

THE PREPARATION OF DIMETHYL (7-²H₃ 2-OXOHEPTYL) PHOSPHONATE

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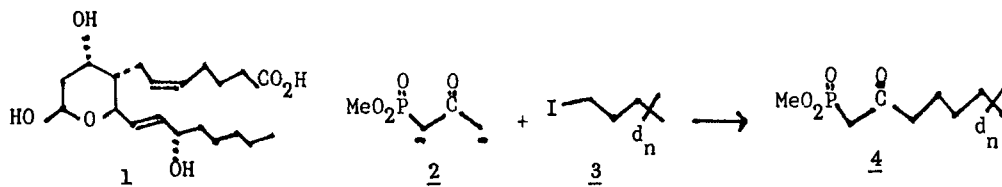
SUMMARY

Dimethyl (7-²H₃ 2-oxoheptyl) phosphonate 4 has been prepared from ²H₃ methyl iodide. The phosphonate should be a useful reagent for the synthesis of deuterium labelled prostaglandins and thromboxanes.

Key Words: Catalytic Deuteration, Prostaglandin, Thromboxane

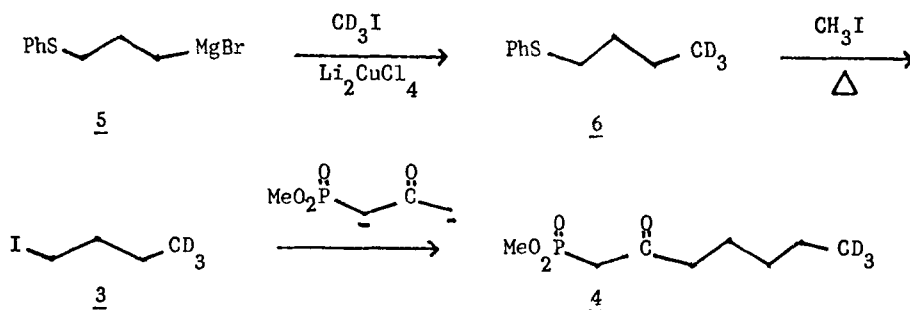
INTRODUCTION

Current interest in the measurement of biological concentrations of prostaglandins and thromboxanes by mass spectrometry has led to the need for the preparation of stable isotope labelled internal standards. In connection with an analysis for thromboxane B₂ 1 currently in use here we required a standard labelled in the lower side chain. We therefore undertook the synthesis of phosphonate 4 (1) using the alkylation of dianion 2 developed by Grieco (2).



As catalytic deuteration of a variety of unsaturated precursors led in our hands to extensive scrambling, even using catalysts alleged not to scramble (3), we chose to pursue a route that involved incorporation of a fully deuterated moiety, the inexpensive ²H₃-methyl iodide (SCHEME).

SCHEME



Thus, coupling (4) of the readily available Grignard reagent 5 (5) with ²H₃ methyl iodide gave the labelled phenylthiobutane 6. Alkylation/displacement of the phenylthio group of 6 with methyl iodide (6) gave the desired labelled iodobutane 3. Alkylation of the dianion of dimethyl methyl phosphonate then led to the desired labelled phosphonate 4.

We expect that 4 (n = 3) will find widespread utility in the synthesis of stable isotope labelled internal standards for mass spectrometric assay.

EXPERIMENTAL

Materials:

The following starting materials were obtained from the indicated commercial sources: ²H₃-methyl iodide, Merck, Sharp and Dohme Canada Limited; dibromopropane, Aldrich Chemical Co.; methyl iodide, Fisher Scientific Co.; dimethyl-(2-oxopropyl)-phosphonate, Aldrich Chemical Co.

1-Bromo-3-phenylthiopropene: 1-Bromo-3-phenylthiopropene was prepared from dibromopropane and thiophenol according to the procedure of Bakuzis (5).

1-Phenylthio-4-²H₃-butane: 1-Bromo-3-phenylthiopropene (23.1 g, 0.100 mol) was added dropwise to dry magnesium turnings (3.6 g, 0.15 mol), distilled THF and a trace of iodine in a dry 100-ml three neck round-bottom flask equipped with a condenser, addition funnel, rubber septum, magnetic stirring bar, and under a nitrogen atmosphere. The mixture was stirred at 50°C for 1 h. The

resulting Grignard reagent was added dropwise via syringe at 0°C to a mixture of ²H₃ - methyl iodide (14g, 0.1 mol) and Li₂Cu Cl₄ (220 mg, 1.0 mmol) in 10 ml THF according to the procedure of Kochi (4). The resulting reaction mixture was stirred at RT for 30 min. The reaction mixture was quenched with an acidic brine solution and extracted with ether (3x20-ml). The ether layers were combined, washed with water (1x20-ml), and dried over magnesium sulfate. After filtration, the ether was evaporated and the remaining yellow liquid was purified by distillation through a 10 cm vigreux column (60-65°C, 0.4 mm) to give the desired product (9.65 g, 57%): NMR (δ) 1.5 (4H,m), 2.90 (2H,m), 7.34 (5H,m), apparently broadened by paramagnetic impurities.

1-Iodo-4-²H₃-butane: 1-Phenylthio-4-²H₃-butane (9.6 g, 0.057 mol) was heated under reflux with methyl iodide (81 g, 0.57 mol) in a suspension of 9g sodium iodide in 50 ml DMF for 18 h according to the procedure of Corey (6). The reaction mixture was quenched with water and extracted with hexane (3x20-ml). The hexane layers were combined and washed with an aqueous solution of sodium thiosulfate (2x20-ml) and dried over magnesium sulfate. After filtration, the hexane was evaporated to give a yellow liquid which was purified by distillation through a 10 cm Vigreux column (58-60°C, 70 mm) to give the desired product (3.73 g, 35%): NMR (δ) 1.36(2H,m), 1.80(2H, quint, J=7), 3.16(2H, t, J=7).

Dimethyl-(7-²H₃-2-oxoheptyl) phosphate: The dianion of dimethyl-(2-oxopropyl)-phosphonate (3.32 g, 0.02 mol) was prepared and alkylated with 1-iodo-4-²H₃-butane (4.2 g, 0.23 mol) following the procedure of Grieco (2). Short path distillation (105-110°C, 0.15 mm) gave the desired product (2.14 g, 48%) NMR (δ) 1.24(4H,m), 1.56(2H,m), 2.56(2H, t, J=6), 3.30(2H, d, J=22), 3.70(6H, d, J=11).

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