Ph.D. Chemistry

Michihiro Fujii

# THE REACTION OF PHENOLS AND PHENYL ETHERS WITH CHLORINE MONOXIDE

## ABSTRACT

Phenol, p-cresol, o-cresol and anisole were each reacted with chlorine monoxide in carbon tetrachloride. From the main reaction, good yields of chlorinated products were obtained. The minor reaction of all phenols was chlorohydroxylation, and, in addition, phenyl-phenyl coupling in the case of p-cresol. The minor reaction of anisole was demethylation, and the demethylated products in turn gave the same type of reaction products as from phenols.

Electron spin resonance spectroscopy, and evidence obtained by using diphenylpicrylhydrazyl as an indicator, as well as the nature of the products have suggested that the reaction proceeds by a free-radical mechanism, and such mechanisms were accordingly proposed and discussed.

Among the reaction products isolated, 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone, 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone, 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol and 2-chloro-4-methylresorcinol were new compounds.

Ph.D. M.Fujii

"Reactions of Chlorine Monoxide with Phenols & Their Ethers"

# THE REACTION OF PHENOLS AND PHENYL ETHERS WITH CHLORINE MONOXIDE

by

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# GENERAL INTRODUCTION

## GENERAL INTRODUCTION

Although chlorine monoxide, the anhydride of hypochlorous acid, has been known since the nineteenth century1), it has seen very little use as a reagent in organic chemistry.

In the field of aromatic chemistry there seem to have been only two publications: one was by Scholl and Nörr13) in 1900, who reported that when benzene was treated with an excess of chlorine monoxide, the main products were benzene hexachloride and an oxygen-containing substance, with 2,4,6-trichlorophenol among the minor products; the other publication was by Chao and Cipriani17), who mentioned the chlorination of N,N'-dimethylaniline with chlorine monoxide without giving any detailed description of the reaction.

In the domain of saturated hydrocarbons, the observation of Goldschmidt and Schüssler, in 192514), that such compounds, on reaction with chlorine monoxide yielded only chlorine-substituted derivatives, lay dormant for more than 35 years until it was subjected to more intensive investigation18,19,20). Tanner and Nychka20) have since concluded that chlorine monoxide is a good chlorinating reagent for saturated hydrocarbons and have summarized the overall stoichiometry of the reaction as in equation (1)

$$Cl_2O + 2RH \longrightarrow H_2O + 2HCl \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

In contrast with chlorination by chlorine, the by-product in this reaction is water and not hydrochloric acid.

Shaw19) has proposed that this chlorination is a free radical chain reaction in which chlorine oxide is a chain carrier; he could detect no products from a reaction such as in equation (2).

$$R\cdot + ClO\cdot \longrightarrow ROCl \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

However, the fact that oxygen-containing substances are formed both from benzene[13)], and from unsaturated hydrocarbons[14)] suggests that with such compounds, chloroxylation may occur as a side reaction. This point was verified in the present work which was undertaken to explore the reaction of chlorine monoxide with phenols and phenyl ethers - compounds which would be expected to be much more reactive than benzene. Phenol, cresol and anisole were studied as representative examples.

The products of the reactions were identified as completely as possible in order to seek clues to the mechanism of the reactions.

# HISTORICAL INTRODUCTION

# CHLORINE MONOXIDE

Chlorine monoxide, $Cl_2O$, was first prepared by Gay-Lussac1) by the reaction of chlorine with dry yellow mercury (II) oxide, protected on the surface by a layer of sand. Later, Goldschmidt2) isolated chlorine monoxide from a distillate of hypochlorous acid, and presented evidence that it was a true anhydride of the acid. He also found that when an aqueous solution of the acid was shaken with carbon tetrachloride, the latter became brown-yellow in color and contained dissolved chlorine monoxide, and that chlorine monoxide was about eight times as soluble in carbon tetrachloride as in water. A standard laboratory method for preparing pure chlorine monoxide has been proposed by Cady3): a mixture of chlorine and an inert gas is passed through a column packed with a mixture of dry mercury (II) oxide and crushed glass chips, and the converted gas mixture is condensed in a trap cooled with dry ice in acetone. The condensate is chlorine monoxide, containing some chlorine and a trace of the inert gas. A solution of chlorine monoxide in carbon tetrachloride is easier to obtain and safer to handle than the gaseous compound. One procedure is to treat a solution of chlorine in carbon tetrachloride with dry yellow mercury (II) oxide according to equation (3).

$$2Cl_2 + (n+1)\,HgO \longrightarrow Cl_2O + HgCl_2 \cdot nHgO \quad \ldots\ldots\ldots \quad (3)$$

Mercury (II) oxide can be recovered and recycled by treating the basic mercury (II) chloride with sodium hydroxide.

Another procedure takes advantage of the reversible hydrolysis of chlorine: $Cl_2 + H_2O \rightleftharpoons HOCl + HCl$. In order to maintain the forward reaction, the hydrochloric acid must be removed by adding an alkali such as $Na_2CO_3$ or $NaHCO_3$. When chlorine is passed into a solution of sodium hypochlorite, the $OCl^-$ ions are converted to HOCl: $OCl^- + HCl \longrightarrow HOCl + Cl^-$. When the solubility of hypochlorous acid is exceeded, decomposition occurs, and continued passage of chlorine into the solution gives chlorine monoxide (equations (4) and (5)).

$$2Cl_2 + 2Na_2CO_3 + H_2O \longrightarrow Cl_2O + 2NaHCO_3 + 2NaCl \quad \ldots\ldots\ldots\ldots \quad (4)$$

$$2Cl_2 + 2NaHCO_3 \longrightarrow Cl_2O + 2CO_2 + H_2O + 2NaCl \quad \ldots\ldots\ldots\ldots \quad (5)$$

Alternatively, when an aqueous solution of sodium carbonate is shaken with chlorine in carbon tetrachloride, the latter is transformed into a solution of chlorine monoxide. This procedure resembles a proposed industrial method for producing chlorine monoxide[4)]. On a large scale, this method would be more economical than the one described earlier, and would avoid the use of toxic mercury compounds. As a laboratory procedure, it has the disadvantages of being difficult to control and of converting only about half of the chlorine dissolved in the carbon tetrachloride into the desired product. In the mercury (II) oxide process, the mercury oxide is recycled, and the net effect is that only sodium hydroxide and chlorine are consumed. In that sense the two processes are similar.

Chlorine monoxide has a reddish yellow color and an odour like that of nitric acid. It boils at 2°[5)] and freezes at -120.6°[6)]. The undiluted gas is very unstable and can be caused to explode by a spark[7)], by heating[7,8)], or by contact with organic materials[9)]. It can be stored for a long time as a liquid at -78°, but it decomposes at a moderate rate at room temperature[3)]. Chlorine monoxide solution in carbon tetrachloride is stable if kept cold and in the dark. Decomposition of chlorine monoxide by heat 8) or light 9) ultimately always liberates chlorine and oxygen. However, photochemical decomposition in carbon tetrachloride solution differs from that in the gaseous phase. The decomposition is generally slower, and is accompanied by the formation of a considerable amount of chlorine dioxide 11).

Wallace and Goodeve 12) devised a procedure for the quantitative analysis of chlorine monoxide. When an amount of chlorine monoxide is mixed with a concentrated solution of potassium iodide containing a known quantity of hydrochloric acid, iodine is liberated (equation (6)),

$$Cl_2O + 4KI + 2HCl \longrightarrow 4KCl + H_2O + 2I_2 \ldots\ldots\ldots\ldots (6)$$

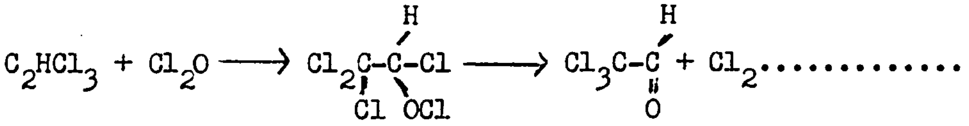
and can be titrated with standard sodium hydroxide; the ratio of the two titrations gives a measure of the purity of the chlorine monoxide. Chlorine also liberates iodine from the potassium iodide but does not consume hydrochloric acid so that the excess of iodine calculated from the equation (6) indicates the chlorine content of the sample.

## REACTION OF ORGANIC COMPOUNDS WITH CHLORINE MONOXIDE

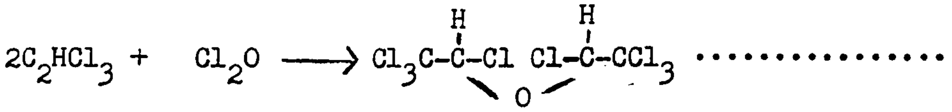
In 1900, Scholl and Nőrr 13) reported having treated benzene with an excess of chlorine monoxide, and having obtained α- and β-benzene hexachloride and an amorphous, poorly characterized compound, $C_6H_6Cl_4O$, as the major products, with 2,4,6-trichlorophenol among the minor products. Goldschmidt and Schüssler 14) later pointed out some ambiguities in Scholl and Nőrr's work, particularly with respect to the source of chlorine monoxide, and the reaction conditions. Nevertheless, the formation of benzene hexachloride suggests that the reaction proceeds by a homolytic addition analogous to the well-known process for producing benzene hexachloride from benzene and chlorine[15,16].

In 1925, Goldschmidt and Schussler[14] found that after long hours of standing chlorine monoxide reacted suddenly with saturated organic compounds and that the reaction products were all chlorine-substituted, viz., monochloroacetone from acetone, chloroacetoacetic ester from acetoacetic ester and a mixture of various chloro-derivatives from cyclohexane. These products are the same as those given by chlorine, and no products were isolated containing newly introduced oxygen.

From the unsaturated organic compounds they obtained more complicated products: trichloroethylene reacted to give pentachloroethane, chloral and an oatachloroethyl ether $(CCl_3CHCl)_2O$ or $(CHCl_2 \cdot CCl_2)_2O$); cyclohexene and indene yielded some oxygen - and chlorine-containing products, but they were not well characterized. They proposed that the first step of the reaction was the addition of chlorine monoxide to the double bond, and the next step was the splitting off of chlorine to form chloral (eq. 7) or further addition of the adduct to another trichloroethylene (eq. 8) to form ethers.



$$C_2HCl_3 + Cl_2O \longrightarrow Cl_2\underset{Cl}{C}-\overset{H}{\underset{OCl}{C}}-Cl \longrightarrow Cl_3C-\overset{H}{\underset{\overset{\|}{O}}{C}} + Cl_2 \ldots\ldots\ldots\ldots \quad (7)$$



$$2C_2HCl_3 + Cl_2O \longrightarrow Cl_3C-\overset{H}{C}-Cl \quad Cl-\overset{H}{C}-CCl_3 \;(\text{bridged by } O) \ldots\ldots\ldots\ldots \quad (8)$$

They also suggested that the formation of oxygen-containing products from unsaturated cyclic compounds might proceed in the same manner.

This explanation may be applied to the formation of oxygen-containing products from benzene, since, on the route to hexachlorobenzene, tetrachlorocyclohexene may be formed, and may then react like cyclohexene.

Tanner and Nychka[20)] have studied the reaction of chlorine monoxide with substituted alkanes (1-chlorobutane, 1-chloropropane and n-butyronitrile) in carbon tetrachloride solution, and compared the ratio of the distribution of isomers in the reaction products with that of the products from treatment with molecular chlorine. They concluded that the former reaction has a free-radical mechanism propagated by a mixed chain involving OCl and chlorine radicals as the chain-carrying species (equations 9 to 15).

$ClOCl \longrightarrow Cl\cdot + ClO\cdot$ .................................. (9)

$RH + ClO\cdot \longrightarrow R\cdot + HOCl$ ............................ (10)

$R\cdot + Cl_2O \longrightarrow RCl + ClO\cdot$ ......................... (11)

$HOCl \longrightarrow HO\cdot + Cl\cdot$ .................................. (12)

$RH + Cl\cdot \longrightarrow R\cdot + HCl$ .............................. (13)

$HCl + HOCl \longrightarrow HOH + Cl_2$ ......................... (14)

$R\cdot + Cl_2 \longrightarrow RCl + Cl\cdot$ .......................... (15)

Their reactions were mainly initiated by photolysis, but they found that the reaction also occurs in the dark. From the distribution of isomers in the products, they calculated the selectivity of chlorine monoxide in abstracting hydrogen from variously substituted carbons, and obtained the value of 1:11:24 for primary:secondary:tertiary substitution. Although this value is not as great as that of the more selective reagent, t-butylhypochlorite (1:8:44), it is greater than that of chlorine (1:3.9:5.1).

At the time of the Tanner and Nychka work, Phillips and Shaw 18) had already reported on the reaction of propane with chlorine monoxide in the gas-phase at 100°, from which hypochlorous acid and chlorine-substituted propane were the reaction products. They proposed a chain reaction in which $ClO\cdot$ radical is the chain carrier (equations 16 to 21).

$$Cl\cdot + CH_3\text{-}CH_2\text{-}CH_3 \longrightarrow HCl + CH_3\text{-}\dot{C}H\text{-}CH_3 \quad \ldots\ldots\ldots\ldots\ldots (16)$$

$$Cl\cdot + CH_3\text{-}CH_2\text{-}CH_3 \longrightarrow HCl + CH_3\text{-}CH_2\text{-}CH_2\cdot \quad \ldots\ldots\ldots\ldots (17)$$

$$ClO\cdot + CH_3\text{-}CH_2\text{-}CH_3 \longrightarrow HOCl + CH_3\text{-}\dot{C}H\text{-}CH_3 \quad \ldots\ldots\ldots\ldots (18)$$

$$ClO\cdot + CH_3\text{-}CH_2\text{-}CH_3 \longrightarrow HOCl + CH_3\text{-}CH_2\text{-}CH_2\cdot \quad \ldots\ldots\ldots\ldots (19)$$

$$CH_3\text{-}\dot{C}H\text{-}CH_3 + ClOCl \longrightarrow CH_3\text{-}CHCl\text{-}CH_3 + ClO\cdot \quad \ldots\ldots\ldots\ldots (20)$$

$$CH_3\text{-}CH\text{-}CH_2\cdot + ClOCl \longrightarrow CH_3\text{-}CH_2\text{-}CH_2Cl + ClO\cdot \quad \ldots\ldots\ldots\ldots (21)$$

Steps (16) and (18), and (17) and (19), constitute non-branching chain reactions carried by the ClO radical.

Later, in 1968, Shaw 19) supplemented this work by a study of the kinetics of the reaction. The measured activation energy was 11 $Kcal.mol^{-1}$, using rate constants for a constant initial pressure of $Cl_2O$ and $C_3H_8$. Since the Cl-O-Cl bond strength is 36 $Kcal.mol^{-1}$, the homogeneous unimolecular decomposition is not the initiation step. Shaw suggested that 0.1% of propene in the propane sample as an impurity might be enough to cause a bimolecular initiation, which is only about 13 $Kcal.mol^{-1}$ endothermic (equation (22)).

$$C_3H_6 + Cl_2O \longrightarrow C_3H_6Cl\cdot + ClO\cdot \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (22)$$

At 78°, for 20 torr. $Cl_2O$ and 200 torr. $C_3H_8$, the observed rate of the overall reaction was $10^{-6.9}$ mol. $1^{-1}$. $sec^{-1}$. The calculated rate of initiation for 0.2 torr. $C_3H_6$ under the same conditions is $10^{-10.8}$ mol. $1^{-1}$. $sec^{-1}$. which gives a chain length of about $10^4$. Consistent with the long chain length, no products from termination reactions (23-25) could be detected.

$$2R\cdot \longrightarrow R_2 \qquad (23)$$

$$R\cdot + ClO\cdot \longrightarrow ROCl \qquad (24)$$

$$2ClO\cdot \longrightarrow Cl_2 + O_2 \qquad (25)$$

Chao and Cipriani17), in 1960, reported that one mole of dimethyl aniline can be chlorinated by one mole of chlorine monoxide in a carbon tetrachloride solution to yield 0.189 moles of 2-chloro-N,N'-dimethylaniline, 0.032 moles of 4-chloro-N,N'-dimethylaniline and 0.012 moles of 2,4-dichloro-N,N'-dimethylaniline, but gave no further details.

Although chlorine monoxide has been known since the nineteenth century, the papers reviewed above constitute all of the literature available on its reaction with organic compounds. They describe the principal reaction as chlorination by a free-radical mechanism. Additional products are obtained from unsaturated compounds and unsubstituted benzene, and substitution products from saturated compounds and substituted benzene. Oxygen-containing by-products have been detected only in reactions of unsaturated compounds.

For the present work, phenols and a phenyl ether were chosen as substrates representative of a group of compounds more reactive than benzene and the alkanes. The purpose was to search for clear evidence of a free-radical reaction and to attempt to isolate oxygen-containing as well as chlorine-containing products.

## CHLORINATION OF PHENOLS AND THEIR ETHERS

Since the reaction of chlorine monoxide with organic compounds generally yields products arising from the substitution or addition of chlorine, the chlorination of phenols and phenyl ethers by other reagents is pertinent to the present research.

### 1. Chlorination by hypochlorous acid

Soper and Smith[21)] have studied the chlorination of phenols by hypochlorous acid in aqueous solutions. When the hydroxyl ion concentration was about $10^{-7}$, the speed of chlorination increased in direct proportion to the hydroxyl ion concentration. In the range of hydroxyl ion concentrations of about $10^{-2}$ the speed was inversely proportional to the hydroxyl ion concentration. It was therefore concluded that reaction occurred either between the hypochlorite ion and unionized phenol, or between unionized hypochlorous acid and the phenoxide ion.

$$v = k_2 [OCl^-] [PhOH] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (26)$$

$$v = k_2' [HOCl][PhO^-] \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (27)$$

Detailed analysis of the kinetics of the reactions supported the second of these alternatives. When a little hydrochloric acid was added to a solution of phenol or anisole and hypochlorous acid a rapid reaction ensued, with a rate independent of the concentration of phenol; the chlorine generated reacted instantaneously with the phenol or phenyl ether.

$$HOCl + HCl \rightleftharpoons Cl_2 + H_2O \text{ ........................ } (28)$$

Hypochlorous acid alone was without action on anisole, a phenyl ether. The chlorine molecule is therefore a more powerful chlorinating agent than the hypochlorous acid molecule.

Harvey and Norman[22)] treated phenol and anisole, respectively, with hypochlorous acid and chloronium ion in order to study the ortho:para ratio of monochlorinated products. The chloronium ion was liberated by treating hypochlorous acid with silver perchlorate and perchloric acid.

$$HOCl + HClO_4 \longrightarrow Cl^+ + ClO_4^- + H_2O \text{ ................ } (29)$$

Chloronium ion treatment of phenol resulted in monochlorinated products in an ortho:para ratio of 1:1; similar treatment of anisole gave a ratio of 1:2. When phenol was treated with hypochlorous acid in 5N NaOH, the ortho:para ratio of the mono-substituted products was 4:1. Harvey and Norman postulated that chloronium ion is so reactive that it has the same chance of attacking either ortho or para positions, but that hypochlorous acid in strong alkali forms hydrogen bonds with phenoxide ion so that the chlorine atom reacts preferentially at the ortho-position.

However, recent results have put this interpretation into question, for from the treatment of guaiacol and creosol, respectively, with aqueous alkaline hypochlorite solution, Asada[23)] isolated carbon-carbon-linked dimers, thus offering rather good evidence of a free-radical reaction[26)].

## 2. Chlorination by t-butyl hypochlorite

In 1931, Clark[24)] reported that t-butyl hypochlorite reacted vigorously with phenol to give 92.3% yield of o-chlorophenol. Ginsburg[25)], in 1951, performed the reaction with several phenols and confirmed that t-butyl hypochlorite is a good ortho-orienting reagent. From the similarity of the reaction of phenols with t-butyl hypochlorite and their benzoyloxylation by benzoyl peroxide, which also usually attacks the position ortho to the hydroxyl group[27)], Ginsburg[25)] suggested that a chlorine atom might be the chlorinating species in this reaction; he did not exclude the possibility that chloronium ions might lead to the same results.

Anbar and Ginsburg[28)] have reported that the reaction of anisole with t-butyl hypochlorite gives rise to 87% yield of o-chloroanisole, but, Harvey and Norman[22)] have found that both of the possible mono-chlorinated products are formed in the same reaction with and without added acid, with the ortho:para ratios ranging from 1:4 to 1:2 as the solvent was varied from polar to non-polar. In Harvey and Norman's experiments, the mono-chlorination of phenol resulted in an ortho:para ratio of 1:1 which was independent of the polarities of the solvents; chlorination of phenoxide ion with t-butyl hypochlorite in 4N sodium hydroxide gave an ortho:para ratio of 4:1.

The reason for the difference in the results reported by Anbar and Ginsburg on the one hand, and Harvey and Norman on the other is not clear. Ginsburg[25)] had described the temperature of the reaction as rising to the boiling point of the solvent. It seems possible that the smaller amounts of reactants used in Harvey and Norman's experiments could have obviated the accumulation of the heat evolved.

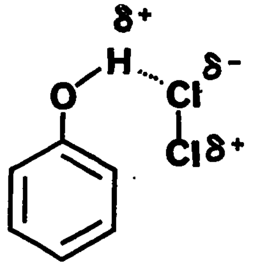
Harvey and Norman proposed that the ortho:para ratio of monochlorophenols of 1:1 in an acidic solvent was possibly due to a chloronium ion mechanism. However, they could not clearly explain the results obtained under non-acidic conditions.

### 3. Chlorination by molecular chlorine

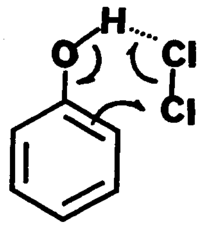
The chlorination of phenol by molecular chlorine without solvent was first reported by Holleman and Rinks29) in 1911. They measured the melting points of the products to determine the ratio of <u>ortho</u>- and <u>para</u>-chlorophenols, and concluded that the <u>ortho</u>:<u>para</u> ratio is always nearly 1:1, and is independent of the reaction temperatures, which they had varied from 40°C to 155°C.

In 1960, Bing, <u>et al</u>.30), reported that the <u>ortho</u>:<u>para</u>-ratio of monochlorophenols produced by the reaction of molten phenol and chlorine at 60° was 1:1.7. Besides monochlorophenols they obtained less than 3% of 2,4- and 2,6-dichlorophenol. Harvey and Norman22), in 1961, had also reported the value of 1:1.5 under the same conditions.

But from the reaction of molecular chlorine with phenol in carbon tetrachloride, Harvey and Norman22) obtained the <u>ortho</u>:<u>para</u> ratio of 2.8:1. They suggested the following explanation: in carbon tetrachloride solution the phenolic hydrogen forms a hydrogen bond with the chlorine molecule, which undergoes polarization, its positively polarized end being suitably placed for reaction at the <u>ortho</u>-position (see (I)), and reaction then takes place by the electron shifts depicted in (II); in molten phenol, the phenolic hydrogen forms a hydrogen bond with the oxygen atom of an adjacent molecule and is not able to assist chlorination at the <u>ortho</u>-position.



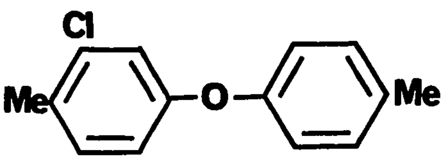
(I)



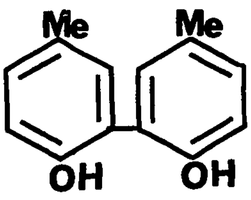
(II)

Campbell and Schields[31], in 1965, studied the effect of solvent on the mechanism of the chlorination of *o*-cresol. They obtained the lowest *ortho*:*para* ratios (1:6.3) in nitromethane, in liquid $SO_2$ (1:6.3) and the highest value (1:0.9)in chloroform and carbon tetrachloride. They concluded that the reason for the varying isomer ratios might be the hydrogen bonding of the -OH of the cresol with solvent. The bound solvent molecules will have a shielding effect on the *ortho*-position but will leave the *para*-position open to attack and thus enhance the yield of the *para*-chloro isomer. They offered the same reasoning as Harvey and Norman for the results of chlorination in the absence of solvent: that the solvating group might be another molecule of *o*-cresol, thus favouring para-substitution. However, their explanation for the high *ortho*-ratio from reaction in carbon tetrachloride was different. They stated that when solvents such as carbon tetrachloride, which do not bond at all with *o*-cresol, are used at a high enough concentration to diminish considerably cresol-cresol bonding, chlorination gives almost equal amounts of *ortho*- and *para*-isomers. If this reasoning be applied to phenol, the ratio of *ortho*-chlorophenol and *para*-chlorophenol becomes 2:1, but the experimental result (2.8:1)[22] does not fit this hypothesis.

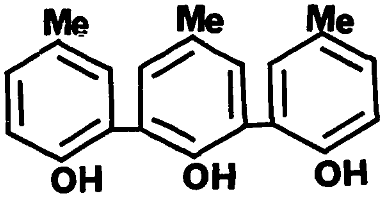
In 1950, Bowden and Reece[32] studied the reaction of *p*-cresol with chlorine, and obtained, besides chlorophenols, the ether (III) and the di- and triphenyl derivatives (IV) and (V).



(III)



(IV)



(V)

These carbon-carbon-coupling products (IV,V) constitute crucial evidence towards establishing a free-radical mechanism for the reaction.[26]

As mentioned earlier, anisole is not attacked by hypochlorous acid alone, but only when a small amount of hydrochloric acid is added. Thus, Soper and Smith[21] concluded that the chlorine molecule is more reactive than hypochlorous acid. Harvey and Norman[22], however, attributed the reactivity to the chloronium ion. They found that the reaction of anisole with chlorine in carbon tetrachloride was slower than with chloronium ion in water. The *ortho*:*para* ratio of the monochloroanisoles is 1:4 when formed by chlorine in carbon tetrachloride and 1:2 when formed by chloronium ion.

Johnes and Richardson[33] have described the chlorination of three ethyl ethers, two phenoxy-acids and four substituted benzyl ethers by chlorine in acetic acid. For these ethers, which fall into three groups, the ortho:para ratios were essentially the same within any one group, namely: 1:4 for alkyl ethers, 1:5 for phenoxy acids and 1:2.7 for benzyl ethers.

Dealkylation of aryl methyl ethers is another important reaction of chlorine in aqueous solution. Sarkanen and Dence34) regarded the reaction as an acid catalyzed cleavage, in which the usual role of the proton is assumed by the chlorine molecule in aqueous solution.

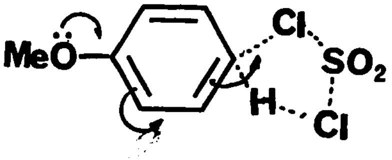
## 4. Chlorination by sulfuryl chloride

Sulfuryl chloride has long been known as a good halogen carrier and has been used in many reactions to introduce chlorine atoms into the phenyl nucleus of phenolic compounds. Since the reaction of phenol with sulfuryl chloride was first reported by Dubois in 186635), it has remained to the present time as a good method for the preparation of p-chlorophenol36).

Campbell and Schields31) studied the solvent effect on the chlorination of phenol and o-cresol with sulfuryl chloride, and concluded that the physical bulk of the chlorinating agent contributes to the larger amounts of p-chlorophenol and 4-chlorocresol.

Bowden and Reece32) obtained a C-C coupled dimer (IV) and a trimer (V) from the reaction products of p-cresol with sulfuryl chloride.

The mechanism of the reaction of sulfuryl chloride with phenols or phenyl ethers is not clear even though Kharasch, et.al.37,38,39) have established a free radical mechanism for the reaction with hydrocarbons and alkylbenzenes. The formation of the carbon-carbon-coupled dimer or trimer obtained by Bowden et al. from p-cresol implies that the reaction must have a free radical mechanism. However, Bolton, et al.$^{40,41)}$, concluded from their kinetic experiments that sulfuryl chloride is an electrophile in reactions with phenol ethers, and that the transition state incorporates one molecule of the aromatic ether and one of the reagent to form a cyclic intermediate, as shown for anisole in (VI).



(VI)

# RESULTS AND DISCUSSION

## IDENTIFICATION OF REACTION PRODUCTS

### 1. Reaction products from phenol and chlorine monoxide

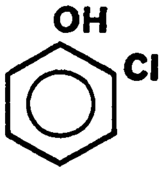
Phenol, treated with one-half molar equivalent of chlorine monoxide in carbon tetrachloride solution at 10°~15° in the dark, reacted so fast that immediately after mixing iodometric titration did not show any active chlorine in the solution. Rapid clouding indicated that water had been produced during the reaction, and, after it had stood undisturbed, the water, with a brown color, floated over the carbon tetrachloride layer.

Without prior separation of the product water, the reaction mixture was extracted with water. Four compounds were then isolated from the carbon tetrachloride solution: <u>o</u>-chlorophenol (I), <u>p</u>-chlorophenol (II), 2,6-dichlorophenol (III) and 2,4-dichlorophenol (IV).

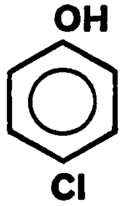
The aqueous extract was re-extracted with ether and proved to contain additional quantities of the same four mono- and di-chlorinated compounds plus 2-chlororesorcinol (V) and 4-chlororesorcinol (VI).

The yields of the mono- and di-chlorinated phenols were quantitatively determined by gas-liquid chromatography, and are shown in Figure 1.

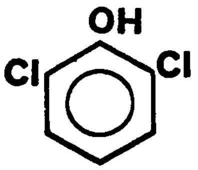
It is significant to note that the ratio of <u>ortho</u>- to <u>para</u>-chlorophenol was 2.9 to 1, closer to the ratio found (2.8:1) for chlorination of phenol by molecular chlorine in carbon tetrachloride (20), than the ratio found in any other known method of chlorination. (See Historical Introduction).



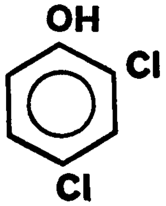
o-Chlorophenol (I).
64.5%



p-Chlorophenol (II).
21.9 %

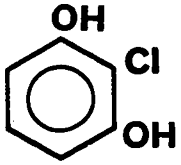


2,6-Dichlorophenol (III).

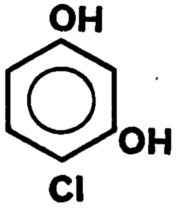


2,4-Dichlorophenol (IV).

( III + IV, 4.7 %)



2-Chlororesorcinol (V)
0.05 %



4-Chlororesorcinol (VI)
0.2 %

Fig. 1. Reaction products (with yields) from phenol and chlorine monoxide.
( Yields of I, II, III, and IV by g.l.c.; yields of V and VI by isolation.)

## 2. Reaction products from p-cresol and chlorine monoxide

When a half molar equivalent of chlorine monoxide in carbon tetrachloride was added to molten p-cresol, the reaction took place very vigorously with the evolution of heat. The solution turned a reddish brown and showed clouding immediately.

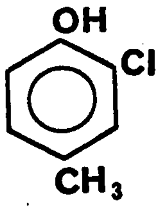
The reaction products were divided into three fractions. One was obtained by extracting the reaction mixture with water; the second by a subsequent extraction with 3% sodium hydroxide solution; the third was the material remaining in the carbon tetrachloride. Individual products, shown with their yields in Fig. 2, were isolated from these fractions.

The major volatile product isolated from the alkali-soluble portion was 2-chloro-p-cresol (VII). The yield was 46% as determined by gas-liquid chromatography, which also indicated that 20% of the p-cresol had not reacted. Only a small amount of 2,6-dichloro-p-cresol (VIII) was found.

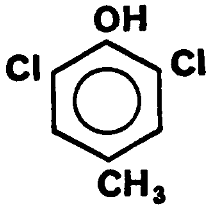
After these three volatile materials had been removed by vacuum distillation, column chromatography of the residue yielded three phenyl-phenyl coupled compounds. They were 5,5'-dimethylbiphenyl-2,2'-diol (IX), 3,3'-dichloro-5,5'-dimethyl-2,2'-diol (X), and 3-chloro-5,5'-dimethyl-2,2'-diol (XI).

The compounds IX and X are known, and the melting points of the compounds isolated here correspond well with those given in the literature[32,62]. Since these compounds were not synthesized independently, evidence from spectra was required to confirm their identities.

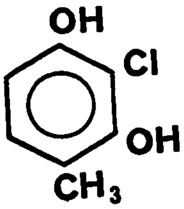
In the infrared spectrum of IX, a pair of bands at 810 $cm^{-1}$



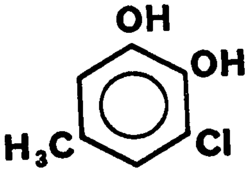
2-Chloro-p-cresol (VII).
46 %



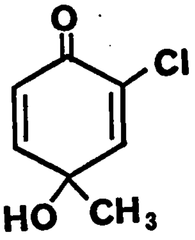
2,6-Dichloro-p-cresol(VIII).
trace



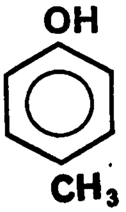
2-Chloro-4-methyl-resorcinol (XIII).
0.35 %.



3-Chloro-5-methylcatechol (XIV).
1 %.

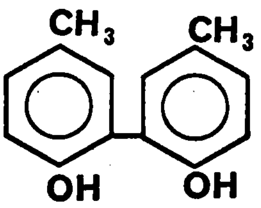


2-Chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone (XV).
0.27 %.

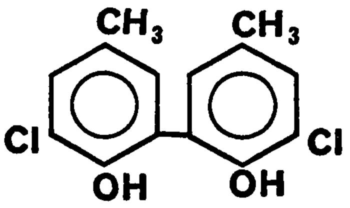


p-Cresol.
20 %.

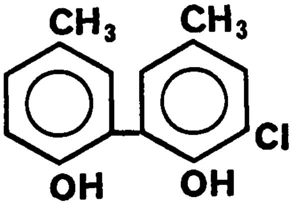
Fig. 2. Reaction products (with yields) from p-cresol and chlorine monoxide.



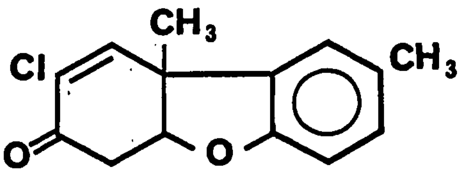
5,5'-Dimethylbiphenyl-2,2'-diol (IX).
0.25 %.



3,3'-Dichloro-5,5'-dimethylbiphenyl-2,2'-diol (X).
1.5 %.



3-Chloro-5,5'-dimethylbiphenyl-2,2'-diol (XI).
4 %.



2-Chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (XII). 1.5 %.

Fig. 2. (Cont'd.).

and 877 $cm^{-1}$ (out-of-plane bending of phenol[42)]) clearly indicates the 1,2,4-trisubstituted phenyl ring structure (Fig. 3), and in its p.m.r. spectrum, an ABC type multiplet at 7.0 p.p.m. corresponds to six phenyl protons, while a singlet at 2.35 p.p.m. corresponds to two methyl groups and a broad band at 5.80 p.p.m. indicates the presence of two hydroxyl groups (Fig. 4). The parent peak in the mass spectrum was at m/e 214, with no indication of the presence of chlorine. Elementary analysis gave an empirical formula of $C_{14}H_{14}O_2$. All evidence supports the structure 5,5'-dimethylbiphenyl-2,2'-diol for IX.

In its out-of-plane H-bending regions, the infrared spectrum of X has only a band at 842 $cm^{-1}$, which indicates a 1,2,3,5-tetrasubstituted phenyl structure[42)]. The p.m.r. spectrum ($CCl_4$) indicates the presence of two methyl groups (singlet, 2.4 p.p.m.), and two hydroxyl groups (singlet, 5.6 p.p.m.). Two doublets of an AB case with a coupling constant of 4 c/s (meta-coupling) at 6.93 p.p.m. and 7.13 p.p.m. correspond to four phenyl protons (Fig. 5). Elementary analysis gave an empirical formula of $C_{14}H_{12}O_2\ Cl_2$. The mass spectrum has a parent peak at m/e 282, a P + 2 peak with an intensity of 2/3 of the parent peak and two intense peaks at m/e 212 each representing successive losses of two chlorine atoms from the parent molecular ion. All the evidence supports the structure 3,3'-dichloro-5,5'-dimethylbiphenyl-2,2'-diol for X.

Compound XI appears to be new. Its infrared spectrum exhibits a pair of out-of-plane bending bands at 805 $cm^{-1}$ and 877 $cm^{-1}$ corresponding to 1,2,4-trisubstituted phenyl and the typical band at 848 $cm^{-1}$ of a 1,2,3,5-tetrasubstituted phenyl ring (Fig. 6). The p.m.r. spectrum

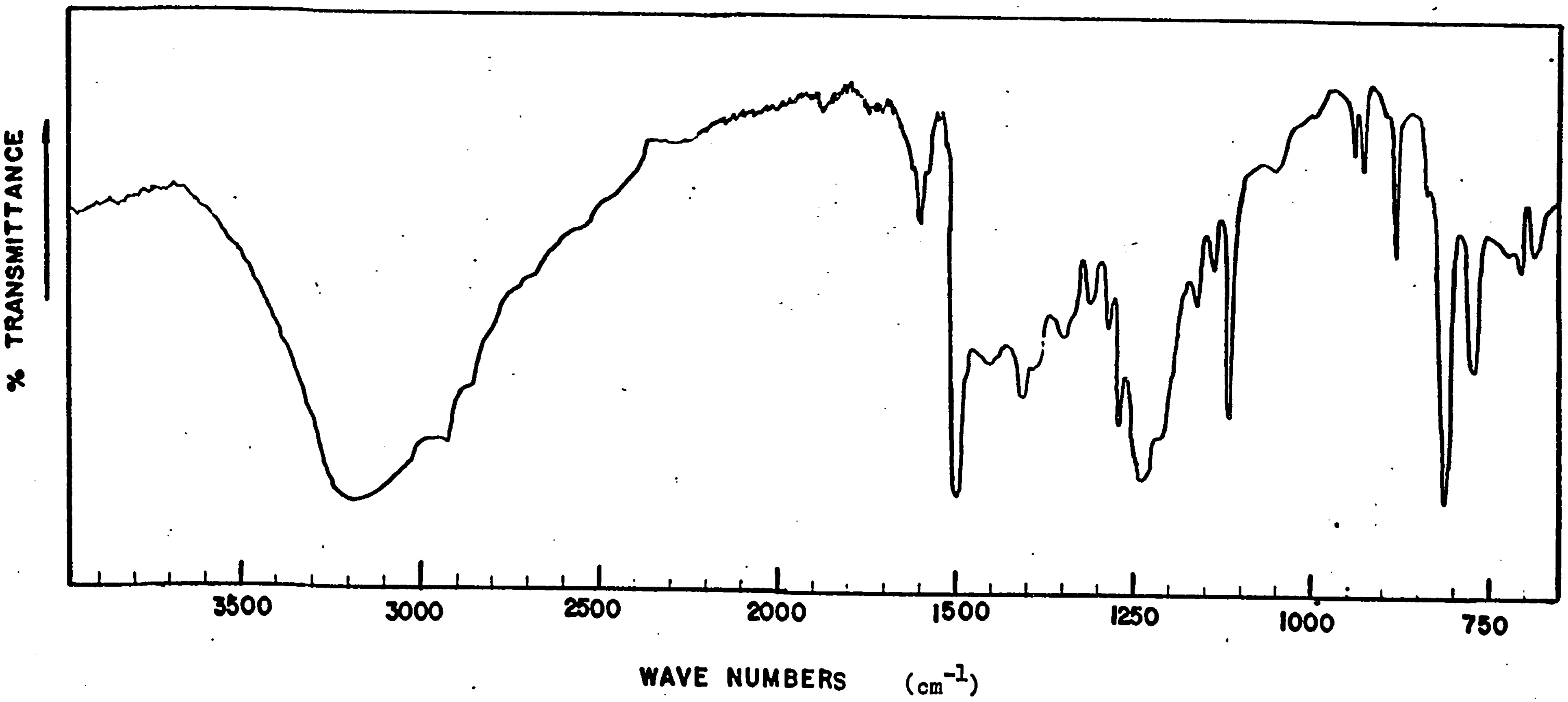


Fig. 3. Infrared spectrum of 5,5'-dimethylbiphenyl-2,2'-diol (KBr).

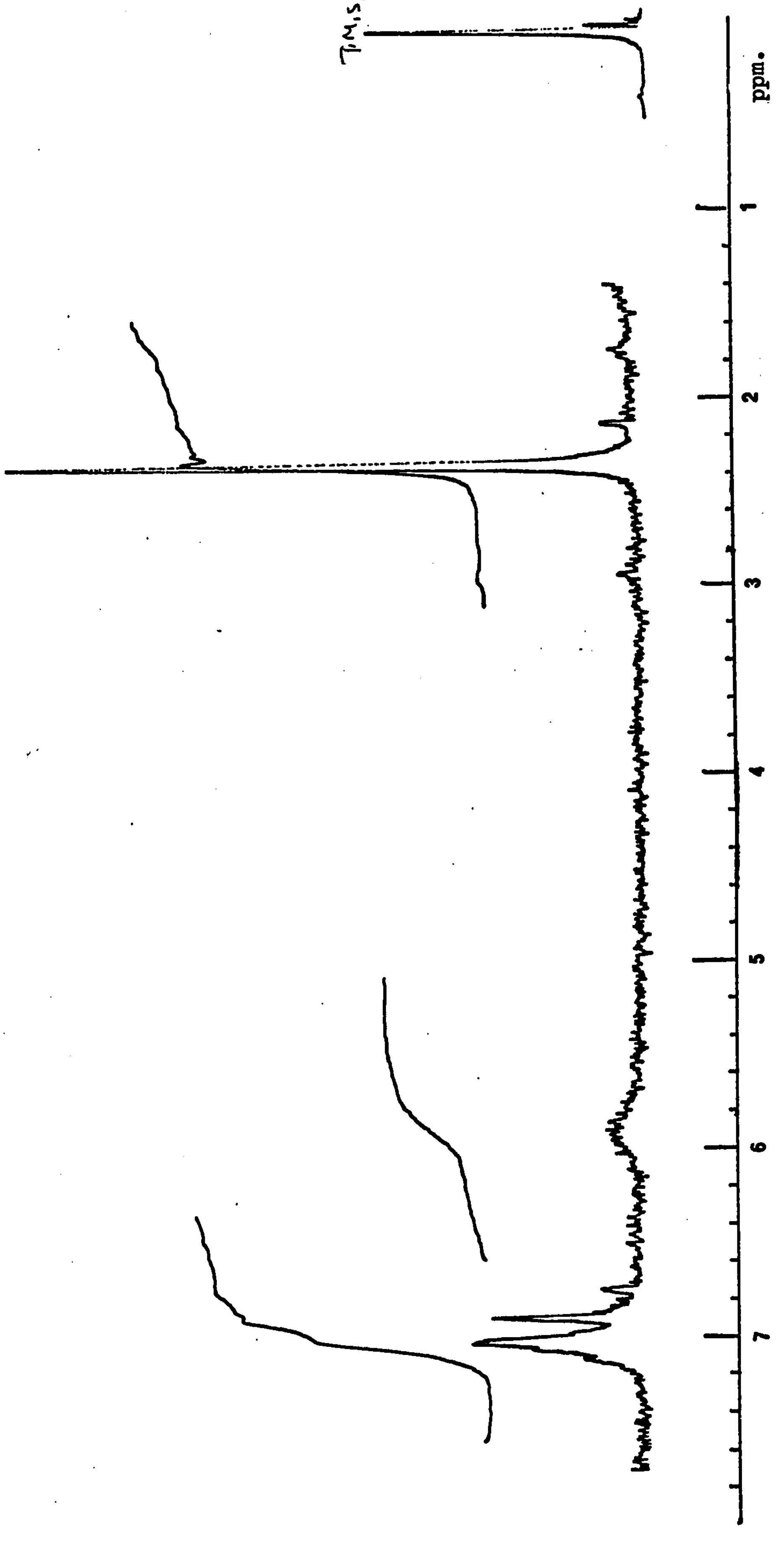


Fig. 4. P. m. r. spectrum of 5,5'-dimethylbiphenyl-2,2'-diol (60 M.Hz., $CCl_4$).

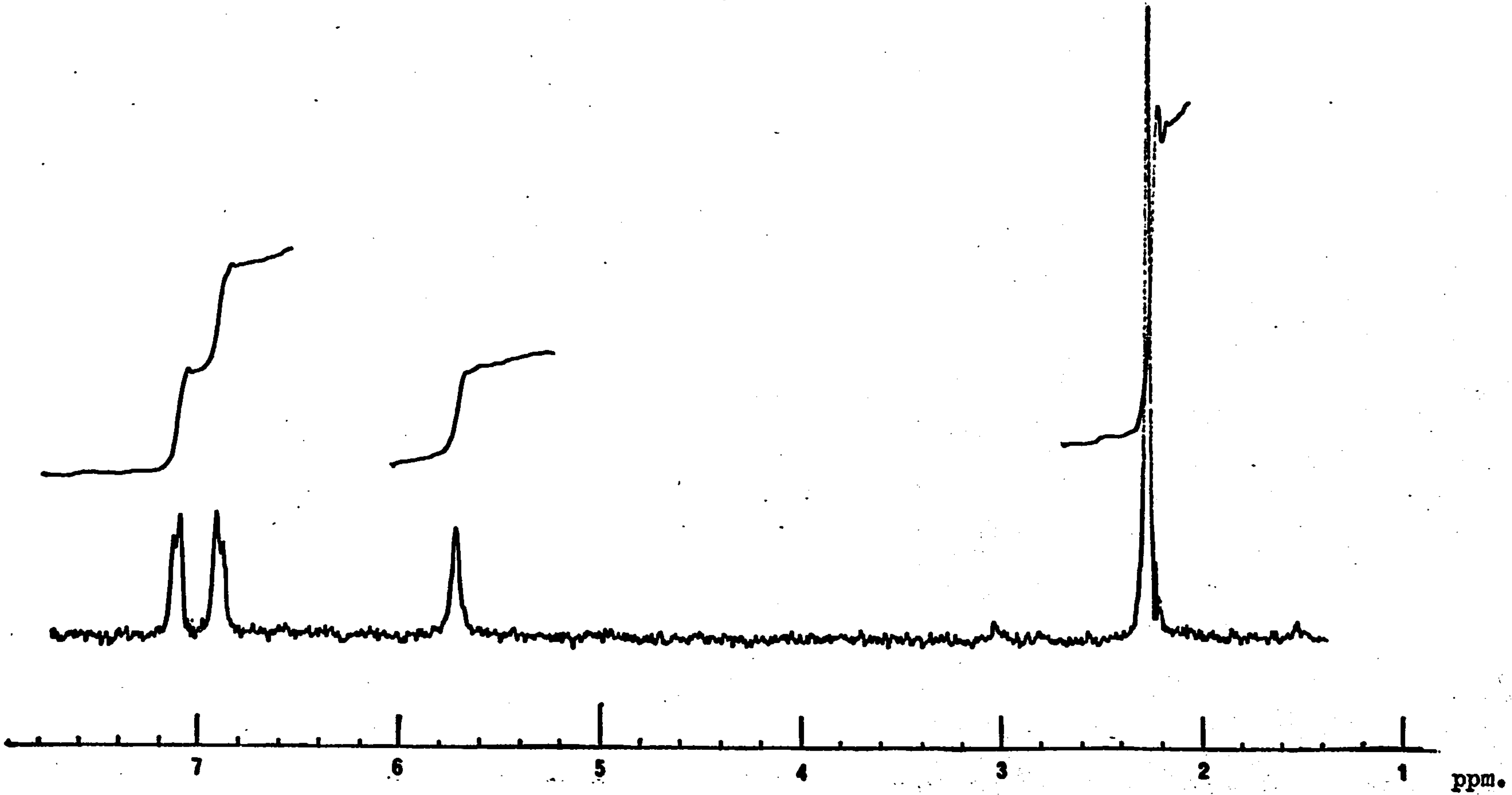


Fig. 5. P. m. r. spectrum of 3,3'-dichloro-5,5'-dimethylbiphenyl-2,2'-diol. (60 M.Hz., $CCl_4$)

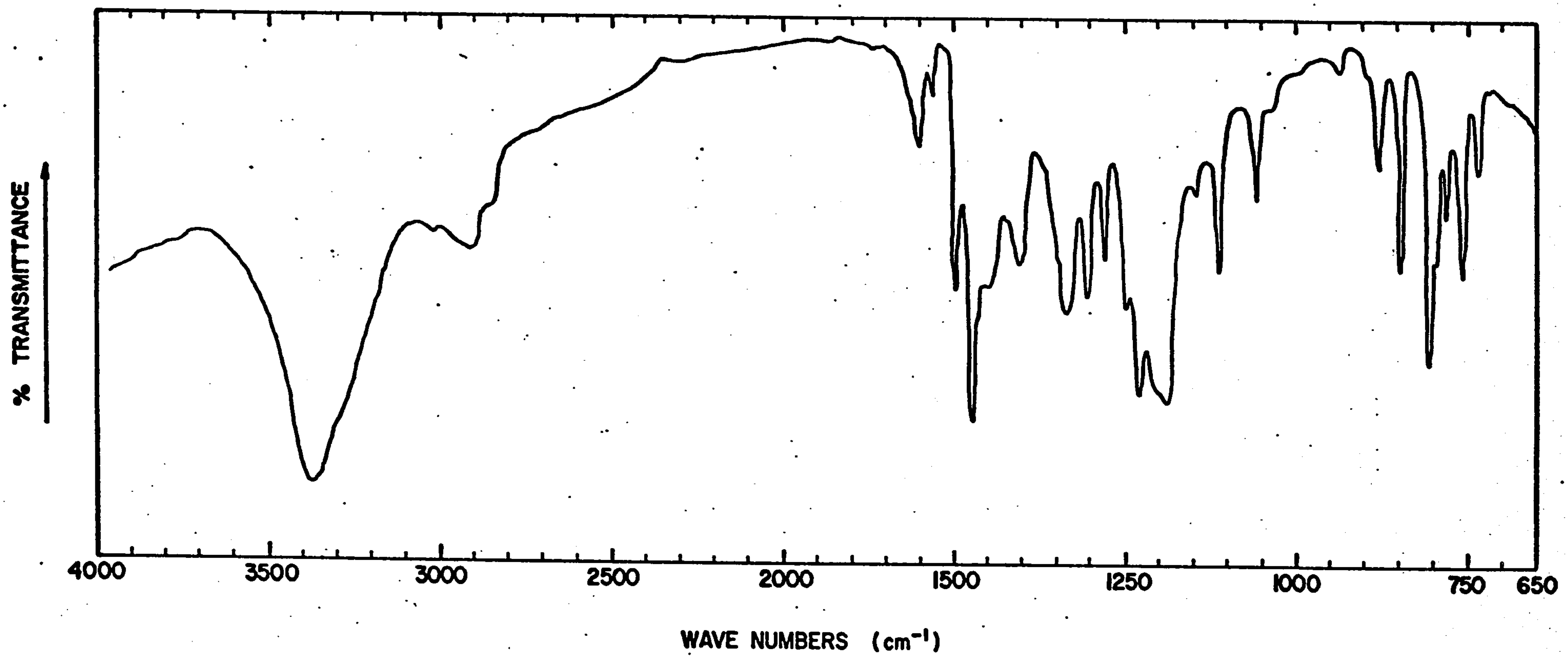


Fig. 6. Infrared spectrum of 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol (KBr).

($CCl_4$) indicates the presence of two methyl groups (singlet, 2.3 p.p.m.), a free OH group (singlet, 5.8 p.p.m.), an intramolecular hydrogen bonding OH group (singlet, 6.1 p.p.m.)[43]. A multiplet in the spectrum, which seems to be an overlap of an ABC case and an AB case with meta-coupling of phenyl protons, at a range of 6.7 and 7.2 p.p.m. corresponds to five phenyl protons (Fig. 7). $D_2O$ exchange demonstrated the disappearance of both OH signals. Elementary analysis gave an empirical formula of $C_{14}H_{13}O_2Cl$. The mass spectrum has a parent peak at *m/e* 248 and a P + 2 peak, of 1/3 the intensity of the parent peak, corresponding to one chlorine atom. An intense peak at *m/e* 213 corresponded to the loss of the single chlorine atom from the molecular ion (Fig. 8). All the evidence suggests that the structure of XI is 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol.

From the neutral fraction of the reaction products remaining in carbon tetrachloride, about 1.5% yield of a new compound, $C_{14}H_{12}O_2Cl_2$ (XII), was isolated. Its infrared spectrum, with two bands at 805 $cm^{-1}$ and 860 $cm^{-1}$, indicates a 1,2,4-trisubstituted phenyl ring, and a pair of bands at 795 $cm^{-1}$ and 840 $cm^{-1}$ suggests a trisubstituted double-bond structure. Bands for phenyl ether (1235 $cm^{-1}$), and a ketone group (1700 $cm^{-1}$) (Fig. 9) were also present. The p.m.r. spectrum (acetone-$d_6$) indicated the presence of one aliphatic methyl group (singlet, 1.68 p.p.m.), one aromatic methyl group (singlet, 2.26 p.p.m.), a cyclic methylene group (AB type peaks at 3.14 p.p.m., further split by another proton), a bridgehead tertiary proton (multiplet, 4.74 p.p.m.), and three phenyl protons (ABC type at 6.6 to 7.2 p.p.m.). A doublet at 6.8 p.p.m. corresponded to the presence of the $\beta$ proton of an $\alpha,\beta$-unsaturated ketone,

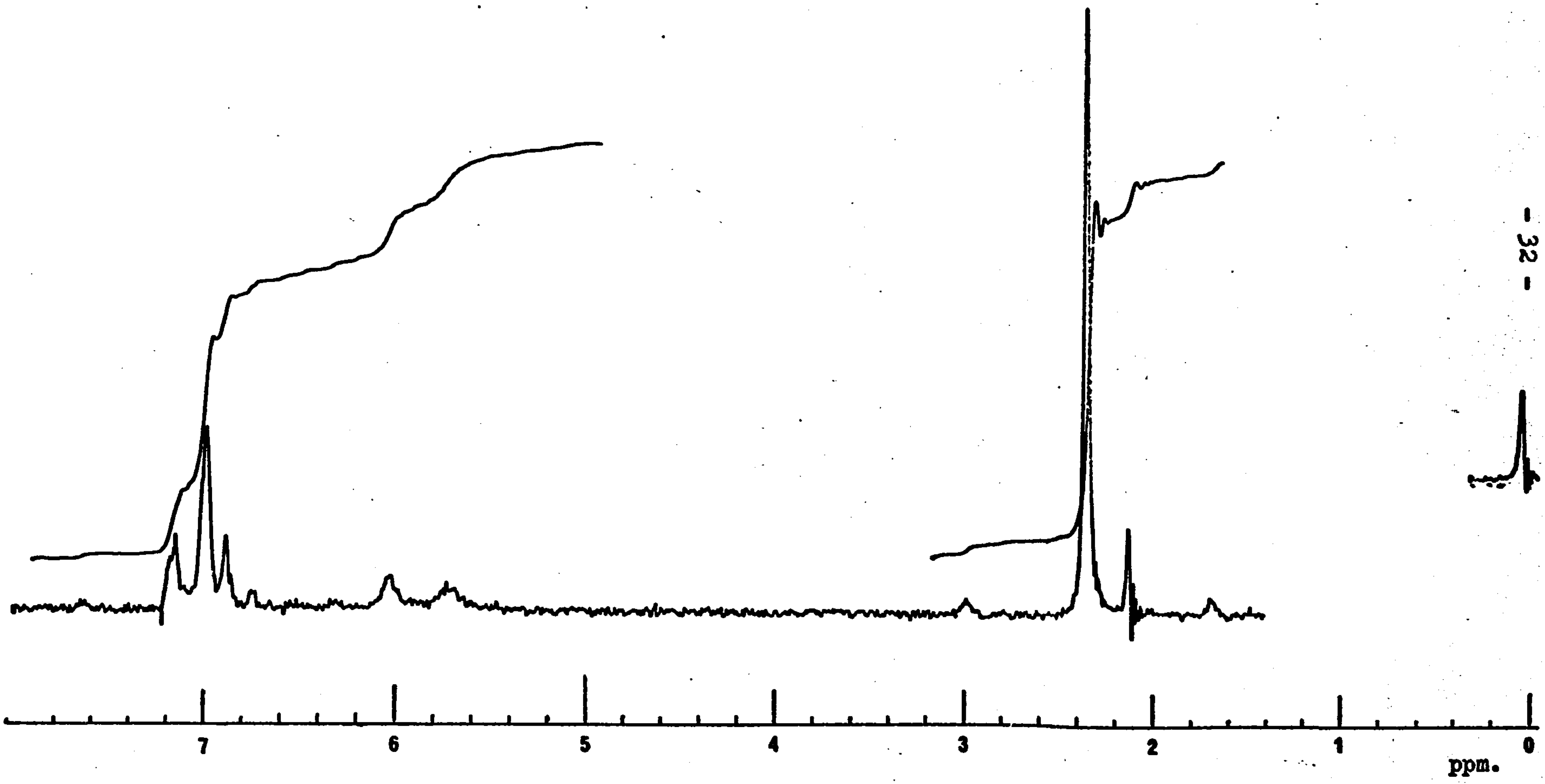


Fig. 7. P.m.r. spectrum of 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol.

(60 M.Hz., $CCl_4$).

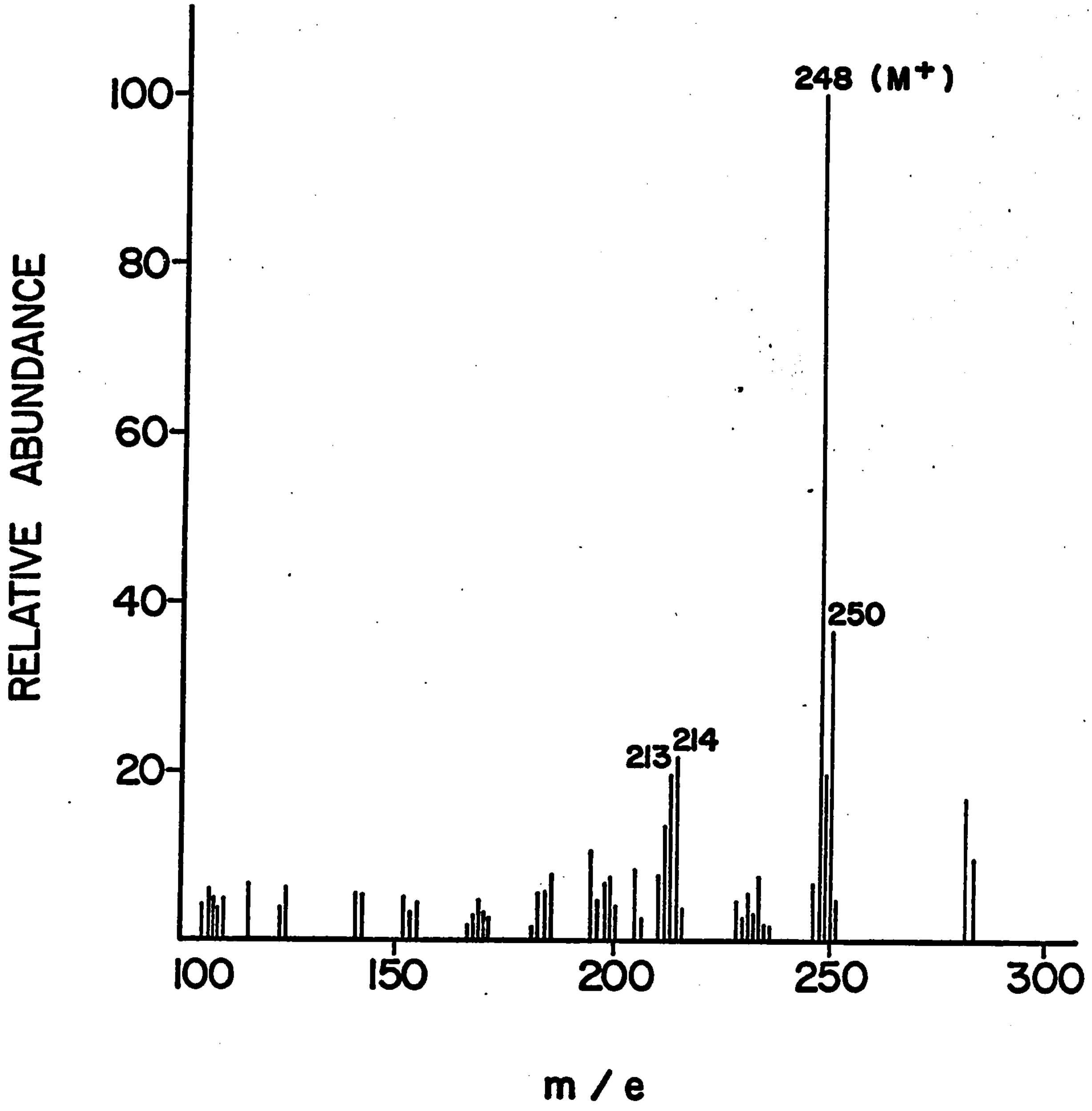


Fig. 8. Mass spectrum of 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol.

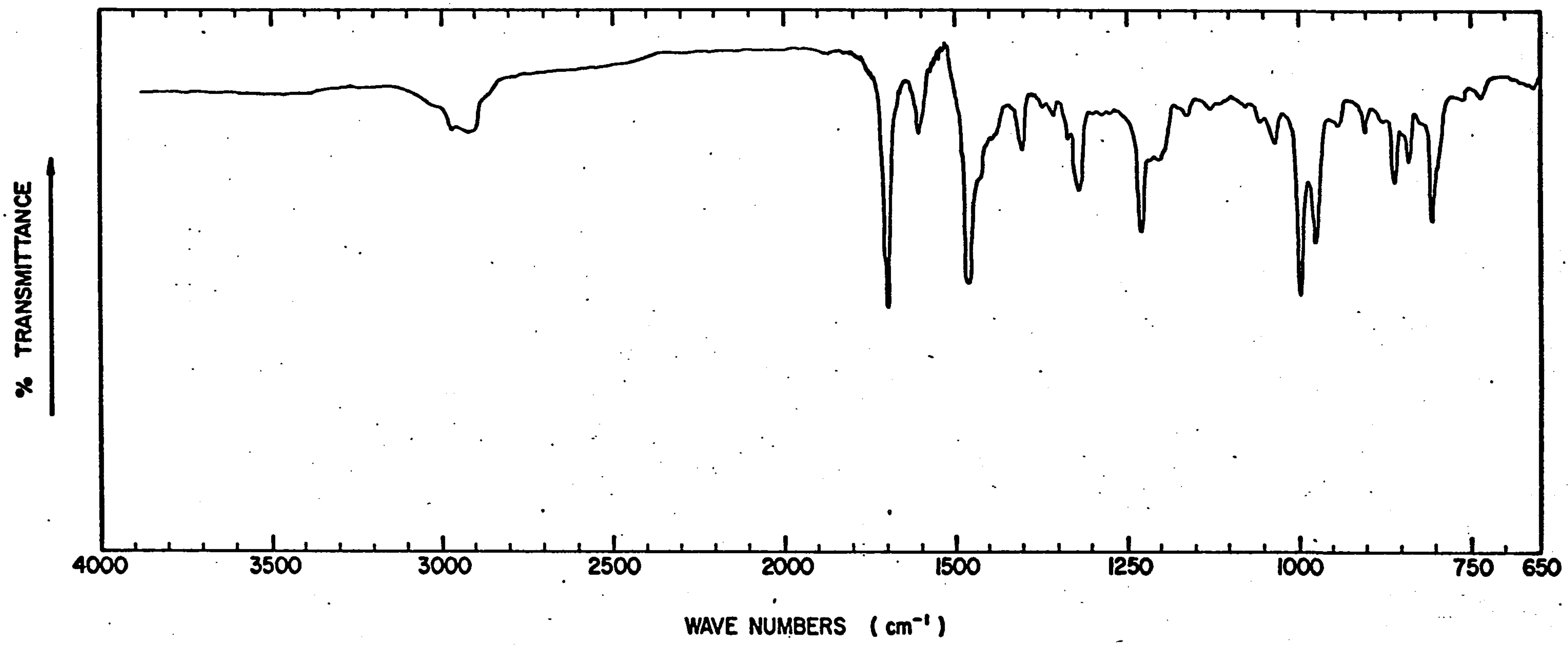
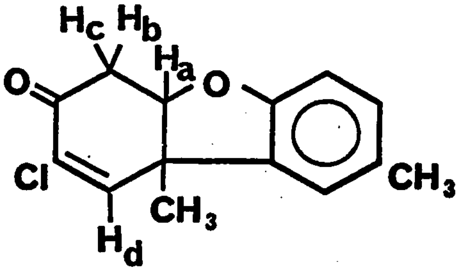


Fig. 9. Infrared spectrum of 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone.



$J_{ab}$ = 3.0 cps.

$J_{ac}$ = 3.5 cps.

$J_{ad}$ = 1.9 cps.

$J_{bc}$ = 17.5 cps.

Table 1. Coupling constants of the protons of 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone

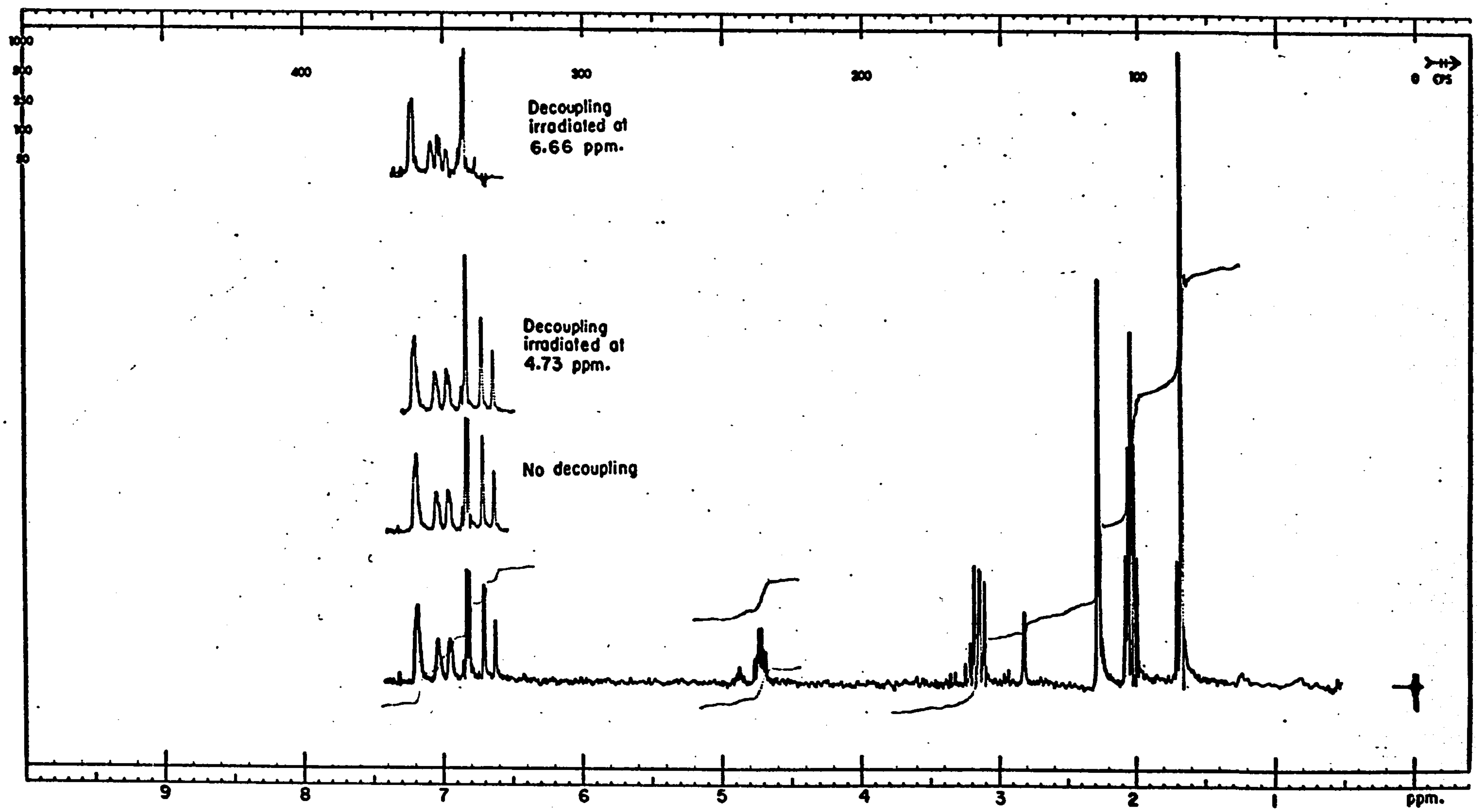


Fig. 10. P. m. r. spectrum of 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (100 M.Hz., Acetone-$d_6$).

but the signal for an α proton was absent. The absence of the latter signal indicated that the α-position was substituted. Spin decoupling experiments revealed that the bridgehead proton coupled with both protons of the methylene group and with the unsaturated proton by a long range coupling. The coupling constants are listed in Table I. The interactions of the 3 phenyl protons were also visualized by the spin decoupling experiment. The p.m.r. spectrum of XII, with the spin decoupling experiment, is shown in Fig. 10. This spectrum, except for the olefin signal, is identical with that of the Pummerer's ketone which as been previously reported[44,45]. The mass spectrum has a parent peak at m/e 248 accompanied by a P + 2 peak with 1/3 the intensity of the parent peak indicating presence of one chlorine atom. An intense peak at m/e 233 indicates the loss of one methyl group from the parent molecular ion, and another intense peak at m/e 205 suggests the loss of CO group from the parent molecular ion (Fig. 11). The ultra-violet spectrum of this compound has λ max 228 mμ (ε14,000) as in an α,β-substituted enone system[46,47](Fig. 12). Thus the compound is 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (XII), a chlorine substituted Pummerer's ketone.

Three compounds were isolated in small yield from the water extracts. All were structural isomers of $C_7H_7O_2Cl$. One of them, 3-chloro-5-methyl catechol (XIV), which melted at 63°, has been mentioned in the literature[48], but not previously characterized in any way. The other two compounds, one with m.p. 83° (XIII), and the other with m.p. 105-107° (XV) were new.

According to its p.m.r. spectrum ($CCl_4$), the compound (XIII)

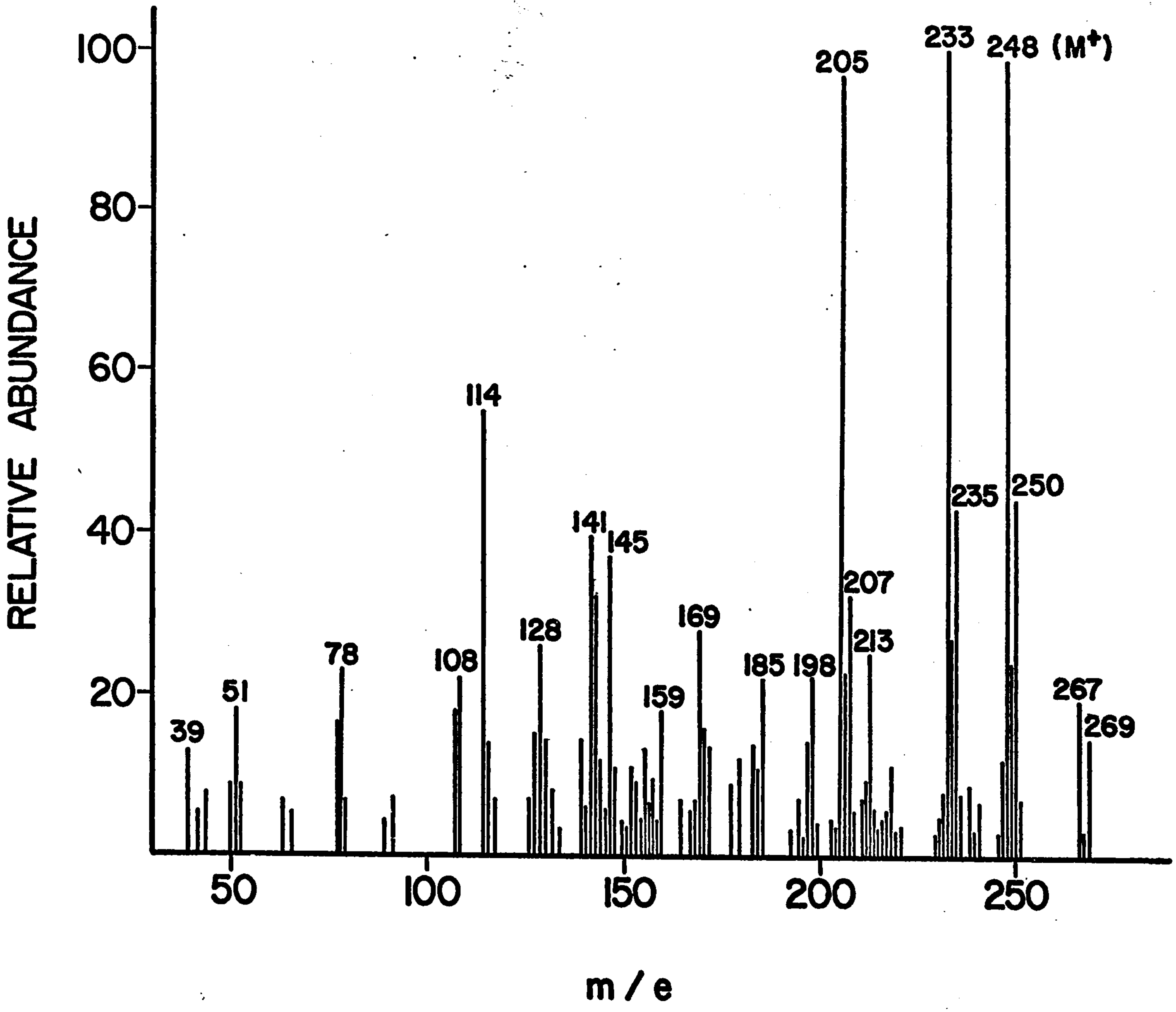


Fig. 11. Mass spectrum of 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone.

Fig.12. Ultra-violet spectrum of 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (ethanol solution).

contains a methyl group (singlet, 2.2 p.p.m.), a free OH proton (singlet, 5.2 p.p.m.), a hydrogen-bonded OH proton (singlet, 5.3 p.p.m.). An AB type quartet with a mid-point at 6.65 p.p.m. (J = 8.4 c/s) corresponded to two ortho-phenyl protons. The mass spectrum had a parent peak at m/e 158 accompanied by a P + 2 peak of 1/3 the intensity of the parent, and corresponding to one chlorine atom. Another intense peak at m/e 123 indicated the loss of the chlorine atom from the parent molecular ion. The infrared spectrum exhibited a band at 800 $cm^{-1}$ representing the two adjacent hydrogen atoms of a 1,2,3,4-tetrasubstituted phenyl group. The absence of a catechol group was indicated by the failure of the compound to reduce silver nitrate in ammonia solution. Thus XIII is 2-chloro-4-methylresorcinol. Its infrared spectrum is shown in Fig. 13.

Compound XIV reduces silver nitrate in ammonia solution. Its p.m.r. spectrum (pyridine $d_5$) shows two doublets (J = 2 c/s) at 6.56 p.p.m. and 6.7 p.p.m. equivalent to meta-phenyl protons and another singlet at 1.9 p.p.m. corresponding to a methyl group. In carbon tetrachloride as solvent, the phenyl proton signal does not resolve but a singlet appears, representing two hydroxyl group protons. The mass spectrum had a parent peak at m/e 158 with a P + 2 peak showing the presence of a single chlorine atom and another intense peak at m/e 123 corresponding to the loss of the chlorine atom. The infrared spectrum had the typical bands at 820 $cm^{-1}$ and 875 $cm^{-1}$ for two isolated phenyl protons in a 1,2,3,5-tetrasubstitution pattern (Fig. 14). Thus, XIV appears to be 3-chloro-5-methylcatechol.

From its infrared spectrum, compound XV was judged not to be

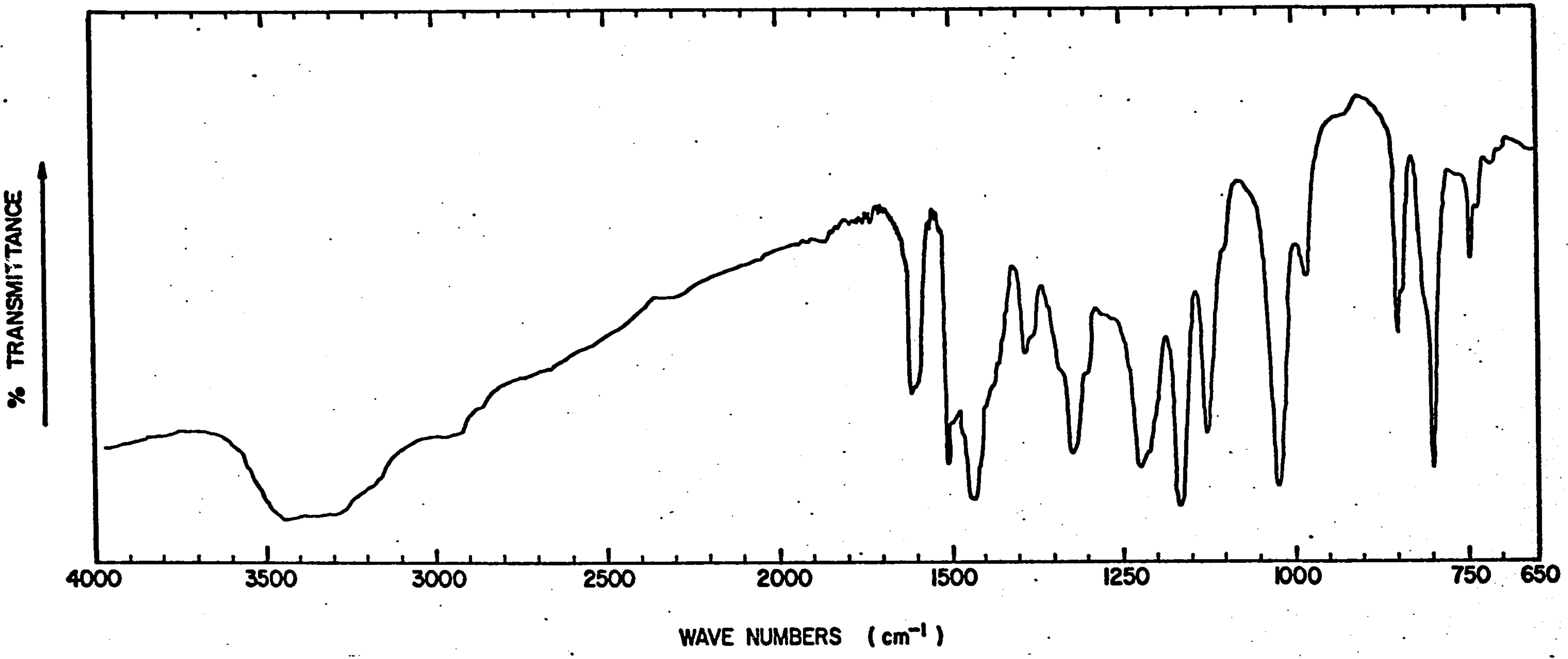


Fig. 13. Infrared spectrum of 2-chloro-4-methylresorcinol.

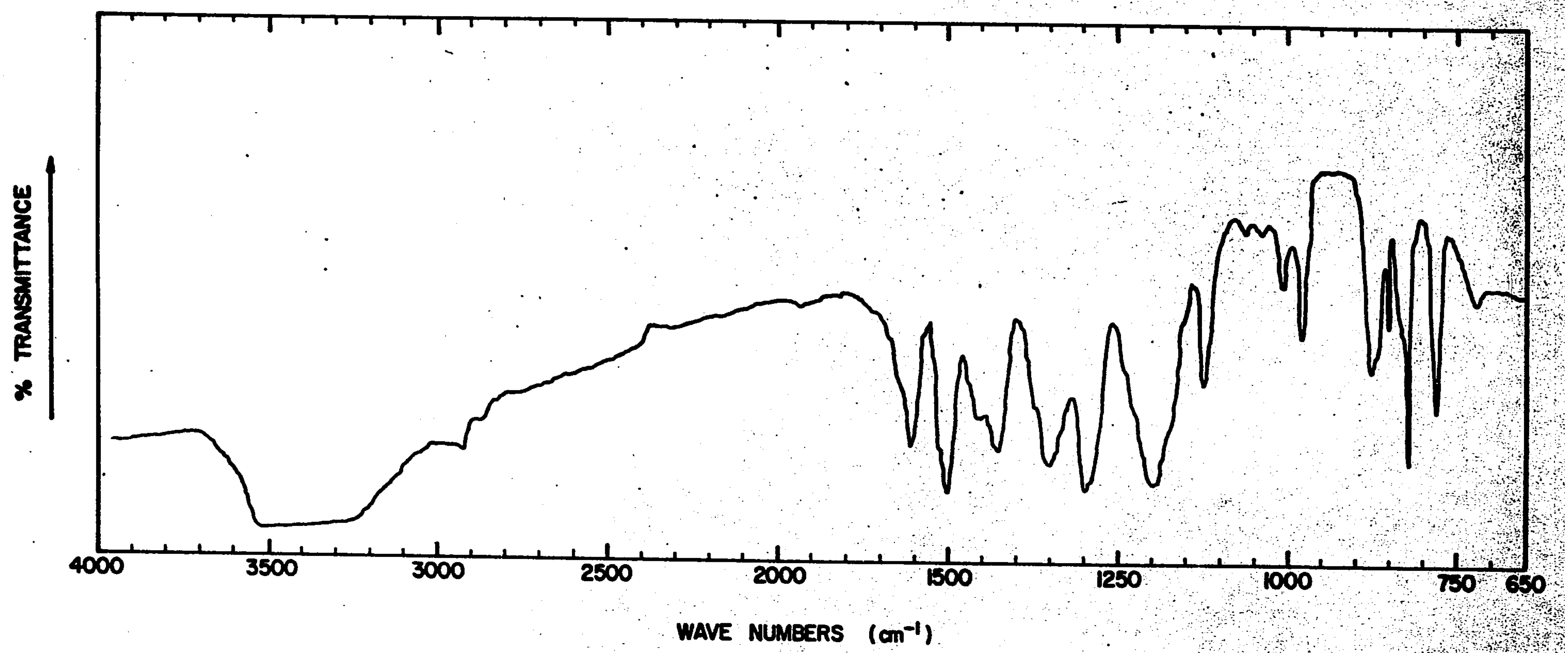


Fig. 14. Infrared spectrum of 3-chloro-5-methylcatechol.

aromatic, but a band at 1660 $cm^{-1}$ suggested the $\alpha,\beta,\alpha',\beta'$ dienone structure (Fig. 15). The ultra-violet spectrum had the absorption maximum at $\lambda$ max 235 $m\mu$ ($\varepsilon$9,200) typical of an $\alpha$-halogen-substituted enone system in accordance with Woodward's rule[46,47,48,49]. In the mass spectrum, the parent peak at m/e 158 was accompanied by a P + 2 peak of 1/3 its intensity, indicating the presence of a single chlorine atom. Peaks at m/e 143, 130 and 123, represented the loss of methyl, carbonyl and chlorine, respectively, from the parent ion. The ion of m/e 143 underwent further fragmentations by two pathways, losing CO (residual ion has m/e 115) in one, and HCl in another (residual ion, m/e 107). The ion at m/e 130 lost a chlorine atom (residual ion m/e 95), and then water (residual ion m/e 77). (Fig. 16). The p.m.r. spectrum (acetone $d_6$) (Fig. 17) exhibited a methyl group (singlet, 1.5 p.p.m.), a hydroxyl group (broad absorption, 2.2 p.p.m.), and the protons of an $\alpha,\beta$-unsaturated ketone. The $\alpha$-proton (doublet, 6.15 p.p.m.) was coupled with the $\beta$-proton (J = 10 c/s). The latter was represented by a quartet at 6.98 p.p.m., which was also coupled with the $\beta'$-proton by long range coupling (J = 3 c/s). The evidence agrees with the structure of 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone for XV.

When XV was heated in dilute sulfuric acid, three phenolic compounds were obtained. One was identified as 5-chloro-2-methylhydroquinone (XVI), and the second as 2-chloro-4-methylresorcinol (XIII), but the third could not be identified because of its small quantity. Both identified compounds were the products of migration of the methyl group or hydroxyl group of XV by the dienone-phenol rearrangement. Wessely and Metlesics have reported that when 4-methyl-p-quinolacetate

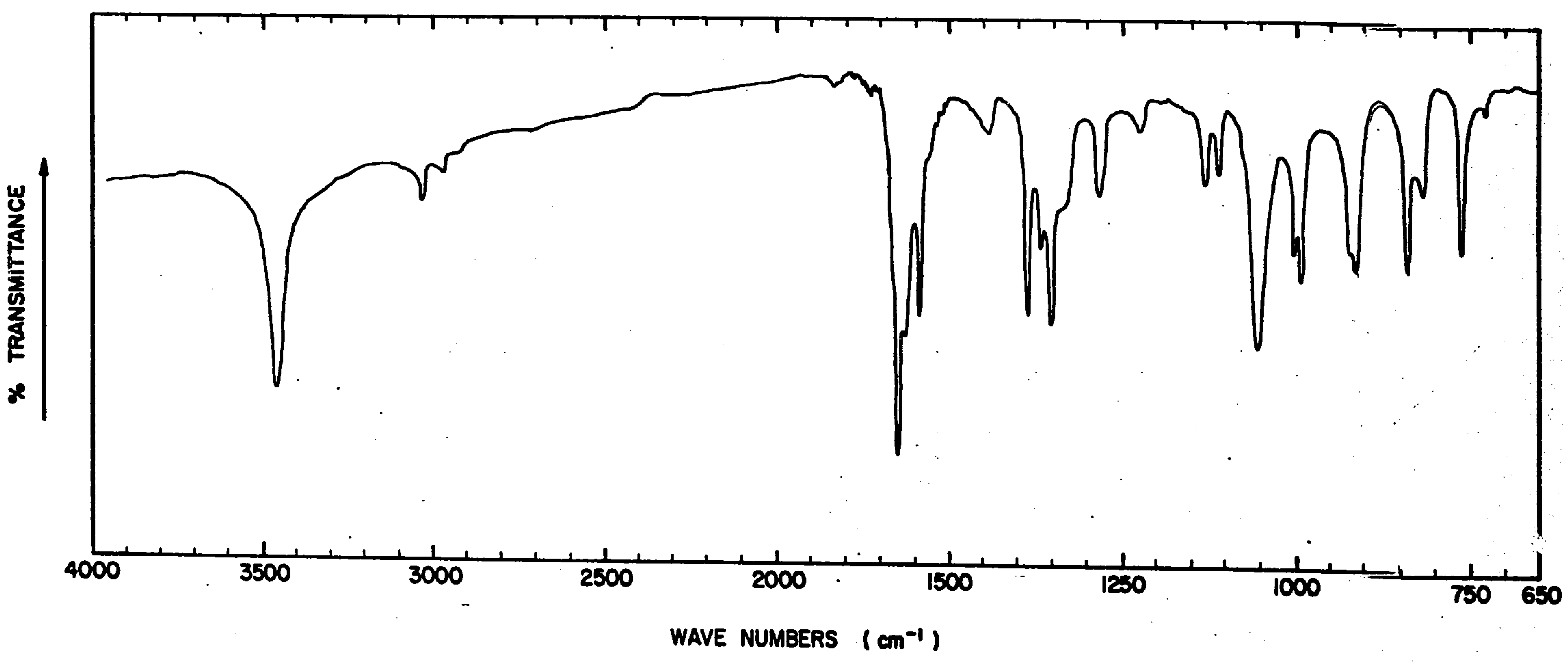


Fig. 15. Infrared spectrum of 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone.

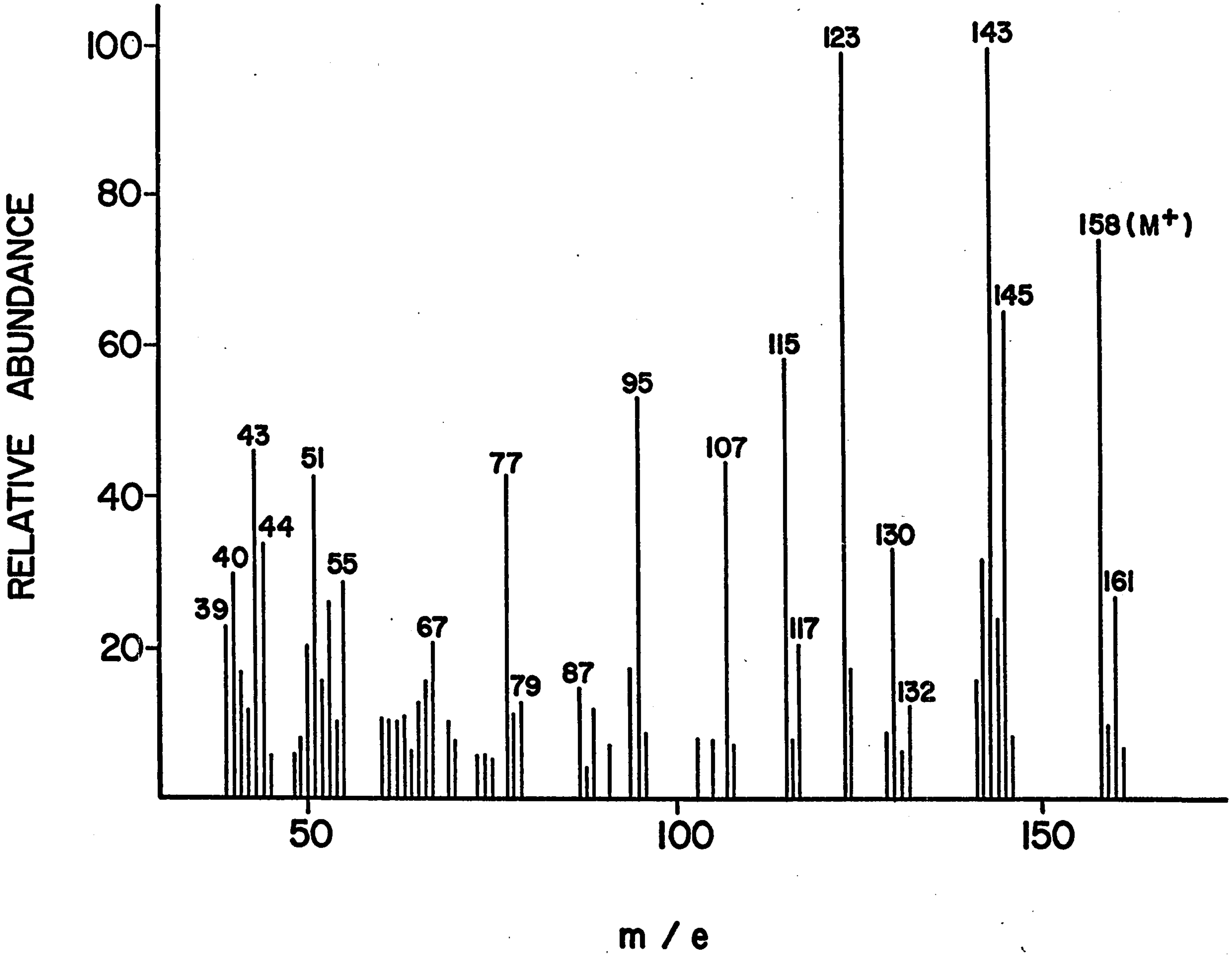


Fig. 16. Mass spectrum of 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone.

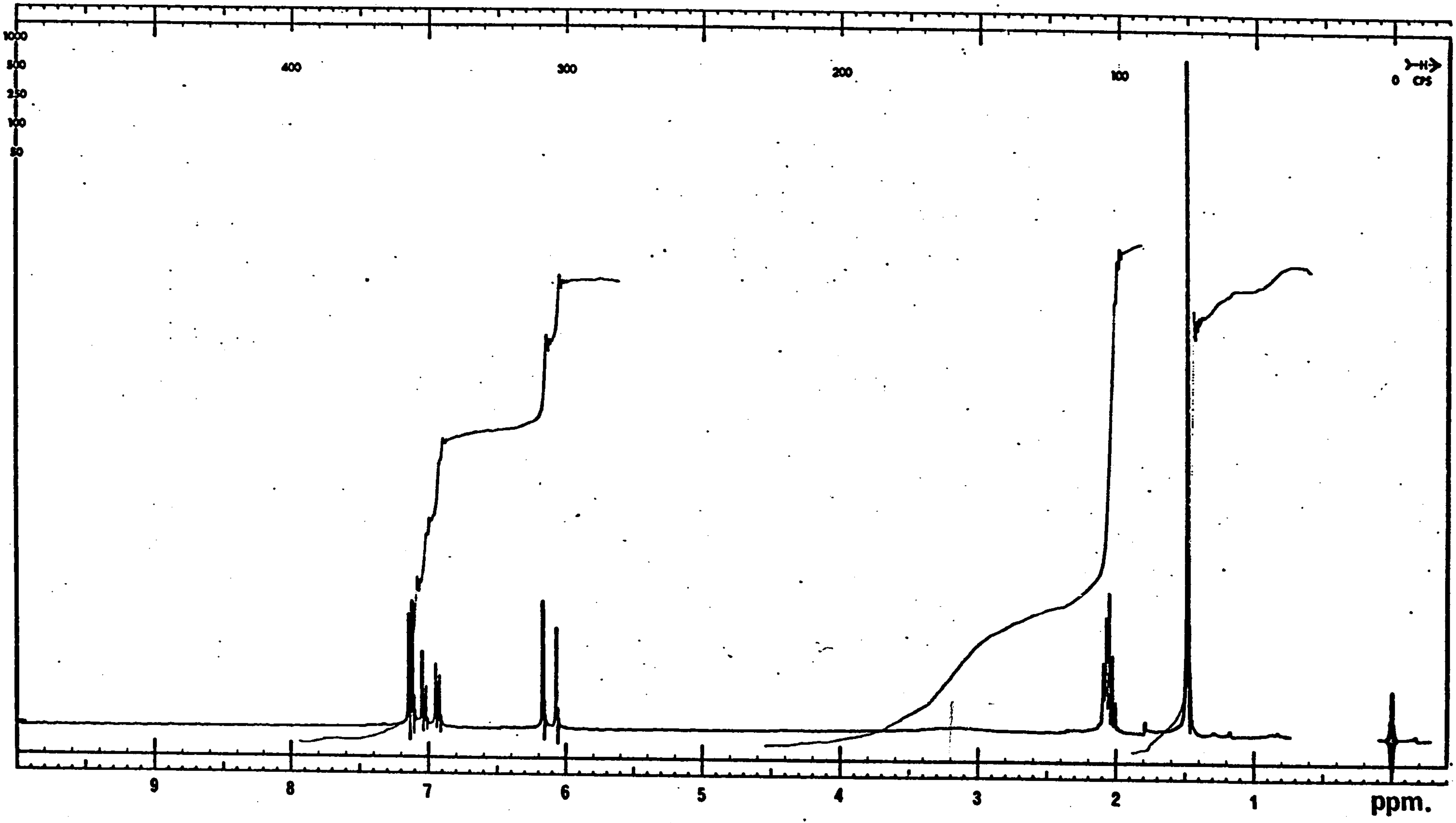
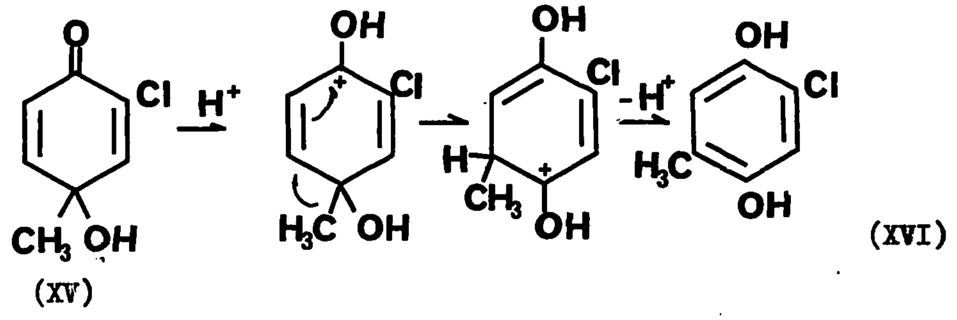
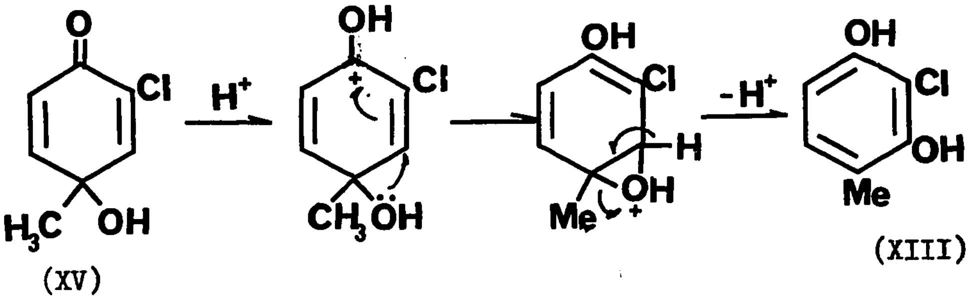


Fig. 17. P. m. r. spectrum of 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone (100 M.Hz., Acetone-$d_6$).

(4-acetyl-4-methyl-2,5-cyclohexadienone) is treated with acid, methyl group migration followed by hydrolysis occurs to form methylhydroquinone, and when 4-methyl-p-quinolacetate is treated with $BF_3$, or acetic anhydride and sulfuric acid, methylresorcinolacetates are obtained[49]. The migration of a methyl group or hydroxyl group directly from 4-methyl-p-quinol has not previously been reported. Possible mechanisms are shown in scheme (1) and (2).



(1)



(2)

The migration of hydroxyl to the position neighbouring the chlorine atom may be favoured by attraction of the hydrogen atom of OH by the chlorine atom to form a hydrogen bond. The above reaction gives further support to the structure proposed for XV.

3. The products from the reaction of o-cresol with chlorine monoxide.

Chlorine monoxide solution in carbon tetrachloride was reacted with molten o-cresol under the same conditions as in the reaction of p-cresol. The reaction proceeded in the same manner.

After the reaction was complete, the solution was extracted with water.

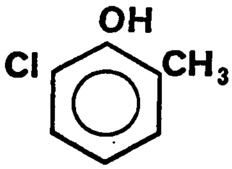
The major products were 6-chloro-o-cresol (XVI) in a yield of 55.0%, and 4-chloro-o-cresol (XVII) in a yield of 22.2%, obtained from the carbon tetrachloride-soluble residue, which also contained 4,6-dichloro-o-cresol (XVIII) (4.0% yield). These compounds were all identified after isolation by comparison with synthesized authentic samples. Quantitative determination of yields was made by gas-liquid chromatography, by means of which 8.2% of unreacted o-cresol was also detected.

From the water extracts, 2-chloro-4-methylresorcinol (XIII) was isolated. The formation of (XIII) from p-cresol by chlorine monoxide has already been described. That it should also have been formed from o-cresol lends further support for its proposed structure.

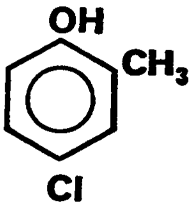
4. The products from the reaction of anisole with chlorine monoxide.

When anisole was treated with chlorine monoxide under the same conditions as phenol, the rate of the reaction seemed to be slower than that of phenol, but all active chlorine was consumed after an hour of addition of the reagent. Within five minutes, the solution became cloudy because of the formation of water. A dark red reaction product was observed in the water layer after the reaction mixture had settled overnight. The reaction mixture was extracted with water to separate all water-soluble material.

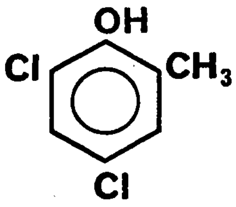
The major products, analyzed by gas-liquid chromatography, were p-chloroanisole (XIX) (41.2%) and o-chloroanisole (XX) (20.1% yield).



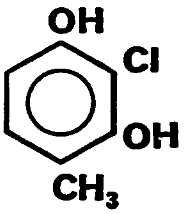
6-Chloro-o-cresol (XVI).
55 %.



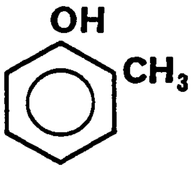
4-Chloro-o-cresol (XVII).
22 %.



4,6-Dichloro-o-cresol
(XVIII).
4 %.



2-Chloro-4-methylresorcinol
(XIII).
0.4 %.



o-Cresol.
8.2 %.

Fig. 18. Reaction products(with yields) from
o-cresol and chlorine monoxide.

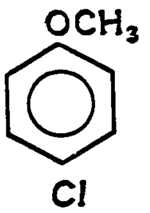
Twenty four percent of unreacted anisole was also detected.

The minor products were all phenolic and water-soluble. They were 2,6- and 2,4-dichlorophenol (III, IV), 2,4,6-trichlorophenol (XXI), 2-chlorohydroquinone (XXII), 2,4-dichlororesorcinol (XXIII), 4-chlororesorcinol (VI), and 2-chlororesorcinol (V).

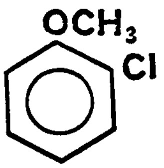
These minor products were all isolated and identified by comparison with the authentic samples.

A synthesis of 2,4-chlororesorcinol, in 80% yield, was achieved by treating 2-chlororesorcinol with sulfuryl chloride. The infrared spectrum and the p.m.r. spectrum of the synthesized product are identical with those of XXIII. This is a new route for the synthesis of 2,4-dichlororesorcinol. The alternative method has been reported by Grover, *et al.*50) They synthesized XIII by chlorination of β-resorcylic acid with sulfuryl chloride followed by decarboxylation of the products. The yield of this method was not reported.

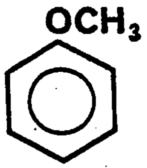
All products, with their yields, are summarized in Fig. 19.



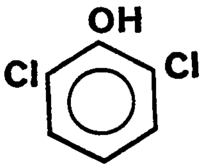
p-Chloroanisole (XIX).
41.2 %.



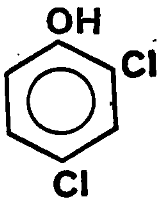
o-Chloroanisole (XX).
20.1 %.



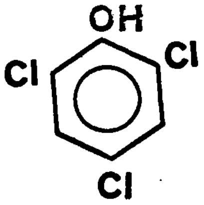
Anisole
24.0 %.



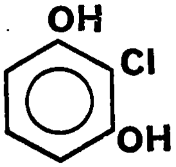
(III).
Trace.



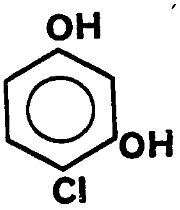
(IV).
Trace.



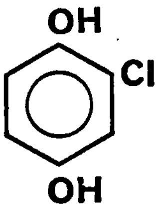
2,4,6-Trichlorophenol
(XXI). 0.2 %.



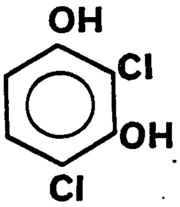
(V).
0.05 %.



(VI).
0.1 %.



2-Chlorohydroquinone
(XXII).
0.7 %.



2,4-Dichlororesorcinol
(XXIII).
0.5 %.

Fig. 19. Reaction products (with yields) from anisole and chlorine monoxide.

## REACTION MECHANISMS

### Evidence of free-radicals

In the reaction of chlorine monoxide with phenols, as well as with anisole, the relative yields of products indicated that chlorination was the main reaction. Partly because of factors limiting the choice of solvent, and partly because the reaction was exceedingly rapid, the study of phenol alone yielded little evidence as to mechanism. However, the study of p-cresol gave clear evidence of the participation of free radicals, and even permitted the isolation of small yields of phenyl-phenyl coupled dimers. All compounds, phenol, the cresols, and anisole, also yielded minor quantitites of hydroxylated products, whose presence additionally points to a free-radical mechanism.

The ortho:para ratio of mono-chlorophenols from phenol was 2.9:1. This ratio is high when compared with that obtained by chlorination of molten phenol with molecular chlorine (1:1), but not when compared with the ratio, 2.8:1, obtained by treating phenol with chlorine in carbon tetrachloride 22). In a study of the chlorination of o-cresol with chlorine, high para-ratios (1:6.6 in nitromethane, 1:5.1 in nitrobenzene) have been found in polar solvents, while in chloroform the ratio was 1:0.9, and explanations have been advanced to account for the effect of solvents 31). The explanations suggest that a solvent which, by hydrogen bonding to the phenolic hydrogen inhibits the hydrogen bonding of chlorine to that of hydrogen, should inhibit chlorination at the ortho-position and lead to a lower ortho:para ratio.

The problem in studying the effect of solvents (or their absence) on the reaction of phenol with chlorine monoxide is that the latter is so reactive that few solvents are suitable. Nevertheless, hexachloroacetone, more polar than carbon tetrachloride, and nearly as stable towards chlorine monoxide seemed an appropriate choice, and the reaction of phenol with chlorine monoxide was performed in it, giving an *ortho*:*para* ratio of monochlorophenols of 2:1, which seemed to indicate that the change of solvent had only a small effect. However, when phenol was chlorinated with chlorine in the same solvent, precisely the same *ortho*:*para* ratio, 2:1, was obtained. Thus, if the change in *ortho*:*para* ratio was related to the degree of hydrogen bonding of solvent to phenol, then that hydrogen bonding must have affected both reactions equally. It might, then, be a reasonable conclusion that the mechanism of chlorination of phenols with chlorine monoxide is similar to the mechanism of chlorination with chlorine, and, if it were possible to conduct the former reaction in molten phenol, or in a polar solvent, the isomer ratio of products would depend only on the solvent, and not on the reagent.

However, the same reasoning ought to apply to *o*-cresol, which gave an *ortho*:*para* ratio of 1:0.9 on chlorination with chlorine in carbon tetrachloride 31), but, in the same solvent, gave an *ortho*:*para* of 2:1 on chlorination with chlorine monoxide.

Therefore, despite the apparent similarity of solvent effects in the chlorination of phenol, reaction with chlorine monoxide may well follow a different course from reaction with chlorine, and neither Harvey and Norman's hypothesis for chlorination by molecular chlorine 22), nor Campbell and Schields' solvent effect theory 31) may apply.

Since a free-radical mechanism had suggested itself, evidence was sought through the use of electron spin resonance spectroscopy. Simply placing a mixture of the reagents in the cavity of an e.s.r. spectrometer failed to give any measurable signal. However, in a mixing cell capable of permitting detection of free radicals with lifetimes greater than $10^{-8}$ seconds, the mixture in carbon tetrachloride of chlorine monoxide and p-cresol exhibited a signal (Fig. 20) which indicated the presence of a secondary free radical derived from the latter.

Chlorine monoxide alone, in carbon tetrachloride, was examined by e.s.r. spectrometry to determine whether the species responsible for the formation of the p-cresol radicals could be detected. At low temperature, -100°, four hyperfine structures ($g_o = 2.0102$, $a = 48.7$ MHz) appeared. They represented the spectrum of the relatively stable chlorine dioxide free radical52), whose presence in carbon tetrachloride solutions of chlorine monoxide is already well-known11). At room temperature, only a broad absorption was observed. Nevertheless, chlorine monoxide is known3) to dissociate at moderate temperatures, and, especially in the light of the following evidence, it can only be concluded that the concentration of the expected chlorine and chlorine oxide radicals must be below the level detectable by the e.s.r. spectrometer employed in these experiments.

That such radicals were present was demonstrated by reaction with diphenylpicrylhydrazyl (DPPH). When a dilute solution of DPPH in carbon tetrachloride was added dropwise to the chlorine monoxide solution, the color (of the DPPH) faded immediately after addition of the first few drops. When more DPPH was added, the purple color persisted at first,

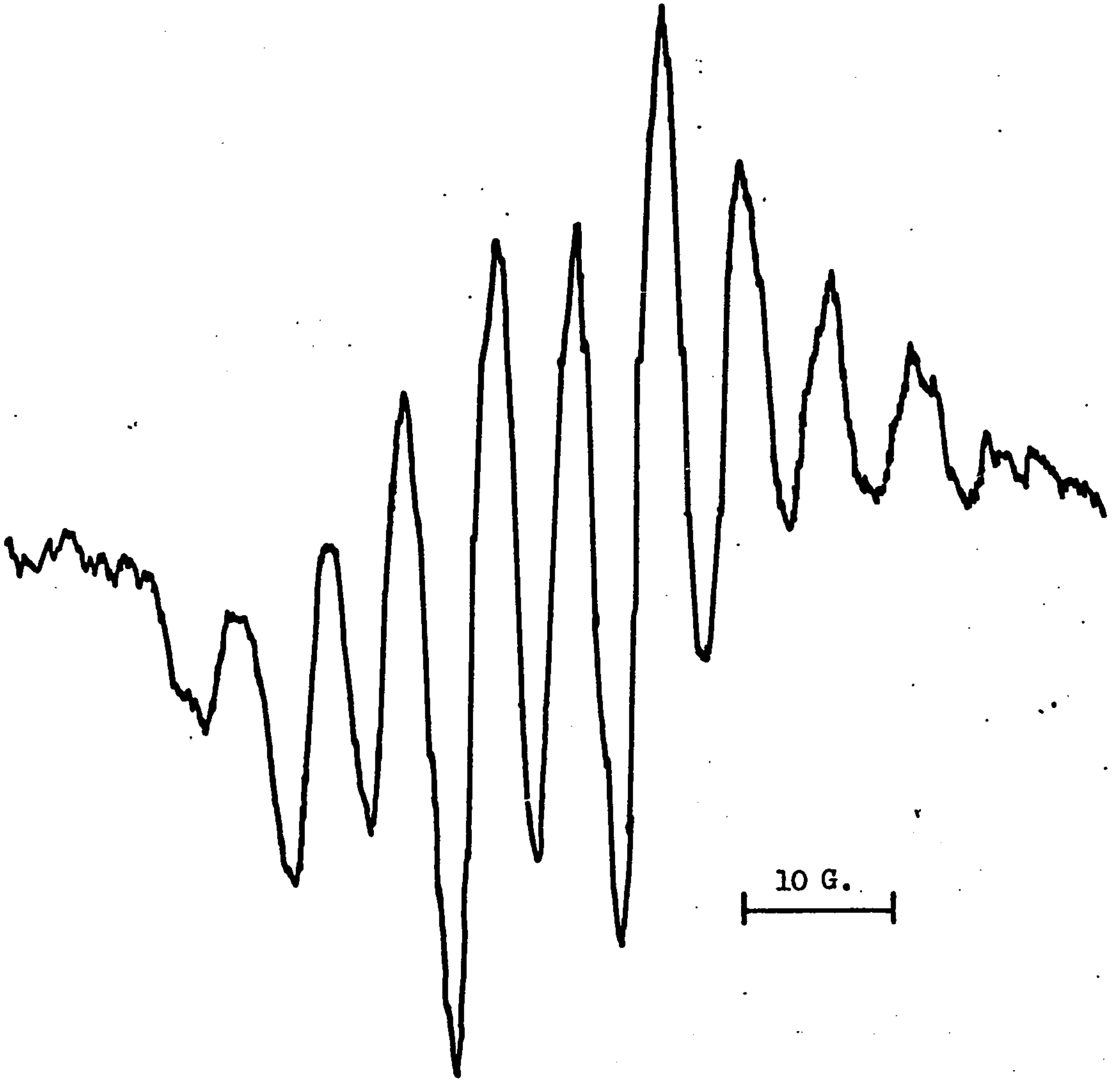


Fig. 20. E. s. r. spectrum of the secondary free-radical produced by the reaction of p-cresol with chlorine monoxide.

then faded very slowly. The initial rapid fading may be attributed to reaction of the DPPH with chlorine dioxide free radicals, and the slow fading to reaction with chlorine and chlorine oxide radicals released by the slow decomposition of chlorine monoxide.

Although phenol and chlorine monoxide in the mixing cell of the e.s.r. spectrometer failed to reveal the presence of any free radicals, the addition of phenol solution to the purple solution of DPPH and chlorine monoxide caused immediate disappearance of the color. In agreement with the direct (e.s.r.) evidence obtained from p-cresol, it must be concluded that free radicals from phenol were responsible for the rapid loss of color.

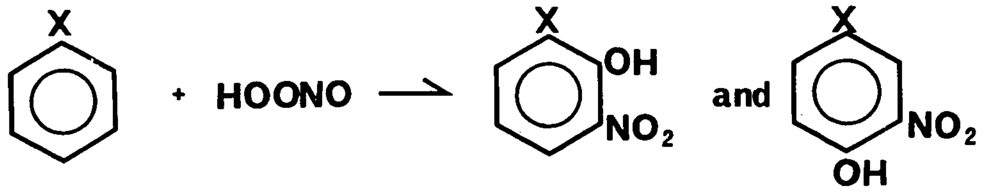
Anisole behaved like phenol in the sense that no free radicals could be detected by means of e.s.r. spectrometry, but caused immediate fading of the color of a solution of DPPH and chlorine monoxide in carbon tetrachloride. Thus, free-radicals participate in the reaction of anisole, although, as will be seen, their nature must be different from those of the phenolic compounds.

Further evidence for the intermediacy of free radicals comes from the isolation of dimers. Again, phenol and anisole gave negative results in this respect, possibly because the amount of dimers formed was too small to permit isolation; more likely because, as in the case of anisole, the reddish-brown syrup obtained in 6 per cent yield, which was soluble in 3 per cent sodium hydroxide solution, was a mixture of polymerized compounds. The syrup was adsorbed strongly by a silica gel column, and was difficult to elute.

The dimers were obtained as minor products only from the reaction of p-cresol, and their formation can be only explained by simple pairing of aryloxy radicals formed during the reaction (Fig. 21).

Some of the phenyl-phenyl coupled compounds, IX and X, isolated in the present work are the same as those obtained by Bowden and Reece[32)] from the reaction of p-cresol with chlorine or sulfuryl chloride. They interpreted the mechanism as ionic, but, by now, a free radical mechanism is more widely accepted[26)]. The Pummerer's ketone must also arise through a free radical mechanism[26)].

The other general types of minor products (aside from polychlorinated phenols), isolated from reaction of all three phenols, were the resorcinols and a catechol. These, too, pointed towards the existence of free-radical intermediates. For, with two exceptions (3-chloro-5-methyl catechol and the quinol XV from p-cresol), chlorine always entered ortho or para to the original phenolic hydroxyl, and hydroxyl always entered meta, and only a free radical mechanism can explain such 1,2-substitution on an aromatic nucleus (see p. 61). An analogous subsitution has been described by Halfpenny and Robinson[51)] for the reaction of pernitrous acid with monosubstituted compounds. When both the hydroxyl and the nitro group enter the ring together, the hydroxyl appears ortho and para to the original substituent, with the nitro groups adjacent to the hydroxyl (equation 30).



(30)

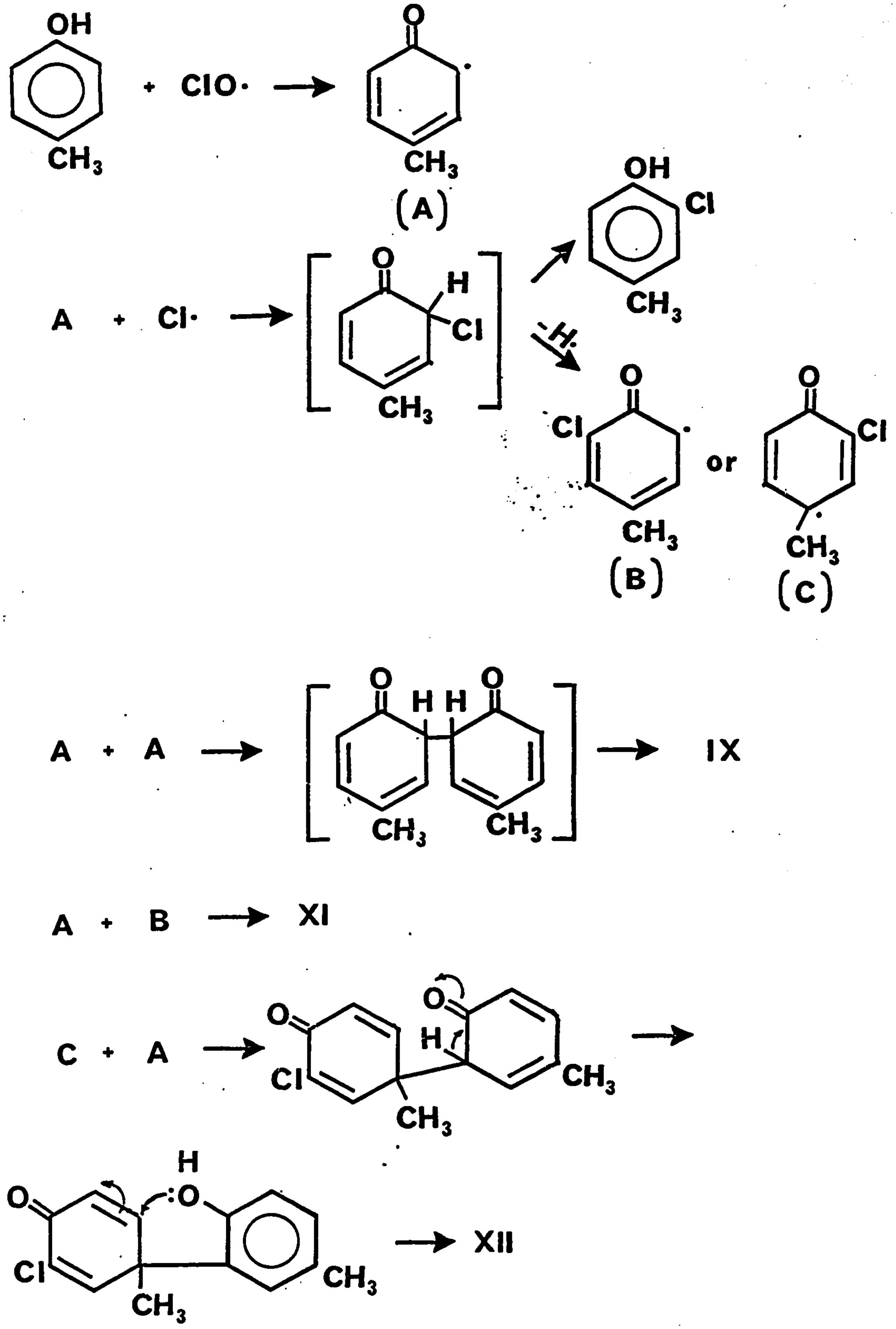


Fig. 21. Reaction mechanisms of the formation of the phenyl-phenyl coupled dimers from p-cresol.

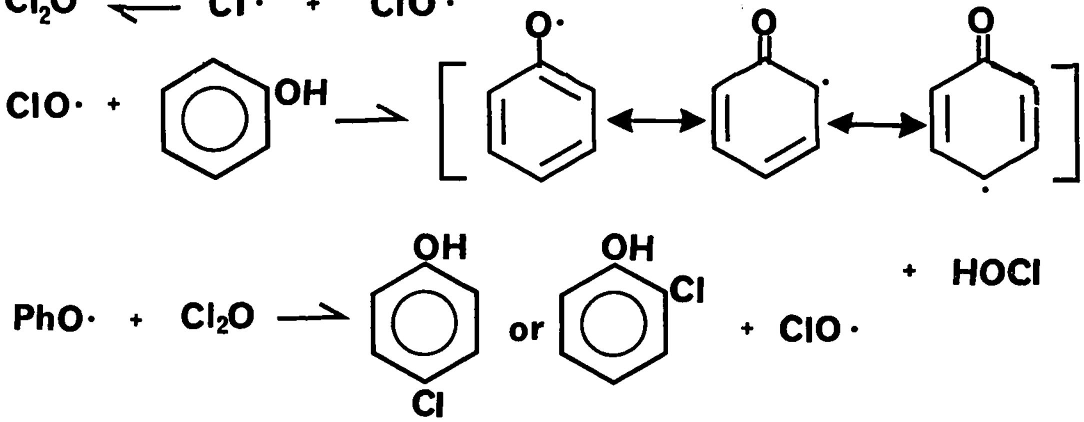
This explanation holds for the formation of 2,4-dichlororesorcinol from anisole, provided it is considered that some demethylation of p-chloroanisole can occur to form p-chlorophenol.

The reaction of phenol and cresols

For both phenol and cresol, initiation of the reaction must depend upon the decomposition of chlorine monoxide to chlorine and chlorine oxide radicals (equation 31).

As described by Shaw19) for the chlorination of saturated hydrocarbons, the chlorine oxide radicals may then be the chain carriers in the propagation steps (equations 32 and 33). In this instance, phenol contains a relatively easily abstractable hydrogen, and the actual chlorination reaction takes place between chlorine monoxide and the phenoxy radical, the latter having been the species whose presence was revealed by DPPH, and, in the case of p-cresol, by e.s.r. spectroscopy. The hypochlorous acid formed readily decomposes to form chlorine monoxide and water (equation 34). The same pathway applies to the formation of the dichlorophenols by chlorination of monochlorophenols.

$$Cl_2O \rightleftharpoons Cl\cdot + ClO\cdot \tag{31}$$



(32)

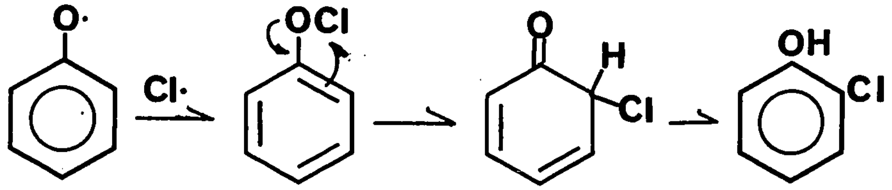
(33)

$$2\,HOCl \longrightarrow H_2O + Cl_2O \tag{34}$$

## The ortho:para ratios

The high ratio of ortho to para among the monochlorinated products of reaction of chlorine monoxide with both phenol and o-cresol has already been noted. Explanation was sought by consideration of the electron spin density of aryloxy radicals.

Aryloxy radicals are stabilized by resonance, and the odd electron is distributed over the oxygen atom and all the carbon atoms of the aromatic ring. Recent developments in electron spin resonance research have revealed that the highest density is found on the oxygen and both ortho positions have only half the spin density of the para position54,55). At the meta position, the spin density is about 10 per cent of the para spin, although of opposite sign56). However, the sum of the spin densities at both ortho positions and on the oxygen is over twice that at the para position. Thus the ortho and oxygen sites have more than twice the probability than the para position of forming a sigma bond with a chlorine atom. Some O-Cl bonds may form, but, because of their instability and their geometry may readily undergo intramolecular rearrangement to form an ortho-substituted product, as indicated in equation (35).

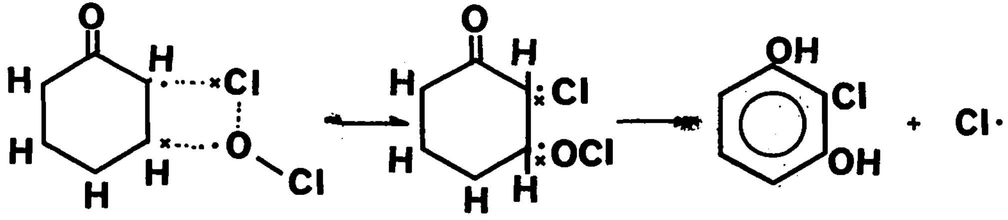


(35)

## The formation of oxygenated products

Shaw[19)] could not detect hydroxylated products from the reaction of chlorine monoxide with saturated hydrocarbons, but oxygenated compounds were isolated from all of the present reactions, and the mechanisms by which they were formed may be regarded as chain termination reactions.

Every phenol studied yielded chlororesorcinols among its minor products, and all of them had an unusual pattern of ortho-, meta- or para-, meta-substitution with two exceptions. No meta-chloro derivatives were observed, but the hydroxyl group always entered the meta position. Further consideration of spin densities of the aryloxy radical may explain this observation, for the meta position has a small spin density of opposite sign to that of the ortho and para positions. Thus, in equation (33), when the phenoxy radical approaches the chlorine monoxide molecule, we can assume that an intermediate exists in which both molecules are located close to each other. If we further assume that at the moment the Cl-O bond of chlorine monoxide breaks to form a new C-Cl bond, the spin state of the odd electron at the ortho carbon is $\alpha$, the spin on Cl must be $\beta$, and the spin on the O (of $Cl_2O$) must be $\alpha$ (where $\alpha$ and $\beta$ designate opposite states of spin.) The odd electron spin at the meta carbon is opposite to the ortho spin, and therefore $\beta$. Since the spin density on the meta carbon is small, in most instances the •OCl radical will simply depart from the product immediately after C-Cl bonding is completed. However, some small proportion, perhaps those OCl radicals located very close to the meta carbon, will instead form a bonding orbital (equation 36).



(36)

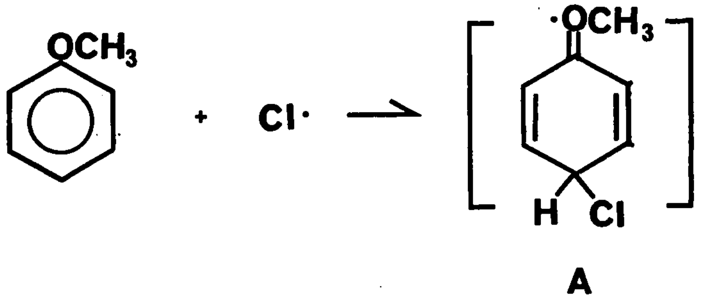
- α spin state
- β spin state

The exceptional cases - the formation of 3-chloro-5-methyl catechol and the quinol XV - may be explained by considering that the •OCl radical released from the normal reaction might tend to combine with another aryloxy radical at its position of densest spin.

The reaction of anisole

For anisole, several experimental observations pointed to a different mechanism from that of the phenols. One was that the ortho: para ratio of the monochlorinated products was 1:2 - quite different from that obtained from phenol. In fact, it was the same ratio as is normally obtained by the action of chloronium ion in water (22), but different from the value of 1:4 resulting from treatment of anisole with chlorine in carbon tetrachloride (22). Another seemingly significant observation was that the rate of reaction of chlorine monoxide with anisole was considerably slower than with phenol. Besides, 24 per cent of the unreacted anisole was recovered from among the reaction products.

The difference in mechanism probably arises from the fact that in the case of anisole there is no readily abstractable hydrogen atom in ring or side chain, and, instead of abstraction, addition of the chlorine radical to the phenyl ring probably occurs (equation 37). This may be the rate determining step, and, as such, the cause of the relatively slow reaction. (This step is analogous to similar ones involved in explaining the hydroxylation[59)] and homolytic aromatic arylation[70)] of anisole). The chlorinated free radical then loses hydrogen to a molecule of chlorine monoxide to form the product chloroanisole, hypochlorous acid, and a chlorine radical (equation 38). The hypochlorous acid becomes water and chlorine monoxide, as previously described (equation 34).



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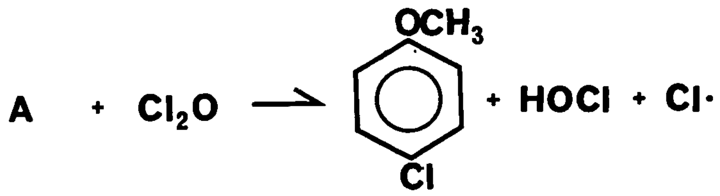
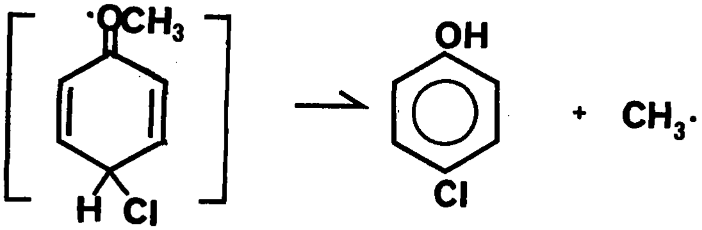


............... (38)

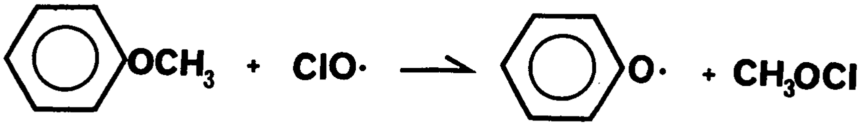
To explain the occurrence of polychlorophenols among the by-products, it may be postulated that a portion of the intermediate A may split off methyl radical instead of hydrogen to form chlorophenol (equation 39). (Demethylation by molecular chlorine, as described earlier, has been observed to occur only in an aqueous medium, so that the mechanism proposed by Sarkanen and Dence[34)] does not apply to the reaction of chlorine monoxide.) Because of the low rate of reaction (37), when reaction (39) occurs there is probably still a considerable concentration of chlorine monoxide in the reaction mixture, and the chlorophenol reacts rapidly to form di- and tri-chlorophenols.



**A**

(39)

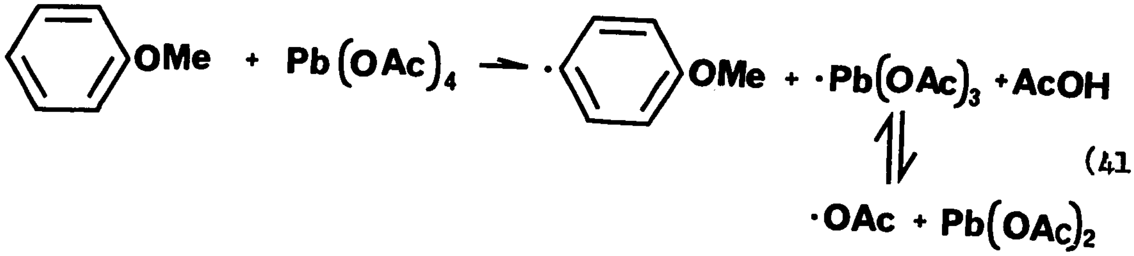
But if the 1,2-addition mechanism is to apply to anisole, then direct demethylation without chlorination must also occur during the reaction (equation 40). The monochlororesorcinols, V and VI, can be considered to arise only from the phenoxy radical. In fact, experimental evidence indicates that V and VI are not formed from chlorophenol, for when both <u>ortho</u>- and <u>para</u>-chlorophenol were reacted with one-half mole of chlorine monoxide, only 2,4-dichlororesorcinol was detected among the reaction products, and no monochlororesorcinols. This experiment, then, suggested the mechanisms of two reactions: the formation of monochlororesorcinols <u>via</u> phenoxy radicals; and the formation of 2,4-dichlororesorcinol, <u>via</u> either <u>ortho</u>- or <u>para</u>-chlorophenol.



(40)

The difficulty in accepting the idea of direct demethylation is that it appears inconsistent with the notion that hydrogen cannot be abstracted from the phenyl nucleus of anisole, and chlorine radical addition (equation 37) is required as a first step.

That the abstraction of hydrogen is possible is suggested by the results of Cavill and Solomon[57)] who reported that anisole reacted with lead tetraacetate to give p-acetoxyanisole, although in poor yield. They suggested that the reaction was not substitution, but involved, as its first stage, the abstraction of the p-hydrogen atom to give p-methoxyphenyl radicals, which then reacted with acetyloxy radicals or lead tetraacetate to give p-acetoxyanisole (equations 41 to 43). The idea of p-methoxypenyl radicals came from evidence that when the reaction was performed in an aromatic solvent, an unsymmetrical diaryl product was obtained.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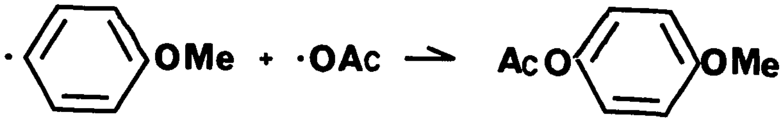
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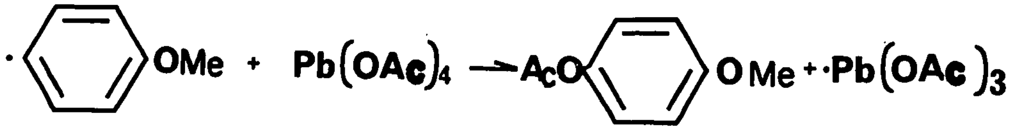
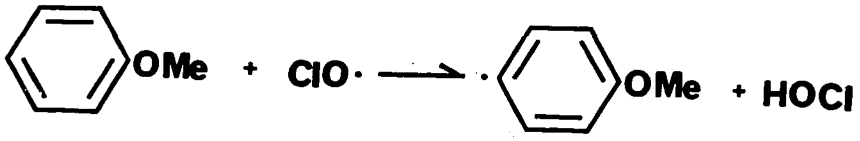

(43)

However, in the present experiments, dimers could not be isolated from the reddish-brown syrup previously described. Nevertheless, the possibility of the participation of methoxyphenyl radicals in the first stage of the reaction is not excluded. A reaction sequence such as in equations 44 to 46 may be visualized, in which step 44 is rate controlling and slow because the hydrogen atom on the aromatic ring is not easily abstractable.



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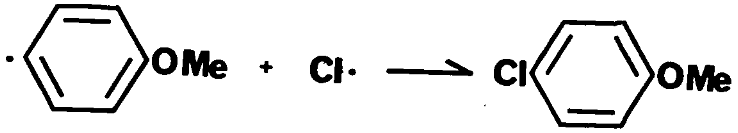
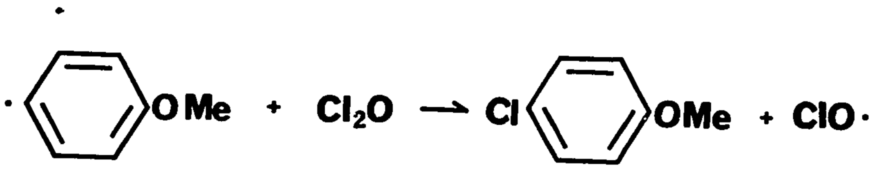


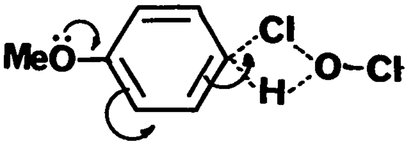
(45)

or



(46)

Another mechanism to consider is that chlorine monoxide may act as an electrophile as in the mechanism of the reaction of anisole with sulfuryl chloride as proposed by Bolton and de la Mare40).



However by this mechanism, demethylation or other side reactions are not explained. Therefore, it may be excluded as an admissible alternative.

# EXPERIMENTAL

Melting points were determined on a calibrated Fisher Johns apparatus. Infrared spectra were recorded on a Unicam SP-200 G infrared spectrometer, and p.m.r. spectra were taken on a Varian A-100 or T-60 spectrometer, with tetramethylsilane as an internal or an external standard. Mass spectra were measured on a AEI Model M3902 mass spectrometer operating at 70 eV. Gas-liquid chromatograms were done on a Perkin-Elmer Vapor Fractometer Model 154 with a High Capacity Golay Column and helium as a carrier gas. Elementary analyses were performed by Schwarzkopf Microanalytical Laboratory of Woodside, N.Y., and Daessle Organic Microanalyses of Montreal, P.Q. Ultra-violet spectra were recorded on a Unicam SP-800 4V spectrometer.

The carbon tetrachloride used as solvent in the reactions was Fisher reagent grade dried with phosphoric oxide and then distilled over phosphoric oxide.

Phenol, p-cresol, o-cresol and anisole used as starting materials were all prepared by distillation of the commercial reagent grade and their purity was checked by thin-layer chromatography.

Preparation of chlorine monoxide

In accordance with Cady[3)], 120 g of dry mercury oxide (yellow) was added to 500 ml of a dry solution of chlorine in carbon tetrachloride ($Cl_2$ 50g/l) at 25° and the mixture was stirred for 45 minutes. The solution was separated from the solid by filtering through a glass-fiber filter. Iodometric titration showed that the concentration of chlorine monoxide was 30.9 g/l (0.435 mol/l) and free of chlorine.

Freshly prepared solution was always used for the reactions.

## Reaction of phenol with chlorine monoxide

Ten grams of phenol (0.13 mol) was dissolved in 200 ml of carbon tetrachloride. The solution was cooled in an ice bath, and stirred. While 150 ml of the chlorine monoxide solution (0.065 mol) was added drop by drop, the temperature of the reaction mixture was kept between 10° and 15°. Soon after the first few drops of reagent had been added, the solution became cloudy. Iodometric titration of the mixture demonstrated that the reaction rate was so fast that no active chlorine could be detected immediately after the chlorine monoxide solution had been added. After the reaction mixture had stood undisturbed overnight, a small amount of water with a yellowish brown color floated on the surface of the carbon tetrachloride solution.

The reaction mixture was washed with water, and the combined washings were extracted with ether. After drying the ether solution over anhydrous sodium sulfate, and evaporating it, the yield of the residue was 4.5 g.

From the carbon tetrachloride solution 10.8 g of residue was obtained after evaporation.

## Isolation of o-, and p-chlorophenol

The carbon tetrachloride-soluble residue was subjected to fractional distillation at normal pressure up to 200°, and then under vacuum of 4.5 mm Hg. A distillate boiling at 173°C had an infrared spectrum identical to that of authentic o-chlorophenol. A fraction boiling at 65-75° at 4.5 mm Hg crystallized. Its m.p. was 37°; its infrared spectrum was idential to that of authentic p-chlorophenol.

Among the water-soluble products, o- and p-chlorophenol were detected by thin layer chromatography and gas-liquid chromatography.

### Isolation of 2,4-, and 2,6-dichlorophenol

Thin layer chromatography, on silica gel G, with benzene as a solvent, of the distillate that boiled at a temperature intermediate to the boiling points of o-chlorophenol and p-chlorophenol, revealed that it was a mixture of those two compounds and dichlorophenols. By means of column chromatography on silica gel, with benzene as an eluant, 2,4- and 2,6-dichlorophenol were isolated and identified by their infrared spectra.

Among the water-soluble products, the two dichlorophenols were also detected by thin layer chromatography.

### Quantitative analysis of o-chlorophenol, p-chlorophenol, 2,4-dichlorophenol and 2,6-dichlorophenol

Quantitative analysis of the water extracts and of the carbon tetrachloride-soluble portion by gas-liquid chromatography at 180°C, with a carrier gas flow rate 30 ml/min, indicated that the total yield of o-chlorophenol was 64.5%, p-chlorophenol, 21.9%, and 2,6- and 2,4-dichlorophenol, 4.7%.

The latter two compounds failed to separate under these conditions.

The retention times on the gas-liquid chromatogram and $R_f$ values on the thin layer chromatogram of the chlorophenols are listed in Table 2.

| | Retention time (min)* | $R_f$ Value** |
|---|---|---|
| Phenol | 4.08 | |
| o-Chlorophenol | 3.75 | 0.36 |
| p-Chlorophenol | 5.95 | 0.23 |
| 2,4-Dichlorophenol | 4.45 | 0.29 |
| 2,6-Dichlorophenol | 4.45 | 0.42 |

* 180°C, Gas flow 30 ml/min.

** Silica gel G. with benzene

Table 2 Retention times and $R_f$ values of chlorophenols in g.l.c. and t.l.c.

## Separation of each component from the water extract

The water extracts, on thin layer chromatography on silica gel G, with a solvent mixture of toluene and ethyl formate (2:1), appeared to contain seven components. Separation was attempted on a silica gel column, with a solvent mixture of benzene and methanol, 20:1. The earliest fractions contained phenol, o-chlorophenol, p-chlorophenol, 2,6-, and 2,4-dichlorophenol. From later fractions two crystalline compounds were isolated.

## Identification of 2-chlororesorcinol (V)

The first crystalline product was purified by sublimation, and yielded 4 mg of 2-chlororesorcinol, m.p. 88°. Its identity was confirmed by mixed m.p. and by comparing its infrared spectrum and mobility on t.l.c. with those of a synthetic sample. Its mass spectrum showed a parent peak at m/e 144, accompanied by a P + 2 peak of 1/3 the intensity of the parent peak.

### Identification of 4-chlororesorcinol (VI)

The second product was also purified by sublimation, and yielded 20 mg of 4-chlororesorcinol (VI) m.p. 102. Its infrared, p.m.r., and mass spectra suggest the structure of VI. The infrared spectrum and $R_f$ value on t.l.c. of this material were identical with those of a synthesized authentic sample. The mixed m.p. showed no depression.

Anal. Found C, 50.1 ; H, 3.6.

Calcd. for $C_6H_5O_2Cl$ C, 49.5; H, 3.4.

### Synthesis of 2-chlororesorcinol

According to the Hemmelmayr's procedure[58)], 20 g of β-resorcylic acid (1.3 mol) was treated with 100 ml of nitric acid (d = 1.4) (1.5 mol) to yield 15 g of 5 nitro-β-resorcylic acid (53 %), m.p. 226° (lit. 215°). The yield was not reported in the literature.

The following experiments followed the method reported by Milligan and Hope[59)]. The yield was not reported in the literature. The compound 3-chloro-5-nitro-β-resorcylic acid was prepared by treating 10 g (0.5 mol) of 5-nitro-p-resorcylic acid with 10 ml (0.45 mol) of sulfuryl chloride. Yield, 8 g, m.p. 251° (dec.) (lit. 252°).

Five grams (0.21 mol) of 3-chloro-5-nitro-β-resorcylic acid was then converted to 3-chloro-5-amino-β-resorcylic acid by reducing the former with stannous chloride. The amino compound was diazotized, and then reduced by stannous chloride to remove the diazo group. After reduction was complete, the reaction mixture was boiled with concentrated hydrochloric acid to cause decarboxylation. Finally, a yield of 200 mg (0.7%) of 2-chlororesorcinol was obtained; m.p. 88° (lit. 97-98° uncorr.).

Synthesis of 4-chlororesorcinol

In a small scale reproduction of the procedure of Kolthoff, *et al.*$^{60)}$, 3.0 g (0.3 mol) of resorcinol was dissolved in 20 g of ethyl ether, cooled in an ice-bath, and 4 g (0.3 mol) of sulfuryl chloride was added drop by drop. One hour after the addition was complete, the ether was evaporated. The resulting syrup, yield, 4 g, was cooled until it crystallized, and then was purified by sublimation, to give a product, m.p. 102° (lit. m.p. 105°$^{61)}$, b.p. 131° at 7 mm Hg$^{60)}$. Yield was not reported.)

Reaction of p-cresol

A chlorine monoxide solution (0.097 mol) in carbon tetrachlorde was poured into 21 g (0.194 mol) of molten *p*-cresol at 45° with agitation. The solution became cloudy immediately, and on completion of the addition the temperature of the solution was 68°. After being allowed to stand overnight, the reaction mixture was extracted with water and then with 3% sodium hydroxide solution. Then the water extracts were extracted with ether, and the ether solution was dried over sodium sulfate and evaporated; yield of residue, 2.5 g. The sodium hydroxide solution was acidified and extracted with ether, and the ether solution, after drying, was evaporated, leaving a residue of 23.6 g. The neutral portion which had remained in carbon tetrachloride solution was recovered by evaporation of the carbon tetrachloride, yielding 0.67 g of residue.

## Separation and identification of each component in the sodium hydroxide-soluble products from p-cresol

The sodium hydroxide-soluble portion was distilled under vacuum at 3 mm Hg. The yield of distillate up to 70° was 15.8 g. Gas-liquid chromatography revealed that it contained 2-chloro-*p*-cresol, cresol and 2,6-dichloro-*p*-cresol in yields of 46%; 20% and 2% respectively. These compounds were separated by column chromatography on silica gel, with benzene as eluent.

The residual non-volatile phenolics were also subjected to chromatography on a silica gel column, with benzene-methanol (20:1) as eluent, and three phenolic dimers were isolated.

### 1. 2-Chloro-*p*-cresol

This compound was obtained as a liquid, and its mass spectrum showed a molecular weight of 142 and one chlorine atom in the molecule. Its infrared spectrum exhibited the typical pattern of the overtone and combination tone bands of 1,2,4-trisubstituted phenyl in the 1660-2000 $cm^{-1}$ region, with a band at 820 $cm^{-1}$ corresponding to the out-of-plane bending of two adjacent hydrogens and a band at 870 $cm^{-1}$ representing an isolated proton. The infrared spectrum, and the retention time of the gas-liquid chromatogram were identical with those of synthetic 2-chloro-p-cresol (see below).

### 2. 2,6-Dichloro-*p*-cresol

Column chromatography of the volatile phenolics yielded a liquid which solidified on standing. The solid was 2,6-dichlorophenol, m.p. 39°. Its p.m.r. spectrum showed a methyl group (singlet, 2.2 p.p.m.), and two phenyl hydrogens (singlet, 6.95 p.p.m.). Its infrared spectrum exhibited a band at 850 $cm^{-1}$ corresponding to 1,2,3,5-tetrasubstituted phenyl C-H out-of-plane bending and the typical pattern of the tetrasubstituted phenyl ring overtone and combination bands in the 1660-2000 $cm^{-1}$ region. The infrared spectrum, and the chromatographic mobility, both thin-layer and g.l.c., were identical with those of a synthetic sample of 2,6-dichloro-p-cresol.

3. 3,3'-Dichloro-5,5'-dimethylbiphenyl-2,2'-diol (X)

The earliest fraction separated from the non-volatile phenolic portion by column chromatography crystallized. It was purified by recrystallization from n-hexane, to yield 0.3 g of 3,3'-dichloro-5,5'-dimethylbiphenyl-2,2'-diol (X), m.p. 133-4° (lit. [32]) 136°). All results of the spectroscopy support the proposed structure (see Discussion).

| | | | |
|---|---|---|---|
| Anal. | C, 59.7; | H, 4.5; | Cl, 24.7 |
| Calcd. for $C_{14}H_{12}O_2Cl_2$ | C, 59.3; | H, 4.2; | Cl, 25.0 |

4. 3-Chloro-5,5'-dimethylbiphenyl-2,2'-diol (XI)

The second fraction from the column chromatography of the non-volatile phenolic portion was also purified by recrystallization from n-hexane, to yield 1.1 g of 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol, m.p. 125-6°. The infrared, p.m.r., and the mass spectra were consistent with the proposed structure (see Discussion).

| | | | |
|---|---|---|---|
| Anal. | C, 67.4; | H, 5.2; | Cl, 13.9 |
| Calcd. for $C_{14}H_{13}O_2Cl$ | C, 67.7; | H, 5.2; | Cl, 14.3 |

### 5. 5,5'-Dimethylbiphenyl-2,2'-diol (IX)

The third fraction of the column chromatography of the non-volatile phenolic fraction was a mixture of XI and another compound. The separation of both compounds was achieved by streaking the mixture on a silica gel thin-layer plate, and developing with a solvent mixture of toluene, ethyl formate, formic acid (5:4:1). The separated compound was recrystallized from n-hexane to yield 55 mg of 5,5'-dimethylbiphenyl-2,2'-diol, m.p. 148-50° (lit.[62]) 152-4°). Spectroscopic experiments support the proposed structure (see Discussion).

| | | |
|---|---|---|
| Anal. | C, 77.6; | H, 6.4 |
| Calcd. for $C_{14}H_{14}O_2$ | C, 78.5; | H, 6.5 |

### Synthesis of 2-chloro-p-cresol

According to the procedure of Sah and Anderson[63]), 20 ml (0.25 mole) of sulfuryl chloride was reacted with 27 g (0.25 mole) of p-cresol. The product, after having been washed with sodium carbonate solution, and dried over calcium chloride, was distilled. A fraction boiling at 195° to 197° was collected in a yield of 20 g (56%)(lit. yield 75%).

## Synthesis of 2,6-dichloro-p-cresol

To 10 g (0.07 mole) of 2-chloro-*p*-cresol, 8 ml (0.1 mole) of sulfuryl chloride was added at room temperature. The reaction mixture was warmed on a water bath until gas no longer evolved. Then the product was washed with a cold solution of sodium carbonate, and dried over calcium chloride. During this drying process, the product solidified. It was warmed until it melted, filtered and distilled, and a distillate boiling between 235° and 240° was collected. On cooling with ice, it solidified to give 8 g (64%) of white needles of 2,6-dichloro-*p*-cresol, m.p. 39° (lit. 39°64)). The p.m.r. spectrum showed three singlets, one of them corresponding to two equivalent protons on the phenyl ring.

The preparation of 2,6-dichloro-*p*-cresol in the previous literature64,65) employed only chlorine for chlorination of *p*-cresol. In the present work sulfuryl chloride was observed to be a convenient and useful reagent to prepare this compound.

## Isolation of 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone (XII)

From the neutral fraction of the *p*-cresol reaction products, a Pummerer's ketone was isolated by column chromatography on silica gel, with benzene as a solvent. The product, purified by recrystallization from n-hexane, yielded 330 mg of the ketone, mp. 136-8°C. Spectroscopic results support the proposed structure (See Discussion).

| | | | |
|---|---|---|---|
| Anal. | C, 66.5; | H, 5.5; | Cl, 15.8 |
| Calcd. for $C_{14}H_{13}O_2Cl$ | C, 67.7; | H, 5.2; | Cl 14.3 |

Separation of components of the water extracts from reaction of p-cresol

The water extracts were subjected to column chromatography on silica gel, with benzene-methanol (10:1) as a solvent. The earliest fraction was a mixture of three components. This mixture was again separated by column chromatography using silica gel and benzene, whereupon 290 mg of 2-chloro-*p*-cresol, 170 mg of *p*-cresol, and a small amount of 2,6-dichloro-*p*-cresol were obtained. From the other fractions of the first column chromatogram, the following compounds were isolated:

1. 2-Chloro-4-methylresorcinol (XIII)

A fraction which gave a red spot with diazotized benzidine on the silica gel G thin-layer chromatogram was purified by sublimation to yield 66 mg of 2-chloro-4-methylresorcinol (XIII), m.p. 83°. The infrared, p.m.r., and mass spectra support the proposed structure (see Discussion).

| | | |
|---|---|---|
| Anal. | C, 54.5; | H, 4.9; |
| Calcd. for $C_7H_7O_2Cl$ | C, 52.9; | H, 4.4 |

2. 3-Chloro-5-methyl catechol (XIV)

A fraction which gave a yellowish brown spot with diazotized benzidine on the silica gel G thin-layer chromatogram was purified by recrystallization from the n-hexane and yielded 200 mg of 3-chloro-5-methyl catechol, m.p. 63°. The spectroscopic results support the proposed structure (see Discussion).

| | | |
|---|---|---|
| Anal. | C, 52.4 | H, 4.5 |
| Calcd. for $C_7H_7O_2Cl$ | C, 52.9; | H, 4.4 |

3. 2-Chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone (XV)

One fraction gave no coloration with diazotized benzidine, but a faint pink color with 2,4-dinitrophenylhydrazine. It was recrystallized from n-hexane, yielding 55 mg of colorless prisms of 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone, m.p. 105-107°. The spectroscopic results support the proposed structure (see Discussion).

| | | |
|---|---|---|
| Anal. | C, 53.8; | H, 4.7 |
| Calcd. for $C_7H_7O_2Cl$ | C, 52.9; | H, 4.4 |

## Treatment of 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone (XV) with dilute sulfuric acid

In 6 ml of 3% sulfuric acid solution, 10 mg of XV was dissolved. The solution was heated for 3 hours on a steam bath, then, after cooling, was extracted with ether. The extract was spotted on a silica gel G thin-layer plate and developed with (1) benzene:methanol (10:1) and (2) toluene:ethylformate:formic acid (5:4:1). Three spots appeared on the chromatogram. One was identical with authentic 2-chloro-5-methylhydroquinone, and the second was identical with XIII but the third could not be identified because of its small quantity.

| Substance | $R_f$ Solvent 1* | $R_f$ Solvent 2** | Color with diazotized benzidine |
|---|---|---|---|
| XIII | 0.31 | 0.41 | red |
| 2-chloro-5-methylhydroquinone | 0.24 | 0.36 | yellow (fading later) |
| unknown | 0.19 | 0.30 | yellow |

* Benzene, methanol 10:1

** Toluene, ethylformate, formic acid 5:4:1

Table 3 Thin-layer chromatogram on silica gel G of dienone-phenol rearrangement products from XV.

### Synthesis of 2-chloro-5-methylhydroquinone

In a modification of the procedure of Clark[66)], 5 g (0.041 mol) of p-toluquinone was dissolved in 50 ml chloroform (a 15% solution was used in the literature). Dry hydrogen chloride gas was passed into the solution until all of the yellow toluquinone was converted to a colorless phenolic compound which precipitated as needle-like crystals. After filtration, it was recrystallized once from water containing sulfurous acid and from ligroin to yield 4.5 (70%) of 2-chloro-5-methylhydroquinone, m.p. 175° (lit. 176°. The yield was not reported[66]).

## Reaction of o-cresol with chlorine monoxide

Under the same conditions as in the reaction of p-cresol, 15 g of o-cresol (0.14 mol) was treated with chlorine monoxide solution. After it had stood overnight, the reaction mixture was extracted with water, and the water solution was, in turn, extracted with ether. The carbon tetrachloride solution itself, on evaporation, gave 17.5 g of residue. A gas chromatogram of the residue indicated that it contained 6-chloro-o-cresol in a yield of 55.0%, 4-chloro-o-cresol in a yield of 22.2%, 4-6-dichloro-o-cresol in a yield of 4.0%, and o-cresol in 8,2% yield.

## Separation of products from the carbon tetrachloride-soluble portion of reaction products from o-cresol

The residue from the fraction soluble in carbon tetrachloride was subjected to column chromatography on silica gel, with benzene as solvent. The following compounds were isolated and identified.

1. 6-Chloro-o-cresol (XVI).

A fraction of the column chromatogram was a liquid whose infrared spectrum had bands at 715 $cm^{-1}$ and 760 $cm^{-1}$ corresponding to 1,2,3-trisubstituted phenyl proton out-of-plane bending bands, with the typical pattern of absorption in the region of 1660-2000 $cm^{-1}$. When 2 g of this compound (0.014 mol) was treated with 1.5 g of sulfuryl chloride (0.011 mol), 4,6-dichloro-o-cresol was obtained in a yield of 1.5 g. From this evidence the compound is 6-chloro-o-cresol.

### 2. 4-Chloro-*o*-cresol (XVII)

A fraction of the column chromatogram was crystalline, m.p. 45° (lit. 48-9°[63]). Its infrared spectrum had a pair of bands at 810 $cm^{-1}$ and at 860 $cm^{-1}$ corresponding to 1,2,4-trisubstituted phenyl C-H out-of-plane bending bands, with the corresponding typical pattern of absorption in the region of 1660-2000 $cm^{-1}$. An authentic sample of 4-chloro-*o*-cresol was synthesized (see below). Both infrared spectra were identical, and the mixed m.p. showed no depression.

### 3. 4,6-Dichloro-*o*-cresol ~~([illegible])~~ (XVIII)

A fraction of the column chromatogram contained two components. One was XVII, and the other was a compound whose mass spectrum indicated a molecular weight of 178 with two chlorine atoms in the molecule. Its chromatographic mobility, both on thin-layer chromatography (silica gel C, benzene) and gas-liquid chromatography, was identical with that of a synthetic 4,6-dichloro-*o*-cresol (see below).

### Synthesis of 4-chloro-o-cresol

According to the procedure of Sah and Anderson[63], 27 g (0.25 mol) of *o*-cresol was reacted with 20 ml (0.25 mol) of sulfuryl chloride. The product, b.p. 220~225°, was collected in a yield of 25 g (70%). It crystallized on standing, and melted at 45° (lit. m.p. 48-9°; yield in the literature was described just as "good yield").

### Synthesis of 4,6-dichloro-o-cresol

To 10 g (0.07 mol) of molten 4-chloro-*o*-cresol, 8 ml (0.1 mol) of sulfuryl chloride was added. The mixture was heated on a water bath until the reaction ended, and, after washing with a sodium carbonate solution, was dissolved in ether. The ether layer was dried over sodium sulfate, and then evaporated. The residue solidified, and was recrystallized from benzene to yield 10 g (81%) of product, m.p. 53° (lit.[67] m.p. 55°. In the literature, chlorine was reacted with o-cresol. The yield was 81%). The infrared spectrum of the product exhibits a band at 850 $cm^{-1}$ corresponding to the out-of-plane bending absorption of a 1,2,3,5-tetrasubstituted phenyl C-H.

### Isolation of 2-chloro-4-methyl resorcinol from the water extracts of products from o-cresol

The water extracts were chromatographed on a column of silica gel, with benzene-methanol (10:1) as solvent. The earliest fraction was a mixture of four compounds, XVII, XVIII, XIX and o-cresol, as detected by thin-layer chromatography on silica gel G, with benzene as solvent.

One fraction gave a red color with diazotized benzidine on a thin layer chromatogram. It was eluted and crystallized, then purified by sublimation to yield 43 mg of 2-chloro-4-methyl resorcinol, m.p. 83°. The mixed m.p. with XIII previously isolated showed no depression. The infrared and p.m.r. spectra were identical with those of XIII.

Another fraction also gave a resorcinol-type color reaction with diazotized benzidine, but the amount was so small that the fraction was not identified.

### Reaction of anisole with chlorine monoxide

In 200 ml of carbon tetrachloride, 13.5 g (0.12 mol) of anisole was dissolved, and the solution was treated with a chlorine monoxide solution in carbon tetrachloride ($Cl_2O$, 0.06 mol) under the same conditions as in the reaction of phenol described above. After the mixture had stood overnight, it was extracted with water. The water solution was re-extracted with the ether extract, after drying over sodium sulfate, was evaporated, leaving 2.0 g of residue. The carbon tetrachloride solution, after evaporation, was subjected to gas chromatography. Column chromatography was applied to the separation of the water-soluble components.

### Gas chromatography of the carbon tetrachloride-soluble portion of the anisole reaction products

Gas chromatography indicated that the carbon tetrachloride soluble portion contained *p*-chloroanisole, *o*-chloroanisole and anisole, with retention times identical to those of authentic samples. Quantitative analysis by gas chromatography gave the yields as *p*-chloroanisole, 41.2%; *o*-chloroanisol, 20.1%; unreacted anisole, 24%.

| Substance | Retention time (min) |
|---|---|
| Anisole | 4.60 |
| *p*-chloroanisole | 5.38 |
| *o*-chloroanisole | 5.55 |

150° Gas flow rate 20 ml/min.

Table 4 Retention time of monochloroanisole

## Separation of components from the water-soluble products from anisole

The water soluble products were subjected to column chromatography on silica gel with benzene-methanol (20:1) as a solvent. The first fraction was a mixture of 2,4- and 2,6-dichlorophenol as detected by thin-layer chromatography on silica gel G, with benzene as a solvent. From other fractions, 2-chlororesorcinol and 4-chlororesorcinol were also detected on a silica gel G thin-layer chromatogram with a solvent mixture of toluene-ethyl formate (2:1). The color developed with diazotized benzidine was characteristic for each compound: a light red for 2-chlororesorcinol, and a deep purple red for 4-chlororesorcinol. The yield of 4-chlororesorcinol was 14 mg, and of 2-chlororesorcinol was 6 mg. Both compounds were identified by comparison with the authentic samples described above.

Compounds isolated from the other fractions and identified, are described in subsequent sections. The rest of the components of the product, remained unidentified. It constituted a major part of the water extracts, was strongly adsorbed on the silica gel in a zone of reddish-brown color. About 1 g of a reddish-brown syrup was recovered by eluting the column with methanol. Attempts were made to isolate pure compounds from the syrup, but failed.

### 1. Chlorohydroquinone

A colorless crystalline substance, m.p. 107°, was isolated from a fraction of the column chromatogram, and purified by sublimation, yielding 80 mg of pure product. The infrared spectrum of this compound exhibited a band at 800 $cm^{-1}$ and a band at 855 $cm^{-1}$ corresponding to a 1,2,4-trisubstituted phenyl. The mass spectrum had a parent peak at <u>m/e</u> 144 accompanied by a P + 2 peak whose intensity was 1/3 of the parent peak, thus showing the presence of a chlorine atom. An authentic sample of chlorohydroquinone was synthesized64). The mixed m.p. showed no depression, and the infrared and p.m.r. spectra of these two materials were identical.

| | | |
|---|---|---|
| Anal. | C, 49.3; | H, 3.6 |
| Calcd. for $C_6H_5O_2Cl$ | C, 49.5; | H, 3.4 |

2. 2,4-Dichlororesorcinol (XXIII)

A fraction from the column chromatogram yielded colorless fine prisms. They were recrystallized from n-hexane and sublimed, to yield 50 mg of product, m.p. 78-9°.

The p.m.r. spectrum ($CCl_4$) of the compound indicated the presence of *ortho*-phenyl protons (an AB type (J = 8.0 c/s) signal at 6.7 p.p.m.) and two hydroxyl groups (two signals at 5.4 p.p.m. and 5.6 p.p.m.). The latter signals disappeared after the compound was treated with deuterium oxide. The compound did not reduce silver nitrate in ammonia solution. Its mass spectrum exhibited a parent peak at *m/e* 178, and showed the presence of two chlorine atoms in the molecule by a P + 2 peak, whose intensity was 2/3 of the parent peak. An authentic sample of 2,4-dichlororesorcinol was synthesized (see below). The mixed m.p. showed no depression, and the infrared and p.m.r. spectra of the two materials were identical.

| | | |
|---|---|---|
| Anal. | C, 39.9; | H, 2.2 |
| Calcd. for $C_6H_4O_2Cl_2$ | C, 40.1; | H, 2.2 |

3. 2,4,6-Trichlorophenol (XXI)

A colorless crystalline compound, m.p., 65-66.5°, was isolated from an early elute from the column, and gave 20 mg of product after purification by recrystallization from n-hexane and sublimation. The mass spectrum of this compound had a parent peak at m/e 196, accompanied by a P + 2 peak of almost the same intensity as the parent peak. The infrared spectrum exhibited a band at 865 $cm^{-1}$ corresponding to 1,2,3,5-tetrasubstituted phenyl C-H out-of-plane bending band. The infrared spectrum was identical with that of authentic 2,4-6-trichlorophenol.

| | | |
|---|---|---|
| Anal. | C, 36.9; | H, 1.7 |
| Calcd. for $C_6H_3OCl_3$ | C, 36.5; | H, 1.5 |

## Synthesis of the chlorohydroquinone

In accordance with Conant and Fieser[68)], dry hydrogen chloride was passed into a solution of 10 g (0.92 mol) of benzoquinone in 100 ml of chloroform. White crystals produced by the reaction were filtered and recrystallized from chloroform, to yield 10 g (75%) of chlorohydroquinone, m.p. 102° (lit. yield 74%, m.p. 101-102°).

## Synthesis of 2,4-dichlororesorcinol

Two hundred milligrams (0.0014 mol) of 2-chlororesorcinol which had been synthesized from β-resorcylic acid as described above was dissolved in 5 ml of anhydrous ether. This solution was cooled in an ice bath, and 0.16 ml (0.002 mol) of sulfuryl chloride was dropped into it. After 10 minutes, the ether was evaporated. Sublimation of the residue gave white crystals, which were recrystallized from n-hexane, to yield 200 mg (80%) of 2,4-dichlororesorcinol, m.p. 76°. (lit.[55)], 80-81°).

The p.m.r. spectrum of this compound showed an AB type of <u>ortho</u>-phenyl protons with a coupling constant of $J = 8.0$ cps. and two individual hydroxyl protons which disappeared on deuteration with $D_2O$.

Grover, <u>et</u> <u>al</u>.$^{50)}$ synthesized 2,4-dichlororesorcinol from β-resorcylic acid through 3,5-dichloro-β-resorcylic acid, which was subjected to decarboxylation. The yield by their procedure was not reported.

### <u>Detection of chlororesorcinols in the reaction products from o- and p-chlorophenol with chlorine monoxide</u>

<u>o</u>-Chlorophenol and <u>p</u>-chlorophenol were treated with chlorine monoxide under the same conditions as in the reaction of phenol. Neither 2-chlororesorcinol nor 4-chlororesorcinol was produced from either starting material, but, 2,4-dichlororesorcinol was detected among the reaction products from <u>p</u>-chlorophenol by thin-layer chromatography.

### <u>Reaction of hydroquinone with chlorine monoxide</u>

In 50 ml of ether, 2 g (0.018 mol) of hydroquinone was dissolved; and while the solution was cooled in an ice bath, chlorine monoxide solution in carbon tetrachloride (0.009 mol) was added. One hour later, the reaction mixture was spotted on a silica gel G thin layer plate and developed by a solvent mixture of toluene, ethylformate, formic acid (5:4:1). Chlorohydroquinone was detected on the chromatogram by spraying with diazotized benzidine.

### <u>Reaction of resorcinol with chlorine monoxide</u>

Resorcinol was treated with chlorine monoxide under the same conditions as above. The formation of 4-chlororesorcinol and 2,4-dichlororesorcinol was detected by t.l.c.

## Electron spin resonance experiments on the reaction mixtures of phenols and anisole with chlorine monoxide

In a mixing cell, a 0.1 M solution of p-cresol and 0.1 M solution of chlorine monoxide, both in carbon tetrachloride, were mixed at a rate of flow of 7 ml/sec. The signal was recorded on a Varian E3 electron spin resonance spectrometer. The signal obtained from p-cresol is shown in Fig. 20. Under the same conditions neither phenol nor anisole exhibited a signal.

## Free radical detection with diphenylpicrylhydrazyl (DPPH)

A solution of DPPH ($4.3 \times 10^{-3}$ mol/l) was gradually added to 1 ml of a solution of chlorine monoxide in carbon tetrachloride ($3.5 \times 10^{-1}$ mol/l). The first 0.1 ml of DPPH was consumed by chlorine monoxide and a light brown color was observed. When 0.2 ml of DPPH had been added, the purple color of DPPH was retained for a time. At this stage, one drop of anisole was added, and the solution immediately turned yellow.

To 10 ml of 5% anisole solution in carbon tetrachloride, 0.2 ml of the DPPH solution was added. When 1 ml of the chlorine monoxide solution was added, the purple color immediately turned yellow.

To 10 ml of 5% phenol in carbon tetrachloride, 0.2 ml of the DPPH solution was added. When 1 ml of the chlorine monoxide solution was added to the solution, the color immediately disappeared to give a colorless solution.

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# CLAIMS TO ORIGINAL RESEARCH

## CLAIMS TO ORIGINAL RESEARCH

1. Reaction of chlorine monoxide with phenols, namely, phenol, p-cresol, and o-cresol, was performed for the first time and investigated. Monochlorophenols were obtained as the major products. As the minor products, dichlorophenols, newly hydroxylated chlorophenols, and phenyl-phenyl coupled dimers were obtained.
2. Reaction of anisole with chlorine monoxide yielded monochloroanisoles as the major products. As the minor products, dichlorophenols, a trichlorophenol and some dihydroxychlorobenzenes were obtained. The formation of these phenols indicates that demethylation is an important side reaction of phenol ethers with chlorine monoxide.
3. Based on the evidence put forward in this thesis, free-radical mechanisms have been proposed for the reaction of both phenols and anisole.
4. The formation of chlororesorcinols from phenols, which is an abnormal 1,2-substitution on the phenyl ring, was explained by distribution of spin densities on the phenyl ring of the aryloxy radical.
5. A Pummerer's ketone, 2-chloro-4a,9b-dihydro-8,9b-dimethyl-3(4H)-dibenzofuranone, was isolated and characterized for the first time.
6. A quinol, 2-chloro-4-hydroxy-4-methyl-2,5-cyclohexadienone, was isolated and characterized for the first time.

7. In a dienone-phenol rearrangement reaction of the above quinol, migration of the hydroxyl group was observed, in addition to methyl group migration. The direct migration of the hydroxyl group of quinol has not previously been reported.

8. The compound 2-chloro-4-methylresorcinol was isolated and characterized for the first time.

9. The compound 3-chloro-5,5'-dimethylbiphenyl-2,2'-diol was isolated and characterized for the first time.

10. The compound 2,4-dichlororesorcinol was prepared by a new route from β-resorcylic acid <u>via</u> 2-chlororesorincol.