Oxidative Coupling of Phenols. Part 9.[1] The Role of Steric Effects in the Oxidation of Methyl-substituted Phenols

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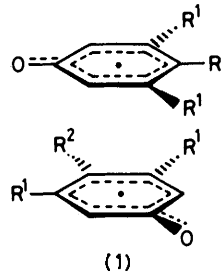
MINDO/3 calculations indicate that for the coupling of 3,5-dimethylphenoxyl radicals the non-bonded methyl–methyl interactions cause the energy difference between the staggered (1b) and eclipsed (2b) geometries of approach to be greater than in the analogous coupling of phenoxyl radicals. The preferential and exclusive formation of the *ortho-ortho*-coupled products from the respective oxidations of 2,3-dimethylphenol and 2,3,5-trimethylphenol with di-t-butyl peroxide also support a mechanism, which proceeds *via* a staggered transition state.

Previous Parts [1-3] have presented experimental and theoretical evidence in support of the postulate that coupling of phenoxyl radicals to form C–C coupled dimers proceeds preferentially *via* the staggered sandwich geometry of approach (1a): this route can account for the formation of the *ortho-ortho*- and *ortho-para*-dimers. Of all the other modes of approach considered, only two, the eclipsed form (2a) and the head-to-tail form (3a) were of any importance but, in both cases, they were shown to be less favourable than (1a). It was shown that the course of the reaction was controlled by the balance between the favourable SOMO–SOMO interactions of the radicals and the unfavourable electrostatic and steric repulsions inherent in these systems and that this balance is at its optimum in species like (1a).

The role of non-bonded interactions between substituents in the phenol are further explored in this paper by a theoretical investigation of the dimerisation of 3,5-dimethyl- and *p*-methyl-phenoxyl radicals and also by an experimental study of the oxidations of 2,3-dimethyl- and 2,3,5-trimethyl-phenol.

Theoretical Study.—A series of MINDO/3 calculations similar to those carried out for the dimerisation of phenoxyl radicals (see Part 8) [1] were performed for 3,5-dimethyl- and *p*-methyl-phenoxyl radicals. The Morse curves corresponding to the three most important geometries of approach (1b)—(3b) for the coupling of 3,5-dimethylphenoxyl radicals are shown in Figure 1 and those for the coupling of *p*-methylphenoxyl radicals *via* the approaches (1c)—(3c) are presented in Figure 2. The results show that the trends observed for the dimerisation of phenoxyl radicals are broadly reproduced. There are, however, some minor differences. In the initial stages of the dimerisation process, the energy difference between the staggered and eclipsed configurations is greater than that for the unsubstituted phenoxyl radical. This can be ascribed to the destabilising effect of the methyl group interactions of (2b) relative to (1b) and of (2c) relative to (1c). The configuration (1b) also possesses one pair of non-bonded methyl–methyl interactions but there are also two pairs of methyl–oxygen interactions. The presence of these could have some stabilising influence on the 'staggered' mode of approach since n.m.r. studies on propanal have shown that the methyl and the carbonyl groups are eclipsed in the most stable conformation of the molecule.[4,5] The C–O bond of phenoxyl radicals has considerable double bond character.

These calculations would therefore suggest that there should be an even greater tendency for the coupling of 3,5-dimethylphenoxyl radicals to proceed *via* the staggered geometry of approach to yield the *ortho-ortho*- and *ortho-para*-C–C coupled products rather than *via* the eclipsed geometry of approach which would give the *para-para*-coupled product. Experimental studies showed that compared with phenol,



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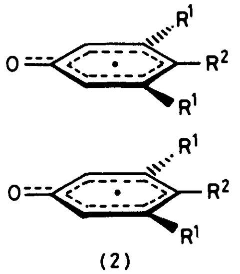

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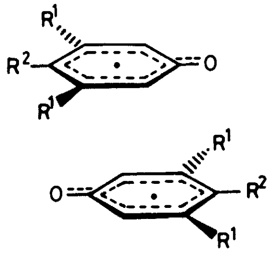


(3)

a; $R^1 = R^2 = H$
b; $R^1 = Me$; $R^2 = H$
c; $R^1 = H$; $R^2 = Me$

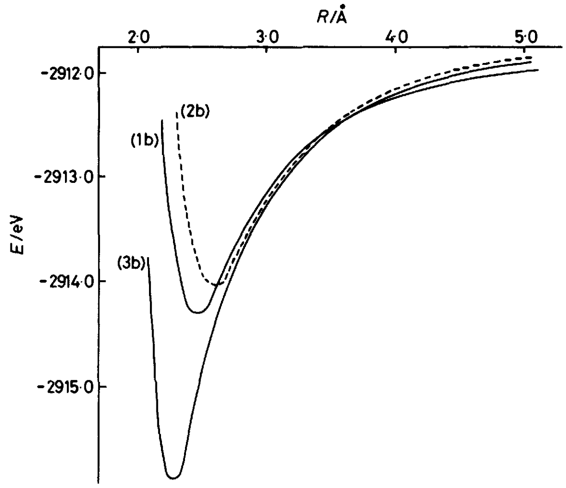


Figure 1. Calculated Morse curves using the MINDO/3 method for the coupling of two 3,5-dimethylphenoxyl radicals *via* staggered (1b), eclipsed (2b) and head-to-tail (3c) approaches

Oxidation products from 2,3-dimethylphenol

Oxidant	Solvent	[ArOH]/M	T/°C	pH	t/h	Products (%)				
						(4)	(5)	(6)	(7)	(8)
$(Bu^tO)_2$	Neat		140		24	77	17	0	5	1
$(Bu^tO)_2$	PhCl	1.0	140		24	85	11	0	4	0
Bu^tOOH	Neat		140		24	69	21	0	9	1
Bu^tOOH	H_2O	1.0	100		24	18	45	21	7	9
$(Bu^tOCO_2)_2$	PhH	1.0	25		24	5	46	26	8	15
$(Bu^tOCO_2)_2$	PhCl	1.0	25		24	11	31	35	9	15
MTA [a]	PhH	0.5	80		16	4	43	28	12	14
MTA	EtOAc	0.5	80		16	27	22	12	24	15
MTA	MeCN	0.5	80		16	9	26	22	27	16
Ag_2CO_3	PhH	0.5	80		3	30	20	10	8	32
Ag_2CO_3	EtOAc	0.5	80		3	6	22	20	13	39
Ag_2CO_3	MeCN	0.5	80		3	1	13	24	9	53
$K_3Fe(CN)_6$	aq. MeCN	0.1	25	9	24	18	18	30	27	8
$K_3Fe(CN)_6$	aq. MeCN	0.1	100	9	24	18	23	27	22	10
$Ce(NO_3)_6{\cdot}(NH_4)_2$	aq. MeCN	0.5	25	4	4	7	42	35	7	11
$Ce(NO_3)_6{\cdot}(NH_4)_2$	aq. MeCN	0.5	−25		4	1	48	35	13	2

[a] MTA = Manganese(III) trisacetylacetonate.

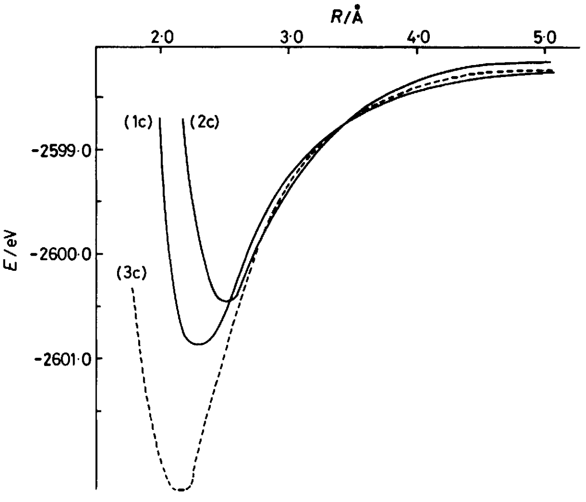
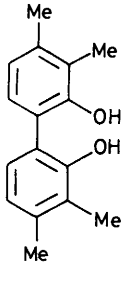


Figure 2. Calculated Morse curves using the MINDO/3 method for the coupling of two *p*-methylphenoxyl radicals *via* staggered (1c), eclipsed (2c), and head-to-tail (3c) approaches

much less *para-para*-coupling is observed in the oxidation of 3,5-dimethylphenol.[2] Similar arguments can be applied to the dimerisation of *p*-methylphenoxyl radicals although *para-para*-C–C coupling of these radicals does not lead to a stable product, so little conclusion can be drawn from this.

It is interesting to note that the depth of the well for the coupling process *via* the staggered approach is lower than for the eclipsed form for both 3,5-dimethyl- and *p*-methylphenoxyl radicals in contrast to the situation for phenoxyl radicals. Once again, this emphasises the effect of non-bonded interactions between methyl groups.



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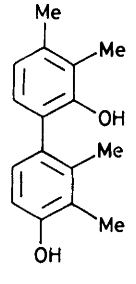

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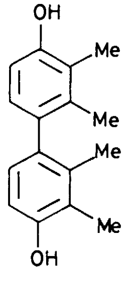

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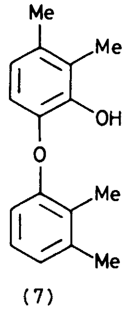

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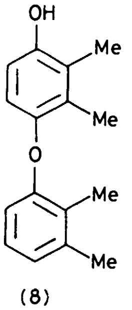

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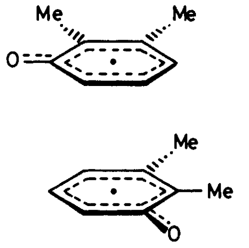
The calculations indicate that the head-to-tail approach of radicals (3) lies in the intermediate position between the staggered and eclipsed forms. This type of approach can result in either *ortho-ortho*-coupling or else *para*-oxygen coupling. It should assume more importance with the substituted phenols than with phenol itself since the energy difference between it and the staggered geometry is reduced as the phenol becomes successively substituted. This is attributed to the increased destabilising forces inherent in the substituted phenols whereas there are little or no such adverse influences present in the head-to-tail type of approach. Some indication as to the importance of this approach will be given in the next section.

Experimental Studies.—A detailed study of the oxidation of 2,3-dimethylphenol was carried out using the procedure described in Part 6 for the oxidations of 3,5-dimethylphenol and phenol.[2]

2,3-Dimethylphenol has free *ortho*- and *para*-positions and hence can give three biphenolic C–C coupled products (4)—(6) and two C–O dimers (7) and (8). One apparent anomalous result is the formation of considerably more of the *para-para*-coupled product (6) (see Table) from the oxidation of 2,3-dimethylphenol with di-t-butyl peroxyoxalate at room temperature than from the comparable oxidation of 3,5-dimethylphenol. The contention given previously that non-bonded interactions in the eclipsed approach are more severe in substituted phenols making this less important appears here to be violated. However, there are two possible



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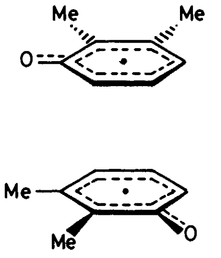

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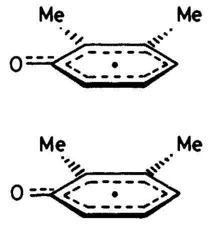

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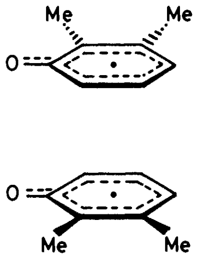

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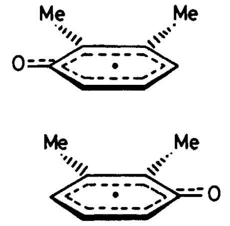

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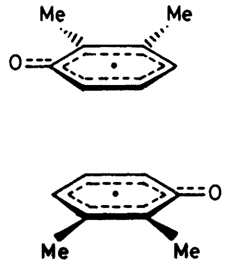

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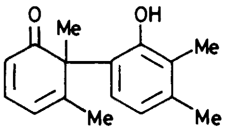
eclipsed geometries of approach (11) and (12) for the *para-para*-coupling of 2,3-dimethylphenoxyl radicals, one of which (12) possesses no methyl–methyl non-bonded interactions. This would favour this particular approach being relatively more favoured than the comparable mode for 3,5-dimethylphenoxyl radicals.

The situation is further complicated by the fact that, due to the unsymmetrical nature of the radicals, there are also two possible staggered geometries of approach (9) and (10) for the coupling of 2,3-dimethylphenoxyl radicals. The more favoured approach (10), in which there are no methyl–methyl interactions, would lead to the *ortho-para*-coupled product (5) while (9) would give the *ortho-ortho*-dimer (4). The experimental results seem at first sight to be at variance with this. It is conceivable that the two 2,3-dimethoxyphenoxyl radicals in the approaches may be slightly tilted towards each other as the result of non-bonded interactions. This tilting, which would be greater for (10) than for (9) would bring the two *ortho*-positions closer to each other and hence might enhance the formation of the *ortho-ortho*-coupled product. No theoretical study of the dimerisation of 2,3-dimethylphenoxyl radicals was undertaken since the lower symmetry of these radicals leads to difficulties in arriving at a suitable geometry.

We have also considered the head-to-tail geometry of approach (3a) for the coupling of phenoxyl radicals. There are two possible configurations (13) and (14) in the case of 2,3-dimethylphenoxyl radicals. The less hindered and energetically more favoured configuration (14) could lead to the *para*-C–O coupled product but not to the *ortho-ortho*-coupled product (4). If coupling *via* this route were important then the oxidation of 2,3-dimethylphenol might be expected to yield significantly more of the *para*-C–O coupled product than the oxidations of 3,5-dimethylphenol and phenol where this type of approach could also lead to the *ortho-ortho*-coupled products. We obtained no evidence for this effect.



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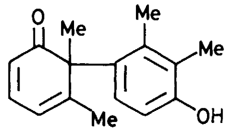

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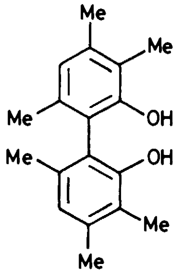

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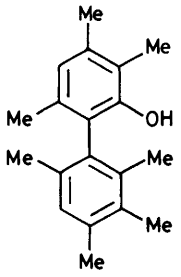

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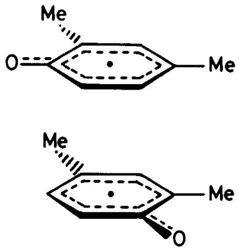
In the oxidations of 2,3-dimethylphenol with potassium ferricyanide and cerium(IV) ammonium nitrate two other dimeric products, in yields of up to 15%, were detected by g.l.c. The retention times of these products indicate that they are isomeric with the other five products and are probably the ketones compounds (15) and (16) formed as a result of *ortho-ortho*- and *ortho-para*-coupling, respectively. These compounds were only obtained under conditions in which ketonic products were found to be produced from the oxidations of *p*-alkylphenols [6] and 2,6-dimethylphenols.[7] These products could be formed *via* the transition states (9) and (10).

We also examined the oxidation of 2,3,5-trimethylphenol with di-t-butyl peroxide at 140° and found that this gave the *ortho-ortho*-coupled compound (17) as the only product. None of the *ortho-para*-coupled isomer (18) was detected. The former could be formed *via* a staggered configuration in which there are one methyl–methyl and two methyl–oxygen interactions. The same steric interactions are present in the staggered approach for the coupling of 3,5-dimethylphenoxyl radicals, which under these conditions, also afford largely the *ortho-ortho*-coupled product.

Comparison of the relative amounts of the two C–O products obtained in oxidations of 2,3- and 3,5-dimethylphenol indicates that rather less C–O coupling occurs in the case of 2,3-dimethylphenol and that the proportion of *ortho*-C–O coupling is greater than in the comparable oxidations of 3,5-dimethylphenol. These observations can be rationalized on the basis that the oxygen in the 2,3-dimethylphenoxyl radical is more sterically hindered than in the 3,5-dimethylphenoxyl radical thus inhibiting slightly C–O coupling. The following paper provides much more dramatic evidence for this effect. The *para*-position is also somewhat more hindered than the *ortho*-position in this radical and hence, if steric effects are important, they may well explain the greater proportion of coupling at the *ortho*-position in the C–O coupling of 2,3- than 3,5-dimethylphenoxyl radicals.

Analysis of the results of oxidations of 2,4- and 3,4-dimethylphenols lends further support to the contention that non-bonding interactions between methyl groups in the transi-



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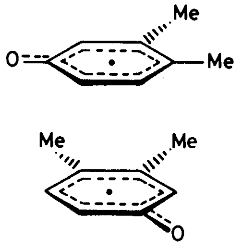

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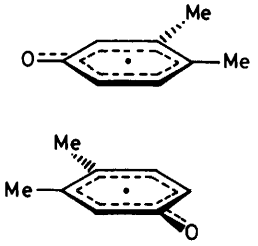

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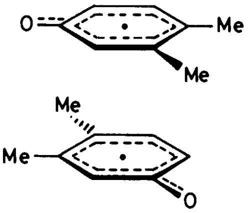

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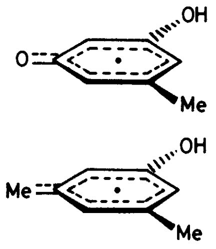
tion state for coupling of methyl-substituted phenoxyl radicals are important. Oxidation of 2,4-dimethylphenol gave a very much higher yield of the C–O coupled product than was obtained with *p*-cresol.[8] Examination of the staggered approach (19) for the *ortho-ortho*-coupling of 2,4-dimethylphenoxyl radicals reveals two sets of non-bonding interactions between the methyl groups. This would result in a higher energy pathway for C–C coupling and consequently relatively more C–O coupling occurs because formation of the latter bond is much less dependent on efficient SOMO–SOMO interactions between two radicals.

Oxidation of 3,4-dimethylphenol has been shown to give all three possible *ortho-ortho*-coupled dimers in comparable yields though intuitively steric considerations would lead one to expect preferential coupling at the 6-position.[8] Examination of the staggered sandwich geometries of approach (20)—(22), however, indicates that the transition state (20) for coupling at the less sterically hindered 6-position is less favoured than are the alternative configurations (21) and (22); these would yield the 2,2′- and 2,6′-dimers respectively together with the ketonic products derived from *ortho-para*-coupling. The approaches (21) and (22) possess no unfavourable methyl–methyl interactions but have one and two of the arguably favourable interactions between a methyl group and an oxygen.

The exclusive formation of the 4,4′-dimer in the oxidation of orcinol has been cited as evidence for the importance of spin density factors on the products obtained in the oxidative coupling of phenols. However, this too can be explained by consideration of the two possible sandwich transition states (23) and (24), the first of which would be less favoured due to the electrostatic repulsion between two sets of oxygen atoms being destabilising and also the methyl–methyl interactions while (24) has two favourable methyl–oxygen interactions. Reaction *via* the approach (24) then proceeds to form a bond at the site of highest electron density. Spin-density considerations are more important in the coupling of radicals derived from orcinol than in the reactions of phenoxyl radicals from monohydric phenols because the ratio of spin densities *ortho* and *para* to the methyl group in the radical from orcinol is 14 : 1, whereas the ratios of spin densities in phenoxyl radicals from monohydric phenols *ortho* and *para* to the oxyl radical are < 1 : 2.



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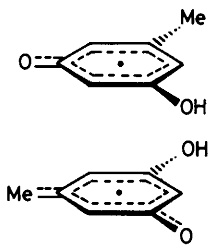

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In conclusion the results presented can be consistently interpreted to indicate that the coupling of phenoxyl radicals proceeds by a staggered sandwich transition state. When more than one such transition state can be considered, reaction proceeds preferentially *via* the transition state possessing the smallest number of non-bonded interactions between the methyl groups of the radicals undergoing coupling. Direct quantum mechanical calculations support these conclusions. It is also interesting to note that whereas t-butyl radicals generally undergo more disproportionation than dimerisation,[7] cumyl radicals give almost exclusively bicumyl.[8] This observation is easy to rationalize if cumyl radicals approach each other in a sandwich geometry since then the exocyclic carbons, which are the sites of highest spin density, are aligned for formation of bicumyl but not for disproportionation. It has previously been suggested that this preferred route for the combination of cumyl radicals could be a result of π-complexation of the radicals.[9]

Experimental

2,3-Dimethyl- and 2,3,5-trimethyl-phenols were commercial materials and were purified by redistillation. Small scale oxidations of 2,3-dimethylphenol were carried out as described previously for 3,5-dimethylphenol[2] and the products analysed by g.l.c. (OV 225) at 225 °C.

Preparative Scale Oxidations of 2,3-*Dimethylphenol to obtain* C–C *Coupled Products.*—(a) The oxidation of 2,3-dimethylphenol (30.6 g, 0.25 mol) with di-t-butyl peroxide (3.65 g, 0.025 mol) was carried out as described for 3,5-dimethylphenol.[2] The crude product (3.0 g) (one major peak on g.l.c.) was chromatographed on a silica gel column. Elution with 9 : 1 light petroleum–ether gave 2,2′-*dihydroxy*-3,3′,4,4′-*tetramethylbiphenyl* (1.1 g, 37%), m.p. 140 °C (Found: C, 79.2; H, 7.4%; M^+, 242.1277. $C_{16}H_{18}O_2$ requires C, 79.3; H, 7.5%; M^+, 242.1307); δ ($CDCl_3$) 2.25 (6 H, s, Me), 2.35 (6 H, s, Me), 5.15 (2 H, exchangeable, s, OH), 6.82 (2 H, d, *J* 8.1 Hz, aromatic), and 6.96 (2 H, d, *J* 8.1 Hz, aromatic).

(b) The method employed was identical to that described for the analogous preparative scale oxidation for 3,5-dimethylphenol with potassium ferricyanide[2] but on half the scale. The residue (2.5 g) was chromatographed on a silica gel column using light petroleum as the eluant. The initial fractions were shown by g.l.c. analysis to consist of a mixture of three dimeric components, one of which was later shown to be one of two possible isomeric diphenyl ethers (7) and the other two thought to be the ketone products (15) and (16). Further elution with 10% ether–light petroleum gave 2,2′-dihydroxy-3,3′,4,4′-tetramethylbiphenyl together with small quantities of (8), the *para*-oxygen coupled ether. Increase of the polarity of the eluant by adding successively more ether resulted in the isolation of a pure sample of *4,4′-dihydroxy-2,2′,3,3′-tetramethylbiphenyl* (0.4 g, 16%) from 1 : 1 ether–light petroleum, m.p. 199—201 °C (Found: C, 79.4; H, 7.7%; M^+, 242.1301); δ (CD_3COCD_3) 1.92 (6 H, s, Me), 2.20 (6 H, s, Me), 6.70 (4 H, s, aromatic), and 7.92 (2 H, s, exchangeable, OH).

(c) 2,3-Dimethylphenol (30.6 g, 0.25 mol) was dissolved in acetonitrile (250 ml) and the solution deoxygenated with nitrogen for 1 h. Manganese(III) trisacetylacetonate (8.65 g, 0.025 mol) was added to the solution at reflux temperature and the reaction mixture stirred at this temperature for 16 h under nitrogen. After cooling, ether (300 ml) was added and the solution filtered. The filtrate was washed with 10% sodium metabisulphite solution (2 × 150 ml) and then with water (3 × 150 ml) and dried (Na_2SO_4). The residue (31.0 g) after solvent evaporation was steam distilled to remove unchanged 2,3-dimethylphenol (28 g). Extraction of the residue with ether (200 ml) followed by drying (Na_2SO_4) and evaporation of the solvent gave a residue (2.7 g) which was chromatographed, as before, on a silica gel column. The first fractions contained a mixture of dimeric products and attempts to separate these (especially the two ketones) proved fruitless. However at a 35% ether–light petroleum solvent composition a pure sample of *2,4′-dihydroxy-2′,3,3′,4-tetramethylbiphenyl* (0.2 g, 7%) was obtained, m.p. 130—131 °C (Found: C, 79.2; H, 7.2%; M^+, 242.1293); δ ($CDCl_3$) 2.08 (3 H, s, Me), 2.24 (6 H, s, Me), 2.31 (3 H, s, Me), 4.84 (1 H, s, exchangeable, OH), 4.90 (1 H, s, exchangeable, OH), 6.66 (1 H, d, *J* 8.1 Hz, aromatic), 6.79 (2 H, s, aromatic), and 6.96 (1 H, d, *J* 8.1 Hz, aromatic).

Preparation of C–O *Coupled Products*.—*2-Hydroxy-2′,3,3′,4-tetramethyldiphenyl ether*. 2-Methoxy-2′,3,3′,4-tetramethyldiphenyl ether was synthesized from the reaction of 2,3-dimethylphenol with 6-bromo-2,3-dimethylanisole using the conditions described previously and obtained as needles (20%), m.p. 44—47 °C; δ ($CDCl_3$) 2.19 (6 H, s, Me), 2.22 (3 H, s, Me), 2.29 (3 H, s, Me), 3.78 (3 H, s, OMe), and 6.44—7.04 (5 H, m, ArH). Demethylation with boron tribromide gave *2-hydroxy-2′,3,3′-4-tetramethyldiphenyl ether* (30%), after sublimation of the crude products, m.p. 55—57 °C (Found: C, 79.1; H, 7.7%; M^+, 242.1289); δ ($CDCl_3$) 2.16 (3 H, s, Me), 2.20 (6 H, s, Me), 2.28 (3 H, s, Me), 5.12 (1 H, s, exchangeable, OH), and 6.30—7.00 (5 H, m, ArH).

4-Hydroxy-2,2′,3,3′-tetramethyldiphenyl ether. 4-Methoxy-2,2′,3,3′-tetramethyldiphenyl ether was obtained as above from 2,3-dimethylphenol and 4-bromo-2,3-dimethylanisole as *crystals* (23%), m.p. 86 °C (Found: M^+, 256.1461. $C_{17}N_{20}O_2$ requires M^+, 256.1463); δ ($CDCl_3$) 2.17 (3 H, s, Me), 2.21 (3 H, s, Me), 2.26 (3 H, s, Me), 2.32 (3 H, s, Me), 3.80 (3 H, s, Me), 2.26 (3 H, s, Me), 2.32 (3 H, s, Me), 3.80 (3 H, s, OMe), and 6.30—7.04 (5 H, m, ArH). Demethylation with boron tribromide gave 4-hydroxy-2,2′,3,3′-tetramethyldiphenyl ether, m.p. 112—113 °C (Found: C, 79.1; H, 7.7%, M^+, 242.1305); δ ($CDCl_3$) 2.16 (3 H, s, Me), 2.22 (3 H, s, Me), 2.27 (3 H, s, Me), 2.32 (3 H, s, Me), 4.58 (1 H, s, exchangeable, OH), and 6.35—7.02 (5 H, m, ArH).

Oxidation of 2,3,5-*Trimethylphenol with Di-t-Butyl Peroxide*.—A single product was obtained (as indicated by g.l.c.) after removal of the excess phenol by steam distillation. Crystallization of the crude product from light petroleum gave *2,2′-dihydroxy-3,3′,4,4′,6,6′-hexamethylbiphenyl*, m.p. 154—155 °C (Found: C, 79.5; H, 8.5%; M^+, 270.1626. $C_{18}H_{22}O_2$ requires C, 80.0; H, 8.2%, M^+, 270.1620); δ ($CDCl_3$) 1.93 (6 H, s, Me), 2.17 (6 H, s, Me), 2.28 (6 H, s, Me), 4.76 (2 H, s, exchangeable, OH), and 6.72 (2 H, s, ArH).

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