LABELLING OF NEUROLEPTIC BUTYROPHENONES. II. SYNTHESIS OF 2'-AMINO-4'-FLUORO-4-[4-HYDROXY-4-(3-TRIFLUOROMETHYLPHENYL)PIPERIDINO]BUTYROPHENONE-(CARBONYL-^{14}C)

Iwao Nakatsuka, Kazuo Kawahara, Takeshi Kamada and Akira Yoshitake
Institute for Biological Science, Sumitomo Chemical Co., Ltd., 2-1, 4-Chome, Takatsukasa, Takarazuka-shi, 665 Japan.

SUMMARY

2'-Amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]butyrophenone (ID-4708)(1), a novel neuroleptic agent, was labelled with carbon-14 at the carbonyl position for use in metabolic studies. The synthesis was achieved according to the reaction scheme shown in Fig. 1. Cyclopropyl 2,4-difluorophenyl ketone-(carbonyl-^{14}C)(2a) was prepared from cyclopropane-carboxylic-^{14}C acid by the Friedel-Crafts reaction with m-difluoro-benzene. Ring-opening of 2a with hydrogen chloride gave 4-chloro-2',4'-difluorobutyrophenone-1-^{14}C (3a). After ketalization of 3a, the resulted ketal (4) was condensed with the piperidine (5) and subsequently hydrolyzed with hydrochloric acid to give 6. Benzylamination of 6 with benzylamine, followed by debenzylation by catalytic hydrogenolysis gave ID-4708-(carbonyl-^{14}C)(1). The overall radiochemical yield of 1 from barium carbonate-^{14}C was 13%.

Key Words: Carbon-14, Butyrophenone Derivatives, Neuroleptics

INTRODUCTION

2'-Amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]-butyrophenone (ID-4708)(1) is a novel butyrophenone derivative which has been synthesized and tested for pharmacological activities in our laboratories. It has been found to possess high anti-apomorphine and anti-metamphetamine activities in animals and is expected to be a potent neuroleptic drug in man[1]. In this paper we report the synthesis of the agent labelled with carbon-14 at the carbonyl position for use in metabolic studies.

0362-4803/79/0316-0407$01.00

Received July 10, 1978
Revised August 4, 1978

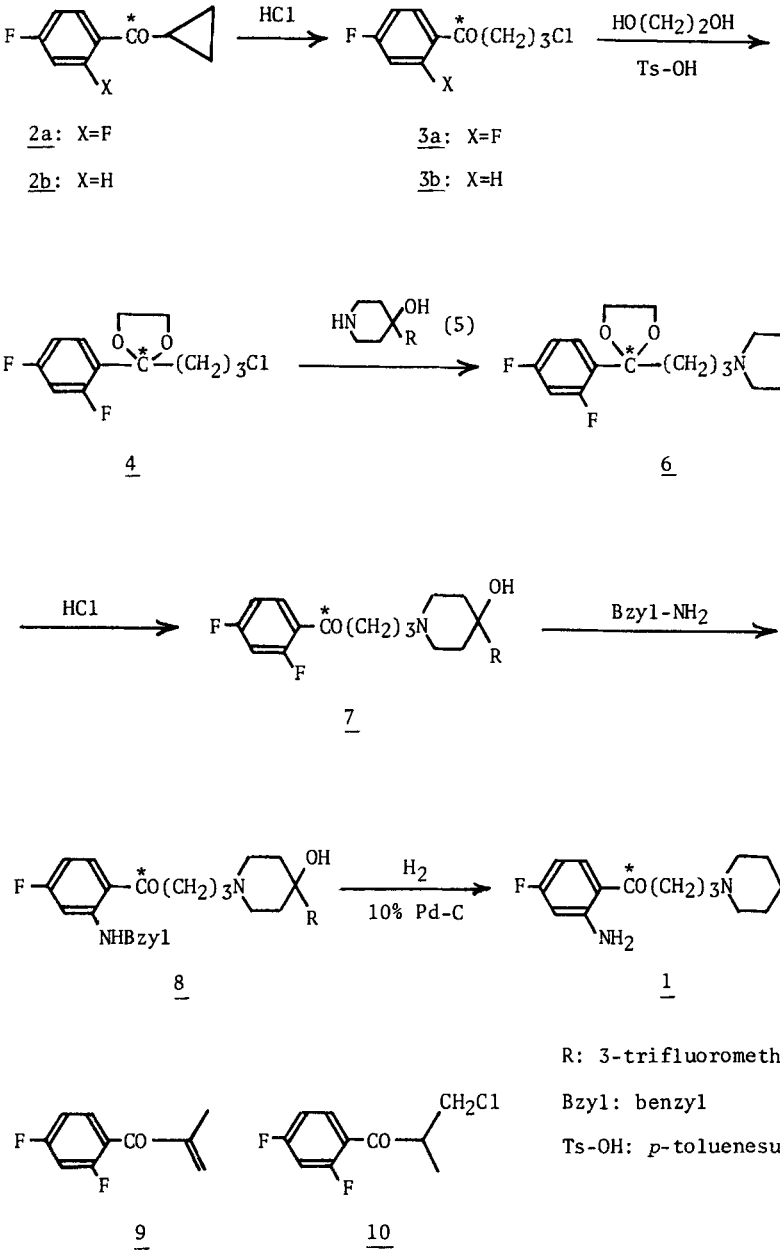
DISCUSSION

The starting material, cyclopropyl 2,4-difluorophenyl ketone-(carbonyl-^{14}C) (2a), was prepared from carbon-^{14}C dioxide according to the procedures basically similar to those described before[2]. Thus, cyclopropanecarboxylic-^{14}C acid, which was readily prepared by carbonation of cyclopropylmagnesium bromide with carbon-^{14}C dioxide, was treated with thionyl chloride and the resulting chloride was allowed to react with an excess of *m*-difluorobenzene at 5-10° for 40 hr to give the desired ketone (2a) in 83% yield.

Conversion of 2a to ID-4708-(carbonyl-^{14}C)(1) was accomplished according to the reaction procedures illustrated in Fig. 1. Preliminary experiments were run in an attempt to obtain the butyrophenone (7) more directly. However, the condensation reaction of 2a with 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine (5) under various reaction conditions gave the butyrophenone (7) only in poor yields (see the Experimental).

As described in the previous paper[2], treatment of cyclopropyl 4-fluorophenyl ketone (2b) with 50% hydrogen chloride-methanol solution containing a small amount of water at room temperature gave 4-chloro-4'-fluorobutyrophenone (3b) in an excellent yield. This method was, therefore, adapted to the ring-opening of cyclopropyl 2,4-difluorophenyl ketone-(carbonyl-^{14}C)(2a). In this case, however, the reaction proceeded more slowly and a considerable amount of the starting material was recovered even in the prolonged reaction time, and the undesired by-products (9 and 10) were yielded under more drastic conditions. After considerable investigation, it was found that the difluorophenyl ketone (2a) when allowed to react with 50% hydrogen chloride-methanol solution *without water* at room temperature for 1 hr gave the best yield of 3a. After purification by column chromatography, the yield of 3a was 73%.

Ketalization of 3a by heating with ethylene glycol and *p*-toluenesulfonic acid in benzene gave the ketal (4) in a quantitative yield. Condensation of 4 with the piperidine (5), followed by acid-hydrolysis of the resulting product



2a: X=F
2b: X=H

3a: X=F
3b: X=H

4

6

7

8

1

9

10

Fig. 1 Scheme for the synthesis of 2'-amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]-butyrophenone-(carbonyl-^{14}C) (1)

(6), afforded the piperidinobutyrophenone-(carbonyl-^{14}C)(7) in 65% yield.

When the piperidinobutyrophenone (7) was allowed to reflux with an excess of benzylamine in *hexane*[3], selective monobenzylamination at the *ortho*-fluorine of the 2,4-difluorophenyl group occurred to give the benzylaminobutyrophenone-(carbonyl-^{14}C)(8) in 79% yield. Catalytic hydrogenolysis of 8 with 10% Pd-C gave crude ID-4708-(carbonyl-^{14}C)(1). Purification of the product by column chromatography on silica gel and subsequent recrystallization from benzene gave 1 in 99% of purity. The overall radiochemical yield of 1 was 13% from carbon-^{14}C dioxide.

EXPERIMENTAL

Cyclopropyl 2,4-Difluorophenyl Ketone-(carbonyl-^{14}C)(2a) -- A mixture of cyclopropanecarboxylic-^{14}C acid[2] (91.0 mCi, 355 mg, 4.13 mmol) and thionyl chloride (540 mg, 4.5 mmol) was heated at 70-75° for 1.5 hr. After cooling, *m*-difluorobenzene (940 mg, 8.3 mmol) and anhydrous aluminium chloride (1.10 g, 8.3 mmol) were added to the reaction mixture. The mixture was stirred at 5-10° for 40 hr, poured into ice-water and extracted with ether. The extract was washed with 5% sodium carbonate solution and water, dried over sodium sulfate, and evaporated under reduced pressure to give cyclopropyl 2,4-difluorophenyl ketone-(carbonyl-^{14}C)(75.5 mCi, 83%). The product was used for the following reaction without any purification.

4-Chloro-2',4'-difluorobutyrophenone-1-^{14}C (3a) -- A mixture of cyclopropyl 2,4-difluorophenyl ketone-(carbonyl-^{14}C)(2a)(75.5 mCi, 624 mg, 3.4 mmol) and 50% hydrogen chloride-methanol solution (5 ml) was stirred at room temperature for 1 hr. The solvent was evaporated under reduced pressure and then the residue was taken up in benzene. The solution was washed with 5% sodium carbonate solution and water, and dried over sodium sulfate. Evaporation under reduced pressure gave an oily residue, which was purified by column chromatography on silica gel with hexane-ethyl acetate (1:1 v/v) to give 4-chloro-2',4'-difluorobutyrophenone-1-^{14}C (3a)(54.8 mCi, 568 mg, 73%); IR νmax (liquid film) cm^{-1}: 1685 (CO), 1610 (phenyl); NMR (δ, $CDCl_3$): 2.20(2H, quint., J=6.0 Hz,-$CH_2\underline{CH_2}CH_2$-),

3.16 (2H, sext., J=6.0 Hz, J=3.4 Hz, $-COCH_2CH_2CH_2-$), 3.68 (2H, t., J=6.0 Hz, $-CH_2CH_2CH_2Cl$), 6.65-7.30 (2H, m., aromatic H), 7.70-8.20 (1H, m., aromatic H); mass spectrum (m/e): 220/218 (M^+), 182, 156, 141 (base peak), 63.

4-Chloro-1,1-ethylenedioxy-1-(2,4-difluorophenyl)butane-1-^{14}C(4) -- A mixture of 4-chloro-2',4'-difluorobutyrophenone-1-^{14}C (3a)(54.8 mCi, 568 mg, 2.6 mmol), unlabelled 4-chloro-2',4'-difluorobutyrophenone (229 mg, 1.1 mmol), ethyleneglycol (450 mg, 7.3 mmol) and *p*-toluenesulfonic acid (70 mg) in anhydrous benzene (40 ml) was refluxed for 6 hr during which water produced was azeotropically removed. After cooling, the mixture was taken up in benzene and the solution washed with 5% sodium carbonate solution and water. The solution was evaporated to dryness under reduced pressure to give 4-chloro-1,1-ethylenedioxy-1-(2,4-difluorophenyl)butane-1-^{14}C (4)(54.5 mCi, 980 mg, 99%), which was used for the following reaction without any purification.

1,1-Ethylenedioxy-1-(2,4-difluorophenyl)-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butane-1-^{14}C (6) -- A mixture of 4-chloro-1,1-ethylenedioxy-1-(2,4-difluorophenyl)butane-1-^{14}C (4)(54.5 mCi, 950 mg, 3.6 mmol), 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine[1] (5)(960 mg, 3.9 mmol), potassium carbonate (500 mg, 3.6 mmol), potassium iodide (10 mg) and anhydrous dimethylformamide (10 ml) was heated with stirring at 90-100° for 6 hr. The mixture was diluted with water and then extracted with ethyl acetate. The extract was washed with water, dried and evaporated under reduced pressure to leave 1,1-ethylenedioxy-1-(2,4-difluorophenyl)-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butane-1-^{14}C (6)(48.0 mCi, 1.56 g, 88%); which was immediately used for the following reaction.

2',4'-Difluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone-1-^{14}C (7) -- A solution of 1,1-ethylenedioxy-1-(2,4-difluorophenyl)-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butane-1-^{14}C (6)(48.0 mCi, 1.56 g, 3.2 mmol) and concentrated hydrochloric acid (2.8 ml) in methanol (17 ml)-water (5 ml) was heated to reflux for 1.5 hr. After cooling, precipitated crystals

were collected by filtration and washed with ether. The crystals were then added to 5% aqueous ammonia and stirred at room temperature for 30 min. The mixture was extracted with ethyl acetate and the extract washed with water and then dried over sodium sulfate. Evaporation of the extract under reduced pressure gave a crystalline residue which was recrystallized from 75% ethanol to give 2',4'-difluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone-1-^{14}C (7)(35.4 mCi, 1.02 g, 65%), mp and mixed mp 90-92°. The product was identical in every respect with the unlabelled authentic sample[3].

2'-Benzylamino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]-butyrophenone-1-^{14}C (8) -- A solution of 2',4'-difluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone-1-^{14}C (7)(35.4 mCi, 1.02 g, 2.4 mmol) and benzylamine (10 g, 96 mmol) in hexane (24 ml) was heated to reflux for 30 hr. The solution was concentrated under reduced pressure to give a residue which was taken up in chloroform. The chloroform solution was washed with 5% hydrochloric acid, 5% sodium carbonate solution and water, successively. The solution was dried over sodium sulfate and evaporated under reduced pressure to give an oily residue of 2'-benzylamino-4'-fluoro-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]butyrophenone-1-^{14}C (8)(35.0 mCi, 1.19 g, 99%); which was used in the next reaction without any purification.

2'-Amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone-(carbonyl-^{14}C) (1) -- A mixture of 2'-benzylamino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone-1-^{14}C (8)(35.0 mCi, 1.19 g, 2.4 mmol), 10% palladium-charcoal (200 mg), concentrated hydrochloric acid (1.8 ml), ethanol (20 ml) and water (0.5 ml) was stirred under atmosphere of hydrogen until the cease of hydrogen uptake. The catalyst was removed by filtration and washed with ethanol. The combined filtrate and washings were evaporated under reduced pressure to leave an oily residue, which was taken up in ethyl acetate and washed with 28% aqueous ammonia and then water. After drying over sodium sulfate, the solution was concentrated under reduced pressure to give an oily residue. The residue was subjected to column chromatography on silica gel and

eluted with chloroform-methanol (95:5 v/v). The main fractions were combined and evaporated to give a crystalline residue, which was recrystallized from benzene to give 2'-amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]butyrophenone-(carbonyl-^{14}C) (1)(13.2 mCi, 375 mg, 14.7 mCi/mmole, 37.7%) as colorless needles; mp and mixed mp 106-107°. The product was identical in every respect with the unlabelled authentic sample[1].

Condensation Reaction of Cyclopropyl 2,4-Difluorophenyl Ketone (2a) with 4-Hydroxy-4-(3-trifluoromethylphenyl)piperidine (5) -- A solution of cyclopropyl 2,4-difluorophenyl ketone (364 mg, 2.0 mmol), 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine (588 mg, 2.4 mmol) and magnesium chloride (20 mg) in anhydrous dimethylformamide (10 ml) was heated at 90-100° for 3 hr. After cooling, the solution was poured into ice-water and extracted with ether. The extract was washed with water, dried over sodium sulfate, and evaporated under reduced pressure to give an oily residue. Chromatography of the residue on silica gel with chloroform gave 2',4'-difluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]butyrophenone (7)(60 mg, 7% yield based on 2a).

Isolation of By-products (9 and 10) in the Ring-opening Reaction of Cyclopropyl 2,4-Difluorophenyl Ketone (2a) -- A mixture of cyclopropyl 2,4-difluorophenyl ketone (1.82 g, 10 mmol), 60% hydrogen chloride-methanol solution (20 ml) and water (2 ml) was refluxed for 2 hr. The mixture was treated by the similar manner as described above to give crude products (1.90 g). Preparative gas-chromatography of the products [column: 2% Silicone SE-30 on Chromosorb (300 cm, 1 cm I.D.), column temperature: 150°, carrier gas: He, detector: FID] gave 4-chloro-2',4'-difluorobutyrophenone (3a)(240 mg), the by-product (9)(32 mg) and the by-product (10)(70 mg). These by-products showed the following physicochemical properties: 1) by-product 9 -- colorless oil; mass spectrum for $C_{10}H_8OF_2$ (m/e): 182 (M^+), 167, 141 (base peak), 113; IR νmax (liquid film): 1670 cm^{-1} (CO); NMR (δ, $CDCl_3$): 2.15 (3H, s., $-CH_3$), 5.68 (1H, broad s., olefinic H), 6.00 (1H, broad s., olefinic H), 6.70-7.20 (2H, m., aromatic H), 7.60-8.03 (1H, m., aromatic H) and 2) by-product 10 -- colorless oil; mass spectrum for

$C_{10}H_9OClF_2$ (m/e): 220/218 (M^+), 183, 141 (base peak), 113; IR νmax (liquid film): 1676 cm^{-1}(CO); NMR (δ, $CDCl_3$): 1.35 (3H, d., J=5.8 Hz, $-CH_3$), 3.52-4.08 (3H, m., methine and methylene H), 6.73-7.22 (2H, m., aromatic H), 7.75-8.02 (1H, m., aromatic H).

ACKNOWLEDGEMENT

The authors wish to thank Dr. J. Katsube, Mr. K. Sasajima and Mr. K. Ono for many helpful discussions and providing the unlabelled authentic materials. We also thank Miss K. Ohsugi for her skillful technical assistance.

REFERENCES

1. Honma T., Sasajima K., Ono K., Kitagawa S., Inaba S. and Yamamoto H. - Arzneim. Forsch. 24: 1248 (1974).
2. Nakatsuka I., Kawahara K., Kamada T. and Yoshitake A. - J. Label. Compds. Radiopharm. 14: 133 (1978).
3. Sasajima K., Ono K., Katsube J. and Yamamoto H. - Chem. Pharm. Bull. (Tokyo): in press.