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RING OPEN ANALOGUES OF DEOXYNUCLEOTIDES

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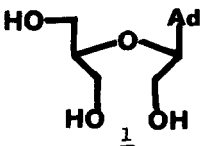
The synthesis of acyclic analogues of 2'-deoxyadenosine and 2'-deoxythymidine which lack only the 2'-CH_2 of the sugar is described. The synthesis of dinucleotides from these analogues is also described.

Adenosine analogues have high potential as chemotherapeutic agents (1) but their practical value is often greatly reduced by their ready deamination in vivo by deaminases (2,3). Consequently, numerous investigations have been carried out to determine the relationship between structure and activity for both substrates and inhibitors of adenosine deaminase (4-10). Many of these studies have involved ring-opened analogues of adenosine (4,8,9,10). De Clercq has recently reported on the antiviral activity of a number of analogues of nucleosides and he found that (S)-9-(2,3-dihydroxypropyl)adenine possesses selective antiviral activity (9). The 9-(2-hydroxyethoxy) derivatives of adenine (10) and guanine (9,11) have proven to be very interesting compounds.

In addition to the interest in adenosine deaminase activity, ring-opened analogues of adenosine have been phosphorylated to provide novel nucleotide analogues (12-14). Smrt and his colleagues have looked at compounds 1 and 2 as flexible analogues (12) of natural enzyme substrates and in modified terminor and initiator codons (13). In addition Pandit reported the synthesis of several 4-hydroxy-3-(hydroxymethyl)butyl derivatives (3) of purines and pyrimidines with the reported intention of preparing nucleotide analogues from them (15).



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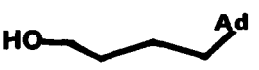

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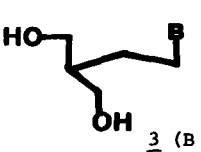
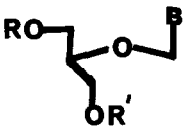


3 (B = Ad,Cy,Th)

We wish to describe the synthesis of the bis-(hydroxymethyl)methoxymethyl derivatives of adenine (A*, 4) and thymine (T*, 5) and several dinucleoside monophosphates derived from them. These compounds contain all of the functional characteristics (5'-hydroxyl,3'-hydroxyl,1'-oxygen) of the natural nucleosides but they lack the rigid ring structure.



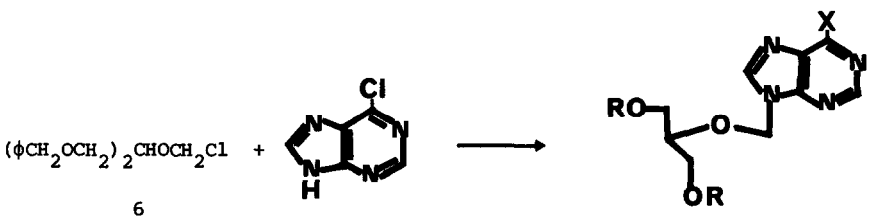
4 = A*; B = Adenine, R = R' = H

5 = T*; B = thymine, R = R' = H

(a) R = monomethoxytrityl (MMT); R' = H

(b) R = H; R' = t-butyldimethylsilyl (TBDMS)

The synthesis of A* involved the condensation of 6-chloropurine (6.5 mmole) with 1,3-dibenzyloxy-2-chloromethoxypropane (16) (6, 6.5 mmole) in DMF (4 ml) containing triethylamine (6.5 mmole) for 16 h at 25°C. The product 7 was isolated from TLC plates as an oil which was heated in a steel bomb at 95°C for 20 h with 60 ml of methanol saturated (0°C) with ammonia. Solvents were evaporated and the product 8 was obtained on precipitation from ethanol with ether. This compound was debenzylated using palladium oxide in methanol at 25 psi of hydrogen for 20 h. The catalyst was removed by filtration and on concentrating and cooling the methanol solution, the product 4 crystallized as a white solid (mp 184-186°C, m/e at 239, λ_{max}^{EtOH} 259 nm, R_f 0.12 ($CHCl_3$-EtOH, 4:1), the overall yield from 6-chloropurine was 27%).

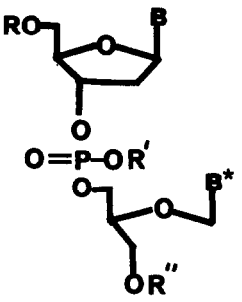


7, X = Cl, R = ϕCH_2

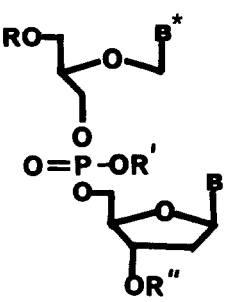
8, X = NH_2, R = ϕCH_2

The compound T* (5, mp 155-156°C, m/e at 230, λ_{max}^{EtOH} 264 nm, R_f 0.19 ($CHCl_3$-EtOH, 4:1) was obtained in two steps from 6 in an overall yield of 57%. The steps involved condensation of thymine wth 6 followed by debenzylation as described for A*.

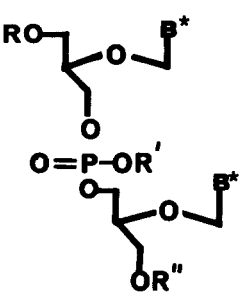
For the synthesis of dinucleotide analogues the compounds 4a,b and 5a,b were prepared by standard procedures (17,18). No attempt was made to resolve the stereoisomers of these compounds. The protected nucleotides 3, 9a-14a were prepared using the dichloridite procedure (19) which does not require protection of amino groups (19,20). The ratios used in all condensations was 1 eq. of tritylated nucleoside (e.g. 4a), 1.1 eq. of trichloroethylphosphorodichloridite and 0.9 eq. of the 3'-silyl nucleoside (eq. 4b). Yields and properties are recorded in the Table. The protected nucleotides were deprotected by successive treatments with 80% HOAc (15 min, 80°C) to remove MMT, Zn/Cu in DMF at 55°C for 2 h to remove TCE and finally tetrabutylammonium fluoride in THF to remove the silyl group. Yields for deprotection were all over 80% and the properties of the nucleotides are recorded in the Table.



9, B = B* = Th
10, B = B* = Ad



11, B* = B = Th
12, B* = B = Ad



13, B* = Th
14, B* = Ad

a) R = MMT, R' = TCE; R" = TBDMS
b) R = R'= R" = H

A* was tested with adenosine deaminase and was found to be a poor substrate with a Km of 1.87×10^{-3} (Km for adenosine 4.83×10^{-5}). A* was also found to be a weak competitive inhibitor of adenosine deaminase (Ki = 2×10^{-4}).

The nucleotides 9b-14b were tested with spleen and snake venom phosphodiesterases and the amount of degradation after 6 h using reported conditions (20) are shown in the Table.

TABLE

Compound	mp. (°C)	λ_{max}^{EtOH} (nm)	R_f [1]	R_m^{Tp} [2]	%degradation [3] spleen	snake venom
9a	110-112	264	0.54[a]	—	—	—
10a	112-116	258	0.62[b]	—	—	—
11a	87-88	265	0.51[a]	—	—	—
12a	92-95	258	0.60[b]	—	—	—
13a	99-100	264	0.30[a]	—	—	—
14a	103-104	258	0.42[b]	—	—	—
9b,TpT*	—	264	0.55[c]	0.44	100	0
10b,dApA*	—	259	0.36[c]	0.20	85	0
11b,T*pT	—	264	0.55[c]	0.44	80	50
12b,A*pdA	—	258	0.33[c]	0.20	0	75
13b,T*pT*	—	264	0.5[c]	0.46	0	0
14b,A*pA*	—	258	0.32[c]	0.22	0	0

(1a,b) TLC on Brinkman silica gel TLC plates in (a) 1:1 Et_2O:Hexane (b) 6:1 $CHCl_3$-EtOH
(1c) Paper chromatography, Whatman 3MM paper, solvent A (20)
(2) Paper electrophoresis, pH 7.5 (3) 6 h, 37°C

Compounds TpT* and dApA* were better substrates for spleen enzyme than T*pT and A*pdA were for snake venom. An interesting observation is that T*pT was a substrate for spleen enzyme while A*pdA was not.

The results of biological screening and physical chemical studies on the modified nucleotides will be reported elsewhere.

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