S 69. *On the Direct Production of Carrierless Organic Radio-halides.*

By E. Glueckauf, R. B. Jacobi, and G. P. Kitt.

Direct production of carrierless organic radio-halides in the thermal column of a pile was generally successful in the cases of simple compounds of not too long half-life. In the cases of radio-halogens of long half-life like ^{82}Br (34 hours) only methyl bromide could be produced in sufficiently large yields utilising a method whereby the methyl bromide vapour is constantly removed from the reaction zone.

Purification of the carrierless halides by distillation and chromatographic separation does not seem to cause any difficulties.

In biological experiments with radio-tracers it is usually desirable to use the radioactive substance with as little dilution as possible by its non-active isotopic compound.

The quantities of pure radioactive material involved, even in the case of highly active preparations, however, are exceedingly small. To give an example: 1 curie of Me^{128}I ($\tau = 25$ min.) weighs $1{\cdot}4 \times 10^{-9}$ g., though in the case of Me^{131}I ($\tau = 8$ days), the quantity reaches $0{\cdot}6 \times 10^{-4}$ g.

The usual methods of organic synthesis are obviously inadequate when dealing with substances on the μg. scale and it was thought worth while to investigate whether Glückauf and Fay's method (*J.*, 1936, 390), utilising the recoil energy of the radio-halogen, would lead to the direct production of amounts of pure radio-halides of substantial activity. Glückauf and Fay had found that irradiation of organic halides or of mixtures of organic substances in the presence of halogens or halides leads to the production of new species of organic compounds, which after the addition of inactive carrier compounds could be easily separated and identified, as shown in the following scheme.

Production of new chemical species by neutron radiation.

Irradiation of ^{127}I	$CH_3I + n$	
	$\downarrow$	
Formation of compound nucleus ^{128}I	$CH_3I\,^*$	
	$\downarrow$	
Emission of γ-ray accompanied by recoil of ^{128}I	$CH_3 + \gamma + I^*_{fast}$	
	$\downarrow$	
Interaction of recoiling ^{128}I with surrounding matter	$\underbrace{I^*_{fast} + CH_3I}$	
	$\downarrow$	
Products isolated by Szilard & Chalmers (1934)	$\left\{\begin{matrix} CH_3 + II^* \\ CH_2I + HI^* \end{matrix}\right\}$	43%
,, ,, Glückauf & Fay (1936)	$\left\{\begin{matrix} I + CH_3I^* \\ H + CH_2II^* \end{matrix}\right.$	46% 11%

New species produced in this way are indicated below :

Some new chemical species produced by neutron irradiation.

$CH_3X \text{ from } \left\{\begin{matrix} CH_3{\cdot}CO_2H + X_2 \\ C_2H_5{\cdot}OH + X_2 \end{matrix}\right.$

$CH_2X_2 \text{ from } \left\{\begin{matrix} CH_3X \\ CH_2X{\cdot}CO_2H \end{matrix}\right.$

$CHX_3 \text{ from } CH_2X_2$

$C_6H_5X \text{ from } \left\{\begin{matrix} C_6H_6 + CH_3X \\ C_6H_6 + X_2 \end{matrix}\right.$

$C_6H_4X_2 \text{ from } C_6H_5X$

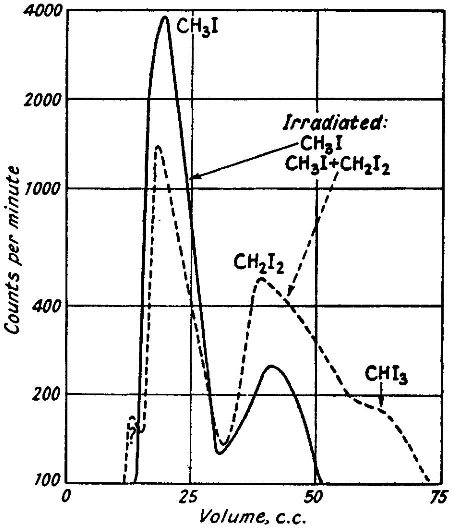
The yields varied between 4 and 20% of the total activity. Experiments of this type have also been carried out by Libby (*J. Amer. Chem. Soc.*, 1940, **62**, 1930) and recently by Reid (*Physical Rev.*, 1946, **69**, 530), who obtained a yield of about 25% of amyl iodide by irradiating iodine in pentane.

When trying to step up these reactions from the tracer-scale by many factors of 10, by utilising the high neutron fluxes in a pile, difficulties arise, which are essentially due to three causes : (1) the *absence* of a protecting carrier material; (2) the *presence*, during the production process, of *ions and radicals* due to the high radiation level inside a pile; (3) *destruction* of the compounds formed by impact of fast particles, in particular protons resulting from collision of fast neutrons with organic matter.

The first fact may lead to the adsorption of the tracer compound by walls and colloidal particles, so that it becomes difficult to separate the radio-halides from the bulk of the irradiated materials. The second results in an increase of chemical exchange after the formation of the new species with inactive halogen, in particular of the ionic form, which in the case of aliphatic halides can result in great losses of activity. The mechanism of these losses of specific activity has been discussed recently by Williams (*J. Physical Coll. Chem.*, 1948, **52**, 603).

FIG. 1.

Chromatographic separation of carrierless radioactive CH_2I_2.



The main problems can therefore be divided under two headings : (*a*) to find conditions where subsequent destruction and exchange is a minimum, and (*b*) to devise methods of separating the minute quantities of active material from the bulk of the irradiated substances.

The obvious answer to the first problem is to carry out irradiation in the thermal column of the pile, though the neutron flux in this region is greatly reduced. If decomposition by γ-rays is not negligible, lead shielding may be provided.

For the separational problem, however, no general solution applies and methods have to be elaborated according to the substance to be produced. Several examples are described which may serve as prototypes for further studies.

(1) *Carrierless* CH_2II^* *from* CH_3I.—5 G. of methyl iodide were irradiated for 30 minutes in the thermal column of the Harwell pile. They were subsequently extracted with aqueous sulphurous acid to remove the Szilard–Chalmers I_2 and I^- (roughly half the activity). 0·2 Ml. of the

extracted organic solution was put on a chromatographic column containing about 40 g. of active charcoal and developed with light petroleum. The eluate was passed through a glass spiral under a Geiger–Müller counter. Two bands of activity were observed (see Fig. 1). The first corresponded to methyl iodide and the smaller, second band to the carrierless methylene iodide. This could be proved by irradiating an approx. 1 : 1 mixture of these two compounds. In this case (see dotted curve of Fig. 1) two bands of approximately equal activity were observed in the same positions as the two bands in the first experiment, which were followed by a much smaller third band which, as one would expect, is due to active iodoform.

An improvement in the separation could be produced by partly distilling off most of the methyl iodide from the carrierless methylene iodide in a similar manner to that described for iodobenzene (see below). This would reduce the width of the methyl iodide band in the subsequent adsorption analysis and thus result in a cleaner separation of the methylene iodide band.

(2) *Iodobenzene from Iodine in Benzene* (*saturated*).—It is known that iodobenzene does not exchange its iodine with either iodine or iodide ions (McKay, *Nature*, 1937, **139**, 283), and it was therefore expected that this reaction would give an excellent yield under pile conditions. This was borne out by the experiments. The irradiated mixture was extracted with aqueous sulphurous acid, whereby consistently 82% of the activity was removed as I^-. The benzene, which retained 18% of the activity, was subjected to various treatments.

(*a*) *Distillation of* 8 *ml. of benzene after addition of* 2 *ml. of decalin and* 2 *ml. of heavy solvent* :

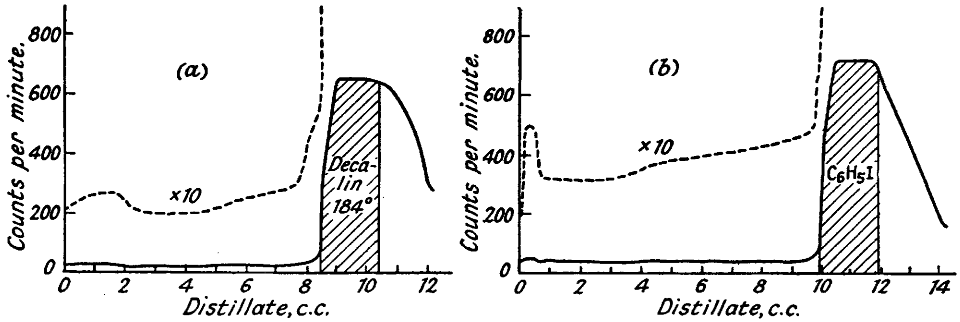
Fraction.	Activity in % of organic activity.	Remarks.
Benzene (80°)	6	Remains practically constant
Decalin (184°)	45	Constant (30 times the activity of benzene)
Heavy solvent (240°)	29	Activity falling off steadily
Residue	19	Coke

(*b*) *Irradiation with carrier* (PhI, 2 *drops*). Aqueous sulphurous acid removed only 77%. The benzene fraction with 23% of organic activity, after addition of 2 ml. of iodobenzene and 3 ml. of heavy solvent gave the following fractions :

Fraction.	Activity in % of organic activity.	Remarks.
Benzene	11	Remains practically constant
PhI (190—210°)	48	Constant (18 times the activity of benzene)
Heavy solvent (210—244°)	36	Activity falling off sharply
Residue	5	Few drops

FIG. 2.

Distillation histograms (a) *without and* (b) *with carrier.*



The distillation histograms are shown in Fig. 2(*a*) and (*b*). Comparison shows that in both cases most of the activity must be iodobenzene, but the yield of organic activity is decidedly greater in the case where carrier had been added. It is also apparent that the distillation proceeds more smoothly in the cases where carrier is present. Chromatographic separation of the irradiated mixtures on alumina shows that the carrierless activity consists to at least 93% of pure iodobenzene (see Fig. 3).

(*c*) After carrierless irradiation, the aqueous sulphurous acid extracted benzene was dried and evaporated in a wash-bottle by an air stream passing over it (at 40°). Less than 10% of the activity was lost during the total evaporation of the benzene. After all the benzene had evaporated no further loss of activity was produced even by prolonged passage of air current, though the vapour pressure of iodobenzene is large enough at this temperature to evaporate the minute quantity in an instant. Apparently the active iodobenzene is retained quantitatively in the trace of resinous material which forms a thin film on the glass after evaporation of the benzene. The activity was quantitatively removed by washing with 5 c.c. of iodobenzene and other solvent, and on distillation of the mixture most of the activity was found in the iodobenzene fraction.

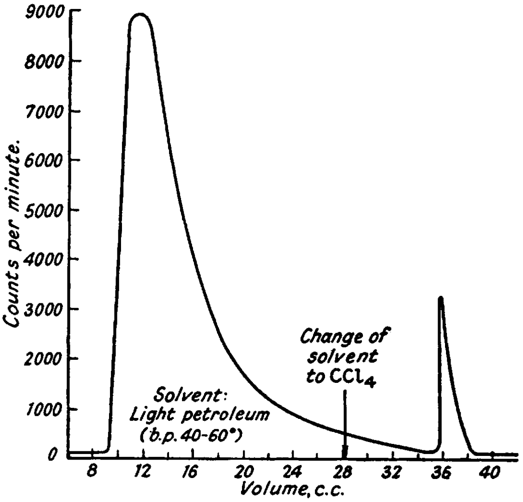


FIG. 3.

Elution curve of $C_6H_5{}^{128}I$ *from charcoal column.*

It would appear that this method provides an excellent means for separating tracer amounts of organic iodine compounds from the bulk of the lighter solvents from which they have been produced. Further purification of the remaining trace activities is then best obtained by chromatographic separation on charcoal, using light petroleum (b. p. 40—60°) as solvent for the development. After chromatographic purification most of the light petroleum can be evaporated without significant loss of activity, but all the activity, *i.e.*, the trace of iodobenzene, disappears together with the last drop of solvent, an indication of the absence of protecting resins.

(3) *Iodobenzene from Benzene and Methyl Iodide* (5% *by vol.*).—Since an attack by iodine on benzene is conceivable under irradiation conditions, an experiment was made in which the iodine was added in the form of methyl iodide. Extraction and distillation gave the following percentages of total activity in the various fractions :

Irradiated mixture.	$C_6H_6 + CH_3I$ (8 mols. %).		$C_6H_6 + I_2$ (satd.).	
Aqueous extract	63	79%	82%	
CH_3I	15			
Benzene			1	
Decalin	11	PhI (est.) 18%	8	PhI (est.) 16%
Heavy solvents	4		5	
Residue	7		4	

Comparison with the iodine experiments shows no essential difference, especially if one takes into account that the decalin fraction would contain methylene iodide to approximately $\frac{1}{4}$ of the methyl iodide fraction, thus bringing the iodobenzene content down to 18%. It is, however, surprising that the yield of active methyl iodide should be as much as 15% of the total activity in spite of the dilution with 13 moles of benzene per mole of methyl iodide, as pure methyl iodide gives a yield of CH_3I^* only 3 times greater (see Glueckauf and Fay, *loc. cit.*).

(4) *Bromobenzene from Benzene and Methyl Bromide.*—An example of the destructive effect of prolonged irradiation is provided by the comparison of the foregoing experiment with the

analogous ^{82}Br experiment which was subjected to 100 times longer irradiation. Separation by distillation and chromatography led to the following distribution of ^{82}Br activity:

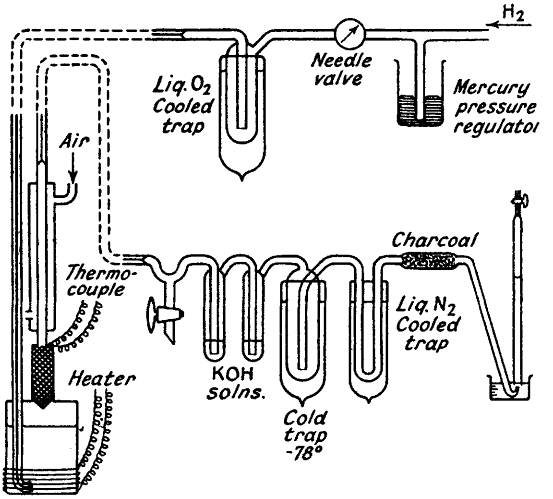
Fraction.	^{82}Br (34 hr.), %.	^{128}I (25 min.), %.
Aqueous extract	11	63
$CH_3(Hal)$	9	14
$CH_2(Hal)_2$		3
$C_6H_5(Hal)$	4	13
$C_6H_4(Hal_2)$	5	7
Resins	71	

We see that not only all the organic radioactive compounds suffer considerable destruction, but practically all the halogen of the aqueous extract apparently interacts with resins formed by the radio-chemical destruction of benzene. This kind of clean-up of inorganic halide is still more pronounced when irradiation is carried out, not in the thermal column, but in a fast neutron flux. After irradiation for 2 hours of a few mc. of ^{131}I dissolved in benzene, no free iodine could be extracted by aqueous solutions, and the benzene solution, which was originally coloured by carrier iodine, was completely colourless after irradiation. It would appear from this that the production of really high activities of long-lived organic radio-halides meets considerable difficulties.

(5) *Carrierless Methyl Bromide.*—Special interest attaches to reactions in which long-lived radioactive methyl bromide is produced, because high volatility of the product renders possible its continuous removal from the reaction zone and thereby offers a possibility of producing considerable quantities of high specific activity. The apparatus used is shown in Fig. 4. 250 Ml. of liquid could be refluxed under irradiation while a very slow stream of dry hydrogen removed the methyl bromide formed. The emerging gas was freed from any hydrogen bromide by passing though a potassium hydroxide solution, organic bromide vapours were removed in a trap cooled with solid carbon dioxide, and the methyl bromide was finally frozen out with liquid nitrogen.

FIG. 4.

Apparatus for continuous production of $CH_3{}^{82}Br$ *in the pile.*



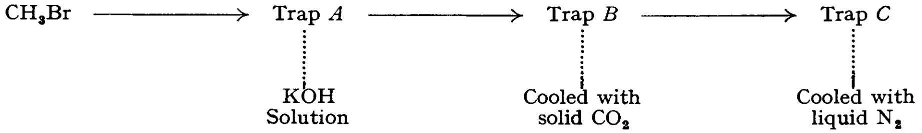
Several reactions were tested by irradiation of (1) $CH_3{\cdot}COBr$, (2) $CH_3{\cdot}CO_2H + CaBr_2$, (3) $CH_3{\cdot}CO_2H$ + 10% $CH_2Br{\cdot}CO_2H$, (4) $CH_3{\cdot}CO_2H$ + 10% $C_6H_4Br_2$. In all these cases the fast-recoiling radioactive bromine atom (or ion) replaces the CO_2H or COBr group, thus resulting in the formation of methyl bromide.

Only insignificant activities of methyl bromide were produced in reactions (1) and (2). Though large quantities of hydrogen bromide were obtained in reaction (1), it was apparent that in this case the methyl bromide formed must have exchanged quickly with either the hydrogen bromide formed by decomposition or, in reaction (2), with the bromide ions present.

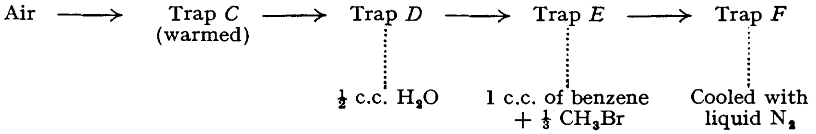
These possibilities of subsequent exchange were reduced in reaction (3) and especially in (4). Reaction (3) yielded quantities of the order of 1—5 mc. of pure methyl bromide, and in reaction (4) as much as 50 mc. of methyl bromide was obtained in an invisible quantity of material. (The activities extracted from the reaction vessel could be doubled by adding 100 mg. of methyl bromide carrier to the mixture before irradiation).

It is conceivable that the greatly increased yield of reaction (4) may be due, not only to the greater stability of dibromobenzene, but also to the clean-up effect of inorganic halogen, described before, which would drastically reduce any possibilities of chemical exchange with the directly formed methyl bromide.

In order to check the chemical identity of the active material so obtained, the following purification train was used :



The trap *C*, in which the methyl bromide was collected, was detached and investigated separately in the following train :



A slow air current was passed through *C*, *D*, *E*, *F*, which quickly removed the activity from *C via D* and *E* to *F*. As less than 1% stayed in *D* and *E*, it was clear that the product in *C* was free from hydrogen bromide and heavier organic bromo-products. It was noticed that *C* remained very active at first, an activity which could not be removed even by flaming the glass tube. However, this activity decayed with an 18-minute period. The obvious explanation is that this was due to the conversion of 4·4-hr. $CH_3{}^{80}Br$ to the 18-min. ^{80}Br which reacts with the glass and therefore cannot be removed.

The activity finally collected in *F* consisted of 4·4-hr. methyl bromide and 34-hr. methyl bromide, the proportion depending on the length of the irradiation.

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Atomic Energy Research Establishment,
Harwell, Didcot, Berks.

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