REACTION OF 6-GLYCOSYLAMINOPYRIMIDIN-4-ONES WITH DIETHYL ETHOXYMETHYLENE-MALONATE IN ACIDIC MEDIUM.

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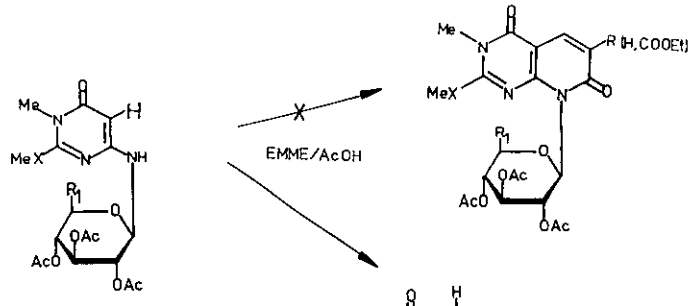
Abstract - Starting from the already known 6-glycopyranosylaminopyrimidin-4-ones, some novel (E)-5-(2-carbethoxyvinyl) derivatives have been synthesized by the reaction with diethyl ethoxymethylenemalonate (EMME) in acetic acid.

The reaction of 4-aminopyrimidines with diethyl ethoxymethylenemalonate (EMME) is one of the procedures employed in the synthesis of pyrido[2,3-d]pyrimidines[1-2] . Certain compounds containing this ring systems have shown antibacterial[3] and anticonvulsive[4] activities.

In the reaction of the 6-glycosylaminopyrimidines **1** - **4** with EMME in glacial acetic acid we have not found 8-glycosylpyrido[2,3-d]pyrimidines and instead isolated the corresponding (E)-5-(2-carbethoxyvinyl) derivatives, homologues of the (E)-5-vinyl uracils so interesting in the treatment of viral infections[5].



1-4

	R_1	X	
1	H	O	5
2	CH_2OAc	O	6
3	H	S	7
4	CH_2OAc	S	8

5-8

The treatment of **1** - **4**[6] with an excess of EMME (1:5) in refluxing acetic acid, only yielded the following identifiable products: (E)-5-(2-carbethoxyvinyl)-2-methoxy-3-methyl-6-β-D-(2,3,4-tri-O-acetyl)xylopyranosylaminopyrimidin-4(3H)-one **5**; (E)-5-(2-carbethoxyvinyl)-2-methoxy-3-methyl-6-β-

Table 1.

Comp.	Reaction time (h)	Yield %	Mp (°C) (solvent)	Molecular Formula*
5	24	18	228-230 Et_2O	$C_{22}H_{29}N_3O_{11}$
6	10	12	180-182 Et_2O	$C_{25}H_{33}N_3O_{13}$
7	24	25	240 EtOH	$C_{22}H_{29}N_3O_{10}S$
8	24	22	169-170 EtOH	$C_{25}H_{33}N_3O_{12}S$

* Satisfactory elemental analyses (C, H, N) and ms data were obtained for all the newly synthesized compounds.

Table 2. ^{1}H-Nmr data of compounds 5 - 8

Comp.	N(3)Me	X-Me	-NH-[a]	C(1')-H	-CH=CH-	-CH=CH-
5	3.3 s	3.9 s	6.4 d J=8.8 Hz	5.4 m	7.3 d ---J=15.4 Hz---	6.8 d
6	3.3 s	4.0 s	6.2 d J=8.8 Hz	5.5 m	7.4 d ---J=16.4 Hz---	6.9 d
7	3.4 s	2.5 s	6.6 d J=8.5 Hz	5.5 m	7.4 d ---J=15.0 Hz---	6.9 d
8	3.4 s	2.6 s	6.3 d J=8.5 Hz	5.5 m	7.5 d ---J=16.0 Hz---	6.9 d

$CDCl_3$, δ (ppm) a) exchangeable

Table 3. Ir and uv data of the compounds 5 - 8

Comp.	IR (KBr, cm^{-1})				UV	
	ν_{N-H}	$\nu_{C=O}$	$\nu_{C=O}$	$\nu_{C=C}$	c M (MeOH)	λ_{max} (nm) (ε)
5	3430	1705	1740	1610	$5x10^{-5}$	229 (13700) 275 (5300) 329 (10400)
6	3440	1700	1750	1610	$6x10^{-5}$	220 (16300) 270 (8240) 324 (7600)
7	3420	1720	1740	1600	$5.8x10^{-5}$	238 (22200) 344 (7600)
8	3400	1705	1750	1640	$5x10^{-5}$	234 (16600) 337 (7900)

D-(2,3,4,6-tetra-O-acetyl)glucopyranosylaminopyrimidin-4(3H)-one 6; (E)-5-(2-carbethoxyvinyl)-3-methyl-2-methylthio-6-β-D-(2,3,4-tri-O-acetyl)xylopyranosylaminopyrimidin-4(3H)-one 7 and (E)-5-(2-carbethoxyvinyl)-3-methyl-2-methylthio-6- β-D-(2,3,4,6-tetra-O-acetyl)glucopyranosylaminopyrimidin-4(3H)-one 8.

The configuration of the 5-carbethoxyvinyl groups has been established by the chemical displacement of the vinylic protons as well as the values of their coupling constants.

The formation of the compounds **5** - **8** is due to an vinylation at C-5 atom of the pyrimidine ring, favoured by the reaction conditions and the higher nucleophilic character of this position in contrast to the other nucleophilic centre of the molecule, C(6)-NH-Gly. The reason for this would be the glycosidic rest takes electronic charge because of its -I effect. The low nucleophilic character of the amino group in C(6) would be the cause by which the cyclization to pyrido[2,3-d] pyrimidine did not occur.

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 AM 300. TMS was used as internal standard. Infrared spectra were recorded with a spectrophotometer ir-Beckman 4250. Ultraviolet (uv) spectra were taken on a Perkin-Elmer lambda 5. Column chromatography was done on Kieselgel 60 silica gel (70-230 mesh) using the solvent systems indicated in each case.

General method of the synthesis of(E)-5-(2-carbethoxyvinyl) derivatives **5** - **8**

To a solution of 1 g of 6-glycosylaminopyrimidine **1** - **4** in 1.5 ml of acetic acid excess EMME (1:5 moles) was added. The mixture was refluxed and stirred for an appropriate time (Table 1). After cooling, the reaction mixture was diluted with 20 ml of $CHCl_3$ and washed with a saturated aqueous $NaCO_3H$ solution, then with H_2O and finally the organic solution was dried with Na_2SO_4. The solution was concentrated to 1 ml and was applied on a chromatography column using as solvent hexane-ethyl ether (0-40%) mixtures for **5** and **6** and dichloromethane-ethyl ether (0-40%) mixtures for **7** and **8**. Yields and physical data are given in the Tables.

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7. ^{13}C-Nmr data of **5** ($CDCl_3$), δ(ppm): 170.58, 170.24, 169.64, 168.59 (CH_3-C=O, COOEt); 161.16, 158.13, 156.18, 92.36 (C-6, C-2, C-4, C-5); 134.15, 115.99 (-CH=CH-); 81.11, 72.49, 70.45, 69.17, 64.48 (C-1', C-2', C-3', C-4', C-5'); 59.83 ($-CH_2-$); 55.55 (CH_3-O); 27.54 (CH_3-N); 20.73, 20.68 (CH_3CO); 14.44 (CH_3-CH_2-).
   ^{13}C-Nmr data of **6** ($CDCl_3$) δ(ppm): 170.79, 170.62, 170.16, 169.44, 168.57 (CH_3CO, COOEt); 161.29, 157.76, 156.23, 92.50 (C-6, C-2, C-4, C-5); 133.70, 117.02 (-CH=CH-); 80.63, 73.58, 72.85, 70.77, 68.53, 62.00 (C-1', C-2', C-3', C-4', C-5', C-6'); 60.04 ($-CH_2-$); 56.61 (CH_3-O); 27.58 (CH_3-N); 20.76, 20.64 (CH_3CO); 14.24 (CH_3-C_2-).

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