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Regiospecific Synthesis of a New Cross-Linked Dinucleoside : 1-(N⁶-Deoxyadenyl)-2-(o⁴-Thymidyl)-Ethane

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REGIOSPECIFIC SYNTHESIS OF A NEW CROSS-LINKED
DINUCLEOSIDE : 1-(N⁶-DEOXYADENYL)-2-(O⁴-THYMIDYL)-ETHANE

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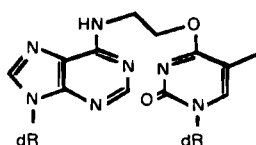
Abstract. The bridged dinucleoside 1-(N⁶-deoxyadenyl) 2-(O⁴-thymidyl)-ethane was prepared from the nucleophilic substitution of a O⁴-triazolyl thymidine by a N⁶-(2-hydroxyethyl) deoxyadenosine derivative via the corresponding 6-halogeno hypoxanthine in ribose and deoxyribose series.

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 O⁴-triazolyl thymidine⁵. The N⁶-(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 salt⁶ with ethanolamine furnished the unexpected 6-chlorophenoxy derivative 8 (44%).

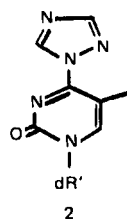
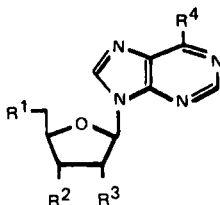
The nucleophilic displacement of sulfonyl moiety of 9 by triazole/ethanolamine led to the AICA-deoxyriboside derivative 10 (54% yield). This type of ring-opening reaction has been described earlier⁷.

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 al⁸. We preferred the faster efficient procedure of Nair et al⁹ to synthesize in one step the 6-iodo deoxyinosine derivative 14 from disilylated deoxyadenosine. The chlorine

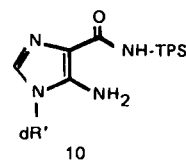


1 dR=2'-deoxyribose

R ¹	R ²	R ³	R ⁴	
TBDMS	TBDMS	H	NH-CH ₂ -OH	3
TPDS		H	NH-CH ₂ -OH	4
TPDS		OH	OH	5
TPDS		OC(S)O∅	OH	6
TPDS		H	OH	7
TPDS		H	OO	8
TPDS		H	OTPS	9
TPDS		OH	Cl	11
TPDS		OC(S)O∅	Cl	12
TPDS		H	Cl	13
TBDMS	TBDMS	H	I	14



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



and iodine displacement by ethanolamine took place (60°C) to give the expected N⁶-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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