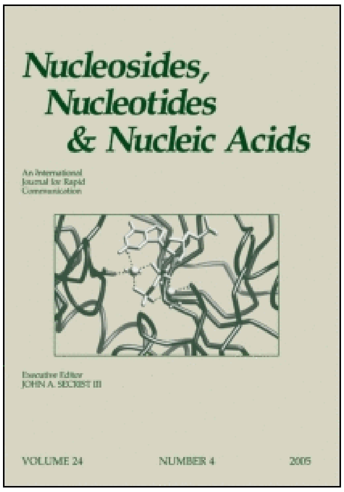

Nucleosides, Nucleotides and Nucleic Acids
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Nucleosides. IL. Synthesis and Properties of 2,4-Quinazolinedione N-1-2' Deoxy-, 3'-Deoxy- and 2',3'-Dideoxynucleosides

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NUCLEOSIDES AND NUCLEOTIDES, 11(2-4), 787-819 (1992)

NUCLEOSIDES. IL[1]
SYNTHESIS AND PROPERTIES OF 2,4-QUINAZOLINEDIONE N-1-2'DEOXY-, 3'-DEOXY- AND 2',3'-DIDEOXYNUCLEOSIDES

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Abstract. A series of 6- and/or 7-substituted 2,4-quinazoline-dione N-1-deoxyribofuranosides have been synthesized and characterized. The 2'-deoxy-ß-D-ribofuranosides 23-28 have been prepared by transformation of the corresponding ribofuranosides by chemical deoxygenation. Direct glycosidation to the ß-anomers with a 2'-deoxyribofuranosyl donor to pure anomers failed due to missing diastereoselectivity and difficult separation of the reaction products. The synthesis of the 3'-deoxy-ß-D-ribofuranosides 54-58, however, was achieved by glycosidation of the trimethylsilylated 2,4-quinazolinediones 43-47 with an appropriate 3'-deoxyribofuranosyl donor (48). The 2',3'-dideoxy-ß-D-ribofuranosyl derivatives 63-66 were again obtained by chemical deoxygenation of the corresponding 2'-deoxy-ß-D-nucleosides, since all experiments of direct glycosidation with a 2',3'-dideoxyribofuranosyl donor as well as the chemical conversion of the corresponding ribonucleosides into the 2',3'-dideoxynucleosides failed due to side reactions. The newly synthesized compounds have been identified by UV and ^{1}H-NMR spectra as well as elemental analyses.

In a recent paper[1] we have described the chemical synthesis and physical properties of various quinazoline N-1 ribofuranosides, which can be regarded as benzo[d]uridine

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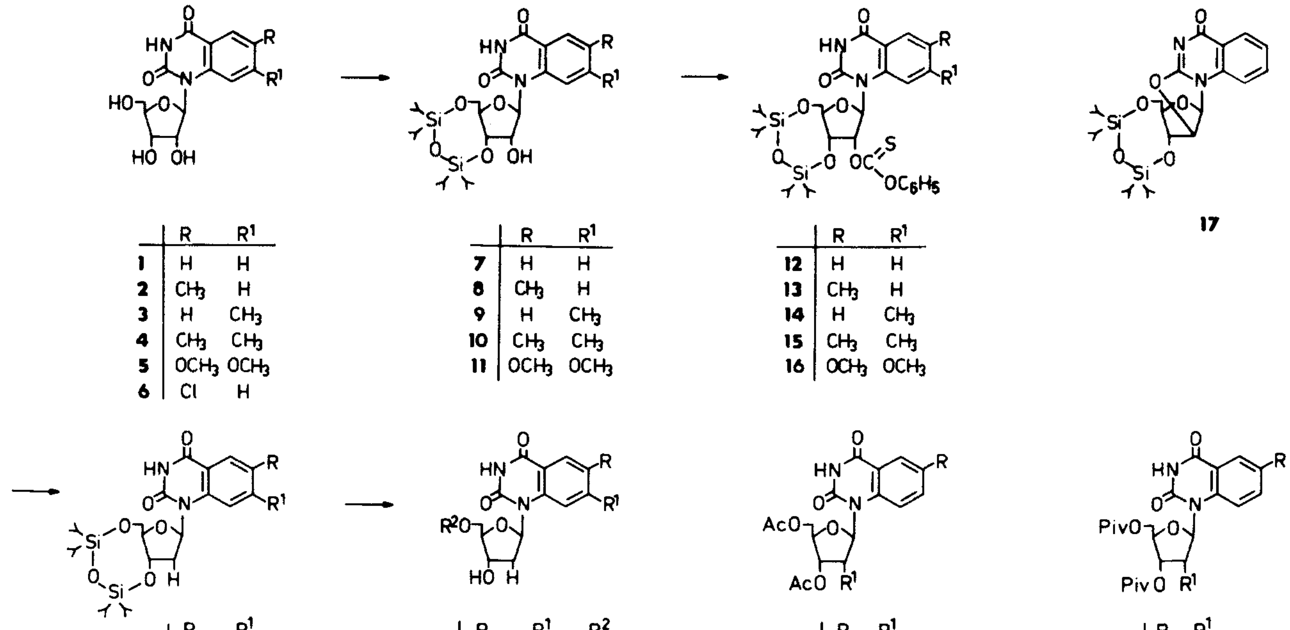
Dedicated in memoriam to Tohru Ueda and in admiration of his scientific achievements.

and -cytidine analogues, respectively. So far, these nucleosides have not shown any biological activity, but there is the potential that the corresponding 2'- and 3'-deoxy, as well as the 2',3'-dideoxyribofuranosides, will reveal the anticipated activity. Since 2',3'-dideoxynucleosides[2] belong to the most potent anti-HIV-1 agents efforts to prepare new types of structural analogues modified in the base moiety can be justified. We report about our studies to gain access to the various types of 2,4-quinazolinedione N-1-ß-D-deoxyribonucleosides.

SYNTHESES

For the preparation of 2'-deoxy-ß-D-ribofuranosides there are currently two general methods in use - the direct glycosylation procedure[3] and the deoxygenation process of an appropriate precursor by radical substitution[4]. The former approach reveals the disadvantage of low diastereoselectivity due to the lack of a 2'-O-acyl function, which controls, by neighbouring participation, glycoside bond formation according to the Tipson-Baker trans-rule[5]. Some catalysts like $ZnCl_2$ and CuI[6] show, in the 2'-deoxyribonucleoside series, a positive effect towards a preferntial ß-orientation between sugar and aglycone giving this method some chance of preparative application.

Our own experiments with various 2,4-quinazoline-diones following the basic work of R.K. Robins et al.[7] as well as by use of several catalysts in the glycosylation reaction of the silylated hetero-bases with 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride, unfortunately, gave no or little ß-diastereoselectivity. The resulting anomeric mixtures of diastereomers were difficult to separate. Separation could only be achieved on small scale by MPLC or preparative TLC. From the physical data of pure 1-(2-deoxy-ß-D-ribofuranosyl)-2,4-quinazolinedione (23) it can be concluded that the direct glycosylation of 2,4-quinazolinedione (43) by R.K. Robins et al.[7] did not lead to the pure ß-ano-



17

	R	R1
1	H	H
2	CH_3	H
3	H	CH_3
4	CH_3	CH_3
5	OCH_3	OCH_3
6	Cl	H

	R	R1
7	H	H
8	CH_3	H
9	H	CH_3
10	CH_3	CH_3
11	OCH_3	OCH_3

	R	R1
12	H	H
13	CH_3	H
14	H	CH_3
15	CH_3	CH_3
16	OCH_3	OCH_3

	R	R1
18	H	H
19	CH_3	H
20	H	CH_3
21	CH_3	CH_3
22	OCH_3	OCH_3

	R	R1	R2
23	H	H	H
24	CH_3	H	H
25	H	CH_3	H
26	CH_3	CH_3	H
27	OCH_3	OCH_3	H
28	Cl	H	H
29	H	H	Tol
30	CH_3	H	Tol
31	H	CH_3	Tol
32	CH_3	CH_3	Tol

	R	R1
33	H	Br
34	CH_3	Br
35	H	Cl
36	CH_3	Cl
37	H	H
38	CH_3	H

	R	R1
39	H	Cl
40	Cl	Cl
41	H	H
42	Cl	H

Ac=ACETYL; Piv = PIVALOYL

mer, which has a melting point of 185-186° and not 167-168°, as reported earlier. Also, the acylation of 23 by p-toluoyl chloride to 1-(2-deoxy-3,5-di-O-p-toluoyl-ß-D-ribofuranosyl)-2,4-quinazolinedione with a melting point of 147-148° indicated that the previously described material (m.p. 129-134°)[7] was not homogeneous.

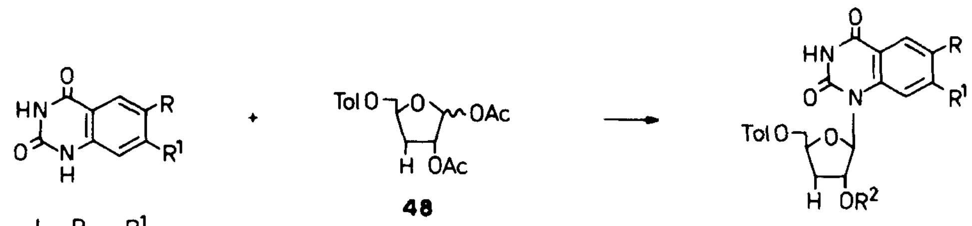
Another general approach to 2'-deoxy-ß-D-ribofuranosyl nucleosides has been demonstrated by the chemical transformations of the 2'-hydroxy group in the corresponding ß-D-ribofuranosides utilizing the reductive removal of 2'-halo- and thiol substituents[8-23]. Finally, Barton's radical deoxygenation process[24,25] of thio- and dithiocarbonates was successfully applied to nucleoside chemistry by M.J. Robins et al.[4] and became, in recent years, a standard procedure for the preparation of deoxy- and dideoxy nucleosides, in general.

When we applied the Robins method to 2,4-quinazolinedione ribofuranosides[1] we encountered some difficulties upon the introduction of the phenoxythiocarbonyl function into the 3',5'-protected nucleosides 7-11, which could be prepared in nearly quantitative yields from the ribosides 1-5 by the Markiewicz reagent. Phenoxythiocarbonylation of 7 under normal conditions led to a mixture of the desired product 12 in 41 % yield, but also a second reaction product was identified as the 3',5'-blocked O^2,2'-anhydronucleoside 17 and was isolated in 40 % yield. Another experiment showed that the anhydronucleoside 17 is formed quantitatively from 12 when treated with 4-dimethylaminopyridine in CH_3CN at room temp.. Variations of the conditions using phenoxythiocarbonyl chloride/pyridine in CH_2Cl_2 at 0°C gave a clean acylation of the 2'-OH group and 12 was isolated in 80 % yield. Reductive cleavage of the phenoxythiocarbonate 12 by tri-n-butylstannane in a radical chain reaction afforded 18 in 83 % yield, which led on subsequent deblocking of the Markiewicz protecting group with tetrabutylammonium fluoride (TBAF) to 1-(2-deoxy-ß-D-ribofuranosyl)-2,4-quinazolinedione

(23)in 75 % isolated yield. The four step procedure 1→7→12→18→23 can also be performed sequentially without isolation and purification of the intermediates to give a good yield of the final product. In the same manner 6-methyl- (24), 7-methyl- (25), 6,7-dimethyl- (26), and 6,7-dimethoxy-1-(2-deoxy-ß-D-ribofuranosyl)-2,4-quinazolinedione (27), respectively, were synthesized in overall yields of 48-70 %.

In a second sequence of reactions the 2,4-quinazolinedione N-1-ribosides 1 and 2 were treated with Mattock's reagent[26] α-acetoxyisobutyryl bromide and acetyl bromide, respectively, as well as acetyl chloride to form the 2'-bromo- (33, 34) and 2'-chloro-3',5'-di-O-acetyl-ribonucleosides (35, 36). All attempts to remove the bromine by catalytic hydrogenation have failed, so far, and led to the formation of the corresponding O^2,2'-anhydronucleosides which have, however, not been characterized further. The reduction of the halo-atoms by tri-n-butylstannane worked well and gave good yields with the more stable 2'-chloro-2'-deoxyribonucleosides 35 and 36 affording in the radical chain reaction 37 and 38, respectively. In order to avoid the formation of peracylated byproducts in the transformations of 1 and 6 into the halo-derivatives acetyl chloride was replaced by the bulky pivaloyl chloride providing a much cleaner reaction to 39 and 40 in excellent yields. Tri-n-butylstannane reduction afforded crystalline 1-(2-deoxy-3,5-di-O-pivaloyl-ß-D-ribofuranosyl)-2,4-quinazolinedione (41) and its 6-chloro derivative (42), both of which led by Zemplen's deacylation procedure[27] to the free 2'-deoxyribonucleosides 23 and 28, respectively. This second method can be regarded as an effective alternative to the Barton-Robins approach, which uses much more expensive reagents and is more time-consuming.

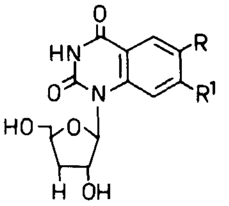
Our investigations have also been extended to the 3'-deoxynucleoside series, since this group of nucleosides[28-35] has attracted some attention after the isolation of cordycepin[36] in 1951. We decided to synthesize 2,4-quinazolinedione N-1-3'-deoxynucleosides 54-58 by direct glycosylation of the



48

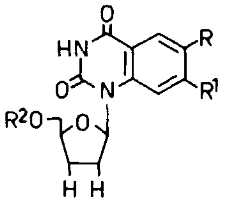
	R	R1
43	H	H
44	CH_3	H
45	H	CH_3
46	CH_3	CH_3
47	OCH_3	OCH_3

	R	R1	R2
49	H	H	Ac
50	CH_3	H	Ac
51	H	CH_3	Ac
52	CH_3	CH_3	Ac
53	OCH_3	OCH_3	Ac



	R	R1
54	H	H
55	CH_3	H
56	H	CH_3
57	CH_3	CH_3
58	OCH_3	OCH_3

Tol = p-Toluoyl



	R	R1	R2
59	H	H	Tol
60	CH_3	H	Tol
61	H	CH_3	Tol
62	CH_3	CH_3	Tol
63	H	H	H
64	CH_3	H	H
65	H	CH_3	H
66	CH_3	CH_3	H

heterobases 43-47 using Vorbrüggen's conditions[37]. The 2,4-quinazolinediones 43-47 were first silylated and then treated with 1,2-di-O-acetyl-3-deoxy-5-O-p-toluoyl-ß-D-ribose[38] in CH_2Cl_2 under trimethylsilyl triflate catalysis to give in moderate to good yields the corresponding protected N-1-3'-deoxy-ß-D-ribofuranosides 49-53. Deacylation according to Zemplen[27] by sodium methoxide led to the free 2,4-quinazolinedione N-1-3'-deoxy-ß-D-ribofuranosides 54-58 in crystalline form.

Finally we have concentrated our efforts towards the synthesis of quinazoline-2',3'-dideoxynucleosides as potential antivirals. Since the first synthesis of a 2',3'-dideoxynucleoside in 1955[39] several approaches[40-58] have been developed to gain access to this interesting groups of compounds. All attempts to convert 2,4-quinazolinedione N-1-ß-D-ribofuranosides (1-6) via reactive intermediates into the 2',3'-dideoxy-2',3'-didehydronucleosides for subsequent reduction to the anticipated 2',3'-dideoxyribofuranosides 63-66 led either to the formation of anhydronucleosides or complex reaction mixtures difficult to be separated into pure components. Also the direct glycosylation of 2,4-quinazolinedione (43) via the Hilbert-Johnson-Birkofer approach using 1,5-di-O-acyl-2-phenylselenyl-3-deoxy-ribofuranose, analogous to recent reports in the pyrimidine series[59], resulted in unidentified product mixtures.

A three step sequence of reactions starting from the 2,4-quinazolinedione-N-1-2'-deoxy-ß-D-ribofuranosides 23-26 was finally successful in preparing the corresponding 2',3'-dideoxynucleosides 63-66. In the first place a selective monoacylation led to the 5'-O-p-toluoyl derivatives 29-32 in 65-75 % yield, which were then reacted at the 3'-OH group with phenoxythiocarbonyl chloride in pyridine and without isolation of the intermediates followed by subsequent reduction with tri-n-butylstannane/AIBN in toluene according to the Barton-Robins conditions[4,24,25] formed the 1-(2,3-dideoxy-5-O-toluoyl-ß-D-ribofuranosyl)-2,4-quinazolinediones 59-62 in 72-99 % yield. Deacylation to the free quinazoline-2',3'-dideoxynucleosides 63-66 could be achieved in the usual manner by transesterification in methanol/sodium methoxide[27].

PHYSICAL PROPERTIES

Characterization of the newly synthesized quinazoline deoxynucleosides was based on elemental analyses, UV and ^{1}H-NMR spectra. The site of attachment of the sugar moiety in the glycosylation reactions of the 2,4-quinazolinediones 43-47 to the corresponding 3'-deoxynucleosides 49-58 at the

Table 1 - Physical Data of Quinazoline N-1-Deoxyribonucleosides

	pK_a in H_2O	UV - Absorption Spectra λ_{max} (nm)				log ε				pH Solvents	Molecular Form
7		217	[242]		306	4.63	[3.96]		3.60	MeOH	o
8		219	[242]		315	4.62	[3.97]		3.57	MeOH	o
9		222	253	[270]	309	4.66	4.10	[4.02]	3.67	MeOH	o
10		224	248	[268]	315	4.65	4.10	[3.95]	3.60	MeOH	o
11		230		[257]	323	4.60		[3.80]	3.79	MeOH	o
12		237	[272]	[281]	305	5.27	[4.07]	[3.92]	3.58	MeOH	o
17		221	[242]	297	308	4.49	[4.15]	3.71	3.64	MeOH	o
18		220	[240]		305	4.60	[3.90]		3.60	MeOH	o
23	9.92	218	[241]		306	4.60	[3.91]		3.60	7.0	o
		221	[241]	[260]	307	4.64	[4.08]	[3.58]	3.65	12.0	-
24	10.02	220	[244]		315	4.61	[3.98]		3.60	7.0	o
		223		[262]	315	4.65		[3.49]	3.63	12.0	-
25	9.89	224	[246]		306	4.62	[3.87]		3.62	7.0	o
		225		[260]	306	4.70		[3.74]	3.68	12.0	-
26	9.98	226	[248]	[259]	313	4.63	[3.93]	[3.76]	3.63	7.0	o
		226		[262]	312	4.70		[3.70]	3.67	12.0	-
27	10.31	235		[261]	318	4.56		[3.89]	3.85	8.0	o
		230	[258]	[269]	317	4.61	[3.81]	[3.66]	3.88	13.0	-
28	9.35	221	244	[252]	317	4.64	4.05	[3.87]	3.56	7.0	o
		224		[252]	317	4.63		[3.90]	3.57	12.0	-
29		217	[236]		305	4.69	[4.40]		3.65	MeOH	o
30		220	[238]		313	4.66	[4.38]		3.58	MeOH	o
31		223	[238]		305	4.71	[4.35]		3.61	MeOH	o
32		224	[240]		311	4.78	[4.39]		3.68	MeOH	o
33		219	[240]		310	4.62	[3.98]		3.58	MeOH	o
34		218	[241]		309	4.61	[3.95]		3.60	MeOH	o
35		216	[240]		303	4.60	[3.87]		3.53	MeOH	o
36		218	[240]		310	4.62	[3.98]		3.58	MeOH	o
37		217	[240]		304	4.51	[3.81]		3.49	MeOH	o
38		219	[241]		314	4.63	[3.93]		3.60	MeOH	o

(continued)

Continuation: Table 1

	pK_a in H_2O	UV - Absorption Spectra λ_{max} (nm)				log ε				pH Sol-vents	Mole-cular Form
39		216	237		303	4.62	3.94		3.58	MeOH	o
40		219	244	[250]	314	4.61	4.02	[3.93]	3.48	MeOH	o
41		217	[239]		304	4.64	[3.95]		3.62	MeOH	o
42		220	245	273	317	4.62	4.05	3.46	3.49	MeOH	o
49		217	[238]		306	4.63	[4.33]		3.54	MeOH	o
50		219	[237]	[265]	302	4.71	[4.44]	[3.68]	3.63	MeOH	o
51		223	[237]		302	4.68	[4.34]		3.60	MeOH	o
52		224	[238]		310	4.68	[4.38]		3.56	MeOH	o
53			235	[260]	317		4.68	[4.02]	3.80	MeOH	o
54	9.97	218	[239]		306	4.59	[3.93]		3.59	7.0	o
		221	[240]	[257]	307	4.63	[4.07]	[3.62]	3.63	12.0	-
55	9.94	220	[241]		315	4.61	[4.01]		3.60	7.0	o
		223		[260]	315	4.65		[3.57]	3.63	12.0	-
56	9.86	224	[246]	[254]	306	4.64	[3.92]	[3.85]	3.63	7.0	o
		225		[260]	306	4.70		[3.74]	3.66	12.0	-
57	9.73	226	[248]	[260]	314	4.63	[3.94]	[3.75]	3.63	7.0	o
		226		[262]	312	4.70		[3.70]	3.68	12.0	-
58	9.92	235		261	319	4.57		3.90	3.86	7.0	o
		230	[258]	[269]	317	4.63	[3.82]	[3.67]	3.89	12.0	-
59		217	[235]		306	4.61	[4.33]		3.57	MeOH	o
60		220	[237]	[271]	311	4.67	[4.41]	[3.65]	3.65	MeOH	o
61		223	[238]	[269]	304	4.74	[4.41]	[4.05]	3.80	MeOH	o
62		225	[240]		311	4.68	[4.30]		3.58	MeOH	o
63	9.96	218	[240]		307	4.59	[3.93]		3.59	7.0	o
		221	[240]	[260]	307	4.63	[4.08]	[3.54]	3.63	12.0	-
64	9.82	221	[244]		316	4.58	[3.96]		3.58	7.0	o
		224		[260]	315	4.63		[3.51]	3.61	12.0	-
65	9.96	224	[246]	[256]	306	4.61	[3.86]	[3.79]	3.60	7.0	o
		225		[260]	306	4.68		[3.69]	3.65	12.0	-
66	9.82	221	[244]		316	4.58	[3.96]		3.58	7.0	o
		224		[260]	315	4.63		[3.51]	3.55	12.0	-

[ ] Shoulder

N-1 ring atom is derived from UV spectral comparison with the structurally proven 1-ß-D-ribofuranosyl-2,4-quinazolinediones[1]. The deprotected deoxynucleosides 23-28, 54-58, and 63-66 were selected for pK_a determination and revealed expectedly very similar values (table 1). The monoanions of these compounds show only a small bathochromic shift of the long wavelength absorption band, which is typical for an N-1 rather than N-3 substitution.

The ^{1}H-NMR spectra of the various types of quinazoline-N-1-nucleosides reveal further information about conformational relations of the flexible parts of the molecules. The anomeric protons in the 3',5'-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl) (TIPDS) derivatives 7-11 appear as singlets analogous to 3',5'-TIPDS-uridine[60] and indicate a ^{3}E or N-conformation of the sugar-pucker. Furthermore the 2'- and 3'-protons resonate in these molecules at much lower field than in the uridine analogue pointing to a high population of syn-conformation of base and sugar moiety leading to a deshielding of the ß-protons induced by the diamagnetic anisotropy of the 2-carbonyl function. The shift of the 3'-protons to lower field is then more pronounced in the N-conformer as stated. The same arguments also explain nicely the strong separation of the 2'- and 2"-proton signals in the 2,4-quinazolinedione N-1-(2-deoxy-ß-D-ribofuranosides) 23-32. We assume that these derivatives prefer again the syn-conformation, wherein the 2'-deoxyribofuranoside moieties adapt the ^{2}E or S-pucker bringing the ß-located 2'-H in close proximity to the 2-carbonyl group of the hetero-base.

The distinct chemical shift differences of the 3'- and 3"-proton signals in the quinazoline N-1-(3-deoxy-ß-D-ribofuranosides) 49-58 could be discussed under the same aspects pointing to an arrangement which indicates the presence of equal amounts of ^{2}E- and ^{3}E-conformers.

The ^{1}H-NMR spectra of the quinazoline N-1(2,3-dideoxy-ß-D-nucleosides) 59-66 allow, so far, no concrete conformational assignments due to the complex patterns of the proton signals, which have not yet been analyzed in detail.

EXPERIMENTAL

^{1}H-NMR spectra were measured with a Bruker WM 250 and a Bruker AC 250 spectrometer with tetramethylsilane as an internal standard and on a δ-scale in ppm. UV-spectra were recorded on a Perkin-Elmer spectrophotometer Lambda 5. The pK-values were determined spectrophotometrically[61]. Thin layer chromatography was performed on silica-gel sheets F 1550 LS 254 of Schleicher & Schüll. Silica Gel 60 (Merck) was used for ordinary column chromatography. Flash chromato graphy was done on Flash silica gel (Baker) according to their instructions. Drying of substances was achieved at 100°C or in a Büchi TO-50 drying oven under vacuum at 40°C. Melting points were measured with a Gallenkamp melting point apparatus and are not corrected.

<u>1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinediones</u> (<u>7</u>-<u>11</u>). <u>General procedure</u>. - A mixture of the 1-ß-D-ribofuranosyl-2,4-quinazolinedione (20 mmole) (<u>1</u>-<u>5</u>) and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (5.9 ml, 22 mmole) in pyridine (100 ml) was stirred overnight at room temperature. After evaporation the residue was partitioned between H_2O (250 ml) and ether (500 ml). The organic layer was washed subsequently with 1N HCl (250 ml), saturated $NaHCO_3$ solution (250 ml) and saturated NaCl solution (250 ml). After drying over Na_2SO_4 the solution was filtered and evaporated in vacuum to give an amorphous solid foam. The products are homogeneous and do not afford chromatographical purification.

<u>1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinedione</u> (<u>7</u>). - Yield 10.5 g (98 %). Amorphous yellowish solid. Column chromatography with $CHCl_3$/MeOH 49:1 gave 85 % colourless material. R_f = 0.79 ($CHCl_3$/MeOH 19:1).

<u>Anal</u>. calc. for $C_{25}H_{40}N_2O_7Si_2$ (536.8): C, 55.94; H, 7.51; N, 5.22. Found: C, 55.58; H, 7.51; N, 5.15.

Table 2 - ^{1}H-NMR Data of Quinazoline N-1-Deoxyribofuranosides

	^{1}H-NMR Spectra in D_6-DMSO or $CDCl_3$* (δ-values in ppm against TMS)															
	NH	1'-H	$J_{1',2'}$	2'-H	2"-H	3'-H	3"-H	4'-H	5'-H	5"-H	Aromatic H				Subst.	
7*	8.14	5.94		4.79d		5.03t		3.97m	4.06m(2H)		7.29t	7.47d	7.68t	8.18dd		
8*	8.26	5.92		4.78d		5.02t		3.95m	3.95-4.09m(2H)		7.35d	7.47dd	7.97d		2.40s(3H)	
9*	8.45	5.91		4.81d		5.05t		4.04m(3H)			7.10d	7.25s	8.06d		2.47s(3H)	
10*	8.17	5.90s		4.81d		5.05t		4.02m(3H)			7.23d	7.90s			2.38s(3H)	2.30s(3H)
11*	8.41	5.82s		4.83d		5.05t		4.05m(3H)			6.84s	7.53s			3.94s(3H)	3.98s(3H)
12*	8.53	6.40s		6.62d		5.24dd		4.05m(3H)			7.24m(2H)		7.69t	8.19d		
17*		6.34d	6.4	4.60m		5.43dd		4.05m(3H)			7.30m(2H)		7.63t	8.12d		
18*	8.97	7.69dd		2.86m	2.31m	4.96m		3.86m	4.08m(2H)		7.21t	7.55d	7.65t	8.18d		
23	11.23	6.76t		2.60m	1.90m	4.33m		3.69m(3H)			7.29t	7.64t	7.85d	8.01d		
24	11.57	6.65t		2.61m	1.92m	4.37m		3.65m(3H)			7.77m(2H)		7.46d		2.33s(3H)	
25	11.54	6.69t		2.62m	1.91m	4.42m		3.68m(3H)			7.10d	7.77s	7.87d		2.37s(3H)	
26	11.47	6.69t		2.60m	1.90m	4.43m		4.11m	3.68m(2H)		7.72s	7.75s			2.23s(3H)	2.29s(3H)
27	11.51	6.71t		2.65m	1.91m	4.42m		3.66m(3H)			7.16s	7.38s			3.80s(3H)	3.88s(3H)
28	11.80	6.16t		2.57m	1.91m	4.37m		3.66m(3H)			7.66dd	7.92m(2H)				
29	11.66	6.68t	7.1	2.76m	2.05m	3.99m		4.61-4.45m(3H)			7.23m	7.37m	7.59d	7.98d		
30	11.59	6.66t		2.72m	2.03m	3.92m		4.58m	4.66dd	4.43dd	7.06dd	7.45d	7.77d		2.25s(3H)	
31	11.54	6.60t		2.78m	2.08m	4.01m		4.54m(2H)		4.43dd	7.09d	7.42s	7.86		2.31s(3H)	
32*	11.48	6.59t		2.76m	2.10m	4.01m		4.55m(2H)		4.43m	7.39s	7.76s			2.23s(6H)	
33*	8.96	6.55d	4.9	5.45m(2H)				4.36m(2H)		4.53dd	7.34t	7.49d	7.69t	8.25dd		
34*	8.95	6.47d	5.1	5.36m(2H)				4.26m(2H)		4.32dd	7.31t	7.41dd	7.97d		2.35s(3H)	
35	11.82	6.45d	5.0	5.42m(2H)				4.31m(3H)			7.35t	7.70m(2H)		8.04d		
36*	8.96	6.30d	5.0	5.31dd		5.48t		4.29m	4.23dd	4.45dd	7.29d	7.41dd		7.97dd	2.35s(3H)	
37	11.67	6.64t	7.3	2.93m	2.20m	5.35m		4.15m	4.31m(2H)		7.30t	7.70m(2H)		8.02d		
38*	9.24	6.72t	7.6	3.06m	2.18m	5.40m		4.18m	4.38d	4.46dd	7.39dd	7.51d		8.00d	2.35s(3H)	

Table 2 - Continuation

	^{1}H-NMR Spectra in D_6-DMSO or $CDCl_3$* (δ-values in ppm against TMS)															
	NH	1'-H	$J_{1',2'}$	2'-H	2"-H	3'-H	3"-H	4'-H	5'-H	5"-H	Aromatic H				Subst.	
39*	8.96	6.37d	4.8	5.40dd		5.53t		4.37m(3H)			7.34t	7.45d	7.69t	8.24dd		
40*	9.08	6.30d		5.40dd		5.50m		4.35m(3H)			7.40d	7.65dd		8.20dd		
41*	8.60	6.71t	7.6	3.11m	2.18m	5.40m		4.18m	4.35dd	4.48dd	7.31t	7.62m(2H)		8.22dd		
42*	9.50	6.64t	7.5	3.02m	2.16m	5.36m		4.25m	4.30dd	4.47dd	7.54m(2H)			8.17d		
49*	9.11	6.18d	2.9	5.82dd		2.88m	2.19dd	4.65m(2H)		4.48dd	7.25m(2H)			8.21d		
50*	8.97	6.14d	3.0	5.78dd		2.84m	2.15dd	4.64m(2H)		4.44dd	7.25m(2H)			7.96d		
51*	8.82	6.00d	2.3	5.89dd		2.87m	2.19dd	4.61m(2H)		4.46dd	7.09d	7.18s		8.08d		
52*	8.46	6.01d	2.5	5.88dd		2.84m	2.23dd	4.61m(2H)		4.46m		7.15s		7.93	2.33s(3H)	2.28s(3H)
53*	9.10	5.99d	2.5	5.90dd		2.85m	2.20dd	4.64m(2H)		4.45m	6.87s	7.57s			3.95s(3H)	3.90s(3H)
54	11.67	6.12d	5.0	4.62m		2.35m	1.83m	4.20m	3.49m(2H)		7.29m	7.68m(2H)		8.01d		
55	11.61	6.09d	4.9	4.61m		2.34m	1.82m	4.19m	3.54m(2H)		7.48dd	7.59d	2.81d		2.34s(3H)	
56	11.57	6.13d	5.0	4.64m		2.43m	1.84m	4.22m	3.61m	3.50m	7.10d	7.62s	7.88d		2.43s(3H)	
57	11.50	6.12d	5.1	4.62m		2.40m	1.83m	4.21m	3.63dd	3.50dd	7.60s	7.74s			2.34s(3H)	2.24s(3H)
58	11.54	6.20d	5.1	4.64m		2.41m	1.79m	4.15m	3.67m	3.50m	7.02s	7.38s			3.80s(3H)	3.88s(3H)
59	11.65	6.57t		2.10 - 2.50 m (4H)				4.39m	4.59dd	4.43dd	7.23t	7.43t	7.61d	7.99d		
60	11.57	6.55t		2.10 - 2.50 m (4H)				4.30m	4.63dd	4.40dd	7.10dd	7.47d	7.78s		2.26s(3H)	
61*	8.78	6.53t		2.20 - 2.65 m (4H)				4.41m	4.64dd	4.50dd	7.08d	7.38s		8.08d	2.38s(3H)	
62	11.47	6.50t		2.10 - 2.50 m (4H)				4.32m	4.52dd	4.42dd	7.38s	7.74s			2.23s(6H)	
63	11.50	6.55t		1.90 - 2.35 m (4H)				3.99m	3.61m(2H)		7.23m	7.61m	7.72m	7.98d		
64	11.55	6.50t		1.90 - 2.35 m (4H)				3.96m	3.60m(2H)		7.49dd	7.68d	7.80s		2.34s(3H)	
65	11.52	6.54t		1.90 - 2.35 m (4H)				3.98m	3.69m	3.55m	7.10d	7.70s	7.88d		2.39s(3H)	
66	11.48	6.52t		1.90 - 2.40 m (4H)				3.97m	3.66m	3.57m	7.69s	7.74s			2.24s(6H)	

s = Singlet; d = doublet; dd = doublet of doublet; t = triplet; m = multiplet.

6-Methyl-1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinedione (8). - Yield 11.0 g (99 %). Amorphous yellowish foam. R_f = 0.86 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{26}H_{42}N_2O_7Si_2$ (550.8): C, 56.70; H, 7.69; N, 5.09. Found: C, 56.40; H, 7.70; N, 5.07.

7-Methyl-1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinedione (9). - Yield 11.0 g (99 %). Amorphous solid. R_f = 0.88 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{26}H_{42}N_2O_7Si_2$ (550.8): C, 56.70; H, 7.69; N, 5.09. Found: C, 56.36; H, 7.69; N, 5.09.

6,7-Dimethyl-1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinedione (10). - Yield 11.06 g (98 %). Amorphous solid. R_f = 0.75 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{27}H_{44}N_2O_7Si_2$ (564.8): C, 57.42; H, 7.85; N, 4.96. Found: C, 56.92; H, 8.16; N, 4.87.

6,7-Dimethoxy-1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinedione (11). Yield 11.32 g (95 %). Amorphous yellowish foam. R_f = 0.67 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{27}H_{44}N_2O_9Si_2$ (596.8): C, 54.33; H, 7.43; N, 4.69. Found: C, 54.12; H, 7.38; N, 4.50.

1-[2-O-Phenoxythiocarbonyl-3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-ribofuranosyl]-2,4-quinazolinedione (12). - (a) To a solution of 7 (1.07 g, 2 mmole) in CH_3CN (30 ml) were added 4-dimethylaminopyridine (DMAP) (0.38 g, 4.1 mmole) and phenoxythiocarbonyl chloride (0.3 ml, 2.2 mmole) with stirring. After reaction for 16 h at room temperature the solution was evaporated and the residue partitioned between H_2O (120 ml) and $CHCl_3$ (150 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated to a small volume for chromatography on a silica-gel column (4.5x9 cm) with $CHCl_3$. The main fraction gave on evaporation a yellowish oil, which could be recrystallized from CH_3CN to give colourless crystals. Yield 0.54 g (40 %), m.p. 112-113°C. R_f = 0.71 ($CHCl_3$/MeOH 99:1).

(b) The same reaction was performed in CH_2Cl_2 (10 ml) at 0°C for 5 h, followed by stirring at room temperature overnight. Work-up and purification according to (a) gave an amorphous solid. Yield 1.15 g (85 %).

Anal.calc. for $C_{32}H_{44}N_2O_8SSi_2$ (672.9): C, 57.11; H, 6.59; N, 4.16. Found: C, 57.08; H, 6.66; N, 4.50.

O^2,2'-Anhydro-1-[3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3-diyl)-ß-D-arabinofuranosyl]-2,4-quinazolinedione (17). - (a) Continued elution of the column in 7 a) led to a second fraction, which gave on evaporation a solid foam. Yield 0.43 g (41 %). R_f = 0.32 ($CHCl_3$/MeOH 99:1).

Anal. calc. for $C_{25}H_{38}N_2O_6Si_2$ (518.8): C, 57.88; H, 7.38; N, 5.40. Found: C, 57.90; H, 7.40; N, 5.28.

(b) A solution of 12 (0.67 g, 1 mmole) in CH_3CN (15 ml) was treated with 4-dimethylaminopyridine (0.244 g, 2 mmole) at room temperature overnight. It was evaporated, the residue extracted with $CHCl_3$ (30 ml) and H_2O (20 ml). The organic phase was dried over Na_2SO_4 and gave on further evaporation an amorphous solid chromatographically identical with fraction a). Yield 0.5 g (95 %).

1-[2-Deoxy-3,5-O-(1,1,3,3-tetraisopropyldisiloxane-1,3 diyl)-ß-D-erythro-pentofuranosyl]-2,4-quinazolinedione (18). A solution of 12 (1.91 g, 2.84 mmole) in toluene (30 ml) was treated with argon for 20 min, then tri-n-butylstannane (2.26 ml, 8.52 mmole) and azo-bis-(isobutyronitrile) (AIBN) added and the mixture heated to 70°C under argon atmosphere for 3 h. After cooling ether (200 ml) and 0.1 N NaOH (100 ml) were added and shaken. The organic phase was dried over Na_2SO_4, filtered and evaporated. The oily residue was purified by column chromatography in $CHCl_3$. The main fraction gave on evaporation an amorphous solid. Yield 1.23 g (83 %).

Anal. calc. for $C_{25}H_{40}N_2O_6Si_2$ (520.8): C, 57.65; H, 7.74; N, 5.38. Found: C, 57.40; H, 7.60; N, 5.31.

1-(2-Deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (23). - (a) A mixture of 2,4-quinazolinedione (43) (2.93 g, 18.1 mmole), a few crystals of ammonium sulfate and acetamide were refluxed in hexamethyldisilazane (HMDS) (70 ml) for 18 h under exclusion of moisture. Excess of HMDS was removed in vacuo, the residue dissolved in $CHCl_3$ (400 ml), then 2-deoxy-3,5-di-O-p-toluoyl-D-erythro-pentofuranosyl chloride (6.61 g, 18.1 mmole) and CuI (3.3 g) added and stirred at room temperature for 20 h. The reaction mixture was treated with saturated $NaHCO_3$ solution, the organic layer separated and the aqueous phase again extracted twice with $CHCl_3$. The combined extracts were dried over Na_2SO_4, evaporated and purified by column chromatography on silica-gel first with $CHCl_3$ and then with $CHCl_3$/ethyl acetate 4:1. The main fraction was evaporated and the residue recrystallized from EtOH to give a 3:1 α,ß-mixture of 1-(3,5-di-O-p-toluoyl-2-deoxy-α,ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione. Yield 7.71 g (80 %). Separation of the anomers could be achieved by chromatography on preparative plates (40x20x0.2 cm) in toluene/EtOAc 4:1. The lower moving band gave pure 1-(3,5-di-O-p-toluoyl-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione. Its structure was proven by acylation of 23 (0.56 g, 2 mmole) with p-toluoyl chloride (0.53 ml, 5 mmole) in pyridine (10 ml) by stirring at 0°C for 2 h and 20 h at room temperature. The reaction mixture was poured on ice, extracted twice with $CHCl_3$ (50 ml), the organic phase dried over Na_2SO_4 and evaporated to dryness. The residue gave on recrystallization from benzene/cyclohexane colourless crystals. Yield 0.73 g (71 %), m.p. 147-148°C, lit.[7] 129-134°C.

Anal. calc. for $C_{29}H_{26}N_2O_7$ (514.5): C, 67.70; H, 5.09; N, 5.44. Found: C, 67.37; H, 5.10; N, 5.70.

(b) A solution of 18 (1.23 g, 2.36 mmole) and tetrabutylammonium fluoride (1.64 g, 5.2 mmole) in tetrahydrofuran (THF) (20 ml) was stirred for 1 h at room temperature. The precipitate was filtered, washed twice with ether. The solid was dissolved in boiling H_2O (8 ml), neutralized by AcOH and then more H_2O added till a clear solution on heating was obtained. On cooling colourless needles separated. Yield 0.48 g (75 %), m.p. 185-186°C, lit.[7] 167-168°C.

(c) In a 0.2 N solution of sodium methoxide in MeOH (150 ml) 37 (12.5 g, 28 mmole) was stirred overnight at room temperature. After evaporation the residue was partitioned between H_2O (50 ml) and ether (200 ml). The organic phase was washed with H_2O (20 ml) and again separated. The combined aqueous layers were neutralized by AcOH and chilled to give colourless needles. Yield 6.66 g (85 %), m.p. 185°C.

(d) In CH_2Cl_2 (200 ml) was dissolved 7 (10.7 g, 20 mmole) and pyridine (2.77 g, 35 mmole). After cooling to 0°C phenoxythiocarbonyl chloride (6.04 g, 35 mmole) was added and the mixture stirred at 0°C for 5 h and then at room temperature for 18 h. After evaporation the residue was taken up in H_2O (350 ml) and ether (500 ml). The eorganic layer was washed with 1 N HCl (200 ml), saturated $NaHCO_3$ solution (200 ml) and saturated NaCl solution (200 ml) and then dried over Na_2SO_4. On evaporation, crude 12 was obtained. It was dissolved in toluene (300 ml), the solution purged with argon, tri-n-butylstannane (17.5 g, 60 mmole) and AIBN (0.3 g) added and then heated to 75°C for 3 h with stirring under argon atmosphere. After cooling it was diluted with ether (400 ml), washed with 0.1 N NaOH (250 ml) and phosphate buffer pH 7 (300 ml). The organic layer was dried over Na_2SO_4, filtered, evaporated to dryness, the residue (18) dissolved in THF (200 ml) and after addition of tetrabutylammonium fluoride (14.2 g, 45 mmole) the solution stirred for 1 h.

The precipitate was collected, washed with ether, dissolved in hot H_2O and then neutralized with AcOH. After cooling, the solid was filtered and then recrystallized from H_2O to give colourless crystals. Yield 6.66 g (85 %), m.p. 185°C.

Anal. calc. for $C_{13}H_{14}N_2O_5$ (278.3): C, 56.11; H, 5.07; N, 10.07. Found: C, 56.03; H, 5.17; N, 10.07.

6-Methyl-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (24). - Analogous to the preceding procedure from 8 (11.1 g; 20 mmole) via the intermediates 13 and 19. Yield 4.11 g (70 %), m.p. 230°C (decomp.).

Anal. calc. for $C_{14}H_{16}N_2O_5$ (292.3): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.07; H, 5.53; N, 9.45.

7-Methyl-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (25). - According to procedure 7 d) from 9 (11.1 g, 20 mmole) via the intermediates 14 and 20. Yield 3.54 g (60 %), m.p. 220°C (decomp.).

Anal. calc. for $C_{14}H_{16}N_2O_5$ (292.3): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.21; H, 5.56; N, 9.53.

6,7-Dimethyl-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (26). - According to procedure 7 d) from 10 (11.3 g, 20 mmole) via the intermediates 15 and 21. Yield 3.64 g (62 %), m.p. 230°C (decomp.).

Anal. calc. for $C_{15}H_{18}N_2O_5$ (306.3): C, 58.82; H, 5.92; N, 9.15. Found: C, 58.51; H, 5.98; N, 9.14.

6,7-Dimethoxy-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (27). - Analogous to procedure 7 d) from 11 (11.9 g, 20 mmole) via the intermediates 16 and 22. Yield 3.17 g (49 %), m.p. 220°C (decomp.).

Anal. calc. for $C_{15}H_{18}N_2O_7 \cdot H_2O$ (356.3): C, 50.56; H, 5.66; N, 7.86. Found: C, 51.01; H, 5.57; N, 7.88.

6-Chloro-1-(2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (28). - (a) In a 0.01 M solution of sodium methoxide in MeOH (20 ml) was dissolved 40 (0.75 g, 1.56 mmole) and the solution was stirred at room temperature overnight. After evaporation, the residue was treated with H_2O (10 ml) and ether (50 ml). The organic phase was washed again with H_2O (5 ml) and then the combined aqueous phases neutralized by AcOH. On cooling, colourless crystals were obtained. Yield 0.313 g (64 %), m.p. 220°C (decomp.).

Anal. calc. for $C_{13}H_{13}Cl\ N_2O_5$ (312.7): C, 49.93; H, 4.19; N, 8.96. Found: C, 49.95; H, 4.34; N, 8.99.

(b) A mixture of 6-chloro-2,4-quinazolinedione (4.33 g, 22 mmole), a few crystals of ammonium sulfate and acetamide was refluxed in 80 ml HMDS under anhydrous conditions for 15 h. It was evaporated under vacuum, the residue dissolved in CH_2Cl_2 (100 ml), and then 2-deoxy-3,5-di-O-p-toluoyl-α-D-erythro-pentofuranosyl chloride (8.54 g, 22 mmole) added. The solution was stirred at room temperature for 24 h, evaporated and the residue recrystallized from EtOH to give a 1:1 mixture of 6-chloro-1-(2-deoxy-3,5-di-O-p-toluoyl-α,ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione. Yield 8.13 g (67 %). A part of this mixture (0.75 g) was separated into the pure components by medium pressure chromatography[62] on silica-gel in toluene/EtOAc 19:1. The faster migrating fraction gave on evaporation a crystalline solid of the ß-anomer. Yield 0.24 g (32 %), m.p. 199°C.

Anal. calc. for $C_{29}H_{25}Cl\ N_2O_7$ (549.0): C, 63.45; H, 4.59; N, 5.10. Found: C, 63.28; H, 4.58; N, 5.13.

The second fraction consisted of the α-anomer. Yield 0.28 g (37 %), m.p. 187°C.

Anal. calc. for $C_{29}H_{25}Cl\ N_2O_7$ (549.0): C, 63.45; H, 4.59; N, 5.10. Found: C, 63.20; H, 4.65; N, 5.13.

The 6-chloro-1-(2-deoxy-3,5-di-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (0.55 g, 1 mmole) was treated analogously to procedure (a) to give colourless crystals. Yield. 0.225 g (72 %), m.p. 220°C (decomp.).

1-(2-Deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinediones (29-32). General procedure. - In pyridine (30 ml) was dissolved the 1-(2-deoxy-ß-D-ribofuranosyl)-2,4-quinazolinedione (23-26) (10 mmole) and after cooling to 0°C p-toluoyl chloride (1.45 ml, 11 mmole) added. The mixture was stirred at 0°C for 3 h and at room temperature for 15 h. After dilution with ice-water (200 ml) the solution was extracted twice with EtOAc (80 ml). The organic extract was dried over Na_2SO_4, evaporated, the oily residue dissolved in CH_2Cl_2 (75 ml) and then the boiling solution further diluted by slow addition of n-hexane (75 ml) forming a colourless precipitate. The crystalline material was collected after cooling.

1-(2-Deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (29). - Yield 2.81 g (71 %), m.p. 180°C. R_f = 0.42 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{21}H_{20}N_2O_6$ (396.4): C, 63.63; H, 5.09; N, 7.07. Found: C, 63.65; H, 5.20; N, 7.37.

6-Methyl-1-(2-deoxy-5-O-p-toluoyl-ß-D-erytho-pentofuranosyl)-2,4-quinazolinedione (30). - Yield 3.25 g (79 %), m.p. 184-187°C. R_f = 0.79 (CH_2Cl_2/MeOH 9:1).

Anal.calc. for $C_{22}H_{22}N_2O_6 \cdot 0.5\ H_2O$ (419.4): C, 63.00; H, 5.53; N, 6.68. Found: C, 62.95; H, 5.42; N, 6.39.

7-Methyl-1-(2-deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (31). - Yield 2.71 g (66 %), m.p. 193-195°C. R_f = 0.58 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{22}H_{22}N_2O_6$ (410.4): C, 64.78; H, 5.40; N, 6.82. Found: C, 64.84; H, 5.68; N, 6.56.

6,7-Dimethyl-1-(2-deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (32). - Yield 3.05 g (69 %), m.p. 199°C. R_f = 0.40 ($CHCl_3$/MeOH 9:1).

Anal. calc. for $C_{23}H_{24}N_2O_6$ (442.5): C, 62.43; H, 5.92; N, 6.33. Found: C, 62.81; H, 5.89; N, 7.25.

1-(3,5-Di-O-acetyl-2-bromo-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (33). - (a) A solution of 1 (2.94 g, 10 mmole) in CH_3CN (150 ml) was heated to 50°C and then a solution of acetyl bromide (4.1 ml) in CH_3CN (15 ml) added dropwise within 15 min with stirring. The reaction mixture was refluxed for 2.5 h, then evaporated and the residue treated with H_2O (100 ml) and $CHCl_3$ (2x100 ml). The organic phase was dried over Na_2SO_4, filtered, evaporated and the resulting residue purified by flash chromatography (80 g silica-gel) in $CHCl_3$/MeOH 49:1. The main fraction gave on evaporation an amorphous solid. Yield 2.6 g (59 %).

(b) A mixture of 1 (0.59 g, 2 mmole), LiBr (0.52 g) and acetyl bromide (0.44 ml) in CH_3CN (20 ml) was boiled under reflux for 1 h. Work-up and purification was performed analogously to (a). Yield 0.74 g (84 %).

(c) Compound 1 (0.59 g, 2 mmole) was heated under reflux with α-acetoxyisobutyryl bromide (0.88 ml) in CH_3CN (20 ml) for 2 h. Work-up and purification according to (a) gave an amorphous foam. Yield 0.45 g (51 %). R_f = 0.82 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{17}H_{17}BrN_2O_7$ (441.2): C, 46.28; H, 3.88; N, 6.35. Found: C, 46.15; H, 3.95; N, 6.09.

6-Methyl-1-(3,5-di-O-acetyl-2-bromo-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (34). - A suspension of 2 (1.54 g, 5 mmole) in CH_3CN (70 ml) was heated to 50°C and then a mixture of acetyl bromide (3.7 ml, 30 mmole) in

CH_3CN (10 ml) added dropwise within 15 min. After refluxing for 2 h, the solution was evaporated, the residue treated with H_2O (70 ml) and $CHCl_3$ (2x80 ml). The organic phase was dried over Na_2SO_4 and then again concentrated to a syrup. Purification was achieved by flash chromatography (80 g silica-gel) in CH_2Cl_2/MeOH 97:3 to give a colourless foam. Yield 1.82 g (80 %). R_f = 0.76 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{18}H_{19}BrN_2O_7$ (455.3): C, 47.49; H, 4.21; N, 6.15. Found: C, 47.24; H, 4.38; N, 5.98.

1-(3,5-Di-O-acetyl-2-chloro-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (35). - A mixture of 1 (4.41 g, 15 mmole) and LiCl (4.24 g, 100 mmole) in CH_3CN (150 ml) was heated to boiling and then a solution of acetyl chloride (7.85 g, 100 mmole) in CH_3CN (10 ml) was added dropwise. It was refluxed for 4 h, then evaporated and the residue taken up in $CHCl_3$ (300 ml) and saturated $NaHCO_3$ solution (200 ml). The organic phase was dried, concentrated and purified by flash chromatography on silica-gel in CH_2Cl_2/EtOAc 4:1. The main fraction gave on evaporation in vacuum an amorphous solid. Yield 4.49 g (75 %). R_f = 0.79 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{17}H_{17}Cl\,N_2O_7$ (396.8): C, 51.46; H, 4.32; N, 7.06. Found: C, 51.33; H, 4.37; N, 7.02.

6-Methyl-1-(3,5-di-O-acetyl-2-chloro-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (36). - Analogous to the preceding procedure was reacted 2 (4.62 g, 15 mmole) with LiCl (4.24 g, 100 mmole) and acetyl chloride (7.85 g, 100 mmole) to give an amorphous solid. Yield 4.28 g (69 %). R_f = 0.49 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{18}H_{19}Cl\,N_2O_7$ (410.8): C, 52.63; H, 4.66; N, 6.82. Found: C, 52.55; H, 4.63; N, 6.62.

A second fraction was also isolated and identified as 6-methyl-1-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)-2,4-quinazolinedione. Yield 1.27 g (20 %). R_f = 0.29 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{20}H_{22}N_2O_9$ (434.4): C, 55.30; H, 5.10; N, 6.45. Found: C, 55.18; H, 5.17; N, 6.49.

1-(3,5-Di-O-acetyl-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (37). - A solution of 35 (3.97 g, 10 mmole) inTHF (100 ml) was purged by argon. Then tri-n-butylstannane (8 ml, 30 mmole) and AIBN (0.2 g) were added and the mixture heated to 65°C for 6 h under argon atmosphere. It was evaporated and the residue recrystallized from n-hexane to give colourless crystals. Yield 2.97 g (82 %), m.p. 120°C.

Anal. calc. for $C_{17}H_{18}N_2O_7$ (362.3): C, 56.35; H, 5.01; N, 7.73. Found: C, 56.28; H, 5.11; N, 7.68.

6-Methyl-1-(3,5-di-O-acetyl-2-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (38). - (a) A solution of 34 (0.71 g, 1.56 mmole) in toluene (50 ml) was gased with argon for 20 min and then tri-n-butylstannane (1.24 ml, 4.7 mmole) and AIBN (60 mg) were added. The mixture was heated to 75°C for 3 h under Ar atmosphere, then evaporated and the residue recrystallized from n-hexane to give colourless crystals. Yield 0.22 g (37 %).

(b) Analogous to the receding prodedure 36 (1.51 g, 3.65 mmole) was heated in toluene (70 ml) with tri-n-butylstannane (2.92 ml, 11 mmole) and AIBN (0.1 g). Colourless crystals were obtained. Yield 1.03 g (75 %).

(c) A solution of 24 (1.17 g, 4 mmole) in pyridine (10 ml) was treated at room temperature with acetic anhydride (10 ml) overnight. The reaction solution was poured onto ice and the resulting precipitate collected. Recrysrallization from EtOH/H_2O gave colourless crystals. Yield 1.35 g (90 %), m.p. 170°C. R_f = 0.65 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{18}H_{20}N_2O_7$ (376.4): C, 57.44; H, 5.36; N, 7.44. Found: C, 57.12; H, 5.48; N, 7.32.

1-(2-Chloro-2-deoxy-3,5-di-O-pivaloyl-ß-D-ribofuranosyl)-2,4-quinazolinedione (39). - A mixture of 1 (1.47 g, 5 mmole), LiCl (0.43 g, 10 mmole) and pivaloyl chloride (6.15 ml, 50 mmole) in CH_3CN (20 ml) was refluxed for 18 h. The suspension was then evaporated and the residue treated with CH_2Cl_2 (150 ml) and saturated $NaHCO_3$ solution (100 ml). The organic layer was dried over Na_2SO_4, filtered, evaporated and the residue purified by flash chromatography (silica-gel column 4.5x14 cm) with CH_2Cl_2/EtOAc 9:1 to give a colourless amorphous solid. Yield 1.17 g (49 %). R_f = 0.39 (CH_2Cl_2/EtOAc 9:1).

Anal. calc. for $C_{23}H_{29}Cl\ N_2O_7$ (480.9): C, 57.44; H, 6.08; N, 5.82. Found: C, 57.18; H, 6.12; N, 5.44.

6-Chloro-1-(2-chloro-2-deoxy-3,5-di-O-pivaloyl-ß-D-ribofuranosyl)-2,4-quinazolinedione (40). - Analogous to the preceding procedure was reacted 6[1] (1.64 g, 5 mmole) to give a colourless foam. Yield 2.45 g (95 %). R_f = 0.77 ($CHCl_3$/-EtOAc 4:1).

Anal. calc. for $C_{23}H_{28}Cl\ N_2O_7$ (515.4): C, 53.60; H, 5.48; N, 5.44. Found: C, 54.13; H, 5.85; N, 5.18.

1-(2-Deoxy-3,5-di-O-pivaloyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (41). - A solution of 39 (0.96 g, 2 mmole) in toluene (20 ml) was gased with Ar for 20 min. Then tri-n-butylstannane (1.6 ml, 6 mmole) and AIBN (50 mg) were added and the mixture heated to 75°C for 6 h under Ar atmosphere. After evaporation the residue was heated in n-hexane till crystallization took place. Colourless crystals. Yield 0.67 g (75%), m.p. 156°C. R_f = 0.61 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{23}H_{30}N_2O_7$ (446.5): C, 61.87; H, 6.77; N, 6.27. Found: C, 61.66; H, 6.70; N, 6.37.

6-Chloro-1-(2-deoxy-3,5-di-O-pivaloyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (42). - Analogous to the preceding procedure with 40 (1.03 g, 2 mmole). The crude product could not be crystallized. Purification was achieved by flash chromatography (silica-gel column 2.5x15 cm) in CH_2Cl_2/-EtOAc 4:1 to give a colourless foam. Yield 0.77 g (80 %). R_f = 0.58 ($CHCl_3$/EtOAc 4:1).

Anal.calc. for $C_{23}H_{29}Cl\ N_2O_7$ (480.9): C, 57.44; H, 6.08; N, 5.82. Found: C, 57.52; H, 6.30; N, 5.99.

1-(2-O-Acetyl-3-deoxy-5-O-p-toluoyl-β-D-erythro-pentofuranosyl)-2,4-quinazolinedione (49-53). General procedure. A mixture of the 2,4-quinazolinedione (43-47) (2 mmole), a few crystals of ammonium sulfate and acetamide was refluxed in hexamethyldisilazane (HMDS) (20 ml) for 20 h under exclusion of moisture. The excess of HMDS was removed in vacuum and the residue dissolved in a solution of 1,2-di-O-acetyl-3-deoxy-5-O-p-toluoyl-D-ribose (48)[38] in 1,2-dichloroethane (60 ml). A solution of trimethylsilyl trifluoromethanesulfonate (0.44 ml, 2.2 mmole) in 1,2-dichloroethane (10 ml) was added dropwise with stirring at room temperature. The reaction was stopped by addition of a saturated solution of $NaHCO_3$ and then extracted twice with $CHCl_3$ (80 ml). The combined organic layers were dried over Na_2SO_4, filtered, evaporated and the residue purified by flash chromatography. The main fraction gave an amorphous solid on evaporation.

1-(2-O-Acetyl-3-deoxy-5-O-p-toluoyl-β-D-erythro-pentofuranosyl)-2,4-quinazolinedione (49). - Flash chromatography (25 g silica-gel) was performed in $CHCl_3$. Yield 0.52 g (59 %). R_f = 0.30 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{23}H_{22}N_2O_7$ (438.4): C, 63.01; H, 5.06; N, 6.39. Found: C, 62.65; H, 5.16; N, 6.20.

6-Methyl-1-(2-O-acetyl-3-deoxy-5-O-p-toluoyl-β-D-erythro-pentofuranosyl)-2,4-quinazolinedione (50). - Purification was done by flash chromatography in $CHCl_3$/MeOH 99:1. Yield 0.56 g (62 %). R_f = 0.40 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{24}H_{24}N_2O_7$ (452.4): C, 63.71; H, 5.35; N, 6.19. Found: C, 63.67; H, 5.38; N, 6.19.

7-Methyl-1-(2-O-acetyl-3-deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (51). - Analogous to the preceding procedure gave an amorphous foam. Yield 0.61 g (67 %). R_f = 0.33 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{24}H_{24}N_2O_7$ (452.4): C, 63.71; H, 5.35; N, 6.19. Found: C, 63.61; H, 5.53; N, 6.25.

6,7-Dimethyl-1-(2-O-acetyl-3-deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (52). - Purification by flash chromatography in $CHCl_3$/MeOH 99:1. Yield 0.68 g (73 %). R_f = 0.45 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{25}H_{26}N_2O_7$. 0.5 H_2O (475.5): C, 63.15; H, 5.72; N, 5.89. Found: C, 63.52; H, 5.71; N, 5.74.

6,7-Dimethoxy-1-(2-O-acetyl-3-deoxy-5-O-p-toluoyl-ß-D-erythro-pentofuranosyl)-2,4-quinazoline-dione (53). - Flash chromatography in $CHCl_3$/MeOH 99:1 gave a solid foam. Yield 0.67 g (68 %). R_f = 0.34 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{25}H_{26}N_2O_9$. H_2O (516.5): C, 58.14; H, 5.46; N, 5.42. Found: C, 58.33; H, 5.17; N, 5.28.

1-(3-Deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinediones (54-58). General procedure. - To a solution of sodium (26 mg, 1.1 mmole) in MeOH (20 ml) was added the appropriate protected quinazoline 3'-deoxynucleoside 49-53 (1 mmole). The solution was stirred at room temperature overnight, then evaporated and the residue partitioned between H_2O (2x10 ml) and ether (50 ml). The combined aqueous layers were neutralized by acetic acid and on chilling overnight colourless crystals were obtained. The solid was collected, washed and dried at 100°C.

1-(3-Deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (54). - Yield 0.16 g (56 %), m.p. 194-195°C.

Anal. calc. for $C_{13}H_{14}N_2O_5$ (278.3): C, 56.11; H, 5.07; N, 10.07. Found: C, 55.91; H, 5.10; N, 9.90.

6-Methyl-1-(3-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (55). - Yield 0.24 g (80 %), m.p. 232°C.

Anal. calc. for $C_{14}H_{16}N_2P_5$ (292.3): C, 57.33; H, 5.52; N, 9.58. Found: C, 57.54; H, 5.58; N, 9.52.

7-Methyl-1-(3-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (56). - Yield 0.22 g (74 %), m.p. 230°C.

Anal. calc. for $C_{14}H_{16}N_2O_5$ (292.3): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.33; H, 5.58; N, 9.77.

6,7-Dimethyl-1-(3-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (57). - Yield 0.22 g (71 %), m.p. 219-221°C.

Anal. calc. for $C_{15}H_{18}N_2O_5$ (306.3): C, 58.84; H, 5.56; N, 9.15. Found: C, 58.81; H, 5.95; N, 8.93.

6,7-Dimethoxy-1-(3-deoxy-ß-D-erythro-pentofuranosyl)-2,4-quinazolinedione (58). - Yield 0.22 g (65 %), m.p. 207-209°C.

Anal. calc. for $C_{15}H_{18}N_2O_7$ (338.3): C, 53.25; H, 5.36; N, 8.28. Found: C, 52.84; H, 5.45; N, 8.29.

1-(2,3-Dideoxy-5-O-p-toluoyl-ß-D-glycero-pentofuranosyl)-2,4-quinazolinediones (59-62). *General procedure.* - A suspension of the appropriate 1-(5-O-p-toluoyl-ß-D-ribofuranosyl)-2,4-quinazolinedione (29-32) (1.5 mmole) and pyridine (0.21 ml, 2.6 mmole) in CH_2Cl_2 (20 ml) was cooled to 0°C and then phenoxythiocarbonyl chloride (0.35 ml, 2.6 mmole) added dropwise with stirring. The reaction mixture was kept 3 h at

0°C and then at room temperature overnight. After evaporation the residue was partitioned between H_2O (30 ml) and EtOAc (2x30 ml). The combined organic layers were dried over Na_2SO_4, filtered, evaporated and the remaining syrup dissolved in toluene/THF 1:1 (50 ml). The solution was treated with argon for 20 min and after addition of tri-n-butylstannane (1.2 ml, 4.5 mmole) and AIBN (50 mg) heated to 75°C for 3 h with stirring under Ar atmosphere. After cooling the solution was evaporated and the residue refluxed in n-hexane (30 ml) till crystallization took place. The crystals were collected and dried in vacuum at 40°C.

1-(2,3-Dideoxy-5-O-p-toluoyl-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (59). - Yield 0.56 g (99 %), m.p. 94-96°C. R_f = 0.27 ($CHCl_3$/EtOAc 4:1).

Anal.calc. for $C_{21}H_{20}N_2O_5 \cdot 0.5\ H_2O$ (380.4): C, 64.77; H, 5.43; N, 7.19. Found: C, 64.56; H, 5.50; N, 7.45.

6-Methyl-1-(2,3-dideoxy-5-O-p-toluoyl-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (60). - Yield 0.44 g (72 %), m.p. 162-165°C. R_f = 0.67 ($CHCl_3$/MeOH 19:1).

Anal. calc. for $C_{22}H_{22}N_2O_5 \cdot 0.5\ H_2O$ (403.4): C, 65.50; H, 5.75; N, 6.94. Found: C, 65.00; H, 5.73; N, 6.57.

7-Methyl-1-(2,3-dideoxy-5-O-p-toluoyl-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (61). - Yield 0.45 g (81 %), m.p. 149°C. R_f = 0.32 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{22}H_{22}N_2O_5 \cdot 0.5\ H_2O$ (403.4): C, 65.50; H, 5.75; N, 6.94. Found: C, 65.48; H, 5.70; N, 6.85.

6,7-Dimethyl-1-(2,3-dideoxy-5-O-p-toluoyl-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (62). - Yield 0.55 g (89 %), m.p. 175°C. R_f = 0.30 ($CHCl_3$/EtOAc 4:1).

Anal. calc. for $C_{23}H_{24}N_2O_5 \cdot H_2O$ (426.5): C, 64.78; H, 6.15; N, 6.57. Found: C, 65.14; H, 6.20; N, 6.64.

1-(2,3-Dideoxy-ß-D-glycero-pentofuranosyl)-2,4-quinazolinediones (63-66). General procedure. - The protected quinazoline 2',3'-dideoxyribonucleoside (59-62) (1 mmole) was stirred at room temperature overnight in a solution of sodium (28 mg, 1.2 mmole) in MeOH (50 ml). The reaction mixture was evaporated and the residue partitioned between ether (20 ml) and H_2O (2x5 ml). The combined aqueous layers were neutralized by AcOH and after cooling the precipitated crystals collected, washed and dried.

1-(2,3-Dideoxy-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (63). - Yield 0.2 g (76 %), m.p. 175°C.

Anal. calc. for $C_{13}H_{14}N_2O_4$ (262.3): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.88; H, 5.43; N, 10.63.

6-Methyl-1-(2,3-dideoxy-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (64). - Yield 0.18 g (66 %), m.p. 196°C.

Anal. calc. for $C_{14}H_{16}N_2O_4$. 0.5 H_2O (285.3): C, 58.94; H, 6.00; N, 9.82. Found: C, 59.20; H, 5.77; N, 9.93.

7-Methyl-1-(2,3-dideoxy-ß-D-glycero-pentofuranosyl)-2,4-quinazolinedione (65). - Yield 0.232 g (84 %), m.p. 198°C.

Anal. calc. for $C_{14}H_{16}N_2O_4$ (276.3): C, 60.85; H, 5.84; N, 10.14. Found: C, 60.40; H, 5.92; N, 10.18.

6,7-Dimethyl-1-(2,3-dideoxy-ß-D-glycero-pentofuranosyl)-2,4-quinazoliendione (66). - Yield 0.25 g (85 %), m.p. 220°C (decomp.).

Anal. calc. for $C_{15}H_{18}N_2O_4$. 0.25 H_2O (294.8): C, 61.11; H, 6.33; N, 9.50. Found: C, 61.04; H, 6.25; N, 9.29.

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