NOTES

THE PREPARATION OF 7-CHLORO-5-(2-CHLOROPHENYL)-1,3-DIHYDRO-2H-1,4-BENZODIAZEPIN-2-ONE-5-^{14}C

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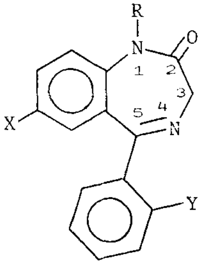
SUMMARY

7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one labeled with carbon-14 in carbon 5 of the diazepine ring has been synthesized. The compound was prepared in a multistep synthesis from barium carbonate-^{14}C in an overall yield of 23%.

Key Words: Benzodiazepine-5-^{14}C, 7-Chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one-5-^{14}C

INTRODUCTION AND DISCUSSION

In a previously submitted paper$^{(1)}$ we described a method for the preparation of N-1 methylated (R=CH_3) benzodiazepines labeled with carbon-14 in the five position of the diazepine ring. We would now like to report an adaptation of this method for the preparation of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one-5-^{14}C (5), a benzodiazepine with no third substituent on nitrogen-1. The synthetic scheme used is depicted in the figure below.



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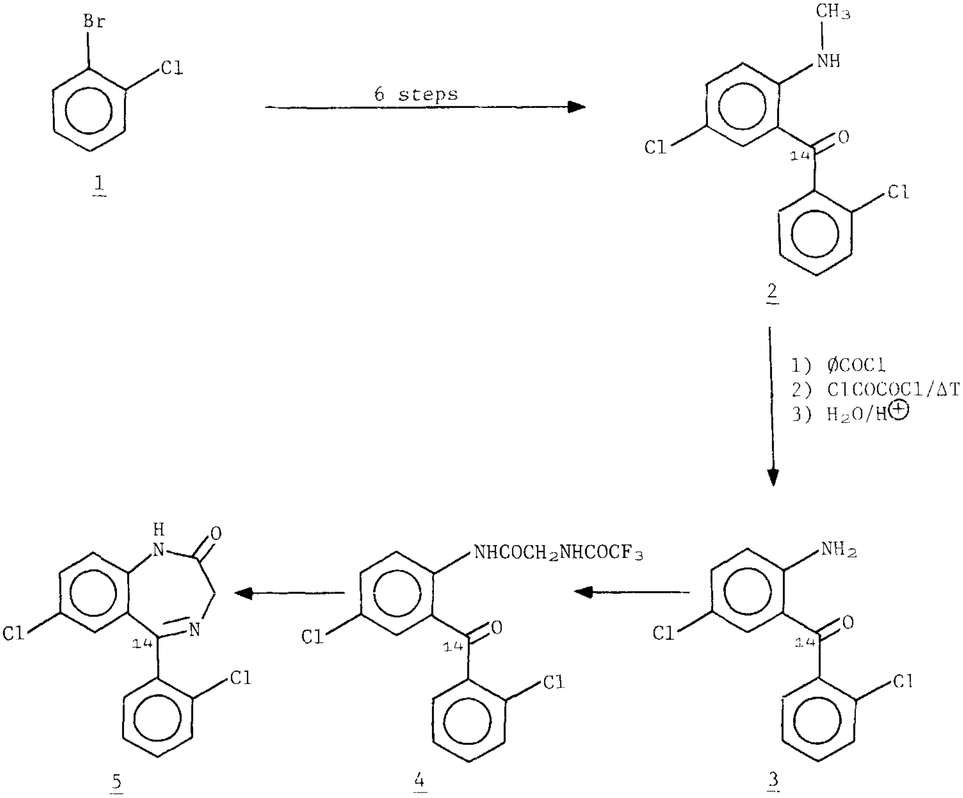
2',5-Dichloro-2-methylaminobenzophenone-carbonyl-^{14}C (2) was prepared in 43% overall yield from o-bromochlorobenzene (1) and carbon-14 dioxide in six steps according to the procedures described in our previous paper.(1) Since the benzodiazepine to be synthesized does not contain a methyl group at N-1, this substituent had to be removed in order to yield the aminobenzophenone 3. This was done by benzoylation, followed by reaction with oxalyl chloride to give a chloroiminium chloride, which upon pyrolysis at 140°C loses methyl chloride and yields an iminochloride. Hydrolysis finally gave the primary amine 3 in overall yield of 86%. These reactions, first described by J. V. Braun(2) for the dealkylation of secondary amines, can be carried out without isolation of any of the intermediates.



The aminobenzophenone 3 was then converted to the desired benzodiazepine (11)(3) with the aid of N-trifluoroacetyl glycinyl chloride,(4) followed by the treatment of the intermediate amide 4 with base. 28.4 mCi of pure product, for an overall yield of 23% calculated from carbon dioxide-^{14}C, was obtained.

EXPERIMENTAL

Melting points are uncorrected. Radioactivity was measured by the liquid scintillation technique using a Packard Tricarb Model 2010 spectrometer. Radiochemical purity was determined on thin layer chromatograms with a Packard Model 7021 Radiochromatogram Scanner System. TLC analyses were conducted on 20 cm TLC plates of Merck Silica Gel GF 254. Unlabeled reference compounds and intermediates were obtained internally or synthesized and structures were confirmed by spectroscopic methods.

2',5-Dichloro-2-methylaminobenzophenone-carbonyl-^{14}C (2)

Starting with barium carbonate-^{14}C (2.05 mmol; 123 mCi) and o-bromochlorobenzene 245 mg of 2',5-dichloro-2-methylaminobenzophenone-carbonyl-^{14}C (2) was prepared following the procedures already described.(1)

2-Amino-2',5-dichlorobenzophenone-carbonyl-^{14}C (3)

A mixture of 245 mg (0.87 mmol) of 2',5-dichloro-2-methylaminobenzophenone-carbonyl-^{14}C and 140 mg (1 mmol) of benzoyl chloride in 10 ml of o-dichlorobenzene was stirred at 140°C overnight. After cooling to room temperature, 1 ml of oxalyl chloride was added and the mixture stirred at 60-70°C for one hr. The temperature was then raised to 140°C and kept there for an additional hr. The solvent was removed in vacuo and the residue refluxed with 5 ml of water for 5 min. After cooling to room temperature 8 ml of conc. sulfuric acid was slowly added and the mixture then heated to 140°C and maintained for 3 hr. The solution was poured onto ice, brought to pH 8 by adding conc. ammonia, and extracted three times each with 40 ml of chloroform. The organic extracts were washed once with 15 ml water, concentrated and evaporated to dryness. The residue, dissolved in a small amount of chloroform, was applied to a column of 20 g of silica gel and developed with chloroform. Small fractions were taken and analyzed by TLC. Those containing the wanted material were combined and evaporated, yielding 201 mg (86%) of 2-amino-2',5-dichlorobenzophenone-carbonyl-^{14}C.

4'-Chloro-2'-(2-chlorobenzoyl-carbonyl-^{14}C)-2-trifluoroacetylaminoacetanilide (4)

A solution of N-trifluoroacetyl glycinyl chloride, prepared as described(4) from 342 mg (2 mmol) of N-trifluoroacetyl glycine in 2 ml of benzene, was added to a solution of 201 mg (0.75 mmol) of 2-amino-2',5-dichlorobenzophenone-carbonyl-^{14}C in 4 ml of benzene and the resulting mixture was refluxed for one hr. After cooling to room temperature, the solution was extracted three times with 15 ml portions of water. All aqueous phases were re-extracted with benzene, the organic layers were combined and evaporated to dryness. The residue was dissolved in a small amount of chloroform and applied to a column of 15 g silica gel. The product was eluted, using a mixture of chloroform/ethyl acetate, 3/1, yielding 269 mg (0.64 mmol, 85%) of pure 4.

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

To the above product, dissolved in 10 ml of methanol, 5 ml of water and 5 ml of 1 N sodium hydroxide were added under cooling in an ice bath. After stirring at room temperature for one hr, most of the methanol was removed *in vacuo* and the aqueous phase was then extracted three times with 20 ml of chloroform. The organic extracts were washed once with water, combined, dried and evaporated to dryness. The product was chromatographed on 20 g of silica gel using chloroform/ethyl acetate, 3/2, as the developing solvent. The first fractions contained 7.7 mCi of 2-amino-2',5-dichlorobenzophenone-carbonyl-^{14}C of greater than 98% radiochemical purity. All later fractions containing the labeled benzodiazepine were combined and evaporated. Recrystallization from chloroform/ether yielded 86.3 mg of pure product, mp 198-199°C (lit 199-201°C(5)), with a specific activity of 204 µCi/mg (17.6 mCi; 14.3% based on carbon dioxide-^{14}C). The mother liquor contained an additional 10.8 mCi of product of >98% purity for a total yield of 23% based on carbon dioxide-^{14}C.

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