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The Alkyl Derivatives of Halogen Phenols and their Bactericidal Action. I. Chlorophenols

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Introduction

We have shown in a recent paper[1] that halogen derivatives of hydroxydiphenylmethane are bactericidal; some of them manifest a highly destructive potency, particularly with respect to the two resistant Gram-positive microörganisms studied, *viz.*, *Staphylococcus aureus* and *Streptococcus hemolyticus*. Since recent research work on the relationship between chemical constitution and antibacterial action of phenol derivatives quite generally seems to point to the great importance of the size of the molecule as one of the major factors influencing the degree of bactericidal efficacy, we expected to find interesting conditions in the series of substituted monohalogen phenols; incidentally, the halogen derivatives of hydroxydiphenylmethane, referred to above, may be regarded as belonging to a sub-group of the series of substituted halogen phenols since they may be also described as benzyl halogen phenol derivatives.

The bactericidal properties of the unsubstituted monohalogen phenols and of some of their simple alkyl derivatives (such as chlorocresol and chloroxylenol) have long been known and utilized. In this connection attention should be called to the work of Laubenheimer,[2] Cooper and Woodhouse,[3] Kuroda,[4] Engelhardt,[5] Klarmann, Shternov and Von Wowern,[6] and Etinger-Tulczynska and Ulrich;[7] this list is not exhaustive. Recently the bacteriological interest in this series of phenol derivatives has been extended to the halogen derivatives of thymol and carvacrol. The bactericidal action of chlorothymol has been referred to in the papers of Laubenheimer,[8] of Klarmann and co-workers[9] and of Etinger-Tulczynska and Ulrich,[7] that of chlorocarvacrol was studied by Kuhn;[10] bromothymol and bromocarvacrol were investigated by Klarmann, Shternov and Von Wowern.[9]

In the present work our interest was directed toward a systematic investigation of the germicidal action of the monohalogen substituted phenol homologs, in relation to their chemical constitution. We prepared, therefore, a complete series of the *o*-alkyl derivatives of *p*-chlorophenol, that of

(1) Klarmann, Gates and Shternov, THIS JOURNAL, **54**, 3315 (1932).
(2) Laubenheimer, "Das Phenol und seine Derivate als Desinfektionsmittel," 1909.
(3) Cooper and Woodhouse, *Biochem. J.*, **17**, 600 (1923).
(4) Kuroda, *Arch. exp. Pathol., Pharmakol.* **112**, 60 (1926).
(5) Engelhardt, *Biochem. Z.*, **190**, 216 (1927).
(6) Klarmann, Shternov and Von Wowern, *J. Bacteriol.*, **17**, 427 (1929).
(7) Etinger-Tulczynska and Ulrich, *Z. Hyg. Infektionskrankh.*, **113**, 437 (1932).
(8) Laubenheimer, *Deut. med. Wochschr.*, **54**, 481 (1928).
(9) Klarmann, Shternov and Von Wowern, *J. Bacteriol.*, **17**, 427 (1929).
(10) Kuhn, *Arch. Hyg.*, **105**, 18 (1930).

p-alkyl derivatives of *o*-chlorophenol and a number of polyalkyl chlorophenol derivatives. Having learned from our previous work[11] that in the case of phenol derivatives a bacterial "group-specificity" may become apparent as the homologous series is ascended, we employed among our test organisms representatives of the groups of Gram-negative, Gram-positive and acid-fast bacteria, and also a pathogenic fungus; the organisms used were *Eberthella typhi*, *Eberthella paradysenteriae* (Flexner), *Staphylococcus pyogenes aureus*, *Streptococcus* (hemolytic strain), *Mycobacterium smegmatis* and *Trichophyton rosaceum*.

All tests were carried out at 37° and the "phenol coefficients" were calculated from the minimum concentrations effective in ten minutes. The details of the bacteriologic technique used will be described elsewhere.

Bactericidal Action of *o*-Alkyl Derivatives of *p*-Chlorophenol.—The relation between the bactericidal action of the compounds of this group (expressed in terms of "phenol coefficient") and their chemical constitution appears in Table I, and is illustrated graphically in Figs. 1 and 2. A consideration of these two graphs and of the numerical values of the phenol coefficients immediately reveals the phenomenon of a "quasi-specific" group parallelism referred to above, and observed in our previous work. Thus in the case of the Gram-negative *Eberthella typhi* and *Eberthella paradysenteriae*, the bactericidal efficacy increases with the increasing weight of the substituting side chain, reaching a maximum with the *n*-amyl, or *n*-hexyl derivatives, respectively, and decreasing rapidly with the substituting alkyl radicals of still greater weight; on the other hand, the maximum of germicidal action upon the other microörganisms studied

TABLE I

BACTERICIDAL ACTION OF *o*-ALKYL DERIVATIVES OF *p*-CHLOROPHENOL (PHENOL COEFFICIENTS)

	Eberthella typhi	*Eberthella paradysenteriae*	*Staphylococcus pyogenes aureus*	*Streptococcus* (hemolytic strain)	*Mycobacterium smegmatis*	*Trichophyton rosaceum*
p-Chlorophenol	4.3	4.7	4.3	4.4	3.9	4.2
Alkyl radical						
Methyl	12.5	14.3	12.5	11.1	13.3	11.7
Ethyl	28.6	32.1	34.4	31.3	25.0	27.5
n-Propyl	93.3	100	93.8	77.8	88.9	83.3
n-Butyl	141	167	257	250	156	160
n-Amyl	156	200	500	556	400	400
Sec-amyl	46.7	80	312	312	389	250
n-Hexyl	(23.2)	333	1250	1333	1111	500
Cyclohexyl		80	438	361	278	300
n-Heptyl		133	1500	2220	1250	667
n-Octyl		(26.7)	1750	>667	156	
Sec-octyl			1000	>555	>100	>50

(11) Klarmann, Gates and Shternov, THIS JOURNAL, **54**, 3315 (1932); **53**, 3397 (1931); **54**, 298, 1204 (1932).

is reached apparently with the *n*-heptyl derivative, although the *n*-octyl derivative is somewhat more effective against *Staphylococcus aureus* than the *n*-heptyl compound. It is of the greatest interest that the behavior of the acid-fast *Mycobacterium smegmatis* and of the fungus *Trichophyton rosaceum* parallels that of the cocci both in a qualitative and a quantitative respect.

From a quantitative point of view it is noteworthy that the lower and the higher alkyl derivatives of *p*-chlorophenol show a relatively different behavior toward the two Gram-negative *Eberthellae* on one hand, and the remaining four microörganisms on the other. Thus, beginning with the unsubstituted *p*-chlorophenol, and up to and including the *n*-butyl derivative, *Eberthella typhi* and *Eberthella paradysenteriae* are killed by lower concentrations than the other organisms. Beginning with the *n*-amyl compound the conditions are reversed; the minimum effective concentrations for the four organisms referred to above continue to decrease until in the case of 2-*n*-heptyl-4-chlorophenol one finds that they are killed in exceedingly low concentrations, as indicated by the extremely high phenol coefficients. Thus the higher alkyl derivatives manifest a "quasi-specific" specific efficacy which agrees entirely with that of the other phenol derivatives of high molecular weight, such as the mono ethers of dihydric phenols and the halogen derivatives of hydroxydiphenylmethane.[11]

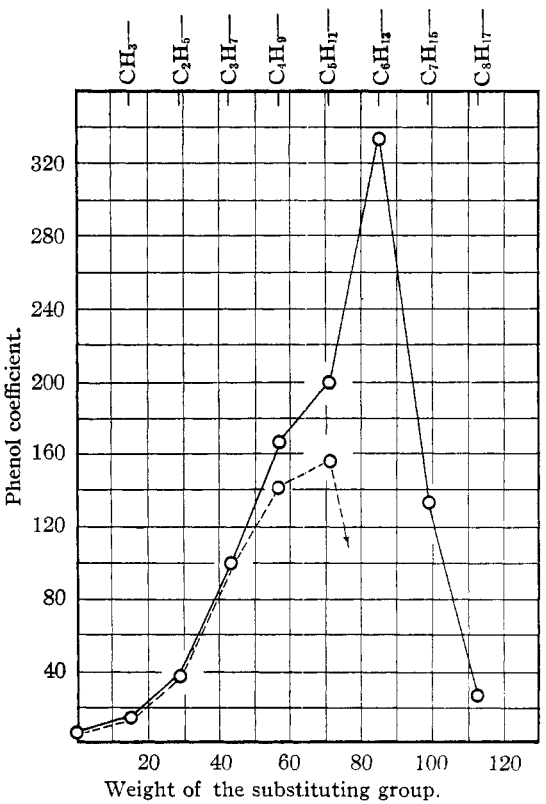


Fig. 1.—The bactericidal action of normal *o*-alkyl derivatives of *p*-chlorophenol. Test organisms: *Eberthella typhi*, dash line; *Eberthella paradysenteriae* (Flexner), full line.

In addition to the straight chain aliphatic derivatives, we have prepared and investigated two compounds with branched side chains. As has

been found in other instances of alkyl substituted phenol derivatives, here, too, the germicidal action upon all test organisms is weaker than that of the corresponding normal derivatives.

2-Cyclohexyl-4-chlorophenol shows only a fraction of the bactericidal potency of the corresponding *n*-hexyl derivative.

Bactericidal Action of *p*-Alkyl Derivatives of *o*-Chlorophenol.—The germicidal action of this group of phenol derivatives resembles that of the preceding one in that here, too, it increases with increasing molecular weight; however, the alkyl derivatives of *o*-chlorophenol are generally less microbicidal than the corresponding derivatives of *p*-chlorophenol.

Table II and Figs. 3 and 4 illustrate the conditions encountered in this series. Again the bacteriological group-specificity is in evidence. The maximum efficacy with respect to *Eberthella typhi* is shown by 4-*n*-butyl-2-chlorophenol, while with respect to *Eberthella paradysenteriae* the butyl and the amyl derivatives appear to be equally effective. Thereafter the action upon these two microörganisms begins to decrease with increasing molecular weight, while with respect to the other four microörganisms it continues to increase, the maximum being reached with 4-*n*-hexyl-2-chlorophenol.

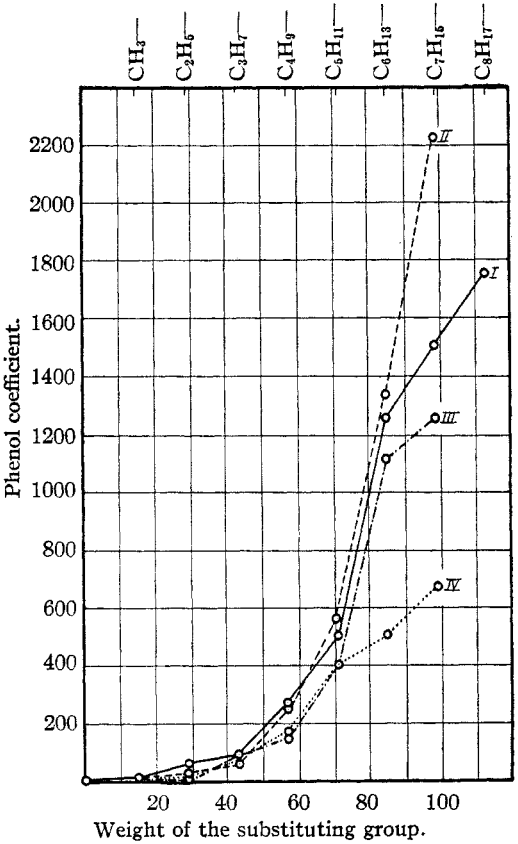


Fig. 2.—The bactericidal action of normal *o*-alkyl derivatives of *p*-chlorophenol. Test organisms: I, *Staphylococcus aureus;* II, *Streptococcus* (hemol.); III, *Mycobacterium smegmatis;* IV, *Trichophyton rosaceum.*

The alkyl derivatives of *o*-chlorophenol up to and including the butyl derivative, kill *Eberthella typhi* and *Eberthella paradysenteriae* in lower concentrations than the other four microörganisms, while the converse is true of the derivatives with five or more carbon atoms in the side chain.

TABLE II

BACTERICIDAL ACTION OF *p*-ALKYL DERIVATIVES OF *o*-CHLOROPHENOL (PHENOL COEFFICIENTS)

	Eberthella typhi	*Eberthella paradysenteriae*	*Staphylococcus pyogenes aureus*	*Streptococcus* (hemolytic strain)	*Mycobacterium smegmatis*	*Trichophyton rosaceum*
o-Chlorophenol	2.5	2.3	2.9	2.0	2.2	<1
Alkyl radical						
Methyl	6.3	5.3	7.5	5.6	6.3	7.0
Ethyl	17.2	13.3	15.7	15.0	15.6	14.0
n-Propyl	37.5	40.0	32.1	35.0	33.3	>33.0
n-Butyl	86.7	80.0	93.8	88.9	125	80.0
n-Amyl	80.0	80.0	286	222	250	>250
Tert-amyl	(32.1)	46.7	125	138	138	145
n-Hexyl		(35.7)	714	625	500	>420
n-Heptyl			375	350	200	>290

Polyalkyl Derivatives of *o*- and *p*-Chlorophenol.—As the data in Table III indicate, this series, too, contains some extremely potent microbicides.

As far as the determining effect of the molecular weight of the substituting groups upon the germicidal potency is concerned, we find here substantially the same conditions as in the case of the monoalkyl derivatives.

It is to be noted further that the bactericidal action is generally weaker when this molecular weight is distributed over two or more substituents. (In Table III the compounds prepared are grouped in the order of increasing molecular weight.) Thus, for example, in the case of normal *p*-chlorophenol derivatives in which the total number of carbon atoms in the substituting groups is four, we have the following derivatives to consider: 2-*n*-butyl-4-chlorophenol, 6-*n*-propyl-3-methyl-4-chlorophenol, and 2-ethyl-3,5-dimethyl-4-chlorophenol. The phenol coefficients with respect to the several microörganisms in the order of the compounds enumerated are: against *Eberthella typhi* 141, 133 and 46.4, against *Staphylococcus aureus* 257, 200 and 106, against *Streptococcus* 250, 178 and 94.4, against *Mycobacterium smegmatis* 156, 156 and 122, and against *Trichophyton rosaceum* 160, 150 and 130, respectively. Here, too, the iso-alkyl derivatives are less effective than those with normal alkyl groups, as follows from the comparison of 6-*n*-propyl-3-methyl-4-chlorophenol and 6-isopropyl-3-methyl-4-chlorophenol (chlorothymol), *i. e.*, the *n*-propyl derivative is distinctly more effective than chlorothymol.

It is also of interest to compare two compounds of equal molecular weight containing an isoalkyl group. Thus 2-isopropyl-3,5-dimethyl-4-chlorophenol is practically as effective a microbicide as 3-methyl-6-*sec*-butyl-4-chlorophenol excepting the case of *Eberthella typhi*, where it is almost twice as potent as the latter. On the other hand, 2-*sec*-butyl-3,5-dimethyl-4-chlorophenol is very much more effective than 6-isopropyl-2-ethyl-3-methyl-4-chlorophenol of the same molecular weight, again except-

ing the case of *Eberthella typhi* against which the latter compound is twice as effective as the former. This, incidentally, furnishes additional evidence for the "quasi-specific" group parallelism referred to before.

6-(Diethylmethyl)-3-methyl-4-chlorophenol is very much more potent than the equimolecular 6-isopropyl-2-ethyl-3-methyl-4-chlorophenol with the exception of the case of *Eberthella typhi*, which fact is quite in line with the observations referred to above. However, the microbicidal action of the former compound with two alkyl groups compares with that of the equimolecular 2-*sec*-butyl-3,5-dimethyl-4-chlorophenol containing three alkyl groups, probably because the diethylmethyl group is more "branched" than the *sec*-butyl radical, the greater extent of "branching" having in turn a more reducing effect on the microbicidal action. On the other hand, the two compounds with seven carbon atoms in the substituting groups, *viz.*, 2-*sec*-amyl-3,5-dimethyl-4-chlorophenol and 2-(diethylmethyl) 3,5-dimethyl-4-chlorophenol, which differ only in the structure of the chains, compare well in respect to their germicidal action.

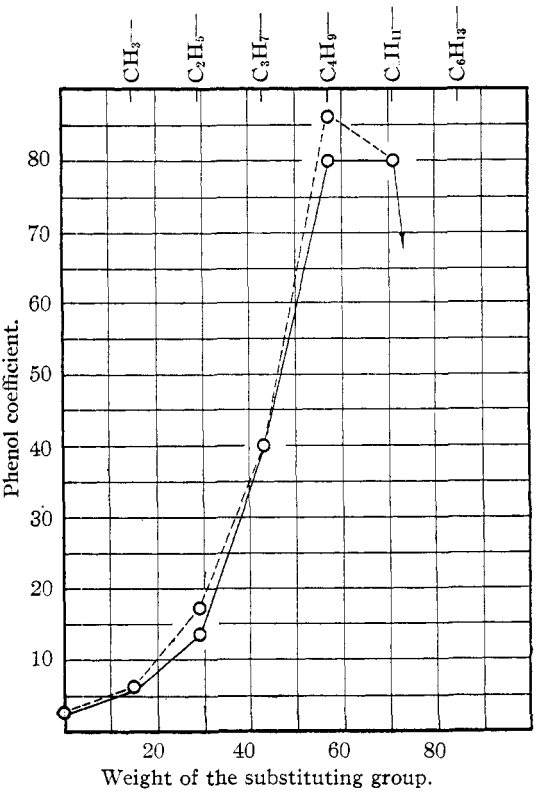


Fig. 3.—The bactericidal action of normal *p*-alkyl derivatives of *o*-chlorophenol. Test organisms: *Eberthella typhi*, dash line; *Eberthella paradysenteriae* (Flexner), full line.

While in the case of the normal monoalkyl derivatives of *p*-chlorophenol the maximum effect upon *Eberthella typhi* was shown by a compound with five carbon atoms in the side chain, this maximum in the case of polyalkyl derivatives is shown by a compound with a total of four substituting carbon atoms. With respect to the other test organisms, the compounds showing the greatest efficacy are those with a total of seven carbon atoms in the substituting groups.

In all the polyalkyl derivatives discussed above, chlorine is present

in the para position. We also prepared one ortho substituted derivative, *viz.*, 4-*n*-propyl-3,5-dimethyl-2-chlorophenol. As was to be expected from the comparison of the germicidal efficacies of the monoalkyl derivatives of *o*- and *p*-chlorophenols, the effect of 4-*n*-propyl-3,5-dimethyl-2-chlorophenol upon the test organisms, except *Eberthella typhi*, is weaker than that of any polyalkyl derivative of *p*-chlorophenol with the same number of substituting carbon atoms. However, in contrast to the observations made elsewhere it is not less effective than 4-*n*-amyl-2-chlorophenol, the corresponding normal alkyl derivative of *o*-chlorophenol with the same number of carbon atoms. It is considerably more potent than 4-*tert*-amyl-2-chlorophenol.

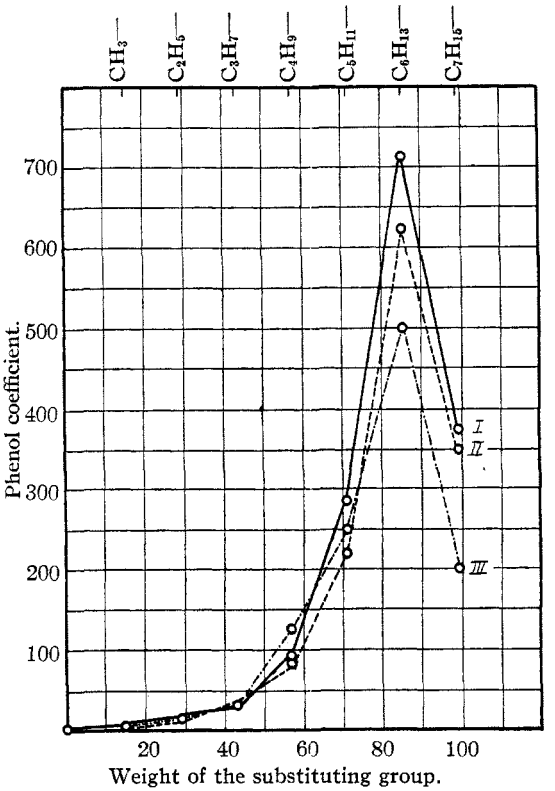


Fig. 4.—The bactericidal action of normal para alkyl derivatives of *o*-chlorophenol. Test organisms: I, *Staphylococcus aureus;* II, *Streptococcus* (hemol.); III, *Mycobacterium smegmatis.*

General Note

The compounds described in this paper comprise some of the most powerful metal-free organic antiseptic agents known to date. Their efficacy in destroying the two Gram-positive cocci and the bacilli of typhoid and paradysenteriae suggests an ultimate extension of this work to experiments on the chemotherapy of infections caused by these and related microörganisms. Nor are the results obtained in the case of *Mycobacterium smegmatis* devoid of a possible chemotherapeutic significance. While this acid-fast microörganism is not itself of a pathogenic character, it was chosen for our experiments because it permits of a comparatively easy cultivation *in vitro* and, therefore, of a quick orientation regarding the probable efficacy of the compounds studied, against the pathogenic members of this class of organisms, such as the germs of tuberculosis and of leprosy.[11a] Similarly, since

(11a) Experiments carried out in the meantime with germs of human and avian tuberculosis, and

Trichophyton rosaceum is known to be one of the most resistant pathogenic fungi some conclusions may be drawn regarding the probable effect of the compounds under discussion upon other pathogenic fungi. Further work in the directions indicated is in progress or in preparation at this time.

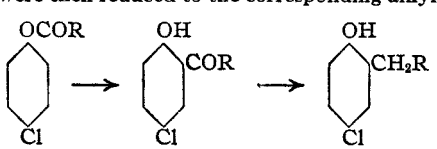
TABLE III

BACTERICIDAL ACTION OF POLY-ALKYL DERIVATIVES OF CHLOROPHENOL (PHENOL COEFFICIENTS)

Derivatives of chlorophenol	*Eberthella typhi*	*Staphylococcus pyogenes aureus*	*Streptococcus* (hemolytic strain)	*Mycobacterium smegmatis*	*Trichophyton rosaceum*
3-Methyl-4-	10.7	11.3	11.3	11.1	11.0
3,5-Dimethyl-4-	30.0	25.7	27.5	28.1	25.0
6-Ethyl-3-methyl-4-	64.3	50.0	55.6	55.6	60.0
6-*n*-Propyl-3-methyl-4-	133	200	178	156	150
6-Isopropyl-3-methyl-4-	107	150	138	138	140
2-Ethyl-3,5-dimethyl-4-	46.4	106	94.4	122	130
6-*Sec*-butyl-3-methyl-4-	42.9	344	333	361	275
2-Isopropyl-3,5-dimethyl-4-	81.3	313	313	325	275
4-*n*-Propyl-3,5-dimethyl-2-	75.0	200	140	222	100
6-Diethylmethyl-3-methyl-4-	26.8	688	556	625	500
6-Isopropyl-2-ethyl-3-methyl-4-	56.7	200	175	200	145
2-*Sec*-butyl-3,5-dimethyl-4-	28.6	563	556	556	545
2-*Sec*-amyl-3,5-dimethyl-4-		750	1111	700	
2-Diethylmethyl-3,5-dimethyl-4-		1143	1000	667	700
6-*Sec*-octyl-3-methyl-4-		>89	122	>70	
2-*Sec*-octyl-3,5-dimethyl-4-		100	>67		

Notes on the Preparation of the Substituted Halogen Phenols

A number of different methods were used in the preparation of the compounds studied. In the synthesis of the normal alkyl halogen phenol derivatives advantage was taken of Behn's[12] method of intramolecular rearrangement of the phenol esters by means of anhydrous aluminum chloride, leading to the corresponding ketones; considerable clarity has been brought into this reaction by the work of Rosenmund and Schnurr.[13] The keto compounds were then reduced to the corresponding alkyl derivatives.



As a result of such rearrangement substitution takes place at lower temperatures preferably in para position to the hydroxyl group if both the ortho and the para positions are open; if the para position is occupied, or if the reaction is conducted at a higher temperature, ortho substitution takes place. In the preparation of almost all the normal

those of human and rat leprosy indicate a bactericidal potency which generally compares with that against *Mycobacterium smegmatis*.

(12) Behn, German Patent 95,901 (1897).

(13) Rosenmund and Schnurr, *Ann.*, **460**, 56 (1928).

ortho substituted derivatives of *p*-chlorophenol, the above course was followed, *i. e.*, *p*-chlorophenol served as the starting material. In synthesizing the normal para substituted compounds derived from *o*-chlorophenol we chose the opposite way, *viz.*, the corresponding alkyl derivative was prepared first and chlorine introduced subsequently by means of sulfuryl chloride.

While the alkyl derivatives with branched side chains, of course, may be prepared by the same general method, starting with the halogen phenol esters of the branched fatty acids, we preferred the method of direct condensation. Thus when using a primary alcohol and concentrated sulfuric acid as the condensing agent, a secondary alkyl derivative is obtained probably due to sulfonation of the carbon atom nearest to the alcohol group[14] or possibly to the intermediate formation of the free unsaturated hydrocarbon which might then condense with the phenol, because of the greater reactivity of the second carbon atom. That such a reaction is possible appears also from the fact that secondary alkyl derivatives are formed at least in part by the condensation of phenols with primary alcohols in the presence of anhydrous zinc chloride.

Several secondary alkyl derivatives were also prepared with the aid of the corresponding alkyl bromides.

Table IV gives a list of the compounds studied and of their intermediates, together with some of their physical constants; the analytical results (halogen determination by Pregl's micro-modification of Carius' method) are also stated.

The several types of reactions leading to the compounds under consideration will be described in the following paragraphs by a number of representative examples.

Method I. Preparation of *o*-*n*-Alkyl Derivatives of *p*-Chlorophenol. Example: Preparation of 2-*n*-Heptyl-4-chlorophenol.—To 43 g. of *p*-chlorophenol was added 52 g. of heptanoyl chloride. A reaction took place immediately with formation of gaseous hydrogen chloride. The reaction mixture was allowed to stand overnight; it was then heated in a steam-bath for thirty minutes. After cooling, the oil was treated with water to decompose the excess acid chloride, then washed free from acid, dried with anhydrous sodium sulfate, and distilled *in vacuo*. The fraction distilling at 155° and 2 mm. was collected.

To 60 g. of 4-chlorophenyl heptanoate, 36 g. of anhydrous powdered aluminum chloride was added in small portions with vigorous stirring and the mixture heated finally to 155° and kept at this temperature (in an oil-bath) for thirty minutes. The reaction mass was decomposed with ice and dilute hydrochloric acid. A dark oil separated which was washed repeatedly and extracted with 10% aqueous potassium hydroxide. The oil which precipitated upon addition of acid to the alkaline extract was shaken out with ether, washed with water and, after evaporation of the ether, subjected to vacuum distillation. The fraction distilling at 140–144° and 3 mm. solidified on standing. After recrystallization from isopropyl alcohol a melting point of 43.5° was obtained.

The 2-hydroxy-5-chloro-oenanthophenone thus obtained was reduced according to Clemmensen's[15] method, with amalgamated zinc and 20% hydrochloric acid. The resulting oil was diluted with ether, washed free of acid and shaken with 10% aqueous potassium hydroxide. The ethereal layer was drawn off and after evaporation of the solvent, taken up in Claisen's methyl alcoholic alkali. This solution was shaken repeatedly with petroleum benzine and then acidified. An oil separated which was extracted with ether, washed free from acid and distilled *in vacuo*. The fraction distilling at 150–152° and 3 mm. was collected.

This method was used in the preparation of all the normal *o*-alkyl-*p*-chlorophenol derivatives (except the *p*-chloro-*o*-cresol), also of the 6-ethyl-3-methyl-, the 6-*n*-propyl-3-methyl-, the 2-ethyl-3,5-dimethyl-, and the 6-isopropyl-2-ethyl-3-methyl-4-chlorophenol.

(14) Meyer and Bernhauer, *Monatsh.*, **53**, 721 (1929).

(15) Clemmensen, *Ber.*, **46**, 1837 (1913); **47**, 687 (1914).

TABLE IV

PHYSICAL AND ANALYTICAL DATA OF THE SUBSTITUTED HALOGEN PHENOLS AND THEIR INTERMEDIATES

	Formula	B. p., °C.	Mm.	M. p., °C.	Chlorine, % Calcd.	Found
o-Alkyl *p*-chlorophenols						
Methyl[1]	$CH_3(2)Cl(4)C_6H_3OH$	220–225	760	45		
Ethyl[2]	$C_2H_5(2)Cl(4)C_6H_3OH$	98–102	2.5	Congeals	22.65	22.75
n-Propyl	$n\text{-}C_3H_7(2)Cl(4)C_6H_3OH$	105	2		20.80	20.78
n-Butyl	$n\text{-}C_4H_9(2)Cl(4)C_6H_3OH$	140	18		19.21	19.24
n-Amyl	$n\text{-}C_5H_{11}(2)Cl(4)C_6H_3OH$	122	3		17.85	17.41
Sec-amyl	$Sec\text{-}C_5H_{11}(2)Cl(4)C_6H_3OH$	120–123	3	61.5	17.85	17.39
n-Hexyl	$n\text{-}C_6H_{13}(2)Cl(4)C_6H_3OH$	132	3		16.68	16.74
Cyclohexyl	$Cyclo\text{-}C_6H_{11}(2)Cl(4)C_6H_3OH$	152–156	4	57.5	16.84	17.31
n-Heptyl	$n\text{-}C_7H_{15}(2)Cl(4)C_6H_3OH$	150–152	3		15.65	15.81
n-Octyl	$n\text{-}C_8H_{17}(2)Cl(4)C_6H_3OH$	165	3		14.74	14.92
Sec-octyl	$Sec\text{-}C_8H_{17}(2)Cl(4)C_6H_3OH$	155–160	3		14.74	14.37
p-Alkyl *o*-chlorophenols						
Methyl[3]	$CH_3(4)Cl(2)C_6H_3OH$	195–196	760		24.88	24.50
Ethyl	$C_2H_5(4)Cl(2)C_6H_3OH$	214–216	760		22.65	22.41
n-Propyl	$n\text{-}C_3H_7(4)Cl(2)C_6H_3OH$	228–230	760		20.80	20.58
n-Butyl	$n\text{-}C_4H_9(4)Cl(2)C_6H_3OH$	247–248	760		19.21	19.13
n-Amyl	$n\text{-}C_5H_{11}(4)Cl(2)C_6H_3OH$	115–116	2		17.85	17.31
Tert-amyl	$Tert\text{-}C_5H_{11}(4)Cl(2)C_6H_3OH$	105–110	2		17.85	17.84
n-Hexyl	$n\text{-}C_6H_{13}(4)Cl(2)C_6H_3OH$	139–142	6		16.68	16.37
n-Heptyl	$n\text{-}C_7H_{15}(4)Cl(2)C_6H_3OH$	147	6		15.65	15.63
Polyalkyl chlorophenols						
6-Ethyl-3-methyl-4-chlorophenol	$C_2H_5(6)CH_3(3)Cl(4)C_6H_2OH$	102	3	73.2	20.80	21.06
6-*n*-Propyl-3-methyl-4-chlorophenol	$n\text{-}C_3H_7(6)CH_3(3)Cl(4)C_6H_2OH$	115	2	49.5	19.21	18.82
2-Ethyl-3,5-dimethyl-4-chlorophenol	$C_2H_5(2)(CH_3)_2(3,5)Cl(4)C_6HOH$			97.5	19.21	19.14
6-*Sec*-butyl-3-methyl-4-chlorophenol	$Sec\text{-}C_4H_9(6)CH_3(3)Cl(4)C_6H_2OH$	120–123	3		17.85	17.98
2-Isopropyl-3,5-dimethyl-4-chlorophenol	$Iso\text{-}C_3H_7(2)(CH_3)_2(3,5)Cl(4)C_6HOH$	125	3	Congeals	17.85	17.35
4-*n*-Propyl-3,5-dimethyl-2-chlorophenol	$n\text{-}C_3H_7(4)(CH_3)_2(3,5)Cl(2)C_6HOH$	125–130	3	81.7	17.85	17.92
6-(Diethylmethyl)-3-methyl-4-chlorophenol	$(C_2H_5)_2CH(6)CH_3(3)Cl(4)C_6H_2OH$	128	2		16.68	16.39
6-Isopropyl-2-ethyl-3-methyl-4-chlorophenol	$Iso\text{-}C_3H_7(6)C_2H_5(2)CH_3(3)Cl(4)C_6HOH$	132	2	Congeals	16.68	17.18
2-*Sec*-butyl-3,5-dimethyl-4-chlorophenol	$Sec\text{-}C_4H_9(2)(CH_3)_2(3,5)Cl(4)C_6HOH$	131–133	2		16.68	16.84

TABLE IV (*Concluded*)

	Formula	B. p., °C.	Mm.	M. p., °C.	Chlorine, % Calcd.	Found
Polyalkyl chlorophenols						
2-(Diethylmethyl)-3,5-dimethyl-4-chlorophenol	$(C_2H_5)_2CH(2)(CH_3)_2(3,5)Cl(4)C_6HOH$	141–142	3		15.65	15.23
2-*Sec*-amyl-3,5-dimethyl-4-chlorophenol	*Sec*-$C_5H_{11}(2)(CH_3)_2(3,5)Cl(4)C_6HOH$	142–145	2		15.65	15.37
6-*Sec*-octyl-3-methyl-4-chlorophenol	*Sec*-$C_8H_{17}(6)CH_3(3)Cl(4)C_6H_2OH$	155–159	2		13.93	13.42
2-*Sec*-octyl-3,5-dimethyl-4-chlorophenol	*Sec*-$C_8H_{17}(2)(CH_3)_2(3,5)Cl(4)C_6HOH$	160–163	3		13.20	12.93
Ketones (intermediates)						
5-Chloro-2-hydroxy-acetophenone[4]	$CH_3CO\cdot C_6H_3Cl(5)OH(2)$	97– 99	2	54	20.80	21.30
5-Chloro-2-hydroxy-propiophenone[5]	$C_2H_5CO\cdot C_6H_3Cl(5)OH(2)$			59.7	19.21	19.34
5-Chloro-2-hydroxy-butyrophenone[5]	n-$C_3H_7CO\cdot C_6H_3Cl(5)OH(2)$	108–112	3	50.5	17.86	17.79
5-Chloro-2-hydroxy-valerophenone	n-$C_4H_9CO\cdot C_6H_3Cl(5)OH(2)$	120–125	2		16.68	17.10
5-Chloro-2-hydroxy-caprophenone	n-$C_5H_{11}CO\cdot C_6H_3Cl(5)OH(2)$			56.5	15.65	15.71
5-Chloro-2-hydroxy-oenanthophenone	n-$C_6H_{13}CO\cdot C_6H_3Cl(5)OH(2)$	140–144	3	43.5	14.74	14.71
5-Chloro-2-hydroxyphenyl n-heptyl ketone	n-$C_7H_{15}CO\cdot C_6H_3Cl(5)OH(2)$			63	13.92	14.23
5-Chloro-4-methyl-2-hydroxy-acetophenone[6]	$CH_3CO\cdot C_6H_2CH_3(4)Cl(5)OH(2)$			71		
5-Chloro-4-methyl-2-hydroxy-propiophenone[6]	$C_2H_5CO\cdot C_6H_2CH_3(4)Cl(5)OH(2)$	110–115	3	65.3	17.86	17.90
5-Chloro-4,6-dimethyl-2-hydroxy-acetophenone[7]	$CH_3CO\cdot C_6H(CH_3)_2(4,6)Cl(5)OH(2)$			89.7	17.86	17.79
5-Chloro-3-isopropyl-6-methyl-2-hydroxy-acetophenone	$CH_3CO\cdot C_6HCH_3(6)$iso-$C_3H_7(3)Cl(5)OH(2)$	127–135	3		15.65	16.12
Esters (intermediates)						
4-Chlorophenyl acetate[8]	$CH_3CO_2\cdot C_6H_4Cl(4)$	90– 92	2.5		20.80	21.25
4-Chlorophenyl propionate[9]	$C_2H_5CO_2\cdot C_6H_4Cl(4)$	76– 78	2		19.21	19.10
4-Chlorophenyl butyrate[9]	n-$C_3H_7CO_2\cdot C_6H_4Cl(4)$	96– 98	3		17.86	17.51
4-Chlorophenyl valerate	n-$C_4H_9CO_2\cdot C_6H_4Cl(4)$	113–118	2		16.68	17.17
4-Chlorophenyl caproate	n-$C_5H_{11}CO_2\cdot C_6H_4Cl(4)$	125–130	2		15.65	15.50
4-Chlorophenyl oenanthate	n-$C_6H_{13}CO_2\cdot C_6H_4Cl(4)$	135	2		14.74	14.95
4-Chlorophenyl caprylate	n-$C_7H_{15}CO_2\cdot C_6H_4Cl(4)$	154–156	2		13.92	14.08
4-Chloro-3-methyl-phenyl acetate[10a]	$CH_3CO_2\cdot C_6H_3CH_3(3)Cl(4)$	94– 96	2.5		19.21	19.10
4-Chloro-3-methyl-phenyl propionate[10b]	$C_2H_5CO_2\cdot C_6H_3CH_3(3)Cl(4)$	102–104	3.5		17.86	18.10
4-Chloro-3,5-dimethyl-phenyl acetate	$CH_3CO_2\cdot C_6H_2(CH_3)_2(3,5)Cl(4)$	102	2.5	48.7	17.86	17.90
4-Chloro-3-methyl-6-isopropyl-phenyl acetate[11]	$CH_3CO_2\cdot C_6H_2CH_3(3)$iso-$C_3H_7(6)Cl(4)$	112–114	2		15.65	15.79

FOOTNOTES TO TABLE IV

[1] Previously referred to by Peratoner and Condorelli, *Gazz. chim. ital.*, **28** I, 211 (1890); Claus and Jackson, *J. prakt. Chem.*, [2] **38**, 328 (1888); Rasik and Miller, THIS JOURNAL, **41**, 2028 (1919); German Patent 302,013 Kl. 30i (1913).

[2] Previously prepared by v. Auwers and Wittig, *Ber.*, **57**, 1270 (1924).

[3] Previously referred to by Zincke and collaborators, *ibid.*, **17**, 2528 (1884); *Ann.*, **328**, 261 (1903); Mazzara, Lamberti and Zanardi, *Gazz. chim. ital.*, **26**, II, 399 (1889); Peratoner and Vitale, *ibid.*, **28**, I, 217 (1890); Autenrieth and Muehlinghaus, *Ber.*, **39**, 4103 (1906); Cain and Norman, *Proc. Chem. Soc.*, **21**, 206 (1905).

[4] Previously prepared by Nencki and Stoeber, *Ber.*, **30**, 1771 (1897); Skraup and Beng, *Bull. soc. chim. Belgique*, **36**, 222.(1927).

[5] Previously prepared by Wittig, *Ann.*, **446**, 155 (1926).

[6] Previously prepared by Rosenmund and Schnurr, *ibid.*, **460**, 56 (1928).

[7] Previously prepared by v. Auwers, Muerbe and Sauerwein, *Fortschr. Chem., Physik physik. Chem.*, **18**, 1 (1924).

[8] Previously prepared by Seelig, *J. prakt. Chem.*, [2] **39**, 175 (1889); Wohlleben, *Ber.*, **42**, 4372 (1910); Wittig, *ibid.*, **57**, 88 (1924).

[9] Previously prepared by Wittig, *Ann.*, **446**, 155 (1926).

[10] Previously prepared by (a) Sulzberger, U. S. Patent 1,498,641 (1924); (b) Rosenmund and Schnurr, *Ann.*, **460**, 56 (1928).

[11] Previously prepared by Bocchi, *Gazz. chim. ital.*, **26** II, 404 (1889).

Method II. Preparation of *p*-*n*-Alkyl Derivatives of *o*-Chlorophenol. Example: Preparation of 4-*n*-Amyl-2-chlorophenol.—Phenyl valerate was prepared by the reaction of 47 g. of phenol with 63.2 g. of *n*-valeryl chloride, and purified in the usual manner. The pure ester distilled at 100–102° and 2 mm.

To 67 g. of phenyl valerate dissolved in 330 g. of freshly distilled nitrobenzene was added 61 g. of anhydrous aluminum chloride. The mixture was allowed to stand overnight. It was then warmed to 50–60° and held at this temperature for eight hours with constant stirring. The 4-hydroxyvalerophenone formed in the course of this reaction was separated and purified in the same manner as described in the preceding example. It distilled at 182–183° and 3 mm. The oil solidified on standing.

This ketone was reduced to the corresponding 4-*n*-amylphenol in the usual manner by means of amalgamated zinc and hydrochloric acid. The pure compound distilled at 119–120° and 3 mm.

To 16.4 g. of 4-*n*-amylphenol diluted with 20 cc. of carbon tetrachloride, 14.8 g. (10% excess) of sulfuryl chloride was added and the mixture warmed to 55° and held at this temperature under reflux for three hours. Finally the temperature was raised to 70° and heating continued for one hour. The reaction mixture was treated with warm water, washed free from acid and distilled. The fraction at 115–116° and 2 mm. was collected.

Method III. Preparation of *o*-Isoalkyl Derivatives. Example I: Preparation of 6-Sec-butyl-3-methyl-4-chlorophenol.—4-Chloro-*m*-cresol (54.6 g.) and 52 g. of anhydrous zinc chloride were mixed and heated to 80°. At this temperature 50 g. of *sec*-butyl bromide was added drop by drop with stirring. After the addition of the alkyl halide heating was continued for four hours. The reaction mixture was allowed to cool and was then decomposed with ice cold water and dilute hydrochloric acid. The reaction product was purified in the usual manner described under the preparation of 2-heptyl-4-chlorophenol. The pure 6-*sec*-butyl-3-methyl-4-chlorophenol distilled at 125–127° at 3 mm.

Example II: Preparation of 2-Isopropyl-3,5-dimethyl-4-chlorophenol.—A mixture of 35 g. of isopropyl alcohol and 87.8 g. of sulfuric acid was allowed to flow slowly into a flask containing 92 g. of *p*-chloro-*sym*-*m*-xylenol at 100° in the course of one hour, the

mixture being stirred mechanically. Heating was continued for another three hours at 90°. After cooling, the reaction mixture was poured into cold water and then washed free from acid. The further steps were the same as described before. The pure 2-isopropyl-3,5-dimethyl-4-chlorophenol distilled at 125° at 3 mm.

Instead of sulfuric acid, anhydrous zinc chloride was used as a condensing agent in several instances.

As indicated before, primary alcohols furnish secondary alkyl derivatives as a result of condensation in the presence of concentrated sulfuric acid. Thus 2-*sec*-amyl-3,5-dimethyl-4-chlorophenol was obtained from *p*-chloro-*sym*-*m*-xylenol and *n*-amyl alcohol. The same compound was prepared using *sec*-amyl alcohol and zinc chloride as a condensing agent.

Similarly 2-*sec*-amyl-4-chlorophenol was obtained in the reaction mixture when either methylpropylcarbinol or *n*-amyl alcohol was condensed with *p*-chlorophenol. The semi-solid mass obtained after vacuum distillation was treated with *n*-heptane, from which the desired compound crystallized, giving in both cases a melting point of 61.5° and the same mixed melting point.

Our thanks are due to Mr. A. Grawehr of our laboratory staff for very efficient assistance in the bacteriological phase of this work.

Summary

A number of alkyl halogen phenol derivatives were prepared and their antibacterial behavior studied with the aid of the following microörganisms: *Eberthella typhi*, *Eberthella paradysenteriae* (Flexner), *Staphylococcus pyogenes aureus*, *Streptococcus* (hemolytic strain), *Mycobacterium smegmatis* and *Trichophyton rosaceum*. The several series of compounds studied comprised the *o*-alkyl derivatives of *p*-chlorophenol, the *p*-alkyl derivatives of *o*-chlorophenol and a number of polyalkyl derivatives of *p*- and *o*-chlorophenols. While all the halogen phenol derivatives studied are germicides, there are among them several which possess this capacity to a rather extraordinary degree.

As in a number of previous instances, the germicidal action of the compounds studied shows several functional regularities. In the first place, the substituting halogen atom considerably intensifies the microbicidal potency of phenol, the substitution in para position to the hydroxyl group being more effective in this respect than ortho substitution. Introduction of alkyl groups into the nucleus of halogen phenols further increases their germicidal action, the increase depending upon the number of carbon atoms introduced. In the majority of instances studied the intensifying effect upon the bactericidal potency of substitution by one normal aliphatic chain with a given number of carbon atoms is greater than that of substitution by one branched chain or by two or more alkyl radicals with the same total number of carbon atoms.

o-Alkyl derivatives of *p*-chlorophenol are more actively germicidal than *p*-alkyl derivatives of *o*-chlorophenol.

The bactericidal action of the normal alkyl derivatives of *p*-chlorophenol upon *Eberthella typhi* reaches a maximum with the amyl derivative

(phenol coefficient 156), that upon *Eberthella paradysenteriae* with the hexyl derivative (phenol coefficient 333), and decreases thereafter. The other four test organisms, in spite of their genetic and morphological differences, show a remarkable parallelism in a qualitative and a quantitative respect in their behavior toward the substances studied. With reference to these organisms the maximum germicidal potency is reached by derivatives of higher molecular weight, *viz.*, the *n*-octyl derivative in the case of *Staphylococcus aureus* (phenol coefficient 1750), and the *n*-heptyl derivative in the case of the remaining three organisms (phenol coefficients: for *Streptococcus* 2220, for *Mycobacterium smegmatis* 1250, for *Trichophyton rosaceum* 667). The germicidal action of the isomeric derivatives with the same number of carbon atoms, but in branched chains, in alicyclic groups or distributed over several radicals, is lower in comparison.

The results thus far obtained appear to be sufficiently significant to suggest an extension of the work outlined into the field of chemotherapy.

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Preparation and Pyrolysis of Dibenzyl Ketone, Phenylacetic Anhydride and Diphenylacetic Anhydride

BY CHARLES D. HURD, ROBERT CHRIST AND CHARLES L. THOMAS

Phenylacetic anhydride was synthesized by the general method of refluxing the acid with acetic anhydride, a method which was also found to give excellent results in the synthesis of diphenylacetic anhydride. Phenylacetic anhydride, but not diphenylacetic anhydride, underwent pyrolysis on vacuum distillation. At sufficiently high temperatures (275°), the latter gave rise to diphenylacetic acid in high yields and to diphenylmethane and tetraphenylethylene in lesser yields.

Staudinger[1] obtained diphenylacetic anhydride from dimethylmalonic diphenylacetic anhydride, $(CH_3)_2C(CO—O—COCH(C_6H_5)_2)_2$, by vacuum distillation and suggested that it decomposed in turn if the bath temperature reached 200–220°, since some diphenylketene then distilled over (20 mm.). In the present work, an initial decomposition temperature of 275° was found and no diphenylketene was isolated as such. Hence, the diphenylketene in Staudinger's work probably came directly from the mixed anhydride.

Phenylacetic anhydride proved interesting to study for it gave good yields of dibenzyl ketone[2] by distillation at reduced pressure. This work

(1) Staudinger, Anthes and Schneider, *Ber.*, **46**, 3539 (1913).

(2) Previously this has been prepared by the dry distillation of calcium or barium phenylacetates: Pohow, *Ber.*, **6**, 560 (1873); Apitzsch, *ibid.*, **37**, 1429 (1904); Stobbe, Russwurm and Schulz, *Ann.*, **308**, 175 (1899).