AMINOPYRIMIDINES AND DERIVATIVES. XVI[1]. SYNTHESIS OF 7-GLYCOSYL-AMINO-OXAZOLO(5,4-d)PYRIMIDINES[2]

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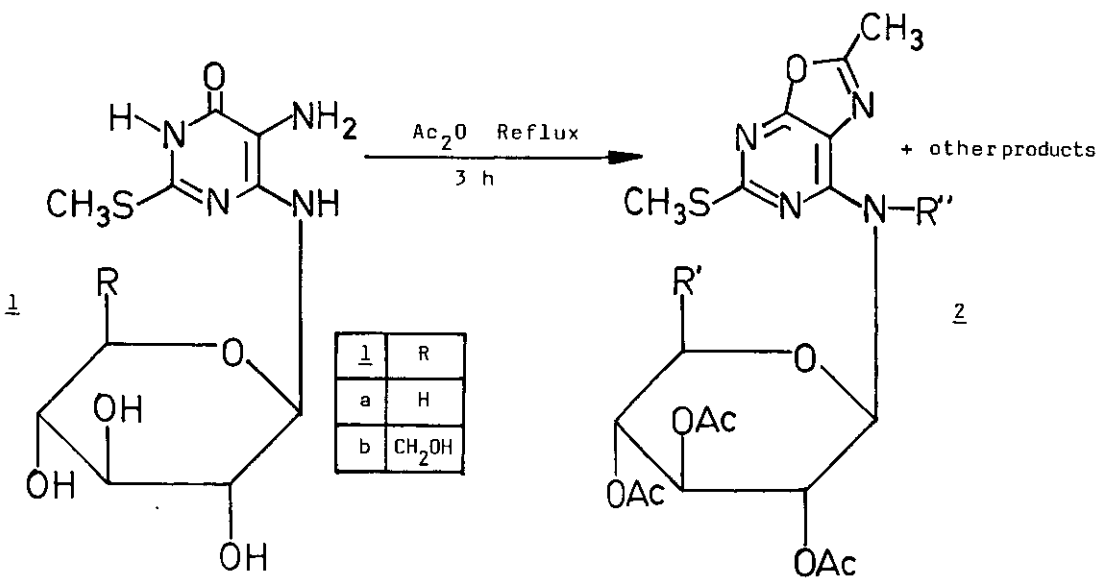
Abstracts - Treatment of 5-amino-4-glycosylamino-6-oxo-pyrimidines 1 with acetic anhydride under reflux has led to 2-methyl-7-glycosylamino-oxazolo (5,4-d)pyrimidines 2.

5-Amino-4-glycosylamino-pyrimidines 1[3] are versatile starting materials for the synthesis of glycosides of various condensed heterocycles. Thus, glycosyl purines[4], glycosyl triazolopyrimidines[5] and glycosyl pteridines[6] have been synthesized from them. We report herein its utility for the synthesis of 7-glycosylamino-oxazolo(5, 4-d)pyrimidines 2, as shown in the Scheme .

SCHEME



2	R'	R''	Yield %	$M^{+\cdot}$	
				Calculated	Found
a	H	H	14	454.11578 $C_{18}H_{22}N_4O_8S$	454.1159
b	H	Ac	20	496.1263 $C_{20}H_{24}N_4O_9S$	496.1262
c	CH_2OAc	H	10	526.1369 $C_{21}H_{26}N_4O_{10}S$	526.1364
d	CH_2OAc	Ac	30	568.14746 $C_{23}H_{28}N_4O_{11}S$	568.1472

Oxazolo(5,4-d)pyrimidines have usually been synthesized by two general methods: by cyclization of 4,5-disubstituted oxazoles[7], or, more often from either 5-amino-6-hydroxypyrimidines[8], or 5-acylamino-6-hydroxypyrimidines[8a-c,9], or 5-imino-6-hydroxypyrimidines[10] by cyclization with either $POCl_3$[8a-b,9] or PhCOCl[8c-d], or $SOCl_2$[10a,10c] or NBS[10b]. The presence on C-4 of the pyrimidine ring of an amino group seems to orientate preferentially the cyclization with $POCl_3$ towards the purine, yielding neverthless a small amount of oxazolopyrimidine[9b]. On the other hand, the action of acid anhydrides on 5-amino-6-hydroxypyrimidines has been reported to produce the N-acylamino derivative[8a-b]. No oxazolopyrimidines have been observed in these reactions, except by Patil et al.[8e]. These authors have obtained an oxazolopyrimidine by mixing $(EtCO)_2O$ with 4,6-dihydroxy-5-aminopyrimidine (HCl salt).

In our case, the action of Ac_2O under reflux on diaminopyrimidines 1 has led to the formation of a significant amount of oxazolopyrimidines 2 and several acetylated products. The reactions have been carried out suspending 1 in Ac_2O and heating and keeping under reflux for 3 h. Ac_2O was completely removed by adding methanol andevaporating several times. The resulting solid was fractionated by column cromatography on silicagel, eluting with mixture of EtOAc/EtOH/hexane (2:1:7). The first fraction which was eluted from the reaction mixture obtained from 5-amino-2-methylthio-4-β-D-xylopyranosylamino-6-oxo-pyrimidine (1a)[3] corresponds to 2-methyl-5-methylthio-7-(2',3',4'-tri-O-acetyl-β-D-xylopyranosylamino)-oxazolo(5,4-d)pyrimidine (2a), the second one corresponding to 7-acetamido-2-methyl-5-methylthio-7-N-(2',3',4'-tri-O-acetyl-β-D-xylopyranosyl)-oxazolo(5,4-d)pyrimidine (2b).

Similarly from 5-amino-2-methylthio-4-β-D-glucopyranosylamino-6-oxo-pyrimidine (1b)[3], the first fraction corresponds to 2-methyl-5-methylthio-7-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosylamino)-oxazolo(5,4-d)pyrimidine (2c), and the second to 7-acetamido-2-methyl-5-methylthio-7-N-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-oxazolo(5,4-d)pyrimidine (2d). Next fractions correspond to diverse acetylated products, but no purines have been detected.

When Ac_2O has been removed by pouring the solution over $NaHCO_3$-ice (and subsequent extraction with $CHCl_3$ several non-glycosidic products, like 7-acetamido-2-methyl-5-methylthio-oxazolo(5,4-d)pyrimidine, have been observed in the mixture, thus indicating that an acetolysis of the glycosidic bond has taken place in some extent. The structural and configurational assignment of 2 has been made on the basis of high resolution mass spectrometry (exact mass measurement) and ^{1}H-nmr data shown in the Scheme and the Table, respectively.

TABLE

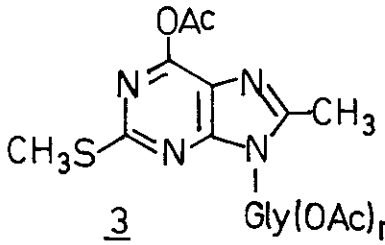
^{1}H-NMR Data of Compounds 2

	Me-2	Me-5	HN-7	Ac-N-7	Sugar protons						
					H-1'	H-2'	H-3'	H-4'	H-5'		H-6'
2a	2.55 s	2.55 s	6.20 d 9Hz	--	5.75 pt	5.25 pq	5.00 m	5.00 m	4.10 pq	5'e	--
									3.52 pt	5'a	
2b	2.66 s	2.71 s	--	2.14	5.90 d 9Hz	5.24 m	5.24 m	4.98 m	4.20 pq	5'e	--
									3.50 pt	5'a	
2c	2.60 s	2.62 s	6.30 d 9Hz	--	5.80 pt	5.14 pq	5.45 pt	5.14 pq	3.97 wide		4.29 pq 4.12 pd
2d	2.67 s	2.67 s	--	2.16	6.05 d 9Hz	5.05--5.35 m	5.05--5.35 m	5.05--5.35 m	3.80--4.00 m		4.15--4.30 m

a = axial; d = doublet; e = equatorial; m = multiplet; s = singlet; pq = pseudo-quadruplet; pt = pseudo-triplet.

The observed coupling in the ^{1}H-nmr spectra of 2a and 2c between the anomeric proton (as a pseudo-triplet) and another proton at lower field (exchangeable by D, therefore corresponding to H-N-C_7) excludes the possibility of the isomeric purines of the formulated oxazolopyrimidines.

As for 2b and 2d, structures 3 could also account for both mass and nmr data.



3

Addition of the nmr shift reagent Eu(DPM)$_3$ has shifted approximately 0.3 ppm downfield one of the -C(O)-C<u>H</u>$_3$ signals, the rest of the acetyl signals remaining almost unchanged. The doublet corresponding to the anomeric proton suffers a similar shift of about 0.5 ppm downfield, strongly suggesting its vicinity to the site of complexation of the Eu chelate. For N- and O-acetylated polyfunctional molecules, the preferential site of complexation has been reported to be the N-Ac rather than O-Ac[11]. The formerly mentioned results allow therefore to reject structures 3. As an additional proof, de-acetylation with NaOMe has been performed on 2b and 2d. Protons corresponding to H-N-C_7 (doublets, exchangeable by D) have been observed in the respective ^{1}H-nmr spectra.

The β-pyranosyl configurations of the sugar moieties have been assigned according to the values of the coupling constants of the anomeric protons ($J_{1,2}$ = 9 Hz in all cases). For 2a and 2c the respective pseudo-triplets became doublets when H-N-C_7 was exchanged by D.

Finally, experiments of double resonance on the 400 MHz ^{1}H-nmr spectra of 2b and 2c have allowed the assignment of the rest of the sugar protons.

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