RELATIONSHIPS BETWEEN THE STRUCTURES AND BACTERICIDAL PROPERTIES OF PHENOLS

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I. INTRODUCTION

Although phenol was suggested as a bactericidal agent by Lister in 1865, a study of the behavior of other phenolic compounds was not begun until the work in Ehrlich's laboratory which was reported in 1906 (11, 12). It was found at that time that a polyhalogenated phenol or β-naphthol was highly effective in its action on *B. diphtheriae* and *Staph. aureus*, one molecule of pentabromophenol being equivalent to five hundred molecules of phenol. It was also observed that the cresols were better germicides than phenol (5, 137). The numerous investigations on the relationship of the structure of phenolic compounds to their bactericidal properties that have been described during the past fifteen years were initiated by the work of Johnson and Lane (70) on the 4-alkylresorcinols. Their results will be discussed later.

The first standardized procedure for determining the effectiveness of a bactericidal agent was due to Rideal and Walker (125), and many of the phenol coefficients reported in the literature were determined by their method. At present a modified procedure adopted by the United States

Food and Drug Administration (160) is commonly employed. The original Rideal and Walker method and its modifications compare the relative germicidal effectiveness of a given compound with that of phenol taken as unity. The results are given on a weight rather than a molecular weight basis. The figure obtained for a given compound may vary greatly with the type of organism used, so that tests with several organisms (*B. typhosus* and *Staph. aureus* are commonly employed) are desirable. The result of an experiment at 20°C., carried out according to the Rideal–Walker method, may differ considerably from a measurement at the temperature of 37°C. commonly used now. The presence of "organic matter" likewise influences the phenol coefficient in some instances. A further complication is introduced by the fact that the bacteriostatic or antiseptic action of a compound is independent of its bactericidal or germ-killing power. A substance may be an excellent preservative, preventing the growth of organisms in high dilutions, without having a strong lethal effect. The

TABLE 1

Phenol coefficients of polyhydroxy phenols

COMPOUND	PHENOL COEFFICIENT AT 37°C.	
	B. typhosus	*Staph. aureus*
Catechol	0.87	0.58
Resorcinol	0.4	0.4
Hydroquinone	12.	0.44
Phloroglucinol	Negligible	Negligible
Pyrogallol	Negligible	Negligible

phenol coefficient refers to the bactericidal function. Despite these limitations, the phenol coefficients are valuable in getting an estimate of the effectiveness of compounds which are soluble enough in water for their solutions to be tested.

II. POLYHYDROXY PHENOLS

It is hardly possible to compare the bactericidal properties of phenol and benzene because of the insolubility of the hydrocarbon in aqueous media, but it is of interest to note the effect of increasing the number of hydroxyl groups attached to the nucleus. Available data (75) are listed in table 1. The behavior of hydroquinone is obviously anomalous. When the experiment was conducted at 20°C., the figures obtained for this compound dropped to 1.4 for *B. typhosus* and 0.34 for *Staph. aureus*. Earlier investigators (35) reported values for *B. typhosus*, *Staph. aureus*, and *B. coli* close to unity. Hydroquinone has a high bacteriostatic action (23) against *B. pestis*, preventing growth in a dilution of 1 to 432,000, while catechol

is about one-tenth as effective. No satisfactory explanation for the behavior of hydroquinone has been advanced. Phloroglucinol does not possess germicidal properties, although it is slightly bacteriostatic (79), as is pyrogallol.

III. HALOGENATED PHENOLS

While fluorophenol differs but little in its germicidal action from phenol (59), the chloro and bromo derivatives of phenol and resorcinol are more effective than the unsubstituted compounds. Little is known about iodinated phenols; they are relatively insoluble in water and possess an unpleasant and persistent odor which decreases the possibility of their practical use. Table 2 summarizes the data of Klarmann (82) on chloro and bromo compounds. Many of these values were greatly reduced when the determinations were made in the presence of organic matter. It is difficult

TABLE 2

Phenol coefficients of halogenated phenols

COMPOUND	PHENOL COEFFICIENTS OF CHLORINE DERIVATIVES		PHENOL COEFFICIENTS OF BROMINE DERIVATIVES	
	B. typhosus	*Staph. aureus*	*B. typhosus*	*Staph. aureus*
2-Halophenol	3.6	3.8	3.8	3.7
3-Halophenol	7.4	5.8		
4-Halophenol	3.9	3.9	5.4	4.6
2,4-Dihalophenol	13	13	19	22
2,4,6-Trihalophenol	23	25		
4-Haloresorcinol	0.7	1.0	1.0	1.3
4,6-Dihaloresorcinol	3.2	3.9	4.0	4.5
2,4,6-Trihaloresorcinol	5.0	4.3	6.4	6.4

to compare these figures with the earlier results of Bechold and Ehrlich (12) already mentioned, who reported that tribromo-β-naphthol kills *Staph. aureus* in 2 to 3 min. in a dilution of 250,000 and that the dibromo compound was active in a dilution of 32,000 toward *B. coli*. 2,4,5-Trichlorophenol (98), and particularly pentachlorophenol (25, 64, 124), have received attention as preservatives for commercial products. Engelhardt (47) reported that *p*-chlorophenol showed germicidal effectiveness only in a solvent of high dielectric constant; this was not the case for phenol. Halogen derivatives of phenols containing other substituents will be considered later.

IV. ALKYLPHENOLS

A considerable amount of information is now available concerning the effect of alkyl groups on the bactericidal properties of mono-, di-, and tri-

hydroxyphenols, and a number of generalizations are possible. In the homologous series of *p-n*-alkylphenols the maximum bactericidal action is reached with the *n*-amyl compound (37) when *B. typhosus* is the test organism, using the Rideal–Walker procedure. The data are listed in table 3. Because of the slight solubility of the phenols in water, they were dissolved in very dilute sodium hydroxide which in itself was not bactericidal. Against *Staph. aureus* at 20°C. a much lower phenol coefficient of 52 has been reported for *p-n*-butylphenol (118, 120), while for measurements at 25°C. a value of 68 has been found (135). More recently, deter-

TABLE 3

Phenol coefficients of alkylphenols against B. typhosus at 20°C.

p-ALKYLPHENOL	PHENOL COEFFICIENT
Methyl	2.5
Ethyl	7.5
n-Propyl	20
n-Butyl	70
n-Amyl	104
n-Hexyl	90
n-Heptyl	20

TABLE 4

Phenol coefficients against Staph. aureus at 37°C.

p-ALKYLPHENOL	PHENOL COEFFICIENT
Ethyl	10
n-Propyl	14
n-Butyl	21
n-Amyl	20
n-Heptyl	21

minations run at 37°C., using 30 per cent alcohol as the solvent for stock solutions of the alkylphenols, have given even lower values for the phenol coefficients (105). These are listed in table 4.

Within the experimental error, the position of the alkyl group has no effect (37, 118, 120). The three cresols and the three *n*-butylphenols are practically identical in their bactericidal action. The *o*- and *p-sec*-butylphenols have a phenol coefficient of 28, and the branching of the carbon side chain, as in *tert*-butylphenol, reduces the effectiveness to about 20. However, the condensation of 2-ethylbutanol with phenol, which might be expected to give *tert*-hexylphenols, gives two products having relatively

high coefficients. One isomer (b.p. 98–100°C. at 1.5 mm.; $n_D^{27°} = 1.5133$) gave 109 against *Staph. aureus* and 86 against *E. typhi*. The other isomer (b.p. 108–110°C. at 1.5 mm.; $n_D^{27°} = 1.5125$) was found to give 118 and 68, respectively, as the coefficients (59a). Since these compounds appear to be exceptions to the generalization that the straight-chain primary alkylphenols are more effective than their isomers, it would be of interest to know their structures. A phenol coefficient of 125 has been found for *o*-cyclohexylphenol against *Staph. aureus* by the F. D. A. method at 37°C. (162).

The *n*-alkylphenols are in general more difficult to prepare than their isomers. The most satisfactory synthesis involves the rearrangement of an aryl ester to the ketone by the Fries method, followed by reduction of the ketone with amalgamated zinc and hydrochloric acid (37). Another general method consists in the condensation of an aldehyde with phenol and the pyrolysis of the polymeric condensation product (105). The yield of crude *p*-alkylphenol amounts to about 40 per cent by weight of the polymer. On the other hand, the secondary and tertiary alkylphenols are obtainable directly by condensing phenol with an alcohol, alkyl halide, or olefin,—reactions that have received extensive investigation in recent years, particularly for patent purposes (18, 21, 22, 61, 94, 101, 107, 110, 113, 141).

It has been claimed that the condensation of phenol with *n*-heptyl alcohol (49) gives *n*-heptylphenol, but it seems likely that the product was a mixture. *n*-Butyl alcohol (121) yields a mixture of *sec*-butyl phenols when zinc chloride is the condensing agent, while it is claimed that aluminum chloride gives the *n*-alkylphenols with both *n*-propyl and *n*-butyl alcohols (158). *o*-Isobutylphenol has been prepared by the rearrangement of methallyl phenyl ether and the reduction of the resulting methallylphenol (8).

The presence of two alkyl groups in the phenol nucleus yields compounds that are highly effective as germicides and incidentally of very low solubility in water. The six isomeric xylenols (91) do not differ greatly in bactericidal properties, the 2,5-dimethylphenol being the most active. Carvacrol and thymol (135) both have a phenol coefficient of 28 at 25°C. against *Staph. aureus*, and the variation in the activity of isomeric *n*-alkylcresols is greater than the experimental error in only a few instances. Data for these compounds (37) are given in table 5A for *B. typhosus* at 20°C.

Three isomeric methylethylphenols (105) have also been tested against *Staph. aureus* at 37°C., with the results shown in table 5B.

The high germicidal effectiveness of the *n*-amylcresols listed in table 5A has led to their extensive study and recommendation for general use (6, 36, 38, 92). The compounds obtained by condensing "amylene" (30) or

an amyl alcohol (57, 142) with a cresol have also been described as useful bactericides. Other patents have dealt with the general preparation of secondary or tertiary alkylcresols (24, 115) as compounds having germicidal

TABLE 5A

Phenol coefficients against B. typhosus at 20°C.

ALKYL GROUP	PHENOL DERIVATIVE			
	4-Alkyl-3-methyl-	2-Alkyl-4-methyl-	4-Alkyl-2-methyl-	2-Alkyl-6-methyl-
Ethyl	12.5	12.5	15	
n-Propyl	34			
n-Butyl	100	95	110	60
n-Amyl	280	250	300	250
n-Hexyl	275	175	100	180

TABLE 5B

Phenol coefficients against Staph. aureus at 37°C.

PHENOL	PHENOL COEFFICIENT
2-Methyl-4-ethylphenol	11
3-Methyl-4-ethylphenol	10
4-Methyl-2-ethylphenol	10

TABLE 6

Phenol coefficients of products formed from cresols and 2-ethyl-1-butanol

PHENOL USED	BOILING POINT OF PRODUCT AT 1.5 MM.	PHENOL COEFFICIENT	
		Staph. aureus	*E. typhi*
	°C.		
o-Cresol	(a) 104–106	94	43
	(b) 110–112	183	45
m-Cresol	(a) 106–108	151	54
	(b) 114–116	231	71
p-Cresol	(a) 106–108	180	47
	(b) 115–117	(Insoluble)	(Insoluble)

properties. Raiziss and Clemence (115) have suggested that the condensation of a cresol with 2-methyl-1-butanol may give the primary alkylcresol, but this is unlikely in view of the results reported in condensations involving phenol. The phenol coefficient of "*sec*-amyl-*o*-cresol" against

Staph. aureus at 37°C. is 125 and for "*sec*-amyl-*p*-cresol" it is 100. For a more complex mixture, "*tert*-amyltricresol", the value of 62.5 was obtained (162).

The condensation of 2-ethyl-1-butanol with the three cresols gives in each instance two products. In table 6 are included the available data for these (59a).

In addition, *m*-cresol was condensed with "*sec*-hexanol" to give two products, boiling at 111–113°C. and at 118–120°C., which gave coefficients of 225 and 237 against *Staph. aureus;* against *E. typhi* the first product gave the coefficient 92. In a large group of methyl- and dimethyl-isobutylphenols (8), the most effective compound tested against *Staph. aureus* at 37°C. was 2-isobutyl-4,5-dimethylphenol, which had a phenol coefficient above 50. It was concluded that the isobutyl compounds were probably less effective than their *n*-butyl isomers.

V. ALKYLRESORCINOLS

Because of the interesting results obtained in the investigation by Johnson and Lane (70), the preparation and properties of alkylated resorcinols have been thoroughly studied. The primary 4-alkylresorcinols, both normal and branched chain, are readily obtained by condensing resorcinol with the proper fatty acids in the presence of zinc chloride (42, 43, 44, 70, 71), followed by reduction according to the method of Clemmensen (34). Secondary and tertiary 4-alkylresorcinols have been prepared by condensing olefins, alkyl halides, or alcohols directly with resorcinol (2, 21, 31, 106, 107, 126, 128), while the synthesis of the 5-*n*-alkylresorcinols (152) and of the 2-alkylresorcinols (130) involves a long series of reactions.

The several investigations on the bactericidal properties of the 4-alkylresorcinols illustrate the variability of the values for the phenol coefficient obtained with various strains of *B. typhosus* (42, 43, 44, 54, 77, 123, 135, 136) and with what appear to be minor variations in the test conditions. Apparently the variation is less serious in the case of tests using *Staph. aureus.* In table 7 are listed the results given by Dohme, Cox, and Miller (44) for *B. typhosus* and those of Schaffer and Tilley (135, 136) for *Staph. aureus.* Whereas the germicidal action toward *B. typhosus* reaches a maximum with the *n*-hexyl compound, the effect on *Staph. aureus* increases continuously with the length of the side chain. As in the alkylphenols, branching of the carbon chain reduces the effectiveness. Because of the bactericidal potency and the low toxicity of 4-*n*-hexylresorcinol, it has come into general use.

The 5-*n*-alkylresorcinols (152) show about the same germicidal activity against *Staph. aureus* as do the 4-isomers as high as the *n*-amyl compound, but above this their effectiveness is less (table 8). Against *B. typhosus* at

20°C., 5-*n*-hexylresorcinol has a coefficient of 22, compared with 50 for the 4-isomer. The 2-alkylresorcinols are relatively ineffective bactericidal agents (130). Although many *sec*-alkylresorcinols have been described (2, 21, 31, 106, 107, 126, 128) as having disinfectant action, phenol coefficients were not given. 4-Cyclohexylresorcinol (7) gave a value of 23 to 27, when tested by the United States Hygienic Laboratory method, which is close to that for isohexylresorcinol. Cyclohexylmethyl-, β-cyclohexyl-

TABLE 7

Phenol coefficients of 4-alkylresorcinols

4-ALKYLRESORCINOL	PHENOL COEFFICIENT	
	B. typhosus	*Staph. aureus*
n-Propyl	5	3.7
n-Butyl	22	10
Isobutyl	15	
n-Amyl	33	30
Isoamyl	24	
n-Hexyl	46 to 56	98
Isohexyl	27	
n-Heptyl	30	280
n-Octyl	0	680
n-Nonyl	0	980

TABLE 8

Phenol coefficients against Staph. aureus at 37°C.

ALKYLRESORCINOL	PHENOL COEFFICIENT	
	4-Isomers	5-Isomers
n-Propyl	4	5
n-Butyl	10	10
n-Amyl	30	35
n-Hexyl	98	49
n-Heptyl	280	128

ethyl-, and cyclopentylmethyl-resorcinols are less effective than *n*-hexylresorcinol (155); exact figures were not given. 4-Hexenylresorcinol is an active bactericide (67); the phenol coefficient was reported to be 150 against *Staph. aureus* at 37.5°C., 200 against *Strep. hemolyticus* at 37.5°C., and 40 against *B. typhosus* at 20.5°C. 4-Pentenylresorcinol was much less active.

A few dialkylresorcinols (2, 3, 74, 140) have been tested; 4,6-diethylresorcinol is as effective as *n*-butylresorcinol, but the di-*n*-propyl compound has a phenol coefficient of only 18; di-*n*-butylresorcinol is no more

bactericidal than the *n*-butyl compound, and the di-*n*-hexyl derivative is less than one-half as effective as *n*-hexylresorcinol. What are presumably di-*sec*-alkylresorcinols have been prepared (117) by condensing alcohols with resorcinol in the presence of zinc chloride. Since there may be some question about the structures of these compounds, particularly since their boiling points are lower than would be expected, there are listed in table 9 the alcohol used in preparing each compound and also the boiling point of the dialkylresorcinol.

The phenol coefficients were determined by the United States Hygienic Laboratory method. The unusually high values shown by the *sec*-hexyl and the heptyl compounds are surprising, in view of the small activity of the lower members of the series. The solubility of these compounds is only one part in 20,000 to 40,000 parts of water, which makes proper evaluation difficult (88, 96).

TABLE 9

Properties of "di-sec-alkylresorcinols"

ALCOHOL	BOILING POINT OF PRODUCT	PHENOL COEFFICIENT	
		Staph. aureus	*Strep. hemolyticus*
	°C.		
C_2H_5OH	135–137 (5 mm.)	60	65
n-C_3H_7OH	156–158 (7 mm.)	20	25
n-$C_5H_{11}OH$	168–175 (7 mm.)		
sec-$C_5H_{11}OH$	119–122 (1 mm.)	190	235
n-$C_6H_{13}OH$	178–182 (7 mm.)	1000	1350
n-$C_7H_{15}OH$	165–175 (2 mm.)	525	525

VI. ALKYLCATECHOLS AND ALKYLHYDROQUINONES

Comparatively recently, several 4-*n*-alkylcatechols have been prepared by both the Clemmensen reduction and catalytic reduction of the corresponding ketones, and the phenol coefficients of three members of the series determined against *Staph. aureus*. These are appreciably higher for the *n*-butyl (29 *versus* 10) and *n*-hexyl (129 *versus* 98) compounds, but lower for the *n*-heptyl (177 *versus* 280) than in the case of the corresponding resorcinol derivatives. Di-*sec*-hexylhydroquinone (117) gave a value of 25 against *Staph. aureus* and 38 against *Strep. hemolyticus*.

VII. ALKYLPHLOROGLUCINOLS AND ALKYLPYROGALLOLS

Several alkyl derivatives of trihydroxyphenols have been investigated as bactericidal agents. The *n*-hexylphloroglucinol (74) has a phenol coefficient of 8, while that for the triethyl compound is 2.5. What is prob-

ably a di-*sec*-hexylphloroglucinol made by condensing *n*-hexyl alcohol with phloroglucinol in the presence of zinc chloride (117) was found to be about ten times as effective against *Strep. hemolyticus* as against *Staph. aureus* (125 *versus* 12). The 4-*n*-alkylpyrogallol series shows a maximum effect

TABLE 10

Phenol coefficients of derivatives of pyrogallol, determined by the F.D.A. method at 37.5°C.

PYROGALLOL DERIVATIVE	PHENOL COEFFICIENT	
	Staph. aureus	*B. coli*
Ethyl	1.0	2.3
n-Propyl	2.5	4.4
n-Butyl	5.0	12.6
n-Amyl	19.0	25.
n-Hexyl	44.	38.
n-Heptyl	50.	26.
Heptenyl	120.	
Dihexenyl I	20.	<11.*
Dihexenyl II	250.	<11.*
Diheptenyl	20.	

* Against *B. typhosus* at 20.5°C.

TABLE 11

Phenol coefficients of di-sec- and di-tert-alkylpyrogallols

ALCOHOL USED	BOILING POINT OF PRODUCT	PHENOL COEFFICIENT	
		Staph. aureus	*Strep. hemolyticus*
	°C.		
n-Butyl	136–140 (2 mm.)	90	100
tert-Butyl	165–170 (4 mm.)	5	3
n-Amyl	146–148 (1.5 mm.)	200	220
tert-Amyl	150–153 (2 mm.)	100	100
Isoamyl	157–159 (2 mm.)	11	15
1-Methylbutyl	157–160 (2 mm.)	215	235
1-Ethylpropyl	154–158 (2 mm.)	118	190
2-Methylbutyl	146–148 (2 mm.)	95	145
n-Hexyl	153–155 (1.5 mm.)	280	320
n-Heptyl	160–164 (1.5 mm.)	360	375
n-Octyl	168–172 (1.5 mm.)	235	

against *B. coli* at the *n*-hexyl compound, while with *Staph. aureus* the effect is still rising with the *n*-heptyl derivative (58). Included in table 10 are figures for some alkenylpyrogallols (66) having high potency against *Staph. aureus* and *Strep. hemolyticus*. Phenol coefficients have been reported for

a number of products believed to be di-*sec*- and di-*tert*-alkylpyrogallols, made by condensing alcohols with pyrogallol in the presence of zinc chloride (117). The properties of these compounds are listed in table 11. The most striking feature of the results is the wide variation in the effectiveness of the isomeric amyl compounds. The products obtained from *n*-amyl and the two *sec*-amyl alcohols are probably all mixtures of di-*sec*-amylpyrogallols, and the phenol coefficients are in accord with this. The product obtained from isoamyl alcohol should be the *tert*-amyl derivative, but it had quite different bactericidal properties from those of the compound made from *tert*-amyl alcohol. Other inconsistencies in the results indicate the necessity for information regarding structures before conclusions can be drawn.

TABLE 12

Properties of 2-alkyl-4-fluorophenols

ALKYL GROUP	SOLUBILITY IN WATER	PHENOL COEFFICIENT	
		B. typhosus at 20°C.	*Staph. aureus* at 37°C.
	grams per liter		
Ethyl	3.51	10	
n-Propyl	1.95	21	
n-Butyl	0.76*	66	60
n-Amyl	0.27†	69	139
n-Hexyl	0.18*	<62	

* In 20 per cent ethyl alcohol.

† 0.41 in 20 per cent ethyl alcohol.

VIII. ALKYLHALOPHENOLS AND ALKYLHALORESORCINOLS

Since alkyl groups and halogen atoms separately increase the bactericidal activity of a phenol, it is interesting to note the cumulative effect when both types of substituents are present. Alkylhalophenols have been prepared by methods analogous to those used in making the unhalogenated compounds.

The presence of fluorine para to the hydroxyl group has a smaller effect on the germicidal properties of alkylphenols (145) than is obtained with the other halogens. The data are given in table 12. A *p*-fluoro-*o*-pentenylphenol has also been prepared (40); it was claimed that it has germicidal activity.

Klarmann and coworkers (81, 84, 86) have reported the behavior of six varieties of microörganisms toward numerous alkylchlorophenols. In table 13 are listed the results obtained with *o*-alkyl-*p*-chlorophenols. In-

spection of these data shows that, as in previous groups of compounds, the first three members of the series have about the same activity toward all microörganisms, but with increasing length of side chain a maximum value is reached for each organism. Since this maximum occurs with different lengths of side chains, certain compounds are highly effective toward some organisms and all but inert to others. Klarmann has used the term "quasi-specific" activity to designate this phenomenon. It has been found among the higher members of all series of alkylated phenols wherever the bactericidal properties have been studied for several organisms.

The bactericidal action of *o*-chloro-*p*-alkylphenols is on the whole less than for the series just described. The data are presented in table 14.

TABLE 13

Phenol coefficients of o-alkyl-p-chlorophenols

ALKYL GROUP	PHENOL COEFFICIENT					
	E. typhi	*E. paradysenteriae*	*Staph. aureus*	*Strep. hemolyticus*	*Mycobacterium smegmatis*	*Trichophyton rosaceum*
None	4.3	4.7	4.3	4.4	3.9	4.2
Methyl	12.5	14.3	12.5	11.1	13.3	11.7
Ethyl	28.6	32.1	34.4	31.3	25.	27.5
n-Propyl	93.	100.	94.	78.	89.	83.
n-Butyl	141.	167.	257.	250.	156.	160.
n-Amyl	156.	200.	500.	556.	400.	400.
n-Hexyl	(23.2)	333.	1250.	1333.	1111.	500.
n-Heptyl		133.	1500.	2220.	1250.	667.
n-Octyl		(26.7)	1750.	>667.	156.	
sec-Amyl	46.7	80.	312.	312.	389.	250.
Cyclohexyl		80.	438.	361.	278.	300.
sec-Octyl			1000.	>555.	>100.	>50.

Here the quasi-specific behavior does not become important until there are more than four carbon atoms in the side chain. It may be that an interaction of the hydroxyl and chloro groups is responsible for the decreased effectiveness of these compounds as compared with their isomers.

Results similar to those shown in table 14 were reported the same year by Blicke and Stockhaus (13). These investigators mentioned the erratic behavior of the hexyl and heptyl derivatives, the phenol coefficients using *Staph. aureus* varying from 444 to 714 and from 375 to 666 for the two compounds.

3-Methyl-4-chlorophenol is slightly less effective than the *o*-cresol derivative (81). Rapps (116) found this compound to be about twice as effective in a castor oil soap solution as in water, the Rideal–Walker phenol coeffi-

cient rising from 13 to 25. Chlorine derivatives of other 3-alkylphenols are not known, chiefly because of the large amount of work that would be involved in preparing them.

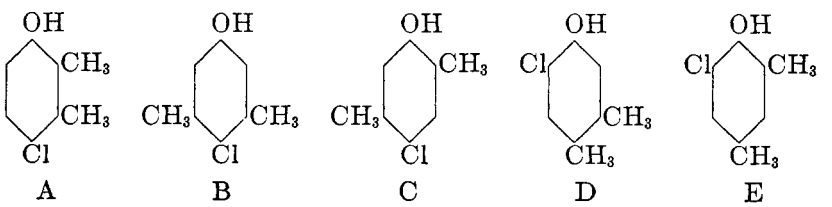
A mixture of chloro-*sec*-butylphenols obtained by the action of sulfuryl chloride upon *sec*-butylphenol has been patented for its bactericidal activity (14). The dichlorination of the cresols has been reported to multiply their germicidal effectiveness by ten (156). Commercial chloro-*o*-cyclohexylphenol gives a phenol coefficient of 437 against *Staph. aureus* (162). A series of 2,4-dichloro-6-alkylphenols has recently been prepared (26), but unfortunately there seems to be no information available concerning their bactericidal power. The preparation of a pentenyl-*m*-chlorophenol has also been described (40) and compounds of this type were claimed as bactericides.

TABLE 14

Phenol coefficients of p-alkyl-o-chlorophenols

ALKYL GROUP	PHENOL COEFFICIENT					
	E. typhi	*E. paradysenteriae*	*Staph. aureus*	*Strep. hemolyticus*	*Mycobacterium smegmatis*	*Trichophyton rosaceum*
None	2.5	2.3	2.9	2.0	2.2	<1
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	38	40	32	35	33	>33
n-Butyl	87	80	94	89	125	80
n-Amyl	80	80	286	222	250	>250
tert-Amyl	(32)	47	125	138	138	145
n-Hexyl		(36)	714	625	500	>420
n-Octyl			375	350	200	>290

A study of the isomeric chloroxylenols has shown that the compounds A, B, and C were about four times as effective against *B. coli* and fifteen times as strong against *Staph. aureus* (60, 90, 91) as the compounds D and E. Here again, the less active substances are those having chlorine ortho to hydroxyl. For B the phenol coefficient by the Rideal–Walker procedure is 38 (116).



Klarmann and coworkers have studied an interesting group of di- and trialkyl-*p*-chlorophenols. The germicidal activity of these compounds is tabulated in table 15. One trialkyl-2-chlorophenol,—namely, the 4-*n*-propyl-3,5-dimethyl compound,—was also studied. The figures obtained were 75, 2000, 140, 222, and 100 for the five microörganisms listed in table 15. It is obvious that when the number of carbon atoms in the side chain totals more than four, the bactericidal effect toward *E. typhi* drops below the maximum value, whereas with the other organisms the maximum is not reached until the carbon atoms total seven. As Klarmann points out, a compound having the side-chain carbon atoms in one alkyl group is

TABLE 15

Phenol coefficients of di- and tri-alkyl-4-chlorophenols

ALKYL GROUPS	PHENOL COEFFICIENT				
	E. typhi	*Staph. aureus*	*Strep. hemolyticus*	*Mycobacterium smegmatis*	*Trichophyton rosaceum*
3,5-Dimethyl	30	26	28	28	25
3-Methyl-6-ethyl	64	50	56	56	60
3-Methyl-6-*n*-propyl	133	200	178	156	150
3-Methyl-6-isopropyl (chlorothymol)	107	150	138	138	140
3-Methyl-6-*sec*-butyl	43	344	333	361	275
3-Methyl-6-*sec*-amyl	27	688	556	625	500
3-Methyl-6-*sec*-octyl		>89	122	>70	
3,5-Dimethyl-2-ethyl	46	106	94	122	130
3,5-Dimethyl-2-isopropyl	81	313	313	325	275
3,5-Dimethyl-2-*sec*-butyl	29	563	556	556	545
3,5-Dimethyl-2-*sec*-amyl*		750	1111	700	
3,5-Dimethyl-2-diethylcarbinyl*		1143	1000	667	700
3,5-Dimethyl-2-*sec*-octyl		100	>67		

* These two phenols are probably mixtures of the two straight-chain *sec*-amyl compounds in varying proportions.

more potent than when these are scattered among two or more substituents. However, because carvacrol and thymol are readily available, chlorine derivatives of these have been advocated for use as germicidal agents (111, 112, 129). Chlorine derivatives of the amylcresols have also been described in the patent literature (114).

The behavior of alkylbromophenols (80, 85) parallels that of the chlorine compounds. Available data for derivatives of *p*-bromophenol are listed in table 16. A comparison with table 13 shows that the maximum effect against *E. typhi* is reached one carbon atom lower in the series but that it is the same maximum. Against *Staph. aureus* the *n*-hexyl chloro and

bromo compounds have identical effects. Because of the lower molecular weights of the chlorine compounds, identical phenol coefficients mean a greater efficiency per molecule for the bromine compounds. The activity of 4-*n*-hexyl-2-bromophenol is just one-half that of the isomer with the bromine in the para-position and slightly less than for the chlorine compound. A series of 2,4-dibromo-6-alkylphenols has been prepared (27), but their germicidal properties were not reported.

TABLE 16

Phenol coefficients of o-alkyl-p-bromophenols

ALKYL GROUP	PHENOL COEFFICIENT			
	E. typhi	*Staph. aureus*	*Mycobacterium tuberculosis*	*Monila albicana*
None	6	5	5.6	6.3
Methyl	12.5	11.3	13.3	13.3
Ethyl	31.	25.	28.	28.
n-Propyl	63.	63.	78.	78.
n-Butyl	156.	313.	278.	222.
n-Amyl	63.	571.	444.	278.
n-Hexyl		1250.	778.	278.
sec-Amyl	>33	150.	156.	150.
Cyclohexyl	>23	429.	278.	222.

TABLE 17

Phenol coefficients of 4-alkyl-6-chlororesorcinols

ALKYL GROUP	PHENOL COEFFICIENT	
	Staph. aureus	*B. typhosus*
None	1.34	1.20
Ethyl	6.	
n-Butyl	35–45	47.
n-Hexyl	240.	
n-Heptyl	625.	
n-Octyl	665.	

The isomeric bromoxylenols differ even more than the chlorine derivatives in their bactericidal properties. Those with the bromine atom para to the hydroxyl group are six times as strong against *B. coli* and fifteen times as active toward *Staph. aureus* as the *o*-bromo compounds. The more active compounds had phenol coefficients in the range 50 to 60.

Iodinated alkylphenols have been little studied. Their solubility in water is low (139). It has been claimed that an iodinated carvacrol (111) has useful germicidal properties.

Some information is available concerning the alkylchlororesorcinols. The presence of the chlorine practically doubles the bactericidal action, as compared to the chlorine-free compounds (99, 103, 119). A comparison of tables 7 and 17 brings out this point. Which member of the series gives the maximum effect against *B. typhosus* apparently has not been determined.

Methods for preparing a number of secondary and tertiary alkylchlororesorcinols have been described (1, 4, 102), but details of the bactericidal activity of these compounds are lacking. In one patent bromine and iodine derivatives are referred to also (87).

IX. HYDROXYCARBOXYLIC ACIDS AND THEIR DERIVATIVES

Many investigations have been made on the antiseptic or preservative effect of the hydroxy acids, their halogen derivatives, and particularly their esters. Most of the results are not easily comparable with phenol coefficient values, as they deal with the bacteriostatic properties of these compounds and are frequently referred to yeast rather than to pathogenic microörganisms. However, the effects of halogen and alkyl groups are comparable to those already described for the simpler phenols and will be discussed briefly.

5-Fluorosalicylic acid has been prepared (154) and was found to have a higher toxicity to white mice than salicylic acid but no bactericidal data were obtained. In cultures of *E. typhi,* chloro- and dichloro-salicylic acids had about the same effect as salicylic acid (127), but 5-bromosalicylic acid was two times and 3,5-dibromosalicylic acid eight times as toxic to the organism. Against *Staph. aureus* both chlorine compounds were about twice as effective as salicylic acid, while 5-bromosalicylic acid was eight times and 3,5-dibromosalicylic acid was sixty-four times as effective. A more recent study (41), using the sodium salts of the acids, showed the superiority of the halogenated salicylic acids over phenol as a growth-arresting or bacteriostatic agent, but salicylic acid and its chlorine derivatives were found to be less germicidal than phenol, while the bromine and iodine derivatives are more active.

A series of *n*-alkylsalicylic acids (39) has been prepared; it was reported that these had higher phenol coefficients than salicylic acid, but no numerical values were given. The synthesis of *sec-* and *tert*-alkylsalicylic acid derivatives has been outlined in a patent (19). The products were claimed to have disinfectant properties.

While esters of salicylic acid have little germicidal or bacteriostatic action, certain alkyl *p*-hydroxybenzoates are highly effective, particularly as preservatives (10, 46, 48, 131, 132, 144, 159). The presence of halogen (88a, 138) in the nucleus increases this effectiveness as does the nitro group

(133) also, while the amino group decreases it. Nuclear-alkylated esters of *p*-hydroxybenzoic acid have been described (53). The action of numerous dihydroxybenzoic acids and their esters on yeast has also been mentioned. A recent determination of the phenol coefficients for several *n*-alkyl 3,5-dihydroxybenzoates (153) against *Staph. aureus* at 37°C. indicated that the figures for the ethyl and *n*-butyl compounds were less than 10, while the *n*-heptyl compound gave a value of 38.

X. NITRO-, AMINO-, AND SULFO-PHENOLS

Not a great deal is known concerning the germicidal properties of nitrophenols. Mazetti (93) found that of the three isomers the para-compound was most active. The ortho- and meta-isomers behaved about the same toward *E. typhi,* whereas against *Staph. aureus* the ortho-isomer was more effective. All three compounds were stronger bactericides than phenol. Since the pH of the nitrophenol solutions was about the same (93), their variation was not due to differences in their acid properties. *o*-Aminophenol and various of its *n*-alkyl derivatives have been described in the patent literature as highly active germicidal agents of low toxicity (109) but have not been studied extensively.

A mixture of phenolsulfonic acids of rather doubtful germicidal value, which contained chiefly the para-isomer (51, 108), was on the market for many years. In a study of sodium *p*-alkylphenolsulfonates (151) from *n*-propyl to *n*-hexyl, it was found that only the *n*-propyl and *n*-butyl compounds had measurable phenol coefficients, the values being 1.8 and 2.4, respectively. At 26°C. the solubility of the four sulfonates in water ranged from 1.5 to 0.5 g. per 100 ml. The solutions foamed readily, indicating a low surface tension. More recently, *n*-hexylresorcinolsulfonic acid has been patented (89) as a germicidal agent.

XI. HYDROXYARYL ALKYL ETHERS AND SULFIDES

Monoalkyl ethers of dihydroxyphenols may be looked upon as alkylphenols in which an oxygen has been introduced between the alkyl group and the ring, or alternatively as alkylphenols in which a methylene has been replaced by oxygen. In table 18 are listed the phenol coefficients for some monoalkyl ethers of the isomeric dihydroxy phenols (75, 77). It is obvious that the effect of the oxygen is complex. While isomeric *n*-alkylphenols exhibit the same germicidal activity, the ortho ethers are definitely less effective than the meta- and para-compounds. On the other hand, the maximum effect against *B. typhosus* in each series occurs at the five-carbon-atom side chain, as with the alkylphenols. Guaiacol and its derivatives have been used medicinally for some time. In the older literature (50) it was described as being a stronger disinfectant than phenol. A series

of 4-alkylguaiacols was found to have its maximum phenol coefficient at the *n*-amyl compound (63), but the value was low. The condensation product of 2-ethyl-1-butanol and guaiacol showed phenol coefficients of 73 and 63 against *Staph. aureus* and *E. typhi*, respectively (59a). The preparation of mono ethers of 4-chlororesorcinol has been described in the patent literature (122). These products are probably mixtures of isomers.

The effect of a second ether oxygen in a phenol side chain is to reduce the bactericidal action still further (20, 65). This is shown in table 19. Ap-

TABLE 18

Phenol coefficients at 37°C. of isomeric hydroxyphenyl alkyl ethers

ALKYL GROUP	PHENOL COEFFICIENT AGAINST *B. typhosus*			PHENOL COEFFICIENT AGAINST *Staph. aureus*		
	Para-compound	Meta-compound	Ortho-compound	Para-compound	Meta-compound	Ortho-compound
None	>12.	0.4	0.87	0.44	0.4	0.58
Methyl	1.0	1.3	0.91	0.8	1.2	0.73
Ethyl	1.5	3.6	1.8	1.5	3.0	1.6
n-Propyl	5.4	6.9	4.1	4.1	5.4	3.8
n-Butyl	14.	20.	9.8	9.	18.	10.
n-Amyl	29.	38.	22.	30.	36.	23.
n-Hexyl	18.	46.	17.	100.	125.	28.
n-Heptyl	17.	21.	9.7	200.	330.	37.
n-Octyl		2.3		360.	580.	
n-Nonyl		3.4			650.	
sec-Amyl	19.	(26)		26.	(31)	
Cyclohexyl		(18)			(20)	

TABLE 19

Phenol coefficients of resorcinol monoethers

ETHER	PHENOL COEFFICIENT	
	B. typhosus (20°C.)	*Staph. aureus* (37°C.)
β-Ethoxyethyl	2.5	5
β-Butoxyethyl	10.	5
γ-Butoxypropyl	6.	5

parently no alkoxyalkylphenol has been studied, so the effect of an ether linkage in the side chain where the oxygen is not attached to the nucleus is not known. One or more alcohol groups in the side chain of an aryl alkyl ether reduces the phenol coefficient to zero (118). Against *Staph. aureus* at 37.5°C. the monoallyl and diallyl ethers of pyrogallol (66) have the phenol coefficients 15 and 6, respectively. Information is not available on other unsaturated ethers.

The results obtained with hydroxyphenyl alkyl ethers made it of interest to determine the germicidal activity of the corresponding sulfides. It is brought out in table 20 that, for the lower members of the series against *B. typhosus*, the sulfides are about five times as effective as the ethers (95, 97, 100, 147). Separating the alkyl group from the phenol nucleus by sulfur results in a rise in the phenol coefficient. The *p*-hydroxy sulfides are more potent than the meta- and ortho-isomers. For the *n*-butyl com-

TABLE 20

Phenol coefficients of p-hydroxyphenyl alkyl sulfides and ethers

ALKYL GROUP	PHENOL COEFFICIENT AGAINST *B. typhosus*		PHENOL COEFFICIENT AGAINST *Staph. aureus*	
	Sulfide	Ether	Sulfide	Ether
Methyl	5	1	4 (8)	0.8
Ethyl	12	1.5	12 (10)	1.5
n-Propyl	25	5.4	25 (36)	4.1
n-Butyl	75	14	60 (77)*	9.3
n-Amyl	75	29	150 (120)	30.
n-Hexyl	40	18	200 (230)*	100.
Isopropyl			(20)	
Isobutyl			(61)	
Isoamyl			(30)	
Benzyl			(20)	

* Here the solvent was 0.01 *N* sodium hydroxide.

TABLE 21

Phenol coefficients of 3-methyl-4-hydroxyphenyl alkyl sulfides

ALKYL	PHENOL COEFFICIENT		
	B. typhosus	*Staph. aureus*	*Strep. hemolyticus*
Methyl	13	12	10
Ethyl	20	50	40
n-Propyl	23	80	80
n-Butyl	14	100	80
n-Amyl	8	250	200

pounds the phenol coefficient decreases from 77 to 40 to 25 as the hydroxyl group approaches the sulfur atom. Introduction of a methyl group into the aryl nucleus decreases greatly the maximum effectiveness of the sulfides against *B. typhosus* (150). The results are shown in table 21.

A series of 3-chloro-4-hydroxyphenyl alkyl sulfides has been prepared (28), but unfortunately no information is available concerning their bactericidal properties. The first attempts to prepare dihydroxyphenyl alkyl

sulfides were unsuccessful (148), but more recently (149) a series of 3,5-dihydroxy compounds has been synthesized by a series of reactions starting with benzenetrisulfonic acid. The phenol coefficients for these compounds are much lower than was anticipated. They are listed in table 22. Monoethers of phloroglucinol are not available for comparison, but the *sym*-alkylresorcinols mentioned earlier did not show abnormally low germicidal activity.

XII. HYDROXY DERIVATIVES OF BIPHENYL

Although there are many claims in the patent literature and some general statements elsewhere to the effect that hydroxybiphenyls are excellent bactericidal agents, the quantitative information available is small. Harris and Christiansen (56) have shown that 2-hydroxybiphenyl kills *B. typhosus* in a dilution of 1:2000 in 5 min., while against *Staph. aureus* the dilution necessary is 1:800. Woodruff gives the phenol coefficient here as 12.5

TABLE 22

Phenol coefficients of 3,5-dihydroxyphenyl alkyl sulfides at 37°C.

ALKYL GROUP	PHENOL COEFFICIENT	
	B. typhosus	*Staph. aureus*
Methyl	5.9	4.3
Ethyl	8.3	5.2
n-Propyl	16.	11.
n-Butyl	17.	14.
n-Amyl	<16.	<11.
n-Hexyl	<34.	<23.

(162). A study of the action of the same compound upon *Mycobacterium tuberculosis* in soap solutions (157) showed it to be lethal after 2 min. in 0.5 per cent concentration in a 1 per cent soap solution; with a 0.5 per cent soap solution, the presence of 0.25 per cent of the phenol was effective in 30 min., while at lower concentrations of soap and the phenol, the results were uncertain. Fuller (52) has reported that *o*-hydroxybiphenyl has remarkable penetrating power on the intact skin and is destructive toward the Streptococcus and Staphylococcus groups of organisms, but no numerical data were given.

A recent (104) determination of the behavior of 3-hydroxybiphenyl toward *Staph. aureus* gave a phenol coefficient of 33, indicating that phenyl is somewhat less effective than *n*-butyl in increasing the germicidal action of phenol. The activity toward *B. typhosus* is only about one-fifth as great (56). Against *Staph. aureus*, *p*-phenylphenol is even less effective than the ortho-isomer (162). Tests made with 2,4-dihydroxybiphenyl

(146) against *Staph. aureus* at 37°C. gave a phenol coefficient of 14, while the 3,5-isomer has a value of less than 12. 2,5-Dihydroxybiphenyl requires a dilution of 1:500 to kill either *B. typhosus* or *Staph. aureus* in 5 min. (56), while for the 3,4-isomer the dilutions were 1:2000 and 1:1200, respectively.

Halogen derivatives of hydroxybiphenyls have been described several times in the patent literature as having bactericidal properties (17, 32, 33, 69, 143). *o*-Bromo-*p*-phenylphenol has a phenol coefficient of 62.5 against *Staph. aureus* at 37°C. (162). A variety of alkylhydroxybiphenyls has also been investigated (16, 29, 33, 56). Against *Staph. aureus*, 3-alkyl-2-hydroxybiphenyls are less active than 2-hydroxybiphenyl itself, while the 5-alkyl isomers are more effective, reaching a maximum with the *n*-propyl derivative. Against *B. typhosus*, both groups of alkyl compounds exhibit decreased bactericidal properties. In general, the regularity in the effect of the alkyl group shown in the simple alkylphenols is no longer in evidence. Many halogenated (15) alkylhydroxybiphenyls have been listed as of potential value as germicides.

XIII. HYDROXY DERIVATIVES OF DIPHENYLMETHANE

It would be of particular interest to be able to compare a series of hydroxybiphenyl derivatives with the corresponding diphenylmethanes, where the two aromatic nuclei are separated by a saturated group which prevents resonance effects from being transferred from one ring to the other. Owing to Klarmann and coworkers (76, 78, 83), information is available for a variety of mono- and di-hydroxydiphenylmethane derivatives. The monohydroxy compounds are listed in table 23. Huston and coworkers (68) have prepared many other benzylphenols.

Several conclusions are obvious from these data. As for the simple halogenated phenols, a halogen ortho to a hydroxyl group increases the phenol coefficient less than when in the para-position. On the whole, it makes little difference which ring bears the halogen atom so long as it is not ortho to the hydroxyl. Multiple substitution of methyl and halogen groups produces substances highly active against *Staph. aureus* and *Strep. hemolyticus*.

A few derivatives of 2,4-dihydroxydiphenylmethane have been investigated. Their relative effectiveness is indicated in table 24. Here a halogen in the second ring raises the bactericidal value more than one adjacent to hydroxyl. The unsubstituted compound has about the same bactericidal action as 2,4-dihydroxybiphenyl (146).

An interesting series of diphenylmethane derivatives has been prepared (55) by condensing 2-hydroxy-3,5-dibromobenzyl bromide with various phenols, giving products having one or more hydroxyls in each ring.

TABLE 23

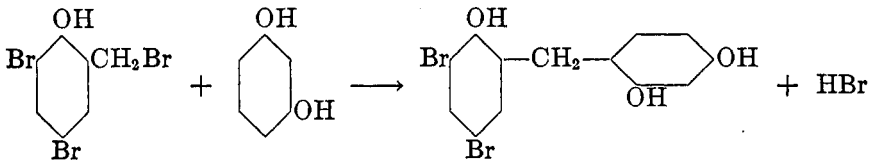
Phenol coefficients of hydroxydiphenylmethane derivatives

SUBSTITUTED HYDROXY COMPOUND	PHENOL COEFFICIENT			
	E. typhi	*E. paradysenteriae*	*Staph. aureus*	*Strep. hemolyticus*
3-Chloro-4-	36	54	125	165
3-Chloro-2-	24	36	71	94
5-Chloro-2-	74	92	215	245
4'-Chloro-4-	83	98	170	165
4'-Chloro-2-	57	90	190	175
3-Bromo-4-	19	37	170	185
5-Bromo-2-	26	55	295	310
3,4'-Dichloro-4-	41	110	345	175
3,5-Dichloro-2-	22	85	65	250
3-Chloro-4'-bromo-4-	17	24	200	565
5-Chloro-3-methyl-2-	16	25	245	300
4'-Chloro-3-methyl-2-	16	26	240	260
5-Chloro-4-methyl-2-	17	34	405	455
5-Chloro-4,6-dimethyl-2-	31	22	920	785
4'-Bromo-4,6-dimethyl-2-			420	600
5 - Chloro - 3 - isopropyl - 6 - methyl-2-	16	15	35	38

TABLE 24

Phenol coefficients of substituted 2,4-dihydroxydiphenylmethanes

SUBSTITUENT	PHENOL COEFFICIENT	
	B. typhosus	*Staph. aureus*
None	18	11
5-Chloro-	48	37
4'-Chloro-	63	40
5-Bromo-	37	45
4'-Bromo-	55	51



In table 25 the compounds made in this manner are listed, together with their "maximum killing dilutions" at 5 min. The first column indicates the phenol used in the condensation. The determinations were made at 37°C. by the F.D.A. method. The presence of a hydroxyl group

in each nucleus apparently reduces the effect toward *E. typhi* to a small value, whereas some of the compounds are quite effective against *Staph. aureus*.

When two aryl groups, one of them containing one or more hydroxyl groups, are separated by more than one methylene group, the germicidal power rises and then falls (74). This is brought out in table 26.

TABLE 25

Bactericidal properties of 2-hydroxy-3,5-dibromodiphenylmethane derivatives

PHENOL	EFFECTIVE DILUTION	
	E. typhi	*Staph. aureus*
Phenol	1:500	1:1200
2,4-Dibromophenol	1:400	1:3000
2,4-Diiodophenol	1:600	1:5000
Resorcinol	1:200	1:250
Dibromoresorcinol	<1:100	1:300
m-Cresol	1:600	1:2000
Dibromo-*m*-cresol	1:200	1:8000
o-Cresol	1:200	1:1000
Bromo-*o*-cresol	1:500	1:5000

TABLE 26

Phenol coefficients of aralkylphenols

COMPOUND	PHENOL COEFFICIENT AGAINST *B. typhosus*
p-Benzylphenol	4.6
4-Benzylresorcinol	22.
4-Phenethylresorcinol	40.
4-Phenpropylresorcinol	31.
Benzylphloroglucinol	7.5
Phenethylphloroglucinol	8.
Phenpropylphloroglucinol	8.8

In the early investigations of Ehrlich and coworkers (11, 12), it was found that when two benzene rings, one bearing a hydroxyl group, were separated by the ketone, sulfone, or carbinol grouping, the bactericidal properties of the compound were reduced to a low value compared with the diarylmethane derivative.

XIV. HYDROXY DERIVATIVES OF ARYL ETHERS AND OF ARYL SULFIDES

It has been pointed out earlier that the bactericidal efficiency of hydroxyphenyl alkyl sulfides is much greater than that of the corresponding ethers.

It is therefore of interest to compare hydroxy derivatives of purely aromatic sulfides with the oxygen compounds. Although the sulfides were found to be more effective (62, 72), the difference is much smaller than in the case of the alkyl aryl compounds. This is brought out in table 27. Walter (161) has extended this comparison for the *p*-hydroxy compound to the

TABLE 27

Phenol coefficients for hydroxy aryl ethers and sulfides against B. typhosus

POSITION OF HYDROXYL	PHENOL COEFFICIENT	
	Ether	Sulfide
Ortho	17	33
Meta	40	68
Para	41	115

TABLE 28

Phenol coefficients of hydroxy diaryl compounds against Staph. aureus

p-HYDROXY DERIVATIVE OF	PHENOL COEFFICIENT
Phenyl ether	40
Phenyl sulfide	100
Phenyl selenide	100
Diphenylamine	10
Diphenylmethane	100

TABLE 29

Phenol coefficients of phenols and corresponding aryl sulfides against Staph. aureus in 30 per cent alcohol

PHENOL	PHENOL COEFFICIENT OF PHENOL	PHENOL COEFFICIENT OF SULFIDE	RATIO
Phenol	1	12.5	12.5
Resorcinol	0.8	3.0	4
m-Cresol	2.1	17	8
p-Chlorophenol	6.2	63	10
p-Bromophenol	4.2	42	10
Thymol	8.3	83	10

selenide, amine, and methane derivatives. In table 28 are shown the results obtained with *Staph. aureus* by the Rideal–Walker technic. The hydroxy ethers are of no value as urinary antiseptics because they are excreted as esters of sulfuric acid. *p*-Hydroxyphenyl *p*-tolyl sulfide has been patented as a germicide (73). Iodine derivatives of hydroxyaryl

sulfides are too insoluble to produce a bactericidal effect in the usual tests (9).

An interesting series of sulfides has been prepared by the action of sulfur dichloride upon phenols (45).

$$2C_6H_5OH + SCl_2 \rightarrow (p\text{-}HOC_6H_4)_2S + 2HCl$$

These compounds, as shown in table 29, are about ten times more effective as bactericidal agents than the original phenols, except in the case of resorcinol; however, 0.8 is about twice the figure found for the phenol coefficient of resorcinol by other investigators (75).

XV. DISCUSSION

On the basis of the evidence presented, a number of generalizations can be formulated.

1. Whatever the reasons for the lack of agreement of the phenol coefficients reported by different investigators for the same compound, it is evident that any conclusion drawn from a comparison of data on different substances when the data are not from the same laboratory must be accepted with reservations. On the other hand, a general trend in bactericidal activity shown in a series of compounds can be relied upon to repeat itself in different sets of data, even though the numerical values of the phenol coefficients may vary.

2. It is clear that the phenol coefficient of a compound must depend upon several properties, which may be physical or chemical or both. A property which is dominant in determining bactericidal activity toward *B. typhosus*, for example, must be relatively unimportant with another type of organism such as *Staph. aureus*. Otherwise the variation in effectiveness toward different organisms shown in a homologous series becomes unintelligible. The use of phenol as a reference standard somewhat clouds the issue here. A compound may have the same phenol coefficient against two types of organisms and still differ markedly in its relative lethal effects because of the difference shown by phenol in its action on the same two types of organism. In other words, the mechanism of bactericidal action must, for the time being, be considered as a separate problem for each type of organism.

3. The introduction of halogen into the nucleus of a phenolic compound without exception increases its bactericidal potency. This increase is less for the ortho-position than the para, perhaps owing to interaction between the hydroxyl groups and halogen atoms. Little evidence is available for meta-compounds. The effect of halogen substitution, in general, increases with increasing atomic weight of the halogen. However, the effect of iodine has been little studied.

4. The introduction of an alkyl group into the phenol nucleus produces a rise in bactericidal action, followed by a decrease as the carbon chain extends beyond five or six carbon atoms when *B. typhosus* and other Gram-negative organisms are employed for testing. For *Staph. aureus* and other Gram-positive varieties, the increase in activity continues somewhat irregularly until the compound becomes too insoluble to test satisfactorily. A normal carbon chain has more effect than a branched one containing the same number of carbon atoms. A primary alkyl group has more effect than a secondary or tertiary alkyl group of the same weight. A given number of carbon atoms produces more effect in a single side chain than when distributed between two or more. The effect of halogen and alkyl on bactericidal properties is more or less independent, i.e., if an alkyl group raises the phenol coefficient a halogen atom increases it still further.

The effect of introducing an alkyl group into a hydroxybiphenyl or hydroxydiphenylmethane is irregular and unpredictable.

5. Separation of an alkyl group from the phenol nucleus by oxygen decreases the germicidal activity, and the presence of oxygen as an alcohol or ether group in the side chain likewise produces this effect. On the other hand, a sulfur atom between the aryl and alkyl group increases the bactericidal action, the sulfur acting somewhat as an additional methylene group.

6. Increasing the number of hydroxyl groups attached to an aromatic nucleus decreases the germicidal activity, a decrease that cannot effectively be compensated for by alkyl and halogen when more than two hydroxyl groups are present.

7. Conclusions about compounds containing two or more aromatic nuclei are subject to the limitations indicated under paragraph 1. It appears that separation of the benzene rings of hydroxybiphenyl by means of groups which do not increase water-solubility or are not strongly polar,—such as methylene, ethylene, possibly trimethylene, sulfur, and selenium,—either does not change or increases bactericidal activity. On the other hand, the effect of the ketone, sulfone, and carbinol groups is just the reverse. The effect of the ether linkage is small and uncertain as to direction. It would be expected that the oxygen of diaryl ethers would have very weakly basic properties and hence influence the water-solubility of these compounds to a relatively small degree. Little systematic information is available concerning hydroxy derivatives of fused ring systems.

Suggestions for further research

Two types of research problems are in need of investigation in the field of phenolic bactericidal agents. In the first place, there are a number of serious gaps in our knowledge of the effect of certain groups. A study of

the effect of halogen meta to hydroxyl would be of interest, as in the one known example the bactericidal value is much higher than for the other isomers. It would be of interest to know whether the effect of halogen in the ring of hydroxyphenyl alkyl sulfides is to increase germicidal action or to decrease it, as does a methyl group. The synthesis of halogenated hydroxybiphenyls in which the halogen is not in the same ring as the phenol group also seems justified, in order to be able to compare such compounds with the diphenylmethane derivatives already investigated. It seems likely that a study of certain naphthalene derivatives,—in particular, 1,3-dihydroxynaphthalene and its substitution products,—would yield results of at least theoretical importance.

The second type of problem to be suggested is that dealing with the mechanism of bactericidal action and the correlation of this action with something other than molecular structure. Data are needed on the physical properties of phenolic compounds; in particular, solubilities, surface tension or interfacial tension effects, the distribution ratio between immiscible solvents, and adsorption phenomena seem worthy of study. From a knowledge of these properties for a relatively few carefully selected compounds, some insight into the mechanism of bactericidal effects may be obtained.

REFERENCES

(1) AUSTIN: U. S. patent 2,060,654, Chem. Abstracts **31**, 507 (1937).
(2) AUSTIN: U. S. patent 2,030,423, Chem. Abstracts **30**, 2325 (1936).
(3) AUSTIN: U. S. patent 2,006,039, Chem. Abstracts **29**, 5601 (1935).
(4) AUSTIN: U. S. patent 2,023,160, Chem. Abstracts **30**, 819 (1936).
(5) BAGLIONI: Z. allgem. Physiol. **3**, 313 (1904).
(6) BAKER: Drug Cosmetic Ind. **34**, 464 (1934).
(7) BARTLETT AND GARLAND: J. Am. Chem. Soc. **49**, 2098 (1927).
(8) BARTZ, MILLER, AND ADAMS: J. Am. Chem. Soc. **57**, 371 (1931).
(9) BASS AND JOHNSON: J. Am. Chem. Soc. **52**, 1146 (1930).
(10) BAYO: Arch. Pharm. **267**, 669 (1929).
(11) BECHOLD: Z. angew. Chem. **22**, 2033 (1909); Münch. med. Wochschr. **61**, 1929 (1914).
(12) BECHOLD AND EHRLICH: Z. physiol. Chem. **47**, 173 (1906).
(13) BLICKE AND STOCKHAUS: J. Am. Pharm. Assoc. **22**, 1090 (1933).
(14) BOOTS PURE DRUG CO. AND MARSHALL: British patent 447,618, Chem. Abstracts **30**, 7285 (1936).
(15) BRITTON, COLEMAN, AND MILLS: U. S. patents 2,092,724,-5, Chem. Abstracts **31**, 8122 (1937).
(16) BRITTON, COLEMAN, AND PERKINS: U. S. patent 2,138,471, Chem. Abstracts **33**, 1885 (1939).
(17) BRITTON AND BRYNER: U. S. patent 1,969,963, Chem. Abstracts **28**, 6160 (1934).
(18) BRUSON: U. S. patent 1,987,228, Chem. Abstracts **29**, 1433 (1935).
(19) BRUSON: U. S. patent 1,998,750, Chem. Abstracts **29**, 3783 (1935).
(20) BRUSON: U. S. patent 2,098,204, Chem. Abstracts **32**, 1360 (1938).

(21) Buc: British patent 398,218, Chem. Abstracts **28,** 1358 (1934); U. S. patent 2,104,412, Chem. Abstracts **32,** 1869 (1938).
(22) Buc and Schuler: U. S. patent 2,045,749, Chem. Abstracts **30,** 5777 (1936).
(23) Caius, Naidu, and Shamser: Indian J. Med. Research **15,** 117 (1927).
(24) Carpenter: U. S. patent 2,064,885, Chem. Abstracts **31,** 900 (1937).
(25) Carswell and Nason: Ind. Eng. Chem. **30,** 622 (1938).
(26) Chien and Yin: J. Chinese Chem. Soc. **7,** 40 (1939).
(27) Chien, Chung, and Tai: J. Chinese Chem. Soc. **4,** 361 (1936).
(28) Chien and Chow: J. Chinese Chem. Soc. **7,** 46 (1939).
(39) Christiansen, Harris, and Lee: U. S. patent 2,073,683, Chem. Abstracts **31,** 3640 (1937).
(30) Christiansen and Lott: U. S. patent 1,922,153, Chem. Abstracts **27,** 5152 (1933).
(31) Christiansen and Harris: U. S. patent 1,897,188, Chem. Abstracts **27,** 2762, (1933).
(32) Christiansen, Moness, and Harris: U. S. patent 1,989,081, Chem. Abstracts **29,** 1942 (1935).
(33) Christiansen, Moness, and Harris: U. S. patent 2,014,720, Chem. Abstracts **29,** 7588 (1935).
(34) Clemmensen: Ber. **46,** 1837 (1913).
(35) Cooper and Woodhouse: Biochem. J. **17,** 600 (1923).
(36) Coulthard: Brit. J. Exptl. Path. **12,** 331 (1931).
(37) Coulthard, Marshall, and Pyman: J. Chem. Soc. **1930,** 280.
(38) Coulthard and Pyman: J. State Med. **39,** 599 (1931).
(39) Cox: J. Am. Chem. Soc. **52,** 352 (1930).
(40) Deichsel: U. S. patent 2,002,447, Chem. Abstracts **29,** 4376 (1935); British patent 428,295.
(41) Delawney: J. pharm. chim. **25,** 254 (1937).
(42) Dohme: U. S. patents 1,649,670-2, Chem. Abstracts **22,** 481 (1928).
(43) Dohme: U. S. patent 1,858,108, Chem. Abstracts **26,** 3876 (1932).
(44) Dohme, Cox, and Miller: J. Am. Chem. Soc. **48,** 1688 (1926).
(45) Dunning, Dunning, and Drake: J. Am. Chem. Soc. **53,** 3468 (1931).
(46) Efron: Thesis, Berlin, 1932 (43 pp.).
(47) Engelhardt: Biochem. Z. **190,** 217 (1927).
(48) Engels and Weijlard: U. S. patent 2,056,176, Chem. Abstracts **30,** 8533 (1936).
(49) Fanto: U. S. patent 1,824,426, Chem. Abstracts **26,** 156 (1932); French patent 721,257, Chem. Abstracts **26,** 4135 (1932).
(50) Frankel: *Arzneimittelsynthese,* 6th edition, p. 576. Julius Springer, Berlin (1927).
(51) Reference 50, p. 542.
(52) Fuller: Ind. Eng. Chem. **26,** 946 (1934).
(53) Gersch: Thesis, Berlin, 1931 (36 pp.).
(54) Hampil: J. Infectious Diseases **43,** 25 (1928).
(55) Harden and Brewer: J. Am. Chem. Soc. **59,** 2379 (1937).
(56) Harris and Christiansen: J. Am. Pharm. Assoc. **23,** 530 (1934).
(57) Hart: U. S. patent 2,082,625, Chem. Abstracts **31,** 5518 (1937).
(58) Hart and Woodruff: J. Am. Chem. Soc. **58,** 1957 (1936).
(59) Harrington: This Laboratory, unpublished results.
(59a) Hartung, Crossley, and Moore (Sharp and Dohme): Private communication.

(60) HEICKEN: Angew. Chem. **52,** 263 (1939).
(61) HESTER: U. S. patent 2,060,573, Chem. Abstracts **31,** 507 (1937).
(62) HILBERT AND JOHNSON: J. Am. Chem. Soc. **51,** 1526 (1929).
(63) HOWELLS AND HOWELLS: J. Am. Chem. Soc. **54,** 401 (1932).
(64) HUBERT: Ind. Eng. Chem. **30,** 1241 (1938).
(65) HURD AND FOWLER: J. Am. Chem. Soc. **61,** 250 (1939).
(66) HURD AND PARRISH: J. Am. Chem. Soc. **57,** 1731 (1935).
(67) HURD AND MCNAMEE: J. Am. Chem. Soc. **59,** 104 (1937).
(68) HUSTON *et al.*: J. Am. Chem. Soc. **55,** 4639 (1939).
(69) JENKINS: U. S. patent 2,084,033, Chem. Abstracts **31,** 5386 (1937).
(70) JOHNSON AND LANE: J. Am. Chem. Soc. **43,** 348 (1921).
(71) JOHNSON AND HODGE: J. Am. Chem. Soc. **35,** 1014 (1913).
(72) JOHNSON: U. S. patent 1,976,732, Chem. Abstracts **28,** 7432 (1934).
(73) JOHNSON: U. S. patent 2,011,582, Chem. Abstracts **29,** 6706 (1935).
(74) KLARMANN: J. Am. Chem. Soc. **48,** 791, 2358 (1926).
(75) KLARMANN, GATES, AND SHTERNOV: J. Am. Chem. Soc. **54,** 298, 1204 (1932).
(76) KLARMANN, GATES, AND SHTERNOV: J. Am. Chem. Soc. **54,** 3315 (1932).
(77) KLARMANN, GATYAS, AND SHTERNOV: J. Am. Chem. Soc. **53,** 3397 (1931).
(78) KLARMANN AND VON WOWERN: J. Am. Chem. Soc. **51,** 605 (1929).
(79) KLARMANN AND FIGDOR: J. Am. Chem. Soc. **48,** 803 (1926).
(80) KLARMANN, GATES, SHTERNOV, AND COX: J. Am. Chem. Soc. **55,** 4657 (1933).
(81) KLARMANN, SHTERNOV, AND GATES: J. Am. Chem. Soc. **56,** 2576 (1933).
(82) KLARMANN: J. Bact. **17,** 440 (1929).
(83) KLARMANN: U. S. patent 1,967,825.
(84) KLARMANN: U. S. patent 2,010,595, Chem. Abstracts **29,** 6607 (1935); U. S. patent 2,139,550, Chem. Abstracts **33,** 2285 (1939).
(85) KLARMANN: U. S. patent 1,969,801, Chem. Abstracts **28,** 6250 (1934).
(86) KLARMANN AND GATES: U. S. patents 1,938,911 and -12, Chem. Abstracts **28,** 1472 (1934).
(87) KYRIDES: U. S. patent 2,093,778, Chem. Abstracts **31,** 8126 (1937); Canadian patent 360,237, Chem. Abstracts **30,** 7285 (1936).
(88) KYRIDES: U. S. patent 2,067,452, Chem. Abstracts **31,** 1557 (1937).
(88a) LEBEDEV: Chem. Abstracts **30,** 5661 (1936).
(89) LEGERLOTZ: Austrian patent 151,971, Chem. Abstracts **32,** 3095 (1938).
(90) LOCKEMANN AND HEICKEN: Zentr. Bakt. Parasitenk., I, Orig. **145,** 61 (1939).
(91) LOCKEMANN AND KUNZMAN: Angew. Chem. **46,** 296 (1933).
(92) MARSHALL AND BOOTS PURE DRUG CO., LTD.: British patent 330,333, Chem. Abstracts **24,** 5939 (1930).
(93) MAZZETTI: Boll. soc. ital. biol. sper. **3,** 1198 (1928); Chem. Abstracts **24,** 879 (1930); **26,** 2761 (1932).
(94) MCGREAL AND NIEDERL: J. Am. Chem. Soc. **57,** 2625 (1935).
(95) MILLER AND READ: J. Am. Chem. Soc. **54,** 4113 (1932); **55,** 1224 (1933).
(96) MILLER, HARTUNG, ROCK, AND CROSSLEY: J. Am. Chem. Soc. **60,** 7 (1938).
(97) MILLER: U. S. patent 2,074,851, Chem. Abstracts **31,** 3212 (1937).
(98) MILLS: U. S. patent 2,039,434, Chem. Abstracts **30,** 4266 (1936).
(99) MONESS: U. S. patent 2,151,137, Chem. Abstracts **33,** 4743 (1939).
(100) MONESS, BRAKER, AND CHRISTIANSEN: J. Am. Pharm. Assoc. **21,** 557 (1932).
(101) MONSANTO CHEMICAL CO.: British patent 452,335, Chem. Abstracts **31,** 485 (1937).
(102) MONSANTO CHEMICAL CO.: British patent 421,965, Chem. Abstracts **29,** 3784 (1935).

(103) MOORE, DAY, AND SUTER: J. Am. Chem. Soc. **56**, 2456 (1934).
(104) MOORE, MAURICE L. (Sharp and Dohme): Private communication.
(105) NIEDERL, NIEDERL, SHAPIRO, AND MCGREAL: J. Am. Chem. Soc. **59**, 1114 (1937).
(106) NIEDERL, NATELSON, AND BEEKMAN: J. Am. Chem. Soc. **55**, 2571 (1933).
(107) NIEDERL: U. S. patent 2,073,316, Chem. Abstracts **31**, 3504 (1937); U. S. patent 2,008,032, Chem. Abstracts **29**, 5994 (1935).
(108) OBERMILLER: Ber. **40**, 3623 (1907).
(109) OSTROMISLENSKY: U. S. patent 2,040,183, Chem. Abstracts **30**, 4629 (1936).
(110) PERKINS, DIETZLER, AND LUNDQUIST: U. S. patent 1,972,599, Chem. Abstracts **28**, 6532 (1934).
(111) PHILLIPP: German patent 582,968, Chem. Abstracts **28**, 859 (1934).
(112) PHILLIPP AND KUHN: Pharm. Presse, Wiss. prakt. Heft (1931) 19; U. S. patent 1,964,999, Chem. Abstracts **28**, 5181 (1934); German patent 583,108, Chem. Abstracts **29**, 553 (1935).
(113) PUTNAM, BRITTON, AND PERKINS: U. S. patent 2,039,344, Chem. Abstracts **30**, 4176 (1936).
(114) RAIZISS AND CLEMENCE: U. S. patent 2,071,939, Chem. Abstracts **31**, 2754 (1937); U. S. patent 2,102,854, Chem. Abstracts **32**, 1409 (1938).
(115) RAIZISS AND CLEMENCE: U. S. patent 2,073,995, Chem. Abstracts **31**, 3214 (1937); U. S. patent 2,106,760, Chem. Abstracts **32**, 2691 (1938).
(116) RAPPS: J. Soc. Chem. Ind. **52**, 175T (1933).
(117) RAWLINS AND HAMILTON: U. S. patent 2,107,307, Chem. Abstracts **32**, 2692 (1938).
(118) READ AND MILLER: J. Am. Chem. Soc. **54**, 1195 (1932).
(119) READ, REDDISH, AND BURLINGAME: J. Am. Chem. Soc. **56**, 1377 (1934).
(120) READ AND MULLIN: J. Am. Chem. Soc. **50**, 1763 (1928).
(121) READ: U. S. patent 1,887,662, Chem. Abstracts **27**, 1453 (1933).
(122) READ: U. S. patent 2,036,827, Chem. Abstracts **30**, 3592 (1936).
(123) RETTGER, VALLEY, AND PLASTRIDGE: Zentr. Bakt. Parasitenk., I., Orig. **110**, 80 (1929).
(124) RHODES: J. Rubber Research Inst. Malaya **8**, 324 (1938).
(125) RIDEAL AND WALKER: J. Roy. Sanit. Inst. **24**, 424 (1903).
(126) ROBINSON AND HESTER: U. S. patent 2,008,337, Chem. Abstracts **29**, 5996 (1935).
(127) ROCHAIX AND PINET: Bull. sci. pharmacol. **34**, 486 (1927).
(128) RÖHM AND HASS: German patent 657,724, Chem. Abstrracts **32**, 6009 (1938).
(129) ROEG: Am. J. Pharm. **110**, 72 (1938).
(130) RUSSELL, FRYE, AND MAULDIN: J. Am. Chem. Soc. **62**, 1441 (1940).
(131) SABALITSCHKA: Pharm. Presse, Wiss. prakt. Heft (1931) 173; Pharm. Acta Helv. **5**, 286 (1930); Pharm. Monatsh. **13**, 225 (1932).
(132) SABALITSCHKA AND SCHWEITZER: Arch. Pharm. **267**, 675 (1929).
(133) SABALITSCHKA AND TIEDGE: Arch. Pharm. **272**, 383 (1934).
(134) SABALITSCHKA AND TIETZ: Arch. Pharm. **269**, 545 (1931).
(135) SCHAEFFER AND TILLEY: J. Bact. **12**, 307 (1926).
(136) SCHAEFFER AND TILLEY: J. Bact. **14**, 259 (1927).
(137) SCHMIEDEBERG: Arch. exptl. Path. Pharmakol. **20**, 203 (1886).
(138) SCHOELLER AND ALLARDT: U. S. patent 1,793,021, Chem. Abstracts **25**, 2155 (1931).
(139) SCHUETZ: M. S. Thesis, Northwestern University, 1939.
(140) SHAH AND MEHTA: J. Indian Chem. Soc. **13**, 358 (1936).

(141) STOCKELBACH: U. S. patent 2,081,284, Chem. Abstracts **31,** 5110 (1937).
(142) STOCKELBACH: U. S. patent 1,982,180, Chem. Abstracts **29,** 556 (1935).
(143) STOESSER: U. S. patent 2,131,258, Chem. Abstracts **32,** 9403 (1938).
(144) SÜSS: Thesis, Berlin, 1931 (29 pp.).
(145) SUTER, LAWSON, AND SMITH: J. Am. Chem. Soc. **61,** 161 (1939).
(146) SUTER AND SMITH: J. Am. Chem. Soc. **61,** 166 (1939).
(147) SUTER AND HANSEN: J. Am. Chem. Soc. **54,** 4100 (1932).
(148) SUTER AND HANSEN: J. Am. Chem. Soc. **55,** 2080 (1933).
(149) SUTER AND HARRINGTON: J. Am. Chem. Soc. **59,** 2575 (1937).
(150) SUTER AND MCKENZIE: J. Am. Chem. Soc. **56,** 2470 (1934).
(151) SUTER AND MOFFETT: J. Am. Chem. Soc. **54,** 2983 (1932).
(152) SUTER AND WESTON: J. Am. Chem. Soc. **61,** 232 (1939).
(153) SUTER AND WESTON: J. Am. Chem. Soc. **61,** 531 (1939).
(154) SUTER AND WESTON: J. Am. Chem. Soc. **61,** 2317 (1939).
(155) TALBOT AND ADAMS: J. Am. Chem. Soc. **49,** 2040 (1927).
(156) TANAKA, MARIKAWA, AND SAKAMATO: J. Chem. Soc. Japan **51,** 275 (1930).
(157) TILLEY, MACDONALD, AND SCHAEFFER: J. Agr. Research **42,** 653 (1931).
(158) TSUKERVANIK AND NAZAROVA: J. Gen. Chem. (U. S. S. R.) **7,** 623 (1937).
(159) TURTIAINEN: Zentr. Bakt. Parasitenk., I, Orig. **139,** 98 (1937).
(160) U. S. Dept. of Agriculture Circular No. 198 (1931).
(161) WALTER: Festschrift Emil C. Barell, p. 266 (1936); Chem. Abstracts **31,** 2349 (1937).
(162) WOODRUFF (The Upjohn Company): Private communication.