SYNTHESIS OF 7-CHLORO-1,3-DIHYDRO-5-(2-FLUOROPHENYL)-1-METHYL-2H-1,4-BENZODIAZEPIN-2-ONE-5-^{14}C (FLUDIAZEPAM-^{14}C).

Iwao Nakatsuka, Kazuo Kawahara, Takeshi Kamada, Fumiaki Shono and Akira Yoshitake,
Institute for Biological Science, Sumitomo Chemical Co., Ltd.,
2-1, 4-Chome, Takatsukasa, Takarazuka-shi, Japan.
Received July 22, 1976
Revised August 16, 1976

SUMMARY

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (Fludiazepam)(I), an anti-anxiety agent, was labelled with carbon-14 at C-5 position for metabolic studies. The reaction sequence for the synthesis is shown in Fig. 2. o-Fluorobenzoic-^{14}C acid (IV) was prepared in 65% yield by carbonation of o-fluorophenyllithium with carbon-^{14}C dioxide. The acid (IV) was condensed with N-(4-chlorophenyl)-N- methyl-ethylenediamine, followed by Bischler-Napieralski cyclization of the resulting amide with phosphorus pentoxide and phosphorus oxychloride to afford 7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-5-^{14}C (VII) in good yield. Oxidation of VII by N-bromosuccinimide in aqueous solution of sodium bicarbonate gave Fludiazepam-^{14}C (I). The overall yield of I was 24% from barium carbonate-^{14}C.

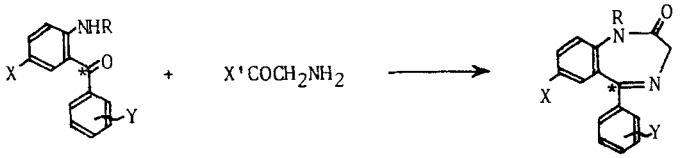
Key Words: Anti-anxiety, Benzodiazepine, Carbon-14

INTRODUCTION

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one (Fludiazepam)(I) is a novel benzodiazepine derivative which has been synthesized and tested for pharmacological activities in our laboratories[1]. It has been found to have central nervous depressant activities and expected to be a potent anti-anxiety drug in human. In order to investigate the metabolic fate of this agent in animals it became necessary to synthesize Fludiazepam labelled with carbon-14 at C-5 position.

Syntheses of some 1,4-benzodiazepin-2-one-5-^{14}C derivatives have already appeared in the literature. For example, E. J. Merrill *et. al.*[2] and H.

Ishihara *et. al.*[3] reported the synthesis of Prazepam-^{14}C (IIa: R=cyclopropyl methyl, X=Cl, Y=H), and A. Yoshitake *et. al.*[4] that of Nimetazepam-^{14}C (IIb: R=methyl, X=NO_2, Y=H). In all of these syntheses, the key intermediates were aminobenzophenone-(carbonyl-^{14}C) derivatives (III) which were condensed with glycine residues and subsequently cyclized to 1,4-benzodiazepin-2-ones (IIa and b) as shown in Figure 1. We first attempted this method for the preparation of



(III) (IIa,b)

Fig. 1. Scheme for the synthesis of 1,4-benzodiazepin-2-one-5-^{14}C derivatives *via* aminobenzophenone-^{14}C derivatives

Fludiazepam-(5-^{14}C)(I) but failed mainly because of a low yield of 2-amino-5-chloro-2'-fluorobenzophenone-(carbonyl-^{14}C)(III: R=H, X=Cl, Y=*o*-F).

This paper describes the synthesis of Fludiazepam-(5-^{14}C)(I) using a different approach from those mentioned above.

DISCUSSION

The reaction sequence for the synthesis of Fludiazepam-(5-^{14}C)(I) is illustrated in Figure 2. 2-Fluorobenzoic-(carboxyl-^{14}C) acid (IV) was selected as the labelled starting material. Although attempts to prepare IV by Grignard reaction of 2-fluorophenylmagnesium bromide with carbon-^{14}C dioxide were unsuccessful, the desired acid (IV) was obtained in 65% yield when treatment of 2-fluorobromobenzene with *n*-butyllithium[5] at -70° for 0.5 hr, followed by carbonation of the resulting 2-fluorophenyllithium with carbon-^{14}C dioxide at the same temperature for 1.5 hr.

By modifing Kaegi's method[6], 2-fluorobenzoic-(carboxyl-^{14}C) acid was treated with thionyl chloride and subsequently allowed to react with N-(4-chlorophenyl)-N-methylethylenediamine (V) in refluxing benzene for 2 hr to give N-(2-fluorobenzoyl)ethylene diamine-^{14}C (VI) in 69% yield. The unlabelled

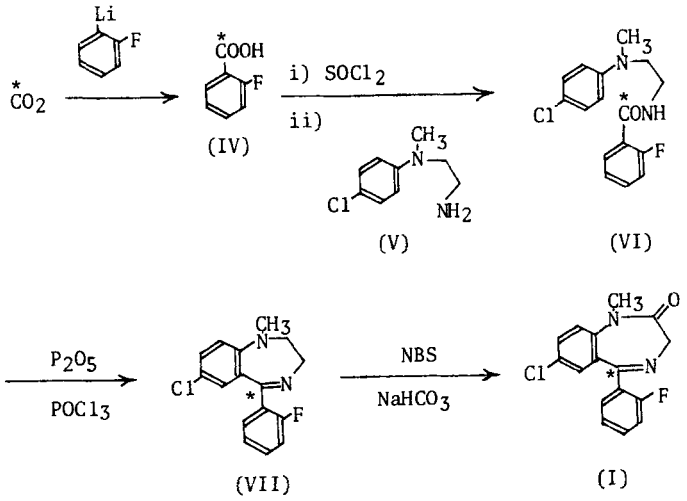


Fig. 2. The reaction sequence for the synthesis of Fludiazepam-(5-^{14}C)

starting material (V) was readily prepared by an improved method as shown in Figure 3. Thus, 4-chloroaniline was allowed to reflux in triethyl orthoformate and the resulting imidate (VIII) reduced with sodium borohydride to give 4-chloro-N-methylaniline (IX). The latter, according to Kaegi's method[6], was aminoethylated with ethyleneimine under aluminum chloride catalysis, giving the ethylenediamine (V) in the overall yield of 60%.

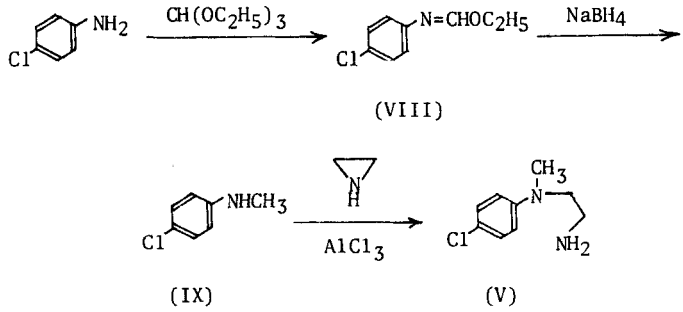


Fig. 3. Scheme for the preparation of N-(4-chlorophenyl)-N-methylethylenediamine

N-(2-Fluorobenzoyl)ethylenediamine-^{14}C (VI) on treatment with phosphorus pentoxide-phosphorus oxychloride at 110° for 6 hr afforded 1,4-benzodiazepine-

5-^{14}C (VII) in excellent yield (93%). In this Bischler-Napieralski cyclization, employment of polyphosphate ester (PPE)[7] was less attractive to give VII in 50% yield.

Oxidation of VII by the use of conventional oxidants such as chromium trioxide[8], potassium permanganate[8], or ruthenium tetroxide[9] led to Fludiazepam-(5-^{14}C)(I) but the yields were never better than 40% in our hand. The only oxidant which was found to be more effective was N-bromosuccinimide (NBS) in aqueous alkaline media. Under the optimal condition (see Experimental) the 1,4-benzodiazepine-5-^{14}C (VII) was oxidized to Fludiazepam-(5-^{14}C)(I) in 59% yield after purification by column-chromatography and recrystallization. The product had a specific activity of 7.48 mCi/mmole and was identical in every respect with the unlabelled authentic sample. The overall yield of I was 24% from barium carbonate-^{14}C.

EXPERIMENTAL

2-Fluorobenzoic-(carboxyl-^{14}C) Acid -- To a 1.5N solution (2 ml) of *n*-butyllithium in hexane which was cooled in a Dry Ice-acetone bath to -70° was added with stirring a solution of 2-fluorobromobenzene (540 mg, 3.1 mmol) in anhydrous ether (6 ml) over a period of 20 min, while not allowing the temperature to rise above -65° during the addition. After stirring at the same temperature for 5 min, the mixture was frozen with liquid nitrogen. To the frozen mixture was introduced, in a vacuum manifold, carbon-^{14}C dioxide which was liberated from barium carbonate-^{14}C (100 mCi, 597 mg, 3.0 mmol). The mixture was then warmed to -70° and stirred for 1.5 hr; during the reaction the temperature was kept below -65°. After hydrolysis with 5% hydrochloric acid, the mixture was extracted with ether. To the extract was added unlabelled 2-fluorobenzoic acid (630 mg, 4.5 mmol) and the solution partitioned with 10% sodium carbonate solution. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. Evaporation of the solvent gave a crystalline residue which was recrystallized from water; giving 2-fluorobenzoic-(carboxyl-^{14}C) acid (65.0 mCi, 875 mg, 10.4 mCi/mmol). The IR spectrum (nujol) showed absorptions at 3100-2500 (COOH) and 1690 cm^{-1}(COOH), and the mass spectrum showed the mole-

cular ion at m/e 140; the spectra were identical with those of the unlabelled authentic sample.

4-Chloro-N-methylaniline -- A mixture of 4-chloroaniline (25.6 g, 0.2 mol), triethyl orthoformate (80 g) and trifluoroacetic acid (5 drops) was refluxed for 5 hr, then concentrated and the residual oil dissolved in absolute ethanol (100 ml). To the solution was added sodium borohydride (20 g) under cooling to 0° and the mixture heated to reflux for 3 hr. After evaporation of the solvent, the residue was suspended in water and extracted with ether. The extract was washed with water, dried and evaporated to give 4-chloro-N-methylaniline (24.1 g, 85%); NMR spectrum (δ, $CDCl_3$): 2.91 (3H, singlet, N-CH_3), 6.60 (2H, doublet, J=9 Hz, aromatic protons) and 7.13 (2H, doublet, J=9 Hz, aromatic protons).

N-(4-Chlorophenyl)-N-methylethylenediamine -- 4-Chloro-N-methylaniline (24.1 g) was converted to N-(4-chlorophenyl)-N-methylethylenediamine according to Kaegi's method[6]. The yield was 70% (22.0 g) after purification by distillation (bp 126° at 0.05 mmHg). The NMR spectrum showed peaks: 2.90 (3H, singlet, NCH_3), 2.87 (2H, triplet, J=6 Hz, -CH_2-), 3.34 (2H, triplet, J=6 Hz, -CH_2-), 6.61 (2H, doublet, J=8 Hz, aromatic protons), 7.14 (2H, doublet, J=8 Hz, aromatic protons) and 1.50 (2H, broad singlet, NH_2).

N'-(4-Chlorophenyl)-N-(2-fluorobenzoyl)-N'-methylethylenediamine-(carbonyl-^{14}C) (VI) -- A mixture of 2-fluorobenzoic-(carboxyl-^{14}C)(29.1 mCi, 435 mg, 3.11 mmol) and thionyl chloride (3.7 g, 30 mmol) in anhydrous benzene (6 ml) was heated to reflux for 3 hr. Removal of the solvent and the excess of thionyl chloride gave an oily residue which was taken up in anhydrous benzene (12 ml), and to the solution was added N-(4-chlorophenyl)-N-methylethylenediamine (V)(630 mg, 3.4 mmol). The mixture was refluxed for 2 hr, cooled and poured into 10% sodium hydroxide solution. The resulting slurry was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate and evaporated to afford an oily residue (23.3 mCi). Chromatography of the residue on silica gel with chloroform gave N'-(4-chlorophenyl)-N-(2-fluorobenzoyl)-N'-methylethylenedi-

amine-(carbonyl-^{14}C)(19.4 mCi, 638 mg, 67%); IR spectrum (liquid film):1650 cm^{-1} (amide carbonyl).

7-Chloro-2,3-dihydro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-5-^{14}C (VII) -- A mixture of N'-(4-chlorophenyl)-N-(2-fluorobenzoyl)-N'-methylethylenediamine-(carbonyl-^{14}C)(19.4 mCi, 638 mg, 2.07 mmol), phosphorus pentoxide (3.0 g, 21 mmol) and phosphorus oxychloride (8.3 ml, 90 mmol) was heated under stirring at 110° for 6 hr. The reaction mixture was poured into ice-water and washed with ether. The aqueous solution was basified with sodium carbonate and extracted with ethyl acetate. The dried extract was evaporated to afford 7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-5-^{14}C (18.1 mCi, 560 mg, 93%), mp 100-103°; NMR spectrum (δ, $CDCl_3$): 2.80 (3H, singlet, NCH_3), 3.42-3.90 (4H, multiplet, $-CH_2CH_2-$) and 6.82-7.73 (7H, multiplet, aromatic H).

Cyclization of N'-(4-Chlorophenyl)-N-(2-fluorobenzoyl)-N'-methylethylenediamine-^{14}C with polyphosphate ester -- A mixture of phosphorus pentoxide (10 g), ether (10 ml) and chloroform (20 ml) was refluxed for 20 hr and evaporated to yield PPE. N'-(4-Chlorophenyl)-N-(2-fluorobenzoyl)-N'-methylethylenediamine-^{14}C (414 μCi, 1.18 g, 3.85 mmol) was added to the PPE and the mixture heated under stirring at 120° for 16 hr. The mixture was then diluted with 10% sodium hydroxide solution and extracted with ethyl acetate. The extract was washed with water, dried and evaporated to give a residue. Chromatography of the residue on silica gel with chloroform gave 7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-5-^{14}C (195 μCi, 528 mg, 47%).

7-Chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one-5-^{14}C, Fludiazepam-(5-^{14}C)(I) -- In a three-necked flask (100 ml) fitted with two dropping funnels and a magnetic stirring bar was placed a solution of N-bromosuccinimide (720 mg, 4.05 mmol) in tetrahydrofuran (20 ml). To the stirred solution was added dropwise at room temperature during 1 hr, simultaneously from the dropping funnels, a solution of 7-chloro-2,3-dihydro-5-(2-fluorophenyl)-1-methyl-1H-1,4-benzodiazepine-5-^{14}C (18.1 mCi, 560 mg, 1.93 mmol) in tetrahydro-

furan (30 ml) and a solution of sodium bicarbonate (730 mg, 8.69 mmol) in water (10 ml). After complete addition, the mixture was stirred at the same temperature for 15 min, diluted with water and extracted with ethyl acetate. The extract was washed with 1% hydrochloric acid, 5% sodium hydroxide solution and water successively, dried over sodium sulfate and evaporated to give a residue (14.4 mCi). The residue, diluted with the unlabelled Fludiazepam (100 mg), was subjected to chromatography on silica gel with chloroform. Evaporation of the main fractions gave a crystalline residue which was recrystallized from isopropyl alcohol-hexane to yield 7-chloro-1,3-dihydro-5-(2-fluorophenyl)-1-methyl-2H-1,4-benzodiazepin-2-one-5-^{14}C (Fludiazepam-5-^{14}C)(10.7 mCi, 435 mg, 7.48 mCi/mmol); its IR spectrum ($CHCl_3$) showing absorptions at 1675 (CON) and 1615 cm^{-1}(phenyl), and being identical with that of the unlabelled authentic sample.

ACKNOWLEDGEMENT

The authors wish to thank Drs, J. Katsube and K. Ishizumi for many helpful suggestions and providing the unlabelled authentic materials. They are indebted to Miss K. Morimoto for her technical help.

REFERENCES

1. Asami Y., Otsuka M., Hirohashi T., Inaba S. and Yamamoto H. - Arzneimittel Forschung 24: 1536 (1974).
2. Merrill E.J. and Vernice G.G. - J. Labelled Comp. 7: 89 (1971).
3. Ishihama H., Kho S. and Tamaki T. - Presented at the 96th Annual Symposium of Pharmaceutical Sciences, Nagoya, Japan, 1976, Abstract Papers vol.4. p 81.
4. Yoshitake A., Makari Y. and Endo M. - J. Labelled Comp. 8: 615 (1972).
5. Gilman H. and Gorsich R.D. - J. Amer. Chem. Soc. 78: 2217 (1956).
6. Kaegi H.H. - J. Labelled Comp. 4: 363 (1968).
7. Kanaoka Y., Sato E., Yonemitsu O. and Ban Y. - Tetrahedron Lett.: 2419 (1964).
8. Fryer R.I., Archer G.A., Brust B., Zally W. and Sternbach L.H. - J. Org. Chem. 30: 1308 (1965).
9. Felix A.M., Early J.V., Fryer R.I. and Sternbach L.H. - J. Heterocyclic Chem. 5: 731 (1968).