SYNTHESIS OF 5,5-DIPHENYLHYDANTOIN-2,4,5-$^{13}C_3$

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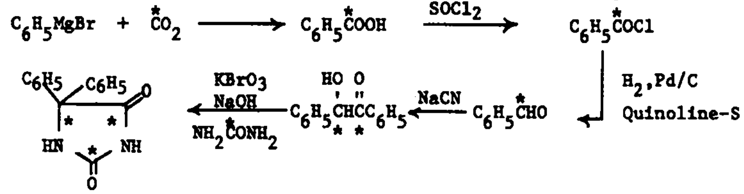
Since its introduction to medicine many years ago diphenylhydantoin has been used in the treatment of epilepsy, both in adults and children. Because of its wide use encompassing a large age group, it has been chosen for studies designed to evaluate the usefulness of the stable carbon-13 isotope as a tracer, in cases which preclude the use of a radioactive isotope.

At present the most useful instrument available for the analysis and detection of stable isotopes is the mass spectrometer. However, the use of the mass spectrometer for the analysis of stable isotopically labeled compounds imposes certain requirements as to the number of atoms to be labeled and the position of the label in the compound. Molecules which contain several carbon atoms have significant peaks at M+1 and M+2 in their mass spectrum due to the natural abundance of carbon-13. For this reason it is necessary, in order to insure adequate sensitivity of the analytical procedure, to use labeled compounds which have a molecular weight three or more mass units greater than the unlabeled compound. A further requirement is that the compound be labeled in positions which also do not readily undergo fragmentation in the mass spectrometer. We have prepared the labeled diphenylhydantoin, 5,5-diphenylhydantoin-2,4,5-$^{13}C_3$, which satisfies the above requirements.

The 5,5-diphenylhydantoin-2,4,5-$^{13}C_3$ was prepared from carbon-^{13}C dioxide and urea-^{13}C according to the scheme outlined in Chart 1.

CHART 1

Preparation of 5,5-Diphenylhydantoin-2,4,5-$^{13}C_3$



Carbonation of phenylmagnesium bromide with carbon-^{13}C dioxide afforded benzoic acid labeled at the carboxyl carbon atom in good yield.(1) Conversion to the corresponding acid chloride with thionyl chloride followed by Rosenmund reduction(2) gave benzaldehyde-^{13}C. The benzaldehyde was then allowed to undergo a benzoin condensation(3) to give 2-hydroxy-1,2-diphenylethanone-1,2-$^{13}C_2$ (benzoin-α,β-$^{13}C_2$). Simultaneous oxidation of the benzoin-α,β-$^{13}C_2$ to benzil-α,α'-$^{13}C_2$ and condensation with urea-^{13}C afforded the desired 5,5-diphenylhydantoin-2,4,5-$^{13}C_3$.(4) Mass spectrometry indicated that 78% of the 5,5-diphenylhydantoin molecules contained three carbon-13 atoms, 20% contained two carbon-13 atoms, 0.9% contained one carbon-13 atom, and 0.9% had no carbon-13 atom.

EXPERIMENTAL

Benzoic-^{13}C Acid

Phenylmagnesium bromide (prepared from 0.2 mol of bromobenzene and 0.22 mol of magnesium turnings) in 800 ml of ether was allowed to react with 4.5 ℓ. (0.2 mol) of carbon-^{13}C dioxide (90 atom % carbon-13) at -20°. After ten minutes the reaction had ceased to absorb carbon-^{13}C dioxide and a dark gum had precipitated. The mixture was acidified with 6N hydrochloric acid to dissolve the precipitates. The ether solution was washed with water and then with 5% aqueous sodium hydroxide. The sodium hydroxide layer was acidified and the precipitated benzoic-^{13}C acid collected and dried (17.7 g). The filtrate was washed with methylene chloride, dried (sodium sulfate) and evaporated to give an additional 2.8 g of product. Total yield 85%.

Benzoyl-^{13}C chloride

A solution of benzoic-^{13}C acid (0.59 mol) thionyl chloride (0.65 mol) and dimethylformamide (0.3 ml) in 350 ml of anhydrous benzene was refluxed for 4 hr. The solvent was removed and the residue distilled under vacuo to give benzoyl-^{13}C chloride (0.46 mol, bp 106°/40 torr). The pot residue was dissolved in 50 ml of anhydrous benzene and 5 ml of thionyl chloride and 0.2 ml of dimethylformamide added. After refluxing for 18 hr the solvent was removed. Distillation of the residue afforded 0.06 mol of benzoyl-^{13}C chloride. Total yield 0.54 mol (89%).

Benzaldehyde-^{13}C

A 500 ml pressure bottle was charged with anhydrous sodium acetate (25 g), 10% palladium on charcoal (3.0 g), benzene (200 ml, distilled and dried over sodium), benzoyl-^{13}C chloride (0.10 mol) and 1.5 ml of quinoline-sulfur.$^{(2)}$ The pressure vessel was placed on a Paar hydrogenation apparatus (model no. 3911), flushed three times with hydrogen and pressurized to 50 psi with hydrogen. The mixture was shaken for 18 hr at ambient temperature. The mixture was filtered through celite with rinsing (benzene). The filtrate was washed with 5% aqueous sodium carbonate (25 ml) and then with water (25 ml) and dried (sodium sulfate). The products from five such reactions were combined and distilled in vacuo to afford 0.28 mol (56%) of benzaldehyde-^{13}C, bp 76°/23 mm.

Benzoin-α,β-$^{13}C_2$

A solution of 0.28 mol of freshly distilled benzaldehyde-^{13}C and 0.09 mol of potassium cyanide in a mixture of 40 ml of 95% ethanol and 32 ml of water was refluxed for 1.5 hr. The solution was cooled and the orange solid removed by filtration. Crystallization from 95% ethanol gave 0.056 mol (40%) of benzoin-α,β-$^{13}C_2$.

5,5-Diphenylhydantoin-2,4,5-$^{13}C_3$

A solution of 0.19 mol of sodium hydroxide and 0.01 mol of potassium bromate in 14 ml of water was heated to 80°. To this solution was added 0.06 mol of urea-^{13}C (90 atom % carbon-13) in one portion and 0.028 mol of benzoin-α,β-$^{13}C_2$, in several portions over a 0.5 hr period. When the addition of the benzoin-α,β-$^{13}C_2$ was complete the temperature was raised to 100° and nitrogen bubbled through the solution. The solvent lost due to evaporation was replaced as necessary during the course of the reaction. After 6 hr the light yellow mixture was diluted with 140 ml of water and filtered. The filtrate was acidified with 6N hydrochloric acid and the precipitated 5,5-diphenylhydantoin-2,4,5-$^{13}C_3$ collected by filtration. Crystallization from ethanol-water afforded 0.019 mol (50%) of 5,5-diphenylhydantoin-2,4,5-$^{13}C_3$, (mp 301° sealed tube).

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J. A. Kepler, J. W. Lytle and G. F. Taylor

Research Triangle Institute
Post Office Box 12194
Research Triangle Park, North Carolina 27709

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