SYNTHESIS OF CARBON-^{14} LABELED DIPHENYLHYDANTOIN AND ITS MAJOR METABOLITE 5-(p-HYDROXYPHENYL)-5-PHENYLHYDANTOIN (HPPH) IN 70 MINUTES

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SUMMARY

A simple and convenient method for the synthesis of carbon-^{14} labeled diphenylhydantoin (DPH) (I) and its major metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH) (II) in 70 minutes is described. This synthesis allows incorporation of carbon-^{11} (physical half-life 20 minutes) into these molecules. Incorporation of short-lived isotopes into drug molecules provides a vastly expanded potential for study of in vivo distribution of drugs and development of tumor specific agents.

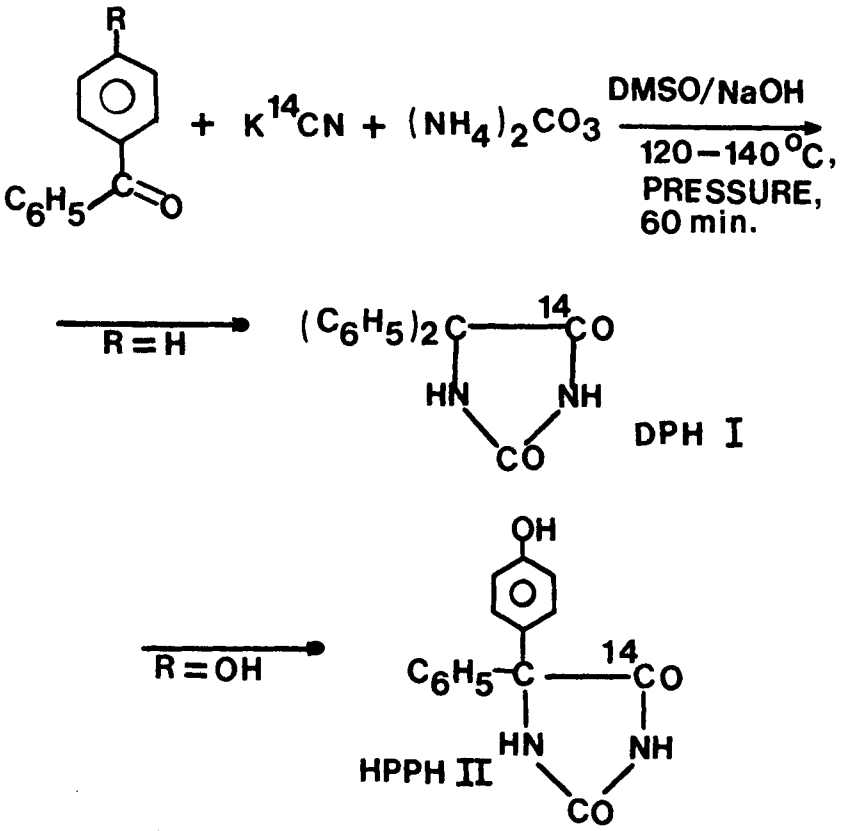
INTRODUCTION

Presently there is interest in introducing the short-lived isotope ^{11}C into agents such as diphenylhydantoin (1) which will localize in the brain and permit scintigraphic imaging. The advantage of ^{11}C lies in its short half-life, which will lower the radiation exposure to the patient, and in the high resolution and sensitivity which can be achieved by virtue of greater photon yield for a given radiation exposure.

Good synthetic methods for diphenylhydantoin and its major metabolite 5-(p-hydroxyphenyl)-5-phenylhydantoin (HPPH) are available in the literature (2, 3, 4, 5, 6). However, these methods are time consuming and do not allow introduction of short-lived isotopes, such as ^{11}C which decays by positron

emission and has a half-life of 20.4 minutes. Due to this short half-life it is imperative to develop rapid organic syntheses which will allow introduction of this isotope into organic molecules. Winstead, et al. (7) reported that ^{11}C hydantoins, including diphenylhydantoin, could be synthesized in 1 1/2 - 2 hours. We now report a convenient synthesis for diphenylhydantoin and its principal metabolite, HPPH, which can be accomplished in 70 minutes for diphenylhydantoin and 80 minutes for HPPH.

REACTION



METHOD

The ^{14}C diphenylhydantoin is synthesized using a modified Bucherer-Bergs synthesis. 66.2 μCi of ^{14}C KCN[a] is dissolved in NaOH 0.01 N/DMSO (5/5) (v/v) containing 0.001 moles (0.065 g) of carrier free KCN. This solution is placed in a Parr bomb (45 ml. capacity) to which 0.0015 moles (0.273 g) of benzophenone dissolved in 5 ml of DMSO[b] is added. Finally 0.047 moles (4.5 g) of ammonium carbonate is added. The bomb is closed and the reaction mixture is heated (120-140° C) under pressure by immersing the bomb in an oil bath (any other convenient way to heat the bomb is adequate). After 60 minutes the bomb is cooled by placing it in an ice bath. The bomb is now opened and the contents transferred to a separatory funnel containing 15 ml of NaOH 1 N. Twenty ml. of ethyl ether is added to the funnel and thoroughly shaken. The aqueous phase containing sodium diphenylhydantoin is separated and transferred to a cold 50 ml beaker. The solution is acidified with a few drops of concentrated HCL. At this point diphenylhydantoin starts to precipitate in fine crystals. The precipitate is filtered through a Buchner funnel and recrystallized in ethanol-water. Crystals from ethanol, mp. 296-298° C, chemical yield 64%, specific activity 0.24 μCi/mg, radioactive yield 59%. Typical synthesis time 70 minutes.

Radioactive purity of final product was determined by thin layer chromatography using silica gel with fluorescent indicator[c] and chloroform-acetone as mobile phase (90 + 10) (8). Only one spot was observed under exposure to short U.V. light. Radioactive scanning of the plate shows over 98% purity.

[a] New England Nuclear Corporation, specific activity 0.18 mCi/mg.

[b] The yield of the reaction is increased if DMSO is used as the solvent.

[c] Eastman Kodak Co., Rochester, N.Y. 14650; Eastman Chromagram Sheet 6060.

Structure determination was confirmed by infrared, nmr, and ultra-violet spectroscopy.

All radioactivity measurements were made using a Packard Tri Carb Scintillation Spectrometer, Model 3375, with efficiency of 90% and background count of 30 cpm. The samples were counted in a liquid scintillation cocktail containing 4 g of 2,5-diphenyloxazole (PPO), 100 mg of 1,4 bis[(4-methyl-5-phenyloxazolyl)]-benzene, and 370 g of Triton X-100 made up to a liter with distilled toluene.

5-(p-HYDROXYPHENYL)-5-PHENYLHYDANTOIN (HPPH)

This compound is prepared by a modified Bucherer-Bergs synthesis with essentially the same technique used in the synthesis of 5,5-diphenylhydantoin. A solution of 0.0015 moles (0.3 g) of 4-hydroxybenzophenone[d] in 5 ml of DMSO is placed in a Parr bomb (45 ml capacity) to which 43 μCi of ^{14}C KCN[a] dissolved in NaOH 0.01 N/DMSO (5/5) (v/v) containing 0.001 moles (0.065 g) of carrier free KCN is added. The bomb is closed and the reaction mixture heated at 130-140° C by means of an oil bath. After 60 minutes the bomb is cooled by placing it in an ice bath. The bomb is now opened and the contents transferred to a separatory funnel containing 15 ml of NaOH 1N. Twenty ml of ethyl ether is added to the funnel and thoroughly shaken. The aqueous phase containing sodium HPPH is separated and transferred to a cold 50 ml beaker.

The solution is acidified with a few drops of concentrated HCL. The light brown precipitate is filtered off using a Buchner funnel. One crystallization from ethanol with Norit yielded white crystals with a melting point of 315-317° C

[d] Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233, U.S.A.

(uncorrected) with decomposition that could not be raised by further crystallization. Chemical yield 46.6%, specific activity 0.137 μCi/mg, radioactive yield 40%. Typical synthesis time 80 minutes.

Radioactive purity of the final product was determined by ascending chromatography using Whatman No. 1 paper and isopropanol-15% ammonia (4:1) as mobile phase (2). Only one spot was observed under exposure to short U.V. light. Radioactive scanning of the paper shows over 95% purity. Structure determination was confirmed by infrared and ultra-violet spectroscopy. Racemic HPPH is obtained using this procedure. All radioactive measurements were performed similarly to those described for 5,5-diphenylhydantoin.

DISCUSSION

Organ imaging procedures have undergone rapid development during the last ten years and are now an important part of nuclear medicine. As a result of pharmacological studies with various drugs, information concerning the mode of action of drugs or their ability to concentrate in various tissues has become available. The potential use of scintigraphic imaging justifies expending considerable effort in the development of rapid organic syntheses such as those described in this paper.

Incorporation of the short-lived isotope ^{11}C into organic molecules provides a vastly expanded potential for development of tumor specific diagnostic agents.

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