

[CONTRIBUTION FROM THE PLAUT RESEARCH LABORATORY OF LEHN & FINE, INC.]

## BACTERICIDAL PROPERTIES OF MONOETHERS OF DIHYDRIC PHENOLS. I. THE MONOETHERS OF RESORCINOL

BY EMIL KLARMANN, LOUIS W. GATYAS AND VLADIMIR A. SHTERNOV

RECEIVED MAY 22, 1931

PUBLISHED SEPTEMBER 5, 1931

### Introduction

During the past several years a considerable amount of work has been carried out dealing with the influence of substitution by alkyl and aryl groups upon the antiseptic properties of mono- and polyphenols. The continued interest in this field of research is due to the occurrence among the mono- and polyhydric phenol homologs of many compounds which combine a remarkable bactericidal potency with a low toxicity for the animal organism. With few exceptions the products in question carry the substituting groups attached to the carbon atoms of the nuclei, while only few data are available on phenol derivatives in which an alkyl or aryl group is attached to another substituting element.

The most potent germ-killing compounds are found in the series of the phenol and resorcinol derivatives.

The first systematic study of alkyl phenol derivatives has been carried out by Laubenheimer.<sup>1</sup> While a number of individual investigations have been published on this subject from time to time, considerable interest in a comprehensive study of the problems involved has been evidenced but recently.

The following is a brief list of the most important recent papers on the effect of the introduction of radicals into the nucleus of phenols upon bactericidal action. Although considerable attention has also been given to the introduction of other substituents, notably halogens, no reference will be made here to these researches, as they are somewhat outside the range of the subject under consideration.

The *p*-alkylphenol derivatives were studied by Schaffer and Tilley,<sup>2</sup> the isomers of butylphenol by Rettger, Plastringe and Valley,<sup>3</sup> the alkyl cresols by Coulthard, Marshall and Pyman.<sup>4</sup>

An extensive study of the antibacterial properties of resorcinol derivatives began with the work of Johnson and collaborators.<sup>5</sup> Additional data were contributed by Dohme, Cox and Miller,<sup>6</sup> Schaffer and Tilley,<sup>2</sup>

<sup>1</sup> Laubenheimer, "Das Phenol und seine Derivate als Desinfektionsmittel," 1909.

<sup>2</sup> J. M. Schaffer and F. W. Tilley, *J. Bacteriol.*, **14**, 259 (1927); **12**, 303 (1926).

<sup>3</sup> L. F. Rettger, W. N. Plastringe and G. Valley, *Zentr. Bakteriolog. Orig.*, **1**, 111, 287 (1929).

<sup>4</sup> C. E. Coulthard, J. Marshall and F. L. Pyman, *J. Chem. Soc.*, 280 (1930).

<sup>5</sup> T. B. Johnson and Hodge, *THIS JOURNAL*, **35**, 1014 (1913); T. B. Johnson and F. W. Lane, *ibid.*, **43**, 348 (1921).

<sup>6</sup> A. R. L. Dohme, E. H. Cox and E. Miller, *ibid.*, **48**, 1688 (1926).

Hampil,<sup>7</sup> and Rettger and co-workers.<sup>8</sup> Resorcinol derivatives with two alkyl groups, and with aromatic groups in the nucleus were studied by Klarmann.<sup>9</sup> Alicyclic derivatives were prepared by Talbot and Adams,<sup>10</sup> and by Bartlett and Garland,<sup>11</sup> combinations with the chaulmoogric radical by Hinegardner and Johnson.<sup>12</sup>

Very few data are available concerning the antiseptic properties of nucleus substituted derivatives of other dihydric and polyhydric phenols. Klarmann and Figdor<sup>13</sup> studied the antibacterial effect of the presence of certain aliphatic and aromatic groups in the nucleus of phloroglucinol.

### Discussion

The above brief description of work accomplished to date indicates that in the study of the effect of side chains upon bactericidal efficiency of phenol derivatives, the attention of the investigators was centered almost exclusively upon substitution in the nucleus. In contrast to this, we were interested in determining the effect of substituting radicals not directly attached to the carbon atoms of the nucleus, in order to ascertain whether or not nucleus substitution is essential for the bactericidal effect. The first group of compounds considered are the monoethers of dihydric phenols. Here the radical is connected with the nucleus by means of an oxygen atom, leaving one hydroxyl group free; the presence of one open hydroxyl group is regarded as essential in bringing about the antiseptic effect<sup>14</sup> of phenol derivatives.

Several monoethers of dihydric phenols have been prepared in the past. Some, as the ethers of pyrocatechol, have also been used for therapeutic purposes, the idea having been primarily to reduce the toxicity of pyrocatechol for the human organism by alkylation. Monoethers of resorcinol, of which only the methyl and ethyl ethers have been described in the literature, do not appear to have been studied bacteriologically before.

The resorcinol monoethers prepared by us to date comprise the normal saturated alkyl derivatives up to the nonyl ether, some secondary and cyclo alkyl derivatives and a number of ethers with aromatic groups. They were obtained (with one exception) by condensation of resorcinol with

<sup>7</sup> B. Hampil, *J. Infectious Diseases*, **43**, 25 (1928).

<sup>8</sup> L. F. Rettger, G. Valley and W. N. Plastringe, *Zentr. Bakteriolog. Orig.*, **110**, 80 (1929).

<sup>9</sup> E. Klarmann, *THIS JOURNAL*, **48**, 791 (1926); **48**, 2358 (1926); E. Klarmann and J. Von Wowern, *ibid.*, **51**, 605 (1929).

<sup>10</sup> R. H. Talbot and R. Adams, *ibid.*, **49**, 2040 (1927).

<sup>11</sup> J. T. Bartlett and C. E. Garland, *ibid.*, **49**, 2098 (1927).

<sup>12</sup> W. S. Hinegardner and T. B. Johnson, *ibid.*, **51**, 1503 (1929).

<sup>13</sup> E. Klarmann, *ibid.*, **48**, 2358 (1926); E. Klarmann and W. Figdor, *ibid.*, **48**, 803 (1926).

<sup>14</sup> E. Klarmann, V. A. Shternov and J. Von Wowern, *J. Bacteriol.*, **17**, 440 (1929).

organic halides. The monophenyl ether of resorcinol (*m*-hydroxydiphenyl oxide) cannot be prepared according to this general scheme since aryl halides do not react easily with resorcinol in the presence of alkali. To obtain the desired compound, condensation of *m*-bromoaniline with phenol was effected in the presence of strong alkali and metallic copper, and the *m*-aminodiphenyl oxide thus obtained was then converted into the hydroxy derivative by diazotization and boiling with water.

The bacteriological investigation of the resorcinol ethers was carried out using *B. typhosus* and *Staphylococcus aureus* as test organisms. The use of two test bacteria has been decided upon since according to previous findings, notably those of Hampil,<sup>7</sup> a distinctly different behavior is observed with Gram positive and Gram negative bacteria. In order to obtain more complete information regarding the compounds of this class, additional bacteria are being included in our further studies of this problem. Experiments *in vivo* are also in preparation.

TABLE I  
BACTERICIDAL ACTION OF MONOETHERS OF RESORCINOL

	<i>B. typhosus</i>				<i>Staph. aureus</i>			
	Bactericidal concentrations			Phenol	Bactericidal concentrations			Phenol
	5 min.	10 min.	15 min.	coeff.	5 min.	10 min.	15 min.	coeff.
Resorcinol	1:50	1:60	1:60	0.4	1:30	1:30	1:35	0.4
Alkyl Ethers								
Methyl	1:160	1:180	1:200	1.3	1:80	1:90	1:90	1.2
Ethyl	1:450	1:550	1:650	3.6	1:200	1:250	1:250	3.0
<i>n</i> -Propyl	1:1000	1:1200	1:1200	6.9	1:400	1:400	1:500	5.4
<i>n</i> -Butyl	1:2750	1:3000	1:3250	20	1:1300	1:1400	1:1500	18
<i>n</i> -Amyl	1:6000	1:6000	1:6500	38	1:2750	1:2750	1:3000	36
<i>sec.</i> -Amyl	1:3750	1:3750	1:4000	(26)	1:2000	1:2000	1:2250	(31)
<i>n</i> -Hexyl	1:6000	1:7000	1:7000	46	1:7500	1:8500	1:9000	125
Cyclohexyl	1:2500	1:2750	1:2750	(18)	1:1500	1:1600	1:1600	(20)
<i>n</i> -Heptyl	1:3000	1:3250	1:3500	21	1:25,000	1:25,000	1:25,000	330
<i>n</i> -Octyl	1:325	1:375	1:375	2.3	1:40,000	1:45,000	1:50,000	580
<i>n</i> -Nonyl	1:500	1:550	1:600	3.4	1:50,000	1:50,000	1:55,000	650
Aromatic Ethers								
Phenyl	1:4500	1:6000	1:6500	40	1:2500	1:2750	1:3000	37
Benzyl	1:2750	1:3250	1:3250	21	1:1100	1:1300	1:1300	16
Phenylethyl	1:4500	1:5000	1:5000	35	1:2250	1:2750	1:2750	39
Phenylpropyl	1:5500	1:5500	1:5500	34	1:5500	1:7000	1:7000	89
<i>p</i> -Chlorobenzyl	1:8000	1:8500	1:9000	61	1:2750	1:3000	1:3000	38
Control (phenol)								
average	1:130	1:140	1:160	1	1:70	1:80	1:90	1

Table I indicates the maximum dilutions which were found to be germicidal for *B. typhosus* and *Staphylococcus aureus* in five, ten and fifteen minutes' exposure at 37°, and the phenol coefficients calculated therefrom.

The data represent practical averages of several experiments. It appears that while the germicidal potency of the parent compound resorcinol is comparatively insignificant, some of its monoethers are highly bactericidal. The relation between the molecular weight of the side chain and the phenol coefficient, particularly in the case of the ethers with aliphatic substituents, manifests itself differently with the two microorganisms. Thus while with *B. typhosus* the germ-killing efficiency increases, reaching a maximum with the hexyl ether and then drops again, no such maximum is reached in the case of *Staphylococcus aureus* with the compounds hitherto prepared; rather the germicidal potency appears to be a direct function of the length of the side chain, at least up to the nonyl ether.

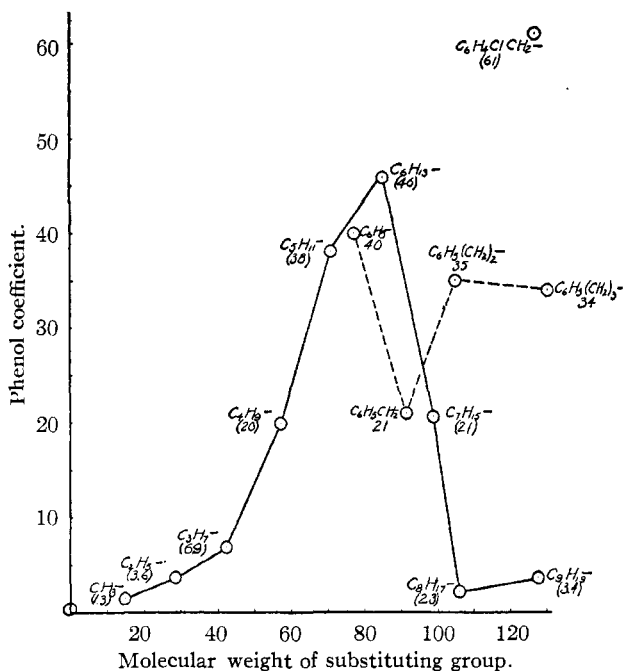


Fig. 1.—The effect of the substituting radical upon the bactericidal action of monoethers of resorcinol. Test organism, *B. typhosus*: —, alkyl derivatives; ---, aromatic derivatives.

Introduction of secondary radicals appears to lead to products the potency of which is lower than that of the straight chain derivatives. Mono substitution with the cyclohexyl group yields a less effective compound than with either the *n*-hexyl or the phenyl radical.

The resorcinol monoethers obtained by introduction of unsubstituted aromatic groups are also powerful germicides. While the phenyl ether appears to be rather strongly bactericidal to both *B. typhosus* and *Staphylo-*

*coccus aureus*, the germicidal potency drops in the case of the benzyl ether, subsequently reaching a new maximum for *B. typhosus* with the phenylethyl ether; for *Staphylococcus aureus* the phenylpropyl ether is more bactericidal than the former compound. The position of the maximum of the effect upon *Staphylococcus aureus* so far is unknown.

As to the substituted alipharyl groups, only the *p*-chlorobenzyl ether has been studied, its bactericidal potency surpassing considerably that of the corresponding unsubstituted derivative.

The conditions encountered in this investigation are also illustrated on the graphs, in which the phenol coefficients are plotted against the weight of the side chains.

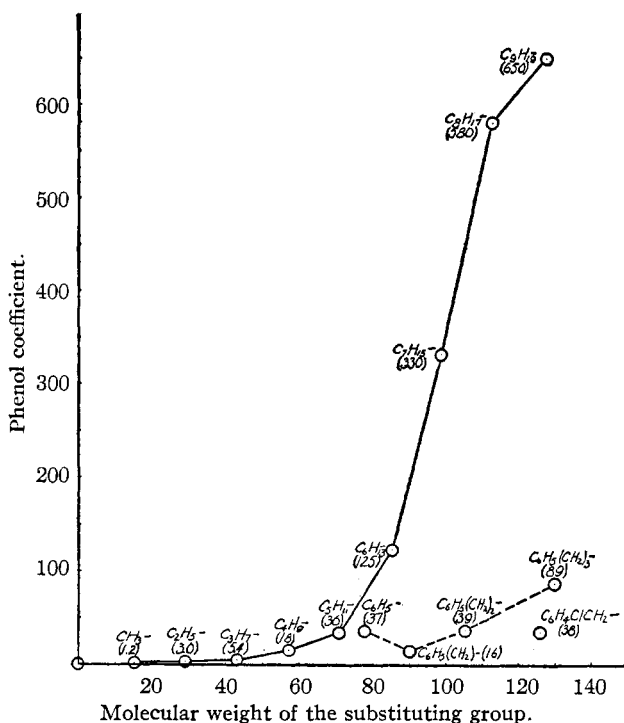
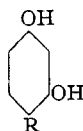
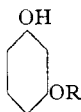


Fig. 2.—The effect of the substituting radical upon the bactericidal action of monoethers of resorcinol. Test organism, *Staph. aureus*: —, alkyl derivatives; ---, aromatic derivatives.

**Comparison with Nucleus Substituted Resorcinol Derivatives.**—As to the numerical values of the phenol coefficients of the resorcinol monoethers, it is noteworthy that they compare quite generally with those determined in the case of the corresponding nucleus substituted derivatives. The two classes of compounds under consideration are represented by the following structural formulas in which R is the substituting radical



Unfortunately, strict comparison with the findings of previous workers is not possible, particularly owing to discrepancies in the methods and in material used in the biological tests. In addition to the well-known effect of temperature, the resistance of the strain and the composition of the nutrient medium are of prime importance, and may influence the results several hundred per cent. either way, especially with very potent germicidal agents. Thus Schaffer and Tilley<sup>2</sup> reported that the phenol coefficient of amyphenol determined with five different strains of *B. typhosus* fluctuated between 42 and 197, that of hexylresorcinol between 52 and 147, that of heptylresorcinol between 31 and 350, etc. It should be added, however, that with four of these strains comparable figures were secured, and that one strain only exhibited an altogether remarkable lack of resistance to the derivatives with longer side chains, although it showed a more normal behavior toward those with shorter chains (butylphenol and lower alkylphenols, amyresorcinol and lower alkylresorcinols). No such fluctuations were noticed with *Staphylococcus aureus*. Hampil<sup>7</sup> reports equally serious differences depending upon the type of peptone used in the preparation of the nutrient medium. We chose, therefore, quite arbitrarily those data

TABLE II

COMPARISON OF THE BACTERICIDAL ACTION EXPRESSED IN PHENOL COEFFICIENTS OF MONOETHERS OF RESORCINOL WITH THAT OF THE CORRESPONDING NUCLEUS SUBSTITUTED DERIVATIVES

	Monoethers		o-p-Nucleus Substituted				Derivatives	
	<i>B. typhosus</i>	<i>Staph. aureus</i>	<i>B. typhosus</i>				<i>Staph. aureus</i>	
			I	II	III	IV	I	IV
Resorcinol	0.4	0.4				0.4		0.4
Methyl	1.3	1.2						
Ethyl	3.6	3.0	(1.6)				1.5	
n-Propyl	6.9	5.4	4.76	5.0	5.0		3.7	
n-Butyl	20	18	15.3	22	17.5		10	
n-Amyl	38	36	40	33	40		30.2	
sec.-Amyl	(26)	(31)			30			
n-Hexyl	46	125	58	46-56	90		98	
Cyclohexyl	(18)	(20)						
n-Heptyl	21	330	34	30	100		280	
n-Octyl	2.3	580		0	110		680	
n-Nonyl	3.4	650		0			980	
Phenyl	40	37						
Benzyl	21	16				18.3		14.5
Phenylethyl	35	39				41		21
Phenylpropyl	34	89				31		
p-Chlorobenzyl	61	38				63		40

from the tables of the authors mentioned which seemed to us most nearly representative and suitable to serve in comparing the monoalkyl ether of resorcinol with the nucleus substituted resorcinol derivatives. In comparing the corresponding alipharyl derivatives the figures reported by Klarman and Von Wown<sup>9</sup> were used.

Table II gives the comparison of phenol coefficients of the monoethers of resorcinol with those of the nucleus substituted derivatives as obtained by previous investigators. Column I gives the data reported by Schaffer and Tilley<sup>2</sup> (*B. typhosus*, strain No. 3, except ethyl; *Staphylococcus aureus*, strain No. 2), II, those by Dohme, Cox and Miller,<sup>6</sup> III, by Hampil,<sup>7</sup> and IV by Klarman and Von Wown.<sup>9</sup> Disregarding, for the sake of making the comparison, the interfering factors referred to above, and taking into account the limits of accuracy of experiments with biologic material, one finds a distinct similarity of the figures obtained with the compounds of the two classes under consideration.

The conclusion, therefore, seems justified that the bactericidal effect of resorcinol compounds with aliphatic or aromatic substituents is practically the same with the substituting radical in the nucleus in ortho-para position to the two hydroxyl groups, or attached to one of the oxygen atoms. It follows also that one hydroxyl group of the resorcinol molecule is sufficient to bring about the antibacterial action, possibly without participation of the other hydroxyl group, if both are open (as in the case of the nucleus substituted resorcinol derivatives), since the effect of the monoethers of resorcinol (with one open hydroxyl group) is similar to that of the corresponding nucleus substituted derivatives (with both hydroxyl groups open).

## Experimental Part

### (a) Chemical

The preparation of the compounds of this series has been carried out (with one exception) by the condensation of resorcinol with the corresponding halide. This condensation may take place in the absence of alkali, preferably using a high-boiling solvent such as xylene. The preferred mode of condensation calls for the use of aqueous or alcoholic potassium hydroxide. The direct condensation has been used where there was reason to believe that the halogen atom was sufficiently mobile as, for example, in the case of the benzyl and the *p*-chlorobenzyl halides. Condensation in the presence of alkali was applied in the case of most of the compounds prepared.

Since a halogen atom directly attached to the benzene nucleus does not react under the conditions described, the phenyl ether of resorcinol (*m*-hydroxydiphenyl oxide) was prepared by a condensation of *m*-bromoaniline with phenol in the presence of alkali and copper and subsequent conversion of the *m*-aminodiphenyl oxide thus obtained into the corresponding hydroxy derivative by means of diazotization and boiling with water.

The following paragraphs contain a description of the three methods which have been applied in the preparation of the resorcinol monoethers.

**Direct Condensation. Preparation of *m*-Hydroxyphenyl Benzyl Ether.**—Resorcinol (55 g.) was dissolved in 150 cc. of xylene. The solution was heated on a sand-bath in a flask equipped with an air condenser. Benzyl chloride (63.3 g.) was added slowly during six hours and heating continued for another half hour. The mixture was allowed to cool and was then poured on ice. It was transferred to a separatory funnel and, after addition of ether, washed with water until the aqueous portion gave a faint reaction with ferric chloride. The ethereal layer was extracted repeatedly with a 5% solution of potassium hydroxide. The alkaline extract was shaken with ether, transferred to another separatory funnel, acidified and the separated oil shaken out with ether. After evaporation of the latter, a heavy red oil remained which was repeatedly distilled in vacuum at 5 mm. pressure. The fraction distilling at 200° was isolated. It crystallized on standing and was purified by recrystallization with carbon tetrachloride. It melted at 69.2°.

**Preparation of *m*-Hydroxyphenyl-*p*-chlorobenzyl Ether.**—This compound was obtained in exactly the same manner as the preceding one. The fraction distilling at 235° and 13 mm. pressure was isolated. The recrystallized product melted at 76.0°.

**Condensation in the Presence of Potassium Hydroxide.**—Equimolecular amounts of resorcinol and organic halide (chlorides, bromides and iodides have been used) are dissolved in alcohol and heated to gentle boiling under reflux. The theoretical amount of a 25% potassium hydroxide solution is added drop by drop in the course of three hours, and boiling under reflux continued for another two hours. While this reaction (like the one described previously) aims at the preparation of monoethers, a simultaneous formation of small quantities of diethers cannot be prevented. In order, therefore, to separate the monoethers from the diethers and the uncombined resorcinol, a similar procedure is followed as is described in the example of direct condensation. The separation is facilitated somewhat in the cases of the lower monoethers (methyl to butyl) since both the diethers and the monoethers are volatile with steam. Thus steam distillation of the alkaline mixture removes first the diether and the unconverted halide; upon acidification the monoether comes over while practically all of the resorcinol remains behind. The other ethers which are not volatile with steam are purified in the same way as described in the case of the benzyl ether, *i. e.*, the resorcinol is removed by washing with water and the monoether separated from the diether by extraction with an aqueous potassium hydroxide solution.

In all cases the isolated crude oils were purified further by repeated distillation under reduced pressure and crystallization wherever possible.

The condensation may also be carried out in the presence of potassium carbonate in acetone. This method has been used as an alternative in the preparation of the methyl and benzylresorcinol monoethers.

**Condensation in the Presence of Alkali and Copper. Preparation of *m*-Hydroxydiphenyl Oxide.**—The aminodiphenyl oxide was prepared using a modification of the method described by Ullmann and Sponagel.<sup>15</sup> Phenol (62 g.) was placed in a flask equipped with a thermometer and 44 g. of 85% potassium hydroxide was added. The mixture was heated until homogeneous and the heating continued until most of the moisture evaporated (180°). The mass was cooled down somewhat and then 57 g. of *m*-bromoaniline and 0.2 g. of finely subdivided copper was added. Heating was continued. The oil-bath thermometer indicated 150° while the temperature inside of the flask rose to 205°. The flask was maintained at this temperature for a half hour

<sup>15</sup> Ullmann and Sponagel, *Ann.*, **350**, 83 (1906).



and then at 180° for two hours. After cooling, water was added which caused an oil to separate. The oil was shaken with ether and treated with a 5% potassium hydroxide solution in order to remove the excess phenol. The amino derivative was then extracted with dilute hydrochloric acid, liberated by the addition of alkali and extracted with ether. The ether solution was washed with water, dried over anhydrous sodium sulfate, evaporated and distilled in a vacuum. The fraction distilling between 152 and 156° at 4.5 mm. pressure was isolated.

*Anal.* Calcd. for  $C_{12}H_{11}NO$ : N, 7.56. Found: N, 7.21.

The *m*-aminodiphenyl oxide was dissolved in dilute hydrochloric acid. The theoretical amount of sodium nitrite solution was added with cooling. The diazotized mixture was heated to boiling for a half hour. A dark oil separated which was extracted with ether. The ether solution was washed with dilute acid, evaporated and the residue distilled in a vacuum. The fraction distilling between 149 and 151° at 4.5 mm. pressure was isolated.

TABLE III  
ANALYTICAL DATA

Alkyl ethers	Formula	Carbon, %		Hydrogen, %		B. p., °C.	Mm.	M. p., °C.
		Calcd.	Found	Calcd.	Found			
Methyl	$C_7H_8O_2$	67.72	67.18	6.50	6.62	102	5	
Ethyl	$C_8H_{10}O_2$	69.54	69.64	7.30	7.51	117	5.5	
<i>n</i> -Propyl	$C_9H_{12}O_2$	71.01	71.49	7.95	8.21	120	5	
<i>n</i> -Butyl	$C_{10}H_{14}O_2$	72.26	72.47	8.49	8.85	130	5	
<i>n</i> -Amyl	$C_{11}H_{16}O_2$	73.31	73.92	8.95	9.32	140	5	
<i>sec.</i> -Amyl	$C_{11}H_{16}O_2$	73.31	72.94	8.95	9.21	138	5	
<i>n</i> -Hexyl	$C_{12}H_{18}O_2$	74.20	74.29	9.34	9.40	145	5	
Cyclohexyl	$C_{12}H_{16}O_2$	74.97	74.33	8.39	8.31	160	6	
<i>n</i> -Heptyl	$C_{13}H_{20}O_2$	75.01	74.78	9.62	9.76	160	5	
<i>n</i> -Octyl	$C_{14}H_{22}O_2$	75.65	75.37	9.98	10.07	170	5	
<i>n</i> -Nonyl	$C_{15}H_{24}O_2$	76.22	76.34	10.24	10.30	171	4.5	
Aromatic ethers								
Phenyl	$C_{12}H_{10}O_2$	77.43	77.45	5.42	5.63	150	4.5	
Benzyl	$C_{13}H_{12}O_2$	78.01	77.51	6.05	6.23	200	5	69.2
Phenylethyl	$C_{14}H_{14}O_2$	78.48	78.69	6.59	6.63	202	6	44.0
Phenylpropyl	$C_{15}H_{16}O_2$	78.92	78.68	7.07	7.12	202	5.5	
		Cl, %	Cl, %					
<i>p</i> -Chlorobenzyl	$C_{13}H_{11}ClO_2$	15.12	15.27			235	13	76.0

Table III contains the analytical data of the compounds prepared.

The halides required for this work were procured from the Eastman Kodak Co. or J. T. Baker Chemical Co. Since no phenylpropyl and nonyl halides were available, we prepared the bromides from the corresponding alcohols.

**Preparation of Phenylpropyl Bromide.**—Bromine (90 g.) and crushed ice (100 g.) are placed in a round-bottomed flask. The flask is kept in an ice-bath and gaseous sulfur dioxide is passed into it until the amber color of bromine has just disappeared.

Phenylpropyl alcohol (121 g.) is added to this mixture containing hydrobromic and sulfuric acids. An additional amount of 45 g. of concentrated sulfuric acid is added in several portions with shaking. The flask is then connected with a reflux condenser and the mixture kept boiling for two hours. It is then washed in a separatory funnel with water and cold concentrated sulfuric acid (in order to remove the unconverted alcohol). Then ether is added and the solution washed repeatedly with water

and sodium carbonate. After evaporation of the ether, the residual oil is distilled in a vacuum. Almost the entire quantity distilled at 83° at 4.5 mm.

*Anal.* Calcd. for  $C_9H_{11}Br$ : Br, 40.2. Found: Br, 39.62.

The *n*-nonyl bromide was obtained in the same manner by treating *n*-nonyl alcohol with a hydrobromic-sulfuric acid mixture.

### (b) Bacteriological

The determination of the bactericidal action of the compounds of this series was carried out using *B. typhosus* and *Staphylococcus aureus*. The method was that described by Reddish.<sup>14</sup> The temperature of medication was 37°. The results were read after forty-eight hours' incubation. The strains of bacteria used in this investigation were procured from the Bacteriological Laboratory of the U. S. Department of Agriculture in Washington.

In some typical instances parallel tests were made with strains from other sources as well, in order to eliminate the possibility of using germs of an irregular behavior, bearing in mind particularly the observations made by previous investigators. In no case, however, did we encounter any significant fluctuations, the data obtained with the various strains being essentially the same.

### Summary

This paper is the first of a series of investigations aiming at the determination of antibacterial action of monoethers of dihydric phenols. A number of monoethers of resorcinol have been prepared and studied. The substituting radicals are: methyl, ethyl, *n*-propyl, *n*-butyl, *n*-amyl, *sec*-amyl, *n*-hexyl, cyclohexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, phenyl, benzyl, phenylethyl, phenylpropyl and *p*-chlorobenzyl. *B. typhosus* and *Staph. aureus* were used as test organisms.

The series comprises a number of compounds of an extraordinary bactericidal potency. There is a distinct relation between the antibacterial action on one hand and the molecular weight and chemical structure of the substituting radical on the other. It is different for the two microorganisms. While the germicidal effect of the aliphatic substituted monoethers upon *B. typhosus* first increases with the length of the chain, reaching a maximum with the hexyl compound, and then decreases, no such maximum is observed in the case of *Staph. aureus*. Generally the germicidal efficacy of the normal compounds surpasses that of the secondary derivatives. The cyclohexyl derivative is a less effective germicide than either the *n*-hexyl or the phenyl ether.

Considerable antibacterial efficacy is found also among the aromatic and aliphatic aromatic resorcinol ethers, the phenyl ether being more effective against *B. typhosus* than the aliphatic aromatic ethers examined; against

<sup>14</sup> G. F. Reddish, *Am. J. Pub. Health*, 17, 320 (1927).

*Staph. aureus* the phenylpropyl ether was found to be more efficacious than other ethers of this group. Halogen seems to enhance the bactericidal action, the *p*-chlorobenzyl ether being a considerably more potent germicide than the benzyl ether.

The antibacterial action of the monoethers of resorcinol has been compared with that of the corresponding nucleus substituted derivatives as reported by previous investigators, and a distinct similarity has been found.

BLOOMFIELD, NEW JERSEY

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

## THE STABILITY OF THE CARBON-SULFUR BOND IN SOME ALIPHATIC SULFONIC ACIDS<sup>1</sup>

BY F. C. WAGNER AND E. EMMET REID

RECEIVED JUNE 4, 1931

PUBLISHED SEPTEMBER 5, 1931

Frequent reference is found in the literature to the preparation and some of the properties of aliphatic sulfonic acids but, with the exception of the study by Spring and Winnsinger<sup>2</sup> of the effect of the sulfonic acid group ( $-\text{SO}_3\text{H}$ ) on the chlorination of the alkyl residue, no one reaction has been applied to a series of these acids to observe the effect of change of structure on the chemical reactivity.

The stability of the carbon-sulfur bond in a series of mercaptans has recently been investigated.<sup>3</sup> It seemed of interest to study the sulfonic acids in comparison with the mercaptans.

### Discussion of Results

The normal alkyl sulfonic acids from methyl to hexyl and the secondary from isopropyl to *sec.*-hexyl and also benzene and benzyl sulfonic acids have been prepared and their sodium salts heated in excess of sodium hydroxide solution at temperatures from 315 to 375°.

The percentages of the sulfonic acids decomposed in three hours at 345° are plotted in Fig. 1. Methyl sulfonic acid is remarkably stable while ethyl is decomposed much more rapidly than the other primary acids. From ethyl on, the decomposition decreases as the carbon chain lengthens, both in the primary and in the secondary series. The secondary sulfonic acids are decomposed much more rapidly than the corresponding primary acids. The percentages of the sulfonic acids decomposed are plotted against the temperatures in Fig. 2. These are the same relations

<sup>1</sup> Taken from the dissertation of F. C. Wagner submitted to the Johns Hopkins University in June, 1929. Reported in part at the Atlanta meeting of the American Chemical Society.

<sup>2</sup> Spring and Winnsinger, *Ber.*, **16**, 327 (1883); **17**, 537 (1884).

<sup>3</sup> Billheimer and Reid, *THIS JOURNAL*, **52**, 4338 (1930).