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# SYNTHESIS OF NOVEL HETEROCYCLES : OXAZOLO[4,5-b]PYRIDINES AND OXAZOLO[4,5-d]PYRIMIDINES

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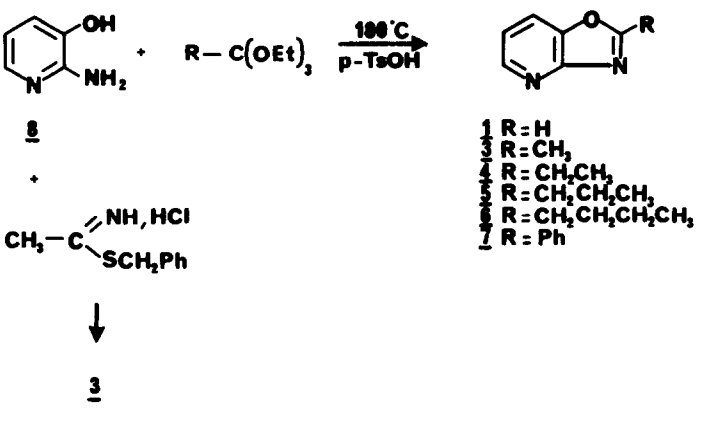
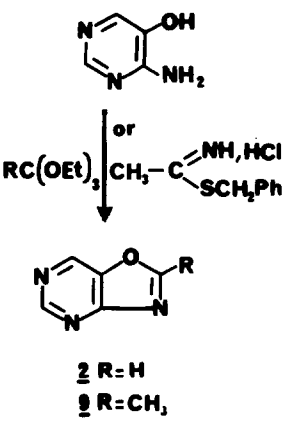
Summary : Novel purine isosters (title compounds) have been prepared by condensation of the appropriate o-hydroxyaminoazine with ethyl orthoformate ; extension to other orthoesters and to benzyl thioacetimidate afford 2-alkyl substituted derivatives of these new fused heterocycles.

We have recently extended the field of our research on new heterocyclic phenols[1-3] to the synthesis of C-nucleoside analogs in which the purine moiety is replaced by an isosteric fused heterocycle such as triazolo[1,5-c] or [4,3-c]pyrimidine[4]. We are now exploring novel series in which the base would be an oxazolo[4,5-b]pyridine or oxazolo[4,5-d]pyrimidine. This paper presents our first results in this field, in particular the synthesis of the desired fundamental fused heterocycles 1 and 2 and some of their 2-alkyl derivatives.

If the literature describes some methods for the preparation of 2-substituted oxazolo [4,5-b]pyridines[5], no mention is made of the unsubstituted parent heterocycle. It is also the case for oxazolo[4,5-d]pyrimidine itself as well as for its derivatives, which hitherto remain unknown.

In order to obtain the fundamental heterocycles in these two series, as well as their 2-substituted derivatives, we have extended to the suitable o-hydroxyaminopyridine and pyrimidine the condensation with ortho esters and thioimidates which have been described for the synthesis of benzoxazoles from o-aminophenol[6,7].



The schemes summarize the results that we got with the commercially available 2-amino-3-hydroxy-pyridine (8). By contrast 4-amino-5-hydroxy-pyrimidine, which is required in the second series, had to be prepared by known procedures[8] in several steps. Among the alternative reagents that we have used, thioimidates are potentialy the most interesting since they are not only known in the alkyl series but also in the sugar chemistry.

The condensation of compound 8 with an excess of various orthoesters (8/1) in the presence of a trace of p-toluene sulfonic acid (p-TsOH) between 140 and 180°C afforded oxazolo[4,5-b]pyridine (in 60% yield) and its 2-substituted derivatives in the respective yields : 42 % (3), 30 % (4), 43 % (5), 42 % (6) and 34 % (7). With thiobenzylacetimidate hydrochloride the reaction led first to an intermediate which was cyclized by further heating at 250°C. When the above reactions were performed with 4-amino-5-hydroxy-pyrimidine, we obtained oxazolo[4,5-d]pyrimidine (in 45% yield) and its 2-methyl derivative (40 %).

All the compounds obtained were fully characterized by $^{1}H$ and $^{13}C$ nmr ir and mass spectroscopy and gave satisfactory analytical results[9].

In conclusion the above results show that this approach is effective for the synthesis of oxazolo[4,5-b]pyridines and oxazolo[4,5-d]pyrimidines both for the parent heterocycles and their 2-substituted derivatives. Extension to thioformimidates in acyclic and sugar series as well as the possibility to use thioesters are presently under investigation.

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9. The following data give the m.p., ir and $^{1}H$, $^{13}C$ nmr characteristics in deuterochloroform solution ( $\delta$, ppm, TMS) for the new fundamental heterocycles.
   1 : m.p. 71°C ; ir : 1620, 1560, 1260 $cm^{-1}$ ; uv $\lambda$ nm ($\varepsilon$) methanol, c = $10^{-4}$ mole/l : 274 (6740) ; $^{1}H$ nmr : 8.25 (s, H-2) ; 8.46 (dd, H-5) ; 7.21 (dd, H-6) ; 7.77 (dd, H-7) with $J_{5-6}$=4.8, $J_{6-7}$=8.2 and $J_{5-7}$=1.3 Hz ; $^{13}C$ nmr : 157.7 (C-2), 160.5 (C-3a), 155.5 (C-5), 140.1 (C-7), 141.2 (C-7a).
   2 : m.p. 110°C ; ir : 1760, 1600, 1580, 1290 $cm^{-1}$ ; uv $\lambda$ nm ($\varepsilon$) methanol, c = $10^{-4}$ mole/l : 282 (5040) ; $^{1}H$ nmr : 8.51 (s, H-2) ; 9.26 (s, H-5) ; 9.12 (s, H-7) ; $^{13}C$ nmr : 155.1 (C-2), 154.2 (C-3a), 146.7 (C-5), 118.8 (C-6), 120.5 (C-7), 141.8 (C-7a).


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