Monatshefte für Chemie 120, 1119 – 1124 (1989)

Monatshefte für Chemie
Chemical Monthly
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Synthesis of 5-Glycopyranosylamino-pyrano[2,3-d]pyrimidin-2-one Derivatives [1]

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Summary. Three series of 3-substituted 5-glycopyranosylamino pyrano[2,3-d]pyrimidin-2-one derivatives, **3a–c**, **4a–c**, and **5a–c** have been prepared by treatment of the corresponding 1,4-dihydro-6-glycopyranosylamino pyrimidin-4-ones **1a–c** with malonic, methyl malonic and ethyl malonic acids, respectively.

Keywords. Pyrano[2,3-d]pyrimidines; 5-Glycopyranosylamino pyrano[2,3-d]pyrimidin-2-ones; Malonic acid derivatives; Nucleosides.

Synthese von Derivaten des 5-Glucopyranosylaminopyrano[2,3-d]pyrimidin-2-on

Zusammenfassung. Es wurden drei Serien von 3-substituierten 5-Glucopyranosylaminopyrano[2,3-d]pyrimidin-2-onen (**3a–c**, **4a–c** und **5a–c**) mittels Behandlung der entsprechenden 1,4-Dihydro-6-glucopyranosylamino-pyrimidin-4-one (**1a–c**) mit Malon-, Methylmalon- bzw. Ethylmalonsäure dargestellt.

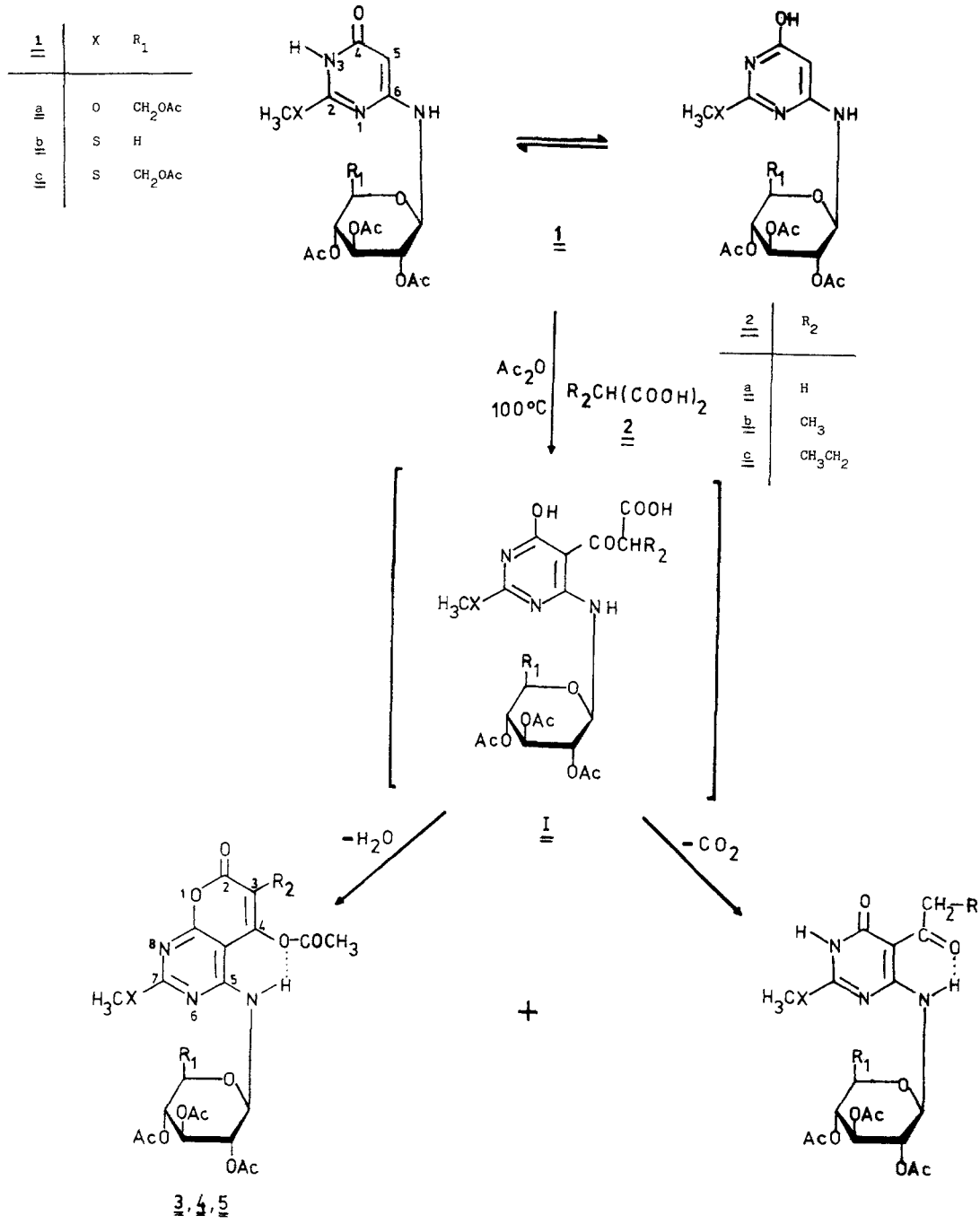
Introduction

Many pyrimidines, pyrimidines nucleosides and their fused bicyclic derivatives are known to show important biological activity. Until now only few syntheses of the pyrano[2,3-d]pyrimidines ring system have been reported; for most of them barbituric acids served as starting materials and usually several steps were needed [2–5]. Other syntheses start from amidoxime ethers which are cyclized with malonyl chloride or malonic acid in the presence of acetic anhydride [6] and by treatment of 6-hydroxypyrimidin-4-ones with bis-2,4,6-tri-chlorophenyl malonates or diethyl malonates [7].

Following our work on the synthesis, reactivity and biological activity [8–11] of 6-glycosylaminopyrimidines, in the present paper we describe the utility of the mentioned products for the synthesis of several 5-glycopyranosylaminopyrano[2,3-d]pyrimidin-2-one derivatives.

Results and Discussion

The 6-glycopyranosylaminopyrimidin-2-ones **1a–c**, used in this study were obtained by a previously reported method [8]. The treatment of these compounds with malonic acid (**2a**), methyl malonic acid (**2b**) and ethyl malonic acid (**2c**), in acetic



3	X	R_1	R_2	4	X	R_1	R_2	5	X	R_1	R_2
a	O	CH_2OAc	H	**a**	O	CH_2OAc	CH_3	**a**	O	CH_2OAc	CH_3CH_2
b	S	H	H	**b**	S	H	CH_3	**b**	S	H	CH_3CH_2
c	S	CH_2OAc	H	**c**	S	CH_2OAc	CH_3	**c**	S	CH_2OAc	CH_3CH_2

anhydride at 100°C afforded the fluorescent 5-glycopyranosylaminopyrano[2,3-d]pyrimidin-2-ones **3a–c**, **4a–c**, and **5a–c**, respectively. The highest yield was observed by using methyl malonic acid (Table 1). Furthermore, in these reactions we have detected the formation of low quantities of 5-acetyl, 5-propionyl and 5-butiryl-6-glycopyranosylaminopyrimidin-2-ones, some of them previously obtained by direct acylation [12].

The 6-glycopyranosylaminopyrimidines **1a–c** present three active sites for electrophilic attack by malonic acids **2a–c**: C(4)−OH, C(5)−H and C(6)−NH. The reaction can pass through the intermediate **I** formed by attack at the C-5 position as we have observed in similar situations [12]. The β-pyrimidinyl-β-ceto acid intermediate **I** can follow three different pathways to give the final products: formation of 5-acylderivatives by decarboxylation (the reaction temperature was 100°C), formation of pyrano[2,3-d]pyrimidine derivatives by intramolecular cyclization "via" C(4)−OH, and formation of pyrido[2,3-d]pyrimidine derivatives by intramolecular cyclization "via" C(6)−NH.

We have obtained pyrano[2,3-d]pyrimidines and small amounts of 5-acyl derivatives but pyrido[2,3-d]pyrimidines were not formed. This class of compounds has been obtained when 6-amino-1,3-dimethyl uracils were acylated with malonic acid or alkyl malonic acids in the presence of acetic anhydride [13]. We have observed that the C(6)−NH-Gly group is less active than C(4)=O ⇄ C(4)−OH due to the presence of the glycosidic moiety [10] and, therefore, in these reactions pyrido[2,3-d]pyrimidines were not obtained. Nevertheless, when the C(4)=O ⇄ C(4)−OH group was not present because of the methyl substitution on N-3, we confirmed the formation of pyrido[2,3-d]pyrimidines [14].

The structures **3**, **4**, and **5** are supported by their ^{1}H-NMR spectra (Table 2). All spectra exhibited an exchangeable doublet at about 8 ppm corresponding to the C(5)−NH proton which is coupled with H-1′, $J_{1'\text{-NH}} = 8.2$ Hz. This signal appears shifted downfield about 2.5 ppm with regard to the same proton in compounds 1 because of the hydrogen bond indicated in the formulas.

The β-configuration of the sugar moieties in all compounds obtained has been confirmed by the values of the coupling constants $J_{1',2'}$ and by the chemical shifts of the anomeric protons and carbons.

Experimental Part

Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. The analysis of C, H and N have been performed in "Servicios Técnicos de la Universidad de Granada" in Granada. The specific optical rotation were measured on a Perkin-Elmer 141 polarimeter. The ultraviolet (UV) spectra were taken on a Perkin-Elmer Lambda 5. The IR spectra were obtained using a Beckman IR-4250 spectrophotometer (KBr pellets). The ^{1}H-NMR spectra were recorded on a Hitachi Perkin-Elmer R-600 spectrometer using *TMS* as internal standard. The ^{13}C-NMR spectra were recorded with a Bruker AM-300 spectrometer. Mass spectra were recorded with Hewlett-Packar HP-5988-A spectrometer. Thin layer chromatography (TLC) was performed on Merck pre-coated TLC aluminium sheets silica gel 60 F_{254}, visualization was accomplished by ultraviolet absorbance followed by charring with a 4% sulfuric acid/methanol solution. Column chromatography was done on silica gel 60 (70–230 mesh).

Table 1. Data for compounds **3–5**

Compound	Time	Yield %	M.p. °C	Formula	Analysis		
					C	H	N
3a	2 h	57	226–227 *Et*OH	$C_{24}H_{27}N_3O_{14}$	49.57 (49.40)	4.68 (4.83)	7.23 (7.03)
3b	30 min	20	243 *Et*OH	$C_{21}H_{23}N_3O_{11}S$	47.99 (47.91)	4.41 (4.61)	8.00 (7.71)
3c	1 h	40	220–221 *Et*OH	$C_{24}H_{27}N_3O_{13}S$	48.24 (48.03)	4.55 (4.79)	7.03 (6.88)
4a	1 h	86	155 hexane	$C_{25}H_{29}N_3O_{14}$	50.42 (50.70)	4.91 (4.98)	7.06 (6.71)
4b	30 min	72	190–195 $CHCl_3$-hexane	$C_{22}H_{25}N_3O_{11}S$	48.97 (48.97)	4.67 (4.80)	7.79 (7.88)
4c	1 h	73	188 hexane	$C_{25}H_{29}N_3O_{13}S$	49.09 (48.96)	4.78 (4.97)	6.87 (6.47)
5a	2 h	56	195 *Et*OH	$C_{26}H_{31}N_3O_{14}$	51.23 (51.15)	5.13 (4.98)	6.89 (7.32)
5b	1 h	39	215–217 *Et*OH	$C_{23}H_{27}N_3O_{11}S$	49.90 (49.84)	4.92 (4.89)	7.59 (7.51)
5c	1 h	63	200-202 *Et*OH	$C_{26}H_{31}N_3O_{13}S$	49.91 (49.92)	4.99 (4.86)	6.72 (6.82)

Table 2. ^{1}H-NMR spectra of compounds **3–5**

Compound	^{1}H-NMR in $CDCl_3$; δ, ppm
3a	8.2 (d, 1, J=8.5 Hz, N−H), 6.0 [s, 1, C(3)−H], 5.8 [st, 1, +D_2O d, J=8.5 Hz, C (1′)−H], 4.0 (s, 3, CH_3−O), 2.4 [s, 3, C(4)−$OCOCH_3$]
3b	8.1 (d, 1, J=8.2 Hz, N−H), 6.0 [s, 1, C(3)−H], 5.7 [st, 1, +D_2O d, J=8.2 Hz, C (1′)−H], 2.6 (s, 3, CH_3−S), 2.4 [s, 3, C(4)−$OCOCH_3$]
3c	8.2 (d, 1, J=8.2 Hz, N−H), 6.0 [s, 1, C(3)−H], 5.7 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 2.6 (s, 3, CH_3−S), 2.4 [s, 3, C(4)−$OCOCH_3$]
4a	7.1 (d, 1, J=8.2 Hz, N−H), 5.7 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 4.0 (s, 3, CH_3−O), 2.5 [s, 3, C(4)−$OCOCH_3$], 1.9 [s, 3, C(3)−CH_3]
4b	7.1 (d, 1, J=8.2 Hz, N−H), 5.7 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 2.6 (s, 3, CH_3−S), 2.6 [s, 3, C(4)−$OCOCH_3$], 1.9 [s, 3, C(3)−CH_3]
4c	7.1 (d, 1, J=8.2 Hz, N−H), 5.7 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 2.6 (s, 3, CH_3−S), 2.6 [s, 3, C(4)−$OCOCH_3$], 1.9 [s, 3, C(3)−CH_3]
5a	7.0 (d, 1, J= 8.2 Hz, N−H), 5.8 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 4.0 (s, 3, CH_3−O), 2.5 [s, 3, C(4)−$OCOCH_3$], 2.4 [cp, 2, C(3)−CH_2−], 1.1 [t, 3, C(3)−CH_2−CH_3]
5b	6.9 (d, 1, J=8.2 Hz, N−H), 5.7 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 2.6 (s, 3, CH_3−S), 2.6 [s, 3, C(4)−$OCOCH_3$], 2.4 [cp, 2, C(3)−CH_2−], 1.1 [t, 3, C(3)−CH_2−CH_3]
5c	6.9 (d, 1, J=8.2 Hz, N−H), 5.8 [st, 1, +D_2O d, J=8.2 Hz, C(1′)−H], 2.5 (s, 3, CH_3−S), 2.5 [s, 3, C(4)−$OCOCH_3$], 2.3 [cp, 2, C(4)−CH_2−], 1.1 [t, 3, C(4)−CH_2−CH_3]

General Procedure for the Synthesis of 5-Glycopyranosylaminopyrano[2,3-d]pyrimidin-2-ones (**3 a–b**, **4 a–b**, *and* **5 a–c**)

1 g of **1 a–c** and the corresponding malonic acid derivative **2 a–c** (double molar amount) were added to 5 ml of acetic anhydride. The mixture was stirred at 100°C for appropiate time until no starting material was detected by TLC (CH_2Cl_2/*Me*OH, 9 : 1) (Table 1). The reaction was concentrated "in vacuo" and a chloroform solution (1 ml) of the above reaction crude was poured into a short chromatographic column which contained 25 g of silica gel. It was eluted with hexane and hexane-$CHCl_3$ (increasing amount of $CHCl_3$). The fraction containing the desired products were pooled, evaporated and crystallized from the appropiate solvent (Table 1). For ^{1}H-NMR see Table 2.

4-Acetoxy-7-methoxy-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrano[2,3-d]pyrimidin-2-one (**3 a**)

$[\alpha]_D^{20} = -73.5°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 222 (11 900), 282 (12 100), 292 (12 400), 357 (15 300), 372 (sh). IR (cm^{-1}): 3 380 w, 3 080 w, 1 785 s, 1 765 s, 1 745 s, 1 630 s, 1 610 s, 1 580 m, 1 550 m. ^{13}C-NMR ($CDCl_3$) δ ppm: 170.4, 169.8, 169.3, 167.4, 167.1, 166.5, 163.9, 161.1, 160.7, 156.6, 103.1, 86.8, 79.3, 73.6, 72.6, 70.6, 68.2, 61.6, 55.8, 20.7, 20.5. Mass spectra *m/z* (%): 580 (M^+-1) (6), 428 (33), 414 (52), 386 (41), 385 (32), 372 (91), 305 (100), 301 (40), 168 (43).

4-Acetoxy-7-methylthio-5-(2,3,4-tri-O-acetyl-β-D-xylopyranosylamino)pyrano[2,3-d]pyrimidin-2-one (**3 b**)

$[\alpha]_D^{20} = -87.6°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 222 (11 900), 265 (12 600), 276 (sh), 359 (sh), 371 (13 600), 382 (sh). IR (cm^{-1}): 3 400 w, 3 095 w, 1 795 s, 1 755 s, 1 630 w, 1 600 s, 1 550 s.

4-Acetoxy-7-methylthio-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**3 c**)

$[\alpha]_D^{20} = -76°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 223 (12 000), 269 (13 100), 281 (13 600), 371 (17 700), 387 (sh). IR (cm^{-1}): 3 370 w, 3 080 w, 1 790 s, 1 770 s, 1 750 s, 1 630 m, 1 590 s, 1 565 s, 1 545 s.

4-Acetoxy-3-methyl-7-methoxy-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**4 a**)

$[\alpha]_D^{20} = -33.6°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 213 (11 300), 235 (sh), 287 (sh), 314 (14 500). IR (cm^{-1}): 3 420 w, 1 790 m, 1 750 s, 1 630 m, 1 595 s, 1 570 s. ^{13}C-NMR ($CDCl_3$) δ ppm: 171.1, 170.4, 169.7, 165.7, 165.6, 165.2, 164.7, 160.6, 159.7, 153.8, 112.3, 90.1, 79.3, 73.5, 72.6, 70.6, 68.4, 61.8, 55.3, 21.1, 20.5, 11.2. Mass spectra *m/z* (%): 595 (M^+) (1), 553 (31); 248 (23), 234 (35), 224 (56), 195 (49), 169 (100), 109 (53).

4-Acetoxy-3-methyl-7-methylthio-5-(2,3,4-tri-O-acetyl-β-D-xylopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**4 b**)

$[\alpha]_D^{20} = -35°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 212 (9 100), 231 (8 600), 258 (14 600), 329 (17 500). IR (cm^{-1}): 3 400 w, 1 795 m, 1 765 s, 1 740 s, 1 630 m, 1 585 s, 1 555 s.

4-Acetoxy-3-methyl-7-methylthio-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**4 c**)

$[\alpha]_D^{20} = -38.6°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 212 (8 900), 232 (sh), 258 (14 700), 330 (17 800). IR (cm^{-1}): 3 420 w, 1 790 m, 1 750 s, 1 630 m, 1 585 s, 1 550 s.

4-Acetoxy-3-ethyl-7-methoxy-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**5a**)

$[\alpha]_D^{20} = -40°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 213 (11 600), 232 (sh), 285 (sh), 317 (17 600). IR (cm^{-1}): 3 440 w, 1 790 m, 1 770 s, 1 745 s, 1 630 m, 1 590 s, 1 560 s. ^{13}C-NMR δ ppm: 171.1, 170.4, 169.7, 169.6, 166.4, 165.7, 164.5, 160.1, 159.7, 153.5, 117.8, 90.2, 79.1, 73.4, 72.6, 70.5, 68.2, 61.7, 55.3, 21.1, 20.6, 20.5, 19.2, 11.4. Mass spectra *m/z* (%): 690 (M^+) (0.4), 169 (31), 109 (20), 43 (100).

4-Acetoxy-3-ethyl-7-methylthio-5-(2,3,4-tri-O-acetyl-β-D-xylopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**5b**)

$[\alpha]_D^{20} = -20.6°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 211 (9 700), 233 (sh), 260 (16 700), 331 (21 200). IR (cm^{-1}): 3 380 w, 1 790 m, 1 760 s, 1 745 s, 1 630 m, 1 585 s, 1 555 s.

4-Acetoxy-3-ethyl-7-methylthio-5-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamino)pyrano[2,3-d]-pyrimidin-2-one (**5c**)

$[\alpha]_D^{20} = -46.9°$ ($c = 1$, $CHCl_3$). UV (*Me*OH) λ_{max} nm (ε): 212 (9 900), 233 (sh), 260 (17 300), 331 (22 300). IR (cm^{-1}): 3 420 w, 1 795 m, 1 760 s, 1 740 s, 1 630 m, 1 585 s, 1 555 s.

Acknowledgment

The authors thanks the "Consejeria de Educación y Ciencia, Junta de Analucía" for the award of a fellowship of the "Plan de Formación del Personal Investigador" to two of them (L. Quijano and M. Melguizo).

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Received March 2, 1989. Accepted March 31, 1989