

ANTISEPTIC PROPERTIES OF BIPHENOL DERIVATIVES

DARWIN D. DAVIS AND ELBERT H. HADLEY
 Southern Illinois University, Carbondale

Carbolic acid, or phenol, is well-known as the standard basis for most of our antiseptics and germicides. The literature includes reports of extensive research in the synthesis of almost every imaginable variation of phenolic compounds and of the tests in the determination of their phenol coefficients. Logically, the next step after phenol was the investigation of compounds containing more than one hydroxy group, such as resorcinol and catechol; however, these compounds were found to be only slightly more effective than phenol. It was soon discovered that by placing an alkyl group on the ring the antiseptic properties of the compound were greatly increased. The preparation of a series of alkyl derivatives showed that the antiseptic power increased steadily with the weight of the side chain until the n-hexyl group was reached, after which a sharp decline was noted. The chemical name for S.T. 37 is n-hexyl resorcinol, an antiseptic which has a relatively high phenol coefficient, but which does not irritate the skin upon application. The unusually high phenol coefficients of certain chlorine substituted compounds indicate that the presence of the halogen greatly intensifies the antiseptic potency of phenols. Klarmann, Shternow, and Gates performed a rather exhaustive search into the antiseptic possibilities of such com-

pounds.¹ They prepared alkyl derivatives of both o- and p-chlorophenol, varying the alkyl group from one to nine carbon atoms. It was found that the p-chlorophenol derivatives were more potent than the ortho isomer; n-nonyl p-chlorophenol has a phenol coefficient of 1750 against the *Staphylococcus aureus* bacteria, whereas n-hexyl o-chlorophenol has a maximum coefficient of 714. They also found that the substitution of a single n-alkyl group was more effective than a branched chain of the same molecular weight or a polyalkyl derivative of the same total weight. Blicke and Stockhaus performed similar experiments on o-chlorophenol at about the same time.²

By the mid 1930's it was deduced that one of the integral necessities of a good antiseptic was a large molecule. This theory was applied in the preparation of alkyl and hydroxy derivatives of diphenylmethane. Moderate but not phenomenal results were obtained. A characteristic example of this series is 5-chloro-4-methyl-2-hydroxy diphenylmethane which exhibits a phenol coefficient of 380. In 1941 work was done on some derivatives of biphenyl, with the possible application as germicides as an objective. Mel-

¹ Klarmann, Shternow, and Gates, *J. Am. Chem. Soc.* 55, pp. 2576-89 (1933).

² Blicke and Stockhaus, *J. Am. Pharm. Assoc.* 22, pp. 1090-2 (1933).

2-hydroxy biphenyl...
 ethyl-2-hydroxy biphenyl...
 propyl-2-hydroxy biphenyl...
 butyl-2-hydroxy biphenyl...
 iso-amyl-2-hydroxy biphenyl...
 dipropyl-2-hydroxy biphenyl...
 chloro-2-hydroxy biphenyl...
 ethyl chloro-2-hydroxy biphenyl...
 propyl chloro-2-hydroxy biphenyl...
 butyl chloro-2-hydroxy biphenyl...
 iso-amyl chloro-2-hydroxy biphenyl...

nikov, Rokitskaya, prepared a series of chloro-derivatives of biphenyl.³ The alkyl groups substituted tended to five carbon atoms. The phenol coefficients varied directly with the size of the alkyl group. The chlorine was present in the ortho position. Table 1. They reported phenol coefficients of 25,400 for 2-hydroxybiphenyl, and 380 for the symmetrical compound 5-chloro-4-methyl-2-hydroxy biphenyl. These compounds exhibit a regular correlation between phenol coefficient and chain length.

Work is being carried on at Southern Illinois University, Carbondale, in the synthesis of a new series of antiseptics related to the or-

³ Melnikov, Rokitskaya, *Dokl. Akad. Nauk SSSR* 34, p. 125 (1941).

TABLE 1.—DERIVATIVES OF 2-HYDROXY BIPHENYL AND THEIR PHENOL COEFFICIENTS

Compound	Monilia Sitophyla	Ustilago Panici Miliacei	Penicillium Expansum
hydroxy biphenyl.....	111	138	14
ethyl-2-hydroxy biphenyl.....	123	8,100	810
propyl-2-hydroxy biphenyl.....	178	75.5	370
butyl-2-hydroxy biphenyl.....	138	71	1,200
iso-amyl-2-hydroxy biphenyl.....	112	98	2,180
dipropyl-2-hydroxy biphenyl.....	740	9,300	930
chloro-2-hydroxy biphenyl.....	460	116	116
ethyl chloro-2-hydroxy biphenyl.....	9,000	25,400
propyl chloro-2-hydroxy biphenyl.....	382	480	9.5
butyl chloro-2-hydroxy biphenyl.....	73	36
iso-amyl chloro-2-hydroxy biphenyl.....	345	172	43

Melnikov, Rokitskaya, and Becker prepared a series of alkyl and alkyl-chloro-derivatives of mono-hydroxy biphenyl.² The alkyl group was extended to five carbon atoms. The phenol coefficients varied considerably with the size of the chain, the bacteria used, and whether or not chlorine was present, as is shown in table 1. They reported a phenol coefficient of 25,400 for ethyl chloro-2-hydroxybiphenyl. These unsymmetrical compounds, however, do not exhibit a regular correlation of antiseptic potency and weight of side chain.

Work is being carried on at Southern Illinois University in the synthesis of a new series of compounds related to the ones in the forego-

ing examples. There is good reason to believe that the application of the better principles of the other series to the biphenyl molecule would result in a very effective antiseptic. The proposed compound is the symmetrical dialkyl-dichloro-dihydroxy derivative of biphenyl. There is no reference in the literature to this particular series of compounds, although the dialkyl derivatives and the dichloro-derivatives of biphenol have been produced separately. Stoughton, Baltzly, and Bass,⁴ and Nara Boon-Long⁵ prepared the alkyl derivatives in 1934 and 1948 respectively, and Cain⁶ prepared the chloro derivatives. After the above series of derivatives

⁴ Stoughton, Baltzly, and Bass, *J. Am. Chem. Soc.* 56, p. 2007 (1934).

⁵ Nara Boon-Long, *J. Pharm. Assoc. Siam* 1, No. 4, pp. 5-18 (1948).

⁶ Cain, *J. Chem. Soc.* 85, p. 10 (1904).

² Melnikov, Rokitskaya and Becker, *Compt. Rend.* 21, p. 125 (1941).

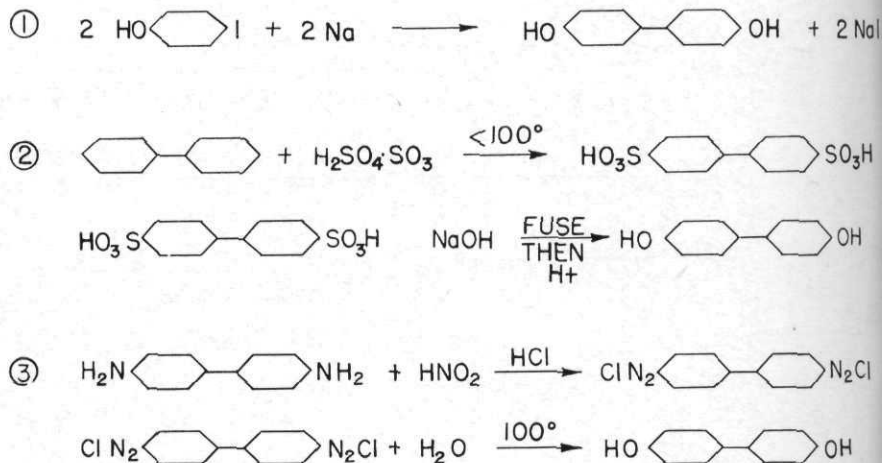


FIG. 1.—Preparation of dihydroxy biphenyl.

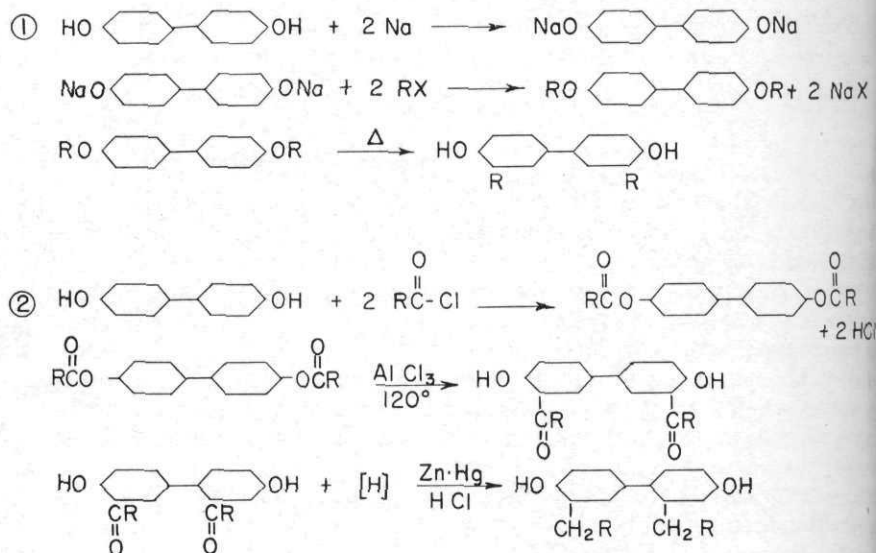


FIG. 2.—Alkylation by rearrangement of the ether or ester.

is prepared, the effect of position of substituent groups will be studied.

The first step in the synthesis of the series was the preparation of *p, p'*-dihydroxy biphenyl, or *p, p'*-biphenol. There are at least three alternatives in this preparation as

shown in figure 1. In the first place, it may be prepared by condensing two molecules of *p*-iodophenol with sodium; however, this reaction was discarded because of the possibility of obtaining too many different products and the subsequent necessity of

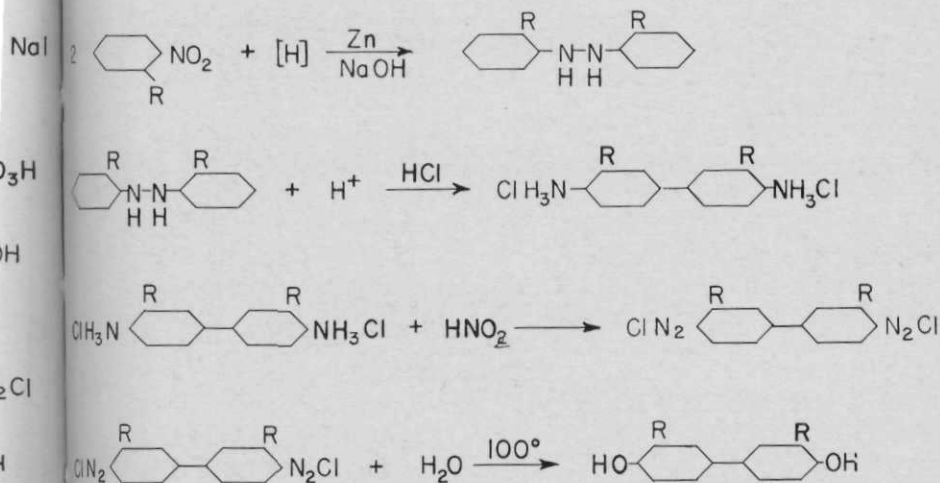


FIG. 3.—Dialkyl dihydroxy biphenyl by the benzidine rearrangement.

a complex purification procedure. Another possibility is the sulfonation of biphenyl⁷ and fusion with sodium hydroxide to obtain the dihydroxy compound. This method was attempted, mainly to ascertain the ease by which the reaction could be carried out; however, it was abandoned for two reasons. First—because it was difficult to prevent the formation of poly-sulfonic acids, and second—because another much more direct method was discovered. The other method is by means of diazotization reactions. Benzidine is the starting material in this case. Benzidine was dissolved in hot 30% HCl and diluted to a large volume. The addition of con. H₂SO₄ formed benzidine sulfate. Sodium nitrite was added, thus giving the benzidine-tetrazonium chloride. The tetrazonium salt was then hydrolyzed by the passage of steam into the hot solution, thus precipitating out the p, p'-dihydroxy biphenyl. The product was purified by recrystallization from

95% alcohol. Yields in excess of 85% were obtained from this reaction.⁸

There are two methods of placing the alkyl groups on the rings after the dihydroxy compound has been prepared, as indicated in figure 2. The method first attempted was the rearrangement of the dialkyl ether of biphenyl. This reaction is analogous to the one reported by Hickenbottom⁹ with respect to naphthols. The p, p'-dihydroxy biphenyl was allowed to react in a toluene solution with metallic sodium for several hours with constant agitation. The sodium salt thus obtained was refluxed for a few hours with two moles of the alkyl bromide, giving the di-ether as a product. The temperature of the boiling toluene is reported to be high enough to effect the rearrangement of the ether, but this was found not to be the case. No definite product could be sepa-

⁸ Beilstein VI: p. 992.

⁹ Hickenbottom, *Reactions of organic compounds*, 2nd ed., p. 93.

⁷ *Organic Reactions III*, p. 180 (1946).

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 MAISON, ILLINOIS

rated which gave indications of being the desired material, so work on this reaction was discontinued in favor of the second possibility.

This method is essentially the Fries rearrangement of the esters of dihydroxy biphenyl. Dimolar quantities of acetyl chloride were mixed with *p, p'*-dihydroxy biphenyl in a reactor equipped with a CaCl_2 drying tube. A drop or two of sulfuric acid was added to hasten the reaction. Good yields of the purified ester were obtained in this manner.¹⁰ Two variations of the rearrangement were attempted. The method of Stoughton, Baltzly, and Bass, which involves the use of nitrobenzene solvent, was first undertaken, but such great difficulty was encountered in the separation of the nitrobenzene and vacuum distillation of the product that an alternative method was used.

According to Nara Boon-Long, the rearrangement may be carried out in a dry reaction, thus bypassing the vacuum distillation of the product. A 2:1 mixture of the ester and anhydrous aluminum chloride was mixed thoroughly in a flask equipped with a drying tube. The mixture was heated at 115-120° for about 30 minutes, at which time the reaction mixture should be orange to green colored. When this reaction was run with granular anhydrous AlCl_3 , no results were obtained under temperatures of 140-150°; however, with the use of powdered AlCl_3 , the specified results were obtained. The excess AlCl_3 was then decomposed with water and the solid separated. At this point the product and the unreacted ester may

theoretically be separated by means of alkali. Sodium hydroxide dissolves the product by reacting with the regenerated OH groups and leaves the unreacted ester behind; however, after several attempts to complete this separation, it became apparent that most of the material which was obtained by the rearrangement is actually for the most part the starting material, dihydroxy biphenyl. Apparently the reaction takes the acetyl group off completely instead of rearranging it.

The last step in the ester synthesis is the Clemmensen reduction of the ketone obtained by rearrangement. The method described by Nara Boon-Long¹¹ was used. The ketone was refluxed for about twenty hours in a mixture of zinc amalgam and conc. HCl containing a little alcohol. The alcohol was distilled off and the product then extracted with petroleum ether, from which it was also recrystallized. Using the material with the correct melting point from the rearrangement of the ester, no material was obtained which could be purified using the specified solvent. After spending a considerable length of time in attempting to make this synthesis work, it was decided to try a completely new approach to the problem.

The method in use at the present time is essentially the coupling of two molecules of the necessary benzene derivatives by means of the preparation of a hydrazo compound and its subsequent rearrangement, as shown in figure 3. Ortho-nitrotoluene was mixed with 15% aqueous NaOH and alcohol and refluxed gently, while zinc dust was added

slowly, thus reducing to sym. di-*o*-tolyl. A sufficient fifty per cent was added just to distill when hot. The product was cooled, giving the product.¹² After the product is prepared, it is arranged as the benzidine. It was stirred vigorously for thirty minutes at room temperature and maintained at 30-40°. The mixture was cooled in water, thus precipitating the product. The pro-

¹⁰ Nara Boon-Long, *J. Pharm. Assoc. Siam* 1, No. 4, pp. 5-18 (1948).

¹¹ Boon-Long, *loc. cit.*

slowly, thus reducing the material to sym. di-o-tolyl hydrazine. Sufficient fifty per cent alcohol was then added just to dissolve the product when hot. The alcohol solution of the product was separated and cooled, giving the crystallized product.¹² After the hydrazo compound is prepared, it is necessary to rearrange it. This reaction is referred to as the benzidine rearrangement. It was stirred vigorously for about thirty minutes with 50% H₂SO₄ at room temperature and then maintained at 30-40° for a few hours. The mixture was then diluted with water, thus precipitating out the product. The product may be dis-

solved in dil. HCl and salted out with NaCl for purification.¹³ The NH₂ groups were then diazotized and hydrolyzed to give the hydroxy compound.

Work is being done at this time on the methyl derivatives. It is apparent that satisfactory results can be obtained from this reaction. No attempt has been made to prepare chloro derivatives but it is anticipated that the chlorine may be substituted on the benzene ring before coupling rather than on the biphenyl molecule itself.

¹² Chao-Lun Tseng and Fu-Min Fam, *Sci. Quant. Nat'l Univ. Peking* 5, pp. 350-7 (1935).

¹³ Lukashovich, *Anilinokrasochynaya Prom.* 4, pp. 605-9 (1934).