LABELLING OF NEUROLEPTIC BUTYROPHENONES. 1. SYNTHESES OF HALOPERIDOL-^{14}C AND TRIFLUPERIDOL-^{14}C

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SUMMARY

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone (haloperidol)(I) and 4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone (trifluperidol)(II), neuroleptic drugs, were labelled at the carbonyl position with carbon-14 for the use of metabolic studies. The syntheses were achieved according to the reaction scheme shown in Fig. 1. Cyclopropionic-1-^{14}C acid (IV) was prepared from cyclopropyl bromide (III) by Grignard reaction with carbon-^{14}C dioxide. Condensation of IV with fluorobenzene, followed by ring-opening with hydrogen chloride, gave 4-chloro-4'-fluorobutyrophenone-1-^{14}C (VI). After ketalization of VI, the ketal (VII) was condensed with corresponding piperidine derivatives (VIIIa and VIIIb) and subsequently hydrolized with hydrochloric acid to give haloperidol-1-^{14}C (I) and trifluperidol-1-^{14}C (II), respectively. The overall radiochemical yields of I and II from barium carbonate-^{14}C were 31 and 27%, respectively.

Key Words: Carbon-14, Butyrophenone Derivatives, Neuroleptics

INTRODUCTION

The typical butyrophenone derivatives, 4-[4-(4-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone (haloperidol)(I) and 4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone (trifluperidol)(II), which possess high neuroleptic activities[1,2], are widely used in therapy as a major tranquilizer. In the course of our metabolic studies on butyrophenone deriva-

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tives, it was required to synthesize radioactive haloperidol and trifluperidol.

Janssen *et al.* reported the metabolic studies of these compounds, in which they employed the compounds labelled with tritium at the fluorophenyl ring[3-6]. However, no report concerning the synthesis of these drugs labelled with carbon-14 has appeared so far.

We now wish to report the syntheses of haloperidol-^{14}C (I) and trifluperidol-^{14}C (II) labelled at the carbonyl position.

DISCUSSION

The general method so far utilized for the synthesis of unlabelled butyrophenone derivatives comprises Friedel-Crafts reaction of 4-chlorobutyryl chloride with fluorobenzene to yield the key intermediate, 4-chloro-4'-fluorobutyrophenone (VI)[7]. In order to apply this method for the radiosynthesis, we tried preliminary experiments with 4-chlorobutyryl-1-^{14}C chloride[8] at tracer level but found that the desired butyrophenone-^{14}C (VI) was obtained only in 20% yield at the highest. The unsatisfactory results forced us to search for an alternate route.

A novel synthetic route devised are shown in Fig. 1. The feature of this route is the use of cyclopropionic acid as a C_4-unit instead of 4-chlorobutyric acid in the Friedel-Crafts reaction and subsequent conversion of the resulting cyclopropyl 4-fluorophenyl ketone to 4-chloro-4'-fluorobutyrophenone by nucleophilic addition of hydrogen chloride.

The unlabelled starting material, cyclopropyl bromide (III), was prepared in 60% yield from cyclopropionic acid by modifying Hunsdiecker reaction[9]. Carbonation of the Grignard reagent prepared from III with carbon-^{14}C dioxide gave cyclopropionic-1-^{14}C acid (IV) in 81% yield. Van Gelder *et al.* [10] reported the preparation of cyclopropyl monohalogenophenyl ketone by Friedel-Crafts reaction of cyclopropionyl chloride with monohalogenobenzene, but in their report no detail on experimental procedure was described. Therefore, we investigated this reaction under various conditions, and it was found that cyclopropionyl-1-^{14}C chloride when allowed to react at 5° with excess of

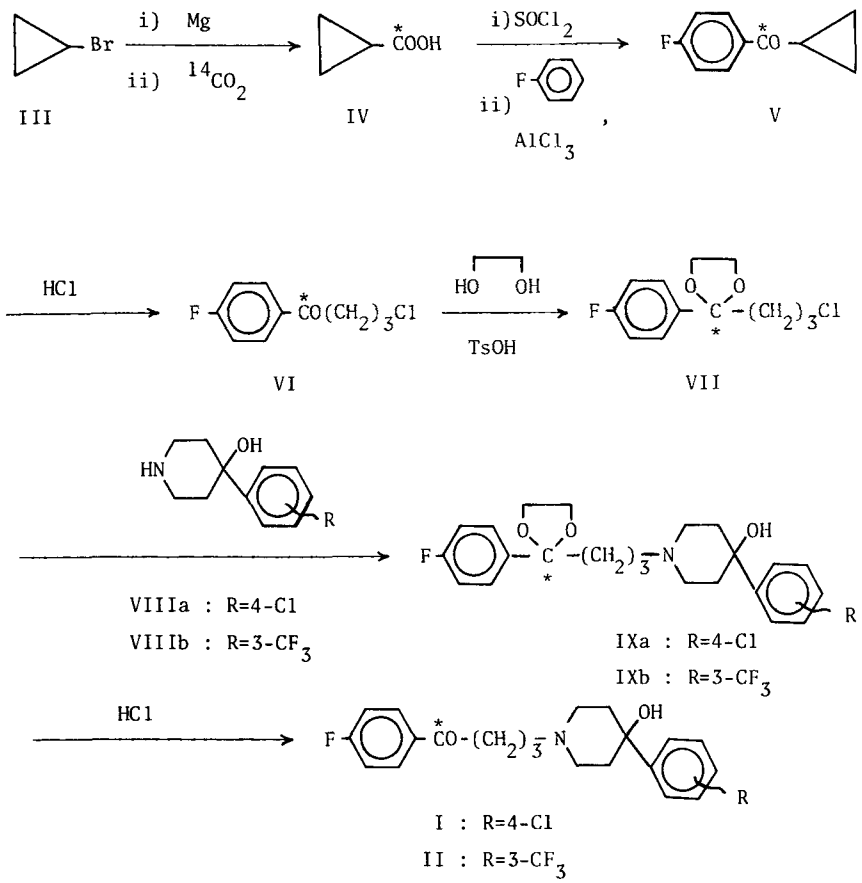

Fig. 1. Scheme for the syntheses of haloperidol-1-^{14}C and trifluperidol-1-^{14}C

fluorobenzene in the presence of aluminum chloride gave cyclopropyl 4-fluorophenyl ketone-(carbonyl-^{14}C)(V) in the most favorable yield (76%). Ring-opening of V with 50% hydrogen chloride-methanol solution containing a small amount of water at room temperature afforded 4-chloro-4'-fluorobutyrophenone-1-^{14}C (VI) in 85% yield. In this reaction the small amount of water seemed to be especially needed, since similar experiments without water led to the increase of unfavorable products. Reaction of VI with ethyleneglycol using *p*-toluenesulfonic acid as a catalyst gave 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane-1-^{14}C (VII) in nearly quantitative yield. Condensation of VII with 4-(4-chlorophenyl)-4-hydroxypiperidine (VIIIa), followed by hydrolysis of the ketal group with

hydrochloric acid, gave haloperidol-1-^{14}C (I). Trifluperidol-1-^{14}C (II) was also prepared by the similar procedure using 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine (VIIIb). Purification of the crude products by chromatography on silica gel afforded I and II in 31 and 27% yield from barium carbonate-^{14}C, respectively. The final products were identical in every respect with the unlabelled authentic samples.

EXPERIMENTAL

The purities of the volatile products were evaluated by radio-gaschromatography which was carried out on a Yanako G-80 chromatograph fitted with a thermal conductivity detector. A glass column (1 m, 3 mm I.D.) packed with 3% DC-550 on Chromosorb W (60-80 mesh) was used. Operating conditions: column temperature 130°, carrier gas helium (28 ml/min). The retention times of the authentic materials were: cyclopropionic acid (2.5 min), cyclopropyl 4-fluorophenyl ketone (2.7 min), 4-chloro-4'-fluorobutyrophenone (8.0 min).

Cyclopropyl Bromide (III) -- To a mixture of cyclopropionic acid (34.4 g, 0.40 mol) and red mercuric oxide (86.6 g, 0.40 mol) in 1,2-dibromoethane (200 ml) was added dropwise bromine (64 g, 0.80 mol) at room temperature and then the mixture heated at 90-100° for 1 hr. After cooling, the inorganic precipitate formed was removed by filtration and washed with ether. Atmospheric distillation of the combined filtrate and washings gave cyclopropyl bromide (29.4 g, 60%); bp 68-70°; NMR spectrum (δ, $CDCl_3$): 0.75-1.15 (4H, m, $-\underline{CH_2}-\underline{CH_2}-$) and 2.70-3.10 (1H, m, $>\underline{CH}Br$).

Cyclopropionic-1-^{14}C Acid (IV) -- A solution of cyclopropyl bromide (1.66 g, 13.8 mmol) in anhydrous ether (6 ml) was added dropwise to a suspension of magnesium turnings (355 mg, 13.8 mmol) in anhydrous ether (10 ml) within 30 min. During the addition, the reaction mixture was maintained at gentle reflux. After further refluxing for 30 min, the mixture was divided into two fractions and placed in two reaction flasks. The flasks were connected to a vaccum

manifold. After frozing with liquid nitrogen, to one of the frozen fraction was introduced carbon-^{14}C dioxide which was liberated from barium carbonate-^{14}C (93 mCi, 1.24 g, 6.30 mmol). The mixture was then warmed to -20° and stirred for 1.5 hr; during the reaction the temperature being kept below -15°. When the reaction rate turned slow, the remaining carbon-^{14}C dioxide was conducted into the other fraction and the mixture allowed to react under the similar condition as above. Both reaction mixtures were combined, hydrolyzed with 5% hydrochloric acid and extracted with ether. The ethereal solution was extracted with 5% sodium carbonate solution. The alkaline layer was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed with water, dried over sodium sulfate and evaporated under reduced pressure to afford cyclopropionic-1-^{14}C acid (75.2 mCi, 440 mg, 14.7 mCi/mmol, yield 81%) as a colorless oil; IR spectrum (liquid film): 1690 cm^{-1}(C=O).

Cyclopropyl 4-Fluorophenyl Ketone-(carbonyl-^{14}C)(V) -- A mixture of cyclopropionyl-1-^{14}C acid (75.2 mCi, 5.1 mmol) and thionyl chloride (667 mg, 5.6 mmol) was heated at 70-75° for 1.5 hr. After cooling, to the reaction mixture were added fluorobenzene (980 mg, 10.2 mmol) and anhydrous aluminum chloride (1.36 g, 10.2 mmol). The mixture was stirred at 0-5° for 40 hr. The reaction mixture was poured into ice-water and extracted with ether. The ethereal extract was washed with 5% sodium carbonate solution and water successively, dried, and evaporated under reduced pressure to give cyclopropyl 4-fluorophenyl ketone-(carbonyl-^{14}C)(57.1 mCi, 640 mg, 14.6 mCi/mmol, yield 76%); IR spectrum (liquid film): 1673 (C=O) and 1610 (phenyl) cm^{-1}; NMR spectrum (δ, $CDCl_3$): 0.91-1.34 (4H, m, $-CH_2-CH_2-$), 2.40-2.80 (1H, m, $>CH-$), 7.00-7.37 (2H, m, aromatic H), 7.55-8.20 (2H, m, aromatic H).

4-Chloro-4'-fluorobutyrophenone-1-^{14}C (VI) -- A mixture of cyclopropyl 4-fluorophenyl ketone-(carbonyl-^{14}C)(57.1 mCi, 640 mg), 50% hydrogen chloride-methanol solution (4.8 ml) and water (0.5 ml) was stirred at room temperature for 3.5 hr. The mixture was taken up in benzene and the solution washed with 5% sodium

carbonate solution and water successively. Evaporation of the solvent under reduced pressure gave an oily residue. Chromatography of the residue on silica gel with ethyl acetate-hexane (1:9 v/v) afforded 4-chloro-4'-fluorobutyrophenone-1-^{14}C (48.5 mCi, 664 mg, 14.6 mCi/mmol, yield 85%) as a colorless oil; IR spectrum (liquid film): 1685 (C=O) and 1600 (phenyl) cm^{-1}; NMR spectrum (δ, $CDCl_3$): 2.00-2.24 (2H, m, $-CH_2\underline{CH_2}CH_2-$), 3.09-3.32 (2H, t, $-COCH_2-$), 3.60-3.80 (2H, t, $-CH_2Cl$), 7.17 (2H, t, aromatic H), 8.00 (2H, m, aromatic H).

4-Chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane-1-^{14}C (VII) -- A mixture of 4-chloro-4'-fluorobutyrophenone-1-^{14}C (48.5 mCi, 664 mg, 3.3 mmol), ethyleneglycol (409 mg, 6.6 mmol), *p*-toluenesulfonic acid (50 mg) and anhydrous benzene (40 ml) was refluxed for 3 hr; water produced being azeotropically removed. The mixture was washed with 5% sodium carbonate solution and then water. After drying, evaporation of the solvent gave 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane-1-^{14}C (47.5 mCi, 802 mg, 89%). The product was used for the following reaction without further purification.

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1,1-ethylenedioxy-1-(4-fluorophenyl)-butane-1-^{14}C (IXa) -- A mixture of 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)-butane-1-^{14}C (26.1 mCi, 440 mg, 1.78 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (376 mg, 1.78 mmol), potassium carbonate (280 mg), potassium iodide (20 mg) and anhydrous dimethyl formamide (5 ml) was heated with vigorous stirring at 90-100° for 4.5 hr. The mixture was then diluted with water and extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid and water, dried, and evaporated to give 4-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1,1-ethylenedioxy-1-(4-fluorophenyl)butane-1-^{14}C (23.5 mCi, 720 mg, yield 90%, purity 90%), which was used for the next reaction without any purification.

1,1-Ethylenedioxy-1-(4-fluorophenyl)-4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]butane-1-^{14}C (IXb) -- Under the same reaction condition as described above, 4-chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane-1-^{14}C (21.4 mCi, 1.46 mmol) was allowed to react with 4-hydroxy-4-(3-trifluoromethylphenyl)piperidine

(358 mg, 1.46 mmol) to give 1,1-ethylenedioxy-1-(4-fluorophenyl)-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butane-1-^{14}C (18.8 mCi, 620 mg, yield 88%, purity 92%).

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone-(carbonyl-^{14}C) (haloperidol-1-^{14}C)(I) -- A mixture of 4-[4-(4-chlorophenyl)-4-hydroxypiperidino]-1,1-ethylenedioxy-1-(4-fluorophenyl)butane-1-^{14}C (23.5 mCi, 1.6 mmol), concentrated hydrochloric acid (1.4 ml) and methanol (8.5 ml) was refluxed for 1.5 hr. After cooling, the mixture was dissolved in ethyl acetate. The solution was washed with 5% aqueous ammonia and water, dried, and evaporated to afford a crystalline residue (22.3 mCi, 550 mg). The residue was subjected to column chromatography on silica gel and eluted with chloroform-methanol (95:5 v/v). Evaporation of the main fraction gave a crystalline residue, which was recrystallized from ethyl acetate to afford 4-[4-(4-chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone-(carbonyl-^{14}C)(15.8 mCi, 409 mg, 14.5 mCi/mmol, 67.2%) as colorless prisms; mp and mixed mp 152-153°. The product was identical in every respect with the unlabelled authentic sample.

4'-Fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)piperidino]butyrophenone-(carbonyl-^{14}C)(trifluperidol-1-^{14}C)(II) -- Hydrolysis of IXb (18.8 mCi, 1.28 mmol), followed by purification, was carried out by the similar procedure as described above to give 4'-fluoro-4-[4-hydroxy-4-(3-trifluoromethylphenyl)-piperidino]butyrophenone-(carbonyl-^{14}C)(11.4 mCi, 319 mg, 14.6 mCi/mmol, 61.1%) as colorless needles; mp and mixed mp 97-99°; identical in all respects with the unlabelled authentic sample.

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REFERENS

1. Janssen P. A. J. - Neuropsychopharmacology 3: 331 (1964).
2. Janssen P. A. J., Niemegeers C. J. E. and Schellekens K. H. L. - Arzneimittel Forschung 15: 104 (1965).
3. Soudijn W. and Van Wijngaarden I. - J. Labelled Compounds 4: 159 (1968).
4. Janssen P. A. J. and Allevijn F. T. N. - Arzneimittel Forschung 19: 199 (1968).
5. Lewi P. J., Heykants J. J. P. and Janssen P. A. J. - Arzneimittel Forschung 20: 1701 (1970).
6. Heykants J., Pardoel L. and Janssen P. A. J. - Arzneimittel Forschung 21: 982 (1971).
7. Janssen P. A. J., Van de Westeringh C., Jageneau A. H. M., Demoen P. J. A., Hermans B. K. F., Van Demoen P. J. A., Schellekens K. H. L., Van der Eycken C. A. M. and Niemegeers C. J. E. - J. Med. and Pharm. Chem. 1: 281 (1959).
8. Yoshitake A., Nakatsuka I., Kamada T. and Kawahara K. - Research Report, unpublished.
9. Cristol S. J. and Firth W. C. - J. Org. Chem. 26: 280 (1961).
10. Van Gelder J. L. H., Josephus L. H., Raeynaekers A. H. M. and Roevens L. F. C. - German Patent 2029637 (1971).