SYNTHESIS OF PINACOLYL [^{14}C]METHYLPHOSPHONOCHLORIDATE

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SUMMARY

A three-step synthetic route to pinacolyl [^{14}C]methylphosphonochloridate (3) from [^{14}C] methyl iodide is described. Condensation of sodium di-n-butyl phosphite with [^{14}C] methyl iodide gave di-n-butyl [^{14}C] methylphosphonate (1) which was converted into [^{14}C] methylphosphonic dichloride (2) by prolonged refluxing with thionyl chloride. Reaction of 2 with pinacolyl alcohol in the presence of N,N-di-n-propylaniline as the base afforded the title compound 3. The radiochemical yield of redistilled 3 was 34,2% based on 1, and the overall radiochemical yield was 20,0% from [^{14}C] methyl iodide.

Key Words: Di-n-butyl- [^{14}C] methylphosphonate, [^{14}C] methylphosphonic dichloride, pinacolyl [^{14}C], methylphosphonochloridate.

INTRODUCTION

For cholinesterase inhibition studies. pinacolyl methylphosphonochloridate (3) labelled with carbon-14 at the methyl group linked to the phosphorus atom was required. Several routes for preparation of inactive 3, have been described (1-3). Most fre

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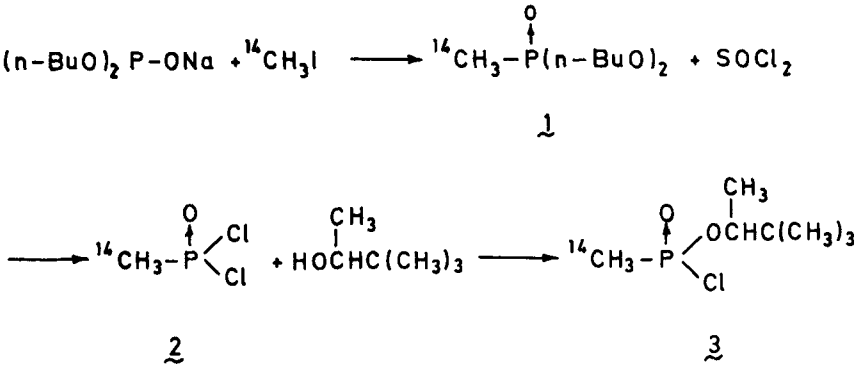
quently used involves the Arbusov reaction of trimethyl phosphite and methyl iodide to give dimethyl methylphosphonate in high yield. The latter compound is then converted into methylphosphonic dichloride (2), either directly or after hydrolysis to methylphosphonic acid, by using phosphorus pentachloride or thionyl chloride as chlorinating agents (3-5). The reaction is, however, not a clean one, and often a variety of side products are formed which cannot be separated from the volatile and hygroscopic dichloride. The final step in the synthesis of 3 involves the condensation of 2 with an equivalent of pinacolyl (1,2,2-trimethylpropyl) alcohol in the presence of a base. The mono-esterification reaction does not proceed (6) so straight-forwardly as just mentioned, and yields of 3 below 50% have been reported in the literature (7,8).

Introduction of the label into the phosphorus-attached methyl group of methylphosphonate cannot be performed by reacting trimethyl phosphite with $[^{14}C]$methyl iodide. If the alkyl halide and alkyls of the phosphite ester are identical, the Arbusov reaction becomes formally catalytic, and traces of methyl iodide are sufficient to convert a large amount of trimethyl phosphite into the isomeric dimethyl methylphosphonate (9). An alternate Arbusov reaction, developed by Kosolapoff (10, 11) for the synthesis of alkylphosphonates having a higher alkyl member was adopted therefore for the synthesis of $[^{14}C]$-labelled methylphosphonate. The advantage of this method, involving condensation of sodium di-*n*-butyl phosphite in hexane with an alkyl halide, is the solubility of the sodium salt in most organic solvents, thus making the preparation and isolation of the product much easier.

The present paper describes a three-step synthesis of $[^{14}C]$-labelled 3, as outlined in Scheme 1, by using $[^{14}C]$methyl iodide as the starting radioactive material. The synthetic route was adapted to the small scale preparation. For the last reaction-step, a more efficient procedure, than that commonly used for the preparation of inactive 3, was developed.

RESULTS AND DISCUSSION

Working on a 10 mmol scale, several runs of low-specific-activity di-n-butyl [^{14}C]methyl phosphonate (1) were prepared in high chemical (70-75%) and radiochemical (73-78%) yields by treating sodium di-n-butyl phosphite in hexane with [^{14}C]methyl-iodide (0.1-0.2 mCi). However, conversion of the procedure to the 4 mmol scale led to a considerable (~ 20%) reduction in yields of 1, which may be due to a partial solubility of the product in aqueous phase. Because extraction of the hexane layer with water is crucial for the purity of 1, the procedure was followed in high-specific-radioactivity preparations, performed on 4-6 mmol scale, to give 1 free of chemical and radiochemical contaminants.



Scheme 1

The initial approach to [^{14}C]methyl phosphonic dichloride (2) involved hydrolysis of the di-n-butyl ester 1 and treatment of the free acid with PCl_5 (2-4). Attempts to prepare 2 on a small scale by this reaction pathway were unsuccessful due to difficulties with removal of hydrochloric acid from the highly hygroscopic methylphosphonic acid and the failure to isolate the volatile dichloride 2 from the partially polymerized reaction mixture by fractional distillation.

Moedritzer and Miller (5) described a one-step, high-yield synthesis of methylphosphonic dichloride from dimethyl methyl-phosphonate by slow addition of the ester in a excess of reflux-

ing thionyl chloride. By ^{1}H and ^{31}P NMR spectroscopic measurements, the authors were able to show that a minimal concentration of dimethyl methylphosphonate in the chlorinating agent is imperative for keeping non-reversible side reactions of the starting methylphosphonate, intermediate methyl methylphosphonochloridate and ultimate methylphosphonic dichloride at the lowest level possible. However, the same procedure did not work so well for diethyl ethylphosphonate and failed completely for di-n-butyl n-butylphosphonate (5).

We studied the above procedure with di-n-butyl methylphosphonate (1) in detail and found that the first O-n-butyl group was readily replaced by the chlorine atom, but the second ester group replacement required a much longer refluxing time (4-6 days). The progress of the reaction was followed by ^{1}H NMR spectra of the reaction mixture: the doublet at 1.85 ppm (J 17 Hz), corresponding to the phosphorus-linked methyl group of the intermediate n-butyl methylphosphonochloridate, decreased with time on the account of a second doublet at 2.5 ppm (J 17 Hz) associated with the CH_3-P group of methylphosphonic dichloride (2). Variation of reaction conditions showed (^{1}H NMR spectra) that a slow addition of 1 to the boiling thionyl chloride and a continuous reflux of the reaction mixture were crucial for a good yield of 2 (55-65% after distillation). However, working on a small scale led to considerable losses of 2 during fractional distillation. Additional inactive and low-activity tracer experiments showed that distillation of 2 from the reaction mixture was unnecessary: removal of thionyl chloride and n-butyl chloride left a residue of a mixture of 2 and some undistillable polymeric material (up to 25%) which was used directly, in the next reaction step.

The widely-used method for preparation of inactive pinacolyl methylphosphonochloridate (3) involves the reaction of methylphosphonic dichloride (2) with triethylamine and pinacolyl alcohol in an inert solvent (usually benzene) under reflux, followed by filtration of the precipitated hydrochloride salt, removal of the

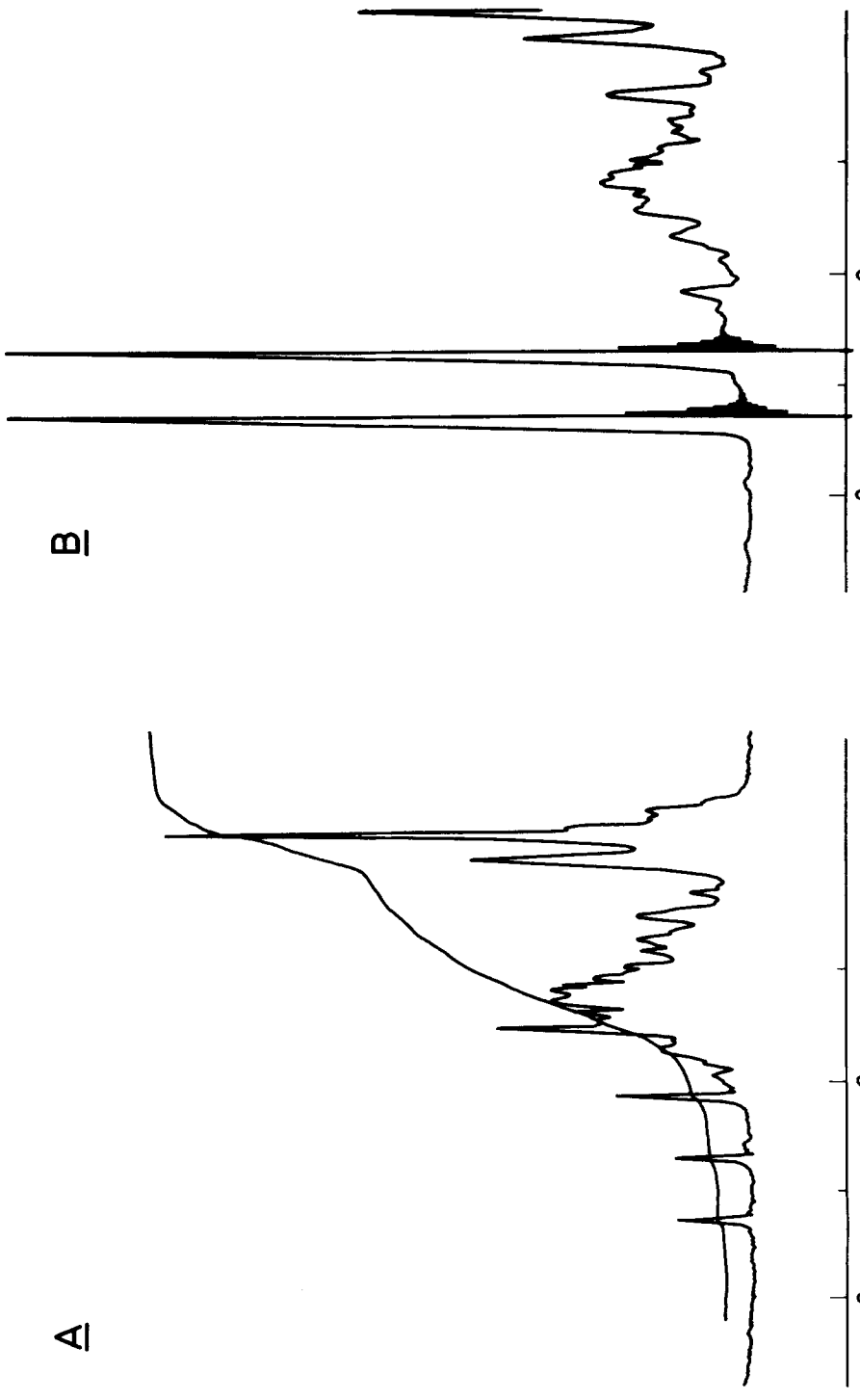


Fig. 1. Partial ^{1}H NMR spectra (phosphorus-linked methyl group) of the samples taken from the reaction of di-n-butyl-[^{14}C]methyl phosphonate (1) with thionyl chloride at various times: (A) after 2 days, (B) after 6 days.

solvent, and isolation of the product by distillation in rather modest [49% (7), 47% (8)] yields. This procedure was found to be unsuitable for small scale work. However, trial experiments, omitting the solvent and by using a less-volatile base than triethylamine - such as N,N-dimethyl- or N,N-diethylaniline - enable direct distillation of the product from the reaction mixture to give 3 in high yields, but contaminated with the corresponding amine salt. By using N,N-di-n-propylaniline in an equivalent proportion to methylphosphonic dichloride, a highly pure pinacolyl methylphosphonochloridate, not contaminated with the amine salt, was obtained.

Based on the above findings, a new procedure for the synthesis of 3, suitable for a small scale work, was developed. The fact that the yields of 3 (75-85%) were considerably higher than those obtained (7,8) by the common route, suggests a general applicability of the procedure for the synthesis of alkyl methylphosphonochloridates.

The reaction of crude [^{14}C]methyl phosphonic dichloride (2) with pinacolyl alcohol in the presence of N,N-di-n-propylaniline, carried out by the above procedure, afforded, after re-distillation, pinacolyl [^{14}C]methyl phosphonochloridate (3) in a 34.2% radiochemical yield based on di-n-butyl [^{14}C]methyl phosphonate (1). The specific activity of 3 was 0.32 mCi (11.7 MBq)/mmol and the overall radiochemical yield from [^{14}C]methyl iodide was 20.0%.

EXPERIMENTAL

All solvents were used dry and distilled. [^{14}C]Methyl iodide (50-60 mCi/mmol) was purchased from Amersham International Limited, Amersham, England. Radioactivity was measured in a Packard Tri-Carb Model 2425 liquid scintillation spectrometer. ^{1}H NMR spectra were recorded using a EM-360 Varian 60 MHz spectrometer.

Di-n-butyl [^{14}C]methyl phosphonate (1)

(a) - Metallic sodium (0.23 g, 10 mmol) was added to n-butanol (5 ml), and, after dissolution, di-n-butyl phosphite (1.94 g, 10 mmol) was added with stirring at 0°C. Stirring was continued for 1 hr at room temperature, excess of butanol was distilled (Rotavapor, bath 50°C), and the remaining viscous oil was dissolved in hexane (20 ml). The solution was transferred under exclusion of moisture into a dry long-neck, round-bottom 50 ml flask containing a magnetic stirring bar and frozen in liquid N_2. The flask was connected to the manifold, and [^{14}C]methyl iodide (2 x 0.1 mCi, 54 mCi/mmol) was transferred in vacuo (10^{-5} mm Hg) into the reaction vessel. The flask was filled with dry air, fitted with a reflux condenser protected by a $CaCl_2$ drying tube, and the reaction mixture was allowed to attain room temperature with occasional stirring. Inactive methyl iodide (0.65 ml, 10 mmol) was then added at 0°C, and the mixture was stirred for 1 hr at room temperature and then 1 hr at mild reflux of hexane. After cooling, water (5 ml) was added, the mixture was thoroughly shaken, and the aqueous layer was quantitatively transferred to an another flask and extracted with hexane (2 x 5 ml). The organic layers were combined, and the solvent, carrying traces of remaining water, was removed in vacuum (water aspirator, bath 40°C) to leave 1 (1.56 g, 75%, radioactive yield: 0.156 mCi, 78%) as a colourless liquid which distilled quantitatively at 59-62°C/0.05 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.34 (d, 3H, J 17 Hz, CH_3-P), partly overlapped with 0.8-1.7 multiplet (14 H, 2 x $-CH_2-CH_2-CH_3$); 3.88 (q, 4 H, $P(OCH_2)_2$).

(b) - By following the above procedure, condensation of sodium di-n-butyl phosphite (0.86 g, 4 mmol) in hexane (15 ml) with [^{14}C]methyl iodide (3 x 1 mCi + 0.5 mCi, spec. act. 55 mCi/mmol, 9 mg, 0.06 mmol) and inactive methyl iodide (0.25 ml, 3.94 mmol) was carried out in a 25 ml reaction flask; NaI and unreacted phosphite were removed by extraction with 3 ml of water. Radiolabelled 1 (400 mg, 47%) was obtained in 58% radioactive yield

(total: 2 mCi) with a specific activity of 1.05 mCi/ mmol. - In a second 6 mmol preparation with 4 mCi [^{14}C]methyl iodide, 1 (640 mg, 51%) was obtained in 50% radioactive yield (total: 2 mCi, spec. act.: 0.65 mCi/ mmol).

[^{14}C]Methyl phosphonic dichloride (2)

Freshly distilled thionyl chloride (2.5 g, 1.5 ml, 21 mmol) was brought to reflux in a magnetically stirred 5 ml round-bottom flask equipped with a Liebig condenser protected from moisture. Di-n-butyl [^{14}C]methyl phosphonate (1) (1.04 g, 5 mmol), 4 mCi - obtained from two preparations) was added in four portions by a long pipette at 1 hr intervals. The flask from which 1 was taken was rinsed with 1 ml of hexane, and the solution was added to the mixture within the next 1 hour. Refluxing and stirring was continued, and samples (50 µl diluted up to 0.4 ml with thionyl chloride) were taken for ^{1}H NMR spectra each 24 hr; after recording, the sample was returned to the flask, and, if necessary, additional thionyl chloride was added to maintain the starting volume. After 6 days of reflux, ^{1}H NMR spectrum of the reaction mixture showed that the process of chlorination was completed.

The bulk of thionyl chloride and n-butyl chloride was removed by distillation at atmospheric pressure, and, after addition of inactive dichloride 2 (133 mg, 1 mmol), traces of thionyl chloride were removed by evacuation (water aspirator) at short intervals until the weight of the residue was constant. The remaining mixture (estimated to contain ~ 3.5 mmol of [^{14}C]methyl phosphonic dichloride (2)) was used immediately in the next reaction step.

Pinacolyl methylphosphonochloridate (3)

In a round-bottom flask (15 ml) were added methylphosphonic dichloride (2.0 g, 15 mmol), pinacolyl alcohol (1.61 g, 15.75 mmol) and N,N-di-n-propylaniline (2.67 g, 15 mmol) under manual

shaking, and the flask was connected to an air condenser equipped with a $CaCl_2$ tube. After ~ 10 min, the exothermic reaction started spontaneously with separation of voluminous crystals of di-n-propylaniline hydrochloride. The solidified, fluffy mixture was kept at 80°C (silicon oil bath) for 1.5 hr, whereupon the flask was connected to a micro distillation unit provided with a short column, air condenser and fraction receiver. The main fraction distilled at 51-53°C/1.6 mm Hg to give 3 as a colourless oil; yield: 2.5 g, 82%, n_D^{23} 1.4418. ^{1}H NMR ($CDCl_3$): δ 1.85 (d, 3 H, J 17 Hz, CH_3-P), 0.92 (s, 9 H, $(CH_3)_3$), 1.32 (d, 3 H, J 6 Hz, CH_3-CH), 4.1-4.6 (m, 1 H, CH). Lit. (8): b.p. 69°C/2 mm Hg, n_D^{23} 1.4417.

Pinacolyl [^{14}C]methyl phosphonochloridate (3)

Crude [^{14}C]methyl phosphonic dichloride (2) (3.5 mmol) was dissolved in pinacolyl alcohol (0.39 g, 0.42 ml, 3.8 mmol), and the solution was transferred to a round-bottom 10 ml flask, followed by N,N-di-n-propylaniline (0.62 g, 3.5 mmol). The mixture was further treated as described for the inactive preparation, except that carrier 3 (500 mg, 2.5 mmol) was added to the reaction mixture before distillation. The product distilled at 50-53°C/1.5 mm Hg as a pale yellow oil (1.033 g) which was submitted to re-distillation to give radiolabelled 3 (870 mg), b.p. 50-52°C/1.5 mm Hg as a colourless oil, n_D^{23} 1.4419 in 34.2% radiochemical yield (total: 1.37 mCi/50.7 MBq) based on di-n-butyl [^{14}C]methyl phosphonate (1) and specific activity of 0.32 mCi (11.8 MBq)/mmol. - Addition of inactive 3 (700 mg), followed by distillation, afforded additional 0.127 mCi of 3 (500 mg) to raise the radiochemical yield to 37.4%. - The overall radiochemical yield of 3, based on [^{14}C]methyl iodide (7.5 mCi/277.5 MBq) was 18.3 + 1.7 = 20.0%.

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