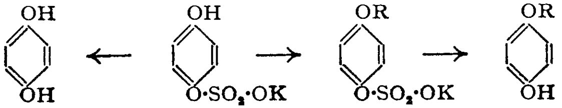
463. *The Elbs Persulphate Oxidation of Phenols, and its Adaptation to the Preparation of Monoalkyl Ethers of Quinols.*

By Wilson Baker and N. C. Brown.

Experiments have been carried out in order to determine the most favourable conditions under which alkaline solutions of persulphates attack phenols with free *p*-positions to give quinols, or *p*-substituted phenols to give catechols (Elbs persulphate oxidation). In the former cases it has now been shown that the free phenolic group in the intermediate *p*-hydroxyphenyl potassium sulphates (I) can be alkylated, and the sulphate group subsequently removed by acid hydrolysis, thus providing a route to the synthesis of quinol monoalkyl ethers of known orientation. A reaction mechanism is put forward involving the participation of the sulphate ion radical $\dot{O}\cdot SO_3^{\ominus}$.

The oxidation of monohydric phenols to dihydric phenols by potassium persulphate in alkaline solution was discovered by Elbs (*J. pr. Chem.*, 1893, **48**, 179). If the *p*-position to the phenolic group is free, then quinol derivatives are produced, but if the *p*-position is occupied a derivative of catechol is formed, though usually in much smaller yield. Patents taken out in 1894 (Chemische Fabrik auf Aktien—vorm. E. Schering, D.R.-PP., 81,068, 81,297, 81,298. See Friedländer, " Fortschritte der Teerfarbenfabrikation ", 1894—1897, **4**, pp. 126, 127, and 121 respectively) showed that the reaction proceeds *via* the intermediate formation of a hydroxyphenyl potassium sulphate (I), which is subsequently hydrolysed in acid solution to the quinol (II).



(II.) (I.) (III.) (IV.)

This reaction has been erroneously attributed both to Bargellini and to Neubauer and Flatow (see later references), but it should be associated solely with the name of its discoverer, and it is suggested that in future it should be called the " Elbs persulphate oxidation ". It cannot be known as the " Elbs reaction ", since this designation has already been applied to the preparation by the same worker of anthracenes by the cyclisation of 2-methylbenzophenones (see Fieser, in Adams's " Organic Reactions ", 1942, **1**, 129). Although the yields are often low, the products are usually isolated in a state of purity, owing to the fact that the intermediate hydroxyphenyl alkali sulphates are not extracted by ether from alkaline or acidified aqueous solutions, so that the other organic products can readily be removed from the reaction mixture.

The reaction was first studied in the favourable case of *o*-nitrophenol, which gave nitroquinol in 30—40% yield, about half the starting material being recovered. The earliest reactants used by Elbs or described in the German patents (*locc. cit.*) were phenol, *o*-, *m*-, and *p*-cresols, *p*-chloro-, *p*-bromo-, and *p*-nitro-phenols, salicylic acid, *p*-hydroxybenzoic acid, and *o*-, *m*-, and *p*-cresotic acids. The following compounds have been successfully oxidised : salicylaldehyde (Neubauer and Flatow, *Z. physiol. Chem.*, 1907, **52**, 375) ; 2-hydroxy-4-methoxyacetophenone (Bargellini and Aureli, *Atti R. Accad. Lincei*, 1911, **20**, 118) ; *p*-hydroxyphenylarsinic acid (D.R.-P., 271,892, 1914) ; coumarin (giving 6-hydroxycoumarin) and 7-methoxycoumarin (Bargellini and Monti, *Gazzetta*, 1915, **45**, 90) ; 2-hydroxy-3 : 4-dimethoxyacetophenone (Bargellini, *ibid.*, 1916, **46**, 249 ; Baker, *J.*, 1941, 667) ; 2-hydroxy-3 : 4-dimethoxybenzophenone (Bargellini, *loc. cit.*) ; *m*-hydroxybenzaldehyde (Hodgson and Beard, *J.*, 1927, 2339) ; 7 : 8-dimethoxycoumarin (Bargellini, *loc. cit.* ; Wessely and Demmer, *Ber.*, 1929, **62**, 120) ; 7-methoxy-8-ethoxycoumarin (Wessely and Demmer, *loc. cit.*) ; *m*-5-xylenol (Bergel, Copping, Jacob, Todd, and Work, *J.*, 1938, 1383) ; 2-hydroxy-3 : 4-dimethoxy- and 2-hydroxy-3 : 4-methylenedioxy-benzoic acid, 2 : 3-dimethoxy- and 2 : 3-methylenedioxy-phenol, and 2-hydroxy-3 : 4-methylenedioxyallylbenzene (Baker and Savage, *J.*, 1938, 1602) ; 2-hydroxy-6-methoxyacetophenone (Baker, *J.*, 1939, 959) ; 2-hydroxy-6-benzyloxy-, 2 : 6-dihydroxy-, 2-hydroxy-3-methoxy-, and 2-hydroxy-5-methoxy-acetophenone, and 2-hydroxy-3-methoxybenzaldehyde (Baker, Brown, and Scott, *J.*, 1939, 1922) ; 8-methoxycoumarin (Mauthner, *J. pr. Chem.*, 1939, **152**, 23) ; 2-hydroxy-3 : 4 : 6-trimethoxyacetophenone (Baker, *J.*, 1941, 669). Of particular interest is the application of the reaction by Seshadri and his co-workers to the flavone and related series, whereby 5-hydroxyflavones and their derivatives were converted into 5 : 8-dihydroxy-derivatives ; the reactants were 5-hydroxy-3 : 7-dimethoxy-, 5 : 7-dihydroxy-3-methoxy-, 5-hydroxy-3 : 7 : 3′ : 4′-tetramethoxy-, 5 : 7-dihydroxy-3 : 3′ : 4′-trimethoxy-, 5-hydroxy-, 5-hydroxy-3 : 7 : 4′-trimethoxy-, 5-hydroxy-3 : 7 : 3′ : 4′ : 5′-pentamethoxy-, and 5 : 7-dihydroxy-3 : 3′ : 4′ : 5′-tetramethoxy-flavone and chrysin, chrysin 7-monomethyl ether, and 4-hydroxy-6-methoxyxanthone (*Proc. Indian Acad. Sci.*, 1947, **25***A*, 417, 427, 432, 444; **26***A*, 288).*

General Reaction Conditions.—A study of the oxidation of a number of simple phenols has established the optimum reaction conditions which are described in the experimental section. No significant advantage is gained by the use of ammonium in place of potassium persulphate, or by addition of ferric chloride as recommended by Bargellini. The yield is sometimes improved by carrying out the oxidation in solutions saturated with sodium chloride or sulphate. With phenols difficultly soluble in aqueous alkali owing to co-ordination with an adjacent carbonyl group, Seshadri recommends addition of pyridine. Where the dihydric phenol is easily soluble in water, and is not readily extracted therefrom, it is an advantage to saturate the solution with carbon dioxide after the oxidation, extract it with ether (an alternative, which frequently removes flocculent material, is to acidify to Congo-red, filter, extract with ether, and make alkaline to litmus with sodium hydrogen carbonate), evaporate the aqueous layer to dryness under diminished pressure, dissolve out the phenyl potassium sulphate derivative with 90% alcohol,

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* *Note added in Proof.*—Further examples have been described by Seshadri *et al.* in *Proc. Indian Acad. Sci.*, 1946, **23***A*, 23, 262; 1948, **27***A*, 37, 85, 91, 209, 217, 375; 1948, **28***A*, 1.

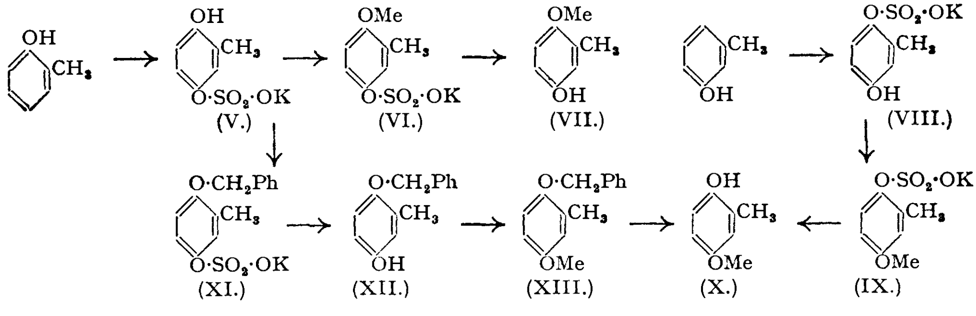
distil off the alcohol, and hydrolyse the residue with a small volume of 2N-acid. The hydrolysis is conveniently effected under a layer of benzene or ether (see Baker, Brown, and Scott, *loc. cit.*).

The Table in the experimental section gives the yields of several dihydric phenols under the standard conditions. In the *p*-oxidations the yields are increased by the presence of electron-attracting groups (this may be due to a general stabilisation of the nucleus), by increasing substitution, and by the effect of substituents on the activity of the position para to the hydroxyl group. The last point is most clearly seen by comparing the yields from the isomeric pair, 2-hydroxy-6-methoxyacetophenone (38%) and 2-hydroxy-3-methoxyacetophenone (4%). The reaction was not successful with α-naphthol.

A side reaction observed during two Elbs persulphate oxidations is an oxidative coupling to give derivatives of diphenyl (Baker, Brown, and Scott, *loc. cit.*); 2-hydroxy-3-methoxybenzaldehyde (*o*-vanillin) gives 2 : 5-dihydroxy-3-methoxybenzaldehyde and a much smaller amount of 4 : 4′-dihydroxy-3 : 3′-dimethoxydiphenyl-5 : 5′-dialdehyde, and 2-hydroxy-5-methoxyacetophenone gives by an ortho-oxidation a very poor yield of 2 : 3-dihydroxy-5-methoxyacetophenone and a much larger amount of 2 : 2′-dihydroxy-5 : 5′-dimethoxy-3 : 3′-diacetyldiphenyl.

The ortho-oxidation of *p*-substituted phenols gives catechol derivatives in very poor yield, and tarry matter is simultaneously produced. The catechols are best isolated and purified by means of their insoluble lead derivatives, which are subsequently decomposed by hydrogen sulphide. No significant yield of catechol derivatives could be obtained from *p-tert.*-butylphenol or β-naphthol.

Preparation of Quinol Monoalkyl Ethers.—The product of interaction of a phenol possessing a free *p*-position and alkaline potassium persulphate is a *p*-hydroxyphenyl potassium sulphate (I), and, owing to the stability of these compounds under alkaline conditions, it is possible to alkylate (I) to (III), and then to hydrolyse (III) in acid solution to the quinol monoalkyl ether (IV), in which the alkyloxy-group occupies the position of the original hydroxyl group. The method, therefore, affords a general process by which quinol monoalkyl ethers of known orientation can be prepared, and the synthetical possibilities are illustrated by the preparation of 5-*benzyloxy*-m-2-*xylenol*, and the two isomeric monomethyl ethers of toluquinol and of 2 : 6-dimethylquinol. *o*-Cresol was oxidised by alkaline potassium persulphate to the intermediate (V), which, after isolation in the crude state, was treated with methyl sulphate in alkaline solution to give (VI), and acid hydrolysis then gave 5-hydroxy-2-methoxytoluene (VII). In a similar manner *m*-cresol gave, *via* the intermediates (VIII) and (IX), 2-hydroxy-5-methoxytoluene (X). By utilising the same series of reactions the two isomeric monomethyl ethers of 2 : 6-dimethylquinol were also obtained, *m*-5-xylenol giving 2 : 6-dimethylquinol 4-methyl ether, and *m*-2-xylenol giving 2 : 6-*dimethylquinol* 1-*methyl ether*.

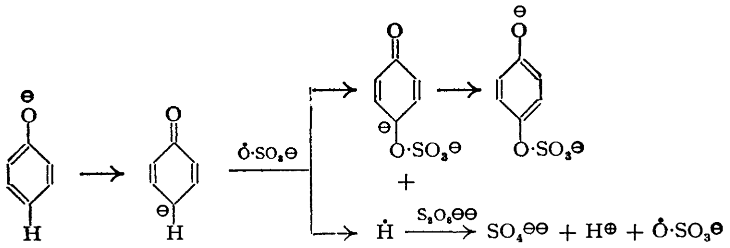


A further synthetical possibility is the preparation of both isomeric monoalkyl ethers of a quinol from the same starting material; this is possible by taking advantage of the fact that a benzyloxy-group is much less readily hydrolysed by acids than is the phenyl sulphate group (see preparation of 2 : 5-dihydroxy-6-benzyloxyacetophenone, Baker, Brown, and Scott, *loc. cit.*). Thus the intermediate (V) from *o*-cresol can be benzylated to (XI), hydrolysed with dilute acid to (XII), methylated to (XIII), and finally hydrolysed in strongly acid solution to (X).

Reaction Mechanism.—The initial and final products of the Elbs persulphate oxidation of phenols are shown in the following ionic equation :

$$\overset{\ominus}{O}\cdot C_6H_5 + S_2O_8^{\ominus\ominus} \longrightarrow \overset{\ominus}{O}\cdot C_6H_4\cdot O\cdot SO_3^{\ominus} + SO_4^{\ominus\ominus} + H^{\oplus}$$

The direct introduction of the group $\cdot O{\cdot}SO_3^{\ominus}$ in place of a hydrogen atom *p*- or *o*-, but never *m*-, to the phenolic oxygen atom strongly suggests that the reaction is due to the sulphate ion radical $\dot{O}{\cdot}SO_3^{\ominus}$ which, although an anion, is yet cationoid in character. The reaction is represented in greater detail in the following scheme (only one of the hydrogen atoms of the phenol nucleus is shown) :



The sulphate ion radical is probably first generated by the interaction of a trace of a metal ion, *e.g.*, a ferrous ion, with a persulphate ion :

$$Fe^{\oplus\oplus} + S_2O_8^{\ominus\ominus} \longrightarrow Fe^{\oplus\oplus\oplus} + SO_4^{\ominus\ominus} + O{\cdot}SO_3^{\ominus}$$

The slow rate of the reaction can be correlated with the requirement that the $\dot{O}{\cdot}SO_3^{\ominus}$ anion radical has to attack an anion (or neutral molecule if the attack were on the free phenol molecule rather than the phenoxide ion) at a negative centre.

The oxidative coupling of the phenol nuclei which occasionally occurs may be due to the production of hydroxyl radicals by the mechanism $\dot{O}{\cdot}SO_3^{\ominus} + H_2O \longrightarrow HSO_4^{\ominus} + \dot{O}H$. Substituted phenyl radicals may then be formed, $\overset{\ominus}{O}{\cdot}C_6H_5 + \dot{O}H \longrightarrow \overset{\ominus}{O}{\cdot}C_6H_4^{\cdot} + H_2O$, which undergo dimerisation (see Discussion, " Oxidation ", *Trans. Faraday Soc.*, 1946, **42**, 196).

EXPERIMENTAL.

General Reaction Conditions.—The phenolic compound (1 mol.) is dissolved in a 10% solution of sodium hydroxide (5 mols.) and oxidised by the slow addition during 3—4 hours of a saturated aqueous solution of potassium persulphate (1 mol.). Throughout the addition the mixture is continually stirred, and the temperature is not allowed to rise above 20°. After standing overnight, the solution is acidified to Congo-red, filtered if necessary, and extracted twice with ether. The aqueous layer is treated with excess of hydrochloric acid, heated on the water-bath for ½ hour, cooled, and extracted with ether. The extracts are then dried and distilled, yielding the dihydric phenol.

The following Table shows a few new results *, and others † where the yields were previously unrecorded or where an appreciable improvement in yield was made.

Phenol.	Product.	Recovered phenol, %.	Yield of dihydric phenol, %.	Yield allowing for recovered phenol, %.
	p-*Oxidations.*			
Phenol †	Quinol	48	18	34
Salicylaldehyde †	2 : 5-Dihydroxybenzaldehyde	24	25	33
m-5-Xylenol †	2 : 6-Dimethylquinol	30	36	51
m-2-Xylenol *	,,	26	30	40
p-Xylenol *	2 : 5-Dimethylquinol	25	42	56
o-Chlorophenol *	Chloroquinol	20	50	62
	o-*Oxidations.*			
p-Cresol †	3 : 4-Dihydroxytoluene	20	9	11
Vanillin *	3 : 4-Dihydroxy-5-methoxybenzaldehyde	48	1·9	3·6
p-Hydroxybenzoic acid †	Protocatechuic acid	71	0·6	2·0

Some of the yields may be raised by isolation of the intermediate phenyl potassium sulphate derivative as previously described, but the process is tedious owing to the evaporation of large volumes of solution.

*5-Benzyloxy-*m*-2-xylenol* (with Dr. R. F. GOLDSTEIN).—4-Hydroxy-2 : 6-dimethylphenyl potassium sulphate was prepared from *m*-5-xylenol, and isolated by extraction with 90% alcohol. This salt (25 g.) was boiled and stirred under reflux with 90% alcohol (60 c.c.) and a solution of sodium hydroxide (7 g.) in water (50 c.c.), during addition of benzyl chloride (14 g.) (¼ hour), and then for a further 2 hours. The mixture was now made weakly acid to Congo-red by addition of hydrochloric acid, stirred just below the boiling point for 2 hours, and cooled in ice. The solid *5-benzyloxy-*m*-2-xylenol* (23 g.) crystallises from benzene or light petroleum and has m. p. 97—99° (Found : C, 78·7 ; H, 6·9. $C_{15}H_{16}O_2$ requires C, 78·9 ; H, 7·1%).

5-*Hydroxy*-2-*methoxytoluene* (VII).—*o*-Cresol (21 g.) was converted into the intermediate phenyl potassium sulphate (V) (6·5 g. of *o*-cresol were recovered), which was isolated (27 g.) by two extractions with 90% alcohol, and methylated by being shaken in 50% alcohol with a large excess of methyl sulphate and concentrated aqueous sodium hydroxide, the mixture (kept alkaline throughout) being finally heated on the water-bath for ½ hour. The solution was then made strongly acid to Congo-red and heated for ½ hour, and the oily product was extracted with ether and distilled twice, giving a product, b. p. 242—244° (7·3 g.; 27% yield), which solidified, and was then crystallised from benzene–light petroleum; m. p. 46° (Bamberger, *Annalen*, 1912, **390**, 175, records m. p. 46—46·5°).

Preparation of 2-*Hydroxy*-5-*methoxytoluene* (X) *from* m-*Cresol.*—(X) was prepared from *m*-cresol (21 g.). *m*-Cresol (6·5 g.) was recovered, and (X) isolated after two distillations, b. p. 240—243° (9·2 g.; 34% yield), and final crystallisation from water. It had m. p. 71° (Bamberger, *loc. cit.*, p. 174, records m. p. 70·5—71·5°).

5-*Hydroxy*-2-*benzyloxytoluene* (XII) (With Mr. F. GLOCKLING).—The crude phenyl potassium sulphate derivative (V) was prepared from *o*-cresol, and a portion (20 g.) was benzylated as in the preparation of 5-benzyloxy-*m*-2-xylenol, using 90% alcohol (60 c.c.), sodium hydroxide (6 g.) in water (50 c.c.), and benzyl chloride (15 g.). After hydrolysis of the sulphate group, the product (XII) was extracted with ether, transferred to aqueous sodium hydroxide, reprecipitated, and again isolated with ether, leaving a dark, partly crystalline solid which was used directly for the preparation of (XIII). Pure 5-*hydroxy*-2-*benzyloxytoluene* (XII) was prepared by shaking the solution of the crude material in chloroform with alumina, and crystallising from light petroleum (b. p. 80—100°) (charcoal); colourless needles, m. p. 69—70° (Found: C, 78·2; H, 6·4. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·5%).

2-*Benzyloxy*-5-*methoxytoluene* (XIII) (With Mr. F. GLOCKLING).—(*a*) The crude phenol (XII) (5·8 g.) was methylated with a large excess of methyl sulphate and 50% aqueous sodium hydroxide in acetone, giving finally crude (XIII) (4·1 g.) which was directly hydrolysed to (X) (below). (*b*) A pure specimen of 2-*benzyloxy*-5-*methoxytoluene* (XIII) was prepared from pure 2-hydroxy-5-methoxytoluene (X) by benzylation, giving a colourless oil, which distilled at 135—138°/0·5 mm., and solidified in solid carbon dioxide–acetone (Found: C, 79·3; H, 7·3. $C_{15}H_{16}O_2$ requires C, 79·0; H, 7·1%).

2-*Hydroxy*-5-*methoxytoluene* (X) *from* (XIII).—The crude compound (XIII) [(*a*) above] (4·1 g.) was heated with acetic acid (30 c.c.) and concentrated hydrochloric acid (15 c.c.) at 60—70° for 2 hours, poured into water (25 c.c.), and extracted with ether. The ethereal extract was shaken with aqueous sodium hydroxide, the aqueous layer acidified, and the product isolated by means of ether and crystallised twice from light petroleum (b. p. 60—80°) (charcoal), giving 2-hydroxy-5-methoxytoluene (X) (0·77 g.), m. p. and mixed m. p. 71°.

5-*Methoxy*-m-2-*xylenol from* m-5-*Xylenol.*—The phenyl potassium sulphate intermediate prepared from *m*-5-xylenol was methylated and hydrolysed as in the preparation of (VII). The neutralised reaction mixture was steam-distilled, yielding 5-methoxy-*m*-2-xylenol, m. p. 77° (Bamberger, *Ber.*, 1903, **36**, 2040 records m. p. 77—77·5°).

2-*Methoxy*-m-5-*xylenol from* m-2-*Xylenol.*—This *compound* was prepared as the preceding isomeride. It separates from water in needles, m. p. 83° (Found: C, 71·2; H, 7·9. $C_9H_{12}O_2$ requires C, 71·1; H, 7·9%).

The authors are indebted to Dr. C. E. H. Bawn and Mr. G. E. Coates for valuable discussions on the reaction mechanism. Their thanks are due to Imperial Chemical Industries Ltd. for permission to record the preparation of 5-benzyloxy-*m*-2-xylenol, which was made in their laboratories at Blackley, and for gifts of specimens of the three isomeric xylenols.

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