

A SIMPLE SYNTHESIS OF PROPIONIC-3-¹⁴C ACID

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SUMMARY

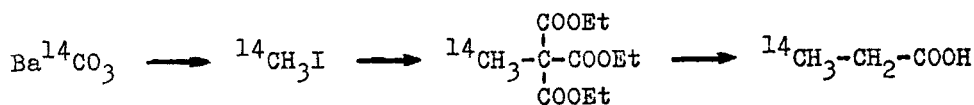
Propionic-3-¹⁴C acid was prepared by methylation of tricarbethoxymethane and subsequent hydrolysis. This method avoids the problems of malonic ester synthesis. A pure monoalkyl derivative was obtained.

INTRODUCTION

The conventional method for the synthesis of propionic-3-¹⁴C acid contains two chain-elongation steps involving one-carbon synthons, consequently the multi-step synthesis is very tiresome and the yield is moderate (20-25 %).¹

Methylation of diethylmalonate and a subsequent hydrolysis would be a shorter way of synthesis, but the by-products of this reaction - unchanged diethylmalonate and diethyl dimethylmalonate - yield acetic acid and isobutyric acid as contamination, whose separation from propionic acid is almost impossible.

Using tricarbethoxymethane instead of diethylmalonate the overmethylation becomes impossible and by applying an excess of methyl iodide the quantity of unchanged ester can be reduced to a negligible amount. This reaction was described for inactive compounds by Prelicz² and Carvalho³ but the hydrolysis of the obtained esters was investigated only kinetically³ and no preparative data were given.



Using this approach pure 1,1,1-tricarbethoxyethane-2- ^{14}C was isolated by reacting methyl- ^{14}C iodide with more than one mole tricarbethoxymethane and then transforming the excess with inactive methyl iodide into 1,1,1-tricarbethoxyethane. Subsequent hydrolysis with dilute sulphuric acid gave propionic-3- ^{14}C acid, which was isolated in the form of its sodium salt. The yield of this simple synthesis is about 40-50 % (calculated on $\text{Ba}^{14}\text{CO}_3$), better than that of the conventional more complicated method.¹

EXPERIMENTAL

Radioactivity was measured by a Packard Tri-Carb (model 3380) liquid scintillation system.

Sodium tricarbethoxymethane

Metallic sodium (0.345 g, 15 mmoles) was dissolved in absolute ethanol (15 ml). Then a solution of tricarbethoxymethane⁴ in ethanol (5 ml) was added under stirring. After several minutes white crystals separated. The mixture was stirred for 30 minutes, then ether (25 ml) was added and stirring was continued for 30 minutes. Then the crystals were filtered off, washed with ether (3x10 ml) and dried in vacuo to yield 3.50 g (92 %) of sodium tricarbethoxymethane as white powder. M.p.: 200-203°C.

1,1,1-Tricarbethoxyethane-2- ^{14}C

A suspension of sodium tricarbethoxymethane (2.54 g, 10 mmoles) in ethanol (10 ml) was cooled with liquid nitrogen, evacuated and methyl- ^{14}C iodide[‡] (1.259 g, 8.85 mmoles, 187 mCi) prepared from $\text{Ba}^{14}\text{CO}_3$ (1.9776 g, 10 mmoles, 200 mCi) was added by vacuum transfer. Then the flask was filled with dry nitrogen, heated to room temperature and capped. The mixture was stirred for 4 hours, until

[‡] Methyl- ^{14}C iodide was prepared as described in the literature.⁵

a clear solution was obtained. Then inactive methyl iodide (1 ml) was added and the mixture was stirred for another hour. The bulk of ethanol was evaporated, the residue was suspended in water (30 ml) and extracted with dichloromethane (4x20 ml). The organic solution was washed with aqueous 25 % NaCl solution (20 ml), dried over Na₂SO₄ and the solvent was evaporated to yield 2.306 g (9.1 mmoles) 1,1,1-tricarbethoxyethane as a colourless oil.

Sodium propionate-3-¹⁴C

1,1,1-Tricarbethoxyethane-2-¹⁴C (2.306 g, 9.1 mmoles, 170 mCi) was refluxed in 20 % aqueous sulphuric acid (30 ml) for 20 hours[✱], then water (100 ml) was added and the product was distilled^{✱✱} from the flask collecting two liters. The distillate was made alkaline (pH 8.8) with 1 N NaOH (5.94 ml was required), and the water was evaporated at reduced pressure. 573.7 mg (5.97 mmoles) of sodium propionate 3-¹⁴C were obtained as white crystals. Measured activity 95.3 mCi (calc. 112 mCi). Specific activity: 166.1 mCi/g, or 15.96 mCi/mmole. Radiochemical yield: 47.7 %^{✱✱✱}. The material contained less than 1 % sodium sulphate and less than 1 % of sodium acetate.

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[✱] A very efficient cooler is required to prevent the loss of the vapour of propionic acid.

^{✱✱} Two liters of water were boiled before the distillation to expell any carbondioxide, and were added continously to the boiling solution.

^{✱✱✱} Yields calculated from sodium tricarbethoxymethane in inactive runs were 60-80 %.

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