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SOME BROMO DERIVATIVES
OF m-CRESOL. II

THESIS FOR THE DEGREE OF M. S.

Walter John Peterson
1933

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SOME BROMO DERIVATIVES OF M-CRESOL. II.

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A Thesis
Submitted to the Faculty of
MICHIGAN STATE COLLEGE

In Partial Fulfillment of the
Requirements for the Degree
of
Master of Science
Department of Chemistry

By

Walter John Peterson

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Historical Data

THE BROMO M-CRESOLS

The investigation of the bromo derivatives of m-cresol was undertaken for several reasons. An examination of the literature revealed that, compared with the number of known halogene derivatives of other phenolic compounds, only a few of the bromo m-cresols had been prepared and conclusively proven.

Huston and Hutchinson, therefore, in 1929 began a series of researches in an attempt to clarify some of the existing inconsistencies in the literature in regard to the structure and properties of some of the bromo-m-cresols. They succeeded in preparing four new derivative. (Huston and Hutchinson. J.A.C.S. 54, 1504, 1932)

It was shown that when m-cresol is treated in the cold with one mole of bromine, two definite mono bromine m-cresols are formed, namely, 4-bromo m-cresol, (m.p. 55 - 56°), and 6 bromo m-cresol, a liquid boiling at 206 - 208°. The structure of these compounds was proven by the preparation thru the corresponding toluidine by diazotization.

It was also shown that when m-cresol is treated in the cold with two moles of bromine two definite dibromo m-cresols are formed. These two isomers are 2-4 and 4-6 dibromo m-cresol. Both of these are crystalline, and each have a melting point of 65°. The formula of the 4-6 dibromo m-cresol was definitely established by the preparation thru the corresponding toluidine.

The results of the researches reported in this thesis are a continuation of the work begun by Huston and Hutchinson on the bromo m-cresols. It was felt that if possible, it would be well to investigate the as yet unreported 2 bromo and 2-6 dibromo m-cresols, and perhaps to further verify the work already completed on the 6 bromo compound.

Before proceeding further it might be well to review briefly the literature on the bromo m-cresols as it stood before the work of Huston and Hutchinson.

Neville and Winther in 1882 (Ber. 15, 2991) prepared a m-bromo m-cresol by the diazotization of m-bromo m toluidine. They obtained a mono bromo m-cresol melting at 56 - 57°.

Claus and Hirsch (f pr. Chem. 2, 39, 59) prepared 2-4-6 tribromo m-cresol by treating m-cresol with bromine in chloroform solution. Their product melted at 84°.

Werner (Bl. Soc. Chem. 2, 46, 276) using much the same method as described by Claus and Hirsch obtained a product melting at 81°- 82°. Werner used water as a solvent instead of chloroform.

2-4-6 tribromo m-cresol has also been prepared by Auwers and Richter (Ber. 32, 3382). These workers obtained the compound by the reduction of 2-4-6 tribromo 3-oxy benzyl bromide. The reduction was accomplished with zinc and acetic acid. Their product melted at 84°.

Gibbs and Robertson (J. Chem. Soc. 1914, 2, 1885) prepared 4-6 dibromo cresol by the diazotization of 4-6 dibromo m-toluidine, which in turn had been prepared by the bromination of acet-m-toluidine in the cold. This dibromo m-cresol melted at 55°.

One year later Walther and Zipper published an article (J. pr. Chem. 91, 364 - 414) in which they described the preparation of 4 bromo m-cresol. This compound, melting at 62° was obtained by the addition of a calculated quantity of bromine in carbon tetra-chloride solution to m-cresol in the same solvent at -5° to -10°.

Bures and Balada (Cas. Ceskoslavenskeko Lekarnistra 6, 107 - 190, 1926) make the statement that by bromination of m-cresol at ordinary conditions without the aid of catalysts or solvents, 2-4-6 tribromo m-cresol is formed.

Hodgson and Moore (J. Chem. Soc., (1926), 2036 - 2040) prepared 4 bromo m-cresol from the corresponding amino compound by diazotization. A melting point of 38° is reported.

Darenzo and Levy, (Compt. rend, 193, 292, 1931) report a melting point of 63° for 4 bromo m-cresol which they claim to have prepared by direct bromination in glacial acetic acid in the cold. Since this work appeared in the literature shortly after Huston and Hutchinson had completed their work on the 4 bromo m-cresol it was thought wise to repeat the work of Darzen and Levy. This was done and a crystalline compound prepared which melted, after repeated crystallization at 53°- 56°, exactly the same melting point as was obtained for 4 bromo m-cresol by the bromination of m-cresol in chloroform in the cold (by H. & H.)

Lures (Chem. Listy. (1927) 21, 221 - 227) makes the following rule for substitution of halogens in m-cresol. "Chloro or bromo substitution products of m-cresol follow the same rule as for halogen substitution in amino or hydroxy derivatives of benzene. In m-cresol, halogen derivatives in the 4 and 6 positions are most likely."

We see then, in a review of the literature that little conclusive evidence is given as to the exact structure of the bromo m-cresols. One finds that whereas considerable work has been done with tribromo m-cresol with quite consistent results, relatively few consistent results have been reported for the mono and dihalogen derivatives. This can probably be explained by the peculiarity of the effect on directing properties when a methyl and a hydroxyl group are situated meta to each other as in m-cresol. Both being strongly para directing, a mixture of 4 bromo and 6 bromo m-cresol usually results in the case of the monobromo derivatives while a mixture of 2-4 and 4-6 occur in the preparation of the dihalogen derivatives. Difficulty in the separation of these isomers has undoubtedly been the reason for the lack and inconsistency of results in the past.

THE SULPHONATION OF M-CRESOL

Considerable work has been done in this laboratory in the preparation of halogenated phenols. Some difficulty has been encountered in obtaining ortho halogen substitution. In most cases this has been accomplished by protecting the para position or the para and one ortho position with sulphonic acid groups.

Maxfield (1930) used this method for the preparation of 2, 6 dibromophenol. His was an adaptation of a method used in the preparation of 2, 6 dichlorophenol (M. Tanaka and K. Kutani, C.A. 21, 2255). Since the halogenation of sulphonated phenols has been quite thoroughly discussed in Ballards' work on "The Preparation and Benzylation of O-Bromophenol" (Thesis 1932) the writer will make no attempt to review this phase of sulphonation, except in as much as it concerns m-cresol. Quite a thorough discussion is also given by Datta and Bhoumick (J. Amer. Chem. Soc. 43, 303, 1921).

Probably the most outstanding work on the sulphonation of m-cresol is that which was accomplished by Claus and Krauss in 1887 (Ber. 20, 3089). These workers state that when one mole of m-cresol is permitted to react with one mole of concentrated sulphuric acid for from three to four days, five-sixths of the cresol is sulphonated, resulting in the 4-sulphonic acid. (para to the OH) Complete sulphonation can also be accomplished by heating two or three hours on the steam bath.

The m-cresol para sulphonic acid crystallizes in three forms depending upon the solvent used in crystallization:

1.	From dil. H_2SO_4	M.P. 75	%H_2O 16
2.	From Conc. H_2SO_4	M.P. 95	%H_2O 12½
3.	Elimination of H_2O	M.P. 118	%H_2O 0

Claus and Krauss treated this m-cresol p-sulphonic acid with phosphorous pentabromide in an attempt to replace the sulphonic and hydroxyl groups with bromine and thus obtain a dibromo toluene. All that they obtained, however, was a mixture of dibromo and tribromo m-cresol, out of which a small amount of the tribromo derivative was isolated, melting at 78°- 81° C.

These workers also prepared a m-cresol disulphonic acid which they decided was the 4-6. This was obtained by treating one mole of m-cresol with four to six moles of sulphuric acid at room temperature for from four to five days or at 120° - 140° for a few hours. Claus and Krauss maintain that overheating may result in a change to the monosulphonic acid.

It is somewhat surprising that though a number of workers have reported a 2-6 dibromo m-cresol sulphonic acid, none of them have succeeded in successfully hydrolizing the sulphonic group and thus obtaining the 2-6 dibromo m-cresol. Claus and Dreher (J. pr. (2) 39, 368) obtained good yields of the dibromo m-cresol sulphonic acid by brominating the potassium salt of the parasulphonic acid in acetic acid. This compound crystallized out of water. A melting point of 140° is reported. Claus and Dreher also reported that bromination (1 mole) of the disulphonic acid gives the 2, 6 dibromo m-cresol 4 sulphonic acid. (J. Pr. (2) 39, 372.)

In more recent years, two English workers, namely Haworth and Lapworth (J.C.S. 125, 1299, '24) have done a great deal to clear up some of the questions in regard to the sulphonated derivatives of m-cresol. It appeared somewhat remarkable to these workers that m-cresol should not yield a sulphonation product corresponding with phenol o-sulphonic acid. Consequently one of their workers, M. L. Wilson, on making a preliminary investigation of the question found that monosulphonation of m-cresol, either with sulphuric acid or with chloro-sulphonic acid, usually led to the mixture of two acids, the nature and proportions of which vary with the agent and the conditions employed during the sulphonation process; by fractional crystallization of their salts a partial separation of the two acids was effected. One of these acids had properties very different from those of the true cresolsulphonic acids and was ultimately found to be identical with Verley's m-tolyl hydrogen sulphate, $C_6H_4CH_3OSO_3H$ (Bull. Soc. Chim., 1901, 25, 46)

The view that phenyl sulphuric acids are formed during the sulphonation of phenols and even that they represent intermediate stages in the sulphonation process, was at one time widely held, receiving its principal support in the formation of the supposed B-naphthylsulphuric acid during the sulphonation of B-naphthol. (Armstrong, Ber., 1882, 15, 202, 204, 207; Nietzki, ibid, p. 305). Since the discovery that this compound was in reality 2-naphthol 1-sulphonic acid, the idea that phenyl sulphuric acids may be formed in appreciable quantities during ordinary sulphonation of phenols, has not been considered very seriously.

Haworth and Lapworth endeavored to replace the sulphonic groups by the OH, Cyano, and amino groups, but these experiments were unsuccessful. In order to determine the constitution of the monosulphonic acids it was necessary to convert them into the corresponding methyl ethers. Haworth and Lapworth found that when the sulphonation was carried out at 120° the main product was the 4-sulphonic acid, but at lower temperatures considerable quantities of the 6 sulphonic acid could be obtained, although the total sulphonation was reduced.

The disulphonic acid prepared by Haworth and Lapworth appeared to be identical with that prepared by Claus and Krauss, and its constitution proven to be 4-6.

These workers were not able to introduce a third sulphonic group by the action of three molecular proportions of chloro-sulphuric acid; only m-cresol 4-6 disulphonic acid being isolated.

Here it might be well to mention something concerning the relative amounts of 4 and 6 obtained when concentrated H_2SO_4 acts on m-cresol. M-cresol sulphonated for one hour at 30° - 35°, yielded the 4 and 6 sulphonic acids in the ratio 2.7 to 1. When the sulphonation was carried out at 100° the two acids were formed in the ratio 19 to 1. At 120° after an hour's heating the main product was the 4 sulphonic acid. No other products than these were detected.

NITRO M-CRESOLS

The nitro derivatives of m-cresol have been prepared by a number of workers.

The proceedure which has been most generally used is that reported by Staedel and Kolb (Ann. 239, 210, 1390). M-cresol was nitrated in glacial acetic acid at -15°. The resulting mixture was poured into several volumes of ice water and the oil which separated steam distilled. The volatile product, which after purification melted at 56° was proven to be the 6 nitro m-cresol. Out of the reaction mixture a good yield of 4 nitro was isolated, melting at 129°. These workers report no 2-nitro m-cresol.

All subsequent work on the isomeric mono-nitro m-cresols does not differ much either in regard to preparation or properties, but it was not until recent years that anything definite was determined in regard to the 2 nitro derivative.

Khotinsky and Jacopson-Jacopmann (Ber., 42, 3097, 1909) claimed to have prepared a crystalline methyl derivative melting at 88°. These authors nitrated m-cresol according to Staedel's directions (Annalen 259, 210, 1831) and separated the volatile 2 and 6 nitro m-cresols by distillation in steam. According to Khotinsky and Jacopson - Jacopmann, the solid which separated from the cold aqueous distillate was 6 nitro m-cresol while the aqueous solution contained 2 nitro nitro m-cresol; and the latter, obtained as an oil by extracting with ether, and treating with methyl sulphate and alkali, yielded the crystalline derivative melting at 88°.

Gibson (J. C. S. 123, 1269, 1923), who repeated the work of Khotinsky and Jacopson-Jacopmann, found that although the yields of 4 and 6 nitro m-cresol were satisfactory, that of the supposed 2 nitro m-cresol was very small. Gibson found that better results were obtained by a method similar to that used by Kauffmann and de Pay (Ber., 37, 725, 1904) for the conversion of resorcinol into 2 nitro resorcinol. M-cresol was first sulphonated, the product was nitrated, and the resulting nitro m-cresolsulphonic acids were hydrolized with superheated steam at 160°- 170°. The yield of the yellow oil thus obtained amounted to 80% of the theoretical and from it Gibson was able to prepare crystalline acetyl, benzoyl and methyl derivatives, accompanied in each case by some oily product. The 2 nitro m-cresol crystallizes in fine yellow needles melting at 39°.

The methyl ether of the 2 nitro m-cresol melted at 54° whereas the methyl ether of the 6 melts at 62°.

Gibson, in order to determine the orientation of the groups in these three nitro compounds oxidized the methyl derivative of each to the corresponding nitro-methoxy benzoic acids, the properties which are known (Ber., 22, 2352, 1889).

Quite recently A. Corbellini and C. Ravazoni (Atti R. Accad. Lincei, 1931 (vi) 13, 132 - 137) reported that a repetition of the series of reactions employed by Gibson (J. C.

S. 1923, 123, 1270) showed that the nitro m-cresol m.p. 41° is not 2 nitro but 6 nitro.

During the course of this work on the bromo m-cresols the writer has been able to demonstrate that Corbellini and C. Ravazzoni were undoubtedly wrong in their conclusions in regard to the work of Gibson. Work by Hodgson and Beard (J. C. S. 127, 498, 1925) in the reduction and subsequent diazotisation of 2 nitro m-cresol also substantiates the work of Gibson.

The 2 amino and 6 amino m-cresols, in which we were particularly interested, have received but little attention in the literature.

Kehrmann and Stampa (Ann. 322, 18) mention the 6 amino m-cresol but give nothing as to preparation or melting point.

Auwers, Borschi and Weller (Ber., 54, 1315, 1921) obtained 6 amino m-cresol by reduction of the 6 nitro compound with stannous chloride and hydrochloric acid. A melting point of 157° - 159° is reported.

The only reference to be found on the preparation of 2 amino m-cresol is that by Hodgson and Beard (J. C. S. 127, 498, 1925). These workers reduced in a water solution of sodium carbonate and sodium hydrosulphite, obtaining a compound melting at 150°. From this they attempted to prepare 2 bromo m-cresol by the Sandmeyer method. A very poor yield of product, melting at 56° - 57° is reported.

In regard to the nitro m-cresols, it was felt that if the para position could be protected by a nitro group and the positions 2 and 6 filled with bromine, subsequent reduction and removal of the amino group through diazotization would result in the as yet unreported 2, 6 dibromo m-cresol.

This compound 2, 6 dibromo, 4 nitro m-cresol has been studied rather extensively by several workers. It was first obtained by Claus and Hirsch (J. pr. (2) 39, 61) by nitrating 2-4-6 tribromo m-cresol with nitric acid in acetic acid solution. These workers also obtained it by bromination of 4 nitro m-cresol.

Zincke also prepared this bromo nitro m-cresol, but the nitration was carried out with sodium nitrate. (J. pr. (2) 61, 564).

Raiford (Amer. Chem. Jour. 46, 426, 1911) in a study of the chlorimidoquinones prepared 2, 6 dibromo 4 nitro m-cresol by a method very similar to that of Zincke. His product melted at 134°.

Reduction of this compound with stannous chloride and hydrochloric acid gives a hydrochloride melting at 225°. The free base liberated by ammonium carbonate melts at 176°.

CHLORO - BROMO M-CRESOLS

Since such very few conclusive results are reported in the literature in regard to either the chloro or bromo m-cresols, we would also expect but little in regard to the chlorobromo m-cresols. Such is actually the case. They are considered briefly here because they provide a convenient means of proving the position of the bromine atoms in some of the compounds to be discussed later.

Walther and Zipper (J. pr. (2) 91, 378) obtained 4 chloro, 6 bromo m-cresol by bromination of 4 chloro m-cresol in carbon tetrachloride. This product melted at 70° - 75.5°.

Raiford and Leavell (J. A. C. S. Soc., 36, 1509) were successful in synthesizing 2, 6 dichloro 4 bromo m-cresol by diazotization of 2 chloro, 4 bromo, 6 amino m-cresol. Needles out of ligroin melted at 65°.

The only remaining chlorobromo m-cresol which is reported in the literature is 4 chloro 2, 6, dibromo m-cresol. This compound, melting at 70° - 75.5° was prepared by Walther and Zipper (J. pr. (2) 91, 378) by bromination of 4 chloro m-cresol in acetic acid.

EXPERIMENTAL PART

THE PREPARATION OF 6-BROMO M-CRESOL

In the preliminary work with the bromo m-cresols, considerable difficulty was encountered in the distillation of the various derivatives under ordinary atmospheric conditions, without obtaining a great deal of decomposition. For this reason it was decided to repeat the work of Huston and Hutchinson in the preparation of 6 bromo m-cresol, thus obtaining enough of this compound for comparison, and determining its boiling point at 4 mm. It was decided to use this pressure throughout the whole of the work.

One mole of m-cresol (108 grams) was brominated with one mole of bromine (160 grams) according to the method reported by Hutchinson. The brominated m-cresol after several distillations under 4 mm. pressure gave the following fractions:

75°- 85° - - - - - - - - - -	16.8 grams	liquid
85°-100° - - - - - - - - - -	44.5 grams	liquid
100°-115° - - - - - - - - - -	27.3 grams	liquid
115°-117° - - - - - - - - - -	65.8 grams	solid

The first fraction boiling at 75 - 85° on refractionation came over at 80 - 81° (4 mm.) This fraction corresponds to that which Hutchinson reports as having a boiling point of 205 - 208° at 731 mm. of pressure, and is undoubtedly the 6 bromo m-cresol.

Analysis by the Parr bomb method gave the following results:

Wt. of Sample	cc. .1 N $AgNO_3$	Calculated Br. in C_7H_7OBr	Found
.2226	11.85	42.78%	42.61%
.2017	10.72	42.78%	42.55%

The large fraction boiling at 115 - 117° (4mm.) gave upon recrystallization, a product melting at 56 - 57°. This corresponds to Hutchinson's 4 bromo m-cresol.

The two fractions which came over between 85° and 115° after repeated fractionation were separated into 6 bromo and 4 bromo m-cresol.

The benzoyl, benzenesulfonyl and toluenesulfonyl esters of the 6 bromo m-cresol were prepared by the method described by Porter, Stewart and Branch (Page 181, Einhorn and Holland, Ann., 301, 95; 1898).

After repeated crystallizations from alcohol the melting points were determined and the compounds analyzed for bromine. Following are the results:

Esters of 6 Bromo M-Cresol

	M. P.	Wt. of Sample	cc..1N $AgNO_3$	Calculated for Br	Found
Benzoyl	87.5°	.2065	7.12	27.49%	27.58%
Small white needles cut of alcohol					
Benzene sulfonyl	92.0°	.1606	4.9	24.46%	24.34%
Small white plates out of alcohol					
Tolyl sulfonyl	72.5°	.2009	5.9	23.43%	23.52%
Fine plate-like needles out of alcohol					

Since the proceedure for the proof of the 6 bromo derivative as given by Hutchinson was long and difficult, and gave but mediocre results, it was felt that some other method might be attempted which would, perhaps give better yields and further substantiate his results.

For this purpose, m-cresol was nitrated in 140 gram lots, in accordance with the method of Staedel and Kolb (Ann. Chem. 259, 210; 1890), and the isomeric nitro products that resulted were separated by steam.

140 grams of m-cresol was placed in a 3-liter, 3-necked balloon flask equipped with an efficient mechanical stirrer. To the cresol was added 140 grams of glacial acetic acid and the mixture cooled to -5° C. A mixture of 400 grams of glacial acetic acid and 200 grams of HNO_3 (Sp. Gr. 1.5) was cooled in the ice box and then added very slowly to the original mixture from a separatory funnel. During the operation the temperature should not rise above 0°. After the addition was complete, the mixture was poured over 1,000 grams of ice and after about an hour a liter and a half of water was added. This was then allowed to stand over night, during which time, a heavy, reddish, black oil separated, which was partly crystalline. The oil was separated from the aqueous portion above it and placed into a flask prepared for steam distillation. The two isomeric products could now be separated since the para compound is not volatile under these conditions and can be obtained in the crude form by allowing the distillation residue to cool.

The ortho compound in the distillate upon recrystallization from petroleum ether, melted at 56°.

The para compound can be further purified by repeated crystallization of its sodium salt from water. These crystals may then be decomposed by treatment of their aqueous solution with dilute hydrochloric acid, and the free nitrocresol subsequently crystallized from hot water, from which it separates in nearly colorless needles melting at 127° - 129°.

The yield of both isomers can be considerably increased by extracting the aqueous portion of the original mixture with ether, evaporating and again steam distilling.

Yields covering a number of nitrations were:

6 nitro --- 38 grams.
4 nitro --- 53 grams.

For the preparation of 6 bromo m-cresol we were naturally especially interested in the 6 nitro product.

From the 6 nitro m-cresol, the 6 amino hydrochloride was prepared by a modification of a method reported by Raiford and Leavell (J. A. C. S. 36, 1505; 1914), also (Am. Chem. Journal 46, 419; 1911).

Thirty grams of the nitro product was dissolved in the smallest possible quantity of hot alcohol. (1 gram to 1 cc) And to the hot solution ¼ more than the calculated amount of stannous chloride (114 grams) dissolved in conc. HCl (114 cc). During this time the flask was shaken and the mixture kept hot in order to prevent the immediate separation of crystalls.

Next one volume of conc. HCl was added and the solution set aside to cool. Fine white crystals separated which were free from tin compounds. The hydrochloride melted at 212° with considerable charring.

Attempts to change this hydrochloride to the amine were unsuccessful. Ammonium carbonate was used for this purpose. A compound of no definite crystalline structure which turned red upon standing in air was repeatedly obtained. Kehrmann (Annalen 322, 19; 1902) claims to have isolated the amine by just such a method but reports no melting point. He does, however, mention that in the ammoniacal filtrate a reddish brown compound was observed which he suggests might be an oxidation product.

Since it seemed impossible to obtain the pure amine by this method an attempt was made to accomplish the reduction by the use of sodium hydrosulphite. Hodgson and Beard (Journal of the Chemical Society 127, 498; 1925) used this successfully in the reduction of 2 nitro m-cresol.

6-nitro m-cresol (33 grams) was dissolved in 400 cc of water containing 60 grams of sodium carbonate. This was treated at the boiling point with 126 grams of solid sodium hydrosulphite. 6 amino m-cresol was deposited on colling in almost colourless, fine needles with a melting point of 157° - 159°. (This agrees with the m. p. reported by Auwers, Borsche and Weller,(B. 54 (1921) 1315).

For the replacement of the amino group with bromine it was found that good yields were obtained by the use of the hydrochloride rather than the amino. To accomplish this diazotization a modification of the method reported for the preparation of p-bromotoluene by Bigelow (Organic Synthesis Vol. V p. 21) was used.

A mixture of 5 grams of crystallized cupric sulfate, 2 grams of copper turnings, 13 grams of sodium bromide, 3 grams of concentrated H_2SO_4 (Sp. Gr. 1.84) and 83 cc of water was reflexed over a flame for three to four hours until the color became yellowish. (If the color of the solution has not been discharged after heating for three to four hours, a few grains of sodium sulfite may be added to complete the reduction).

When the hydrobromic acid - cuprous bromide solution was ready for use, the diazonium solution was prepared. A solution of 10 grams of amine hydrochloride and 16 grams of concentrated sulfuric acid (Sp. Gr. 1.84) in 80 cc of water was cooled below 20° and diazotized with a solution of 6 grams of sodium nitrite in 125 cc of water. This required about twenty to thirty minutes when the temperature was maintained between 15° and 20° by means of an ice bath.

A one liter round-bottom flask containing the hydrobromic acid cuprous bromide solution, was arranged for steam distillation. After the copper solution was gradually added from a separatory funnel and a vigorous current of steam passed through the mixture at the same time. This proceedure required about an hour. The oil in the aqueous distillate was separated with ether, washed, and upon evaporation of the ether and distillation 4 grams of yellow oil boiling at 81° - 82° (4mm.) was obtained. Analysis for bromine by the Parr bomb method gave the following results:

Wt. of Sample	cc .1 N $AgNO_3$	Calculated Br. in C_7H_7OBr	Found
.1950	10.41	.4278	.4270

To further prove the structure, a portion was brominated in chloroform solution with one mole of bromine. Crystals were separated from a large fraction of oil (undoubtedly 2, 6 dibromo m-cresol) which melted at 64° - 65°. The crystalline product was the 4, 6 dibromo product, described by Hutchinson.

The 4, 6 dibromo m-cresol was proven by preparation of its benzoyl ester. Repeated crystallization from ethyl alcohol gave a melting point of 84° - 85°.

Various attempts to nitrate the 6 bromo m-cresol were unsuccessful. In each case 2-4-6 trinitro m-cresol (m. p. 109° - 110°) was isolated.

THE PREPARATION OF 2-BROMO M-CRESOL

Since the preparation of 6 bromo m-cresol was so easily accomplished by working through the corresponding amino compound, it was felt that a similar method might be worked successfully for the preparation of 2 bromo m-cresol.

For the preparation of 2 nitro m-cresol, a method was used which was first suggested by Gibson (J. C. S. 123, 1269; 1923) and later modified by Hodgson and Beard (J. C. S. 127, 498, 1925).

The original method used fuming sulphuric acid which contained 6 - 7% SO_3. Although reasonably good protection in the four and six positions is accomplished with this strength of sulphuric acid the crude nitro product does not crystallize readily but has to be purified by preparation of the acetyl derivative, which is later hydrolized with alcoholic sodium hydroxide solution. The method of Hodgson and Beard, which obviates the troublesome process of purification by acetylation consists in using stronger oleum (15% SO_3 instead of 6-7%) for the initial disulphonation.

The author found that an even stronger oleum (23% SO_3 instead of 15%) gave improved protection. Following is the method eventually decided upon.

To a cold solution of 108 cc of m-cresol in 400 cc of fuming sulphuric acid (23% SO_3), a mixture of 100 cc of fuming sulphuric acid and 46 cc of nitric acid (d. 1.5) was gradually added. After twenty hours, the liquid was diluted with 500 cc of water and superheated steam passed through the heated solution. Below about 145° a little unchanged cresol distilled, but above this temperature up to 180° nitrocresol passed over, leaving a black tar from which no crystalline compound could be isolated. Only the first third of the steam distilled 2 nitro m-cresol comes over as an oil (which partly solidifies); the bulk of the distillate solidifies immediately. The 2 nitro m-cresol can be recrystallized from petroleum ether in bright yellow, fern-like, rhombic groups of needles melting at 39°.

After purification of all fractions 43 grams of 2 nitro m-cresol and 39.9 grams of oil (m-cresol) were gotten from a typical nitration experiment like that just discussed. The m-cresol fraction boiled at 80° - 89° at 4 mm.

A method adapted from the work of Hodgson and Beard was also used in the reduction of the 2 nitro m-cresol to the corresponding amine.

Thirty-three grams (33) of 2 nitro m-cresol were dissolved in 400 cc of water containing 30 grams of sodium carbonate. This mixture was then treated at the boiling point with solid sodium hydrosulphite (126 grams). 2 amino m-cresol was deposited, on cooling, in colorless, elongated, hexagonal plates, m.p. 150°, yield 20 grams.

The 2 amino compound was then converted into the corresponding bromo derivative by application of the method used by Bigelow (Org. Synthesis Vol. V, p. 21) for the preparation of p-bromotoluene from the corresponding toluidene.

A mixture of 5.6 grams of crystallized cupric sulphate, 2 grams of copper turnings, 14 grams of sodium bromide, 3 grams of sulphuric acid and 90 cc of water was refluxed over a flame for from three to four hours.

When the hydrobromic acid - cuprous bromide solution was ready for use, a diazonium solution was prepared. A solution of 11 grams of 2 amino m-cresol and 17.6 grams of concentrated sulphuric acid (Sp. Gr. 1.84) in 90 cc of water was cooled below 20° and diazotized with a solution of 6.3 grams of sodium nitrite in 12 cc of water. This required about twenty to thirty minutes when the temperature was maintained between 15 and 20° by means of an ice bath.

A one liter round bottom flask containing the hydrobromic acid - cuprous bromide solution was arranged for steam distillation. After the copper solution was heated to boiling, the diazonium solution was gradually added from a separatory funnel and a vigorous current of steam passed through the reaction mixture at the same time. This proceedure required about one hour. The aqueous solution was then washed with dilute sodium carbonate and water and extracted with ether. Distillation gave a yield of 7.5 grams boiling at 83° - 84° (4 mm.), all of which became solid.

Recrystallization from alcohol gave characteristic large, hexagonal plates, m. p. 58.5° - 59°.

Since protection of the 4 and 6 positions was so easily accomplished in the preparation of 2 nitro m-cresol by the use of fuming sulphuric acid, it was felt that a similar proceedure might be used for the preparation of 2 bromo m-cresol directly.

To a cold solution of 108 grams of m-cresol in 450 cc of fuming sulphuric acid (23% SO_3) 53 cc of bromine were added very slowly. After twenty-four hours, the liquid was diluted with 500 cc of water and superheated steam passed through the heated solution. The bulk of the 2 bromo m-cresol came over at 180° or above. It was often found necessary to allow steam distillation to go on for as long as 2 to 3 hours at 180° in order to secure complete hydrolysis. The distillate, which was a yellow oil, was extracted with ether, and eventually distilled, using an eight inch column and vacuum of 4 mm. Following are the fractions from 93 cc of oil (one run):

80° - 85° - - - - 34.7 grams
85° - 95° - - - - 29.0 grams
95° -103° - - - - 36.8 grams
103° -112° - - - - 4.0 grams
112° -114° - - - - 13.5 grams

The first three fractions consisted of a mixture of 2 bromo and 6 bromo m-cresol. These two isomers were separated in the following manner:

The three fractions were refractionated a number of times until the bulk was separated into an 80° - 85° fraction. This fraction which had consistently refused to crystallize of its own accord, was then seeded with a crystal of the 2 bromo m-cresol prepared by diazotization. The fraction crystallized immediately. After standing in the ice box over night a fraction (representing about one third of the weight) of uncrystallizable oil was decanted from the crystalline portion. This oil fraction, which it was decided, must be the 6 bromo m-cresol was fractionated, using an eight inch column and a 4 mm. vacuum. The bulk of the oil came over at 80° - 81°, This was proven to be the six by preparation of its benzene sulfonyl ester, which when crystallized out of alcohol, melted at 92° - 93°.

The crystalline fraction or 2 bromo m-cresol upon recrystallization from alcohol gave a melting point of 58.5° to 59°.

The fraction from 112° - 114° was analyzed by the Parr bomb method and found to be 2,6 dibromo m-cresol, the proof and preparation of which will be discussed later.

A method suggested by Ballard for the preparation of ortho bromo phenol was also used in the preparation of 2 bromo m-cresol. This method yields very good results but the proceedure is long and inefficient as compared to the sulphonation proceedure just described.

One mole (108 grams) of m-cresol and 3½ moles (350 grams) of concentrated sulphuric acid in a three liter, three necked flask were heated on a steam bath for three to four hours. At the end of this time the reaction mixture was cooled, the stirring motor attached and the mixture made alkaline by adding a solution of seven moles (280 grams) of sodium hydroxide dissolved in 700 cc of water. This was done very slowly.

The alkaline solution was then cooled to room temperature and brominated by adding slowly one mole (160 grams), of bromine, stirring constantly. (During this operation the temperature may be permitted to rise to 40° - 50°) Stirring was continued for about half an hour after all the bromine had been added. (The mixture should still be alkaline).

The reaction mixture was then transferred to a three liter flask set for steam distillation. During this distillation the reaction mixture was heated on an oil bath to about 150°. This removed any tribromo m-cresol which should not appear as more than a trace.

When no more tribromo m-cresol was observed in the distillate, the steam distillation was stopped and the reaction mixture, still on the oil bath was evaporated to a thick pasty mass. This was allowed to cool and was then acidified with about 800 cc of concentrated sulfuric acid. This had to be accomplished slowly on account of the rapid evolution of HBr.

The mixture was again steam distilled, this time from an oil bath heated to 200° - 210°.

When no more oil appeared in the distillate, steam distillation was stopped. The brominated m-cresols were then extracted with ether, the ether evaporated off and the residue distilled under vacumm of 4 mm. The following fractions were separated from a yield of 103 cc of oil:

80 - 85°	35.7 grams	solid
85 - 100°	21.4 grams	liquid
100 - 110°	20.0 grams	liquid
110 - 120°	43.9 grams	liquid

The fraction 80 - 85° remained liquid until seeded with a crystal of 2 bromo m-cresol. When placed in the ice box overnight, 13.1 grams of the 35.7 gram fraction was separated as an oil by simple decantation from the crystalline portion. This oil upon distillation boiled at 80 - 81° (4 mm.) and was proven to be 6 bromo m-cresol by the benzene sulfonyl ester preparation used in the previous sulfonation.

The crystalline 2 bromo m-cresol fraction gave large, characteristic hexagonal plates out of ethyl alcohol, melting at 58.5° - 59°. By repeated fractionation with a column the three other fractions can be separated into 2 bromo and 2,6 dibromo m-cresol, (b. p. 114° - 116°) the proof and preparation of which will be discussed later.

Several Parr bomb analyses were run on the crystalline 2 bromo m-cresol fractions (b. p. 83° at 4 mm.).

Wt. of Sample	cc .1 N $AgNO_3$	Calculated Br. in C_7H_7OBr	Found
.2314	12.42	42.78%	42.94%
.2005	10.68	42.78%	42.62%
.1803	9.62	42.78%	42.57%

Since Hodgson and Beard (J. C. S. 127, 499, 1925) had prepared 2 bromo-3-methoxy toluene by diazotization of the methyl ether of 2 amino m-cresol, it was felt that this compound might be prepared by a simple methylation of 2 bromo m-cresol.

2 bromo m-cresol (10 grams) was dissolved in 15 cc of methyl alcohol and 1.2 grams of sodium added to form the sodium cresolate. When this reaction was complete the theoretical amount, (7 grams) of methyl iodide was added, the mixture refluxed for five hours and allowed to stand overnight. The alcohol was then evaporated off and the residue washed with water to remove the sodium iodide formed in the reaction. The ether was extracted with ethyl ether and was obtained by evaporation of the solvent. Recrystallization in ethyl alcohol gave long flat plates, melting at 39.5° - 40°. Hodgson and Beard reported a melting point of 35.5° - 36.5° for this product.

Analysis of the methyl ether of 2 bromo m-cresol for bromine yielded the following:

Wt. of Sample	cc .1 N $AgNO_3$	Calculated Br. in C_8H_9OBr	Found
.2283	11.7	41.13%	40.98%

A small portion of 2 bromo m-cresol brominated in CCl_4 solution in the cold with one mole of bromine yielded a portion of uncrystallizable oil (probably 2, 6) and a crystalline fraction which upon purification in petroleum ether gave a melting point of 65°. This agrees with the melting point for 2, 4 dibromo m-cresol. Once purified, it crystallized very easily out of most solvents, differing from the 4, 6 dibromo m-cresol in that respect.

The benzoyl, benzene sulfonyl and toluene sulfonyl esters of 2 bromo-m-cresol with their melting points and analyses for bromine are reported below:

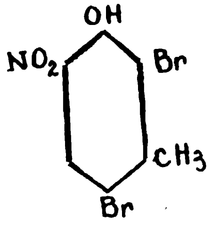
	M. P.	Wt. of Sample	cc .1 N $AgNO_3$	Calcu. for Br	Found
Benzoyl ester	59°	.1836	6.33	27.49%	27.58%
Small white plates from alcohol					
Benzene sulfonyl	71°	.2131	6.5	24.46%	24.39%
Small white plates from alcohol					
Toluene sulfonyl	85°	.1988	5.8	23.43%	23.34%
Small needle like plates from alcohol					

THE PREPARATION OF 2-6 DIBROMO M-CRESOL

It was felt that a convenient method for the preparation of this compound would be through 4 nitro, 2, 6, dibromo m-cresol, by subsequent reduction and finnally replacement of the amino group by hydrogen through the diazotization reaction.

For the preparation of this nitrobromo derivative a method was first used which had been reported by Raiford (Am. Chem. Journal, 46, 426, 1911).

Pure tribromo m-cresol was the starting point in the preparation of this compound. Thirty grams was dissolved in 300 cc glacial acetic acid, the liquid cooled to 10°and then 10% more than the calculated amount of sodium nitrite added during half an hour, while the flask was continually shaken and the temperature kept down to that given above. When the nitrite had all dissolved, the dark liquid was poured with stirring into 5 volumes of water, and the mixture set aside for some hours to allow the precipitate to subside. At the end of this time the yellow solid was filtered off and dried on a clay plate. A yield of 90% was obtained. The crude product softened at 65° and was completely melted at 113° (when it appeared to decompose), which suggested the possible presence of two compounds. It may be stated at once that isomeric mononitrodibromo m-cresols, viz;



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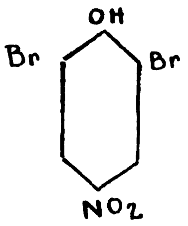


were isolated from the mixture.

The best method of separating the compounds present was found to consist in dissolving the dried crude product in hot chlorofomr (1 gram to 1 cc) and treating the solution with two volumes of ligroin (40 - 60°). Precipitation of the high melting isomer (para compound) took place at once. After half an hour this was filtered off and crystallized from benzene, when a compound melting at 128° with decomposition was secured. Repeated crystallization from the same solvent gave pale yellow plates melting at 134° with decomposition. The substance so obtained has the nitro group in the para position as respects hydroxyl, and is 2, 6 dibromo 4 nitro m-cresol. A small yield was obtained.

When the filtrate from the chloroform-ligroin mixture specified above was allowed to evaporate, it left a yellowish red, sticky mass which, after repeated crystallizations from alcohols, gave a small yield of deep yellow needles melting at 87°. This compound is isomeric with the nitro product mentioned above, and has the nitro group adjacent to the hydroxyl.

Due to difficulties encountered in the separation of the isomers it was decided to use some other method to obtain the desried nitro dibromo product.

Para nitro m-cresol, (m. p. 129°) the nonvolatile product previously mentioned in the nitration of m-cresol, was the starting point for this proceedure. Fifty-eight grams of the compound were dissolved in 450 cc of glacial acetic acid. The mixture was cooled to about 15° - 20° and a mixture of 40 cc of bromine dissolved in 200 cc of glacial acetic acid was slowly added. After the addition was complete, the whole was poured with stirring into 5 volumes of water, and the mixture set aside for some hours to allow the precipitate to subside. At the end of this time, the yellow brown solid was filtered off, and dried on a clay plate. The crude product was then crystallized several times in ethyl alcohol. A yield of 56.9 grams of pure product was obtained, melting at 134°.

It was decided that this proceedure was much more efficient than the method suggested by Raiford.

The hydrochloride of 2, 6 dibromo, 4 amino m-cresol was naxt prepared by the following proceedure - Fifty grams of the p-nitro compound was dissolved in 200 cc of hot alcohol, and to this solution was added 130 grams of stannous chloride dissolved in 130 cc of concentrated hydrochloric acid, during the addition, the flask was shaken and the mixture kept hot in order to prevent the immediate separation of crystals. Next one volume of concentrated hydrochloric acid was added and the solution set aside to cool. Crystals of the amino hydrochloride soon separated out. These were filtered off and recrystallized as follows: The crude material was dissolved in warm water and the solution filtered through paper, after which one volume of concentrated hydrochloric acid was added to the filtrate. Upon standing, colorless needles were separated. When heated above 225° the substance blackened but did not melt. (Raiford, Am. Chem. Journal, 46, 426; 1911)

The free amine was easily prepared from the hydrochloride by treatment of an aqueous solution of the latter with ammonium carbonate. The precipitated base, after being filtered off, washed well with water and dried on a clay plate melted at 175° - 176° with blackening. It is readily soluble in alcohols, benzene, chloroform and a solution of sodium hydroxide, less soluble in ligroin and practically insoluble in colorless crystals melting at 176°. (Raiford, Am. Chem. Journal, 46, 426; 1911)

For the replacement of NH_2 with hydrogen it was found that the diazotization could be carried out just as efficiently from the hydrochloride as from the free base. The ammonium carbonate method of releasing the free amine was found to give very small yields, and the operation itself was cumbersome.

The diazotization was carried out according to a procedure used by Bigelow, Johnson and Sandborn (Org. Synthesis, Vol. 6, 16) for the preparation of m-bromo-toluene.

To a cold mixture of 48 cc of 95% ethyl alcohol and 12 cc of sulphuric acid in one liter round bottom flask, provided with an efficient mechanical stirrer, was added 20 grams of the hydrochloride of 2, 6 dibromo, 4 amino m-cresol. The solution was stirred and cooled to 10° and a solution of 9 grams of U.S.P. sodium nitrite in 16 cc of water was added from a separatory funnel. During this addition, the temperature of the mixture was not allowed to rise above 10°. After all the nitrite solution had been added, the mixture was stirred twenty minutes longer to complete the diazotization.

To the diazotized solution was added 3 grams of copper (reduced copper powder) which had been washed with ether. The stirrer was replaced by a long efficient, reflux condenser. A bath of ice water was prepared for cooling the flask when the reaction became too vigorous. The flask was warmed cautiously until a vigourous evolution of gas began. It was then immersed in the ice water to prevent loss through the condenser by too rapid evaporation of nitrogen and acetaldehyde. When the reaction had moderated, the flask was again warmed, and finally the mixture was heated for ten minutes on a steam bath. At the end of the reaction the color changed from reddish brown to yellow.

After the addition of 120 cc of water, the mixture was steam distilled as long as any oil came over. The crude, heavy yellow oil was washed with water, extracted with ether, and after the evaporation of the ether was distilled at 4 mm. The bulk of the yellow oil (8.3 grams) came over at 114°-116°. This boiling point corresponds with that of the fractions

assumed to be 2, 6 dibromo m-cresol, obtained in the preparation of the 2 bromo m-cresol by sulfonation.

To further prove the positions of the bromine a portion was brominated in carbon tetrachloride solution with one mole of bromine. The product after repeated crystallization from ethyl alcohol had a melting point of 81°, which corresponds to the melting point of 2-4-6 tribromo m-cresol.

Analysis for the 2, 6 dibromo m-cresol by the Parr bomb method gave the following results:

Wt. of Sample	cc .1 N $AgNO_3$	Calculated Br in $C_7H_6OBr_2$	Found
.2057	15.5	60.15%	60.32%

Since, in the preparation of 2 bromo m-cresol by sulphonation, a portion was consistently separated which gave evidence of being 2, 6 dibromo m-cresol, an attempt was made to develop a proceedure which would give a fairly good yield of this product. The following method was eventually decided upon.

One mole (108 grams) of m-cresol and one mole (98 grams) of concentrated sulphuric acid in a two liter three necked flask were heated on a water bath for three hours. At the end of this time the reaction mixture was cooled and made alkaline by adding a solution of 160 grams NaOH in 373 cc of water. (This must be done very slowly). The alkaline solution was then cooled to room temperature and brominated by

adding slowly two moles (320 grams), of bromine, still stirring constantly. (During this operation the temperature may rise to 40° - 50°). Stirring was continued for about half an hour after all the bromine was added.

The reaction mixture was then transferred to a three-liter flask set for steam distillation. During the steam distillation the reaction mixture was heated on an oil bath to about 150°. This removed the tribromo m-cresol which appeared as only a trace.

As soon as no more tribromo m-cresol appeared in the distillate, the steam distillation was stopped and the reaction mixture, still on the oil bath was evaporated to a thick pasty mass. This was allowed to cool and then acidified with about 800 cc of concentrated sulphuric acid. This had to be done slowly on account of the rapid evolution of hydrogen bromide.

The mixture was again steam distilled, this time from an oil bath heated to 200° - 210°. The sulphonic acid was hydrolysed by this proceedure and the brominated cresols distilled over as a heavy, pale yellow oil.

After the distillation was complete, the brominated cresols were extracted with ethyl ether, the ether evaporated and the residue distilled under 4 mm. pressure.

Following are the fractions from 80 cc of distillate (one run):

100 - 110° - - - - - - - - 16.3 grams
110 - 120°(mostly 114-115°) 45.8 grams
120 - 130° - - - - - - - - 4.3 grams
130 - 145° - - - - - - - - 16.9 grams

The last portion crystallized and on purification from ethyl alcohol was found to be tribromo m-cresol (2, 4, 6).

Analysis of the 110 - 120° fraction which on distillation with an eight inch column (4 mm.) boiled at 114 - 115° gave the following Parr bomb analysis:

Wt. of Sample	cc .1 N $AgNO_3$	Calculated Br. in $C_7H_6OBr_2$	Found
.2145	16.07	60.15%	59.95%

A portion of 2, 6 dibromo m-cresol chlorinated in carbon tetrachloride with one mole of chlorine, gave a crystalline compound which, when recrystallized repeatedly from alcohol had a melting point of 70.5°. (Walther and Zipper J. pr (2) 91, 378).

To recheck this 4 chloro, 2, 6 dibromo m-cresol, a portion of 4 chloro m-cresol (m. p. 55°) obtained from H. Chen of this laboratory, was brominated in carbon tetrachloride with two moles of bromine. Identical crystals of the same melting point were obtained.

The benzoyl, benzene-sulfonyl and toluenesulfonyl esters of 2, 6 dibromo m-cresol were prepared. Following are the melting points and results of analysis by the Parr bomb method:

Esters of 2,6 dibromo m-cresol

	m.p.	Wt. of Sample	cc .1 N Ag NO3	Calcul. for Br	Found
Benzoyl	91°	.2354	12.77	43.24%	43.40%
Fine white needles from alcohol					
Benzene sulfonyl	95°	.1633	8.07	39.41%	39.52%
Small white plates from alcohol					
Toluenesulfonyl	122°	.2190	10.43	38.00%	38.09%
Fine white needles from alcohol					

Several attempts to nitrate the 2, 6 dibromo m-cresol yielded rather peculiar results. When four moles of nitric acid were used in glacial acetic acid, a compound of fine yellow crystals was separated. An analysis for bromine suggested that two bromine atoms were present and one nitro group. It melted at 78 - 78.5°.

Wt. of Sample	cc .1 N $AgNO_3$	Calculated Br in $C_7H_5O_3NBr$	Found
.2189	13.9	51.47%	50.79%

The only nitro-bromo m-cresol reported in literature with this melting point is 2, 6 dinitro 4 bromo m-cresol. The writer will make no attempt to explain these peculiar results.

Since the benzoyl, benzene sulfonyl, and toluenesulfonyl esters of 2, 4 dibromo m-cresol and 2, 4, 6 tribromo m-cresol had not yet been prepared, these esters were prepared by the usual method. Following is a table of melting points and results of Parr bomb analyses:

Esters of 2, 4 dibromo m-cresol

	m.p.	Wt. of Sample	cc .1 N $AgNO_3$	Calcul. for Br	Found
Benzoyl	81°	.1806	9.75	43.24%	43.18%
Fine white needles from alcohol					
Benzene sulfonyl	92°	.2445	12.07	39.41%	39.49%
Small white plates from alcohol					
Toluenesulfonyl	89½°	.2269	10.8	38.00%	38.13%
Small white plates from alcohol					

Esters of 2, 4, 6 tribromo m-cresol

	m.p.	Wt. of Sample	cc .1 N $AgNO_3$	Calcul. for Br	Found
Benzoyl	85°	.2063	13.77	53.45%	53.39%
Small white needles from alcohol					
Benzene sulfonyl	117°	.2996	18.42	49.28%	49.20%
Small white plates from alcohol					
Toluene sulfonyl	113°	.2225	13.4	48.09%	48.17%

THE BACTERICIDAL PROPERTIES OF DERIVATIVES OF M-CRESOL

In the preparation of the bromo derivatives of m-cresol, a number of nitro, amino and sulphonic acid derivatives were also prepared. It was felt that if the phenol coefficients were determined for each of these, some interesting conclusions might be drawn as to the relationship between bactericidal properties and chemical constitution.

The method used for these determinations is known as the F. D. A. method.

Organism - A twenty-four hours old broth culture of Staphylococcus pyogenes aureus.

Temperature - 37°.

Proportion of culture to Disinfectant - Five-tenths cc of the broth culture was used, added to 5 cc of the disinfectant solution.

Incubation - The subcultures were incubated forty-eight hours at 37° C and the results tabulated.

Determination of the coefficient - Subcultures were made every five minutes up to and including fifteen minutes. To determine the coefficient, the figure representing the degree of the weakest strength of the disinfectant that killed in the ten minutes was divided by the figure representing the degree of dilution of the weakest strength of the phenol control that killed within the same time.

Following are the results:

	Compound	Phenol Coefficient
1.	3 methyl 4 bromo phenol	9
2.	3 methyl 6 bromo phenol	6
3.	3 methyl 2 bromo phenol	5
4.	3 methyl 2 nitro phenol	4.5
5.	3 methyl 4 nitro phenol	5.0
6.	3 methyl 6 nitro phenol	4.5
7.	3 methyl 2 amino phenol	6.0
8.	3 methyl 6 amino phenol	5.5
9.	3 methyl 6 amino (hydrochloride) phenol	3.8
10.	3 methyl 4 Na sulphonate phenol - less than	2.0
11.	3 methyl 4 Na sulphonate 2, 6 dibromo phenol - less than	2.0
12.	3 methyl 2-4 dibromo phenol	16.0
13.	3 methyl 2-6 dibromo phenol	19.0
14.	3 methyl 2-4-6 tribromo phenol	23.0
15.	3 methyl 4 nitro, 2, 6 dibromo phenol	7.5
16.	3 methyl 4 amino, 2, 6 dibromo phenol	5.0
17.	3 methyl 4 amino (HCl) 2, 6 dibromo phenol	6.5

Conclusions:-

1. The halogenated cresols increase in bactericidal efficiency with the increase in number of halogen atoms added to the ring.

2. Amino, nitro, and SO_2ONa groups added to the ring retard very greatly the efficiency of a brominated m-cresol.

3. Nitro, amino, and monobromo groups substituted into any one of the isomeric 2, 4, 6 positions approximately double the phenol coefficient of m-cresol; additional bromine substitution does not increase the phenol coefficient except in the case of dibromo and tribromo m-cresols.

The fact that the sodium sulphonates of m-cresol and their bromine derivatives show a phenol coefficient of less than mOcresol itself can be explained in part to the fact that sulphonates though quite easily prepared, crystallize with one (1) to three (3) moles of water.

SUMMARY

The results of this work on the bromo m-cresols may be summarized in the following way.

6 bromo m-cresol has been prepared by the following methods:

1. Diazotization of 6 amino m-cresol
2. Bromination of the disulphonic acids in alkaline solution and subsequent hydrolysis.
3. Bromination of the disulphonic acid in the presence of fuming sulphuric acid and subsequent hydrolysis.

2 bromo m-cresol has been prepared by the following methods:

1. Diazotization of 2 amino m-cresol.
2. Bromination of the disulphonic acid in alkaline solution and subsequent hydrolysis.
3. Bromination of the disulphonic acid in the presence of fuming sulphuric acid and subsequent hydrolysis.

2, 6 dibromo m-cresol has been prepared by the following methods:

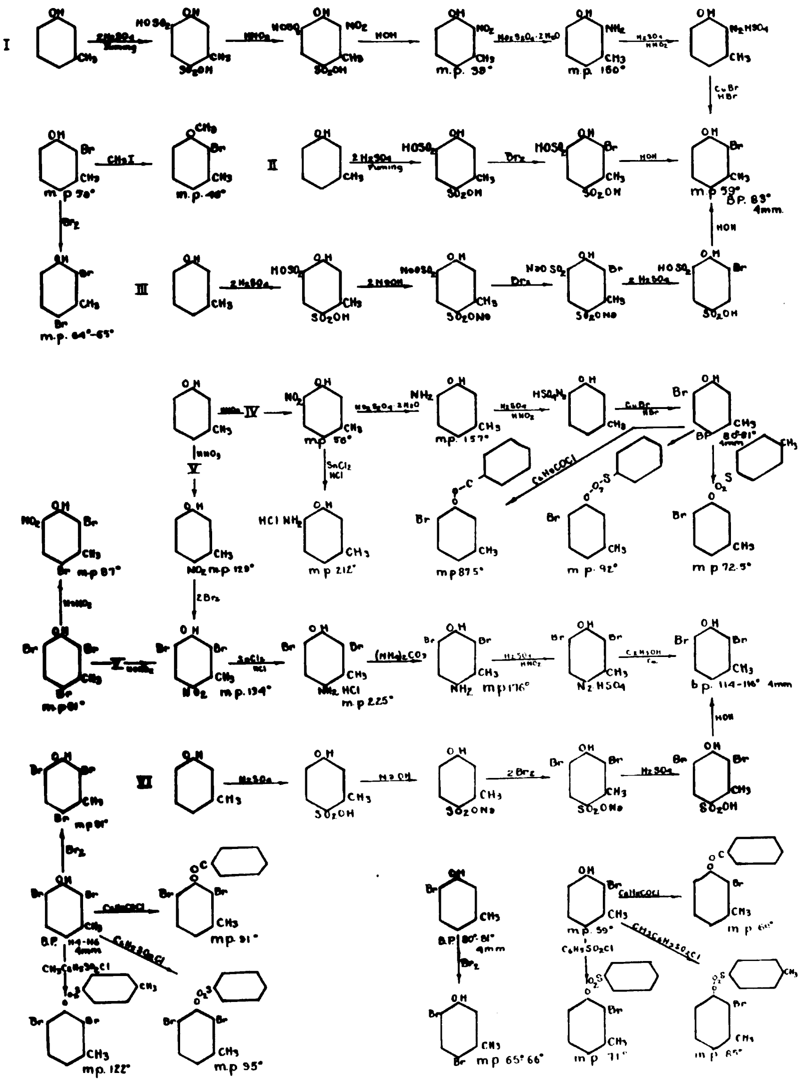
1. Diazotization of 2, 6 dibromo 4 amino m-cresol
2. Bromination of the para-sulphonic acid and subsequent hydrolysis.

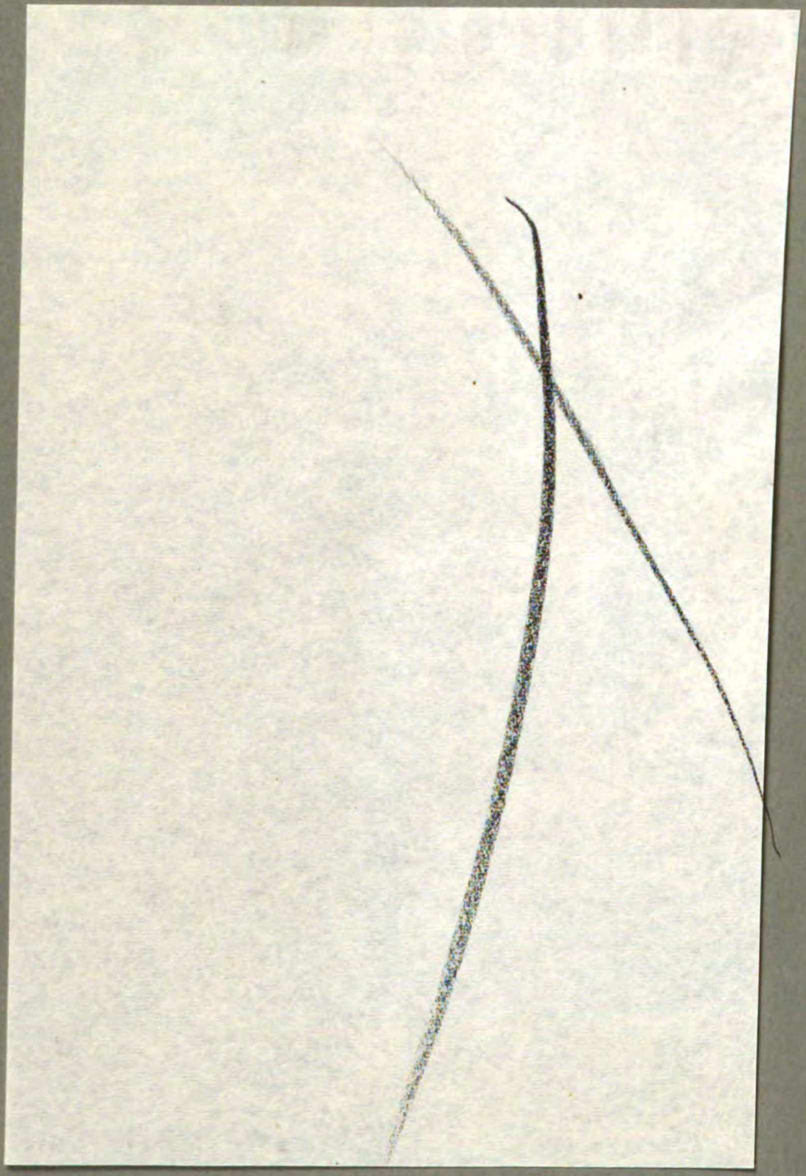
The benzoyl, benzene sulfonyl and toluenesulfonyl esters of these compound have been prepared.

The phenol coefficients of all intermediates produced in this problem have been determined.

SOME BROMO DERIVATIVES OF m-CRESOL. II.

W.J. Peterson.





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