Canadian Journal of Chemistry

Issued by THE NATIONAL RESEARCH COUNCIL OF CANADA

VOLUME 35 JULY 1957 NUMBER 7

THE ATTEMPTED SYNTHESIS OF TWO HEXOSE PHOSPHONATE ESTERS[1]

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ABSTRACT

The synthesis of glucose-1-methylphosphonate and isopropyl glucose-1-methylphosphonate has been attempted. Although the intermediates were successfully prepared, deacetylation failed to give the desired products.

The formation of biologically important phosphate derivatives of lipids, carbohydrates, and other substances is well known. However, it has recently been shown that under circumstances where hexose phosphate esters are enzymatically produced from phosphate, no analogous esters are formed from methylphosphonate (5).

The present report describes the attempted chemical synthesis of barium or potassium glucose-1-methylphosphonate and of isopropyl glucose-1-methylphosphonate. Although intermediates analogous to those encountered in the chemical preparation of glucose-1-phosphate were synthesized without difficulty, neither acid nor alkaline treatment (3, 8) gave the two desired compounds from the corresponding acetylated intermediates. In repeated attempts, white solids were obtained which proved to be either inorganic salts or rather impure glucose.

EXPERIMENTAL

Phenyl Methylphosphonochloridate

Equimolar amounts of phenol and methylphosphonyl dichloride (7) were allowed to react in a manner analogous to that described for the reaction of phenol with phosphorus oxychloride (2). After degassing and the removal of unreacted methylphosphonyl dichloride at about 90° C. (temperature of distillation flask) and 8–10 mm. pressure, the material distilling at 60–80° C. and 0.01–0.02 mm. was collected. A rather large non-volatile fraction probably represented diphenyl methylphosphonate. The crude material was redistilled and, except for a small forerun and residue, was collected at 67–69° C. and 0.01 mm.; $n_D^{27} = 1.5234$; final yield 49%. Calc. for $C_7H_8O_2ClP$: C, 44.12; H, 4.23. Found: C, 43.84; H, 4.52.

Silver Phenyl Methylphosphonate

Phenyl methylphosphonochloridate (80 g., 0.42 mole) was poured over 200 g. ice with shaking. When all of the ice had melted, the cloudy aqueous mixture was extracted several times with ether, the combined ether extracts were back-extracted once with water, and the ether solution was dried with anhydrous magnesium sulphate. After filtration the ether was evaporated and the remaining oily material was dried *in vacuo*

[1]*Manuscript received January 21, 1957.*
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at about 65° C. A portion was heated in a distilling apparatus to 200° C. at 0.005 mm. but no distillate was obtained. On cooling, the material showed only slight discoloration but had become quite viscous. Probably a considerable amount of phenyl methylphosphonic anhydride, $(CH_3P(O)OC_6H_5)_2O$, had been formed.

The remaining impure phenyl methylphosphonic acid was converted to its silver salt by being heated on a steam bath with an excess of freshly prepared silver oxide suspended in a large volume of hot water. After being heated for 15 minutes, the slurry was filtered hot and the filtrate was evaporated to dryness. Following vacuum desiccation the yield of crude silver phenyl methylphosphonate was nearly quantitative. A hot aqueous solution of this salt was treated with norite, filtered, recrystallized by reduction of the solvent volume and cooling, and was desiccated *in vacuo* over silica gel. Yield was 82% based on phenyl methylphosphonochloridate, allowance being made for the fraction used for the attempted distillation. The silvery white platelets darkened slightly at about 150° C. and melted sharply at 221° C. with decomposition. Calc. for $C_7H_8O_3AgP$: C, 30.13; H, 2.89. Found: C, 30.34; H, 3.11.

2,3,4,6-Tetraacetylglucose-1-methylphosphonate Phenyl Ester

A total of 9.5–10 g. (approximately 0.035 mole) of silver phenyl methylphosphonate was reacted with 10.0 g. (0.0243 mole) acetobromoglucose (6) according to the directions of Posternak (8) for the reaction of silver diphenyl phosphate and acetobromoglucose. The resulting sirup crystallized readily. The product was recrystallized twice from anhydrous ether – absolute ethanol, treated with norite, and recrystallized once more. The resulting white crystalline powder was readily soluble in ethanol and only slightly soluble in ether or water giving a neutral solution in the latter which yielded no precipitate on addition of silver nitrate. Yield 39%; m.p. 89–93° C. without elevation on subsequent recrystallizations, $[\alpha]_D$ −7.5° (*c*, 0.4, ethanol–water).* Calc. for $C_{21}H_{27}O_{12}P$: C, 50.20; H, 5.42. Found: C, 50.15; H, 5.53.

2,3,4,6-Tetraacetylglucose-1-methylphosphonic acid

2,3,4,6-Tetraacetylglucose-1-methylphosphonate phenyl ester (4.2 g., 0.008 mole) was exhaustively hydrogenated in absolute ethanol in the presence of 0.4–0.5 g. platinum oxide catalyst (1). The uptake of hydrogen was complete within the first hour. The alcoholic solution was filtered hot to remove catalyst. The filtrate was cooled and the product crystallized readily. The product, after filtration, was washed several times with anhydrous ether, recrystallized from absolute ethanol, and desiccated *in vacuo* over silica. Yield 87%; needles, m.p. 152° C., $[\alpha]_D$ −4.7° (*c*, 0.4, water). Calc. for $C_{15}H_{23}O_{12}P$: C, 42.26; H, 5.44. Found: C, 42.28; H, 5.62.

Silver Isopropyl Methylphosphonate

The silver salt of isopropyl methylphosphonic acid, referred to briefly in a previous publication (4), was synthesized and purified by reactions analogous to those described for the synthesis of silver phenyl methylphosphonate. Isopropyl methylphosphonic acid was collected at 80° C. and 0.008 mm.; $n_D^{25} = 1.4232$. Calc. for $C_4H_{11}O_3P$: C, 34.78; H, 8.03. Found: C, 34.66; H, 7.95. The silvery white platelets of silver isopropyl methylphosphonate darkened slightly at about 120° C. and melted with decomposition at 210–220° C. Calc. for $C_4H_{10}O_3AgP$: C, 19.61; H, 4.11. Found: C, 19.62; H, 4.17.

**A small-bore, 4 dm. polarimeter tube was used for this and subsequent determinations.*

2,3,4,6-Tetraacetylglucose-1-methylphosphonate Isopropyl Ester

A total of 8.5–9 g. (approximately 0.035 mole) of silver isopropyl methylphosphonate was reacted with 10.0 g. (0.0243 mole) acetobromoglucose. After thorough drying the resulting sirup crystallized with some difficulty on addition of petroleum ether. The product was recrystallized twice from ether – petroleum ether and desiccated *in vacuo* over silica. The fine white crystals were readily soluble in ether, ethanol, or water, giving a neutral solution in the latter which yielded no precipitate on addition of silver nitrate. Yield, 60%; m.p. 73–75° C. Calc. for $C_{18}H_{29}O_{12}P$: C, 46.15; H, 6.24. Found: C, 46.43; H, 6.34. Successive recrystallizations finally gave a product melting at 77–79° C., $[\alpha]_D$ −4.2° (*c*, 3.1, ethanol–water). Found: C, 46.34; H, 6.56.

Attempted Deacetylation

Repeated attempts to deacetylate 2,3,4,6-tetraacetylglucose-1-methylphosphonic acid with hydrochloric acid in methanol (3) or with dilute sodium hydroxide (8) according to the methods described for the preparation of glucose-1-phosphate led only to inorganic salts which, when subjected to qualitative tests, appeared to be either barium chloride or potassium sulphate, depending on the method employed. Similar attempts to deacetylate 2,3,4,6-tetraacetylglucose-1-methylphosphonate isopropyl ester and to isolate a neutral product yielded a white amorphous substance. Elemental analysis and optical rotation indicated that the product was rather impure glucose.

ACKNOWLEDGMENTS

For the general methods of preparation of methylphosphonic acids and their silver salts from the corresponding methylphosphonohalidates, I have drawn on unpublished results of Mr. A. H. Ford-Moore. Analyses were performed by Mr. Tom Stewart of the Suffield Experimental Station, Ralston, Alberta.

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