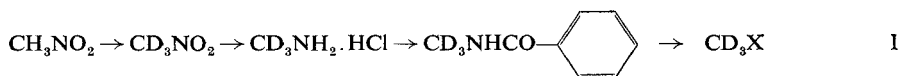


Synthesis of Methyl-T Chloride on a Micro Scale

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Triated methyl chloride of relatively high specific radioactivity was required for a research on reaction mechanism. For this labelled compound, several methods of preparation are available in the literature, but all are unsatisfactory in some respects. Noether reported a preparative method for deuterated methyl halides starting with nitromethane according to the reaction scheme I (X = Cl or Br) ⁽¹⁾.



This method is inconvenient owing to its length and the low over-all yield. The synthetic processes passing through labelled methanol were reported by Harman and his coworkers (scheme II) ⁽²⁾ and Beersmans and Jungers (scheme III) ⁽³⁾.



Nystrom and his coworkers proposed an alternative method of reduction of carbon dioxide to deuterated methanol using lithium aluminium deuteride ⁽⁴⁾. These methods were considered not to be appropriate to the micro and radioactive synthesis, since, in these processes, the primary reaction product is the labelled alcohol and the low expected yield in conversion of the alcohol to the chloride in a micro scale synthesis can hardly justify the use of these processes.

Harman and his coworkers, although they consequently employed the above mentioned process (scheme II), suggested a preparative method starting with diazomethane for tritium labelled methyl iodide ⁽²⁾. According to the method, the intended methyl chloride-T can be obtained directly from diazomethane and tritiated hydrogen chloride which is readily prepared by the distillation of tritiated water onto phosphorus pentachloride ⁽⁵⁾, (scheme IV).



It was therefore decided to adopt this process which later proved to be successful for the micro scale preparation of methyl-T chloride.

Materials. An ethereal solution of diazomethane was prepared from p-totyl sulfonylmethyl nitrosoamide in the usual way and an aliquot of the solution was assayed by titration before use. Commercially available phosphorus pentachloride was used after sublimation. Tritiated water having a specific radioactivity of 5 mCi/ μ l was purchased from the Radiochemical Centre, Amersham England.

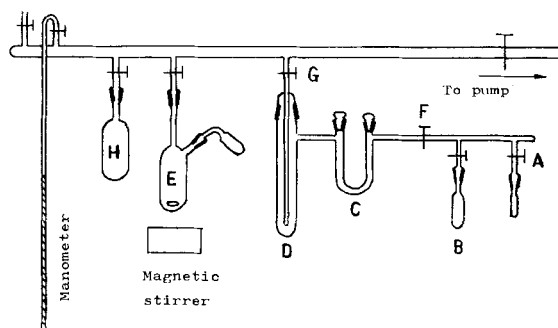


FIG. 1. Apparatus for methyl chloride-T preparation.

A high vacuum manifold, shown in figure 1, equipped with a reaction flask, a tritiated hydrogen generator and a product receiver was mounted on a rack, and the reactions were all carried out in this vacuum system.

Preparation of Methyl-T Chloride. A bulb containing 50 μ l (2.8 mmoles, 250 mCi) of tritium water was attached at A, 1.8 g (6.5 mmoles) of phosphorus pentachloride was placed in the tritium chloride generator B, and the U-shaped tube C was filled with phosphorus pentachloride. The reaction flask E containing 25 ml of an ethereal solution of diazomethane (7 mmoles of diazomethane was included) was attached to the manifold, and the flask was equipped with a side tube containing 1g of benzoic acid.

The bulb containing tritium water and the flask E were cooled with liquid nitrogen; then the whole vacuum system was evacuated to 0.1 μ . Stopcock F was closed, and the liquid nitrogen bath was moved from tritium water container to tritium chloride generator. When tritium water was wholly transferred into the generator, stopcock A was closed and F was opened. The cooling bath was removed, and the temperature of the mixture was allowed to rise to room temperature. Resulting tritiated hydrogen chloride, dried and freed from phosphoryl chloride by passage through the phosphorus pentachloride tube C and a freeze-out trap D cooled in a dry ice-acetone mixture, was introduced into the reaction flask E which was cooled by liquid nitrogen. When the last of tritiated hydrogen chloride was evolved by war-

ming the generator and the U-shaped tube, stopcock G was shut, and the mixture in the flask E was thawed with a dry ice-acetone mixture.

As the reaction mixture melted, the reaction occurred, and nitrogen gas began to generate smoothly. After stirring for 20 min, when the manometer reading was constant, the mixture was again frozen with liquid nitrogen to draw any remaining tritiated hydrogen chloride into the reaction flask, then the mixture was stirred for another 20 min at the dry ice-acetone temperature to ensure complete absorption. The side tube containing benzoic acid was arranged downwards, benzoic acid was added slowly to decompose the excess diazomethane.

The reaction flask was cooled with liquid nitrogen and the system was evacuated again then methyl-T chloride with ether was transferred to the receiver H, leaving methyl benzoate and the excess benzoic acid in the reaction flask.

Separation of Methyl-T Chloride. To separate methyl-T chloride from the solvent, the solution was submitted to preparative gas-chromatography on a silicon DC 550 column (3 × 100 cm), and the component containing pure methyl chloride was collected into a trap cooled by liquid nitrogen; 104 ml (converted to N.T.P.) of methyl-T chloride having 171 mCi of radioactivity was obtained. The yield was estimated as 82.8 % as chemical and 68.5 % as radiochemical.

The decrease of specific radioactivity from the expected value may result from the dilution with hydrogen chloride included in phosphorus pentachloride and/or generated by ordinary water which get into the system.

The infrared spectrum of the product was consistent with the expected structure, and the gas-chromatogram, of course, showed only one peak.

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REFERENCES

1. NOETHER, H. D. — *J. Chem. Phys.*, **10** : 664 (1942).
2. HARMAN, D., STEWART, T. D. and RUBEN, S. — *J. Am. Chem. Soc.*, **64** : 2293 (1942).
3. BEERSMANS, J. and JUNGERS, J. C. — *Bull. Soc. Chim. Belges*, **56** : 72 (1947).
4. NYSTROM, R. F., YANKO, W. H. and BROWN, W. G. — *J. Am. Chem. Soc.*, **70** : 441 (1948).
5. KLEIN, F. S. and WOLFSBERG, M. — *J. Chem. Phys.*, **34** : 1494 (1961).