ortho-HYDROXYLATION OF PHENOLS.

with an addendum on the cyclisation of

2-aryloxy-5-nitrobenzaldehydes.

A Thesis for the Degree of Ph.D.

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September 1952.

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Acknowledgments.

The author wishes to express his sincere thanks to his supervisor, Dr. J.D. Loudon, for help, advice, and encouragement during this work.

Thanks are also due to Mr. J.M.L. Cameron, Miss R.H. Kennaway, and Miss Christie for performing the microanalyses.

The author is indebted to the Department of Scientific and Industrial Research for a Maintainance Allowance during the period October 1949 to September 1952.

Summary.

In the method of ortho-hydroxylation studied, phenol, its derivatives or homologues, are condensed with 2-chloro-5-nitrobenzophenone, ($Ph.CO.C_6H_3.NO_2.Cl$ or, for convenience, RCl) giving aryloxy-nitrobenzophenones of type 1. These, on successive treatment with concentrated sulphuric acid, acetic acid, and hydrogen peroxide, afford o-hydroxyaryloxy-nitrobenzophenones of type 2, which undergo scission in boiling piperidine to give simple derivatives or homologues of catechol. Methylation of type 2 affords compounds of type 3 which on scission yield guaiacol derivatives. Diazomethane is the most reliable methylating agent since it is shown that in suitable compounds of type 2 and in alkaline media, the group R may migrate from one to the other oxygen atom. A preliminary investigation into the possible advantages of 2-chloro-3:5-dinitrobenzophenone over the mono-nitro compound gave promising results.

1. $R.O.C_6H_5$ 2. $R.O.C_6H_4.OH$

3. $R.O.C_6H_4.OMe$ 4. $R.O.C_6H_3.(OH)_2$

5. $R.O.C_6H_3.OH.OMe$

Renewed hydroxylation, applied to compounds of types 2 and 3, yields those of types 4 and 5 respectively.

When heated with piperidine compounds of type 4 in general were not cleaved to pyrogallols, but underwent rearrangement followed by cyclisation, the products finally isolated being derivatives of 4-hydroxy-7-nitro-9-phenylfluorone. The latter process was blocked by the presence of methyl substituents in the positions flanking the two free hydroxyl groups, and in this case with piperidine normal scission to 4:6-dimethylpyrogallol took place. The presence of bromo substituents in these positions did not prevent fluorone formation which was attended by expulsion of one bromine atom. Methylation or tosylation of the hydroxyl groups before treatment with piperidine resulted in normal scission, affording partial O-derivatives of pyrogallol.

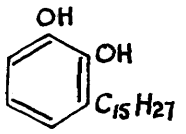
In one case 1:2:3:4-tetramethoxybenzene was synthesised from phenol by a combination of three hydroxylations and one rearrangement.

In an addendum the cyclisation by concentrated sulphuric acid of 2-aryloxy-5-nitrobenzaldehydes is described and is shown to take a different course from that of the 2-arylthio- analogues.

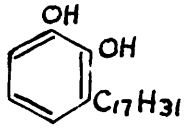
Contents.

Introduction.

Aromatic ortho dihydroxy compounds are widely distributed in Nature. Catechol itself occurs in crude wood tar and crude beet sugar, while its monomethyl ether guaiacol is present in the crude creosote of beech tar. Similarly Japanese lacquer contains urushiol (I), laccol (II), and thitsiol (III); and the catechol derivative adrenaline (IV) is a physiologically important substance.



(I)



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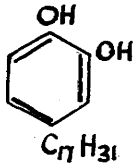

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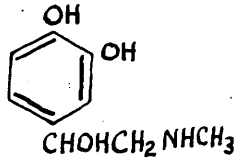


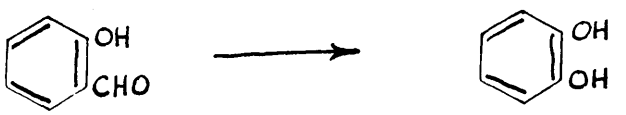
(IV)

Catechol and certain of its alkyl derivatives, for example butyl catechol, are widely used as antioxidants in petrol, lubricating oils, rubber, plastics, soap, etc., and as polymerisation inhibitors and pharmaceutical

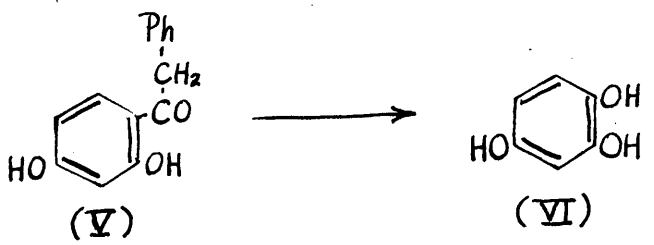
intermediates. Guaiacol and its derivatives are of value as antiseptics and antipruritics.

It is desirable here to review briefly the methods available for the synthesis of catechol derivatives. Industrially alkyl catechols may be prepared by the interaction of catechol with olefines, alkyl halides, alcohols, or esters, but such methods are not used on the laboratory scale.

The Dakin reaction as originally employed involved the oxidation of ortho (or para) hydroxyaldehydes with hydrogen peroxide in alkali. Dakin [1,2] noted that although

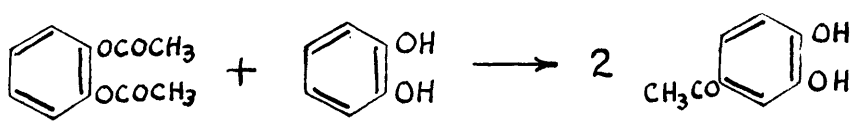


the corresponding hydroxyketones could be similarly oxidised the yields were poor, but Baker, Jukes, and Subrahmanyam [3] have shown that it is readily possible to oxidise such compounds successfully. Thus for example (V) gives (VI) in good yield. Since hydroxyacetophenones are generally much more readily accessible than the corresponding aldehydes, this extension of the reaction is most useful.



(V) (VI)

Although it is not a hydroxylation reaction mention must be made of the Fries Rearrangement which is an excellent method for the preparation of acyl and alkyl derivatives of catechol. It involves the rearrangement of catechol esters in the presence of aluminium chloride to give the corresponding 4-acyl catechols which may be



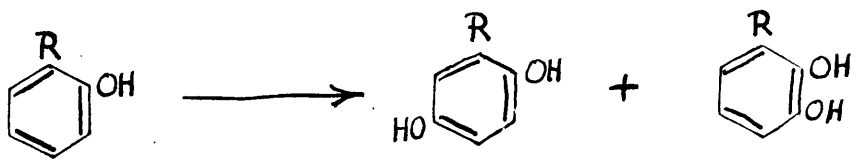
reduced to give 4-alkyl catechols. (See Miller, Hartung, Rock, and Crossley [4]). This method may be used to prepare p-hydroxyacetophenones which can be further used in the Dakin reaction for the preparation of trihydroxy compounds.

The Elbs persulphate oxidation involves the oxidation of mono- to di-hydric phenols by potassium persulphate

in alkali. According to Baker and Brown [5] a quinol derivative is produced if the para position is free, but if not a catechol derivative is formed in very poor yield. Thus (VII) gives (VIII) in fair yield. However,

(VII) (VIII)

Forrest and Petrow [6] have shown that the reaction can give appreciable quantities of catechols as well as the expected quinols, even when the para position is vacant.



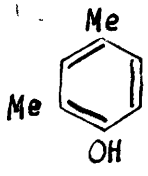
(IX)

Thus oxidation of (IX, R=Cl or NO_2) gives, in addition to the quinol, some 15% of the catechol derivatives.

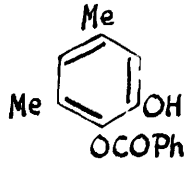
It may be noted that <u>in vivo</u> phenolic oxidases can change phenols to catechols, and the action of such enzymes leads to the loss of estrogenic activity in estrone. Niederl and Vogel [7] have described the synthesis

of estracatechol, thought to be the product so derived from estrone.

Merz and Waters [8] have studied the direct hydroxylation of aromatic nuclei by hydrogen peroxide in the presence of ferrous ions, that is by free hydroxyl radicles. Toluene gave cresols among the products, while benzoic acid, benzamide, nitrobenzene, and chlorobenzene all gave the ortho-hydroxy compound. They found that the oxidation of phenol was complex, although the products included catechol. Cosgrove and Waters [9] have described the reaction of monohydric phenols with benzoyl peroxide in boiling chloroform to give monobenzoates of catechol derivatives. Thus both (X) and (XII) give (XI). The



(X)



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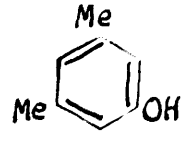


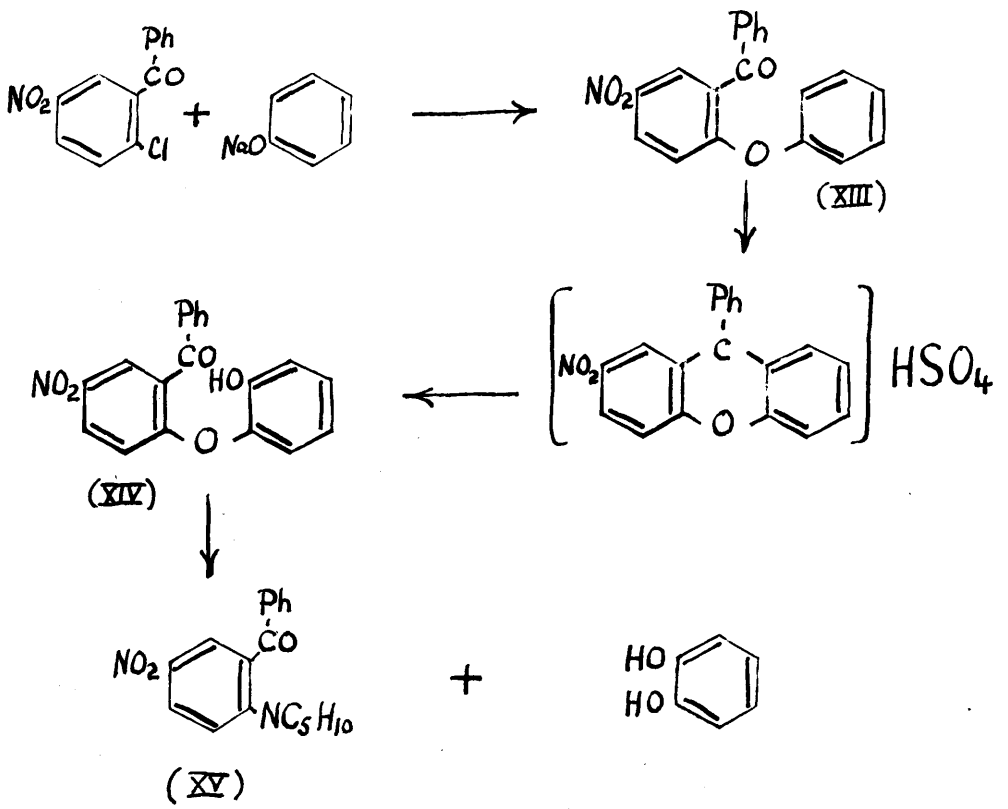
(XII)

oxidation of phenol by this method resulted in the formation of much resin but catechol monobenzoate and, to a much lesser extent, quinol monobenzoate, were isolated.

Baker and collaborators [10,11,12,13,14,15] have described the application of a variety of hydroxylation reactions

to the preparation of various tetrahydroxybenzene derivatives.

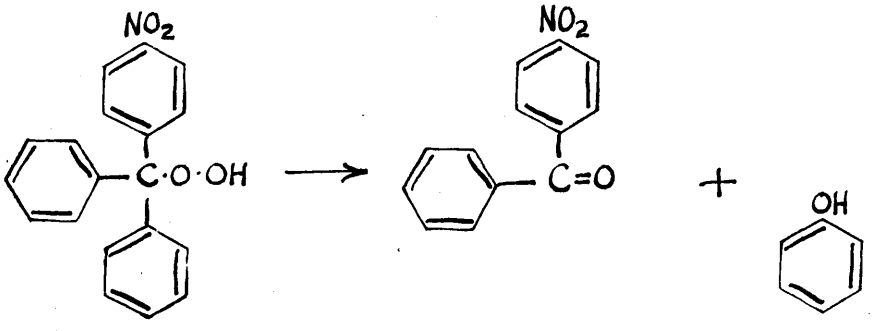
Recently Loudon, Robertson, and Watson [16] described a new method for the ortho-hydroxylation of phenols. The sodium salt of the phenol is condensed with 2-chloro-5-nitrobenzophenone to give the 2-aryloxy-5-nitrobenzophenone (XIII). This dissolves readily in concentrated sulphuric acid yielding a solution of the xanthylium



sulphate. Glacial acetic acid is added, and the solution

treated with hydrogen peroxide, when the 2-(2"-hydroxyaryloxy)-5-nitrobenzophenone (XIV) is formed. This is readily split on boiling with piperidine giving the appropriate catechol derivative and 2-piperidino-5-nitrobenzophenone (XV). Methylation of (XIV) before scission affords a guaiacol derivative.

It may be noted that there is some similarity between the hydroxylation step and the observation of Bartlett and Cotman [17] that in the presence of acid as catalyst triarylmethyl peroxides are converted into diaryl ketones and phenols. Thus for example (XVI) gives (XVII) and phenol.



(XVI) (XVII)

The complete reaction scheme described by Loudon et.al.[16] therefore comprises three main steps:

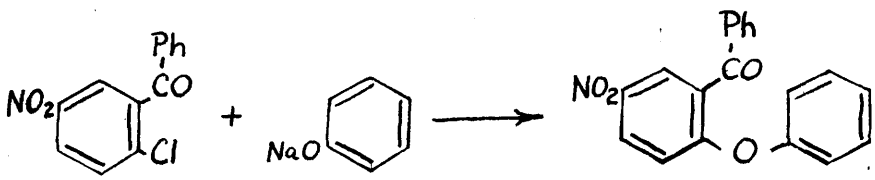
(i) preparation of the aryloxynitrobenzophenone,

(ii) hydroxylation,

(iii) liberation of the hydroxylated phenol.

The published work sufficed to show that the process was practicable in a few simple cases. In the work about to be described the various steps have been re-examined and improved, and the potentialities of the reaction when applied to a range of phenol homologues investigated.

Preparation of 2-aryloxy-5-nitrobenzophenones.



These compounds were prepared by heating the potassium salt of the appropriate phenol, dissolved in excess phenol, with 2-chloro-5-nitrobenzophenone, the following homologues of phenol being employed:-

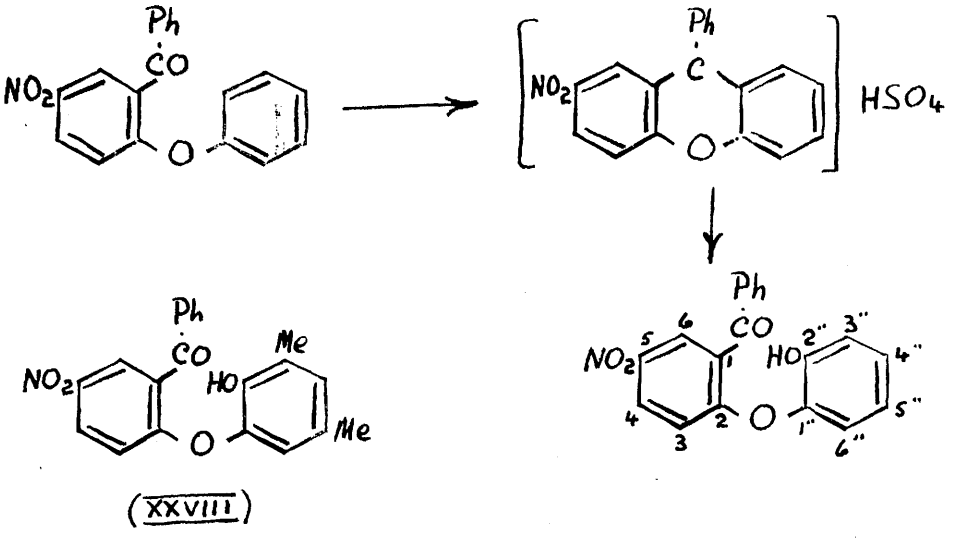
2:4-dimethyl	p-tert.butyl
2:5-dimethyl	p-tert.octyl
3:4-dimethyl	o-phenyl
3:5-dimethyl	m-phenyl
p-isopropyl	p-phenyl.

All the products were obtained in yields of 80% or over, and generally they solidified readily when the warm reaction mixture was treated with dilute sodium hydroxide solution, thereafter being crystallised from aqueous acetic acid. The m-phenyl compound proved to be somewhat intractable and could only be crystallised after chromatography of the crude material on an alumina column.

The use of excess phenol as a solvent in this reaction is rather wasteful if the phenol concerned is scarce or

expensive, so attempts were made to find more satisfactory conditions; for example by heating the reactants under reflux in aqueous alkali or in diethylaniline, but these were not successful. It was found, however, that the excess of phenol used could be reduced to about 0.5 mol., and although in a few cases this was insufficient to maintain all of the potassium salt in solution initially, it dissolved smoothly as the reaction proceeded. In selected cases it was shown that a proportion of the excess phenol could be recovered from the alkali used in the purification of the product.

Preparation of 2-(2"-hydroxyaryloxy)-5-nitrobenzophenones.



In order to avoid frequent repetition of the rather clumsy full names of these compounds they will be referred to in this chapter by the substituents in the hydroxylated ring. Thus (XXVIII) is described as the 3"+5"-dimethyl compound.

The compounds were prepared by dissolving the appropriate 2-aryloxy-5-nitrobenzophenone in concentrated sulphuric acid, diluting with glacial acetic acid, and oxidising this solution with hydrogen peroxide. The reaction is complete in about 15 minutes, the crude product being obtained by pouring on to crushed ice.

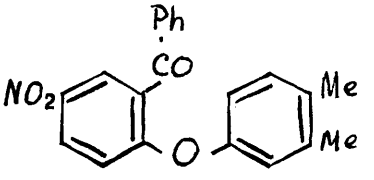
Of the several variables concerned in this reaction the most critical, and that least amenable to standard-

isation, is the ultimate concentration of sulphuric acid. If this is too high, coloured by-products are formed and the product may be crystallisable only with great difficulty or not at all: if too low, considerable amounts of insoluble peroxides may be produced, as described by Loudon et. al.[16] . It is desirable that the quantity of sulphuric acid used should dissolve the aryloxybenzophenone readily, and the set of conditions ultimately adopted was satisfactory in this respect, and was applicable to the facile hydroxylation of all of the compounds described in the previous section with the exception of the 4"-isopropyl, 4"-tert.butyl, and 4"-tert.octyl compounds. The volume of acetic acid employed is greater than that described by Loudon et.al.[16] . This assists in preventing local precipitation of solid during the addition of the hydrogen peroxide, and for the same reason slow, dropwise addition of the latter reagent is desirable. When appropriate conditions have been found the process is simple, quick, and efficient.

In the cases of the 4"-isopropyl, 4"-tert.butyl, and 4"-tert.octyl compounds the quantity of concentrated sulphuric acid used had to be reduced by half before satisfactory hydroxylations were acheived.

The cyclisation of the two compounds 2-(3":4"-dimethylphenoxy)- and 2-(3"-phenylphenoxy)-5-nitro-

benzophenone, (XX) and (XXVII) respectively, can obviously take place in two directions. The product from (XXVII) has, however, been shown to have the structure (XXIX) by the fact that on scission it affords the known 4-phenyl



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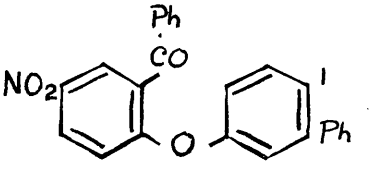
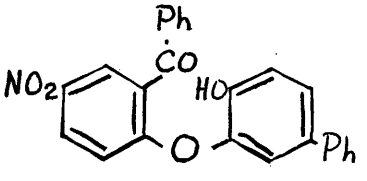


(XXVII)



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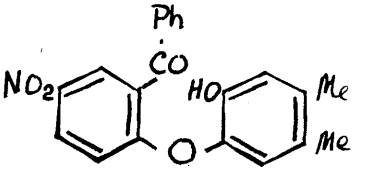


(XXX)

catechol. In the case of (XX) the ambiguity remains, although the product is more likely to have the structure (XXX).

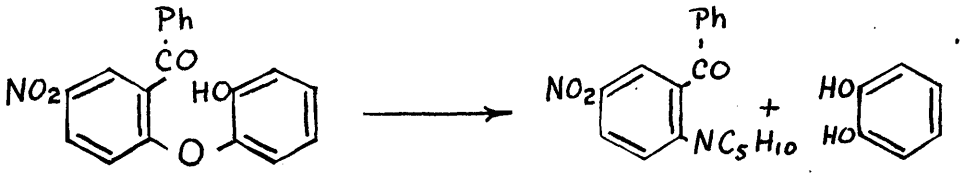
In the cases of the 3":4"-dimethyl, 3":5"-dimethyl, and 6"-phenyl compounds the products crystallised directly from the reaction mixture in good yield, whereas it was noticed that all compounds containing an alkyl group ortho to the ether link were difficult to crystallise, and had the same conglomerate crystalline

form.

The hydroxylated tert.butyl and tert.octyl compounds clung most tenaciously to traces of the solvent (benzene) from which they had been srystallised, and satisfactory analyses were obtained only after the samples had been melted in vacuo. In all other cases the solvent was methanol or ethanol and no trouble of this nature was encountered.

The colours of these hydroxyaryloxybenzophenones range in an interesting fashion from white to bright yellow. The 3":5"-dimethyl Compound forms pure white needles but affords a yellow solution in ethanol, and it was found that the 5"-phenyl compound can exist in two forms, one white of m.p.144° and the other golden yellow, m.p.125°. The white form appears to be slightly the more stable, but either may be obtained from a solution of the other by seeding with the appropriate material. If crystals of the yellow form are warmed for a short while in benzene they change to the white form without dissolving. Both materials have the same analysis and give the same methyl ether on treatment with diazomethane.

Preparation of substituted catechols and guaiacols.



(XIV) (XV)

The aryloxynitrobenzophenones having been successfully hydroxylated, it remains to liberate the catechol derivatives. The scission of o- or p-nitrated diaryl ethers by means of piperidine is well known (Le Fevre, Saunders, and Turner [18] ; Groves, Turner, and Sharp [19]), and Loudon et.al.[16] showed that in a few test cases compounds of type (XIV) were split on boiling with piperidine, affording the appropriate catechol and 2-piperidino-5-nitrobenzophenone (XV). Similarly scission of compounds of type (XIV) which had been methylated yielded guaiacol derivatives.

In the present work a number of 2-(2"-methoxy-aryloxy)-5-nitrobenzophenones were prepared from the corresponding hydroxy compounds using dimethyl sulphate in alkali, or diazomethane where there was the possibility of rearrangement in alkali. (See following chapter on the Smiles rearrangement). The yields were

uniformly good, and in all cases investigated the scission of these methoxy compounds was accomplished satisfactorily by boiling the material under reflux with piperidine for one hour. The cooled piperidine solution was then diluted with benzene and extracted successively with dilute sulphuric acid and dilute sodium hydroxide solution. Acidification of the alkaline extract followed by recovery with chloroform or ether afforded the crude guaiacol which was then sublimed or distilled on to a cold finger *in vacuo* and crystallised from benzene/petroleum (60-80°) where practicable. The following derivatives of guaiacol were produced:-

2-methoxy-3:5-dimethylphenol

2-methoxy-3:6-dimethylphenol

2-methoxy-4:6-dimethylphenol

2-methoxy-5-phenylphenol

2-hydroxy-3-methoxytoluene

3-hydroxy-2-methoxytoluene.

Catechol derivatives may be prepared by following the same proceedure with the appropriate 2-(2"-hydroxy-aryloxy)-5-nitrobenzophenones, but yields are not high. It was found that the scission took place fairly rapidly and that the time of heating could be reduced from one hour to about five minutes, thus effecting

some improvement, but the extraction process was still unsatisfactory, as catechols are fairly readily oxidised in alkaline solution, and losses were being introduced at this stage. The extraction proceedure was therefore modified as follows. The cooled piperidine reaction mixture was diluted with benzene and washed several times with water. Acidification of the aqueous extract afforded the crude catechol which was isolated and purified in similar fashion to the guaiacol derivatives. The following catechols were prepared:-

3:5-dimethylcatechol

3:6-dimethylcatechol

4:5-dimethylcatechol

3-phenylcatechol

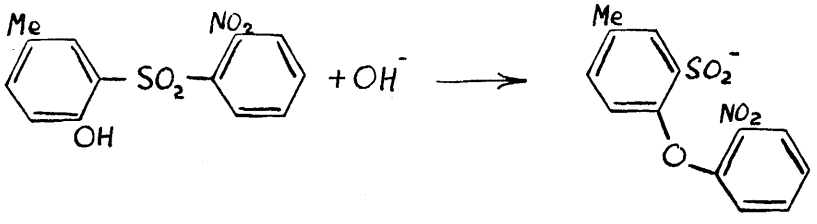
4-phenylcatechol.

From these results it seems clear that the method under investigation is capable of being successfully applied to the production of a considerable range of alkyl and aryl substituted catechols and guaiacols, although its use for large scale preparations is limited by the fact that 2-chloro-5-nitrobenzophenone is not readily available in quantity. The products, whether catechols or guaiacols, are normally of unambiguous structure, and the process is specially suited

to the preparation of vicinal polysubstituted derivatives of benzene - compounds often only laboriously accessible.

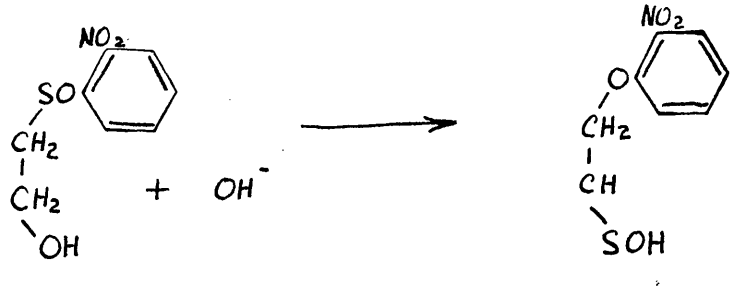
The Smiles Rearrangement.

Samuel Smiles and collaborators have shown that certain classes of compound (fully detailed below) can undergo rearrangement in suitable conditions. Thus for example 2-nitrophenyl-4-hydroxy-m-tolyl sulphone (XXXI) is transformed into 2-nitrophenyl 3-sulphino-p-tolyl ether (XXXII) in the presence of a slight excess of aqueous sodium hydroxide at 50°.



(XXXI) (XXXII)

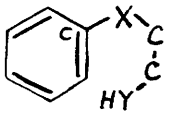
A similar case is the rearrangement of 2-hydroxyethyl 2-nitrophenyl sulphoxide (XXXIII) to 2-(2-nitrophenoxy)-ethanesulphenic acid (XXXIV).



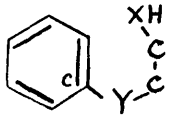
(XXXIII) (XXXIV)

The rearrangement has been the subject of a recent review by Bunnett and Zahler [20] who give a comprehensive list of references.

The general case of the Smiles rearrangement may be represented by the transformation of (XXXV) to (XXXVI) where the carbon atoms joining X and Y may be saturated, or form part of an aromatic ring.



(XXXV)



(XXXVI)

Smiles has shown that the mechanism is firstly the removal of a proton from -YH by sodium hydroxide or other strong base to give Y^-, followed by nucleophilic attack by this on the carbon atom C in (XXXV), resulting in the displacement of $-X^-$ in its anionic condition. The following factors influence the ease of rearrangement:

(a) the activation present in the aromatic ring, that is the positive character of carbon atom C in (XXXV);

(b) the positive character of X;

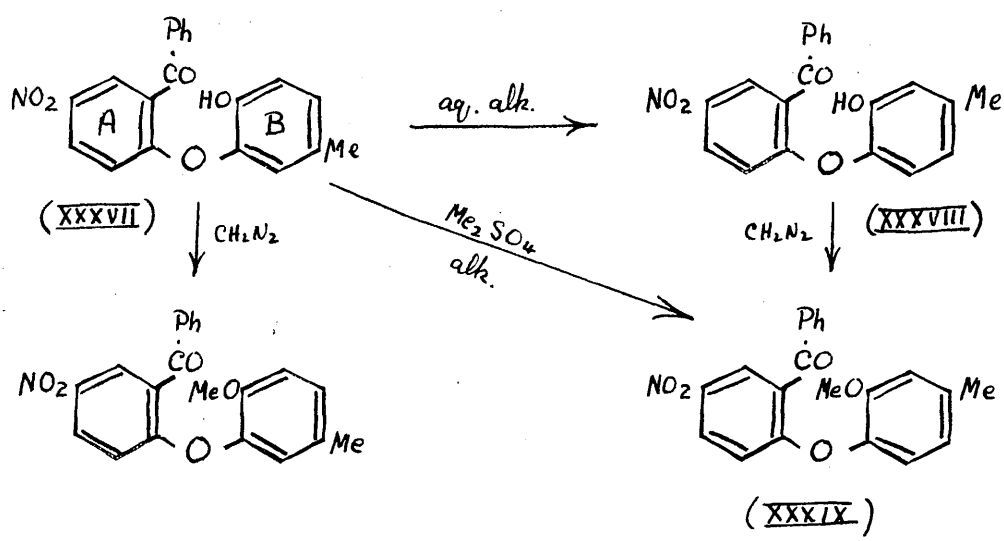
(c) the strength of $-Y^-$ as a nucleophilic reagent; and

(d) the acidity of -YH.

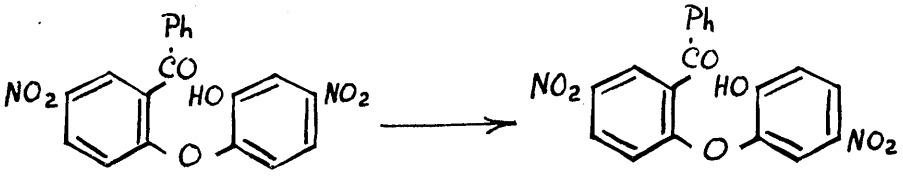
YH and X may represent a variety of different groups, and a summary of the various combinations with which rearrangement has been observed is given below.

If YH is	NHacyl	X may be	SO_2, SO, or O
"	$CONH_2$	"	SO_2, S, or O
"	SO_2NH_2	"	O
"	OH (alkyl)	"	SO_2, or SO
"	NH_2 (aryl)	"	SO_2, or O
"	OH (aryl)	"	SO_2, -COO-, $-SO_2O-$, or O
"	SH	"	O
"	SO_2H	"	O

It is apparent that certain 2-(2"-hydroxyaryloxy)-5-nitrobenzophenones satisfy the conditions for rearrangement. Thus in (XXXVII) the carbon atom attached



to the oxygen atom in ring A is activated by the nitro group, and although X and Y are atoms of the same element they are differently situated in the molecule and have different electron donor capacities. Loudon, Robertson, and Watson [16] showed that in aqueous alkali the compound (XXXVII) rearranged almost completely to (XXXVIII) and that both gave the same methyl ether (XXXIX) when methylated with dimethyl sulphate in alkali. When treated with diazomethane each gave its own methyl ether. The same authors also found some evidence that (XL) rearranged to (XLI).

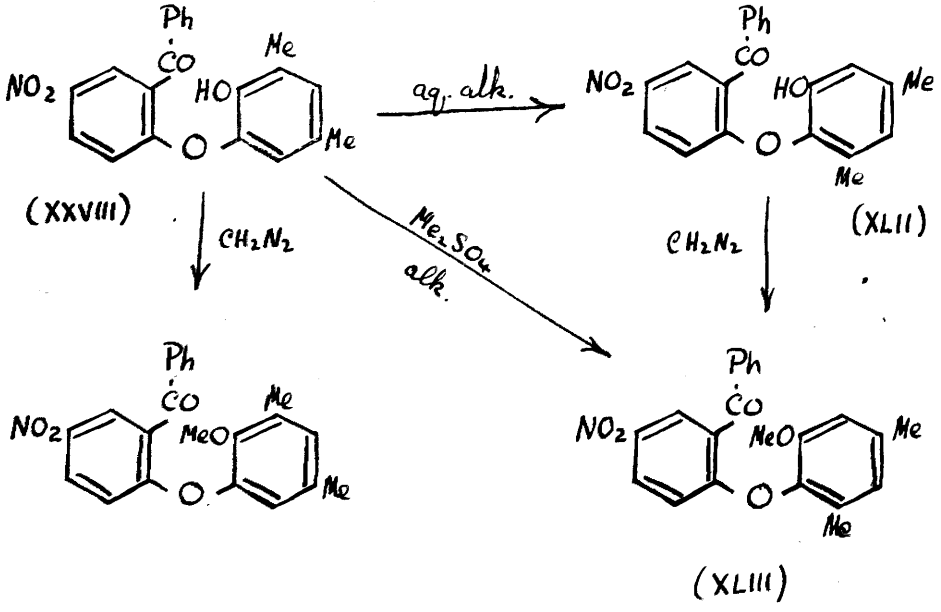


(XL) (XLI)

These facts are in accord with the assumption that in alkali the benzoylated nitrophenyl radicle migrates to the oxygen atom with the greater donor capacity. In (XXXVII) this will be the atom in the position <u>para</u> to the methyl group since electrons will tend to be repelled by the methyl group, whereas in (XL) electrons

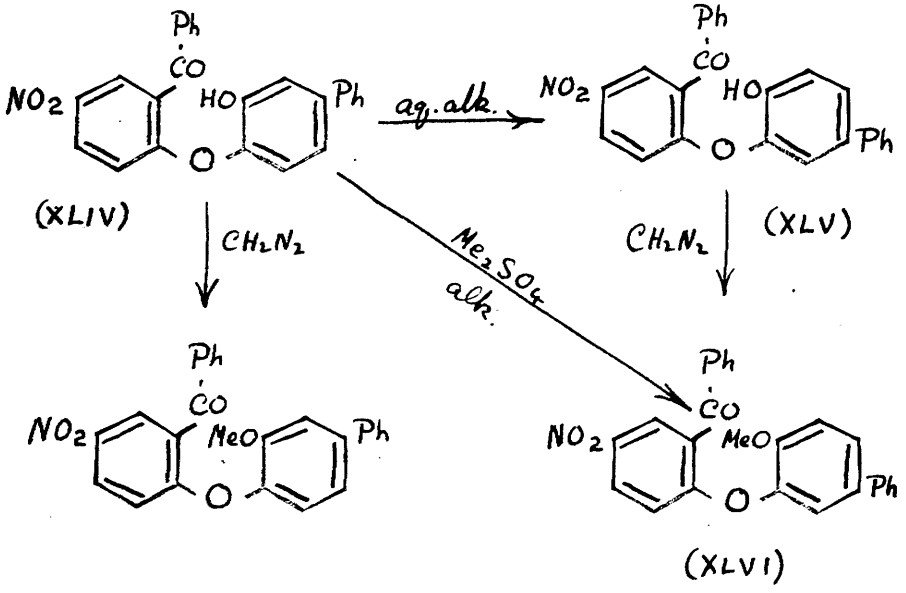
will be withdrawn from the oxygen atom <u>para</u> to the nitro group, leaving the other oxygen atom with the greater donor capacity.

In the present work it has been shown that in alkali (XXVIII) rearranges largely, but not completely, (as shown by a rather low m.p.), to (XLII). Both (XXVIII) and (XLII) are of unambiguous structure, and were prepared from 3:5-dimethylphenol and 2:5-dimethylphenol respectively. With diazomethane the two compounds gave



their individual methyl ethers, but with dimethyl sulphate in alkali both gave (XLIII).

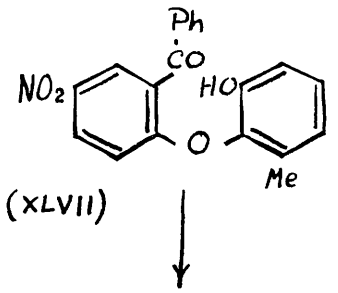
A similar state of affairs obtains with (XLIV) and (XLV). Recovery of either of these compounds from alkali afforded an oily and impure product which on crystallisation gave (XLV). Methylation of the crude



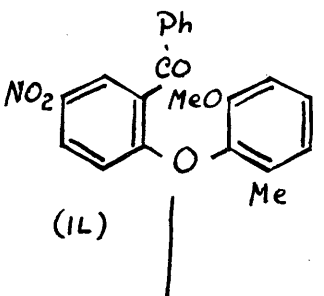
product with diazomethane gave (XLVI) and this was also obtained by treatment of (XLIV) or (XLV) with dimethyl sulphate in alkali, although with diazomethane each gave a distinct methyl ether. In this case the phenyl group tends to withdraw electrons from the <u>para</u> position, thereby reducing the donor capacity of the oxygen in that position, so that in alkali the benzoylated nitrophenyl radicle migrates to the other oxygen atom

whose donor capacity is relatively greater.

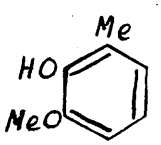
It is clear that these rearrangements are seldom complete, but probably reach an equilibrium dependant on the substituents in the molecule. The behaviour of the compound (XLVII) supports this view. When dissolved in alkali it was recovered largely unchanged, except on one isolated occasion when a high yield of (XLVIII)



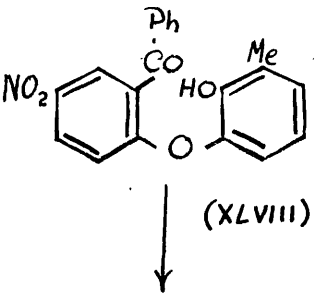
(XLVII)



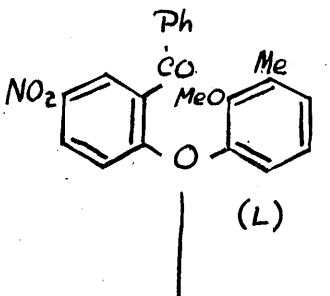
(IL)



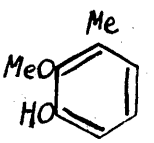
(LI)



(XLVIII)



(L)

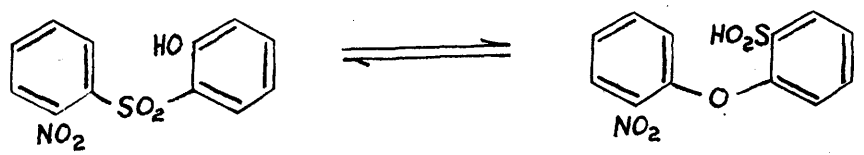


(LII)

was obtained. Eventually it was found that under certain conditions (XLVII) could be readily rearranged to (XLVIII). If a saturated methanolic solution of (XLVII) was made just alkaline with a drop of aqueous potassium hydroxide, and the solution left to stand, the very much less soluble (XLVIII) crystallised in high yield. Presumably the precipitation of one component from the equilibrium as it is formed accounts for the completeness of the reaction in the unexpected direction. It has not been possible to synthesise (XLVIII) but there is considerable evidence in support of the structure assigned to it. Thus it dissolved in concentrated sulphuric acid to give a red solution and on oxidation gave a gum which when treated with piperidine yielded a fluorone derivative; whereas (XLVII), which has no free ortho position, gave only a pale yellow solution with sulphuric acid. Further, methylation of (XLVII) and (XLVIII) with diazomethane gave methyl ethers which on scission afforded 2-hydroxy-3-methoxytoluene (LI) and 3-hydroxy-2-methoxytoluene (LII) respectively.

In the two cases recorded on pp. 23 and 24 where rearrangement was shown to take place, attempts were made to reverse the transformation by adding an appropriate seed to a concentrated, slightly alkaline solution of

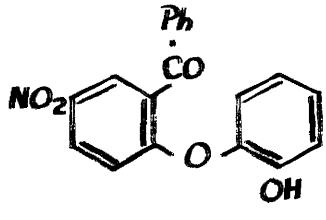
the material concerned. These were not successful, but in both cases there was little difference in the solubilities of the two isomers, whereas with (XLVII) and (XLVIII) this difference was very marked. It is worthy of note that Coats and Gibson [21] showed that the rearrangement of o-hydroxysulphones to sulphinic acids, for example (LIII) to (LIV), as described by Smiles, could be reversed under suitable conditions of temperature and pH.



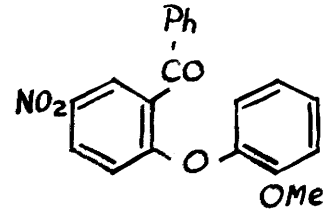
(LIII) (LIV)

Preparation of derivatives of pyrogallol.

It was shown in earlier chapters that the method being investigated was likely to be useful for the preparation of a range of catechol and guaiacol derivatives. The value of the reaction would obviously be greatly enhanced if intermediates of types (XIV) and (LV) proved capable of renewed hydroxylation, giving ultimately derivatives of pyrogallol. This possibility was therefore investigated.

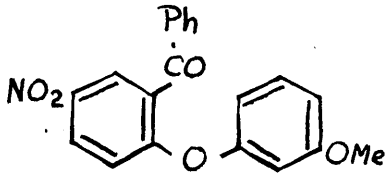


(XIV)

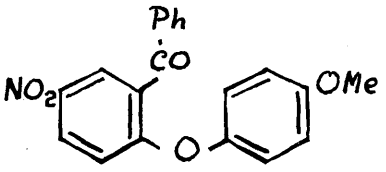


(LV)

Guaiacol, resorcinol monomethyl ether, and hydroquinone monomethyl ether were each condensed with chloronitrobenzophenone by the usual method, giving good yields of (LV) and (LVII). The yield of (LVI) was not high and it was difficult to crystallise. Dissolution of (LV) in concentrated sulphuric acid followed by oxidation by the standard technique proceeded smoothly and cleanly to give a phenolic amber oil in high yield.

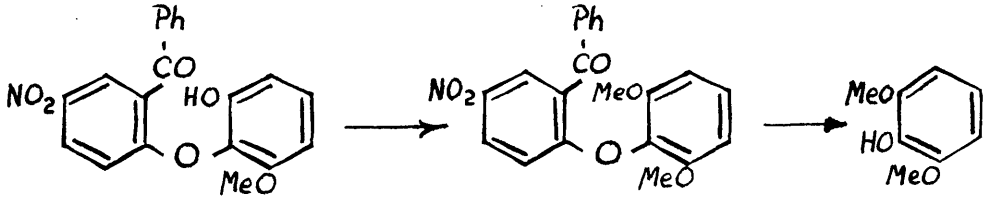


(LVI)



(LVII)

This could not be induced to crystallise but it was presumed to have the structure (LVIII) and this was supported by a variety of observations. Thus when methylated either in alkali with dimethyl sulphate, or with diazomethane, it gave the crystalline methyl ether (LIX) which on scission afforded pyrogallol 1:3-dimethyl ether, identified as the benzoyl derivative.

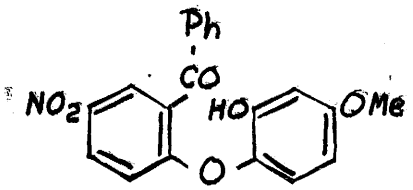


(LVIII) (LIX)

Scission of crude (LVIII) gave pyrogallol 1-methyl ether as a liquid which could not be solidified. It yielded a diacetyl derivative whose melting point coincided with that recorded in the literature, but

afforded a dibenzoate of m.p. 83° whereas Herzig and Klimosch [22] give m.p. 156-8°. Pyrogallol 1-methyl ether was therefore prepared by methylation of pyrogallol carbonate followed by hydrolysis, as described by Hilleman [23], and on benzoylation afforded a dibenzoate of m.p. 83° identical with that previously obtained. The product described by Herzig and Klimosch [22] was prepared by treating pyrogallol 1:3-dimethyl ether with benzoyl chloride and aluminium chloride over a long period, the monobenzoate being an intermediate product. These authors give no experimental details, but based their structural conclusions only on analytical results which indicated that the compound contained a single methoxyl group.

Compounds (LVI) and (LVII) were cyclised and oxidised in the usual way, affording crystalline samples of hydroxylated materials. Cyclisation of (LVI) can take place in either of two directions and the structure of the product from it is therefore ambiguous, although that from (LVII) must have structure (LX). Yields were poor and considerable amounts of red insoluble by-products were obtained. Although a variety of different conditions was used for the oxidation, no improvement could be achieved. Possibly some fission of



(LX)

the ether linkage occurs, followed by oxidation of the resultant catechol derivative. Zeigler et.al [24] have noted the ease of fission of methoxylated aryl ethers. Alternatively, Fernholz [25] describes the peracetic acid oxidation of phenol ethers, red quinones being among the intermediate products.

When the standard method of cyclisation and oxidation was applied to the various hydroxy- and methoxy-aryloxy-benzophenones described in the previous chapter (pp. 11 - 16), the results were not encouraging, but using the modified proceedure which was successful for the preparation of the isopropyl, tert.butyl, and tert.octyl mono-hydroxylated compounds, good yields were obtained of the desired dihydroxyaryloxynitrobenzophenones and hydroxymethoxy-aryloxynitrobenzophenones. A list of the compounds prepared is shown in Table I, on the following page. In most cases the product was difficult to crystallise but only three compounds did not finally do so, and of

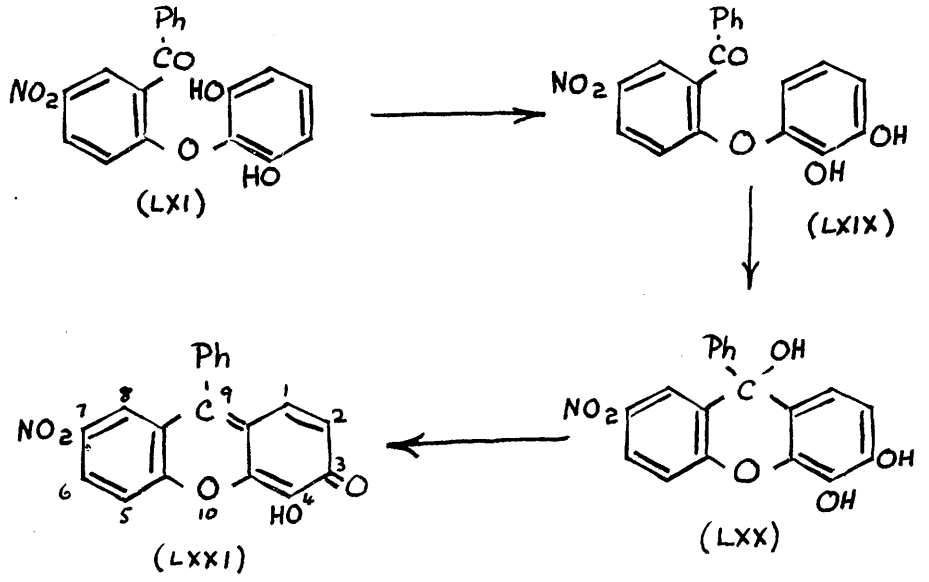
No.	Substituents in aryloxy nucleus
LXI	2":6"-dihydroxy
LXII	2":6"-dihydroxy-3"-methyl
LXIII	2":6"-dihydroxy-4"-methyl
LXIV	2":6"-dihydroxy-3":4"-dimethyl
LXV	2":6"-dihydroxy-3":5"-dimethyl
LXVI	2"-hydroxy-6"-methoxy
LXVII	2"-hydroxy-6"-methoxy-4"-methyl
LXVIII	2"-hydroxy-6"-methoxy-4":5"-dimethyl

Table I.

these, two afforded crystalline methyl ethers, compounds (LXVI) and (LXVII). Compound (LXVIII) was prepared only in yields of about 50%, as considerable amounts of insoluble peroxide were produced, and various alterations to the reaction conditions effected no improvement. This problem was not encountered in any other case. In the course of these preparations it was observed that the colour of the sulphuric / acetic acid solutions before oxidation ranged from blue - green to plum red, with no apparent correlation of colour with structure. These dihydroxy- and hydroxymethoxy-aryloxynitrobenzophenones are yellow compounds with melting points over 100°. Some of them decompose on melting, but they

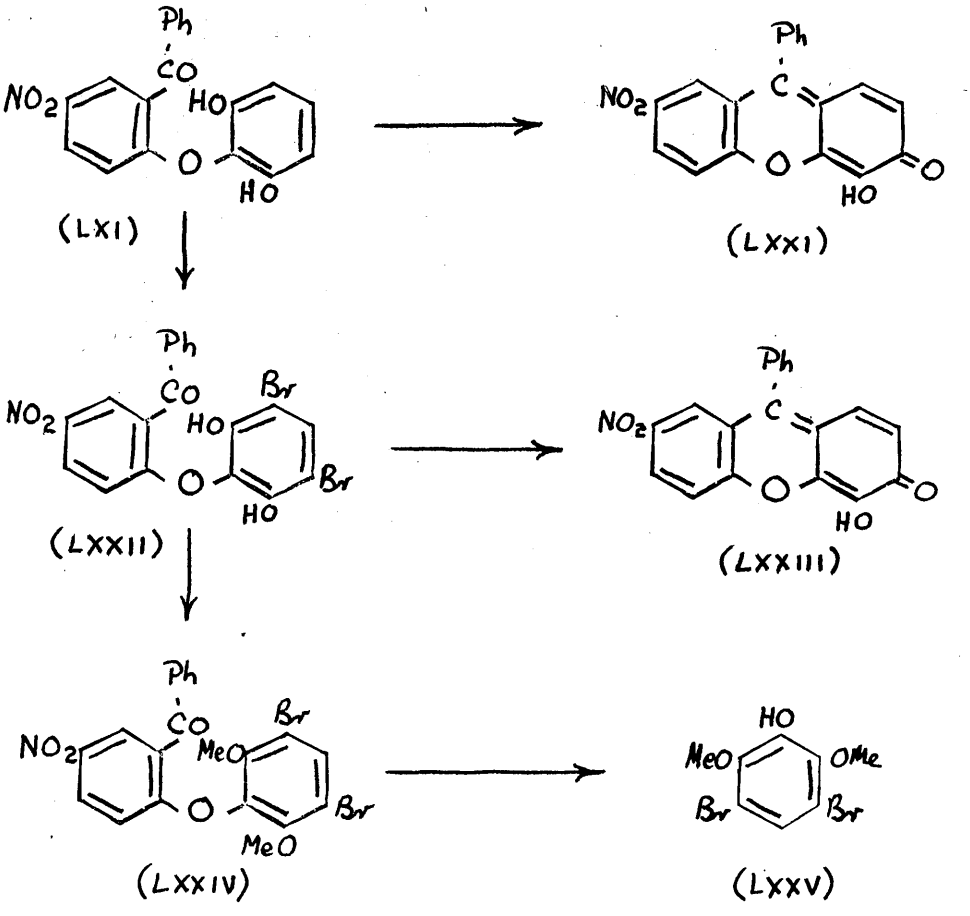
are perfectly stable in air at normal temperatures. Both types of compound can be methylated with dimethyl sulphate in alkali, or with diazomethane, to give the corresponding dimethoxy compounds. The use of diazomethane is preferable, as in the absence of alkali there is no possibility of rearrangement and the structure of the product is therefore unambiguous.

As described earlier (p. 29) scission of the appropriate compounds produced pyrogallol 1-methyl ether and pyrogallol 1:3-dimethyl ether. However, when 2-(2":6"-dihydroxyphenoxy)-5-nitrobenzophenone (LXI) was treated with piperidine no pyrogallol was produced, a dark - red, insoluble, high - melting material being isolated instead. This was considered to have the structure (LXXI), that is, 4-hydroxy-7-nitro-9-phenyl-

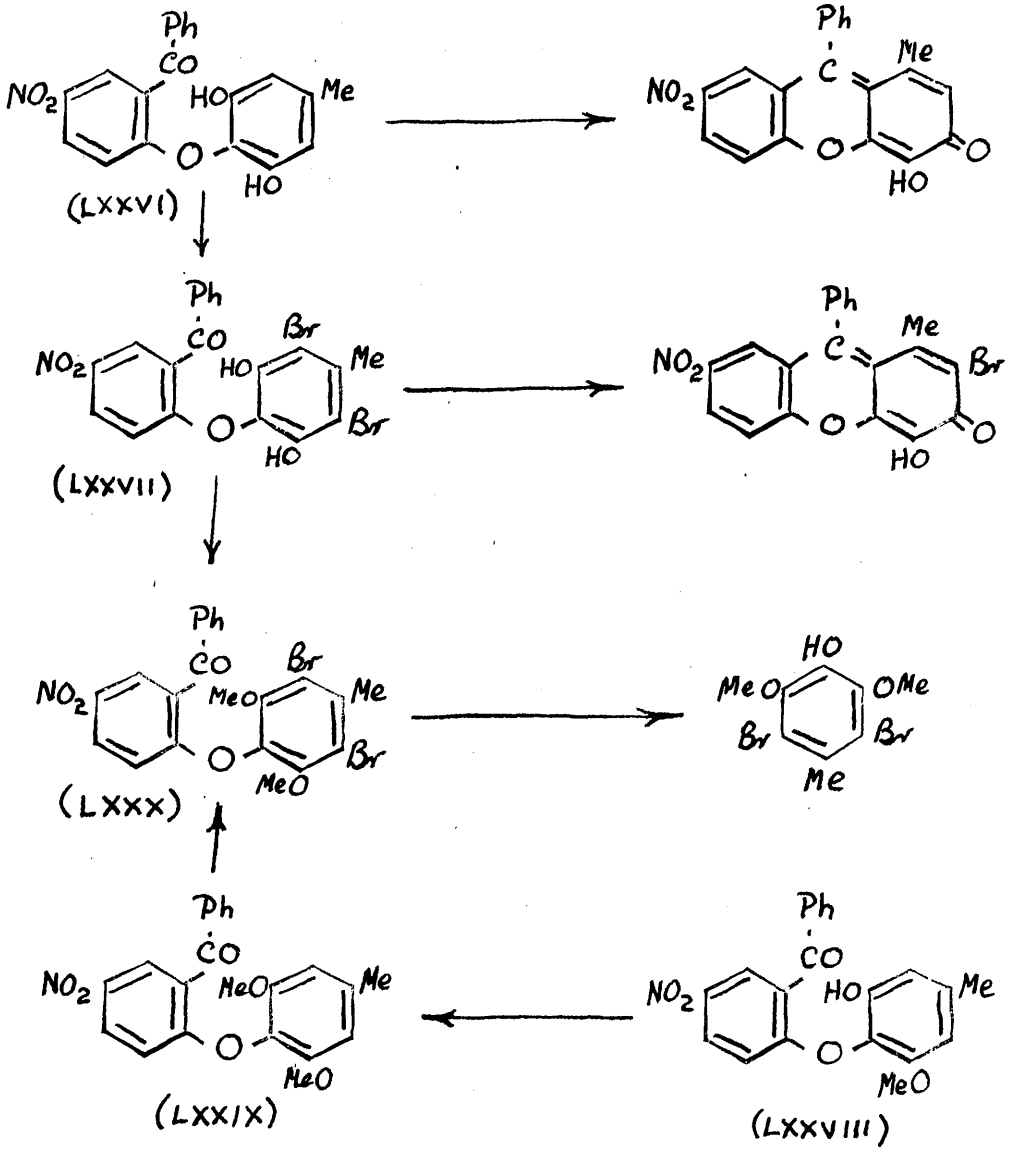


fluorone, and it is thought to be produced in the following manner. As was noted in an earlier chapter (p. 19), suitable hydroxyaryloxynitrobenzophenones can undergo rearrangement in alkali, the benzoylated nitrophenyl radicle migrating from one oxygen atom to the other. In the present case it is presumed that in the alkaline piperidine solution (LXI) rearranges to (LXIX), wherein the free ortho position (6") is simultaneously the reactive para position of a phenolic ion. Although cyclisations of this type in alkaline solution are rare, the degree of activation present in this case is sufficiently great, and ring closure takes place, yielding (LXX), a derivative of 3-hydroxy-9-phenyl-xanth-hydrol. Such compounds are known to dehydrate readily, forming fluorone derivatives of type (LXXI). See Baeyer [26] and Kropp and Decker [27].

Attempts to prevent fluorone formation by brominating positions 3" and 5" were not successful; when (LXXII) was treated with piperidine it gave (LXXIII), one bromine atom having been expelled. Methylation of (LXXII) gave the dimethyl ether (LXXIV) which underwent scission normally to give 4:6-dibromopyrogallol 1:3-dimethyl ether (LXXV).



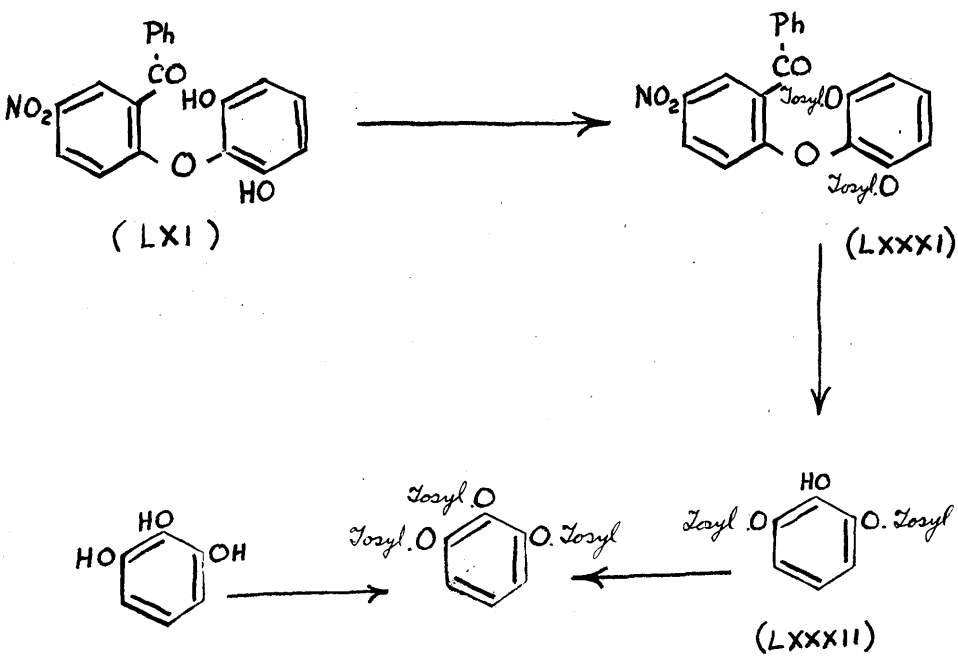
The analogous series of reactions shown below was carried out, starting from (LXXVI) and yielding eventually 4:6-dibromo-5-methylpyrogallol 1:3-dimethyl ether. It may be noted that in this case the structure of the dibromo - compound (LXXVII) is quite unequivocal, since the bromine atoms occupy the only two vacant places in the appropriate ring. The dimethyl ether (LXXIX) had been prepared by the action of dimethyl sulphate in alkali on (LXXVIII) and there was therefore some doubt



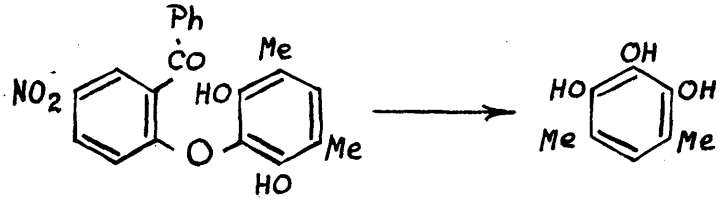
about its structure, but on bromination it gave (LXXX), thereby removing any possibility of rearrangement incidental to the methylation process.

Since methylation of one or both of the free hydroxyl groups in compounds of type (LXI) prevents fluorone formation, the effect of acetylation and

benzoylation of these groups was tried, but preliminary experiments gave no promise of success. However, treatment of (LXI) with p-toluenesulphonyl chloride in pyridine yielded the ditosyl ester (LXXXI) which underwent normal scission at the ether link to give a product which is provisionally regarded as the 1:3-ditosyl ester of pyrogallol (LXXXII). The possibility that rearrangement might have taken place during tosylation must be borne in mind. On further tosylation (LXXXII) gave a tri-ester identical with that produced from pyrogallol.

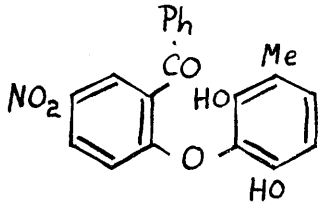


It would be expected from the postulated series of reactions that (LXXXIII) would not undergo fluorone formation since positions 3" and 5", at one of which cyclisation would require to take place, are both occupied by methyl groups. On scission the compound did in fact afford 4:6-dimethylpyrogallol.

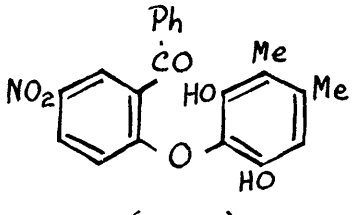


(LXXXIII)

The two remaining dihydroxylated compounds (LXXXIV) and (LXXXV), obtained respectively from 2-(2"-hydroxy-3"-methylphenoxy)- and 2-(2"-hydroxy-4":5"-dimethylphenoxy)-5-nitrobenzophenones as described on p.31, yielded the appropriate fluorones on treatment with piperidine.

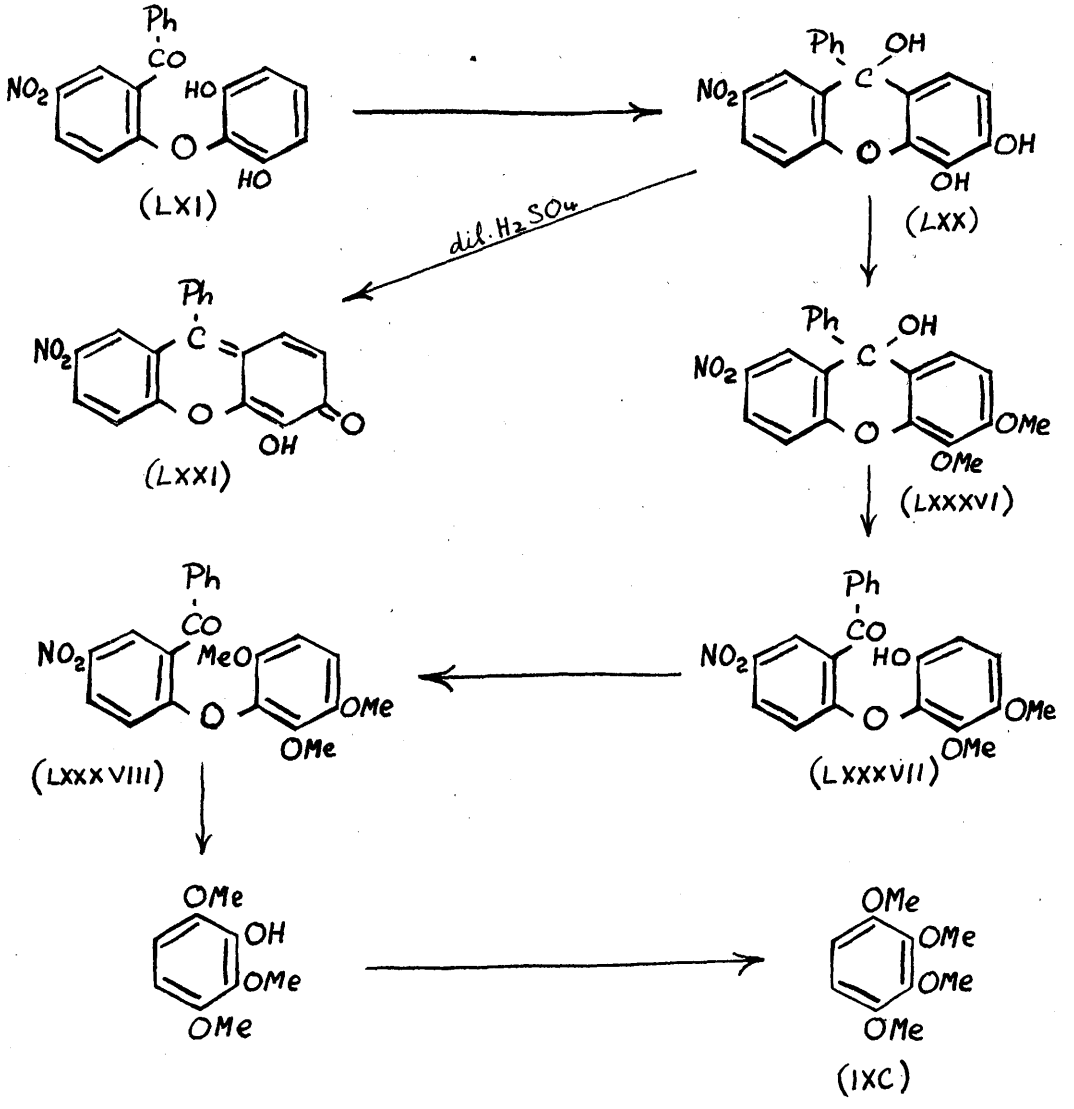


(LXXXIV)



(LXXXV)

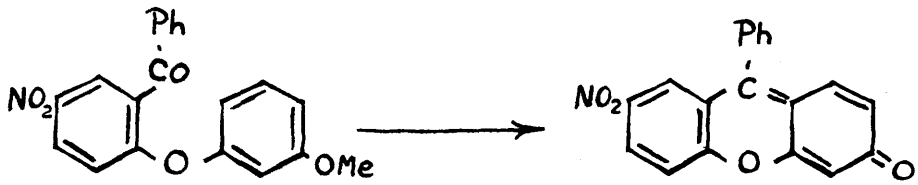
During a further preparation of (LXXI) it was noticed that although the piperidine reaction mixture was very dark in colour, the red fluorone did not appear until the solution had been poured into dilute sulphuric acid. This suggested that the xanth-hydrol intermediate (LXX) might be stable in the piperidine, so the reaction solution was mixed with benzene and washed exhaustively with water. A black tar was deposited, which yielded the fluorone whentreated with acid and reacted with diazomethane in ether / methanol to give 3:4-dimethoxy-7-nitro-9-phenylxanth-hydrol (LXXXVI). If the piperidine was not removed completely before methylation a different product, apparently containing piperidine, was produced. It yielded (LXXXVI) on treatment with concentrated sulphuric acid. Since (LXXXVI) does not contain a free hydroxyl group in position 3 it cannot undergo fluorone formation in contact with acid, and it should therefore be possible to hydroxylate it. This was achieved, the yellow gummy product affording 2-(2":3":6"-trimethoxyphenoxy)-5-nitrobenzophenone ((LXXXVIII) on methylation. Scission of this with piperidine followed by methylation gave 1:2:3:4-tetramethoxybenzene (IXC). The isolation of a derivative of tetrahydroxy-benzene is strong evidence that the postulated re-



arrangement has in fact taken place.

During the investigation into the method of fluorone formation it was observed that if (LVI) could be demethylated and ring-closed it would give a derivative of 3-hydroxy-9-phenylxanth-hydrol which should dehydrate to give a fluorone derivative. (LVI) was therefore treated

with constant boiling hydrobromic acid in boiling glacial acetic acid for several hours, when it afforded a high-melting, neutral substance presumed to be (XC).



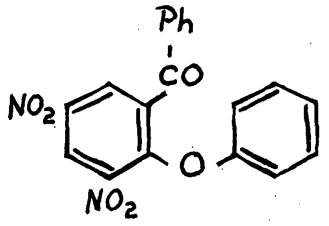
(LVI) (XC)

It is apparent from the work described in this chapter that the di-ortho-hydroxylation of phenols by this method is perfectly practicable and likely to be of value, and although the inability to isolate free pyrogallols is unfortunate, the range of compounds made potentially available is still considerable.

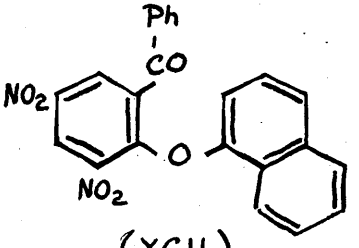
Use of 2-chloro-3:5-dinitrobenzophenone.

As was pointed out earlier, the conditions for the preparation of aryloxynitrobenzophenones are rather too violent to be used with sensitive phenols, and in any case the use of an unproductive excess of the phenol makes the method wasteful. Attention was therefore turned to the possibility of using 2-chloro-3:5-dinitrobenzophenone, in which the chlorine atom is further activated by the second nitro group, and which can be prepared as readily as the mono-nitro compound. An attempt to condense phenol with this reagent by dissolving equimolecular quantities in cold pyridine and leaving overnight was completely successful, the desired product (XCI) being isolated in high yield; and when applied to other phenols including 7-hydroxycoumarin and the sensitive 1-phenanthrol, the compounds (XCII) to (XCV) were likewise obtained in excellent yield. This clearly represents a significant advance over the former method, and makes the hydroxylation reaction potentially applicable to a much wider and more interesting range of phenols.

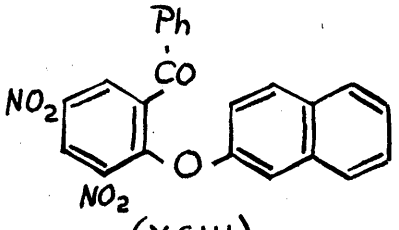
The aryloxydinitrobenzophenones are slightly more difficult to cyclise in concentrated sulphuric acid than their mono-nitro analogues, but the oxidation step takes place normally, and (XCI) gives (XCVI) in good yield.



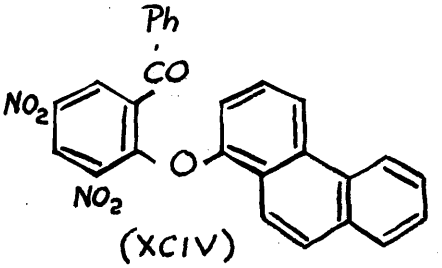
(XCI)



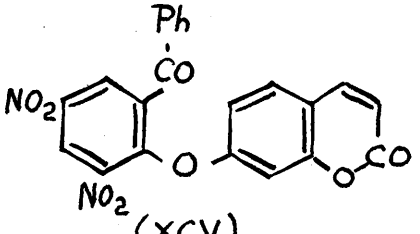
(XCII)



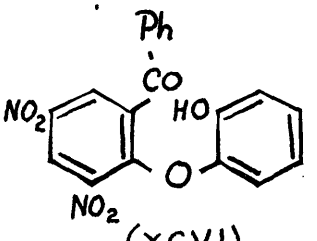
(XCIII)



(XCIV)



(XCV)

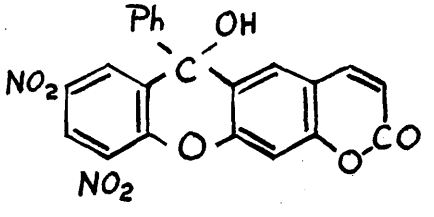


(XCVI)

The structure of the latter compound has been confirmed by Mr. W. Hamill in this department who prepared it from chlorodinitrobenzophenone and catechol, a reaction which, incidentally, could not be achieved under the more destructive conditions of the mono-nitro series. The hydroxylation of (XCII), (XCIII), and (XCIV), appeared to take place normally, giving phenolic products which were, however, very sensitive, and tended to decompose

on standing in contact with a solvent. The compound from (XCIV) was analysed after crystallisation from benzene, but the results suggested that it had retained some of the solvent, and it decomposed when an attempt was made to dry it at 60° in vacuo. It may be remembered that on previous occasions when benzene was used to crystallise a hydroxylated material great difficulty was encountered in removing the solvent.

The compound (XCV), derived from 7-hydroxycoumarin (umbelliferone), was cyclised only after heating in concentrated sulphuric acid at about 100° for some fifteen minutes. Cyclisation was shown to have taken place by treating the resultant red solution with water, when the xanth-hydrol (XCVII)was isolated. So far the hydroxylation of (XCV) has not been achieved.



(XCVII)

Lack of time has prevented these compounds from being given the thorough study which they obviously merit, and for the same reason their scission has not been investigated. One preliminary experiment showed that when (XCVI) was dissolved in cold piperidine a reaction took place and considerable heat was developed. This tends to confirm the expectation that scission of these compounds would be sensibly easier than in the mono-nitro series by virtue of the extra activation of the appropriate position. If further experience proves this to be so, it affords another strong reason for preferring the dinitro compound, since the milder the conditions of scission the greater is the possibility of isolating a sensitive polyhydroxy compound in good yield.

Conclusions.

The method of ortho-hydroxylation of phenols investigated has been shown to be readily applicable to the production of a variety of alkyl and aryl derivatives of catechol and guaiacol. The fact that 2-chloro-5-nitrobenzophenone has to be prepared and is not recoverable tends to restrict the reaction to the preparation of small quantities, but the method is quick and the structure of the products, with certain exceptions noted earlier, unambiguous. Among the new compounds which were prepared are:-

3:6-dimethylcatechol,

3-phenylcatechol,

2-methoxy-3:6-dimethylphenol,

2-methoxy-4:6-dimethylphenol,

2-methoxy-5-phenylphenol.

The method appears to be of much greater value when extended to the preparation of partially or wholly methylated derivatives of pyrogallol, and although unmethylated pyrogallols cannot be produced except in special cases, the range of compounds made available is likely to include several which are otherwise obtainable only with considerable difficulty. Thus for example the following new compounds were prepared:-

4:6-dimethylpyrogallol,

4:6-dibromopyrogallol 1:3-dimethyl ether,

4:6-dibromo-5-methylpyrogallol 1:3-dimethyl ether.

The preparation of tetramethoxybenzene suggests the possibility of preparing some other derivatives of tetrahydroxybenzene by a similar route.

Although only preliminary experiments have been made on 2-aryloxy-3:5-dinitrobenzophenones, these were promising, and the compounds appear to be worthy of further investigation. Their use may well extend the range of phenols to which the hydroxylation reaction can be applied.

Experimental Section.

2-Aryloxy-5-nitrobenzophenones

No.	Substituents in aryl group	M.Pt.	Found C	Found H	Reqd. C	Reqd. H
XVIII	2":4"-dimethyl	109°	72.7	5.0	72.6	4.9
XIX	2":5"-dimethyl	120°	72.7	5.0	72.6	4.9
XX	3":4"-dimethyl	133°	72.7	4.9	72.6	4.9
XXI	3":5"-dimethyl	117.5°	72.45	4.8	72.6	4.9
XXII	4"-isopropyl	82°	73.0	5.4	73.1	5.3
XXIII	4"-tert.butyl	85°	73.75	5.7	73.6	5.6
XXIV	4"-tert.octyl	117°	75.2	7.1	75.1	6.8
XXV	2"-phenyl	97-98°	75.9	4.4	76.0	4.3
XXVI	4"-phenyl	126°	76.2	4.35	76.0	4.3
XXVII	3"-phenyl	58-60°	76.1	4.45	76.0	4.3

Table II

2-(2"-Hydroxyaryloxy)-5-nitrobenzophenones

Source	Substituents in aryl group	M.Pt.	Found C	Found H	Reqd. C	Reqd. H
XVIII	4":6"-dimethyl	108°	69.6	4.8	69.4	4.7
XIX	3":6"-dimethyl	132°	69.6	4.6	69.4	4.7
XX	4":5"-dimethyl	166°	69.5	5.0	69.4	4.7
XXI	3":5"-dimethyl	166°	69.35	4.6	69.4	4.7
XXII	4"-isopropyl	75°	70.3	5.05	70.0	5.1
XXIII	4"-tert.butyl	115°	70.45	5.2	70.6	5.4
XXIV	4"-tert.octyl	145°	72.5	6.7	72.5	6.5
XXV	6"-phenyl	141°	72.8	4.0	73.0	4.2
XXVI	4"-phenyl	119°	73.1	4.0	73.0	4.2
XXVII	5"-phenyl	*144°	73.1	4.3	73.0	4.2
XXVII	"	†125°	72.8	4.2	73.0	4.2

*colourless †yellow variety

Table III

Preparation of derivatives of catechol and guaiacol.

Preparation of 5-nitro-2-aryloxybenzophenones.

These were prepared by adding 2-chloro-5-nitrobenzophenone (1 mol.) to a fused mixture of the appropriate phenol (1.5 - 2 mol.) and potassium hydroxide (1.2 mol.). The mixture was warmed sufficiently to initiate and then to maintain the reaction (15 - 20 minutes) before being cooled and treated with aqueous sodium hydroxide. The product was collected, washed, and crystallised from aqueous acetic acid. Where necessary it was further crystallised from benzene (charcoal) - petrol (60-80°). The compounds described in Table II were thus prepared.

Preparation of 5-nitro-2-(2"-hydroxyaryloxy)-benzophenones.

The finely powdered 5-nitro-2-aryloxybenzophenone (0.0015 mol.) was dissolved in 1ml. of concentrated sulphuric acid with shaking and gentle warming. In the cases of compounds XXII, XXIII, and XXIV , 0.5 ml. of sulphuric acid was used. After ½ hour acetic acid (8 ml.) was added and the mixture was treated with 30% hydrogen peroxide (ca. 0.002 mol.) added dropwise and with shaking until, on standing for five minutes, the original red colour lightened to a pale amber. The mixture was left

Derivatives of 5-nitro-2-(2"-methoxyphenoxy)benzophenone.

Substituents in aryl group	M.Pt.	Found C	Found H	Reqd. C	Reqd. H	Method
4":6"-dimethyl	131°	70.1	5.2	70.0	5.1	(a)
3":6"-dimethyl	104°	70.1	5.5	70.0	5.1	(b)
4":5"-dimethyl	125°	70.1	5.1	70.0	5.1	(b)
3":5"-dimethyl	101°	70.0	5.0	70.0	5.1	(b)
5"-phenyl	120°	73.7	4.5	73.4	4.5	(a)

(a) Diazomethane (b) Dimethyl sulphate in alkali.

Table IV

left for 20 minutes, poured on to crushed ice, and the washed and dried solid was crystallised from methanol. Compounds from XX, XXI and XXV crystallised directly from the reaction mixture and were further crystallised from ethanol. Compounds from XXIII and XIV were crystallised from benzene/petrol (60 - 80°) and the last traces of solvent could only be removed by melting the sample in vacuo. The compounds thus prepared are described in Table III.

Preparation of 5-nitro-2-(2"-methoxyaryloxy)-benzophenones.

These were prepared by methylating the appropriate 5-nitro-2-(2"-hydroxyaryloxy)benzophenone by one or both of the following methods, as noted in Table IV.

(a) A solution of the compound in ether, containing a little methanol, was mixed with a large excess of diazomethane in ether and left at 0° for two days. Removal of the solvent gave the methylated product which was crystallised from ethanol.

(b) The compound was treated with rather more than the minimum amount of 5% aqueous potassium hydroxide and sufficient methanol was added where necessary to render the solution homogeneous at 0°. A slight excess of

dimethyl sulphate was then added with shaking. The initially formed oil solidified on standing or on rubbing with ethanol, from which the product was crystallised.

Scissions with piperidine.

The appropriate 5-nitro-2-(2"-hydroxyaryloxy)- or 5-nitro-2-(2"-methoxyaryloxy)-benzophenone was heated under reflux with piperidine for one hour and the product was recovered using method (a) for guaiacols and method (b) for catechols:-

(a) The cooled piperidine solution was diluted with benzene and this solution was washed with dilute sulphuric acid and then with dilute sodium hydroxide solution. The acidified alkaline extract afforded the guaiacol which was recovered with ether or chloroform. The crude product was distilled or sublimed *in vacuo* and, where practicable, was crystallised from petrol (60-80°) or from benzene/petrol (60-80°).

(b) The cooled piperidine solution, diluted with benzene, was washed with water several times and the aqueous extract was acidified. The catechol was recovered from this solution with ether or chloroform and was purified as for the guaiacols.

3:5-Dimethylcatechol, m.p. 55° rising to 70.5-71° by prolonged standing over concentrated sulphuric acid, was prepared from 5-nitro-2-(2"-hydroxy-4":6"-dimethylphenoxy)benzophenone. (Hodgkinson and Limpach [28] record m.p. 73-74° after dehydration).

3:6-Dimethylcatechol, m.p. 104° (Found: C,69.3; H,7.7. $C_8H_{10}O_2$ requires C,69.55; H,7.3%), was prepared by scission of 5-nitro-2-(2"-hydroxy-3":6"-dimethylphenoxy)benzophenone.

4:5-Dimethylcatechol, m.p. 85-86°, was prepared by scission of 5-nitro-2-(2"-hydroxy-4":5"-dimethylphenoxy)benzophenone. (Diepolder [29] gives m.p. 79-82°; Karrer and Schick [30] give m.p. 86-87°).

3-Phenylcatechol, m.p. 111°(Found: C,77.2; H,5.3. $C_{12}H_{10}O_2$ requires C,77.4; H,5.4%), was prepared by scission of 5-nitro-2-(2"-hydroxy-3"-phenylphenoxy)-benzophenone.

4-Phenylcatechol, m.p. 135°, was prepared by scission of 5-nitro-2-(2"-hydroxy-4"-phenylphenoxy)- and 5-nitro-2-(2"-hydroxy-5"-phenylphenoxy)-benzophenones. (Found: C,77.55; H,5.4; Calc. for $C_{12}H_{10}O_2$: C,77.4; H,5.4%). (Yasuo [31] records m.p. 141°).

2-Methoxy-3:5-dimethylphenol, a viscous liquid, b.p. 180° (bath temp.)/20 mm. (Found: C,70.7; H,8.2.

Calc. for $C_9H_{12}O_2$: C,71.0; H,7.95%, was formed by scission of 5-nitro-2-(2"-methoxy-3":5"-dimethylphenoxy)-benzophenone. (Hodgkinson and Limpach [28] record b.p. 227-228°).

2-Methoxy-3:6-dimethylphenol, m.p. 48° (Found: C,70.8; H,7.8. $C_9H_{12}O_2$ requires C,71.0; H,7.95%) was prepared by scission of 5-nitro-2-(2"-methoxy-3":6"-dimethylphenoxy)benzophenone.

2-Methoxy-4:6-dimethylphenol, m.p. 29°, (Found: C,70.75; H,8.4. $C_9H_{12}O_2$ requires C,71.0; H,7.95%) was prepared by scission of 5-nitro-2-(2"-methoxy-4":6"-dimethylphenoxy)benzophenone.

2-Methoxy-5-phenylphenol, m.p. 111° (Found: C,78.3; H,6.0. $C_{13}H_{12}O_2$ requires C,78.0; H,6.0%) was prepared by scission of 5-nitro-2-(2"-methoxy-5"-phenylphenoxy)-benzophenone.

2-Hydroxy-3-methoxytoluene, m.p. 41°, was prepared by scission of 5-nitro-2-(2"-methoxy-6"-methylphenoxy)-benzophenone. (Majima and Okazaki [32] give m.p. 41-42°).

3-Hydroxy-2-methoxytoluene, m.p. 36.5°, was prepared by scission of the non-crystalline methyl ether of 5-nitro-2-(2"-hydroxy-3"-methylphenoxy)benzophenone obtained by treating the latter compound with diazomethane. (Limpach [33] gives m.p. 39°). Mixed m.p. with preceeding isomer ca. 25°.

Rearrangements.

Rearrangement of 5-nitro-2-(2"-hydroxy-3":5"-dimethylphenoxy)benzophenone (a) to 5-nitro-2-(2"-hydroxy-4":6"-dimethylphenoxy)benzophenone (b).

Acidification of a solution of (a) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 24 hours, afforded a gummy solid which was crystallised from methanol, m.p. 106-108°, undepressed by admixture with (b) but depressed to m.p. 95-102° by admixture with (a). Methylation of (a) with dimethyl sulphate and alkali, but not with diazomethane, involved rearrangement to the ether of (b), m.p. and mixed m.p. 131°, depressed to m.p. 85-90° by admixture with the methyl ether of (a). See Table IV .

Rearrangement of 5-nitro-2-(2"-hydroxy-4"-phenylphenoxy)benzophenone (c) to 5-nitro-2-(2"-hydroxy-5"-phenylphenoxy)benzophenone (d).

Acidification of a solution of (c) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 1½ hours, afforded yellow crystals, m.p. 115° from methanol, unchanged by admixture with the yellow form of (d) and depressed to m.p. 104-109° by admixture with (c). Methylation of (c) with dimethyl

sulphate in alkali gave the methyl ether of (d), m.p. and mixed m.p. 120°, depressed to m.p. 103-110° by admixture with the methyl ether of (c).

Rearrangement of 5-nitro-2-(2"-hydroxy-6"-methylphenoxy)benzophenone (e) to 5-nitro-2-(2"-hydroxy-3"-methylphenoxy)benzophenone (f).

Acidification of a solution of (e) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 1 hour, yielded pale yellow crystals, m.p. 112-116°, after one crystallisation from methanol. After repeated crystallisations this material afforded about 10% of (f) as colourless needles of m.p. 144-145°, depressed to m.p. 110-115° by admixture with (e). (Found: C, 68.65; H, 4.25. $C_{20}H_{15}O_5N$ requires C, 68.8; H, 4.3%).

To an almost saturated solution of (e) in methanol at room temperature was added a small drop of N sodium hydroxide solution. Crystallisation was initiated by stirring or rubbing and proceeded slowly to give (f) in 90% yield, m.p. and mixed m.p. 144-145°.

Dihydroxy- and hydroxymethoxy-aryloxynitrobenzophenones.

Substituents in aryl nucleus	M.Pt.	Found C	Found H	Reqd. C	Reqd. H	ml.	Notes
2":6"-dihydroxy	180°(d)	65.1	3.85	65.0	3.7	0.5	---
2";6"-dihydroxy-3"-methyl	106°	-	-	-	-	0.5	1
2":6"-dihydroxy-4"-methyl	166°(d)	65.9	4.3	65.6	4.1	0.5	2
2":6"-dihydroxy-3":4"-dimethyl	175°(d)	66.6	4.5	66.5	4.5	0.6	3
2":6"-dihydroxy-3":5"-dimethyl	196°	66.5	4.5	66.5	4.5	0.6	---
2"-hydroxy-6"-methoxy	-	-	-	-	-	1.0	4
2"-hydroxy-6"-methoxy-4"-methyl	-	-	-	-	-	0.7	4
2"-hydroxy-6"-methoxy-4":5"-dimethyl	149°	67.35	5.0	67.15	4.9	0.5	5

Table V

Preparation of Pyrogallol Derivatives.

Preparation of 5-nitro-2-(2":6"-dihydroxyphenoxy)- and 5-nitro-2-(2"-hydroxy-6"-methoxyphenoxy)-benzophenones.

The appropriate 5-nitro-2-(2"-hydroxyaryloxy)- or 5-nitro-2-(2"-methoxyaryloxy)-benzophenone (0.5g.) was dissolved by warming in concentrated sulphuric acid (ca. 0.5ml., see table), and glacial acetic acid (8ml.) added. To the cold mixture was then added 30% hydrogen peroxide (0.5 ml.) dropwise and with shaking. After some ten minutes, when the initial intense colour had faded to pale red or yellow, the solution was poured on to crushed ice and the dried product crystallised from methylated spirits or methanol. The compounds thus prepared are described in Table V, to which the following notes refer.

1. Satisfactory analyses could not be obtained although two separate samples were prepared.
2. The product was crystallised from chloroform.
3. The initial colour of the sulphuric/acetic acid solution was intense blue instead of the usual red. The product crystallised from benzene/petrol (60-80°).
4. The product could not be crystallised.
5. The considerable amount of yellow peroxide formed was removed by filtration, treatment of the filtrate

Derivatives of 7-nitro-9-phenylfluorone.

Source	Compound	M.Pt.	Found C	Found H	Reqd. C	Reqd. H
LXI	4-hydroxy	320 (d)	68.2	3.4	68.5	3.3
LXIII	4-hydroxy-1-methyl*	277 (d)	69.0	3.6	69.2	3.8
LXII	4-hydroxy-2-methyl	295 (d)	69.5	3.9	69.2	3.8
LXIV	4-hydroxy-1:2-dimethyl	300 (d)	69.7	4.4	69.8	4.2
LXXII	4-hydroxy-2-bromo	324 (d)	55.5	2.7	55.4	2.45
LXXVII	4-hydroxy-2-bromo-1-methyl†	300 (d)	56.5	3.0	56.4	2.8

*The product was amorphous †The product was microcrystalline

Table VI

with water giving the desired product in yields of about 50%.

Preparation of derivatives of 7-nitro-9-phenylfluorone.

The appropriate 5-nitro-2-(2":6"-dihydroxyaryloxy)-benzophenone was boiled with excess piperidine for two minutes, and the cooled solution was then poured into dilute sulphuric acid. The maroon-coloured precipitate thus formed was collected, dried, and warmed with anisole. A certain amount of tar was deposited. The anisole solution was decanted from this, and on cooling deposited highly lustrous, almost black, crystals of the product. The compounds thus prepared are described in Table VI.

7-Nitro-9-phenylfluorone was prepared by boiling 5-nitro-2-(3"-methoxyphenoxy)benzophenone under reflux with constant-boiling hydrobromic acid and glacial acetic acid for 2½ hours and then pouring into water. The crude product crystallised from benzene in stout orange needles of m.p. 308°. (Found: C,71.9; H,3.9. $C_{19}H_{11}O_4N$ requires C,71.9; H,3.5).

1:2-Dimethyl-4-hydroxy-7-nitro-9-phenylxanth-hydrol was prepared by dissolving 5-nitro-2-(2"-hydroxy-4":5"-

dimethylphenoxy)benzophenone in concentrated sulphuric acid and pouring on to crushed ice. The crude product crystallised from aqueous acetic acid in yellow prisms of m.p. 221°. (Found: C,69.1; H,4.9. $C_{21}H_{17}O_5N$ requires C,69.4; H,4.7).

5-Nitro-2-(2":6"-dimethoxyphenoxy)benzophenone was produced by methylating crude 5-nitro-2-(2"-hydroxy-6"-methoxyphenoxy)benzophenone with dimethyl sulphate in alkali. It was crystallised from ethanol, affording small white cubes, m.p. 170°. (Found: C,66.5; H,4.7. $C_{21}H_{17}O_6N$ requires C,66.5; H,4.5).

Methylation of 5-nitro-2-(2",6"-dihydroxyphenoxy) benzophenone with diazomethane in ether yielded identical material, m.p. and mixed m.p. 170°.

Scission of this material by boiling with piperidine for ½ hour, followed by extraction as previously described for guaiacol derivatives, yielded pyrogallol 1:3-dimethyl ether as an oil which could not be solidified. It was benzoylated in alkali, affording the benzoyl derivative, m.p. 115°. (lit. 118°).

Similarly, scission of crude 5-nitro-2-(2"-hydroxy-6"-methoxyphenoxy)benzophenone, followed by extraction as previously described for catechol derivatives, gave pyrogallol 1-methyl ether. This could not be solidified,

but on acetylation with acetic anhydride it yielded the diacetate, m.p. 91-2°. (lit. 91-3°). When treated with benzoyl chloride in pyridine it afforded a dibenzoate, m.p. 83° from ethanol. (Found: C,72.25; H,4.5. $C_{21}H_{16}O_5$ requires C,72.4; H,4.6).

Pyrogallol carbonate was prepared according to the method of Einhorn [34] and from it pyrogallol 1-methyl ether was produced as described by Hilleman [23]. Benzoylation of this by the Schotten-Baumann technique gave a dibenzoate identical with that previously obtained, m.p. and mixed m.p. 83°.

4:6-Dimethylpyrogallol was prepared by the scission of 5-nitro-2-(2":6"-dihydroxy-3":5"-dimethylphenoxy)-benzophenone. Extraction was carried out as described for catechol derivatives. The crude product, which sublimed at 80°/30 mm.,was crystallised from benzene affording white needles of m.p. 123°. The yield was not high as considerable tar was also produced. (Found: C,62.5; H,6.7. $C_8H_{10}O_3$ requires C,62.4; H,6.5).

5-Nitro-2-(2":6"-dimethoxy-4"-methylphenoxy)-benzophenone was prepared by methylating 5-nitro-2-(2":6"-dihydroxy-4"-methylphenoxy)benzophenone in alkali with dimethyl sulphate. It crystallised from ethanol in white prisms, m.p. 200-1°. (Found: C,66.9;

H,4.7. $C_{22}H_{19}O_6N$ requires C,67.15; H,4.9).

Crude 5-nitro-2-(2"-hydroxy-6"-methoxy-4"-methylphenoxy)benzophenone was similarly methylated and afforded the same product, m.p. and mixed m.p. 200°.

5-Nitro-2-(3":5"-dibromo-2":6"-dihydroxyphenoxy)-benzophenone was prepared by treating 5-nitro-2-(2":6"-dihydroxyphenoxy)benzophenone in chloroform with a slight excess of bromine in chloroform, and removing the solvent by distillation. The product crystallised from benzene in pale yellow needles, m.p. 206°. (Found: C,44.9; H,2.3. $C_{19}H_{11}O_6NBr_2$ requires C,44.8; H,2.2).

Methylation of this material with excess diazomethane in ether/methanol afforded 5-nitro-2-(3":5"-dibromo-2":6"-dimethoxyphenoxy)benzophenone which crystallised from ethanol in white needles, m.p. 139°. (Found: C,47.05; H,2.7. $C_{21}H_{15}O_6NBr_2$ requires C,46.95; H,2.8).

Scission of this compound followed by extraction as described for guaiacol derivatives gave 4:6-dibromopyrogallol 1:3-dimethyl ether which crystallised from benzene/petrol (60-80°) in white needles, m.p. 132°. (Found: C,31.0; H,2.7. $C_8H_8O_3Br_2$ requires C,30.8; H,2.6).

In an exactly similar series of reactions 5-nitro-2-(2":6"-dihydroxy-4"-methylphenoxy)benzophenone afforded

5-nitro-2-(3":5"-dibromo-2":6"-dihydroxy-4"-methylphenoxy)benzophenone as yellow cubes from benzene, m.p. 204°. (Found: C,46.0; H,2.5. $C_{20}H_{13}O_6NBr_2$ requires C,45.9; H,2.5%). Methylation of this gave 5-nitro-2-(3":5"-dibromo-2":6"-dimethoxy-4"-methylphenoxy)-benzophenone which crystallised from ethanol in white prisms, m.p. 144°. (Found: C,48.2; H,2.9. $C_{22}H_{17}O_6NBr_2$ requires C,47.9; H,3.1%). Bromination in chloroform of 5-nitro-2-(2":6"-dimethoxy-4"-methylphenoxy)benzophenone yielded identical material, m.p. and mixed m.p. 143-4°. Scission of this ether afforded 4:6-dibromo-5-methylpyrogallol 1:3-dimethyl ether as long white needles of m.p. 130°. (Found: C,33.1 H,3.0. $C_9H_{10}O_3Br_2$ requires C,33.2; H,3.1%).

The di-tosyl ester of 5-nitro-2-(2":6"-dihydroxyphenoxy)benzophenone was prepared by warming a mixture of 5-nitro-2-(2":6"-dihydroxyphenoxy)benzophenone (1 mol.) and p-toluene sulphonyl chloride (2.2 mol.) in pure dry pyridine on the steam bath for 15 minutes, and then treating with excess dilute hydrochloric acid. The resultant gum solidified on rubbing with ethanol and was crystallised from that solvent, yielding white prisms of m.p. 144°. (Found: C,60.0; H,4.0. $C_{33}H_{25}O_{10}NS_2$ requires C,60.1; H,3.8%). This compound was split at the

ether linkage by boiling under reflux with piperidine for one hour. The cooled solution was diluted with benzene and extracted with dilute sulphuric acid. Subsequent treatment of the benzene solution with dilute sodium hydroxide solution precipitated an insoluble sodium salt which was collected, washed,, and shaken with a mixture of chloroform and dilute sulphuric acid. From the dried chloroform layer was obtained pyrogallol 1:3-di-tosyl ester, which crystallised from methanol in large white prisms, m.p. 126°. (Found: C,55.1; H,4.1. $C_{20}H_{18}O_7S_2$ requires C,55.3; H,4.2%). This material was further treated with p-toluenesulphonyl chloride (1.1 mol.) in pyridine, and afforded pyrogallol tri-tosyl ester which crystallised from ethanol in gleaming white prisms, m.p. 139°. (Found: C,54.9; H,4.05. $C_{27}H_{24}O_9S_3$ requires C,55.1; H,4.1%). Pyrogallol (1 mol.) and p-toluenesulphonyl chloride (3.2 mol.) were warmed with pyridine on the steam bath for fifteen minutes and then treated with excess dilute hydrochloric acid, affording identical material, m.p. and mixed m.p. 139°.

3:4-Dimethoxy-7-nitro-9-phenylxanth-hydrol. 5-Nitro-2-(2":6"-dihydroxyphenoxy)benzophenone was heated with piperidine for two minutes, cooled, diluted with benzene, and washed with water (a) exhaustively, when a

black tar finally separated; and (b) until the tar just began to form. In the case of (a) the tar, after being separated by decantation, was dried in vacuo and treated with ethereal diazomethane. After some hours the colour of the solution faded to pale yellow, and on evaporation the xanth-hydrol was obtained. It formed colourless needles, m.p. 184° from benzene (charcoal) / petrol (60-80°). (Found: C,66.3; H,4.7. $C_{21}H_{17}O_6N$ requires C,66.5; H,4.5%). In acetic acid, saturated with hydrogen chloride, it gave with ferric chloride red plates of the chloride-ferrichloride. With perchloric acid in acetic acid it afforded red needles of the perchlorate.

In case (b) evaporation of the dried benzene solution followed by methylation (in ethereal diazomethane) of the residue gave yellow prisms, m.p. 227°, which have not yet been identified. (Found: C,67.3; H,6.45; N,6.3. $C_{21}H_{17}O_6N, C_5H_{11}N$ requires C,67.3; H,6.1; N,6.0%). The compound yielded the xanth-hydrol described above when its solution in concentrated sulphuric acid was poured on to ice, but it could not be prepared from that compound by heating with piperidine, or from 4-hydroxy-7-nitro-9-phenylfluorone by similar treatment followed by methylation.

1:2:3:4-Tetramethoxybenzene. The flocculent precipitate produced by adding hydrogen peroxide (0.2 ml.) to a solution of 3:4-dimethoxy-7-nitro-9-phenylxanthhydrol (0.2g.) in concentrated sulphuric-acetic acid (0.25:3.5 ml.) and pouring the whole on to ice, could not be crystallised but with methyl sulphate in alkali gave 5-nitro-2-(2":3":6"-trimethoxyphenoxy)benzophenone as pale yellow prisms, m.p. 134° from methanol. (Found: C,64.4; H,4.9. $C_{22}H_{19}O_7N$ requires C,64.5; H,4.7%). This compound was heated for one hour with piperidine, benzene was added, and the solution successively extracted with dilute sulphuric acid and alkali. To the alkaline extract methyl sulphate was added with shaking and after brief heating tetramethoxybenzene was recovered in chloroform as colourless prisms, micro-m.p. 85°(Found: C,60.5; H,6.95. Calc for $C_{10}H_{14}O_4$: C,60.0; H,7.1%). Baker, Jukes, and Subrahmanyam [3] record m.p. 89°.

Use of 2-chloro-3:5-dinitrobenzophenone.

2-Chloro-3:5-dinitrobenzophenone was prepared from 2-chloro-3:5-dinitrobenzoic acid (produced as described by Ullmann [43]) by the method used for the preparation of 2-chloro-5-nitrobenzophenone.

2-Phenoxy-3:5-dinitrobenzophenone was prepared by dissloving phenol (1.1 mol.) and 2-chloro-3:5-dinitrobenzophenone (1 mol.) in pyridine, leaving overnight, and treating with excess dilute hydrochloric acid. The crude product crystallised from acetic acid in almost colourless needles, m.p. 141-142°. (Found: C,62.5; H,3.2. $C_{19}H_{12}O_6N_2$ requires C,62.6; H,3.3%).

In similar fashion were prepared 2-α-napthoxy-3:5-dinitrobenzophenone, golden yellow leaflets, m.p. 154-5°, from acetic acid. (Found: C,67.0; H,3.7. $C_{23}H_{14}O_6N_2$ requires C,66.7; H,3.4%); 2-β-napthoxy-3:5-dinitrobenzophenone, shining yellow leaflets, m.p. 188°, from acetic acid. (Found: C,66.9; H,3.0. $C_{23}H_{14}O_6N_2$ requires C,66.7; H,3.4%); 2-(1-phenanthroxy)-3:5-dinitrobenzophenone, yellow needles, m.p. 248°, from xylene. (Found: C,70.0; H,3.7. $C_{27}H_{16}O_6N_2$ requires C,69.8; H,3.5%); 2-(7-coumarinoxy)-3:5-dinitrobenzophenone, fine white needles, m.p. 167°, from ethanol. (Found: C,61.0; H,2.7. $C_{22}H_{12}O_8N_2$ requires C,61.1; H,2.8%).

2-(2"-Hydroxyphenoxy)-3:5-dinitrobenzophenone was prepared by dissolving the phenoxy compound (0.5g.) in concentrated sulphuric acid (1.0 ml.), adding glacial acetic acid (15.0 ml.) followed by hydrogen peroxide (1.0 ml.). The crude product, obtained by pouring into water, crystallised from ethanol in pale yellow prisms, m.p. 180°.

Attempted hydroxylation of 2- -napthoxy- and 2- -napthoxy-3:5-dinitrobenzophenones.

The same method was used in each case. The substance (0.2g.) was dissolved in concentrated sulphuric acid (0.4 ml.), acetic acid (2.0 ml.) added, and the whole treated with hydrogen peroxide (0.2 ml.). On pouring into water the crude product was obtained as an orange powder, soluble in alkali. In neither case was satisfactory crystals obtained.

Attempted hydroxylation of 2-(1-phenanthroxy)-3:5-dinitrobenzophenone.

The substance (0.35g.) in sulphuric-acetic acid (2.0:8.0 ml.) was treated with hydrogen peroxide (0.5 ml.) and the whole poured on to ice. The crude product was dried and extracted repeatedly with benzene. Evaporation of this gave, with some difficulty, yellow crystals, m.p. 147° (d), soluble in alkali.

Cyclisation of 2-(7-coumarinoxy)-3:5-dinitrobenzophenone.

The substance was dissolved in excess concentrated sulphuric acid by warming at about 100° with shaking for twenty minutes, and then pouring on to ice. The crude product was dried and crystallised from aqueous acetic acid. It formed fine white crystals, m.p. 240-244° (d). (Found: C,61.1; H,2.9. $C_{22}H_{12}O_8N_2$ requires C,61.1; H,2.9%). The product, 4-hydroxy-4-phenyl-6:8-dinitrochromano-2:3-6':7'-coumarin, is shown on p. 44, no. (XCVII).

Miscellaneous preparations.

2-Chloro-5-nitrobenzophenone was prepared as described by Rupe [35].

m-Phenylphenol. m-Nitrodiphenyl was prepared according to Elks and Hey [36]. This was catalytically hydrogenated, and then treated as described by Jacobson and Loeb [37].

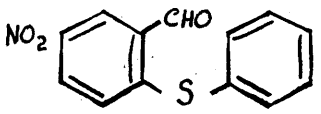
7-Hydroxycoumarin was prepared by the method of Pechmann [38].

1-Phenanthrol. 1-Keto-1:2:3:4-tetrahydrophenanthrene was prepared according to Haworth [39], using the modified Clemmensen proceedure of Martin [40]. It was then treated as described by Mosettig and Duvall [41] using Pd/C prepared by the method of Linstead and Thomas [42], giving 1-phenanthrol in rather poor yield.

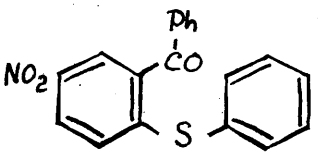
Cyclisation of 2-aryloxy-5-nitrobenzaldehydes.

Campbell, Dick, Ferguson, and Loudon [44] have shown that thio-ethers of types (I) and (II), prepared from 2-chloro-5-nitrobenzaldehyde and 2-chloro-5-nitrobenzophenone respectively, dissolve in cold concentrated sulphuric acid yielding bright red solutions of the corresponding thioxanthylium sulphates. Solutions of sulphates derived from type (II) were hydrolysed when poured into water, 9-phenylthioxanth-hydrols, for example (III), being produced. Under similar conditions sulphates derived from type (I) did not yield the thioxanth-hydrols, for example (IV), since the latter immediately underwent dismutation, affording a mixture of thioxanthene, e.g. (V), and thioxanthone, e.g. (VI), in equimolecular proportions.

In view of these results an investigation was made of the behaviour of the analogous aryloxybenzaldehydes under similar conditions. 2-Phenoxy-5-nitrobenzaldehyde (VII) was readily prepared by the condensation of sodium phenate and 2-chloro-5-nitrobenzaldehyde. A number of methylphenoxy- and methoxyphenoxy- nitrobenzaldehydes were also similarly produced. Dissolution of (VII) in cold concentrated sulphuric acid afforded a bright red solution of the xanthylium sulphate which yielded, on



(I)



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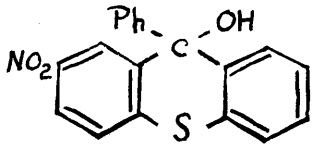

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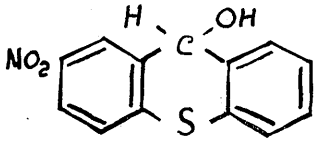

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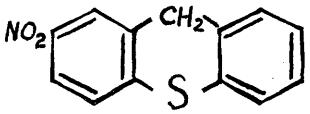

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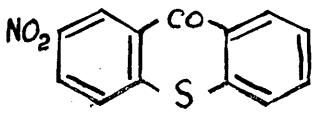

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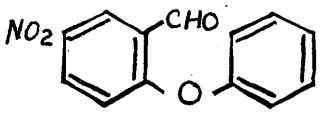

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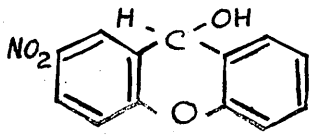

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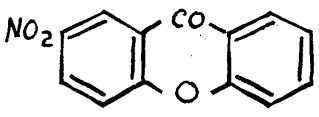

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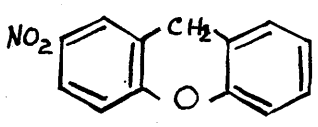

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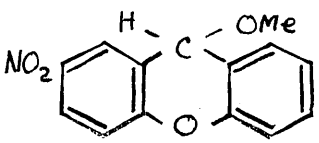

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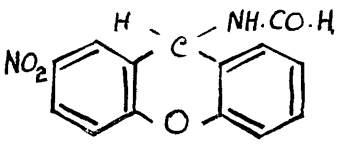


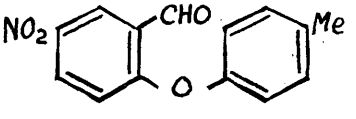
(XII)

pouring into water, a white substance (A) of m.p. 170°. Repeated crystallisation of this from dioxan gave a small amount of 2-nitroxanthone, m.p. 203 (IX). No trace of the corresponding nitroxanthene (X) could be found, so it would appear that disproportionation of the xanth-hydrol (VIII) does not take place, as was the case with the analogous sulphur compound. When (A) was recrystallised from methanol / dioxan the methyl ether (XI) was produced, while using ethanol / dioxan the corresponding ethyl ether was isolated. When (A) was treated with formamide in boiling acetic acid it afforded the formamide derivative (XII).

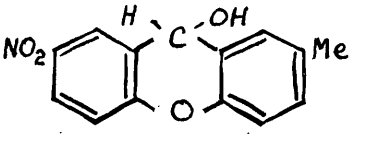
These facts are in accord with the assumption that (A) is the xanth-hydrol (VIII), but attempts to prepare a perchlorate or a chloride-ferrichloride were not successful, and the substance did not appear to react with sodium in toluene, although all of these reactions take place readily with xanth-hydrol itself. Kny-Jones and Ward [45] have shown that xanth-hydrol undergoes disproportionation on boiling in dilute mineral acid, but after being so treated (A) was recovered unchanged.

(A) could not be obtained in a crystalline form suitable for analysis, but cyclisation of 2-(p-tolyloxy)-5-nitrobenzaldehyde (XIII) gave a product which could be

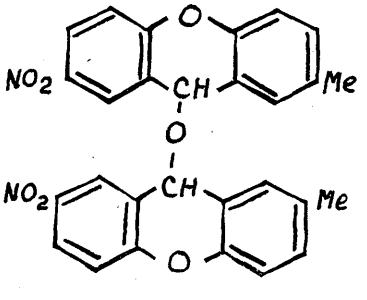
crystallised from acetic acid. The analysis figures for this substance corresponded to the dixanthyl ether (XV), but the molecular weight, as determined by the Rast method, was 288. This is fairly close to that of the xanth-hydrol (XIV), (257), allowing for experimental error; but it is very different from that of the dixanthyl ether (496).



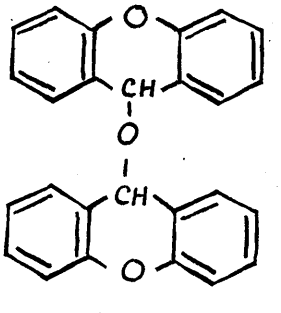
(XIII)



(XIV)



(XV)



(XVI)

Kny-Jones and Ward [45] note that the dixanthyl ether (XVI) yields xanth-hydrol on boiling under reflux in dilute alcoholic hydrochloric acid, and they also quote

evidence to show that such ethers are ionised, and therefore presumably can react to give derivatives of the corresponding xanth-hydrol.

Sufficient evidence has not been obtained to enable a decision to be made about the structure of (A), as work on this line was discontinued in order that attantion might be turned to a more profitable field.

Derivatives of 5-nitrobenzaldehyde.

Compound	M.Pt.	Formula	Found C	Found H	Reqd. C	Reqd. H
2-Phenoxy	68°	$C_{13}H_9O_4N$	64.5	3.7	64.2	3.7
2-(p-Tolyloxy)	80°	$C_{14}H_{11}O_4N$	not satisfactory			
2-(o-Tolyloxy)	122°	$C_{14}H_{11}O_4N$	not satisfactory			
2-(2'-Methoxyphenoxy)	114°	$C_{14}H_{11}O_5N$	61.6	4.1	61.55	4.1
2-(4'-Methoxyphenoxy)	98°	$C_{14}H_{11}O_5N$	61.3	4.0	61.55	4.1

Table VII.

Cyclisation of 2-aryloxy-5-nitrobenzaldehydes.

2-Chloro-5-nitrobenzaldehyde was prepared according to Erdmann [46].

Preparation of 2-aryloxy-5-nitrobenzaldehydes.

The appropriate phenol (0.01 mol.) and sodium hydroxide (0.012 mol.) were dissolved in 20 ml. of water, 2-chloro-5-nitrobenzaldehyde (0.01 mol.) was added, and the whole boiled under reflux for two hours. Recovery with ether afforded the crude product which was distilled *in vacuo* and crystallised from benzene/petrol (60-80°). The compounds described in Table were thus prepared.

Cyclisation of 2-phenoxy-5-nitrobenzaldehyde.

The substance (1.0 g.) was dissolved in the minimum amount of cold concentrated sulphuric acid, left for four hours, and then poured on to crushed ice. The crude product (A) was thoroughly washed with sodium bicarbonate solution, dried, and crystallised from dioxan, yielding 0.85 g. of white microcrystalline material, m.p. 170°. Repeated crystallisations from dioxan finally afforded a small amount of 2-nitroxanthone, m.p. 203°. (Dhar [47] records m.p. 200°). (Found: C, 64.6; H, 2.9. Calc. for $C_{13}H_7O_4N$ C, 64.7; H, 2.9%).

Preparation of methylnitroxanthyl ether.

The crude product (A) was crystallised froma mixture of methanol and dioxan, yielding small cubic crystals of the methylnitroxanthyl ether, m.p. 119.5°. (Found: C,65.0; H,4.3. $C_{14}H_{11}O_4N$ requires C,65.4; H,4.3%). When (A) was crystallised from ethanol/dioxan a different substance, m.p. 86°, was produced. This was presumed to be the ethyl ether.

Attempted purification of (A) by chromatography.

Crude (A) in dry benzene was passed through a column of acid-washed alumina. Prolonged washing with benzene developed two bands. The first, and larger, was bright orange on the column but when washed through the column gave a colourless solid, m.p. 170°, identical with the starting material. The other small band was found to be 2-nitroxanthone.

During the preparation of (A) for chromatography ca. 5% did not dissolve in benzene. After crystallisation from anisole this had m.p. 265°.

Preparation of formamide derivative of (A).

(A) was dissolved in glacial acetic acid and boiled under reflux with excess formamide for from 5 to 10 minutes. Water was then added and the mixture was

allowed to cool, when crystals were deposited. Recrystallised from dioxan/water these yielded the formamide derivative of 7-nitroxanth-hydrol, m.p. 189-190°. (Found: C,62.4; H,3.7. $C_{14}H_{10}O_4N$ requires C,62.2; H,3.7%).

Cyclisation of 2-(p-tolyloxy)-5-nitrobenzaldehyde.

The substance was dissolved in the minimum amount of cold concentrated sulphuric acid and left overnight. It was then poured on to ice and the recovered product was crystallised from dioxan, giving m.p. 176-178°. This was raised to m.p. 179° by three crystallisations from aqueous acetic acid. (Found: C,68.0; H,4.0. $C_{28}H_{20}O_7N_2$ requires C,67.7; H,4.1%).

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