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PHOTO-INDUCED REACTIONS—IX

THE HYDROXYLATION OF PHENOLS BY THE PHOTO-DECOMPOSITION OF HYDROGEN PEROXIDE IN AQUEOUS MEDIA[1, 2]

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Abstract—The photolysis of hydrogen peroxide in the presence of phenols in aqueous solution was used for the hydroxylation of various phenols on a preparative scale. Irradiation with the light at 2537 Å resulted in the formation of *ortho-* and *para*-dihydroxy compounds as the main products. The *ortho*-hydroxylation is predominant. Dihydroxybenzenes were also hydroxylated. In the case of *p*-substituted phenols, only an *ortho*-hydroxylated derivative was obtained. *p*-Carboxy- and *p*-methoxy-phenols gave hydroquinone in addition to the usual catechol derivative. Photolysis under various conditions of *p*-cresol, gave the best yield of the catechol at pH 3–8. Irradiation of *p*-cresol in aqueous hydrogen peroxide with the light over 2800 Å at pH ca. 1, in the presence or the absence of uranyl sulphate, resulted in the formation of a mixture of dimers as the main products. The mechanisms, including hydrogen abstraction and addition of hydroxyl radicals, are discussed.

THE direct hydroxylation methods of phenols[3] include (1) Fenton's reagent,[4] (2) radiolysis of water,[4, 5] (3) Udenfriend system,[6] (4) photolysis of hydrogen peroxide,[7] (5) organic peracids,[8] and (6) inorganic peroxides.[9] The first four reactions are considered to proceed by homolytic mechanisms, the hydroxyl radical being the actual hydroxylating agent.[10] In general, the yield of dihydroxybenzenes is limited because of further oxidation and side reactions. In the case of the Fenton and Udenfriend systems, the ferric ion formed can form a complex with phenols and can eventually oxidize them.[11] Although the radiolytic and photolytic procedures are less complex, the rate of hydroxyl radical formation is relatively slow, but the radicals are produced more effectively with lower energy photochemically and this procedure is therefore preferred for the preparative hydroxylation of organic compounds including phenols.*

The hydroxylation of aromatic compounds by the photolysis in aqueous hydrogen peroxide,[7, 13, 14] has been applied to benzene, anisole, fluorobenzene, and benzoic acid to give corresponding phenols, but the relatively low solubility of these substrates in water renders the method of little preparative use. Finally, Boyland and Sims[7] have reported that hydroxybenzoic acids are hydroxylated during photolysis in aqueous hydrogen peroxide at the *ortho-* and *para*-positions with respect to the original OH groups. We report here the hydroxylation of various phenols with this system.

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* In the course of our study, the oxidation of epoxides on a preparative scale by the photolysis of hydrogen peroxide was reported.[12]

Prior to the preparative experiments, we examined the effect of a few organic solutes on the decomposition rate of aqueous hydrogen peroxide with the light at 2537 Å. The results are shown in Fig. 1. It is obvious that the decomposition rate is decreased by the addition of organic compounds. The consumption of hydrogen peroxide has been regarded as due to a chain reaction initiated by an active species (presumably OH radical) which is generated from hydrogen peroxide by light absorption.[15, 16] The results indicate that phenol is apparently an effective inhibitor for radical chain reactions,[15] though the effect of the absorption of the light by phenol itself must be considered.

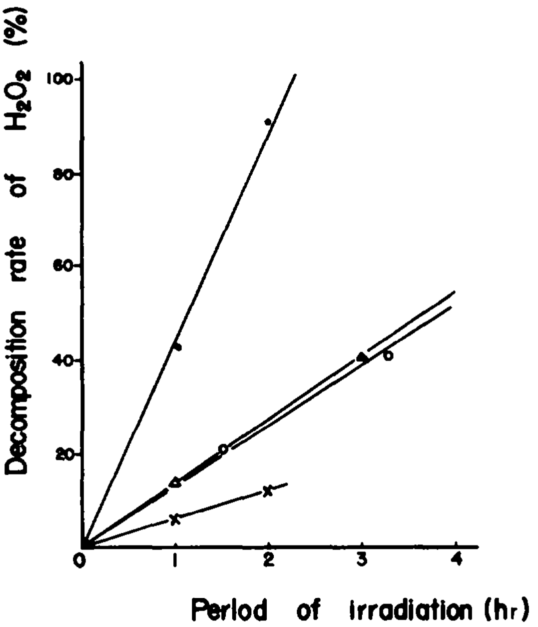
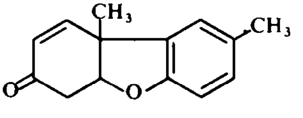


FIG. 1 The effect of organic solutes on the decomposition of aqueous H_2O_2 by a 2537 Å light.

The aqueous solution (200 ml) containing about 0·3 mole of hydrogen peroxide and 1 g of each solute was photolysed with a low pressure mercury lamp of quartz housing: ●, in the absence of solute; △, Allyalcohol (17·2 mmole); ○, dioxane (11·4 mmole); × phenol (10·6 mmole).

Irradiation with a low-pressure mercury lamp (mainly 2537 Å)

In a typical preparative run, a solution of *p*-cresol (37 mmoles) and excess of hydrogen peroxide (ca. 0·3 mole) in distilled water (230 ml) was irradiated with a low-pressure mercury lamp of quartz housing under bubbling nitrogen at about 40° for 8 hours. The initial colorless solution turned dark with some turbidity. VPC of the volatile product showed that this consisted of the starting material (0·63 g, 16%) and 4-methylcatechol (0·96 g, 25%) besides several minor products. The non-volatile material which consisted of polymers weighed 1·72 g. In the case of the oxidation of *p*-cresol with Fenton's reagent, it is known that dimeric compounds such as Pummerer's ketone (I) and 2,2′-dihydroxy-5,5′-dimethybiphenyl (II) are obtained without yielding the normal hydroxylated product.[17] Therefore, it seemed to be important for the mechanistic consideration of the present reaction to know whether these dimers are formed or not. VPC indicated that the minor products include three dimers (ca. 0·1% yield), I, II and presumably 2,5′-dihydroxy-2′,5-dimethylbiphenyl (III). This indicates the intermediary formation of cresoxyl radicals in this case.



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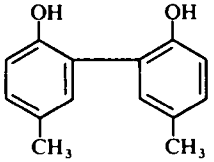

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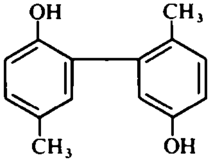

III

The results of a similar procedure applied to a number of water-soluble phenols are summarized in Table 1. The reactions in the dark were carried out with *p*-cresol, phloretic acid, and tyrosine. In each case, most of the starting material was recovered unchanged. In the case of phenol, small amounts of pyrogallol and 1,2,4-trihydroxybenzene were obtained in addition to catechol and hydroquinone but no resorcinol was detected (Exp. 2). As was expected from this result, catechol gave further hydroxylated products, i.e. pyrogallol and 1,2,4-trihydroxybenzene (Exp. 3). It appears rather rare that pyrogallol is obtained in a fairly good yield by the direct hydroxylation of catechol which on oxidation often leads to the formation of *o*-benzoquinone or its further degraded products.* In the case of hydroquinone, 1,2,4-trihydroxybenzene was the only product isolated (Exp. 4). The low yield might be due to the instability of the product under the conditions employed. The hydroxylation of a phenol, which bears a methoxyl or carboxyl group at the *para*-position, resulted in replacement of the group by an OH group to give hydroquinone in addition to the formation of the normal *ortho*-hydroxylated product (Exp. 5, 6).

The pH of the reaction mixture falls in the course of the reaction. The hydroxylation of phenolic acids was not affected by the addition of one equivalent of alkali (Exp. 6, 7, 8 and 9), although the reaction is much faster at a higher pH. In the case of sparingly soluble tyrosine, the photolysis at a temperature up to 67° yielded 3,4-dihydroxyphenylalanine (Exp. 10),[18] but if the photolysis of tyrosine was carried out in the presence of three mole equivalents of alkali (pH 10) the destruction of the phenolic ring yielded aspartic acid and no dihydroxyphenylalanine was detected (Exp. 11).

In order to investigate the pH dependence of this reaction, *p*-cresol was irradiated in aqueous hydrogen peroxide varying the pH and other conditions (Table 2). The photolysis in the presence of an excess or an equimolar amount of hydrogen peroxide gave 3,4-dihydroxytoluene in a similar yield, although a longer period of irradiation was needed in the latter case (Exp. 13 and 14). As seen from Table 1 and 2, the nature of the reaction is not altered at the initial pH 3–8. However, the yield of the catechol

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* As an example of hydroxylation of polyphenols, gallic acid is hydroxylated to 2,3,4,5-tetrahydroxybenzoic acid by radiation-induced oxidation in an aqueous solution saturated with oxygen.[5]

TABLE 1. HYDROXYLATION OF PHENOLS IN AQUEOUS HYDROGEN PEROXIDE BY PHOTOLYSIS USING A LOW-PRESSURE MERCURY LAMP WITH QUARTZ HOUSING (MAINLY 2537 Å)[a]

Exp. No.	Phenol (g)	NaOH added	Irrad. time (hr)	Initial pH	Final pH	Recovered phenol (%)	Products (Yield, %)[b]	Non-volatile product (g)
1	*p*-Cresol (4·0)	—	9·0	5·7	2·7	16	3,4-dihydroxytoluene(25)	1·7
2	Phenol (5·0)	—	6·0	5·6	*c*	22	catechol(26), hydroquinone(14), pyrogallol(5), 1,2,4-trihydroxybenzene (3)	0·6
3	Catechol (4·5)	—	5·7	5·6	*c*	35	pyrogallol(22), 1,2,4-trihydroxybenzene(3)	0·6
4	Hydroquinone (4·0)	—	5·0	5·6	*c*	33	1,2,4-trihydroxybenzene(6)	1·2
5	*p*-Methoxyphenol (3·2)	—	6·0	5·2	*c*	18	4-methoxycatechol(9), hydroquinone(5)	—
6	*p*-Hydroxybenzoic acid (4·0)	—	5·8	2·9	*c*	37	3,4-dihydroxybenzoic acid(38), hydroquinone(10), 2,3,4- and 3,4,5-trihydroxybenzoic acid (trace)	—
7	*p*-Hydroxybenzoic acid (4·0)	1 mole	2·0	8·2	7·0	29	3,4-dihydroxybenzoic acid(24), hydroquinone(9), 2,3,4- and 3,4,5-trihydroxybenzoic acid (trace)	—
8	Phloretic acid (3·3)	—	6·5	3·0	*c*	20	3-(3,4-dihydroxyphenyl)propionic acid(28)	—
9	Phloretic acid (3·3)	1 mole	2·5	7·1	5·2	19	3-(3,4-dihydroxyphenyl)propionic acid(26)	—
10	Tyrosine (4·0)[d]	—	1·3	5·8	*c*	20	3,4-dihydroxyphenylalanine(20)	—
11	Tyrosine (5·0)	3 mole	1·8	10·2	9·1	33	aspartic acid(22)	—
12	N-Acetyltyrosine (2·9)	1 mole	5·0	5·0	3·9	*c*	N-acetyl-3,4-dihydroxyphenylalanine(9)	—

[a] A solution of a phenol and hydrogen peroxide (0·3 mole) in water (ca. 230 ml) was irradiated under bubbling nitrogen at about 40°.

[b] The yields are based on the consumed starting phenol.

[c] Not determined.

[d] The reaction was carried out at 51–67°.

TABLE 2. IRRADIATION OF *p*-CRESOL UNDER VARIOUS CONDITIONS USING A LOW-PRESSURE MERCURY LAMP WITH QUARTZ HOUSING (MAINLY 2537 Å)[a]

Exp No.	H_2O_2 (mole)	Additive (mole eq.)	Irrad. time (hr)	Initial pH	Final pH	H_2O_2 decomposed (mmole)	Cresol oxidized (mmole)[b]	Cresol recovered (%)	Yield of 3,4-dihydroxytoluene (%)[c]	Yield of dimers (%)[c]	Non-volatile product (g)
13	0·3	—	9·0	5·7	2·7	64	31	16	25	~0·1	1·7
14	0·04	—	11·5	5·8	3·3	27	21	42	29	0~0·3	0·8
15	0·3	NaOH (0·01)	6·5	8·0	2·7	*d*	28	25	22	*d*	1·5
16	0·3	NaOH (1·0)	6·5	10·1	7·6	*d*	32	13	5	~0·5	1·1
17	0·3	NaOH (1·0)	3·0	10·1	7·8	*d*	24	35	2	*d*	0·7
18	0·3	H_2SO_4 (1·0)	6·5	1·2	1·1	53	24	35	1	~0·9	1·3
19	0·3	H_2SO_4 (8·0)	6·5	0·8	0·8	48	23	38	trace	~1	1·4
20	0·3	NaCl (0·3)	6·0	4·5	2·3	93	34	8	4	~0·7	1·4
21	—	O_2[e]	9·0	5·8	3·4	—	8	79	~1	~7	0·2
22	—	—	8·5	5·8	5·5	—	4	89	trace	~4	0·0

[a] A solution of *p*-cresol (4·0 g, 37 mmole) in water (ca 230 ml) was irradiated at 40–50° under bubbling nitrogen, unless otherwise indicated.

[b] Calculated on the basis of the recovered cresol.

[c] Yields are based on the consumed cresol.

[d] Not determined.

[e] Irradiation was carried out under bubbling oxygen.

was decreased at pH H 10 (Exp. 16), and it was not improved when the reaction period was shortened (Exp. 17). Addition of a mineral acid (pH ca. 1) decreased the yield of the catechol (Exp. 18 and 19). The rate of the photo-decomposition of hydrogen peroxide does not seem to be accelerated in strongly acidic media. Dark reactions under acidic and basic conditions gave only the recovered starting material. The addition of a large excess of sodium chloride seemed to stimulate the decomposition of hydrogen peroxide, and the catechol was obtained only in a low yield (Exp. 20).

Recently, Joscheck and Miller[19] reported that irradiation of an aqueous solution of various phenols with a light of 2537 Å, results in the formation of a phenoxyl radical leading to dimers and dihydroxybenzene derivatives. This reaction using *p*-cresol on an experimental scale, led to the formation of a small amount of 3,4-dihydroxytoluene and a mixture of dimers (Exp. 21 and 22) although a large amount of *p*-cresol was recovered. The yield of the dimers was considerably higher than in the presence of hydrogen peroxide (Exp. 13–20).

Irradiation with a high-pressure mercury lamp (ca. > 2800 Å)

The results of photolysis of *p*-cresol in aqueous hydrogen peroxide with the light (ca. > 2800 Å) from a high-pressure mercury lamp under various conditions are shown in Table 3. Under normal conditions (pH 5·7), *p*-cresol was largely recovered and the catechol and the usual dimeric products were obtained in low yields (Exp. 23). This is probably due to the low efficiency of the decomposition of hydrogen peroxide with the longer wavelength light. On the other hand, in an acidic medium (pH ~ 1), the yield of the catechol was decreased but the yield of the dimer mixture was increased (Exp. 24 and 25).

The photolysis in the presence of uranyl sulfate, which in an acidic solution, is known to sensitize the decomposition of hydrogen peroxide to OH radicals,[20] showed that in the absence of sulfuric acid, the decomposition of hydrogen peroxide (Exp. 26) is retarded. But in strongly acidic solution, the rate of the reaction was considerably increased and the cresol dimers, I, II and III, were obtained in 20, 3, and 12% yields, respectively, and only a trace of the catechol was detected (Exp. 27).

If persulphate, the oxygen–oxygen bond of which is known to be cleaved by irradiation,[21] was used for the photo-oxidation of *p*-cresol, 3,4-dihydroxytoluene was again a minor product and the cresol dimers were obtained in 9% yield.

DISCUSSION

The results (Tables 1 and 2) obtained with the light at 2537 Å can be summarized as follows: (1) The hydroxylation of phenols occurs at the *ortho*- and *para*-positions but not at the *meta*-position. (2) The *ortho*-hydroxylation is preferential. (3) The best yield is obtained at the initial pH between 3 and 8. At the higher or lower pH, the yield is much decreased. (4) The reaction is accelerated at higher temperature. (5) A methoxyl or carboxyl group at the *para*-position with respect to the phenolic group is replaced by a hydroxyl group in addition to usual *ortho*-hydroxylation.

The primary reaction for the photo-decomposition of hydrogen peroxide in an aqueous solution is considered as a fission of the O—O bond of the excited molecule to form two OH radicals (Eq. 1), which initiate the chain decomposition (Eqs 2, 3 and 4).[22]

TABLE 3. IRRADIATION OF *p*-CRESOL UNDER VARIOUS CONDITIONS USING A 100 W HIGH-PRESSURE MERCURY LAMP WITH A PYREX FILTER (>2800 Å)[a]

Exp. No.	H_2O_2 (mole)	Additive	Irrad. time (hr)	Initial pH	Final pH	H_2O_2 decomposed (mmole)	Cresol oxidized (mmole)[b]	Cresol recovered (%)	Yield of 3,4-dihydroxytoluene (%)[c]	Yield of dimers (%)[c]	Non-volatile product (g)
23	0·3	—	7·5	5·7	3·0	10	8·2	78	2·5	~0·6	0·3
24	0·3	H_2SO_4 (1 eq)	6·5	1·0	1·0	8·4	7·2	81	trace	32	0·2
25	0·3	H_2SO_4 (8 eq)	6·7	0·5	0·3	8·4	8·5	77	trace	13	0·3
26	0·3	$UO_2SO_4H_2O$ (1 g)	7·5	1·6	1·6	3·2	6·8	82	trace	~14	0·0
27	0·3	$UO_2SO_4H_2O$ (0·8 g)	6·5	0·7	0·8	28	24	35	trace	35	1·1
28[d]	—	H_2SO_4 (8 eq) $(NH_4)_2S_2O_8$ (25 g)	6·0	1·4	1·3	Not det.	28	25	trace	9	1·2

[a] A solution of *p*-cresol (4·0 g; 37 mmole) in water (ca 230 ml) was irradiated at room temperature under bubbling nitrogen.

[b] Calculated on the basis of the recovered cresol.

[c] Yields are based on the consumed cresol.

[d] A solution of *p*-cresol (4·0 g) in water (300 ml) was irradiated with a 450 w high-pressure mercury lamp with a Pyrex filter.

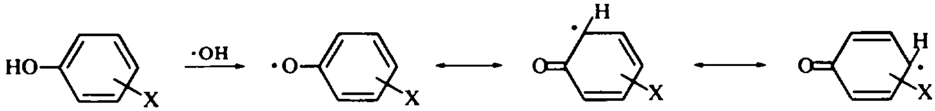
$$H_2O_2 \xrightarrow[(<4000\ \text{Å})]{h\nu} 2\cdot OH \tag{1}$$

$$\cdot OH + H_2O_2 \longrightarrow \cdot OOH + H_2O \tag{2}$$

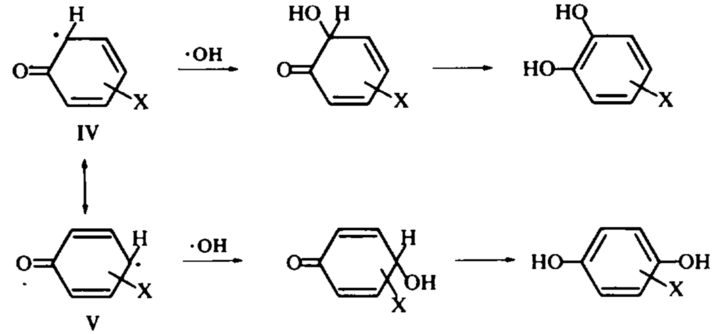
$$\cdot OOH + H_2O_2 \longrightarrow \cdot OH + H_2O + O_2 \tag{3}$$

$$2\cdot OOH \longrightarrow H_2O_2 + O_2 \tag{4}$$

Considering the high inhibition effect of phenol on the decomposition of hydrogen peroxide (Fig. 1), the active oxidizing species of the present hydroxylation reaction will be the OH radical. In this resepct there are two possible mechanisms for the hydroxylation of phenols with OH radicals. One is known as "transfer substitution", that is, the abstraction of the H atom of the phenolic group to form a phenoxyl radical (Eq. 5), giving the *ortho*- and *para*-dihydroxy compounds by combination of a second OH radical with the two canonical forms (IV and V) of the phenoxyl radical (Eq. 6),[3,4,*] but not the *meta*-dihydroxy compounds. Such a mechanism is



(5)



(6)

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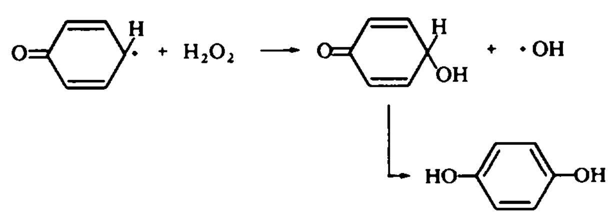
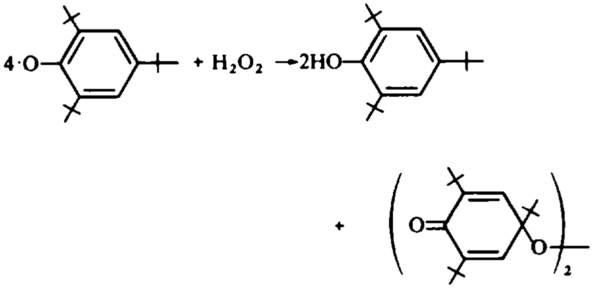
[*] Another possible pathway, in which a phenoxyl radical reacts with hydrogen peroxide to give dihydroxybenzenes as Eq. (i), seems improbable, since 2,4,6-tri-t-butylphenoxyl reacts with hydrogen peroxide to form the parent phenol and a peroxide as in Eq. (ii).[23]



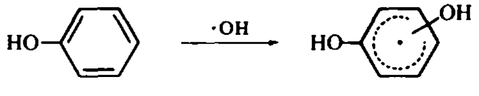
(i)



(ii)

recognized as general for the reaction of phenols with many free radicals.[24] In fact, the formation of phenoxyl radicals from phenol and cresol with the OH radical has been confirmed by electron spin resonance spectroscopy.[25] This pathway rationalizes that the *ortho* and *para*-, but not the *meta*-hydroxylations take place in the reaction.

An alternative mechanism, the attack of the OH radical to a phenol results in the formation of a cyclohexadienyl radical (Eq. 7), which is eventually converted into *ortho*- and *para*-dihydroxy compounds (Eq. 8). Such a mechanism has often been considered in the hydroxylation of various benzene derivatives which usually give a *meta*-dihydroxy compound besides *ortho*- and *para*-derivatives.[3d, 25] An electrophilic character of the OH radical can explain why no *meta*-dihydroxy compound was found in the present reaction. In fact, it has been reported that only *ortho*- and *para*-methoxyphenols are obtained in the reaction of anisole with the OH radical, which is generated either by photolysis of aqueous hydrogen peroxide or by Fenton reagent.[14] Furthermore, Dorfman presented evidence for the formation of the cyclohexadienyl radical from phenol and the OH radical generated by an electron-pulse radiolysis of water.[26]



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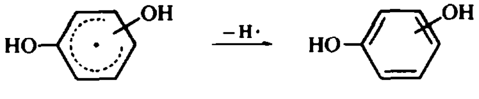
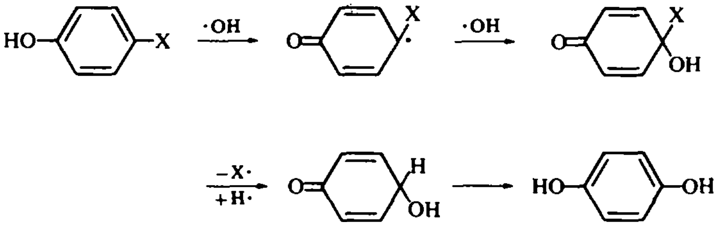


(8)

ortho and *para*

The second mechanism does not explain the formation of phenol dimers which are inevitably obtained in low yields with a light at 2537 Å. The dimers may be derived by coupling of phenoxyl radicals which can be formed either by the hydrogen abstraction of phenols with the OH radical (Eq. 5) or by direct photolysis of phenols.[19] The formation of hydroquinone from *p*-hydroxybenzoic acid and *p*-methoxyphenol can be explained by Eqs. 9 or 10.



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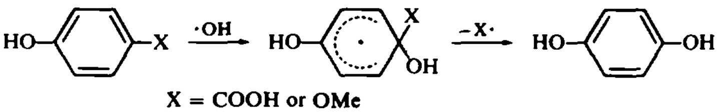

(10)

X = COOH or OMe

The reaction is faster at a higher pH. The absorption spectrum of hydrogen peroxide in an aqueous solution is shifted to a longer wavelength as the pH becomes higher and the absorption intensity at 2537 Å consequently increases. This may result in the increase of the quantum yield of the decomposition. The reaction may be accelerated by lowering of the oxidation potential of phenols at a higher pH.

The results obtained in the photolysis with the longer wavelength light (2800 Å) are more puzzling. Under standard conditions (at the initial pH 5·7), the reaction is slow and the yield of the catechol is low. Under acidic conditions in the presence or the absence of uranyl sulfate, the main products are the mixture of dimers and the formation of the catechol is a side reaction. Although Schenck tentatively suggested that OH radicals are generated by the uranyl sulfate-sensitized photodecomposition of hydrogen peroxide[20] and benzene was hydroxylated by this system,[27] the nature of this reaction seems to differ from the photolysis with the light at 2537 Å.

EXPERIMENTAL

M.ps are uncorrected. The starting materials and the reagents were commercially available, unless otherwise indicated. The products were identified or detected by a comparison with authentic samples by mixed m.ps, IR spectroscopy (Japan Spectroscopic Co., Model IRS), high-voltage electrophoresis (Pherograph-Original-Frankfurt; borate buffer at pH 8·7 or pyridine–acetic acid–H_2O, 10:1:78, at pH 6·2), VPC (stationary phase, silicon DC on celite; carrier gas, He; temp 180–250°), TLC (silica gel; solvent, toluene–ethyl formate-formic acid, 5:4:1, unless otherwise indicated), or paper chromatography (PPC). The following color reagents were used for the detection: I_2 vapor, ethanolic $FeCl_3$, modified Pauli reagent,[28] or ethanolic ninhydrin.

General procedure

A. Table 1. An aqueous soln (ca. 230 ml) of a phenol (3–5 g) and H_2O_2 (ca. 0·3 mole) was placed in a cylindrical vessel, into which a ca. 40 W low-pressure mercury lamp with quartz housing was inserted. During irradiation N_2 was bubbled through a sintered glass jointed at the bottom of the vessel. The reaction temp was kept at 40–50° under these conditions. In some cases, brown material was deposited on the surface of the lamp tube during the reaction and wiped off occasionally. After irradiation, the remaining peroxide was decomposed below 50° by the addition of $NaHSO_3$aq (ca. 30 g). The mixture was extracted with ether. The ethereal layer was separated, dried over Na_2SO_4, and evaporated to dryness. The residue after distillation or immediately was chromatographed on silica gel (ca. 100 g unless otherwise indicated), or analyzed by VPC.

B. Table 2. An aqueous soln (ca. 230 ml) of *p*-cresol (4·0 g, 37 mmole), H_2O_2 (0·3 mole), and other additive, if needed, was irradiated with a ca. 40 W low-pressure mercury lamp in a similar manner to A, An aliquot (40 ml) was iodometrically titrated for the H_2O_2 analysis. The reaction mixture was treated as described above and the products was distilled *in vacuo*. The distillate was analyzed by VPC.

C. Table 3. A soln, as described in B, was irradiated with a 100 W high-pressure mercury lamp surrounded with a water-cooled Pyrex jacket under N_2. The reaction mixture was treated as described in B, unless otherwise indicated.

Isolation of the products

With phenol (Exp. 2). Distillation of the product yielded two fractions: (i) 1·03 g of a colorless liquid, b.p. 35–70°/5 mm, which was identified as phenol (VPC); (ii) 3·05 g of a semi-crystalline solid, b.p. 83–116°/0·1 mm. The fraction (ii) was found to consist mainly of catechol and hydroquinone but not resorcinol (electrophoresis). Column chromatograhy of the fraction (ii) gave 67 mg of phenol (VPC) by elution with $CHCl_3$–acetone (20:1) and 1·19 g of catechol, m.p. 104–107° (IR), by elution with $CHCl_3$–acetone (9:1). Further elution with the same solvent mixture yielded 0·58 g of crystals, m.p. 106–149°, which were found by VPC and TLC to consist of 0·23 g hydroquinone and 0·25 g pyrogallol. Pyrogallol was isolated by preparative VPC, m.p. 134–135° (IR). Further elution yielded 0·40 g hydroquinone, m.p. 173–175° after recrystallization from water (IR). Elution with acetone gave 98 mg of a mixture of products in which 1,2,4-trihydroxybenzene was detected as the major component by TLC and IR.

With catechol (Exp. 3). Distillation of the product yielded 2·89 g of crystals, b.p. 130–220°/0·1 mm, which were separated by column chromatography. Elution with $CHCl_3$ yielded 1·59 g catechol, m.p. 107–108° (TLC). Elution with $CHCl_3$–acetone (5:1) gave 0·99 g of crystals which were purified by rechromatography (silica gel, 30 g) to give almost pure pyrogallol (0·72 g). Further purification by sublimation gave 0·65 g pyrogallol (IR) as needles, m.p. 133–135·5°. Further elution with $CHCl_3$–acetone (10:3) yielded 0·18 g of semi-crystals, which were purified by chromatography to give 0·10 g 1,2,4-trihydroxybenzene (IR).

With hydroquinone (Exp. 4). Distillation of the product yielded 2·29 g of crystals, b.p. 90–110°/0·1 mm, which were chromatographed to give 1·33 g hydroquinone, m.p. 175–177°, after elution with $CHCl_3$–acetone (4:1). Elution with $CHCl_3$–acetone (5:2) yielded 0·19 g 1,2,4-trihydroxybenzene (IR).

With p-*methoxyphenol* (Exp. 5).* Distillation of the product yielded 1·04 g of a distillate, which on digesting with benzene deposited 0·12 g hydroquinone, m.p. 170–172° (IR). The filtrate from the hydroquinone was evaporated and chromatographed. Elution with $CHCl_3$–acetone yielded 0·60 g of a liquid which was identified as the starting material (TLC). Further elution gave 0·28 g 4-methoxycatechol (TLC).

With p-*hydroxybenzoic acid* (Exp. 6). Half (1·50 g) of the product was directly chromatographed (silica gel, 80 g). Elution with $CHCl_3$–acetone (9:1) yielded 0·82 g of crystals, which consist of 0·72 g of the recovered acid and 0·10 g hydroquinone by VPC. This fraction was shown to be contaminated with a trace of 2,3,4-trihydroxybenzoic acid† by TLC. Hydroquinone was isolated by careful sublimation (110°/6 mm) of the fraction and was identified by IR. Further elution yielded 0·54 g of crude protocatechuic acid (TLC and IR), which on recrystallization from water gave 0·40 g of colorless crystals, m.p. 207°. Elution with acetone yielded 70 mg of a mixture of two products (TLC), from which 3,4,5-trihydroxybenzoic acid was identified as the major one (TLC). Irradiation at a higher pH (Exp. 7) gave a similar result which is shown in Table 1.

With phloretic acid (Exp. 8). Column chromatography of the product gave 0·65 g of the recovered acid after elution with $CHCl_3$–acetone (10:1). Recrystallization from water gave crystals, m.p. 125–127°. Further elution gave 0·14 g of a mixture of phloretic acid and 3-(3,4-dihydroxyphenyl) propionic acid (TLC). The next eluate gave 0·81 g of crystals, m.p. 126–134°, which on recrystallization from acetone–$CHCl_3$ gave pure dihydroxy-acid m.p. 133–136°, identical with authentic sample‡ (IR). Irradiation at a higher pH (Exp. 9) gave a similar result which is shown in Table 1.

A soln of phloretic acid and H_2O_2 in water was allowed to stand at room temp for 6 hr. The starting material was recovered in 97% yield.

With tyrosine (Exp. 10). After decomposing the remaining H_2O_2, the dark colored soln was adjusted to pH 4·7 by the addition of NaOH aq. No precipitation occurred at this point. An aqueous soln of neutral lead acetate (160 g) was then added and the ppt filtered off. The filtrate was adjusted to pH 8·3 by the addition of 3% NH_4OH aq. The lead salt of 3,4-dihydroxyphenylalanine formed was collected by centrifugation and treated as described by Raper[18a] to give 0·71 g 3,4-dihydroxyphenylalanine, m.p. 278° (dec), which was identified by IR and TLC (solvent, phenol–H_2O, 3:1). The filtrate from the lead salt was acidified with 6N HCl and evaporated under reduced press to 400 ml. Insoluble materials were filtered off and the filtrate was adjusted to pH 5·0 by the addition of NaOH aq, yielding 0·80 g tyrosine, m.p. 294° (dec), which was identified by TLC.

When the reaction mixture was concentrated under reduced press under N_2 before treatment with lead acetate, the yield of dihydroxyphenylalanine was less (7%), but tyrosine was recovered in 22% yield. When irradiation time was prolonged, the dark colored reaction mixture turned colorless again and the products were found to be more complex (TLC).

An aqueous soln (200 ml) of tyrosine (1 g) and H_2O_2 (0·1 mole) was heated at 78–92° for 1·5 hr in the dark. Pure tyrosine (78%) was recovered and the filtrate contained only tyrosine and no dihydroxyphenylalanine, by TLC.

Experiment 11. The reaction mixture was treated with $NaHSO_3$ to give white ppts. The whole mixture was extracted with ether. Evaporation of the ethereal layer left a dark brown oil (73 mg), which was a complex mixture containing a trace of p-hydroxybenzaldehyde (TLC). The ppts (1·27 g) were collected by filtration, and identified as tyrosine (IR and PPC). The filtrate was shown to contain tyrosine, asparatic

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* The authors are indebted to Mr. Tomoaki Nagamachi for these experiments.

† The authentic sample was prepared according to the literature.[29]

‡ The authentic sample, m.p. 135–137°, was prepared by the demethylation of 3-(3,4-dimethoxyphenyl)-propionic acid with HBr.

acid and several unidentified minor products but no 3,4-dinydroxyphenylalanine (by PPC and electrophoresis). Concentration of the filtrate at pH 5·0 yielded 0·40 g tyrosine. One fifth of the final filtrate was evaporated to dryness. The residue was treated according to the procedure by Johnson *et al.*[30] for the preparation of n-amyl ester of N-acetylamino acid, giving 1·12 g of a dark brown oil, which was chromatographed on silica gel (35 g). Elution with benzene yielded 67 mg of semi-crystals which on alkaline hydrolysis gave 11 mg oxalic acid (IR and TLC). Elution with $CHCl_3$ yielded 0·24 g of an oil, which was identified as n-amyl acetylaspartate[31] by comparison with an authentic sample (IR and TLC).

With N-*acetyltyrosine* (Exp. 12). The reaction mixture was continuously extracted with EtOAc. Evaporation of the extract yielded 2·64 g of a reddish oil, which was chromatographed on silica gel. Elution with $CHCl_3$–acetone (9:1) yielded 0·15 g of an oil which contained the starting material (TLC). Elution with $CHCl_3$–acetone (1:1) yielded 1·12 g of a colored oil, which was hydrolyzed by refluxing in 3N HCl (40 ml). The hydrolysate was treated as described above (Exp. 10) to give 0·22 g dihydroxyphenylalanine.

With p-*cresol* (Exp. 1 and 13). After the titration of an aliquot (40 ml), the reaction mixture was treated as usual. Distillation of the product gave 1·34 g of an oil, b.p. 41–220°/10^{-3} mm, which was shown by VPC to consist of 0·53 g *p*-cresol and 0·79 g 3,4-dihydroxytoluene. VPC at 240° revealed the presence of 5 minor products showing retention times at 7·4, 9·3, 10·9, 12·8 and 21·0 min. The first 4 were identical with the products obtained by ferricyanide oxidation of *p*-cresol at pH 8·0.[31] These products were assigned as Pummerer's ketone (I; ret time, 9·3 min), 2,2′-dihydroxy-5,5′-dimethylbiphenyl (II; ret time, 10·9 min), and 2,5′-dihydroxy-2′,5-dimethylbiphenyl (III; ret time, 12·8 min), but the structure of the product (ret time, 7·4 min) is still unknown. The total yielded of I, II, and III was estimated as ca. 3 mg.

Column chromatography of the distillate on silica gel (50 g) yielded 0·41 g *p*-cresol (IR and VPC) by elution with $CHCl_3$. Further elution with $CHCl_3$ yielded 0·54 g of semi-crystals which showed only one peak by VPC. Distillation (51–83°/10 mm) gave 0·41 g pure 3,4-dihydroxytoluene, m.p. 60–62° (IR and TLC).

Isolation of dimers I, II *and* III (Exp. 27). The products obtained from a part (21/25) of the reaction mixture were distilled *in vacuo* to give 1·17 g *p*-cresol as a yellow oil, b.p. up to 120°/1 mm, and a viscous oil, b.p. 120–210°/10^{-3} mm, which was shown by VPC and TLC to consist of a mixture of dimers and a trace of 3,4-dihydroxytoluene. The latter fraction (1·1 g) was chromatographed on silica gel (45 g). Elution with benzene yielded 0·57 g of a mixture of I and II (VPC), which was dissolved in ether and extracted with NaOH aq. Evaporation of the ethereal layer gave 0·48 g of Pummerer's ketone (I), which on recrystallization from MeOH gave crystals, m.p. 120–122°. Acidification of the alkaline layer yielded 75 mg 2,2′-dihydroxy-5,5′dimethylbiphenyl (II). Further elution with benzene yielded 0·29 g 2,5′-dihydroxy-2′,5-dimethyl biphenyl (III), which on recrystallization from benzene gave crystals, m.p. 154–157°. All the dimeric products were identified by a comparison with the authentic samples.[32]

In Exp. 28, the reaction mixture was treated as above (Exp. 27). Dimers I, II, and III were isolated in 1·9, 2·3, and 4·5% yield, respectively. A reaction in the dark was carried out for Exp. 28 and most of the starting material was recovered (IR).

Reactions in the dark

With p-*cresol.* An aqueous soln (230 ml; pH 5·5) of *p*-cresol (4·0 g) and H_2O_2 (0·3 mole) was allowed to stand in the dark under N_2 for 22 hr. Treatment of the reaction mixture as usual yielded 3·76 g (94%) of pure *p*-cresol. Similar reactions in the dark under acidic (pH 1·1) and alkaline (pH 10·2) conditions recovered *p*-cresol in 92 and 91%, respectively.

With 3,4-*dihydroxytoluene.* An aqueous soln (50 ml; pH 1) of 3,4-dihydroxytoluene (0·2 g) and H_2O_2 (0·1 mole) was allowed to stand in the dark at 50° under N_2 for 6 hr. From the reaction product 0·12 g (62%) of catechol was recovered (VPC).

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