I. THE PREPARATION OF ORTHO-, META-, AND PARABROMOBENZYLRESORCINOLS

II. A STUDY OF THE PEROXIDE CATALYZED CHLORINATION OF THE BROMOTOLUENES WITH SULFURYL CHLORIDE

Thesis for the Degree of M. S.

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Richard Charles Nametz

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I. The Preparation of Ortho-, Meta- and Parabromobenzylresorcinols.

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Richard Charles Nametz

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By

Richard Charles Nametz

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PART I

THE PREPARATION OF ORTHO-, META-, AND PARABROMOBENZYLRESORCINOLS

INTRODUCTION

It is well known that resorcinol and several of its alkyl derivatives, especially hexylresorcinol, show a remarkable improvement in germicidal action over the corresponding phenols. Klarmann (1) has shown that by the introduction of the benzyl group into the resorcinol nucleus a compound of high germicidal activity coupled with low toxicity could be obtained. Germicidal potency is also known to be increased in phenols and their alkyl derivatives by the introduction of a halogen into the nucleus. Florestano (2) has tested twenty-eight derivatives of diphenylmethane for antibacterial activity against tubercle bacilli. It was found that activity seemed to be dependent on halogen and hydroxyl group substitution in the parent compound, and more particularly upon position.

It was felt that with the introduction of a bromobenzyl group into the resorcinol nucleus, a compound of high antibacterial activity would be obtained.

The main purpose of this work was to synthesize the ortho-, meta-, and parabromobenzylresorcinols. The method chosen for the synthesis was the condensation of the appropriate benzyl chloride and resorcinol in the presence of aluminum chloride. Much work has been done in this laboratory on the aluminum chloride condensation of phenols with alkyl halides and with alcohols.

A literature survey of the aluminum chloride condensation of phenols and alkyl halides will not be given here as this is very ably covered by Gyorgy (3). Only those references pertinent to this work will be cited.

In 1926, Klarmann (1) prepared benzylresorcinol in a 50% yield by the aluminum chloride condensation of resorcinol and benzyl-chloride. This reaction was carried out at 50-70° for two hours using nitrobenzene as a solvent. Klarmann also prepared benzylresorcinol by an application of the Hoesch (4) synthesis. In this method benzo-nitrile and resorcinol were condensed to form the ketimine hydro-chloride in the presence of anhydrous zinc chloride by passing dry hydrogen chloride gas through the mixture in an ethereal solution. The benzylresorcinol was obtained in a 30% overall yield by hydroly-sis of the ketimine hydrochloride to the ketone and a subsequent Clemmensen reduction.

In this laboratory benzyl alcohol was substituted for benzyl chloride in the aluminum chloride condensation. Houk (5), following closely the method of Klarmann, condensed benzyl alcohol and resorcinol to obtain a 25% yield (based on the resorcinol used) of benzyl re-sorcinol.

A few years later Klarmann and v. Wowern (6) introduced a halo-gen substituent into the unsubstituted benzylresorcinol. p-Chloro-benzyl chloride and resorcinol were condensed in the presence of aluminum chloride to obtain a 55% yield of p-chlorobenzylresorcinol. As in his previous work, nitrobenzene was the solvent but the tempera-ture (50 - 70°) was maintained for four hours. By applying the Hoesch synthesis, Klarmann was also able to obtain p-chlorobenzylresorcinol and p-bromobenzylresorcinol in yields of 33% and 55%, respectively, from the appropriate benzonitrile and resorcinol.

Klarmann and v. Wowern also introduced a bromine and a chlorine atom into the resorcinol nucleus of benzylresorcinol. Thus 5-chloro-2,4-dihydroxydiphenylmethane was prepared in a 51% yield by the action of a calculated amount of sulfuryl chloride on benzylresorcinol in ether with cooling. In the same manner 5-bromo-2,4-dihydroxydiphenylmethane was obtained in a 71% yield by the action of a calculated amount of bromine on benzylresorcinol.

Thus, one of the three compounds to be prepared, namely p-bromobenzylresorcinol, had already been synthesized, although by the Hoesch synthesis, followed by Clemmensen reduction, rather than by the Friedel Crafts method.

EXPERIMENTAL

I. Chemicals

Aluminum Chloride (anhydrous pellets) Baker's Analyzed.

Benzoyl Chloride, E. K., 293.

p-Bromobenzoic Acid, E. K., 1351.

Bromobenzyl Chlorides and Bromides. Prepared as described in Part II of this thesis.

Charcoal, Norite "A" and Darco.

Ether, Baker's Anhydrous Reagent.

Ether, Baker's U. S. P. "Solvent."

Ligroin, b.p. 60-90°, E. K., P513.

Nitrobenzene, Carrier Stevens Co. (redistilled).

Potassium Thiocyanate, C. P., Baker's.

Pyridine, E. K., P214. Refluxed for two hours over barium oxide and distilled (b.p. 112-114° at 740 mm.).

Resorcinol, E. K., 222. Dried at 95° for at least twelve hours.

Silver Nitrate, Merck, Reagent.

Sodium Hydroxide (pellets), Merck, Reagent.

Sodium Peroxide, C. P., Baker.

Toluene, Merck, Reagent.

Xylene, Merck, Reagent.

p-Bromobenzoyl Chloride. It was necessary to prepare this reagent by a modification of the method given by Adams and Jenkins (7) for the preparation of p-nitrobenzoyl chloride.

In a 500 ml. round-bottomed flask were mixed 20.1 g. (0.1 mole) of p-bromobenzoic acid, and 20.8 g. (0.1 mole) of phosphorus pentachloride. The flask was fitted with a cork bearing a

calcium chloride drying tube and placed on a steam bath. After a few minutes the mixture melted, a vigorous reaction occurred, and much hydrogen chloride was evolved. After heating for about ten minutes, the reaction was complete and the contents of the flask poured into a 50 ml. Claisen flask and distilled. When all the phosphorus oxychloride had been collected, b.p. 104-108° at 740 mm., the water condenser was changed to an air condenser and the acid chloride distilled. p-Bromobenzoyl chloride was collected at 220 - 225° at atmospheric pressure and solidified quickly in the receiver and condenser. Eighteen grams or an 82% yield of product was obtained. This material was not further purified, but was used directly to make the di-p-bromobenzoates.

II. Preparation of p-Bromobenzylresorcinol

For all condensations a 1-l. three-necked, standard-tapered (24/40 - 34/45 - 24/40), round-bottomed flask was used. This was equipped with a 250 ml. dropping funnel, an addition tube, reflux condenser protected by a calcium chloride drying tube, thermometer, and a mechanical stirrer of the Hershberg (8) type. Heat was supplied by a Glascol mantle. Since all condensations were carried out in the same manner, only the first one is described in detail.

Condensation of p-Bromobenzyl Chloride and Resorcinol.

Reactants:

Resorcinol 70 g. (0.63 mole)

p-Bromobenzyl chloride 64.7 g. (0.31 mole)

Nitrobenzene 400 g. (334 ml.)

Anhydrous aluminum chloride 50 g. (0.37 mole)

Seventy grams (0.63 mole) of resorcinol which had previously been dried at 95° for at least twelve hours was dissolved with stirring in 300 g. of freshly distilled nitrobenzene. To this solution was quickly added 50 g. (0.37 mole) of aluminum chloride pellets. Immediately thereafter, a solution of 64.7 g. (0.31 mole) of p-bromobenzyl chloride in 100 g. of nitrobenzene was added dropwise to the reaction mixture. The addition of the halide solution required about two hours. As the solution of p-bromobenzyl chloride in nitrobenzene was added, the temperature rose slowly to 48° and then dropped to 35-40°.

After the latter solution had been added, the temperature of the reaction mixture was raised to and maintained at 65-70° for four hours.

At the end of this time the mixture was a deep red color. The reaction mixture was allowed to cool slightly and then poured onto cracked ice with stirring. This mixture was allowed to stand over night and then the water layer (upper) was siphoned off, using an aspirator. The oily layer was washed twice with 250 ml. portions of 10% hydrochloric acid and then with water. Each wash was siphoned off with the aspirator and discarded. An equal volume of ether was then added to the oily layer and the whole shaken repeatedly with 500 ml. of a 10% sodium hydroxide solution. Since the resulting layers were very dark, it was difficult to make a separation. In order to facilitate seeing the layers in the extraction, a good source of light at a higher level than the separatory funnel was used. The alkaline solution was drawn off and extracted several times with ether until all the nitrobenzene had been removed. The last ether extract was colorless.

The mixture was transferred to a large beaker and acidified to Congo paper with 1:1 hydrochloric acid. Upon acidification a heavy dark red oil was liberated. The mixture was then placed on a hot plate and boiled for twenty-five minutes with frequent stirring. After cooling, the water was decanted and the oily layer washed once with distilled water. The heavy oil was poured into a 125 ml. Allihn flask and any material clinging to the beaker was dissolved in ether and added to the flask. The ether and traces of water were removed by an aspirator with some heating of the flask being necessary to remove the last traces of moisture.

The crude oil was distilled through a modified Allihn flask using a three-pronged type fraction cutter and 50 ml. Erlenmeyer flasks as

receivers. Due to the high temperature at which the distillation was carried out, it was found necessary to wrap the column of the distilling flask with asbestos tape and to heat it with a nichrome wire winding. For a heating bath, Crisco was found very suitable as it withstood temperatures of 275-280° quite well without darkening or smoking very badly. An oil vacuum pump was used and the pressure obtained was read from a finger type manometer.

The following fractions were collected:

Fraction	B.p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	120-200 (2)	248-250	< 1
2	200-217[a] (2)	250-256	26.4
3	217-219 (2)	256-271	7.3

a Major portion distilled at 217°

It was necessary to heat the side arm with a free flame in order to prevent clogging. Fraction 1 solidified upon collection and was probably mostly resorcinol. Fractions 2 and 3 distilled as light yellow viscous oils which solidified after standing several days or after repeated stirring. The yield of crude p-bromobenzylresorcinol was 33.7 g. or 38.9% based on the p-bromobenzylchloride used. After recrystallizing fraction 2 from a 1:1 ligroin-xylene mixture, 22 g. of p-bromobenzylresorcinol, m.p. 90 - 92°, was obtained in clusters of needles which were slightly yellowish-green in appearance. A charcoal ("Darco") treatment seemed to remove most of the color but the product still retained a slight greyish cast even after repeated recrystallization. After three recrystallizations the melting point was raised to 92.5 - 93.5° on a Fischer-Johns melting point block. Klarmann and

v. Wowern (6) reported a melting point of 96°. Anal. Calcd. for $C_{13}H_{11}BrO_2$: Br, 28.62. Found: 28.35, 28.60.

Another condensation was carried out in the same manner using the following quantities of reactants:

Resorcinol 70 g. (0.63 mole)

p-Bromobenzyl chloride 94.4 g. (0.46 mole)

Nitrobenzene 400 g. (334 ml.)

Anhydrous aluminum chloride 50 g. (0.37 mole)

The following fractions were collected. A mantle was used to heat the flask.

Fraction	B.p., ° C. (mm.)	Distillate (g.)
1	150-200 (5)	< 1
2	200-227 (5)	51

The yield of crude p-bromobenzylresorcinol was 51 g., or 39.6% based on p-bromobenzyl chloride. This material, which solidified on rubbing, was used in determining the solvent most suitable for recrystallization.

Condensation of p-Bromobenzyl Bromide and Resorcinol.

This condensation was carried out in the same manner as the other condensations using the same equipment and the following quantities of reactants:

Resorcinol 70 g. (0.63 mole)

p-Bromobenzyl bromide 77.5 g. (0.31 mole)

Nitrobenzene 400 g. (334 ml.)

Anhydrous aluminum chloride 50 g. (0.37 mole)

The p-bromobenzyl bromide, m.p. 61-62°, was prepared by the method described on page 48. After working up the reaction mixture in the manner previously described, the following fractions were collected.

Fraction	B. p., ° C. (mm)	Bath, ° C.	Distillate (g.)
1	130-200 (3)	200-265	0.3
2	200-218 (3)	265-275	29.5

The yield of crude p-bromobenzylresorcinol was 29.5 g. or 34.2% based on the p-bromobenzyl bromide. As before, this product solidified upon rubbing. By recrystallizing fraction 2 from toluene, 18.4 g. of p-bromobenzylresorcinol, m.p. 92.5-94°, was obtained. This product was slightly colored as in the other condensations. An additional 1.95 g. of a slightly darker product, m.p. 89.5-91°, was obtained from the mother liquor.

III. Preparation of o-Bromobenzylresorcinol.

Condensation of o-Bromobenzyl Chloride and Resorcinol.

The following quantities of reactants were used:

Resorcinol 88 g. (0.80 mole)

o-Bromobenzyl chloride 82 g. (0.40 mole)

Nitrobenzene 520 g. (438 ml.)

Anhydrous aluminum chloride 64.0 g. (0.48 mole)

The o-bromobenzyl chloride, b.p. 112-114° at 17 mm. and n_D^{20} = 1.5880, was dissolved in 130 g. of the nitrobenzene and added dropwise to the reaction vessel over a period of an hour. The temperature of the mixture was raised and maintained between 60-70° for four hours.

The reaction mixture was worked up in the manner described in the previous condensations and distilled.

Fraction	B.p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	74-202 (2)	193-229	0.3
2	202-212.5 (2)	229-254	36.9
3	213-215 (2)	257-265	4.5

A black tarry material which amounted to 31.1 g. was left in the distilling flask. This material, which was somewhat soluble in concentrated sodium hydroxide solution, was not identified. The yield of crude o-bromobenzylresorcinol was 41.4 g. or 35.7% based on the o-bromobenzyl chloride used.

Fraction 2 was redistilled using a 50 ml. Claisen flask having the column leading to the side arm filled with glass beads and wrapped with asbestos tape. The fractions collected were as follows:

Fraction	B.p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	108-191 (1)	200-254	3.4
2	191-195.5 (1)	252-267	24.3
3	195.5-196 (1)	267-275	1.9

Fraction 2 was crystallized and decolorized by rubbing under toluene to obtain 16.2 g. of o-bromobenzyl-resorcinol, m.p. 103.5-107°. By evaporating the mother liquor, 2.3 g. of product, m.p. 96-100°, was obtained. It was found that the melting point of the product of m.p. 103.5-107° could be raised to 109.5-111° by one recrystallization from toluene. However, repeated recrystallization from various solvents (carbon tetrachloride, water) did not raise the melting point

above 112°. These values do not agree too closely with the melting point of the product obtained in the condensation of o-bromobenzyl bromide and resorcinol, 112-114.5° (page 13). However, no depression was shown in the melting point of the dibenzoates prepared from both products. Evidently the product obtained by condensing o-bromobenzyl chloride and resorcinol must have been slightly contaminated, and this impurity is difficult to remove.

Another condensation was carried out in the same manner using the following quantities of reactants:

Resorcinol 70 g. (0.63 mole)

o-Bromobenzyl chloride 63.7 g. (0.31 mole)

Nitrobenzene 400 g. (334 ml.)

Anhydrous aluminum chloride 50 g. (0.37 mole)

The following fractions were collected:

Fraction	B.p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	140-195 (3)	to 236	2.4
2	195-216 (3)	236-240	8.4
3	216-228 (3)	240-265	18.0

The yield of crude o-bromobenzylresorcinol obtained was 28.4 g. or 30.4% based on the o-bromobenzyl chloride used.

Condensation of o-Bromobenzyl Bromide and Resorcinol.

Reactants:

Resorcinol 70 g. (0.63 mole)

o-Bromobenzyl bromide 77.5 g. (0.31 mole)

Nitrobenzene 400 g. (334 ml.)

Anhydrous aluminum chloride 50 g. (0.37 mole)

The equipment and method used for this condensation were the same as in previous condensations. The o-bromobenzyl bromide, b.p. 129-130° at 16.5 mm., was prepared as described on page 49. The following fractions were obtained:

Fraction	B. p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	133-211 (3)	to 232	< 1.0
2	211-212 (3)	232-246	23.9

The yield of crude o-bromobenzylresorcinol was 23.9 g. or 27.5% of theory based on the o-bromobenzyl bromide. By dissolving this material in a large volume of boiling water and decanting away from the dark insoluble oils, 10 g. of o-bromobenzylresorcinol, m.p. 112.5-114°, was obtained. This compound crystallized as fine, slightly colored needles from water. A small portion of this was again recrystallized from water to obtain fine white needles, m.p. 113.5-114.2°. This material was analyzed after drying in a vacuum desiccator. Anal. Calcd. for $C_{13}H_{11}BrO_2$: Br 28.62. Found: Br, 28.67, 28.72.

IV. Preparation of m-Bromobenzylresorcinol.

Condensation of m-Bromobenzyl Chloride and Resorcinol.

This condensation was carried out in the manner described previously using the following quantities of reactants:

Resorcinol 70 g. (0.63 mole)

m-Bromobenzyl chloride 64.7 g. (0.31 mole)

Nitrobenzene 400 g. (334 ml.)

Anhydrous aluminum chloride 50 g. (0.37 mole)

The m-bromobenzyl chloride, b.p. 116-118.5° at 17 mm., was obtained from the distillation described on page 47. This condensation proceeded essentially the same as all the others, except that a dark semicrystalline solid was isolated after acidification of the alkaline extract, boiling, and chilling the mixture in an ice bath. This solid was filtered, transferred to the distilling flask, and distilled as before.

Fraction	B.p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	85-205 (2.5)	to 225	0.3
2	205-209 (2)	225-247	3.3
3	209-215 (2)	247-261	28.3

The tarry material left in the flask amounted to 16.5 g. and was not identified. The yield of crude m-bromobenzylresorcinol, isolated as a light yellow viscous oil, was 31.6 g. or 36.4% based on the m-bromobenzyl chloride used. After repeated rubbing fraction 3 solidified. Recrystallization from toluene gave 21.7 g. of light yellow plates, m.p. 59.5-63.5°. Upon decolorizing a small portion of this material with Norite "A" in toluene, white, glistening plates were obtained. These melted from 59-66.5°.

Believing that perhaps the m-bromobenzyl chloride used had been contaminated with a small amount of m-chlorobenzyl bromide, and that the condensation had yielded a mixture difficult to separate, the dibenzoate of this material was prepared by the method described on

page 17 and purified. The melting point of the dibenzoate was 95.5-96°. This dibenzoate was hydrolyzed as follows, using a modification of the procedure described by Shriner and Fuson (9).

Twenty-five milliliters of diethylene glycol, 8 ml. of water, and 4.8 g. of solid potassium hydroxide were placed in a 50 ml. round-bottomed flask and a boiling chip added. This mixture was shaken until most of the potassium hydroxide had dissolved. Three grams of the dibenzoate of m-bromobenzylresorcinol was added, a reflux condenser placed in position, and the mixture refluxed for one hour. Almost immediately the solution became deep red in color. The solution was cooled and acidified with dilute sulfuric acid. A white, finely divided precipitate was thrown down. The mixture was extracted with ether and the ether extract washed with water. In order to remove the benzoic acid formed, the ether layer was extracted twice with sodium bicarbonate solution and finally with water. Upon evaporation of the ether solution, a light red viscous oil was obtained. Glistening plates, m.p. 59-66°, were obtained by dissolving this oil in hot toluene and cooling.

A second condensation was carried out in the same manner, using the same reactants in the same quantities. The following fractions were collected in the distillation:

Fraction	B.p., ° C. (mm.)	Bath, ° C.	Distillate (g.)
1	125-190 (2)	220-240	1
2	190-225[a] (2)	240-254	6.6
3	225-229 (2)	254-270	12.4

a Major portion distilled at 222-225°.

The yield of crude m-bromobenzylresorcinol was 19.0 g. or 21.9% based on m-bromobenzyl chloride.

Condensation of m-Bromobenzyl Bromide and Resorcinol.

It was believed that a product having a better melting point might be isolated by carrying out this condensation. The following quantities of reactants were used:

Resorcinol 110 g. (1.01 moles)

m-Bromobenzyl bromide 125 g. (0.50 mole)

Nitrobenzene 573 g. (480 ml.)

Anhydrous aluminum chloride 80 g. (0.6 mole)

The m-bromobenzyl bromide, b.p. 125-126° at 12 mm., was prepared by the procedure described on page 50. The m-bromobenzyl bromide was dissolved in 165 g. of the nitrobenzene and added dropwise to the reaction mixture over a period of two hours. The rest of the reaction was carried out as described above. Upon distillation of the semi-crystalline solid, 8.4 g. of light red oil was collected, boiling at 190-210° at 1 mm. Considering this as crude m-bromobenzylresorcinol, a yield of 10.3% was obtained based on m-bromobenzyl bromide. A small portion of this crude distillate was recrystallized from toluene and decolorized with Norite "A" to give slightly colored, glistening plates, m.p. 59-64°.

A small amount of the recrystallized m-bromobenzylresorcinol from the first condensation was placed in a vacuum desiccator over mineral oil for several days. This material exhibited the following melting point: Some of the crystals melted at 60-64°. The crystals that were

left were clearly defined and did not melt until 75° and then melted at 75-77°. After melting some of the compound in an oven at 125° for ten minutes and cooling the product until crystallization was complete, a melting point of 59-60.5° and 77-79° was again obtained. It is possible that two polymorphic forms of this compound exist. The material which had been dried over mineral oil was analyzed and gave the following bromine value. Anal. Calcd. for $C_{13}H_{11}BrO_2$: Br, 28.62. Found: Br, 28.41, 28.54.

V. Derivatives

Attempts were made to prepare five different types of derivatives of the bromobenzylresorcinols. These were the dibenzoates, the di-p-bromobenzoates, the diacetates, the diaryloxyacetic acids, and the p-tosyl derivatives. Of these only the dibenzoates and di-p-bromobenzoates were satisfactory. The diacetates, prepared by the method of Chattaway (10), were apparently oils. The p-tosyl derivative of m-bromobenzylresorcinol failed to crystallize, while the diaryloxyacetic acid of m-bromobenzylresorcinol was obtained in a yield too small for halogen determination. The product obtained upon reacting m-bromobenzylresorcinol and chloroacetic acid according to the method of Koelsch (11) melted at 172-174.5°.

Dibenzoates

The dibenzoates were prepared using essentially the method given by Gyorgy (3).

The following materials were placed in a dry 10-inch pyrex test

tube: 1.5 g. of the bromobenzylresorcinol, 5 ml. of dry pyridine, and 2 ml. of benzoyl chloride. As soon as the acid chloride was added, the tube became quite warm, the mixture solidified and turned light brown in color. The reaction mixture was protected by a calcium chloride tube and placed on a steam bath for an hour. At the end of this time the contents had darkened somewhat.

After allowing the mixture to cool, 10 ml. of water was added to the tube. The mixture was transferred to a separatory funnel, 20 - 30 ml. of ether added and the whole shaken . The water layer was drawn off and the ether layer washed twice with a 6 N sulfuric acid solution, a 10% sodium carbonate solution, and then with water.

After evaporating the ether from the solution a light tan oil was left. Only the dibenzoate of m-bromobenzylresorcinol could be made to crystallize on rubbing. The dibenzoates of the ortho- and para-bromobenzylresorcinols were found to crystallize from 95% ethanol as granular crystals. The dibenzoate of the meta isomer was recrystallized from 95% ethanol in the form of shiny plates. In all cases the yields were excellent and purification quite easy.

Di-p-bromobenzoates

The di-p-bromobenzoates were prepared essentially the same as the dibenzoates, except that 2.4 g. of p-bromobenzoyl chloride, prepared by the method given on page 4, 1.5 g. of the bromobenzylresorcinol and 6.5 ml. of pyridine were used. The mixture was heated for a period of two hours on the steam bath and then worked up. The di-p-bromobenzoates were all found to be only slightly soluble in absolute ethanol

TABLE I

DERIVATIVES OF BROMOBENZYLRESORCINOLS

Compound	Dibenzoate		Di-p-bromobenzoate	
	M.p., °C.	%Br [a]	M.p., °C.	%Br [b]
o-Bromobenzylresorcinol	87.5-88.5	17.09, 17.23	115.5-116.6	37.14, 37.08
m-Bromobenzylresorcinol	95.5-96.0	17.05, 17.29	153.5-154.5 [c]	37.11, 37.20
p-Bromobenzylresorcinol	101 - 102	17.10, 17.14	154 - 155°	36.97, 37.08

a. Calculated for $C_{27}H_{19}BrO_4$: Br, 17.25.

b. Calculated for $C_{27}H_{17}Br_3O_4$: Br, 37.16.

c. Mixed melting point, 135 - 145°.

and much solvent had to be used to recrystallize them. The di-p-bromobenzoates crystallized as granular crystals. In all cases, the yields were only fair.

VI. Method of Determination for Bromine

The method used for the determination of bromine was that given by Lemp and Broderson (12). This method involves a fusion of the organic compound with sodium peroxide in a Parr bomb in the presence of potassium nitrate and cane sugar. The fusion was then followed by a Volhard determination for halogen.

Approximately 1.5 g. of finely ground potassium nitrate, 0.4 to 0.45 g. of cane sugar, and 0.2 to 0.25 g. (accurately weighed) of the compound to be analyzed was placed in the fusion cup of the bomb. About 10 g. of sodium peroxide was then added quickly and the bomb sealed. After shaking the bomb thoroughly for about five minutes, the cup was tapped lightly on the desk to get materials to the bottom and ignited in the hottest part of a Bunsen flame until fusion had taken place (one to three minutes).

The bomb was then cooled immediately under the water tap, opened, the cup and top rinsed with distilled water, and placed in a 600 ml. beaker. The beaker was covered with a watch glass and enough hot water added to cover the fusion cup. After the evolution of gases had ceased the solution was digested for several minutes and the cup and top rinsed and removed. An excess of standard 0.1N silver nitrate solution was added and the mixture boiled gently for fifteen minutes.

The mixture was cooled, acidified with concentrated nitric acid, and hydrazine sulfate added in small portions until frothing had ceased. The determination was completed by a titration of the excess silver nitrate with standard potassium thiocyanate in the presence of ferric ion (3-5 ml. of ferric alum solution for each 200 ml. of solution). The addition of 3 ml. of nitrobenzene facilitated seeing the endpoint by surrounding the silver bromide and holding it on the bottom of the beaker.

DISCUSSION

During the course of this work, the three isomeric bromobenzylresorcinols have been prepared from resorcinol, the appropriate bromobenzyl chloride or bromide and anhydrous aluminum chloride, using nitrobenzene as the solvent. Of the above compounds, only p-bromobenzylresorcinol has been reported previously (6). The yields and melting points of these bromobenzyl-resorcinols are given in Table II. In all cases the yield from the bromobenzyl chloride was higher than from the corresponding bromide.

From Table II it may be observed that the melting point of the bromobenzylresorcinol increases in the order meta<para<ortho. The o-bromobenzylresorcinol prepared from o-bromobenzyl bromide melted at a slightly higher temperature than that prepared from the o-bromobenzyl chloride. All attempts to raise the melting point of the compound prepared from the chloride were futile. These attempts included recrystallization from water, toluene, and carbon tetrachloride, then redistillation followed by recrystallization from the above solvents. m-Bromobenzylresorcinol appeared to be rather impure from the melting point of 59-66.5°. However, after being melted completely and then permitted to cool and solidify, the melting point was observed to be 59-60.5° for some crystals and 77-79° for the rest of the crystals. This peculiarity in melting point may be due to polymorphism. p-Bromobenzylresorcinol was prepared in a 39.2% average yield from p-bromobenzyl chloride by the Friedel-Crafts method. Klarmann and v. Wowern (6) reported that a 55% yield of this compound was obtained from

TABLE II

BROMOBENZYLRESORCINOLS

Compound	From Chloride		From Bromide	
	Yield,% [a]	M.p., °C. [b]	Yield,% [a]	M.p., °C. [b]
o-Bromobenzylresorcinol	35.7 30.4	109.5-111	27.5	113.5-114.2
m-Bromobenzylresorcinol	21.9 36.4	59-60.5 and 77-79 [c]	10.3	59-64
p-Bromobenzylresorcinol	38.9 39.6	92.5-93.5	34.2	92.5-94

a. Yield of crude product obtained on distillation.

b. Melting point of purified product taken on Fisher-Johns melting point apparatus.

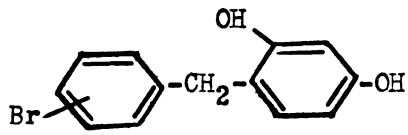
c. See discussion.

p-bromobenzonitrile and resorcinol via the Hoesch synthesis and a Clemmensen reduction of the ketone obtained. Their compound was reported to melt at 96° whereas the highest melting point obtained in the present work was 92.5-94°.

No systematic study for determining the optimum quantities of reactants was made, the quantities being similar to those used by Klarmann and v. Wowern (6) in the preparation of p-chlorobenzylresorcinol by the Friedel-Crafts method. However, it was observed that increasing the amount of p-bromobenzyl chloride from 0.31 to 0.46 mole, while holding the resorcinol constant at 0.63 mole, did not materially increase the yield of the desired product. On the other hand, in the preparation of o-bromobenzylresorcinol, it was found that by increasing the o-bromobenzyl chloride from 0.31 to 0.40 mole and the other reactants proportionately, the yield was increased from 30.4% to 35.7%.

In general the bromobenzylresorcinols are solids. They distil, usually with superheating, at 200 to 220° at 2 mm. as light yellow oils which crystallize slowly. They are so easily soluble in solvents containing oxygen, such as alcohols and esters, that they cannot be recovered from them. They are very insoluble in aliphatic hydrocarbons such as petroleum ether, hexane, heptane, etc. They can be crystallized with difficulty from toluene, xylene-ligroin, carbon tetrachloride, and large volumes of water. Although the pure solids are relatively stable, the solutions appear to be easily oxidized. It is very difficult to remove traces of color from them.

The structure of the bromobenzylresorcinols



is assumed to be that shown. This is in agreement with structure assigned by Klarmann (1, 6) to benzylated resorcinols, with the structure of hexylresorcinol, and with the fact that substitution in resorcinol is ortho to one hydroxyl group and para to the other, or in the 4 position.

The antibacterial action of the bromobenzylresorcinols is being investigated.

SUMMARY

The preparation of ortho-, meta-, and parabromobenzylresorcinols by the Friedel-Crafts method has been described. Of these, the ortho and meta isomers are reported for the first time.

The di-benzoates and di-p-bromobenzoates have been prepared as derivatives.

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PART II

A STUDY OF THE PEROXIDE CATALYZED CHLORINATION OF THE BROMOTOLUENES WITH SULFURYL CHLORIDE

INTRODUCTION

In 1939, Kharasch and Brown (1) described a method for the side chain chlorination of aromatic hydrocarbons. The method consisted essentially of heating together the hydrocarbon and sulfuryl chloride in the presence of catalytic amounts of benzoyl peroxide (other peroxides were employed but benzoyl peroxide was found to be the most suitable).

Thus toluene, p-chlorotoluene, ethyl benzene, isopropylbenzene and m-xylene were readily chlorinated in good yields by sulfuryl chloride. In some cases carbon tetrachloride, methylene chloride, and benzene were used as inert solvents. The purpose of the solvent was to decrease the vigor of the reaction by dilution and also to keep oxygen, which is an inhibitor, away from the reaction mixture. Kharasch and Brown proposed the following mechanism for side chain chlorination, where C_6H_5-, R-, Cl-, etc., represent free radicals. It involves the decomposition of the benzoyl peroxide at the reaction temperature initiating a chain reaction.

$$C_6H_5CO\text{-}O\text{-}O\text{-}COC_6H_5 \longrightarrow 2C_6H_5\text{-} + 2CO_2 \quad (1)$$

$$C_6H_5\text{-} + SO_2Cl_2 \longrightarrow \text{-}SO_2Cl + C_6H_5Cl \quad (2)$$

$$\text{-}SO_2Cl \longrightarrow SO_2 + Cl\text{-} \quad (3)$$

$$Cl\text{-} + RH \longrightarrow R\text{-} + HCl \quad (4)$$

$$R\text{-} + SO_2Cl_2 \longrightarrow RCl + \text{-}SO_2Cl \quad (5)$$

$$Cl\text{-} + RH \longrightarrow RCl + H\text{-} \quad (6)$$

$$H\text{-} + SO_2Cl_2 \longrightarrow HCl + \text{-}SO_2Cl \quad (7)$$

These authors considered equations (6) and (7) as being very unlikely. The chain could be broken by the following steps.

$$R\text{-} + R\text{-} \longrightarrow R\text{-}R \qquad (8)$$

$$R\text{-} + Cl\text{-} \longrightarrow R\text{-}Cl\text{ , etc.} \qquad (9)$$

$$H\text{-} + H\text{-} \longrightarrow H_2 \qquad (10)$$

$$H\text{-} + Cl\text{-} \longrightarrow HCl\text{ , etc.} \qquad (11)$$

In addition, impurities could break the chain reaction by combining with the atoms or free radicals.

In this laboratory, Gyorgy (2) first employed this method for the chlorination of the bromotoluenes. In all runs three moles of the bromotoluene, one mole of sulfuryl chloride, and 0.002 mole of benzoyl peroxide were used. This ratio was used supposedly to keep dichlorination of the side chain at a minimum and to reduce the vigor of the reaction by dilution. The reaction mixture was heated slowly to 93° - 97° C. (depending on the bromotoluene) in a round-bottomed flask equipped with an efficient condenser. As the initiation temperature was approached, the reaction mixture underwent a color change from a light yellow to a reddish orange. When the initiation temperature was reached a vigorous reaction occurred as evidenced by a rapid evolution of gases and the appearance of some liquid in the condenser. The liquid was noted to be deep red in color, but this color rapidly disappeared. At the end of about thirty minutes, the reaction was complete and the mixture was heated to gentle reflux for a short time. Any remaining gases were sucked off by means of an aspirator and the mixture distilled.

The reaction mixture from the chlorination of p-bromotoluene was distilled from a normal Claisen flask, and those from the ortho and meta bromotoluenes through a 6" heated column. The average yields of the bromobenzyl chlorides after rectification were reported as 78% for the para, 63% for the ortho, and 57% for the meta isomer. Gyorgy mentionedthat low boiling fractions and high boiling fractions were obtained in all cases, but these fractions were not identified.

During the course of the preparation of p-bromobenzylresorcinol, it became necessary to prepare p-bromobenzyl chloride as an intermediate. After several attempts to synthesize the intermediate in good yields by the method mentioned above, it became apparent that side reactions were also taking place. Several of the low boiling fractions were carefully investigated and p-chlorotoluene was isolated and identified.

It seemed desirable, after noting nuclear bromine displacement in this reaction, to further investigate the products formed in the sulfuryl chloride chlorination of the bromotoluenes.

Replacement of bromine by chlorine in chlorinations involving gaseous chlorine and aromatic bromides has frequently been observed.

Eibner (3) showed that chlorine could replace bromine from bromobenzene completely so that mono-chlorobenzene was obtained in addition to small quantities of other substances.

Srpek (4), in the chlorination of p-bromotoluene to form the benzylchloride, obtained p-bromobenzyl bromide as one of the products. Boeseken (5), Jacobs and Heidelberger (6), and Berger (7) all obtained products in the chlorination of para, ortho, and meta bromotoluenes, respectively, that had an increased bromine content in the side chain.

Also Olivier (8), hoping to prepare 3,5-dibromobenzyl chloride by the chlorination of 3,5-dibromotoluene at high temperature, always obtained a mixture of products that he could neither separate nor identify.

Asinger (9), hoping to prepare 3-bromo-5-chlorobenzaldehyde from 3-bromo-5-chlorotoluene by chlorination to the corresponding benzal chloride and subsequent hydrolysis to the benzaldehyde obtained 3,5-dichlorobenzaldehyde as a final product. A closer investigation showed that the nuclear bromine did not escape along with the hydrogen chloride given off but entered the side chain.

Asinger made a study of the side chain chlorination of ortho, meta, and para bromotoluenes and also 3,5-dibromotoluene. He found that partial or complete replacement of the nuclear bromine could occur and that the products formed were mixtures from which the benzyl or benzal chloride could not be isolated in pure form. Also the nuclear bromine, after being replaced, entered the side chain. Chlorination to the benzyl chlorides and benzal chlorides was carried out at 180° - 200° C. (in some cases at 160° - 170°). Replacement of nuclear bromine was shown to occur less at lower temperatures than at higher temperatures. Total halogen and side chain halogen were determined after the theoretical amount of chlorine had been taken up. For example, in the chlorination of p-bromotoluene to form the benzyl chloride, the following analysis of the reaction mixture was obtained after it had been freed of hydrogen halide gases by placing it over alkali.

Total chlorine-bromine value

Calculated on C_7H_6ClBr

Calc.	Cl	17.26%	Br	38.91%
Found	Cl	17.58%	Br	38.45%

One would assume that pure p-bromobenzyl chloride had been formed. However, upon side chain halogen determination, Asinger showed this was not the case.

Side chain halogen

Calc.	Cl	17.26%	Br	0.00%
Found	Cl	6.78%	Br	14.12%

After recrystallizing the mixture twice from ethanol, a product was obtained that melted at 43° - 44° C. and gave the following chlorine-bromine value.

Total chlorine-bromine value

Calculated on C_7H_6ClBr

Calc.	Cl	17.26%	Br	38.91%
Found	Cl	14.64%	Br	42.87%

Side chain halogen

Calc.	Cl	17.26%	Br	0.00%
Found	Cl	6.92%	Br	22.48%

EXPERIMENTAL

I. Chemicals

Bromine, N. F. V., Dow.

o-Bromotoluene, Dow (redistilled).

m-Bromotoluene, E. K. 1142 (redistilled).

p-Bromotoluene, Dow (redistilled).

o-Chlorobenzoic Acid, E. K. 552.

p-Chlorobenzoic Acid, E. K. 627.

Ethyl Alcohol, 95% and Absolute, Commercial Solvents.

Ether, Baker's Anhydrous Reagent.

Ether, Baker's U. S. P. "Solvent."

Magnesium Metal Turnings (for Grignard's reaction), Baker's Analyzed.

Picric Acid, C. P. Baker.

Potassium Permanganate, C. P. Baker.

Sodium Hydroxide (pellets), Merck, Reagent.

Sulfuryl Chloride, E. K., P322.

Thiourea, E. K., P497.

II. Chlorination of p-Bromotoluene

A. Preliminary Investigation.

For a preliminary investigation of the products formed in this reaction, the low boiling fractions of several runs were obtained from Gyorgy and vacuum distilled. For the distillation, a Fenske type column, 31 cm. long and packed with 1/16 in. I. D. case hardened glass

helices was used. The take-off was of the cold finger type arranged so that small fractions could be taken under vacuum.

The following definite fractions were obtained in the distillation.

Fraction	Identified as	B.p., °C.	(mm.)	n_D
1	p-Chlorotoluene[a]	47-48	(12)	1.5209[b]
2	p-Bromotoluene[c]	63-65	(12)	-----
3	p-Chlorobenzyl chloride[d]	94.5-95.5	(12)	-----

a. Large fraction. b. At 20.2°. c. Large fraction which solidified upon collection. d. A small fraction that solidified upon standing.

1. Identification of p-Chlorotoluene.

Since the boiling point and refractive index of fraction 1 agreed closely with the values given by Huntress (10) for p-chlorotoluene (b.p. 45.5-48°/12 mm., and n_D^{20} = 1.521), there was good reason to believe that p-chlorotoluene had been formed in the chlorination.

An alkaline permanganate oxidation of fraction 1 was carried out using the procedure of Cheronis and Entriken (11).

In a 50 ml. round-bottomed flask equipped with a reflux condenser were placed 1.5 g. of solid potassium permanganate, 25 ml. of water, 0.5 ml. of 6 N sodium hydroxide, and a boiling chip. Five hundred milligrams of fraction 1 was added and the mixture refluxed for an hour and three quarters. At the end of this time, the permanganate color had almost disappeared, and the characteristic brown precipitate of manganese dioxide was present.

After the reaction mixture cooled, it was acidified to Congo red paper with dilute sulfuric acid. Sodium bisulfite was then added in small quantities to the mixture until the solution cleared. The solution was boiled for a few minutes, filtered, and cooled. Upon cooling, the oxidation product crystallized in white needles which were filtered and recrystallized from 10 ml. of hot alcohol. Water was then added drop-wise to the filtered, hot alcoholic solution until a slight turbidity resulted. The solution was cooled and the product filtered and dried at room temperature.

The melting point of the product (taken in a sealed capillary) was 235-236.5°. When admixed with an authentic sample of p-chlorobenzoic acid, m.p. 235-236°, it melted at 233.5-235°.

2. Identification of p-Bromotoluene.

Unreacted p-bromotoluene, fraction 2, constituted a very large fraction and solidified on collection in the receiver. The boiling point checked closely with that given by distillation of the known p-bromotoluene. This material was noted to melt on a warm day in the laboratory when the temperature was over 28°. Bigelow (12) lists a melting point of 25-26°. Gyorgy (13) reported a boiling point of 70-74° at 12 mm., but mentioned that he could never get the recovered p-bromotoluene to solidify.

3. Identification of p-Chlorobenzyl Chloride.

Due to the fact that p-chlorotoluene had been identified as one of the products in the chlorination reaction, and the boiling point of fraction 3 agreed closely with that given by Huntress (14) for

p-chlorobenzyl chloride (94-96° at 14 mm.), there was good reason to believe this fraction to be p-chlorobenzyl chloride. Fraction 3 (b.p. 94.5-95.5° at 12 mm.) was characterized by conversion to the Grignard reagent, carbonation, and subsequent hydrolysis to the phenylacetic acid. The procedure was essentially the same as that given by Cheronis and Entriken (15) for the preparation of phenylacetic acid.

Two hundred and forty milligrams of magnesium turnings was placed in a 10 in. pyrex test tube that had been dried by heating with a flame. A solution of 1.4 g. of fraction 3 in 8 ml. of anhydrous ether was added all at once to the magnesium. The reaction started very easily after crushing a few magnesium turnings with the end of a stirring rod. A cork bearing a finger condenser and a soda-lime tube was placed tightly in the mouth of the tube. After about twenty minutes, the reaction ceased and the solution was refluxed for a short period and allowed to cool. The reagent was a dark green color.

The carbonation of the Grignard reagent was effected by dropping small pieces of dry ice into the tube after each piece had been wiped with a dry cloth. A vigorous reaction occurred and most of the ether was lost. After the reaction had ceased, the mixture was stirred, 10 ml. of ether added, and the addition product decomposed with a mixture of 8 g. of ice and 4 ml. of concentrated sulfuric acid. The resulting mixture was filtered from the unreacted magnesium into a 250 ml. separatory funnel. The ether layer was separated, the water layer extracted once with ether, and the ether extracts combined.

The water layer was tested for bromide ion in the following manner. One milliliter of the solution and 1 ml. of chloroform were placed in

a small test tube and two drops of chlorine water added. After several minutes the organic layer became light brown in color. This would indicate that fraction 3 was probably slightly contaminated with a bromide.

In order to isolate the acid, the ether solution was extracted once with a 5% sodium hydroxide solution, once with water and the extracts combined.

Upon careful acidification of these extracts with dilute hydrochloric acid, followed by cooling, the acid crystallized as fine, white needles which were filtered and dried at room temperature. After recrystallization from dilute alcohol, the compound melted at 101.5-103.5°.

When admixed with p-chlorophenylacetic acid, prepared in the same manner as above from p-chlorobenzyl chloride and melting at 103-105°, it melted at 102-105°.

B. Chlorination of p-Bromotoluene in the Dark.

The following reaction was carried out using only an 8 candle power red safety light for illumination. Due to the large amount of gases given off, it was necessary to carry out the chlorination in the hood.

In a 3-l. one-necked, round-bottomed flask equipped with a ground glass bulb condenser, a thermometer extending through the condenser to the bottom of the flask, and heated by a Glascol mantle were placed 514 g. (3 moles) of p-bromotoluene, 135 g. (1 mole) sulfuryl chloride, and 0.5 g. of benzoyl peroxide. The p-bromotoluene used was redistilled (b.p. 82° at 27 mm.) from a Claisen flask, and the sulfuryl chloride

was distilled through a 30 cm. Fenske column immediately before use (b.p. 67° at 739.6 mm.). The reactants were heated slowly to 100°. At this temperature the reaction commenced. The mantle was removed and the reaction flask cooled with an ice bath. Even with external cooling the reaction proceeded violently, being accompanied by the evolution of gases and vigorous reflux in the condenser. At 40°, the reaction still proceeded but not as vigorously as before. After about thirty minutes, spontaneous reaction had ceased and the mixture was heated to 110° for a short time.

The reaction mixture was transferred to a 500 ml. two-necked, round-bottomed flask equipped with a thermometer well and capillary tube, the corrosive vapors pulled off by the water aspirator and the material distilled through the Fenske column previously described (page 33). The pressure was reduced by means of an oil vacuum pump. The following fractions were obtained:

Fraction	Identified as	B.p., ° C.	(mm.)	Distillate (g.)	No. of moles
1	p-Chlorotoluene	47.5-50	(12)	27.9	0.22
2		50 -62	(12)	8.5	
3	p-Bromotoluene[a]	62 -64.5	(12)	317.4	1.85
4		75 -92	(12)	2.1	
5		92 -94	(12)	.83	
6	p-Chlorobenzyl chloride[b]	94 -97	(12)	2.55	0.02
7	[c]	97 -100	(12)	1.66	
8	p-Bromobenzyl chloride[d]	100 -115	(12)	77.2	0.38
9	p-Bromobenzyl bromide[e]	115 -124	(11)	46.2	0.18

a,b,c,d,e. These fractions solidified upon collection.

Fraction 1, identified as p-chlorotoluene in the preliminary investigation (page 34), amounted to 0.22 mole of p-chlorotoluene produced.

Fraction 2 can be considered as a mixture of p-chlorotoluene and p-bromotoluene.

Fraction 3, p-bromotoluene, solidified upon collection in the receiver and amounted to 1.8 moles.

The fractions intermediate between those of p-bromotoluene and p-chlorobenzyl chloride, fractions 4 and 5, were considered as mixtures of p-bromotoluene and p-chlorobenzyl chloride.

Fraction 6, which amounted to 2.55 g., was considered as p-chlorobenzyl chloride. This fraction was collected at approximately the same boiling point as that identified as p-chlorobenzyl chloride on page 35 .

1. Identification of p-Bromobenzyl Chloride.

Upon recrystallizing fraction 8 from 95% alcohol, 71.8 g. of long needles was obtained, m. p. 40-41° on a Fischer-Johns melting point block. Some of the literature values for p-bromobenzyl chloride are as follows: 38-39° (16), 40° (17), 41° (5), 40-42° (18). The total yield of recrystallized p-bromobenzyl chloride was 34.9%, based on the sulfuryl chloride used.

2. Identification of p-Bromobenzyl Bromide.

By recrystallizing fraction 9 from 95% alcohol, 40.9 g. of a product crystallizing in long needles was obtained. This material gave a melting point of 60-62°. This value agrees closely with that found by the bromination of p-bromotoluene, m.p. 61-62° (page 48).

The material obtained by recrystallizing fraction 9 was identified as p-bromobenzyl bromide by a mixed melting point with a sample of

known p-bromobenzyl bromide, prepared as on page 48, and by analysis. This material when admixed with known p-bromobenzyl bromide, m.p. 61-62°, melted at 60.5-62.5°.

Analysis of this material after drying in a vacuum desiccator gave the following bromine value. Anal. Calcd. for $C_7H_6Br_2$: Br, 63.96. Found: Br, 63.78 and 64.01.

C. Chlorination of p-Bromotoluene in the Light.

Another chlorination was carried out in daylight using the same equipment and the same quantities of reactants as described on page 37.

This time the reaction mixture was noted to undergo a characteristic color change from light yellow to deep orange as it was slowly heated to 93°. At this temperature the reaction commenced, the mantle was removed, and the reaction flask was cooled with an ice bath. Even with external cooling the evolution of gases was very vigorous and much red liquid flooded the condenser.

After the reaction had ceased (about twenty minutes), the mantle was again adjusted and the mixture heated to 110° for a short time. Upon working up the reaction mixture in the previously described manner, the same products were recovered as before in the yields indicated.

Fraction	Identified as	B.p., °C.	(mm.)	Distillate (g.)	No. of moles
1	p-Chlorotoluene	53-55	(16)	35.6	0.28
2	--	61-63	(16)	1.7	--
3	p-Bromotoluene	70-74	(18)	327.6	1.91
4	a.	87-102	(16)	2.0	--
5	p-Bromobenzyl chloride	107-120	(12)	96.0[b]	0.47
6	p-Bromobenzyl bromide	120-130	(12)	26.6[b]	0.11

a. This was probably a mixture of p-bromotoluene and p-chlorobenzyl chloride. The amount of material boiling at the temperature and pressure given for p-chlorobenzyl chloride was very small.

b. Yield of unrecrystallized product.

D. Effects of a Solvent on the Chlorination of p-Bromotoluene.

To determine the effect of a solvent on the chlorination, carbon tetrachloride was used. The reaction was carried out as in the previous cases, using the following quantities of reactants:

p-Bromotoluene	-- 342	g.	(2 moles)
Sulfuryl chloride	-- 135	g.	(1 mole)
Carbon tetrachloride	-- 100	ml.	(approx. 1 mole)
Benzoyl peroxide	-- 0.5	g.	(0.00203 mole)

The reactants were placed in a 2 l. three-necked flask equipped with two ground glass bulb condensers and thermometer. At 75° some refluxing occurred. As the temperature was raised, the same color change from light yellow to deep orange took place, and the refluxing increased. At 93° the vigorous reaction again occurred, much red liquid flooded the condenser, and no diminution in the violence of the reaction was observed. The flask was cooled with an ice bath for a short time, the ice bath removed, and the reaction allowed to proceed by itself. The liquid was still bubbling after five hours.

The reaction mixture was worked up in the manner previously described, the solvent removed at atmospheric pressure and the material boiling below 105° at 12 mm. distilled from a Claisen flask. This material was redistilled through a Fenske column and the following quantities of products were obtained:

Fraction	Identified as	B.p., ° C.	(mm.)	Distil-late (g.)	No. of Moles
1	p-Chloro-toluene	56.5-59	(17)	38.2	0.30
2	p-Bromo-toluene	65-70	(15)	106.5	0.63

Due to the hold up in a column of this type, and the small amount of p-chlorobenzyl chloride probably produced, no fraction corresponding to that of p-chlorobenzyl chloride was obtained.

The material boiling above 105° at 12 mm. from the reaction was distilled from a Claisen flask using a three-pronged type fraction cutter and 125 ml. Erlenmeyer flasks to collect the following fractions.

Fraction	Identified as	B. P., ° C.	(mm.)	Distil-late (g.)	No. of Moles
3	p-Bromobenzyl chloride	106-121	(12)	108.5	0.53
4	p-Bromobenzyl bromide	121-131	(12)	39.6	0.16

Upon recrystallizing fraction 3 from 95% alcohol, there was obtained 94.5 g. (45.9% yield) of p-bromobenzyl chloride, m.p. 41-42.5°.

There was obtained 27.8 g. of material melting at 54.5-56.5° upon recrystallizing fraction 4 from 95% alcohol. This material evidently was p-bromobenzyl bromide contaminated with p-bromobenzyl chloride.

III. Chlorination of o-Bromotoluene.

A. Preliminary Investigation.

The material from several chlorination reactions was obtained from Gyorgy and distilled through the Fenske column previously described.

The following definite fractions were obtained:

Fraction	Identified as	B.p., ° C.	(mm.)	n_D^{20}
1	o-Chlorotoluene	54.5-55	(20)	1.5263
2	o-Bromotoluene	68.5	(19)	1.5560
3	o-Chlorobenzyl chloride	98.5-100	(17)	1.5621
4	o-Bromobenzyl chloride	112-114	(17)	1.5880
5	o-Bromobenzyl bromide	123-127	(17)	--

1. Identification of o-Chlorotoluene.

The physical properties of fraction 1 were in agreement with those given by Huntress (19) for o-chlorotoluene (b.p. 41° at 11 mm., n_D^{20} = 1.52691).

An alkaline permanganate oxidation was carried out on fraction 1 using the procedure described on page 34 for the oxidation of p-chlorotoluene.

The product obtained from the oxidation of fraction 1 melted at 137-139° in a sealed capillary. When admixed with an authentic sample of o-chlorobenzoic acid, m.p. 137-139°, it showed no depression.

2. Identification of o-Bromotoluene.

Since fraction 2 constituted such a large one and the boiling point and refractive index checked closely with the values given by Gyorgy (20), namely 70-72° at 20 mm. and n_D^{20} = 1.5550, for known o-bromotoluene, this material was considered as the o-bromotoluene recovered from the chlorinations.

3. Identification of o-Chlorobenzyl Chloride.

Since o-chlorotoluene had been isolated and identified in the chlorination and since the boiling point of fraction 3 agreed closely

with that given by Austin and Johnson (96-98° at 14 mm.) (21) and Bennett and Jones (94° at 15 mm.) (22), it was believed that fraction 3 was o-chlorobenzyl chloride.

Fraction 3 was identified as o-chlorobenzyl chloride by nitration to 2-chloro-5-nitrobenzyl chloride using essentially the procedure described by Meisenheimer, Zimmermann, and v. Kummer (23).

Five grams of fraction 3 was placed in a 10 in. pyrex test tube and heated to 30°. While maintaining the temperature between 30 and 35°, 10 ml. of fuming nitric acid was added dropwise from a separatory funnel to the tube with shaking. After the acid had been added, the mixture was allowed to cool and then poured on cracked ice. By stirring and scraping, a heavy gummy precipitate was obtained. This was recrystallized twice from 95% alcohol to give light yellow needles, m.p. 64-66°.

Nitration of a known sample of o-chlorobenzyl chloride by the above procedure gave a product melting at 66°. A mixed melting point gave a value of 65-66°.

4. Identification of o-Bromobenzyl Chloride.

Fraction 4 constituted the major fraction in the distillation. The boiling point found was in agreement with that reported by Bennett and Jones (105-106° at 12 mm.) (22) for o-bromobenzyl chloride.

5. Identification of o-Bromobenzyl Bromide.

The boiling point of fraction 5 was in agreement with that found for known o-bromobenzyl bromide prepared as described on page 49. Also, a capillary boiling point was taken and a value of 233-234° at 743 mm.

was obtained. A sample of known o-bromobenzyl bromide was found to boil at 235-236° at 743 mm.

Fraction 5 was identified as o-bromobenzyl bromide by conversion to the S-o-bromobenzylisothiourea picrate using a procedure described by Levy and Campbell (24).

One gram of powdered thiourea, 1 g. of fraction 5, 10 ml. of ethanol, and a boiling chip were placed in a 10 in. pyrex test tube. A finger condenser was placed in position and the mixture refluxed for five minutes. At the end of this time, 1.0 g. of picric acid was introduced and heating continued for an additional five minutes.

Upon cooling, the tube filled with a mass of yellow needles. These were filtered, recrystallized once from alcohol, and dried at room temperature. The melting point of the product in a sealed capillary was 221.5-223°. Levy and Campbell (24) reported 222° as the melting point for S-o-bromobenzylisothiourea picrate.

B. Chlorination of o-Bromotoluene.

In order to determine the amounts of the products of the reaction, a chlorination in daylight was carried out. The equipment was the same as that described on page 41 for the chlorination of p-bromotoluene, and the quantities of reactants were as follows:

o-Bromotoluene	--	256.4 g.	(1.5 moles)
Sulfuryl chloride	--	67.5 g.	(0.5 mole)
Benzoyl peroxide	--	0.242 g.	(0.001 mole)

Upon heating the reaction mixture to 60-65°, the characteristic color change from light yellow to deep orange occurred. At 70°

evolution of gases began but did not become vigorous until 95° was reached. At this temperature the reaction was violent and external cooling of the reaction vessel with an ice bath was necessary. When it was noted that the reaction was not proceeding spontaneously, the mantle was adjusted and the mixture heated once more to 95°. Again the reaction started violently and external cooling was necessary. However, this time the reaction proceeded smoothly for about twenty minutes. The mixture was then heated to 120° for ten minutes and after cooling transferred to a 500 ml. two-necked round-bottomed flask fitted with a thermometer well and capillary tube. After pulling off the corrosive gases with an aspirator, the distillation was carried out through a Fenske column.

Fraction	Identified as	B.p., ° C.	(mm.)	Distillate (g.)	No. of moles
1	o-Chlorotoluene	54-57.5	(20)	15.5	0.13
2	o-Bromotoluene	71-75	(21)	121.7	0.71
3	o-Chlorobenzyl chloride	97.5-100	(17)	2.0	0.012
4	o-Bromobenzyl chloride	110-114	(17)	32.9	0.16
5	o-Bromobenzyl bromide	124-128	(17)	11.8	0.047

IV. Chlorination of m-Bromotoluene.

For an investigation of the products formed in this reaction, the material from several reactions was obtained from Gyorgy and vacuum distilled through a Fenske column. The following fractions were collected:

Fraction	Identified as	B.p., ^{o} C. (mm.)		Remarks
1		97-99.5	(17.5)	$n_D^{19.6}$ = 1.5610
2	m-Chlorobenzyl chloride	99.5-101	(17.5)	$n_D^{19.6}$ = 1.5625
3		101-102	(17.5)	n_D^{19} = 1.5635
4		102-105	(17)	$n_D^{19.6}$ = 1.5661
5		105-116	(17)	
6	m-Bromobenzyl chloride	116-118.5	(17)	main fraction
7		118.5-129	(17)	
8	m-Bromobenzyl bromide	129-131.5	(17)	large fraction, solidified.

Evidently all the m-chlorotoluene and m-bromotoluene had been stripped from the reaction mixture by Gyorgy.

A. Identification of m-Chlorobenzyl Chloride.

Bennett and Jones (22) list a value of 104° at 17 mm. for the boiling point of this compound. Although the refractive index of fraction 1 agreed more closely to the value given by Robinson (n_D^{20} = 1.5568) (25), fraction 2 was chosen for the identification. This was necessary because fraction 1 was very small.

The identification of m-chlorobenzyl chloride was carried out by the alkaline permanganate oxidation of fraction 2. The procedure used was about the same as that described on page 34 for the oxidation of p-chlorotoluene except that the solution was more alkaline; 16 drops of 6 N sodium hydroxide being used. The product melted at 156-157° while that from the oxidation of known m-chlorotoluene melted at 153-154°. A mixed melting point gave a value of 153.5-157°.

The material evidently must have been the m-chlorobenzyl chloride and not the m-chlorobenzyl bromide which boils much higher (103-105° at 8 mm.) (26, 27).

B. Identification of m-Bromobenzyl Chloride.

Fraction 6 constituted the main fraction in the distillation. This was considered as the m-bromobenzyl chloride since its boiling point agreed with that given by Olivier (119° at 18 mm.) (28).

C. Identification of m-Bromobenzyl Bromide.

Fraction 8 which constituted a large fraction solidified as collected. Known m-bromobenzyl bromide, prepared as described on page 50, distilled at 125-127° at 12 mm. and also solidified when collected.

Fraction 8 was identified by its conversion to the S-m-bromobenzylisothiourea picrate by the method employed on page 45. The yellow needles obtained were lighter in color than the corresponding ortho isomer and melted at 204-205°. Levy and Campbell (24) list 205° for the melting point of S-m-bromobenzylisothiourea picrate.

V. The Preparation of the Bromobenzyl Bromides.

The bromobenzyl bromides were prepared by a modification of the method given by Coleman and Honeywell (29) and Brewster (30).

A. Preparation of p-Bromobenzyl Bromide.

Two-hundred-fifty-six and one half grams (1.5 moles) of p-bromotoluene was placed in a 1 l. three-necked, round-bottomed flask (ground glass joints), which was fitted with an addition tube and bulb condenser,

a separatory funnel that reached below the surface of the p-bromotoluene, a thermometer, and an efficient mechanical stirrer.

The p-bromotoluene was heated slowly to 95° by means of a mantle. At this temperature, 51.7 ml. (79.9 g., 1.0 mole) of bromine (N.F.V.) was added with stirring at a rate that just kept the solution void of bromine color (about two hours). The temperature rose rapidly to 110° and was maintained between 110-120° during the addition. Throughout the addition of bromine, the reaction mixture was illuminated with two 150-watt, unfrosted, tungsten lamps.

After all the bromine had been added, heating was discontinued and the reaction mixture stirred for fifteen minutes. The contents of the reaction flask was poured while still warm into a 250 ml. Claisen flask, freed of gases with an aspirator and vacuum distilled using a three-pronged fraction cutter and 125 ml. Erlenmeyer flask to collect the fractions. The following fractions were obtained after the p-bromotoluene had been removed.

Fraction	B.p., °C.	(mm.)	Distillate (g.)	Recrystallized (g.)	M.p., °C.
1	125-130	(12)	157	124.5	61-62
2	130-135	(12)	11	5.3	61.5-62.5

The above fractions recrystallized from 95% alcohol as long colorless needles, m.p. 61-62.5°, and amounted to 129.8 g. or 51.9%, based on the bromine used.

B. Preparation of o-Bromobenzyl Bromide.

The same equipment was used as for the preparation of p-bromobenzyl bromide. The following quantities of reactants were used:

o-Bromotoluene	299.3 g.	(1.75 moles)
Bromine	51.7 ml., 158.4 g.	(1.0 mole)

The o-bromotoluene was heated with stirring to 100° and the bromine added slowly. As the reaction proceeded, the temperature rose quickly to 135° and was maintained between 135-140° throughout the addition of the bromine. This required about three and a half hours. After the bromine had been added, heating was discontinued and stirring continued for about ten minutes. The mixture was poured into a 500 ml. two-necked, round-bottomed flask equipped with a thermometer well and a capillary tube. After drawing off the gases with an aspirator, the material was vacuum distilled through a Fenske column.

Fraction	Product	B.p., ° C. (mm.)	Distillate (g.)
1	o-Bromotoluene	70-74 (17)	137
2	--	74-129 (17)	1.7
3	o-Bromobenzyl bromide	129-130 (16.5)	198

The yield of o-bromobenzyl bromide, b.p. 129-130° at 16.5 mm., was 137 g. (79.2% based on bromine used or 95% based on the o-bromotoluene consumed).

C. Preparation of m-Bromobenzyl Bromide.

Two hundred six grams (1.20 moles) of m-bromotoluene, $n_D^{20} = 1.5521$, was brominated with 35.5 ml. (108.5 g., 0.685 mole) of bromine using the procedure and equipment described above. The addition of bromine was started as soon as the m-bromotoluene had reached 100°. The temperature rose quickly to 175° and remained between 175-180° until all the bromine had been added. This required an hour and a half. The reaction

mixture was distilled as previously described.

Fraction	Product	B.p., °C.	(mm.)	Distillate (g.)
1	m-Bromotoluene	65-67	(12)	93.7
2	m-Bromobenzyl bromide	125-127	(12)	128

The product, m-bromobenzyl bromide, was collected at 125-127° at 12 mm. and weighed 128 g. (74.7% theory based on the bromine used, or 95.2% on the m-bromotoluene consumed.) This product soon crystallized on standing.

DISCUSSION

This investigation of the peroxide catalyzed chlorination of the bromotoluenes with sulfuryl chloride has shown that the products obtained are similar to those obtained by chlorination with molecular chlorine. In addition to the recovered bromotoluenes and the expected bromobenzyl chlorides as many as three other products were obtained from each of the bromotoluenes. These are shown in Table I.

It is evident from the products identified in the chlorination that nuclear bromine replacement by chlorine takes place to a considerable extent. This phenomenon is indeed strange when one considers the work of Kharasch and Brown (1). By reacting 3.0 moles of n-propyl bromide and 0.75 mole of sulfuryl chloride and using 0.001 mole of benzoyl peroxide as a catalyst, they obtained a 50% yield of 1-bromo-2-chloropropane and a 30% yield of 1-bromo-3-chloropropane. No n-propyl chloride was isolated.

The recovery of relatively large amounts of the chlorotoluenes and very small amounts of the chlorobenzyl chlorides may be explained by one or both of the following: (1) The initial concentration of the chlorotoluene is very small and is increased during the course of the reaction. Hence the amount of chlorotoluene present to be chlorinated at the start of the reaction is very small and the chlorination proceeds only as the concentration of chlorotoluene increases. (2) The reaction between free radicals of chlorine and the

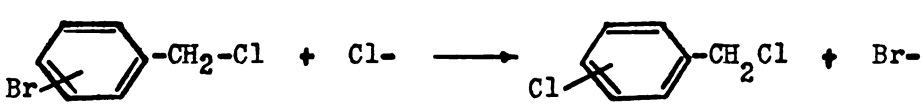


TABLE I

MINOR PRODUCTS FROM THE CHLORINATION OF THE BROMOTOLUENES

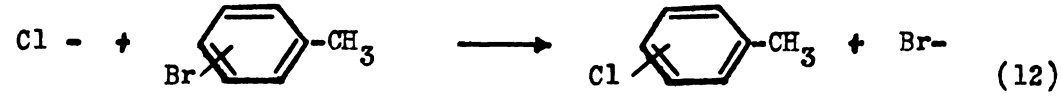
Compound Chlorinated	Products Identified	Method of Identification
o-Bromotoluene	o-Chlorotoluene	Oxidation of o-chlorobenzoic acid.
	o-Chlorobenzyl chloride	Nitration to 2-chloro-5-nitro-benzyl chloride.
	o-Bromobenzyl bromide	Conversion to S-o-bromo-benzylisothiourea picrate.
m-Bromotoluene	m-Chlorobenzyl chloride	Oxidation to m-chlorobenzoic acid.
	m-Bromobenzyl bromide	Conversion to S-m-bromo-benzylisothiourea picrate.
p-Bromotoluene	p-Chlorotoluene	Oxidation to p-chloro-benzoic acid.
	p-Chlorobenzyl chloride	Formation of the Grignard reagent, carbonation, and hydrolysis to p-chlorophenyl-acetic acid.
	p-Bromobenzyl bromide	Analysis and mixed m.p. with a known sample.

bromobenzyl chloride to yield chlorobenzyl chloride and free radicals of bromine does not occur to any appreciable extent.

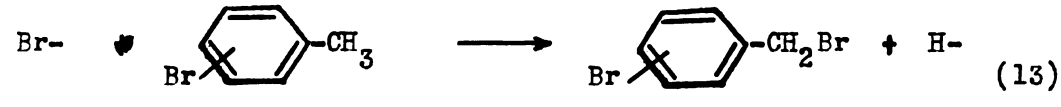
Bromination of the side chain also occurs during this chlorination reaction. The bromine atom, after being replaced, is quite reactive and enters the side chain on it to form the bromobenzyl bromides, which were isolated from the chlorination of each of the bromotoluenes. No chlorobenzyl bromides were isolated. The bromobenzyl bromides are evidently the high boiling products thought by Gyorgy to be the bromobenzal chlorides.

Little or no effect was noted in the reaction when the chlorination of p-bromotoluene was carried out in the dark or in the presence of a solvent such as carbon tetrachloride. It is interesting to note, however, that the initiation temperature was higher (100° as compared to 93°) when the chlorination of p-bromo-toluene was performed in the dark.

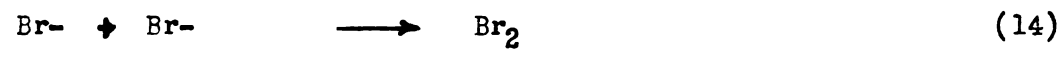
In addition to the eleven possible equations suggested by Kharasch and Brown (1) (see page 28) for explaining how the chlorination reaction using sulfuryl chloride might proceed, the following four equations should be added for the bromotoluenes:



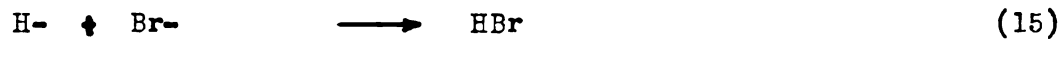
(12)



(13)



(14)



(15)

Equations (14) and (15) represent chain-breaking or chain terminating reactions. Although no evidence was obtained in favor of equation (15), equation (14) probably does occur. The evidence for this was the change of the reaction mixture from a light yellow to a deep orange color as the temperature was raised and also the red-colored liquid which flooded the condenser at the height of the chlorination reaction.

This method of chlorination appears to be quite useful in the preparation of the chlorobenzyl chlorides (25). However, in the chlorination of the bromotoluenes the yields are reduced considerably by the side reactions, and the products formed are difficult to separate.

The bromobenzyl bromides have been prepared in good yields from the bromotoluenes by bromination in light from the unfrosted tungsten lamps at temperatures near the boiling point. These bromobenzyl bromides were useful in identifying like products which were formed in the chlorination reaction.

SUMMARY

1. The peroxide catalyzed chlorination of the bromotoluenes with sulfuryl chloride has been investigated.

2. Nuclear bromine replacement by chlorine has been found to occur. The bromine atom after being replaced enters the side chain of the bromotoluenes.

3. In addition to the bromobenzyl chlorides, chlorotoluenes, chlorobenzyl chlorides and bromobenzyl bromides have been identified as products of the chlorination reaction.

4. The preparation of the bromobenzyl bromides in good yields is described.

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