NOTE

SYNTHESIS OF DEUTERIUM LABELLED CLOFIBRATE

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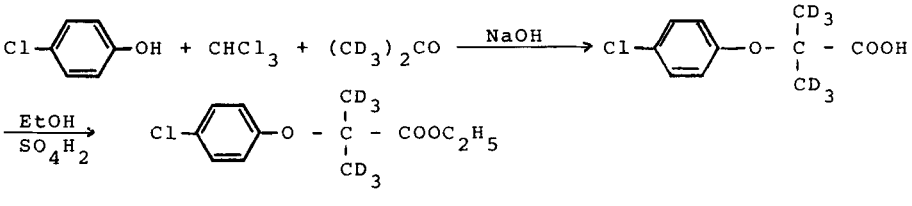
Summary
The synthesis of deuterium labelled clofibrate using fully deuterated acetone, $(CD_3)_2CO$, as labelling agent is described. Purification of labelled material was accomplished by recrystallization and fractional distillation.

Key words: clofibrate, acetone-d_6, 2-(p-chlorophenoxy)-2-methyl propionic acid.

Introduction

Clofibrate(ethyl chlorophenoxy isobutyrate) has a significant effect upon a number of the symptoms of atherosclerotic disease[1]. Its effects on blood coagulability suggest that it may reduce the hypercoagulability frequently associated with the disease[2]. Unfortunately little is known about the fate of this valuable drug in the body, and the details of its mechanism of action are largely lacking[3].

As drugs labelled with either radioactive or stable isotopes have found wide use in studies of drug metabolism[4], we now report a convenient synthesis of deuterated clofibrate fully labelled in both methyl groups by using acetone-d_6 as the labelling source[5,6]. The preparation of deuterated clofibrate is shown in the following scheme:



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Experimental

A mixture of p-chlorophenol (2.7g), acetone-d_6 (15g, Stohler Isotope Chemicals), chloroform (1.68g) and sodium hydroxide (3g) were refluxed with stirring for 4 hrs. The additional acetone-d_6 was distilled off and the viscous residue diluted with water (10ml). The mixture was then stirred for 2 hrs until it becomes homogenous. It was filtered and acidified with hydrochloric acid (6N) to congo red. Clofibric acid was finally recrystallized from petroleum ether (b.p. 60-80 °C), yield 2g, m.p. 120 °C.

Deuterated clofibric acid (2g), absolute ethyl alcohol (6ml), toluene (3ml) and concentrated sulphuric acid (0.2ml) were mixed in a 25 ml flask equipped with a condenser and heated in an oil bath at 110 °C for 2.5 hrs. The mixture was then cooled and distilled off. The azeotropic mixture of alcohol, toluene and water commenced to distil at 75-80 °C. After that the temperature rose abruptly and the deuterated ethyl p-chlorophenoxy isobutyrate distilled at 158-160 °C as a pale yellow liquid, yield 2.35g. For n.m.r. analysis of the deuterated and non-deuterated drugs a 10 mg sample was dissolved in a deuterated solvent ($CDCl_3$), a trace of TMS was added and ^1H n.m.r. spectra recorded at 60 MHz employing a Varian T-60 spectrometer. The relative intensities of the corresponding ^1H m.m.r. peaks for labelled and unlabelled materials were determined and showed no resonance of the two methyl groups at 2.1 ppm confirming that the compound is fully deuterated at the relevant positions.

References

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