AMINOPYRIMIDINES AND DERIVATIVES.XVIII[1]. REACTIONS OF 1,6-DIHYDRO-4- β -D-(2',3',4',6'-TETRA-O-ACETYL)GLUCOPYRANOSYLAMINO-2-METHYLTHIO-6-OXOPYRIMIDINE WITH ELECTROPHILES

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Abstract - Reactions of 1,6-dihydro-4- β -D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthio-6-oxopyrimidine with electrophiles may take place on four positions: N_1-H, N_3-H, C_6-OH and/or C_5-H. Acidic media induce electrophilic substitution on C_5 and basic media on C_6-OH. Neither N_1 nor N_3 are substituted under the above mentioned conditions.

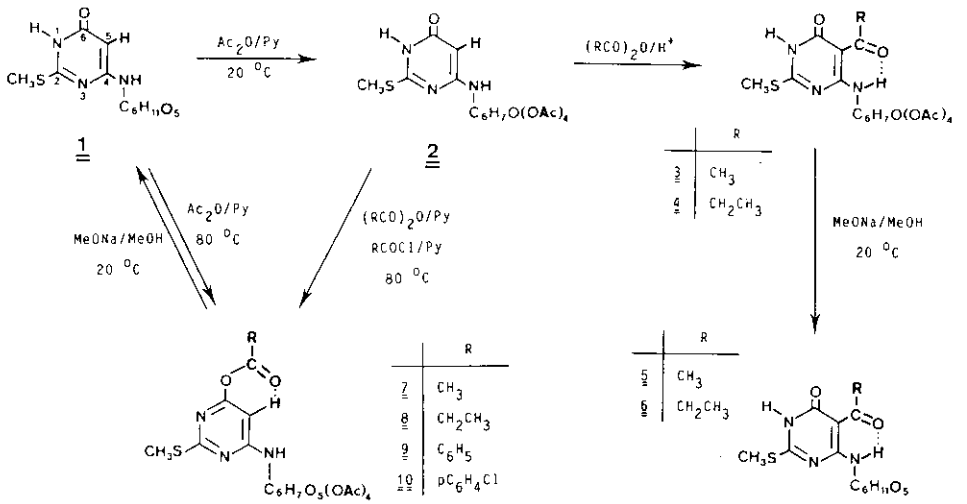
Studies on reactivity and synthetic applications of several 4-glycosylaminppyrimidines[2,3,4,5,6] have been carried out. Our interest is focused on the preparation of derivatives with potential biological activity. One of the aims consists of the functionalization with different reagents of the position C_5 of the ring[7]. We report herein the results of the reactions of 1,6-dihydro-4- β -D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthio-6-oxopyrimidine 2 with electrophiles in both acidic and basic media.

Product 2 has been obtained from 1,6-dihydro-4- β -D-glucopyranosylamino-2-methylthio-6-oxopyrimidine 1 by the method reported by Melgarejo and co-workers[6]. Reaction of 2 with acetic anhydride and propionic anhydride, using perchloric acid as a catalyst, under reflux for 1 h, yielded 5-acetyl-1,6-dihydro-4- β -D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthio-6-oxopyrimidine 3, and 1,6-dihydro-4- β -D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthio-5-propionil-6-oxopyrimidine 4, respectively.

De-O-acetylation of 3 and 4 with molar amounts of sodium methoxide in methanol at 25°C, produced 5-acetyl-4- β -D-glucopyranosylamino-2-methylthio-6-oxopyrimidine 5, and 1,6-dihydro-4- β -D-glucopyranosylamino-2-methylthio-5-propionyl-6-oxopyrimidine 6, respectively.

Reaction of 2 with acetic anhydride, propionic anhydride, benzoyl chloride and p-chlorobenzoyl chloride in pyridine at 80° C for 1~ 3 h yielded 6-O-acetyl-4-β -D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthiopyrimidine 7, 4-β -

SCHEME 1



D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthio-6-O-propionylpyrimidine 8, 6-O-benzoyl-4-β -D-(2',3',4',6'-tetra-O-acetyl)glucopyranosylamino-2-methylthiopyrimidine 9 and 6-O-(p-chlorobenzoyl)-4- β -D-(2',3',4',6'-tetra-O-acetyl) glucopyranosylamino-2-methylthiopyrimidine 10, respectively. De-O-acylation of 7 and 8 with molar amounts of sodium methoxide in methanol at 25° C, yielded 1,6-dihydro-4- β -D-glucopyranosylamino-2-methylthio-6-oxopyrimidine 1.

TABLE I

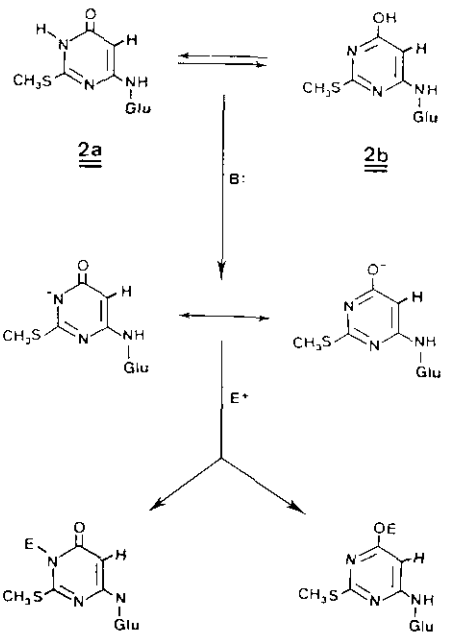
COMPOUND	Mp °C	YIELD %	MOLECULAR FORMULA[a]	$[\alpha]_D^{25}$ c 1, $CHCl_3$
3	238	50	$C_{21}H_{27}N_3O_{11}S$	-10.2°
4	255	45	$C_{22}H_{29}N_3O_{11}S$	- 6.5°
5	298	77	$C_{13}H_{19}N_3O_7S$	-52.2° [b]
6	278	49	$C_{14}H_{21}N_3O_7S$	+18.5° [c]
7	155	78	$C_{21}H_{27}N_3O_{11}S$	-18.9°
8	174	70	$C_{22}H_{29}N_3O_{11}S$	-19.5°
9	171-172	42	$C_{26}H_{30}N_3O_{11}S$	-17.4°
10	170	50	$C_{26}H_{29}ClN_3O_{11}S$	-19.1°

a) Calculated by elemental analysis and mass spectrometry

b) c 1, H_2O : c) c 1, DMS

Two tautomeric forms of 2, 2a and 2b, are posible (Scheme 2). In acidic media 2b predominates, and the electrophilic attack must therefore take place on the typically aromatic position C_5.

SCHEME 2



Basic media induce the abstraction of the N_1-H proton, and an anion (whose charge is delocalized between N_1 and C_6-O) is formed. The nitrogen atom at position 1, as well as the oxygen at C_6 are then susceptible of electrophilic attack. Reactions of this types are seldom found in bibliography[8].

The structures shown in scheme 1 for 7, 8 and 10 are proposed on the basis of the following considerations:

a) The IR spectra of 3, 4, 5 and 6 show different stretching bands for C=O, C=N and C=C. However, those of 7, 8, 9 and 10, show only one band of stretching for C=N and C=C about 1600 cm^{-1}, indicating the disappearance of the 6-oxo group, and the total aromatization of the pyrimidine ring.

The spectra of 3, 4, 5 and 6 show a broad stretching band of N-H at 3100 - 3200 cm^{-1}, owing to the association by intramolecular hydrogen bond, as indicated in scheme 1. For 7, 8, 9 and 10, a broad band about 3400 Cm^{-1}, corresponding to the non-associated C_4-N-H, is observed instead.

T A B L E II

IR SPECTRA (KBr, absortion bands in cm^{-1})

COMPOUND	νN-H	νC_6=O	νC_5-C=O	νC=C	νC=N
3	3100[a]	1670		1580	
		1640		1560	
4	3150[a]	1660		1555[a]	
		1620			
5	3200[a]	1690		1600	
		1630		1560	
6	3300[a]	1670		1550[a]	
		1610			
7	3380[b]	1780		1590	
		1750[a,c]			
8	3385[b]	1765		1575	
		1745[a,c]			
9	3400[b]	1775[a,d]		1600	
10	3400[b]	1755[a,d]		1600	

a) broad; b) sharp; c) C=O, acetate, sugar;

d) C_6-O-CO-R and sugar acetate

T A B L E III

^{1}H-NMR (δ ppm)

COMPOUND	R	SOLVENT	CH_3- S	C_6-OCOR	C_5-COR	C_1' - H	C_5-H	C_4-NH	N_1-H
2	CH_3	Cl_3CD	2.6 s	-	-	5.4 m	5.3 s	5.7 d	9.5 s broad
		DMS-d_6+D_2O				5.4 d			
3	CH_3	Cl_3CD	2.5 s	-	2.6 s	5.6 m	-	11.3 d	12.6 s broad
		DMS-d_6+D_2O				5.6 d			
4	CH_2CH_3	Cl_3CD	2.6 s	-	1.2 t 3.2 cp	5.5 m	-	11.4 d	12.0 s broad
		Cl_3CD+D_2O				5.5 d			
5	CH_3	DMS-d_6	2.5 s	-	2.5 s	5.2 m	-	11.0 d	12.0 s broad
		DMS-d_6+D_2O				5.2 d			
6	CH_2CH_3	DMS-d_6	2.5 s	-	1.0 t 3.2 cp	5.3 m	-	11.1 d	14.4 s broad
		DMS-d_6+D_2O				5.3 d			
7	CH_3	Cl_3CD	2.5 s	2.3 s	-	5.5 m	6.0 s	6.3 d	-
		DMS-d_6+D_2O				5.7 d			
		Cl_3CD+Eu(THD)$_3$*					5.4 s		
8	CH_2CH_3	Cl_3CD	2.5 s	1.3 t 2.6 cp	-	5.5 m	6.0 s	5.9 d	-
		DMS-d_6+D_2O				5.9 d			
9	C_6H_5	Cl_3CD	2.5 s	7.6-8.2	-	5.5 m	6.1 s	5.9 d	-
		DMS-d_6+D_2O				5.8 d			
10	pC_6H_4Cl	Cl_3CD	2.5 s	7.4-8.3 dd	-	5.5 m	6.1 s	5.9 d	-
		DMS-d_6+D_2O				5.8 d			

d: doublet J= 8.2 Hz; cp: quadruplet; t: triplet; dd: double doublet

* molar amount

b) The ^{1}H-NMR of 2 show a signal of C_5-H at 5.3 ppm. In the ^{1}H-NMR of 7, 8, 9 and 10, the signal of this proton is shifted 0.6 ppm downfield (δ 6.1 ppm), because of the hydrogen bond indicated in scheme 1. The addition of a molar amount of $Eu(thd)_3$ to the $CDCl_3$ solution of 7 and 8, shifted the signal in question 0.6 ppm upfield, as a result of the breaking of the hydrogen bond, and the subsequent formation of an Eu^{3+} chelate, wich involves the carbonyl of the $C_6O\underline{C}O\underline{C}H_3$ group and the N_1-H. Signals of C_4N-H in 7, 8, 9 and 10, appear between 5.9 and 6.3 ppm each as a doublet (J= 8.2 Hz). In 3, 4, 5 and 6 these signals are observed at 11 ppm (doublet, J=8.2 Hz), due to the hydrogen bond indicated in scheme 1.

c) In ^{13}C-NMR, the presence of an acetyl group on C_5 in 3, shifts the signal of that carbon 11 ppm in relation to the signal of the equivalent carbon in 2. In 7, the signal is shifted only 5.5 ppm. C_6 in 2, 3 and 7 appears at 166.1, 165.4 and 167.6 ppm respectively. The values of these chemical shifts agree with those found in bibliography[9] for structures similar to those proposed by us.

TABLE IV

^{13}C-NMR (δ ppm) (in $CDCl_3$)

COMPOUND	$\underline{C}H_3S$	$OC\underline{O}CH_3$	$C_5C\underline{O}CH_3$	$C_6OC\underline{O}CH_3$	C_6'	C_2'	C_3'	C_4'	C_5'	C_1'	C_5	C_4	C_2	C_6	$\underline{C}OCH_3$	$C_5\underline{C}OCH_3$	$C_6\underline{C}OCH_3$
2	13.2	20.6	-	-	62.1		68.8			81.4	85.3	161.4	162.5	166.1	169.5	-	-
		20.7					70.8								170.0		
							73.0								170.7		
							73.4								170.9		
3	13.2	20.5	32.6	-	62.2		68.7			79.8	96.7	162.9	164.4	165.4	169.3	199.6	-
							70.4								169.4		
							73.2								170.1		
							73.8								170.5		
7	14.1	20.5	-	21.3	62.1		68.7			80.5	91.2	163.4	164.5	167.6	169.5	-	172.6
		20.6					70.8								169.9		
							73.0								170.5		
							73.4								171.0		

EXPERIMENTAL

Melting points were determined in a Melting Point Apparatus Gallemkamp and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra have been made in the following spectrometers: Hitachi Perkin-Elmer R-600 and Bruker WP.80-SY. TMS was used as internal standard. Infrared spectra were recorded with a spectrophotometer IR-Beckman 4250. Elemental analyses was performed in a Mycroanalysis apparatus Carlo Erba mod. 1106. Values of specific rotation were determined in a Polarimeter Perkin-Elmer 141. Mass spectra were recorded in a mass spectrometer Hewlett-Packard mod. 5930 at 70 ev.

General method of acylation in acid medium.

To a mixture of 1.25 moles of acylating agent and 5 drops of perchloric acid, left at room temperature for 10 min, 0.01 moles of 2 were added. The suspension was refluxed for 1 h until all the solid dissolved. The solvents were evaporated at reduced pressure. Traces of solvents were removed by dissolving in ethanol and evaporating several times. The final product was crystallized from ethanol. Compounds 3 and 4 were obtained from 2 using acetic and propionic anhydrides respectively. Yields and physical data are shown in the tables.

Acylations in basic medium.

a) Acylation with acetic and propionic anhydrides: To a mixture of 10 ml of pyridine and 0.2 moles of acylating agent heated at 80°C, 1 g (2.05 mmoles) of 2 was added. The temperature was kept at 80 °C for 1 h when using acetic anhydride, and 3 h when using propionic anhydride. The reaction mixture was then evaporated to dryness at reduced pressure. The residue was extracted with chloroform, and the solution was washed with aqueous HCl, then with aqueous $NaCO_3H$, and finally with H_2O. The organic solution was dried with Na_2SO_4. After evaporating chloroform, the residue was crystallized from EtOH. Compounds 7 and 8 were obtained. Yields and physical data are given in the tables.

b) Acylation with benzoyl and p-chlorobenzoyl chlorides: To a mixture of 10 ml of pyridine and 3 mmoles of acyl chloride heated at 80 C, 1 g (2.05 mmoles) of 2 was added. The temperature was kept at 80 °C for 1 h when using benzoyl chloride, and 3 h when using p-chlorobenzoyl chloride. In both cases the reaction mixtures were worked up as in a). Compounds 9 and 10 were obtained. Yields and physical data are given in the tables.

General method of de-O-acylation.

To a solution of 2 mmoles of sodium methoxide in 75 ml of methanol, 2 mmoles of O-acylated product (3, 4, 7 and 8), were added. The mixture was stirred 3 h at room temperature, and the resulting solution was evaporated to dryness at reduced pressure. The final residue was dissolved in hot water, and neutralized with Amberlite IR-120 (H^+). The filtrate was concentrated at reduced pressure, and crystallized from ethanol. Compounds 3 and 4 afforded 5 and 6, respectively. The yields and physical data are given in the tables. Compounds 7 and 8, afforded 1.

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