SYNTHESIS OF ^{14}C-LABELED 4-ACETYL-5,6-BIS(4-CHLOROPHENYL)-2-(2-HYDROXYETHYL)-2H-PYRIDAZIN-3-ONE

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SUMMARY

A simple and convenient synthesis of a radiolabeled antihypertensive pyridazinone was developed. The product was purified chromatographically, and the chemical and radiochemical purities of the sample were determined.

Key words: Antihypertensives, ^{14}C-Labeling, Pyridazinones

INTRODUCTION

As part of a program to discover novel, pharmaceutically active compounds, a series of pyridazinones was shown to exhibit a high level of antihypertensive activity.[1-4] These compounds also exhibited low acute toxicity and were structurally dissimilar to the classical antihypertensive agents. 4-Acetyl-5,6-bis-(4-chlorophenyl)-2-(2-hydroxyethyl)-2H-pyridazin-3-one (4)[1] was chosen as the best candidate for additional development based upon antihypertensive activity and acute toxicity data. In order to acquire information relating to the metabolism and pharmacokinetics of this compound, a simple and convenient synthesis of radiolabeled 4 was developed.

DISCUSSION

The synthesis of 4 is illustrated in Scheme 1. Following optimization of reaction conditions with unlabeled materials, uniformly ring ^{14}C-labeled 4,4'-dichlorobenzil (1) was utilized to prepare the desired pyridazinone. The

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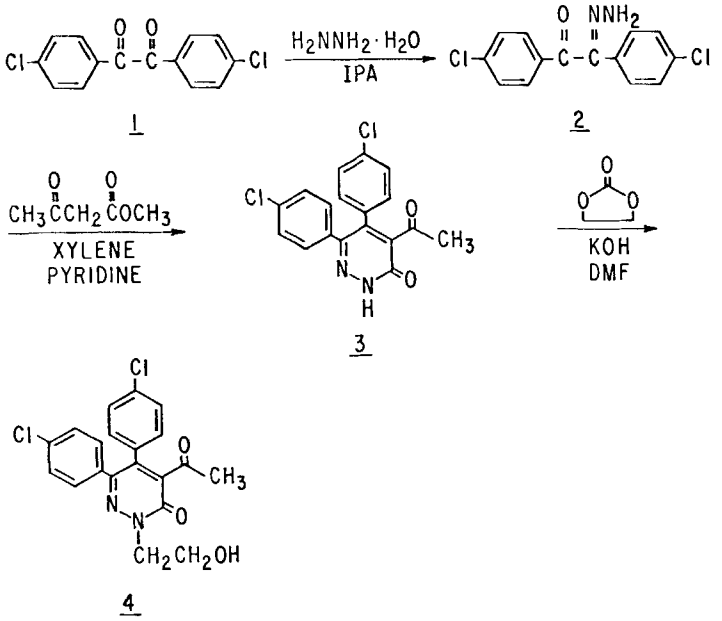
synthetic route outlined in Scheme 1 constitutes a simple and convenient preparation of 5,6-diarylpyridazinones with a radiolabel in the aromatic substituents.

The preparation of 4 involved condensation of 1 with $H_2NNH_2 \cdot H_2O$ to afford the hydrazone 2. Crude 2 was reacted with methyl acetoacetate/pyridine to give the pyridazinone 3. Alkylation of crude 3 with ethylene carbonate/KOH afforded the desired antihypertensive 4.

The chemical and radiochemical purity of radiolabeled 4 was determined by chromatographic and spectral means and by differential scanning calorimetry (DSC). TLC analysis demonstrated the sample to be homogeneous in four solvent systems. The only significant impurity detected by ^1H NMR was the retention of approximately 0.5% solvent of recrystallization (CH_3CN).

Scheme I



EXPERIMENTAL

TLC (Analtech silica gel GHLF, UV visualization, 254 nm) was performed using toluene/EtOAc/90% HCO_2H : 15/10/1, EtOAc/CH_3OH : 98/2, $CHCl_3$/isopropanol : 90/10, and C_6H_6/CH_3OH : 85/15. DSC data were obtained on a Perkin-Elmer DSC 2. ^1H NMR spectra were obtained on a Bruker WH-90 (90 MHz) spectrometer in $CDCl_3$ using TMS as an internal standard. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Specific activity was determined on a Searle Analytic Liquid Scintillation Counter Isocap Model 300 at ambient temperature. Counting efficiency was determined by the external standard ratio method, and corrections were made for background. Radiochemical purity was determined by TLC (Brinkman silica gel 60/ Kieselguhr F 254, aluminum backing, hexane/acetone : 1/1). The method consisted of developing a plate and determining the amount of radioactivity of the spot with the R_f of the product. This value was then compared with the total amount of radioactivity originally applied to the plate.

4,4'-Dichlorobenzil Monohydrazone (2)

Uniformly ring ^{14}C-labeled 4,4'-dichlorobenzil (3 mg, 10.8 mol, 9.44 mCi/ mmol, Pathfinder Laboratories, Inc., St. Louis, Missouri, Lot No. 70213) was diluted with unlabeled 4,4'-dichlorobenzil (346 mg, 1.24 mmol). To this mixture (349 mg, 1.25 mmol) was added isopropanol (20 mL) and 100% $H_2NNH \cdot H_2O$ (100 mg, 2.0 mmol, 0.10 mL) and the resulting mixture stirred under reflux for 2 hr. TLC (silica gel, toluene/EtOAc/90% HCO_2H : 15/10/1) indicated the reaction was complete (R_f: 1 = 0.95, 2 = 0.83). The yellow solution was cooled to room temperature and evaporated *in vacuo* to dryness. The crude 2 was used without further purification.

4-Acetyl-5,6-bis(4-chlorophenyl)-2H-pyridazin-3-one (3)[1,4]

A mixture of crude 2, from the above procedure, anhydrous xylene (20 mL), anhydrous pyridine (1 mL) and methyl acetoacetate (320 mg, 2.75 mmol, 0.30 mL) was

stirred under reflux for 15 hr. An additional portion of methyl acetoacetate (160 mg, 1.38 mmol, 0.15 mL) was added and refluxing continued for 4 hr. TLC (silica gel, toluene/EtOAc/90% HCO_2H : 15/10/1) indicated the reaction was complete (R_f: 3 = 0.52). The amber solution was cooled to room temperature and evaporated *in vacuo* to dryness. The crude 3 was used without further purification.

4-Acetyl-5,6-bis(4-chlorophenyl)-2-(2-hydroxyethyl)-2H-pyridazin-3-one (4)[1,4]

A mixture of crude 3, from the above procedure, anhydrous DMF (20 mL), ethylene carbonate (330 mg, 3.75 mmol) and 86% KOH (1/2 pellet, pulverized) was stirred and submerged in a preheated oil bath (90°C) for 1 hr. TLC (silica gel, toluene/EtOAc/90% HCO_2H : 15/10/1) indicated the reaction was complete (R_f: 4 = 0.33). The dark brown mixture was cooled to room temperature and distilled H_2O (100 mL) was added. The resulting mixture was stirred at room temperature for 30 min and filtered. The tan amorphous solid obtained was washed with distilled H_2O until the washings were clear and colorless and air dried overnight. The crude 4 was dissolved in $CHCl_3$ (7 mL) and chromatographed on a dry silica gel column (38 mm x 150 mm) with $CHCl_3$/EtOAc : 3/1 (800 mL). Fractions containing product were eluted from the adsorbent with EtOAc and the EtOAc solution evaporated *in vacuo* to dryness. The resulting light yellow amorphous solid was recrystallized from CH_3CN (10 mL). The excess solvent was removed by decantation and the crystalline solid obtained washed with CH_3CN (3 x 2 mL) and dried at 140°C/0.25 mm Hg for 3 days to give 162 mg (32% based on 1) of yellow prisms: mp 191-193°C (Lit. 191-193°C[1,4]); ^1H NMR δ 2.23 (3, s, CH_3), 2.86 (1, t, J=5.7, OH), 4.02-4.19 (2, m, $CH_2\underline{CH_2}OH$), 4.22-4.55 (2, m, $\underline{CH_2}CH_2OH$), 6.93-7.07 (4, m, aromatic H), 7.18-7.34 (4, m, aromatic H). DSC analysis indicated a chemical purity of 99.8%. The radiochemical purity was demonstrated to be 99.6%. The specific activity was determined to be 66.3 μCi/mmol.

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REFERENCES

1. R. Buchman, J. A. Scozzie, Z. S. Ariyan, R. D. Heilman, D. J. Rippin, and L. J. Powers, J. Med. Chem., 23, 1398 (1980).

2. S. W. Fogt, J. A. Scozzie, R. D. Heilman, and L. J. Powers, J. Med. Chem., 23, 1445 (1980).

3. L. J. Powers, D. J. Eckert, and L. Gehrlein, J. Pharm. Sci., 70, 419 (1981).

4. L. J. Powers, Z. S. Ariyan, R. Buchman, J. A. Scozzie, R. E. Moser, and W. J. Pyne, U.S. Patent 4,238,490 (1980).