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Reaction of 6-Glycopyranosylaminopyrimidin-4-ones with Malonic Acids. Synthesis of 8-Glycopyranosylpyrido[2,3-d]pyrimidin-4-one Derivatives [1]

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Summary. Reactions of 6-glycopyranosylaminopyrimidin-4-ones **1a–d** with malonic, methyl malonic and ethyl malonic acids are discussed in this paper. These reactions have been carried out in acetic anhydride at 100°C affording the 8-glycopyranosylpyrido[2,3-d]pyrimidin-4-ones **2a–d**, **3c–d** and the 5-acyl-6-glycopyranosylaminopyrimidin-6-ones **4a–d**, **5a–d**.

Keywords. Pyrido[2,3-d]pyrimidines; 8-Glycopyranosylpyrido[2,3-d]pyrimidin-4-ones; Malonic acid derivates; Nucleosides.

Reaktion von 6-Glycopyranosylaminopyrimidin-4-onen mit Malonsäuren. Synthese von 8-Glycopyranosylpyrido[2,3-d]pyrimidin-4-on-Derivaten

Zusammenfassung. Es werden Reaktionen der 6-Glycopyranosylaminopyrimidin-4-one **1a–d** mit Malonsäure, Methylmalonsäure und Ethylmalonsäure diskutiert. Die Reaktionen wurden in Essigsäureanhydrid bei 100°C ausgeführt und ergaben 8-Glycopyranosylpyrido[2,3-d]pyrimidin-4-one **2a–d**, **3c–d** und die 5-Acyl-6-glycopyranosylaminopyrimidin-6-one **4a–d** und **5a–d**.

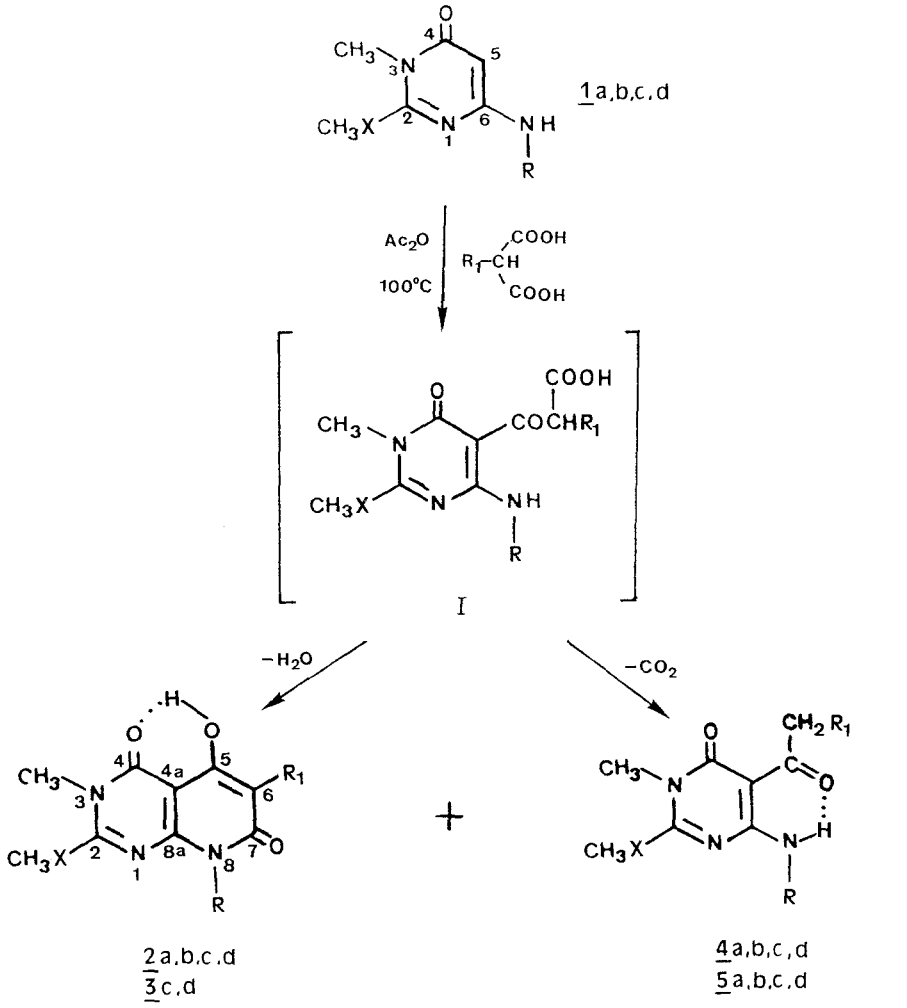
Introduction

Pyrido[2,3-d]pyrimidines are an important class of fused bicyclic derivates known to show important biological activity [2]. One of the main synthetic ways possible for this system is the reaction of 6-aminopyrimidines with 1,3-dicarbonylic compounds [3]. This method has not been extended to 6-glycosylaminopyrimidines.

In an earlier publication, we have reported about the synthesis of some pyrano[2,3-d]pyrimidines by treatment of the corresponding 6-glycosylaminopyrimidines with malonic acid derivates [4]. In continuation of our work on the synthesis, reactivity, and biological activity of 6-glycosylaminopyrimidines [5–9], we describe now the utility of the above mentioned method for the synthesis of several 8-glycopyranosylaminopyrido[2,3-d]pyrimidines, which can be seen as special nucleoside analogues.

Results and Discussion

The 6-glycopyranosylaminopyrimidin-4-ones **1a–d** used in this study were obtained by a previously reported method [5]. The treatment of these compounds with methyl malonic acid and ethyl malonic acid in acetic anhydride at 100°C afforded the 8-glycopyranosylaminopyrido[2,3-d]pyrimidines **2a–d**, **3c–d** and the 5-acyl derivates **4a–d**, **5a–b** (Scheme 1). Futhermore, in the reaction of **1c** and **1d** we



	X	R		R_I
a	O	β-D-(tri-O-acetyl)xylopyranosyl	2	CH_3
b	O	β-D-(tetra-O-acety)glucopyranosyl	3	CH_2CH_3
c	S	β-D-(tri-O-acetyl)xylopyranosyl	4	CH_3
d	S	β-D-(tetra-O-acetyl)glucopyranosyl	5	CH_2CH_3

Scheme 1

have detected by TLC the formation of low quantities (not isolable) of 5-propionyl- (**4c–d**) and 5-butyryl-6-glycopyranosylaminopyrimidin-4-ones (**5c**). On the other hand, in the reaction of compound **1d** with ethyl malonic acid an unresolved mixture determined by ^{1}H-NMR (86% total yield) of 5-butyryl derivative **5d** (17%) and the corresponding pyrido[2,3-d]pyrimidine **3d** (69%) was obtained.

Attempts to react malonic acid were unsuccessful leading to a complex mixture with nonseparable components.

To corroborate the structures of **4a** and **4b**, direct acylations of **1a** and **1b** were carried out. When **1a** or **1b** (1 g) reacts with propionic anhydride (20 ml) in the presence of perchloric acid (1–2 drops) under reflux, 16% **4a** or 36% **4b** were obtained.

The structures **2–5** are supported by their ^{1}H-NMR and ^{13}C-NMR spectra. The β-configuration of the sugar moieties has been confirmed in all compounds by the values of the coupling constants $J_{1',2'}$ and by the chemical shifts of the anomeric proton an carbon [4–10].

In the ^{1}H-NMR spectra of compounds **4** and **5** the C(6)−NH protons appear at 11.5 ppm as an exchangeable doublet. This signal appears downfield shifted in comparison with the same proton in compounds **1** because of the intramolecular hydrogen bond indicated in Scheme 1. The above signal is not observed in the spectra of compounds **2** and **3** because of the involvement of the C(6)−NH in the formation of the second heterocyclic ring. Likewise, the C(5)−OH proton signals in compounds **2** and **3** appear downfield shifted at 11.9 ppm as expected for intramolecular hydrogen bonds between this hydrogen and the C(4)=O group.

Formation of compounds **2–5** can be explained as follow. The 6-glycopyranosylaminopyrimidines **1a–d** present two active sites for electrophilic attack by malonic acids: C(5)−H and C(6)−NH. The reaction can pass through the intermediate **I** (Scheme 1) formed by attack at the C-5 position as we have observed in a similar case [10]. The β-pyrimidinyl-β-ketoacid **I** can follow two different pathways leading to the final products: formation of pyrido[2,3-d]pyrimidine derivates **2** and **3** by a heterocyclization reaction with the C(6)−NH group and 5-acyl derivates **4** and **5** by decarboxylation at 100°C.

We have obtained in fact both possible types of compounds: pyrido[2,3-d]pyrimidines **2** and **3** and 5-acyl derivates **4** and **5**. In contrast to this result, pyrido[2,3-d]pyrimidines were obtained [11] when 6-amino-1,3-dimethyl uracils were acylated with malonic acid or alkyl malonic acids in the presence of acetic anhydride.

Experimental Part

Melting points (uncorrected) were determined using a melting point apparatus Gallenkamp. Proton nuclear magnetic resonance spectra were recorded with Hitachi Perkin-Elmer R-600 and Bruker AM-300 spectrometers using tetramethylsilane as internal standard. Carbon-13 nuclear resonance spectra were determined with a Bruker AM-300 spectrometer. Ultraviolet spectra were recorded with a Perkin-Elmer Lamda 5 spectrophotometer. Infrared spectra were recorded using a Beckman 4250 spectrophotometer (KBr pellets). The analysis of C, H, and N have been performed in the "Servicios Técnicos de la Universidad de Granada" using a Perkin-Elmer 240C equipment. Mass spectra were recorded using a Hewlett-Packard HP-5988-A spectrometer. Thin layer chromatography (tlc) was run on silica gel Merck 60 GF_{254}, visualization was accomplished by ultraviolet absorbance followed by charring with a 4% sulfuric acid-methanol solution. Finally, column chromatography was done on Kieselgel 60 silica gel (70–230 mesh).

General Procedure for the Reaction of 6-Glycopyranosylaminopyrimidines **1 a–d** *with Methyl and Ethyl Malonic Acids*

1 g of **1 a–d** and the corresponding malonic acid derivate (double molar amount for **1 a–d** and 10 mol per mol for **1 c–d**) were added to 5 ml of acetic anhydride. The mixture was stirred at 100°C until no starting material was detected by TLC (CH_2Cl_2/*Me*OH, 9 : 1). After evaporation of the solvent in a rotatory evaporator the residue was dissolved in chloroform (1 ml), poured into a short chromatographic column (5 cm diameters) which contained 50 g of silica gel and eluted with CH_2Cl_2/Ethyl Ether (0–40%) in the case of **1 a**, **b** or CH_2Cl_2/*Me*OH (0–2%) in the case of **1 c**, **d**. The fraction containing the desired products were pooled, evaporated and crystallized from the appropiate solvent.

3,4,7,8-Tetrahydro-5-hydroxy-3,6-dimethyl-2-methoxy-4,7-dioxo-8-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)pyrido[2,3-d]pyrimidine (**2 a**)

Reaction time 2–3 h. Crystallized from *Et*OH. 0.32 g (27%), m.p. 184–186°C. ^{1}H-NMR ($CDCl_3$): δ = 1.8 [s, 3 H, C(6) − CH_3], 3.4 [s, 3 H, CH_3 − N(3)], 4.0 (s, 3 H, CH_3 − O), 6.6 [d, 1 H, J = 6.9 Hz, C(1′)-H], 11.9 [s, 1 H, C(5) − OH]. ^{13}C-NMR ($CDCl_3$): δ = 8.6 [CH_3 − C(6)], 65.6 (C-5′), 80.4 (C-1′), 92.5 (C-4 a), 103.2 (C-6), 151.8 (C-8 a), 154.7 (C-2), 161.3, 163.6, 163.9 (C-4, C-5, C-7). Anal. calc. for $C_{21}H_{25}N_3O_{11}$: C 50.90, H 5.08, N 8.48; found: C 50.83, H 5.16, N 8.82. $[\alpha]_D^{25} = -70.8°$ (c = 1, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 234 (26 800), 290 (11 500), 308 (sh). IR (cm^{-1}): 2 970 w, 1 760 s, 1 690 s, 1 665 s, 1 635 s, 1 585 s, 1 550 s, 1 495 m, 1 450 w, 1 415 m, 1 380 m. Mass spectrum m/z (abundance %): 495 (M^+) (4), 373 (23), 237 (100), 236 (20), 222 (14), 97 (36), 43 (43).

3,4,7,8-Tetrahydro-5-hydroxy-3,6-dimethyl-2-methoxy-4,7-dioxo-8-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)pyrido[2,3-d]pyrimidine (**2 b**)

Reaction time 2–3 h. Crystallized from ethyl ether. 0.35–0.47 g (30–40%), m.p. 172–174°C. ^{1}H-NMR ($CDCl_3$): δ = 1.8 [s, 3 H, C(6) − CH_3], 3.4 [s, 3 H, CH_3 − N(3)], 4.0 (s, 3 H, CH_3 − O), 6.6 [d, 1 H, J = 6.9 Hz, C(1′) − H], 11.9 [s, 1 H, C(5) − OH]. ^{13}C-NMR ($CDCl_3$): δ = 8.6 [CH_3 − C(6)], 62.0 (C-6′), 79.8 (C-1′), 92.7 (C-4 a), 103.2 (C-6), 151.8 (C-8 a), 154.7 (C-2), 161.3, 163.6, 164.0 (C-4, C-5, C-7). Anal. calc. for $C_{24}H_{29}N_3O_{13}$: C 50.79, H 5.15, N 7.40; found: C 51.01, H 5.20, N 7.67. $[\alpha]_D^{25} = -39.5°$ (c = 1, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 223 (29 900), 290 (13 100), 311 (sh). IR (cm^{-1}): 2 980 w, 2 900 w, 1 760 s, 1 690 s, 1 665 s, 1 640 s, 1 590 m, 1 550 s, 1 500m, 1 465 m, 1 420 m, 1 385 s. Mass spectrum m/z (abundance %): 567 (M^+) (1), 448 (21), 348 (15), 238 (78), 237 (100), 169 (27), 109 (29), 43 (49).

3,4,7,8-Tetrahydro-5-hydroxy-3,6-dimethyl-2-methylthio-4,7-dioxo-8-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)pyrido[2,3-d]pyrimidine (**2 c**)

Reaction time 30 min. Crystallized from *Et*OH. 1.01 g (85%), m.p. 208–211°C. ^{1}H-NMR ($CDCl_3$): δ = 1.8 [s, 3 H, C(6) − CH_3], 2.8 (s, 3 H, CH_3 − S), 3.5 [s, 3 H, CH_3 − N(3)], 6.6 [d, 1 H, J = 7.4 Hz, C(1′) − H], 11.9 [s, 1 H, C(5) − OH]. ^{13}C-NMR ($CDCl_3$): δ = 8.8 [CH_3 − C(6)], 65.8 (C-5′), 80.6 (C-1′), 93.6 (C-4 a), 104.5 (C-6), 150.7 (C-8 a), 160.9 (C-2), 162.5, 163.1, 163.6 (C-4, C-5, C-7). Anal. calc. for $C_{21}H_{25}N_3O_{10}S$: C 49.31, H 4.93, N 8.22; found: C 49.06, H 4.96, N 8.19. $[\alpha]_D^{20} = -63.2°$ (c = 1, $CHCl_3$). UV (*Me*OH) $\lambda_{max.}$ nm (ε): 227 (25 100), 295 (10 000), 333 (12 000). IR (cm^{-1}): 2 970 w, 2 930 w, 1 755 s, 1 680 s, 1 650 s, 1 620 m, 1 530 s, 1 460 m, 1 415 m, 1 370 m. Mass spectrum m/z (abundance %): 511 (M^+) (9), 332 (41), 254 (91), 253 (100), 43 (78).

3,4,7,8-Tetrahydro-5-hydroxy-3,6-dimethyl-2-methylthio-4,7-dioxo-8-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)pyrido[2,3-d]pyrimidine (**2 d**)

Reaction time 1 h. Crystallized from *Et*OH. 1.10 g (95%), m.p. 122–125°C. ^{1}H-NMR($CDCl_3$): δ = 1.8 [s, 3 H, C(6)-CH_3], 2.8 (s, 3 H, CH_3-S), 3.6 [s, 3 H, CH_3 − N(3)], 6.6 [d, 1 H, J = 7.8 Hz, C(1′)-H],

11.9 [s, 1 H, C(5)−OH]. ^{13}C-NMR($CDCl_3$): δ = 8.8 [CH_3−C(6)], 61.8 (C-6′), 79.9 (C-1′), 93.7 (C-4a), 104.5 (C-6), 150.7 (C-8a), 161.0 (C-2), 162.5, 163.1, 163.5 (C-4, C-5, C-7). Anal. calc. for $C_{24}H_{29}N_3O_{12}S$: C 49.40, H 5.01, N 7.20; found: C 48.95, H 5.16, N 6.51. $[\alpha]_D^{20} = -22.1°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 227 (22 000), 295 (8 700), 324–330 (10 300). IR (cm^{-1}): 2 930 w, 1 750 s, 1 670 s, 1 650 s, 1 615 m, 1 530 s, 1 460 m, 1 410 m, 1 370 m. Mass spectrum *m/z* (abundance %): 583 (M^+) (7), 464 (46), 254 (100), 253 (76), 208 (23), 168 (26), 43 (96).

6-Ethyl-3,4,7,8-tetrahydro-5-hydroxy-3-methyl-2-methylthio-4,7-dioxo-8-(2,3,4-tri-O-acetyl-β-D-xylopyranosyl)pyrido[2,3-d]pyrimidine (**3c**)

Reaction time 1 h. Crystallized from *Et*OH. 0.61–0.83 g (50–68%), m.p. 175–180°C. ^{1}H-NMR($CDCl_3$): δ = 1.1 (t, 3 H, CH_3), 2.5 (c, 2 H, CH_2), 2.8 (s, 3H, CH_3−S), 3.6 [s, 3 H, CH_3−N(3)], 6.6 [d, 1 H, J = 7.4 Hz, C(1′)-H], 11.9 [s, 1 H, C(5)−OH]. ^{13}C-NMR ($CDCl_3$): δ = 12.6 [CH_3-CH_2-C(6)], 17.0 [CH_2−C(6)], 65.8 (C-5′), 80.6 (C-1′), 93.7 (C-4a), 110.6 (C-6), 150.8 (C-8a), 160.7 (C-2), 162.5, 163.1, 163.2 (C-4, C-5, C-7). Anal. calc. for $C_{22}H_{27}N_3O_{10}S$: C 50.28, H 5.17, N 7.99; found: C 50.10, H 5.23, N 8.20. $[\alpha]_D^{20} = -43.9°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 228 (27 200), 295 (10 400), 323–332 (11 700). IR (cm^{-1}): 2 960 w, 2 930 w, 2 870 w, 1 760 s, 1 740 s, 1 675 s, 1 655 s, 1 615 m, 1 535 s, 1 460 m, 1 435 m, 1 410 m, 1 365 m, 1 325 w. Mass spectrum *m/z* (abundance %): 525 (M^+) (6), 406 (10), 568 (62), 267 (52), 252 (100), 43 (91).

3,4-Dihydro-3-methyl-2-methoxy-4-oxo-5-propionyl-6-(2,3,4-tri-O-acetyl-β-D-xylopyranosylamino)pyrimidine (**4a**)

Reaction time 2–3 h. Crystallized from ethyl ether. 0.18 g (16%), m.p. 190–192°C. ^{1}H-NMR($CDCl_3$): δ = 1.1 (t, 3H, CH_3), 3.0 (c, 2 H, CH_2), 3.3 [s, 3 H, CH_3−N(3)], 4.0 (s, 3 H, CH_3−O), 5.8 [st, 1 H, +D_2O d, J = 7.5 Hz, C(1′)-H], 11.6 [d, 1 H, J = 8.2 Hz, C(6)−NH]. ^{13}C-NMR($CDCl_3$): δ = 8.7 [CH_3−CH_2-CO−C(5)], 36.7 [CH_2−CO−C(5)], 62.6 (C-5′), 78.5 (C-1′), 95.4 (C-5), 157.4, 162.5, 162.9 (C-2, C-4, C-6), 202.7 [CO−C(5)]. Anal. calc. for $C_{20}H_{27}N_3O_{10}$: C 51.16, H 5.79, N 8.95; found: C 51.03, H 5.91, N 8.94. $[\alpha]_D^{25} = -16.0°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 226 (35 300), 261 (sh), 291 (11 400). IR (cm^{-1}): 3 200 w, 2 980 w, 2 930 w, 2 850 w, 1 745 s, 1 675 s, 1 635 s, 1 605 m, 1 555 s, 1 490 m, 1 455 m, 1 410 w, 1 380 m. Mass spectrum *m/z* (abundance %): 469 (M^+) (3), 350 (38), 290 (21), 240 (67), 222 (91), 210 (28), 208 (28), 194 (37), 182 (73), 97 (52), 72 (32), 43 (100).

3,4-Dihydro-3-methyl-2-methoxy-4-oxo-5-propionyl-6-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrimidine (**4b**)

Reaction time 2–3 h. Crystallized from *Et*OH. 0.40 g (36%), m.p. 158°C. ^{1}H-NMR ($CDCl_3$): δ = 1.1 (t, 3 H, CH_3), 3.0 (c, 2 H, CH_2), 3.3 [s, 3 H, CH_3-N(3)], 4.0 (s, 3 H, CH_3−O), 5.7 [st, 1 H, +D_2O d, J = 8.2 Hz, C(1′)−H], 11.4 [d, 1 H, J = 8.2 Hz, C(6)−NH]. ^{13}C-NMR ($CDCl_3$): δ = 8.8 [CH_3−CH_2−CO−C(5)], 36.8 [CH_2−CO−C(5)], 62.1 (C-6′), 79.6 (C-1′), 95.6 (C-5), 157.4, 162.4, 163.1 (C-2, C-4, C-6), 202.9 [CO−C(5)]. Anal. calc. for $C_{23}H_{31}N_3O_{12}$: C 51.01, H 5.77, N 7.76; found: C 50.98, H 5.57, N 7.76. $[\alpha]_D^{25} = +12.7°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 226 (32 300), 261 (sh), 289 (10 700). IR (cm^{-1}): 3 470 w, 2 970 w, 2 920 w, 1 745 s, 1 675 s, 1 615 s, 1 600 s, 1 555 s, 1 490 m, 1 450 w, 1 410 w, 1 370 m. Mass spectrum *m/z* (abundance %): 541 (M^+) (7), 422 (65), 362 (32), 348 (75), 302 (39), 210 (44), 240 (77), 222 (100), 194 (60), 182 (79), 169 (30), 141 (33), 109 (32), 43 (99).

5-Butyryl-3,4-dihydro-3-methyl-2-methoxy-4-oxo-6-(2,3,4-tri-O-acetyl-β-D-xylopyranosylamino)pyrimidine (**5a**)

Reaction time 2–3 h. Crystallized from *Et*OH. 0.47–0.76 g (40–65%), m.p. 202–204°C. ^{1}H-NMR ($CDCl_3$): δ = 1.0 (t, 3 H, CH_3), 3.0 (c, 2 H, CH_2), 3.3 [s, 3 H, CH_3−N(3)], 4.0 (s, 3 H, CH_3−O), 5.8 [st, 1 H, +D_2O d, J = 8.2 Hz, C(1′)−H], 11.6 [d, 1 H, J = 8.9 Hz, C(6)−NH]. ^{13}C-NMR($CDCl_3$):

$\delta = 14.0$ [$CH_3-CH_2-CH_2-CO-C(5)$], 18.0 [$CH_2-CH_2-CO-C(5)$], 45.5 [$CH_2-CO-C(5)$], 62.6 (C-5'), 78.5 (C-1'), 95.5 (C-5), 157.4, 162.5, 163.0 (C-2, C-4, C-6), 202.2 [$CO-C(5)$]. Anal. calc. for $C_{21}H_{29}N_3O_{10}$: C 52.16, H 6.04, N 8.69; found: C 52.21, H 5.91, N 8.97. $[\alpha]_D^{25} = -14.8°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 227 (32 000), 264 (sh), 291 (11 700). IR (cm^{-1}): 2 960 w, 2 870 w, 1 760 s, 1 740 s, 1 680 s, 1 615 s, 1 565 s, 1 490 m, 1 455 w, 1 415 w, 1 375 m. Mass spectrum *m/z* (abundance %): 483 (M^+) (3), 364 (42), 304 (23), 264 (52), 254 (55), 236 (89), 224 (38), 208 (49), 182 (64), 97 (54), 72 (24), 43 (100).

5-Butyryl-3,4-dihydro-3-methyl-2-methoxy-4-oxo-6-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl-amino)pyrimidine (**5b**)

Reaction time 2–3 h. Crystallized from *Et*OH. 0.34 g (30%), m.p. 152–155°C. ^{1}H-NMR($CDCl_3$): $\delta = 1.0$ (t, 3 H, CH_3), 3.0 (c, 2 H, CH_2), 3.3 [s, 3 H, $CH_3-N(3)$], 4.0 (s, 3 H, CH_3-O), 5.6 [st, 1 H, $+D_2O$ d, $J = 8.9$ Hz, C(1')−H], 11.4 [d, 1 H, $J = 8.9$ Hz, C(6)−NH]. ^{13}C-NMR ($CDCl_3$): $\delta = 14.0$ [$CH_3-CH_2-CH_2-CO-C(5)$], 18.1 [$CH_2-CH_2-CO-C(5)$], 45.5 [$CH_2-CO-C(5)$], 62.1 (C-6'), 79.6 (C-1'), 95.6 (C-5), 157.3, 162.4, 163.2 (C-2, C-4, C-6), 202.3 [CO-C(5)]. Anal. calc. for $C_{24}H_{33}N_3O_{12}$: C 51.88, H 5.98, N 7.56; found: C 52.19, H 5.86, N 7.85. $[\alpha]_D^{25} = +1.3°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 227 (37 400), 262 (sh), 292 (12 200). IR (cm^{-1}): 2 960 w, 2 870 w, 1 745 s, 1 675 s, 1 630 m, 1 605 m, 1 555 s, 1 490 m, 1 455 w, 1 410 w, 1 380 m, 1 365 m. Mass spectrum *m/z* (abundance %): 555 (M^+) (1), 264 (37), 254 (22), 236 (37), 224 (31), 208 (40), 182 (39), 109 (28), 81 (36), 72 (25), 43 (100).

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