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The Preparation of F^{18}-labelled Aryl Fluorides

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Various methods used in the preparation of F^{18}-labelled aryl fluorides are described. Neutron-irradiated lithium carbonate is dissolved in a small quantity of glacial acetic acid; the solution is diluted with acetone containing ethanol, and then passed through a column of cellulose powder in order to remove the lithium. The adsorbed F^{18} is eluted with acetone containing a trace of fluoroboric acid and a diazonium fluoroborate is dissolved in the effluent, precipitated by adding ether, and converted into the F^{18}-labelled aryl fluoride by the Schiemann decomposition. A simpler process is described which can be applied when the diazonium fluoroborate is relatively stable in acetonic solution containing lithium. Other possible methods are also discussed. In the course of the experiment, it is proved that the Schiemann decomposition proceeds via the ionic mechanism.

LA PREPARATION DES FLUORURES ARYLIQUES MARQUES DE F^{18}

On décrit une variété de méthodes employées à la préparation des fluorures aryliques marqués de F^{18}. Du carbonate de lithium irradié de neutrons est dissous dans une petite quantité d'acide acétique glacial; on fait une dilution de la solution avec de l'acétone contenant de l'éthanol, puis on la fait passer par une colonne de poudre de cellulose afin d'en enlever le lithium. On fait l'élution du F^{18} absorbé, avec de l'acétone contenant une trace d'acide fluoroborique et un fluoroborate de diazonium se trouve dissous dans l'effluent, lequel on précipite en ajoutant de l'éthère puis on convertit par la décomposition de Schiemann en le fluorure arylique marqué de F^{18}.

On décrit un procédé plus simple qui peut s'employer quand le fluoroborate de diazonium est rélativement stable en solution acétonique contenant du lithium. On discute aussi des autres méthodes qui seraient possibles. Au cours de l'expérience on montre que la décomposition de Schiemann prend lieu par le mécanisme ionique.

ПРИГОТОВЛЕНИЕ ФТОРИСТЫХ АРИЛОВ С ВВЕДЕННЫМИ МЕЧЕНЫМИ АТОМАМИ F^{18}

Описываются различные методы, применяемые для приготовления фтористых арилов с введенными меченными атомами F^{18}. Облученный нейтронами углекислый литий растворяется в небольшом количестве ледяной уксусной кислоты. Этот раствор разбавляется содержащим этанол ацетоном и затем пропускается через колонну целлюлозы для устранения лития. Поглащенный F^{18} извлекается ацетоном, содержащим следы фторборной кислоты, а фтороборат диазония растворяется в вытекающем потоке, осаждается прибавкой эфира и конвертируется во фтористый арил с введенными меченными атомами F^{18} расщеплением по Шиманну. Описывается простой процесс, который можно применять, когда фтороборат диазония сравнительно устойчив в ацетоновом растворе, содержащим литий.

Обсуждаются также другие возможные методы. В течение опыта было доказано, что расщепление по Шиманну проходит через ионный механизм.

DIE VORBEREITUNG VON MIT F^{18} MARKIERTEN ARYLFLUORIDEN

Es werden verschiedene Methoden für die Herstellung von mit F^{18} markierten Arylfluoriden beschrieben. Neutronenbestrahltes Lithiumkarbonat wird in ein wenig Eisessig aufgelöst,

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die Lösung mit Äthanol enthaltendem Aceton verdünnt und dann durch eine Kolonne mit Zellulosepulver geleitet, um das Lithium zu entfernen. Das adsorbierte F^{18} wird mit Spuren von Fluorborsäure enthaltendem Aceton ausgewaschen und ein Diazoniumfluorborat wird in dem Ausfluss aufgelöst, durch Zusatz von Äther ausgeschieden und durch die Schiemann Zersetzung in das mit F^{18} markierte Arylfluorid verwandelt. Ein einfacheres Verfahren wird dann beschrieben, das verwendet werden kann, wenn das Diazoniumfluorborat in einer Lithium enthaltenden Acetonlösung verhältnismässig stabil ist. Andere mögliche Methoden werden ebenfalls erörtert. Im Laufe des Experiments wurde bewiesen, dass die Schiemann Zersetzung über den Ionenmechanismus vor sich geht.

1. INTRODUCTION AND THE PRINCIPLE OF THE PRESENT METHODS

Although F^{18}-labelled organic compounds are regarded as useful in tracer study,⁽¹⁾ their use has as yet been limited. In order to make a fuller use of them, it is essential to develop suitable methods of synthesizing them. In this paper, convenient methods will be presented for the synthesis of F^{18}-labelled aryl fluorides. The processes are simple and can be carried out within a half-life of F^{18} (1·8 hr).

F^{18} is usually produced by irradiating lithium carbonate in an atomic reactor. It can also be produced efficiently by irradiating pure lithium oxide with an α- or He^3-beam of a convenient energy.⁽²⁾ These lithium compounds are soluble in a small quantity of glacial acetic acid, and the solution can be diluted with acetone containing ethanol without forming any precipitates. The F^{18} in such a non-aqueous solution is highly adsorbable on many kinds of polar substances, such as ionic crystals and cellulose. This property can be made use of in the preparation of many kinds of F^{18}-labelled organic compounds including aryl fluorides.

When the non-aqueous solution is passed through a column of cellulose powder, the F^{18} is adsorbed in the column and the lithium passes through it. The F^{18} is easily eluted with acetone containing a trace of fluoroboric acid. A diazonium fluoroborate can be labelled with the F^{18} by dissolving it in the effluent. By adding ether to the solution, the labelled diazonium fluoroborate is precipitated. It yields the F^{18}-labelled aryl fluoride by the Schiemann decomposition.

Another, simpler method is also applicable when the diazonium fluoroborate is relatively stable in a non-aqueous solution containing lithium. By stirring ether rapidly into the solution, the diazonium fluoroborate is precipitated together with most of the F^{18}. The F^{18}-labelled aryl fluoride is obtained by the Schiemann decomposition of the precipitate.

1.1 *The diazonium fluoroborate and aryl fluoride*

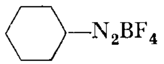
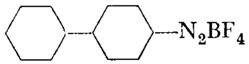
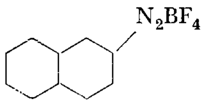
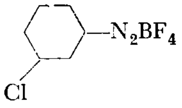
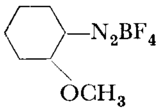
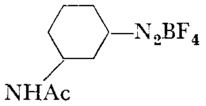
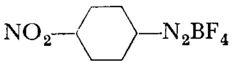
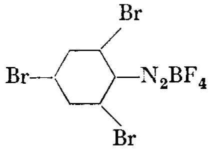
The diazonium fluoroborates listed in Column 2 of Table 1 were chosen as the starting substances of our experiment, because most of them give aryl fluorides useful in organic or biological chemistry and because their substituents are markedly different from one another in properties. Most of the diazonium fluoroborates are obtained⁽³⁾ as precipitate from an aqueous solution, but some are synthesized in acetic acid and precipitated by adding ether. They are soluble in acetone in general, the measured solubility being given in Column 3 of Table 1. Acetonitrile is a still better solvent. On adding ether or kerosine to the acetonic or acetonitrile solution, the diazonium fluoroborate precipitates in a purified state.

Most kinds of aryl fluorides are prepared via the Schiemann decomposition:⁽³⁾

$$ArN_2BF_4 \xrightarrow{\text{heat}} ArF + N_2 + BF_3.$$

This reaction is also the most widely useful in the preparation of F^{18}-labelled aryl fluorides. It can be completed within several minutes for a few grammes of diazonium fluoroborate. Remarkably different values have sometimes been reported for the decomposition point of a given diazonium fluoroborate.⁽³⁾ In our experiment also, the decomposition point varied considerably according to the rate of heating; the higher the rate, the higher the apparent decomposition point. The values in Column 4 of Table 1 were observed at the heating rate of about 2°C/min.

TABLE 1. The properties of the diazonium fluoroborates and aryl fluorides, and the yield of F^{18}-labelled aryl fluorides

Diazonium fluoroborate					[m.p.] or (b.p.) of aryl fluoride			
Compound No.	Formula	S* (g/l.)	Decomp. point (°C)	Y.S.D.† (%)	Crude	Pure	M.A.Y.‡ & preprn. method	Overall Y§ (%)
I		39·8	107–108	60	(84)	(85·2)	A: 1·00	6·7
II		54·4	117–118	69	[73–74]	[74–75]	A: 1·00 B: 0·97	10·0
III		27·2	108	35	[58–60]	[61]	A: 1·00 B: 0·79	3·8
IV		19·7	146–147	56	(122–125)	(123–125)	A: 1·00	6·3
V		274	125 m.p.: 95–96	60	(158)	(157)	A: 1·00 B: 1·03	9·0
VI		19·0	96	39	[85–87]	[87]	A: 1·00 B: 0·47	4·4
VII		491	99–100	65	[181–182]	[182·6]	A: 0·87	6·1
VIII		20·5	141–142	33	[23]	[27]	A: 1·00 B: 0·13	3·4
IX		32·4	244	49	[62–64]	[68·5]	A: 0·79	4·3

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* S: solubility in acetone at 23°C; † Y.S.D.: yield in the Schiemann decomposition; ‡ M.A.Y.: molar activity yield; § Overall Y: overall F^{18}-yield for the preferable method.

The yield of a reaction usually varies according to the scale and the required purity of the product. Column 5 of Table 1 gives the observed yield in the Schiemann decomposition, when a few grammes of the diazonium fluoroborate were converted into the aryl fluoride with the melting or boiling point shown in Column 6. The purification involved was carried out within 30 min. The melting points or boiling points for a further purified state (or the commonly accepted values) are given in Column 7.

2. THE LABELLING PROCEDURE

2.1 *Method A* (*a widely applicable method*)

This method is applicable to all of the diazonium fluoroborates that can be obtained in acetonic or acetonitrile solutions. Since diazonium fluoroborates are usually unstable in a basic solution, the F^{18} is made free from lithium before it is brought into contact with them.

The irradiated lithium carbonate (about 100 mg) was dissolved in glacial acetic acid (2 ml) in a polyethylene beaker. The solution was then diluted with a mixture of acetone (25 ml) and ethanol (3 ml) to give a non-aqueous solution. Only a minute fraction of the F^{18} was adsorbed onto the polyethylene produced by the high-pressure polymerization. A polyethylene column (11 mm in diameter) was impregnated tightly with cellulose powder (for chromatographic purposes, 4 g) with the aid of benzene. The non-aqueous solution was passed through the column, which was then washed with acetone (20 ml). The F^{18} was found to be in the upper part of the column. It was then eluted with acetone containing a trace (0·6 vol. %) of fluoroboric acid (40 per cent). The flow rate was about 2·5 ml/min. Figure 1 shows the elution curve. The process required 35–40 min; more than 98 per cent of the lithium was thus removed (as determined by the thoron spectrophotometric method(4)).

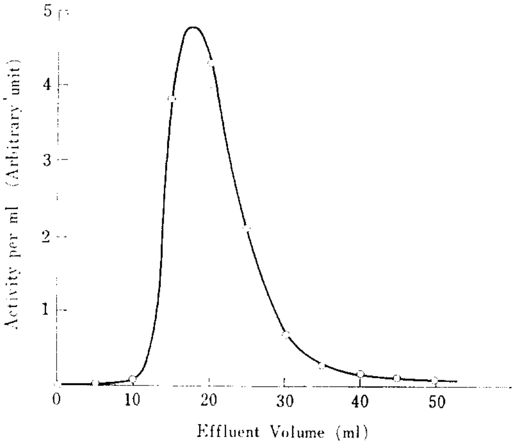


FIG. 1. Elution curve of F^{18} from a cellulose column. Eluent—acetone containing a trace of fluoroboric acid.

A diazonium fluoroborate (a few grammes) was dissolved in the effluent (about 30 ml), additional acetone or acetonitrile being added for a compound with a low solubility. After several minutes, the diazonium fluoroborate was precipitated in the F^{18}-labelled state by adding ether. When the volume of ether was more than twice that of the diazonium solution, the recovery exceeded 80 per cent. The F^{18} activity per mole of the diazonium fluoroborate was measured both in the solution and in the precipitate state; the two values always agreed within the limits of experimental error (2 per cent). No significant decrease was observed in the specific activity of the precipitated diazonium fluoroborate when its acetonic solution was passed through a column of cellulose or silica gel. Hence, the true isotopic exchange was the main cause of the labelling.

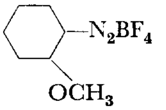
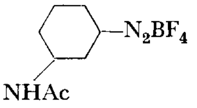
2.2 *Method B* (*a simpler but less widely applicable method*)

The diazonium fluoroborate (1–3 g) was dissolved in acetone (30–70 ml), and the solution mixed with a non-aqueous solution of F^{18} which had been prepared from irradiated lithium carbonate (about 100 mg), glacial acetic acid (2 ml), ethanol (5 ml), and acetone (20 ml). The mixture was deeply coloured. Immediately, ether was stirred into the mixture. The diazonium fluoroborate precipitated with a minute fraction of the lithium (as determined by the thoron method(4)), leaving deeply coloured substances in the solution. A varying fraction of the F^{18} was caught in the precipitate according to the conditions of the ether addition and the nature of the diazonium fluoroborate. When the addition was rapid with good stirring, most of the F^{18} was usually caught.

The desired F^{18}-labelled aryl fluoride was obtained by the Schiemann decomposition of the precipitate. Its specific activity sometimes appeared to indicate that the isotopic exchange was complete, but also sometimes much lower. In the latter case, however, the specific activity was made higher by dissolving the precipitate in acetone containing a trace of acetic acid and by then reprecipitating it prior to the decomposition.

Figure 2 shows the F^{18}-activity per mole of II (4-phenylbenzenediazonium fluoroborate) and its product (4-fluorobiphenyl) after treatment under various conditions. The correction due to the decay of F^{18} has already been applied to the observed activity. The "original solution" in Fig. 2 is the mixture containing the irradiated lithium compound and the diazonium fluoroborate; its F^{18}-activity per mole diazonium fluoroborate is taken as 100. Hence, if a complete isotopic exchange had taken place, the F^{18}-activity per mole would always have been 100 for the diazonium fluoroborate and 25 for the aryl fluoride. In Table 2, the F^{18}-activity per mole is given for V (2-methoxybenzenediazonium fluoroborate) and VI (3-acetaminobenzenediazonium fluoroborate) treated by this process under suitable conditions.

TABLE 2. Chemical yield and specific activity in Method B

				
Compound	Chem. yield (%)	Activity per mole	Chem. yield (%)	Activity per mole
Original Solution (ArN$_2$BF$_4$)	100	100	100	100
1st p.p.t. (Ar N$_2$BF$_4$)	68	119	90	47
2nd p.p.t (Ar N$_2$BF$_4$)	63	126	↓	↓
ArF	39	103 × ¼	35	47 × ¼

The diazonium fluoroborate precipitated together with F^{18} was made almost free from the F^{18} by treating its acetonic solution with a column of cellulose or silica gel (Fig. 2). Therefore, the F^{18} was coprecipitated; no significant degree of the isotopic exchange had taken place. The specific activity of the precipitated diazonium fluoroborate sometimes exceeded the value corresponding to the complete isotopic exchange. Minute dusts, especially fibres from filter paper, when they were present in the solution, caught a considerable part of the F^{18} and lowered the specific activity of the final product.

Method B, although very simple, was not applicable to some of the compounds. When treated with an acetonic solution containing lithium, VII precipitated as lithium salt, which gave aryl fluoride in a poor yield, while IX gave a yellow, explosive precipitate, probably the diazonium acetate or oxide. Further, VI gradually precipitated into fairly large crystals, no matter how rapidly ether was stirred into the acetonic solution. In such a case, a considerable part of the F^{18} was lost, remaining in the solution as is obvious from Table 2.

3. THE YIELD FOR THE F^{18}

On assuming that the complete isotopic exchange had taken place, the molar activity (the F^{18}-activity per mole) of the aryl fluoride was calculated. The observed molar activity of the aryl fluoride was then divided by the calculated one; the quotient is shown in Column 8 of Table 1 as the molar activity yield (M.A.Y.). The method of labelling is also shown in the same column, A and B denoting Method A and Method B respectively. For two of the compounds, VII and IX, the molar activity yield in Method A differs from 1·00. The product from IX, 2,4,6-tribromofluorobenzene, was not obtained in a pure state; probably a small quantity of tribromobenzene was simultaneously formed and remained persistently after careful purification. For VII, it is possible that the isotopic exchange was rather slow and that some of the F^{18} was caught by

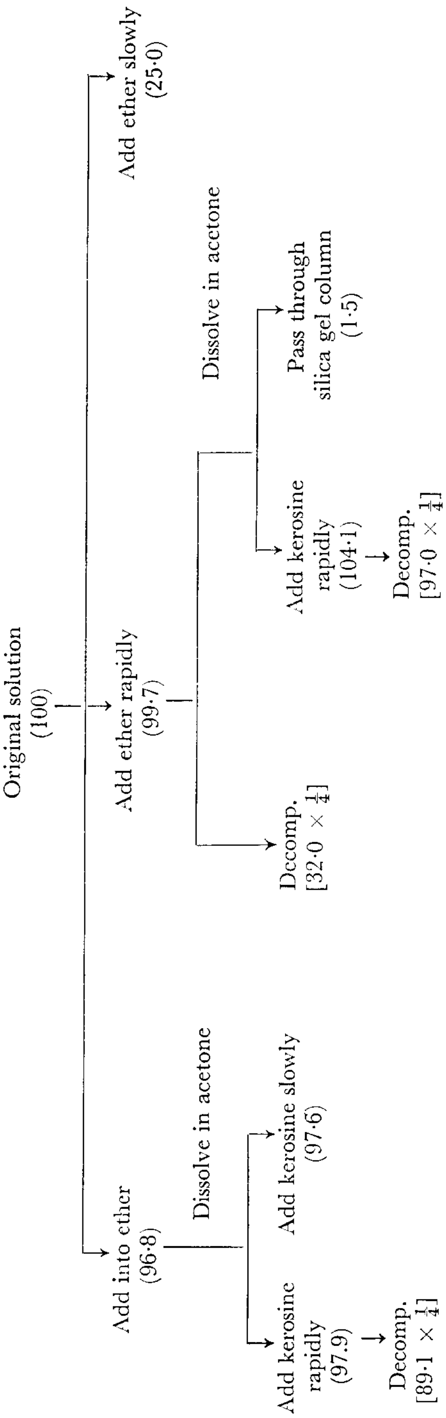
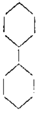


FIG. 2. Variation in the F^{18}-yield according to the conditions in Method B.

( )—Activity per mole of —N_2BF_4.

[ ]—Activity per mole of —F.

coprecipitation; in repeated experiments considerably different values (0·78, 0·71 and 0·59) were obtained.

The entire process can be carried out within 1 hr for Method B and 1·5 hr for Method A, unless a remote-controlled operation is required. The overall chemical yield, based on the initial diazonium fluoroborate, is smaller than the yield in the Schiemann decomposition, usually by a factor of 0·7–0·9, due to the loss of the diazonium fluoroborate in the precipitation and, in some cases, reprecipitation. Therefore,

$$
\begin{aligned}
&[F^{18}\text{-activity in the aryl fluoride}]\\
&= \begin{bmatrix}F^{18}\text{-activity in the}\\ \text{lithium compound}\end{bmatrix} \times (0{\cdot}7\text{–}0{\cdot}9)\\
&\times \tfrac{1}{4}[\text{yield in the Schiemann decomp.}]\\
&\times [\text{molar activity yield}] \times (0{\cdot}7\text{–}0{\cdot}5).
\end{aligned}
$$

The last factor, 0·7–0·5, is due to the decay of F^{18} during the process. In Method A, the entire process requires a longer time, but the loss of diazonium fluoroborate is smaller than in Method B. Hence, for both of the methods,

$$
\begin{aligned}
&[\text{overall } F^{18}\text{-yield}]\\
&= \frac{[F^{18}\text{-activity in the aryl fluoride}]}{[F^{18}\text{-activity in the lithium compound}]}\\
&= \alpha[\text{yield in the Schiemann decomp.}]\\
&\times [\text{molar activity yield}]
\end{aligned}
$$

where α has a value between 0·12 and 0·16. The overall F^{18}-yield is given in Column 9 of Table 1.

4. OTHER POSSIBLE METHODS

After the Schiemann decomposition, the product aryl fluoride contains only one quarter of the fluorine in the diazonium fluoroborate. The loss of fluorine in the decomposition would be lowered by the use of diazonium fluorosilicate, fluoroberyllate or fluoride instead of fluoroborate if the chemical yield were the same. The chemical yield when they were employed was, however, found to be too poor for general use. The boron trifluoride formed in the decomposition can be caught by a liquid nitrogen trap or by a suitable liquid or solution. The utilization of the recovered boron trifluoride, however, usually involves more tedious procedures than the production of F^{18} by neutron irradiation.

There are other methods of preparing F^{18}-labelled aryl fluorides: (1) by means of the recoil effect of the F^{18} following the nuclear reaction; (2) by the use of already-labelled fluoroborate ions in an aqueous solution; (3) by the derivation from another, already-labelled aryl fluoride, and (4) (in a few special cases) by using the halogen interchange.

The recoil labelling was studied by Anbar and Netta,[5,6] who also compared it[1] with other possible methods as to the usefulness in preparing the labelled compounds. The recoil labelling, in general, gives a mixture of many compounds similar to one another, and their separation is tedious. Hence, unless no other method is practicable, this method seems to be of little use in preparing a compound labelled at a desired definite position.

An aqueous solution of the F^{18}-labelled fluoroborate ion is produced very effectively by irradiating a borate with α- or He^3-particles from a cyclotron[2] and then by dissolving it in a small quantity of hydrofluoric acid. Also, a very dilute aqueous solution of labelled fluoroboric acid is prepared by a similar irradiation of water containing a trace of the acid, the isotopic exchange of fluorine between fluoride and fluoroborate being fast in an acid solution.[7] When such an irradiation is possible, an F^{18}-labelled, sparingly soluble diazonium fluoroborate can be conveniently prepared as the precipitate from an aqueous solution.

There are many aryl fluorides for which the only practical synthetic method is derivation from another aryl fluoride. For example, F^{18}-labelled 3-fluoroaniline and 2-fluorophenol should be prepared by the hydrolysis of the F^{18}-labelled 3-fluoroacetanilide and 2-fluoroanisole respectively.

Few aryl fluorides can be prepared by the halogen interchange. A proper F^{18}-labelled fluorinating agent is necessary for obtaining F^{18}-labelled aryl fluoride by this method, and the reaction usually requires a rather long time.[8] Thus, F^{18}-labelled 2,4-dinitrofluorobenzene should be prepared by the nitration of the 4-nitrofluorobenzene.

4.1 *A note on the mechanism of the Schiemann decomposition*

Three reaction mechanisms have been proposed for the Schiemann decomposition:(9,10) (1) an ionic (carbonium ion) reaction; (2) a radical (aryl free radical) reaction, and (3) an intramolecular rearrangement. In the decomposition of the diazonium fluoroborate, as has been described above, the adsorbed (coprecipitated) F^{18} can be taken in the product aryl fluoride with almost the same probability as the fluorine in the fluoroborate. Hence, the intramolecular rearrangement mechanism must be rejected. The coprecipitated F^{18} can be regarded to be in an anionic state, probably in the form of lithium fluoride. Therefore, the ionic reaction appears to be the most probable mechanism for the decomposition of the solid diazonium fluoroborate.

5. EXPERIMENTAL

5.1 *The preparation and purification of the diazonium fluoroborate*

I–IV, VI and VIII were prepared by the diazotization of the corresponding amines in hydrochloric acid, followed by precipitation with fluoroboric acid. V was obtained as precipitate by treating a concentrated solution of *o*-anisidine in fluoroboric acid with sodium nitrite. *p*-Aminobenzoic acid fluoroborate (10 g) was suspended in acetic acid (50 ml); then iso-amyl nitrite was rapidly stirred into the mixture to give momentarily a clear solution, from which VII soon precipitated. 2,4,6-Tribromoaniline (15 g) was suspended finely in acetic acid (100 ml) containing fluoroboric acid (46 %, 15 ml), and treated with iso-amyl nitrate (10 g); the resulting mixture was stirred for 30 min and diluted with ether to give IX.

The diazonium fluoroborates were dissolved in acetone or acetonitrile and precipitated by adding ether in the crystalline state. The purification was also carried out every time just before use. The solubility was measured by weighing the solid obtained by drying up a known volume of the saturated solution under reduced pressure.

5.2 *Irradiation*

Lithium carbonate was prepared from lithium chloride and ammonium carbonate and purified by the use of its reverse solubility in water.(11) It (about 100 mg) was placed in a polyethylene tube and neutron-irradiated under a 4×10^{12} n/cm^2-sec or a 5×10^{11} n/cm^2-sec flux for about 10 min.

5.3 *The Schiemann decomposition*

The vessel used for the decomposition was a suitably bent glass tube with a side-arm also shaped suitably in view of properties of the product. For a volatile product (from I or IV), the arm was long and was wound for efficient cooling with ice water. For a less volatile liquid product (from V or VIII), the arm was Y-shaped and closed in order to collect the product in one side and to then distill it into the other. For a solid product with a relatively high vapour pressure (from II, III or VII), the arm was short and closed; for that with a relatively low vapour pressure (from VI or IX), the arm was long and open in order to collect the product in it by vacuum sublimation. The outlet of the vessel was stuffed with glass wool and cooled to minimize the escape of the product along with the stream of the boron trifluoride and nitrogen.

The decomposition was effected by heating with a small flame. In some cases, it was performed under reduced pressure (with the aid of a water aspirator). After the decomposition, the product was caused to condense in the side-arm by cooling it and by heating the other parts of the vessel. The side-arm was then cut open to take out the product, which was treated with a sodium hydroxide solution (3 N) and distilled or sublimed.

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