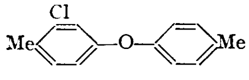
341. *Reactions of Halogens with Phenols.*

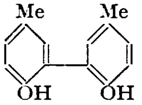
By K. Bowden and C. H. Reece.

Chlorine or sulphuryl chloride with *p*-cresol at room temperature gives, besides chlorocresols, the ether (I) and the di- and ter-phenyl derivatives (II) and (III). The general applicability of the reaction to a variety of phenols and to bromine has been examined and a possible mechanism put forward to account for the formation of these compounds.

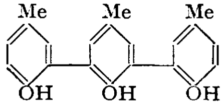
The reaction of halogens with phenols under mild conditions has long been known to yield simple halogen-substituted phenols. The present investigations have shown that chlorine or chlorine-generating compounds can give, from some phenols, a variety of more unusual products under these conditions. Thus sulphuryl chloride or chlorine gives with *p*-cresol, not only 3-chloro-*p*-cresol, but also 3-chloro-4 : 4′-dimethyldiphenyl ether (I), the diphenyl derivative (II), and the terphenyl derivative (III).



(I.)



(II.)



(III.)

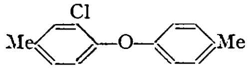
The general procedure adopted for the preparation of these types of compounds is reaction with sulphuryl chloride at 20—30° in the presence of a small amount of zinc chloride. Although zinc chloride is not essential for the reaction, better yields are obtained in its presence : the combined yields of (I)—(III) from *p*-cresol approximate to 26%, and that of 3-chloro-*p*-cresol to 13%.

The formation of compounds (I)—(III) appears to be little affected by temperature over the range investigated (20—100°), and variation in the molecular ratio of sulphuryl chloride to *p*-cresol alters mainly the ratio to each other in which these compounds are formed and not their combined yields (see Table, p. 1689).

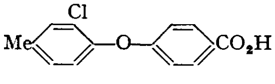
Distillation of the *p*-cresol reaction mixture, after removal of zinc salts, gave four fractions, (*A*)—(*D*).

The first, (*A*), consisted of unchanged *p*-cresol and chlorocresol which were separated by distillation of their methyl ethers.

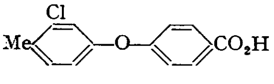
Fraction (*B*) had the empirical formula $C_{14}H_{13}OCl$, gave no colour with ferric chloride solution, and was insoluble in dilute sodium hydroxide. It was recovered almost quantitatively after being refluxed with 20% alcoholic potash or hydrogen iodide. It is thus probably the ditolyl ether (I) or (IV) with the halogen in the nucleus. It did not yield a picrate and decomposed on attempted nitration with fuming nitric acid in sulphuric acid at 0° [Reilly, Drumm, and Barrett (*J.*, 1927, 67) obtained a similar result when they attempted to nitrate di-*p*-tolyl ether]. Oxidation by potassium permanganate in aqueous pyridine gave a monocarboxylic acid which did not melt below 300° and which gave an *S*-benzylthiuronium salt, m. p. 184°. The ethers (I) and (IV) were synthesised and oxidised to their respective acids (V) and (VI). The acid from fraction (*B*) was unexpectedly found to have the structure (VI).



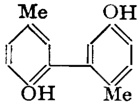
(IV.)



(V.)



(VI.)



(VII.)

The only chloro-4 : 4′-dimethylphenyl ether recorded in the literature, is that obtained by chlorinating 4 : 4′-dimethyldiphenyl ether, when the halogen was thought to enter position 2, giving (IV) (Mailhe and Murat, *Bull. Soc. chim.*, 1912, [iv], **11**, 288). Chlorination of di-*p*-tolyl ether with sulphuryl chloride in the presence of iodine gave an oil, b. p. 311—314°/758 mm., which was identical with the chlorodimethyldiphenyl ether obtained from 2-amino-4 : 4′-dimethyldiphenyl ether by a Sandmeyer reaction and therefore had the structure (IV). Oxidation of this ether gave the carboxylic acid (V), characterised as its *S*-benzylthiuronium salt.

The ether (IV) was also prepared from the potassium salt of 3-chloro-*p*-cresol and *p*-bromotoluene. This general method of preparing chloroditolyl ethers was found to be satisfactory for preparation of (I) from 2-chloro-*p*-cresol and *p*-bromotoluene after other syntheses had failed.

Fraction (*C*) after crystallisation had m. p. 154°, was soluble in dilute sodium hydroxide solution, and gave a greenish-blue colour with dilute ferric chloride solution. It had the empirical formula C_7H_7O and gave a crystalline benzoate and acetate. It was identical with the diphenyl derivative (II) obtained by Pummerer *et al.* (*Ber.*, 1922, **55**, 3116) and by Westerfield and Lowe (*J. Biol. Chem.*, 1942, **145**, 463) by different processes, and differed from the isomer (VII) in its ultra-violet absorption spectrum.

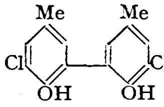
Fraction (*D*) after crystallisation had m. p. 197°. It was a phenol, of formula $C_{21}H_{20}O_3$. It has been recorded by Pummerer *et al.* and by Westerfield and Lowe (*locc. cit.*), the latter authors concluding that it was the terphenyl derivative (III).

The compounds (II) and (III) were obtained from *p*-cresol by potassium ferricyanide (Pummerer *et al.*) and the enzyme peroxidase (Westerfield and Lowe) and could conceivably have been formed by free-radical mechanisms (see Harington, *J.*, 1944, 193). Our investigations of the reaction between sulphuryl chloride and *p*-cresol preclude free-radical mechanisms. The presence of sulphur or organic nitro-compounds, known to inhibit free-radical mechanisms (Kharasch and Brown, *J. Amer. Chem. Soc.*, 1939, **61**, 2142), did not influence the course of the reaction to any large extent (see Table). Again, the addition of benzoyl peroxide, known to promote the formation of free radicals, had no influence. This, and the unexpected configuration of the product (I), having the chloro-group in position 3 and not the expected position 2, indicated that the halogen atom had not been introduced by simple substitution into either *p*-cresol or 4 : 4′-ditolyl ether, and led us to consider mechanisms other than those involving free radicals to explain the formation of all three types of product.

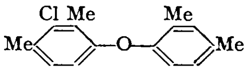
When chlorine was passed into *p*-cresol in the presence of a trace of zinc chloride the same products were formed as when sulphuryl chloride was used, showing that the sulphuryl chloride was acting solely as a source of molecular chlorine.

From 3-chloro-*p*-cresol, sulphuryl chloride in the presence of a small amount of zinc chloride gave a 13·7% yield of 3 : 5-dichloro-*p*-cresol and a 9·6% yield of 3 : 3′-dichloro-2 : 2′-dihydroxy-5 : 5′-dimethyldiphenyl (VIII). In this experiment less than 1% of the expected ether (XIV) was formed.

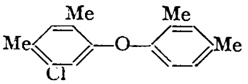
From *m*-4-xylenol, an ether, presumably (IX) or (X), was formed in 4·7% yield, together with a dihydroxytetramethyldiphenyl (XI) (cf. Bamberger and Brun, *Ber.*, 1907, **40**, 1952).



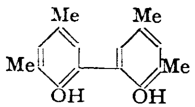
(VIII.)



(IX.)



(X.)



(XI.)

On the other hand phenol, *o*- and *m*-cresols, *p*-*tert.*-butylphenol, and *p*-tolyl methyl ether with sulphuryl chloride and zinc chloride gave only simple chlorinated derivatives, and 3 : 5-dichloro- and 3-nitro-*p*-cresol did not react.

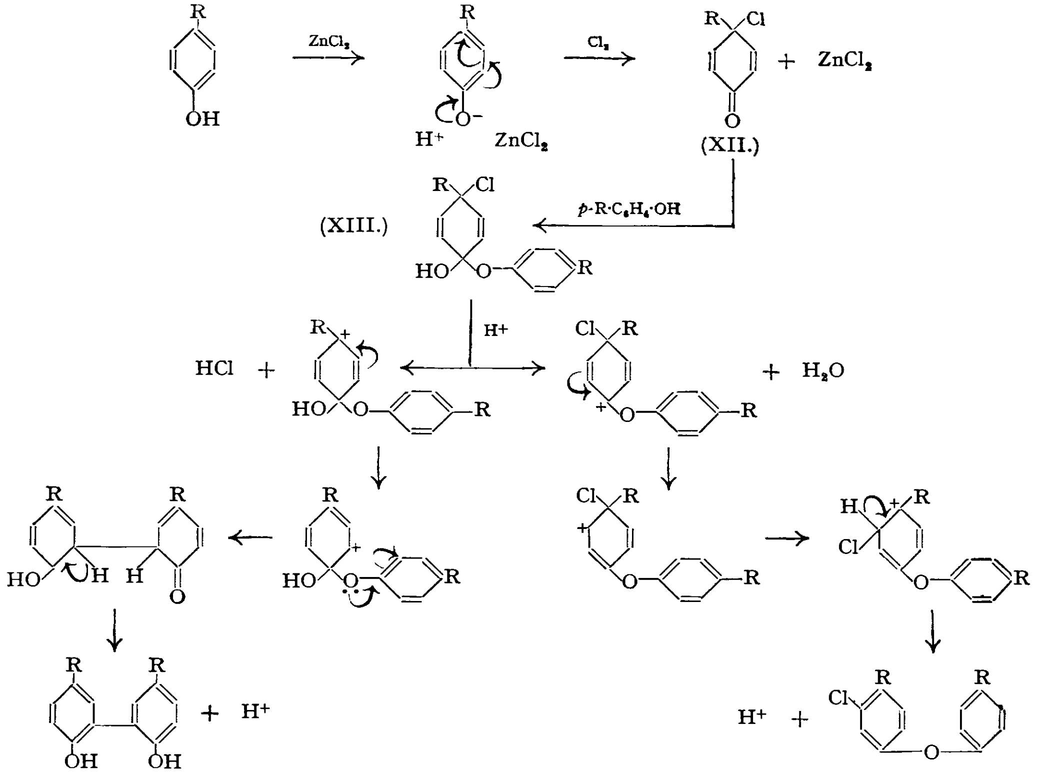
Either bromine or *N*-bromosuccinimide with *p*-cresol in the presence of the same catalyst gave only simple bromocresols and hydrogen chloride was without effect on a mixture of *p*-cresol and zinc chloride.

Discussion.—From the above results it appears that for products of the type (I)—(III) to be produced by the action of chlorine, the phenol must have a side chain in the *para*-position to a free hydroxyl group.

The negligible effect of substances which promote or inhibit free-radical formation is evidence against the products being formed by free-radical mechanisms. Again the possibility of the reactions proceeding *via* the derived *p*-methylene-quinones was discounted in view of the readiness with which such compounds react with hydrochloric acid (which is produced in large amounts during the reaction) to give *p*-hydroxybenzyl chlorides.

From the experimental results obtained the mechanism shown in the chart seems to be the most suitable hypothesis. Repetition of the process giving diphenyl derivatives will obviously give ter- and poly-phenyl derivatives.

This hypothesis explains (see Table) why only small amounts of zinc chloride are necessary; also why copper and cobalt chlorides do not act as catalysts, since their affinity for electrons is much less than that of aluminium chloride, zinc chloride, or sulphur dichloride (formed from sulphur when it was added to the reaction mixture). It can be seen that according to this mechanism the reaction will proceed in the absence of a catalyst but the yields will be decreased as the molecule is less activated.

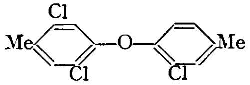


The non-formation of compounds similar to (XII) from phenol or *o*- or *m*-cresol explains why they yield only mononuclear chlorinated products. In the case of *tert.*-butylphenol it is considered that the reaction is sterically hindered.

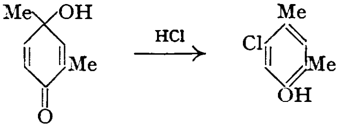
The mechanism also explains why 3-chloro-*p*-cresol gives so much less of the ether (XIV) than of the diphenyl derivative (VIII); for, although the halogen atom in 3-chloro-*p*-cresol tends to deactivate the whole ring, it has a greater effect on adjacent position than on others, *Effects of various reagents and conditions on the reaction between sulphuryl chloride and* p-*cresol* (21 *g.*).

Mol. ratio, SO_2Cl_2/*p*-cresol.	Temp.	Catalyst.	Yields, mol.-%. (I.)	(II.)	(III.)
1 : 2	30°	$ZnCl_2$, 2 g.	5·5	16·8	3·8
,,	,,	Nil	1·5	4·6	—
,,	100	$ZnCl_2$, 2 g.	5·6	15·1	3·7
,,	,,	$ZnCl_2$, 28 g.	6·0	16·8	3·6
,,	30	$ZnCl_2$, 2 g. + Bz_2O_2, 0·5 g.	5·6	16·8	2·9
1 : 1	,,	$ZnCl_2$, 2 g.	6·0	11·5	8·5
1 : 2	,,	$CoCl_2$, 2 g.	0·9	3·2	—
,,	,,	Cu_2Cl_2, 2 g.	1·3	3·6	—
,,	,,	$AlCl_3$, 2 g.	11·5	8·0	—
,,	,,	S, 2 g.	4·8	15·5	2·8
,,	,,	$Ph{\cdot}NO_2$, 2 c.c.	0·9	3·2	—
,,	,,	$ZnCl_2$, 2 g. + $Ph{\cdot}NO_2$, 25 c.c.	4·9	17·4	3·8

so that in the intermediate (XIII) the affinity of the hydroxyl group for the hydrogen ion is decreased more than is that of the halogen in the *para*-position. Therefore only (VIII) is obtained in any quantity, although the yield of this is less than that of the corresponding ether obtained from *p*-cresol.



(XIV.)



(XV.) (XVI.)

The aromatic ring of 3-nitro- or 3 : 5-dichloro-*p*-cresol is deactivated to such an extent as to prevent the formation of compounds similar to (XII).

From the above hypothesis it can be deduced that the chloro-ether obtained from *m*-4-xylenol and sulphuryl chloride has the structure (X) since Bamberger and Reber (*Ber.*, 1907, **40**, 2268) obtained 6-chloro-*m*-4-xylenol (XVI) by heating *m*-xylene-*ψ*-quinol (XV) with hydrogen chloride.

EXPERIMENTAL.

(Analyses by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

Reaction of Sulphuryl Chloride with p-*Cresol in the Presence of Zinc Chloride.*—Sulphuryl chloride (13·5 g.) was added during 45 minutes to a stirred mixture of *p*-cresol (21·0 g.) and powdered anhydrous zinc chloride (2·0 g.) starting at 30°, at which temperature the mixture is liquid. During the addition the temperature fell to 20°, the mixture remaining liquid. After about 20 minutes hydrogen chloride and sulphur dioxide were evolved and the temperature rose to 25°, the mixture darkening and the zinc chloride slowly dissolving. The mixture was stirred at room temperature overnight and then shaken with water and light petroleum (b. p. 60—80°). The light petroleum layer, after being dried (Na_2SO_4), was distilled to give the following fractions : (*A*) b. p. 94—97°/15 mm. (15·8 g.), (*B*) b. p. 110—120° (air-bath temp.)/2 × 10^{-4} mm. (1·28 g.), (*C*) b. p. 160—175° (air-bath temp.)/2 × 10^{-4} mm. (3·67 g.), and (*D*) b. p. 200—230° (air-bath temp.)/2 × 10^{-4} mm. (0·78 g.). The higher-boiling residue (1·3 g.) was not investigated.

Fraction (A). The total fraction, dissolved in a solution of sodium hydroxide (6·0 g.) in water (30 c.c.), was cooled to 5° and methylated with methyl sulphate (20 g.) (stirring) at that temperature for 2 hours and then at the b. p. for 2 hours. The resulting ethers were fractionally distilled giving *p*-tolyl methyl ether, b. p. 172—177°/748 mm. (11·3 g.), followed by an intermediate fraction, b. p. 177—212°/748 mm. (0·9 g.), and 3-chloro-*p*-tolyl methyl ether b. p. 212—217°/748 mm. (4·0 g.).

Fraction (B). This was a colourless oil, b. p. 133—136°/0·1 mm., m. p. 17°, sparingly soluble in aqueous alcohol (Found : C, 72·6; H, 5·4; Cl, 16·1%; *M*, 205. $C_{14}H_{13}OCl$ requires C, 72·2; H, 5·6; Cl, 15·2%; *M*, 232).

To the oil (0·6 g.) and water (3 c.c.), pyridine was added until a homogeneous solution was formed. Potassium permanganate (1·7 g.) was added and the stirred solution heated on the steam-bath for 1 hour. After filtration hot, the filtrates were decolorised with sulphur dioxide and acidified with hydrochloric acid, to give a precipitate (0·52 g.) which was dissolved in hot 8% sodium hydroxide solution (4·0 c.c.) and allowed to cool, to give white needles of the sodium salt of the carboxylic acid. These were filtered off and then dissolved in hot water, and the carboxylic acid was precipitated as a white solid by hydrochloric acid. p-*Carboxyphenyl* 2-*chloro*-p-*tolyl ether* (VI), crystallised from glacial acetic acid, had m. p. >300° (0·32 g.) (Found : C, 64·1; H, 4·5; Cl, 13·5. $C_{14}H_{11}O_3Cl$ requires C, 64·2; H, 4·2; Cl, 13·1%). Acidification of the alkaline filtrates from the crystallisation of the sodium salt gave material which was probably a mixture of mono- and di-carboxylic acids. The S-*benzyl*iso*thiuronium* salt of the carboxylic acid crystallised from aqueous alcohol as colourless rosettes, m. p. 184° (Found : C, 62·6; H, 5·1. $C_{22}H_{21}O_3N_2ClS$ requires C, 62·2; H, 4·9%).

Fraction (C). The crude material had m. p. 150°. It crystallised as a colourless solid, m. p. 154°, from *cyclo*hexane (Found : C, 78·7; H, 6·4. Calc. for $C_{14}H_{14}O_2$: C, 78·5; H, 6·6%). Light absorption :

Max. at 2930 A.; ε = 8200 (alcohol). Westerfield and Lowe (*J. Biol. Chem.*, 1942, **145**, 464) give m. p. 154° for the diphenyl derivative (II), and cite a maximum at 2950 A. (ε = 6000). The acetyl derivative had m. p. 88° (Westerfield and Lowe, *loc. cit.*, give m. p. 88°). The *dibenzoate* crystallised from *cyclo*hexane or methyl alcohol in long colourless needles, m. p. 133° (Found: C, 79·2; H, 5·3. $C_{28}H_{22}O_4$ requires C, 79·6; H, 5·3%).

Fraction (D). The crude material had m. p. 194° and crystallised from methyl alcohol–benzene as colourless plates, m. p. 197°. It was soluble in dilute sodium hydroxide and gave a pale green colour with ferric chloride solution (Found: C, 78·5; H, 6·4%; *M*, 306. Calc. for $C_{21}H_{20}O_3$: C, 78·7; H, 6·8%; *M*, 320). Light absorption: Max. at 2930 A.; ε = 13,000 (alcohol). Westerfield and Lowe (*loc. cit.*) give m. p. 198° for the terphenyl derivative (III) and a maximum at 2950 A. (ε = 12,400).

Reaction of Chlorine with p-*Cresol in the Presence of Zinc Chloride.*—Dry chlorine was slowly passed into a mixture of *p*-cresol (21 g.) and finely powdered anhydrous zinc chloride (2 g.) at 30—20° until it had increased by 4 g. The reaction mixture was stirred overnight at room temperature and worked up in the usual manner. After removal of the more volatile fraction the residue was distilled at 2×10^{-4} mm., giving the following fractions: air-bath temp. 110—120°, ditolyl ether (I) (1·2 g.); 160—170°, diphenyl derivative (II), m. p. 153° (2·5 g.); and 200—220°, terphenyl derivative (III), m. p. 197° (1·6 g.).

2-*Chloro*-4 : 4′-*dimethyldiphenyl Ether* (IV).—(*a*) Di-*p*-tolyl ether in carbon tetrachloride was chlorinated with sulphuryl chloride at room temperature, giving 2-chloro-4 : 4′-dimethyldiphenyl ether, b. p. 311—314° (42%) (Found: C, 73·0; H, 5·6. Calc. for $C_{14}H_{13}OCl$: C, 72·2; H, 5·6%).

(*b*) 2-Nitro-4 : 4′-dimethyldiphenyl ether was obtained in 42% yield from 4-bromo-3-nitrotoluene and potassium hydroxide in an excess of *p*-cresol at 150—175°, in the presence of a small amount of water (cf. Reilly, Drumm, and Barrett, *J.*, 1927, 67) and was reduced to 2-amino-4 : 4′-dimethyldiphenyl ether with iron and hydrochloric acid (yield, 92%) (cf. Reilly and Barrett, *J.*, 1927, 1399). Diazotisation of the amine followed by a Sandmeyer reaction gave 2-chloro-4 : 4′-dimethyldiphenyl ether, b. p. 130—133°/0·5 mm. (30%) (Found: C, 72·5; H, 5·9; Cl, 14·3. Calc. for $C_{14}H_{13}OCl$: C, 72·2; H, 5·6; Cl, 15·2%).

(*c*) Potassium hydroxide (5·6 g.) was dissolved in 3-chloro-*p*-cresol (29 g.) on the steam-bath. Copper bronze (5 g.) and *p*-bromotoluene (17·1 g.) were added and the stirred mixture heated on a wax-bath to 160°; at this temperature a slight reaction commenced, so the bath was removed until the internal temperature began to fall, the flask being then re-immersed and the temperature raised to 175°. The mixture was stirred at this temperature for 30 minutes and after cooling was shaken with water and ether. The ethereal layer was washed with dilute sodium hydroxide solution, then with water, and dried (Na_2SO_4). The ethereal solution was distilled to give unchanged bromotoluene and later a fraction, b. p. 140—143°/0·8 mm., consisting of an oil containing a little solid. The methanol-soluble material, on distillation at 1 mm. pressure, gave 2-chloro-4 : 4′-dimethyldiphenyl ether, b. p. 143—145° (3·9 g., 17%) (Found: C, 72·3; H, 5·8%).

Oxidation. To the ether (5 g.) and water (30 c.c.) was added pyridine until the mixture became homogeneous. Potassium permanganate (14·2 g.) was added and the solution heated on the steam-bath for 1 hour by which time the pink colour had disappeared. The mixture was filtered hot and the colourless filtrates were acidified with concentrated hydrochloric acid, a white solid being precipitated. This was filtered off and dissolved in hot 8% sodium hydroxide solution (40 c.c.) from which the sodium salt of the carboxylic acid crystallised out on cooling. After filtration, the crystals were dissolved in hot water and the solution was acidified with concentrated hydrochloric acid, giving a white precipitate, which was filtered off and dried (yield, 2·8 g.). p-*Carboxyphenyl* 3-*chloro*-p-*tolyl ether* (V) crystallised from dilute acetic acid but did not melt below 300° (Found: C, 64·2; H, 4·1. $C_{14}H_{11}O_3Cl$ requires C, 64·2; H, 4·2%). The S-*benzyl*iso*thiuronium* salt crystallised from aqueous methyl alcohol as small needles, m. p. 169° (Found: C, 62·1; H, 4·8. $C_{22}H_{21}O_3N_2ClS$ requires C, 62·2; H, 4·9%).

3-*Chloro*-4 : 4′-*dimethyldiphenyl Ether* (I).—Potassium hydroxide (5·6 g.) was dissolved in 2-chloro-*p*-cresol (29 g.) on the steam-bath. Copper bronze (5 g.) and *p*-bromotoluene (17·1 g.) were added and the stirred mixture was treated as in preparation (*c*) of the ether (IV). The resulting ethereal solution was distilled, giving 3-*chloro*-4 : 4′-*dimethyldiphenyl ether*, b. p. 148—151°/1 mm., m. p. 16—17° (9·8 g., 42%) (Found: C, 72·0; H, 6·1; Cl, 15·5%).

Oxidation. The foregoing ether (3 g.) was oxidised with potassium permanganate in aqueous pyridine as was the isomer (IV), and the resulting carboxylic acid was dissolved in hot 8% sodium hydroxide solution (20 c.c.). The sodium salt crystallised on cooling of the mixture and was filtered off and dried (yield, 1·8 g.). The *S*-benzyl*iso*thiuronium salt crystallised from aqueous alcohol as colourless needles, m. p. 184°, not depressed on admixture with the salt of the oxidised material obtained by the action of sulphuryl chloride on *p*-cresol.

Reaction of Sulphuryl Chloride with m-4-*Xylenol in the Presence of Zinc Chloride.*—Sulphuryl chloride (13·5 g.) was added to a stirred mixture of *m*-4-xylenol (24·5 g.) and powdered zinc chloride (2 g.) at 30°. After the mixture had been stirred overnight it was worked up as in the reaction with *p*-cresol. After removal of the lower-boiling phenolic fractions distillation of the residue gave: (*a*) 5-*chloro*-2 : 4 : 2′ : 4′-*tetramethyldiphenyl ether* (X) (1·2 g., 4·7%), a neutral oil, b. p. 110—125° (air-bath temp.)/2×10^{-4} mm. (Found: C, 73·4; H, 6·1; Cl, 13·8. $C_{16}H_{17}OCl$ requires C, 73·7; H, 6·5; Cl, 13·6%); (*b*) the diphenyl derivative (XI) (3·9 g., 16·1%), b. p. 160—175° (air-bath temp.)/2×10^{-4} mm., a colourless oil which solidified on cooling. (XI) crystallised from ligroin in white needles, m. p. 136° (Bamberger and Brun, *Ber.*, 1907, **40**, 1952, give m. p. 137°) (Found: C, 79·0; H, 7·4. Calc. for $C_{16}H_{18}O_2$: C, 78·8; H, 7·2%).

Reaction of Sulphuryl Chloride with 3-*Chloro*-p-*cresol in the Presence of Zinc Chloride.*—The chlorocresol (43 g.) was mixed with powdered anhydrous zinc chloride (2 g.), and sulphuryl chloride (20·5 g.) added to the stirred mixture at 30°. After being stirred overnight the mixture was shaken with water and light petroleum (b. p. 60—80°), and the organic layer extracted with 8% sodium hydroxide solution (200 c.c.) and then dried (Na_2SO_4). After removal of the solvent a yellow oil (0·2 g.), which solidified on cooling and had the characteristic odour of a diphenyl ether, remained.

The sodium hydroxide solution was acidified with concentrated hydrochloric acid and the oily mixture extracted with ether. The ethereal extract was dried (Na_2SO_4) and distilled to give unchanged chlorocresol, b. p. 96—99°/14 mm. (29 g., 67·5%), followed by 3 : 5-dichloro-*p*-cresol, b. p. 120—125°/14 mm. (7·3 g., 13·7%), and **3** : 3′-***dichloro***-2 : 2′-***dihydroxy***-5 : 5′-***dimethyldiphenyl*** (VIII), b. p. 165—180° (air-bath temp.)/2 × 10^{-4} mm., as an oil which solidified on cooling and crystallised from *cyclo*hexane in white rosettes, m. p. 136° (4·0 g., 9·6%) (Found : C, 59·4 ; H, 4·2 ; Cl, 25·8. $C_{14}H_{12}O_2Cl_2$ requires C, 59·4 ; H, 4·2 ; Cl, 25·1%). The *dibenzoate* of (VIII), crystallised from methyl alcohol, had m. p. 140° (Found : C, 68·0 ; H, 4·1. $C_{28}H_{20}O_4Cl_2$ requires C, 68·4 ; H, 4·0%).

The authors are indebted to Dr. E. A. Braude for light-absorption data.

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[*Received, March* 17*th*, 1950.]