SYNTHESIS OF 1-[(1,4-BENZODIOXAN-2-YLMETHYL)AMINO]-3-(3-PYRIDAZINON-2-YL)-[3-^{14}C]PROPANE HYDROCHLORIDE (GYKI-12743), A NEW ANTIHYPERTENSIVE AGENT

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SUMMARY

A new antihypertensive agent, GYKI-12743, has been labelled with carbon-14 via a six-step synthesis. The label was introduced by chain elongation of an appropriate precursor using potassium [^{14}C]cyanide as radioactive starting material. A satisfactory overall yield, 44.7 %, relative to KCN was achieved.

Key words: Carbon-14, antihypertensive, chain elongation.

INTRODUCTION

1-[(1,4-Benzodioxan-2-ylmethyl)amino]-3-(3-pyridazinon-2-yl)-propane hydrochloride (GYKI-12743; 1a . HCl) is one of the compounds of general formula 1 prepared in our laboratories (1) searching for new substances for the treatment of cardiovascular diseases. Results of animal studies have proved GYKI-12743 to be a potent α_1-adrenoceptor and calcium antagonist exhibiting antihypertensive activity. In order to further explore the possibilities of the utilization of the putative therapeutic value of this compound, the synthesis of a radioisotopically labelled analogue, suited for metabolic and pharmacokinetic evaluation was required.

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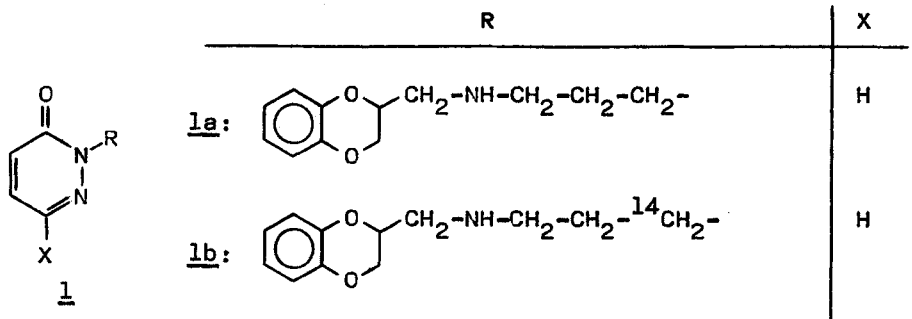
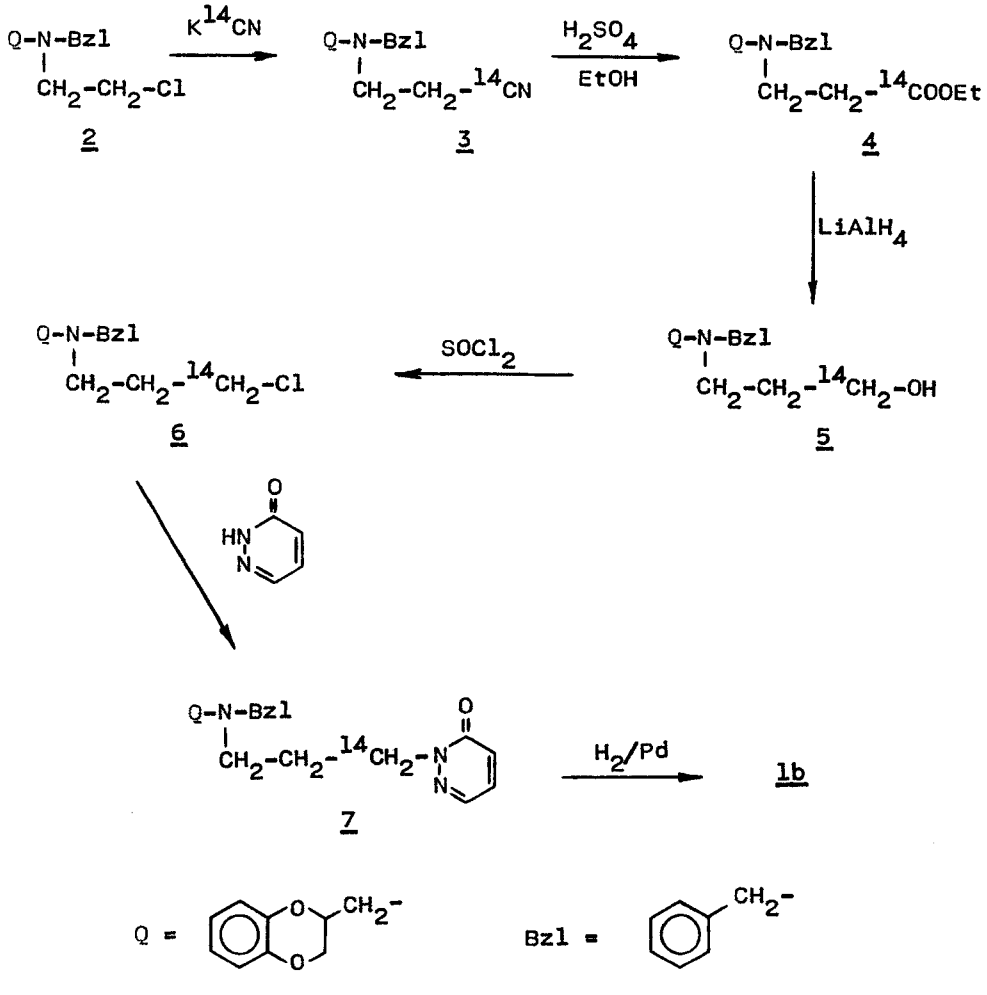

R
X
1a:
1b:
1

SCHEME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2
K14CN
Q-N-Bzl
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3
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CH2-CH2-14COOEt
4
LiAlH4
Q-N-Bzl
CH2-CH2-14CH2-OH
5
SOCl2
Q-N-Bzl
CH2-CH2-14CH2-Cl
6
Q-N-Bzl
CH2-CH2-14CH2-N
7
H2/Pd
1b
Q =
Bzl =

DISCUSSION

In compound 1a the trimethylene chain was considered as metabolically stable position, and thus, suitable for labelling. Although we had elaborated the preparation of a carbon-labelled bifunctional 1,3-propylene derivative, i.e. 3-chloro[1-^{14}C]-propyl p-toluenesulfonate (2), in this case a chain elongation was thought to be a more advantageous synthetic approach for introducing carbon-14 into the propylene moiety. For this purpose a suitable precursor (2) had to be synthesized and, subsequently, the synthetic route outlined in the scheme was carried out.

The reaction of 2-[(1,4-benzodioxan-2-ylmethyl)amino]-ethanol, prepared as described by Marini-Bettolo et al. (3), with benzyl chloride in the presence of phase transfer catalyst gave the corresponding N-benzyl derivative which was then treated with thionyl chloride to obtain 2. By reacting with $K^{14}CN$ this compound served as starting material for the preparation of the labelled intermediate 3. The nitrile was purified by chromatography, then converted into ester in one step and the crude product was first reduced with $LiAlH_4$, thereafter chlorinated with thionyl chloride and finally condensed with 3-pyridazinone by means of phase transfer catalyst. All these reaction steps could be carried out without purification, which was fortunate because the products were liquid; however the last product had to be carefully purified by chromatography, because, according to the results of "cold" runs, debenzylation of the crude 7 by hydrogenolysis took place very slowly resulting in a mixture of 1b and its dihydro derivative, which could not be easily separated. For this reason, the compound 7 had to be exposed to hydrogen over Pd catalyst only for a relatively short period (not more than 2 hours) and the hydrogen consumption during deprotection should not exceed the calculated one. In this manner the last step of the synthesis afforded pure 1b that was isolated as hydrochloride in an overall radiochemical yield of 44.7 %

calculated relative to $K^{14}CN$.

The progress of each reaction step as well as the chemical and radiochemical purity of the final product were monitored by thin-layer chromatography followed by radiometric scanning.

EXPERIMENTAL

The melting points were determined on a Boëtius hot stage and are uncorrected. Radioactivity was measured by liquid scintillation technique using a Packard TRI-CARB Model 2660 spectrometer. IR spectra were recorded with a Bruker Model IFS 85 spectrometer. TLC was carried out on precoated silica gel 60 F_{254} sheets (Merck) and a Berthold TLC scanner Model LB-2723 was used for evaluation. $K^{14}CN$ was prepared in our laboratories (4). All evaporations were carried out under reduced pressure.

2-[Benzyl(1,4-benzodioxan-2-ylmethyl)amino] ethyl chloride hydrochloride (2.HCl)

A mixture of 2- (1,4-benzodioxan-2-ylmethyl)amino ethanol (10.46 g; 50 mmol), sodium iodide (0.76 g), tetrabutylammonium bromide (TBAB) (0.76 g), anhydrous potassium carbonate (21.0 g) and benzyl chloride (7.00 g; 55 mmol) was stirred in hot toluene (100 ml) for 3 hours. After cooling, the mixture was filtered and the filtrate was washed with water (2 x 25 ml) and extracted with 1 N HCl (2 x 30 ml). The combined extracts were made alkaline to pH 9 with 1 N NaOH and extracted again with dichloromethane (3 x 20 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to give 8.15 g of a yellow oil that was redissolved in dichloromethane (30 ml) and, after addition of thionyl chloride (3.24 g; 1.96 ml; 27.0 mmol), refluxed for 4 hours. After allowing to stand in a refrigerator overnight, the crystals were filtered off and recrystallized from acetone to afford 2.HCl (6.50 g; 36.7 %). M.p. 134-136°C. The compound found to be pure by TLC (benzene/methanol 8:2) was identified by IR spectrum.

3-[Benzyl(1,4-benzodioxan-2-ylmethyl)amino] [cyano-^{14}C]propionitrile (3)

A mixture of 2 (freshly prepared from 5.5 mmol, 1.95 g of 2.HCl by dissolving it in water, adding excess NaOH to the solution, extracting the base with ether and evaporating the extract), $K^{14}CN$ (0.326 g; 5.00 mmol; 5.27 GBq; 1.054 GBq/mmol), 98 % ethanol (18 ml) and a catalytic amount of KI was heated at 90°C for 4 hours and evaporated. The residue was mixed with water (10 ml) and extracted with benzene (5 x 10 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to an oil which was chromatographed on a silica gel column using benzene as eluting solvent. Evaporation of the appropriate fractions gave a pale yellow homogeneous oil (1.570 g) (TLC: benzene).

Ethyl 3-[benzyl(1,4-benzodioxan-2-ylmethyl)amino] [carboxyl-^{14}C]-propionate (4)

The above nitrile was dissolved in 95 % ethanol (3.2 ml) and after dropwise addition of conc. H_2SO_4 (1.35 ml) the mixture was heated at 90°C for 3 hours, then cooled to room temperature and diluted with water (15 ml). Ether (25 ml) was layered over the solution and the pH was adjusted to 8 with Na_2CO_3. After shaking, the layers were separated and the aqueous phase was extracted with additional portions of ether (3 x 10 ml). The combined extracts dried over anhydrous Na_2SO_4 were evaporated to afford 4 as a pale yellow oil (1.70 g). The main radioactive spot detected by TLC (benzene/acetic acid 9:1; butanol/acetic acid/water 4:1:1) in the crude product accounted for approximately 90 % of the radioactivity.

3-[Benzyl(1,4-benzodioxan-2-ylmethyl)amino]-1-[1-^{14}C]propyl chloride (6)

The crude ester and $LiAlH_4$ (0.50 g) in dry ether (30 ml) were

heated under reflux for 2 hours. Then, while cooling the flask in an ice-bath, excess $LiAlH_4$ was destroyed by dropwise addition of 10 % aqueous Seignette salt solution (1.6 ml). The coagulated solid was filtered off, the filtrate was dried over anhydrous Na_2SO_4 and evaporated to give a colourless oil (1.60 g) which was subsequently reacted with thionyl chloride (0.66 g; 0.4 ml) in hot dichloromethane for 4 hours. After cooling, the reaction mixture was mixed with water (10 ml) and its pH was adjusted to 8-9 by the addition of Na_2CO_3. The separated aqueous phase was extracted with dichloromethane (3 x 10 ml), the combined organic layers were dried over Na_2SO_4 and evaporated. The residue, 1.60 g of a yellow oil, was found to be pure enough by TLC (benzene/ methanol 8:2) for the next step.

1-[Benzyl(1,4-benzodioxan-2-ylmethyl)amino]-3-(3-pyridazinon-2-yl)-[3-^{14}C]propane (Z)

A solution of 3-pyridazinone (0.721 g; 7.5 mmol) in dry methanol (10 ml) containing a stoichiometric amount of KOH (0.420 g; 7.5 mmol) was stirred at 20°C for 30 minutes and evaporated to dryness. The last trace of moisture was removed by azeotropic distillation with toluene. About half of the residue as well as TBAB (0.34 g) were added to the above radioactive intermediate dissolved in toluene (26 ml). After refluxation for 4 hours, the remaining 3-pyridazinone potassium salt was added and refluxing was continued for an additional 3 hour period. The reaction mixture was then cooled and washed successively with 2 N NaOH (2 x 10 ml), saturated $NaHCO_3$ (10 ml) and water (10 ml). Removing the solvent by evaporation afforded a brown oil which was applied to a silica gel column and eluted with ethyl acetate. The appropriate fractions were evaporated to constant weight yielding 1.47 g (3.76 mmol) of a yellowish oil.

1-[(1,4-Benzodioxan-2-ylmethyl)amino]-3-(3-pyridazinon-2-yl)-[3-^{14}C]propane hydrochloride (1b.HCl)

The above product (7; 1.47 g; 3.76 mmol) dissolved in a mixture of ethanol (10 ml), distilled water (1.3 ml) and conc. HCl (0.6 ml) was hydrogenated over 10 % Pd/C catalyst (0.24 g) until hydrogen consumption attained the calculated one (90 ml at room temperature). The mixture was then filtered, neutralized with NaOH and evaporated. Water (10 ml) was added to the residue, the solution was made alkaline to pH 9 and the oil that separated was extracted with chloroform (5 x 15 ml). The organic layers were combined, dried over K_2CO_3 and evaporated to give a yellow oily residue (1.08 g) which was dissolved in ethyl acetate (4 ml) and acidified to pH 3 with alcoholic HCl. After being kept in a refrigerator overnight, the crystals were filtered off and recrystallized from ethanol. The white crystalline substance after drying in a vacuum desiccator over P_2O_5 and KOH weighed 0.774 g (2.29 mmol) and proved to be identical in every respect except radioactivity with an authentic sample of 1a.HCl. No radioactive contaminants could be detected by TLC (ethyl acetate/methanol/conc. NH_4OH/water 80:20:5:5). M.p. 125-27°C. Radioactivity: 2.358 GBq (3.047 GBq/g; 1.029 GBq/mmol). Overall radiochemical yield: 44.7 %.

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