SYNTHESIS OF ^{14}C-LABELLED 2-(3-BENZOYLPHENOXY)-2-METHYL PROPIONIC ACID (LF.599)

C.LUU DUC and Cl.CHARLON

Groupe d'Etude et de Recherche du Médicament (G.E.R.M.)
U.E.R. des Sciences Pharmaceutiques et Biologiques de Grenoble,
Domaine de la Merci, F-38700 La Tronche, France.

J.P.BOURGOGNE and R.SORNAY
Laboratoires Fournier, B.P. 130, 21004 Dijon Cédex, France.

SUMMARY

The title product was labelled with ^{14}C at the ketone group, from 3-methoxybromobenzene in six steps. Complete synthetic techniques of the labelled drug are presented.

Key Words: Benzophenone, Carbon-14, Analgesic.

INTRODUCTION

The importance of Procetofen (LF.178) as an antilipemic drug has been well established (1,2,3). The title product, a structural analogue of Procetofen, is the most effective agent in analgesic field. In order to investigate its metabolism, we were interested in a labelled sample of 2-(3-benzoylphenoxy)-2-methyl propionic acid 1. This synthesis is a derivative method of the labelling of Procetofen (4). Labelling of the carbon atom of the ketone function was chosen on the basis of ease of labelling and biostability.(Scheme 1).

EXPERIMENTAL

(with the technical contribution of Ch.Béney)

All solvents were used dried and distilled. Radioactivity was measured using the Intertechnique ABAC SL.40 liquid beta scintillation spectrometer. For proof of structure, NMR spectra were recorded using a Hitachi Perkin Elmer R-24 A 60 MHz spectrometer.

3-Methoxy[^{14}C]benzoic acid 2

The 3-methoxyphenylmagnesium bromide was obtained from 3.6 g of freshly distilled 3-bromoanisole and from 0.6 g of magnesium. Carbonation was performed with 90 mCi of barium carbonate (0.316 g of $Ba^{14}CO_3$ and 3.5 g of cold $BaCO_3$) according to Dauben et al. (5). After hydrolysis and extraction, 2.44 g of the labelled product were isolated (83 % yield).

0362-4803/81/040583-04$01.00

Received December 4, 1979
Revised January 21, 1980

3-Methoxy[^{14}C]benzoylchloride 3

A mixture containing 2.44 g of acid 2 in 20 ml of anhydrous toluene and 2.90 g of thionyl chloride were refluxed during 8 hours. After evaporation to dryness, 2.73 g of chloride 3 were obtained (100 % yield). This material was used in the subsequent reaction without further purification.

3'-Methoxy[^{14}C]benzophenone 4

To a stirred solution of 2.6 g of aluminium chloride in 20 ml of anhydrous benzene,maintained at 0-5°, 2.73 g of chloride 3 were added dropwise. The stirring is maintained during another day at room temperature. After hydrolysis with HCl 10 %, the crude ketone was extracted with ether (3 x 10 ml). The organic layer was dried over anhydrous sodium sulfate and then evaporated to give 2.24 g of ketone (66 % yield).

3'-Hydroxy[^{14}C]benzophenone 5

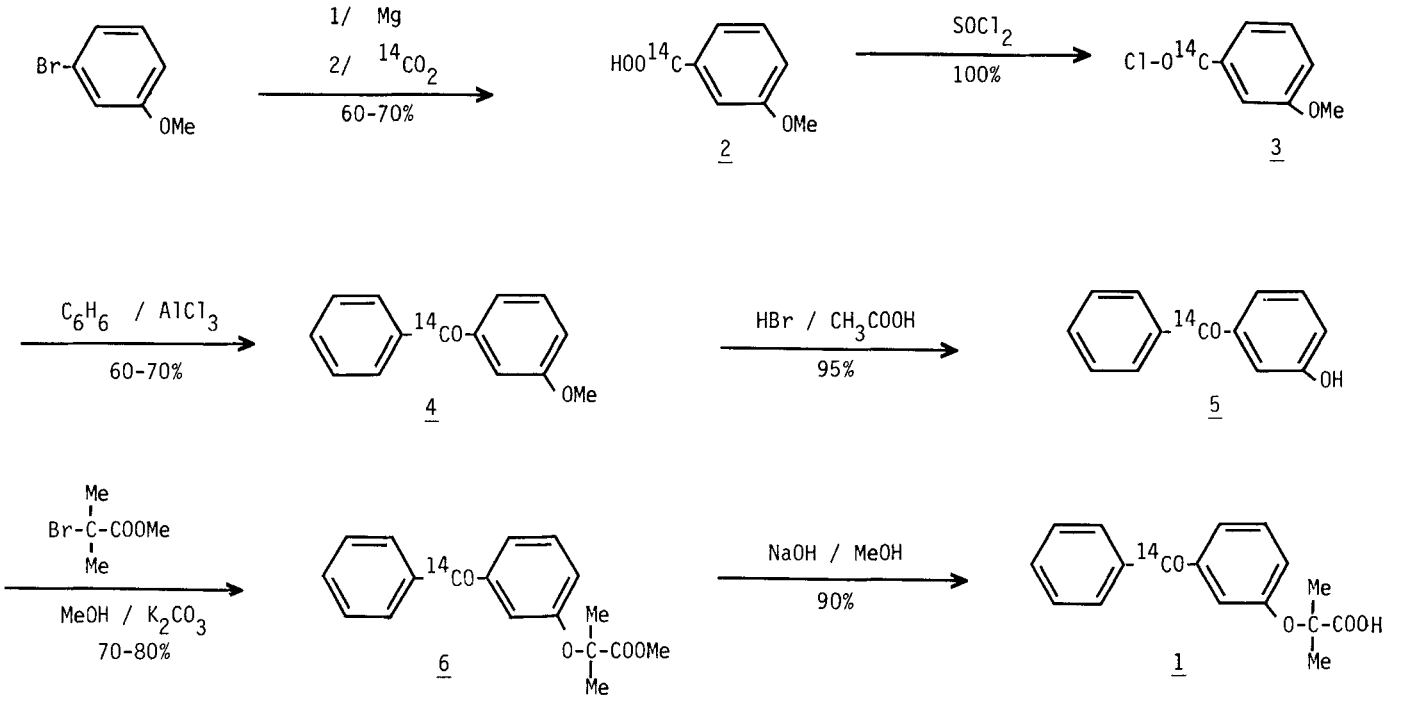
A mixture of the ketone 4 (2.24 g), 7.9 ml of glacial acetic acid and 1.5 ml of hydrobromic acid (48 %) were refluxed for 60 hours. The reaction product was poured into 40 ml of ice. Hydroxybenzophenone 5 was extracted with ether (3 x 8 ml). The organic layer was dried over anhydrous sodium sulfate, and distilled to give a dark residual solid which when treated with Norit in isopropyl ether gave 1.6 g of an orange coloured solid (76 % yield).

2-(3-[^{14}C]Benzoylphenoxy)-2-methyl propionate 6

In a 100 ml flask, the benzophenone 5 previously prepared (1.6 g) was added to 20 ml of methanol and 1.55 g of potassium carbonate. The mixture was heated under reflux for five days with 4.17 g of methyl 2-bromo-2-methylproprionate and 0.5 g of pyridine. After this time, 1 g of a mixture of the bromo-ester and pyridine was added and refluxed for a further two days. Methanol and water were then evaporated and ether (15 ml) was added to the residual product. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated to give 1.94 g of an oily liquid (80 % yield).

2-(3- [^{14}C]Benzoylphenoxy)-2-methylpropionic acid 1 (LF.599)

In a 50 ml flask, 1.94 g of ester 6, 5 ml of sodium hydroxyde (40 %) and 20 ml of methanol were refluxed for 3 hours. The solvent was then evaporated and 15 ml of water were added. The mixture was washed once with 5 ml of ether and then acidified with hydrochloric acid (pH = 2). The propionic acid was extracted with ether (2 x 5 ml), dried and the solvent removed in vacuo. The crude labelled acid was dissolved in 2 ml of absolute ethanol and then chromatographed on 20 TLC silicagel 60 PF_{254} plates. Eluant system used for the development of the preparative chromatography plates contained hexane (60), chloroform (15) and acetic acid (15).



Scheme 1: Synthetic Pathways

The pure acid was recrystallized in a mixture of petroleum ether and isopropyl ether, 0.28 g of labelled acid were obtained according to this procedure (5,2 % overall yield from barium[^{14}C]carbonate).

The radiochemical purity was determined by autoradiography of a thin layer chromatogram over silicagel (Merck F_{254}) in eluant mixture (hexane/chloroform/acetic acid) (60:15:15). The total radioactivity, measured by liquid beta scintillation was 5.07 mCi, corresponding to a specific radioactivity of 17.8 µCi/mg (5.06 mCi/mmol.). M.p. 90°C (uncorrected).

^{1}NMR (Acetone-d_6, TMS): δ = 1.62 (s, 6H, CH_3), 7.4 ppm (m, 9H, arom).

REFERENCES

1. Sornay R., Gurrieri J., Tourne C., Renson F.J., Majoie B. and Wulfert E., Arzneim.Forsch.,(Drug Research) 26: (5), 885 (1976).
2. Gurrieri J., Lelous M., Renson F.J., Tourne C. Voegelin H., Majoie B. and Wulfert E., ibid. 26: (5), 889 (1976)
3. Brodie R.R., Chasseaud L.F., Elsom F.F., Franklin E.R. and Taylor T., ibid. 26: (5) 896 (1976)
4. Luu Duc C., ibid. 26: (5) 894 (1976)
5. Dauben W.G.,Reid J.C., Yankwick P.E., Anal.Chem., 19: 828 (1947) in Organic Syntheses with Isotopes, Murray A. III and Williams D.L., Interscience Publisher, New York 1958.