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

Iwao Nakatsuka, Kazuo Kawahara 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-2-^{14}C]butyrophenone [ID-4708-(piperidine-^{14}C], a neuroleptic agent, was synthesized for use in metabolic studies. The synthesis was achieved by the reaction scheme shown in Fig. 1. 1-Benzyl-4-piperidone-2-^{14}C was prepared by Mannich reaction of paraformaldehyde-^{14}C with ethyl acryloylacetate and benzylamine, followed by treatment with hydrochloric acid, in 65% yield. Grignard reaction of the product with 3-trifluoromethylphenylmagnesium bromide followed by hydrogenolysis gave 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (8), which was condensed with 3-(6-fluoro-2-methyl-3-indolyl)propionic acid to give the 3-indolylpropionylpiperidine-^{14}C (10). Conversion of 10 by reduction, oxidation and then hydrolysis led to ID-4708-(piperidine-^{14}C) (1) in the overall yield of 9.6% from paraformaldehyde-^{14}C.

Key Words: Carbon-14, Butyrophenone Derivatives, Neuroleptics

INTRODUCTION

Some 4-piperidinobutyrophenones including haloperidol and trifluperidol are extensively used as neuroleptics in clinical fields. In our laboratory, new 4-piperidinobutyrophenones have been synthesized to search for more effective and characteristic neuroleptics, one of which is 2'-amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone (ID-4708)(1). This compound has been found to possess higher anti-apomorphine and anti-metamphetamine activities than haloperidol, and is expected to be a potent neuroleptic [1].

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In our previous paper[2], we described a method to label this compound with carbon-14 at the carbonyl carbon of the butyrophenone moiety for use in metabolic studies. The metabolic studies of ID-4708-(carbonyl-^{14}C) have revealed that it is oxidatively biodegradated at C_4-N bond to give 4-oxo-4-phenylbutyric acids which are further biotransformed up to fluorophenylacetic acids. Soudijn *et al.* reported similar observations in the metabolic studies of ^{3}H-labelled neuroleptics of this type[3]. However, no report on the metabolism of the piperidine moiety has appeared so far. To clarify the metabolic fate of the piperidine moiety, it became necessary to synthesize ID-4708-(piperidine-^{14}C).

In the present paper, we describe the synthesis of ID-4708-(piperidine-^{14}C) *via* 1-benzyl-4-piperidone-2-^{14}C (6). The latter compound seems to be a useful key-intermediate for ^{14}C-labelling of other 4-substituted-piperidine derivatives of medical use.

DISCUSSION

The reaction scheme for the synthesis of ID-4708-(piperidine-^{14}C) (1) is shown in Figure 1. Oehring reported that 2-benzyl-3-carbethoxy-1-methyl-4-piperidone was prepared in a considerable yield by a modified Mannich reaction using phenylacetaldehyde, ethyl acryloylacetate and methylamine[4]. We applied this reaction to construct the 4-piperidone-^{14}C ring from paraformaldehyde-^{14}C. In the preliminary experiment, it was found that reaction of paraformaldehyde with ethyl acryloylacetate (3) and benzylamine (4) in methanol at room temperature gave a crude mixture containing 1-benzyl-3-carbethoxy-4-piperidone (5) which was immediately hydrolyzed and decarboxylated with 20% hydrochloric acid at 95° to yield 1-benzyl-4-piperidone (6) though the yield was as low as 5%.

In order to improve the yield of 1-benzyl-4-piperidone based on paraformaldehyde, we studied the effects of the solvent, reaction temperature, reaction time, and molar ratios of reactants (3 and 4) to paraformaldehyde on the yield. Solvents strongly influenced on the reaction; in hydrocarbons and ethers the reaction did not proceed but did slightly in alcohols with less than 10% yields, and polar solvents such as dimethylsulfoxide and dimethylformamide were found to give much better results. The reaction sufficiently

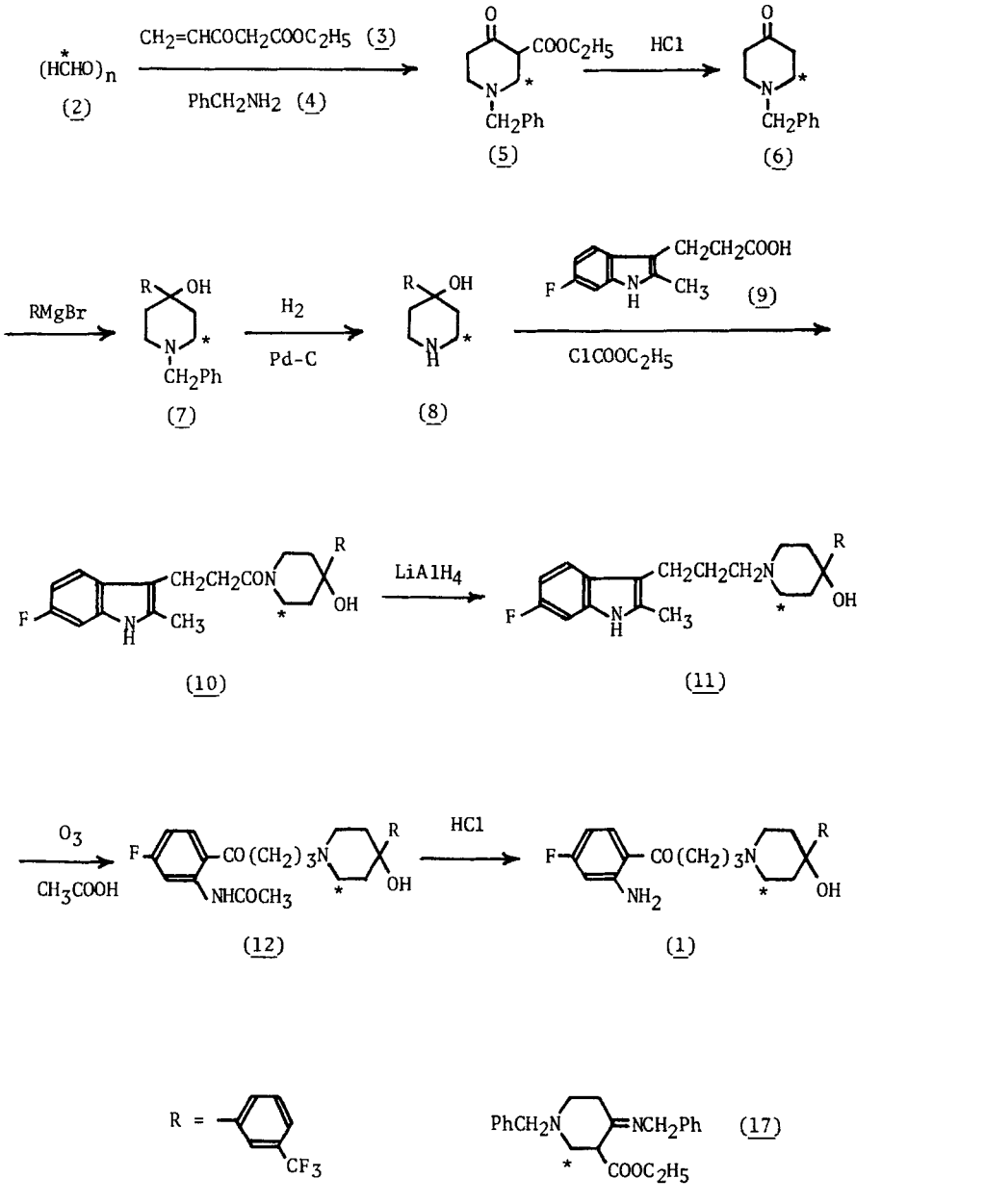

Fig. 1. Scheme for the synthesis of 2'-amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino-2-^{14}C]butyrophenone (1)

proceeded at 25° but higher or lower temperatures served only to decrease the yield. The best reaction time was 16 hr and the increase of the time afforded no positive result. Yields of 6 markedly depended on the molar ratios of the reactants: the representative results are shown in Table 1. Use of larger equivalents of the reactants increased the yield of 6, which reached 70% when four equivalents of ethyl acryloylacetate and benzylamine were used. The increase of the reactants, however, led to the formation of a by-product (16) in unfavorable amounts. Although the by-product formation was considerably prevented by addition of a small amount of triethylamine, it was difficult to separate the desired product (6) from 16 effectively because of their similar mobilities on column chromatography. Attempts were, therefore, made to purify the products at an earlier stage, before hydrolysis, where 1-benzyl-3-carbethoxy-4-piperidone (5) might exist with a precursor of the by-product (16). When the crude crop obtained by the Mannich reaction was immedeately chromatographed on a silica gel column with hexane-ethyl acetate (9/1 v/v), the carbethoxypiperidone (5) and two by-products (14 and 17) were effectively isolated. Treatment of 5 with 20% hydrochloric acid at 95° gave the piperidone (6) in an excellent yield.

Table 1 Effect of molar ratios of ethyl acryloylacetate (3) and benzylamine (4) to paraformaldehyde on a yield of 1-benzyl-4-piperidone (6) in a Mannich reaction

Run No.*	Molar ratio $(HCHO)_n$: 3 : 4	Addition of $(C_2H_5)_3N$	Yield (%) 6	Yield (%) 16
1	1 : 1 : 1	-	18	0
2	1 : 2 : 2	-	23	6
3	1 : 2 : 2	+	28	1
4	1 : 3 : 3	+	45	5
5	1 : 4 : 4	+	70	12

* In all runs the Mannich reaction was carried out in dimethylsulfoxide at 25° for 16 hr, and the products were hydrolyzed and decarboxylated with 20% hydrochloric acid.

The fact that hydrolysis of the by-product (14) under the same condition gave 16 indicates that 14 was the precursor of 16 which was formed *via* an intermediate (13) by the process shown in Figure 2. Another by-product (17), a Schiff-base of 5, was also found to be hydrolyzed and decarboxylated by hydrochloric acid to give the desired product (6).

Based on these results, we chose the following method for the radioactive preparation of 1-benzyl-4-piperidone-2-^{14}C (6). Paraformaldehyde-^{14}C was allowed to react with four equivalents of ethyl acryloylacetate and benzylamine in dimethylsulfoxide, in the presence of triethylamine, at 25° for 16 hr. Chromatography of the crude products on silica gel with hexane-ethyl acetate gave 1-benzyl-3-carbethoxy-4-piperidone-2-^{14}C (5) and the Schiff-base (17) in the radiochemical yields of 46 and 28%, respectively. Both products were combined and treated with 20% hydrochloric acid at 95° to give 1-benzyl-4-piperidone-2-^{14}C (6) in 89% yield. The product thus obtained was radiochemically and chemically pure enough to be used for the following reaction.

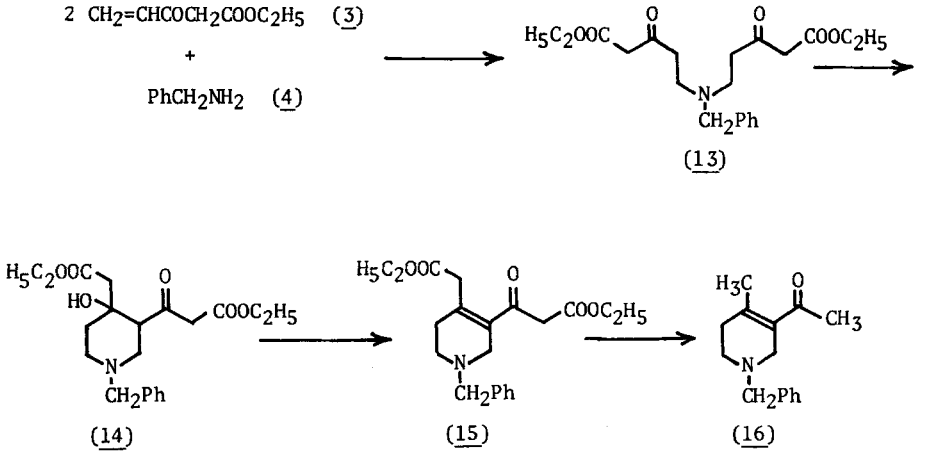

Fig. 2. A proposed process for the formation of by-products in the Mannich reaction

Ziering *et al.* reported that reaction of arylmagnesium halides or aryllithiums with 1-alkyl-4-piperidones yielded the corresponding 4-aryl-4-hydroxypiperidines[5]. We selected the Grignard reaction for the preparation of 1-benzyl-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (7). Thus, reaction of 6 with 3-trifluoromethylphenylmagnesium bromide in ether below -5° gave the desired product (7) in 75% yield. Elimination of the benzyl group of 7 was achieved by catalytic hydrogenolysis. Hydrogenolysis of 7 with 10% palladium on charcoal under the atmospheric hydrogen pressure gave a poor yield of 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (8). However, it was found that the rate of the hydrogenolysis was markedly increased by increasing the hydrogen pressure. In fact, when the pressure was arranged at 5 kg/cm^2, the piperidine-^{14}C (8) could be obtained in 94% yield.

Conversion of 8 to ID-4708-(piperidine-^{14}C (1) was carried out according to Yamamoto's method[1], with some modifications suitable for the radioactive preparation. The piperidine-^{14}C (8) was condensed with a slightly excess of the mixed anhydride which was prepared by reaction of 3-(6-fluoro-2-methyl-3-indolyl)-propionic acid (9) with ethyl chloroformate; giving the 3-indolylpropionylpiperidine-^{14}C (10) in 82% yield. Reduction of 10 with lithium aluminum hydride in refluxing ether-tetrahydrofuran gave the 3-indolylpropylpiperidine-^{14}C (11) in 70% yield after purification. Oxidative ring-opening of 11 in acetic acid with ozone afforded a crude product of the piperidinobutyrophenone-^{14}C (12). The product was contaminated with radioactive by-products (about 20%) but was used for the next reaction without any purification. Hydrolysis of 12 in ethanol with hydrochloric acid gave a crude product which was immediately subjected to a column chromatography on silica gel and then recrystallization; giving ID-4708-(piperidine-^{14}C) (1) in 48% yield from 12. The overall yield of 1 was 9.6% from paraformaldehyde-^{14}C, and the final product was completely identical with the unlabelled authentic sample.

EXPERIMENTAL

1-Benzyl-3-carbethoxy-4-piperidone-2-^{14}C (5) and 1-Benzyl-4-benzylimino-3-carbethoxypiperidine-2-^{14}C (17) -- A mixture of paraformaldehyde-^{14}C (26.0 mCi, 85 mg, 2.83 mmol, The Radiochemical Centre, Amersham), ethyl acryloylacetate (804 mg, 5.66 mmol), benzylamine (606 mg, 5.66 mmol), triethylamine (280 mg, 2.8 mmol) and powdered molecular sieves (450 mg) in anhydrous dimethylsulfoxide (12 ml) was vigorously stirred under nitrogen at 25° for 2 hr. After adding the same amounts of ethyl acryloylacetate and benzylamine, the mixture was stirred continuously at 25° for 14 hr. The mixture was filtered to remove the molecular sieves, diluted with 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, which was chromatographed on silica gel. The first fraction eluted with hexane-ethyl acetate (19/1 v/v) was evaporated to give 1-benzyl-3-carbethoxy-4-piperidone-2-^{14}C (5)(11.9 mCi, 339 mg, 46.0%); IR νmax (cm^{-1}, liquid film): 1720 and 1730 (CO); NMR (δ, $CDCl_3$): 1.20 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 2.10-3.00 (6H, m, methylene H),3.13 (1H, broad s, methine H), 3.56 (2H, s, benzyl H), 4.13 (2H, q, J=7 Hz, $-\underline{CH_2}CH_3$) and 7.25 (5H, broad s, aromatic H). The second eluate with hexane-ethyl acetate (9/1 v/v) afforded 1-benzyl-4-benzylimino-3-carbethoxypiperidine-2-^{14}C (17)(7.20 mCi, 274 mg, 27.7%); IR νmax (cm^{-1}, liquid film): 1650 (CO); NMR (δ, $CDCl_3$): 1.25 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 2.45-3.30 (6H, m, methylene H), 3.62 (2H, s, benzyl H), 4.10 (2H, q, J=7 Hz, $-\underline{CH_2}CH_3$), 4.30 (2H, d, J=7 Hz, benzyl H), 7.30 (10H, broad s, aromatic H) and 9.20 (1H, d, J=7 Hz, NH); mass spectrum (m/e): 350 (M^+), 259, 243, 242, 107, and 91 (base peak). The third eluate with hexane-ethyl acetate (3/2 v/v) gave the non-radioactive by-product (14)(250 mg).

1-Benzyl-4-piperidone-2-^{14}C (6) -- A mixture of 1-benzyl-3-carbethoxy-4-piperidone-2-^{14}C (11.9 mCi, 339 mg, 1.30 mmol), 1-benzyl-4-benzylimino-3-carbethoxypiperidine-2-^{14}C (7.20 mCi, 274 mg, 0.78 mmol) and 20% hydrochloric acid (12 ml) was refluxed for 1 hr. After cooling, the mixture was diluted with water and washed with ether. The aqueous solution was basified with 30% sodium hydroxide

solution and extracted with ether. The extract was washed with water, dried, and evaporated, giving a pale-yellow oil. Chromatography of the oil on silica gel with hexane-ethyl acetate (4/1 v/v) gave 1-benzyl-4-piperidone-2-^{14}C (6) (16.9 mCi, 349 mg, 88.5%); purity 99% on radio-TLC (silica gel, hexane/ethyl acetate=3/2 v/v, R_f-value=0.35); IR νmax (cm^{-1}, liquid film): 1710 (CO); NMR (δ, $CDCl_3$): 2.32-2.97 (8H, m, methylene H), 3.69 (2H, s, benzyl H) and 7.38 (5H, s, aromatic H); mass spectrum (m/e): 189 (M^+), 112, 98, and 91 (base peak).

1-Benzyl-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (7) -- A solution of 3-trifluoromethylbromobenzene (828 mg, 3.68 mmol) in anhydrous ether (1.5 ml) was added dropwise to a mixture of magnesium turnings (90 mg, 3.70 mmol) in anhydrous ether (3 ml) at such a rate that the solvent refluxed gently. When the addition was complete, the mixture was heated at gentle reflux for 1 hr. After cooling, to the mixture was added dropwise at -10- -5° a solution of 1-benzyl-4-piperidone-2-^{14}C (16.9 mCi, 349 mg, 1.84 mmol) and unlabelled 1-benzyl-4-piperidone (230 mg, 1.22 mmol) in anhydrous ether (1.5 ml). The mixture was stirred at the same temperature for 2 hr and then at room temperature for 1 hr. The excess of the Grignard reagent was decomposed by an addition of 10% ammonium chloride solution, and the mixture extracted with ethyl acetate. The extract was washed with water, dried and evaporated. Chromatography of the residue on silica gel with hexane-ethyl acetate (1/1 v/v) gave 1-benzyl-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (7)(12.6 mCi, 770 mg, 5.53 mCi/mmol, 74.5%) as colorless prisms; mp and mixed mp 92-93°; purity 99% on radio-TLC (silica gel, ethyl acetate, R_f-value=0.25); identical in every respect with the unlabelled authentic sample[1].

4-Hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (8) -- A mixture of 1-benzyl-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (12.6 mCi, 770 mg, 2.28 mmol) and 10% palladium on charcoal (200 mg) in ethanol was shaken, at room temperature, with hydrogen at the pressure of 5 kg/cm^2 until hydrogen uptake was ceased. The catalyst was removed by filtration, and the filtrate evaporated under reduced pressure to give 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-

^{14}C (8)(11.9 mCi, 534 mg, 94.4%) as colorless needles; purity 98% on radio-TLC (silica gel, ethanol/water/28% NH_4OH=12/5/1, R_f-value=0.21); mp and mixed mp 64-67°. The product was used for the next reaction without any purification.

1-[3-(6-Fluoro-2-methyl-3-indolyl)propionyl]-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (10) -- To a mixture of 3-(6-fluoro-2-methyl-3-indolyl)-propionic acid (575 mg, 2.60 mmol) and triethylamine (121 mg, 2.60 mmol) in anhydrous tetrahydrofuran (5 ml) was added dropwise a solution of ethyl chloroformate (140 mg, 1.30 mmol) in tetrahydrofuran (1.5 ml) at 0-5°, and the mixture stirred at the same temperature for 20 min. To the mixture was added dropwise a solution of 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (11.9 mCi, 534 mg, 2.17 mmol) in anhydrous tetrahydrofuran (6 ml) at -5-0°. The mixture was warmed with stirring over a period of 30 min to room temperature and stirred for 2 hr. The solvent was removed under reduced pressure, and the residue taken up in ethyl acetate. The solution was washed successively with 5% hydrochloric acid, 5% sodium hydroxide solution and water, dried over sodium sulfate, and evaporated. The crystalline residue was recrystallized from isopropanol to afford 1-[3-(6-fluoro-2-methyl-3-indolyl)propionyl]-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (10)(9.76 mCi, 745 mg, 82.0%) as yellow prisms; mp and mixed mp 148-150°; purity 99% on radio-TLC (silica gel, chloroform/methanol/triethylamine=40/14/1 v/v/v, R_f-value=0.41); IR νmax (cm^{-1}, nujol): 1625 (CON); identical in every respect with the unlabelled authentic sample[1].

1-[3-(6-Fluoro-2-methyl-3-indolyl)propyl]-4-hydroxy-4-(3-trifluoromethylphenyl)-piperidine-2-^{14}C (11) -- To a suspension of lithium aluminum hydride (205 mg, 5.40 mmol) in anhydrous tetrahydrofuran (3 ml) was added dropwise with stirring a solution of 1-[3-(6-fluoro-2-methyl-3-indolyl)propionyl]-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (9.76 mCi, 745 mg, 1.78 mmol) in anhydrous tetrahydrofuran (6 ml) at room temperature, and the mixture heated at reflux for 3 hr. After cooling, the excess of the reagent was decomposed with ice-water, and the mixture filtered. The filtrate was concentrated under reduced pressure,

and the residue taken up in ethyl acetate. The solution was dried over sodium sulfate and evaporated. Chromatography of the residue on silica gel with ethyl acetate gave 1-[3-(6-fluoro-2-methyl-3-indolyl)propyl]-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (11)(6.80 mCi, 542 mg, 69.7%) as colorless prisms; mp and mixed mp 139-141°; purity 99% on radio-TLC (silica gel, chloroform/methanol =2/1 v/v, R_f-value=0.48); identical in every respect with the unlabelled authentic sample[1].

2'-Acetamido-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino-2-^{14}C]-butyrophenone (12) -- To a solution of 1-[3-(6-fluoro-2-methyl-3-indolyl)propyl]-4-hydroxy-4-(3-trifluoromethylphenyl)piperidine-2-^{14}C (6.80 mCi, 542 mg, 1.24 mmol) in glacial acetic acid (6 ml) was introduced 2% ozonized oxygen through a bubbling tube at room temperature for 30 min. At the end of the reaction, the color of the reaction mixture changed to dark-red. The mixture was diluted with water (20 ml), basified with 10% sodium hydroxide solution, and extracted with ether. The extract was washed with water, dried, and evaporated to yield a crude product, 2'-acetamide-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino-2-^{14}C]butyrophenone (12)(5.33 mCi, purity 82%). The product was used for the next reaction without any purification.

2'-Amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino-2-^{14}C]-butyrophenone (1) -- A mixture of 2'-acetamido-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino-2-^{14}C]butyrophenone (5.33 mCi) and concentrated hydrochloric acid in ethanol (15 ml) was refluxed for 2 hr. After cooling, the mixture was concentrated under reduced pressure, diluted with water, basified with 10% sodium hydroxide solution, and extracted with ether. The extract was washed with water, dried, and evaporated to leave an oily residue (4.31 mCi). The residue was chromatographed on silica gel and eluted with chloroform-methanol (97/3 v/v). Removal of the solvent of the main fraction gave a crystalline product, which was recrystallized from benzene-hexane to give 2'-amino-4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino-2-^{14}C]butyrophenone (1)(2.56

mCi, 196 mg, 5.53 mCi/mmol, 48.0%) as colorless prisms; mp and mixed mp 105-107°; IR νmax (cm^{-1}, nujol): 1655 (CO); identical in every respect with the unlabelled authentic sample[1].

Preparation of By-products (14 and 16) -- A mixture of ethyl acryloylacetate (2.84 g, 20 mmol), benzylamine (0.54 g, 5 mmol) and molecular sieves (0.5 g) in anhydrous dimethylsulfoxide (10 ml) was stirred at 25° for 16 hr. The mixture was filtered to remove the molecular sieves. The filtrate was diluted with water and extracted with ether. The extract was dried and evaporated to give an oily residue, which was chromatographed on silica gel and eluted with hexane-ethyl acetate (3/2 v/v). Removal of the solvent of the main fraction gave the by-product (14)(0.41 g) as a colorless oil (Found: C, 64.22; H, 7.34. $C_{21}H_{29}O_6N$ requires C, 64.43; H, 7.47%); IR νmax (cm^{-1}, liquid film): 1740 and 1720 (CO); NMR (δ, $CDCl_3$): 1.30 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 1.33 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 1.70-2.90 (11H, m, methylene and methine H), 3.52 (2H, s, benzyl H), 3.88-4.20 (4H, q, J=7 Hz, $-\underline{CH_2}CH_3$), 7.34 (5H, broad s, aromatic H); mass spectrum (m/e): 391 (M^+), 373, 345, 281, 258 and 91. A mixture of the by-product (14)(0.40 g) in 20% hydrochloric acid (5 ml) was refluxed for 1 hr. After cooling, the mixture was diluted with water and then washed with ether. The aqueous solution was basified with 30% sodium hydroxide solution and extracted with ether. The extract was washed with water, dried and evaporated to give an oily residue. Chromatography of the residue on silica gel with hexane-ethyl acetate (4/1 v/v) gave the by-product (16)(0.14 g) as a colorless oil (Found: C, 78.93; H, 8.22. $C_{15}H_{19}ON$ requires C, 78.56; H, 8.35%); IR νmax (cm^{-1}, liquid film): 1720 (CO); NMR (δ, $CDCl_3$): 1.93 (3H, t, J=2 Hz, $-\underline{CH_3}$), 2.08 (3H, s, $-COCH_3$), 2.00-2.82 (4H, m, methylene H), 3.07 (2H, q, J=2 Hz, methylene H), 3.51 (2H, s, benzyl H) and 7.29 (5H, broad s, aromatic H); mass spectrum (m/e): 229 (M^+), 214, 186, 138, and 91 (base peak).

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