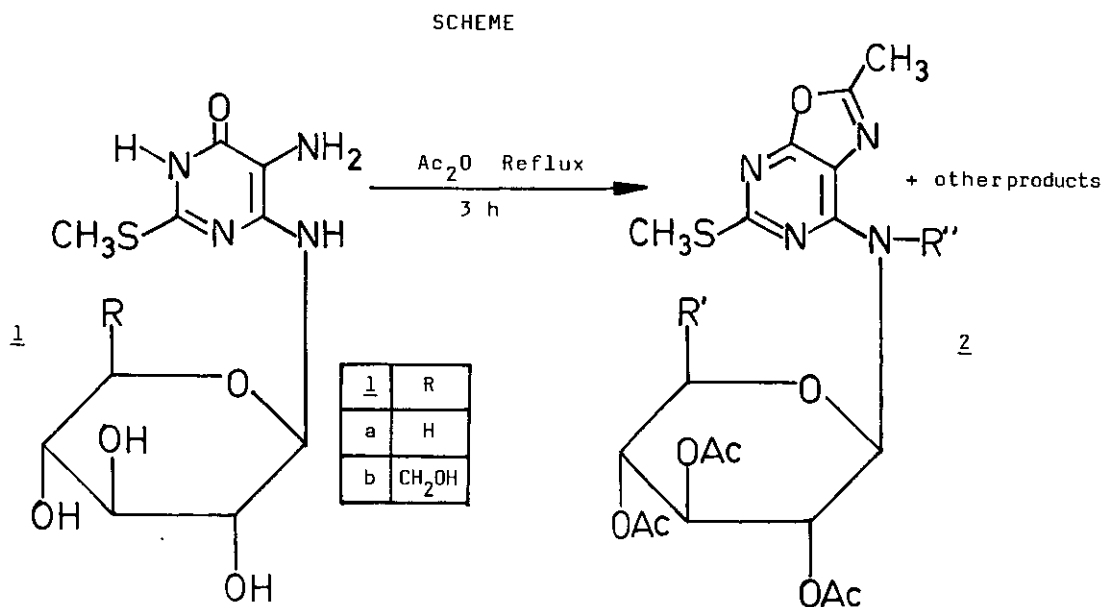


AMINOPYRIMIDINES AND DERIVATIVES. XVI<sup>1</sup>. SYNTHESIS OF 7-GLYCOSYL-AMINO-  
OXAZOLO(5,4-d)PYRIMIDINES<sup>2</sup>

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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<sup>3</sup> are versatile starting materials for the synthesis of glycosides of various condensed heterocycles. Thus, glycosyl purines<sup>4</sup>, glycosyl triazolopyrimidines<sup>5</sup> and glycosyl pteridines<sup>6</sup> 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 .



| <u>2</u> | R'                  | R'' | Yield<br>% | M <sup>+</sup>  |          |
|----------|---------------------|-----|------------|---|----------|
|          |                     |     |            | Calculated  | Found    |
| a        | H                   | H   | 14         | 454.11578<br>C <sub>18</sub> H <sub>22</sub> N <sub>4</sub> O <sub>8</sub> S  | 454.1159 |
| b        | H                   | Ac  | 20         | 496.1263<br>C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> O <sub>9</sub> S   | 496.1262 |
| c        | CH <sub>2</sub> OAc | H   | 10         | 526.1369<br>C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> O <sub>10</sub> S  | 526.1364 |
| d        | CH <sub>2</sub> OAc | Ac  | 30         | 568.14746<br>C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>11</sub> S | 568.1472 |

Oxazolo(5,4-d)pyrimidines have usually been synthesized by two general methods: by cyclization of 4,5-disubstituted oxazoles<sup>7</sup>, or, more often from either 5-amino-6-hydroxypyrimidines<sup>8</sup>, or 5-acylamino-6-hydroxypyrimidines<sup>8a-c,9</sup>, or 5-imino-6-hydroxypyrimidines<sup>10</sup> by cyclization with either POCl<sub>3</sub><sup>8a-b,9</sup> or PhCOCl<sup>8c-d</sup>, or SOCl<sub>2</sub><sup>10a,10c</sup> or NBS<sup>10b</sup>. The presence on C-4 of the pyrimidine ring of an amino group seems to orientate preferentially the cyclization with POCl<sub>3</sub> towards the purine, yielding nevertheless a small amount of oxazolopyrimidine<sup>9b</sup>. On the other hand, the action of acid anhydrides on 5-amino-6-hydroxypyrimidines has been reported to produce the N-acylamino derivative<sup>8a-b</sup>. No oxazolopyrimidines have been observed in these reactions, except by Patil et al.<sup>8e</sup>. These authors have obtained an oxazolopyrimidine by mixing (EtCO)<sub>2</sub>O with 4,6-dihydroxy-5-aminopyrimidine (HCl salt).

In our case, the action of Ac<sub>2</sub>O 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<sub>2</sub>O and heating and keeping under reflux for 3 h. Ac<sub>2</sub>O was completely removed by adding methanol and evaporating several times. The resulting solid was fractionated by column chromatography 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)<sup>3</sup> 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- $\beta$ -D-glucopyranosylamino-6-oxo-pyrimidine (1b)<sup>3</sup>, the first fraction corresponds to 2-methyl-5-methylthio-7-(2;3;4;6-tetra-O-acetyl- $\beta$ -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- $\beta$ -D-glucopyranosyl)-oxazolo(5,4-d)pyrimidine (2d). Next fractions correspond to diverse acetylated products, but no purines have been detected.

When Ac<sub>2</sub>O has been removed by pouring the solution over NaHCO<sub>3</sub>-ice (and subsequent extraction with CHCl<sub>3</sub> 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 <sup>1</sup>H-nmr data shown in the Scheme and the Table, respectively.

TABLE

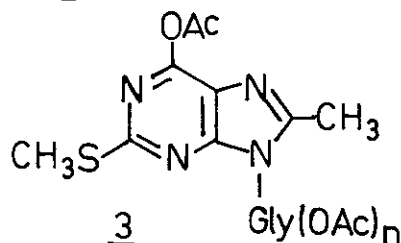
<sup>1</sup>H-NMR Data of Compounds 2

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

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

The observed coupling in the  $^1\text{H}$ -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  $\text{H-N-C}_7$ ) 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.



Addition of the nmr shift reagent  $\text{Eu}(\text{DPM})_3$  has shifted approximately 0.3 ppm downfield one of the  $-\text{C}(\text{O})-\text{CH}_3$  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<sup>11</sup>. 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  $\text{H-N-C}_7$  (doublets, exchangeable by D) have been observed in the respective  $^1\text{H}$ -nmr spectra.

The  $\beta$ -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  $\text{H-N-C}_7$  was exchanged by D.

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

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