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A NEW SYNTHESIS OF 9-ß-D-RIBOFURANOSYLURIC ACID AND ITS 5'-MONOPHOSPHATE

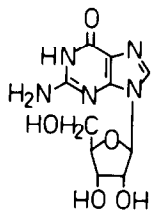
BERND S. SCHULZ AND WOLFGANG PFLEIDERER*
Fakultät für Chemie, Universität Konstanz, Postfach 5560, D-7750 Konstanz/West Germany

Abstract. Syntheses for 9-ß-D-ribofuranosyluric acid (16) and its 5'-monophosphate 14 starting from guanosine and by applying the p-nitrophenylethyl blocking group are described.

Naturally occurring uric acid ribosides and ribotides have so far been isolated from beef blood [1-6] and the bacterium Lactobacillus plantarum [7]. The structural assignment of the beef blood component turned out to be a long term problem of controversy [3-6] and could only recently be proven as 3-ß-D-ribofuranosyluric acid [8] besides very small amounts of its 5'-monophosphate [9]. The product from the bacterial source on the other hand has been recognized as the 9-ß-D-ribofuranosyluric acid 5'-monophosphate [7] by enzymatic dephosphorylation and spectroscopic comparisons with synthetic model substances. Synthetic efforts led on direct ribosylation of uric acid [10] and by an unambiguous route [11] to the 3-ß-D-ribosyl derivative, whereas the isomeric 9-ß-D-ribofuranosyluric acid (16) has been derived from guanosine [12, 13] and 8-bromoxanthosine [14] respectively via various structural modifications in relatively low yields. Finally conversion of 8-hydroxyguanosine-5'-monophosphate into the uric acid 9-ribotide 14 [15] proceeded also not satisfactorily due to the unusual properties of all these compounds of this field.

Since the encountered synthetic difficulties are primarily based upon the three amide functions of the aglycone we investigated the possibility to protect this moiety completely by appropriate blocking groups for better handling of this molecule in general and in approaches towards nucleotide and oligonucleotide syntheses.

Guanosine (1) was chosen as a cheap starting material and was converted by known procedures first into the 8-bromo derivative 2 followed by acetylation at the ribose moiety to give



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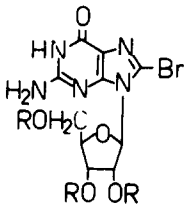
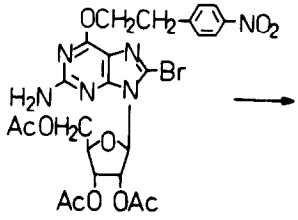


	R
2	H
3	Ac



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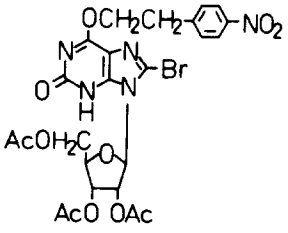

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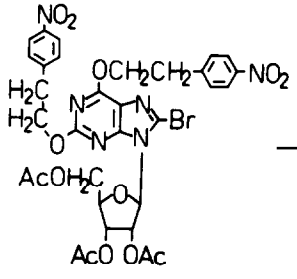

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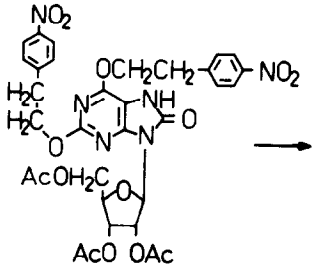

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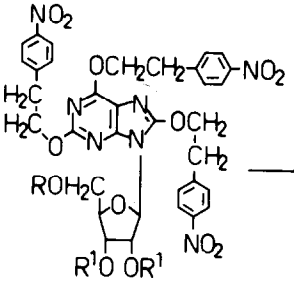

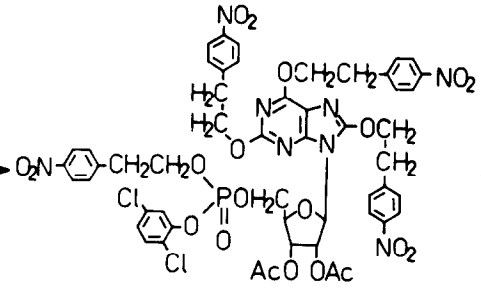

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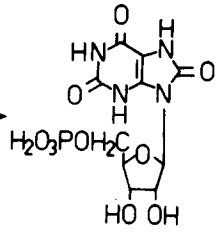
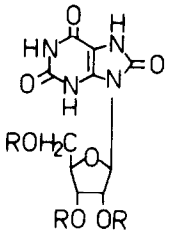


14

	R	R^1
8	Ac	Ac
9	H	H
10	MTr	H
11	MTr	Ac
12	H	Ac



	R
15	Ac
16	H

Physical Data of 9-β-D-Ribofuranosyluric Acid Derivatives

	UV - Absorption Spectra		Solvent
	λ_{max} (nm)	lg ε	
4	259 285	4.27 4.29	MeOH
5	[250] 270 [277]	[4.15] 4.34 [4.31]	MeOH
6	269	4.48	MeOH
7	[218] [244] 276	[4.25] [4.19] 4.49	MeOH
8	[218] [242] 270	[4.39] [4.31] 4.59	MeOH
9	[248] 272	[4.35] 4.60	MeOH
10	236 271	4.45 4.59	MeOH
11	235 272	4.48 4.60	MeOH
12	[220] [244] 272	[4.37] [4.34] 4.61	MeOH
13	[218] [230] 271	[4.51] [4.32] 4.61	MeOH
14	232 286 238 293	3.90 3.99 4.00 3.98	pH 1 pH 10
16	233 287 239 293	3.92 4.05 4.01 4.04	pH 1 pH 10

2',3',5'-tri-O-acetyl-8-bromoguanosine (3) in 73 % overall yield. The Mitsunobu reaction [16] proceeded with 3 and p-nitrophenylethanol in the usual manner and led in 84 % yield to O^6-protection [17] to give 4. The critical part was then the deamination of the guanosine derivative 4 to the corresponding xanthosine 5, which could be achieved by nitrous acid in acetone/water at 10°C in 93 % yield.

O^2-protection of the new amide function resulted from a silver ion catalysed alkylation with p-nitrophenylethyl iodide to give in 90 % yield 9-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-8-bromo-2,6-bis-p-nitrophenylethoxypurine (6), which on reflux in glacial acetic acid in presence of sodium acetate formed the corresponding 8-oxo-7,8-dihydro derivative 7

in 92 % yield. Further O^8-alkylation proceeded in an analogous manner to the fully protected uric acid derivative 8 (88 %). Deprotection of the sugar moiety can be achieved by sodium methoxide in methanol to 9 (86 %), whereas cleavage of the p-nitrophenylethyl groups by ß-elimination works best with DBU in pyridine to give 15 and on subsequent ammonia treatment 16 respectively. Conversion of 9 into 9-ß-D-ribofuranosyluric acid 5'-monophosphate (14) resulted from another sequence of reactions including 5'-O-monomethoxytritylation to 10 (68 %), acetylation to 11 (93 %), detritylation to 12 (98 %), phosphorylation with 2,5-dichlorophenylphosphorodichloridate and subsequent treatment with p-nitrophenylethanol to the mixed phosphotriester 13 (81 %), which on final cleavage of all blocking groups subsequently by ammonia and DBU treatment resulted in the formation of 9-ß-D-ribofuranosyluric acid 5'-monophosphate 14.

All new compounds showed correct elementary analyses and have furthermore been characterized by UV and ^{1}H-NMR spectra.

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