ONE-POT PROCEDURE FOR THE PREPARATION OF ^{14}C -LABELLED TRISODIUM PHOSPHONOFORMATE HEXAHYDRATE (FOSCARNET).

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SUMMARY

Trisodium phospho[^{14}C]formate is synthesized from [^{14}C]phosgene in 4 steps. All reactions are performed *in situ* in an overall radiochemical yield of 51%.

INTRODUCTION

Foscarnet, trisodium phosphonoformate hexahydrate **1**, is an antiviral agent which exerts its activity by inhibition of herpesvirus DNA polymerase.(1) In order to study the distribution of foscarnet *in vivo* a radioactive form of the compound was required. This paper describes a high yield synthesis of ^{14}C-labelled foscarnet from [^{14}C]phosgene in four steps.

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SYNTHESIS

$$Cl^{14}COCl + HOCH_2C_6H_5 \longrightarrow Cl^{14}COOCH_2C_6H_5 \xrightarrow{(CH_3CH_2O)_3P}$$

2

$$(CH_3CH_2O)_2PO^{14}COOCH_2C_6H_5 \xrightarrow{(CH_3)_3SiI} [(CH_3)_3SiO]_2PO^{14}COOSi(CH_3)_3 \longrightarrow$$

3 4

$$\xrightarrow[H_2O]{NaOH} (NaO)_2PO^{14}COONa \cdot 6H_2O$$

1

A solution of [^{14}C]phosgene in toluene was treated with one equivalent of benzyl alcohol at low temperature. Before bringing the reaction to completion by warming, the HCl formed was removed by means of a slow stream of gaseous nitrogen. Triethyl phosphite was added to the product, benzyl chloro [^{14}C]formate 2, and the reaction mixture heated to give benzyl diethyl phosphono [^{14}C]formate 3 by the Arbuzov reaction (2). The injection of 3 equivalents of iodotrimethylsilane into the solution of 3, initially at -25° C and then at room temperature, led to the tristrimethylsilyl ester 4 in high yield as monitored by ^{1}H NMR on cold runs. By employing iodotrimethylsilane as reagent, which has been shown very effective in dealkylation of phosphonic acid esters (3) and carboxylic benzyl esters (4) under very mild conditions, the loss in yield accompanying basic (5,6) and acidic (5) hydrolysis of alkyl phosphonoformate esters is avoided. Subsequent treatment of 4 with sodium hydroxide in water at ice-water temperature gave 1 in an overall radiochemical yield of 51%.

EXPERIMENTAL

[^{14}C]Phosgene (11.5 mCi/mmol) in toluene was purchased from Amersham International plc , Amersham, England. Iodotrimethylsilane was used as received (Aldrich Chemical Co.). Thin layer chromatography was carried out on cellulose plates (DC-Fertigplatte Cellulose F, Merck 0.10 mm) developed in Cl_3CCOOH;NH_3;H_2O;CH_3OH, (5 g of Cl_3CCOOH; 15 ml 10% NH_3; 30 ml H_2O; 50 ml CH_3OH).

Radioactivity was determined in a Packard liquid scintillation counter (Model 3320) using Biofluor (New England Nuclear) as the counting medium. The radiochemical purity was determined by scanning (Berthold Dünnshicht-Scanner II) of the TLC plates.

Trisodium phosphono[^{14}C]formate hexahydrate 1

To a 20% solution of phosgene (15 mCi, 1.30 mmol) in toluene at -55°C (dry ice-alcohol bath), benzylalcohol (135 mg, 1.25 mmol) was added with stirring . After 5 min the dry ice-alcohol bath was replaced by an ice-water bath and the reaction mixture was kept at 0°C for 25 minutes and for 75 minutes at room temperature. While passing a slow stream of N_2-gas through the reaction flask, the temperature was raised to 40°C during 15 min. After cooling with ice-water triethyl phosphite (232 mg, 1.40 mmol) was added. The reaction mixture was heated and kept at 80-100°C for 100 min. After cooling, a sample corresponding to 10% of the product was withdrawn from the reaction mixture for other applications. At -25°C the remaining reaction mixture was treated with iodotrimethylsilane (705 mg, 3.53 mmol) and allowed to attain room temperature. After 4 hours the initially brown mixture had become colourless and was cooled to -12°C. NaOH (150 mg, 3.75 mmol) in H_2O (1.5 ml) was added and the stirring was continued at room temperature

for 20 minutes. The half-solid mixture was washed with ether (3x1.5 ml) and, after recrystallisation from water, gave 158 mg of 1 with spec. activity 357.2 MBq (9.65 mCi)/mmol. Addition of 150 mg inactive 1 to the mother liquor and recrystallisation gave another 145 mg of 1 with spec. activity 146.2 MBq (3.95 mCi)/mmol. The identity and radiochemical purity of the two crops were checked by thin layer chromatography and scanning the plate for radioactivity. They were found to be at least 98% pure. The total radiochemical yield from [^{14}C]phosgene with the withdrawn sample accounted for, was 51%.

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