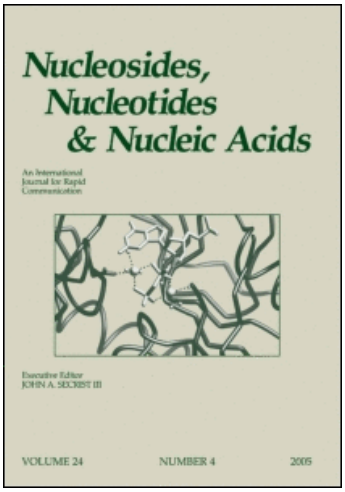

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AMINOPYRIMIDINES AND DERIVATIVES. 19[1]. REACTION OF 1,6-DIHYDRO-4-β-D-(2,3,4,6-TETRA-O-ACETYL)GLUCOPYRANOSYLAMINO-1-METHYL-2-METHOXY-6-OXO PYRIMIDINE WITH CHORACETYL CHLORIDE[2].

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Abstract: Reaction between 1,6-dihydro-4-β-D-(2,3,4,6-tetra-O-acetyl) glucopyranosylamino-1-methyl-2-methoxy-6-oxo pyrimidine and chloracetyl chloride yields the corresponding 5-α-chloracetyl derivative and 2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine. The first compound has been cyclized to the corresponding 7-β-D-glucopyranosyl-pyrrolo[2,3-d]pyrimidine and the second one to 3-β-D-glucopyranosyl-vic-triazolo[4,5-d]pyrimidine.

Pyrrolo[2,3-d]pyrimidines (7-deazapurines) and vic-triazolo[4,5-d] pyrimidines (8-azapurines) are an important class of compounds, structurally and chemically related to naturally nucleosides and some antibiotics[3-6]. The biological activity of such nucleosides is well known and they have been intensively investigated as antitumoral, antiallergi and antiviral agents[7-10].

Several methods have been described in the literature for the synthesis of 7-deazapurine nucleosides; the most interesting being the phase transfer glycosylation used by F. Seela[11]. The use of this method leads usually to an anomeric mixture. 8-azapurine nucleosides are fundamentally obtained by cyclization of 5-amino-4-glycosylamino pyrimidines with nitrous acid[12].

Due to the interest of this class of compounds and following our previous works on reactivity and synthetic applications of 4-glycosylamino pyrimidines[13], the reaction of 1,6-dihydro-4-β-D-(2,3,4,6-tetra-O

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-acetyl)glucopyranosylamino-1-methyl-2-methoxy-6-oxo pyrimidine 1 with chloracetyl chloride has been carried out. Appropiates intermediates for cyclization to 7-glycosyl-pyrrolo[2,3-d]pyrimidines[14] and 3-glycosyl-vic-triazolo[4,5-d]pyrimidines has been obtained.

The reaction of 1 with fresh distilled $ClCOCH_2Cl$, in anhydrous ethyl acetate, produces a precipitate (43%) identified as: 2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine 3. On the other hand 5-α-chloracetyl-1,6-dihydro-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-2-methoxy-6-oxo pyrimidine 2 (42%) was isolated from the mother liquors. The estructure of 3 has been confirmed by acid hidrolysis of 1 with HCl in $HCCl_3$.

In the ^{1}H-NMR (table 1) of compound 2, the signal assigned to C_4N-H (10.9 ppm, doublet, $J_{NH,1'}$= 8.2 Hz) appears shifted downfield compared with the corresponding signal in the spectrum of its precursor 1 (5.7 ppm, doublet, $J_{NH,1'}$= 9 Hz). This shift is attributed to the six membered hydrogen bond formed between C_4-NH and C_5-COCH$_2$Cl groups, as shown in Scheme 1.

Compound 2, is formed by electrophilic aromatic substitution on C-5 of the pyrimidine ring. The HCl molecule reacts with the CH_3-O-C_2 group, yielding $HCCl_3$ and produce 3. This has been evidences by the easy hydrolysis of 2-methoxy pyrimidines in acidic medium[15], as well as in hot water[16].

The selective de-O-acetylation of 2 and 3 has been carried out with molar amount of sodium methoxide in methanol at room temperature, yielding: 5-α-chloracetyl-1,6-dihydro-4-β-D-glucopyranosylamino-1-methyl-2-methoxy-6-oxo pyrimidine 4 and 2,6-dioxo-4-β-D-glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine 5 respectively, in high yield.

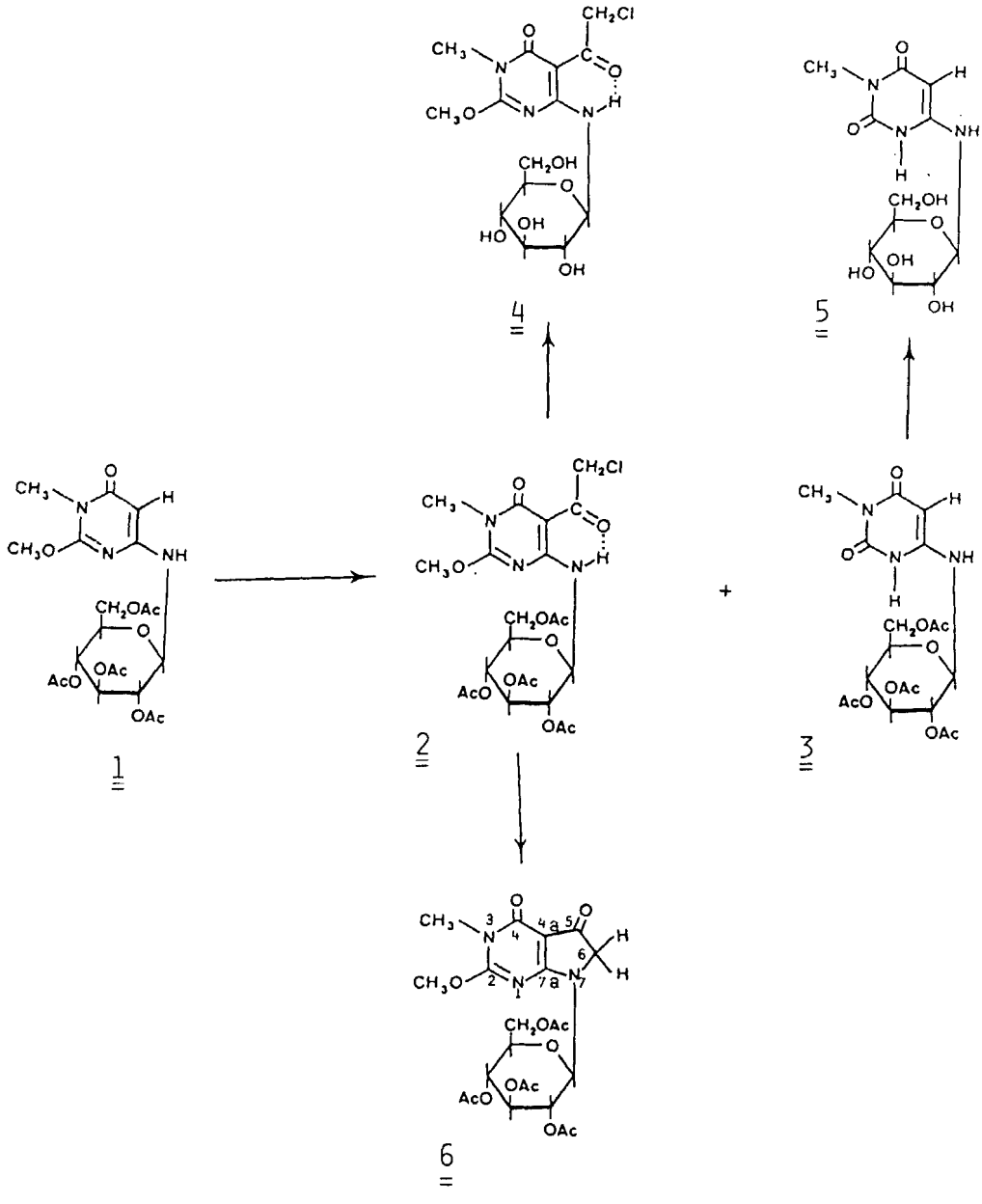
This method allows to obtain the nucleoside 5, impossible to obtain by direct condensation between 4-amino-1-methyl uracile and glucose, 5 is intermediate in the syntheses of interesting compounds, such as 8 and others[17].

The intermediates 2, 3, 4 and 5 are structural analogues to other nucleosides showing antitumoral and antiviral activities[18]. The probable biological activity of the above compounds is being studied[19].

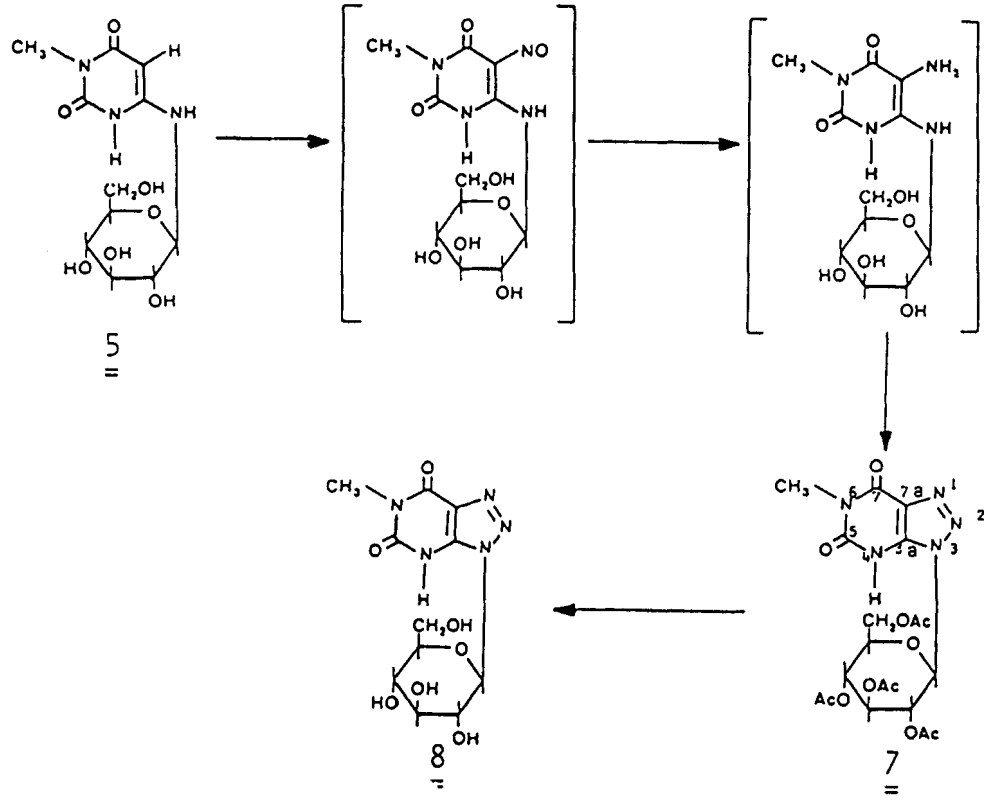
Table 1.- ^{1}H-NMR DATA. δ(ppm). J(Hz). INTERNAL. STANDARD Me_4Si

Compound	Solvent	NMe	OMe	H-5	C_4N-Ha (J1',NH)	$COCH_2$	N_3-H[a]	H1' (J1',2')	AcO
1	$CDCl_3$	3,3 s	4,0 s	5,3 s	5,7 d (9)	--	--	5,2-5,4 ■	2,1 s 12H
	$(CD_3)_2SO$	3,2 s	4,0 s	5,2 s	7,6 d (9)	--	--	5,3-5,7 ■	2,0 s 12H
2	$CDCl_3$	3,3 s	4,1 s	--	10,9 d(8,2)	4,9 s	--	5,9 ■ +D_2O d(8,2)	2,0 s 12H
	$(CD_3)_2SO$	3,2 s	4,1 s	--	10,6 d(8,2)	4,9 s	--	5,9 st +D_2O d(8,2)	2,0 s 12H
3	$(CD_3)_2SO$	3,0 s	--	4,9 s	6,8 d(8,2)	--	10,3 s broad	5,3 ■ +D_2O d(8,2)	2,0 s 12H
4	$(CD_3)_2SO$	3,2 s	4,0 s	--	10,7 d(8,2)	4,9 s	--	5,3 ■ +D_2O d(8,2)	--
5	$(CD_3)_2SO$	3,1 s	--	4,8	6,8 d(8,2)	--	10,3 s broad	4,4 ■ +D_2O d(8,2)	--
6	$CDCl_3$	3,4 s	4,2 s	--	--	4,0[a] s (C_6-H_2)	--	5,6 d(8,2)	2,0 s 12H
	$(CD_3)_2SO$	3,2 s	4,2 s	--	--	3,9 s (C_6-H_2)	--	5,9 d(8,2)	2,0 s 12H
7	$(CD_3)_2SO$	3,2 s	--	--	--	--	b	6,1 d (9)	1,8 s 2,0 s 12H
8	$(CD_3)_2SO$	3,1 s	--	--	--	--	b (N_4-H)	5,3 d (9)	--

a) Protons exchangeable by D; b) These signals are included in that of H_2O remaining in the $(CD_3)_2SO$; s = Singlet; d = Doublet; st = Pseudo-triplet; ■ = Multiplet.



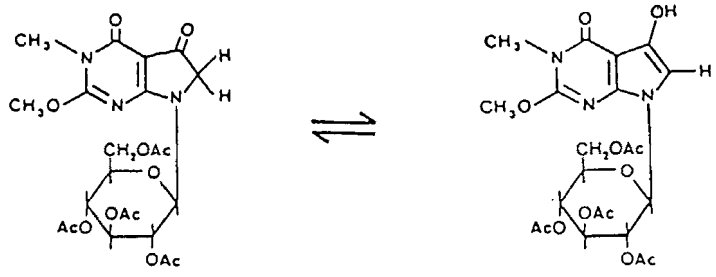
SCHEME 1



SCHEME 2

Cyclization of 2 to 4,5-dioxo-7-β-D-(2,3,4,6-tetra-O-acetyl)gluco-pyranosyl-3-methyl-2-methoxy-3,4,5,6-tetrahydro-pyrrolo[2,3-d]pyrimidine 6 has been carried out with anhydrous K_2CO_3 in DMF at 70 °C. This procedure is similar to that reported in the literature[14] for other 4-amino-5-α-chloracetyl pyrimidines.

In the ^{1}H-NMR spectra of 6, does not appear any signal for C_4-NH (table 1). The signal for the methylenic protons in C-6 is changed by deuterium on adding D_2O. The enolic forme may account for this fact.



The compound 5,7-dioxo-3-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosyl-6-methyl-4,5,6,7-tetrahydro-vic-triazolo[4,5-d]pyrimidine 7 has been obtained from 5 by successive treatments with $NaNO_2$/HOAc, $(NH_4)_2S$ (10% aqueous solutions), $NaNO_2$/HOAc, and finally Ac_2O/Py; none of the intermediates were isolated.

The selective de-O-acetylation of 7 using molar amount of sodium methoxide in methanol yields 5,7-dioxo-3-β-D-glucopyranosyl-6-methyl-4,5,6,7-tetrahydro-vic-triazolo[4,5-d]pyrimidine 8.

The β-configuration of the sugar moieties in all compounds has been confirmed by the value of the coupling constants $J_{1',2'}$, of the anomeric protons (table 1) and by the chemical shifts of the anomeric proton and carbon. The α-anomers have not been detected in the crystalline products.

EXPERIMENTAL

Melting points were determined in a Melting Point Apparatus Gallemkamp and are uncorrected. Proton nuclear magnetic resonance spectra were recorded with a Hitachi Perkin-Elmer R-600 Spectrometer. Carbon-13 nuclear magnetic resonance spectra were recorded with a Bruker WP 805 Spectrometer. Specific rotation values were determined with a Polarimeter Perkin-Elmer 141. Ultraviolet spectra were recorded with a Model 25 Spectrophotometer Beckman. Infrared spectra with a Spectrophotometer Beckman 4250 (KBr pellets). The analysis of C, H and N have been performed in "Instituto Nacional de Química Orgánica" in Madrid. Thin layer chromatogrphy (TLC) was runned on silica gel Merck 60 G, using chloroform/hexane/ethanol (8:1:0.5) as eluent. Compound 1 was prepared following the published method[13].

Reaction of 1 with chloracetyl chloride.

To a solution of 1, 4.8 g (0.01 mmol) in 100 mL of anhydrous ethyl acetate, 0.81 mL (0.01 mmol) of freshly distilled $ClCOCH_2Cl$ were added. The mixture was stirred under reflux for 5 h. At the end of this time a white solid precipitated which was filtered hot, washed with ethyl acetate and recristallized from $DMSO/H_2O$. This compound was identified as: 2,6-dioxo-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine 3. 2.03 g (43%); M.P.:280-5°C; $[\alpha]_D^{20}$ =-14.3° (c 1, DMSO). U.V. ($4.5x10^{-5}$M, H_2O): λ_{max}: 264 (ε 27200) and 201 (ε 20400) nm. I.R.:ν (cm^{-1}): 3270 m, 1760 s, 1715 s, 1690 s, 1600 s, 1570 s, 1375 m, 1250-1210 s broad, and 1035 s. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{19}H_{25}N_3O_{11}$: C, 48.41; H, 5.34; N, 8.91. Found: C, 48.24; H, 5.27; N, 8.82.

The mother liquors were neutralized with a saturated solution of $NaHCO_3$, washed with water, dried over $CaCl_2$ and evaporated under reduced pressure. The syrupy residue was crystallized from EtOH/AcOET (2:1) and recrystallized from $DMSO/H_2O$. The compound obtained was identified as: 5-α-chloracetyl-1,6-dihydro-4-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylamino-1-methyl-2-methoxy-6-oxo pyrimidine 2. 2.36 g (42%). M.P.: 205-7 °C. $[\alpha]_D^{20}$ = 4° (c 1, $HCCl_3$). U.V. ($4x10^{-5}$ M, H_2O): λ_{max}: 272 (ε 8000) and 227 (ε 18700) nm, ($5.16x10^{-5}$ M, MeOH): λ_{max}: 226 (ε 38000), 263 (shoulder) and 290 (ε 15300) nm. I.R.: ν(cm^{-1}): 3200 w, 1755 s, 1730 s, 1675 s, 1635 s, 1600 s, 1565 s, 1375 m, 1240 s, 1210 s, 1070 m, 1035 s. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{22}H_{28}N_3O_{12}Cl$: C, 47.03; H, 5.03: N, 7.47. Found: C, 47.10; H, 4.75; N, 7.31.

5-α-chloroacetyl-1,6-dihydro-4-β-D-glucopyranosylamino-1-methyl-2-methoxy-6-oxo pyrimidine 4.

To a suspension of 1.12 g (2 mmol) of 2 in 20 mL of MeOH, 2 mL (2 mmol) of 1 M solution of sodium methoxide in methanol was added, the mixture was stirred during 1 h at room temperature. Then the precipitate was filtered off. This compound was recrystallized fron DMSO/EtOH. 0.65 g (82%). M.P.: dec..$[\alpha]_D^{20}$ = 30.4° (c 1, DMSO). U.V. ($6.3x10^{-5}$ M, H_2O): λ_{max}: 290 (ε 10700), 227 (ε 26600) and 201 (ε 11600) nm; ($5.33x10^{-5}$ M, MeOH): λ_{max}: 226 (ε 31000), 264 (shoulder) and 294 (ε 11300) nm. I.R.: ν

TABLE 2. ^{13}C-NMR DATA. δ(ppm). INTERNAL STANDARD Me_4Si

Compound	Solvent	NMe	OMe	C-2	C-4	C-5	C-6	C-1'	C-2',C-3' C-4',C-5'	C-6'	$\underline{C}OCH_2$	$\underline{C}OCH_2$	$\underline{Me}CO$	$Me\underline{C}O$
1	$CDCl_3$	27,1	55,4	159,4	157,9	82,7	163,6	81,2	73,0 72,9 70,6 68,5	61,9	--	--	20,5 20,4	170,5 170,4 169,8 169,3
2	$(CD_3)_2SO$	27,1	56,6	161,7	157,8	93,6	162,8	77,9	72,3 70,0 68,3	61,9	51,1	190,3	20,2	169,2 169,5 169,9
3	$(CD_3)_2SO$	26,1	--	151,6	150,7	79,5	163,3	75,8	72,7 71,8 70,2 68,1	61,8	--	--	20,3	170,0 169,6 169,4
4	$(CD_3)_2SO$	27,2	56,5	162,1	157,7	93,1	163,1	80,9	79,1 77,6 73,1 70,1	61,0	51,3	190,3	--	--
5	$(CD_3)_2SO$	26,1	--	152,3	150,8	82,2	163,3	77,8	77,2 75,0 72,9 69,9	60,8	--	--	--	--
6	$CDCl_3$	27,3	57,0	161,6	156,3 (C-7a)	95,9 (C-4a)	169,3 (C-4)	79,6	74,0 73,2 68,6 68,0	61,7	53,1 (C-6)	189,5 (C-5)	20,6	173,5 170,5 170,1
7	$(CD_3)_2SO$	27,2	--	158,2 (C-5)	152,6 (C-3a)	122,4 (C-7a)	168,3 (C-7)	79,7	73,0 69,0 67,7	61,7	--	--	20,3 20,0	170,1 169,6 169,3
8	$(CD_3)_2SO$	27,3	--	158,4 (C-5)	152,4 (C-3a)	122,7 (C-7a)	158,6 (C-7)	83,4	79,6 77,6 70,7 69,9	60,9	--	--	--	--

(cm^{-1}): 3560-3180 s broad, 1655 s, 1625 s, 1590 m, 1565 s, 1230 m, 1080 s, 1035 s. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{14}H_{20}N_3O_8Cl$: C, 42.70; H, 5.12; N, 10.67. Found: C, 42.83; H, 4.97; N, 10.39.

2,6-dioxo-4-β-D-glucopyranosylamino-1-methyl-1,2,3,6-tetrahydro pyrimidine 5.

To a suspension of 1.89 g (4mmol) of 3 in 50 mL of MeOH, 4 mL (4 mmol) of 1 M solution of sodium methoxide in methanol was added. The mixture was stirred for 5 h at room temperature, neutralized with acetic acid and then evaporated under reduced pressure. The syrupy residue was crystallized fron water with active charcoal. 0.9 g (74%); M.P.: dec., $[\alpha]_D^{20}$ = -56° (c 1, DMSO). U.V. (1.02×10^{-4} M, H_2O): λ_{max}: 266 (ε 15900) and 202 (ε 10200) nm. I.R.: ν(cm^{-1}): 2940-2840 s broad, 1720 s, 1640 s, 1595-1560 s broad, 1460 s, 1355 m, 1295 m, 1115 m, 1095 m, 1075 s, 790 m. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{11}H_{17}N_3O_7$: C, 43.56; H, 5.65; N, 13.85. Found: C, 43.72; H, 5.93; N, 13.72.

4,5-dioxo-7-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosyl-1-methyl-2-3,4,5,6-tetrahydro-pyrrolo[2,3-d]pyrimidine 6.

1.1g (2 mmol) of 2 was added to 5 mL of DMF. To this solution 0.28 g (2 mmol) of anhydrous K_2CO_3 was added. The reaction mixture was stirred for 90 minutes at 70 °C, then, the mixture poured into cold water and extracted with $HCCl_3$ (15 mL, five times). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The syrupy residue was crystallized from EtOH/ether/hexane and recrystallized from EtOH with active charcoal. 0.78 g (75%); M.P.: 193-5 °C;$[\alpha]_D^{20}$ ◻ - 10° (c 1, $HCCl_3$). U.V. (5.3×10^{-5} M, H_2O): λ_{max}: 290 (ε 8100), 262 (ε 6300), 231 (ε 32100) and 200 (ε 14200) nm. I.R.: ν(cm^{-1}): 3600 - 3400 w broad, 1750 s, 1730 s, 1665 m, 1580 s, 1545 s, 1525 s, 1235 s, 1040 m. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{22}H_{27}N_3O_{12}$: C, 50.29; H, 5.18; N, 7.99. Found: C, 49.99; H, 5.20; N, 7.60.

5,7-dioxo-3-β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosyl-6-methyl-4,5,6,7-tetrahydro-vic-triazolo[4,5-d]pyrimidine 7.

To 15 mL of a solution of 5, in hot water (0.6 g, 2 mmol), 0.14 g (2 mmol) of $NaNO_2$ and acetic acid (0.12 g, 2 mmol) were succesively

added. The resulting solution was evaporated under reduced pressure, yielding a red syrupy, which was dissolved in 3 mL of 10% $(NH_4)_2S$ aqueous solution. This solution was stirred during 15 minutes at 60 °C. At this point the solution became decolorated, and then was evaporated under reduced pressure. 10 mL of boiling water were added to the solid residue and then filtered. After this, 4 mmol of $NaNO_2$ and 4 mmol of acetic acid were added to the resulting solution. The mixture was concentrated and the water eliminated by adding methanol and evaporating several times. The dry residue was directly acetylated by adding 10 mL of acetic anhydride and 10 mL of pyridine and stirring for 24 h at room temperature. The solution was evaporated at reduced pressure. The excess of solvents were removed by dissolving in methanol and evaporating several times. The final product was crystallized from ethanol with active charcoal. 0.86 g (88%); M.P.: 200 °C; $[\alpha]_D^{20}$ = - 9.9° (c 1, DMSO). U.V.: (4.6×10^{-5} M, H_2O): λ_{max}: 279 (ε 9100), 255 (ε 7500) and 214 (ε 15800) nm. I.R.: ν (cm^{-1}) : 3440 m broad, 1750 s, 1690 s, 1590 s, 1365 m, 1235 s, 1205 m, 1075 m, 1035 m, 905 m. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{19}H_{23}N_5O_{11}$: C, 45.87; H, 4.66; N, 14.08. Found: C, 44.65; H, 4.68; N, 14.41.

5,7-dioxo-3-β-D-glucopyranosyl-6-methyl-4,5,6,7-tetrahydro-vic-triazolo[4,5-d]pyrimidine 8.

0.98 g (2 mmol) of 7 were dissolved in 10 mL of methanol. then 2 mL (2 mmol) of 1 M solution of sodium methoxide in methanol were added. The mixture was stirred at room temperature during 12 h. The solid precipitated was filtered and washed with ethanol and ether. this compound was recrystallized from ethanol/methano (1:1). 0.56 g (85%); M.P.: dec., $[\alpha]_D^{20}$ = - 13.7° (c 1, DMSO). U.V. (6.2×10^{-5} M, H_2O): λ_{max}: 277 (ε 8000), 252 (ε 6700) and 214 (ε 14800) nm. I.R.: ν(cm^{-1}): 3550-3200 m broad, 1680 s, 1620 s, 1580 s, 1510 m, 1290 m, 1270 m, 1080 m, 1075 m, 1060 m, 780 m. ^{1}H-NMR see table 1. ^{13}C-NMR see table 2. Anal. Calcd. for $C_{11}H_{15}N_5O_7$: C, 40.12; H, 4.59; N, 21.27. Found: C, 40.08; H, 5.12; N, 21.45.

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