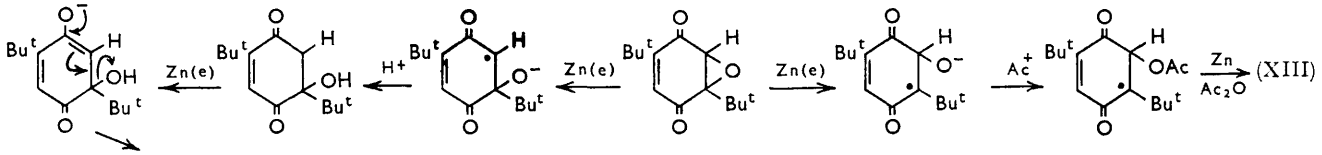
(XVII) R = Ac (XVIII) R = H

reaction of lead tetra-acetate with this phenol to introduce the third oxygen function. This reaction proved complex, and is described in the following paper. The mixture of monoacetates (XV) and (XVI) obtained in this way could not be demethylated by pyridinium chloride or hydrobromic acid without loss of a t-butyl group, and was therefore oxidised to the acetoxy-quinone (XVII) using Frémy's salt. Reductive acetylation gave the triacetate (XIII).

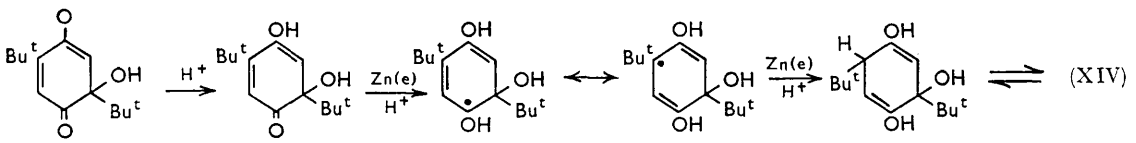
is evidently sufficient to slow down formation of the normal product (XIII), and allow the less usual reactions of Scheme 3 to become significant. Elimination of an α-substituent has been observed in the reduction of a hindered ketone by zinc and acetic acid.[11]

The reduction of the monoepoxide (IX) by other reagents was also investigated. Sodium dithionite, and hydrogenation over palladium–charcoal, both gave substantial amounts of 2,5-di-t-butylhydroquinone, and smaller quantities of the hydroxy-dione (XIV), but the associated reduction products could not be purified, and appeared to be mixtures of alicyclic compounds. The hydroquinone was the only identified product from lithium aluminium hydride reduction. Reduction by chromous acetate gave, as well as the hydroquinone, some of the hydroxy-quinone (XVIII), whose structure was proved by the conversion of (XVIII) into the acetoxy-quinone (XVII) on acetylation. It seems likely that the hydroxy-quinone (XVIII) is an artifact produced by oxidation of the corresponding hydroxy-hydroquinone during extraction. The failure of the monoepoxide (IX) to react with acetic acid alone under these conditions indicates that the formation of the hydroxy-hydroquinone is not simply the result of hydrolysis followed by elimination.

Reaction of the monoepoxide (IX) with hydrobromic



SCHEME 2



SCHEME 3

The structure of the hydroxy-dione (XIV) is indicated by its n.m.r. spectrum. This (in carbon tetrachloride) showed a hydroxy-resonance (removed on exchange with deuterium oxide) at τ 6·82, resonances between τ 7·04 and 7·68 which were ascribed to five alicyclic ring protons, and two t-butyl resonances at τ 8·96 and 9·01. The absence of any resonance below τ 6·82 indicates the tertiary nature of the hydroxy-group. The i.r. spectrum, showing carbonyl absorption at 1710 $cm.^{-1}$, bonded hydroxy at 3520 $cm.^{-1}$ and a small bonded hydroxy at 3460 $cm.^{-1}$, also supports this structure.

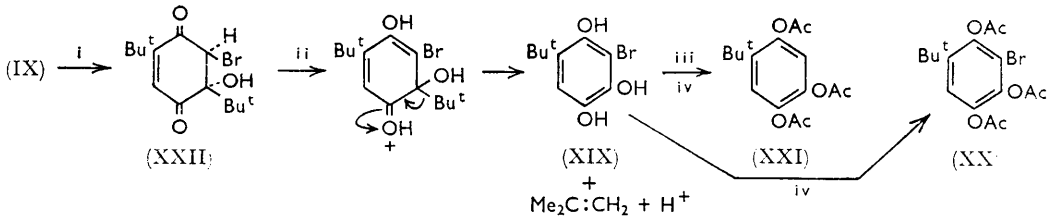
We ascribe the variety of the reductive acetylation products to the unusually hindered nature of the oxygen atoms in the epoxide (IX). Three competing reactions may be envisaged, and these are shown in Schemes 2 and 3. The steric compression in the triacetate (XIII) acid in acetic acid gave the bromophenol (XIX), which was not isolated but converted into the triacetate (XX). The location of the bromine at position 2 and not 3 was revealed when hydrogenolysis of the bromophenol (XIX), followed by acetylation, gave 2,4,5-triacetoxy-t-butylbenzene (XXI). The debutylation involved in the formation of the bromophenol is thought to proceed as in Scheme 4, where it will be seen that, in the initial *trans*-bromohydrin (XXII), elimination of hydrogen bromide or water is precluded by the stereochemistry imposed by the opening of the epoxide ring. A similar reaction occurred with hydrochloric acid.

These reactions with hydrogen halides clearly indicate that this oxidation product is the monoepoxide (IX) and not the cyclic peroxide (XXIII); a structure that cannot be excluded on evidence from the n.m.r. spectrum and reduction products alone. Like Moore [8] we have

[9] F. R. Hewgill and B. R. Kennedy, *J. Chem. Soc.*, 1965, 2921.
[10] E. Muller, H. Kaufmann, and A. Rieker, *Annalen*, 1964, **671**, 61.
[11] R. S. Rosenfeld and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1955, **77**, 4367.

also obtained the monoepoxide by reaction of the quinone (VIII) with alkaline hydrogen peroxide.

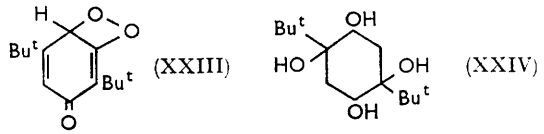
Similar reactions were employed to confirm the structures of the diepoxides. Reductive acetylation of both the *cis*- (X) and the *trans*-diepoxide (XI) gave the diacetate (XII), the yield being higher (90%) in the latter case. Rather surprisingly, neither the triacetate (XIII) nor hydroxy-dione (XIV) were formed, from



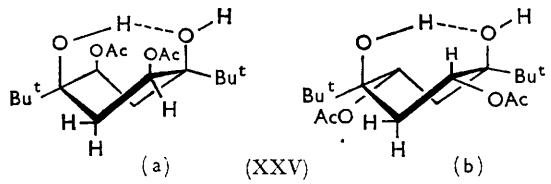
Reagents: i, HBr; ii, H^+; iii, H_2–Pd, KOH; iv, Ac_2O

SCHEME 4

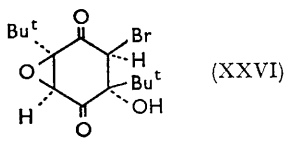
which we can only conclude that the monoepoxide (IX) is not an intermediate in these reductions. When reduced with lithium aluminium hydride the *trans*-diepoxide (XI) gave a mixture of products which could



not be separated. Similar reduction of the *cis*-diepoxide (X) gave a mixture from which a product believed to be the tetrol (XXIV) was isolated. The n.m.r. spectrum showed only one t-butyl resonance, but the insolubility of the compound prevented a reliable assessment of its stereochemistry by either i.r.[12] or n.m.r. spectroscopy. However, the diacetate derived from (XXIV) was soluble enough for a tentative assignment of its configuration and conformation to be made from spectroscopic data, without invoking uncertain arguments based on the sterically preferred mode of reduction of the *cis*-diepoxide. The i.r. spectrum showed hydroxy-absorption at 3592 and 3506 cm.$^{-1}$ but no significant broadening or shift of the carbonyl frequency. From the frequency shift of the bonded hydroxy-absorption we conclude that the hydroxy-groups are intramolecularly bonded to each other, and rather closer together than in cyclohexane-*cis*-1,3-diol ($\nu_{max.}$[13] 3544 cm.$^{-1}$). The strength of the hydrogen bond is similar to that described by Stolow [12] for *cis,cis,cis*-2,5-di-t-butyl-1,4-cyclohexanediol, which has $\nu_{max.}$ 3480 cm.$^{-1}$, and to which he assigns a twist–boat conformation. By analogy, the diacetate of (XXIV) must also have a twist–boat conformation. The symmetry of the molecule is evident from its n.m.r. spectrum, which shows only one acetate and one t-butyl resonance. Both pairs of methine and methylene protons appear as one ABX system, with J_{AX} −4·5 and J_{BX} 2·5 c./sec. The dihedral angle between the methine and either neighbouring methylene C–H bond is therefore small, indicating that the acetate possesses structure (XXVa), in which the methine C–H bond approximately bisects the angle subtended by the C–H bonds of the neighbouring methylene group. In the alternative isomer (XXVb) both acetate groups are *trans* to the hydroxy-groups. Here the most stable twist–boat conformation requires an approximately *trans*-antiparallel relationship between the methine hydrogens and one of the neighbouring methylene hydrogens, which would imply a much larger coupling constant. This dihedral angle can only be reduced at the expense of forcing the acetate groups into pseudo-axial positions. Thus the acetate,



and the tetrol from which it was derived, are thought to have all four oxygens on the same side of the ring.



Reaction of the *trans*-diepoxide (XI) with hydrobromic acid gave the monobromohydrin (XXVI) which was reconverted into the *trans*-diepoxide by acetic anhydride in pyridine. Similar treatment of the *cis*-diepoxide (X) gave a mixture of bromohydrins which could not be crystallised, and which was largely reconverted into the *cis*- diepoxide on chromatography.

Epoxidation of the monoepoxide (IX) with hydrogen peroxide gave a mixture of the *cis*- and *trans*-diepoxides (X) and (XI) in the ratio 3 : 2. Autoxidation of 2,5-di-t-butylhydroquinone gave the same products as autoxidation of 4-methoxy-2,5-di-t-butylphenol. In these autoxidations it was noticed that the use of stronger alkali decreased the yield of the *trans*-diepoxide (XI). Like Moore [8] we have found that the diepoxides are not isomerised by alkali. However, on prolonged autoxidation, the *trans*-diepoxide is destroyed more rapidly than the *cis*-, which explains the variation in the ratio of these products.

[12] R. D. Stolow and M. M. Bonaventura, *J. Amer. Chem. Soc.*, 1963, **85**, 3636.
[13] L. P. Kuhn, *J. Amer. Chem. Soc.*, 1952, **74**, 2492.

As neither the quinone (VIII) nor the monoepoxide (IX) react with oxygen under the conditions used for autoxidation, we conclude that the mechanism of autoxidation of 4-methoxy-2,5-di-t-butylphenol involves initial demethylation to the quinone (VIII) by a process such as that described in Scheme 1. This is supported by the rapid appearance of the characteristic triplet of 2,5-di-t-butyl-1,4-benzosemiquinone when an alkaline alcoholic solution of 4-methoxy-2,5-di-t-butylphenol, briefly shaken with air was examined by e.s.r. spectroscopy. As no secondary radicals were observed, and because autoxidation of the phenol and epoxidation of the quinone gave the same products, further oxidation must involve epoxidation of quinone (VIII) by the anion of hydrogen peroxide, produced in the initial oxidation.

$$ArO^- + O_2 \longrightarrow ArO\cdot + (O_2)\cdot^-$$
$$ArO^- + (O_2)\cdot + H^+ \longrightarrow ArO\cdot + HO_2^-$$

EXPERIMENTAL

I.r. spectra were determined with a Perkin-Elmer Infracord, Model 337. Carbon disulphide solutions were used unless otherwise stated. N.m.r. spectra were determined with a Varian Associates A-60 Spectrometer at 60 Mc./sec. for carbon tetrachloride solutions unless stated to the contrary. Tetramethylsilane was used as an internal standard. Melting points were determined with a Kofler hot-stage apparatus. Light petroleum refers to the fraction of b.p. 56—60°.

Autoxidation of 4-*Methoxy*-2-*t*-*butylphenol*.—The phenol (3·47 g.) in ethanol (30 ml.) and 15M-aqueous potassium hydroxide (5 ml.) was vigorously shaken in the presence of oxygen. The reaction was stopped when 1 mol. of oxygen (480 ml.) had been absorbed. The dark brown solution was poured into water, neutralized with dilute hydrochloric acid, and extracted with ether. Concentration of the washed and dried (Na_2SO_4) solution gave 2,2′-dihydroxy-5,5′-dimethoxy-3,3′-di-t-butylbiphenyl (I) (1·66 g.), m.p. and mixed m.p. 229—230°. Chromatography of the residue from the mother liquor on alumina yielded no crystalline product.

Autoxidation of 2,2′-*Dihydroxy*-5,5′-*dimethoxy*-3,3′-*di*-*t*-*butylbiphenyl* (I).—The diol (I), (3·26 g.) in t-butyl alcohol (150 ml.) and 12·5M-aqueous potassium hydroxide (4 ml.) was autoxidised as described above for 4-methoxy-2-t-butylphenol. Concentration of the ether extract gave the unchanged diol (I) (1·24 g.). Adsorption of the evaporated mother liquor on alumina and elution with benzene gave 8-methoxy-2,6-di-t-butyldibenzofuran-1,4-quinone (II) (25 mg.), m.p. and mixed m.p. 178—179°.

Autoxidation of 4-*Methoxy*-3-*t*-*butylphenol*.—The phenol (7·3 g.) in t-butyl alcohol and 1,2-dimethoxy-ethane (1 : 1; 160 ml.) containing potassium t-butoxide (8·4 g.) was autoxidised as described above. The ether extract was evaporated to leave a dark gum, which was washed with light petroleum, and the remainder was crystallised from ether–light petroleum to give 3-*hydroxy*-2-(4-*methoxy*-3-*t*-*butylphenoxy*)5-*t*-*butyl*-1,4-*benzoquinone* (IV) (1·65 g.) as dark purple plates, m.p. 150—151° (Found: C, 70·2; H, 7·5. $C_{21}H_{26}O_5$ requires C, 70·4; H, 7·3%), $\nu_{max.}$ (CCl_4) 3390 (bonded OH) and 1660 cm.$^{-1}$ (C=O); τ 8·67, 8·65 (2 Bu^t), 6·20 (OMe), 3·63 (vinylic H), 3·41—3·07 (AB_2 system, *J* 2·0 c./sec., 3 ArH). Chromatography on alumina of the residue from the evaporated light petroleum washings, and elution with light petroleum gave 2,2′-dihydroxy-5,5′-dimethoxy-4,4′-di-t-butylbiphenyl (III) (310 mg.), m.p. and mixed m.p. 167·5—168·5°. Elution with benzene gave starting material (1·64 g.), and elution with ether gave the phenoxy-quinone (IV) (0·84 g.).

Reactions of 3-*Hydroxy*-2-(4-*methoxy*-3-*butylphenoxy*)-5-*t*-*butyl*-1,4-*benzoquinone* (IV).—(a) *Acetylation*. The hydroxy-phenoxy-quinone (IV) (200 mg.) in acetic anhydride (10 ml.) and pyridine (1 ml.) was left at room temperature for 14 hr. to give 3-*acetoxy*-2-(4-*methoxy*-3-*t*-*butylphenoxy*)-5-*t*-*butyl*-1,4-*benzoquinone* (120 mg.) as brown prisms, m.p. 84—85°, from light petroleum (Found: C, 69·1; H, 7·2. $C_{23}H_{28}O_6$ requires C, 69·0; H, 7·1%), $\nu_{max.}$ (CCl_4) 1775 (OAc) and 1665 cm.$^{-1}$ (C=O); τ 8·68, 8·66 (2 Bu^t), 8·08 (OAc), 6·18 (OMe), 3·56 (vinylic H), and 3·32—3·10 (AB_2 system, *J* 2·0 c./sec., 3 ArH).

(b) *Hydrogenation*. The hydroxy-phenoxy-quinone (IV) (80 mg.) in ethanol was hydrogenated over palladium–charcoal at room temperature and pressure to give 2,3,6-*trihydroxy*-4′-*methoxy*-3′,4-*di*-*t*-*butyldiphenyl ether* (70 mg.) as needles, m.p. 161—163°, from benzene–light petroleum (Found: C, 70·0; H, 7·7. $C_{21}H_{28}O_5$ requires C, 70·0; H, 7·8%), $\nu_{max.}$ 3540 cm.$^{-1}$; τ 8·64, 8·60 (2Bu^t), 6·18 (OMe), 3·54 (ArH), and 3·42—3·00 (AB_2 system, *J* 2·0 c./sec., 3 ArH).

This triol (50 mg.) was acetylated as described above to give 2,3,6-*triacetoxy*-4′-*methoxy*-3′,4-*di*-*t*-*butyldiphenyl ether* (45 mg.) as prisms, m.p. 187—188°, from benzene–light petroleum (Found: C, 67·0; H, 7·1. $C_{27}H_{34}O_8$ requires C, 66·70 H, 7·0%), $\nu_{max.}$ 1775 cm.$^{-1}$ (OAc); τ 8·14, 8·08, and 7·77 (3 OAc).

Synthesis of 2,5-*Dihydroxy*-4′-*methoxy*-3′-4-*di*-*t*-*butyldiphenyl Ether* (V).— 2-Bromo-5-t-butylhydroquinone [14] (11·2 g.) in ethanol (50 ml.) was treated with sodium (2·7 g.) under nitrogen, and benzyl chloride (13·3 g.) in ethanol (20 ml.) was added. The mixture was heated under reflux for 3 hr. The cooled mixture was diluted with water and extracted with ether. Evaporation of the washed, and dried (Na_2SO_4) ether extract gave a brown solid, recrystallisation of which from benzene–light petroleum gave 2,5-*dibenzyloxy*-4-*bromo*-*t*-*butylbenzene* (11·6 g.) as plates, m.p. 135—137° (Found: C, 67·4; H, 6·2. $C_{24}H_{25}BrO_2$ requires C, 67·8; H, 5·9%); τ 8·68 (Bu^t), 5·00, 4·95 (2 CH_2Ph), 3·14, 2·90 (2 ArH), and 2·64 (2 Ph).

This bromo-compound (1·30 g.), 4-methoxy-3-t-butylphenol (0·72 g.) and cuprous oxide (0·85 g.) were heated in refluxing *s*-collidine (30 ml.) in an atmosphere of nitrogen for 68 hr. The cooled mixture was poured into concentrated hydrochloric acid (50 ml.) and extracted with ether. The extract was washed with concentrated hydrochloric acid, aqueous sodium hydrogen carbonate, water, and then dried (Na_2SO_4). Removal of the solvent gave a brown oil. Adsorption on alumina and elution with light petroleum gave unchanged bromo-compound (0·45 g.). Elution with benzene–light petroleum (1 : 1) gave an oil (0·55 g.) which was hydrogenolysed in AnalaR acetic acid (20 ml.) over palladium–charcoal at room temperature and pressure to give 2,5-*dihydroxy*-4′-*methoxy*-3′,4-*di*-*t*-*butyldiphenyl ether* (V) (0·21 g.) as plates, m.p. 137—139°, from benzene–light petroleum (Found: C, 72·7; H, 8·2. $C_{21}H_{26}O_4$ requires C, 73·2; H, 8·2%), $\nu_{max.}$ 3590 and 3550 cm.$^{-1}$; τ 8·65

[14] C. J. R. Adderley and F. R. Hewgill, to be published.

(2 Bu^t), 6·18 (OMe), 3·95, 3·21 (2 ArH), and 3·32—3·02 (AB_2 system, J 2·0 c./sec., 3 ArH).

Synthesis of 3-*Hydroxy*-2-(4-*methoxy*-3-*t*-*butylphenoxy*)-5-*t*-*butyl*-1,4-*benzoquinone* (IV).—The diphenyl ether (V) (50 mg.) and potassium t-butoxide (35 mg.) in t-butyl alcohol and 1,2-dimethoxyethane (1 : 1, 10 ml.) was autoxidised under the condition described for 4-methoxy-3-t-butylphenol. Chromatography of the extracted product on alumina and elution with ether gave the hydroxy-phenoxy-quinone (IV) (7 mg.), m.p. and mixed m.p. 149—151°. The i.r. spectrum was identical with that of the autoxidation product of 4-methoxy-3-t-butylphenol.

Preparation of 2-(4-*Methoxy*-3-*t*-*butylphenoxy*)-5-*t*-*butyl*-1,4-*benzoquinone* (VII).—The diphenyl ether (V) (120 mg.) and silver oxide (200 mg.) were shaken in dried ether (20 ml.) for 20 min. Filtration and evaporation of the yellow solution gave an orange gum which on crystallisation from n-pentane gave 2-(4-*methoxy*-3-*t*-*butylphenoxy*)-5-*t*-*butyl*-1,4-*benzoquinone* (VII) (50 mg.) as yellow prisms, m.p. 132—133° (Found: C, 73·9; H, 7·6. $C_{21}H_{26}O_4$ requires C, 73·7; H, 7·7%), $\nu_{max.}$ 1670 cm.$^{-1}$ (C=O); τ 8·71, 8·62 (2 Bu^t), 6·10 (OMe), 4·43, 3·50 (2 vinylic H), and 3·13—3·03 (AB_2 system, J 1·0 c./sec., 3 ArH).

The phenoxy-quinone (VII) (50 mg.) failed to react with acetic anhydride (8 ml.) in the presence of concentrated sulphuric acid (0·5 ml.) during 16 hr. at room temperature. It was also unaffected by the conditions in which 4-methoxy-3-t-butylphenol was autoxidised. No identifiable product was obtained when the phenoxy-quinone (100 mg.) was shaken in ethanol (20 ml.) containing aqueous sodium hydroxide (0·1M, 5 ml.) under nitrogen.

Autoxidation of 2,2′-*Dihydroxy*-5,5′-*dimethoxy*-4,4′-*di*-*t*-*butyl*-*biphenyl*.—Alkaline solutions of this phenol in ethanol did not absorb oxygen. When autoxidised in t-butyl alcohol–1,2-dimethoxyethane containing potassium t-butoxide, uptake of oxygen was slow, and more than half of the original phenol was recovered. No product could be isolated.

Autoxidation of 4-*Methoxy*-2,5-*di*-*t*-*butylphenol*.— The phenol (9·4 g.) in ethanol (200 ml.) and 0·1M-aqueous sodium hydroxide (100 ml.) was shaken in the presence of oxygen until 1 mol. had been absorbed. External cooling with cold water was necessary when the solution became hot. The precipitated fine yellow needles were filtered from the dark brown solution, washed with water and then dried *in vacuo* to give a mixture (6·5 g.) of 2,5-di-t-butyl-1,4-benzoquinone (VIII) (*ca.* 20% by n.m.r. spectroscopy) and monoepoxy-2,5-di-t-butyl-1,4-benzoquinone (IX) (*ca.* 80%). Repeated recrystallisation from light petroleum gave the monoepoxide (IX) (2·5 g.) as pale yellow needles, m.p. 121—122° (lit.,[8] 114—117°). The dark brown filtrate from the autoxidation was diluted with water, neutralized with dilute hydrochloric acid, and extracted with ether. Evaporation of the washed and dried (Na_2SO_4) solution gave a dark brown oil (2·4 g.). Adsorption on alumina and elution with light petroleum gave starting material (1·2 g.) and a mixture of *cis*- and *trans*-diepoxide (0·8 g., *ca.* 3 : 1 by n.m.r. spectroscopy). Recrystallisation from light petroleum gave *trans*-diepoxy-2,5-di-t-butyl-1,4-benzoquinone (XI) (80 mg.) as needles, m.p. 146—147° (lit.,[8] 141—142°). Repeated recrystallisation from the same solvent of the residue from the mother liquors gave large and small prisms of the *trans*- and *cis*-isomers. Mechanical separation gave cis-*diepoxy*-2,5-*di*-*t*-*butyl*-1,4-*benzoquinone* (X) (25 mg.), m.p. 102·5—103° (Found: C, 66·9; H, 8·0. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%), $\nu_{max.}$ 1720 cm.$^{-1}$ (C=O); τ 8·89 (2 Bu^t) and 6·59 (2 alicyclic H).

Reductive Acetylation of Monoepoxy-2,5-*di*-*t*-*butyl*-1,4-*benzoquinone* (IX).—The monoepoxide (IX) (240 mg.) was heated with zinc dust and sodium acetate in refluxing acetic anhydride for 15 min. A little acetic acid was then added and the mixture poured into cold, dilute sulphuric acid. The product was extracted into ether and the ether solution was washed with water, aqueous sodium hydrogen carbonate, and water, then dried (Na_2SO_4), and the ether evaporated to leave a colourless gum (250 mg.). Adsorption on alumina and elution with benzene gave a mixture of acetates (150 mg.), and elution with benzene–ether (9 : 1) gave 2-*hydroxy*-2,5-*di*-*t*-*butyl*-*cyclohexa*-1,4-*dione* (XIV) as prisms (20 mg.), m.p. 128—131°, from light petroleum (Found: C, 69·7; H, 10·1. $C_{14}H_{24}O_2$ requires C, 70·0; H, 10·1%), $\nu_{max.}$ 3520, 3460 (bonded OH), 1710 cm.$^{-1}$ (C=O); τ 9·01, 8·96 (2 Bu^t), 7·68—7·04 (5 alicyclic H), and 6·82 (OH, removed on exchange with deuterium oxide). The chromatographed mixture of acetates was washed with hot, light petroleum to give the light petroleum-soluble 2,5-di-t-butylhydroquinone diacetate (XII) (56 mg.), m.p. and mixed m.p. 173—174°, and the light petroleum-insoluble 1,3,4-*triacetoxy*-2,5-*di*-*t*-*butylbenzene* (XIII) (25 mg.) as prisms, m.p. 168—170°, from methanol (Found: C, 66·1; H, 7·8. $C_{20}H_{28}O_6$ requires C, 65·9; H, 7·7%), $\nu_{max.}$ 1775 cm.$^{-1}$ (OAc); τ 8·70, 8·64 (2 Bu^t), 7·80, 7·78, 7·76 (3 OAc), and 3·16 (ArH).

Attempted Selective Demethylation of a Mixture of 2-*Acetoxy*-5-*methoxy*-3,6-*di*-*t*-*butylphenol* (XV) *and* 2-*Acetoxy*-4-*methoxy*-3,6-*di*-*t*-*butylphenol* (XVI).—The mixture of acetates (500 mg.) in acetic acid (35 ml.) and 48% hydrobromic acid (3 ml.) was heated at 100° for 30 min. Removal of solvent under reduced pressure gave a dark green oil (450 mg.) which was acetylated upon being heated in acetic anhydride–pyridine for 2 hr. to give 2,3,5-triacetoxy-t-butylbenzene, m.p. and mixed m.p. 105—106°.

When the mixture of acetates (100 mg.) was heated with pyridinium chloride (500 mg.) at 210° for 4 hr. and then acetylated, 2,3,5-triacetoxy-t-butylbenzene, m.p. and mixed m.p. 105—106° was obtained again.

Synthesis of 1,3,4-*Triacetoxy*-2,5-*di*-*t*-*butylbenzene* (XIII).—The mixture of acetates (XV) and (XVI) (370 mg.) in acetone (100 ml.) was added dropwise to a stirred solution of Frémy's salt (860 mg.) in 0·04M-aqueous potassium dihydrogen phosphate (100 ml.) at 10°. After 15 min., water (60 ml.) was added, and stirring was continued at room temperature for 1·5 hr. The solution was diluted with water and extracted with chloroform. Evaporation of the washed, and dried (Na_2SO_4) solution gave an orange oil (300 mg.). Recrystallisation from light petroleum gave starting material (XV) and (XVI) (75 mg.) Adsorption of the evaporated mother liquor on alumina and elution with light petroleum gave 3-*acetoxy*-2,5-*di*-*t*-*butyl*-1,4-*benzoquinone* (XVII) (180 mg.) as an orange oil (Found: C, 69·5; H, 7·9. $C_{16}H_{22}O_4$ requires C, 69·0; H, 8·0%), $\nu_{max.}$ 1775 (OAc) and 1660 cm.$^{-1}$ (C=O); τ 8·73, 8·66 (2 Bu^t), 7·73 (OAc), and 3·61 (vinylic H).

Reductive acetylation of this acetoxy-quinone (XVII) (160 mg.) with refluxing acetic anhydride, sodium acetate, and zinc dust gave the triacetate (XIII) (105 mg.), m.p. and mixed m.p. 168—170°. The i.r. and n.m.r. spectra were identical with those of the triacetate obtained by reductive acetylation of the monoepoxide (IX).

Reduction of the Monoepoxide (IX).—(a) *By lithium*

aluminium hydride. A solution of the monoepoxide (IX) (460 mg.) in dry ether was added dropwise to lithium aluminium hydride (200 mg.) in refluxing ether (50 ml.). After being heated for 40 min. the mixture was cooled, and ethyl acetate (5 ml.) was slowly added, followed by dilute sulphuric acid. Extraction with ether, and evaporation of the washed and dried (Na_2SO_4) extract gave a colourless residue (440 mg.) which was adsorbed on alumina and eluted with benzene to give 2,5-di-t-butylhydroquinone (80 mg.) and a mixture of unidentified aliphatic compounds (230 mg.).

(b) *By sodium dithionite*. A solution of the monoepoxide (IX) (300 mg.) in ethanol (50 ml.) and water (20 ml.), containing sodium dithionite (1·2 g.), was warmed on a water-bath for 30 min., cooled, diluted with water and the insoluble 2,5-di-t-butylhydroquinone (77 mg.) was filtered off. The filtrate was extracted with ether and evaporation of the dried (Na_2SO_4) extract gave an orange oil (200 mg.). Adsorption on alumina and elution with benzene–light petroleum gave an unidentified mixture (135 mg.), and elution with benzene–ether (1 : 1) gave the hydroxy-dione (XIV) (30 mg.).

(c) *Catalytic*. The monoepoxide (300 mg.) in ethanol (60 ml.) was hydrogenated over palladium–charcoal at room temperature and pressure. Evaporation of the filtered solution gave a yellow residue (290 mg.). Adsorption on alumina and elution with benzene gave 2,5-di-t-butylhydroquinone (56 mg.) and an unidentified mixture (160 mg.), and elution with benzene–ether (1 : 1) gave the hydroxy-dione (XIV) (20 mg.).

(d) *By chromous acetate*. Chromous acetate (2·0 g.) was added to the monoepoxide (500 mg.) in acetic acid (60 ml.) under an atmosphere of carbon dioxide. The reaction mixture was left at room temperature for 4 hr., then poured into water and extracted with ether. The extract was washed with water, aqueous sodium hydrogen carbonate, water, and then dried (Na_2SO_4). Evaporation gave an orange solid (470 mg.) which was washed with hot light petroleum and the insoluble 2,5-di-t-butylhydroquinone (180 mg.) was filtered off. Chromatography of the evaporated light petroleum washings on alumina, and elution with benzene–light petroleum (1 : 1) gave starting material (40 mg.) and a yellow gum, $\nu_{max.}$ 3330 (bonded OH) and 1660 $cm.^{-1}$ (C=O), τ 8·71, 8·65 (2 Bu^t), 3·65 (vinylic H), and 2·40 (OH, removed on exchange with deuterium oxide). This yellow gum was left in acetic anhydride and pyridine at room temperature for 16 hr. to give the acetoxy-quinone (XVII)—shown by n.m.r. and i.r. spectroscopy to be identical with the sample described above.

Reaction of the Monoepoxide (IX) *with Hydrobromic Acid*.—A solution of the monoepoxide (1·0 g.) in acetic acid (50 ml.) and hydrobromic acid (1 ml.) was heated at 100° for 20 min. The cooled solution was poured into water, and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water, and dried (Na_2SO_4). Evaporation gave a brown gum (1·1 g.) which did not crystallise even after chromatography. Treatment of this gum (250 mg.) with acetic anhydride (10 ml.) and pyridine (1 ml.) for 18 hr. at room temperature gave an oil (240 mg.), which was adsorbed on alumina and eluted with benzene to give 2,4,5-*triacetoxy*-3-*bromo*-*t*-*butylbenzene* (XX) (110 mg.) as prisms, m.p. 127—129°, from benzene–light petroleum (Found: C, 50·1; H, 5·1. $C_{16}H_{19}BrO_6$ requires C, 49·6; H, 4·9%), $\nu_{max.}$ 1775 $cm.^{-1}$ (OAc); τ 8·65 (Bu^t), 7·83, 7·75, 7·61 (3 OAc), and 2·81 (ArH).

The brown gum (290 mg.) in methanol (15 ml.) containing potassium hydroxide (460 mg.) was hydrogenolysed over palladium–charcoal. Removal of solvent under reduced pressure followed by acetylation with acetic anhydride and pyridine gave a brown oil (250 mg.). Adsorption of the oil on alumina and elution with benzene gave 2,4,5-triacetoxy-t-butylbenzene (XXI) (120 mg.), m.p. and mixed m.p. 120—122°.

Reaction of the Monoepoxide (IX) *with Hydrochloric Acid*.—The monoepoxide (1·10 g.) in acetic acid (50 ml.) and concentrated hydrochloric acid (1 ml.) was heated at 100° for 1·5 hr. The cooled solution was poured into water and extracted with ether. Evaporation of the washed (aqueous sodium hydrogen carbonate) and dried (Na_2SO_4) extract gave an orange residue (1·08 g.) which was adsorbed on alumina and eluted with light petroleum to give starting material (420 mg.). Elution with ether gave a yellow oil (200 mg.) which was acetylated to give 2,4,5-*triacetoxy*-3-*chloro*-*t*-*butylbenzene* as rectangular prisms, m.p. 114—115°, from benzene–light petroleum (Found: C, 56·5; H, 5·7. $C_{16}H_{19}ClO_6$ requires C, 56·1; H, 5·6%), $\nu_{max.}$ 1775 $cm.^{-1}$ (OAc); τ 8·64 (Bu^t), 7·81, 7·74, 7·61 (3 OAc), and 2·86 (ArH).

Synthesis of Monoepoxide (IX).—To 2,5-di-t-butyl-1,4-benzoquinone (VIII) (1·1 g.) in ethanol (350 ml.), 0·1M-sodium hydroxide (50 ml.), and 30% hydrogen peroxide (2 ml.) were added. The reaction mixture was left at room temperature for 20 hr., poured into water (500 ml.) and then the solid was filtered off. The n.m.r. spectrum showed that the dried solid (1·0 g.) contained the monoepoxide (IX) (*ca.* 40%), the *cis*-diepoxide (X) (45%), and the *trans*-diepoxide (XI) (15%). When a large excess of hydrogen peroxide was used, and the reaction was stopped after 30 min., an almost quantitative yield of *cis*- and *trans*-diepoxides in 1 : 1 ratio, was obtained and no monoepoxide was detected.

Reduction of the cis- *and* trans-*Diepoxides* (X) *and* (XI).—(a) *Reductive acetylation*. The *cis*-diepoxide (X), (340 mg.) was reductively acetylated as described for the monoepoxide (IX) to give a solid (440 mg.). Adsorption on alumina and elution with benzene gave 2,5-di-t-butylhydroquinone diacetate (XII) (240 mg.).

The *trans*-diepoxide (250 mg.) was similarly reductively acetylated to give the diacetate (XII) (240 mg.).

(b) *Reduction by lithium aluminium hydride*. The *cis*-diepoxide (X) (500 mg.) was reduced by lithium aluminium hydride (500 mg.) as described for the reduction of the monoepoxide (IX) to give a solid (450 mg.) which could not be purified by chromatography on alumina. Repeated recrystallisation from methanol gave cis,cis,cis-1,2,4,5-*tetrahydroxy*-1,4-*di*-*t*-*butylcyclohexane* (XXIV) (120 mg.) as prisms, m.p. 254—257° (Found: C, 64·3; H, 10·7. $C_{14}H_{28}O_4$ requires C, 64·6; H, 10·8%), τ (pyridine) 8·72 (Bu^t). The material was too insoluble for clear observation of the other resonances, and so insoluble in carbon tetrachloride that even with a 5-cm. cell no interpretation of the OH region was possible. This tetrol (20 mg.) was heated in acetic anhydride (5 ml.) and pyridine (1 ml.) at 100° for 1 hr. to give cis-2,5-*diacetoxy*-cis,cis-1,4-*dihydroxy*-1,4-*di*-*t*-*butylcyclohexane* (XXVa) (18 mg.) as prisms, m.p. 217—219°, from benzene–light petroleum (Found: C, 62·4; H, 9·3. $C_{18}H_{32}O_6$ requires C, 62·8; H, 9·4%), $\nu_{max.}$ (76 mg./l. CCl_4. Perkin-Elmer 521 Grating Infrared Spectrometer, 5-cm. quatz cell) 3592, 3506 $cm.^{-1}$ calibrated against water vapour, and 1750 $cm.^{-1}$ (normal cell); τ 9·05

(2 Bu^t), 7·90 (2 OAc), 7·00 (2 OH, removed on exchange with D_2O), and an ABX system (ν_B 7·83 and ν_A 7·82, 4 methylene H, J_{AX} −4·5 and J_{BX} 2·5 c./sec., ν_X 4·70, 2 methine H).

The *trans*-diepoxide (XI) (500 mg.) was similarly reduced to give a mixture which could not be separated by chromatography or recrystallisation.

Reactions of the cis- *and* trans-*Diepoxides* (X) *and* (XI) *with Hydrobromic Acid.*—(a) The *trans*-diepoxide (XI) (450 mg.) in acetic acid (80 ml.) and excess of 48% hydrobromic acid (6 ml.) was left at room temperature for 18 hr. The reaction mixture was poured into water and extracted with ether. The extract was washed with aqueous sodium hydrogen carbonate and water and then dried (Na_2SO_4). Removal of ether gave a solid (440 mg.) and recrystallisation from light petroleum gave *3-bromo-5,6-epoxy-2-hydroxy-2,5-di-t-butylcyclohexa-1,4-dione* (XXVI), (320 mg.) as prisms, m.p. 135—136° (Found: C, 50·6; H, 6·7. $C_{14}H_{21}BrO_4$ requires C, 50·5; H, 6·4%), $\nu_{max.}$ (CCl_4) 3440 (bonded OH) and 1725 $cm.^{-1}$ (C=O); τ 8·83, 8·82 (2 Bu^t), and 6·34, 5·35 (2 alicyclic H).

Acetylation of the bromohydrin (XXVI) in acetic anhydride and pyridine at room temperature, or adsorption on alumina, converted the bromohydrin to the *trans*-diepoxide (XI).

(b) The *cis*-diepoxide (X) (140 mg.) in acetic acid (30 ml.) was allowed to react with excess of 48% hydrobromic acid (2 ml.) at room temperature for 48 hr. to give a mixture (160 mg.). The n.m.r. spectrum showed t-butyl resonances at τ 8·98, 8·87, 8·81, 8·70, 8·60, and 8·52, and alicyclic proton resonances at 6·20, 5·83, and 5·28, and absence of the *cis*-diepoxide (X). Chromatography of the mixture on alumina and elution with benzene gave the *cis*-diepoxide (X) (53 mg.), and an unidentified mixture (70 mg.).

Epoxidation of the Monoepoxide (IX).—The monoepoxide (IX) (1·4 g.) in ethanol (300 ml.), 0·1M-aqueous sodium hydroxide (60 ml.), and 30% hydrogen peroxide (5 ml.) was left at room temperature for 25 min. The reaction mixture was poured into water (800 ml.) and the solid was filtered off. The n.m.r. spectrum showed that the dried solid (1·3 g.) was a mixture of *cis*- and *trans*-diepoxides (X) and (XI) in 2 : 3 ratio.

The monoepoxide (IX) was not autoxidised when subjected to the conditions described for 4-methoxy-2,5-di-t-butylphenol.

Autoxidation of 2,5-Di-t-butylhydroquinone.—The hydroquinone (2·2 g.) was autoxidised as described for 4-methoxy-2,5-di-t-butylphenol to give more than 95% (by n.m.r. spectroscopy) of 2,5-di-t-butyl-1,4-benzoquinone (VIII), and a very small amount of the *cis*- and *trans*-diepoxides (X) and (XI).

When the hydroquinone (4·4 g.) was autoxidised in ethanol (50 ml.) containing 10M-aqueous potassium hydroxide (5 ml.), the quinone (VIII) (3·9 g.), the monoepoxide (IX) (80 mg.), and *cis*-diepoxide (X) (300 mg.) were obtained. No *trans*-diepoxide was isolated.

2,5-Di-t-butyl-1,4-benzoquinone (VIII) was not autoxidised when subjected to the conditions described for 4-methoxy-2,5-di-t-butylphenol.

Comparative Stability of the cis- *and* trans-*Diepoxides* (X) *and* (XI).—A mixture of the diepoxides (X) and (XI) in 3 : 2 ratio (220 mg.) in ethanol (60 ml.) and 0·1M-aqueous sodium hydroxide (5 ml.) was shaken in oxygen for 2 hr. The reaction mixture was neutralized with dilute hydrochloric acid and extracted with ether. Evaporation of the washed, and dried (Na_2SO_4) solution left a residue (230 mg.). The n.m.r. spectrum showed that the *cis*-diepoxide (X) was stable and that the *trans*-isomer was autoxidised to an unidentified mixture.

We thank Dr. L. H. Little for measuring the i.r. spectrum of compound (XXV), and the Australian Research Grants Committee for the Varian e.s.r. spectrometer.

[7/1648 *Received, December 18th,* 1968]