2. The mercury compound from 3-nitrophthalic acid is obtained in good yield and reacts with bromine and with iodine to give good yields of the otherwise difficultly obtainable 2-bromo-3-nitrobenzoic acid and 2-iodo-3-nitrobenzoic acid.
3. Anhydro-2-hydroxymercuri-3-nitrobenzoic acid can be refluxed with fuming nitric acid without breaking the C-Hg linkage. On the other hand a short heating with concd. hydrochloric acid removes the mercury completely from the organic molecule.
4. The results obtained with the 3-substituted phthalic acids show that the mercuration reaction consists in the replacement of the 2-carboxyl by mercury.

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[CONTRIBUTION FROM THE PLAUT LABORATORY OF LEHN AND FINK, INC.]

THE PREPARATION OF CERTAIN CHLORO AND BROMO DERIVATIVES OF 2,4-DIHYDROXYDIPHENYLMETHANE AND -ETHANE AND THEIR GERMICIDAL ACTION[1]

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Introduction

The introduction of aryl groups into the nucleus of resorcinol leads to compounds showing a very pronounced germicidal action.[2] It has been shown that of the three aryl groups, *viz.*, benzyl, phenylethyl and phenylpropyl, the introduction of the second produces the most active aryl derivative of resorcinol, the phenol coefficient of which was reported as being 41, against *B. typhosus*.[3]

It is well known that halogen substitution of phenol and its alkyl derivatives leads to compounds, the germicidal potency of which is very considerably greater than that of the unsubstituted compounds. While the germicidal action increases with the number of halogen atoms introduced (one molecule of pentabromophenol has the same effect upon *B. diphtheriae* as 500 molecules of phenol), the toxicity first drops but later rises again. Thus monohalogen phenol is less toxic than phenol, while the general toxicity of trihalogen phenol approximately equals that of phenol itself; tetra- and pentahalogen phenol derivatives are more toxic than phenol.[4]

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[1] Presented in part before the Division of Biological Chemistry at the meeting of the American Chemical Society in Swampscott, Massachusetts, September, 1928.

[2] E. Klarmann, THIS JOURNAL, **48**, 791 (1926).

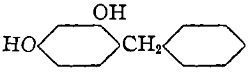
[3] E. Klarmann, *ibid.*, **48**, 2358 (1926).

[4] R. Koch, *Mitt. Kais. Gesundheitsamt*, **1**, 234 (1881); H. Bechhold and P. Ehrlich, *Z. physiol. Chem.*, **47**, 173 (1906); K. Laubenheimer, "Phenol und seine Derivate als Desinfektionsmittel." Berlin-Wien, **1909**.

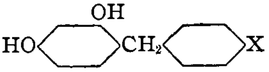
In continuing our work on the relationship between the germicidal action and chemical constitution we have taken another factor into consideration, *viz.*, inactivation of the disinfectant in the presence of organic matter (particularly of protein character), which may be regarded as eminently important from both a practical and theoretical viewpoint. It is well known that many chemicals which are strong germicides in the absence of organic matter may be greatly or even totally inactivated in its presence. Bechhold and Ehrlich found that the very pronounced germicidal efficacy of polyhalogen substituted phenols and phenol derivatives is greatly reduced in the presence of serum; such reduction need not necessarily be accompanied by a precipitation of the protein. On the other hand, there is evidence that the inactivation by organic matter of unsubstituted phenol or cresol takes place to a much less degree.

Discussion

We were interested in determining the influence of monohalogen substitution upon the germicidal action of certain aryl derivatives of resorcinol. Considering the structural formula, *e. g.*, of 2,4-dihydroxydiphenylmethane



the halogen may be introduced either into the benzene nucleus which bears the hydroxyl groups or into the unsubstituted one. In this paper we have considered halogen substitution in the positions 4′ and 5, respectively; thus the compounds studied belong to one of the two types



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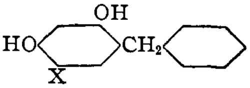

wherein X stands for either Cl or Br. The difference in germicidal action resulting from such substitution is indicated in Table I. The figures under I are phenol coefficients determined according to a modified Rideal-Walker procedure using *B. typhosus*, under II the same in the presence of standard organic matter, under III phenol coefficients against *Staphylococcus pyogenes aureus*, under IV the same as under III in the presence of organic matter.

TABLE I

DIFFERENCES IN GERMICIDAL ACTION

	I	II	III	IV
2,4-Dihydroxydiphenylmethane	18.3	14.5	11.3	7.3
5-Chloro-2,4-dihydroxydiphenylmethane	48.2	36.0	36.7	19.6
4′-Chloro-2,4-dihydroxydiphenylmethane	63.1	27.1	40.1	16.7
5-Bromo-2,4-dihydroxydiphenylmethane	37.3	15.7	44.6	18.3
4′-Bromo-2,4-dihydroxydiphenylmethane	54.8	18.9	51.4	13.6

It appears that the presence of halogen very considerably enhances the germicidal effect; the introduction of the halogen into the nucleus which bears the hydroxyl group leads to derivatives with a lower germicidal potency than substitution in p'-position. There is no very distinct difference between *B. typhosus* and *Staph. pyog. aureus;* this fact tends to indicate that the substances dealt with may probably be regarded as general disinfectants rather than specifics.

Organic matter causes a very considerable reduction of germicidal action of the halogen substituted derivatives (in all cases but two, more than 50%); in contrast to this the inactivation of the unsubstituted 2,4-dihydroxydiphenylmethane is much less pronounced.[5]

We attempted to extend our investigation to the corresponding halogen derivatives of 2,4-dihydroxydiphenylethane. The germicidal action of this compound is indicated in Table II.

TABLE II

GERMICIDAL ACTION OF 2,4-DIHYDROXYDIPHENYLETHANE

	I	II	III	IV
2,4-Dihydroxydiphenylethane	40.8	16	22.1	8.5

The figures under I, II, III and IV correspond with those under the respective headings in Table I. It appears that the presence of organic matter impairs the germicidal action of the 2,4-dihydroxydiphenylethane

[5] While this work was in progress a paper was published by Bettylee Hampil, *J. Infectious Diseases,* **43,** 25 (1928), according to which the disinfectant action of the higher alkylresorcinols is also very considerably impaired by organic matter, *e. g.,* about 70% in the case of hexylresorcinol and more than 80% in that of heptylresorcinol at 37°. Great differences were also found depending upon the kind of peptone used in compounding the "organic matter." The present bacteriological concept of "organic matter" is rather vague from a chemical viewpoint. Both constituents of the so-called "organic matter," required by certain bacteriological methods for standardization of disinfectants, *viz.,* gelatin and peptone, represent products of partial hydrolysis of protein and probably consist of a mixture of amino acids, polypeptides and amino acid anhydrides which will differ qualitatively and quantitatively depending upon the initial material and the method and duration of the protein hydrolysis.

We assume that the impairment of disinfectant action of phenols, polyphenols and their derivatives is due to the fixation of their hydroxyl group or groups by means of secondary valencies by a reactive group in protein (NH_2, possibly COOH, OH, NH, SH). The stability of this, what may be termed additive (molecular) compound under the conditions of the bacteriological experiment, is regarded as one factor which influences the extent to which the impairment of the disinfectant action takes place. It is obvious that this idea of the impairment of disinfecting action by reactive groups in proteins may be used in a hypothetical explanation of the disinfecting action proper, since it is possible that the reactive groups in "organic matter" which hinder the disinfecting action may resemble those which attach the disinfecting chemical to the microörganism; this is probably the first step in disinfection.

We expect to continue our investigations with the view of contributing experimental evidence in support of this theory.

to a much greater extent than that of the corresponding methane derivative. We also succeeded in obtaining the 5-chloro and bromo derivatives of 2,4-dihydroxydiphenylethane but experienced great difficulties in their bacteriological investigation because of the insolubility of these compounds.

The synthesis of the 4′-halogen substituted derivatives of 2,4-dihydroxydiphenylmethane was carried out according to a method applied by one of us for the preparation of 2,4-dihydroxydiphenylmethane proper, *viz.*, condensation of *p*-chloro- or *p*-bromobenzonitrile with resorcinol in the presence of dry hydrogen chloride, according to Hoesch,[6] transformation of the 4′-halogen-2,4-dihydroxybenzophenone-imide hydrochloride into the 4′-halogen-2,4-dihydroxybenzophenone and reduction of the latter with amalgamated zinc and hydrochloric acid to the 4′-halogen-2,4-dihydroxydiphenylmethane. Direct condensation of the halogen benzyl chloride with resorcinol in nitrobenzene solution in the presence of anhydrous aluminum chloride may also be used for the synthesis of these compounds.

The 5-halogen derivatives of 2,4-dihydroxydiphenylmethane and -ethane were obtained by direct action of sulfuryl chloride or of bromine upon the respective compounds.

Experimental Part

A. Chemical

Preparation of 4′-Chloro-2,4-Dihydroxydiphenylmethane, $C_6H_3(OH)_2CH_2C_6H_4Cl$.—This compound was prepared according to the following two methods.

Method I.—Seventy g. of resorcinol, which was previously dried at 100° for a period of twelve hours, and 50 g. of anhydrous aluminum chloride were dissolved in 300 g. of freshly distilled, dry nitrobenzene. The solution was placed in a flask fitted with a dropping funnel and connected with an air condenser and a calcium chloride tube. A solution of 50 g. of *p*-chlorobenzyl chloride in 100 g. of dry nitrobenzene was added drop by drop under continuous stirring. After addition of the total quantity, the flask was heated on the water-bath and kept at a temperature of 70° for four hours. The resulting dark liquid was poured upon chopped ice and allowed to stand; the watery portion was drawn off and the oil washed with dilute hydrochloric acid and then with water. After addition of an equal volume of ether, the liquid was shaken repeatedly with a 10% solution of sodium hydroxide. The alkaline extract was shaken with ether repeatedly in order to remove the adhering nitrobenzene completely. Then hydrochloric acid was added and the whole boiled for half an hour. The precipitated dark oil was washed with water and distilled in a vacuum at 5 mm. The main part distilled at 200–225° as a heavy oil; by dissolving this in a large quantity of boiling water and cooling, the 4′-chloro-2,4-dihydroxydiphenylmethane crystallized in white needles; yield, 55%. After drying in a micro vacuum desiccator, the melting point is 80.4° (uncorr.). The halogen determination was carried out according to Pregl's micro modification of Carius' method.

Anal. Subs., 4.166 mg.: AgCl, 2.550 mg. Calcd. for $C_{13}H_{11}O_2Cl$: Cl, 15.11. Found: Cl, 15.14.

Method II.—Sixty g. of dry resorcinol and 50 g. of *p*-chlorobenzonitrile, previously

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[6] R. Hoesch, *Ber.*, **48**, 1122 (1915).

dried in a vacuum desiccator over phosphorus pentoxide, were dissolved in 200 cc. of dry ether and 10 g. of zinc chloride, previously fused and powdered, was added. A current of hydrogen chloride, dried by means of sulfuric acid, was passed through the mixture for a period of about five hours. A heavy oil formed. The vessel was allowed to stand in an ice box for twenty-four hours; then cold hydrochloric acid (15%) was added, whereby the oily keto imide hydrochloride was transformed into a crystalline mass. The crystals were filtered off and washed repeatedly with cold ether in order to remove the unchanged nitrile; yield, 72%.

The 4′-chloro-2,4-dihydroxybenzophenone-imide hydrochloride thus obtained was boiled with approximately 1 liter of water for half an hour, whereby the imide hydrochloride was transformed into the ketone. The latter was recrystallized from water; yield, 65% of the imide hydrochloride. The 4′-chloro-2,4-dihydroxybenzophenone forms pinkish needles which after drying in a micro vacuum desiccator melt at 155° (uncorr.). A solution in dilute alcohol gives a purple coloration with ferric chloride.

This keto compound was reduced by boiling with 150 g. of amalgamated zinc and hydrochloric acid (10%) until a sample of the oil when dissolved in alcohol and diluted with water gave no distinct coloration with ferric chloride. The mixture was shaken with ether, the ether solution washed with dilute hydrochloric acid (2%) and finally with water. The ethereal layer was drawn off, dried with sodium sulfate, the solvent evaporated and the residue distilled in a vacuum at 5 mm. Further purification was carried out as described under Method I; yield, 70% of the keto compound; total yield, 33%.

Preparation of 4′-Bromo-2,4-dihydroxydiphenylmethane, $C_6H_3(OH)_2CH_2C_6H_4Br$.—This compound was prepared according to the procedure given under Method II. The 4′-bromo-2,4-dihydroxybenzophenone melts at 169° (uncorr.); yield, 89% of the corresponding imide hydrochloride. The 4′-bromo-2,4-dihydroxydiphenylmethane melts at 96° (uncorr.); yield, about 70% of the keto compound; total yield, 45%.

Anal. Subs., 4.227 mg.: AgBr, 2.855 mg. Calcd. for $C_{13}H_{11}O_2Br$: Br, 28.67. Found: Br, 28.74.

Preparation of 5-Chloro-2,4-dihydroxydiphenylmethane, $C_6H_2(OH)_2ClCH_2C_6H_5$.—One part of 2,4-dihydroxydiphenylmethane was dissolved in 10 parts of dry ether. The theoretical quantity of sulfuryl chloride was added drop by drop under continuous stirring and cooling. The ether solution was washed with water repeatedly, dried over sodium sulfate, decolorized with Darco and the solvent evaporated. The residue was recrystallized from carbon tetrachloride. The compound crystallizes in white needles which after drying melt at 122° (uncorr.); yield, 51%.

Anal. Subs., 5.785 mg.: AgCl, 3.583 mg. Calcd. for $C_{13}H_{11}O_2Cl$: Cl, 15.11. Found Cl, 15.32.

Preparation of 5-Chloro-2,4-dihydroxydiphenylethane, $C_6H_2(OH)_2ClCH_2CH_2C_6H_5$.—This compound was prepared by chlorination of 2,4-dihydroxydiphenylethane according to the method used for the corresponding methane derivative. It crystallizes in needles melting at 136.7° (uncorr.); yield, 40%.

Anal. Subs., 5.637 mg.: AgCl, 3.331 mg. Calcd. for $C_{14}H_{13}O_2Cl$: Cl, 14.25. Found: Cl, 14.62.

Preparation of 5-Bromo-2,4-dihydroxydiphenylmethane, $C_6H_2(OH)_2BrCH_2C_6H_5$.—The bromination was carried out in exactly the same way as the chlorination, using the theoretical quantity of bromine. The same method of purification was used. The compound melts at 122.4° (uncorr.); yield, 71%.

Anal. Subs., 15.329 mg.: AgBr, 10.415 mg. Calcd. for $C_{13}H_{11}O_2Br$: Br, 28.67. Found: Br, 28.92.

Preparation of 5-Bromo-2,4-dihydroxydiphenylethane, $C_6H_2(OH)_2BrCH_2CH_2C_6H_5$.—This compound was prepared exactly like the foregoing one from 2,4-dihydroxydiphenylethane. It melts at 152.1° (uncorr.).

Anal. Subs., 14.774 mg.: AgBr, 9.408 mg. Calcd. for $C_{14}H_{13}O_2Br$: Br, 27.27. Found: Br, 27.10.

B. Bacteriological

The determination of the phenol coefficients was carried out according to a modified Rideal-Walker procedure, using 0.5 cc. of broth culture to 5 cc. of diluted disinfectant. The dilutions of disinfectant were prepared in such a way that first the solid substance was dissolved in a small quantity of alcohol and then diluted with water. In no case was the concentration of alcohol more than 5% at the final dilution when the killing of the germ took place. The organic matter used in the investigation of the impairment of germicidal efficacy was a solution of 5% gelatin (French Gold Label) and 10% peptone "Difco." One cc. of this solution was added to 4 cc. of the dilute disinfectant, so that the final solution before introduction of the culture contained 1% of gelatin and 2% of peptone. Subcultures were made after five, ten and fifteen minutes of contact of bacteria and disinfectant, one loop being transplanted into fresh media.

Our thanks are due to Dr. V. A. Shternov and Mr. A. Grawehr for the determination of the phenol coefficients.

Summary

It appears from previous experiments that certain aryl derivatives of resorcinol show a very pronounced germicidal action. Since it is known that halogenation leads to derivatives, the germicidal efficacy of which is more pronounced than that of the unsubstituted compounds, we were interested in determining the influence of the introduction of chlorine and bromine into 2,4-dihydroxydiphenylmethane and -ethane (benzyl- and phenylethylresorcinol). Another point studied was the difference resulting from the introduction of the halogen into the unsubstituted or the dihydroxyl substituted nucleus. It has been found that halogenation greatly increases the germicidal efficacy of these compounds against *B. typhosus* and *Staph. pyog. aureus.* Some interesting observations have been made regarding reduction of the germicidal efficacy of these substances by "organic matter." The methods of preparation of the new compounds 4′-chloro- and 4-bromo-2,4-dihydroxydiphenylmethane and 5-chloro- and 5-bromo-2,4-dihydroxydiphenylmethane and -ethane have been described.

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