# SYNTHESIS OF ORGANIC DEUTERIUM COMPOUNDS

## IV. METHYL-$d_3$ BROMIDE[1]

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## ABSTRACT

Silver acetate-$d_3$ and bromine react readily in the dry state in a sealed tube to give methyl-$d_3$ bromide in high yield. This method is more convenient than the reduction of carbon dioxide to deuterated methyl alcohol with lithium aluminum deuteride, followed by the conversion of the alcohol into the halide, or other methods hitherto reported.

## INTRODUCTION

As potential sources of deuteromethyl groups, methyl-$d_3$ halides are very valuable compounds in deuterium chemistry. Deuterated methyl halide of high isotopic purity was needed in these laboratories for research on reaction mechanisms, free radicals, and infrared absorption spectra of organic molecules.

Two methods of preparation are available in the chemical literature but both are unsatisfactory in some respects. In 1942, Noether (9) reported the synthesis of two deuterated methyl halides from nitromethane according to the reaction scheme I (X = Cl, or Br).

$$CH_3NO_2 \rightleftharpoons CD_3NO_2 \rightarrow CD_3NH_2.HCl \rightarrow CD_3NHCOC_6H_5 \rightarrow CD_3X \qquad I$$

This method is inconvenient owing to its length and the low over-all yield.

Beersmans and Jungers later prepared the methyl-$d_3$ halides (2) via methyl-$d_3$ alcohol (1) according to the reaction scheme II (X = Cl, Br, or I).

$$CO + 2D_2 \rightarrow CD_3OD \rightarrow CD_3X \qquad II$$

The reduction of carbon monoxide was carried out in the presence of a copper–zinc–chromium (49:43:8) catalyst in a specially designed apparatus at 280°C. under a pressure of 3.5 atm. of deuterium gas. The yield of alcohol was very good and the methyl group contained 98 atom % deuterium as determined by infrared absorption. This method, however, requires elaborate apparatus and gives a low daily yield of alcohol (1.5–2.0 ml.). The synthesis of a large amount of alcohol requires many days of continuous operation, while the preparation of a small quantity can hardly justify the use of this process. Moreover, the primary reaction product is the alcohol, whereas in many cases the material required is the halide; the conversion usually gives a yield of 80%.

The reduction of carbon dioxide with lithium aluminum hydride in diethyl carbitol solution was reported to give methanol in 80% yield based on carbon dioxide (11); the yield based on the hydride is however only 40%. Isotopically labeled carbon dioxide was later reduced in a similar way, the yields of methanol and methyl iodide being respectively about 90% and 80% (3, 4); on the basis of the hydride used, they are reduced by half.

In the present work, lithium deuteride was prepared in nearly quantitative

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yield from lithium metal and deuterium gas (99.7 atom % deuterium) in a specially designed reactor at 750°C. The finely ground material was reacted with a diethyl ether solution of aluminum chloride, essentially as described for the preparation of lithium aluminum hydride (5), to give lithium aluminum deuteride in 70% yield, based on lithium deuteride. The compound contained 94.4 atom % deuterium as determined by mass analyses of the deuterium gas evolved on pyrolysis (5).

Carbon dioxide was reduced with lithium aluminum deuteride in diethyl carbitol solution essentially as described for the reduction of isotopically labeled carbon dioxide with lithium aluminum hydride (3), except for the use of a smaller excess (1.33 equivalents) of the reducing agent. The crude deuterated methanol was converted into the iodide by means of a Zeisel reaction in an over-all yield of 40%. This method is tedious and somewhat hazardous. The yield is low and the contamination of the final product with about 5% of normal ethyl iodide is inherent to the use of diethyl carbitol as solvent. This contamination can be reduced to a certain extent by the use of tetrahydrofurfuryloxytetrahydropyran (3, 4), but this solvent is not available commercially and does not improve the yield significantly.

The isotopic purity of the deuterated methyl iodide corresponded to 94.3 atom % deuterium, which is in agreement with the figure found for lithium aluminum deuteride. However, this is lower than that of the deuterium gas used in the preparation of lithium deuteride. No sure explanation is offered for this dilution effect, as precautions were taken during the synthetic process to exclude any obvious source of contamination. The lithium metal might have occluded some hydrogen which eventually diluted the deuterium gas.

In a previous paper from these laboratories (10), one of us mentioned the preparation of deuterated methyl bromide in 25% yield from deuterated silver acetate and bromine in carbon tetrachloride solution; the isotopic content amounted to 90 atom % deuterium. The reaction was not further investigated at the time, but it was felt that a procedure might be developed to give satisfactory yields of pure deuterated methyl bromide of high isotopic purity. This paper describes experiments made in this direction.

Silver salts of monobasic carboxylic acids react with two equivalents of bromine as represented in the simplified scheme III (8).

$$\begin{gathered} \mathrm{RCOOAg} + \mathrm{Br_2} \rightarrow [\mathrm{RCOOBr}] + \mathrm{AgBr} \\ [\mathrm{RCOOBr}] \rightarrow \mathrm{RBr} + \mathrm{CO_2} \end{gathered} \qquad \mathrm{III}$$

The reaction is usually carried out in carbon tetrachloride solution. According to Hunsdiecker *et al.* (7) however, methyl bromide was prepared in 80% yield in the absence of solvents in a *suitable vessel,* the nature of which was not specified in the patent.

In the present procedure, silver acetate-$d_3$ is treated in the dry state with a slight excess of bromine in the apparatus illustrated in Fig. 1. This tube permits both reagents to be present under reduced pressure in the same reaction vessel so that their contact may be controlled as desired. Features of the decomposition of the intermediate complex [RCOOBr] are the low temperature at which it

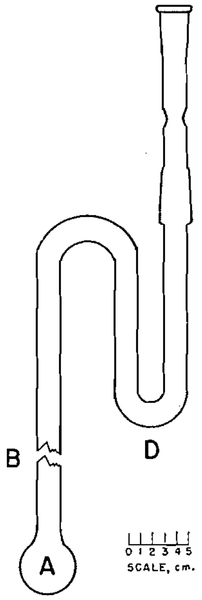

FIG. 1. Apparatus for the reaction of bromine with silver acetate-$d_3$.

occurs, and the fact that as the chain length of the acid is shortened, the decomposition occurs with increasing violence (12, 13). Under the conditions described in the experimental part, the reaction of bromine with silver acetate-$d_3$ is smooth and complete in about half an hour. The crude material is readily purified and 75–82% yields of methyl-$d_3$ bromide are consistently obtained. Its isotopic purity was 99.3 atom % deuterium, which is assumed to be also the deuterium content of its precursors, namely deuterated silver acetate, acetic acid, and malonic acid.

The latter acid was easily prepared on the one-mole scale by repeated exchange of normal malonic acid with deuterium oxide. By decarboxylation, deuterated acetic acid was obtained in nearly quantitative yield. Deuterated malonic acid could also be prepared by direct synthesis from carbon suboxide and heavy water (6, 14).

## EXPERIMENTAL

### *Silver Acetate-$d_3$*

A given weight of deuterated acetic acid is diluted with cold water and the solution neutralized carefully with cold dilute ammonia. On adding silver nitrate deuterated silver acetate is precipitated; it is isolated by filtration, washed with cold water, and dried. The material present in the filtrate is easily recovered by concentration. The yield of the silver salt is practically quantitative. If the silver salt, for some reason, is not free from acetic acid, it is preferably purified by further washing with or crystallization from water, as traces of the acid have been found to reduce the yield of the subsequent preparation.

### *Methyl-$d_3$ Bromide*

The preparation is carried out in the apparatus illustrated in Fig. 1.

Silver acetate-$d_3$ (0.05 mole, 8.5 gm.) is placed in the 25 ml. flask $A$, which is sealed to an inverted S-shaped tube at $B$, and dried by heating in boiling water under vacuum. Bromine (0.06 mole, 3.1 ml.), dried over phosphorus pentoxide, is distilled from a vacuum line through $C$ and frozen at $D$ with liquid nitrogen (a dry ice – acetone mixture could likely be used). The reactor is then sealed off at $E$. The bromine is melted by plunging $D$ into an acetone bath at room temperature and, by cooling the reaction flask till the bulk of bromine begins to boil, some is frozen above $A$. This portion of bromine is melted and reacted slowly with the silver salt while the tube is being swirled. The process is repeated about ten times and by then the reaction mixture has already yielded some methyl bromide. The reaction is thereafter continued as follows: $A$ is cooled up to $B$ and some bromine* is allowed to run down to the reaction flask and frozen above $A$; the more volatile methyl bromide is frozen at $D$, which facilitates the reaction of the bromine frozen above $A$. The process is repeated till all the liquid at $D$ is used up. The reaction time, as estimated from 10 runs, varies from 30 to 45 min.** The reaction mixture was generally allowed to stand overnight in the dark.

The reaction tube is cooled at $D$, opened, and attached quickly to the evacuated manifold. The system is completely evacuated and all the volatile material is allowed to distill out. The yellow residue in $A$ is heated with a free flame to liberate any remaining methyl bromide from the intermediate complex.

The crude material is passed through a U-tube filled with Ascarite, where carbon dioxide and most of the excess bromine are removed. A similar treatment with Ascarite and Drierite removes the last traces of bromine and any water, the presence of which is however unlikely under the conditions described above. In some runs, a yellow coloration persisted, which disappeared on further treatment with Ascarite. Vapor pressure measurements and mass analyses indicated that the deuterated methyl bromide thus obtained is slightly contaminated with deuterated ethane, acetic acid, and possibly methyl acetate. These by-products are easily removed in the following manner. The material is cooled at − 78°C. and its vapor is allowed to expand four times into a manifold, the fractions being discarded. Four distillations at − 78°C. are then carried out from bulb to bulb to remove the less volatile impurities. Yield, 4.0 gm., 81.7%.

The above treatment yields a product of high chemical purity, as judged by its mass spectrum and its vapor pressure at 0°C., 681.5 mm. This figure is in agreement with that reported by Beersmans and Jungers (2) for pure methyl bromide of comparable deuterium content. Mass analyses have indicated an isotopic purity of 99.3 atom % deuterium (98.0% $CD_3Br$ and 2.0% $CD_2HBr$). This is the equivalent of 2.98 deuterium atoms per methyl group, while the theoretical requirement is 3.

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**Very small portions of bromine are introduced at first, but larger amounts can be added when the reaction subsides.*

***One must not be anxious to bring about the reaction in a shorter time, even when it seems to proceed smoothly. It is preferable to warm up the reaction flask to room temperature before further addition of bromine; this avoids the accumulation of much undecomposed complex in the reaction mixture.*

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