376. *The Oxidation of Phenols with the Free Hydroxyl Radical.**

By Stanley L. Cosgrove and William A. Waters.

p-Cresol, *m*-4-xylenol, *m*-2-xylenol, and mesitol have been oxidised with hydrogen peroxide in the presence of acidified ferrous sulphate in either water or 20% acetic acid solution, and their simpler oxidation products have been isolated and identified as far as possible.

p-Cresol gives dimeric products identical with those obtained by Pummerer (*Ber.*, 1922, **55**, 3116; 1925, **58**, 1808) by alkaline ferricyanide oxidation, and *m*-4-xylenol oxidises similarly. *m*-2-Xylenol gives 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-diphenoquinone, the corresponding 4 : 4′-diphenol and also 2 : 6-dimethylquinol; mesitol gives two diphenols, one of which has been definitely identified as 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenylmethane. Unsuccessful attempts have been made to identify the second product by synthetic methods.

It is concluded that this oxidation of phenols involves the formation of free aryloxy-radicals which, being mesomeric systems, then dimerise by union at any of the possible atomic centres near which the odd electron may become localised.

A study of the reactions of phenols with free radicals is of fundamental importance in connection with the elucidation of the modes of action of phenolic substances in inhibiting autoxidation and olefin polymerisation.

We have recently shown (*J.*, 1949, 3189) that when phenols react with benzoyl peroxide in hot chloroform solution the distinctive reaction is the introduction of a benzoate group into the aromatic nucleus in an *ortho*-position to the hydroxyl group, though often a migration of a benzoyl group occurs as well. *ortho*-Attack is also the first stage in the oxidation of phenols with peracetic acid (Boeseken and Metz, *Rec. Trav. chim.*, 1935, **54**, 345) and by air in the presence of the enzyme, tyrosinase (Pugh and Raper, *Biochem. J.*, 1927, **21**, 1370), whereas other oxidations of phenols have given dimeric or polymeric products. Thus diphenols result from electrolytic oxidation (Fichter and Stocker, *Ber.*, 1914, **47**, 2003; Fichter and Ackermann, *Helv. Chim. Acta*, 1919, **2**, 583) and also from some oxidations with neutral potassium persulphate (Raudnitz, *Ber.*, 1930, **63**, 517), ferric chloride (Bowden and Reece, *J.*, 1950, 2249), or alkaline potassium ferricyanide. It has been suggested that the latter processes involve mesomeric free phenolic radicals (Pummerer *et al.*, *Ber.*, 1914, **47**, 1472, 2957; 1919, **52**, 1414; 1922, **55**, 3116; 1925, **58**, 1808), and since such free radicals can be obtained quite simply by treating aromatic compounds in aqueous solution with hydrogen peroxide and a ferrous salt (Merz and Waters, *J.*, 1949, 2427) it was of interest to study the oxidation of substituted phenols with this reagent. Goldhammer (*Biochem. Z.*, 1927, **189**, 81) obtained catechol, pyrogallol, and purpurogallin from phenol by this oxidation, and Chwala and Pailer (*J. prakt. Chem.*, 1939, **152**, 45) obtained about equal yields of quinol and catechol. From the cresols Ono and Oyamada (*Bull. Soc. chim., Japan*, 1936, **11**, 132) obtained only dark complexes containing iron.

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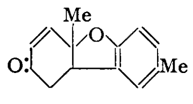
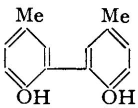
We have adopted the more convenient simultaneous addition technique of Merz and Waters, which can be justified on theoretical grounds, for our phenol oxidations, and by working in dilute sulphuric acid solution we have avoided the production of iron complexes. Our main reaction products are phenol dimers, which can be separated by distillation at low pressure and correspond to the oxidation products obtained by Pummerer (*Ber.*, 1922, **55**, 3116; 1925, **58**, 1808) by the use of alkaline potassium ferricyanide. Thus *p*-cresol yields a mixture of the tetrahydroketodibenzofuran derivative (I) and 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (II), which were also obtained from *p*-cresol by Westerfield and Lowe (*J. Biol. Chem.*, 1942, **145**, 463) by the use of hydrogen peroxide and a peroxidase catalyst, and more recently by Bowden and Reece (*loc. cit.*) by the prolonged action of neutral ferric chloride.

(I.)

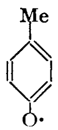


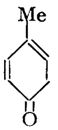


(II.)

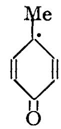
Our work thus accords with the view that there is a close connection between peroxidase-catalysed reactions and oxidations involving hydroxyl radicals, and fully substantiates the view expressed by Pummerer and his co-workers that phenols oxidise *via* mesomeric radicals, such as (III; canonical forms, *a*, *b*, and *c*), which can dimerise by coupling at any of the possible localities at which the odd electron may be found. Thus (I) arises from (III*a* + III*c*) and (II) from (III*b*) :

(III*a*.)



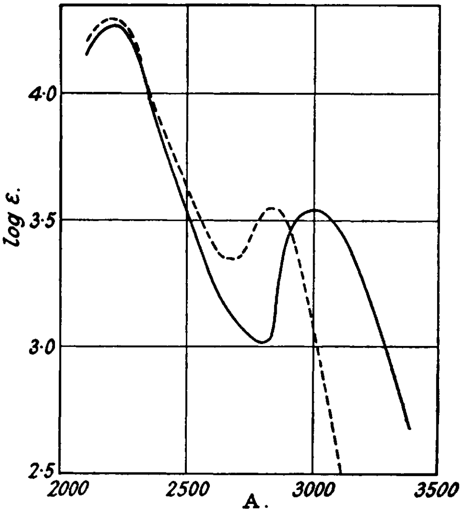


(III*b*.)



(III*c*.)

Homocatechol could not be isolated as a reaction product from *p*-cresol; it would probably be further oxidised and destroyed in the course of the reaction. It was noticeable that the relative



Full curve = ketonic product (I) *from* p-*cresol* ($\lambda_{max.}$ 2,200; 3,000. $\varepsilon_{max.}$ 19,100; 3,550).
Dotted curve = oxidation product from m-4-*xylenol* ($\lambda_{max.}$ 2,210; 2,835. $\varepsilon_{max.}$ 19,900; 3,550).

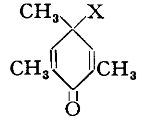
yields of (I) and (II) were appreciably different when the reaction was carried out in 20% acetic acid instead of in water.

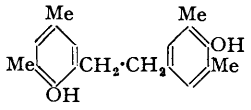
m-4-Xylenol (2 : 4-dimethylphenol) on oxidation in 20% acetic acid gave mainly 2 : 2′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl, corresponding to the dimer (II), and a very small proportion of a non-phenolic compound which, judged by its ultra-violet absorption spectrum (cf. figure), may be a homologue of (I). *m*-2-Xylenol (2 : 6-dimethylphenol) however gave 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-diphenoquinone, together with the corresponding quinol, 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl, and 2 : 6-dimethylquinol.

These products indicate that the blocking of the *ortho*-positions favours *para*-coupling.

The oxidation of mesitol (2 : 4 : 6-trimethylphenol) in 20% acetic acid solution gave a mixture of two diphenols which, after isolation by vacuum distillation, were separated by fractional crystallisation of their diacetates. The minor product, m. p. 173° (identical with a minor product of the oxidation of mesitol with benzoyl peroxide at 100°), was identified as 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenylmethane, by a direct synthesis of the latter from *m*-2-xylenol and formaldehyde (Auwers, *Ber.*, 1907, **40**, 2524). The major product, m. p. 152°, which formed a diacetate, m. p. 132°, may be identical with a compound obtained by Fries and Brandes (*Annalen*, 1939, **542**, 48) by the treatment of (IV; X = Br) with ice-water. They suggested tentatively that their product might have the unsymmetrical structure (V), but failed to establish this conclusively.

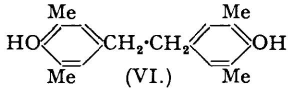
(IV.)



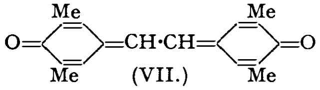


(V.)

We have not been able to establish the structure of our major product conclusively, but by synthetic work we have been able to eliminate a number of plausible structures; thus: (*a*) The symmetrical dibenzyl compound (VI), m. p. 167°, was prepared by the reduction of the red-purple stilbenequinone (VII). The latter was obtained by oxidation of mesitol with moist silver oxide (cf. Porter and Thurber, *J. Amer. Chem. Soc.*, 1921, **43**, 1194), but was not a product of the oxidation with Fenton's reagent.



(VI.)



(VII.)

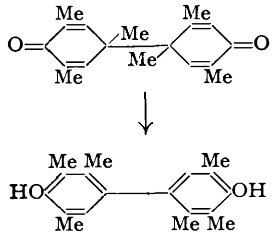
(*b*) The *ortho–ortho* (to the hydroxyl groups) coupled isomer of (VI) has been described by Fries (*loc. cit.*) as having m. p. 167°, and forming a diacetate, m. p. 125°.

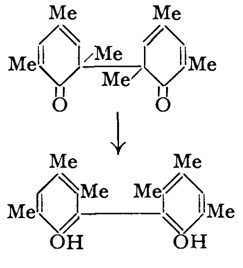
(*c*) Although the production of 3 : 3′-dihydroxydimesityl seemed unlikely we synthesised it from 3 : 3′-diaminodimesityl (Moyer and Adams, *J. Amer. Chem. Soc.*, 1929, **51**, 632; Adams and Joyce, *ibid.*, 1938, **60**, 1490); it had m. p. 161° and formed a diacetate, m. p. 134°.

(*d*) The coupling of two mesitol residues in the positions *para* or *ortho* to the hydroxy-group to give quinonoid products, such as (VIII) or (IX), is quite possible in view of the course of oxidation of *p*-cresol, and of the oxidation of mesitol with benzoyl peroxide to give a nearly quantitative yield of (IV; X = O·CO·Ph) (Cosgrove and Waters, *J.*, 1951, 388). In the acid solutions which we have used the consequent rearrangements of (VIII) to (X) and of (IX) to (XI) might be expected. The synthesis of (X) is not very practicable but we have synthesised (XI) by oxidation with ferric chloride of *pseudo*cumenol (Auwers, *Ber.*, 1884, **17**, 2976), prepared from *pseudo*cumene. The product had m. p. 172°, as described by Bamberger (*Ber.*, 1903, **36**, 2038), and formed a diacetate, m. p. 137°.

(VIII.)

(X.)





(IX.)

(XI.)

Other possible structures can be envisaged by postulating reactions involving migrations, or losses, of methyl groups, and since our micro-analytical data for the major product of the oxidation of mesitol are equally consistent for $C_{18}H_{20}(OH)_2$ and $C_{17}H_{18}(OH)_2$ the possibility of demethylation, as must occur in the concurrent formation of the minor product, cannot as yet be ignored.

Though the results obtained from our study of the oxidation of mesitol are not quite clear, nevertheless they are significant, for they show that the blocking of all positions *ortho* and *para* to a hydroxyl group in a phenol does not prevent the occurrence of far-reaching free-radical reactions.

EXPERIMENTAL.

Oxidation of p-*Cresol.*—3% Hydrogen peroxide solution (150 ml.; 0·75 mol.) and ferrous sulphate solution (150 ml.; 0·1 mol.) were simultaneously added, dropwise, to a mechanically stirred solution of *p*-cresol (18 g.; 1 mol.) in 0·2N-sulphuric acid (1 l.). After some hours, the mixture was extracted with ether, and the extracts were evaporated and then steam-distilled to remove unchanged cresol (12·2 g.). There remained a brown resin which was collected and distilled at 0·1-mm. pressure from an oil-bath at 200—220°. The thick distillate (2 g.) was extracted with 5% sodium hydroxide solution and so separated into the tetrahydroketodibenzofuran (I) (0·7 g., 13%), m. p. 122° (phenylhydrazone, m. p. 182°), and 2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (II) (1·07 g., 20%), m. p. 153°. The melting points of all three compounds were unchanged after admixture with authentic specimens prepared by Pummerer and Raudnitz's methods (*loc. cit.*). In the absence of sulphuric acid only a jet-black powdery resin was obtained (cf. Ono and Oyamada, *loc. cit.*). When only traces of ferrous sulphate were used there was no appreciable reaction; with as much as 0·5 mol. of ferrous sulphate the yields were lower, *i.e.* 8% of ketone and 11% of the dicresol. Ferric salts alone, in acid solution, gave only traces of these same products. When 20% acetic acid was used as the solvent, together with the original proportions of sulphuric acid, hydrogen peroxide, and ferrous sulphate, the yields were 18% of ketone and 14% of dicresol.

Oxidation of m-4-*Xylenol.*—*m*-4-Xylenol (30·5 g.) in 20% acetic acid made 0·2N. with respect to sulphuric acid was oxidised with similar proportions of hydrogen peroxide and ferrous sulphate. The pasty product was separated by vacuum distillation into unchanged xylenol (6 g.), 2 : 2′-*dihydroxy*-3 : 5 : 3′ : 5′-*tetramethyldiphenyl* (13 g.; m. p. 134°, after crystallisation from xylene) (Found: C, 79·4; H, 7·4%; *M*, 238. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%; *M*, 242), and non-phenolic material (3 g.). The diphenyl gave a *diacetate*, m. p. 107·5° (Found: C, 72·9; H, 6·8. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). Contrary to the statements of Bamberger (*Ber.*, 1907, **40**, 1926, 1952) dehydration of the diphenol into a dibenzofuran derivative did not take place even on heating it to 400° in the presence of zinc dust.

The non-phenolic material, after repeated crystallisation from methyl alcohol, in which it was sparingly soluble, gave a dimeric *compound*, $C_{16}H_{18}O_2$ (0·2 g.), m. p. 166° (Found: C, 79·4; H, 7·1. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·4%). This was stable to a boiling mixture of hydrochloric and acetic acids, and neither formed a phenylhydrazone nor was reduced catalytically (palladised charcoal) in ethyl alcohol solution by the use of hydrogen at room temperature and pressure. Its ultra-violet absorption spectrum (see figure) nevertheless showed marked similarities to that of the tetrahydroketodibenzofuran (I).

Oxidation of m-2-Xylenol.—This compound (12·2 g.) was oxidised in a similar way to its isomer. The organic products were collected in ether, and the red, insoluble 3 : 5 : 3′ : 5′-tetramethyl-4 : 4′-diphenoquinone (1·5 g.) was removed by filtration. It crystallised from glacial acetic acid in needles, m. p. 210—215° (decomp.) (Found: C, 79·7; H, 6·3. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). The ethereal solution was evaporated and the residue was steam-distilled. A little potassium iodide was added to the distillate, which was then saturated with sulphur dioxide and left overnight. Unchanged xylenol (6·0 g.) was removed from this mixture by steam-distillation, and the residue yielded 2 : 6-dimethylquinol (0·8 g.) as needles, m. p. 148—149° (from xylene). For comparison, an authentic specimen of the latter was prepared by converting *m*-2-xylenol into 4-hydroxy-3 : 5-dimethylbenzyl alcohol with formaldehyde by Bamberger's method (*Ber.*, 1903, **36**, 2028), oxidising this to 2 : 6-dimethyl-*p*-benzoquinone with hot aqueous ferric chloride, and then reducing the quinone to the dimethylquinol. The two specimens had identical properties.

The material from the original oxidation which did not distil in steam was collected in ether and distilled at 0·05 mm. (bath-temp. 150°). It yielded 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl, which crystallised from xylene in needles, m. p. 218°. This same product was also obtained by reducing the red diphenoquinone with zinc dust in boiling glacial acetic acid solution. It was also obtained by oxidising *m*-2-xylenol with benzoyl peroxide in boiling chloroform solution (Cosgrove and Waters, *J.*, 1951, 388).

Oxidation of Mesitol.—Mesitol (27·2 g.) was oxidised in 20% acetic acid solution in the foregoing manner. The products were collected in ether, dried, and steam-distilled to remove unchanged mesitol (8·0 g.). The residue was distilled at 0·05 mm. from a bath at 180° and gave a brown gummy distillate which solidified on being rubbed with xylene. The crude material (9·4 g.) was acetylated by refluxing it with an excess of acetic anhydride and fused sodium acetate, and the mixed acetates were separated by fractional crystallisation from methanol.

The less soluble acetate (0·5 g.) formed needles, m. p. 143° (Found: C, 74·7; H, 6·9. Calc. for $C_{21}H_{24}O_4$: C, 74·1; H, 7·1%). Its m. p. was not depressed by an authentic specimen of 4 : 4′-diacetoxy-3 : 5 : 3′ : 5′-tetramethyldiphenylmethane (see below). Hydrolysis with 10% aqueous sodium hydroxide solution containing a little alcohol yielded the corresponding diphenol, which crystallised from methanol as needles, m. p. 172°; this m. p. was unchanged after admixture with authentic 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenylmethane (Found: C, 79·8; H, 7·9. Calc. for $C_{17}H_{20}O_2$: C, 79·7; H, 7·8%).

The main *product* of the acetylation (4·8 g.) formed needles, m. p. 132° (Found: C, 74·2; H, 7·4. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·3. $C_{21}H_{24}O_4$ requires C, 74·1; H, 7·1%). Hydrolysis with 10%

sodium hydroxide solution containing a little alcohol yielded the corresponding *diphenol* which crystallised from methanol in rods, m. p. 152° (Found : C, 79·8; H, 8·0. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·15. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%). No substituted quinone could be obtained from this diphenol by prolonged oxidation with moist silver oxide in benzene solution at room temperature.

Both these diphenols were methylated, by using dimethyl sulphate and alkali at 80°, and gave gummy products. On oxidation with chromic acid in acetic acid solution the product from the diphenol, m. p. 172°, yielded material which gave a bright-red, granular dinitrophenylhydrazone, indicative of the oxidation of a diphenylmethane to a benzophenone derivative. The methylated product from the other diphenol did not give a similar oxidation product.

Syntheses of Reference Compounds.—3 : 3′-*Dihydroxydimesityl.* Bromomesitylene (*Org. Synth.*, Coll. Vol. II, 95) was converted into 3 : 3′-diaminodimesityl by the methods of Mayer, Adams, and Joyce (*locc. cit.*). The diamine (3·6 g.) in a mixture of sulphuric acid (9·9 g.), hydrochloric acid (3 ml.), and water (240 ml.) was diazotised with sodium nitrite (1·91 g.). The diazonium salt solution was steam-distilled and 3 : 3′-*dihydroxydimesityl* (2·5 g.) was collected in ether. It was purified by distillation *in vacuo* and crystallised from aqueous methanol in pale yellow tablets, m. p. 161° (Found : C, 79·8; H, 8·4. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·15%). Its *diacetate* crystallised from aqueous alcohol as micro-hexagonal plates, m. p. 134° (Found : C, 75·2; H, 7·3. $C_{22}H_{26}O_4$ requires C, 74·6; H, 7·3%).

Di-ψ-cumenol. ψ-Cumene was nitrated by Schultz's method (*Ber.*, 1909, **42**, 3606), but in agreement with Fisher and Walling (*J. Amer. Chem. Soc.*, 1935, **57**, 1700) we found the yield of 5-nitro-*pseudo*cumene to be much lower than that claimed by Schultz. The nitro-compound was reduced with tin and hydrochloric acid, and the resultant *pseudo*cumidine, after distillation in steam, was purified by distillation under reduced pressure. It was converted into *pseudo*cumenol, *via* the diazonium salt, by Auwers's method (*Ber.*, 1884, **17**, 2976). Dimerisation of the *pseudo*cumenol was effected by treatment with a threefold excess of 10% aqueous ferric chloride solution. Traces of the unchanged phenol were removed by steam-distillation, and the residue was collected by filtration. It crystallised from glacial acetic acid in needles, m. p. 171° (Found : C, 79·3; H, 8·0. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·15%). Its diacetate crystallised from methanol in prisms, m. p. 137° (Found : C, 75·1; H, 7·4. Calc. for $C_{22}H_{26}O_4$: C, 74·6; H, 7·3%).

4 : 4′-*Dihydroxy*-3 : 5 : 3′ : 5′-*tetramethyldibenzyl* (VI). The stilbenequinone (VII) obtained from the oxidation of mesitol with moist silver oxide (Porter and Thurber, *loc. cit.*) was quantitatively reduced to 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethylstilbene with zinc dust in glacial acetic acid. Further catalytic reduction with hydrogen, palladised charcoal and an alcohol solution being used, gave a quantitative yield of the dibenzyl (VI) which crystallised from benzene in needles, m. p. 168° (Found : C, 79·9; H, 8·1. Calc. for $C_{18}H_{22}O_2$: C, 80·0; H, 8·15%). Its diacetate crystallised from methanol in needles, m. p. 148°. Fries and Brandes (*loc. cit.*) report m. p. 167° and m. p. 150°, respectively.

4 : 4′-*Dihydroxy*-3 : 5 : 3′ : 5′-*tetramethyldiphenylmethane.* *m*-2-Xylenol (7·5 g.), 10% aqueous sodium hydroxide (15 ml.), and 40% formaldehyde solution (15 ml.) were heated to 100° for two hours in a sealed tube (cf. Auwers, *Ber.*, 1907, **40**, 2528). The product (7·2 g.) was removed by filtration; it crystallised from benzene as needles, m. p. 171°. There was no depression of the m. p. on admixture with the product (m. p. 172°) obtained by the Fenton oxidation of mesitol (p. 1729). The diacetate crystallised from methanol in needles, m. p. 143°, and this was unchanged by admixture with the corresponding product from mesitol.

We wish to report also that Dr. D. G. Jones, of Imperial Chemical Industries Limited (Billingham), has submitted to us for identification samples of diphenolic products which he has prepared by heating phenols with benzoyl peroxide at 100° in the absence of any solvent. From *m*-4-xylenol he obtained a diphenol, m. p. 135°, giving a diacetate, m. p. 109° (Found : C, 73·3; H, 6·7%); this we have identified as 2 : 2′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenyl by mixed m. p. comparison with our own reaction products (p. 1729). From mesitol he obtained a diphenol, m. p. 172°, identical with our diphenol, 4 : 4′-dihydroxy-3 : 5 : 3′ : 5′-tetramethyldiphenylmethane. Since we ourselves obtained rather different products by working in boiling chloroform solution (*J.*, *locc. cit.*) it is evident that the exact courses of these free-radical oxidations of phenols are sensitively dependent upon the reaction conditions.

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