CHAPTER 2

THE PERSULFATE OXIDATION OF PHENOLS AND ARYLAMINES (THE ELBS AND THE BOYLAND–SIMS OXIDATIONS)

E. J. BEHRMAN

The Ohio State University, Columbus, Ohio

CONTENTS

Organic Reactions, Vol. 35, Edited by Andrew S. Kende et al.
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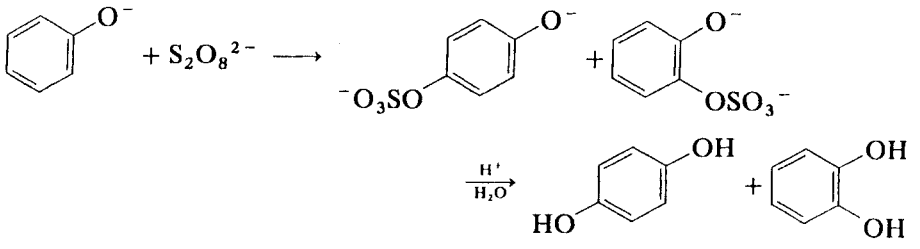
ACKNOWLEDGMENTS

I thank the following: the Editorial Board of Organic Reactions for their advice, and in particular Drs. Robert Joyce and Ralph Hirschmann for the meticulous care that they devoted to my typescript, the late Dr. Burnett M. Pitt for introducing me to the Elbs oxidation, and Prof. J. O. Edwards, to whom this paper is dedicated, for invaluable help over the years.

THE ELBS OXIDATION: INTRODUCTION

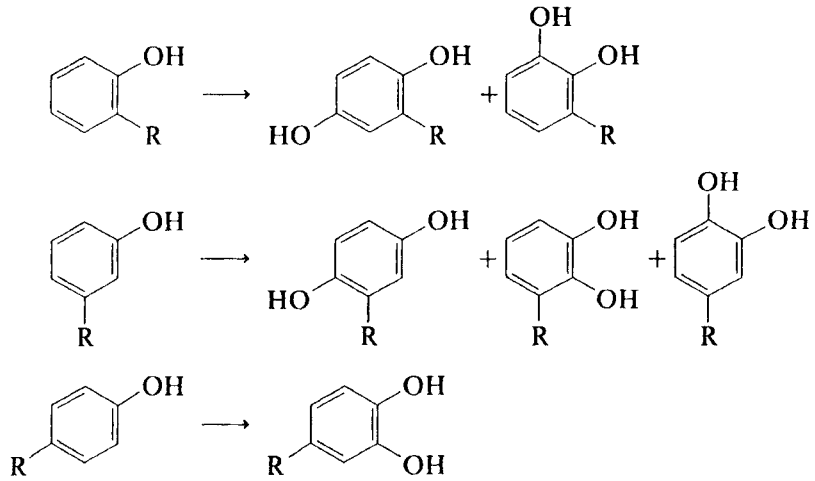
A phenolate anion reacts with persulfate ion in alkaline solution to yield a product in which a sulfate group enters the ring *para* or *ortho* to the phenolic group. *Para* substitution predominates. Subsequent acid-catalyzed hydrolysis yields the dihydric phenol.



The reaction was discovered by Karl Elbs* in 1893[1] and named the *Elbs persulfate oxidation.*[2] The reaction is generally applicable to *ortho*-, *meta*-, and

* A brief obituary of Karl Elbs appears in *Ber.*, **66**, 74 (1933). For further bibliographical material, see J. S. Fruton, *A Bio-Bibliography for the History of the Biochemical Sciences Since 1800,* American Philosophical Society, Philadelphia, 1982, p. 191.

para-substituted phenols with isomer distributions as shown:



The yields are not very high, particularly from *para*-substituted phenols, but the major contaminant is usually unchanged starting material that can be separated easily from the intermediate sulfate ester by solvent extraction. Other generally oxidizable groups such as an aldehyde or a double bond are usually not affected under the reaction conditions. The reaction was last thoroughly reviewed in 1951.[3] Subsequent partial reviews include Refs. 4–8. T. R. Seshadri [see W. Baker and S. Rangaswami, *Biograph. Memoirs Fell. Roy. Soc.*, **25**, 505 (1979) and Fruton, *loc. cit.*, p. 661] has made major contributions to the development of the Elbs oxidation. Nearly 30% of the references in this review are due to him and his colleagues.

MECHANISM

Studies of the kinetics of the reaction[9–11] reveal a first-order dependence on both persulfate and phenol and a positive salt effect. The relationship between pH and reaction rate shows that the phenolate ion is the reactive species. Allyl acetate, a reagent that reacts rapidly with sulfate radical ions, has no effect on either the rate of disappearance of persulfate or the rate of product formation (for *o*-nitrophenol as substrate). These data and the substituent effects discussed below make it clear that the reaction proceeds via electrophilic attack of the persulfate ion on the phenolate ion.

The observed ionic strength effect is consistent with a reaction between two ions of the same charge. The phenolate ion is, of course, much more susceptible to electrophilic attack than is the undissociated phenol. Accordingly, the pH at which a maximum rate is achieved is dependent on the pK_a. The effect of a series of substituents on the reaction rate has been reported,[10] and representative second-order rate constants are given in Table A. Again, the substituent effects are in the expected direction for electrophilic attack by the persulfate ion. The

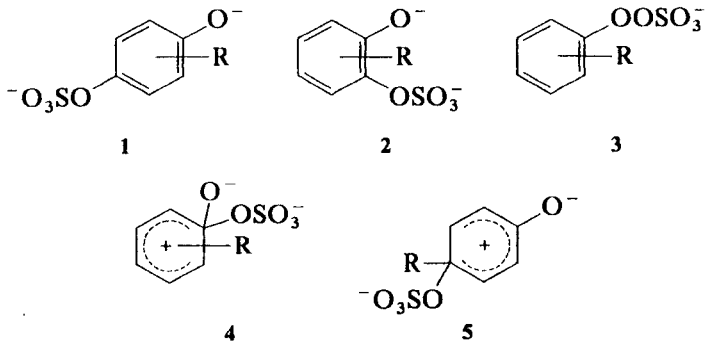
TABLE A. REPRESENTATIVE RATE CONSTANTS FOR REACTION OF PHENOLS AND PERSULFATE ION[a]

Substituent	Rate Constant $10^2 k_2$ ($L\,mol^{-1}\,s^{-1}$)
H	1.93
o-NO_2	0.15
m-NO_2	0.32
o-CN	0.24
m-CN	0.38
o-CHO	0.53
m-CHO	0.73
o-CO_2^-	4.08
m-CO_2^-	0.55
o-Cl	1.60
m-Cl	0.58
o-Br	1.56
m-Br	0.64
o-I	2.12
m-I	0.66
o-F	1.61
m-F	1.25
o-CH_3	8.42
m-CH_3	2.40
o-C_4H_9-*t*	16.40
m-C_4H_9-*t*	1.63
o-OCH_3	31.70
m-OCH_3	4.25

[a] Conditions: 30°, 1.7 *M* KOH, Ref. 10.

question of whether initial attack is at carbon or at oxygen followed by rearrangement has not been definitely settled. This point is discussed in further detail below.

Electrophilic attack by the persulfate ion on each of the three resonance forms of the phenolate anion will give rise to products **1**, **2**, and **3**:



1 **2** **3**

4 **5**

There are, in addition, possibilities for electrophilic attack by persulfate at two sets of *ipso* positions to give **4** and **5**.

The final product could arise by direct attack at either carbon or oxygen (or an *ipso* position) followed by rearrangement. The evidence bearing on the site of initial attack rests principally on the kinetic effects of substitutents in the *ortho* and *meta* positions. The overall correlation with Hammett substituent constants is much better for the assumption of attack at oxygen (or the oxygen *ipso* position) than for attack at carbon. Thus the order of reactivity of each pair of *ortho*- and *meta*-substituted phenols (except for carboxylate) in Table A is consistent with what would be expected on the assumption of attack at oxygen. This conclusion is based on the fact that the substituent with the more negative Hammett sigma constant should give the higher rate and that the relative rates should be reversed depending on whether rate-limiting attack at carbon or oxygen is assumed.[10] The principal contrary evidence[10] originally adduced to support attack at carbon came from a comparison of the rates of oxidation of 2,4- and 2,6-disubstituted phenols. Less reliance must be placed on these data because the yields from *para*-substituted phenols are too low to provide a basis for reliable conclusions.[12] This *caveat* also applies to arguments in support of attack at oxygen based on the relative reactivity of *p*-fluorophenol.[13] The preponderance of the evidence appears to support attack at the phenolic oxygen followed by inter- or intramolecular rearrangement.

Although *para*-substituted phenols react at normal rates, the yields of *o*-sulfate are typically very low, and little unchanged starting material is generally recovered. These yields can be substantially increased by increasing the persulfate:phenol ratio,[14] in contrast to the result for *ortho*- and *meta*-substituted phenols, where increasing the persulfate:phenol ratio usually decreases the yield of *p*-sulfate. These facts argue for a pathway in which reaction with 1 mol of persulfate leads to an intermediate that neither gives the normal Elbs product nor reverts to starting material. It is possible to view structures **3**, **4**, and **5** as intermediates of this sort. An *ipso* intermediate of type **5** has also been implicated in the reaction of persulfate with 2,4,6-trichlorophenol by the formation of substantial quantities of chloride ion[12] and in the formation of 2,5-dihydroxy-3-iodo-4-methoxybenzoic acid by persulfate oxidation of 2-hydroxy-3,5-diiodo-4-methoxybenzoic acid.[15]

SCOPE AND LIMITATIONS

Phenols substituted with a wide variety of functional groups are successfully oxidized by the Elbs procedure in spite of the large redox potential of persulfate ion. This is due to the fact that, although persulfate ion is capable of oxidizing many substituents, these reactions do not take place at significant rates under the typical conditions of the Elbs oxidation. Alcohols, aldehydes, and olefins are essentially inert to the action of persulfate at room temperature and below in aqueous alkali. Some oxidative cleavage of the double bond of stilbenes is reported,[16] but coumarins, which react as the *o*-hydroxycinnamic

acid dianions, generally give good yields (Table IV). Some functional groups, however, undergo reaction with persulfate more rapidly than do typical Elbs substrates. Among these are thiol groups, which are oxidized by persulfate to disulfides.[17] Aliphatic amines also appear to be oxidized sufficiently rapidly (to unknown products) to suggest effective competition with the Elbs oxidation.[18] *p*-Nitrosophenol is oxidized to *p*-nitrophenol without any observable formation of the *o*-sulfate.[19] For summaries of the reactions of persulfate with a variety of organic substrates, see Refs. 8 and 20–22.

Another source of interference is the instability of some substrates under alkaline conditions, for example, 4-methoxycoumarins.[23,24] When this instability is due to reaction of the phenolate anion with oxygen, the difficulty can be circumvented by working in an inert atmosphere. Thus 1,3,5-trihydroxybenzene is successfully oxidized under nitrogen,[25] and the yield of 5,8-dihydroxyflavone is increased 15% by purging the system with nitrogen.[26] On the other hand, certain quinones react rapidly with hydroxyl ion. The oxidation of 5-hydroxy-1,4-naphthoquinone (juglone) is unsuccessful because of this fact.[27] Hydroquinone can be oxidized to quinhydrone by persulfate.[28]

There are a number of other examples in which the substrate is recovered unchanged (Table XV). It is not known why these compounds fail to react, but perhaps increasing the persulfate:substrate ratio might be beneficial.[14]

Isomer Distribution

There are only a few reports on the isomer distribution in the Elbs persulfate oxidation.[11,29–32] Ratios of *para* to *ortho* isomers are reported for seven subtrates based on isolated yields.[29] Table B lists those subtrates for which ratios have been determined by methods that do not depend on the isolation procedure. The *para*:*ortho* ratio is reported to increase with decreasing ionic strength.[11]

Ratios of *para* to *ortho* isomer determined by isolation are in the range 6–22 and are thus not widely different from the three examples determined by analytical methods, with the following notable exception. In the oxidation of two *meta*-substituted phenols, the 3,4-dihydroxy isomer could not be found.[29] It has since been shown that this isomer is indeed formed in substantial proportion.[30] Failure to detect it earlier was simply a result of the isolation scheme.

TABLE B. ISOMER DISTRIBUTION

Substrate	Products (Relative Yield)	Method	Ref.
Phenol	Hydroquinone (5.9–2.3), catechol (1)[a]	GLC	11
m-Hydroxybenzoic acid	2,5-Dihydroxybenzoic acid (8), 3,4-dihydroxybenzoic acid (3), 2,3-dihydroxybenzoic acid (1)	GLC, HPLC	30
2-Pyridone	2,5-Dihydroxypyridine (11.5), 2,3-dihydroxypyridine (1)	Colorimetric	31

[a] The *para*:*ortho* ratio is a function of pH, ionic strength, temperature, and ratio of reactants.

Byproducts

Substantial quantities of apparently polymeric material of the humic acid type have been noted as products in the persulfate oxidation of phenols. For example, a 40% yield of a dark brown amorphous material is produced in the oxidation of *m*-hydroxybenzaldehyde.[33] Similar observations have been noted incidently throughout the literature, but the products have not been well characterized. The only extensive studies show that dihydric phenols, aminophenols, and even monohydric phenols such as phenol itself, *o*-cresol, and salicylic acid all give rise to substantial quantities of "humic acids" when oxidized at persulfate:phenol ratios greater than 1.[34,35] It should be recalled that the yield of the Elbs product (the sulfate ester) generally increases as the persulfate: phenol ratio is decreased.[9] In addition to the humic acids, biphenyls have been detected as byproducts,[36] especially with activated phenols. These presumably arise from radical coupling reactions, and their formation might possibly be prevented by the inclusion of radical trapping agents such as allyl alcohol. The biphenyls, however, do not appear to be formed in large quantities.

COMPARISON WITH OTHER METHODS

Many methods exist for the synthesis of hydroquinones. A superb and extensive summary can be found in Wedemeyer's volume of Houben-Weyl.[37] There are also less detailed treatments.[38–42] The methods can be divided into those that involve replacement of some substituent other than hydrogen and those in which hydrogen is replaced (direct methods). The first group includes alkali fusion of halophenols and phenolsulfonic acids, the Dakin oxidation of phenolic aldehydes and the related Baeyer–Villiger oxidation of hydroxyacetophenones, diazotization and hydrolysis of aminophenols, the Bucherer reaction, and hydrolysis of halophenols via Grignard reagents. The direct methods, which include the Elbs oxidation, usually offer the considerable advantage of fewer steps from starting material to product. Direct methods other than the Elbs oxidation include the use of Fenton's reagent, oxidation by hydrogen peroxide or peracids, electrochemical oxidation of phenols, reduction of quinones available by oxidation of phenols with Fremy's salt, and three promising newer methods: (1) benzeneselenic anhydride oxidation of phenols to *o*-quinones;[43] (2) an *ortho*-hydroxylation procedure[44] using copper(I) chloride and oxygen in acetonitrile at 0–50° with yields of 70–90%; and (3) a *para*-hydroxylation method [45] involving alkylation with cyclopentadiene, isomerization, and finally oxidation with hydrogen peroxide in acetonitrile. These latter two methods have not yet been tested for generality.

The Elbs oxidation remains a useful procedure, in spite of its generally moderate yields, because of the simplicity of the process and the fact that the conditions for the synthesis are compatible with a number of sensitive functional groups that might not survive other procedures. It offers the unique advantage that the sulfate ester is produced on the way to the hydroquinone.

This means that the water solubility of the sulfate ester can be used to advantage in separating the product from both unchanged starting materials and from byproducts. Beyond this, the production of the unsymmetrical alkali-stable hydroquinone sulfate ester can be used to synthetic advantage as it allows distinction to be made between the hydroxyl groups in what otherwise might be a symmetrical molecule.[2]

EXPERIMENTAL CONDITIONS

Most of the studies reported in the literature deal with isolated yields. There are few consistent trends to be derived from these data. In a few reactions, yields have been determined by an analytical method that is not subject to the variables of a particular isolation method (Table B). The major factors that have been shown to influence yield are pH, ratio of reactants, free-radical traps, metal ion chelators, and, perhaps, ionic strength. In addition, small effects have been noted by varying the temperature.

pH and Nature of the Base

The stoichiometry of the reaction is

$$R(H)OH + S_2O_8^{2-} + 2OH^- \longrightarrow {}^-OROSO_3^- + SO_4^{2-} + 2H_2O$$

One mole of alkali is needed to ionize the phenol and a second mole to neutralize the proton displaced from the ring. A quantity of base less than this requirement will decrease the yield correspondingly; the addition of alkali in excess of this requirement appears to offer no advantage and may actually decrease the yield as the result of an ionic strength effect.[11] The identity of the base may influence the yield. Tetramethylammonium hydroxide is reported to give better yields than either potassium hydroxide or sodium hydroxide in some reactions.[46] Tetraethylammonium hydroxide gives much better yields than does tetramethylammonium hydroxide in the oxidation of 5-hydroxyflavone.[26] Sodium hydroxide is reported to give better yields than potassium hydroxide.[47]

Ratio of Reactants

With 2-pyridone as substrate, substrate:persulfate ratios in the range 10–20 give yields of 85–90%; a 1:1 ratio gives a yield of only about 55%, and excess persulfate sharply decreases the yield.[9] With phenol as substrate, however, excess substrate appears to lower the yield slightly.[11] The reason for this apparent discrepancy is not known. The former result is probably usually true for *ortho*- and *meta*-substituted phenols since the monosulfate formed as the initial product can undergo further attack by persulfate to yield a disulfate.[32,48,49] However, for four *p*-substituted phenols, increased yields are obtained with a substrate:persulfate ratio of 0.3.[14]

Under typical synthetic conditions, the phenol will usually be the cost-limiting component, so that it will seldom prove practicable to use excess phenol. The presence of excess phenol during the initial stages of the reaction,

at least, can be achieved by adding a solution of the persulfate slowly to the solution of phenol. Alternatively, one can add potassium persulfate as a solid to the solution of phenol in alkali and take advantage of the fact that this salt dissolves slowly relative to the sodium and ammonium salts. However, improved yields can sometimes be obtained with the more concentrated solutions of persulfate made possible by using the more soluble ammonium salt.[50] At 20°, saturated solutions of potassium, sodium, and ammonium persulfates in water are 0.17, 2.3, and 2.5 *M* respectively.[51]

Nature and Position of Ring Substituents

Reactions of a set of *ortho*-, *meta*-, and *para*-substituted phenols with persulfate, using a colorimetric method to determine the dihydric phenol produced following acid hydrolysis, show that the *ortho*- and *meta*-substituted phenols give yields in the range 60–75% regardless of the nature of the substituent.[12] The yields from the *para*-substituted phenols are, however, in only the 15–20% range.

Free-Radical Traps and Metal Ion Chelators

The yield of 2-phenylhydroquinone from *o*-phenylphenol is increased by about 9% on the addition of allylbenzene to the reaction mixture and by about 5% by the addition of ethylenediaminetetraacetic acid (EDTA).[50] Allyl alcohol decreases the formation of dark-colored materials during the oxidation of guaiacol and *o-tert*-butylphenol.[10] By contrast, allyl acetate has no effect on yield in the oxidation of *o*-nitrophenol.[9] This result may reflect a difference between activated and deactivated phenols.

Temperature and Ionic Strength

Temperature variation over the range 0–70° appears to affect the yield only slightly, perhaps by a decrease of 3–5% as temperature increases. The oxidation of water by persulfate may be a competing reaction at the upper end of this temperature range, especially for phenols that react very slowly.[52]

A significant drop in yield with an increase in ionic strength amounting to about 15% for an increase from 0.05 to 0.3 *M* is reported,[11] but this effect has been questioned.[9] These studies should be repeated, using a wider range of substrates.

Effects of Ferrous Ion

It has been recommended that ferrous ion be added to reaction mixtures.[53] This addition may have been rationalized on the assumption that the Elbs oxidation is a free-radical process with ferrous ion serving as initiator. However, it has since been shown that the reaction does not involve free-radical intermediates and further that the addition of ferrous ion does not affect the rate of the reaction.[9,10] Indeed, there is evidence that metal ions reduce the yield, presumably by the promotion of competing free-radical processes leading to other organic products and also by direct consumption of persulfate.[47] See, however, Ref. 53a.

Solvents Other Than Water

Although Elbs oxidations are usually carried out in aqueous solution, pyridine[54] or 1,4-dioxane[10] can be used as cosolvents to aid in solubilizing certain phenols. Kinetic studies in aqueous mixtures of ethanol, *tert*-butyl alcohol, and acetonitrile give linear plots of log k versus $1/D$ (where D is the dielectric constant) with a negative slope.[55] There exists the possibility, as yet unexplored, for carrying out the Elbs oxidation in pure organic solvents since persulfate can be solubilized by crown ethers and quaternary ammonium salts.[56]

Conditions for the Hydrolysis of Aryl Sulfates

Rate constants for the acid-catalyzed hydrolysis of a variety of aryl sulfates vary by a factor of about 10 from the *p*-nitrophenyl sulfates (highest) to the *p*-methoxyphenyl sulfates (lowest).[57] Hydrolysis takes place with cleavage of the sulfur–oxygen bond.[58]

EXPERIMENTAL PROCEDURES

Phenylhydroquinone.[50] A solution of 17.0 g (0.1 mol) of *o*-phenylphenol, 0.5 g (0.0017 mol) of EDTA, 34.0 g (0.85 mol) of sodium hydroxide, and 2.4 g (0.02 mol) of allylbenzene in 180 mL of distilled water was prepared. This solution was cooled to 5° and kept under nitrogen while a solution of 22.8 g (0.1 mol) of ammonium persulfate in 100 mL of distilled water was added over a period of 1 hour. The resulting solution was kept at 5° for an additional 4 hours. Then 100 mL of methylene chloride was added and the mixture acidified with 2 *N* HCl to pH 1. A small amount of tar was filtered off on glass wool and the filter washed with water. The filtrate was extracted with methylene chloride, after which the aqueous phase was treated with 25 mL of concentrated HCl and hydrolyzed on a steam bath for 1 hour under nitrogen. The solution was cooled and extracted with methylene chloride (4 × 150 mL). Evaporation of the methylene chloride left the product, which crystallized to give 7.9 g of brown crystals of 95% purity (38.4% yield of pure product).

The yield dropped to 29% in the absence of allylbenzene and to 25% in the absence of both allylbenzene and EDTA.

2,5-Dihydroxypyridine (5-Hydroxy-2-pyridone).[31] In this procedure, 38 g (0.4 mol) of 2-pyridone and 80 g (2 mol) of sodium hydroxide were dissolved in 1.5 L of water. The solution was cooled to 5°, and then 135 g (0.5 mol) of potassium persulfate was added all at once. The mixture was stirred for 20 hours while the temperature was allowed to rise to 20°. The reaction mixture was filtered, cooled, and brought to pH 0.75 with concentrated sulfuric acid. The mixture was hydrolyzed at 100° for 30 minutes. The hydrolysate was cooled to 5°, brought to pH 6.5 with 10 *N* sodium hydroxide under nitrogen, and evaporated to dryness *in vacuo*. After a final drying over phosphorus pentoxide, the salt cake was thoroughly extracted with 2-propanol in a Soxhlet apparatus. The

2-propanol extract was decolorized with charcoal and then concentrated until crystals began to form. After standing overnight at −10°, the solution deposited 19 g (42%) of crude 2,5-dihydroxypyridine, which, after two recrystallizations from ethanol, gave 8 g of nearly colorless crystals that darkened at 230° and decomposed at 250–260° without melting. UV (water) nm max (ε): 230.5 (7390), 320 (5620).

The original procedure recommended the addition of 2 g of ferrous sulfate. As discussed earlier, ferrous ion offers no advantage and indeed merely decreases the yield by reduction of persulfate.

Hydrogen Cytosine-5-sulfate Monohydrate and 5-Hydroxycytosine.[59] To a solution of 2 g (0.018 mol) of cytosine in 100 mL of 1.0 *N* KOH was added 7.3 g (0.027 mol) of potassium persulfate. The solution was stirred at 25° for 18 hours. The pale yellow solution was acidified by the addition of 9 mL of concentrated HCl with cooling. Hydrogen cytosine-5-sulfate precipitated from the solution. It was washed with cold water, acetone, and ether to give 3.3 g (89%) of crude material. One recrystallization from 45 mL of water gave 2.6 g (70%) of pure product as the monohydrate. UV (water, pH 6.8) nm max (ε): 277 (5400).

A 3-g sample of hydrogen cytosine-5-sulfate monohydrate (0.014 mol) and 7 mL of 6 *N* HCl was heated in a boiling water bath for 15 minutes. Cooling produced 2 g (85%) of 5-hydroxycytosine hydrochloride. This material was dissolved in 30 mL of warm water and the pH adjusted to 7 with 4 *N* potassium hydroxide. The precipitate of 5-hydroxycytosine (1.2 g, 77%) was washed with water, acetone, and ether. UV (water, pH 6.8) nm max (ε): 288 (5000).

5,8-Dihydroxy-3-ethoxy-7,3′,4′,5′-tetramethoxyflavone.[60] To a solution of 1.4 g (0.0035 mol) of 5-hydroxy-3-ethoxy-7,3′,4′,5′-tetramethoxyflavone in 20 mL of pyridine was gradually added a solution of 1 g of potassium hydroxide in 250 mL of water. To this mixture was added during 2 hours a solution of 1.4 g (0.0052 mol) of potassium persulfate in 50 mL of water. After 24 hours, the solution was acidified, filtered, and then extracted three times with ether to remove unchanged starting material. Concentrated HCl (25 mL) and sodium sulfate (2 g) were then added to the aqueous phase, and the mixture was heated on a boiling water bath for 30 minutes. A yellow precipitate of product separated. This was combined with some further material obtained by ether extraction to yield 0.7 g (48%) of product. Recrystallization from ethanol gave deep yellow short needles, mp 190–192°.

5,8-Dihydroxy-2-methyl-4′,5′-dihydro[furano-3′2′:6,7-chromone](8-Hydroxydihydronorvisnagin).[61] To a solution of 1 g of dihydronorvisnagin (5-hydroxy-2-methyl-4′,5′-dihydro[furano-3′,2′:6,7-chromone]) in 20 mL of pyridine and 18 mL of 10% aqueous tetramethylammonium hydroxide was added 2.2 g of potassium persulfate dissolved in 150 mL of water during 4 hours. The reaction mixture was kept for 20 hours under nitrogen at 15–20°. The deep red solution was then acidified to pH 2 (Congo red) and filtered to remove 0.4 g of a brown precipitate. The filtrate was extracted twice with ether, the ether evaporated,

and the residue combined with the brown precipitate. The combined residues were extracted with chloroform. On chromatographic purification of the chloroform solution on alumina, 0.3 g of starting material was recovered.

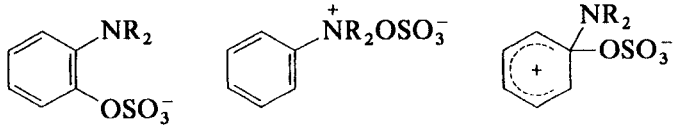
The aqueous filtrate was treated with 2 g of sodium sulfite, 30 mL of concentrated HCl, heated for 30 minutes at 90°, and cooled. Extraction with ether (5 × 30 mL) gave 0.45 g (42%) of 8-hydroxydihydronorvisnagin, which, following treatment with Norit, crystallized from methanol containing sulfurous acid in deep yellow thin plates, mp 260–262°.

THE BOYLAND–SIMS OXIDATION: INTRODUCTION

By analogy with the Elbs persulfate oxidation of phenols, it might be expected that aromatic amines would react with persulfate to give *p*-aminoaryl sulfates. Although the Elbs reaction had been known since 1893, it was not until 60 years later that Boyland et al.[62] reported the extension of this reaction to aromatic amines. In accordance with expectations, aminoaryl sulfates were indeed the major products of the reaction, but, unexpectedly, the substitution took place exclusively *ortho* to the amino group rather than predominantly in the *para* position as in the phenol oxidation. *Para* substitution takes place only if the *ortho* positions are occupied by substituents other than hydrogen. Boyland and Sims explored the preparative aspects of this reaction in a series of papers.[16,62–65] It seems appropriate to name the reaction the Boyland–Sims oxidation.[66] Primary, secondary, and tertiary aromatic amines are all converted to the corresponding *o*-aminoaryl sulfates under conditions similar to those used for the Elbs oxidation, that is, room temperature or below, aqueous alkali, and equimolar quantities of amine and persulfate.

MECHANISM

The mechanistic evidence favors a polar rather than a free-radical reaction involving electrophilic displacement by the peroxide oxygen on the unprotonated amine.[66] In particular, radical traps have no effect on either the rate or extent of product formation. However, a single electron transfer mechanism is possible provided that the radicals are confined to a solvent cage.[66a] The rate law, like that for the Elbs persulfate oxidation, is $v = k[S_2O_8^{2-}]$ [amine]. Selected rate constants are given in Tables C–E. The exclusive *ortho* orientation of the entering sulfate group could, in principle, arise from attack at the (1) *ortho* carbon atom assisted by interaction with the amino group (**6**), (2) nitrogen atom followed by rearrangement (**7**), or (3) *ipso* carbon atom followed by rearrangement (**8**).



6 **7** **8**

TABLE C. SELECTED RATE CONSTANTS FOR OXIDATION OF PRIMARY ANILINES BY PERSULFATE[a]

Substituent	Rate constant $10^3 k_2$ (L mol^{-1} s^{-1})		
	o	*m*	*p*
—H	12	12	12
—OCH_3	56	17	165
—CH_3	27	18	32
—F	4	5	17
—Cl	3	5	15
—CO_2^-	3	3	4
—NO_2	0.15	1	0.3

[a] Conditions: 30°, pH 7, 20% aqueous ethanol (v/v).[67]

TABLE D. SELECTED RATE CONSTANTS FOR OXIDATION OF PRIMARY, SECONDARY, AND TERTIARY ANILINES BY PERSULFATE.[a]

Substrate	Rate Constant, $10^3 k_2$ (L mol^{-1} s^{-1})
Aniline	5
N-Methylaniline	70
N,*N*-Dimethylaniline	28

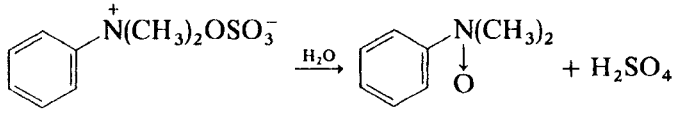
[a] Conditions: 30°, pH 7, 50% aqueous ethanol (v/v).[68] The data in Ref. 69 suggest that rate constants obtained in 50% ethanol can be converted to those expected in 20% ethanol by multiplying by a factor of about 2.

TABLE E. RATE CONSTANTS FOR OXIDATION OF SUBSTITUTED *N*,*N*-DIMETHYLANILINES BY PERSULFATE.

Substituent	Rate Constant, $10^3 k_2$ (L mol^{-1} s^{-1})	Ref.
4-OCH_3	91.5	70
3-OCH_3	18	70
4-CH_3	38.5	70
3-CH_3	24	70
4-Cl	18	70
2-CH_3-4-Cl	1.8	71
2-CH_3-3-Cl	1	71
2,4-$(CH_3)_2$	2.5	71
2,3-$(CH_3)_2$	2.1	71

[a] Conditions: 30°, pH 7,[70] or 0.1 *M* KOH, 50% aqueous ethanol (v/v).[71]

The observed effects of substituents on the rate of reaction eliminate rate-limiting attack at the *ortho* carbon atom[66–71] for primary and tertiary anilines. The choice between the other two possibilities appears to have been solved for tertiary anilines and may be generally applicable. Intermediate **7**, R = methyl, was synthesized and was shown under the reaction conditions not to rearrange to the *o*-sulfate but rather to hydrolyze as shown.[72] Inasmuch as the substituent effects for a series of tertiary anilines are the same as those for primary anilines, *ipso* attack followed by rearrangement seems the most likely alternative.[70,71]



When a substrate such as 2,6-dimethylaniline is oxidized, the *para* sulfate is formed. This might occur either by direct attack of persulfate at the *para* carbon or by an intermolecular rearrangement. Kinetic measurements of the oxidation of 2,6- and 2,4-disubstituted anilines would be revealing. Since no *p*-substituted products are ordinarily formed, direct attack at the *para* position must be slow compared with the rate of *ortho* substitution. If, however, the rate of oxidation of the 2,6 isomer is approximately equal to that of the 2,4 isomer (as the limited data in Ref. 73 suggest), we might assume an intermolecular rearrangement.

SCOPE AND LIMITATIONS

The Boyland–Sims oxidation of aromatic amines is not as well represented in the literature as the Elbs oxidation of phenols. Consequently, the scope and limitations of the reaction are less well known. The general limitations on the Elbs oxidation apply since the two reactions are usually carried out under similar conditions. The principal possible difference in the reaction conditions (although most Boyland–Sims reactions have been run in dilute alkali) is due to the widely different values for the pK_a of typical aromatic amines compared with phenols: phenol has a pK_a of 10, while aniline has a pK_a of 4.6. Thus, while the Elbs oxidation of phenol should be run above pH 11, the Boyland–Sims oxidation of aniline can be carried out at neutrality because the reactive species are the phenolate anion and the uncharged amine, respectively. Therefore, the Boyland–Sims reaction can be performed in the presence of alkali-sensitive functional groups, in contrast to the Elbs oxidation.

Overall yields in the Boyland–Sims oxidation appear to be lower than those in the Elbs oxidation. Thus 2-pyridone gives a yield of 85% of 2,5-dihydroxypyridine,[9] in contrast to a yield of 55% of 2-amino-3-hydroxypyridine from 2-aminopyridine.[66] It is reasonable to attribute this difference to the more facile formation of condensation polymers of the humic acid type from aromatic amines.

Isomer Distribution

When there is a free *ortho* position, *ortho* substitution is generally exclusive, although small quantities of *para*-substituted products have been detected in the oxidations of three related anilines: anthranilic acid, *o*-aminoacetophenone, and kynurenine.[64] 3-Methylindole is attacked at all free positions in the benzene ring and so may be reacting by a different mechanism.[74] The ratio of the two possible *ortho* isomers for *meta*-substituted anilines has not been studied to any extent; however, the 6-sulfate (the least sterically hindered) is the major product in the oxidation of 3-methylaniline and 3-chloroaniline.[63]

Byproducts

In addition to sulfation of the ring, competitive oxidation reactions occur at the nitrogen atom. A number of these byproducts have been isolated under typical Boyland–Sims conditions; others, under more acidic conditions and include imines, quinones, and their condensation products. The final stages of condensation are a humic acid-like polymer. Typical structures are shown in Table F. While the structures of these products are well established, the mechanisms by which they are formed are not well understood. Kinetic investigations of the formation of these colored products have been carried out by monitoring the increase in absorbance in the vicinity of 400 nm.[75–81] Mechanistic schemes for the reaction based on these studies include the following points: (1) there is some free-radical involvement as judged by the inhibitory effects of allyl acetate and allyl alcohol;[81] (2) the rates are first order in both amine and persulfate, but the derived second-order "constants" are a function of initial concentrations;[81] (3) electron-withdrawing substituents generally increase the rate, although there is conflicting evidence on this point,[79,80] especially by the fact that the protonated amine is unreactive[78,81a]; and (4) the quantity of polymer increases with increasing persulfate:amine ratio.[81] Resolution of some of the conflicting evidence may lie in the interpretation of the kinetic data. The method measures the formation of both the imine and quinone intermediates as well as the condensation products. The reactions leading to these products probably have different electronic requirements. Attack by persulfate at the amine nitrogen is probably accelerated by electron-donating substituents on the ring, while the condensation reactions leading to polymer formation could be dominated by the electrophilicity of the quinones formed in the initial reactions. It is not clear at what stage free radicals are involved, but it must be remembered that allyl acetate has no effect on the rate of disappearance of persulfate so that radical involvement must follow any steps requiring persulfate.

Only brown amorphous material is formed from the persulfate oxidation of 2-aminofluorene and 4-amino-4′-fluorobiphenyl, while 2-aminoanthracene, 2-aminoanthraquinone, 2-aminochrysene, and 4-aminoazobenzene all fail to react appreciably.[16] Likewise, 4-dimethylaminostilbene is not attacked, except with some cleavage of the double bond to yield 4-dimethylaminobenzoic acid.[16]

A tentative overall view of the reactions between persulfate and aromatic amines can be seen as a partitioning of products due to competition between

attack at the *ipso* carbon atom leading to ring sulfation (the Boyland–Sims oxidation) and attack at nitrogen leading eventually to polymeric products.

COMPARISON WITH OTHER METHODS

The principal alternative methods for synthesis of aminophenols are the reduction of nitrophenols and diazophenols. Summaries of methods for the synthesis of aminophenols are to be found in Refs. 37, 38, 40, 41, 82, and 83. Monoperphosphoric acid reacts with some aromatic amines (only a few have been looked at) in the presence of carbonyl compounds and acid to give aminophenols and their *O*-phosphate esters.[83a] The advantage of the Boyland–Sims oxidation lies in the mild conditions under which it can be run. While the yields for some compounds are respectable, generally better yields are often obtained by these other methods.

EXPERIMENTAL CONDITIONS

Experimental conditions have been varied in only a few studies. The only factors known to influence the yield are the ratio of reactants and pH. The yield of sulfate ester drops markedly as the amine:persulfate ratio is decreased.[66] Concomitantly, the yield of polymeric product increases.[78] The yield of sulfate ester falls as the pH is increased,[66] but this might conceivably be an ionic strength effect. Considering the stoichiometry of the reaction, however, in the absence of other data, it would appear prudent to use no more than 1 equivalent of base.

$$HO^- + S_2O_8^{2-} + R(H)NH_2 \longrightarrow H_2O + SO_4^{2-} + R\begin{matrix}NH_2\\ \diagdown\\ \diagup\\ OSO_3^-\end{matrix}$$

The reaction can be carried out in water or in acetone–water mixtures. Other water–solvent mixtures can be used as well, but the rate of reaction decreases with decreasing dielectric constant.[69] Temperature does not appear to influence the yield over the range 30–50°.[66]

EXPERIMENTAL PROCEDURES

It has been the usual practice, in contrast to the Elbs oxidation, to isolate the intermediate sulfate and subsequently hydrolyze it to the aminophenol.

The general procedure is as follows.[63] The amine (5 g) in water (250 mL) is brought into solution by the addition of acetone, or, in the case of amines containing an acidic group, by the addition of 2 *N* sodium or potassium hydroxide. Sodium or potassium hydroxide (2 *N*, 20% molar excess) is added, followed by 1 molar equivalent of persulfate in aqueous solution during 8 hours with continuous stirring. The mixture is kept overnight, evaporated to 200 mL under

reduced pressure, and filtered. The solution is washed with ether and further treated according to the nature of the amine. Toluidine *o*-sulfates can be extracted from the ether-washed solution with butanol, aminobenzoic acid *o*-sulfates can be isolated by extracting the dried reaction mixture with methanol, and some sulfates can be crystallized directly from the ether-extracted reaction mixture (diphenylamine *o*-sulfate). The aminophenol is then formed by acid-catalyzed hydrolysis of the sulfate.

Comparative experiments in which the aminophenol is isolated directly have not been reported.

o-Dimethylaminophenyl Hydrogen Sulfate and o-Dimethylaminophenol.[62] *N,N*-Dimethylaniline (5 g, 0.04 mol) in a mixture of 250 mL of water, 400 mL of acetone, and 30 mL of 2 *N* potassium hydroxide (0.06 mol) were mixed with a saturated aqueous solution of 11.2 g of potassium persulfate (0.04 mol) and the mixture stirred for 8 hours at room temperature. The mixture was kept overnight, filtered, concentrated to 250 mL, washed with ether (3 × 150 mL), and then evaporated to dryness under reduced pressure. The residue was extracted with hot 95% ethanol (3 × 50 mL). The combined extracts were diluted with 1.5 L of ether, yielding *o*-dimethylaminophenyl potassium sulfate (4.2 g, 40%), which was recrystallized from 95% ethanol.

The potassium salt (0.46 g) was dissolved in 2 mL of water and treated with 2 mL of concentrated HCl to yield *o*-dimethylaminophenyl hydrogen sulfate (0.31 g, 82%). Recrystallization from aqueous ethanol gave prisms, mp 217–219° (dec.).

The hydrogen sulfate (0.4 g) was heated at 100° with concentrated HCl (5 mL) for 1 hour, and the solution was then cooled to near 0° and partially neutralized with 2 *N* NaOH. *o*-Dimethylaminophenol (0.21 g, 83%) separated as needles, mp 44–45°, which was raised to 46° by crystallization from aqueous ethanol.

TABULAR SURVEY

The literature has been searched through mid-1984. Some oxidations of phenols and aromatic amines may have been missed because they were not indexed if incidental to the principal theme of the reference. In addition to Chemical Abstracts, the ISI citation index was found very valuable.

In each table, entries are arranged in order of increasing number of carbon atoms and, within each carbon-number group, in order of increasing number of hydrogen atoms. Yields are given in parentheses, and conversions based on recovered starting material are in brackets. Yields marked with a double dagger (‡) are for the phenol sulfate ester; those marked with an asterisk (*) were determined by a chromatographic or colorimetric procedure. A dash in parentheses (—) in the yield column indicates that no yield was reported. Since most reactions have been carried out under similar conditions, no details are given in the tables. Table XV lists a number of unsuccessful oxidations together with comments.

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