SYNTHESIS OF 2-n BUTYL 3-(3,5-^{125}DIIODO 4-(N,N-DIETHYLAMINO 2-ETHOXYBENZOYL)) BENZOFURAN HYDROCHLORIDE (^{125}I AMIODARONE)

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SUMMARY

^{125}I Amiodarone was prepared by iodination of 2-n butyl 4-hydroxy 3-benzoyl benzofuran with Na^{125}I in alkaline medium. By amination with N,N-diethyl 2-amino 1-chloroethane, ^{125}I amiodarone was obtained with 30 % yield and a specific activity of about 1 Ci/mmol.

INTRODUCTION

Amiodarone (Cordarone ®) is a benzofuran developped as antianginal and antiarrhythmic agents particularly used for the treatment of supraventricular and ventricular tachyarrhythmias (1)(2).

A previous report (3) describes a method using ^{125}iodine in an exchange reaction between ^{127}I and ^{125}I of the 2-butyl 3-(3,5-diiodo 4-hydroxybenzoyl) benzofuran [1] with Chloramine T as oxidation agent. The specific activity obtained was 50 µCi/mmol.

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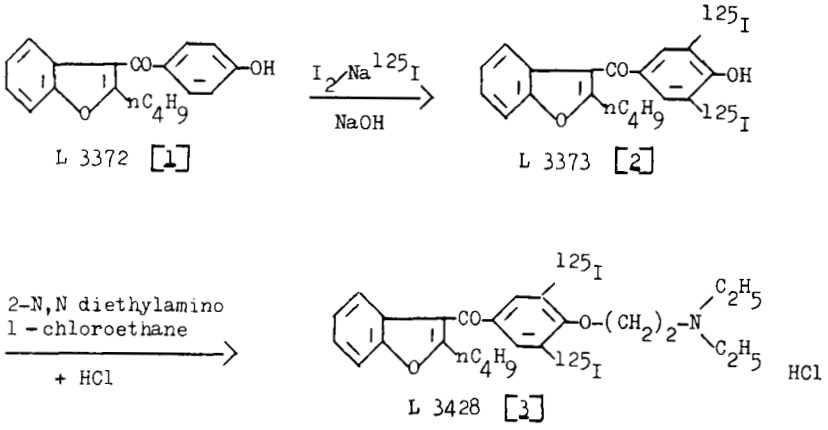
In the present report, a synthesis of ^{125}I Amiodarone [2] based on the industrial preparation of the non-labelled compounds (4) (5) (6) is described. This route allows to obtain a higher specific activity in order to meet the requirements of the users.

Indeed, higher specific activities were asked for researches on drug proteins binding, radioimmunoassays and partition coefficient measurements.

SCHEME FOR SYNTHESIS OF ^{125}I LABELLED AMIODARONE



PRODUCTS - MATERIAL

- 2-butyl 4-hydroxy 3-benzoylbenzofuran for synthesis Labaz-Sanofi product, L 3372 [1].
- ^{125}I sodium iodide
  Isotope Institute (Hungary) code I.RB-3
  batch M-1028/2 in solution in NaOH free of reducing agents (pH 8-10); Max. 0.9 % ^{126}I.
- Bisublimate iodine for synthesis
- Sodium iodide for analysis
- Sodium hydroxyde in pellets for analysis
- Sodium hydrogenosulfite for synthesis
  (38 % aqueous solution)

- Potassium carbonate for analysis
- Benzene for analysis dried on sodium
- Diethyl ether for analysis
- 2-N,N-diethylamino 1-chloroethane prepared following the procedure described in Organic Synthesis, 31:37 (Wiley & Sons, 1951).
  Recristallized in a mixture propranol-2/petroleum ether or propanol-2/heptane.
- Gamma spectrometer : Berthold LB MAG 510.
- Radioactivity counter : Berthold LB 2722-2738.
- Liquid chromatograph : Hewlett Packard 1082 A or Spectra-Physics 3500 B.

EXPERIMENTAL

2-n butyl 3-(3,5-^{125}diiodo 4-hydroxybenzoyl)benzofuran [3]

In a glass tube, the following mixture was prepared :

Iodine : 5.59 mg (22 micromoles)
NaI : 3.65 mg (24.3 micromoles) in 0.1 ml of water
$Na^{125}I$: 30.8 mCi (0.4 ml), 1.7 µg (0.0115 micromole)
Specific activity : 2500 Ci/mmol

2.94 mg (10 micromoles) of [1] were dissolved in a solution of NaOH (38.5 micromoles) and 0.100 ml of water, drop by drop, to the above mixture with vigorous stirring at a constant temperature of 65°C. This temperature was maintained and the mixture was stirred for 4 hours. After cooling, 4.16 mg (40 micromoles) of sodium hydrogenosulfite in 0.1 ml of water were added and the mixture was stirred for 5 minutes. The solution was acidified by addition of 0.1 ml of 1 M HCl and stirred for 5 minutes. L 3373 was extracted with five 1 ml portions of diethyl ether. The combined ether layers were washed with a small volume of water, dried over anhydrous sodium sulfate and evaporated to dryness.

Chemical yield : 5.33 mg [2], 97,6 %
Observed activity : 8 mCi.

2-n butyl 3-(3,5-^{125}diiodo 4-(N,N-diethylamino 2-ethoxy benzoyl))benzofuran hydrochloride [3]

The diiodo compound obtained (L 3373) was dissolved in 1 ml of benzene. The solution was refluxed for 30 minutes with 5.6 mg (40 micromoles) of potassium carbonate to obtain the salt. After cooling, 3.44 mg (20 micromoles) of 2-N,N-diethylamino 1-chloroethane dissolved in 0.1 ml of water were added.

The mixture was refluxed for 4 hours (oil bath at 85°C). After cooling, 0.1 ml of 1 M NaOH were added and the aqueous phase was extracted with five 1 ml portions of diethyl ether. The combined ether layers were washed with some water, dried over anhydrous sodium sulfate and evaporated to dryness under a nitrogen flow.

Chemical yield : 5.51 mg, 87,4 % (free base)
Observed activity : 7 mCi.

Hydrochloride salt preparation :

^{125}I Amiodarone (free base) was dissolved in 1 ml of methanol and 0.010 ml of 1 M HCl to obtain amiodarone hydrochloride salt. Methanol and HCl in excess were eliminated to dryness.

Chemical yield : 5.81 mg [3], 100 %
Observed activity : 7 mCi.

PURIFICATION

Labelled amiodarone [3] was purified by high performance liquid chromatography (HPLC) using the following experimental conditions :

Apparatus	: Liquid chromatograph - HP 1082 A
Column	: LOBAR Merck Lichroprep. RP 8 (40-63 microns) Size : 240 x 10 mm
Mobile phase	: water/diethylamine/methanol (7/0.02/92.98; v/v/v)
Flow	: 2 ml/min
Pressure	: 14 atm

Detector : UV at 242 nm
Recording speed : 0.5 cm/min
Temperature : 20°C
Loading volume : 200 microlitres (methanol)
Retention time of [3] : 27.0 min
Yield : 37 %

PURITY CONTROL

Radiochemical purity

The radiochemical purity was verified by thin layer chromatography (figure 1) using Merck plates (Si 60 F 254)

Solvent : hexane/2-propanol/ammonia 25 %
(100/15/1; v/v/v)
Rf [3] : 0.67 (figure 1).

The radioactivity recording and the localization of ^{125}I labelled amiodarone on the chromatography plate were realized with a Berthold counter, type window-less "Flow counter" (Berthold LB 2722 - 2738).

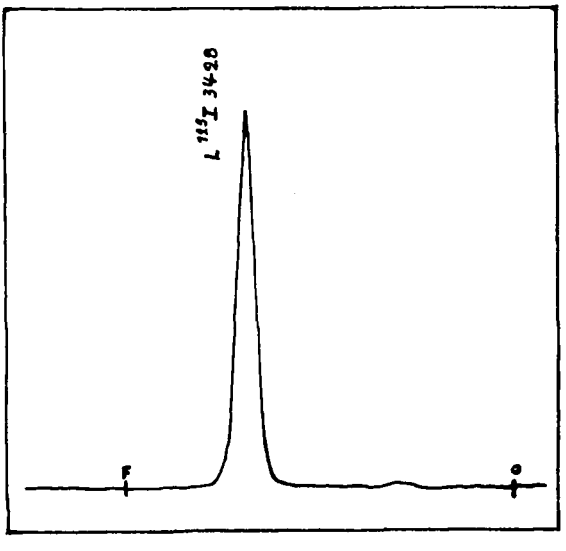


Figure 1 : Radiochemical purity of ^{125}I Amiodarone checked by TLC

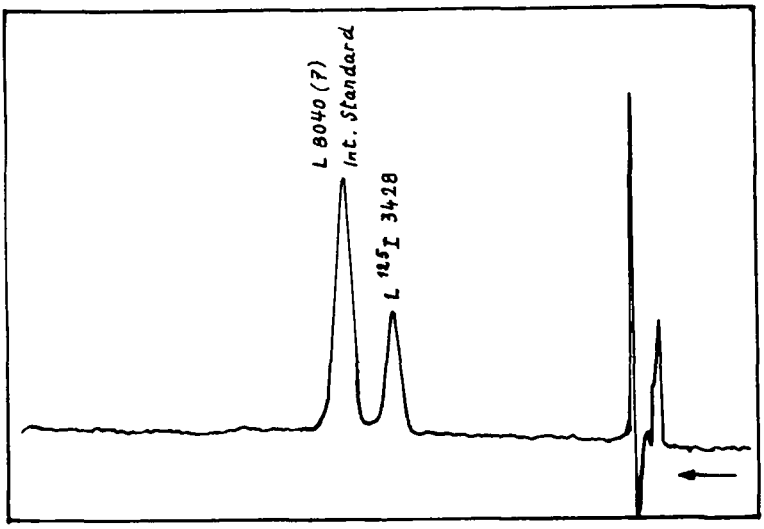


Figure 2 : Chemical purity of ^{125}I Amiodarone checked by HPLC

Chemical purity

The chemical purity was established by high performance liquid chromatography (figure 2).

Apparatus : HPLC SPECTRA-PHYSICS model 3500 B
Column : Hibar Si 100 (10 microns)
250 mm in lenght and 4 mm in diameter
Mobile phase : ethanol/ammonia 25 %/chloroform
(0.90/0.01/99.09; v/v/v)
Flow : 1 ml/min
Detector : UV at 250 nm, 0.04 aufs
Recording speed : 0.5 cm/min
Temperature : 20°C
Retention time of [3] : 15.8 min

RESULTS

The radioactivity measured with a Berthold gamma counter was 2.59 mCi.

Chemical yield [3] : 2.15 mg (3.15 micromoles) or 31 % (total)
Specific activity : 820 mCi/mmol
Chemical purity : 99.8 %
Radiochemical purity : 99 %
Self-decomposition : 5 % each month when stored at -20°C

DISCUSSION

This direct iodination procedure allows to obtain specific activity higher than with the oxidation by the Chloramine T method.
This is a fact which migh be attributed to the substituted phenol group of [1].
However, if it is yet possible to obtain specific activities above 1 Ci/mmol; in practice, the self-decomposition increases so fast that the use of a such compound is to be avoided for the fixed purposes.
For the same reason, the synthesis and the purification of the compound must be realized in about four days because the impurified compound was subject to a faster degradation than the pure ^{125}I amiodarone.

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(7) Internal standard for quantitative analysis of amiodarone
L 8040 = 2-ethyl 3-(3,5-dibromo 4-(N,N-di-n-propyl 3-propoxybenzoyl))thiophene.