

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

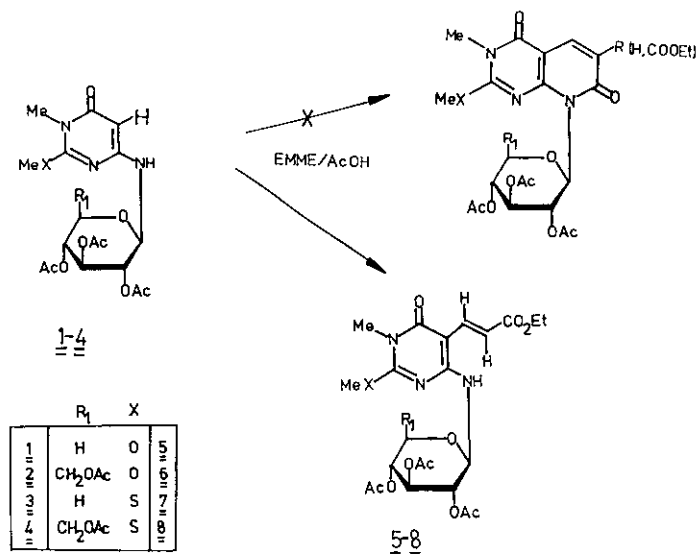
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Abstract - Starting from the already known 6-glycopyranosylaminopyrimidin-4-ones, some novel (E)-5-(2-carbethoxyvinyl) derivatives have been synthesized by the reaction with diethyl ethoxymethylenemalonate (EMME) in acetic acid.

The reaction of 4-aminopyrimidines with diethyl ethoxymethylenemalonate (EMME) is one of the procedures employed in the synthesis of pyrido[2,3-d]pyrimidines¹⁻². Certain compounds containing this ring systems have shown antibacterial³ and anticonvulsive⁴ 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 infections⁵.



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 *
<u>5</u>	24	18	228-230 Et ₂ O	C ₂₂ H ₂₉ N ₃ O ₁₁
<u>6</u>	10	12	180-182 Et ₂ O	C ₂₅ H ₃₃ N ₃ O ₁₃
<u>7</u>	24	25	240 EtOH	C ₂₂ H ₂₉ N ₃ O ₁₀ ^S
<u>8</u>	24	22	169-170 EtOH	C ₂₅ H ₃₃ N ₃ O ₁₂ ^S

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

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

Comp.	N(3)Me	X-Me	-NH- ^a	C(1')-H	-CH=CH-	-CH=CH-
<u>5</u>	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
<u>6</u>	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
<u>7</u>	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
<u>8</u>	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

CDCl₃, δ (ppm) a) exchangeable

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

Comp.	IR (KBr, cm ⁻¹)					UV		
	ν _{N-H}	ν _{C=O}	ν _{C=O}	ν _{C=C}	c M (MeOH)	λ _{max} (nm) (ε)		
<u>5</u>	3430	1705	1740	1610	5x10 ⁻⁵	229 (13700)	275 (5300)	329 (10400)
<u>6</u>	3440	1700	1750	1610	6x10 ⁻⁵	220 (16300)	270 (8240)	324 (7600)
<u>7</u>	3420	1720	1740	1600	5.8x10 ⁻⁵	238 (22200)	344 (7600)	
<u>8</u>	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 Gallekamp and are uncorrected. ^1H -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.

REFERENCES

1. A. D. Broom, J. L. Shim, and G. L. Anderson, *J. Org. Chem.*, **41**, 1095 (1976); G. L. Anderson, *J. Heterocyclic Chem.*, **22**, 1469 (1985); G. L. Anderson and S. G. Richardson, *J. Heterocyclic Chem.*, **22**, 735 (1985).
2. S. Nishigaki, K. Ogiwara, K. Senga, S. Fukazawa, K. Aida, Y. Machida, and F. Yoneda, *Chem. Pharm. Bull.*, **18**, 1385 (1970).
3. N. Suzuki, *Chem. Pharm. Bull.*, **28**, 761 (1980).
4. E. Kretzchmar, *Pharmazie*, **35**, 253 (1980).
5. E. De Clerq and R. T. Walker, *Pharmac. Ther.*, **24**, 1 (1984).
6. R. Asenjo, M. Melgarejo, C. Rodriguez, M. Nogueras, and A. Sánchez, *An. Quím.*, **79C**, 417 (1983).
7. ^{13}C -Nmr data of 5 (CDCl_3), δ (ppm): 170.58, 170.24, 169.64, 168.59 ($\text{CH}_3\text{-C=O}$, COOEt); 161.16, 158.13, 156.18, 92.36 (C-6 , C-2 , C-4 , C-5); 134.15, 115.99 ($-\text{CH=CH}-$); 81.11, 72.49, 70.45, 69.17, 64.48 (C-1' , C-2' , C-3' , C-4' , C-5'); 59.83 ($-\text{CH}_2-$); 55.55 ($\text{CH}_3\text{-O}$); 27.54 ($\text{CH}_3\text{-N}$); 20.73, 20.68 (CH_3CO); 14.44 ($\text{CH}_3\text{-CH}_2-$).
 ^{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 ($-\text{CH=CH}-$); 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 ($-\text{CH}_2-$); 56.61 ($\text{CH}_3\text{-O}$); 27.58 ($\text{CH}_3\text{-N}$); 20.76, 20.64 (CH_3CO); 14.24 ($\text{CH}_3\text{-C}_2-$).

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