HALOGENATION OF PHENOL SULFONIC ACIDS

IN NITRO BENZENE

A Thesis

Submitted to the Faculty of the

Michigan State College of Agriculture and Applied Science

in partial fulfillment of the requirements for

the Degree of

Doctor of Philosophy

by

Arthur House Neeley

1935

ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. R. C. Huston for his advice and supervision in the accomplishment of this investigation.

TABLE OF CONTENTS

I N T R O D U C T I O N

For the most part, the methods recorded in the literature for the preparation of these halogenated phenols in which the halogens occur adjacent to the hydroxyl group are unsatisfactory. Either the preparation requires the use of expensive chemicals or the method is too involved or laborious and quite often the yields are extremely low.

This investigation was undertaken with the view of developing a more convenient efficient procedure for the production of these compounds, together with a study of the properties and structure of the less well known ones.

H I S T O R I C A L

A review of the literature reveals a great many methods for the preparation of ortho-mono- and dihalogenated phenols. A brief resume of this material follows:

O-BROMOPHENOL.

1. Direct bromination of phenol in various solvents.

Hübner, Brenken, Ber., 6, 171.

Gerdan, Proc., (1891), 64.

Holleman, Rinkes, Chem. Zentr., 1910 II

Meldola, Streatfield, J. Chem. Soc., 73, 681 (1898).

Dinwiddie, Kastle C. A. 6, 482 (1912).

Haines, J. Chem. Soc., 121, 2813 (1922).

Skraup, Beifuss, Bul. Soc. Chim., 48, 809 (1927).

2. Heating of 3-bromo-2-hydroxy benzoic acid in the presence of water at 180° for several hours.

Sellman, Grothman, Ber., 17, 2726.

3. Replacement of the amino group in o-bromoaniline with hydroxyl by means of a diazonnium intermediate.

Körner, Gazz. chim. ital., 4, 388.

Fettig, Mager, Ber. 8, 362.

Holleman, Rinkes, Rec. trav. chim. 30, 51.

4. Replacement of the amino group in 2-amino phenol with bromine by the Sandmeyer reaction.

Meldola, Streatfield, J. Chem. Soc., 75, 685.

5. Passing of bromine vapor through phenol at a temperature of 150-180°.

Merck D.R.P. 76597; Ber. 27, R 957.

Holleman, Rinkes, Rec. trav. chim., 30, 77.

6. Bromination of phenol sulfonic acid and carboxylic acid with a mixture sodium bromide and sodium hypobromite.

Obermiller, Ber., 42, 4361.

7. Slow bromination of a water solution of the sodium salt of phenoldisulfonic acid at room temperature and subsequent acid hydrolysis at high temperature.

Takagi, Kutani, J. Pharm. Soc. Japan, 517, 247 (1925).

Takagi, Kutani, C. A. 20, 2669.

Ballard, Organic Syntheses, Vol. XIV, page 14.

3. Bromination of phenol with a mixture of potassium bromide and dichlorourea.

Likhosherstov, J. Russ. Phys. Chem. Soc., 61, 1019, (1929). C. A. 24, 856.

2, 6-DIBROMOPHENOL.

1. Replacement of the amino group in 2,6-dibromoaniline with hydroxyl through a diazonnium intermediate.

Hienichen, Ann., 255, 281.

Orton, Coates, Burdett, J. Chem. Soc. 91, 51.

2. Replacement of the amino group of 2,6-dibromo-4-amino-phenol with hydrogen through a diazonnium intermediate.

Mohlau, Ber., 15, 2494.

3. Distillation of tetra bromophenolphthalien with concentrated sulfuric acid.

Baeyer, Ann., 202, 138.

4. Heating of tetra bromocyclohexane to 120-130°.

Wallach, Chem. Zentr., 1905 II, 676.

5. Heating of 3,5-dibromo-4-hydroxy benzoic acid to 165° in the presence of NaOH.

Pope, Wood, J. Chem. Soc., 101, 1827.

O-CHLOROPHENOL.

1. Direct chlorination of phenol in various solvents.

Faust, Müller, Ann., 175, 303.

Varnholt, J. prakt. Chem.(2) 36, 22.

Lossen, D.R.P. 156631, Chem. Zentr., 1904 II, 1486.

2. Treatment of phenol with sodium hypochlorite solution.

Chandelon, Ber., 16, 1749.

3. Heating of 2-chloro-phenol sulfonic acid-4 in an autoclave.

Hazard, Flamand D.R.P. 141751, Chem. Zentr., 1903 I, 1324.

4. Replacement of the amino group in o-chloroaniline by an hydroxyl group.

Beilstein, Kulatow, Ann., 176, 39.

5. Replacement of the amino group in o-aminophenol with chlorine.

Sandmeyer, Ber., 17, 2651.

6. Passing of chlorine through molten phenol at 150-160°.

Merck, D.R.P., 76597.

7. Chlorination of an 2,4-phenol disulfonic acid with subsequent hydrolysis of the sulfonic groups at 200°.

Takagi, Kutani, J. Pharm. Soc. Japan, 517, 247.

C. A. 20, 2669.

2,6-DICHLOROPHENOL.

1. Direct chlorination of melted phenol.

Holleman, Rec. trav. chim., 37, 97.

Fischer, Ann. (spl.), 7, 181.

2. Replacement of the amino group in 2,6-dichloro-4-amino-phenol with hydrogen by means of a diazonnium intermediate.

Seifert, Ann. (spl.), 7, 208.

3. Treatment of phenol with sodium hypochlorite.

Chandelon, Ber., 16, 1752.

4. Heating of 3,5-dichloro-4-hydroxy benzoic acid with calcium oxide.

Zincke, Ann., 261, 251.

5. Chlorination in alkaline solution of the sodium salt of p-phenol sulfonic acid and the removal of the sulfonic group by hydrolysis at a high temperature.

Tanaki, Kutani, J. Pharm. Soc. Japan, 541, 196 (1927).

C. A. 21, 2255.

6-BROMO-O-CRESOL.

1. Heating 5-bromo-4-hydroxy-3-methyl benzoic acid with lime.

Robertson, J. Chem. Soc., 93, 789.

6-CHLORO-O-CRESOL.

1. Heating the potassium salt of 3-chloro-2-hydroxy toluene sulfonic acid (5) with dilute sulfuric acid to about 150°.

Fahlberg, List & Co., D.R.P. 256345, Chem. Zentr.

1913 I, 866.

Kaschig, D.R.P. 160304, Chem. Zentr., 1905 I, 1448.

2-BROMO-M-CRESOL.

1. Reduction of 2-nitro-m-cresol to the corresponding amino and replacement of the amino group with bromine.

Hodgson, Beard, J. Chem. Soc., 127, 498 (1925).

2. Direct bromination of m-cresol in four volumes of fuming sulfuric acid and removing the sulfonic groups by hydrolysis

with steam at 180-200°.

Huston, Peterson, J. Am. Chem. Soc., 55, 3380 (1933).

4-BROMO-M-CRESOL.

1. Direct bromination of m-cresol in carbon tetrachloride at -5° to -10°. The compound melted at 62°. No proof of structure was given.

Walther, Zipper, J. pr. Chem. 91, 364-414.

2. Replacement of the amino group of 4-amino-m-cresol with bromine by diazotization. A melting point of 38° was obtained.

Hodgson, Moore, J. Chem. Soc., (1926) 2036.

3. Direct bromination of m-cresol in chloroform at -10°.

Huston and Hutchinson, J. Am. Chem. Soc. 54, 1504, (1932).

4. Bromination acet-m-toluidine in acetic acid to form 2-bromo-5-aminotoluene, followed by the replacement of the amino group with hydroxyl by the diazonnium reaction.

Huston, Hutchinson, J. Am. Chem. Soc., 54, 1504 (1932).

5. Direct bromination of m-cresol in glacial acetic acid in the cold. A melting point of 65° is reported.

Darenzo and Levey, Compt. rend., 193, 292 (1931).

6-BROMO-M-CRESOL.

1. Along with 4-bromo-m-cresol by bromination of m-cresol in chloroform at -10°. The product did not solidify.

Huston, Hutchinson, J. Am. Chem. Soc., 54, 1504 (1932).

2. By replacement of the amino group in the hydrochloride of 6-amino-m-cresol with bromine by the Sandmeyer reaction.

Huston, Peterson, J. Am. Chem. Soc., 55, 3880 (1933).

2,6-DIBROMO-M-CRESOL was reported from this laboratory by Huston and Peterson. It was obtained as an oil.

Huston, Peterson, J. Am. Chem. Soc., 55, 3880 (1933).

2-CHLORO-M-CRESOL.

1. Along with 4-chloro- and 6-chloro-m-cresol by the chlorination of m-cresol in carbon tetra chloride with a saturated solution of chlorine in carbon tetra chloride.

Gibson, J. Chem. Soc., 1424 (1926).

2. Replacement of the amino group in 2-amino-m-cresol with chlorine by the diazonnium reaction.

Huston, Chen, J. Am. Chem. Soc., 55, 4214 (1933).

3. Direct chlorination of the sodium salt of 4,6-phenol disulfonic acid with subsequent hydrolysis of the sulponic groups at 200°.

Huston, Chen, J. Am. Chem. Soc., 55, 4214 (1933).

4-CHLORO-M-CRESOL.

1. Direct chlorination of m-cresol in the vapor state.

Bredermann, Ber., 6, 325 (1873).

2. Chlorination of m-cresol in a cold solution of glacial acetic acid. M.p. 66°.

Kalle and Co., D.R.P. 90847; 93694.

5. Action of sulfuryl chloride on m-cresol. M.p. 52-53°.

Peratoner and Condorelli, Gazz. chim. ital., 28 I, 213 (1898).

4. Chlorination of a technical mixture of m- and p-cresols with sulfuryl chloride. Only the m-cresol was found to be attacked.

Raschig, D.R.P., 232071.

5. Chlorination of mixed cresols followed by sulfonation. Only the 4-chloro-m-cresol is sulfonated and can be readily separated.

Siebrecht, D.R.P., 233118.

6. Along with 2-chloro- and 6-chloro-m-cresol by chlorinating a carbon tetra chloride solution of m-cresol with a saturated solution of chlorine in carbon tetra chloride.

Gibson, J. Chem. Soc. 1424 (1926).

7. Treatment of m-cresol with a mixture of sulfuryl chloride and chlorine.

Laschinger, M. S. 1847566.

8. Nitration of o-chlorotoluene to form 2-chloro-5-nitrotoluene. Reduction of this compound and replacement of the amine group by hydroxyl by means of a diazonnium intermediate.

Huston, Chen, J. Am. Chem. Soc. 55, 4214 (1933).

2,4-DICHLORO-M-CRESOL.

1. Passing a calculated amount of chlorine into a warm solution of 4-chloro-m-cresol in aqueous sodium hydrogen carbonate. M.p. 45-46°.

Walther, Zipper, J. prakt. chem., 91, 374 (1864).

2. Chlorination of m-cresol in carbon tetra chloride in the cold.

Tanaki, Morakawa, Sakamoto, J. Chem. Soc. Japan, 51, 275 (1930). C. A. 26, 706.

3. Direct chlorination of 2-chloro-m-cresol with a calculated amount of chlorine in chloroform in the cold. M. p. 58°.

Huston, Chen, J. Am. Chem. Soc., 55, 4217 (1933).

4. Direct chlorination of 4-chloro-m-cresol with a calculated amount of chlorine in chloroform in the cold. M.p. 58°.

Huston, Chen, J. Am. Chem. Soc., 55, 4217 (1933).

MIXED BROMO-CHLORO-M-CRESOLS.

1. Replacement of amino group in 2-chloro-4-bromo-6-amino-m-cresol with chlorine yielded 2,6-dichloro-4-bromo-m-cresol, melting at 65°.

Raiford, Leavell, J. Am. Chem. Soc., 36, 1509.

2. Direct bromination of 4-chloro-m-cresol in glacial acetic acid gave 2,6-dibromo-4-chloro-m-cresol melting at 70-75.5°.

Walther, Zipper, J. pr. Chem.(2) 91, 378.

SULFONATION OF PHENOLS.

Investigations into the use of sulfonic acid groups as protecting agents in halogenation and nitration of phenols has been carried out by a number of workers. It is well known that replacements of sulfonic acid groups by halogen take place with more or less ease in the presence of aqueous acid.

Datta (J. Am. Chem. Soc., 43, 305 (1921)) reported quanti-

tative yield of 2,4,6-tribromophenol when an aqueous solution of phenol mono- and di-sulfonic acids are treated with bromine; 2, 4, 6-trichlorophenol when they are chlorinated. He found that the ring was activated in the position occupied by the sulfonic group, allowing the bromine to enter with greater ease than in the unoccupied positions. The chlorination of 2,6-m-cresol desulfonic acid in aqueous solution (Datta, Mitter, J. Am. Chem. Soc., 41, 2055 (1919)) yielded a compound melting at 45° which was assumed to be 2,6-dichloro-m-cresol.

On the other hand it has been found that if the sulfonic groups are in the form of their sodium salts, they are not readily replaced by halogen and serve as efficient blocking agents. Tanaki and Kutani (J. Pharm. Soc. Japan, 541, 196 (1927); C. A. 21, 2255) obtained good yields of 2,6-dichloro phenol by chlorinating the sodium salt of p-phenol sulfonic acid in alkaline solution and removing the sulfonic group by hydrolysis at high temperature in the presence of acid. By a modification of this method, Takagi and Kutani (J. Pharm. Soc. Japan, 517, 260 (1925); C. A. 20, 2669) have prepared 2-chloro phenol in good yield and 2-bromo phenol in somewhat lower yield.

Ballard (Organic Syntheses, Vol. XIV, p. 14) has developed a technique for the efficient production of 2-bromophenol.

Modifying a method developed by Kauffmann and DePay (Ber., 37, 725 (1904)) for the preparation of 2-nitroresorcinol, Gibson (J. Chem. Soc., 123, 1269, (1923)) and later Hodgson and Beard (J.

Chem. Soc. 127, 498 (1925)) used fuming sulfuric acid to protect the four and six positions of m-cresol during nitration.

Good yields of 2-bromo-m-cresol (Huston, Peterson, J. Am. Chem. Soc., 55, 3880 (1933)) and 2-chloro-m-cresol (Huston, Chen, 55, 4214 (1933)) were obtained in this laboratory by brominating or chlorinating m-cresol directly with one mol of halogen in four volumes of fuming sulfuric acid and then removing the sulfonic acid groups by hydrolysis with superheated steam at 180-200°.

E X P E R I M E N T A L

Numerous attempts to adapt this method to the preparation of 2,6-dibromophenol and 2-bromophenol failed to give satisfactory results. It was found that if enough sulfuric acid was used to keep the phenols in solution during the bromination, that sulfonation took place to too great an extent and the phenols would react with only a small portion of the calculated bromine. If only enough sulfuric acid was used to sulfonate one position, the phenols would solidify after a small amount of bromine had been added and further addition of bromine would result in the formation of tribromophenol. Finally, however, a small amount of 2,6-dibromophenol was obtained by the following procedure:

31 grams of phenol was treated with 65 grams of concentrated sulfuric acid at 100° for 3 hours, cooled, and a mixture of 45 grams

of fuming sulfuric acid (40%) and 25 grams of conc. sulfuric acid added. 55 grams of bromine was added before the mass solidified. Bromination was discontinued and the mass subjected to steam distillation at 200°. 20 grams of 2,6-dibromophenol was obtained, boiling at 80-90° (4 mm.).

This reaction indicated that the sulfonic acid groups were effectively blocking the para position of the phenol and that the halogenation might take place as desired if carried out in an inert anhydrous solvent. Accordingly, a number of runs were made in various solvents, including petroleum, ether, gasoline, kerosene and nitrobenzene. It was found that freshly distilled nitrobenzene was very well suited to the purpose and the following procedure was developed which gave excellent yields of 2,6-dibromophenol. Slight modifications gave satisfactory yields of 2-bromophenol, 2,6-dichlorophenol, 2-chlorophenol, 6-bromo-o-cresol, and 6-chloro-o-cresol.

2,6-DIBROMOPHENOL AND 2-BROMOPHENOL: A mixture of 31.3 grams (1/3 mol) of phenol and 50 grams of concentrated sulfuric acid (d. 1.84) was heated with stirring at 100-110° for two hours on an oil bath. It was cooled and 100 grams of freshly distilled nitrobenzene added. Cooling was continued while 15 grams of fuming sulfuric acid (49%) was added at such a rate that the temperature did not rise above 10°. 107 grams (2/3 mol) of bromine dissolved in 50 grams of nitrobenzene was added dropwise over a period of 2 hours, and stirring was continued for an hour to complete bromination. One liter of water in which 5-10 grams of sodium bisulfite

had been dissolved was added. The water and reaction mixture was thoroughly stirred for 15 minutes to facilitate extraction of the brominated phenol sulfonic acids. For the most part the tribromophenol remained in the nitrobenzene. This was drawn off by means of a separating funnel and the solution of sulfonic acids was evaporated from a 2-liter flask, suitably equipped for steam distillation, on an oil bath maintained at 200°. The distillate obtained during the evaporation contained a small amount of nitrobenzene and was discarded. When the temperature of the sulfonic acid solution reached 115°, steam, superheated in a copper coil, was passed through it. The temperature of the oil bath was maintained at 200°, while the temperature of the contents of the flask continued to rise to 175-180° during the hydrolysis. The brominated phenols were extracted from the distillate with ether and the phenol residue, after evaporation of the ether, was distilled under reduced pressure (4 mm.) from a modified Claisen flask having a 35 cm. column. Under these conditions a 10.4% yield of 2-bromophenol boiling at 55-60° (4 mm.)-190-191 (740 mm.)- and a 72.7% yield of 2,6-dibromophenol (M.p. 55-56°) boiling at 80-90° (4 mm.)-255-256° (740 mm.)- were obtained.

Analysis. Calc. for $C_6H_4OBr_2$: Br, 63.4. Found: Br, 62.9.

In order to determine the effect of the amount of sulfuric acid on the yields of 2,6-dibromo- and 2-bromophenol, a number of runs were made using the above procedure with the exception that increasing amounts of sulfuric acid were used in succeeding runs, starting with 45 grams. As would be expected, the amount of bromine can be gradually reduced, without reducing the yield, as the amount of sulfuric acid is increased.

I. BROMOPHENOLS

Order of runs	Grams of H_2SO_4 used	Yield of 2,6-Dibromophenol (%)	Yield of 2-Bromophenol (%)
1	45	60.0	10.0
2	50	72.7	10.4
3	55	69.5	14.0
4	60	64.8	18.2
5	65	54.9	25.4
6	70	51.4	29.3
7	75	40.0	32.6
8	80	35.0	34.8
9	85	32.8	36.0
10	90	29.6	45.0
11	95	9.5	46.5
12	100	8.5	46.0

2,6-DICHLOROPHENOL, 2-CHLOROPHENOL: Reactants were used in the same quantities and under the same conditions as in the preparation of the bromophenols except that 200 grams of nitrobenzene and the nitrobenzene solution of sulfonic acids was maintained at 55° while chlorine was passed until no further reaction took place.

The following table gives the yields resulting from the use of increasing amounts of sulfuric acid:

II. CHLOROPHENOLS

Order of runs	Grams of H_2SO_4 used	Yield of 2,6-Dichlorophenol (%)	Yield of 2-Chlorophenol (%)
1	55	63	19
2	59	65.4	20
3	62	64	18
4	68	70.3	17
5	71	66.6	18
6	80	50	39
7	85	39	52.8
8	90	39	55.1
9	95	31	59
10	100	24	72
11	105	27.4	66.8
12	110	29	64
13	115	33	62

A maximum yield of 70.3% of 2,6-dichlorophenol (M.p. 66-67°) boiling at 80-85° (4 mm.)-219-220° (740 mm.) and 72.0% of 2-chlorophenol boiling at 50-55° (4 mm.)-177-178° (740 mm.) were obtained.

Analysis. Calc. for $C_6H_4OCl_2$: Cl, 45.5. Found: Cl, 45.4.

6-BROMO-O-CRESOL: Bromination of 36 grams of o-cresol at 5-10°, using 55 grams of concentrated sulfuric acid, 100 grams of nitrobenzene and 60 grams of bromine in 50 grams of nitrobenzene gave a 60% yield of crude 6-bromo-o-cresol boiling at 55-65° (4 mm.) which contained about 8% o-cresol. When redistilled through a

90 cm. column (surrounded by an evacuated jacket) a pure product was obtained. B. p. 206-207 (740 mm.).

Analysis. Calcd. for C_7H_7OBr: Br, 42.77. Found: Br, 42.3.

A small amount of 4,6-dibromo-o-cresol was obtained boiling at 105° (4 mm.).

6-CHLORO-O-CRESOL: 36 grams of o-cresol chlorinated at 55°, using 60 grams of concentrated sulfuric acid and 200 grams of nitrobenzene, yielded 30% 6-chloro-o-cresol boiling at 45-50° (4 mm.)- 188-189° (740 mm.)-and 12% 4,6-dichloro-o-cresol boiling at 75-78° (4 mm.).

2-BROMO-M-CRESOL, 4-BROMO-M-CRESOL, 6-BROMO-M-CRESOL and 2,6-DIBROMO-M-CRESOL: Several runs were carried out using 36 grams of m-cresol, 36 grams of concentrated sulfuric acid, (Ber., 20, 3089 (1887)) and other reagents in the amounts given in the procedure for bromophenols. It was found necessary to brominate at 55-60° to prevent precipitation of the sulfonic acids before the reaction was completed. Two fractions were obtained. The first, boiling at 60-65° (4 mm.) - 214-215° (743 mm.) - was identified as 2-bromo-m-cresol. It was obtained in an average of 7% and solidified on standing in the receiver. When crystallized rapidly from a small amount of petroleum ether, it formed a sheaf of tetragonal crystals. Slower crystallization from a greater amount of solvent gave large solid prisms, m. p. 61-62°.

Analysis. Calcd. for C_7H_7OBr: Br, 42.77. Found: Br, 42.4.

The second fraction, boiling at 102-105° (4 mm.) also

solidified in the receiver. However, toward the end of the distillation a small amount of material came over at about the same temperature which did not solidify. (This was assumed to be due to the presence of a small amount of 4-bromo-m-cresol and 2,4-dibromo-m-cresol, which have approximately the same boiling point.) This solid fraction was shown by analysis and the following series of reactions to be 2,6-dibromo-m-cresol. Yield 25%. It crystallized from petroleum ether in clusters of needles which melted at 36.5-37.5° and formed a p-toluene sulfonyl ester (Einhorn and Holland, Ann., 301, 95 (1898)) melting at 131-132°.

Analysis. Calcd. for $C_7H_6OBr_2$: Br, 60.15. Found: Br, 59.7.

PROOF OF STRUCTURE OF 2,6-DIBROMO-M-CRESOL: Pure 4-nitro-m-cresol, prepared by the method of Staedel and Kolb (Ann., 259, 210 (1890)) was brominated with two mols of bromine in glacial acetic acid (Claus, J. prakt. Chem.(2) 39, 61 (1888)) at 15-20° and the resulting 2,6-dibromo-4-nitro-m-cresol was reduced by means of stannous chloride and hydrochloric acid (Raeford, Am. Chem. J., 46, 419 (1911)).

The hydrochloride of 2,6-dibromo-4-amino-m-cresol was diazotized by the procedure of Bigelow, Johnson and Sandborn (Organic Syntheses, Vol. VI, p. 16) and an unsuccessful attempt was made to prepare 2,6-dibromo-m-cresol by reducing the diazonnium group with alcohol in the presence of finely divided copper. (Huston and Peterson, J. Am. Chem. Soc., 55, 3881 (1933)). The first fraction obtained by the steam distillation of the reaction mixture re-

mained an oil, while subsequent fractions solidified in the receiver and were shown by analysis to be 2,6-dibromo-4-chloro-m-cresol. Recrystallization from petroleum ether gave needle clusters melting at 68½-69½°. Analysis of the liquid fraction coming over in the first stages of the steam distillation for halogen indicated a mixture of 2,6-dibromo-m-cresol and 2,6-dibromo-4-chloro-m-cresol. Direct chlorination of this fraction in chloroform, after repeated attempts to purify it had failed, gave 2,6-dibromo-4-chloro-m-cresol melting at 68½-69½°. The p-toluene sulfonyl ester (Einhorn and Holland, Ann., 301, 95, (1898)) recrystallized from alcohol melted at 108-109°.

Conclusive proof of the structure of the 2,6-dibromo-m-cresol was obtained by chlorinating it directly in chloroform to the 2,6-dibromo-4-chloro-m-cresol which was also prepared by the bromination of 4-chloro-m-cresol with two mols of bromine. In all cases the identity of the products was checked by ester formation and analysis.

An attempt to prepare 2-bromo- and 6-bromo-m-cresol was made by brominating 36 grams of m-cresol (1/3 mol) and 36 grams of concentrated sulfuric acid in nitrobenzene at 5-10°. However, the reaction was found to yield a mixture of 25 grams (40%) of 2-bromo-m-cresol boiling at 67-70° (4 mm.) and 5 grams (8%) of 4-bromo-m-cresol boiling at 103-105° (4 mm.). The latter formed a mass of very fine needles when recrystallized from petroleum ether which melted at 58½-59½°. Its p-toluene sulfonyl ester melted at 112-113°. Recrystallization of 4-bromo-m-cresol, prepared by Huston

and Hutchinson (J. Am. Chem. Soc., 54, 1505 (1932)) gave the same melting point from the same solvent, and its p-toluene sulfonyl ester also melted at 112-113°. To further prove the structure of the 103-105° fraction, 4-nitro-m-cresol was reduced by tin and hydrobromic acid in alcoholic solution, the method used being adapted from that of Raiford, (Am. Chem. J., 46, 419 (1911)). The hydrobromide of 4-amino-m-cresol was diazotized in hydrobromic acid solution. Replacement of the diazonnium group with bromine by the Sandmeyer reaction (Organic Syntheses, Coll. Vol. I, p. 131.) yielded 4-bromo-m-cresol, which was identified by the melting point and that of its p-toluene sulfonyl ester.

In order to prove the structure of 2,4-dichloro-m-cresol obtained in the chlorination of m-cresol sulfonic acid-6, 6-bromo-m-cresol was prepared by the following sequence of reactions:

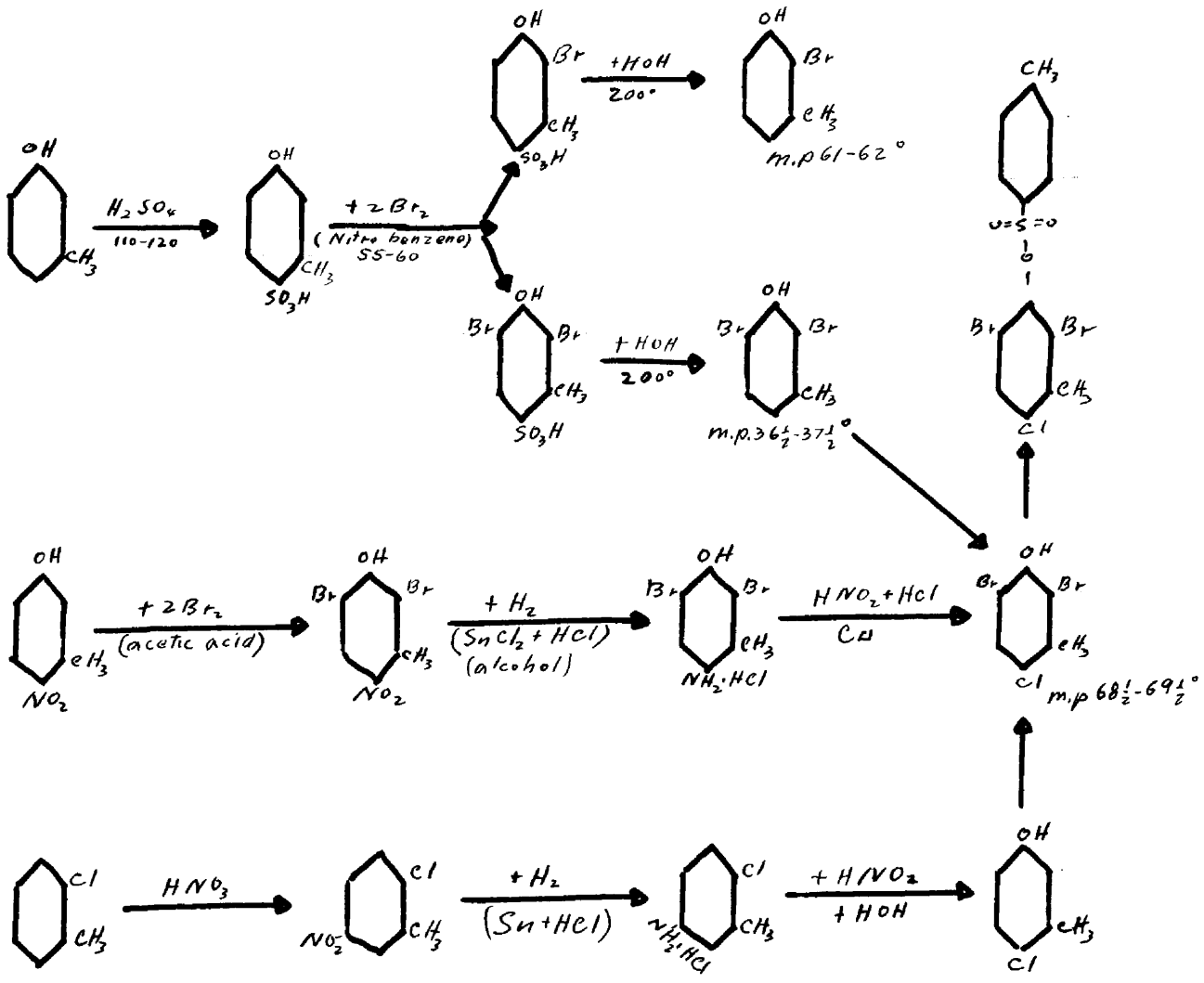
6-nitro-m-cresol, the volatile fraction obtained in the nitration of m-cresol by the method of Stadel and Kolb (Ann., 259, 210 (1890)) was reduced to the corresponding amino compounds with sodium hydrosulfite (Anwers, Borsche and Weller, Ber. 54, 1315 (1921)); (Huston and Petersen, J. Am. Chem. Soc., 55, 3880 (1933)). The 6-amino-m-cresol thus obtained was diazotized in sulfuric acid solution and the diazonnium group replaced by bromine in the presence of cuprous bromide and hydrobromic acid according to the method reported by Bigelow (Organic Syhtheses, Coll. Vol. I, p. 131). The product was obtained as an oil by extraction with ether and was purified by distillation under reduced pressure (4 mm.) B. p. 70-75° (4 mm.) - 210-212° (745 mm.). Upon standing in the

receiver the 6-bromo-m-cresol solidified. It formed in solid angular prisms when recrystallized from petroleum ether. M. p. $38\frac{1}{2}$-$39\frac{1}{2}^{0}$.

Its p-toluene sulfonyl ester melted at 89.5-90.5 when crystallized from alcohol.

Analysis. Calcd. for C_7H_7OBr: Br 42.77. Found: Br, 42.8.

SCHEME OF REACTION



2-CHLORO-M-CRESOL, 2,4-DICHLORO-M-CRESOL, 2,6-DICHLORO-M-CRESOL AND 4-CHLORO-M-CRESOL: A number of chlorinations of m-cresol sulfonic acid were carried out by a procedure similar to that used for the brome-m-cresols. 56 grams of m-cresol, 36 grams of concentrated sulfuric acid and 200 grams of nitro benzene were used. Chlorination was carried on to saturation at room temperature.

In this case three fractions were obtained from carefull distillation under reduced pressure in a modified Claisen flask having a 56 cm. column (2 cm. bore), the first fraction boiling at 53-57° (4 mm.) - 195-196° (740 mm.) - solidified in the receiver and upon rapid crystallization from a small amount of petroleum ether gave a sheaf of fine tetragonal crystals melting at 49-50°. From a greater amount of solvent large solid prisms were obtained. Analysis and properties of this compound identifies it as 2-chloro-m-cresol. Yield - 14%.

Analysis. Calcd. for C_7H_7OCl: Cl, 24.91. Found: Cl, 24.8.

The second fraction, coming over at 75-80° (4 mm.) - 235-236° (745 mm.) - also solidified in the receiver and crystallized from petroleum ether in clusters of needles melting at 58-59°. Its p-toluene sulfonyl ester formed in small platelets from alcohol which melted at 101-102°. These constants and the sequences of reactions below show it to be 2,4-dichloro-m-cresol. Yield - 25%.

Analysis. Calcd. for $C_7H_6OCl_2$: Cl, 40.11. Found: Cl, 39.35.

The third fraction boiling at 80-85° (4 mm.) - 239.5-240.5

(745 mm.) - remained an oil at room temperature. Analysis and the reactions given below show it to be 2,6-dichloro-m-cresol. Yield - 6%.

PROOF OF STRUCTURE OF 2,4-DICHLORO-M-CRESOL: 2,4-dichloro-m-cresol obtained in the chlorination of m-cresol sulfonic acid-6 in nitro benzene was brominated with one mol of bromine in chloroform at 0°. Clusters of feathery crystals crystallized from petroleum ether which melted at 58-59°, the p-toluene sulfonyl ester of which melted at 96-96°. Analysis of the compound showed it to be a monobromo-dichloro-m-cresol.

Analysis. Calcd. for $C_7H_5OBrCl_2$: halogen, 58.98.

Found: halogen, 59.6.

6-bromo-m-cresol prepared from 6-nitro-m-cresol by the reactions discussed above, was directly chlorinated in chloroform at 0° with an amount of chlorine calculated to occupy two positions. (Houben Die Methoden der organischen Chemie, Vol. III, p. 799; Ber., 35, 43u, 2754 (1902)). The compound obtained was shown by melting point, analysis and ester formation to be the same as the one obtained by brominating 2,4-dichloro-m-cresol.

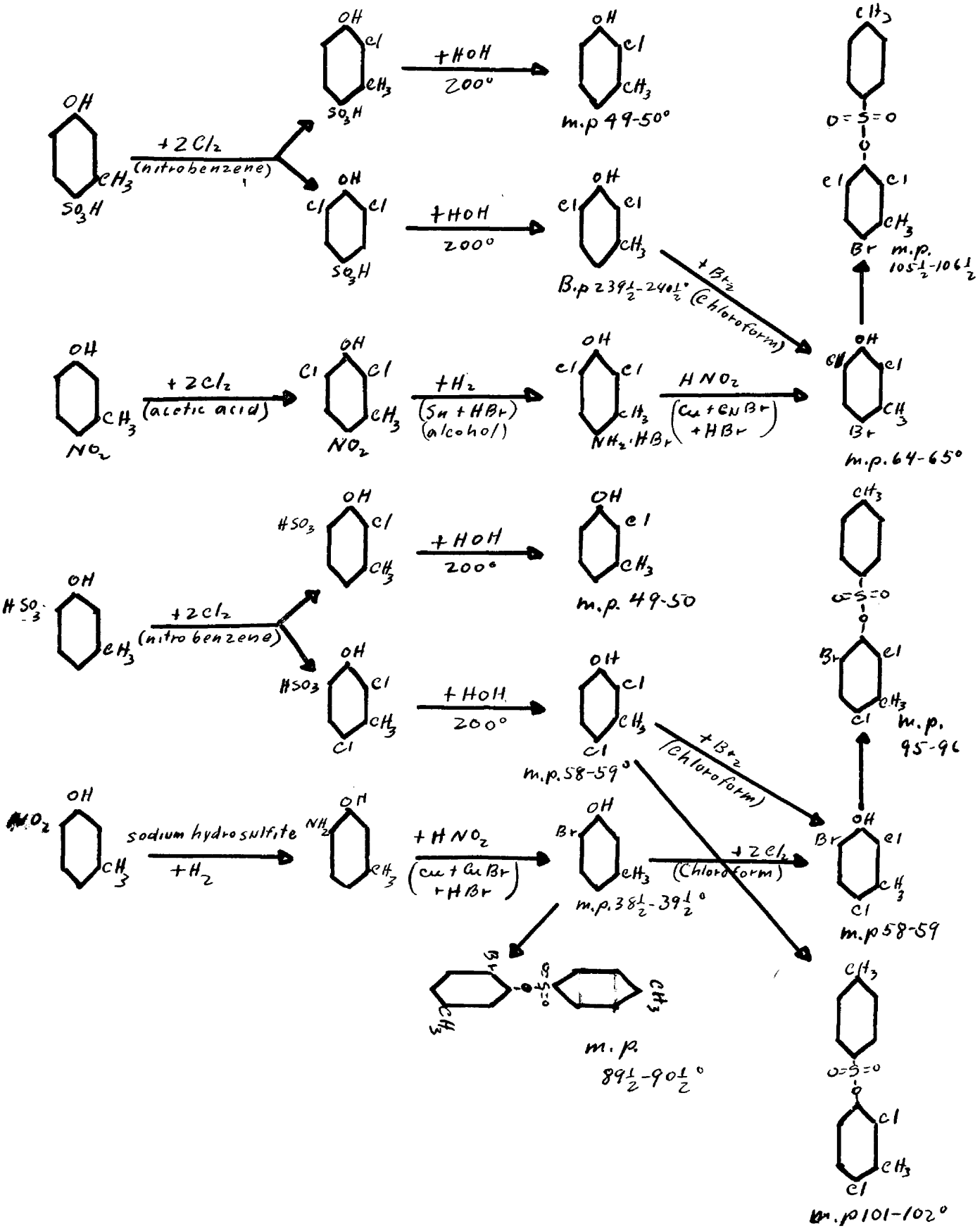
PROOF OF STRUCTURE OF 2,6-DICHLORO-M-CRESOL: 2,6-dichloro-m-cresol was isolated along with 2,4-dichloro-m-cresol in the reactions described above. It was brominated directly with one mol of bromine in chloroform at 0° to 4-bromo-2,6-dichloro-m-cresol which crystallized in needle clusters from petroleum ether melting at 64-65°. The p-toluene sulfonyl ester of 4-bromo-2,6-dichloro-m-cresol formed in needles from alcohol which melted at 105½-106½°.

Analysis. Calcd. for $C_7H_5OBrCl_2$: halogen, 58.98.

Found: halogen, 59.6.

4-nitro-m-cresol (Staedel, Kolb, Ann., 259, 210 (1890)) was chlorinated with two mols of chlorine in glacial acetic acid (Huston, Chen, J. Am. Chem. Soc., 55, 4217 (1933)). The 4-nitro-2,6-dichloro-m-cresol thus obtained was reduced with tin and hydrobromic acid. (135 grams of 4-nitro-2,6-dichloro-m-cresol was dissolved in 500 cc. of alcohol and 105 grams of mossy tin added. 450 cc. of 48% hydrobromic acid was added to the boiling mixture dropwise, with continued refluxing. After reduction was complete the hot solution was poured in an equal volume of 48% hydrobromic acid. The crystals of the hydrobromide formed in fine needles upon cooling overnight in a refrigerator, and were removed by filtration.) Replacement of the amine with bromine was accomplished by the procedure of Bigelow (Organic Syntheses, Coll. Vol. I, p. 131) and the oil obtained was fractionated at 4 mm. to remove the underchlorinated portion. The desired 4-bromo-2,6-dichloro-m-cresol came over at 110-120° (4 mm.). It crystallized from petroleum ether in needle clusters melting at 64-65° and its p-toluene sulfonyl ester melted at 105½-106½°.

SCHEME OF REACTION



M-cresol was chlorinated by the procedure used for the preparation of 2,4-dichloro-m-cresol, 2,6-dichloro-m-cresol and 2-chloro-m-cresol with the exception that 45 grams of sulfuric acid was used for 36 grams of m-cresol and chlorination was carried out at 80°. At this temperature about 5% of the m-cresol was chlorinated in the 4 position, the greater part being recovered unchlorinated. The 4-chloro-m-cresol boiled at 83-86° (4 mm.) and formed a mass of fine needles from petroleum ether which melted at 55-56°.

During the chlorination of m-cresol at 25°, a mass of yellow leaflets precipitated from the nitrobenzene which were removed by filtration. They were slightly soluble in alcohol and ether, but insoluble in petroleum ether, hot water, and cold concentrated sulfuric acid. They dissolved in hot concentrated sodium hydroxide, the solution darkening to green-black.

Qualitative analysis for elements showed carbon, hydrogen and chlorine to be present; sulfur to be absent. Saponification tests indicated chlorination of the side chain. Decomposition occurred at 196° when crystallized from alcohol. It is possible the compound may be m-hydroxy-benzo-trichloride.

D I S C U S S I O N

It is reported by Claus and Krauss (Ber., 20, 3089 (1887)) that sulfonation of m-cresol with an equal amount of sulfuric acid at 110-120° for 2 to 3 hours produces a 5/6 yield of m-cresol sulfonic acid-4. Since similar conditions yield p-phenol sulfonic acid, bromination and chlorination of m-cresol sulfonic acid in anhydrous nitro benzene was expected to yield mainly 2,6-dibromo- and 2,6-dichloro-m-cresols. This was true in the bromination reactions although a small amount of oil was obtained along with the 2,6-dibromo-m-cresol fraction which would not solidify. In the chlorination reactions 2,4-dichloro-m-cresol was obtained in greatest yield along with an oil which was shown to be 2,6-dichloro-phenol. Under modified conditions both 4-bromo- and 4-chloro-m-cresol were obtained. It would seem in the light of these results that m-cresol sulfonic acid is not formed in the amounts reported by Claus and Krauss but that a mixture of the 4 and 6 sulfonic acids is formed. This conclusion is supported by the work of Haworth and Lapworth (J. Chem. Soc., 125, 1299 (1924)), who studied the action of concentrated sulfuric acid on m-cresol at various temperatures. Treatment for one hour at 30-35° gave the 4 and 6 sulfonic acids in a ratio of 1 to 2.7; 1 to 2 at 100°, while at 120° the product was mainly m-cresol sulfonic acid-6. That 2,6-dibromo-, 4-bromo- and 2,4-dibromo-m-cresol could come over in the same fraction, and 2,6-dichloro-, 2,4-dichloro- and 4-chloro-m-cresol could come over at approximately the same temperature is shown by the following boiling points for these substances:

4-bromo-m-cresol	135-140° (16 mm.)
2,4-dibromo-m-cresol	130-140° (16 mm.)
2,6-dibromo-m-cresol	140-145° (16 mm.)
4-chloro-m-cresol	231-233° (745 mm.)
2,4-dichloro-m-cresol	235-236° (745 mm.)
2,6-dichloro-m-cresol	239.5-240.5° (745 mm.)

S U M M A R Y

I - Bromination and chlorination of p-phenol sulfonic acid in anhydrous nitro benzene gave excellent yields of 2,6-dibromo-, 2,6-dichloro-, 2-bromo- and 2-chlorophenols.

II - Bromination and chlorination of the para sulfonic acid of o-cresol in anhydrous nitro benzene gave 6-bromo-o-cresol and 6-chloro-o-cresol.

III - Bromination and chlorination of a mixture of m-cresol sulfonic acid-4 and m-cresol sulfonic acid-6 in anhydrous nitro benzene under various conditions gave 2-bromo-m-cresol, 4-bromo-m-cresol, 2,6-dibromo-m-cresol, 2-chloro-m-cresol, 4-chloro-m-cresol, 2,4-dichloro-m-cresol and 2,6-dichloro-m-cresol.

IV - 6-bromo-m-cresol was prepared in crystalline form from 6-nitro-m-cresol.

V - Sulfonic acid groups on the benzene ring of phenol and phenol derivatives were shown to be stable toward halogenation if carried out in an inert anhydrous solvent.