SYNTHESIS OF ^{14}C-LABELLED BUTOXYETHOXYETHANOL

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SUMMARY

Butoxyethoxyethanol[1], an organic solvent used as carrier in the levamisole pour-on formulation, was synthesized via a Makosza etherification of 1-^{14}C-labelled bromobutane with mono tetrahydropyranyl (T.H.P.) protected diethylene glycol and subsequent removal of the T.H.P. protecting group. The compounds' synthetic yield was 88.8 %; it had a specific activity of 32.5 mCi/mmol. The reaction product was radiochemically pure (99.6 %) according to high-performance liquid chromatography and thin-layer chromatography in three solvent systems.

Key words: [^{14}C]butoxyethoxyethanol, 1-[1-^{14}C]bromobutane, levamisole

INTRODUCTION

Butoxyethoxyethanol (IV) is an organic solvent used as the carrier in the levamisole pour-on formulation.[2] This formulation, when applied topically on the skin of the back of cattle, has anthelmintic properties against lungworms and gastrointestinal nematodes.

Although butoxyethoxyethanol has many industrial applications, little is known about its metabolic fate in animals and man. To evaluate the metabolism in animals, the synthesis of [^{14}C]butoxyethoxyethanol was indicated. The selection of a suitable radiolabel position is difficult, since it may be anticipated that the compound will be broken down into numerous small metabolic fragments, many of them being candidate for entering the endogenous

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pool of the body. Based on the complexity of the proposed metabolism[3] of butoxyethoxyethanol and in order to minimize the formation of volatile radioactivity ($^{14}CO_2$), the 1-carbon atom of the butyl moiety was selected as the most appropriate position for the ^{14}C-label. Utilizing available 1-[1-^{14}C]bromobutane at high specific activity, the desired product could be obtained by a two step reaction (Figure 1).

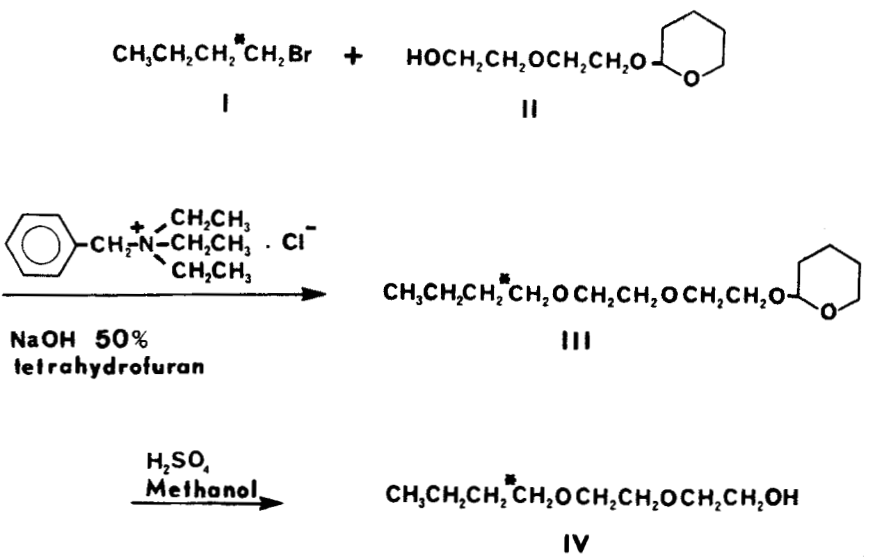

Fig. 1. Reaction scheme for the synthesis of [^{14}C]butoxyethoxyethanol (IV).

Makosza etherification[4] of 2-[2-[(tetrahydro-2H-pyran-2-yl)oxy]ethoxy]ethanol (II)[5] with 1-[1-^{14}C]bromobutane (I) and subsequent removal of the tetrahydropyranyl (THP) protecting group in 2-[2-[2-([1-^{14}C]butoxy) ethoxy]ethoxy] tetrahydro-2H-pyran (III) afforded 99.6 % radiochemically pure 2-[2-([1-^{14}C]butoxy)ethoxy]ethanol. The reaction product was diluted with unlabelled butoxyethoxyethanol to a specific activity of 3.25 mCi/mmol which has been used in various pharmacokinetic studies.

EXPERIMENTAL

ANALYTICAL PROCEDURES

Radioactivity measurements

Liquid scintillation counting (Packard Tri-Carb 460 CD) was used to determine the specific activity of labelled butoxyethoxyethanol. The radioactivity of the samples was measured in 10 ml of Insta-Gel II (Packard).

Determination of the radiochemical purity

A. High-performance liquid chromatography (HPLC). The apparatus consisted of two Waters Associates model 6000 A pumps with a Waters model 660 solvent programmer for gradient elution. Stainless-steel columns (4.6 mm I.D. x 30 cm) were packed with ODS-Hypersil (5 µm) bonded phase. The samples (about 0.15 µCi) were injected using a Waters model U6K universal injector and eluted with a linear gradient running from 100 % of water:diisopropylamine (100:0.2; v/v) to 70 % of water:diisopropylamine (100:0.2; v/v) and 30 % of acetonitrile:diisopropylamine (100:0.2; v/v) over a 30-minute period (flow rate: 1 ml/minute).

On-line radioactivity detection of the HPLC-eluates was carried out with a Berthold Radioactivity Monitor LB 5025 HP system using a flow-through cell of 400 µl. The eluate was mixed with a scintillation cocktail (Pico-fluor $^{TM}30$, Packard) in a LKB ultrograd mixing unit. The normalized areas of the radioactivity peaks were computed by a SP 4270 system (Spectra-Physics).

B. Thin layer chromatography (TLC). An appropriate amount of the labelled compound was chromatographed on silica gel plates (Merck 60 F 254, 20 x 10 cm and 0.25 mm thickness) using as eluate chloroform:methanol (90:10; v/v), chloroform:methanol:ammonia (85:15:1; by volume) and hexane:ethyl acetate (50:50; v/v).

The radioactivity on the plates was scanned with a Berthold radiochromatogram scanner (LB 2723).

SYNTHESIS

2-[2-[2-([1-^{14}C]butoxy)ethoxy]ethoxy]tetrahydro-2H-pyran (III)

To a suspension of N,N,N-triethylbenzenemethanammonium chloride (139 mg; 0.61 mmol) and II[5] (1273 mg; 6.69 mmol) in sodium hydroxide 50 % (4 ml) was added a solution of 1-[1-^{14}C]bromobutane (747 mg; 5.45 mmol, 300 mCi) [ICI Billingham, Cleveland (U.K.)] in tetrahydrofuran (2 ml). After vigorous stirring for 25 hours, gas chromatographically no bromobutane could be detected. Then the reaction was continuously stirred for 18 hours with added excess of unlabelled 1-bromobutane (747 mg; 5.45 mmol). The reaction mixture was subsequently diluted with water (4 ml) and extracted with diethyl ether (5 x 10 ml). The combined organic layers were washed with a saturated sodium chloride sol-

ution (2 ml), dried over magnesium sulphate and evaporated in vacuo at 40° C. The residue (1.55 g; chemical yield: 95.4 %) contained mainly the THP-protected III, and was used immediately in the next reaction step.

2-[2-([1-^{14}C]butoxy)ethoxy]ethanol (IV)

The THP-derivative III was dissolved in methanol (10 ml) containing two drops of sulphuric acid (95-97 %). After three hours at room temperature the solution was neutralized by stirring with solid sodium hydrogen carbonate (200 mg; 2.38 mmol). The solvent was evaporated under reduced pressure, the residue was dissolved in diethyl ether (10 ml), filtered to remove insoluble salts, and concentrated at aspirator pressure. The residue contained 963 mg of pure IV corresponding to an overall chemical yield of 88.8 %.

The radiochemical yield of 2-[2([1-^{14}C]butoxy)ethoxy]ethanol (IV) was 193 mCi (64.3 %*), at a specific activity of 200 µCi/mg, 32.5 mCi/mmol, and was shown to be 99.6 % radiochemically pure by high-performance liquid chromatography and by thin-layer chromatography.

REFERENCES

1. Butoxyethoxyethanol is known chemically as well as industrially under a wide variety of names; e.g.:

   Chemical Synonymes: 2-(2-Butoxyethoxy)ethanol, Diethylene glycol n-butyl ether, 2-ß-butoxyethoxy ethanol, Butoxydiethylene glycol, Butoxydiglycol, Butyl diglycol, O-butyl diethylene glycol, Diglycol monobutylether, Butyl diethyl cellosolve.

   Industrial Nomenclature: Butyldioxytol, Butyl Carbitol, Dowanol DB, Poly-Solv DB, Ektasolve DB, Jeffersol DB.

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The observed large discrepancy between chemical and radiochemical yield was ascribed to irradiative degradation of part of the highly radioactive 1-bromobutane to 1-butene prior to reaction.

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