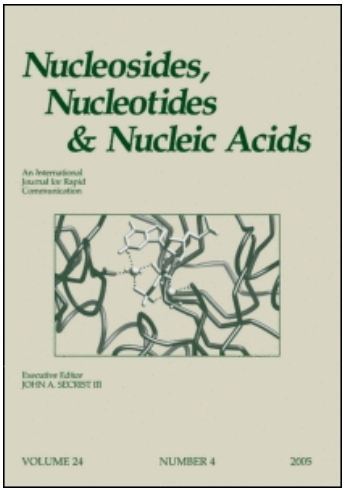

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1,4:3,6-Dianhydrohexitol Nucleosides

Peter Stoss[a]; Elmar Kaes[a]
[a] Chemical Research and Development, Heinrich Mack Nachf., Chem. Pharm. Fabrik, Illertissen, West Germany

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1,4:3,6-DIANHYDROHEXITOL NUCLEOSIDES

Peter Stoss* and Elmar Kaes

Chemical Research and Development, Heinrich Mack Nachf.,
Chem. Pharm. Fabrik, P.O.Box 2064, D-7918 Illertissen, West Germany

Abstract:

Novel types of nucleoside analogues, being potential anticancer and antiviral candidates and exhibiting a 1,4:3,6-dianhydrohexitol moiety as the carbohydrate part of the molecule, are described. The synthesis has been performed by reacting the appropriate chloromethylated, protected dianhydrohexitol with silylated bases.

Amongst antiviral and anticancer agents, structures related to naturally occurring nucleosides play an important role. In addition to the well-known and therapeutically useful compounds, e.g. Ara-A, Ara-C, TFT, Azacytidine and others, there are some newer types, such as BVDU, FIAC, FMAU, Ribavirin, Tiazofurin etc. which are potential candidates for the future or which have already been introduced into the market. It is obvious from these few examples as well as from the fast growing literature that this class of compounds is subject of current interest.

Numerous attempts have been directed towards increasing the potency and simultaneously lowering the side effects by enhancing the selectivity for infected cells as opposed to normal cells. To achieve this, modifications of the nucleobases as well as variations of the sugar part of the molecule have been widely investigated[1]. Different heterocyclic systems, substituted derivatives of nucleosides, replacement of ribose and deoxyribose by other carbohydrates, tetrahydrofuryl and carbocyclic rings and also C-nucleosides have been taken into consideration[2-4]. The most

promising newer analogues for antiviral chemotherapy belong to a group with an open chained sugar moiety, for which the term acyclonucleosides[5,6] is commonly used. One of these, Acyclovir[7] was introduced as a drug in 1982, another, DHPG (Biolf-62)[8-11] is presently under clinical development. Furthermore DHPA[12] is the subject of intensive investigation.

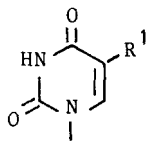
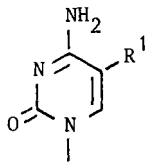
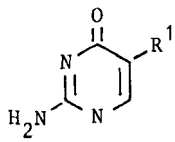
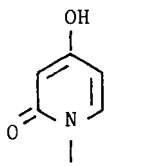
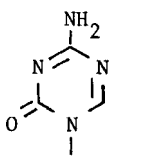
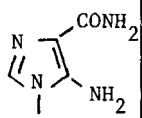
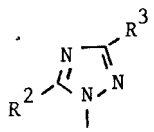
The activity in this area has been stimulated by the success of the above mentioned efforts and will certainly generate further novel structures with superior properties. As a major challenge, higher selective toxicity for virus and cancer cells should be achieved. However, suitable stability against metabolic degradation and the ability of cellular penetration is also a necessary requirement for the achievement of therapeutical success.

To the best of our knowledge, no attempt has been undertaken until now to incorporate a dianhydro sugar derivative into a nucleoside molecule. We therefore started to investigate this possibility. In this first approach we would like to present our results of the pyrimidine series, including some other one-ring heterocycles.

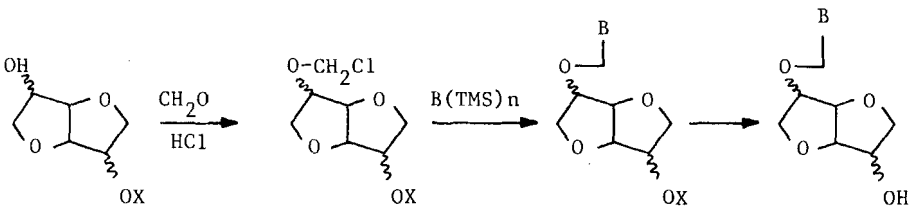
The ring system of the 1,4:3,6-dianhydrohexitols, used in this study, consists of two cis-fused tetrahydrofurane rings, forming a V-shaped molecule with a 120° angle. Thus for both the OH-substituents, attached at the 2- and 5-position of the bicyclic ring system, endo/exo configurations are possible. Our approach includes the 1,4:3,6-dianhydro-D-glucitol (isosorbide, 2-exo, 5-endo), -D-mannitol (isomannide, 2- and 5-endo) and -L-iditol (isoidide, 2- and 5-exo) systems. Like the carbohydrates, incorporated in common nucleosides, the dianhydrohexitols exhibit chiral properties. In contrast to the naturally occuring carbohydrate-linked nucleosides and the acyclonucleosides, the ring system presented here is more bulky and rigid. It still contains one free hydroxyl group, which possibly could be phosphorylated in the organism. The influence of these structural modifications on biological properties is presently being investigated.

The synthesis of the target molecules started with monoacylated or monobenzylated 1,4:3,6-dianhydrohexitols 1[13] and proceeded via chloromethylation to the novel intermediates 2 (Table 2). The glycosidation step was performed by reacting 2 with the appropriate silylated bases,

TABLE 1

Nucleobases B		Compound No. in Table 3	Compound No. in Table 4		Substituents R^1	R^2	R^3
Uracils		3	10	a	H		
				b	CH_3		
Cytosines		4	11	c	C_2H_5		
				d	$CH_2CH(CH_3)_2$		
				e	C_6H_{13}		
Isocytosines		5	12	f	CH_2OH		
				g	$CH{=}CH_2Br$		
Pyridine		6	13	h	F		
				i	Cl		
				k	Br		
5-Azacytosine		7	14	l	I		
				m	CF_3		
Imidazole		8	15	n		H	$COOCH_3$
				o		H	$CONH_2$
				p		$COOCH_3$	H
Triazoles		9	16	q		$CONH_2$	H

using conventional conditions. Products 3-9 (Table 3) were subsequently deprotected, in the case of x = acyl by sodium methylate/methanol or basic ion exchange resins, and when x = benzyl, by catalytic hydrogenation. O-acylated methoxycarbonyl-triazoles (9 n, 9 p) were converted to the corresponding carbamoyl derivatives and deprotected simultaneously by reacting with ammonia in methanol, yielding 16 o, 16 q.



1 2 3-9 10-16

Compounds 10-16 (Table 4), which we conveniently and trivially refer to as "isohexide nucleosides" instead of the more precise name given in the title of this paper, were fully characterized by elemental analysis, IR, ^{1}H-NMR and MS. An analogue structural assignment was performed for all the intermediates.

The following nucleobases B have been incorporated into this investigation (Table 1):

Compounds 10-16 were tested for anticancer properties and found to be inactive[14]. Potential antiviral activities are presently under evaluation.

EXPERIMENTAL

The following abbreviations are used in the tables: Ring systems: G: 1,4:3,6-Dianhydro-D-glucitol; M: 1,4:3,6-Dianhydro-D-mannitol; I: 1,4:3,6-Dianhydro-L-iditol; Solvents: MeOH-Methanol; EtOH-Ethanol; 2-PrOH-2-Propanol; EtOAc-Ethylacetate; Et_2O-Diethylether; Hex-n-Hexane. TLC was performed on Sil G-25 UV_{254} (Macherey-Nagel) plates using $CHCl_3$/MeOH 9:1 (v/v) or EtOAc as solvent systems.

5(2)-O-Protected-2(5)-O-chloromethyl-1,4:3,6-dianhydrohexitols 2 (General Method).

A suspension of the appropriate O-acylated[13] or O-benzylated[15] 1,4:3,6-dianhydrohexitol 1 (0,25 mol) and 15 g paraformaldehyde in 120 ml CH_2Cl_2 was chilled to 0° C and saturated at this temperature with gaseous HCl. The resulting solution was kept for 15-20 hrs. at 0-5° C. The water formed was separated and the organic phase was dried over $CaCl_2$. Filtration and evaporation i.vac. afforded a syrup in nearly quantitative yield, which was used immediately in the next step. Normally no attempts were undertaken to purify the material. In some cases it was possible to recrystallize the product from a suitable solvent (Table 2).
2(5)-O-(Pyrimidin-1-yl-methyl)-5(2)-O-protected-1,4:3,6-dianhydrohexitols and related pyridine-, imidazole- and triazole-derivatives 3-9 (General Method).

A solution of 5(2)-O-protected-2(5)-O-chloromethyl-1,4:3,6-dianhydrohexitol 2 (0,05 mol) and an equimolar amount of the appropriate trimethyl silylated nucleobase was stirred at room temperature in 50 ml $CHCl_3$ until complete reaction was indicated by TLC (between 1 and 20 hrs.). The mixture was evaporated i.vac. and the remaining syrup was taken up in 100 ml CH_2Cl_2. After adding 100 ml of saturated aqueous $NaHCO_3$ solution the system was vigorously stirred until evolution of gas had ceased. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated. The syrupy residue was crystallized from an appropriate solvent or reacted directly in the next synthetic step (Table 3).

2(5)-O-(Pyrimidin-1-yl-methyl)-1,4:3,6-dianhydrohexitols and related pyridine-, imidazole- and triazole-derivatives 10-16 (General Method).
The O-acylated compound 3-9 (0,03 mol) was suspended in 150 ml MeOH and 9 ml of a 30% sodium methylate solution in MeOH was added. The mixture was stirred at room temperature until TLC indicated complete conversion (30 min - 2,5 hrs.) and subsequently neutralized by the addition of 90 ml Amberlite IR-120 (H^+-form, methanol wet). The ion exchange resin was filtered off, the filtrate was evaporated and the residue crystallized from a suitable solvent (Table 4).

5-O-(Uracil-1-yl-methyl)-1,4:3,6-dianhydroglucitol(10 a)

TABLE 2 5(2)-O-Protected-2(5)-O-chloromethyl-1,4:3,6-dianhydrohexitols 2

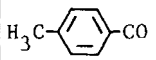
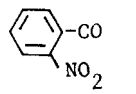
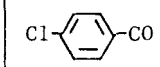
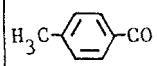
Compound No.	Ring-system	X	Position OX	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c = 2, CH_2Cl_2
2.1	G		endo	$C_{15}H_{17}ClO_5$ 312,8	85-7 CH_2Cl_2/Hex	+ 63,0
2.2	G		endo	$C_{14}H_{14}ClNO_7$ 343,7	Syrup	
2.3	G		endo	$C_{14}H_{14}Cl_2O_5$ 333,2	66-9 CH_2Cl_2/Hex	+ 35,0
2.4	G	C_6H_5-CO	endo	$C_{14}H_{15}ClO_5$ 298,7	Syrup	
2.5	G		exo	$C_{15}H_{17}ClO_5$ 312,8	100-2 CH_2Cl_2/Hex	+ 157,0
2.6	G	H_3C-CO	exo	$C_9H_{13}ClO_5$ 236,7	Syrup	
2.7	G	C_6H_5-CH_2	exo	$C_{14}H_{17}ClO_4$ 284,7	Syrup	
2.8	M	C_6H_5-CO	endo	$C_{14}H_{15}ClO_5$ 298,7	Syrup	
2.9	I	C_6H_5-CO	exo	$C_{14}H_{15}ClO_5$ 298,7	Syrup	

TABLE 3 5(2)-O-Protected-2(5)-B-substituted 1,4:3,6-dianhydrohexitols 3-9

Compound No.	Ring-system	X Position OX	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
3.1 a	G	4-Toluyl endo	$C_{19}H_{20}N_2O_7$ 388,4	134 MeOH	+ 59,8 2, CH_2Cl_2	65,4
3.7 a	G	Benzyl exo	$C_{18}H_{20}N_2O_6$ 360,4	Oil	+ 58,0 2, CH_2Cl_2	71,0
3.2 b	G	2-Nitro-benzoyl endo	$C_{19}H_{19}N_3O_9$ 433,4	169-70 EtOH	+ 30,3 2, CH_2Cl_2	78,4
3.3 b	G	4-Chlor-benzoyl endo	$C_{19}H_{19}ClN_2O_7$ 422,8	75-80 chromat.	+ 51,0 2, CH_2Cl_2	72,5
3.5 b	G	4-Toluyl exo	$C_{20}H_{22}N_2O_7$ 402,4	Syrup		47,2
3.8 b	M	Benzoyl endo	$C_{19}H_{20}N_2O_7$ 388,4	Syrup		
3.9 b	I	Benzoyl exo	$C_{19}H_{20}N_2O_7$ 388,4	Syrup		
3.1 c	G	4-Toluyl endo	$C_{21}H_{24}N_2O_7$ 416,4	134 MeOH	+ 68,0 2, CH_2Cl_2	64,6
3.1 d	G	4-Toluyl endo	$C_{23}H_{28}N_2O_7$ 444,5	169-70 MeOH/H_2O	+ 45,3 2, CH_2Cl_2	77,8
3.1 e	G	4-Toluyl endo	$C_{25}H_{32}N_2O_7$ 472,5	104-6 Et_2O	+ 48,0 2, CH_2Cl_2	80,5
3.1 f	G	4-Toluyl endo	$C_{20}H_{22}N_2O_8$ 418,4	192-3 MeOH/H_2O	+ 49,3 2, DMF	62,1
3.1 g	G	4-Toluyl endo	$C_{21}H_{21}BrN_2O_7$ 493,3	117-20 MeOH	+ 42,0 1, CH_2Cl_2	56,8
3.1 h	G	4-Toluyl endo	$C_{19}H_{19}FN_2O_7$ 406,4	Foam		90,1
3.1 k	G	4-Toluyl endo	$C_{19}H_{19}BrN_2O_7$ 467,3	Foam		quant.

(continued)

TABLE 3 (continued)

Compound No.	Ring-system	X Position OX	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
3.1 1	G	4-Toluyl endo	$C_{19}H_{19}IN_2O_7$ 514,3	Amorphous		92,6
3.5 1	G	4-Toluyl exo	$C_{19}H_{19}IN_2O_7$ 514,3	Amorphous		98,4
3.6 1	G	Acetyl exo	$C_{13}H_{15}IN_2O_7$ 438,2	Foam		89,0
3.8 1	M	Benzoyl endo	$C_{18}H_{17}IN_2O_7$ 500,3	150-2 Toluene	+ 110,8 2, CH_2Cl_2	42,8
3.9 1	I	Benzoyl exo	$C_{18}H_{17}IN_2O_7$ 500,3	80-5 2-PrOH	+ 33,8 2, CH_2Cl_2	78,2
3.1 m	G	4-Toluyl endo	$C_{20}H_{19}F_3N_2O_7$ 456,4	Foam		99,2
4.1 a	G	4-Toluyl endo	$C_{19}H_{21}N_3O_6$ 387,4	214-5(dec.) MeOH/H_2O	+ 68,5 2, DMF	43,7
4.1 h	G	4-Toluyl endo	$C_{19}H_{20}FN_3O_6$ 405,4	237,5-8 MeOH	+ 56,0 2, DMF	61,2
4.4 i	G	Benzoyl endo	$C_{18}H_{18}ClN_3O_6$ 407,8	199-201 2-PrOH	+ 62,o 1, CH_2Cl_2	22,6
4.1 1	G	4-Toluyl endo	$C_{19}H_{20}IN_3O_6$ 513,3	190-1(dec.) MeOH	+ 42,5 2, CH_2Cl_2	44,0
5.1 a	G	4-Toluyl endo	$C_{19}H_{21}N_3O_6$ 387,4	223-5(dec.) MeOH	+ 53,5 2, DMF	26,9
5.1 b	G	4-Toluyl endo	$C_{20}H_{23}N_3O_6$ 401,4	165-6 MeOH	+ 56,5 2, DMF	45.6
6.1	G	4-Toluyl endo	$C_{20}H_{21}NO_7$ 387,4	100-1(dec.) EtOAc	+ 48,5 1, MeOH	54,4
7.1	G	4-Toluyl endo	$C_{18}H_{20}N_4O_6$ 388,4	212-3 MeOH	+ 65,0 1, CH_2Cl_2	16,5
7.5	G	4-Toluyl exo	$C_{18}H_{20}N_4O_6$ 388,4	215-8 2-PrOH	+ 56,0 0,5, CH_2Cl_2	13,4

TABLE 3 (continued)

Compound No.	Ring-system	X Position OX	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
8.1	G	4-Toluyl endo	$C_{19}H_{22}N_4O_6$ 402,4	142-3 MeOH/H_2O	+ 34,5 1, CH_2Cl_2	14,2
9.1 n	G	4-Toluyl endo	$C_{19}H_{21}N_3O_7$ 403,4	138-9 MeOH	+ 53,0 2, CH_2Cl	24,6
9.1 p	G	4-Toluyl endo	$C_{19}H_{21}N_3O_7$ 403,4	110 MeOH	+ 48,0 2, CH_2Cl_2	19,3
9.5 n	G	4-Toluyl exo	$C_{19}H_{21}N_3O_7$ 403,4	88-9 MeOH	+ 113,0 2, CH_2Cl_2	40,0
9.5 p	G	4-Toluyl exo	$C_{19}H_{21}N_3O_7$ 403,4	Oil		21,8
9.8 n	M	Benzoyl endo	$C_{18}H_{19}N_3O_7$ 389,4	125-6 EtOH	+ 113,8 2, CH_2Cl_2	20,8
9.8 p	M	Benzoyl endo	$C_{18}H_{19}N_3O_7$ 389,4	Oil	+ 98,5 2, CH_2Cl_2	31,9
9.9 n	I	Benzoyl exo	$C_{18}H_{19}N_3O_7$ 389,4	Oil	+ 17,3 2, CH_2Cl_2	36,8
9.9 p	I	Benzoyl exo	$C_{18}H_{19}N_3O_7$ 389,4	90-90,5 Et_2O	+ 44,8 2, CH_2Cl_2	18,5

TABLE 4 1,4:3,6-Dianhydro-hexitol nucleosides 10-16

Compound No.	Ring-system	Position OH	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
10 a	G	endo	$C_{11}H_{14}N_2O_6$ 270,2	161 MeOH	+ 41,0 1, H_2O	75,3
10 a	G	exo	$C_{11}H_{14}N_2O_6$ 270,2	136-7 MeOH	+ 65,0 2, H_2O	40,2
10 b	G	endo	$C_{12}H_{16}N_2O_6$ 284,3	132-3 MeOH	+ 39,0 1, H_2O	56,1
10 b	G	exo	$C_{12}H_{16}N_2O_6$ 284,3	48-55[a] lyophylized	+ 69,5[a] 1, H_2O	19,4

(continued)

TABLE 4 (continued)

Compound No.	Ring-system	Position OH	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
10 b	M	endo	$C_{12}H_{16}N_2O_6$ 284,3	141-142,5 EtOAc	+ 92,0 1, H_2O	38,1
10 b	I	exo	$C_{12}H_{16}N_2O_6$ 284,3	165,5-166,5 EtOH	+ 16,0 1, H_2O	59,5
10 c	G	endo	$C_{13}H_{18}N_2O_6$ 298,3	48-60[a] lyophylized	+ 38,0[a] 1, H_2O	65,1
10 d	G	endo	$C_{15}H_{22}N_2O_6$ 326,4	53-62[b] lyophylized	+ 34,5[b] 1, H_2O	53,6
10 e	G	endo	$C_{17}H_{26}N_2O_6$ 354,4	50-55[a] CH_2Cl_2	+ 29,5[a] 2, CH_2Cl_2	24,6
10 f	G	endo	$C_{12}H_{16}N_2O_7$ 300,3	177-8 MeOH/H_2O	+ 36,5 1, H_2O	47,5
10 g	G	endo	$C_{13}H_{15}BrN_2O_6$ 375,2	141-141,5 MeOH	+ 34,5 0,33, H_2O	43,4
10 h	G	endo	$C_{11}H_{13}FN_2O_6$ 288,2	133-5 lyophylized	+ 38,0 1, H_2O	23,1
10 k	G	endo	$C_{11}H_{13}BrN_2O_6$ 349,2	169 MeOH/H_2O	+ 35,5 1, H_2O	81,7
10 l	G	endo	$C_{11}H_{13}IN_2O_6$ 396,2	148-9 MeOH	+ 30,0 1, H_2O	48,7
10 l	G	exo	$C_{11}H_{13}IN_2O_6$ 396,2	169-70 H_2O	+ 52,0 1, H_2O	32,8
10 l	I	exo	$C_{11}H_{13}IN_2O_6$ 396,2	115-7[c] H_2O/MeOH	+ 22,5[c] 1, MeOH	57,6
10 l	M	endo	$C_{11}H_{13}IN_2O_6$ 396,2	60-80 lyophylized	+ 62,5 2, H_2O	66,7
10 m	G	endo	$C_{12}H_{13}F_3N_2O_6$ 338,3	155-8 CH_2Cl_2	+ 55,0 1, MeOH	28,4
11 a	G	endo	$C_{11}H_{15}N_3O_5$ 269,3	255-6(dec.) MeOH/H_2O	+ 47,5 1, H_2O	74,1

TABLE 4 (continued)

Compound No.	Ring-system	Position OH	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
11 h	G	endo	$C_{11}H_{14}FN_3O_5$ 287,3	250-1(dec.) MeOH/H_2O	+ 39,5 1, H_2O	54,6
11 i	G	endo	$C_{11}H_{14}ClN_3O_5$ 303,7	214 EtOH	+ 49,5 1, H_2O	50,7
11 l	G	endo	$C_{11}H_{14}IN_3O_5$ 395,2	181(dec.) MeOH	+ 32,0 1, H_2O	54,4
12 a	G	endo	$C_{11}H_{15}N_3O_5$ 269,3	192-3(dec.) EtOH	+ 45,5 1, H_2O	63,9
12 b	G	endo	$C_{12}H_{17}N_3O_5$ 283,3	197-8 MeOH	+ 42,5 1, H_2O	48,1
13	G	endo	$C_{12}H_{15}NO_6$ 269,3	178-9 EtOH	+ 43,5 1, H_2O	60,2
14	G	endo	$C_{10}H_{14}N_4O_5$ 270,3	195 MeOH	+ 41,8 2, H_2O	62,9
14	G	exo	$C_{10}H_{14}N_4O_5$ 270,3	160-2 EtOH	+ 60,0 1, H_2O	49,7
15	G	endo	$C_{11}H_{16}N_4O_5$ 284,3	130-2 2-PrOH	+ 36,5 1, H_2O	40,4
16 n	G	endo	$C_{11}H_{15}N_3O_6$ 285,3	109-10 MeOH/Et_2O	+ 40,5 1, H_2O	45,9
16 o	G	endo	$C_{10}H_{14}N_4O_5$ 270,3	173 MeOH/H_2O	+ 38,0 1, H_2O	69,0
16 o	G	exo	$C_{10}H_{14}N_4O_5$ 270,3	145-7 MeOH	+ 80,0 1, H_2O	50,6
16 o	M	endo	$C_{10}H_{14}N_4O_5$ 270,3	135,5-137,5 EtOH	+ 104,0 2, H_2O	78,8
16 o	I	exo	$C_{10}H_{14}N_4O_5$ 270,3	189-91 MeOH	+ 7,0 1, H_2O	54,6
16 p	G	endo	$C_{11}H_{15}N_3O_6$ 285,3	106 MeOH/Et_2O	+ 37,5 1, H_2O	53,0

(continued)

TABLE 4 (continued)

Compound No.	Ring-system	Position OH	Molecular Formula MW	MP °C Solvent	$[\alpha]_D^{20}$ c/Solvent	Yield %
16 q	G	endo	$C_{10}H_{14}N_4O_5$ 270,3	158-9 MeOH/H_2O	+ 41,0 1, H_2O	65,7
16 q	G	exo	$C_{10}H_{14}N_4O_5$ 270,3	132-3 MeOH	+ 72,0 1, H_2O	64,8
16 q	M	endo	$C_{10}H_{14}N_4O_5$ 270,3	144-5 MeOH	+ 93,5 2, H_2O	49,8
16 q	I	exo	$C_{10}H_{14}N_4O_5$ 270,3	126-126,5 EtOH	+ 16,5 2, H_2O	63,8

a) · 0,5 H_2O, hygroscopic; b) · 0,25 H_2O hygroscopic; c) · H_2O

A solution of 11 g 2-O-benzyl-5-O-(uracil-1-yl-methyl)-1,4:3,6-dianhydroglucitol (3.7 a) in 150 ml MeOH was mixed with 2 g of 5% palladium on charcoal and hydrogenated until the uptake of hydrogen had ceased. The catalyst was filtered off and the solution was evaporated to dryness. The residue was recrystallized (Table 4).

2-O-(3-Carbamoyl-1,2,4-triazol-1-yl-methyl)-1,4:3,6-dianhydroglucitol (16 o)

7,5 g gaseous NH_3 was bubbled into a suspension of 8 g 2-O-(3-methoxycarbonyl-1,2,4-triazol-1-yl-methyl)-5-O-(4-toluyl)-1,4:3,6-dianhydroglucitol (9.1 n) in 60 ml MeOH at 20-25° C, whereby solution occurred. After standing for 30 hrs. a precipitate had formed, which was filtered off and re-crystallized. (Table 4).

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