SYNTHESIS OF A NEW RING SYSTEM: 1,2,4-OXADIAZOL-[2,3a]PYRIMIDIN-4-ONE

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The preparation of 2,7-diphenyl-1,2,4-oxadiazol-[2,3a]pyrimidin-4-one is described and its ring opening by hydrogenation and hydrolysis examined.

N-(1,2,4-oxadiazol-3-yl)-β-enamino esters of the type (1) were shown to undergo hydrogenolysis to yield pyrimidine-4-one derivatives[1] (2) and base-induced rearrangement into imidazole derivatives[2] (3).

The latter reaction is believed to occur *via* attack by nucleophilic center in the activated side-chain on the ring nitrogen atom.

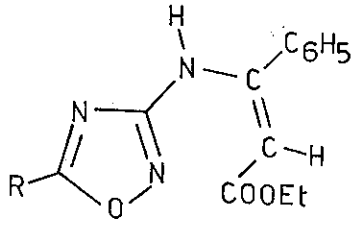
We decided to investigate on the reactivity of compounds (1a-b) in the presence of strong acids, since it was foreseen that, similar to enamino esters of other α-amino azoles, protonation of the ester carbonyl in the side-chain would favor

nucleophilic attack by the ring nitrogen atom yielding ring closure to bicyclic compounds of the type (4). However, owing to tendency shown by 1,2,4-oxadiazole derivatives to undergo ring opening reactions, it was anticipated that the initially formed bicyclic compounds (4) might also give rise to pyrimidin-6-one derivatives under the reaction conditions.

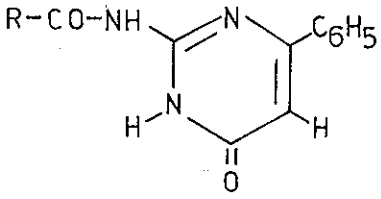
We have observed that refluxing a solution of (1a) in anhydrous toluene (Markusson apparatus, 100 hr) in the presence of p-toluenesulphonic acid resulted in the formation of 2,7-diphenyl-1,2,4-oxadiazol-[2,3a]pyrimidin-4-one (4a)[3]. The product precipitates by removal of solvent under vacuum [yield 30%; m.p. 218° (ethanol). I.R.(nujol mull): 1686 cm^{-1} (C=O); U.V.λ_{max}^{EtOH} nm (log ε): 264 (4.32), 310sh (3.70). NMR (DMSO): 6.90 δ (s,1H,CH), 7.40-8.40 δ (m,10H,ArH)].

We also found that hydrogenation of (4a) using 10% Pd/C in the Parr apparatus (40 p.s.i.) gives the benzoylamino derivative (2)[1]. Furthermore we observed that the oxadiazole ring can be cleaved by hydrolysis. In fact, by refluxing (4a) with aqueous potassium hydroxide in ethanol (2 hr)yields benzoic acid and 1-hydroxy-2-amino-pyrimidin-6-one (5)[3], m.p. 292° (ethanol) [I.R. (hexachlorobutadiene): 3289, 3049, 2500 (br), 1656 cm^{-1}. Mass spectrum: 203 (M^+), 187 (M^+ - O), 186 (M^+ - OH), 158 m/e] .

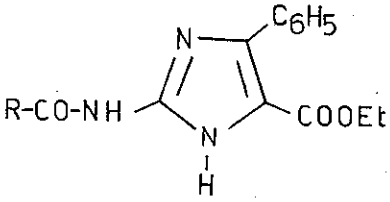
By way of contrast, treatment of (1b) with p-toluenesulphonic acid, using the same procedure and reaction conditions as described for (1a), resulted in direct formation of (5). Compound (5) can be isolated by extraction of the crude reaction mixture with petroleum ether (to remove starting material) and crystallization from ethanol.



(1)



(2)



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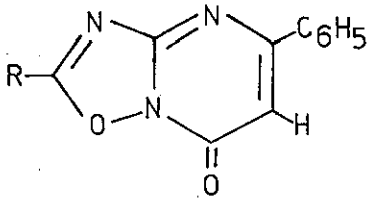
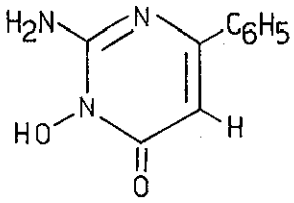


(4)



(5)

a: R = C_6H_5

b: R = CH_3

As it is likely that in this case (5) arises from the initially formed bicyclic compound (4b), this result indicates that 1,2,4-oxadiazole rings in (4a) and (4b) have a remarkable different stability under the same reaction conditions.

The lability of the five-membered heterocyclic ring in (4b) can be ascribed to the absence of diaryloid stabilization. The same effect has been previously invoked to rationalize the course of related heterocyclic transformations[4].

Researches in progress aim to generalize the formation of bicyclic compounds of the type (4) in the 1,2,4-oxadiazole series and to study the influence of the substituents present on the course of the reaction.

References

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3 Satisfactory analytical data were obtained.

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