SYNTHESIS OF CARBON-14 LABELLED ACETAMINOPHEN (4-HYDROXYPHENYLACETAMIDE, CARBONYL-^{14}C)

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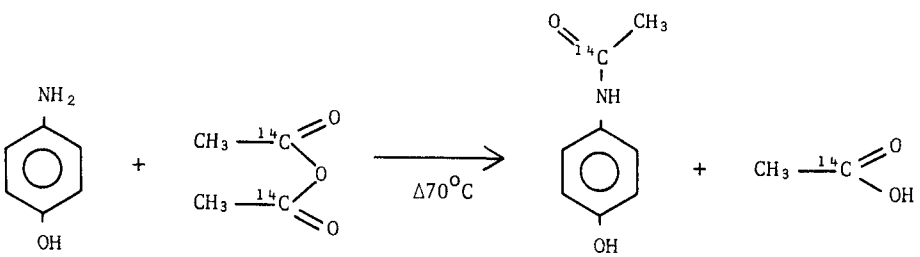
SUMMARY

A simple and convenient method for the condensation of p-aminophenol (I) with ^{14}C-acetic anhydride (II) yields up to 76% of ^{14}C-labelled 4-hydroxyphenylacetamide (carbonyl-^{14}C) (III). Typical synthesis time is 60 minutes. Radioactive yield is 51%, and specific activity is 0.22 μCi/mg.

Key Words: ^{14}C-hydroxyphenylacetamide (carbonyl-^{14}C), ^{14}C-acetaminophen

REACTION



(I) (II) (III)

INTRODUCTION

Application of labelled compounds is still a sensitive and selective tool for metabolic and pharmacokinetic studies. Although ^{3}H-acetaminophen is available commercially, the inherent impurity, which is described (1), restricts its usefulness. Although a purification method is available, it is time consuming.

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Numerous synthetic methods for acetaminophen have been reported in the literature (2-7). However improvements are needed in purity, yield and synthetic time.

We now present a simple and convenient method for the synthesis and purification of ^{14}C-acetaminophen.

EXPERIMENTAL

Purification of p-aminophenol

In a 250 ml beaker, 21.8 g of p-aminophenol[a] was dissolved in 130 ml of deionized water at 90°. To this solution 0.04 g of sodium dithionite[a] was added as antioxidant. Finally, 1 g of Fe-free charcoal was added. The resulting solution was heated to boiling for five minutes, filtered and cooled to yield p-aminophenol. This procedure was repeated several times until the product was colorless.

Preparation of Fe-free charcoal

A small amount of citric acid (approximately 1 g) was dissolved in a dilute solution of hydrochloric acid. This solution was then used to wash the charcoal in order to eliminate any Fe present.

Synthesis of 4-hydroxyphenylacetamide

A "break seal" glass ampoule containing 1 mCi of ^{14}C-acetic anhydride[b] (specific activity 28.6 mCi/m mole), filtered with a reflux condenser, was cooled (dry ice bath), the seal broken and 0.94 ml of acetic anhydride, 1.09 g of dry, freshly purified p-aminophenol and 10-15 drops of deionized water was added. The reaction mixture was stirred and heated to 70° for 20 minutes and cooled. The ^{14}C-labelled 4-hydroxyphenylacetamide which precipitates was filtered and recrystallized from deionized water with Fe-free charcoal to yield white crystals (mp 166-169°, chemical yield 76%, specific activity 0.22 μCi/mg, radioactive yield 51%).

Radioactive purity of the final product was determined by thin layer chromatography using silica gel with fluorescent indicator[c] and 2-butanone as

[a] Aldrich Chemical Co., Milwaukee, Wisconsin, USA
[b] Amersham Searle Co., Arlington Heights, Illinois, USA
[c] Silica gel GF, Analtech Inc., Newark, Delaware, USA

mobile phase. Only one spot was observed under exposure to short UV light. This separation was characterized by an R_f value of 0.55. In addition, two dimensional ascending chromatography was performed using chloroform-acetone-cyclohexane (50:30:20), followed by benzene-ether-methanol acetic acid (60:30:5:5) as mobile phases (1). These solvent systems gave separation characterized by R_f values of 0.2 and 0.3, respectively. Only one spot was observed under exposure to short UV light. Radioactive scanning of the plate showed over 95% purity. No radioactive impurities were detected on the tlc plates.

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 30.3 g of 2-(4'-t-butylphenyl)-5-(4"-biphenyl)-1,3,4-oxidiazole and 1.9 g of 2-(4'-biphenyl-6-phenyl)-6-phenylbenzoxazole made up to a gallon with freshly distilled toluene.

REFERENCES

1. Singh H.P. and Gault M.H. - J. Labelled Compounds 8: 595 (1972).
2. Leoveanu O., Pusca V. and Cociasu C. - Farmacia (Bucharest) 11: 397 (1963).
3. Freifelder M. and Robinson R.M. (Abbott Laboratories) Patent, US 3,079,435 (Feb. 26, 1963).
4. Bialik J. and Jedszejewski A. (Farmaceutyczna Spoldizielnia Pracy "Galena") Patent, Poland 54,012 (Oct. 31, 1967).
5. Wilbert G. and De Angelis J. (Warner-Lambert Pharmaceutical Company) Patent, US 2,998,450 (Aug. 29, 1961).
6. Duesel B.F. and Wilber G. (Nepera Chemical Company, Inc.) Patent, US 3,341,587 (Sep. 12, 1967).
7. Young D.W. (Sinclair Research, Inc.) Patent, US 3,113,150 (Dec. 3, 1963).