SOME BROMO DERIVATIVES OF M-CRESOL

THESIS FOR THE DEGREE OF M. S.

James Alfred Hutchinson

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THESIS

R.C. History

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SOME BROMO DERIVATIVES OF m-CRESOL

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HISTORICAL

Very little is known of the bromine derivatives of m-cresol. There may be two explanations of this peculiar circumstance. Either the previously high cost of m-toluidine or the difficulties encountered in the preparation and proof of their structures. At any rate the literature contains very little on the subject. The very discouraging results which I have obtained, has led me to believe that it is perhaps the latter reason as to why more previous work has not been done on such a common organic substance.

Neville and Winther in 1882 (Ber. 15, 2991) prepared a m-brom-cresol by the diazotization of m-brom-m-toluidine. The diazoting agent used was sodium nitrite, and the diazonium salt thus formed was decomposed with water. They obtained a mono brom m-cresol melting at 56-57°.

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

2-4-6 tribrom m-cresol was also prepared by Werner (Bl. Soc. Chem. 2, 46, 276). Much the same method as that described by Claus and Hirsch was used. The only difference being that water was used as a solvent instead

of chloroform. They obtained a product which melted at 81-82°.

In 1898, Bodroux (Compt. rend. 126, 1282-85) found that when m-cresol was treated with bromine in the presence of aluminum chloride, a tetra brom m-cresol was formed which melted at 194°.

Auwers and Richter (Ber. 32, 3382) prepared 2-4-6 tribrom m-cresol but the reduction of 2-4-6 tribrom 3-oxy benzyl bromide. The reduction was accomplished by the use of zinc and acetic acid. Their product melted at 84°, thus checking the work of Claus and Hirsch.

Gibbs and Robertson (J. Chem. Soc. 1914, 2, 1885) prepared a dibrom m-cresol to which they assigned the formula 4-6 dibrom m-cresol. This was accomplished through the diazotization of 4-6 dibrom m-toluidine which was prepared by the bromination of acet-m-toluidine in the cold. The dibrom m-cresol thus prepared 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 6-brom m-cresol which under our system of naming would be 4-brom m-cresol. They prepared this compound by the addition of the calculated quantity of bromine in carbon tetra-chloride solution to m-cresol in the same solvent at-5° to -10°. They obtained a

compound melting at 62°. The melting point of the benzoyl derivative is given as 83-83.5°. However, they gave no proof of the structure of the compound whatsoever.

Bures and Balada (Cas. Ceskoslavenskeko Lekarnistra 6, 107-190, 1926) state that by bromination of m-cresol at ordinary conditions, without the aid of solvents or catalysts, 2-4-6 tribrom m-cresol is formed. Thus proving that the rule valid for amino derivatives of benzene is applicable in this case. The abstract from which this material was taken gives no proof for this assumption.

Hodgson and Moore (J. Chem. Soc. (1926), 2036-40) 4-brom m-cresol from the corresponding amino compound by diazotization. They give as the melting point of the cresol thus obtained 38°. The melting point of the corresponding amino derivative is given as 46°. Nothing in the literature which I have been able to find, in any way corresponds to these figures. They give no proof of their structures of either the cresol or the amino compounds.

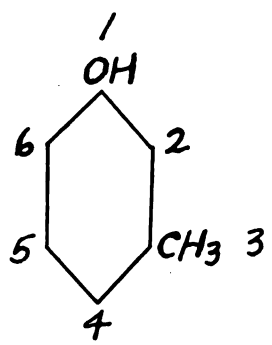
Bures (Chem. Listy. (1927) 21, 221-227) makes the following rule for substitution of halogens in m-cresol. "Chloro or bromo substitution products of m-cresol follow the same rule as for halogen substitution

in amino or hydroxy derivatives of benzene. In m-cresol halogen derivatives in the 4 and 6 positions to the hydroxy group are most likely."

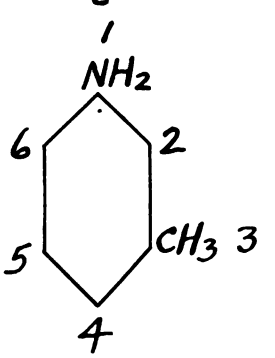
I believe this to be a fairly thorough review of the literature on the subject of bromination of m-cresol. It is very plainly seen that there is little if any conclusive evidence as to the exact structure of the brom m-cresols described. It will also be noted that in many cases the material is very conflicting.

EXPERIMENTAL

Throughout this work we will speak of the derivatives of m-cresol as occupying one of the positions as indicated below.



For the toluidines we will use a similar method of numbering starting with the amino group.



This will, I hope, make it much easier for those reading this work to understand. Since some writers prefer to start numbering with the methyl group rather than the hydroxyl.

MONO BROM - META CRESOLS

One mole of m-cresol (108 gm.) was dissolved in chloroform and placed in a tall-form liter beaker, which was fitted with a mechanical stirrer. The beaker was placed in a freezing mixture of salt and ice and cooled to 0° to -10°. This temperature was maintained throughout the addition of bromine.

One mole of bromine (160 gm.) in chloroform solution was then slowly added from a dropping funnel. The mixture being stirred very rapidly during the addition to prevent local heating. A copious evolution of hydro bromic acid followed. When all the bromine was added, the mixture was stirred for half an hour to insure complete reaction. The mixture was then allowed to stand over night to eliminate most of the hydrobromic acid.

The brominated m-cresol was then transferred to a distilling flask and the chloroform removed. The remaining oil was then distilled in vacum (16 mm), the following fractions collected:

below 100° ---------- liquid

100-120° ---------- liquid

120-130° ---------- liquid

130-140° ---------- solid

The fourth fraction was recrystalized several times from petroleum ether to a constant melting point of 56-57°. The second and third fractions were combined and distilled at ordinary pressure. In this fraction was found a small quantity of unchanged m-cresol and 26 gm. of material which had a constant boiling point of 205-208° at 731 mm. of pressure. This fraction, I believe, is the 6-brom m-cresol. The proof of this compound will be taken up later.

The 4-brom m-cresol crystalized in long white silky needles, which matted together when brought down out of concentrated solutions. Petroleum ether was found to be the best solvent for the 4-brom m-cresol, however it is soluble to some extent in water and may be crystalized from hot water.

Analysis by the Parr bomb method showed this compound to be a monobrom cresol.

Wt. of sample	cc .1N $AgNO_3$	Calculated for Br.	Found
.2314	12.51	.4278	.4259
.2165	11.71	.4278	.4265

As has been noted in the historical part of this paper, Wather and Zipper (J. pr. chem. (1915) 91, 364-414) prepared a brom m-cresol in much the same

manner. They assigned the formula 6-brom m-cresol. The formula is possible by numbering from the methyl group. However, they give as the melting point of the compound 62°. The compound which I obtained in almost the same manner melts about 6° lower or 56-57°. The melting point of the in benzoyl derivative 83-83.5° however, checks rather closely to the one which I obtained 82.5-83°. There was no proof of the structure of the compound given in the article.

To prove the structure of the 4-brom m-cresol, I attempted its preparation through the diazotization of 4-brom m-toluidine. This task was accomplished in the following manner.

Acet-m-toluidide was prepared according to the procedure outlined by Gibbs and Robertson (J. Chem. Soc. 1914 2, 1885) from the preparation of 4-6 dibrom m-toluidine. Thirty grams of m-toluidine was boiled four hours with slightly more than the theoretical amount of acetic anhydride. Water was added to decompose the unchanged anhydride and the volume made up to 500 cc with glacial acetic acid. Bromine (45 gm. 1 mole) in acetic acid solution was then slowly added in the cold. Upon addition of water the compound separated out as a white crystaline solid. The crystals were filtered off and dried between pads of filter paper. When recrystalized from alcohol the 4-brom

acet-m-toluidide melted at 107-108°.

For the general purposes of this experiment, purification is not necessary. The dried 4-brom acet-m-toluidide was boiled for two hours with the calculated amount of 20% alcoholic potassium hydroxide to remove the acyl group. Upon cooling the 4-brom m-toluidine seperated out and was filtered off. The mother liquor was concentrated and a second crop of crystals obtained. After several recrystalizations from alcohol the 4-brom m-toluidine melted at 79-80°.

After purification of the amine by crystalization, it was dissolved in much boiling dilute hydrochloric acid. Upon cooling the hydrochloride separates as fine white needles. The calculated quantity of sodium nitrite in water solution was then added in the cold. The mixture was stirred constantly until all the hydrochloride dissolved. After about two hours standing the diazonium chloride was decomposed by heating on the water bath for half an hour. During this period of heating, nitrogen was evolved and the solution took on a reddish brown color with a layer of dark oil on the top.

The mixture was then subjected to distillation with steam. A yellow oil came over, which on standing turned to a brown. The oil was salted out and extracted with ether. The ether was removed on the water bath and

the resulting oil treated with dilute sodium hydroxide to dissolve out the substituted m-cresol. The alkaline solution was filtered and the filtrate acidified with hydrochloric acid. (It is best to again salt out the oil before extraction with ether, as it was found that the brom cresol was quite soluble in water).

The ether was evaporated off. The remaining oil solidified on standing. After repeated crystalizations from petroleum ether the 4-brom m-cresol melted at 55-56°. It will be noted here that the 4-brom m-cresol prepared in this way has the same melting point as the solid brom m-cresol obtained by direct bromination.

Analysis of the 4-brom m-cresol prepared in this manner showed it to be a mono brom m-cresol.

Wt. of sample	cc .1N $AgNO_3$	Calculated for Br.	Found
.2384	12.9	.4278	.4266
.2018	10.95	.4278	.4272

The yield was exceptionally good for this type of reaction. Ten grams of the amine yielding two and one half grams of the brom cresol or a 25% yield.

Further proof that these were the same compounds was afforded through the preparation of the benzoyl, benzene sulfon, and the toluene sulfon esters of both

Compounds. The esters were all prepared by the Schotten-Baumenn reaction.

The benzoyl esters crystalized from alcohol in fine white fluffy needles. The melting point was found to be 82.5-83°. Analysis gave the following results:

Wt. of Sample	cc .1N Ag NO_3	Calculated for Br.	Found
.2015	6.98	.2749	.2732

The benzene sulfon esters crystalized from alcohol in fine white needles very similar to the benzoyl ester. The melting point of this compound was found to be 79-80°.

Wt. of sample	cc. .1N Ag NO_3	Calculated for Br.	Found
.2205	6.84	.2446	.2419

The toluene sulfon ester crystalized from alcohol in small shinny plates which matted together. The melting point was 84-85°.

Wt. of sample	cc .1N $AgNO_3$	Calculated for Br.	Found
.2113	6.23	.2346	.2325

The next task was to prepare and prove the structure of the 6-brom m-cresol. This proved to be a very difficult one but I believe it has been accomplished. Because there are so many steps to be taken in arriving at the desired end, the yields are cut down to such an extent that only very small quantities of the desired products are obtained.

p-Toluidine was acylated according to the directions given by Johnson and Sandborn (Org. Syn. Vol. 6, 8). 214 gms. of p-toluidine was boiled two hours with 800 cc of glacial acetic acid. On cooling the acet-p-toluidine separated as a crystaline mass. The crystals were filtered off and dried between pads of filter paper. When recrystalized from alcohol the acylated toluidine melted at 145-146°. However, for our general purpose this is not necessary.

The dried acet-p-toluidide was then nitrated according to the method described by Kuhlberg (Am. 158, 134). 100 gms. of acet-p-toluidide was added in small quantities (5 gm) to 400 gm. of concentrated nitric acid (sp. gr. 1.45). The temperature was maintained between 30 and 40 degrees during the addition. (The nitro group

will enter the ring in the ortho position to the amino group since the para position is already filled by the methyl group). The acid solution was then poured into cold water. The o-nitro acet-p-toluidide separated out in fine yellow crystals. When crystalized from alcohol the compound melted at 92-93°.

The acyl group was then removed by cooking with alcoholic potassium hydroxide . It is very essential in this hydolysis that only slightly more than the theoretical amount of alkali be used. After two hours heating, the o-nitro p-toluidine separated as a brick-red substance. This compound when recrystalized from alcohol melted at 114-115°.

The amino group was then replaced with bromine. This was accomplished by the diazonium perbromide reaction as described by Bulow and Schmactenberg (Ber. 41, 2609). Sixteen and four tenths grams of nitro toluidine was treated with 30 gms. of concentrated hydrochloric acid and warmed. The nitro toluidine changed from a brick-red color to a salmon color. The mixture was cooled and 60 gms. of ice added, and the vessel placed in an ice bath. Ten grams of sodium nitrite in 30 cc of water was then added with constant stirring. The temperature being maintained at 0°.

Bromine (29.7 gm.) in a water solution of

17.8 gm. of potassium bromide was then slowly added from a dropping funnel. When all the bromine had been added the mixture was stirred for several minutes to make certain all the bromine had reacted. The orange-red percipitate, (diazonium perbromide), was filtered by suction and washed with water, absolute alcohol, and ether. Small amounts of the washing agents being used. The diazonium perbromide was then placed in a beaker and covered with absolute alcohol. The alcohol was warmed to effect decomposition of the perbromide. (It will be interesting to note that 95% alcohol works equally as well in this decomposition). Care must be exercised in heating that the decompisition does not become too violent. During the decomposition, nitrogen was evolved and the odor of acet aldahyde became very prominent.

When nitrogen ceased to be evolved, the alcohol was removed by distillation and the resulting oil distilled with steam. The p-brom m-nitro toluene distilled over as a very insoluble yellow oil, which settled to the bottom. The oil was separated from the water layer. On standing it solidified. (Chilling is some times necessary to cause the compound to solidify). When recrystalized from alcohol the p-brom m-nitro toluene melted at 31-32°. I found that the perbromide

method affords an excellent means of replacing an amino group with bromine. From a number of runs and average yield of 60% was obtained.

The p-brom m-nitro toluene was then reduced by tin and hydrochloric acid to 6-brom m-toluidine. The reduction appears to take place very smoothly, but yields were very low. Some trouble was also encountered in causing the amine to crystallize. One sample did crystallize and a melting point of it was obtained. The melting point 32-33° checks very well with that given by Neville and Winther (Ber. 13, 972) 31-32°, considering the temperature at which the compound melts. On other runs the 6-brom m-toluidine remained as an oil and would only solidify upon freezing. This liquid had a boiling point of 115-118° at 16 mm. Wroblewsky (Ann. 168, 177) gives a melting point of 68° for this compound but in refuting Neville and Winthers work fails to give any proof of the structure.

The 6-brom m-toluidine was then dissolved in much boiling dilute hydrochloric acid. Upon cooling the hydrochloride separated as white crystaline solid. The mixture was cooled to 0° and the calculated amount of sodium nitrite in water solution was added with constant stirring. After standing about two hours the

the diazonium salt was decomposed by heating on the water bath. During the period of heating nitrogen was evolved and the solution took on a dark color.

The mixture was then subjected to steam distillation. A yellow-red oil distilled over. The oil was salted out and extracted with ether. The ether was removed on the water bath and the resulting oil dissolved in dilute sodium hydroxide. The alkaline solution was filtered and the filtrate acidified with hydrochloric acid. The oil was again salted out and extracted with ether. The ether was removed on the water bath and the resulting oil distilled at ordinary conditions. It came over at 206-208° at 731 mm.

Analysis by the Carius method for bromine proved the compound to be a mono brom cresol.

Wt. of sample	gm. Ag. NO_3	Calculated for Br.	Found
.2855	.12586 .2829	.4278	.4220

The boiling points of the oil obtained by direct bromination and the 6-brom m-cresol prepared in this way gave every indication that they were the same compounds;

Boiling point of brom cresol from direct bromination 205-208°. Boiling point of brom cresol from amine

bromination 206-208°. Both boiling points were taken on the same day, the pressure being 731 mm.

Further proof of the two compounds was attempted by preparation of the benzoyl esters of both compounds. Due to the quantity of the two compounds at hand very small amounts of them were used in preparing the esters. Neither one has solidified as yet, and the quantity of oil is much too small to determine a boiling point.

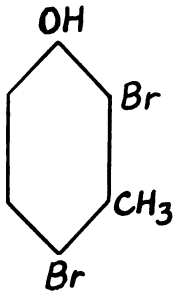
The toluene sulfon esters were also prepared in small quantities, and they too remain as a liquid.

DI BROM META CRESOLS

Our attention next turned to the dibrom m-cresols. It was discovered that when m-cresol was treated with two moles of bromine in chloroform solution, two definite dibrom m-cresols were formed. Because one appeared to be a solid and the other a liquid, it was decided that the solid dibrom m-cresol had the structure 2-4 dibrom m-cresol. This left the only probable structure of the liquid dibrom cresol to be 4-6 dibrom m-cresol.

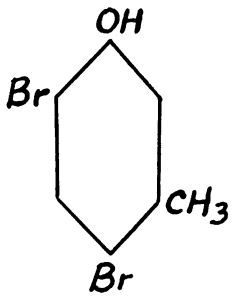
These assumptions were made in view of the following structures.

I



M.P. 64-65

II



B.P. 132-135 16 mm.

Because formula I was more compact it was only reasonable to believe that it was the solid compound. It will also be noted that formula II is very symetrical, and therefore should also be a solid compound.

The formation of dibrom m-cresol by direct bromination was accomplished in much the same manner as that described for the preparation of 4-brom m-cresol. One mole of m-cresol was dissolved in chloroform and cooled to 0°. Two moles of bromine in the same solvent was slowly added with constant stirring. After evolution of hydrobromic acid had ceased, the chloroform was removed and the resulting oil fractionally distilled at 16 mm of pressure.

Fraction	
below 100°	liquid
100 - 120°	liquid
120 - 130°	liquid
130 - 140°	solid

The first three fractions were very small and were disregarded. The fourth fraction was recrystallized several times from petroleum ether to a constant melting point 64-65°. At the end of the crystallizing the mother liquor contained a quantity of oil which would not solidify. The oil had a boiling point of 132-135° at 16 mm of pressure.

Analysis of the solid compound showed it to be a dibrom cresol:

Wt. of sample	cc .1N $AgNO_3$	Calculated for Br.	Found
.2545	19.7	.6015	.5993
.2312	17.61	.6015	.6001

An attempt was then made to distinguish between these two dibrom m-cresols. Gibbs and Robertson (J. Chem. Soc. 105, 1885) outlined a method for the preparation of 4-6 dibrom m-cresol. Since the two assumptions already made, gave one of the dibrom cresols this structure it was decided to follow these direction for the preparation of the compound.

Thirty grams of m-toluidine were boiled four hours with slightly more than the theoretical of acetic anhydride. Water was added to decompose the unaltered anhydride and the volume made up to 500 cc. with glacial acetic acid. Two moles of bromine (90 gm.) in acetic acid solution were then slowly added in the cold with constant stirring. The temperature was maintained about 0° during the addition of the bromine. On addition of water the product separated as a white crystaline solid. Recrystallized from alcohol the 4-6 dibrom acet-m-toluidide melted at 167-168°.

Upon cooking with alcoholic potassium hydroxide the acyl group was removed and the 4-6 dibrom m-toluidine

was obtained by distillation with steam. After several crystallizations from alcohol the 4-6 dibrom m-toluidine melted at 74.5-76°. Neville and Winther (Ber. 13, 972) give 75-76° for the melting point of this compound. The procedure was varied slightly from that given by Gibbs and Robertson, since they did not purify the amine before proceeding with the diazotization.

After purification of the amine by crystallization from alcohol, it was dissolved in much boiling dilute hydrochloric acid. Upon cooling the hydrochloride separates as fine white needles. The calculated quantity of sodium nitrite in water solution was then slowly added in the cold. After about half an hour of stirring practically all the hydrochloride had dissolved. The diazotized mixture was then allowed to stand for two hours before decomposition by heating was started. When heated on the water bath nitrogen was evolved and the solution became dark colored with a layer of dark oil on the top. The mixture is then subjected to distillation with steam.

A yellow-red oil distills over which has a very characteristic quinone odor. This oil was salted out and extracted with ether. The ether was removed on a water bath and the resulting mixture dissolved in dilute alkali and filtered. (This separates the 4-6

dibrom m-cresol from the 4 brom toluquinone). The filtered alkaline solution was acidified with hydrochloric acid and the oil again salted out. The 4-6 dibrom m-cresol was then extracted from the acid solution with ether. Upon evaporation of the ether the 4-6 dibrom m-cresol solidified and was pressed between pads of filter paper to remove any oily impurities.

After several recrystallizations from petroleum ether the 4-6 dibrom m-cresol melted at 65-66°. Gibbs and Robertson, whose procedure was followed in preparing this compound, gave 55° as the melting point. The first melting point taken checked this figure very well, but after several crystallizations from petroleum ether the constant melting point was 65-66°.

When the oil obtained from direct bromination of m-cresol was seeded with a crystal of the 4-6 dibrom m-cresol, it readily solidified. After chilling in the ice chest, the crystals were pressed between pads of filter paper to remove the oily impurities and recrystallized from petroleum ether. When pure, the crystals melted at 65-66°. This gave every indication that the two previous assumptions were correct.

That there are two dibrom m-cresols can readily be seen in the manner in which they come down when crystallized from petroleum ether. The 2-4 dibrom

m-cresol crystallizes in long, fine white or slightly pink cyrstals, which matt together. The 4-6 dibrom m-cresol, when crystalized from petroleum ether, comes down in fine white crystals which cling to the sides of the beaker. The 2-4 dibrom m-cresol crystallizes very easily, while the 4-6 dibrom m-cresol is very hard to crystallize. When the crystals of 4-6 dibrom m-cresol are scraped from the sides of the beaker, the crystals come down very rapidly and a pure product is hard to obtain.

To further prove the identity of the two compounds, the benzoyl ester of each was prepared. The ester of the 2-4 dibrom m-cresol when pure melted at 80-81°. The ester of the 4-6 dibrom m-cresol obtained from direct bromination melted at 84-85°, as did the ester of the 4-6 dibrom m-cresol which was prepared from the 4-6 dibrom m-toluidine.

Further proof was also afforded by the direct bromination of the 6-brom m-cresol previously prepared. In the 6-brom m-cresol, the bromine is in the ortho position to the hydoxyl group. This leaves vacant the para position, which should be the most reactive if m-cresol is to be considered as reacting the same as phenol. This being the case, when 6 brom m-cresol is treated with bromine we should have formed 4-6

dibrom m-cresol. This was found to be true, as when 6 brom m-cresol was brominated, a dibrom m-cresol was formed which melted at 65-66°, the same as the 4-6 dibrom m-cresol.

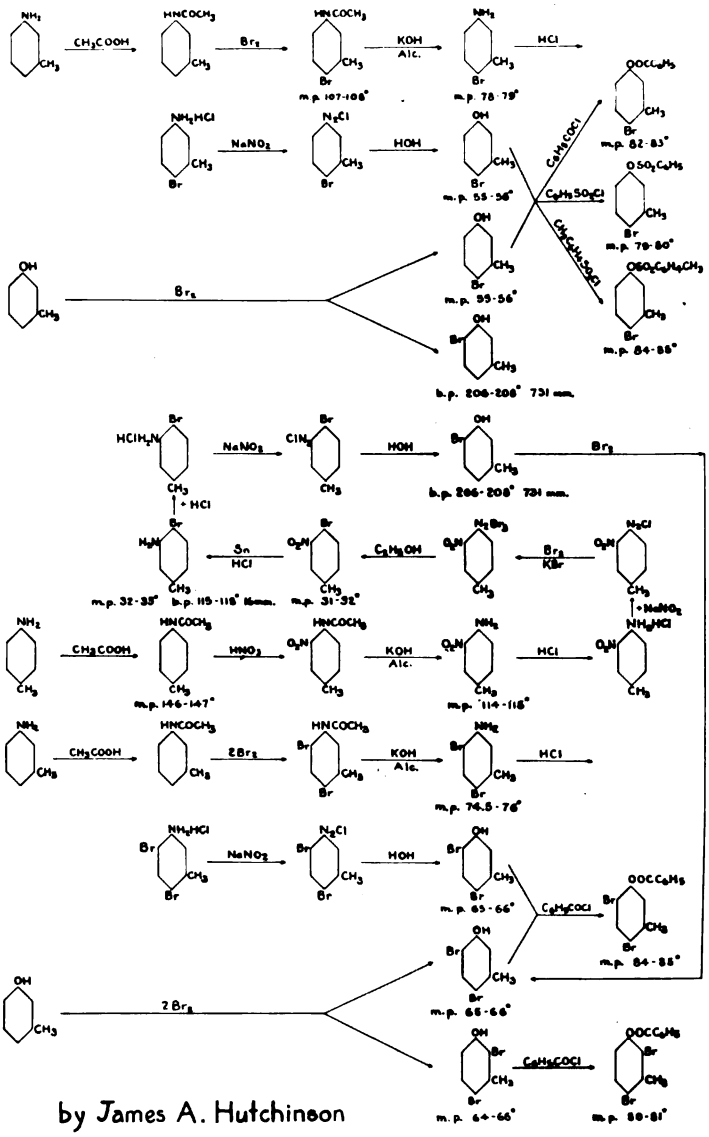
Following this same line of reasoning, it was thought that when the 4-brom m-cresol was brominated, both the 2-4 and the 4-6 dibrom m-cresols should be obtained. However, when the calculated quantity of bromine was added to 4 brom m-cresol, observing the usual precautions as to temperature, a very unusual result was obtained. A goodly quantity of the 4 brom m-cresol was recovered, and a small amount of material which melted at 83-84° was obtained. On further investigation it was found that the material checked very closely the melting point given in the literature for 2-4-6 tribrom m-cresol. I will not attempt to explain why such a reaction should take place, but may be taken up in future investigations.

SUMMARY

It has been shown that when m-cresol is treated in the cold with one mole of bromine, two definite mono brom m-cresols are formed. Namely, 4-brom m-cresol and 6-brom m-cresol being formed. I have attempted to prove the structure of both of these compounds by preparing them by diazotization of the corresponding toluidine.

It has also been shown that when m-cresol is treated in the cold with two moles of bromine two definite dibrom m-cresols are formed. The two dibrom cresols being 2-4 and 4-6 dibrom m-cresol. I have definitely established the formula of the 4-6 dibrom m-cresol by preparing it from the corresponding toluidine. The structure of the 2-4 dibrom m-cresol has also been established if the laws of substitution of organic chemistry hold.

Some Bromo Derivatives of m-Cresol



by James A. Hutchinson