NOTE

Synthesis of [2-^{14}C]Nimodipine

D.Scherling

Institute of Pharmacokinetics, Bayer AG,
Postfach 10 17 09, D-5600 Wuppertal, FRG

SUMMARY

[2-^{14}C]Nimodipine (8) was synthesized from isopropyl [3-^{14}C]acetoacetate (5), which was converted to isopropyl 3-amino[3-^{14}C]crotonate (6) by reaction with gaseous ammonia in toluene. The ^{14}C-labelled drug 8 was prepared by the cyclising Michael addition of the 3-aminocrotonate 6 onto 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate (7) in boiling ethanol.

Key words: Carbon-14, Dihydropyridine, Calcium antagonist

INTRODUCTION

Nimodipine - (±) 3-isopropyl 5-(2-methoxyethyl) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-pyridine-3,5-dicarboxylate - is a calcium antagonistic compound with a preferential effect on cerebral vessels (1, 2).

DISCUSSION

Reaction partners of the final cyclising Michael addition in the synthesis of nimodipine were isopropyl 3-aminocrotonate and 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate. Both were readily accessible starting from the corresponding aceto-acetates by enamine formation with ammonia and Knoevenagel condensation with 3-nitrobenzaldehyde, resp.

The labelled ß-ketoester 5 was converted to isopropyl 3-amino [3-^{14}C]crotonate (6) with gaseous ammonia in toluene (cf.

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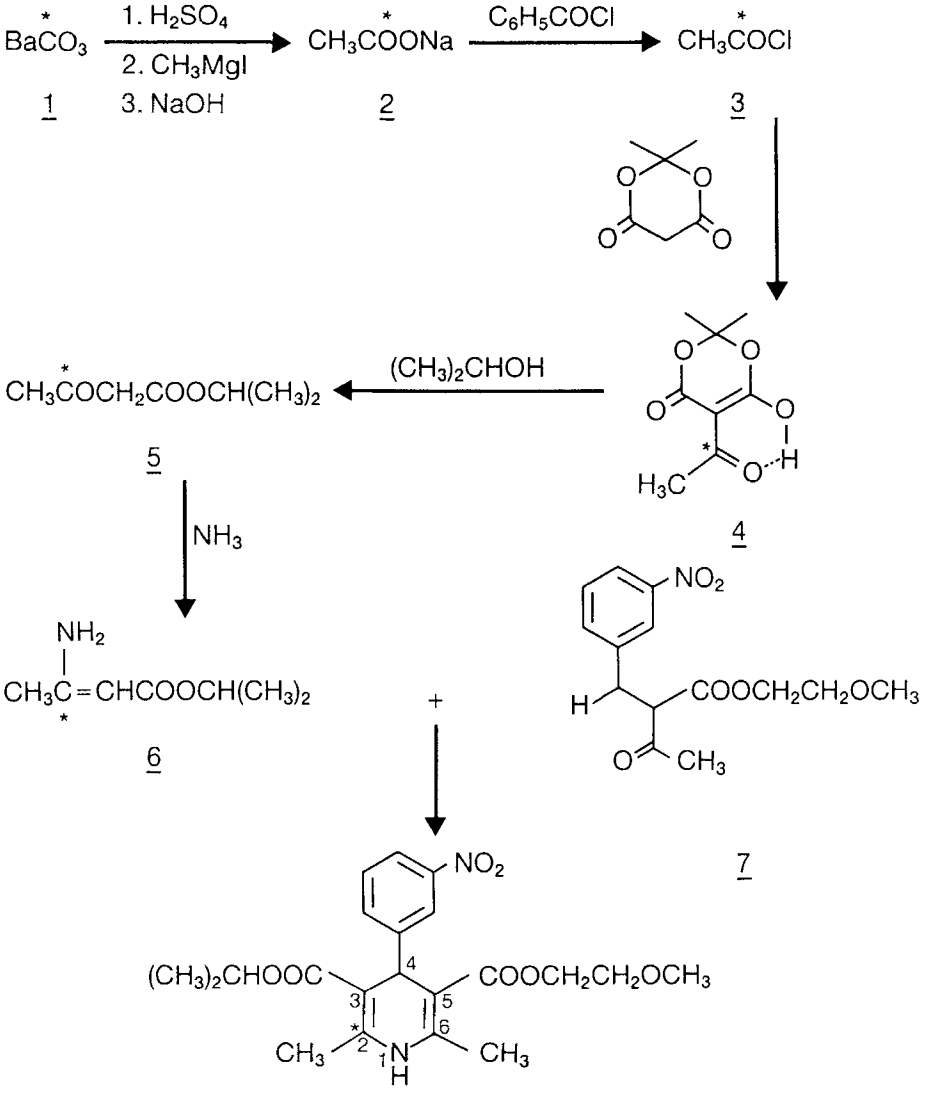
Scheme 1: Synthesis of [2–^{14}C]nimodipine



[2–^{14}C]nimodipine (8) * indicates 14C-label

scheme 1). The reaction with 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate (7) yielded nimodipine (8) labelled at the 2-position with a specific activity of 1.92 MBq/mg (51.85 µCi/mg). The radiochemical purity exceeded 98.5 % (TLC).

EXPERIMENTAL PART

All reagents used were of analytical grade and supplied by E.Merck (Darmstadt, FRG) unless otherwise stated.

Gas liquid chromatography was performed on the HP 5750 A gas chromatograph (Hewlett-Packard, Waldbronn, FRG) with flame-ionization detection (FID operated at 300 °C) using helium as carrier gas (30 ml/min), hydrogen (30 ml/min) and air (300 ml/min), resp., as combustion gases. Chromosorb(R) W-AW-DMCS (45/60 mesh) coated with 5 % Carbowax(R) 20 M THP was used as stationary phase (column length: 3 m, i.d.: 3 mm, polarity of the liquid phase: 464, using pyridine as reference standard according to Rohrschneider (3)). The gas chromatograph was operated in a temperature programming mode (post injection time: 8 min, 100 °C -----> 180 °C with 10 °C/min.). The retention indices of 4, 5, and 6 (cf. scheme 1), resp., were measured using the n-alkanes as reference standards (4).

Radioactivity of liquid samples was measured by liquid scintillation spectrometry (LS-counters PW 4502 and 4700, resp., Philips) using the external standard channel ratio method at 10 °C and Quickszint(R) 294 (Zinsser, Frankfurt, FRG) as scintillation cocktail.

Purity checks by TLC were performed on precoated TLC-plates (silica gel 60, F 254, layer thickness 0.25 mm) using toluene-acetic acid-dist. water 5+5+1 (by volume, organic phase). Radioactive spots were detected by apposition autoradiography using Agfa Curix(R) RP 1 Cb X-ray film. Zones of silica gel corresponding to radioactive areas were scraped off, mixed with 10 ml Unisolve(R) I (Zinsser)/4 ml dist. water and counted by LS-technique. Alternatively the purity checks were established by the Berthold TLC-scanner II LB 2723 with dual ratemeter-integrator LB 242 K (Labor Prof. Berthold, Wildbad, FRG).

The preparation of sodium[1-^{14}C]acetate (2) and [1-^{14}C]acetyl chloride (3), resp., from barium[^{14}C]carbonate (1) has been described in (5).

Isopropyl [3-^{14}C]acetoacetate (5)

2.1 ml (24.7 mmol) pyridine were added to a cooled (2 °C) and stirred solution of 1.78 g (12.35 mmol) Meldrum´s acid in 10 ml dichloromethane. 880 µl (12.35 mmol) [1-^{14}C]acetyl chloride

(3) in 2 ml dichloromethane were introduced dropwise within 10 min. Stirring at 2 °C was continued for 30 min and at room temperature for additional 40 min.

The reaction mixture was extracted once with 15.5 ml 1 N hydrochloric acid and twice with 10 ml dist. water. The organic phase was dried (sodium sulfate), filtered (glass wool) and evaporated under reduced pressure (55 °C/2 kPa). The orange-red intermediate 4 (1.95 g = 11.18 mmol, yield: 90.5 %, GLC: retention index 1654) was dissolved in 15 ml isopropanol and refluxed for 60 min. The excess of reagent was removed under reduced pressure (40 °C/2 kPa) to obtain 1228 mg isopropyl [3-^{14}C]acetoacetate (5) (yield: 76.3 %) with 90 % purity (GLC: retention index 1390).

Isopropyl 3-amino[3-^{14}C]crotonate (6)

Gaseous ammonia was introduced into a stirred solution of 1228 mg (8.53 mmol) isopropyl [3-^{14}C]acetoacetate (5) and 55 mg (2.75 mmol) p-toluene sulfonic acid in 18 ml boiling toluene within 4 hours. The cooled (room temperature) reaction mixture was extracted with 2.5 ml saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate), filtered (glass wool) and the excess of solvent was removed in vacuo (40 °C/2 kPa) to obtain 975.6 mg isopropyl 3-amino[3-^{14}C]crotonate (6) (yield: 80 %) with 94 % purity (GLC: retention index 1729).

2-Methoxyethyl 2-(3-nitrobenzylidene)acetoacetate (7)

A solution of 151 g (1 mol) 3-nitrobenzaldehyde and 160 g (1 mol) 2-methoxyethyl acetoacetate in 1000 ml toluene was saturated with gaseous hydrochloric acid at 0 °C over 3 hours. After 40 hours the reaction mixture was extracted with a diluted sodium hydroxide solution and dist. water. The organic extract was dried (sodium sulfate) and evaporated under reduced pressure. The residue was crystallized from isopropanol to give 223.5 g (yield: 76.5 %) 2-methoxyethyl 2-(3-nitrobenzylidene)-acetoacetate (7) (m.p. 69-70 °C, purity: approx. 100 % by TLC).

3-Isopropyl 5-(2-methoxyethyl) 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-[2-^{14}C]pyridine-3,5-dicarboxylate (8)

Nimodipine is sensitive to daylight, this reaction step has to be carried out under exclusion of daylight. The light of a sodium vapor lamp may be used.

A solution of 975.6 mg (6.82 mmol) isopropyl 3-amino[3-^{14}C]crotonate (6) and 2 g (6.82 mmol) 2-methoxyethyl 2-(3-nitrobenzylidene)acetoacetate (7) in 5 ml ethanol was refluxed for 20 hours. The reaction mixture was cooled to 0 °C. After 2 hours the pale yellow crystals of [2-^{14}C]nimodipine (8) were filtered off, washed with cold ethanol and dried (2049 mg 8 = 71.8 % and 32.3 %, resp., based on barium[^{14}C]carbonate, radiochemical purity 98.5 %, specific activity 1.92 MBq/mg = 51.85 /uCi/mg).

REFERENCES

1. Kazda S. and Toward R. - Acta Neurochirurgica 63: 259 (1982)
2. Allen G.S., Ahn H.S., Preziosi T.J. and Batty R. - New Engl. J. Med. 308: 619 (1983)
3. Rohrschneider L. - J. Chromatogr. 22: 34 (1966)
4. Ettre L.S. - Chromatographia 6: 489 (1973) and 7: 39 (1974), resp.
5. Maul W. and Scherling D. - J. Lab. Comp. Radiopharm. in press