SYNTHESIS OF ^{11}C-PINDOLOL

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SUMMARY

A method is described by which 100 mCi of pindolol may be obtained from about 1.5 Ci $^{11}CO_2$ in 30 minutes. The product is chromatographically pure, sterile and apyrogenic with a specific activity between 600 and 1000 mCi/μmole at the time of use.

The synthesis involves the preparation of ^{11}C-acetone followed by fixation of the isopropyl group on the precursor : 2 hydroxy-3 (4-indolyoxy) propylamine by formation of an imine, the reduction of the latter by sodium cyanoborohydride.

I - INTRODUCTION

The advent of the use of Positron Emission Tomography has allowed direct approaches to the characterization of receptor properties in the living brain and heart of animals and man. The in vivo characterization of beta-adrenergic receptors is difficult because most radioligands used for in vitro binding studies (e.g. ^{3}H-dihydroalprenolol) cannot be employed in vivo. Pindolol (4-[2-hydroxy-3-(isopropylamino)-propoxy] indole) could be convenient for PET studies because it has a higher affinity than practolol for the beta adrenergic

0362-4803/87/020227–05$05.00

Received March 24, 1986

receptor and a lower liposolubility than propranolol (1, 2). We report here the synthesis of Pindolol labeled with the short-lived isotope, carbon 11.

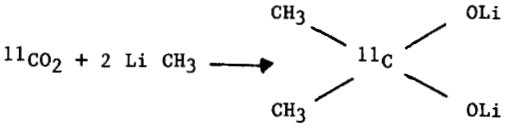
II - PRINCIPLE OF THE METHOD

Carbon eleven is obtained by the nuclear reaction :

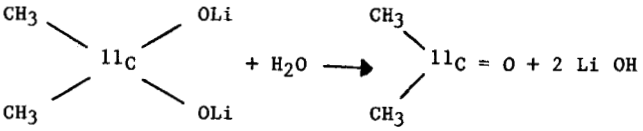
$^{14}N\ (p, \alpha)\ ^{11}C$

and combines immediately with traces of oxygen present in the target to give $^{11}CO_2$.

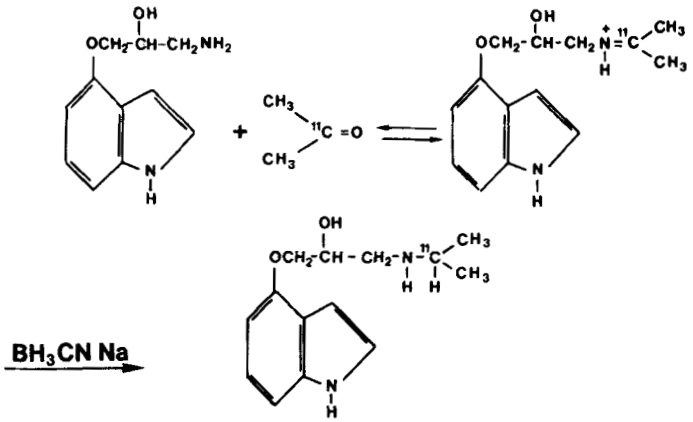
In the presence of methyl lithium, we have :



The complex is then hydrolysed and the excess methyl lithium destroyed.



Acetone reacts with D.L. 2 hydroxy-3 (4-indolyoxy) propylamine (I)



and gives an imine which is reduced by cyanoborohydride into D.L. pindolol.

The reductive amination of ketones described by F. Borch et al (3) has been adapted here to this synthesis.

III - MATERIALS AND METHODS

1) Apparatus

The apparatus used is that described earlier (3). The reactions take place in cylindroconical tubes (1.5 ml) closed by chromatographic septa (Carlo Erba) and interconnected by teflon tubes (int Ø : 0.08 cm) fixed onto medical needles.

The passage of gases is controlled by compressed air-operated electrovalves.

The reaction tubes are fixed on a mobile rod and may be transferred from a cold bath (-10°C) to a hot bath (80°C).

The radioactivity is measured by 3 ionisation chambers : one beside the $^{11}CO_2$ trap, another near the tube in which Pindolol is synthetized and the third at the chromatograph column outlet. All this apparatus is contained in a hermetically closed shielded cell (5 cm lead).

2) Preparation

Nitrogen (Air Liquide, purity N60) is irradiated for 30 min, under 8 bars pressure, with 20 MeV protons at 30 µA intensity.

The $^{11}CO_2$ formed is carried by the nitrogen current through a P_2O_5 trap (int Ø = 0.4 cm, L = 5 cm) where all traces of water are stopped, and collected in a metal loop (int Ø = 0.1 cm, L = 40 cm) cooled with liquid argon (-186°C).

This operation takes about 5 minutes and gives approximately 1.5 Ci $^{11}CO_2$.

The loop is then removed from the liquid argon and brought back to room temperature. The radioactivity is carried by a nitrogen flow (N48, 20 ml/min) into a first tubes (previously oven dried), cooled

to -10°C and containing about 5 µmoles methyl lithium in 100 µl anhydrous ether (distilled over sodium, kept under nitrogen).

The transfer is over in less than 10 seconds. The tube is placed for a few seconds in the hot bath to evaporate the ether, then cooled ; 50 µl water are added, then the tube is heated again and connected up with the second tube through an electrovalve. A nitrogen current (20 ml/min) transfers the ^{11}C acetone in less than 2 min. A calcium chloride trap (int Ø = 0.4 cm, L = 5 cm) stops the water vapour carried on the gas stream.

The second tube contains 2 µmoles precursor (0.5 mg) (I), 2 µmoles sodium cyanoborohydride and 4 µl acetic acid in 300 µl tetrahydropyran (T H P). The second reagent has previously been dissolved in a T H P/water mixture (9/1) thus the final mixture contains traces of water (0.5 µl).

The reaction is carried out for 15 minutes at 80°C, the tube being closed by electrovalves.

After cooling, an air pressure is applied over the solution, which is then sent through a catheter and a chromatographic needle into the injector of a liquid phase chromatograph. The valves are closed from the outside of the shielded cell.

The eluent used here with the partisil PAC.M9 50 cm Whatman column is made up of 85 % dichloromethane and 15 % ethanol (the latter containing 1.5 % ethylamine and 2.5 % water). The flow-rate is 8 ml/min. The eluate radioactivity and optical density at 280 nm are recorded and the fraction corresponding to ^{11}C-pindolol is collected (t_R = 6 min). The solvent is evaporated by nitrogen bubbling and the radiopharmaceutical redissolved in 5 ml physiological serum buffered by a 2.10^{-3} M phosphate at pH 3.0. The solution is sterilised by passage through a millipore filter.

IV - RESULTS

- Chromatography of the reaction mixture reveals ^{11}C-pindolol

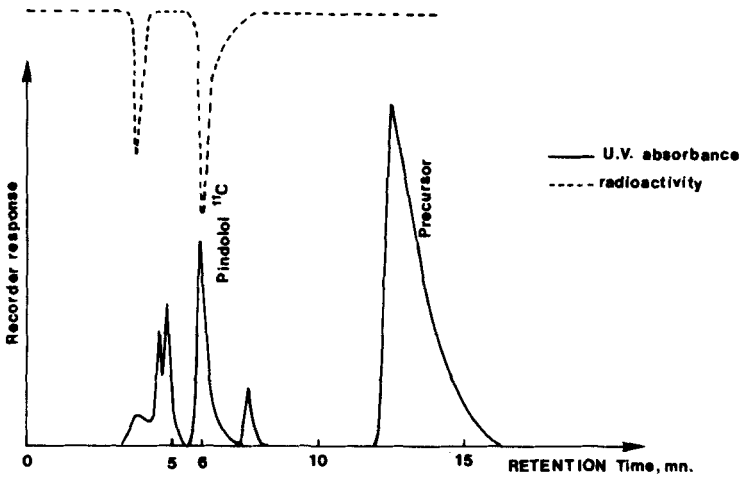


Fig. 1 : Chromatogram of synthetic mixture.

Conditions described in the text.

and a complex peak including at least the acetone which has not reacted plus tert butyl alcohol (fig. 1) (4).

- The radiopharmaceutical obtained is chromatographically pure, giving a shoulder free peak when chromatographed in the presence of the reference product.

- All samples tested were sterile and apyrogenic.

- 20 MeV protons irradiation of nitrogen target under 8 bars for 30 minutes at 30 µA gives about 1.5 Ci $^{11}CO_2$. 100 mCi of pindolol are obtained 30 minutes after the end of bombardment with a specific radioactivity of 600-1000 mCi/µmole.

Acknowledgements

The authors wish to thank Dr. Voges from Sandoz LTD for pindolol and precurssor supply.

BIBLIOGRAPHY

1. Berger G., Mazière M., Prenant C., Sastre J., Syrota A., Comar D. - J. Radioanal. Chem. 74 (1) : 301-306 (1982).

2. Berger G., Prenant C., Sastre J., Syrota A., Comar D. - Int. J. Appl. Radiat. Isot. 34 : 1556 (1983).

3. Borch R.F., Bernstein M.D., Dupon-Durst H. - J. Am. Chem. Soc. 93 : 2897 (1971).

4. Berger G., Mazière M., Prenant C., Comar D. - Int. J. Appl. Radiat. Isot. 31 : 577 (1980).