SYNTHESIS OF 1-[4-[3-(N-METHYL N-[3,4-DIMETHOXY β-PHENETHYL] AMINO] [3-^{14}C]PROPYLOXY] BENZENESULFONYL]-2-ISOPROPYL INDOLIZINE or [^{14}C]SR 33557

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SUMMARY

[^{14}C]SR 33557 was synthesized in six steps and in an overall yield of 3.8 % from sodium [^{14}C]cyanide.

Key-words : indolizine, carbon-14, calcium antagonist.

INTRODUCTION

SR 33557 belongs to a class of compounds for whom calcium channel blocking activity has recently been demonstrated (1,2).
The structure of SR 33557 differs from that of known calcium antagonists such as dihydropyridines, phenylalkylamines and benzothiazepines. The compound is therefore of interest in the treatment of cardiovascular pathologies.

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SR 33557 labelled with carbon-14 was prepared for pharmacokinetic studies in man and animals. The labelling of the indolizine ring, better suited to the type of study envisaged, was abandoned due to chemical difficulties. Instead, a more accessible lateral site was labelled. It is possible that the labelled position will be not suitable. As a function of the results of the metabolic study, the position of the labelled site will be reexamined.

DISCUSSION

As the lateral chain was to be labelled, the first route attempted consisted of condensing the 1,3[1,3-^{14}C]dibromopropane with 1-(4-hydroxybenzenesulfonyl)-2-isopropylindolizine. However, the yields were poor due, amongst others, to the formation of a dimer as shown by mass spectrometry.

We opted instead for another route involving the acylation of the secondary amine 4 to the appropriate tertiary amide with an ω-chloro-acid chloride (3,4,5).

Then, the reduction of the amide 5 with lithium aluminium hydride gave us to the desired tertiary amine 6. Finally, the phenolic position was alkylated by a Williamson reaction on the alkyl chloride (5).

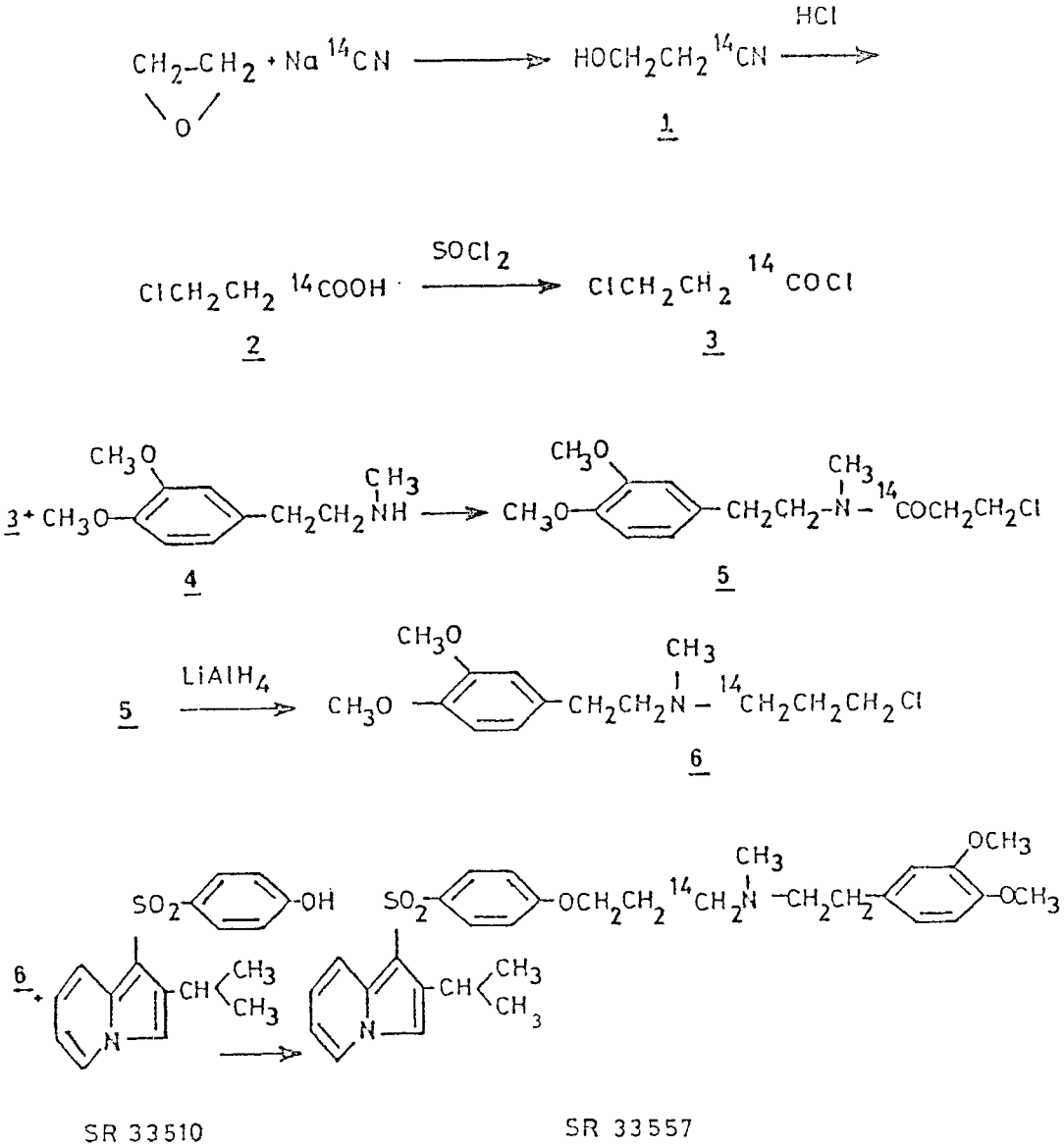
EXPERIMENTAL SECTION

Thin layer chromatography

This was performed on Merck F 254 silica gel plates, dimensions 200 x 50 x 0.25 mm. The elution solvents were :

A)	Ethyl acetate/cyclohexane	80/20	(v/v)
B)	Chloroform/methanol	95/ 5	(v/v)
C)	Dichloromethane/ethyl acetate	80/20	(v/v)
D)	Acetone	100	(v)

SCHEME



SR 33510 SR 33557

High pressure liquid chromatography

E) Reverse phase RP 15
Flow rate 1 ml min^{-1}
Detection 232 nm
Mobile phase Acetonitrile/water/diethylamine 60/40/0.05 (v/v/v)

Ultraviolet

The spectra were measured with a Beckman Acta III apparatus.

3-Chloro[1-^{14}C]propionic acid : 2

Starting with 400 mCi (14 800 MBq) of [^{14}C]NaCN (IRE, Belgium) (6), reaction with ethylene oxide gave 3-hydroxy[1-^{14}C]propionitrile. Hydrolysis of the nitrile with concentrated hydrochloric acid in a sealed flask at 105 °C during 45 hours and extraction with ether gave 325 mCi (12 000 MBq) of the acid 2.

3-Chloro[1-^{14}C]propionyl chloride : 3

The crude acid (325 mCi) in dry benzene (30 ml) was heated at reflux for 30 minutes under a Dean-Stark trap. After cooling, thionyl chloride (1.4 ml) was added dropwise, and the resulting solution heated at reflux for 2 hours. After evaporation of the benzene and excess thionyl chloride under vacuum, the product 3 (171 mCi (6.325 MBq), 43 %) was used directly for the following step.

3-Chloro-N-methyl-N-(2-(3,4-dimethoxyphenyl)ethyl) [1-^{14}C]propionamide : 5

A solution of 3 in cold dry benzene (10 ml) was added dropwise to a solution of N-methylhomoveratrylamine (957 mg, 4.9 mM) in benzene (5 ml) at 0 °C. The resulting solution was refluxed 2 hours, whereupon the solvent was evaporated under vacuum. The residue was partitioned between methylene chloride and 5 % aqueous sodium hydroxide solution. The organic phase was dried ($MgSO_4$), filtered and evaporated, and the residue chromatographed on a column of Merck silica gel (10 cm x 3.5 cm, 230-400 mesh) with hexane/ethyl acetate 70/30 (v/v) as eluant to give the desired product 5 (42 mCi (1.550 MBq), 343 mg (25 %)).
TLC A) 1 radioactive peak identical to the reference.

Reduction of amide 5 to 6

A solution of 5 in diethylether (5 ml) was added slowly to a solution of $LiAlH_4$ (94 mg, 2.4 mM) in ether (5 ml) at 0 °C under dry nitrogen. The temperature and agitation were maintained for 2 hours, then the mixture was warmed to room temperature for 1.5 hours. The excess $LiAlH_4$ was destroyed by the addition of 0.1 ml of H_2O and 0.3 ml of 10 % NaOH. After 1 hour of stirring at room temperature, the salts were filtered off, and the solvent evaporated in vacuum to give 6 (40 mCi, 1.480 MBq ; 320 mg, 1.18 mM, 98 % yield).
TLC B) Radiochemical purity 85 %

[^{14}C]SR 33557

To a solution of non-purified 6 in DMSO (5 ml) was added successively 1-(4-hydroxybenzene-sulfonyl)-2-isopropylindolizine (410 mg,

1.3 mM) and potassium carbonate (345 mg, 2.5 mM). The mixture was stirred for 72 hours at room temperature, then dissolved in water and extracted five times with methylene chloride. The combined extracts were washed with 5 % NaOH then water and dried with K_2CO_3. Filtration and evaporation of the solvant gave the crude product which was purified by HPLC under the following conditions :

Column	Altech RP 18 10 μ 20 x 2.2 cm
Eluant	Acetonitrile/Water/DEA 75/25/0.5 (v/v/v)
Detection	Waters Lambdamax 232 nm
Flow rate	Perkin Elmer LC Series 1 20 ml min^{-1}
Retention volume	300 ml

The specific activity was determined from the UV spectrum and the measurement of the radioactivity.

UV λ max : 232 nm ϵ max : 38700

15 mCi (555 MBq) of [^{14}C]SR 33557 was obtained radiochemically pure at 98 % by C), D) and HPLC E) and with a specific activity of 31 mCi/mM.

The overall radiochemical yield was 3.8 % calculated from the sodium [^{14}C]cyanide.

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