

SYNTHESIS OF 2,3-BIS(p-METHOXYPHENYL) INDOLE-2-¹⁴C

Richard C. Thomas

Pharmaceutical Research and Development Division, The Upjohn Company, Kalamazoo, Michigan 49001, U.S.A.

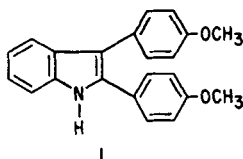
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SUMMARY

2,3-Bis(p-methoxyphenyl)indole-2-¹⁴C was prepared at a specific activity of 1.71 mCi/mM from Ba¹⁴CO₃ by a 4-step synthetic sequence in 33% overall radiochemical yield.

INTRODUCTION

Metabolism studies with the nonsteroidal, antiinflammatory agent, 2,3-bis(p-methoxyphenyl)indole (I), required the preparation of a radioactive form of the



drug. Carbon-14 was chosen as the label since probable routes for biotransformation of I would involve hydroxylation of the aromatic rings; a tritium label would possibly be lost. The synthetic route chosen involved introducing carbon-14 into the 2-position of the indole ring by the Fischer indole synthesis, as described by Szmuszkovicz, *et al.* (1) for preparing I in a nonradioactive form.

EXPERIMENTAL

Radioactivity Measurements

All counting was performed with Packard Tri-Carb, Model 314EX2A and 3375, liquid scintillation spectrometers using conditions suitable for measuring carbon-14. Appropriate aliquots of samples were dissolved in 15 ml of scintil-

lation solvent [toluene-dioxane-methanol (350:350:210 by volume) containing 73 g of naphthalene, 4.6 g of 2,5-diphenyloxazole, and 0.08 g of 1,4-bis-2-(5-phenyloxazolyl)-benzene per L.] The absolute counting efficiency for each sample was determined by recounting following addition of an internal standard of carbon-14 labeled toluene and results then expressed as millicuries (mCi).

Thin-layer chromatograms were scanned for radioactivity with a Vanguard Model 885 radiochromatogram scanner.

Thin-Layer Chromatography

Thin-layer chromatograms were developed by the ascending method on 5 x 20 cm glass plates having 0.25-mm layers of silica gel G in the following systems: (a) ethyl acetate-cyclohexane (1:4 by volume) and (b) acetone-hexane-ammonium hydroxide (200:200:1 by volume). Zones absorbing ultraviolet light were located as fluorescence-quenched areas when thin-layer chromatograms were viewed under short-wavelength UV light.

Synthesis

p-Methoxybenzyl Chloride (III) - This was prepared by the method of Grice and Owen (2) from *p*-methoxybenzyl alcohol and SOCl_2 . The final product was purified by distillation through a 30-cm Vigreux column; b.p., 114-115° (15 mm). This material was stored under nitrogen in the refrigerator until used.

p-Methoxybenzylmagnesium Chloride (IV) - This was prepared by the reaction of equimolar quantities of magnesium and *p*-methoxybenzyl chloride in tetrahydrofuran using the usual anhydrous conditions. It was necessary to activate the magnesium by allowing it to react with a drop of methyl iodide in a few ml of ethyl ether prior to adding the tetrahydrofuran solution of *p*-methoxybenzyl chloride. A 3-hour reflux period was required to completely consume the magnesium. The Grignard solution was found to be 0.24 M by titration.

p-Methoxyphenylacetic-1- ^{14}C Acid (V) - This was prepared from 0.60 g (3 mM) of $\text{Ba}^{14}\text{CO}_3$ (20 mCi) and 5 mM of the Grignard reagent (IV) using the procedure and apparatus described by Ebersson (3). Following carbonation, the complex of V was decomposed with 1N H_2SO_4 and the reaction mixture was transferred to a separatory funnel with ether. Carrier *p*-methoxyphenylacetic acid (1.21 g) was added and the

reaction mixture was extracted with ether. The combined ether extracts were reduced in volume and extracted with 3 portions of 1*N* Na₂CO₃. The combined alkaline extracts were acidified with 6*N* H₂SO₄ and extracted with ether. After drying over Na₂SO₄, the ether was evaporated and the residue was recrystallized from water to yield 1.58 g of V having a specific activity of 1.74 mCi per mM. The radiochemical yield was 83%.

Desoxyanisoin-carbonyl-¹⁴C (VII) - The bulk of the above *p*-methoxyphenyl-acetic-1-¹⁴C acid (1.55 g, 9.3 mM) and 2.1 ml (28 mM) of SOCl₂ were refluxed for 2 hours. Excess SOCl₂ was then removed by evaporation on a rotary evaporator at 50° *in vacuo*. Two 5-ml portions of CS₂ were added successively and removed by evaporation to eliminate the last traces of thionyl chloride. CS₂ (14 ml) and 2.1 ml (19mM) of anisole were added to the crude acid chloride in the reaction flask and the reaction mixture was cooled in an ice bath. Anhydrous AlCl₃ (4.3 g) was added very carefully in portions with stirring and the reaction mixture was allowed to stir under a reflux condenser and drying tube at room temperature overnight. The reaction mixture was poured onto cracked ice containing 3 ml of HCl and then transferred to a separatory funnel with methylene chloride. The phases were separated and the aqueous phase was extracted 2 additional times with methylene chloride. The combined organic extracts were washed successively with 1*N* NaOH solution and water and then dried over Na₂SO₄. The methylene chloride was removed *in vacuo* and the residue was recrystallized from EtOH-H₂O with the aid of Darco G-60 to obtain 1.51 g (5.9 mM, 63% yield) of product having a melting point of 109-110° (capillary, uncorrected; authentic VII melted at 109-110°).

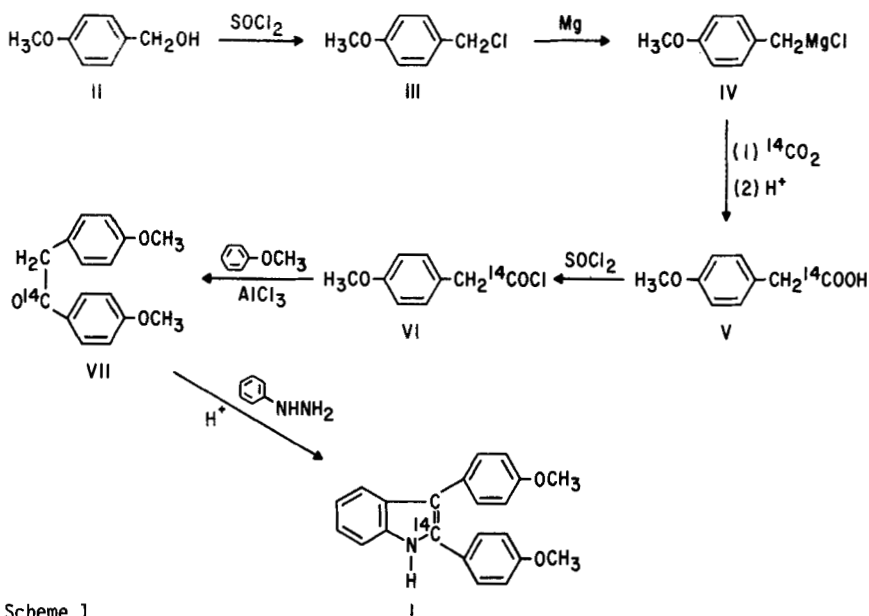
2,3-Bis (*p*-Methoxyphenyl) Indole-2-¹⁴C (I) - Into a round-bottom flask equipped with a water-separating trap, reflux condenser, and drying tube were added 1.50 g (5.86 mM) of desoxyanisoin-carbonyl-¹⁴C, 0.64 g (5.91 mM) of phenylhydrazine, 0.05 ml of acetic acid and 7 ml of benzene. The reaction mixture was carefully refluxed for 3 hours. At the end of this period, 11.5 ml of 3*N* ethanolic HCl was added and the reaction mixture was refluxed 1.25 additional hours with stirring. The solvent was evaporated with a nitrogen stream and 5 ml of water and 5 ml of methylene chloride were added. The layers were separated

and the aqueous phase was extracted 3 additional times with methylene chloride. A white crystalline material separated and was removed by filtration during this procedure. The methylene chloride extracts were combined and washed successively with 1N NaOH solution, water, 5% HCl, water, and brine. The organic phase was dried over Na_2SO_4 , evaporated to 5 ml, and applied to a 75-cm column of Florisil packed in methylene chloride. The column was of a special design such that the top one-third had a 30 mm diameter, the middle one-third a 20 mm diameter, and the bottom one-third a 10 mm diameter. The column was eluted with methylene chloride while collecting 5-ml fractions. Progress of elution was followed by viewing the column with a long-wavelength ultraviolet lamp. Following removal of solvent from the individual tubes, fractions 24-30 deposited solids whereas those beyond tube 30 deposited oil. Fractions 24-30 were combined (0.98 g) and recrystallized from ethanol to obtain 0.83 g (2.52 mM, 43% yield) of product having a melting point of 151-151.5° (capillary, uncorrected; authentic I melted at 149.5-150.5°). A second crop of 0.075 g was obtained from the mother liquor for a total yield of 47%. The specific activity of the product was 1.71 mC per mM. Its ultraviolet and infrared absorption spectra corresponded to authentic I. Thin-layer chromatography on silica gel GF using the systems described revealed in each case a single radioactive and ultraviolet-absorbing zone corresponding to authentic I. *Anal.* Calcd. for $\text{C}_{22}\text{H}_{19}\text{NO}_2$: C, 80.2; H, 5.8; N, 4.2. Found: C, 79.9; H, 6.1; N, 4.2.

RESULTS AND DISCUSSION

The sequence for synthesis of 2,3-bis(*p*-methoxyphenyl)indole-2- ^{14}C (I) is shown in Scheme 1. The overall yield of I, based on $\text{Ba}^{14}\text{CO}_3$, was 23%.

p-Methoxybenzyl chloride (III) was found to be rather unstable. Even when stored under dry nitrogen and in the refrigerator a precipitate formed within several days. It was therefore used within 2 days of its preparation. *p*-Methoxyphenylmagnesium chloride (IV) could not be prepared in ethyl ether because of its insolubility in that solvent. Tetrahydrofuran proved to be a satisfactory solvent, however, even though it was necessary to activate the magnesium and required 3 hours of reflux to consume the magnesium. Carbonation of the Grignard reagent



Scheme 1

(IV) with ¹⁴C₂O₂ using the apparatus of Ebersson (3) went smoothly to give p-methoxyphenylacetic acid (V) in 83% yield. The conversion of V to the acid chloride (VI) and its condensation with anisole using AlCl₃ resulted in a 63% yield of desoxyanisoin (VII). Condensation of the free acid (V) with anisole in liquid HF might have been a better approach but the 63% yield using AlCl₃ proved satisfactory.

ACKNOWLEDGEMENTS

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