

Preparation of Labelled Compounds by Tritioboration Procedures

I. Cyclohexene-1-³H

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SUMMARY

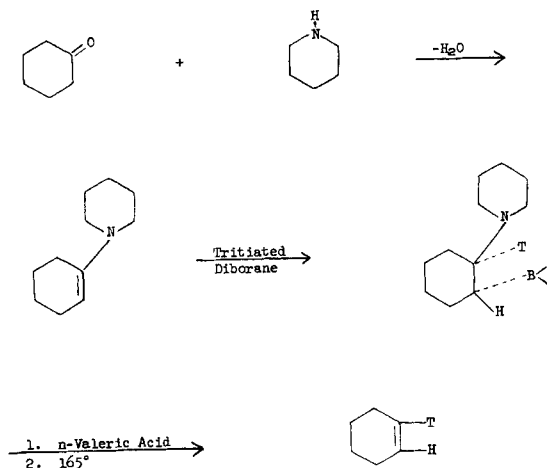
Cyclohexene-1-³H has been synthesized with a yield of 88 % by tritioboration of 1-(N-piperidino)-cyclohexene followed by heating with n-valeric acid. Other unsaturated compounds can be labelled at one olefinic carbon atom with tritium by this method.

INTRODUCTION.

A novel hydroboration procedure reported by J. W. LEWIS and A. A. PEARCE ⁽¹⁾ has been utilized to prepare cyclohexene-1-³H. Briefly summarized, the reaction sequence is : (a) conversion of cyclohexanone to 1-(N-piperidino)-cyclohexene; (b) reduction of the enamine with tritiated diborane; and (c) reaction between 2-N-piperidylcyclohexylborane-³H and n-valeric acid followed by heating to furnish cyclohexene-³H. When the reaction is carried out on a 10 millimole scale, the yield of cyclohexene-1-³H is 88 % based on 1-(N-piperidino)-cyclohexene and 73 % based on sodium borotritide.

This process appears to be a promising method for preparing certain unsaturated compounds labelled at one olefinic carbon atom with tritium in a stereospecific manner. Thus, *cis* 2-pentene-3-³H and α -(*trans*)-crotonic acid-3-³H have been made. The *cis*-acid is probably isomerized to the *trans*-form during the work-up procedure. However, attempts to prepare *cis*-stilbene-³H by this process furnished a mixture of the *cis* and *trans* isomers.

Alternate methods for synthesizing cyclohexene-1-³H are the pyrolysis of cyclohexyl-1-³H S-methyl xanthate ⁽²⁾ (with 98 % of the tritium attached to the olefinic carbon atoms), the sulfuric acid dehydration of cyclohexanol-1-³H ⁽³⁾ (with 92 % of the tritium attached to the olefinic carbon atoms ⁽⁴⁾), and the phosphoric acid dehydration of cyclohexanol-1-³H (with 54 % of the tritium attached to the olefinic carbon atoms ⁽²⁾).



EXPERIMENTAL.

1-(N-piperidino)-1-Cyclohexene.

In a 500-ml round-bottomed flask to which was attached a water separator and a reflux condenser was placed 16.3 g (0.17 mole) of cyclohexanone, 25.5 g (0.30 mole) of piperidine, and 0.25 g of *p*-toluenesulfonic acid dissolved in 50 ml of toluene. The mixture in the flask was heated by means of an electric heating mantle so that a reflux was maintained. The theoretical amount of water was collected in 4 hours. Then, most of the toluene was removed by distillation at atmospheric pressure. The flask was next heated slowly while the system was evacuated to a pressure of 1 mm Hg. The 1-(N-piperidino)-1-cyclohexene was distilled and collected at 83-85° C, in a yield of 21 g (51 %) ⁽⁵⁾.

Cyclohexene-1-³H.

The lower part of the apparatus was constructed from a 50-ml flask fitted on one side with a 25 mm × 13 cm neck attached to a 24/40 standard taper outer joint and on the other side with a 25 mm × 4 cm tip. The upper part was a 24/40 standard taper inner joint equipped with a gas inlet tube which almost reaches to the bottom of the reaction vessel, a gas outlet tube, and an opening for a modified eye dropper assembly. A small magnetic stirring bar was placed in the reaction vessel, the top attached, and the entire apparatus flamed dry in a stream of dry nitrogen. Into the tip of the reaction vessel was placed 12 ml of a 1 M solution of sodium borotritide ⁽⁶⁾ in diethylene glycol dimethyl ether (diglyme) and 1.65 g (10 millimoles) of 1-(N-piperidino)-1-cyclohexene. The system was flushed with dry nitrogen gas and a nitrogen atmosphere was maintained during the dropwise addition of 2.5 ml of boron trifluoride etherate over a period of two hours. A white precipitate formed

near the end of the reaction. After the addition of boron trifluoride was complete, the top of the apparatus was removed. Next, the diglyme was removed by distillation at 50° C and 10⁻⁴ mm Hg. All the volatile materials must be removed at this stage. The residue was then treated with 7 ml of n-valeric acid before attaching the reaction vessel, equipped with a gas inlet and outlet tube, to two traps in series connected to a high vacuum line. A slow stream of helium was passed through the apparatus and the traps cooled by means of liquid nitrogen. The reaction vessel was then heated by means of an oil bath to 165° C. At a temperature of about 90° C a vigorous reaction took place. After sweeping the mixture for 1 hour with helium, the condensate collected in the cold traps was vacuum distilled at 10⁻⁴ mm Hg through a trap cooled at 0° C and the product collected in a tube cooled by liquid nitrogen. The yield of cyclohexene-1-³H was 0.72 g (88 % based on the enamine).

The radiochemical purity of the cyclohexene-1-³H was established by radiogas chromatography ⁽⁷⁾; by isotope dilution assay using a distillation column with 100 theoretical plates to effect purification of the diluted cyclohexene-1-³H before conversion to the 1,2-dibromocyclohexane-³H derivative with approximately the same millimolar radioactivity as calculated for the diluted cyclohexene-1-³H; and by degradation to adipic acid with complete loss of the tritium radioactivity.

ACKNOWLEDGMENT

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