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Preparation of 5,5-Bis(2-deuterophenyl)hydantoin

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Abstract

Preparation of the anticonvulsant 5,5-diphenylhydantoin specifically labelled with deuterium in a metabolically stable position is described.

Introduction

With the increasing availability of combined gas chromatography–mass spectrometric instruments, the use of stable-isotope labelled drugs has become an attractive alternative method for following biotransformation reactions. Our interest in microbial transformation reactions of drugs, and their associated enzymes, led us to look for a method where biotransformation products could be readily identified from the wealth of endogenous compounds often present in crude biological extracts. A synthesis of 5-pentadeuterophenyl-5-phenylhydantoin has recently been reported.[1] However, for metabolic studies this compound suffers from the disadvantage of having an isotopic label which is potentially metabolically labile, while dilution with unlabelled drug gives a complex mass spectrum.

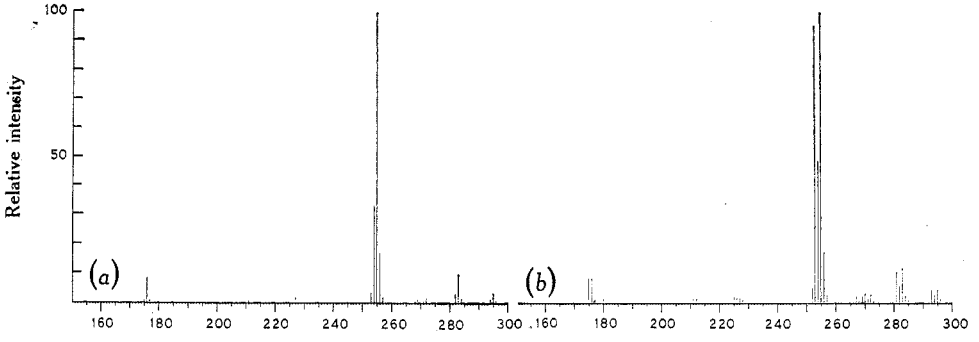

Fig. 1. Chemical ionization mass spectrum of 5,5-bis(2-deuterophenyl)hydantoin: (*a*) undiluted; (*b*) diluted with unlabelled diphenylhydantoin 3 : 2.

5,5-Bis(2-deuterophenyl)hydantoin does not suffer from the objections described above, and we now present a simple synthesis of this substance. Fig. 1*a* shows the

[1] Baty, J. D., and Robinson, P. R., *Biomed. Mass Spectrom.*, 1977, **4**(1), 36.

chemical ionization spectrum of undiluted 5,5-bis(2-deuterophenyl)hydantoin and Fig. 1*b* the labelled material diluted 3 : 2 with unlabelled diphenylhydantoin.

Experimental

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 grating spectrometer as a paraffin mull. The p.m.r. spectrum was recorded on a Varian HA60 instrument at 60 MHz. Low-resolution mass spectra were obtained on a Finnigan quadrupole 3200D instrument, operating in the chemical ionization mode, with methane as reagent gas, from a solid probe inlet. The system was interfaced with a Finnigan 6110 interactive data system. High-resolution mass spectra were measured at 70 eV on an AEI MS 902 mass spectrometer.

2-Deuterotoluene

2-Bromotoluene (115 g) was converted into the corresponding Grignard reagent in the usual manner. Decomposition with deuterium oxide (80 ml), followed by ether extraction, then fractional distillation of the ether extract, gave 2-deuterotoluene (47 g, 75%), b.p. 110–111°/760 mm. P.m.r. spectrum (neat liquid) δ 1·67, s, 3H, CH_3; 6·65, m, 4·13H (relative to methyl protons) (aromatic), deuterium incorporation 87%.

1,2-Bis(2-deuterophenyl)-2-hydroxyethan-1-one

2-Deuterotoluene (10 g) was mixed with a solution of dry benzene (30 ml) containing *N*-bromosuccinimide (24 g) and dibenzoyl peroxide (0·1 g). Benzene was distilled from the mixture until the distillate was water-free (about 5 ml). The reaction mixture was illuminated with a 40-W tungsten lamp and refluxed for 30 min, then filtered to remove succinimide which was washed with chloroform (40 ml). The combined filtrate and washings were distilled and 40 ml of solvent collected and discarded. Hexamethylenetetramine (18 g) in a mixture of acetic acid (27 g) and water (32 ml) was added to the residual solution and distillation continued until the temperature rose sharply above 80°. The mixture was then refluxed for 2 h, 10 M hydrochloric acid (11 ml) added and the refluxing continued for a further 15 min. The reaction mixture was then diluted with water (100 ml), the pH adjusted to about 7 with solid potassium carbonate, and the mixture extracted with ether. The extract was washed with water and dried over anhydrous sodium sulphate; the solvent was removed at room temperature to give approximately 10 g of 2-deuterobenzaldehyde. This was then directly made to react, without further purification, with a mixture of sodium cyanide (1 g) in water (10 ml) and ethanol (13 ml) and refluxed for 30 min. After cooling, the mixture was poured into ice-water and worked up in the usual way to give 1,2-bis(2-deuterophenyl)-2-hydroxyethan-1-one (dideuterobenzoin) (7·7 g, 66%), m.p. 135–137°; infrared spectrum: ν_{max} 3410s, 3375s, 3060m, 1675s, 1685m, 1670m, 1255m, 1205m, 1085m, 975m, 780m, 752m, 672m, 635s, 620s, 600s cm^{-1}.

2,2-Bis(2-deuterophenyl)-2-hydroxyacetic Acid

Dideuterobenzoin (2 g) was oxidized to the corresponding dideuterobenzil, then rearranged to 2,2-bis(2-deuterophenyl)-2-hydroxyacetic acid (dideuterobenzilic acid) by standard methods.[2] Yield 1·5 g (70%), m.p. 149–150°.

5,5-Bis(2-deuterophenyl)hydantoin

Dideuterobenzilic acid (0·4 g) was condensed with urea (0·243 g) in the presence of acetic anhydride (0·390 g) as catalyst, the mixture being contained in a thick-walled screw-cap-sealed vessel, capacity 10 ml, following the method of Raymahasay and Mukherjee[3] to give 5,5-bis(2-deuterophenyl)-hydantoin (0·294 g, 67%), m.p. 293–298° (dec.) (diphenylhydantoin, m.p. 294–298° (dec.)). The

[2] Vogel, A. I., 'Elementary Practical Organic Chemistry, Part I: Small Scale Preparations' 2nd Edn (Longmans: London 1966).
[3] Raymahasay, S., and Mukherjee, S. L., *Manuf. Chem.*, 1954, **25**, 293.

compound was shown to be homogeneous by t.l.c. when run in the system chloroform/methanol/acetone 3 : 1 : 1.

Found: mol. wt (mass spectrometry) 254·1039 ± 0·002. $C_{15}H_{10}D_2N_2O_2$ requires 254·1034. Infrared spectrum: ν_{max} 3270s, 3200s, 3065m, 1770s, 1740s, 1718s, 1448s, 1400m, 1235m, 1195m, 1015m, 775s, 743s, 721s, 700m, 655s, 640s, 628s, 595s cm^{-1}.

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