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Synthesis of Cis-diamino-[1,1-[1-^{14}C]cyclobutane-dicarbonyloxy (2)-O,O] platinum II

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SUMMARY

The synthesis of the title compound (4) is described. [2-^{14}C]Diethyl malonate was treated simultaneously with a freshly prepared solution of sodium ethoxide and 1,3-dibromopropane to give 1 1-[1-^{14}C]cyclobutanedicarboxylic acid diethyl ester (1). Treatment with potassium hydroxide saponified the ester leaving the dipotassium salt (2). Conversion of potassium tetrachloroplatinate II with potassium iodide followed by ammonium hydroxide resulted in cis-diamino-diiodoplatinum II[1] (3). Reaction of (3) with 1,1-[1-^{14}C]cyclobutanedicarboxylic acid dipotassium salt in the presence of silver nitrate resulted in the title compound (4).

Key Words:

Cis-diamino-[1,1-[1-^{14}C]cyclobutanedicarbonyloxy(2)-O,O] platinum II, antitumor, carboplatin, cisplatin, phosphorylation, nephrotoxicity.

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INTRODUCTION

The title compound (carboplatin) is a second generation cisplatin derivative. It has been selected for further clinical testing because it showed less toxicity, especially nephrotoxicity, in comparison to the parent compound cisplatin, while retaining antitumor activity. It enhanced nuclear protein phosphorylation in the tumor cells more than cisplatin, but caused much less protein phosphorylation in the normal liver and kidney cells. This suggests some selective toxicity towards tumor cells and may explain the decreased nephrotoxicity[1]. In order to determine the protein-binding, degradation in urine, degradation in plasma and the formation of both 1-cyclobutane carboxylic acid and 1,1-cyclobutane dicarboxylic acid the ^{14}C-labelled compound was synthesized.

EXPERIMENTAL

Materials

[2-^{14}C] Diethyl malonate was purchased from Amersham Corporation. All chemicals used in the synthesis were purchased commercially and used without any purification. All other solvents were either distilled or analytical reagent quality. Thin layer chromatography plates used were Analtech silica gel GF scored 10 x 20 cm and high pressure liquid chromatography was carried out on Waters Associates instrumentation. Radioactivity was measured by a Beckman LS 9000 liquid scintillation counter. Weighings were carried out on a Sartorius 200 balance and a Mettler Microanalytical M5AS Balance.

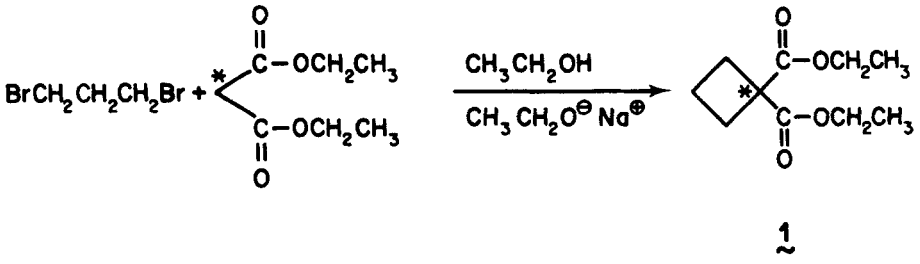
1,1-[1-^{14}C]Cyclobutanedicarboxylic acid diethyl ester(1).

Into a 100 ml round bottom flask was added absolute ethyl alcohol (42 ml), freshly prepared sodium ethoxide solution (17 ml, 0.05 molar solution), [2-^{14}C]diethyl malonate (186.5 mg, 55 mCi) and a solution of non-radioactive diethyl malonate (7.81 g) in absolute ethyl alcohol (2 ml). This mixture was heated under reflux for 90 min. During this 90 min period 1,3-dibromopropane (8.4 g) and sodium ethoxide solution (17 ml, 0.05 molar sol.) were added simultaneously. The reaction was then heated under reflux for an additional 2 hrs. and then concentrated under reduced pressure, yielding a yellow oily solid. This solid was dissolved in water (50 ml) and the solution extracted with diethyl ether (3 x 100 ml). The combined ether extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure yielding an oil. Purification was achieved by flash chromatography (silica gel, Whatman 30μ - 63μ) in toluene (4.7 g., yield 47%).

Thin Layer Chromatography

Eluent- toluene - methylene chloride (9:1), Plates- Analtech silica gel, Visualization-iodine vapor, Compound Rf = 0.9.

SYNTHETIC PATHWAY



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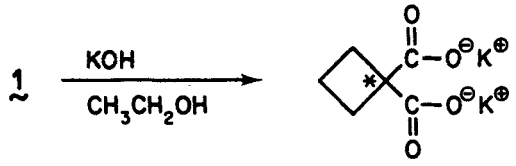

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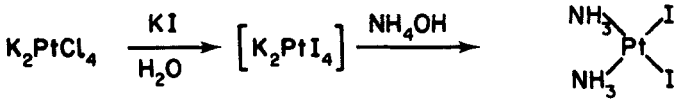

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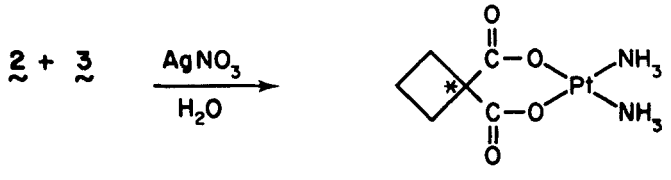

4

* = Position of radiolabel

1,1-[1-^{14}C]Cyclobutanedicarboxylic acid dipotassium salt (2).

Into a 25 ml round bottom flask was added absolute ethyl alcohol (6 ml), 1,1-[1-^{14}C]cyclobutanedicarboxylic acid diethyl ester (4.7g), and a solution of potassium hydroxide (2.6 g) in water (3 ml). This mixture was heated at 60°C for 15 min. and then concentrated under reduced pressure to dryness. The residue was dissolved in water (10ml) and extracted with ethyl acetate (2 x 10 ml). The aqueous portion was concentrated under reduced pressure to a volume of 5 ml and used as is in the following reaction.

Cis-diamino-diiodoplatinum II(3)

To a solution of potassium tetrachloroplatinate II (9.6g) in water (120 ml) was added potassium iodide (18.0g), and the mixture was stirred until solution occurred. To this was then added a solution of ammonium hydroxide (3.9 ml) in water (3.9 ml). The resulting yellow precipitate was removed by filtration, washed with water (20 ml), absolute ethyl alcohol (20 ml), and then dried under reduced pressure, yielding a mustard-colored powder (9.2 g). This material was used as is in the following reaction.

Cis-diamino-[1,1-[1-^{14}C]cyclobutanedicarbonyloxy(2)-0,0] platinum II (4)

Cis-diamino-diiodoplatinum II (3) (9.2 g) was slurried in a solution of silver nitrate (6.4 g) in water (30 ml). After heating at 60°C for 2 hrs. the reaction mixture was cooled to room temperature and filtered through a bed of diatomacious earth. The filtrate was heated to 60°C and to this was added 1,1-[1-^{14}C]cyclobutanedicarboxylic acid dipotassium salt (2) as an aqueous solution (5 ml), and this mixture was stirred at 60°C for 3 hr, after which it was cooled to 5°C and stirred at this temperature for 64 hrs. The resulting colorless solid was removed by filtration, redissolved in hot water (11), filtered and concentrated to a volume of approximately 10ml under reduced pressure. The resulting crystalline solid was recovered by filtration and dried. Wt = 2.4 g. Radiochemical purity was 99.2%. Specific activity was 3.1 μCi/mg.

High Pressure Liquid Chromotography was carried on Waters Associates instrumentation with the following parameters: Eluent-87% acetonitrile - 13% water. Flow Rate-2 ml/min. Detector-Ultraviolet at 230 nm. Temperature-22.5°C. Column-Waters Associates μBondapak amine. Retention Time-7 min.

RESULTS AND DISCUSSION

A mixture of [2-^{14}C]diethyl malonate[2] and non-radioactive diethyl malonate was reacted simultaneously with freshly prepared sodium ethoxide solution and 1,3-dibromopropane under reflux in absolute ethyl alcohol as described[3]. Purification of the resulting 1,1-[1-^{14}C]cyclobutanedicarboxylic acid diethyl ester (1) was achieved by flash chromatography utilizing silica gel in toluene. A colorless oil resulted. Saponification took place rapidly by heating with aqueous potassium hydroxide at 60°C for 15 min. The dipotassium salt was isolated and used in the following reaction without any purification. Treatment of potassium tetrachloroplatinate II with potassium iodide and then ammonium hydroxide resulted in cis-diamino-diiodoplatinum II (3) as a mustard colored powder. The reaction of potassium tetrachloroplatinate II with potassium iodide is rapid and complete. Displacement with ammonia is highly stereospecific due to the strong trans directing effect of the iodide. Treatment of the cis-diamino-diiodoplatinum II with 1,1-[1-^{14}C]cyclobutanedicarboxylic acid dipotassium salt in the presence of silver nitrate at 60°C in water for 3 hrs yielded the title compound in an overall yield of 34%. This was a colorless solid having only a slight solubility in water. Purification was achieved by dissolving in a large volume of hot water (1l), filtered through a Nylon -66 filter and concentrated to a volume of approximately 10 ml. This produced crystalline cis-diamino-[1,1-[1-^{14}C]cyclobutanedicarbonyloxy (2)-O,O] platinum II (2.4 g) (4) having a specific activity of 3.1 μCi/mg and a radiochemical purity of 99%. All experimental conditions were optimized using non-radiolabelled materials.

REFERENCES

1. "Data Brochure on Carboplatin" Oct. 1983 prepared by Bristol-Myers Company 841704

2. [2-^{14}C]diethyl malonate was purchased from Amersham Corp.

3. H. Schwarz et al, Chem. Berichte, 114 p. 2820 (1981).