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Synthesis of 2'-Deoxynucleoside 5'-Methylenebis-(phosphonate)s Using 2-(4-Nitrophenyl)ethyl Methylenebis(phosphonate) as the Phosphonylating Agent.

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SYNTHESIS OF 2'-DEOXYNUCLEOSIDE 5'-METHYLENEBIS-(PHOSPHONATE)S USING 2-(4-NITROPHENYL)ETHYL METHYLENEBIS(PHOSPHONATE) AS THE PHOSPHONYLATING AGENT.

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Abstract: 2-(4-Nitrophenylethyl) methylenebis(phosphonate) (**1**) has been prepared by reaction of 2-(4-nitrophenyl)ethyl alcohol with methylenebis(phosphonyl) tetrachloride. Compound **1** was treated with diisopropylcarbodiimide (DIC) to give bicyclic intermediate **2**, which in reaction with suitably protected 2'-deoxynucleosides **3** gave P¹,P²-disubstituted methylenebis(phosphonate)s **4**. Removal of the nitrophenylethyl group by β -elimination with DBU afforded the corresponding 2'-deoxynucleoside 5'-methylenebis(phosphonate) analogues **5**.

INTRODUCTION

Recently, we synthesized several P¹, P²-disubstituted methylenebis(phosphonate)s of biological interest using a new method of activation of nucleoside 5'-methylenebis(phosphonate)s with dehydrating agents such as dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC).^{1,2}

Although our method of coupling of nucleoside 5'-methylenebis(phosphonate)s with nucleosides or alcohols was efficient,^{1,2} the synthesis of the starting nucleoside 5'-methylenebis(phosphonate)s was rather problematic especially in the case of purine nucleosides. It is known that the DCC coupling of nucleosides with methylenebis(phosphonic acid) is inefficient due to formation of polyphosphates.³ The more attractive approach, described by Poulter,⁴ was nucleophilic displacement of the 5'-tosyloxy group of nucleosides with tris(tetra-butylammonium) salt of methylenebis(phosphonic acid). In the case of purine nucleosides, however, such 5'-tosylates

This paper is dedicated to the 60th birthday of Professor Jacques H. van Boom.

readily form cyclic 3,5'-nucleosides giving low yield of the desired nucleoside 5'-methylenebis(phosphonate)s.⁵ Almost exclusive formation of 3,5'-cyclic purine nucleosides has been reported in an attempted phosphorylation of the 5'-hydroxyl group of purine nucleosides *via* the Mitsunobu reaction (carried out in DMF or HMPA).⁶ Recently, however, the Mitsunobu reaction (in pyridine) has been successfully applied for phosphorylation and phosphonylation of purine nucleosides.⁷ This approach, however, requires the synthesis of tribenzyl ester of methylenebis(phosphonic acid)⁸ followed by debenzylation.

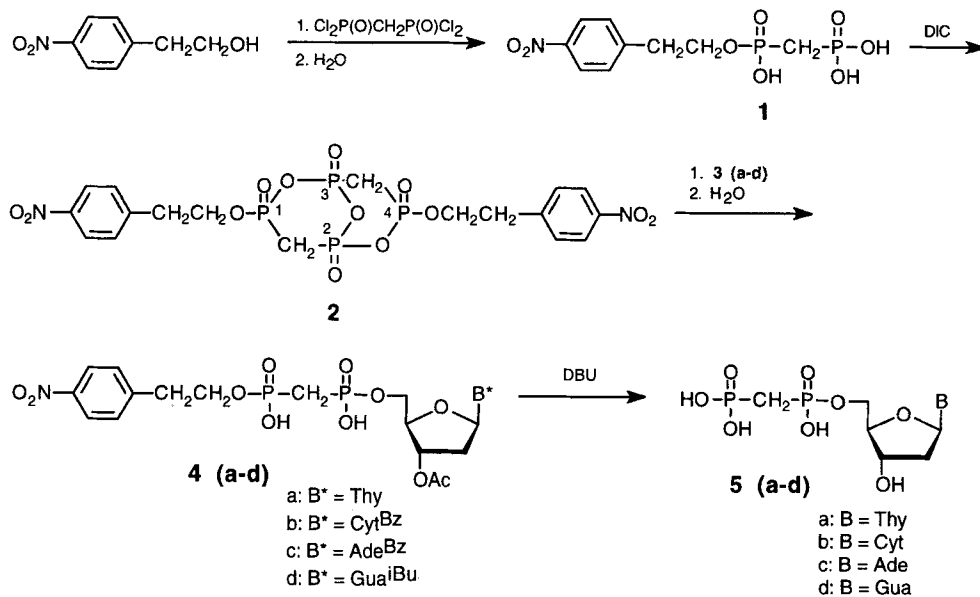
Herein we report a general synthesis of 2'-deoxynucleoside 5'-methylenebis(phosphonate)s using anhydride **2** prepared from 2-(4-nitrophenyl)ethyl methylenebis(phosphonate) (**1**, **SCHEME 1**).

RESULTS AND DISCUSSION

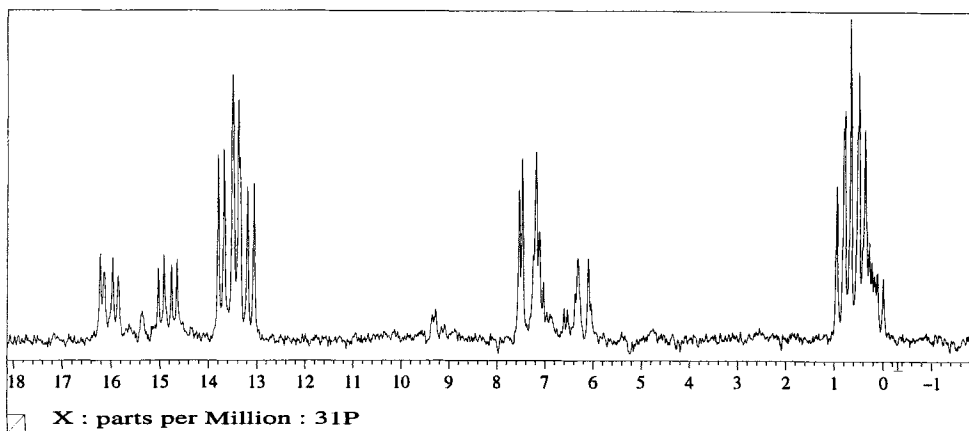
2-(4-Nitrophenyl)ethyl methylenebis(phosphonate) (**1**) was prepared from equimolar amounts of 2-(4-nitrophenyl)ethyl alcohol and methylenebis(phosphonyl) tetrachloride.⁹ After hydrolysis of methylenebisphosphonyl chlorides, with 1M triethylammonium bicarbonate a mixture of mono-, di-, and tri-nitrophenylethyl esters of methylenebis(phosphonic acid) was obtained. The major product, the desired mono-ester derivative **1**, was isolated by HPLC in 36% yield.

Treatment of **1** with DIC in pyridine afforded **2** as a mixture of diastereomers due to presence of four chiral phosphorus atoms. The ³¹P NMR spectrum of the mixture shows multisignal resonances (**FIGURE 1**).

Addition of 3'-O-acetylthymidine¹⁰ (**3a**) at this stage of the reaction caused gradual simplification of ³¹P NMR spectrum which showed two narrow multiplets at δ 7 and 18 ppm. Finally, addition of water to the reaction mixture resulted in the ³¹P NMR showing an AB system (as a major signal) of the desired product **4a**. In the same manner, reaction of **2** with 3'-O-acetyl-2'-deoxy-N⁴benzoylcytidine¹⁰ (**3b**), 3'-O-acetyl-2'-deoxy-N⁶-benzoyladenosine¹⁰ (**3c**), and 3'-O-acetyl-2'-deoxy-N²-iso-butyrylguanosine¹⁰ (**3d**) afforded the corresponding 4-nitrophenylethyl protected nucleotide analogues **4b-d** in good yields. Treatment of **4a-d** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) caused removal of the 4-nitrophenylethyl group by β -elimination. The base labile 3'-O-acetyl, N-acetyl, N-benzoyl, and N-isobutyryl protecting groups were also removed simultaneously. Thus, the desired 5'-methylenebis(phosphonate) of thymidine (**5a**), 2'-deoxycytidine (**5b**), 2'-



SCHEME 1

Figure 1. ^{31}P NMR spectrum of the reaction mixture of **1** with DIC in pyridine.

deoxyadenosine (**5c**), and 2'-deoxyguanosine (**5d**) were obtained in overall 53%, 53%, 45% and 31% yields, respectively.

On the basis of the known reactivity of nucleoside bicyclic trisanydrides¹ it is reasonable to assume that our 4-nitrophenylethyl intermediate **2** would also react with a variety of nucleosides, alcohols, and carbohydrates. Therefore, 2-(4-nitrophenyl)ethyl methylenebis(phosphonate) (**1**), as a precursor of **2**, is expected to have a broad application as a versatile reagent for the synthesis of methylenebis(phosphonate) analogues of variety of nucleoside pyrophosphates and related derivatives.

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10. Nucleosides **3a-d** were synthesized from commercially available 2'-deoxy-5'-O-dimethoxytritylthymidine, 2'-deoxy-5'-O-dimethoxytrityl-N⁴-benzoylcytidine, 2'-deoxy-N⁶-benzoyladenine, and 2'-deoxy-N²-isobutyrylguanosine by acetylation with acetic anhydride in pyridine followed by removal of dimethoxytrityl group by treatment with 80% acetic acid.