SYNTHESIS OF 7-CHLORO-1,3,-DIHYDRO-3-HYDROXY-1-METHYL-5-PHENYL-2H-1,4-BENZODIAZEPIN-2-ONE-2-^{14}C (2-^{14}C-TEMAZEPAM)

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SUMMARY

Temazepam-2-^{14}C, 7-Chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one-2-^{14}C, was prepared in a five-step synthesis. Chloroacetic-1-^{14}C acid was converted to the acid chloride with thionyl chloride. The acid chloride was allowed to react with 2-methylamino-5-chloro-benzophenone to form the amide. The amide was reacted with hydroxylamine and directly cyclized to the benzodiazepine N-oxide which was converted to the acetate with acetic anhydride. The acetate was hydrolyzed with concentrated sulfuric acid to give the final product (3.8% radiochemical yield at 52. mCi/mmol). This procedure provides temazepam with the radiolabel in a metabolically stable position.

Key Words: 2-methylamino-5-chlorobenzophenone, chloroacetic acid-1-^{14}C, temazepam.

INTRODUCTION

The synthesis of 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazapine-2-one (temazepam, the active component of Restoril®, the trade name of Sandoz Pharmaceuticals Corp.) with the carbon-14 label in the 2-position (7) has not been previously reported. Earlier work demonstrated the feasibility of obtaining 2-^{14}C-7 via methylation of either 7-chloro-1,3-dihydro-3-hydroxy-5-phenyl-2H-1,4-benzodiazpine-2-one-2-^{14}C (1,2) or

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7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazapine-2-one-4-oxide-2-^{14}C (1,3). In the latter case, rearrangement of the N-oxide to the ester of 7 with acetic anhydride followed by hydrolysis would be necessary to obtain the final product. We wish to describe a direct synthetic route to 2-^{14}C-7 which avoids the methylation step by starting with 2-methylamino-5-chlorobenzophenone.

RESULTS AND DISCUSSION

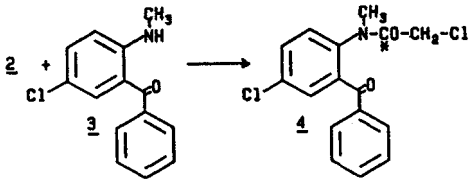
Chloroacetic acid-1-^{14}C (1) was converted to the acid chloride (2) using thionyl chloride (Scheme 1). In order to minimize nucleophilic displacement of the 2-chloro group the reaction mixture was cooled with a dry ice-acetone bath prior to the addition of a solution of 2-methylamino-5-chlorobenzophenone (3). Following the addition of 3 the reaction flask was placed in an ice water bath and stirred for 2 h; the amide (4) was purified by column chromatography. The amide was converted directly to the N-oxide (5) without isolating the intermediate hydroxylamine as described by Bell, et al. (4). Treatment of the N-oxide (5) with acetic anhydride gave quantitative conversion to the ester (6) which was demonstrated by TLC. The ester was not isolated but was hydrolyzed to (7) using sulfuric acid. The overall radiochemical yield was 3.8%. The specific activity of the final product was 52.7 mCi/mmol and the radiochemical purity was 96.7%. The radiosynthesis provides 2-^{14}C-7 with the radiolabel in a metabolically stable position. Drug metabolism studies have shown that demethylation of temazepam occurs in animals and man with an extent that is dependent upon the species (5). Introduction of a label into the 1-position would therefore give a modification that would not be metabolically stable.

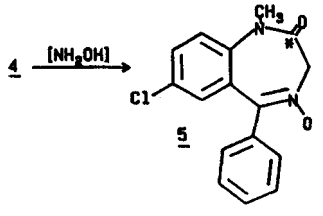
EXPERIMENTAL

Radioactivity determinations were carried out with a liquid scintillation spectrometer (Packard, Model 3320). Purity determinations were performed by thin-layer chromatography (TLC)

Scheme 1


Cl-CH2-CO2H
SOCl2
Cl-CH2-COCl
1
2


2
+
Cl
CH3
NH
O
3
CH3
N-CO-CH2-Cl
Cl
O
4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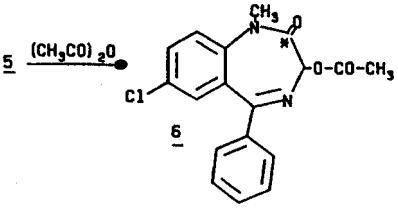
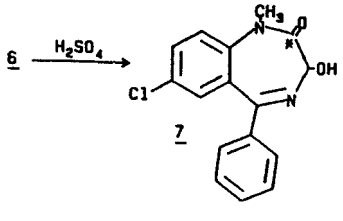
[NH2OH]
CH3
N
O
Cl
N
O
5


5
(CH3CO)2O
CH3
N
O
Cl
O-CO-CH3
N
6


6
H2SO4
CH3
N
O
Cl
OH
N
7

analyses on silica gel GF (Whatman). Visualization of zones on a TLC plate was accomplished by UV (254 nm) and by iodine vapors. The radiochemical purity of each product was determined by scanning the TLC plate with Varian Model 6000 TLC scanner. Yields of product are radiochemical yields. Radiochemical purity of the final product was determined by reverse isotope dilution analysis.

2-(N-Methylchloroacetamido-1-^{14}C)-5-chlorobenzophenone (4)

Chloroacetic-1-^{14}C acid (1), 0.372 g, 3.92 mmol, specific activity 51 mCi/mmol and 1 ml of thionyl chloride were heated for 1 hr under reflux at 100°C in an oil bath. The reaction mixture was cooled in a dry ice-acetone bath and 25 ml of methylene chloride was used to wash down the walls of the double surface condenser. A solution of 2-methylamino-5-chlorobenzophenone (3), 1.25 g, 5.1 mmol, in 20 ml of methylene chloride-ether (1:1, v/v) was added dropwise to the flask containing 2. After the addition of 3 ml of water, the reaction mixture was stirred for two hours in an ice bath. The organic phase was separated, washed once with brine and then dried over anhydrous sodium sulfate. The sample was filtered and the solvent was removed by evaporation *in vacuo*. The residue was dissolved in chloroform and applied to a 25 x 2.5 cm Silica Gel G column (30 g) conditioned in ligroine. The column was eluted with 100 ml of ligroine and then with 500 ml of toluene-ligroine (1:1, v/v). The solvent was changed to methylene chloride and eleven-100 ml fractions were collected. Each fraction was analyzed by TLC using toluene-ethyl acetate (5:1, v/v) as the developing solvent. Fractions 3-10 which contained 4 were combined and evaporated *in vacuo* to dryness. The residue was dissolved in 10 ml of carbon tetrachloride at the boiling point, and 20 ml of ligroine was added. The sample was seeded and one crop of crystals was obtained (0.885 g, 67% yield).

7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one-2-^{14}C-4-oxide (5)

A mixture of 4 0.885 g, 2.74 mmol, 50 ml of isopropyl alcohol, 1.19 g of sodium iodide, 2.21 g of hydroxylamine sulfate and 2.21 g of potassium carbonate hemihydrate were stirred for 24 hours. Fifty milliliters of chloroform were added to the sample and the mixture was filtered. The solvent was evaporated *in vacuo*. The residue was dissolved in chloroform and applied to a 25 x 2.5 cm Silica Gel G column (30 g) conditioned in toluene. The column was eluted with 100 ml of toluene followed by 500 ml of chloroform-toluene (1:1, v/v). The solvent was changed to chloroform and eleven-100 ml fractions were collected. Each fraction was analyzed by TLC using chloroform-methanol (95:5, v/v) as the developing solvent. Fraction 3-7 which contained 5 were combined and evaporated *in vacuo* to dryness. The residue was dissolved in 10 ml of boiling ethanol; upon cooling and seeding 5 was obtained (0.254 g, 25.5% yield).

7-Chloro-1,3-dihyro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one-2-^{14}C (7)

A mixture of 5 (0.229 g, 0.76 mmol) and 2.4 ml of acetic anhydride was heated at 120° in an oil bath for 10 min. Heptane was added to the flask to assist in the azeotropic removal of the excess acetic anhydride *in vacuo*. TLC of the residue with chloroform-methanol (95:5, v/v) as the developing solvent demonstrated that quantitative conversion of 5 to 6 had occurred. Compound 6 and 1.7 ml of concentrated sulfuric acid were stirred at room temperature for 1.5 hours. Ten milliliters of chloroform were added and 15.4 g of sodium bicarbonate was added slowly with efficient mixing. The neutral mixture containing 7 was extracted with chloroform. The chloroform extracts were evaporated to

dryness in vacuo. The residue was dissolved in chloroform and applied to a 25 x 2.5 cm Silica Gel G column (30 g) conditioned in toluene. The column was eluted with 100 ml of toluene and then with 250 ml of chloroform-toluene (1:1, v/v). The solvent was changed to chloroform-toluene (9:1, v/v) and 100 ml fractions were collected. The fractions were analyzed by TLC using chloroform-methanol (95:5, v/v) as the developing solvent. Those fractions which contained 7 were combined and evaporated in vacuo to dryness. The residue was dissolved in dimethylformamide, diluted with water-methanol (1:1, v/v), and, after seeding, 0.116 g, 22.7% of 7 was obtained (52.7 mCi/mmol).

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