SYNTHESIS OF [4"-^{3}H]- AND [4,4,5,5-$^2H_4$]-2-(1'-[2",6"-DICHLOROPHENOXY]-ETHYL)-Δ^2-IMIDAZOLINE

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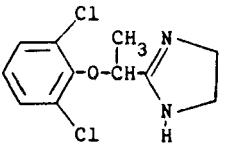
SUMMARY

[4"-^{3}H]-2-(1'-[2",6"-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline was prepared from [4-^{3}H]-2,6-dichlorophenol in two different ways. By reaction of 2,6-dichlorophenol with 2-(α-chloroethyl)-Δ^2-imidazoline, the radiochemical yield, at a specific activity of 173.9 mCi/mmole, was 12.8 %. With the two-step-procedure (reaction of 2,6-dichlorophenol with 1.) 2-chloropropionitrile and 2.) ethylenediamine), the radiochemical yield of product, at a specific activity of 185.8 mCi/mmole, was 30.0 %.

[4,4,5,5-$^2H_4$]-2-(1'-[2",6"-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline was prepared in one step from [1,1,2,2-$^2H_4$]-ethylenediamine in 49 % yield.

INTRODUCTION

In the course of investigations into the action of various compounds as possible drugs in the treatment of hypertension[1)], it was necessary to prepare both the tritiated and the deuterated form of 2-(1'-[2",6"-dichlorophenoxy]-ethyl)-Δ^2-imidazoline (I) (lofexidine)[1,2,3)] for a study of its pharmacokinetic and metabolic behaviour in various species.



(I)

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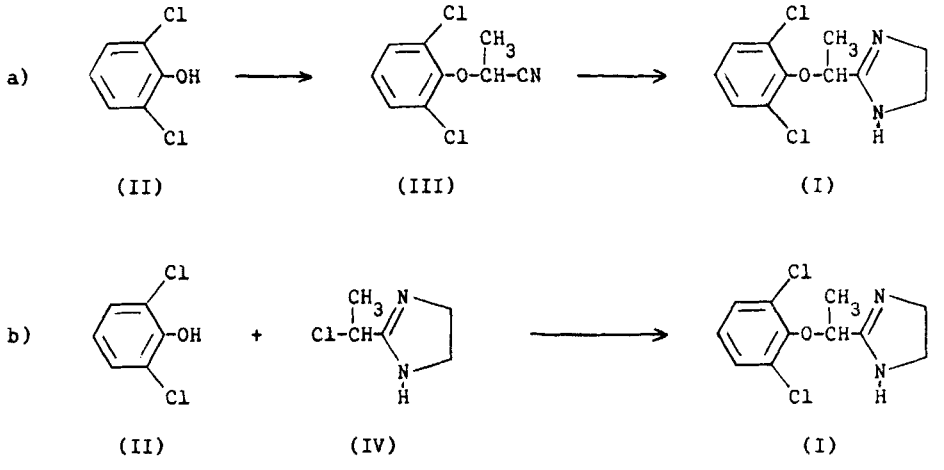
Since lofexidine, like its structural analogue clonidine[3], is active in rather small doses (about 2 µg/kg body weight in man), the tritiated compound is only useful for bioavailability studies and elucidation of metabolite structure, whereas the determination of unchanged drug in plasma is only possible by use of gas chromatography/mass spectrometry (glc/ms). In the present paper we report the preparation of the labelled compounds according to the scheme given below; study results on pharmacokinetics and metabolism of lofexidine will be published elsewhere.



(II) (III) (I)

(II) (IV) (I)

Scheme

MATERIALS AND METHODS

[4-^{3}H]-2,6-Dichlorophenol (specific activity 277.5 mCi/mmole) was obtained from Farbwerke Hoechst, Frankfurt. A small amount of label was present in the 3- and 5-position as well. Later, we prepared [4-^{3}H]-2,6-dichlorophenol ourselves by reduction of 4-bromo-2,6-dichlorophenol[4] with tritium gas according to Stiasni and Stähle[5]. The specific activity of this preparation was 179.1 mCi/mmole.

[1,1,2,2-$^2H_4$]-Ethylenediamine (98 % isotopic enrichment) was obtained from Sharp and Dohme, München. All solvents were of analytical grade; they were obtained from Merck, Darmstadt.

Scanning of radiochromatograms was performed on Dünnschichtscanner II (Berthold, Wildbad).

Liquid scintillation counting was done in a Packard TriCarb model 3390 using Unisolve 1 scintillation cocktail (Koch-Light). Quench was corrected for by the external standard ratios method.

Mass spectra were recorded on a Varian MAT 331 A spectrometer. EI-ionization was performed at 70 eV and 250 °C.

Chromatography systems:

a) tlc

system A: silica gel (Kieselgel Merck 60 F_{254}):
chloroform : hexane 1 : 1

system B: silica gel (Kieselgel Merck 60 F_{254}):
ethanol : chloroform : conc. NH_3 70 : 50 : 2

c) glc

system C: Varian Aerograph 2700; column length 1.5 m filled with 3 % OV 17; temperature gradient 200 - 300 °C (10 °C min^{-1}). (I) was derivatized with trifluoroacetic anhydride.

Radiochemical purity was determined by tlc with subsequent scanning of the radiochromatograms.

EXPERIMENTAL

1. One-step procedure

[2"-^{3}H]-2-(1'-[2",6"-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline (I)

To a solution of 110 mg (0.67 mmole; 120 mCi) [4-^{3}H]-2,6-dichlorophenol in 2 ml of a 3 : 1 mixture of dimethylformamide and benzene, 185 mg (1.34 mmole) finely powdered K_2CO_3 were added. The mixture was heated at 100 °C for 1 h. After cooling, 103 mg (0.67 mmole) 2-(α-chloroethyl)-Δ^2-imidazoline · HCl were added; the reaction mixture was heated at 100 °C for 18 h.

After cooling, the reaction mixture was diluted with 1 ml of $CHCl_3$; solids were filtered off. The filtrate was evaporated to dryness using a rotary evaporator. The residue was taken up in chloroform. It was chromatographed over a column of silica gel (Woelm 63 - 100 mesh) (1 x 25 cm) first with pure chloroform, then with chloroform : isopropanol 95 : 5. The isolated product was converted to its hydrochloride by addition of anhydrous HCl in diethyl ether. The raw product was recrystallized three times from isopropanol. Yield: 26 mg = 12.8 % (with respect to [4-^{3}H]-2,6-dichlorophenol), specific activity: 173.9 mCi/mmole = 0.59 mCi/mg, radiochemical purity: ≥ 95 % (the nature of the impurity is unknown).

The substance is identical to authentic (I) · HCl according to mass spectrometry.

2. Two-step procedure

[4'-^{3}H]-2-(2',6'-Dichlorophenoxy)-propionitrile (III)

To a solution of 40 mg (0.245 mmole; 68 mCi) [4-^{3}H]-2,6-dichlorophenol in 2 ml anhydrous 2-butanone, 51 mg (0.37 mmole) of finely powdered K_2CO_3 and 4 mg KJ were added. This mixture was stirred for 10 min at room temperature. A solution of 49.2 mg (0.55 mmole) 2-chloropropionitrile in 400 µl 2-butanone was added. The resulting mixture was heated at 80 °C for 8 h. The solution was filtered; solvent was evaporated under vacuum. The oily residue weighed 143 mg and contained a relative large amount of polymers of 2-butanone, the separation of which was impossible at this point of the synthesis. The only radioactive compound according to tlc (system A) was (III).

[4"-^{3}H]-2-(1'-[2",6"-Dichlorophenoxy]-ethyl-Δ^2-imidazoline (I)

143 mg of crude [4'-^{3}H]-2-(2',6'-dichlorophenoxy)-propionitrile were placed in a 2 ml vial. 20 µl ethylendiamine and 5 µl CS_2 (both freshly distilled) were added. This mixture was heated at 60 °C for 4 h. At this time, the glc (system C) of this mixture revealed the presence of approximately 30 % starting mate-

rial (III). Therefore, another 20 µl ethylenediamine and 5 µl CS_2 were added. The mixture was heated at 60 °C for another 3 h, after which time the glc (system C) revealed 95 % conversion into product (I).

The resulting melt was placed in a desiccator for 2,5 h to remove excess ethylenediamine. The residue was taken up in dichloromethane. The resulting solution was washed three times with 1-ml-portions of water. After filtering over heated cotton, the solution was evaporated to dryness. The residue was recrystallized from n-hexane. Yield: 19.1 mg = 30.0 % (with respect to [4-^{3}H]-2,6-dichlorophenol), specific activity: 185.8 mCi/mmole ◻ 0.72 mCi/mg, radiochemical purity: > 95 % (a small amount [< 5 %] of (III) is detected by tlc (system A) and glc (system C).

This substance is identical to authentic (I) according to mass spectrometry.

The specific activity of the product (I) is significantly lower than that of starting material (II), since some of the ^{3}H-label in (II) was still present in the phenolic hydrogen position.

(I) has to be kept strictly anhydrous, since the imidazoline moiety is easily hydrolyzed to the corresponding ß-aminoethylamide of 2-(2',6'-dichlorophenoxy)-propionic acid, which is inactive as an antihypertensive drug.

[4,4,5,5-$^2H_4$]-2-(1'-[2",6"-Dichlorophenoxy]-ethyl)-Δ^2-imidazoline

1.68 (7.8 mmole) 2-(2',6'-dichlorophenoxy)-propionitrile (III), 557 mg (8.7 mmole) [1,1,2,2-$^2H_4$]-ethylenediamine and 60 µl CS_2 were placed in a 10 ml round-bottom-flask and heated at 60 °C for 6 h. The glc (system C) of this melt showed more than 95 % of the desired product. The yellow semicrystalline melt was taken up in 15 ml dichloromethane; this solution was washed twice with 5-ml-portions of water. After filtering over cotton, the solution was evaporated to dryness. The residue was recrystallized from di-iso-propyl ether. Yield: 990 mg = 49 %. The substance is pure according to glc (system C). Mass spectrum and nmr spectrum are consistent with the assigned structure.

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