A CONVENIENT SYNTHESIS OF DEUTERIUM LABELLED DIPHENYLHYDANTOIN

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SUMMARY

A simple, inexpensive method for the synthesis of deuterated diphenylhydantoin is described. Ten deuterium atoms are introduced to the 5,5-diphenyl moiety of the diphenylhydantoin molecule.

KEY WORDS

Deuterated diphenylhydantoin; Mass fragmentographic analysis

INTRODUCTION

Patients on chronic diphenylhydantoin (DPH) medication eventually achieve steady state plasma concentrations of drug (1). Subsequent to achieving steady state, marked deviation from these plasma concentrations is indicative of significant alteration in either the absorption, distribution, metabolism, or excretion of DPH. To identify which of the four processes is implicated, cessation of the DPH therapy is necessary and an examination of the pharmacokinetics of a single dose is required. Clearly such a procedure is not possible for patients whose therapy requires chronic administration of DPH.

It was conceived that the administration of a non-radioactive, stable isotope of DPH, the plasma concentration of which could be measured independently of relatively large amounts of the natural isotope (using GC-mass spec), and yet would have identical pharmacokinetic properties would provide the requisite information. In this way the pharmacokinetic function which has been altered can be identified without interrupting the patient's therapy.

Although the synthesis of deca-deuterated DPH has not been reported in the literature, it seemed a likely choice for our purposes due to the fact that

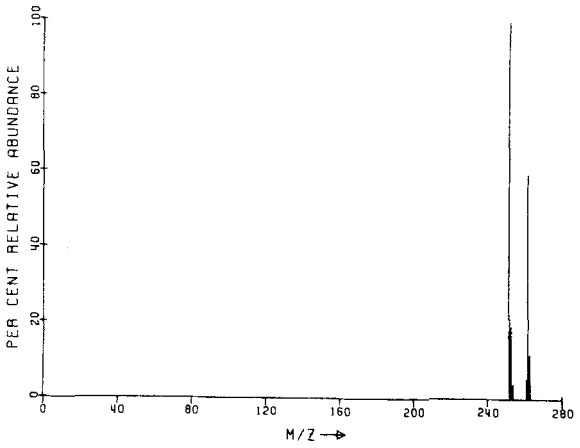

Fig. 1 Molecular ion region of the mass spectrum of a mixture of deca-deuterated DPH (m/z = 262) and non-deuterated DPH (m/z = 252). This figure clearly illustrates the ease with which the two molecular ions can be simultaneously monitored, without any interference from the naturally occurring p + 1 and p + 2 ions of the non-deuterated DPH (m/z = 253 and 254).

it would give a mass fragmentographic pattern ideally suited for the simultaneous determination of deuterated and non-deuterated DPH concentrations. The incorporation of ten deuterium atoms separates the two molecular ions to be measured by ten mass units as can be seen in fig. 1. This eliminates any interference due to the naturally occurring p + 1 and p + 2 ions of the non-deuterated DPH. An added advantage and reason for choosing deuterium as the stable isotope is that deuterated precursors are generally less expensive and more readily available than the corresponding ^{13}C labelled precursors. Due to the reasons mentioned above, the following synthesis of deca-deuterated DPH was developed.

METHOD

Deuterated benzophenone[1] was synthesized by carrying out a Friedel and

[1] In our particular case deca-deuterated benzophenone (the immediate precursor to deca-deuterated DPH) was synthesized from deuterated benzene (supplied from Stohler Isotope Chem., Inc.). However, deuterated benzophenone is now commercially available (from, for example, Stohler Isotope Chemicals) simplifying further the total synthesis of deuterated DPH.

Crafts Ketone synthesis starting with deuterated benzene and carbon tetrachloride in the presence of $AlCl_3$ in excess carbon tetrachloride (2). The deuterated benzophenone was then used in a modified Bucherer-Bergs synthesis (3) to produce diphenylhydantoin with both phenyl rings fully deuterated.

Potassium cyanide, 0.0653 g (0.01 mol) was dissolved in NaOH 0.01 N/DMSO (5/5) (V/V). The KCN solution was placed in a 45 ml capacity Paar bomb. A solution containing 0.288 g (0.0015 mol) of deuterated benzophenone in 5 ml DMSO was then added to the bomb. Finally, 4.5 g (0.045 mol) of ammonium carbonate was added and the bomb was sealed and heated at 140° C for 60 min. The bomb was cooled in an ice bath, opened, and the contents transferred to a separatory funnel containing 15 ml of 1.0 N NaOH and 20 ml diethyl ether. After thorough shaking, the aqueous phase containing the sodium salt of DPH was separated and transferred to a cold 50 ml beaker. A few drops of concentrated HCl were added to acidify the solution and precipitate the deuterated DPH. The fine white crystals were filtered, washed with water and then recrystallized from ethanol-water. The yield of DPH was 60-70%.

The structure of the product was confirmed spectrally (IR and NMR). No proton signals were observed in the aromatic region of the NMR spectrum. The IR was identical to that of authentic DPH. The isotopic purity of the starting material (D_6-Benzene)[1] was 99.5%. The absence of any peaks in the mass spectrum of the product in the region between 252-261 me/z (which would have arisen if any deuterium loss had occurred) prove that the isotopic purity of the product was at least 99.5%.

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