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A GENERAL CHEMICAL METHOD  
FOR THE PREPARATION OF THE  
DEUTERATED BENZENES

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## Survey of the Method.

The Raman spectra of the deuterium derivatives of benzene should furnish valuable information concerning the internal vibrations of the benzene molecule, and from these one should also be able to make direct inferences concerning the structure of benzene. We have therefore prepared each of the derivatives in pure form and have investigated their spectra. In this paper we shall report only the methods of preparation.

The introduction of deuterium into the benzene nucleus has usually been effected by exchange between benzene and some deuterium compound, with or without a catalyst. The exchange method is quite satisfactory for preparing hexadeuterobenzene. For the preparation of the intermediate deuterium derivatives in pure form, however, the method of direct exchange is not applicable, since one can obtain thereby only mixtures of the various compounds. It is therefore necessary to resort to chemical procedures which can be depended upon to introduce deuterium into definite places in the ring. Two such procedures which immediately suggest themselves are: (1) the decarboxylation of the various calcium benzene-carboxylates with  $\text{Ca}(\text{OD})_2$ , and (2) the replacement of halogen atoms with deuterium by means of a Grignard reaction.

The first of these methods was used by ERLÉNMEYER (Helv. chim. acta 18, 1464 (1935)) to prepare hexadeutero-

benzene. However, the attempts of REDLICH (Monatsh. 68, 374 (1936)) to prepare *p*-tetra deuterobenzene in this way led to a mixture of the three tetra compounds, a result which is not surprising in view of the high temperatures required for decarboxylation. The decarboxylation method therefore appears to us to be unsafe for the preparation of any pure deuterium derivatives except the hexa compound.

The first use of the Grignard method was that of REDLICH (Monatsh. 67, 213 (1936)) who prepared mono-deuterobenzene by hydrolyzing  $C_6H_5MgBr$  with  $D_2O$ . He also used the same procedure for making the para-di derivative since it is possible to prepare  $p-C_6H_4(MgBr)_2$ . The Grignard method has the strong disadvantage that save for one or two exceptions such as the preceding, only one of the halogens in a polyhalogenated benzene will react with magnesium to form a Grignard reagent. In order to replace more than one halogen with deuterium, it is necessary to carry out the reaction stepwise, preparing a new Grignard reagent after each hydrolysis. This entails the wasteful and troublesome purification and drying of each intermediate halogen-deuterium compound from which the succeeding Grignard reagent is to be prepared. A further disadvantage is that the hygroscopic nature of the basic magnesium halide produced by the hydrolysis necessitates the use of a large excess of  $D_2O$ . This excess, as well as the deuterium in the basic halide, is extremely troublesome to recover.

All of these difficulties are obviated by using  $DCl$  rather than  $D_2O$  for breaking up the Grignard complex. The decomposition of the complex with dry  $DCl$  gas may be carried out in the ether solution in which the complex has been formed. We have found that magnesium does not react with  $DCl$  in the dry ether solution and more-

over that it is still possible for the magnesium under these circumstances to form a new Grignard compound. Therefore if the introduction of the DCl is begun as soon as the appropriate polyhalogenated benzene has been transformed to the first Grignard complex, one will obtain straightaway a monodeutero-halogen-compound. The latter will react again with magnesium, forming a new Grignard complex which will in turn be decomposed by the DCl. The replacement of several halogen atoms by deuterium can thus proceed in an effectually continuous fashion. The fact that the reaction can be carried out in a single vessel without isolation of the intermediate compounds results in tremendous saving of time and materials.

The DCl required for the decomposition of the Grignard compound is generated by addition of  $D_2O$  to  $SOCl_2$ . In this way the gas can be produced in a high state of purity with little loss of deuterium (ca. 10—15%). This loss is quite small in comparison with the previously mentioned losses of deuterium attendant upon the hydrolysis of the Grignard compound, inasmuch as here the final magnesium compound is a normal rather than a basic salt.

A further convenience of the method is the ease with which the deuterated benzene may be obtained in purified form from the reaction mixture. It is only necessary to distill off the ether solution in vacuo from the crystalline magnesium salts, wash and dry it, and then remove the ether from the benzene by fractionation through an efficient column.

There is one feature of the DCl method which might lead to a rather considerable loss of deuterium. If the DCl be introduced into the reaction vessel so rapidly that an excess is present, some of it may react with magnesium

iodide to form DI. The DI in turn reacts with the diethyl ether to produce ethyl iodide (cf. the well-known ZEISEL method for the estimation of alkoxy groups); from the latter, mono-deuteroethane is formed by Grignard reaction. The amount of ethane given off depends only on the extent of the excess of DCl, and consequently the stream of gaseous ethane may serve as a rather sensitive indicator for the excess. With help of this indicator, the most effective rate of admission of DCl gas to the reaction vessel may be closely determined. Furthermore it is obvious that the replacement of halogen by deuterium in the benzene nucleus has been completed when it is no longer possible to cut off the evolution of ethane by slowing down the addition of DCl.

Following the program we have just outlined, we have prepared all of the deuterated benzenes in amounts varying from seven to fourteen grams. The success of the preparations depends largely on careful control of the rate of addition of DCl. Therefore it should be emphasized that close attention must be paid to the details of the addition which are described in the experimental part.

The purity of the products may be indicated briefly by saying that their boiling point ranges were quite narrow, and that their Raman spectra showed only the presence of small amounts of benzenes with lower deuterium content, but no traces of isomers or of extraneous impurities. It is quite important to appreciate the fact that the usual criteria are of little value in judging the purity of these preparations. Analyses of the deuterium content, determinations of density, refractive index and boiling point, and the other customary methods of organic chemistry can in general only confirm that the material under consideration has

the proper hydrogen-deuterium ratio. The boiling point range (not the absolute value of the boiling point, which is not known to us a priori) is a helpful indication of purity, but it must be realized that the great differences in the Raman spectra of different isomers furnish by far the most reliable criterion of the purity of the several preparations.

### Experimental.

#### Preparation of Deuterated Benzenes by Modified Grignard Reaction.

(1) Preparation of DCl by decomposition of  $\text{SOCl}_2$  with  $\text{D}_2\text{O}$ . We prepared DCl by adding  $\text{D}_2\text{O}$  very slowly to nearly-boiling  $\text{SOCl}_2$ . The dropping funnel *A* (Fig. 1) contained the  $\text{D}_2\text{O}$  (99.0—99.6 %). The funnel's outlet had been extended some fifty centimeters by means of a capillary tube (to give increased hydrostatic pressure), and the part of the outlet tube which dipped below the surface of the  $\text{SOCl}_2$  in the flask *B* was drawn to a fine nozzle to prevent the occurrence of any reaction in the tube itself. The oil bath *C* was kept at a temperature of 80—85° during the endothermic hydrolysis of the  $\text{SOCl}_2$ . The reflux condenser *D* returned to *B* any  $\text{SOCl}_2$  carried away by the DCl and  $\text{SO}_2$ . The traps *E* and *F* were cooled by a solid  $\text{CO}_2$ -acetone bath. *E* was maintained at a temperature of —65° to —55° to remove the  $\text{SO}_2$  without attendant condensation of any appreciable amount of DCl. For the same reason the height of the acetone bath was kept a centimeter or so below the end of the inlet tube. The last traces of  $\text{SO}_2$  in the DCl were eliminated in *F*, whose temperature was —78°. The rate of evolution of DCl could be closely regulated by the rate of addition of  $\text{D}_2\text{O}$ . The entire DCl

generator was set up ready for instantaneous use before any attempt was made to start the Grignard reaction.

(2) The modified Grignard reaction. The Grignard reaction was carried out in the three-necked flask *K*. The central neck was attached by means of a ground

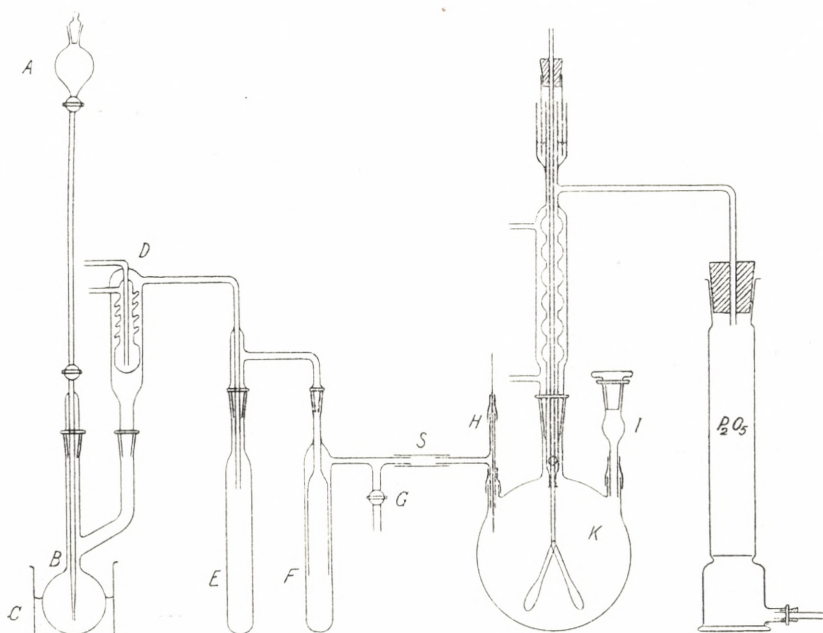


Figure 1.

joint to a reflux condenser through which a mercury seal stirrer extended into the flask. A  $P_2O_5$ -tower closed the exit tube of the condenser to insure the exclusion of atmospheric moisture. The halogen compounds were introduced through the side neck *I*, which was equipped as illustrated in Fig. 1 for the ready introduction of solid material. In case the halogen compound could be added in solution, the introduction was effected by means of a dropping funnel. The inlet tube for the  $DCl$  gas entered



the flask through the side neck *H*. The tube was fitted out with a glass rod with which cakes of the magnesium salts could be removed when they threatened to clog the side neck. To keep the ether vapor out of the trap *F*, a slow stream of dry nitrogen was passed into the system through the stopcock *G*; if in spite of this precaution a counter-distillation of ether took place, the tube could be closed for the time being by means of a pinch clamp at *S*.

The amount of magnesium (equivalent to the quantity of halogen compound) used in each preparation was freshly turned out on a lathe, and immediately covered with dry ether in the flask *K*. In some cases we tried the use of magnesium turnings activated by heating them with a little iodine, but the essential thing appears to be the use of freshly turned magnesium. About one fourth of the halogen compound was then added to the ether together with a small crystal of iodine. Stirring was begun, and continued throughout the entire course of the preparation. The reaction started automatically with the simpler halogen derivatives. With the other compounds, however, it was necessary to keep the ether solution gently boiling by steady electrical heating. A zone of condensation in the reflux condenser was noticed. When this zone began to rise, the reaction was known to have started. If this rise did not occur within half an hour, one c. c. of ethyl bromide and a little more iodine were added to etch the surface of the magnesium turnings. As a rule this procedure caused the reaction to start within a few minutes. If not, the procedure was repeated once or twice until the formation of the Grignard complex had definitely begun. After a short lapse of time, heating was no longer required and it was occasionally necessary to cool the flask. The remainder of the

halogen compound was then added as rapidly as possible without provoking too violent a reaction. Some time later the zone of condensation was observed to fall; this was taken as an indication that the first halogen had reacted with the magnesium.

At this point the introduction of DCl was started. For the quantities of material which we have used (cf. Table I), it was found that the most suitable flow of DCl was obtained by adding  $D_2O$  to the  $SOCl_2$  at the rate of ten grams an hour. Ordinarily this flow of DCl kept the reaction mixture boiling. The heat evolved was in certain cases so considerable that the reaction vessel had to be cooled to prevent too vigorous boiling. For a few of the reactions, however, it was found necessary to supply heat.

The supply of DCl was diminished or cut off altogether if more than a trace of iodine made its appearance in the ether in the reflux condenser. The free iodine originated in the oxidation of DI by a small amount of oxygen present in the stream of the nitrogen. The occurrence of the free iodine was an indication that the DCl was not being used completely for the decomposition of the Grignard complex. The liberation of iodine was always accompanied by the evolution of a gas through the  $P_2O_5$ -tower.

We have mentioned in the introduction that a side reaction something like a ZEISEL reaction occurs when an excess of DCl is present. Such a reaction should produce mono-deuteroethane, and in agreement with expectation, we have found that the gas evolved is inflammable and has about the same density as air. Furthermore if the introduction of DCl be continued after all the magnesium has been consumed, the presence of some ethyl iodide is to be expected in the ether solution. Because of the proximity of

the boiling points of ethyl iodide and benzene, it is difficult to separate these compounds by distillation only. In the first deuterated benzene which we prepared, we observed the presence of ethyl iodide which had failed to be removed by fractionation. This observation confirmed the nature of the side reaction. Henceforth the deuterated benzenes were freed from all ethyl iodide by distillation over freshly turned magnesium.

Although an excess of DCl is thus undesirable, it is not to be presumed that the DCl should be added so slowly as to avoid all possibility of this excess. If the Grignard compound is not decomposed by DCl soon after its formation, subsidiary reactions of the Grignard compound with the halogen atoms on other benzene nuclei may lead to the formation of considerable amounts of compounds of the type of diphenyl and thus reduce the yield of the deuterated benzene.

As we have remarked, the generation of DCl may be closely controlled by the rate of addition of  $D_2O$  to the  $SOCl_2$ . This close control is essential to the success of the whole preparation, and was maintained in the following way. As soon as the first Grignard compound had been formed, the introduction of DCl was begun as previously described. While the decomposition of the Grignard complex was taking place, the gas coming out of the reaction vessel was normally only the nitrogen which was being introduced at *G*. The flow of nitrogen was small, i. e. less than 1 c. c. of gas per second. When the reaction had continued for some time, however, a very considerable increase (ten fold or more) in the outflow of gas was noticed to which attention was directed by the appearance of free iodine in the reflux condenser. Since the increase was due

to the liberation of ethane, the evolution of DCl was cut off completely to allow the excess of DCl to be used up. Ten or fifteen minutes later, the generation of DCl at a somewhat slower rate was resumed and continued until the evolution of ethane again become noticeable. The supply of DCl was again cut off, and the entire procedure repeated. However, if the ethane began coming off with little delay (i. e. within a minute or two), the displacement of halogen by deuterium was known to be complete, and the addition of DCl was stopped. The boiling reaction mixture was allowed to cool, and the process of recovering the deuterated benzene began.

(3) Recovery and Purification of the Deuterated Benzenes. The flask *K* was removed from the apparatus, and the ether solution distilled off as follows: The flask was incorporated in a simple vacuum-tight still, the receiving vessel of which was immersed in an ice-salt mixture. The system was evacuated and then closed off. Distillation was hastened by heating the flask with a water bath, whose temperature was raised gradually to the boiling point. It was found that this procedure removed all of the benzene from the magnesium salts, and left behind only ether of crystallization and certain of the byproducts to which we have referred. Stronger cooling of the receiving vessel merely resulted in the undesirable distillation of these byproducts.

The distillate, yellow to orange in color, was shaken with dilute sodium hydroxide solution, which removed DCl and at the same time eliminated the color. The ether solution was then dried with calcium chloride, and after the addition of fresh magnesium turnings and a little iodine, the

greater part of the solvent was removed by distillation through an efficient column 1.4 meters long.

The remaining solution was transferred in vacuo from the large still to a small one. The latter was designed particularly for the efficient fractionating of small quantities. An indication of its efficiency may be given by remarking that the middle fraction between ether and benzene was in general only a few drops when the rate of distillation was a half dozen drops per minute. Little benzene was lost in the column of the still since the column had been wound with a thermal element by means of which it could be heated at the end of the distillation. The samples of the various deuterated benzenes as a rule were collected within a boiling point range of  $0.2^\circ$ , most of the material distilling within a range of  $0.05^\circ$ .

In table 1 the chief data for the syntheses of the various benzenes are given. Column II lists the halogen compounds which have been used as the starting point for the syntheses. The preparation of these compounds will be described in the Appendix.

The number of moles of the halogen compounds and of half-moles of  $D_2O$  employed are given respectively in the next two columns. The ratio of the theoretical number of gram-atoms of deuterium to be substituted for halogen to the number of half-moles of  $D_2O$  actually used is listed in column V to illustrate the economy of each preparation. The ratio can of course never exceed unity.

The boiling point range over which the compounds were collected is given in column VI. The temperature at which most of the material distilled is given as the boiling point in the next column. All temperatures have been reduced

Table 1.

Deuterated Benzene (I)	Halogen Compound (II)	Moles of Halogen Compound (III)	Halfmoles of D <sub>2</sub> O (IV)	G-atoms D Halfmoles D <sub>2</sub> O (V)	B. p. range (VI)	B. p. (VII)	Yield		Yield per step % (X)
							g. (VIII)	% (IX)	
C <sub>6</sub> H <sub>5</sub> D	C <sub>6</sub> H <sub>5</sub> Br	0.30	0.60	0.50	79.45-79.65	79.60	13.3	56.1	56.1
1,2-C <sub>6</sub> H <sub>4</sub> D <sub>2</sub>	1,2-C <sub>6</sub> H <sub>4</sub> BrI	0.37 <sub>5</sub>	1.23	0.61	79.85-80.00	79.95	10.6	35.3	59.4
1,3-C <sub>6</sub> H <sub>4</sub> D <sub>2</sub>	1,3-C <sub>6</sub> H <sub>4</sub> BrI	0.30	1.00	0.60	79.65-79.80	79.75	9.0	37.5	61.2
1,4-C <sub>6</sub> H <sub>4</sub> D <sub>2</sub>	1,4-C <sub>6</sub> H <sub>4</sub> Br <sub>2</sub>	0.30	1.03	0.58	79.65-79.75	79.70	13.6	56.6	75.2
1,2,3-C <sub>6</sub> H <sub>3</sub> D <sub>3</sub>	2,6-C <sub>6</sub> H <sub>3</sub> Br <sub>2</sub> I	0.38	2.00	0.57	79.60-79.85	79.80	7.2	23.4	61.6
1,2,4-C <sub>6</sub> H <sub>3</sub> D <sub>3</sub>	2,5-C <sub>6</sub> H <sub>3</sub> Br <sub>2</sub> I	0.40	2.00	0.60	79.60-79.95	79.85	7.3 <sub>5</sub>	22.8	61.1
1,3,5-C <sub>6</sub> H <sub>3</sub> D <sub>3</sub>	1,3,5-C <sub>6</sub> H <sub>3</sub> Br <sub>3</sub>	0.30	1.51	0.60	79.50-79.65	79.55	13.4	55.1	82.0
1,2,3,4-C <sub>6</sub> H <sub>2</sub> D <sub>4</sub>	2,3,6-C <sub>6</sub> H <sub>2</sub> Br <sub>3</sub> I	0.50	2.50	0.80	79.50-79.65	79.60	11.4	27.8	72.6
1,2,3,5-C <sub>6</sub> H <sub>2</sub> D <sub>4</sub>	2,4,6-C <sub>6</sub> H <sub>2</sub> Br <sub>3</sub> I	0.50	2.50	0.80	79.60-79.65	79.65	12.9	31.5	74.9
1,2,4,5-C <sub>6</sub> H <sub>2</sub> D <sub>4</sub>	2,4,5-C <sub>6</sub> H <sub>2</sub> Br <sub>3</sub> I	0.50	3.13	0.64	79.60-79.65	79.60	14.4	35.2	77.0
C <sub>6</sub> H <sub>5</sub> D <sub>5</sub>	2,3,4,6-C <sub>6</sub> HBr <sub>4</sub> I	0.50	3.00	0.83	79.50-79.60	79.60	13.0	31.4	79.3

to standard barometric pressure with the help of the assumption that  $\frac{dT}{dp}$  has the same value as for benzene, namely 0.0043 °/mm at 80°. The boiling points may be seen to vary quite irregularly.

The yield in grams and percent based on the initial amount of halogen compound is given in columns VIII and IX. Since the entire preparation of benzene substituted by  $n$  D-atoms may be regarded as  $n$  consecutive reactions, the mean percentage yield per step may be computed by taking the  $n^{\text{th}}$  root of the entire percentage yield. This quantity is found in the last column. It is seen to lie between 60 % and 80 %.

It may be seen from the table that in the earlier preparations, in which the yield per step is comparatively small, a rather large amount of  $D_2O$  has been used. In these cases we had not yet learned to utilize the evolution of ethane as a guide to the most efficient introduction of  $DCl$ , by means of which the latter portion of each preparation can be regulated in the best way. The greater yield per step for the higher deuterated benzenes, in the preparation of which the detailed directions were followed strictly, shows clearly that the best results are obtained by using 1.2—1.4 halfmoles of  $D_2O$  per gram-atom of deuterium to be introduced.

## Appendix.

### The preparations of the intermediate halogen compounds.

In order to prepare a given deuterated benzene in the manner just described, it is first necessary to select an analogous halogen compound which will react readily with magnesium, give little by-products and be comparatively easy to synthesize. It is well-known that in general a chlorine atom attached to the benzene nucleus will not form a Grignard compound, while a bromine or iodine atom in the same place does react with magnesium. We may therefore eliminate the chlorine derivatives from consideration, and restrict our choice to bromo- and iodo-compounds. We have previously remarked that iodine compounds may produce through

side reactions considerable amounts of by-products which make the deuterated benzene difficult to purify and which reduce the final yield. For these reasons it is advisable to select a halogen compound containing as little iodine as is compatible with satisfactory reactivity.

In this connection we remark that we were not able to get 1.2.4.5-tetrabromobenzene to react with magnesium. By using instead a compound in which one of the bromine atoms had been replaced by iodine, namely 2.4.5-tribromo-iodobenzene, it was possible for us to carry through the synthesis of the corresponding deuterobenzene, although the formation of the first Grignard reagent in this instance required an unusually long time. The nature of the variation in reactivity of different halogen derivatives indicates that not only the kind and number of halogen atoms but also their relative positions in the benzene nucleus must surely play an important role in determining the reactivity of the compounds. Thus we have found that two isomers of 2.4.5-tribromo-iodobenzene, as well as a bromo derivative of the compound, react readily with magnesium. Perhaps this reactivity may be connected with the fact that these three compounds all have a vicinal Br-I-Br arrangement, in contradistinction to 2.4.5-tribromo-iodobenzene.

The importance of having as little iodine as possible in the halogen compounds is clearly evident from table 1, in which it may be observed that para-di- and sym-tri-deuterobenzene have been prepared in relatively high yield from pure bromo compounds. In these cases the iodides in the reaction mixture could be formed only from the small amount of iodine used for activating the magnesium. However, in several cases, even in the simpler preparations, we have used compounds containing one iodine atom purely because it is so much easier to introduce iodine than bromine into benzene by means of the diazo reaction.

In the following the preparation and properties of the intermediate halogen compounds are described. It is true that these compounds have been prepared by methods which are familiar to every chemist. We have described the preparative details, however, because they do not appear to be readily accessible in the literature, and because, in some cases, considerable improvements have been made in procedure. The order of description is determined by the partially deuterated benzenes obtained from the intermediates.



(1) Bromobenzene. The bromobenzene used for the Grignard reaction was the middle fraction obtained from a large amount of commercial bromobenzene by distillation through an efficient column.

(1.2) *o*-Bromo-iodobenzene. *o*-Bromo-nitrobenzene (commercial product of Fraenkel & Landau) was recrystallized once from alcohol (m. p. 40.8–41.2°) and then reduced with iron powder and a little sulfuric acid by the method of Holleman (*Recueil des trav. chim.* **25**, 186).

The *o*-Bromoaniline obtained from one mol of *o*-Bromonitrobenzene was suspended in water (1–1.5 liters) and concentrated hydrochloric acid (500 c. c.) added. The suspension was chilled in an icebath, and then diazotized by the addition, during the course of 10 to 15 minutes, of sufficient sodium nitrite (ca. 0.95 mol — as indicated by KI-paper). Aqueous potassium iodide (170 g. in 200 c. c.) was added, and after the reaction had been allowed to proceed for one hour, the water layer was decanted and the oil remaining washed with dilute sodium hydroxide. The product was distilled in vacuo (1–2 mms) over  $P_2O_5$ . First fraction: 16 g.; middle fraction: 165 g.; final fraction: 7 g. Total: 188 g. or 71 %; m. p. of middle fraction 9–10°. Holleman (*Recueil des trav. chim.* **34**, 228) gives 5°.

(1.3) *m*-Bromo-iodobenzene. A similar procedure was followed in preparing *m*-Bromo-iodobenzene from *m*-Bromo-nitrobenzene. It was found more efficient, however, to pour the diazotized bromoaniline slowly into a large volume of cold dilute potassium iodide solution. The crude product was distilled with steam. Yield: 165 g. or 57 % m. p. –12° to –10°. Holleman (*loc. cit.*) gives –18°.

(1.4) *p*-Dibromobenzene. Benzene (270 c. c., dried over  $CaCl_2$ ) and iron powder ("Ferrum reductum", 6 g.) were placed in a one liter two-necked flask equipped with reflux condenser (ground joint) and a dropping funnel. By means of the funnel, whose tip extended beneath the surface of the benzene, enough bromine (5 c. c.) to start the reaction was introduced. When the temperature of the reaction mixture rose and hydrogen bromide began to come off, the remainder of the bromine (290 c. c.) was added during the course of 40 to 50 minutes. When all the bromine had been added, the mixture was poured into a large mortar and macerated with water (ca. 1 liter). The water was drained off, and the crude crystals

were washed and dried with suction; in this way nearly all the ortho-compound may be removed. The material was then recrystallized from alcohol (1 liter) and dried between filter papers. Yield: 390 g. or 55 %/o, m. p. 88°.

(1.2.3) Potassium salt of 2.6-Dibromo-sulfanilic acid. To sulfanilic acid (191 g. — 1 mol.) suspended in water (3 liters), bromine (102 c. c.) dissolved in concentrated hydrobromic acid (200 c. c.) was added with constant stirring during the course of an hour. A small amount of crystalline tribromoaniline formed by a side reaction was filtered off, and potassium hydroxide (60 g.) added to the solution. The latter was concentrated over a flame until crystals appeared. The concentrate was then cooled, and the crude crystals filtered, washed with cold water and recrystallized once or twice from water (until free from bromide ion.) Yield: 65 %/o.

2.6-Dibromo-iodobenzene. The potassium salt (370 g. — 1 mol.) was refluxed with dilute sulfuric acid (340 c. c. conc. sulfuric acid in 160 c. c. water) until complete solution was effected (about 2 hours). The warm solution was poured slowly into a large amount of water, whereupon 2.6-dibromoaniline was precipitated in the form of very fine crystals. The precipitate was washed several times by decantation and then collected on a filter with suction. The moist dibromoaniline was immediately suspended in water (ca. 2 liters) and concentrated hydrochloric acid (400 c. c.) added. The mixture was then chilled and sodium nitrite solution (65—70 g. in sufficient water) added through a dropping funnel over a period of an hour, during which the temperature of the mixture never rose above 5°. A small amount of insoluble material was removed by filtration and the clear solution poured into a cold solution of potassium iodide (250 g.), iodine (250 g.) and concentrated sulfuric acid (250 c. c.) in water (6—8 liters). Steam was passed into the mixture until evolution of nitrogen had ceased, and the free iodine remaining was removed by the addition of a solution of sodium sulfite. The crystalline precipitate of 2.6-Dibromo-iodobenzene was collected on a filter, washed with water and then recrystallized from alcohol. Yield: 195 g. The alcoholic mother liquor could be made to yield 60 g. additional. Total yield: 255 g. or 70 %/o. m. p. 98—99°. WILLGERODT (J. für prakt. Chem. (2) 71,540 (1905)) gives 99°.

Note: It is highly important that the potassium salt be enti-

rely bromide-free, as the presence of a trace of bromide ion will cause the transformation of the dibromoaniline, during the liberation of the sulfonic acid group, into a mixture of mono- and tribromoaniline.

(1.2.4) 2.5-Dibromo-nitrobenzene. To fuming nitric acid (800 c. c.) in a two-liter three-necked flask p-dibromobenzene (400 g) was added, with constant stirring, during the course of 10–15 minutes. The temperature of the reaction mixture was kept below 15° during the nitration by cooling the flask with an ice-salt bath. The stirring was continued for an hour without further cooling, and the mixture was then poured into ice-water. The precipitated 2.5-dibromo-nitrobenzene was washed first by decantation, filtered and then washed free from acid on the filter. Yield: approximately theoretical.

2.5-dibromoaniline. The dibromo-nitrobenzene (281 g. — 1 mol.) was reduced by ordinary iron powder (250 g.) in a large flask containing five liters of water. Sulfuric acid (1 mol.) was added in small portions with continued stirring over a period of an hour. After three hours' further stirring, the mixture was made basic with sodium hydroxide (120 g.) and allowed to settle. After decantation of the supernatant solution the dibromoaniline was distilled with steam. Yield of crude material: 85 %.

2.5-dibromo-iodobenzene. The crude dibromoaniline (126 g. — 0.5 mol.) was dissolved in a little alcohol (150 c. c.) and filtered to remove insoluble impurities (trace of iron powder carried over during steam distillation). The alcoholic solution was poured into dilute hydrochloric acid (250 c. c. conc. HCl in one liter water) with stirring. The temperature was kept below 5° with ice during the diazotization. The correct amount (ca. 35 g.) of sodium nitrite was determined by using potassium iodide paper, as before. The diazotized mixture was poured into aqueous potassium iodide (125 g. in 5 liters) and allowed to stand overnight. The precipitated 2.5-dibromo-iodobenzene was steam-distilled after addition of some dilute sodium hydroxide. Yield: 75% — The melting point was not sharp, however, so the material was recrystallized as follows. The crude product (300 g) was dissolved in petroleum ether (400 c. c.) at about 30°. After the solution was cooled to 10°, a large part (160 g.) of the solute crystallized out. The crystals were filtered off, washed with ice cold petroleum ether (100 c. c.) and dried, first between filter papers and then in vacuo over sulfuric acid. m. p.

37.5-37.9°. WILLGERODT (l. c.) gives 38°. Concentration of the mother liquor yielded 80 g additional. The melting point of this latter material extended over a somewhat wider range.

(1.4.5) sym-Tribromobenzene. The preparation of this compound followed Organic Syntheses vol. 13, p. 96.

(1.2.3.4) 2.3.6-Tribromo-iodobenzene. 2.6-Dibromo-iodobenzene (362 g. — 1 mol.) was dissolved in carbon tetrachloride (375 c. c.) in a one-liter two-necked flask, to which a reflux condenser was attached through a ground joint. To this solution were added a little bromine (4 c. c.) and aluminium chloride (2-3 g.). Reaction began at once, and thereupon more bromine (50 c. c.) was introduced without delay through a dropping funnel. Ten minutes after the start of the reaction, the whole mixture was poured into dilute hydrochloric acid. Any free halogen remaining was removed with a little sodium sulfite, and the clear pale yellow carbon tetrachloride was drawn off by means of a separatory funnel. To prevent any crystallization the temperature of the solution was not allowed to drop below 40°. The solution was boiled down to 250-300 c. c., and allowed to stand overnight in an icebox. The crystalline 2.3.6-Tribromo-iodobenzene was filtered off, washed twice with high-boiling (b. p. 60°-70°) petroleum ether and dried first in air and then in vacuo over phosphorus pentoxide. Yield: ca. 70% m. p. 78-79.5°.

(1.2.3.5) 2.4.6-Tribromoaniline. To a solution of aniline (93 g — 1 mol.) in methyl alcohol (1.5 liters) cooled by an ice-bath, bromine (153 c. c.) was added with constant stirring during the course of fifteen minutes. When continued stirring had reduced the temperature of the mixture to 15°, the crystals of the tribromoaniline were filtered off and washed with cold methyl alcohol. Further material was recovered by dropping an equal volume of water into the mother liquor. Total yield: 219 g + 108 g., or 96% m. p. 119°.

2.4.6-Tribromo-iodobenzene. The diazotization was carried out in glacial acetic acid, in the manner suggested by HANTZSCH (Ber. **34**, 3337 (1901)). Tribromoaniline (330 g — 1 mol.) was dissolved in boiling acetic acid (1 liter) and concentrated sulfuric acid (60 c. c.) added. The solution was poured into a further quantity (0.5 liter) of acetic acid and cooled. Amyl nitrite (150 c. c.) was dropped slowly (1-2 hours) with stirring into the mixture, the temperature being kept constant at 15°. The diazotized mixture

was stirred for half an hour longer, and then added to a cold solution of potassium iodide (250 g), iodine (250 g) and concentrated sulfuric acid (200 c. c.) in water (5 liters). The reaction mixture was warmed to 60° and decolorized with sodium sulfite (ca. 300 g.). The precipitate of 2.4.6-Tribromo-iodobenzene was collected on a filter, washed, dried and then recrystallized from alcohol in which decolorizing carbon was suspended. Yield: 260 g. or 59%. m. p. 104—105°. SILBERSTEIN (J. für prakt. Chem. **27**, 120 (1883)) gives 103.5°.

(1.2.4.5) 2.4.5-Tribromo-iodobenzene. The technique used in preparing this compound was the same as that for 2.3.6-Tribromoiodobenzene. Iodobenzene (306 g. — 1.5 mol.), prepared according to Organic Syntheses Coll. Vol. 1, p. 316, was dissolved in carbon tetrachloride (300 c. c.) and "ferrum reductum" (6 g.) added. Bromine (240 c. c.) was introduced through a dropping funnel, the addition requiring half an hour. The reaction mixture was kept at boiling temperature during the addition of the bromine and for ten minutes thereafter, and was then poured into carbon tetrachloride (100 c. c.). The whole volume of carbon tetrachloride solution was shaken with dilute sodium hydroxide, and cooled. The crystals of 2.4.5-Tribromo-iodobenzene were filtered off and recrystallized from carbon tetrachloride to which had been added some decolorizing carbon. Yield: 207 g or 31%. m. p. 165.0—166.7°. WILLGERODT (Chem. Centr. Blatt 1885, 836) gives 164—165°. The yield could be increased to 36% by working over the mother liquors.

(1.2.3.4.5) 2.3.4.6-Tetrabromoaniline. A solution of m-bromoaniline (69 g. — 0.4 mol.) in glacial acetic acid (750 c. c.) was mixed very rapidly with an acetic solution of bromine (64 c. c. in 250 c. c.). The mixture was stirred for two minutes and then poured into a large volume of water. The precipitated 2.3.4.6-Tetrabromoaniline was filtered off and dried with suction. It was recrystallized from alcohol (2 liters). Yield 142 g., + 17 g. from the solvent alcohol, or 96% m. p. 115—116°. CLAUS and WALLBAUM (J. für prakt. Chem. (2) **56**, 50 (1897)) give 115°.

2.3.4.6-Tetrabromo-iodobenzene. This compound was prepared in very nearly the same way as 2.4.6-Tribromo-iodobenzene, except that the amounts of the solvent acetic acid were doubled. The diazotization was judged to be complete when a test sample removed from the mixture was entirely soluble in a small volume

of water. If the sample was not soluble, more amyl nitrite was added. Twice the previous quantity of water was used in making up the iodide solution to which the diazotized mixture was added. The precipitated 2.3.4.6-Tetrabrome-iodobenzene was filtered, washed with alcohol and recrystallized from carbon tetrachloride containing decolorizing carbon. Yield from 1 mol. of tetrabromaniline (410 g.): 279 g. having m. p. 148—149°, and 120 g. recovered from the solvent. m. p. 144—148°. Total yield: 399 g. or 77%.

### SUMMARY

The preparation of the deuterated benzenes from analogous halogen compounds by a modified Grignard reaction is described. The essential feature of the method is that deuterium chloride rather than deuterium oxide is used for the decomposition of the Grignard compounds. The advantages of the method are: 1) the initial compounds are simple to prepare; 2) the replacement of halogen by deuterium is carried out continuously in a single chemical operation; 3) the deuterated benzenes are obtained in pure state and with good yields. Their purity has been ascertained by a study of their Raman spectra.

In an Appendix the preparation of the initial halogen compounds is described in detail.

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