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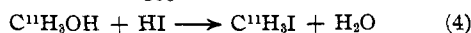
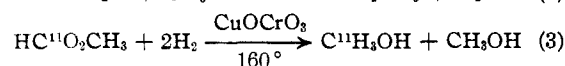
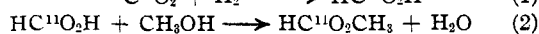
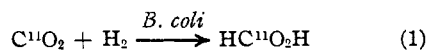
Tracer Studies with Radioactive Hydrogen. The Synthesis of Labeled Methyl Iodide

BY D. HARMAN, T. D. STEWART AND S. RUBEN

In connection with our work on the Menschutkin reaction¹ it was necessary to prepare methyl iodide with the methyl group labelled by the inclusion of a radioactive carbon or hydrogen atom.

There are two radioactive isotopes of carbon whose half-lives are such that they can be used as isotopic tracers, C¹¹ (half-life 20.5 minutes) and C¹⁴ (half-life 10⁸ years). Since the supply of C¹⁴ is limited we attempted to use the shorter lived isotope. The isotopes have already been employed in a rapid synthesis of other organic compounds.^{2,3,4}

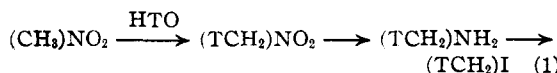
The synthesis of C¹¹H₃I used may be summarized by the equations



The reduction of CO₂ to formic acid was accomplished by a fresh suspension of *Bacterium coli*.^{5,6}

While the above process is practicable, the time required is about three hours. It was therefore decided to label the methyl groups with radioactive hydrogen.⁷ The half life of H³ is about thirty years⁸ and, moreover, samples of high specific radioactivity can be prepared. The chief difficulty in the use of H³ is in the measurement. It emits very soft beta particles (upper energy limit 10–15 Kev)^{7,8,9} and, consequently, it must be counted in gaseous form.

With radioactive hydrogen as a tracer for methyl groups there are several possible modes of preparation in addition to the one above.



(1) Harman, Stewart and Ruben, *THIS JOURNAL*, **64**, 2294 (1942).

(2) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 549 (1941).

(3) Wood, Werkman, Hemingway, Nier and Stuckwisch, *THIS JOURNAL*, **63**, 2140 (1941).

(4) Allen and Ruben, *ibid.*, **64**, 948 (1942).

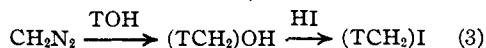
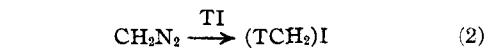
(5) Woods, *Biochem. J.*, **30**, 515 (1936).

(6) We are indebted to Professor H. A. Barker for the *B. coli* and for his helpful cooperation.

(7) Alvarez and Cornog, *Phys. Rev.*, **56**, 613 (1939).

(8) O'Neal and Goldhaber, *ibid.*, **57**, 1086 (1940).

(9) Brown, *ibid.*, **58**, 954 (1941).



The process used here employs the apparatus developed for C¹¹H₃I, substituting HT for H₂.

Experimental

Preparation of C¹¹H₃I.—About 50 cc. of the aqueous solution of radioactive formic acid was titrated to phenolphthalein and the solution evaporated to dryness *in vacuo* at 100°. The residual sodium formate (about 0.5 g.) was placed in a semi-micro distillation apparatus and to it was added 1 cc. of a solution prepared from 25 g. of sulfuric acid and 50 g. of methanol. The first distillate of about 0.2 cc. was redistilled to give about 0.1 cc. of liquid which contained approximately 60% yield of methyl formate. This yield could be improved. The ester was converted to methanol and methyl iodide by essentially the same process as described below for the tritium derivative.

Preparation of (TCH₂)₂I.—The apparatus used, shown in Fig. 1, was designed to recover unused radioactive hydrogen which was stored in bulb I.

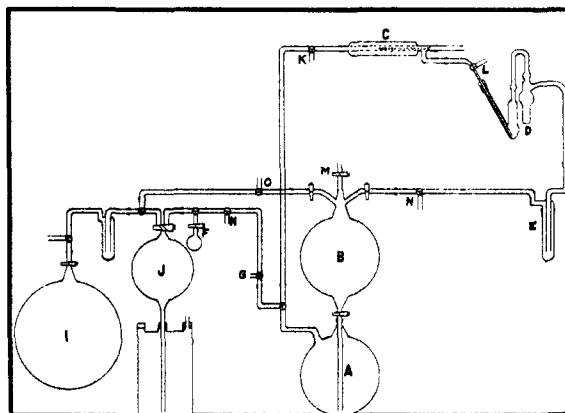


Fig. 1.

A bulb containing the methyl formate was attached at F and cooled in liquid air. The line including J, A and B was filled with hydrogen three times and evacuated. The line from K to N was swept out with a stream of hydrogen. Initially, bulb B is filled with mercury and bulb A has only enough to cover the end of the tube leading from B to A.

The reaction mixture of methyl formate and tritium (HT) was prepared in bulb A by admitting the ester to a pressure of 7.6 cm. of mercury and transferring the tritium with the help of the Toepler pump to give a total pressure of 76 cm. of mercury. This mixture was passed over the catalyst in C and through the Zeisel apparatus¹⁰ at a rate

(10) J. B. Niederl and V. Niederl, "Organic Quantitative Micro-analysis," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 187.

of about 10 cc. per minute by admitting mercury from B to A. In order to maintain atmospheric pressure mercury is added to B through M. The liquid air trap at E condensed the methyl iodide formed and unused tritium was returned through B eventually to I.

The active methyl iodide containing tritium was made in about 2 g. quantities in better than 75% yield. The crude material of d^{20} 1.5268 melted at about -60° . It was redistilled and the vapor passed over phosphorus pentoxide *in vacuo*.

Preparation and Use of Catalyst.—The catalyst was prepared by dissolving 120 g. of cupric nitrate in 100 cm. of water and adding a saturated solution containing 60 g. of potassium carbonate at about 50° . The precipitated basic copper carbonate was filtered off, washed well and dried; 45 g. of the pulverized material was added to 100 cc. of quartz chips (0.5 to 1 mm.) and 50 cc. of chromic acid

solution containing 2 g. of CrO_3 . The mixture was well stirred and dried on a steam-bath. The catalyst chamber of 3.5-cc. capacity was filled with this material and the catalyst reduced by passing about 20 cc. of hydrogen per minute over it at a temperature of 325° for six hours. Tank hydrogen was passed over the catalyst at 160° , the temperature used for the reduction of the ester, for two hours before each preparation.

Summary

Radioactive methyl iodide has been prepared by two processes, the one leading to a compound containing short-lived C^{11} , the other to a compound containing radioactive hydrogen. Each process is designed for small amounts of material.

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A Study of the Menschutkin Reaction Using Radioactive Hydrogen as a Tracer

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The reaction between amines and organic halides



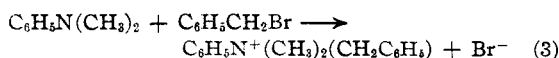
has been the subject of considerable experimentation and speculation.¹⁻¹⁰

The kinetics of this reaction are of particular interest because the probability factor in the rate expression

$$\frac{d(\text{I}^-)}{dt} = k(\text{R}_3\text{N})(\text{RX}) = PZe^{-E/RT} (\text{R}_3\text{N})(\text{RX}) \quad (2)$$

is unusually low, and, moreover, markedly affected by the solvent. For example, in the reaction between $\text{C}_6\text{H}_5\text{NH}_2$ and $\text{C}_6\text{H}_5\text{COCH}_2\text{Br}$ the factor P varies from 4×10^{-11} in benzene to 5×10^{-5} in benzyl alcohol.¹⁰

The values of $\log P$ and E in different solvents for the reaction



as given by V. A. Gol'tschmidt and N. K. Vorob'ev⁹ are reproduced in Table I.

- (1) N. Menschutkin, *Z. physik. Chem.*, **6**, 41 (1890).
- (2) Moelwyn-Hughes and Hinshelwood, *J. Chem. Soc.*, 239 (1932).
- (3) G. E. Edwards, *Trans. Faraday Soc.*, **33**, 1294 (1937).
- (4) R. G. W. Norrish, *ibid.*, **33**, 1521 (1937).
- (5) C. N. Hinshelwood, *ibid.*, **33**, 970 (1937).
- (6) Moelwyn-Hughes and Sherman, *J. Chem. Soc.*, 101 (1936).
- (7) Stern and Eyring, *J. Chem. Phys.*, **5**, 113 (1937).
- (8) Scatchard, *ibid.*, **2**, 657 (1934).
- (9) V. A. Gol'tschmidt and N. K. Vorob'ev, *J. Phys. Chem.* (U. S. S. R.), No. 4, 473 (1939).
- (10) R. G. Cox, *J. Chem. Soc.*, **119**, 142 (1921).

TABLE I

THE ACTIVATION ENERGY AND PROBABILITY FACTOR FOR THE REACTION OF EQUATION 3

Solvent	$(\text{CH}_3)_2\text{-CO}$	$\text{C}_6\text{H}_5\text{-COCH}_3$	$\text{C}_6\text{H}_5\text{NO}_2$	$\text{C}_2\text{H}_5\text{OH}$
$k \times 10^4$ (30°)	80.5	84.5	118	650
E	9747	9929	11,200	13,800
$-\log P$	4.94	5.08	6.16	8.78

For other types of reaction the value of P is usually close to unity; the very low values in the Menschutkin reaction imply that very few "activated" collisions result in reaction. Many theories have been advanced to account for this abnormality and the present paper presents experimental results which offer a test of some of these explanations.

Moelwyn-Hughes and Sherman⁶ have assumed that at least one of the reactants forms an unstable complex with the solvent and that the true reactant is this solvated portion. In such a case the evaluation of the product $(\text{R}_3\text{N})(\text{RX})$ of the rate expression is in error and the true value of P could be unity.

Hinshelwood,⁵ from a consideration of Eucken's¹¹ work on the variation of the velocity of sound with frequency in the gas phase, and Norrish,⁴ by analogy with a number of photochemical reactions, account for the apparent inefficiency of the activated collisions by assuming an intermediate collision complex which can yield the

(11) Eucken and Jaacks, *Z. physik. Chem.*, **B30**, 85 (1935).