Preparation of Nucleoside 3′,5′-Cyclic Phosphates *via* Phosphotriester Intermediates

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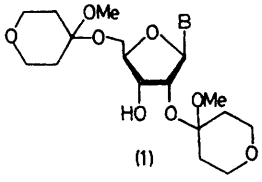
Summary Several ribonucleoside 3′,5′-cyclic phosphates (**7b**) have been prepared in good yields by the action of base on the corresponding 2′-protected 3′-diphenyl phosphates (**5**); thymidine 3′,5′-cyclic phosphate (**7**; R = H, B = thymine-1) has similarly been prepared from both thymidine 3′- and 5′-diphenyl phosphates (**8a** and **8b**).

IN connection with our work on the synthesis of oligoribonucleotides, we have developed methods[1,2] for the preparation of 2′,5′-protected nucleoside building blocks (**1**) and (**2**). We have previously shown[3] that the diacetals (**1**) are suitable intermediates for the preparation of ribonucleoside 2′,3′-cyclic phosphates and now report that the 2′-acetal-5′-esters (**2**) may readily be converted into the corresponding 3′,5′-cyclic phosphates (**7b**) in good overall yields.

The uridine derivative[2] [**2**; B = (**3**)] was treated (20°, 16 h) with diphenyl phosphorochloridate (1·3 molecular equivalents) in acetonitrile solution, in the presence of 5-chloro-1-methylimidazole[3] (3 molecular equivalents). The product was purified by chromatography on silica gel, and then treated with dilute aqueous ammonia to give 2′-*O*-methoxytetrahydropyranyluridine 3′-diphenyl phosphate‡ [**5**; B = (**3**)] which was obtained as a colourless crystalline solid, m.p. 123—125°, in 79% yield. Treatment of this compound with an excess of potassium t-butoxide in anhydrous dimethyl sulphoxide solution at 20° gave the cyclic phosphotriester [**6**; B = (**3**)] which was isolated as a colourless solid in 61% yield. Unless rigorous precautions were taken to exclude water, no cyclic phosphotriester was obtained but [**5**; B = (**3**)] was quantitatively converted into the cyclic phosphodiester [**7a**; B = (**3**)]. Hydrolysis of [**5**; B = (**3**)] under mild acidic conditions gave unprotected uridine 3′,5′-cyclic phosphate [**7b**; B = (**3**)] as the sole nucleotide product which was then isolated as its pure triethylammonium salt in 90% yield, based on [**5**; B = (**3**)].§

The general usefulness of this approach to the synthesis of nucleoside 3′,5′-cyclic phosphates was demonstrated by the preparation of the biologically-important adenosine compound [**7b**; B = (**4b**)] and three of its derivatives. The crystalline 2′-*O*-methoxytetrahydropyranyl 3′-diphenyl phosphate esters of N^6-*p*-anisoyl-, N^6-methyl- and N^6N^6-dimethyl-adenosines [**5**; B = (**4a**), (**4c**), and (**4d**)] were obtained in 65, 70 and 71% yields, respectively, from the appropriate ketal esters [**2**; B = (**4a**), (**4c**), and (**4d**)]. These phosphotriester intermediates were converted into the corresponding 3′,5′-cyclic nucleotides [**7b**; B = (**4a**), (**4c**), and (**4d**)] which were then isolated as pure triethylammonium salts in 82, 90 and 80% yields, respectively.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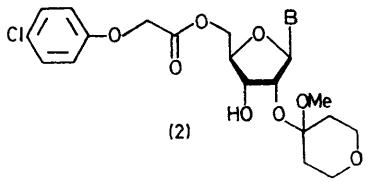
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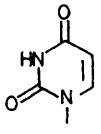
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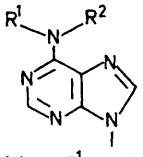
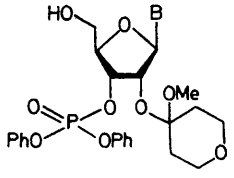

(4) a; R^1 = *p*-MeO·C_6H_4CO, R^2=H
b; R^1 = R^2 = H
c; R^1 = Me, R^2 = H
d; R^1 = R^2 = Me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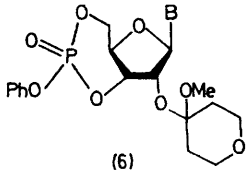
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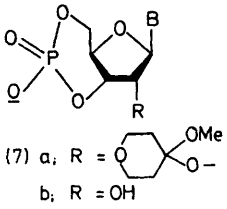
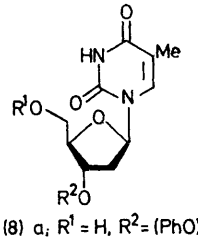

(7) a; R = Ado
b; R = OH


(8) a; R^1 = H, R^2 = $(PhO)_2P(O)$-
b; R^1 = $(PhO)_2P(O)$-, R^2 = H

Adenosine 3′,5′-cyclic phosphate [**7b**, B = (**4b**)] itself was obtained in quantitative yield by treating its N^6-*p*-anisoyl derivative [**7b**; B = (**4a**)] with aqueous ammonia.

† Alternatively, the 5′-*O*-*p*-chlorophenoxyacetyl protecting group may conveniently be removed by treatment with K_2CO_3–MeOH.

‡ Satisfactory analytical data were obtained for all the phosphotriester intermediates described.

§ The experimental procedure adopted for the conversion of [**5**; B = (**3**)] into uridine 3′,5′-cyclic phosphate [**7b**; B = (**3**)] was as follows. A solution of [**5**; B = (**3**)] (0·5 mmol) in dimethyl sulphoxide (2 ml) was stirred at 20° with a suspension of potassium t-butoxide (7 mmol) in dimethyl sulphoxide (7 ml). After 90 min, the products were neutralized (Dowex 50, pyridinium form; 5 g) and the solvent removed. After an acidic hydrolysis step (pH 2, 20°, 16 h), pure uridine 3′,5′-cyclic phosphate [**7b**; B = (**3**)] was isolated by chromatography on DEAE-cellulose. This procedure is general but the acidic hydrolysis step is unnecessary in the case of the preparation of thymidine 3′,5′-cyclic phosphate.

The present method was also found to be suitable for the preparation of deoxyribonucleoside 3′,5′-cyclic phosphates (**7**; R = H). Thus thymidine 3′, 5′-cyclic phosphate (**7**; R = H, B = thymine-1) was obtained when either thymidine 3′-or 5′-diphenyl phosphate [(**8a**) or (**8b**)] was treated with potassium t-butoxide in dimethyl sulphoxide solution under the above conditions; it was isolated as its pure triethylammonium salt in 90 and 80% yields from the respective starting materials.

Nucleoside 3′,5′-cyclic phosphates have previously been prepared by the cyclization of phosphomonoester[4] and phosphodiester[5] derivatives. The present phosphotriester approach has the advantage that all the intermediates, such as [**5**; B = (**4a**)—(**4d**)], (**8a**) and (**8b**), so far prepared can be isolated as pure crystalline solids. A more important advantage suggested by some very recent experiments is that the cyclization reaction does not seem to be affected significantly by the presence of substantial quantities of water. Thus, when [**5**; B = (**3**)] was treated with potassium hydroxide in Me_2SO–H_2O (9:1, v/v), the corresponding 3′,5′-cyclic phosphate [**7a**; B = (**3**)] accounted for nearly all (*ca.* 98%) of the nucleotide products obtained.

(*Received*, 20*th May* 1974; *Com.* 574.)

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