aniline was converted into the *m*-nitro-*sec.*-butylbenzene in the usual manner by diazotization in alcohol:[6] *m*-nitro-*sec.*-butylbenzene; b. p. 132–134° (19 mm.). *Anal.* Calcd.: N, 7.8. Found: N, 8.0. This was reduced to the amine with tin and hydrochloric acid: *m-sec.*-butylaniline, b. p. 120° (18 mm.). *Anal.* Calcd.: N, 9.4. Found: N, 8.8.

[6] Bigelow, THIS JOURNAL, **41**, 1559 (1919).

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[CONTRIBUTION FROM THE LABORATORIES OF SHARP AND DOHME, INC.]

SOME SUBSTITUTED PHENOLS AND GERMICIDAL ACTIVITY

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An increasing interest in the germicidal activity of substituted phenols led the writers to undertake a study of the relation between this property and the nature of certain substituted groups as well as their positions on the ring.

Since it was found, in the case of the alkylresorcinols[1,2,3] that the weight of the hydrocarbon side chain determined the degree of germicidal activity, it seemed desirable to study the influence of weight alone by comparing the effects of differing groups of approximately the same molecular weight. For this purpose a series of substituted phenols, containing oxygen in the side chain, was prepared and compared with normal, secondary and tertiary butylphenols. The activity of a number of other phenols is also included for comparative purposes.

Also in order to study the influence of position in the ring, the ortho, meta and para isomers were prepared in several instances. These compounds and their phenol coefficients are listed in the accompanying table.

Experimental

The preparation of the three normal butylphenols[4] and of the ortho and para secondary butylphenols from secondary butylbenzene[5] has been reported previously.

The various ethers were all prepared by the usual procedure. One mole of sodium was dissolved in about 15 moles of absolute alcohol and one mole of the phenol added to the solution. The solution was refluxed on a steam-bath while one mole of the alkyl chloride or chlorohydrin was added during one hour. Heating was continued during two hours. The precipitated salt was filtered off and the alcohol removed under reduced pressure. The

[1] Johnson and Lane, THIS JOURNAL, **43**, 348 (1921).

[2] Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926).

[3] See also the work of Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930), which appeared since the work here described was completed.

[4] Read and Mullin, THIS JOURNAL, **50**, 1763 (1928).

[5] Read, Hewitt and Pike, *ibid.*, **54**, 1194 (1932).

TABLE I

STRUCTURAL, PREPARATIONAL, PHYSICAL AND ANALYTICAL DATA

Side chain on phenol	Position	Weight of side chain	Phenol coefficient[a]	Melting point, °C.	Crystallizing solvent[b]	Analyses, % Calcd. C	Calcd. H	Found C	Found H
$CH_2CH_2CH_2CH_3$	*o*	57	52 (a)	B. p. 234–237					
	m	57	52 (a)	B. p. 247–249					
	p	57	52 (a)	B. p. 246–250[c]					
$CH(CH_3)CH_2CH_3$	*o*	57	28.1 (a)	B. p. 226–228		80.0	9.3	79.6	9.2
	p	57	27.5 (a)	B. p. 240–242	e				
				61–62					
$C(CH_3)_3$	*p*	57	19 (b) 22 (c)	99	e				
OCH_2CH_2OH	*o*	61	0 (b)	96–97	h i	62.3	6.5	62.1	6.7
	m	61	0 (b)	83–85	h	62.3	6.5	62.9	6.8
	p	61	0 (b)	B. p. 202–205 (14 mm.)		62.3	6.5	62.5	6.5
$OCH_2CHOHCH_2OH$	*o*	91	0 (b)	B. p. 245–255 (18 mm.)		58.7	6.5	58.5	6.5
$OCH_2CH_2CH_3$	*o*	59	5.5 (b)[d]	B. p. 228–229 (corr.)					
	p	59	4.4 (b)	55	e f g	71.1	7.9	70.9	7.9
$OCOCH_3$	*o*	59	0 (b)	B. p. 148 (25 mm.)					
	m	59	0 (b)	B. p. 174 (24 mm.)					
	p	59	0 (b)	B. p. 167–170 (20 mm.)					
				53–54					
$COOCH_3$	*o*	59	0 (b)	B. p. 109–111 (16 mm.)					
$COOCH_3$	*p*	59	0 (b)	123–124					
Cyclohexyl	*p*	83	0 (b)[e]	126	e				
Cyclohexyl	*o*	..	32 (b)	52	e				
$OCH_2CH_2CH_2CH_2CH_2CH_3$	*p*	101	67 (c)	44	e				
$OCH_2CH_2CH_2CH_2CH_3$	*p*	87	40 (c)	48	e				
$C_6H_3(OH)_2(OCH_2CH_2OH)$			0 (b)	B. p. 195–205 (13 mm.)		56.4	5.9	56.7	5.8
CH_2OH	*o*	31	0 (b)	85					
OCH_3	*o*	31	0.8 (c)	26–28					
	m	31	0.7 (c)	B. p. 140–142 (15 mm.)					
	p	31	0.8 (c)	47–48					
C_2H_5	*p*	29	7[f]						
CH_3	*o*	15	2.2 (a)	29					
	m	15	2.2 (a)	6					
	p	15	2.2 (a)	33					

[a] Phenol coefficients by the Hygienic Laboratory Method, 20°; organism, *Staph. aureus;* (a), (b), (c), refer to the bacteriologist making determinations.

[b] Crystallizing solvents: e, ligroin; f, water; g, ethyl alcohol; h, benzene; i, carbon tetrachloride.

[c] Due to a typographical error, this value was stated to be 746–750° by Read and Mullin, THIS JOURNAL, **50**, 1764 (1928).

[d] Klarmann, THIS JOURNAL, **53**, 3402 (1931), gives a value of 5.4 for the meta isomer using the same test organism, *Staph. aureus*.

[e] Bartlett and Garland, *ibid.*, **49**, 2100 (1927), also found *p*-cyclohexylphenol inactive. Solubility at 25° is 6:100,000. The ortho isomer is active at 1:3200.

[f] Schaffer and Tilley, Ref. 7,

phenol then was distilled in vacuum and crystallized from the solvent indicated. Analyses are given if the compounds have not been described previously.

Tertiary butylphenol, tertiary amylphenol and cyclohexylphenols were prepared by the condensation of the corresponding alcohols with phenol in the presence of zinc chloride, as will be described in a later report. Ortho and para secondary butylphenols can also be obtained by the condensation of secondary or primary butyl alcohol with phenol but the separation of the isomers is difficult.

Discussion

As the three cresols gave practically identical values,[6,7,8] it was hoped that if the bactericidal activity were sufficiently enhanced, a variation would appear. The normal butylphenols[9] did not show such a variation, having an average value of fifty for each isomer on one series of determinations and a value of fifty-two on a second series.[10]

It appears then that in the case of certain alkyl phenols (monohydroxybenzene derivatives) the relative position on the ring of the alkyl and

[6] An average of six determinations gave values 2.16, 2.17 and 2.20 for the *o*, *m* and *p* isomers. These values are taken from determinations reported by Leo F. Rettger.

[7] Schaffer and Tilley, *J. Bact.*, **14**, 266 (1927), give the values 2.2 for ortho cresol and 2.4 for meta cresol. The somewhat higher values reported by these investigators are probably due to the use of a higher temperature, 25°. It is interesting that their values for thymol and carvacrol, which differ only in the position of the OH group, are so nearly identical, 28.5 and 27.5.

[8] It has been the writers' experience that determinations of the phenol coefficient of a single lot of a phenol by the same bacteriologist made on different occasions may vary over a range of 10%. This is particularly true when the coefficient is high. The variation between different workers may be even greater. A very extreme case was noted when a sample was divided among three well-known bacteriologists who reported values from twenty-two to forty.

[9] The normal butylphenols were prepared for Rettger, Plastridge and Calley [*Centr. Bakt. Parasitenk.*, 287 (1929)], who investigated the properties of the butylphenols which one of the writers (R.) prepared for them.

[10] Schaffer and Tilley, *J. Bact.*, **12**, 307 (1926), assign a value of sixty-eight to the *p*-*n*-butylphenol. These workers used a temperature of 25° instead of the 20° used in the work reported here. B. Hampil, *J. Infectious Diseases*, **43**, 9 (1928), discusses some effects of temperature variation. Coulthard, Marshall and Pyman have recently assigned the values of 70 for the para and 75 for the ortho isomer using *B. typhosus* as the test organism.

hydroxyl groups has little effect on the germicidal activity: all three isomers are of approximately equal activity.

In the case of certain sulfur-containing phenols, a dependence is evident. The three hydroxydiphenyl sulfides[11] offer a striking variation in activity, having coefficients of 33, 68 and 115 for the *o*, *m* and *p* isomers. A later report on certain sulfur-containing germicides by the authors will show a similar variation in activity between isomers.

It has been observed previously that the mass of the side chain attached to the phenolic nucleus is only one factor in determining the activity of a phenol as a germicide. Particularly has it been pointed out that branching of the side chain lowers the activity in the resorcinol series.[2,12] This effect of a branching alkyl chain is demonstrated more clearly in the series of butylphenols, in which the values decrease in the order normal, secondary, tertiary in a ratio 5:3:2.

Frequently phenols which should be very active as tested by the usual[13] procedure are inactive due to low solubility. The two cyclohexylphenols offer an odd illustration of what is apparently such a case: the ortho isomer is active[14] while the para is not.[15] The para isomer is soluble to the extent of 6 mg. in 100 cc. of water while the coefficient of thirty would require a solubility of approximately 48 mg. per 100 cc. The still less soluble *p*-*n*-hexylphenol is also inactive according to this method of testing, although in the presence of alkali this phenol is reported to have a coefficient of 90.[16] Secondary hexylphenol (a mixture of the *o* and *p* isomers) is likewise inactive at 20° but at 37° and in the presence of 0.2% sodium carbonate is markedly active.[17] Coulthard, Marshall and Pyman[16] and also Hampil[18] found it necessary to use a dilute solution of alkali as the solvent in order to make comparisons of many alkyl cresols, resorcinols and guaiacols. This procedure probably alters the activity of the phenol as is indicated by tertiary butylphenol and its sodium salt.[19]

The replacement of a methylene group by oxygen lowers the activity of the substituted phenol markedly: *p*-*n*-butylphenol 50, and *p*-hydroxyphenyl *n*-propyl ether 5; *p*-ethylphenol 7, and *p*-methoxyphenol 1. When, in addition, the terminal methyl group of such an ether or one of the hydrogen atoms of that group is replaced by an hydroxyl group, the germicidal

[11] Johnson and Hilbert, THIS JOURNAL, **51**, 1534 (1929).

[12] Leonard, *A. M. A.*, **83**, 2005 (1924); *J. Urology*, **585**, 12 (1924).

[13] Hygienic Laboratory Method.

[14] Coefficient 32.

[15] Bartlett and Garland also report the para isomer as inactive, THIS JOURNAL, **49**, 2098 (1927).

[16] Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).

[17] Coefficient 78, less than *p*-*n*-hexylphenol as would be expected.

[18] Hampil, *J. Infectious Diseases*, **43**, 25 (1928).

[19] *p*-Tertiary butylphenol 19, sodium salt 13.

activity goes down to less than one—less than if no side chain were present: *p*-hydroxylphenyl *n*-propyl ether 5, *p*-hydroxyphenyl *n*-γ-hydroxypropyl ether 0; *o*-cresol 2.2, saligenin 0.

Summary

While it is true that no concise "rules" can result from such limited data, certain conclusions are perhaps permissible.

1. The mass of a group substituted into a phenol has little relation to the germicidal activity of the resulting compound.
2. Position isomerism has little effect on the bactericidal activity of alkyl and alkoxy substituted phenols.
3. Side chain isomerism affects the activity of alkyl phenols markedly. The more compact the group, the lower the activity.
4. The group CH_2R is much more effective than OR in enhancing the activity of a phenol.
5. The carbomethoxy and acetoxy groups are ineffective in enhancing the activity of phenol.

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THE NITRATION OF PHENYLACETIC ACID

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Latimer and Porter have shown that the directive influence of a group substituted for hydrogen in the benzene ring depends upon the residual charge of the atom attached to the ring.[1] The method of determining the residual charge is based upon the unequal sharing of electrons between two unlike atoms. It was found that if the residual charge on the atom attached to the ring has a high positive value, the substituent directs the incoming group mainly to the meta position and if the residual charge is zero or negative the substituent is ortho–para in its orienting influence. The method used in calculating the residual charge does not take into account the influence of atoms beyond those directly connected with the key atom. In order to evaluate the influences of remote atoms it is necessary to have exact data on the behavior of border-line groups. As a start in this direction we have studied the nitration of phenylacetic acid.

Radziszewski[2] found that the nitration of phenylacetic acid yielded mostly the para isomer, which is quite insoluble, and a small amount of the ortho isomer, which remained behind in the mother liquor. Maxwell,[3]

[1] Latimer and Porter, THIS JOURNAL, **52**, 206 (1930).

[2] Radziszewski, *Ber.*, **2**, 207 (1869); **3**, 648 (1870).

[3] Maxwell, *ibid.*, **12**, 1764 (1879).