in chloroform, benzene, alcohol, acetic acid, acetone and insoluble in water.   On hydrolysis with 1:1 hydrochloric acid they yield 2,4-dinitrobenzaldehyde and the respective substituted amines.

The condensing medium was alcohol for all but Nos. 2 and 3.   The products consisted of yellow needles except in 2 and 8; these were orange needles.

These compounds like many other similar condensation products are affected to a considerable extent by the action of light.   It was noted that the halogenated derivatives were particularly susceptible to light.

PITTSBURGH. PA.

THE PREPARATION OF SOME ALKYL DERIVATIVES OF RESORCINOL AND THE RELATION OF THEIR STRUCTURE TO ANTISEPTIC PROPERTIES.

BY TREAT B. JOHNSON AND FREDERICK W. LANE.[1]

Introduction.

A review of the literature reveals the fact that, in spite of the work of Ehrlich[2] and others, our knowledge of the relation of the structure of phenolic bodies to their antiseptic and toxic properties is still very incomplete.   Therefore, any additional facts contributing to a better understanding of this relationship should be of considerable assistance in directing the search for new and more valuable antiseptics.   It is believed by the writers that the present work adds a new and fundamental conception in the relationship consideration.

It is well understood,[3] that the substitution of one or more methyl groups into the nucleus of phenol increases the germicidal value as well as lowers the toxic properties of that substance.   Nothing, however, appears to be definitely known as to how the *antiseptic* strength would be affected by replacing the methyl group with alkyl radicals of greater weight.   It is this phase of the subject in which the writers are especially interested.

Inasmuch as phenol and many of its derivatives have been found

[1] This paper is constructed from a thesis presented by Frederick W. Lane in 1920 to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the Degree of Doctor of Philosophy.   T. B. J.

[2] Bechold and Ehrlich, *Z. physiol. Chem.*, **47**, 173 (1906); Baglioni, *Z. allgem. Physiol.*, **3**, 313 (1904); Pyman, *J. Chem. Soc.*, **111**, 1103 (1917); Bechhold, *Z. angew. Chem*, **22**, 2033 (1909); May, "The Chemistry of Synthetic Drugs," p. 152.   Longmans, 1918; Frankel, "Die Arzneimittel-Synthese," p. 483, Springer, Berlin, 1906.

[3] Bechhold and Ehrlich, *loc. cit.;* Baglioni, *loc. cit.;* May, *loc. cit.;* compare also Schmiedeberg, *Arch. exp. Path. Pharm.*, **20**, 203 (1886).

to be rather highly toxic,[1] we have chosen the less poisonous resorcinol[2] as our starting point or standard phenol, and, in order to reveal the relationship between germicidal properties and the molecular weight of the respective alkyl groups, we have prepared the methyl, ethyl, normal propyl, and normal butyl derivatives of this dihydroxy benzene, and have determined their "phenol coefficients" by a modification of the Rideal-Walker method.[3] In each of the prepared substances, the alkyl group is substituted directly in the benzene nucleus and occupies in every case a position *ortho* to one hydroxyl group and *para* to the other. We have not investigated the isomeric ether combinations which can be obtained from resorcinol.

A comparison of antiseptic values is not, however, the only interest developed in the present work. The chemistry of many of the substances met with as intermediate products is very obscure; some of the compounds utilized in our research had not been prepared, and a part of our research, therefore, deals with the synthesis and chemistry of the different resorcinol compounds investigated.

II. Preparation, Properties and Antiseptic Qualities of Methyl-, Ethyl-, *N*-Propyl and *N*-Butyl Derivatives of Resorcinol.

Several methods suggest themselves at once, or have been applied, for the introduction of alkyl groups into the nucleus of resorcinol. Of these, the most efficient mode of procedure is undoubtedly that in which an acyl group is first introduced into the nucleus, and is then reduced to the corresponding alkyl group. It will be evident that, in the case of the substitution of the methyl radical, it is the aldehyde radical which must be subjected to reduction. In our research the following intermediate products have been prepared and reduced to the corresponding alkyl derivatives: resorcyl aldehyde, $C_6H_3(CHO)(OH)_2.(1,2,4)$, methyl resorcinol, $C_6H_3(CH_3)(OH)_2.(1,2,4)$; resacetophenone, $C_6H_3(COCH_3)$-$(OH)_2.(1,2,4)$, ethyl resorcinol, $C_6H_3(C_2H_5)(OH)_2.(1,2,4)$; N propionyl resorcinol, $C_6H_3(COC_2H_5)(OH)_2.(1,2,4)$, N propyl resorcinol, $C_6H_3(C_3H_7)$-$(OH)_2.(1,2,4)$; N butyryl resorcinol, $C_6H_3(COC_3H_7)(OH)_2.(1,2,4)$, N butyl resorcinol, $C_6H_3(C_4H_9)(OH)_2.(1,2,4)$.

The acyl groups were introduced into the resorcinol nucleus by condensing the phenol with the proper fatty acid in the presence of zinc chloride. This general method has been applied extensively by Nencki

[1] Bechhold and Ehrlich, *Z. physiol. Chem.*, **47**, 173 (1906).

[2] There appears to be some disagreement in the literature regarding the relative toxicities of phenol and resorcinol. See Baglioni, *Z. allgem. Physiol.*, **3**, 332 (1904); Brieger, *Arch. Anat. Physiol. Supp.*, **1879**, pp. 61; Cooper, *British Med. J.*, **1**, 1235 (1912); U. S. Dispensatory, 20th Edition, pp. 948, Lippincott, **1918**; Frankel, *loc. cit.;* May, *loc. cit.*

[3] We are indebted to the Department of Bacteriology of Yale University for its assistance with this phase of our investigation.   T. B. J

and other investigators.[1] The ketones formed by application of this reaction were reduced according to the method of Clemmensen,[2] which involves treatment of them in hydrochloric acid solution with amalgamated zinc.

In the preparation of resorcyl aldehyde for our research, attention was first directed to the apparently simple process of Dimroth and Zoeppritz,[3] but, although these investigators claim for their method an efficiency of 80%, repeated trials failed to produce anything except large amounts of tarry matter. An investigation of their process showed that the quantity of alakli recommended for the hydrolysis of the Schiff base produced in their reaction was much too small. When this defect was remedied, 40% yields of resorcyl aldehyde were obtained, and we have accordingly modified and amplified the original directions to correspond with our experience. However, we have not been successful in obtaining yields much over 40%. The lately published method of P. Karrer[4] for the preparation of resorcyl aldehyde was also given a trial but proved not very satisfactory.

The production of resorcyl aldehyde by the well-known method of Gattermann[5] was attended with considerable success. In order to avoid the disagreeable preparation of liquid hydrogen cyanide, we modified the method of operation so that this substance may be used directly in the gaseous state. The yields thus obtained have been very satisfactory, though they are somewhat smaller than those quoted by Gattermann. Undoubtedly these can be greatly increased after we have improved the technique of our method of operation.

An attempt to prepare resorcyl aldehyde in a new way, namely, by the interaction of phenyl-isonitrile with resorcinol in the presence of hydrochloric acid, was unsuccessful. It was predicted that hydrochloric acid would form an addition product with the isonitrile and that this in turn would take part in a Friedel-Crafts' reaction with the resorcinol. Theoretically, a Schiff base, identical with that produced in the Dimroth and Zoeppritz process should result, which could then be hydrolyzed with the formation of resorcyl aldehyde and aniline. A single trial of

[1] Nencki, *Monatsh.*, **10**, 906 (1889); Nencki and Schmid, *J. prakt. Chem.*, **23**, 546 (1881); Gukassiantz, *Ber.*, **11**, 1184 (1878); Nencki and Sieber, *J. prakt. Chem.*, **23**, 147 (1881); Crepieux, *Bull. soc. chim.*, [3] **6**, 151 (1891); Nencki, *J. prakt. Chem.*, **25**, 273 (1882); Rasinski, *ibid.*, **26**, 53 (1882); Goldzweig and Kaiser, *ibid.*, **43**, 86 (1891); D. R. P., 49149, 50450, 50451; Frey and Horowitz, *J. prakt. Chem.*, **43**, 113 (1891).

[2] Clemmensen, *Ber.*, **46**, 1837 (1913); *ibid*, **47**, 681 (1914); see also Johnson and Hodge, THIS JOURNAL, **35**, 1014 (1913), and Majima and Nakamura, *Ber.*, **46**, 4089 (1913).

[3] Dimroth and Zoeppritz, *ibid.*, **35**, 993 (1902).

[4] Karrer, *Helvetica Chim. Acta*, **11**, 89 (1919).

[5] Gattermann and Köbner, *Ber.*, **32**, 278 (1899); see also Gattermann and Berchelmann, *ibid.*, **31**, 1765 (1898); and Gattermann, *Ann.*, **357**, 313 (1907).

this new reaction failed to produce the aldehyde although there was a reaction between the isonitrile and resorcinol. It is very probable that the further study of the change which takes place here will throw additional light on the mechanism of the reactions which occur between isonitriles and the halogen acids.[1] The work of Tiemann and Lewy,[2] as well as the patented process of Scholl and Bertsch,[3] were considered in connection with the preparation of resorcyl aldehyde, and 2 other German patented methods,[4] but Gattermann's method, as modified by us, gave such satisfactory results that a further extension of this phase of our work appeared unnecessary.

Methyl resorcinol was obtained by reducing resorcyl aldehyde according to the method recommended by Clemmensen.[5] The most characteristic behavior of this substance prepared in this way was its widely varying melting point, which ranged between 70° and 104°, depending upon the solvent and the number of crystallizations. Consultation of the literature dealing with methyl resorcinol reveals the fact that our experience in this respect has been shared by others,[6] and that the chemistry of this substance is in a very unsatisfactory condition. Analyses of our products and also those obtained by other investigators showed that the high- and low-melting samples have identical compositions; and their general appearance, as well as the definiteness of their fusion points, would be quite satisfactory evidence that one was dealing with a pure substance in every case. The obvious explanation of this behavior would seem to be that our methyl resorcinol was contaminated with its isomers, orcinol or 2,6-dihydroxy-toluene, though the attempts to isolate such impurities by fractional crystallization were unsuccessful. If one or both of these isomers be present in our methyl resorcinol, then either the accepted formula for resorcyl aldehyde is incorrect, or else a partial rearrangement of the molecule occurs during the reduction. Clemmensen[7] himself saw a difficulty here, and the subject needs to be investigated further.

Apparently, the proof for the structure of resorcyl aldehyde rests on the work of Tiemann and Lewy,[8] who, using the Perkin reaction, converted the aldehyde into a substance similar to, but not entirely identical

[1] Nef, THIS JOURNAL, 26, 1557 (1904).

[2] Tiemann and Lewy, Ber., 10, 2210 (1877).

[3] Scholl and Bertsch, ibid., 34, 1441 (1901); D. R. P. 114,195.

[4] D. R. P. 105,798, and 155,731.

[5] Ber., 47, 62 (1914).

[6] Senhofer, Ann., 164, 132 (1872); Blomstrand and Hakansson, Ber., 5, 1086 (1872); Knecht, ibid., 15, 298 (1882); Ann., 215 92 (1882); Wallach, Ber., 15, 2835 (1882); Nevile and Winther, ibid., 15, 2980 (1882); Nölting, ibid., 19, 136 (1886); Clemmensen, ibid., 47, 62 (1914).

[7] Clemmensen, ibid., 47, 62 (1914).

[8] Tiemann and Lewy, Ber., 10, 2216-20 (1877).

with, hydroxycumarin. Furthermore, there is so much difference of opinion regarding the properties of 2,6-dihydroxy-toluene, that this substance can hardly claim to have been identified. Ullman[1] gives its melting point as 63–66°, while Herzig and Wenzel[2] claim that it fuses at 116° to 121°. It would seem almost necessary, therefore, that the constitutions of all 3 substances, namely, resorcyl aldehyde, methyl resorcinol and 2,6-dihydroxy-toluene, be more thoroughly investigated.

The synthesis of resacetophenone,[3] and ethyl resorcinol,[4] was accomplished without difficulty. The efficiency of these transformations, as well as some of the factors that influence them, have been determined. The same may be said regarding the preparation of propionyl resorcinol[5] and n-propyl resorcinol.[6]

N-butyryl resorcinol, its oxime, as well as n-butyl resorcinol, have been prepared. Reference to the first of these compounds was made by Nencki and Sieber[7] as follows: "Similarly, as with acetic acid, resorcinol when warmed with butyric acid and zinc chloride gives a new product, which, however, is a liquid." Inasmuch as we have shown butyryl resorcinol to be a white crystalline solid, the above description is incorrect. However, it is the only information we can find regarding the substance in question. The details of the process for producing butyryl resorcinol have been worked out and its identity has been established. The same may be said regarding the oxime of this ketone and its reduction product, n-butyl resorcinol.

The bacteriological tests on these alkyl resorcinols are of considerable interest and importance. Because of the uncertainty which appears to exist regarding the constitution of methyl resorcinol, it was not thought advisable to include this phenol with the rest in our bacteriological tests. The results of the other tests show very conclusively that the length, or weight, of the alkyl group incorporated in the resorcinol test has a very marked influence in increasing the antiseptic value of resorcinol. The ethyl, n-propyl, and b-butyl derivatives are respectively 5, 14, and 26 times as strongly germicidal as resorcinol itself. It is believed that the establishment of this fact adds a new and fundamental conception in the relationship of structure to antiseptic properties.

[1] Ber., 17, 1964 (1884).

[2] Herzig and Wenzel, Monatsh., 24, 906 (1903).

[3] Nencki and Sieber, J. prakt. Chem., 23, 147 (1881); von Pechman and Duisberg, Ber., 16, 2123 (1883); Nencki, ibid., 27, 2732 (1894); Bülow, ibid., 36, 730 (1903); Kehrmann, Ann., 372, 347 (1910).

[4] Johnson and Hodge, THIS JOURNAL, 35, 1020 (1913); Clemmensen, Ber., 47, 54 (1914).

[5] Nencki. Monatsh., 10, 906 (1889); Goldzweig and Kaiser, J. prakt. Chem., 43, 90 (1891); Hantzsch, Ber., 39, 3094 (1906).

[6] Johnson and Hodge, loc. cit.

[7] Nencki and Sieber, J. prakt. Chem., 23, 151 (1881).

Experimental Part.

Preparation of Resorcyl Aldehyde, $C_6H_5(CHO)(OH)(OH)(1,2,4)$.—

The first method applied for the production of this substance was that of Dimroth and Zoeppritz.[1] Starting with 44 g. of resorcinol, 48.5 of formanilide, and 20.5 g. of phosphorus oxychloride dissolved in 125 cc. of absolute ether, the directions of these investigators were followed as closely as possible. No difficulty was encountered until we attempted to hydrolyze the Schiff base, $C_5H_5N = CH(C_6H_3)(OH)_2.HCl$ with alkali when we obtained a red amorphous substance, which yielded after pressing on tile and crystallization from water a crystalline product melting at 99° to 101°. The melting point assigned in the literature to resorcyl aldehyde is 134–5°. This experiment was repeated several times without success.

A quantitative determination of aniline formed during hydrolysis revealed the fact that the cause of our failure was an insufficient quantity of alkali to bring about complete hydrolysis. The directions of Dimroth and Zoeppritz[2] call for 20 parts of a 3% solution of sodium hydroxide, based on a unit of 22 g. of resorcinol. However, it is apparent by calculation that this proportion of alkali is too small for effective neutralization of hydrochloric and phosphoric acids, and render the solution alkaline and the reaction calls for an increase of $1/3$ of a mole of alkali or 13.3 g. In the light of these facts, a series of experiments was conducted in which the quantity of alkali was varied within certain limits. The results are recorded in Table I.

Twenty-two g. of resorcinol was used in each case except Expt. 1, in which 44 g. was employed. The weight of formanilide used was equivalent to the weight of resorcinol multiplied by the factor 1.102. These are the proportions used by Dimroth and Zoeppritz.[3] Except where otherwise stated, the alkali employed was dissolved in 400 cc. of water.

TABLE I.

Expt.	POCl₃. G.	NaOH. G.	Tar formed during distillation.	Aniline recovered. G.	Pure Resorcyl-aldehyde. G.	Yield. %.
1[a]	20.5	..[b]	Large	....	0	0
2	12.0	45	None	....	6.0	22
3	14.0	45	None	16.4	10.0	36
4	10.5	60	None	17.2	7.8	28
5	10.5	75	None	17.3	10.1	37
6	10.5	45	None	17.3	12.0	43
7	10.5	35	None	17.6	4.0	14
8	10.5	120 g. dry Na₂CO₃	Large	13.0	Lost	
9	10.5	Ba(OH)₂[c]	None	18.0	9.0	33

[a] This experiment repeated 4 times with similar results.
[b] As per Dimroth and Zoeppritz.
[c] 185 g. of Ba(OH)2.8 H₂O in 325 cc. of H₂O.

From the results recorded in Table I, it is readily seen that where the original directions were adhered to no resorcyl aldehyde was obtained. On the other hand this compound was formed in fair yield when the process was applied with an increased amount of alkali. In addition to

[1] Dimroth and Zoeppritz, *Ber.*, **35**, 995 (1902).
[2] *Ber.*, **35**, 994 (1902).
Loc. cit.

the influence of alkali concentration, the temperature and volume of the solution, and the strength and temperature of the sulfuric acid at the time of neutralization, have an important influence on the production of tar and therefore on the yield of resorcyl aldehyde.

The largest yield of resorcyl aldehyde was obtained in Expt. 6, and the details of the method by which this was accomplished may be stated as follows:

Twenty-two g. of resorcinol. 24.2 g. of formanilide, and 10.5 g. of phosphorus oxychloride were dissolved in 65 cc. of absolute ether. The solution was warmed slightly on a water-bath for 10 to 15 minutes to start the reaction, which then proceeded spontaneously at ordinary temperature. After standing overnight the Schiff base separated completely. The ether was evaporated, and the reaction-product was digested with a solution of 45 g. of sodium hydroxide in 400 cc. of water. This operation was conducted so that the aniline formed by hydrolysis of the base was permitted to distill with water until 200 cc. of liquid had been collected. To the residue left in the digestion flask 100 cc. of water was added and this solution, thoroughly cooled, was neutralized with a *cold* mixture of 30 cc. concd. sulfuric acid in 200 cc. of water. The whole was cooled constantly during neutralization and the resulting solution allowed to stand several hours, or better overnight. After the resorcyl aldehyde which separated had been removed by filtration, the filtrate was saturated with sodium chloride and extracted with ether. The aldehyde filtered off was also extracted with ether to remove small quantities of sodium sulfate, and the 2 ether solutions were combined and evaporated. This final product was recrystallized from a small amount of water, when it showed a melting point of 134–5°.

Preparation of Resorcyl Aldehyde by Karrer's Method.[1]—This new method, which is said to give excellent results, was carried through three times with careful observation of the directions given in the original paper.

The yields obtained in 3 experiments using 10, 20 and 30 g. of resorcinol, were 1.6, 4.7 and 8.0 g. of resorcyl aldehyde, respectively, or 13, 18 and 21%. The melting points of the products from Expts. 1 and 2 were 120–3° and 124–9°, respectively.

It will be noted that, aside from the small yields, the melting points obtained were not very satisfactory, and were markedly lower than that of resorcyl aldehyde (134–5°).

Preparation of Resorcyl Aldehyde by Gattermann's Method.[2]—Aside from the disagreeable feature involved in the use of liquid hydrogen cyanide. this method has proved very advantageous for the introduction of the aldehyde group into phenols and their derivatives.[3] In the present work. the procedure has been so modified that this poisonous acid can be used directly in the gaseous form. The method of operation was as follows:

Two hundred g. of potassium ferrocyanide was heated in a flask with a mixture of 160 g. of concd. sulfuric acid and 280 cc. of water. The flask was fitted with an air condenser, from the upper end of which the hydrogen cyanide was led first through an empty wash-bottle, then through 3 small calcium chloride towers, and finally into a flask, kept

¹ Karrer, *Helvetica Chim. Acta.*, **11**, 89 (1919).

² Gattermann and Berchelmann, *Ber.*. **31**, 1768 (1898); Gattermann and Köbner, *ibid.*, **32**, 278 (1899).

³ Gattermann, *Ann.*, **357**, 313 (1907).

at —5°, containing one part of resorcinol dissolved in 3 parts of absolute ether. The passage of the gas was continued until the increase in weight of the flask and contents indicated a 50% excess of hydrocyanic acid. The flask containing the ether solution of resorcinol should be fitted with an outlet tube leading into a draught flue, and the whole apparatus requires well-fitting rubber stoppers.

Hydrogen chloride was then led slowly through the same drying train until it ceased to be absorbed by the ether solution. During this operation, the contents of the flask became slightly warm and finally because of the separation of the imide, nearly solidified. When the reaction mixture had stood for several hours, at the end of which time the presence of hydrochloric acid was still very evident, the imide was decomposed by the addition of boiling water. In this way a solution was obtained which was filtered and allowed to deposit crystals.

Since hydrogen cyanide liquefies at 26°, the drying train was kept above this temperature by placing in a water-bath at 35° to 40°. At first, hydrogen chloride should be led into the reaction mixture while it is thoroughly cooled. After the reaction has progressed somewhat, the flask may safely be lifted from the cooling-bath. A too rapid inflow of hydrogen chloride may remove so much hydrogen cyanide from the reaction mixture that the resorcinol will be in excess. Under these conditions the final product is a substance intensely red in color which has not been investigated by us. It is not unlikely that, as Gattermann[1] suggests, the excess of resorcinol condenses with the resorcyl aldehyde. If this is the case, the colored substance is probably a derivative of rosolic acid.

Methyl Resorcinal.—A 6 g. sample of resorcyl aldehyde was reduced according to the method of Clemmensen.[2] The product, at first a red oil, crystallized on long standing and was pressed on a porous plate to remove oil impurities. After 2 crystallizations from benzene it melted at 85–7°. Three more crystallizations were made from toluene and the fusing points of the samples were respectively, 95–7°, 101–3° and 103–4°. In a second experiment, 20 g. of resorcyl aldehyde was reduced in the same manner, and the resulting red oil distilled twice at 18 mm. The boiling points were 160° to 175° and 158° to 163°, respectively. The distillate was very light yellow in color and crystallized from toluene in 2 distinct forms, each of which melted at 83–4°. The main portion of the distilled oil was recrystallized twice from chloroform and showed a melting point of 78° to 79°. It was then subjected to 6 additional crystallizations from toluene; the respective fusing points of the products were 78° to 80°, 78-9°, 78–80°, 87–8°, 95° and 101–3°.

In the third experiment, 30 g. of resorcylaldehyde were treated exactly as described above. Distillation of the product at 18 mm. confirmed the value found for the boiling point in the preceding experiment. At ordinary pressure it distilled at 270–5°, which agrees well with the statements given in the literature by Knecht,[3] Blomstrand,[4] and Senhofer.[5] After a single crystallization from toluene, the substance, dried over sulfuric acid, melted at 68° to 70°.

Thus samples of methyl resorcinol have been prepared which possess melting-points ranging from 70° to 104°. Judged by the ordinary criteria, nearly all of these specimens would be regarded as pure substances.

It now remained to determine whether a sample melting, say, at 70°.

[1] Gattermann, *Ber.*, **32**, 279 (1899).
[2] Clemmensen, *ibid.*, **47**, 62 (1914).
[3] Knecht, *Ann.*, **215**, 94 (1882).
[4] Blomstrand and Hakansson, *Ber.*, **5**, 1087 (1872).
[5] Senhofer, *Ann.*, **164**, 133 (1872).

would show the same analysis as the higher-melting material. While samples of methyl resorcinol, melting above 100°, were analyzed by Knecht[1] and Nevile and Winther,[2] Senhofer[3] was the only one to analyze the low-melting substance.

A determination of the carbon and hydrogen made with a sample which melted at 68° to 70°, gave the following results:

> Subs., 0.1849: CO_2, 0.4577; H_2O, 0.1006.
> Calc. for $C_7H_8O_2$: C, 67.72; H, 6.50.   Found: C, 67.51; H. 6.09.

The remainder of the substance after crystallization from chloroform with the use of boneblack, gave a beautiful white material melting at 72-4°. This sample was also analyzed with the following results:

> Subs., 0.1770: CO_2, 0.4408; H_2O, 0.0993.
> Calc. for $C_7H_8O_2$: C, 67.72; H, 6.50.   Found: C, 67.92; H, 6.29.

Taking into account also the above cited analyses of Knecht, Senhofer, and Nevile and Winther, it can be said that the analytical results are identical whether the sample melts at 68° to 70°, 72° to 74°, 87°, or 103° to 105°.

We were not able to duplicate exactly Clemmensen's[4] experiment in which a sample of methyl resorcinol when sublimed, gave a product that melted sharply at 83-4°. In 2 trials, the substance prepared according to his directions melted very indefinitely at 77-9° and 81-4° respectively, and the quantity obtained was too small in amount to be subjected to recrystallization. Lastly, our experiments have shown that, when applied to resorcyl aldehyde, the Clemmensen reduction process is not more than 50% efficient.

Resacetophenone.—The method of Nencki and Sieber[5] for the preparation of this ketone was applied with success, and the results recorded in Table II illustrate the efficiency of the condensation:

<div align="center">TABLE II.</div>

Expt.	Acetic acid. G.	Zinc chloride. G.	resorcinol. G.	Crude resaceto-phenone G.	Purified resaceto-phenone. G.	Yields. Crude. %.	Yields. Purified.[a] %.
1.......	15	15	10	9.0	7.9	65	57
2.......	75	75	50	...	38.6	..	56
3.......	100	100	100	8.7	....	63	..

[a] M. p. 140–1°.

Ethyl Resorcinol.—This phenol is formed smoothly when the corresponding ketone is reduced.

[1] Knecht, *Ann.*, **215**, 94 (1882).
[2] Nevile and Winther, *Ber.*, **15**, 2981 (1882).
[3] Senhofer, *Ann.*, **164**, 133 (1872).
[4] Clemmensen, *Ber.*, **47**, 62 (1914).
[5] Nencki and Sieber, *J. prakt. Chem.*, **23**, 147 (1881).

Thus, 46.5 g. of resacetophenone reduced according to the Clemmensen[1] process yielded 44 g. of crude product. Inasmuch as the theoretical yield is 42 g., the transformation can be considered nearly quantitative. Ethyl resorcinol crystallizes from hot water, is light brown in color, and melts at 97–8°.

Propionyl Resorcinol.—The condensation of resorcinol with propionic acid in the presence of zinc chloride takes place readily when a mixture of the 2 substances is heated in an open flask.[2]

Excessive charring may be avoided if the source of heat is removed as soon as the mixture starts to boil and the product is allowed to cool. When the cold melt is treated with water, the ketone separates as a dark colored oil which soon crystallizes. It may be purified by recrystallization from hot water; it yields light yellow needles melting at 95–6°. In Table III are summarized the results obtained.

TABLE III.

Expt.	Propionic acid. G.	Resorcinol. G.	Zinc chloride. G.	Crude propionyl resorcinol. G.	Yield crude product. %.
1	18	10	18	12	80
2	25	25	50	20	53
3	37	25	37	23	61
4	46	25	46	30	80
5	25	10	25	13	86
6	25	10	15	10	66
7	30	20	50	22	72

Experiment 2 followed the procedure of Goldzweig and Kaiser[3] and is the least satisfactory of all those presented. It is clear that too large a proportion of zinc chloride results in excessive charring and reduces the yields.

The propionic acid employed in this work was obtained from a commercial sample repeatedly fractionated through a Hempel column. The portion distilling between 138° and 143° was used in these experiments.

Propyl Resorcinol.—This phenol was obtained from the crude propionyl resorcinol by the reduction method of Clemmensen.[4]

Yields of over 60% were obtained, calculated on the basis of impure propionyl resorcinol. The product crystallizes well from benzene and shows a melting point of 82–3°. It is light brown in color.

Normal Butyryl Resorcinol.—This new ketone was prepared by dissolving pulverized zinc chloride in warm N butyric acid. When solution was complete. the resorcinol was added and the whole was heated on the sand-bath until it commenced to boil gently. The flame was removed at once, the melt allowed to cool, and 200 cc. of water was added for each 10 g. of resorcinol employed in the condensation, which caused the separation of an oil consisting of the desired ketone mixed with butyric acid and a little water. Distillation of this oil under diminished pressure removed the acid and moisture. The ketone then distilled as a light yellow oil. In Table IV are recorded the details and results of 6 experiments.

[1] Clemmensen, *Ber.,* **47,** 54 (1914).

[2] Goldzweig and Kaiser, *J. prakt. Chem.,* **43,** 90 (1891).

[3] *Loc. cit.*

[4] Johnson and Hodge, THIS JOURNAL, **35,** 1020 (1913).

TABLE IV.

Expt.	Butyric acid. G.	Resorcinol. G.	Zinc chloride. G.	B. p.	Pressure. Mm.	Actual yield.[a] G.	Theo. yield. G.	% yield.[a]
1........	25	10	25	200–3°	30	..	..	..
2........	50	20	50	200–15°	25	24	32.7	73[b]
3........	50	25	50	210–15°	25	27	40.9	66[c]
4........	30	12	30	200–5°	10	15	19.6	76[b]
5........	70	24	70	180–5°	8	29	39.3	74[b]
6........	50	20	50	189–192°	9	22	32.7	67[b]

[a] In terms of yellow oil.
[b] After one distillation.
[c] After 2 distillations.

The oil crystallizes slowly, but some difficulty was experienced in obtaining the solid substance in a pure condition. If, however, the oil is dissolved in a warm mixture of 3 parts of carbon tetrachloride and one part of benzene, and the solution is cooled and stirred, the substance separates as a colorless solid. After 5 crystallizations from the same solvents, it was dried for 8 hours at 35°; the melting point was then constant at 69° to 70°.

Subs., 0.1842: CO_2, 0.4487; H_2O, 0.1137.
Calc. for $C_{10}H_{12}O_3$: C, 66.64; H, 6.72. Found: C, 66.40; H. 6.90.

The ketone obtained in the process outlined above is a colorless, crystalline substance which in time turns slightly brown. It is very soluble in benzene, ethyl alcohol, chloroform, acetone, and ethyl acetate, and slightly soluble in carbon tetrachloride and hot water. It melts sharply at 69° to 70°, apparently without decomposition.

The butyric acid employed in the preparation of this ketone was obtained by fractional distillation of several samples of crude commercial acid. The portion distilling between 157° and 167° was used in the present work. It was, therefore, necessary to show that the product obtained in the condensation with resorcinol was the N-butyryl derivative. This was done as follows. A sample of N-butyric acid, prepared by means of the malonic ester method of synthesis, was heated with resorcinol and zinc chloride in the manner just described. Recrystallization of the condensation product gave a substance melting at 69° to 70°, which was the same temperature as that obtained for the ketone made from the fractionated crude acid. To eliminate the possibility that the N-butyryl and iso-butyryl derivatives might melt at the same temperature, the melting point of a mixture of the 2 samples of ketone was taken and found to be 69° to 70°.

Oxime of Normal Butyryl Resorcinol, $C_6H_3C(NOH)(CH_2C_2H_5)$. (OH)·(OH). (1,2,4).—The identity of the new ketone was further established by the preparation of its oxime.

Five g. of butyryl resorcinol, 25 cc. of absolute alcohol, 2 g. of hydroxylamine hydrochloride, and 2.9 g. of potassium acetate were heated on the steam-bath for 5 hours. The liquid was filtered hot, and the filtrate was allowed to stand until crystallization took place. The crude product, after filtration, was pressed on a porous plate; it weighed 3.5 g. Small portions were recrystallized from ethyl alcohol, from chloroform, and from hot benzene, and in each case showed a melting point of 189° to 190°. The oxime is nearly colorless when first prepared, but becomes slightly colored on exposure to the air. It is not appreciably soluble in cold water.

Calc., $C_{10}H_{13}O_3N$: N, 7.18. Found: 7.24.

Normal Butyl Resorcinol, $C_6H_3(CH_2CH_2C_2H_5)(OH)(OH).(1,2,4).$—
Twenty-nine g. of the distilled butyryl resorcinol, 250 g. of freshly amalgamated mossy
zinc, 150 cc. of hydrochloric acid (sp. gr. 1.20), and 150 cc. of water were placed in a
flask connected with a return condenser. To effect reduction this mixture was boiled
for 26 hours with the occasional addition of 20 cc. portions of hydrochloric acid (sp.
gr. 1.20). It is probable that the reduction is complete in far less time than this, but
the failure of the butyl resorcinol to dissolve in the aqueous acid was misleading and was
at first supposed to indicate unreduced ketone.

At the end of this time, the dark red oil remaining on the surface of the solution
was separated and distilled 4 times under diminished pressure. The respective pressures
and boiling points were as follows: 175–190° at 12 mm., 165–185° at 8 mm., 155–175°
at 7 mm., and 155–175° at 7 mm. The weight of crude oil before distillation was 21 g.,
representing a yield of over 78%. The distilled oil gave the following results on analysis:

Subs., 0.1843: CO_2, 0.4920; H_2O, 0.1406.

Calc. for $C_{10}H_{14}O_2$: C, 72.24; H, 8.43. Found: C, 72.81; H, 8.53.

Butyl resorcinol is practically insoluble in water, but dissolves readily in ethyl
alcohol, in benzene, and in chloroform.

Comparative Antiseptic Values of Resorcinol, Methyl Resorcinol, Ethyl Resorcinol, Normal Propyl Resorcinol, and Normal Butyl Resorcinol.

In order to determine the influence of side-chain alkyl groups on the
germicidal activity of resorcinol, and also to ascertain whether a relation-
ship exists between antiseptic action and length of side chain, the di
hydroxy-phenols mentioned
above were submitted to a bac-
teriological examination. This
work was done in coöperation
with the Department of Bac-
teriology of Yale University
and consisted of determining the
phenol coefficient by a modi-
fication of the Rideal-Walker
method.

These tests revealed the fol-
lowing interesting facts: (1) the
antiseptic strength of resorcinol
is markedly increased by the
incorporation of an alkyl group
into the aromatic nucleus; (2)
the increase in disinfecting prop-
erties is a function of the size
of the group introduced. The
"phenol coefficients" of the sub-

Fig. 1.

stances examined are given in Col. A of Table V, while in Col. B are
recorded the more striking values obtained by arbitrarily placing the
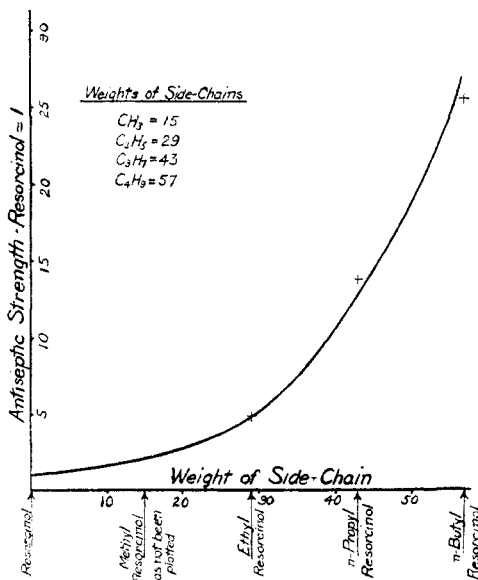antiseptic value of resorcinol equal to unity:

TABLE V.

Substance.	A.	B.
Resorcinol	0.3	1.0
Ethyl resorcinol	1.5	4.9
n-Propyl resorcinol	4.3	13.8
n-Butyl resorcinol	8.0	25.6

When the values under B, are plotted as ordinates against the weight of the side chains as abscissas the curve in Fig. 1 is obtained.

It is clear, therefore, that the antiseptic properties of the compounds investigated are very definitely determined by the length or weight of hydrocarbon side chain introduced into the resorcinol molecule. Just what effect will be produced by the introduction of branched side chains remains to be established. This investigation will be continued.

Summary.

1. Of the various methods applied for the preparation of resorcyl aldehyde, that of Gattermann, as modified by the writers, has proved the most successful.

2. The process of Dimroth and Zoeppritz for preparing resorcyl aldehyde has been investigated, and, while it is found to be unsatisfactory as described in the literature, it has been so modified as to give fair results.

3. Methyl resorcinol was prepared by reducing resorcyl aldehyde as suggested by Clemmensen. Difficulty was encountered, however, in isolating what would be concluded as a pure phenol; the products melting at different temperatures ranging from 70° to 104°. The results obtained by analysis of various samples showed uniformity of constitution, but the melting points indicate the presence of other isomeric substances as impurities. Fractional crystallization, however, failed to reveal the presence of a foreign substance.

4. Although the structure of orcinol appears to be well established, the writers believe that the constitutions of methyl resorcinol, 2,6-dioxytoluene and resorcyl aldehyde should be more thoroughly investigated.

5. Three entirely new substances have been described, namely, butyryl resorcinol, the oxime of butyryl resorcinol, and butyl resorcinol.

6. Finally, the antiseptic values of resorcinol, and ethyl, propyl-, and butyl derivatives of this phenol have been determined. The results obtained show that the germicidal properties of resorcinol are distinctly dependent upon the weight of alkyl side chain incorporated in the aromatic nucleus.