NOTES

AN EFFICIENT SYNTHESIS OF 5-(PHENYL-$^{13}C_6$)-5-PHENYLHYDANTOIN.

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SUMMARY

A procedure is described to convert benzene-$^{13}C_6$ into 5-(phenyl-$^{13}C_6$)-5-phenylhydantoin in 80% overall yield.

Key words : Anticonvulsant, Phenytoin, Friedel-Crafts reaction, Bücherer-Berg synthesis.

INTRODUCTION

The use of stable isotopes in biomedical research has proliferated in recent years specially in connection with the increasing availability of gas chromatography mass spectrometry (GCMS) computer systems. This technique can be utilized for both metabolism and pharmacokinetics studies[1-5].

Clinical problems associated with the chronic administration of anticonvulsant drugs are particularly acute in the case of 5,5-diphenylhydantoin (DPH, Phenytoin) due mainly to erratic resorption, non-linear pharmacokinetics and unpredictable metabolism rate[6]. In order to achieve proper drug monitoring without withdrawing antiepileptic agents (which is not clinically acceptable), some authors have proposed different deuterio-analogs of Phenytoin for quantitative analysis of DPH and its major metabolite in man, 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH)[7-10]. Recent work in our department has drawn the attention on pharmacokinetic deviations of 5-(p-deuteriophenyl)-5-phenyl- and 5-(pentadeuteriophenyl)-5-phenylhydantoin compared to the parent drug phenytoin. Consequently, the synthesis of a ^{13}C

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analog of phenytoin was undertaken using benzene-U-$^{13}C_6$ as starting material. The synthetic approach was based on a classical Friedel-Craft synthesis [12] of the intermediate benzophenone-U-$^{13}C_6$, followed by its conversion according to the Bücherer-Berg synthesis [13] as modified by Henze[14]. The title compound was obtained in 80% overall yield.

METHOD.

To 6g (0.045 mole) of anhydrous aluminum chloride was added 3g (0.036 mole) of benzene - $^{13}C_6$ (90% isotopic purity, CEA, France) and 15 ml of dry carbon disulfide in a 100 ml, one-necked flask, fitted with a reflux condenser and calcium chloride tube. The suspension was magnetically stirred and through the reflux condenser was added in three portions at 15 min. interval 7.27g (0.052 mole) of benzoyl chloride. The dark solution was refluxed for 6 h and, under dryness conditions, most of the carbon disulfide was slowly distilled (60 min). The residue was treated with 100 ml of 10% hydrochloric acid and extracted three times with 60 ml of ether. The organic extract was concentrated in vacuo, treated with 100 ml of 10% aq. sodium hydroxyde and reextracted to yield 7g of the crude benzophenone, that was sufficiently pure (GLC) for the Bücherer -Berg hydantoin synthesis.

In a 100 ml steel bomb were placed 7g (N 0.036 mole) of the crude benzophenone dissolved in 15 ml of dimethylformamide, 4g (0.061 mole) of potassium cyanide dissolved in 8 ml of water and 16 g (0.167 mole) of solid ammonium carbonate. The closed steel bomb was immersed in an oil bath and heated at 125°C for 2.5 days. After cooling to room temperature, the bomb was opened and the content was diluted in 400 ml of hot water, acidified and filtered. The crude product was dissolved in 200 ml of aqueous sodium hydroxyde and the resulting solution was extracted with 100 ml of toluene and twice with 100 ml of ether. Acidification of the aqueous phase yielded 7.42 g (80% yield) of dry and pure (HPLC, 10μ-RP-18, 250 x 4.6 mm, solvent : acetonitrile-water, 15:85 (v/v), flow rate 1.0 ml/min, Rt 9.8 min) material. Recrystallization from 120 ml of ethanol afforded a first crop of 5.20 g (56% yield) of crystalline material, mp 293-295°C. IR (KBr) 3270, 3200(νN-H), 1775, 1740, 1720 (νC = O) cm^{-1}. MS (70eV, direct inlet) m/e 258 (m^+), 229, 215, 186, 171, 110, 104. Isotopic purity 89.9 ± 0.2%.

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