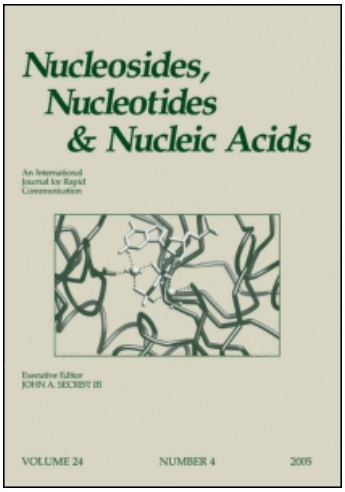


Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Nucleosides, XLVIII. Syntheses and Properties of Quinazoline N-1-Ribofuranosides

Martin Dunkel[a]; Wolfgang Pfleiderer[a]
[a] Fakultät für Chemie, Universität Konstanz, Konstanz, FRG

To cite this Article Dunkel, Martin and Pfleiderer, Wolfgang(1991) 'Nucleosides, XLVIII. Syntheses and Properties of Quinazoline N-1-Ribofuranosides', Nucleosides, Nucleotides and Nucleic Acids, 10: 4, 799 — 817
To link to this Article: DOI: 10.1080/07328319108046663
URL: http://dx.doi.org/10.1080/07328319108046663

NUCLEOSIDES & NUCLEOTIDES, 10(4), 799-817 (1991)

NUCLEOSIDES, XLVIII[1]
SYNTHESES AND PROPERTIES OF QUINAZOLINE N-1-RIBOFURANOSIDES

Martin Dunkel and Wolfgang Pfleiderer
Fakultät für Chemie, Universität Konstanz
Postfach 5560, D-7750 Konstanz/FRG

Abstract. Several 6- and 7-substituted quinazoline-2,4-(1H,3H)-diones (1-7) have been ribosylated with 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose (8) via the "silyl"-method and Lewis acid catalysis in a highly regioselective manner to give the corresponding protected N-1 ribosides 9-15. Debenzoylation to the free nucleosides 16-22 was achieved by sodium methoxide. Thiation of 9-15 by Lawesson's reagent effected the conversion of the 4-oxo into the 4-thioxo function (23-29). Removal of the sugar protecting groups in these derivatives worked best with potassium carbonate in anhydrous MeOH to form in high yields 30-35. Treatment of the peracylated 4-thioxo quinazoline nucleosides with methanolic ammonia resulted in deacylation of the sugar moiety and in displacement of the sulfur function to give the corresponding 4-amino-1-ß-D-ribofuranosyl-quinazolin-2(1H)-ones 36-41. The newly synthesized nucleosides have been characterized by elemental analysis, UV- and ^{1}H-NMR-spectra.

It has been known for several years that AIDS is caused by the human immunodeficiency virus (HIV-1), but so far only 3'-azido-3'-deoxythymidine (AZT) has been licensed to treat this disease. Many structurally related nucleosides have recently been synthesized leading to the 2',3'-dideoxy-nucleosides[2] as the most potent anti-HIV-1 agents. Also a series of 3'-halo-2',3'-dideoxy-[3-5] and 2',3'-dideoxy-2',3'-didehydropyrimidine-nucleosides[6] were discovered as potent and selective inhibitors of HIV-1. Since other active antiviral compounds like ara-thymidine[7], 5-iodo-2'-deoxyuridine (IDU)[8], *E*-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)[9] and 2'-fluoro-5-iodo-ara-cytidine (FIAC)[10] belong also to the pyrimidine

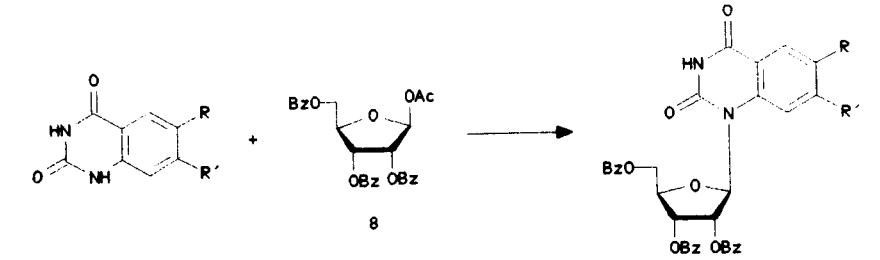
nucleoside group there is a good reason from a structural point of view to extend the investigations to the quinazoline series, which can be regarded as benzo-uridines and -cytidines respectively.

Relatively little is known about quinazoline nucleosides, of which the uridine analog 1-β-D-ribofuranosyl-quinazoline-2,4-dione (16) was first synthesized by Stout and Robins[11] in 1968. They also reported about chemical interconversions of various functionalities at the sugar and aglycone moiety of this molecule and detected some activity against the herpes-simplex-virus[12]. Despite these facts only a few more papers[13-18] are concerned with this field of potentially active antiviral compounds.

S Y N T H E S E S

The basic work of Robins et al.[11,13] was used as a guideline for the ribosylations of quinazoline-2,4(1H,3H)-dione (1) and its 6- and/or 7-substituted derivatives (2-7). The first efforts have been directed towards a simplification and optimization of the described reaction conditions. Application of the Hilbert-Johnson-Birkofer method[19] to the trimethylsilylated heterocyclic starting materials and 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (8) under trimethylsilyl triflate catalysis[20] in 1,2-dichloroethane afforded the corresponding quinazoline-2,4-dione N-1-β-D-ribofuranosides in a highly regio- and stereoselective manner.

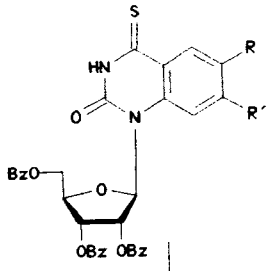
Thus 6-methyl-(2)[21], 7-methyl-(3)[22], 6,7-dimethyl-(4)[23], 6,7-dimethoxy-(5)[23], 6-chloro-(6)[24], 6-bromo-(7)[25] and the unsubstituted quinazoline-2,4-dione (1) reacted in a one-pot-two-step procedure to the peracylated N-1-β-D-nucleosides 9-15. Silylation was achieved by hexamethyldisilazane (HMDS) and catalytic amounts of ammonium sulfate and acetamide and led on evaporation of excess of HMDS to viscous oils or amorphous solids in quantitative yield. The subsequent ribosylation was complete in one to two hours by stirring at room temperature and gave with usual work-up and



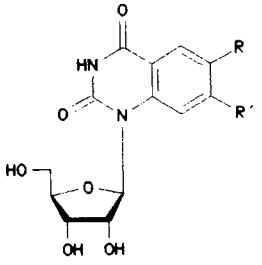
8

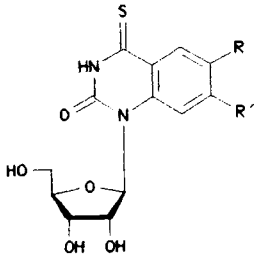
	R	R′
1	H	H
2	CH_3	H
3	H	CH_3
4	CH_3	CH_3
5	OCH_3	OCH_3
6	Cl	H
7	Br	H

	R	R′
9	H	H
10	CH_3	H
11	H	CH_3
12	CH_3	CH_3
13	OCH_3	OCH_3
14	Cl	H
15	Br	H

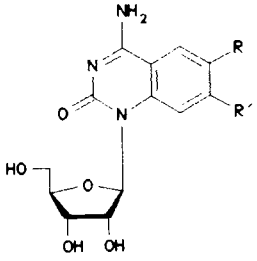


	R	R′	
23	H	H	16
24	CH_3	H	17
25	H	CH_3	18
26	CH_3	CH_3	19
27	OCH_3	OCH_3	20
28	Cl	H	21
29	Br	H	22





	R	R′	
30	CH_3	H	36
31	H	CH_3	37
32	CH_3	CH_3	38
33	OCH_3	OCH_3	39
34	Cl	H	40
35	Br	H	41



recrystallization from ethanol/water the blocked nucleosides in 70-90 % yield.

Debenzoylation by Zemplen's procedure[26] with sodium methoxide in methanol afforded the free quinazoline-2,4-dione N-1-ß-D-ribofuranosides 16-22 in yields of 80-90 %.

Substitution of the 4-oxo function by sulfur was accomplished in the peracylated nucleosides 10-15 by Lawesson's reagent[27] in toluene, which allows an easy work-up of the reaction mixture and is therefore preferable to phosphorus pentasulfide. The crude reaction products could be recrystallized from methanol to give the analytically pure 1-(2',3',5'-tri-O-benzoyl-ß-D-ribofuranosyl)-4-thioxo-quinazolin-2(1H)ones (23-29) in high yields. Deprotection of 23-29 was carried out under mild basic conditions and worked best with potassium carbonate in dry methanol to give 30-35. Attempted removal of the benzoyl group by sodium methoxide led to partial displacement of the thioxo group and formation of the corresponding methoxy derivative.

Finally the synthesis of the 4-amino-1-ß-D-ribofuranosyl-quinazolin-2(1H)ones 36-41 was also achieved from 24-29 by heating with methanolic ammonia in an autoclave at 100°C for 18 hours.

PHYSICAL PROPERTIES

Characterization of the newly synthesized quinazoline nucleosides was based on elemental analyses, UV and ^{1}H-NMR spectra.The site of attachment of the sugar moiety at N-1 is derived from UV spectral comparisons with the proven structure of 1-ß-D-ribofuranosyl-quinazoline-2,4(1H,3H)-dione[11] indicating a high degree of similarity. The determinations of the pK_a values of the deprotected nucleosides 16-22 reveal the minor influence of the electron-donating and electron-attracting substituents on the acidity of the N_3-H function. The fact that anion formation is not associated with a pronounced bathochromic shift of the long wavelength absorption band is also in agreement with N-1 rather than N-3 substitution.

The introduction of a 4-thioxo function causes an increase in acidity and the usual red shift of the absorption spectrum. The 4-amino-quinazolin-2(1H)one nucleosides encounter weakly basic properties evident from their pK_a in the range of 3.2-3.8. Protonation takes places in these molecules at N-3 giving rise to the normally observed hypsochromic shift of the long wavelength absorption maximum.

The ^{1}H-NMR spectra can be taken for further characterization of the various nucleosides but are in general of complex nature and do not reveal many distinct fine structural features. It is noteworthy to mention that the coupling constants of the anomeric proton of the protected and free quinazoline N-1-ribofuranosides are much larger than those of the corresponding lumazine N-1-ribofuranosides[29,30] indicating a higher conformational population towards the S-type conformer in the quinazoline N-1-ribofuranoside series. Furthermore the increase in acidity of the N-3 proton going from the amide to the thioamide function is reflected, expectedly, in the chemical shifts of these acidic protons.

E X P E R I M E N T A L

UV-spectra were recorded on a Perkin Elmer spectrophotometer Lambda 5; ^{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. The pK-values were determined spectrophotometrically.[28] Thin layer chromatography was performed on silica-gel sheets F 1550 LS 254 of Schleicher & Schüll. 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.

General procedure for substituted 2,4-quinazoline-diones (1-7).[22-25] A solution of 2.4 g potassium cyanate in H_2O (10 ml) was dropped slowly into a stirred suspension of the substituted anthranilic acid[18] (15 mmol) in a mixture of

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

	pK$_a$	UV Absorption Spectra												pH	Mole-cular
	in H_2O	λ ... [nm]					log ε							solv.	Form
9		218	[274]	[281]	304	[312]	4.79	[3.52]	[3.52]	3.57				MeOH	o
10		221	274	312	[322]		4.82	3.51	3.60	[3.54]				MeOH	o
11		225		[274]	303		4.87		[3.55]	3.64				MeOH	o
12		225		[274]	310		4.90		[3.57]	3.61				MeOH	o
13		230		[260]	317		4.87		[4.01]	3.82				MeOH	o
14		221	[251]	[273]	316		4.87	[4.11]	[3.50]	3.56				MeOH	o
15		224	[252]	[274]	317		4.87	[4.16]	[3.47]	3.54				MeOH	o
16	9.93	218	[240]		307		4.58	[3.91]		3.58				8.0	o
		221		[256]	307		4.60		[3.63]	3.61				12.0	-
17	9.74	220	[242]		315		4.60	[3.99]		3.60				8.0	o
		223		[260]	315		4.64		[3.57]	3.62				12.0	-
18	9.78	224	[246]		306		4.65	[3.90]		3.63				7.0	o
		225		[261]	306		4.70		[3.74]	3.69				11.0	-
19	9.84	226	[248]	[260]	313		4.63	[3.94]	[3.75]	3.63				8.0	o
		226		[262]	315		4.64		[3.57]	3.62				12.0	-
20	9.99	230		[258]	[317]	324	4.59		[3.79]	[3.85]	3.81			7.0	o
		235		[261]	318		4.53		[3.87]	3.83				12.0	-
21	9.09	221	244	[252]	318	[328]	4.60	4.08	[3.89]	3.58	[3.51]			7.0	o
		224		[252]	318	[326]	4.64		[3.92]	3.59	[3.52]			12.0	-
22	9.08	224	246	[250]	319		4.62	4.09	[4.02]	3.51				7.0	o
		228		[254]	318		4.07		[3.95]	3.55				11.0	-
23		229		[261]	[324]	351	[374]	4.59		[3.80]	[3.78]	4.02	[3.73]	MeOH	o
24		223		265		360	[378]	4.76		4.20		4.10	[3.94]	MeOH	o
25		221		273	356	[367]	[376]	4.69		4.04	4.20	[4.07]	[3.91]	MeOH	o
26		225		274	323	359	[377]	4.70		3.99	3.83	4.10	[3.96]	MeOH	o

Table 1 Continuation

27			257			367	[385]	4.63				4.25	[4.22]	MeOH	o
28		225			310	363	[374]	4.80			3.79	4.08	[3.95]	MeOH	o
29		227			[310]	364	[382]	4.79			[3.74]	4.07	[3.88]	MeOH	o
30	9.04	211	238	270	326	361	[374]	4.46	4.17	3.72	3.86	4.06	[3.98]	7.0	o
		222	242	274	326	354	[368]	4.52	4.16	3.75	3.92	4.08	[3.95]	12.0	-
31	9.08	211	239	275	[324]	355	[368]	4.45	4.10	3.89	[3.90]	4.19	[4.09]	7.0	o
		222	[238]	282	[318]	346	[355]	4.49	[4.18]	3.92	[3.94]	4.14	[4.08]	11.0	-
32	9.04	212	242		277	360	[376]	4.47	4.17		3.90	4.15	[4.09]	7.0	o
		222	[239]	283		352	[365]	4.50	[4.22]	3.93		4.11	[4.01]	12.0	-
33	9.12	[222]	255	286	321	370	385	[4.46]	4.25	3.91	3.81	4.25	4.26	7.0	o
		225	243	292	319	358	[368]	4.41	4.25	3.98	3.98	4.19	[4.14]	11.0	-
34	8.45	220	243	[264]	327	363	[374]	4.49	4.24	[3.77]	3.80	4.06	[3.96]	7.0	o
		226	[244]	[272]	328	357	[371]	4.61	[4.24]	[3.59]	3.90	4.06	[3.94]	11.0	-
35	8.41	220	[243]	[264]	327	364	[374]	4.48	[4.27]	[3.79]	3.76	4.00	[3.91]	7.0	o
		204	[250]	[269]	330	358	[369]	4.31	[4.18]	[3.64]	3.86	4.00	[3.90]	11.0	-
36	3.69	222		[260]	336			4.58		[3.84]	3.69			1.0	+
		225	[247]	[262]	326	[336]		4.64	[4.10]	[3.84]	3.67	[3.59]		7.0	o
37	3.83	222		269	324			4.52		4.01	3.73			1.0	+
		227	[251]	[264]	316			4.67	[4.06]	[3.94]	3.72]			6.0	o
38	3.70	225		271	333			4.52		3.98	3.72			1.0	+
		228	[249]	[270]	323			4.68	[4.13]	[3.88]	3.74			6.0	o
39	3.75	210	242	283	340	[347]		4.29	4.52	3.99	3.98	[3.96]		1.0	+
		233	[256]	275	328	[334]		4.61	[4.07]	3.88	3.96	[3.93]		6.0	o
40	3.18	226		[264]	339			4.64		[3.65]	3.66			1.0	+
		227	[250]	[270]	329	[336]		4.67	[4.10]	[3.64]	3.64	[3.59]		5.0	o
41	3.39	228	252		341			4.63	4.16		3.64			1.0	+
		229	[252]	[272]	330	[338]		4.67	[4.14]	[3.60]	3.63	[3.57]		6.0	o

Table 2 - Physical Data of Quinazoline N-1-Ribofuranosides

	^{1}H-NMR Spectra in D$_6$-DMSO or in CDCl$_3$* (δ-values in ppm against TMS)											
	NH NH$_2$	1'-H	J$_{1',2'}$ [Hz]	2'-H	3'-H	4'-H	5'-H	5''-H	aromatic H			aromatic substituent(s)
9*	8.78	6.51d	3.7	6.30dd	6.19t	4.68-4.76m(2H)		4.92dd	8.22dd	7.22-7.60(3H)**		
10*	8.80	6.45d	3.6	6.20-6.30m(2H)		4.60-4.90m(3H)			7.20-8.00m(3H)**			2.30s(3H)
11*	8.55	6.30d	2.6	6.40m	6.25m	4.60-4.90m(3H)			7.10d	7.20s	7.35-7.55(1H)**	2.40s(3H)
12*	8.60	6.20-6.40m(3H)				4.60-4.90m(3H)			7.15s	7.95s		2.25s(6H)
13*	8.75	6.20-6.40m(3H)				4.65-4.95m(3H)			6.80s	7.60s		3.95s(6H)
14*	8.80	6.45d	3.6	6.15-6.25m(2H)		4.60-4.90m(3H)			7.25-8.15m(3H)**			
15*	9.10	6.45d	3.7	6.15-6.30m(2H)		4.65-4.95m(3H)			7.25-7.60m(2H)**	8.30s		
16	11.68	6.16d	6.2	4.50pq	4.13pq	3.77m	3.57-3.73m(2H)		7.30t	7.66t	7.80d 8.01d	
17	11.60	6.18d	6.1	4.45pq	4.15pq	3.70m	3.55-3.65m(2H)		7.45s	7.75d	7.80s	2.33s(3H)
18	11.58	6.19d	6.3	4.47pq	4.16pq	3.80m	3.58-3.72m(2H)		6.18d	7.71s	7.88d	2.38s(3H)
19	11.60	6.17d	6.1	4.47pq	4.15pq	3.78m	3.60-3.70m(2H)		7.65s	7.74s		2.24s(3H) 2.29s(3H)
20	11.55	6.20d	6.1	4.45pq	4.20pq	3.55-3.85m(3H)				7.05s	7.45s	3.80s(3H) 3.90s(3H)
21	11.85	6.20d	6.4	4.45pq	4.15pq	3.75m	3.55-3.70m(2H)		7.70dd	7.90d	7.95s	
22	11.85	6.15d	6.4	4.45pq	4.15pq	3.80m	3.60-3.75m(2H)		7.80m(2H)	8.05s		
23*	9.97	6.39d	3.5	6.26dd	6.16t	4.60-4.69m(2H)		4.85dd	7.14-7.52m(3H)**	8.52d		
24*	9.90	6.35d	3.4	6.20-6.30m(2H)		4.65-4.90m(3H)			7.20-7.55m(2H)	8.40s		2.30s(3H)
25*	10.00	6.20-6.45m(3H)				4.65-4.95m(3H)			7.10d	7.20s	8.50d	2.40s(3H)
26*	9.75	6.20-6.45m(3H)				4.60-4.90m(3H)			7.10s	8.30s		2.30s(6H)
27*	10.00	6.20-6.45m(3H)				4.65-4.95m(3H)			6.75s	8.05s		3.90s(3H) 3.95s(3H)
28*	9.95	6.40d	3.3	6.15-6.35m(2H)		4.60-4.90m(3H)			7.20-7.55m(2H)**	8.50s		
29*	9.95	6.40d	3.4	6.20-6.30m(2H)		4.65-4.95m(3H)			7.20-7.55m(2H)**	8.70s		
30	13.05	6.10d	6.4	4.55pq	4.15pq	3.85m	3.55-3.80m(2H)		7.55d	7.75d	8.25s	2.40s(3H)

Table 2 - Continuation

	^{1}H-NMR Spectra in D_6-DMSO (δ-values in ppm against TMS)										
	NH NH_2	1'-H	$J_{1',2'}$ [Hz]	2'-H	3'-H	4'-H	5'-H	5''-H	aromatic H			aromatic substituent(s)
31	13.00	6.15d	6.3	4.50pq	4.15pq	3.80m	3.50-3.75m(2H)		7.10d	7.75s	8.35d	2.35s(3H)
32	12.95	6.15d	6.7	4.50pq	4.15pq	3.85m	3.55-3.80m(2H)		7.75s	8.20s		2.30s(3H) 2.35s(3H)
33	12.90	6.21d	6.0	4.45pq	4.20pq	3.55-3.80m(3H)			7.05s	7.89s		3.82s(3H) 3.90s(3H)
34	13.25	6.15d	6.1	4.50pq	4.15pq	3.80m	3.55-3.75m(2H)		7.70d	7.90d	8.40s	
35	13.30	6.15d	6.4	4.45pq	4.15pq	3.80m	3.55-3.75m(2H)		7.80m(2H)		8.50s	
36	7.95	6.10d	5.5	4.50pq	4.20pq	3.75m	3.50-3.70m(2H)		7.40d	7.55d	7.85s	2.30s(3H)
37	7.85	6.15d	5.8	4.50pq	4.15pq	3.50-3.80m(3H)			7.05d	7.55s	7.95d	2.35s(3H)
38	8.05	6.15d	5.8	4.48pq	4.15pq	3.75m	3.58-3.70m(2H)		7.54s	7.84s		2.23s(3H) 2.29s(3H)
39	8.00	6.25d	5.8	4.45pq	4.20pq	3.50-3.80m(3H)			7.00s	7.65s		3.80s(3H) 3.90s(3H)
40	8.10	6.15d	6.1	4.45pq	4.15pq	3.75m	3.50-3.70m(2H)		7.60d	7.70d	8.20s	
41	8.10	6.10d	6.1	4.50pq	4.10pq	3.45-3.80m(3H)			7.60d	7.70d	8.30s	

s = singlet; d = doublet; dd = doublet of doublet; pq = pseudo quartet; m = multiplet

** = signals are covered by sugar benzoyl protons

additional signals of the benzoyl protons appear for 3-8 and 16-21 at 7.20-7.55m(9H) and 7.80-8.05m(6H)

H_2O (90 ml) and glacial AcOH (1.5 ml) at 35°C and stirred for another 30 min. Sodium hydroxide (26.6 g) was added portionwise to the suspension to give a colourless precipitate. After cooling to room temperature the suspension was adjusted to pH 4 with concentrated hydrochloric acid. The precipitate was filtered after standing for 1 h, thoroughly washed with H_2O and dried at 100°C. The purity of the products was sufficient for the next step. Yield: 85-95 %.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazoline-diones (9-15). General procedure. A mixture of the 2,4-quinazolinedione (5 mmol) (1-7), some crystals of ammonium sulfate and acetamide respectively in hexamethyldisilazane (15 ml) was stirred overnight under reflux. The mixture was evaporated and the resulting residue was dissolved in a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (8) (5 mmol) in 30 ml of 1,2-dichloroethane. A solution of trimethylsilyl triflate (6 mmol) in 1,2-dichloroethane (10 ml) was added dropwise and the mixture was stirred at room temperature for 2 h. A cooled saturated sodium bicarbonate solution (70 ml) was added and then the mixture extracted three times with $CHCl_3$ (70 ml). The collected organic layers were dried over sodium sulfate, filtered and evaporated to yield an amorphous solid foam. The crude product was heated in ethanol/water 4:1 until crystallization began. After cooling to room temperature the crystals were filtered, washed with a little ethanol and dried at 100°C.

1-(2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (9).[11] Yield 2.71 g (88 %), m.p. 183°C, lit.[11], m.p. 180-182°C.

Anal. calc. for $C_{34}H_{26}N_2O_9 \times 1/2\ H_2O$ (615.6): C, 66.34; H, 4.42; N, 4.55. Found: C, 66.68; H, 4.43; N, 4.76.

6-Methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (10). Yield 2.57 g (83 %), m.p. 202°C.

Anal. calc. for $C_{35}H_{28}N_2O_9$ (620.6): C, 67.74; H, 4.55; N, 4.51. Found: C, 67.61; H, 4.68; N, 4.34.

7-Methyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (11). Yield 2.73 g (88 %), m.p. 229°C.

Anal. calc. for $C_{35}H_{28}N_2O_9$ (620.6): C, 67.74; H, 4.55; N, 4.51; Found: C, 67.09; H, 4.57; N, 4.55.

6,7-Dimethyl-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (12). Yield 2.57 g (81 %), m.p. 227°C.

Anal. calc. for $C_{36}H_{30}N_2O_9$ (634.6): C, 68.13; H, 4.76; N, 4.41. Found: C, 67.87; H, 4.81; N, 4.47.

6,7-Dimethoxy-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (13). The crude product was purified by column chromatography (silica-gel, eluated with chloroform/methanol 97:3) to yield 2.83 g (85 %) of a solid foam. The product can be recrystallized from EtOH/H_2O 4:1, m.p. 116-122°C.

Anal. calc. for $C_{36}H_{30}N_2O_{11}$ (666.6): C, 64.86; H, 4.54; N, 4.20. Found: C, 64.64; H, 4.53; N, 4.06.

6-Chloro-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (14). Yield 2.24 g (70 %), m.p. 191-192°C.

Anal. calc. for $C_{34}H_{35}ClN_2O_9$ (641.0): C, 63.71; H, 3.93; N, 4.37. Found: C, 63.79; H, 4.04; N, 4.13.

6-Bromo-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (15). Yield 2.33 g (68 %), m.p. 190-191°C.

Anal. calc. for $C_{34}H_{25}BrN_2O_9$ (685.5): C, 59.57; H, 3.68; N, 4.09. Found: C, 59.55; H, 3.65; N, 4.04.

1-(β-D-Ribofuranosyl)-2,4-quinazolinedione (16-22). General procedure. The 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinediones (9-15, 15 mmol) were stirred

under reflux in a solution of sodium (0.414 g, 18 mmol) in dry MeOH (150 ml) for 2 h. The mixture was evaporated to dryness and partitioned between H_2O (150 ml) and diethyl-ether (300 ml). The organic layer was again extracted with H_2O (30 ml) and the collected aqueous layers were then neutralized with AcOH to pH 6. After standing in a refrigerator for 24 h the colourless crystals were collected, washed with H_2O and dried at 100°C.

1-(β-D-Ribofuranosyl)-2,4-quinazolinedione (16). Yield 3.8 g (85 %), m.p. 225°C, lit.[11], m.p. 226-227°C.

Anal. calc. for $C_{13}H_{14}N_2O_6$ x 1/4 H_2O (298.8): C, 52.26; H, 4.89; N, 9.37. Found: C, 52.50; H, 5.32; N, 9.57.

6-Methyl-1-(β-D-ribofuranosyl)-2,4-quinazolinedione (17). Yield 3.7 g (80 %), m.p. 230°C.

Anal. calc. for $C_{14}H_{16}N_2O_6$ (308.3): C, 54.54; H, 5.23; N, 9.09. Found: C, 54.44; H, 5.34; N, 9.15.

7-Methyl-1-(β-D-ribofuranosyl)-2,4-quinazolinedione (18). Yield 4.09 g (86 %), m.p. 255°C (decomp.).

Anal. calc. for $C_{14}H_{16}N_2O_6$ x 1/2 H_2O (317.3): C, 53.00; H, 5.40; N, 8.83. Found: C, 53.23; H, 5.09; N, 8.79.

6,7-Dimethyl-1-(β-D-ribofuranosyl)-2,4-quinazolinedione (19). Yield 4.45 g (92 %), m.p. 240°C.

Anal. calc. for $C_{15}H_{18}N_2O_6$ (322.2): C, 55.90; H, 5.63; N, 8.69. Found: C, 55.65; H, 5.57; N, 8.50.

6,7-Dimethoxy-1-(β-D-ribofuranosyl)-2,4-quinazolinedione (20). Yield 4.15 g (78 %), m.p. 220-222°C.

Anal. calc. for $C_{15}H_{18}N_2O_8$ (354.3): C, 50.85; H, 5.12; N, 7.91. Found: C, 50.35; H, 5.14; N, 7.75.

6-Chloro-1-(β-D-ribofuranosyl)-2,4-quinazolinedione (21). Yield 3.45 g (70 %), m.p. 232°C.

Anal. calc. for $C_{13}H_{13}ClN_2O_6$ (328.7): C, 47.50; H, 3.99; N, 8.52. Found: C, 47.38; H, 4.00; N, 8.48.

6-Bromo-1-(β-D-ribofuranosyl)-2,4-quinazolinedione (22). Yield 4.93 g (88 %), m.p. 219-220°C.

Anal. calc. for $C_{13}H_{13}BrN_2O_6$ (373.2): C, 41.84; H, 3.51; N, 7.51. Found: C, 41.79; H, 3.55; N, 7.45.

4-Thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolones (23-29). General procedure. A mixture of substituted 1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2,4-quinazolinedione (5 mmol) (9-15) and Lawesson's reagent (1.14 g, 2.81 mmol) in toluene (50 ml) was stirred under reflux for 20 h. After cooling to room temperature the solution was partitioned between $CHCl_3$ (200 ml) and H_2O (150 ml). The aqueous layer was again extracted with $CHCl_3$ (30 ml) and the combined organic layers then dried over sodium sulfate, filtered and evaporated to yield a solid foam. The crude product was recrystallized from MeOH.

4-Thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (23). Yield 3.05 g (98 %), m.p. 182°C, lit.[11], m.p. 180°C.

Anal. calc. for $C_{34}H_{26}N_2O_8S$ (622.7): C, 65.59; H, 4.21; N, 4.50. Found: C, 65.11; H, 4.23; N, 4.52.

6-Methyl-4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (24). Yield 3.20 g (99 %), m.p. 187-188°C.

Anal. calc. for $C_{35}H_{28}N_2O_8S \times 1/2\ H_2O$ (645.7): C, 65.10; H, 4.53; N, 4.34. Found: C, 65.21; H, 4.40; N, 4.22.

7-Methyl-4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (25). Yield 2.8 g (88 %), m.p. 183°C.

Anal. calc. for $C_{35}H_{28}N_2O_8S$ (636.7): C, 66.03; H, 4.43; N, 4.40. Found: C, 65.88; H, 4.52; N, 4.49.

6,7-Dimethyl-4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (26). Yield 1.85 g (57 %), m.p. 131-133°C.

Anal. calc. for $C_{36}H_{30}N_2O_8S$ (650.7): C, 66.45; H, 4.65; N, 4.31. Found: C, 66.10; H, 4.71; N, 4.21.

6,7-Dimethoxy-4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (27). Yield 2.73 g (80 %), m.p. 197-198°C.

Anal. calc. for $C_{36}H_{30}N_2O_{10}S$ (682.7): C, 63.34; H, 4.43; N, 4.10. Found: C, 63.36; H, 4.50; N, 4.01.

6-Chloro-4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (28). Yield 2.53 g (77 %), m.p. 188°C.

Anal. calc. for $C_{34}H_{25}ClN_2O_8S$ (657.1): C, 62.15; H, 3.84; N, 4.24. Found: C, 62.01; H, 3.98; N, 4.21.

6-Bromo-4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (29). Yield 3.27 g (92 %), m.p. 204-205°C.

Anal. calc. for $C_{34}H_{25}BrN_2O_8 \times 1/2\ H_2O$ (710.6): C, 57.47; H, 3.69; N, 3.94. Found: C, 57.67; H, 3.56; N, 3.96.

4-Thio-1-(β-D-ribofuranosyl)-2-quinazolones (30-35). General procedure. A mixture of 4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (1 mmol) (24-29) and potassium carbonate (0.18 g) in dry MeOH (20 ml) was stirred for 20 h at room temperature. It was evaporated and the residue partitioned between H_2O (50 ml) and diethylether (50 ml). The organic layer was again washed with H_2O (10 ml) and the combined aqueous layers were neutralized with 3N hydrochloric acid to pH 5. The yellow precipitate was filtered, washed with H_2O and dried at 100°C.

6-Methyl-4-thio-1-(β-D-ribofuranosyl)-2-quinazolone (30). Yield 0.233 g (72 %), m.p. 228°C.

Anal. calc. for $C_{14}H_{16}N_2O_5S$ (324.4): C, 51.94; H, 4.97; N, 8.64. Found: C, 51.40; H, 5.07; N, 8.45.

7-Methyl-4-thio-1-(β-D-ribofuranosyl)-2-quinazolone (31). Yield 0.266 g (82 %), m.p. 231°C (decomp.).

Anal. calc. for $C_{14}H_{16}N_2O_5S$ (324.4): C, 51.84; H, 4.97; N, 8.64. Found: C, 51.73; H, 5.00; N, 8.57.

6,7-Dimethyl-4-thio-1-(β-D-ribofuranosyl)-2-quinazolone (32). Yield 0.253 g (71 %), m.p. 225-227°C.

Anal. calc. for $C_{15}H_{18}N_2O_5 \times 1\ H_2O$ (356.4): C, 50.55; H, 5.66; N, 7.86. Found: C, 50.45; H, 5.61; N, 7.90.

6,7-Dimethoxy-4-thio-1-(β-D-ribofuranosyl)-2-quinazolone (33). Yield 0.318 g (82 %), m.p. 204°C.

Anal. calc. for $C_{15}H_{18}N_2O_8 \times 1\ H_2O$ (388.4): C, 46.39; H, 5.19; N, 7.21. Found: C, 46.46; H, 5.23; N, 7.19.

6-Chloro-4-thio-1-(β-D-ribofuranosyl)-2-quinazolone (34). Yield 0.241 g (70 %), m.p. 219°C.

Anal. calc. for $C_{13}H_{13}ClN_2O_5S$ (344.8): C, 45.29; H, 3.80; N, 8.13. Found: C, 45.28; H, 3.85; N, 8.02.

6-Bromo-4-thio-1-(β-D-ribofuranosyl)-2-quinazolone (35). Yield 0.32 g (82 %), m.p. 230°C.

Anal. calc. for $C_{13}H_{13}BrN_2O_5S$ (389.2): C, 40.12; H, 3.37; N, 7.20. Found: C, 40.09; H, 3.27; N, 7.10.

4-Amino-1-(β-D-ribofuranosyl)-2-quinazolones (36-41). General procedure. A solution of 4-thio-1-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-2-quinazolone (1.5 mmol) (24-29) in saturated methanolic ammonia (50 ml) was heated in a sealed bomb at 100°C for 18 h. After cooling, the mixture was eva-

porated, the residue treated with CH_2Cl_2 (200 ml), filtered, washed with a little CH_2Cl_2 and dried at 100°C to give the crude material. Further purification was achieved by recrystallization.

4-Amino-6-methyl-1-(β-D-ribofuranosyl)-2-quinazolone (36). The crude material (0.46 g, 100%) was chromatographically pure. An analytical sample was recrystallized from CH_3OH/H_2O to give colorless crystals, m.p. 234-235°C.

Anal. calc. for $C_{14}H_{17}N_3O_5$ (307.3): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.28; H, 5.63; N, 13.52.

4-Amino-7-methyl-1-(β-D-ribofuranosyl)-2-quinazolone (37). Yield 0.368 g (80 %), m.p. 235°C (decomp.).

Anal. calc. for $C_{14}H_{17}N_3O_5$ (307.3): C, 54.72; H, 5.58; N, 13.67. Found: C, 54.17; H, 5.72; N, 13.52.

4-Amino-6,7-dimethyl-1-(β-D-ribofuranosyl)-2-quinazolone (38). Yield of chromatographically pure product 0.495 g (98 %). An analytical sample was recrystallized from MeOH/H_2O to give colorless crystals of m.p. 221°C.

Anal. calc. for $C_{15}H_{19}N_3O_9$ x 1/2 H_2O (330.3): C, 54.54; H, 6.10; N, 12.72. Found: C. 54.65; H, 6.16; N, 12.68.

4-Amino-6,7-dimethoxy-1-(β-D-ribofuranosyl)-2-quinazolone (39). Yield of chromatographically pure product 0.522 g (96 %). An analytical sample was recrystallized from CH_3OH/H_2O, m.p. 229°C.

Anal. calc. for $C_{15}H_{19}N_3O_7$ x 1/2 H_2O (362.3): C, 49.72; H, 5.56; N, 11.60. Found: C, 50.06; H, 5.54; N, 11.80.

4-Amino-6-chloro-1-(β-D-ribofuranosyl)-2-quinazolone (40). Yield of chromatographically pure product 0.487 g (99 %). An analytical sample was recrystallized from CH_3OH/H_2O, m.p. 220°C (decomp.).

Anal. calc. for $C_{13}H_{14}ClN_3O_5$ (327.7): C, 47.64; H, 4.31; N, 12.82. Found: C, 47.30; H, 4.46; N, 12.64.

4-Amino-6-bromo-1-(ß-D-ribofuranosyl)-2-quinazolone (41). Yield of chromatographically pure product 0.566 g (99 %). An analytical sample was recrystallized from CH_3OH/H_2O, m.p. 300°C (decomp.).

Anal. calc. for $C_{13}H_{14}BrN_3O_5 \times 1/2\ H_2O$ (381.2): C, 40.96; H, 3.97; N, 11.02. Found: C, 40.96; H, 3.84; N, 11.12.

ACKNOWLEDGEMENT

We thank Mrs. M. Bischler for the pK_a determinations and measurements of the UV spectra, and the Fonds der Chemischen Industrie for financial support.

R E F E R E N C E S

1. Part XLVII: Al-Masoudi, N.A.; Pfleiderer, W. Pteridines (1990) 2, 9.
2. Mitsuya, H.; Broder, S. Proc.Natl.Acad.Sci. USA (1986), 83, 1911.
3. Herdewijn, P.; Balzarini, J.; De Clercq, E.; Pauwels, R.; Baba, M.; Broder, S.; Vanderhaeghe, H. J.Med.Chem. (1987) 30, 1270.
4. Herdewijn, P.; Balzarini, J.; Baba, M.; van Aerschot, A.; Jansen, G.; De Clercq, E. J.Med.Chem. (1988) 31, 2040.
5. Horwitz, J.P.; Chua, J.; Noel, M. J.Org.Chem. (1964) 29, 2076.
6. Balzarini, J.; Pauwels, R.; Herdewijn, P.; De Clercq, E.; Conney, D.A.; Kang, G.J.; Dalal, M.: Johns, D.G.; Broder, S. Biochem.Biophys.Res.Commun. (1986) 140, 735.
7. Gentry, G.A.; Aswell, J.F. Virology (1975) 65, 294.
8. Prusoff, W.H.; Goz, B. Fed.Proc,Am.Soc.Exp.Bibl. (1973) 32, 1679.
9. De Clercq, E. Arch.Int.Physiol.Biochim. (1979) 87, 353.

10. Watanabe, K.A.; Reichmann, U.; Hirota, K.; Lopez, C.; Fox, J.J. J.Med.Chem. (1979) 22, 21.
11. Stout, M.G.; Robins, R.K. J.Org.Chem. (1968) 33, 1219.
12. Diwan, A.R.; Robins, R.K.; Prusoff, W.H. Experientia (1969) 25, 98.
13. Stout, M.G.; Robins, R.K. J.Heterocycl.Chem. (1969) 6, 89.
14. Wagner, G.; Suess, F. Pharmazie (1969) 24, 35.
15. Wittenburg, E. Collect.Czech.Chem.Commun. (1971) 93, 246.
16. Takahashi, H.; Nimura, N.: Ogura, H. Chem.Pharm.Bull. (1979) 27, 1143.
17. Marmet, D.; Boullanger, P.; Descotes, G. Tetrahedron Lett. 1980, 1459.
18. Marmet, D.; Boullanger, P.; Descotes, G. Can.J.Chem. (1981) 59, 373.
19. Birkofer, L.; Ritter, A. Angew.Chem. (1965) 77, 414.
20. Vorbrüggen, H.; Höfle, G. Chem.Ber. (1981) 114, 1256.
21. Oakes, V.; Rydon, H.N.; Undheim, K. J.Chem.Soc. 1962, 4678.
22. Curd, F.H.S.; Landquist, J.K.; Rose, F.L. J.Chem.Soc. 1948, 1759;
V. Niementowski, S. J.pr.Chem. II (1889) 40, 4.
23. Hess, H.-J.; Cronin, T.H.; Scriabine, A. J.Med.Chem. (1968) 11, 130.
24. Curd, F.H.S.; Landquist, J.K.; Rose, F.L. J.Chem.Soc. 1948, 1759;
Endicott, M.M.; Alden, B.W.; Sherill, M.L. J.Am.Chem. Soc. (1946) 68, 1303.
25. Scott, J.R.; Cohen, J.B. J.Chem.Soc. 1923, 3187;
Jacini. Gazz.Chim.Ital. (1943) 73, 85.
26. Zemplen, G.; Geres, A.; Hadacsy; J. Ber.Deut.Chem.Ges. (1936) 69, 1827.
27. Scheibye, S.; Pedersen, B.S.; Lawesson, S.-O. Bull.Soc. Chim.Belg. (1978) 87, 229.

28. Albert, A.; Serjeant, E.P. in "The Determination of Ionization Constants", Chapman and Hall Ltd., London 1977, p. 44.
29. Al-Masoudi, N.A.; Pfleiderer, W. Nucleosides & Nucleotides (1989) 8, 1485.
30. Ritzmann, G.; Ienaga, K.; Pfleiderer, W. Liebigs Ann. Chem. 1977, 1217.

Received August 10, 1990.