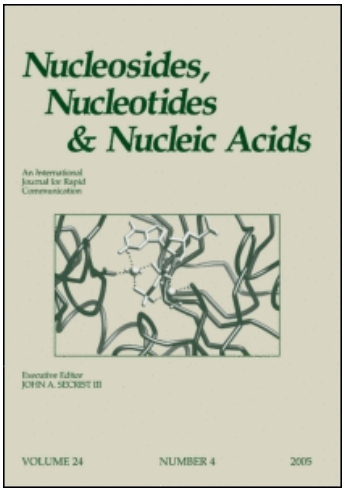

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Synthesis Aitd Properties of C'-Methylhuclsosides and Their Phosphoric Esters

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SYNTHESIS AND PROPERTIES OF C'-METHYLNUCLEOSIDES AND THEIR PHOSPHORIC ESTERS

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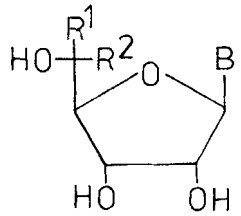
ABSTRACT. A brief review on the synthesis and properties of C'-methylnucleosides is given.

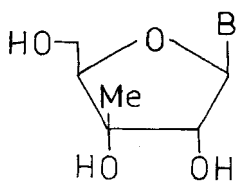
A traditional approach in preparing the analogs of nucleosides and nucleotides is to replace, or remove, functional groups. Although this approach has its merits, our purpose is to synthesize functionally competent analogs, preserving all the functionalities of the naturally occurring compounds in order to retain all possible sites of binding with the enzymes catalyzing the synthesis and decomposition of nucleic acids. In this short review we wish to give an account of the synthesis and properties of some functionally competent analogs: C'-methylnucleosides and their phosphoric esters.

The first reports were mainly focused on adenosine derivatives. Starting from L-rhamnose 5'-C-methyladenosines 1 and 2 were obtained[1], later it was shown[2] that it was possible to synthesize these compounds from adenosine derivatives.



1 R^1=Me, R^2=H

2 R^1=H, R^2=Me



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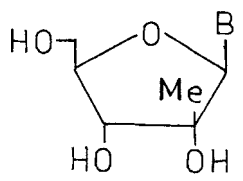

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The defined Baker's scheme was used for the preparation of 1 and 2 (B=Ura, Cyt, Ade)[3]. Nearly the same approach was utilized for the synthesis of cytidine derivatives 1 and 2[4]. Recently it was shown that purine 5'-C-methylnucleosides could be prepared from uridine derivatives 1 and 2 by microbilogical transglycosylation[5].

Walton and coauthors prepared[6a,b] 3 (B=Cyt, Ade) starting from D-xylose, the same group synthesized[6b,c] 4 from available 2-C-methyl-D-ribonolactone. Recently we have developed a general scheme for the preparation of 3'-C-alkylnucleosides[7] starting from 3-C-alkyl-D-allose derivatives. Moreover, it has been shown that starting from 3-C-methyl-D-allose it is possible also to prepare 2'-C-methylnucleosides 4 (B=Ura, Cyt, Ade)[8a,b]. The key step in another scheme[8b] for the synthesis of 4 is aldol condensation of 2,3-O-isopropylidene-5-O-trityl-D-ribose with formaldehyde. Very recently 4 (B=Cyt) was obtained by a multistep synthesis starting from uridine[8c]. The structure of 1-4 were unambiguously proved by X-ray analysis[7c,8b,9].

It appeared to be of interest to compare the conformational properties of C'-methylnucleosides with those of naturally occurring compounds. As for 5'-C-methylnucleosides 1 and 2, their conformation in solution is nearly the same as can be seen from the CD and PMR spectra[3]: almost the same Cotton effects, chemical shifts of 1',2',3'-protons and $J_{1',2'}$, $J_{2',3'}$ and $J_{3',4'}$ values as in the case of natural nucleosides. As can be seen from the PMR spectra of 3 the large values of $J_{1',2'}$=7.5-8.0 Hz might be due to the preferential S-type conformation[7], $^2T_3$ conformation was found in crystal of 3'-C-methylcytidine[7c]. An opposite conformation of N-type can be deduced from PMR spectra of 4 in solution[8a,b]. In crystal 2'-C-methyluridine adopted the rare $^3T_4$ conformation[8b]. These conformational peculiarities must be taken into account while considering the substrate properties of 1-4 and their phosphoric esters.

5'-C-Methyl derivatives of UMP and UTP were prepared[3c]. It was shown[10a] that E.coli RNA polymerase discriminates

D-allo- and L-talo-5'-triphosphates of 1 and 2. RNA polymerase does not support long-chain RNA synthesis from 5'-C-methyl-NTP in the absence of natural NTP. Not more than two analog residues can be attached to the 3'-end of the presynthesized RNA. Copolymerization of ATP and 5'-C-methyl-UTP(D-allo) yields a long poly-A-U analog. In the case of L-talo-isomer, RNA elongation is not inhibited only if the distance between the analog residues in the RNA chain is not shorter than five natural nucleotide residues[10a].

3'-C-Methyl-UTP was prepared[7c] and found to be a terminator of RNA synthesis, it can be used[10b] for nucleic acid sequencing with DNA-dependent RNA polymerase from E. coli. This termination of RNA synthesis may be associated with the antiviral activity of 3'-C-alkylnucleosides[6b,11].

Using the conventinal methodology, several dinucleosides monophosphates were prepared[12] on the basis of 1,2 and the kinetic parameters for their hydrolysis catalysed by RNAases with different specifity were measured[13].

REFERENCES

1. E.J.Reist, L.Goodman, R.R.Spencer, and B.R.Baker, J.Am.Chem.Soc., 1958, 80, 3962; E.J.Reist, L.Goodman, and B.R.Baker, ibid, 1958, 80, 5775.
2. P.Howgate and A.Hampton, Carbohydr.Res., 1972, 21, 309; R.S.Ranganathan, G.H.Jones, and J.G.Moffatt, J.Org. Chem., 1974, 39, 290.
3. (a) M.Ya.Karpeisky and S.N.Mikhailov, Bioorgan.Chem. (USSR), 1979, 5, 895; (b) S.N.Mikhailov, N.Sh.Padyukova, M.I.Struchkova, and S.V.Yarotsky, ibid, 1982, 8, 926; (c) M.Ya.Karpeisky, S.N.Mikhailov, and N.Sh.Padyukova, ibid, 1982, 8, 933.
4. S.David and G.deSennyey, J.Chem.Soc.Perkin I, 1982,385.
5. A.I.Zinchenko, V.N.Barai, L.A.Eroshevskaya, L.N.Beigelman, S.N.Mikhailov, M.Ya.Karpeisky, and I.A.Mikhailopulo, Proc. USSR Acad.Sci., 1987, 297, 731.
6. (a) R.F.Nutt, D.J.Dickinson, F.W.Holly, and E.Walton, J.Org.Chem., 1968, 33, 1789; (b) E.Walton, S.R.Jenkins,

R.F.Nutt, F.W.Holly, and M.Nemes, J.Med.Chem., 1969, 12, 306; (c) S.R.Jenkins, B.Arison, and E.Walton, J.Org. Chem., 1968, 33, 2490.

7. (a) A.Rosenthal and S.N.Mikhailov, Carbohydr.Res., 1980, 79, 235; (b) L.N.Beigelman, M.Ya.Karpeisky, and S.N. Mikhailov, Bioorgan.Chem.(USSR), 1981, 7, 1701; (c) S.N. Mikhailov, L.N.Beigelman, G.V.Gurskaya, N.Sh.Padyukova, G.I.Yakovlev, and M.Ya.Karpeisky, Carbohydr.Res., 1983, 124, 75; (d) L.N.Beigelman and S.N.Mikhailov, Proc. USSR Acad.Sci., 1987, 296, 1379.
8. (a) L.N.Beigelman, M.Ya.Karpeisky, and S.N.Mikhailov, Bioorgan.Chem.(USSR), 1986, 12, 1359; (b) L.N.Beigelman, B.S.Ermolinsky, G.V.Gurskaya, E.N.Tsapkina, M.Ya. Karpeisky, and S.N.Mikhailov, Carbohydr.Res., 1987, 166, 219; (c) A.Matsuda, K.Takenuki, H.Itoh, T.Sasaki, and T.Ueda, Chem.Pharm.Bull., 1987, 35, 3967.
9. G.V.Gurskaya, A.S.Zhdanov, S.N.Mikhailov, and E.N.Tsapkina, Cryst.Struct.Comm., 1982, 11, 1245; G.V.Gurskaya, G.M.Javadova, and S.N.Mikhailov, ibid, 1982, 11, 1253.
10. (a) V.A.Aivazashvili, S.N.Mikhailov, N.Sh.Padyukova, R.Sh. Beabealashvili, and M.Ya.Karpeisky, Mol.Biol.(USSR),1987, 21, 1080; (b) Bioorgan.Chem.(USSR), 1986, 12, 708.
11. E.DeClercq, unpublished results.
12. N.Sh.Padyukova and J.Smrt, Coll.Czech.Chem.Comm., 1980, 45, 2550.
13. G.I.Yakovlev, A.L.Bocharov, G.P.Moiseyev, and S.N.Mikhailov, FEBS Letters, 1985, 179, 217; Bioorgan.Chem. (USSR), 1985, 11, 205.