SYNTHESIS OF STABILIZED TRITIUM-LABELLED 1,3-DIOXA-2-HYDROXYPROPANE DERIVATIVES FOR USE AS LYMPHATIC ABSORPTION ADJUVANTS

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SUMMARY

The synthesis of stabilized tritium-labelled 2-monoglycerides which may be used as lymphatic absorption adjuvants, using [carbonyl-^{3}H]-benzaldehyde is described. A simple method of analysis for the regeneration of these compounds from their stabilized forms is also proposed.

Key Words: [carbonyl-^{3}H] benzaldehyde, 1',3'-dioxa-2'-phenyl-[2'-^{3}H]-cyclohexyl-5'-hexadecanoate, 2-monopalmitin, lymphatic absorption adjuvants.

INTRODUCTION

The absorption of triglycerides by the lymphatic route has been well documented[1,2]. On the other hand, when certain drugs have been administered along with triglycerides higher blood levels of the drug may result[3]. In some cases, the increased amount of drug in the blood has been due to co-absorption of drug by lymphatic absorption adjuvants[4]. It has been recently reported that agents such as 2-monoglycerides (2-monopalmitin) may enhance the oral absorption of suitable drugs via the lymphatic system[4]. In these cases, a problem has arisen due to transesterification of 2-monopalmitin to 1-monopalmitin. The compound therefore requires storage at 0°C in order to prevent isomerisation[4]. 1-Monoglycerides are rapidly hydrolysed to 1,2,3-trihydroxypropane and fatty acid after ingestion[4].

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To solve this problem,it has been suggested[4] that such compounds should first be stabilized by blocking the transesterification reaction and then be regenerated to 2-monopalmitin *in vivo*. To test this hypothesis the benzylidene adduct of 2-monopalmitin has been prepared and the desired compound has been regenerated by acid catalysed hydrolysis. HPLC and colorimetric assay have been applied for the detection of benzaldehyde[4].

EXPERIMENTAL

Preparation of [methylene-^{3}H] benzyl alcohol[5,6]

Benzyl alcohol(2g) was mixed with tris(triphenylphosphine)ruthenium dichloride(0.07g) and [^{3}H]water(100μl,5Ci/ml) in a sealed tube and heated for ¾h at 200°C. The tube was then cooled and opened. The product was dried over magnesium sulphate and distilled,b.p. 92°C /11mm, yield 1.9g,specific activity 186 mCi/mmol.

Preparation of [carbonyl-^{3}H]benzaldehyde[6,7]

[methylene-^{3}H] Benzyl alcohol(1.9g) was oxidized to [carbonyl-^{3}H] benzaldehyde at room temperature for ½h with a complex of chromium trioxide(10g) and pyridine(15g) in methylene chloride(150ml) under nitrogen. The solution was then decanted from the residue. The decanted methylene chloride solution was condensed *in vacuo* and the residue then taken up in ether(100ml),filtered to remove insoluble chromium salts,washed with dilute aqueous base and saturated brine,and dried over magnesium sulphate. Evaporation of the solvent at reduced pressure afforded the [carbonyl-^{3}H] benzaldehyde(I),b.p. 63°C/10mm,yield 1.7g, specific activity 172 mCi/mmol.

Preparation of 5-hydroxy-2-phenyl-[2-^{3}H]-1,3-dioxacyclohexane[4]

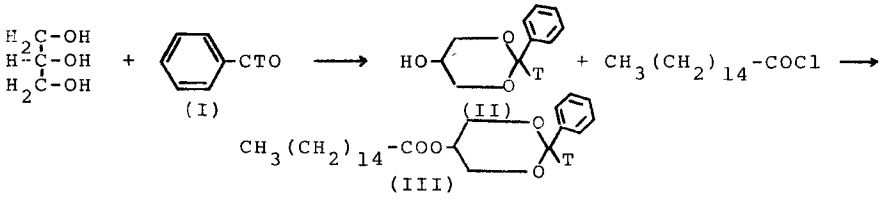
[carbonyl-^{3}H] Benzaldehyde(1.7g) and 1,2,3-trihydroxypropane(1.5g) with p-toluene sulphonic acid(0.3g) in toluene(10ml) were heated to reflux in a micro Dean-Stark apparatus. After three hours the mixture was dried over anhydrous sodium sulphate. Thin layer chromatography(acetonitrile:isopropanol:water in a 75:15:10 ratio) showed that no benzaldehyde remained,indicating the reaction was complete. The solution was cooled in a dry ice-bath(-50°C) forming a white crystalline mass. The crystals were collected on a cold filter funnel,dissolved in ether(10ml) and washed with 2% sodium sulphate solution(2X15ml). The ether solution was dried over anhydrous magnesium sulphate and evaporated to yield white crystals(II),m.p.63°C,yield 2g, specific activity 149 mCi/mmol.

Preparation of 1',3'-dioxa-2'-phenyl- [2'-^{3}H] -cyclohexyl-5'-hexadecanoate[4]

5-Hydroxy-2-phenyl- [2 -^{3}H] -1,3-dioxacyclohexane(1g) was added to chloroform(3ml). Pyridine(0.5g) was then added to the solution followed by dropwise addition of palmitoyl chloride(1.65g). After ½h the mixture was diluted with petroleum ether(b.p.60-80°C):ether(1:1,75ml) and washed with dilute hydrochloric acid (50ml) and water(2X25ml) to remove pyridine. The organic layer was dried over anhydrous sodium sulphate and evaporated under vacuum yielding a white residue. The residue was recrystallized from petroleum ether(b.p.60-80°C) which gave white crystals(III), m.p.50°C,yield 0.6g, specific activity 105mCi/mmol. Tritiated samples were counted with a Beckman LS 100 Liquid Scintillation Counter by using NE-250 as liquid scintillator.

RESULTS AND DISCUSSION

Pearlman et al[4] have reported the use of buffers of the desired pH in a range of pH 1 to pH 4 in order to regenerate 2-monopalmitin from its stabilized form. In their paper they have applied HPLC and colorimetric analysis for the detection of benzaldehyde. With respect to this report,we have investigated a simple method of analysis by using [carbonyl-^{3}H] benzaldehyde to stabilize the triglyceride thus preparing 1',3'-dioxa-2'-phenyl-[2'-^{3}H]-cyclohexyl-5'-hexadecanoate(scheme 1).



Scheme 1

It is worthy to note that,whilst the main product in experiment 3 was 5-hydroxy-2-phenyl- [2-^{3}H] 1,3-dioxacyclohexane some small quantity of 2-phenyl- [2-^{3}H] -4-hydroxymethyl-1,3-dioxacyclopentane was also prepared. In the present paper it is suggested that after acid catalysed hydrolysis of 1',3'-dioxa-2'-phenyl- [2'-^{3}H]-cyclohexyl-5'-hexadecanoate in a range of pH 1 to pH 4 and isolation of the product,the amount of radioactivity in the solution

which corresponds to [carbonyl-^{3}H] benzaldehyde at appropriate times can be measured and the amount of regenerated 2-monopalmitin can be accurately determined.

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