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NOTE

Labelling of Benzocaine with Tritium

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SUMMARY

A convenient method is described to label a local anesthetic, benzocaine, with tritium. The bromoester of *para* - aminobenzoic acid (PABA) was prepared from *para*-nitrotoluene and was reduced with tritium. The generation of isotopic hydrogen and labelling of benzocaine was achieved in one-step. A mixture of sodium borohydride (NaB^3H_4) with cobalt (II) chloride was used to generate tritium gas. 5% Pd/C was used as a catalyst. This constitutes the first report of tritium labelled benzocaine.

Key words: Hydrogen isotopes, tritium, bezocaine, local anesthetics, PABA, microscale.

INTRODUCTION

Local anesthetics are commonly divided into two main classes, amino-esters and amino-amides. Benzocaine (ethyl *para*-aminobenzoate) belongs to the first group. It is a local anesthetic of low water solubility and lower toxicity. This makes it one of the most significant anesthetics used in its class. Benzocaine is used in large number of topical preparations. There are several over the counter products available in the USA which contain benzocaine. They include hemorrhoid creams, teething gels, first aid ointments, vaginal creams, mouth rinses and throat lozenges. Chemically it is an ester of *para*-aminobenzoic acid (PABA). PABA and its derivatives are also used in sunscreens. Skin absorption and metabolism of Benzocaine and PABA has been reported (1). ^{14}C-labelled PABA is commercially available and ^{14}C-labelled benzocaine can be prepared by its esterification. To my knowledge tritium label benzocaine and its derivatives are not commercially available. This constitutes the first report of tritium labelled benzocaine. A convenient method has been established to label bezocaine, using our recently reported new approach to label organic compounds with hydrogen isotopes (2). PABA and other benzoic acid derivatives can also be labelled with this simple technique.

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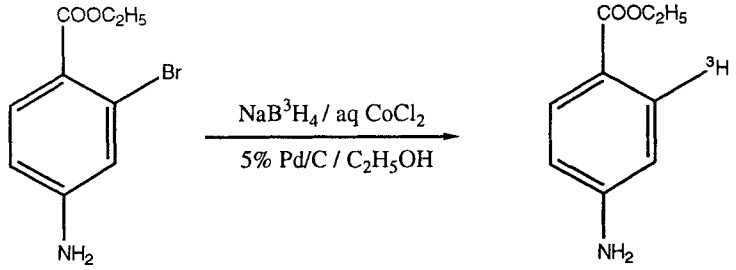
EXPERIMENTAL

The ethyl 4-amino-2-bromobenzoate (1) was synthesized from 4-nitrotoluene as described earlier (3). Compound 1 (1.0mg, 4.09 x 10^{-3} mmol) was dissolved in ethanol with 5% Pd/C in a small vial. This was placed in a larger vial with NaB^3H_4 (10 mCi, 600 mCi/mmol). The larger vial was tightly capped with a rubber septum. $CoCl_2$ (0.4 mg, 3.17 x 10^{-2} mmol) in 0.5 ml water was added and the reaction mixture was stirred for 5 hrs. at room temperature. The details of methodology and reaction have been described previously (2). Catalyst was removed by filtration and the resulting tritiated benzocaine (2) was purified by small silica gel column, using a mixture of chloroform-methanol as eluent. The amount of radioactivity recovered in the tritiated product (2) was 1.68mCi/mmol.



(1) (2)

RESULTS AND DISCUSSION

The approach used here to label benzocaine is simple and can be performed conveniently in any ordinary laboratory. Brominated compounds, commercially available or synthetically prepared , can be labelled with hydrogen isotopes (deuterium or tritium) by this method. This reaction is particularly useful for small scale labelling where high specific activity is not a major concern. The one-step method of tritium gas generation and labelling of organic compounds was first developed in our laboratory (2) and proves to be very successful for small scale labelling of variety of different compounds of pharmaceutical interest. Procaine, commonly known as novocaine, also belongs to the same group of anesthetics. It is structurally analogous to benzocaine with an additional terminal diethylamino group. Likewise, procaine can be labelled with tritium. In addition to benzocaine and procaine, this simple and rapid approach to label organic compounds can be applied to benzoic acid and wide variety of its derivatives.

REFERENCES

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