NOTE

SYNTHESIS OF ^{11}C-SURICLONE*

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SUMMARY

^{11}C-Suriclone was synthetised in a short time (30 minutes) with a high specific activity (750 mCi/ μMol) for studies in man with the Positron Emission Tomography technic. The starting material was the N-demethylated product 35489 RP. The radioactive reagent was either ^{11}C-formaldehyde or ^{11}C-methyl iodide.

Key words : ^{11}C, Suriclone 31264 RP, (chloro-2, naphthyridin |1,8| yl-7)-6-(^{11}C-methyl-4 piperazinyl-1) carbonyloxy-5, oxo-7 tetrahydro-2,3,6,7 dithiino |1,4| |2,3-c| pyrrole, cyclopyrrolone, Positron, Receptor.

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* Suriclone is the commercial name of Rhône-Poulenc product.

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INTRODUCTION

Suriclone (31264 RP) or (chloro-2, naphthyridin |1,8| yl-7)-6 (methyl-4 piperazinyl-1) carbonyloxy-5, oxo-7 tetrahydro-2, 3, 6, 7 dithiino |1, 4| |2, 3-c| pyrrole is a drug of the cyclopyrrolones family with anxiolytic and hypnotic properties.

It has been labelled with carbone-11 to be studied in man by the Positron Emission Tomography technic. The both methods of labelling which have been considered consist of a methylation of nitrogen in 4 position of piperazine ring of precursor 35489 RP by ^{11}C-formaldehyde or ^{11}C-methyl iodide (fig. 1).

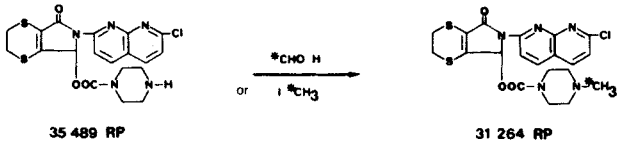

Fig. 1 - Scheme of the synthesis

EXPERIMENTAL AND RESULTS

Method I

The methylation is carried out by ^{11}C-formaldehyde, the synthesis of $H^{11}CHO$ has been already described (2). 200µL of a chloroform solution containing 2 µMol of 35489 RP are disposed in the reaction flask with 50-100µL water, 4 µL $NaBH_3CN$ solution (15.7 mg/mL C_2H_5OH) and 5µL acetic acid.

The ^{11}C-formaldehyde is transferred into this solution with the aid of a helium stream at a 20 mL/min flow rate. The recovery of ^{11}C-formaldehyde is proving difficult into this heterogeneous reaction mixture. All the attempts carried out with homogeneous mixtures such CH_3CN-C_2H_5OH - $CHCl_3$; 200 : 50 : 200 v/v with 50 µL water remained unfruitful.

Thus the reaction mixture retained has been CH_3Cl - H_2O (200 µL : 50 µL), the water being indispensable to trap the ^{11}C-formaldehyde.

When the formaldehyde is recovered, the reaction mixture is heated during 6 minutes at 60°C. Then the solvent is evaporated to dryness and the residue dissolved by a few hundred µL of CH_2Cl_2 - 3 % B mixture used as eluent (B : ethanol - water - ethylamin ; 96 : 2 : 2). This mixture is injected on the chromatography system using a silica column (Partisil M9 10/50 Whatman - flow rate : 8 mL/min).

The radioactivity of the products going out of the column is detected with a small ionisation chamber and their mass measured with a UV detector at 280 nm. The retention time of suriclone is 6.5 min and those of nor-suriclone derivative (35489 RP) 11 min.

The chemical yield obtained with regard to $^{11}CO_2$ vary from 5 to 30 %. This variation proceed from the difficulty to trap ^{11}C-formaldehyde into the reaction mixture.

This difficulty led us to try the labelling with ^{11}C-methyl iodide.

Method II

The method of synthesis of ^{11}C-methyl iodide has been described elsewhere (2).

Into 2 mL flask, closed with silicon septa equiped with needles, are introduced 400 µL tributyl phosphate, 0.8 mg (1.7 µMol) 35489 RP compound and 15 µMol NaOH. Labelled methyl iodide, carried away by a nitrogen stream, is trapped into the reaction mixture at ambient temperature. When the radioactivity of $I^{11}CH_3$ is maximum, the solution is heated at 110°-115°C during 5 minutes. After cooling in an ice-alcohol bath, the mixture is injected with the aid of a catheter onto the column (same chromatographic system as the one described in method I). The chromatogram obtained is represented on fig. 2.

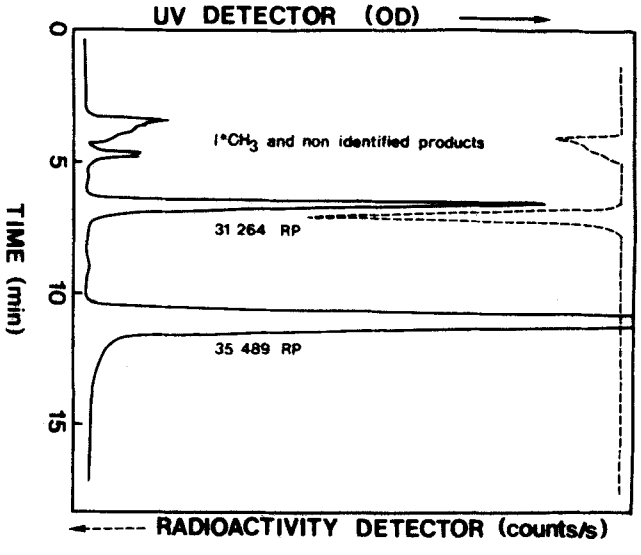

Fig. 2 - HPLC chromatogram of ^{11}C-suriclone

The labelled product, separated from the others constituents of the solution, is recovered into a flask. After eluent evaporation at 80°C under a nitrogen stream, the radioactive fraction corresponding to suriclone is dissolved in a hot physiological serum (3-5 mL) containing 300 µL of propanediol and 0.3 µMol of methanesulfonic acid. The final solution is sterilised by passage through a Millipore filter (0.22 µM PTFE).

The synthesis of ^{11}C-suriclone has been optimized by previous experiments using non radioactive products. The melting point and the mass spectra of the obtained product are similar to those of authentic samples. The synthesis of labelled suriclone ready for injection lasts 30 minutes after the end of bombardment of target for the production of ^{11}C as $^{11}CO_2$ form. The radioactive fraction recovered has been tested for pyrogen and sterility. The synthesis using 30 min of proton bombardment (30 µA, 20 MeV) of a nitrogen target (pressure : 7 bars, lenght 30 cm, diameter 4.5 cm) gave 150 to 220 mCi of ^{11}C-suriclone with a specific activity of 750 mCi/µMol (chemical yield 40 to 55 % with regard to $^{11}CO_2$). All synthetic operations were carried out semiautomatically in a well shielded cell (3).

Acknowledgements

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