SYNTHESIS OF 4-ALLYLOXY-3-CHLOROPHENYLACETIC-1-^{14}C ACID.

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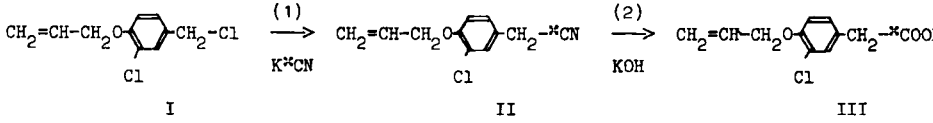
In the course of our research on new non-steroid anti-inflammatory and analgetic agents we found that certain substituted phenylacetic acids show strong analgesic and antipyretic properties ; one of them 4-allyloxy-3-chlorophenylacetic acid # (III) (Alclofenac) is of great interest for its high potency in these fields and for its low toxicity [1][2][3]. Metabolic patterns in different animal species [4][5] and kinetic studies on the absorption and excretion of this compound in man [6] have been undertaken with 1-^{14}C labelled compound synthetized according the following sequence.



I II III

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Tottoli apparatus and are uncorrected as are boiling points. Paper chromatography was made on Whatman n° 2 paper and thin-layer chromatography on pre-coated plates Merck with Kieselgel F 254 (0,25 mm tickness).

The scanning of the chromatograms was achieved using a Packard Radiochromatogram scanner Model 7201. Specific activities were determined using a secondary ^{14}C standard by liquid scintillation counting on a Tri-Carb Packard Model 3375.

Starting compound I was made by chloromethylation of 4-allyloxy-3-chlorobenzene[7] (bp 117-118°/1 mm, n_D^{25} 1.5600, > 99 % pure by gas liquid chromatography).

#Mervan^R, Manufacturer : Continental Pharma s.a. Brussels (Belgium).

4-allyloxy-3-chlorophenylacetonitrile-1-^{14}C (II)

A suspension of 97 mg of potassium cyanide - ^{14}C (6,4 mCi, 1,42 mM) and 326,5 mg of I (1,5 mM) in 1 ml of dimethylsulfoxide was stirred at 50°C for 16 h. Then 40 ml of water was added and the mixture extracted with five 10 ml portions of ether (total activit of the residual water phase 0,5 mCi). The organic extract was dried with magnesium sulfate, filtered and the solvent removed. The crude nitrile was used directly without purification in the next step.

Thin-layer chromatography did not detect any major impurity (solvent:chloroform-cyclohexane-methanol-Acetic Acid = 60 : 40 : 10 : 10)

4-allyloxy-3-chlorophenylacetic-1-^{14}C acid (III)

The crude nitrile II was dissolved in a mixture of 0,25 ml water and 1,6 ml ethanol together with 300 mg of potassium hydroxide in a 10 ml sealed glass container and brought in a oil bath at 90°C for 15 h. After cooling and opening 10 ml water was added and the mixture extracted three times with 5 ml portions of ether in order to remove the non acidic by-products (total activity of the organic extract 0,18 mCi). The alkaline water layer (total activity 5,25 mCi) was acidified with 0,3 ml concentrated sulfuric acid in 5 ml water, extracted five times with 15 ml portions of ether. The combined organic phases were dried on magnesium sulfate, concentrated and sprayed as a band on a preparative silica gel plate Merck GF 254(thickness 2 mm).

After five runs with a mixture of pentane 70 parts and acetic acid 10 parts a very good separation of the impurities was observed and the acid band was scratched and extracted with three 10 ml portions of methanol-acetone (50/50). After dilution with 4 g of the unlabelled acid the solution was lyophilized.
Yield : 4,21 g m.p. : 92-93°- Total activity : 4,7 mCi - Specific activity : 0,261 mCi/mM
Radiochemical yield : 75 % -Radiochemical purity : $\geq$ 99,9 %
Chromatographic analyses on paper and thin layer in four solvent systems, detected only one spot (U V and iodine vapor revelation).

System 1 : Dioxan : benzene : acetic acid = 10 : 30 : 10
System 2 : Pentane : acetic acid = 70 : 10
System 3 : Chloroform : cyclohexane : methanol : acetic acid = 60 : 40 : 10 : 10
System 4 : Ethanol : water : ammonia (25 %) = 30 : 5 : 5

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