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SYNTHESIS OF O^6-p-NITROPHENYLETHYL GUANOSINE AND 2'-DEOXYGUANOSINE DERIVATIVES

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The p-nitrophenylethyl group is introduced into the O^6-position of 2'-deoxyguanosine and guanosine via the Mitsunobu-reaction to yield valuable building blocks for oligonucleotide syntheses.

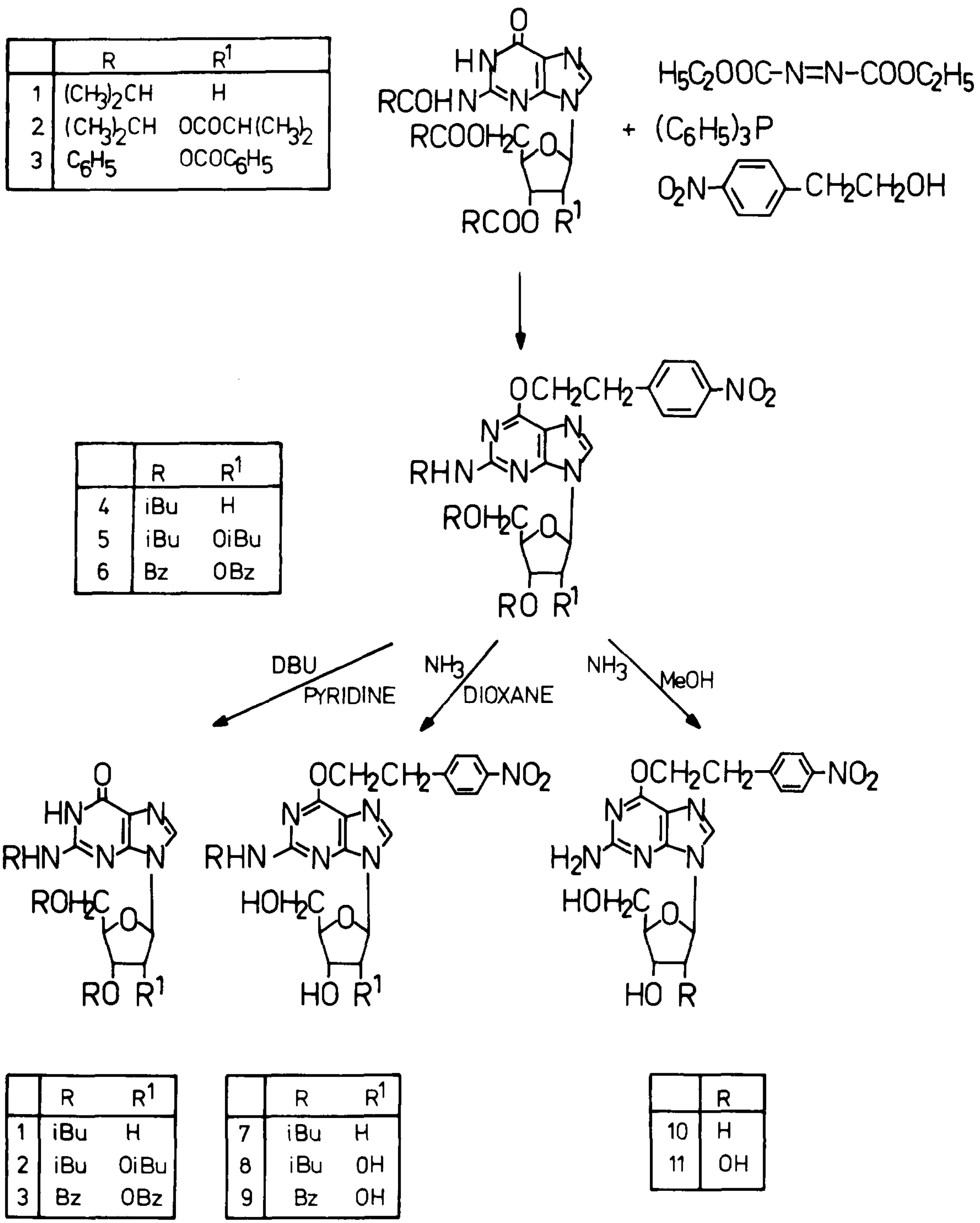
Recent development of new methodologies such as introduction of new protecting groups [1] and new coupling reagents [2] improved the synthesis of oligonucleotides [3] enormously. However, syntheses of guanosine containing oligomers reveal a long-standing problem of various side-reactions involving the guanine moiety during the phosphorylation and condensation steps.

Reese [4] reported that guanosine derivatives were sulfonylated at O^6 with arene sulfonyl chlorides in pyridine and can even react further to form 6-(3-nitro-1,2,4-triazol-1-yl)-derivatives [5] by use of an excess of 1-(mesithylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) especially in presence of phosphodiesters. Therefore protection of the amide function in the guanine moiety seems to be an obvious necessity to eliminate such type of side reactions.

Various research groups approached recently the problem of O-6 protection differently including the 6-O-(2-nitrophenyl) group by Reese [6], various 6-O-substituted silyl, sulfonyl, phosphoryl, and phosphino-thioyl derivatives by Hata [7] and the trimethylsilylethyl as well as properly substituted ethyl groups prone to ß-elimination cleavage reactions by Jones [8].

Our own contribution to this problem is based on the new type of phosphate protecting groups [9] which have recently successfully been applied in the phosphotriester approach [10,11] and have their most prominent representative in the p-nitrophenylethyl groups [12,13]. The exceptionally good properties of this blocking group signalized a more universal applicability to other functions including the amide group. O^6 protection in guanosine and deoxyguanosine by the p-nitrophenylethyl group has now been investigated to achieve also a higher solubility of such guanosine and deoxyguanosine derivatives in organic solvents for further condensation reactions to oligonucleotides.

After a series of unsuccessful attempts to displace the 6-substituent in 6-chloro- and 6-methylsulfonyl-2-amino-9-ß-D-ribofuranosylpurine nucleophilicly



	R	R^1
1	$(CH_3)_2CH$	H
2	$(CH_3)_2CH$	$OCOCH(CH_3)_2$
3	C_6H_5	$OCOC_6H_5$

	R	R^1
4	iBu	H
5	iBu	OiBu
6	Bz	OBz

	R	R^1
1	iBu	H
2	iBu	OiBu
3	Bz	OBz

	R	R^1
7	iBu	H
8	iBu	OH
9	Bz	OH

	R
10	H
11	OH

by p-nitrophenylethanol under various reaction conditions we encountered that the "Mitsunobu reaction" [14] offers good chance of O^6 alkylation if the 2-amino group is acylated and hinders this way a possible reaction on the adjacent N-1 ring-atom. Treatment of N^2, 3',5'-tri-O-isobutyroyl-2'-deoxy-guanosine (1) and N^2, 2',3',5'-tetra-O-isobutyroyl-guanosine (2) respectively with 1.5 moles of diethyl azodicarboxylate, 1.5 moles of triphenylphosphine and 1.5 moles of p-nitrophenylethanol in dioxane at room temp. led after 24 h to the O^6-p-nitrophenylethyl guanosine derivatives 4 and 5 in 85 and 72 % yield respectively. The p-nitrophenylethyl group could be cleaved selectively in 40 min by 0.5 M DBU in pyridine to yield the starting materials 1 and 2 back. Treatment with conc. ammonia in dioxane gave after 20 h N^2-isobutyroyl-O^6-p-nitrophenylethyl-2'-deoxyguanosine (7) and -guanosine (8) as crystalline products, whereas conc. ammonia in methanol achieves deacylation at the sugar moiety already after 3 h. Prolonged treatment under the latter conditions finally cleaves also the N^2-acyl group without harming the O^6 blocking group and yielding O^6-p-nitrophenylethyl-2'-deoxyguanosine (10) and-guanosine (11) respectively.

A similar reaction sequence starting from N^2, 2',3',5'-tetra-O-benzoylguanosine (3) proceeded analogously and yielded 6, 3 and 9. The preparation of the most valuable building blocks 7 and 8 for oligonucleotides synthesis can be performed in a one-pot reaction starting from 1 and 2 respectively in good overall yields.

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