54. ortho-*Hydroxylation of Phenols. Part II.* Derivatives of Catechol.*

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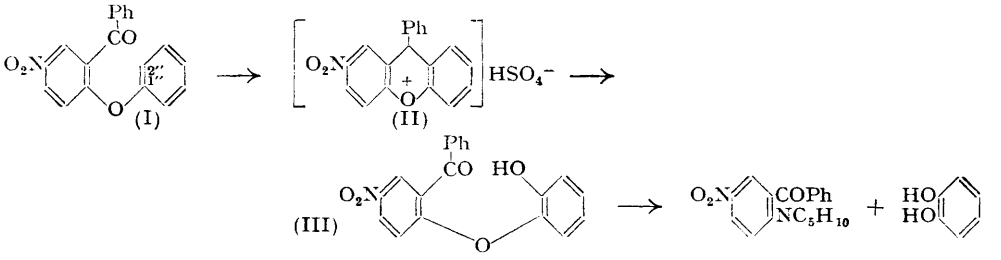
In development of work described in Part I * a number of homologues of phenol have been converted into their catechol or guaiacol analogues through intermediates of the 2-aryloxy- and 2-(2-hydroxy-aryloxy)-5-nitrobenzophenone types. In certain intermediates of the latter class further examples of the Smiles rearrangement have been noted.

In a preliminary survey, now regarded as Part I,* the practicability of a new method of preparing catechols from phenols was established for a few simple cases. The method consists of three practical steps exemplified by (*a*) conversion of the phenol into an aryloxynitrobenzophenone of type (I), (*b*) hydroxylation of (I) to (III) through the intermediate but unisolated xanthylium sulphate (II), and (*c*) scission of (III) by piperidine, thereby liberating the catechol. Inclusion of an alkylation step, prior to scission, leads to monoalkyl ethers of catechols. The whole process is simple, rapidly carried out, and suitable for preparations on the small scale. Its extension to certain derivatives of pyrogallol, through renewed hydroxylation at stage (III), is discussed in the following paper. Meanwhile a more comprehensive study has been made of the method in its application to homologues of phenol. This was primarily designed to discover optimum conditions for the critical hydroxylation step in this class of compound, but incidentally minor improvements were made in other phases of the process (see Experimental).



The 2-aryloxy-5-nitrobenzophenones of type (I), listed in Table 1, were prepared in satisfactory yield from the appropriate phenols by reaction with 2-chloro-5-nitrobenzophenone. Hydroxylation was effected by dissolving the compound in concentrated sulphuric acid, diluting the solution with acetic acid, and adding hydrogen peroxide. Of the variables examined the ultimate concentration of sulphuric acid appears to be the most significant and the least easy to standardise. It must be sufficiently high to prevent the precipitation of colourless peroxides (Part I, *loc. cit.*) and yet low enough to avoid the formation of red by-products. The tendency to form these coloured by-products was troublesome only in hydroxylating the compounds (VIII), (IX), and (X) where a relatively low concentration of sulphuric acid was advantageous. Otherwise the hydroxylated products, listed in Table 2, were prepared under uniform conditions, the yield in all cases being high although those compounds in which a substituent is present in position 6, *viz.*, (XIV), (XV), and (XXI), proved difficult to crystallise. An interesting variation was observed in the colour of the compounds of type (III). In general it ranged from pale to bright yellow but two compounds, *viz.*, (XVII) and (XXII), were obtained colourless. In both cases, however, there was also evidence of a yellow form: thus the colourless form of (XVII) afforded a yellow solution in ethanol and, in the case of (XXII), the colourless variety was interconvertible, through crystallisation, with a yellow form. Possibly chromoisomerism is more general in this class of compound than has so far been detected.

* *J.*, 1950, 55, is regarded as Part I.

It was previously shown (Part I, *loc. cit.*) that in presence of alkali the benzoylated nitrophenyl group of compounds of type (III) may migrate from one to the other oxygen atom when the phenolic ring is unsymmetrically substituted. Such rearrangement renders ambiguous the structures of *O*-alkylation products prepared in presence of alkali but it

TABLE 1. *2-Aryloxy-5-nitrobenzophenones.*

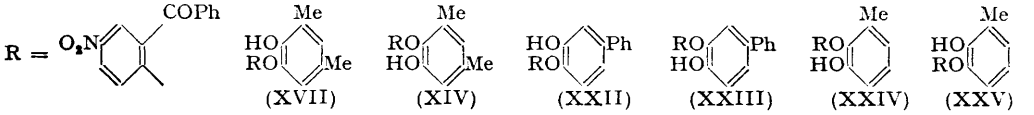
No.	Subst.	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
IV	2″ : 4″-Me_2	109°	$C_{21}H_{17}O_4N$	72·7	5·0		
V	2″ : 5″-Me_2	120	,,	72·7	5·0	72·6	4·9
VI	3″ : 4″-Me_2	133	,,	72·7	4·9		
VII	3″ : 5″-Me_2	117·5	,,	72·45	4·8		
VIII	4″-Pr^i	82	$C_{22}H_{19}O_4N$	73·0	5·4	73·1	5·3
IX	4″-Bu^t	85	$C_{23}H_{21}O_4N$	73·75	5·7	73·6	5·6
X	4″-$CMe_2{\cdot}CH_2Bu^t$	117	$C_{27}H_{29}O_4N$	75·2	7·1	75·1	6·8
XI	2″-Ph	97—98	$C_{25}H_{17}O_4N$	75·9	4·4		
XII	3″-Ph	58—60	,,	76·1	4·45	76·0	4·3
XIII	4″-Ph	126	,,	76·2	4·35		

TABLE 2. *2-(2″-Hydroxyaryloxy)-5-nitrobenzophenones.*

No.	Subst.	Source	M. p.	Formula	Found, % C	Found, % H	Required, % C	Required, % H
XIV	4″ : 6″-Me_2	IV	108°	$C_{21}H_{17}O_5N$	69·6	4·8		
XV	3″ : 6″-Me_2	V	132	,,	69·6	4·6		
XVI	4″ : 5″-Me_2	VI	166	,,	69·5	5·0	69·4	4·7
XVII	3″ : 5″-Me_2	VII	166	,,	69·35	4·6		
XVIII	4″-Pr^i	VIII	75	$C_{22}H_{19}O_5N$	70·3	5·05	70·0	5·1
XIX	4″-Bu^t	IX	115	$C_{23}H_{21}O_5N$	70·45	5·2	70·6	5·4
XX	4″-$CMe_2{\cdot}CH_2Bu^t$	X	145	$C_{27}H_{29}O_5N$	72·5	6·7	72·5	6·5
XXI	6″-Ph	XI	141	$C_{25}H_{17}O_5N$	72·8	4·0		
XXII	5″-Ph	XII	144 [a]	,,	73·1	4·3	73·0	4·2
		XII	125 [b]	,,	72·8	4·2		
XXIII	4″-Ph	XIII	119	,,	73·1	4·0		

[a] Colourless. [b] Yellow.

is not encountered in methylations effected by diazomethane. Further experience has confirmed the view that rearrangement is seldom complete and presumably reaches an equilibrium position which is individually determined. When either (XVII) or (XIV) was dissolved in alkali subsequent acidification afforded in each case a substance which was readily identified as slightly impure (XIV). Likewise methylation of (XVII) or (XIV) by means of methyl sulphate and alkali afforded the methyl ether (XIV*a*) of the latter compound. By the action of diazomethane the same methyl ether was obtained from (XIV),



(XVII) (XIV) (XXII) (XXIII) (XXIV) (XXV)

(**XVII***a*; MeO for HO) (XIV*a*; MeO for HO) (XXII*a*; MeO for HO) (XXIII*a*; MeO for HO)

whereas (XVII) gave the different methyl ether (XVII*a*). In this case, (XIV) clearly predominates over (XVII) in alkaline solution and a similar situation obtains in regard to compounds (XXII) and (XXIII). With diazomethane these compounds gave the corresponding ethers, (XXII*a*) and (XXIII*a*) respectively, whereas with methyl sulphate and alkali they both gave (XXIII*a*) as the only product identified. The substance recovered from an alkaline solution of (XXII) or (XXIII) was oily and when induced to solidify was obviously heterogeneous but it gave impure (XXIII) on recrystallisation, and (XXIII*a*) on treatment with diazomethane. Thus in alkaline solution (XXIII) appears to predominate over (XXII).

The compound (XXIV), obtained in the course of hydroxylation of *o*-cresol (Part I, *loc. cit.*), has provided an interesting example of rearrangement. When it is dissolved in aqueous alkali acidification yields a mixture of (XXIV) and (XXV) in which the former

greatly predominates. Nearly complete rearrangement can be achieved, however, by adding a trace of alkali to a fairly concentrated solution of (XXIV) in ethanol whereupon the much less soluble (XXV) gradually crystallises. Although no convenient alternative synthesis of (XXV) is available, the structure assigned is supported by several observations. In concentrated sulphuric acid (XXV) affords a red solution indicative of the formation of a xanthylium salt, whereas with (XXIV) where analogous cyclisation is impossible the corresponding solution is pale yellow. Furthermore by methylation of (XXIV) and (XXV) with diazomethane and subsequent scission, in each case with piperidine, different methoxycresols were obtained and were recognised as 2-hydroxy-3-methoxy- and 3-hydroxy-2-methoxy-toluene respectively.

Scission of the 2-(2''-hydroxyaryloxy)-5-nitrobenzophenones and of their methyl ethers by piperidine was not attempted in all cases, but a number of catechol and guaiacol homologues, prepared in this way, are described in the Experimental section.

Experimental

2-Aryloxy-5-nitrobenzophenones (Table 1) 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 min.) before being cooled and treated with aqueous sodium hydroxide. The product was washed with water and crystallised first from acetic acid (diluted with water where necessary) and then from benzene (charcoal)–light petroleum (b. p. 50—80°).

2-(2''-Hydroxyaryloxy)-5-nitrobenzophonones (Table 2).—The finely powdered 2-aryloxy-5-nitrobenzophenone (0·0015 mole) was dissolved by shaking and gentle warming in 1 c.c. of concentrated sulphuric acid [0·5 c.c. for compounds (VIII), (IX), and (X)]. After ½ hour acetic acid (8 c.c.) was added and the mixture was treated with 30% hydrogen peroxide (*ca.* 0·002 mole) added dropwise and with shaking until, after 5 minutes, the original red colour lightened to a pale amber. The mixture was left for 20 minutes, then poured on crushed ice, and the washed and dried solid was crystallised from methanol. Compounds (XVI), (XVII), and (XXI) crystallised directly from the reaction mixtures and were further crystallised from ethanol. Compounds (XVIII) and (XIX) were crystallised from benzene–light petroleum (b. p. 60—80°), and the last traces of solvent could only be removed by melting the samples *in vacuo*.

Methylation of Compounds of Type (III).—(*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 2 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 methyl sulphate was then added with shaking. The oil, initially formed, solidified on storage or when rubbed with ethanol from which the product was crystallised. The results are summaried in the following Table.

2-(2''-Methoxyaryloxy)-5-nitrobenzophenones.

					Found, %		Required, %	
No.	Subst.	M. p.	Source	Formula	C	H	C	H
XIV*a*	4'' : 6''-Me_2	131°	XIV * †	$C_{22}H_{19}O_5N$	70·1	5·2	70·0	5·1
XV*a*	3'' : 6''-Me_2	104	XV †	,,	70·1	5·5		
XVI*a*	4'' : 5''-Me_2	125	XVI †	,,	70·1	5·1		
XVII*a*	3'' : 5''-Me_2	101	XVII *	,,	70·0	5·0		
XXIII*a*	4''-Ph	120	XXIII *	$C_{26}H_{19}O_5N$	73·2	4·8	73·4	4·5
XXII*a*	5''-Ph	120	XXII * †	,,	73·7	4·5		
XXIV*a*	6''-Me	130	XXIV *	$C_{21}H_{17}O_5N$	69·6	4·8	69·4	4·7

In reaction with : * diazomethane, † methyl sulphate and alkali.

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

(XXIII) ⟶ (XXII). Acidification of a solution of (XXIII) 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 (XXII) and depressed to m. p. 104—109° by admixture with (XXIII). Methylation of (XXIII) with methyl sulphate in alkali gave (XXII*a*), m. p. and mixed m. p. 120°, depressed to m. p. 103—110° by admixture with (XXIII*a*).

(XXIV ⟶ (XXV). (*a*) Acidification of a solution of (XXIV) in 5% aqueous potassium hydroxide, which had been kept at room temperature for 1 hour, yielded pale yellow crystals, m. p. 112—116° (once crystallised from methanol). After repeated crystallisations this material afforded 2-(2″-*hydroxy*-3″-*methylphenoxy*)-5-*nitrobenzophenone* (XXV) (*ca.* 10%) as colourless needles of m. p. 144—145°, depressed to m. p. 110—115° by admixture with (XXIV) (Found: C, 68·65; H, 4·25. $C_{20}H_{15}O_5N$ requires C, 68·8; H, 4·3%). (*b*) To an almost saturated solution of (XXIV) in methanol at room temperature was added a small drop of N-sodium hydroxide. Crystallisation, initiated by stirring or rubbing, proceeded slowly and gave (XXV) (90%), m. p. and mixed m. p. 144—145°.

Scissions with Piperidine.—The 2-(2″-hydroxy- or 2″-methoxy-aryloxy)-5-nitrobenzophenone was heated under reflux with piperidine for 1 hour and the product was recovered by method (*a*) for guaiacols and method (*b*) for catechols. (*a*) The cooled piperidine solution was diluted with benzene and was washed with dilute sulphuric acid and then with dilute sodium hydroxide solution. The acidified alkaline extract afforded the guaiacol on recovery in ether or chloroform. The crude product was distilled or sublimed *in vacuo* and, where practicable, crystallised from light petroleum or from benzene–light petroleum (b. p. 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 in ether or chloroform and was purified as for the guaiacols. The following were thus prepared.

3 : 5-Dimethylcatechol, m. p. 55° rising to 70·5—71° on prolonged storage over concentrated sulphuric acid; from (XVII) (Hodgkinson and Limpach, *J.*, 1893, **63**, 108, 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%); from (XV).

4 : 5-Dimethylcatechol, m. p. 85—86° (Diepolder, *Ber.*, 1909, **42**, 2916, gives m. p. 79—82°; Karrer and Schick, *Helv. Chim. Acta*, 1943, **26**, 800, give m. p. 86—87°); from (XVI).

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%); from (XXI).

4-Phenylcatechol, m. p. 135° (Found: C, 77·55; H, 5·4%) (Yasuo, *Bull. Chem. Soc. Japan*, 1943, **18**, 93, records m. p. 141°); from (XXII) and (XXIII).

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%) (Hodgkinson and Limpach, *loc. cit.*, record b. p. 227—228°); from (XVII*a*).

2-*Methoxy*-3 : 6-*dimethylphenol*, m. p. 48° (Found: C, 70·8; H, 7·8%); from (XV*a*).

2-*Methoxy*-4 : 6-*dimethylphenol*, m. p. 29° (Found: C, 70·75; H, 8·4%); from (XIV*a*).

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%); from (XXII*a*).

2-Hydroxy-3-methoxytoluene, m. p. 41° (Majima and Okazaki, *Ber.*, 1916, **49**, 1488, give m. p. 41—42°); from (XXIV*a*).

3-Hydroxy-2-methoxytoluene, m. p. 36·5°, was prepared by scission of the non-crystalline methyl ether of (XXV) obtained by treating the latter compound with diazomethane (Limpach, *Ber.*, 1891, **24**, 4137, gives m. p. 39° for the toluene). A mixed m. p. with the preceding isomer was *ca.* 25°.

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