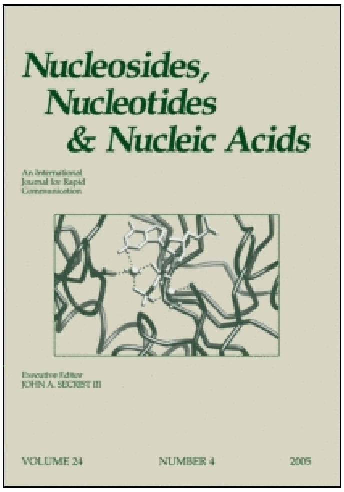

Nucleosides, Nucleotides and Nucleic Acids

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Regiospecipic Synthesis of a New Cross-Linked Dinucleoside : 1-(N^6-Deoxyadenyl)-2-(o^4-Thymidyl)-Ethane

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REGIOSPECIFIC SYNTHESIS OF A NEW CROSS-LINKED DINUCLEOSIDE : 1-(N^6-DEOXYADENYL)-2-(O^4-THYMIDYL)-ETHANE

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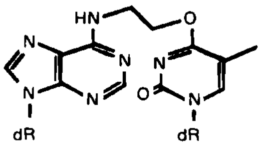
Abstract. The bridged dinucleoside 1-(N^6-deoxyadenyl) 2-(O^4-thymidyl)-ethane was prepared from the nucleophilic substitution of a O^4-triazolyl thymidine by a N^6-(2-hydroxyethyl) deoxyadenosine derivative via the corresponding 6-halogeno hypoxanthine in ribose and deoxyribose series.

During the course of our studies on cross-linked dinucleosides[1,2], we required a regiospecific synthesis of the bridged dinucleoside 1. This compound has been previously suggested[3,4] to be formed in the reaction of N,N'-bis(2-chloroethyl)-N-nitrosourea (BCNU) with DNA. In this paper, we wish to report the synthesis of the dimer 1 from appropriate protected 6-substituted (deoxy) inosine and O^4-triazolyl thymidine[5]. The N^6-(2-hydroxyethyl) deoxyadenosine derivative 3 and 4 are theoretically available either from triazolation of deoxyinosine or from 6-halogeno deoxyinosine.

Triazolation of the 3',5'-di-O-TBDMS deoxyinosine failed and the reaction of the resulting intermediate 6-pyridinium salt[6] with ethanolamine furnished the unexpected 6-chlorophenoxy derivative 8 (44%).

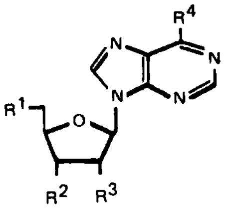
The nucleophilic displacement of sulfonyl moiety of 9 by triazole/ethanolamine led to the AICA-deoxyriboside derivative 10 (54% yield). This type of ring-opening reaction has been described earlier[7].

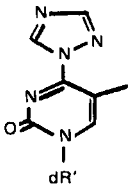
From 6-chloro-9-β-D-ribofuranosylpurine we synthesized the 3',5'-TPDS 6- chloro deoxyadenosine 13 via the intermediates 11 and 12, by the deoxygenation procedure of Robins et al[8]. We preferred the faster efficient procedure of Nair et al[9] to synthesize in one step the 6-iodo deoxyinosine derivative 14 from disilylated deoxyadenosine. The chlorine



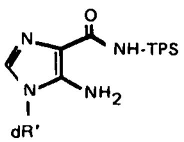
1 dR=2'-deoxyribose

R^1	R^2	R^3	R^4	
TBDMS	TBDMS	H	NH∿OH	3
TPDS		H	NH∿OH	4
TPDS		OH	OH	5
TPDS		OC(S)OØ	OH	6
TPDS		H	OH	7
TPDS		H	OO	8
TPDS		H	OTPS	9
TPDS		OH	Cl	11
TPDS		OC(S)OØ	Cl	12
TPDS		H	Cl	13
TBDMS	TBDMS	H	I	14





2



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dR' =3',5'-di-O-TBDMS 2'-deoxyribose

and iodine displacement by ethanolamine took place (60°C) to give the expected N^6-substituted deoxyadenosine 3 and 4 in 80-86% yield.

The two synthons 2 and 3 (or 4) were reacted together in acetonitrile and DBU (6 eq.) to give the protected dinucleoside (35%). After deprotection, the unprotected dimer 1 was obtained and its structure confirmed by its spectroscopic datas.

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