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A Multistep Rearrangement in the Nitropyrimidine System

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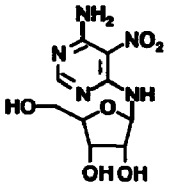
Abstract : The 4-chloro5-nitropyrimidines 2 and 5 upon treatment with sodium azide, rearrange to give nitromethylene tetrazole 4 and 6 respectively.

Clitocine 1 is a nucleoside with insecticidal and antiviral properties extracted from a clitocybe mushroom.[1] Recently, we were involved in the chemistry of clitocine and its analogues in the quest for novel insecticides and antiviral agents. Chloro compound 2 was selected as a convenient starting material and prepared as described.[2]



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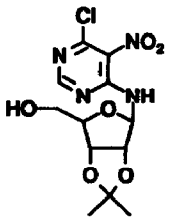
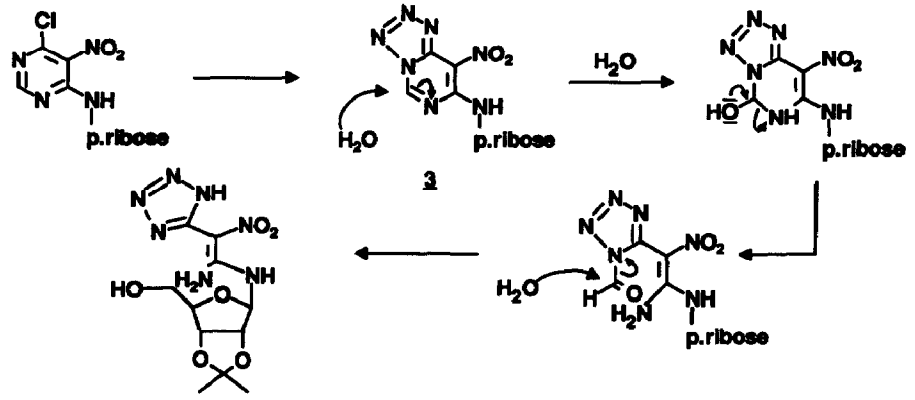


2

Compound 2 readily undergoes nucleophilic substitution of the chlorine atom. Thus we tried to synthesize the azido compound by reaction of sodium azide in DMF. We did not obtain the azido compound and no product was found in the organic phase after work-up. But in the aqueous phase after three days, white crystals appeared in very good "yield". The spectroscopic and elemental analyses[3] of these crystals showed no alteration of the ribose moiety but indicated the disappearance of the pyrimidine ring with incorporation of three more nitrogens and a loss of one carbon atom. The presence of a tetrazole ring was postulated because its formation is well described in pyrimidine chemistry[4] but the unknown product did not correspond to the fused tetrazole derivative 3. A careful literature search of nitropyrimidine chemistry gave us access to an article by C. Temple [5] describing the formation of a fused oxadiazole oxide (furoxan) which could also be ruled out. However, in the same paper, these authors reported the formation of a rearranged product by acidic sodium azide treatment of the chloronitropyrimidine system and then decomposition in DMF at 145° or further acidic treatment. Despite their probably wrong conclusion about the position of the double bond outside the tetrazole ring (as us they did not see any proton α to the nitro group by NMR), it seems likely that it is this rearrangement which occurred in our case and so, we postulate the structure 4 for our white crystals. The formation of such a compound can be described as in scheme 1.

To confirm our proposed structure, we attempted an X-Ray study of compound 4. Unfortunately, the crystals were too small and only partial resolution was obtained. However, the poor resolution concerned the ribose moiety and the data clearly showed the presence of a nitro group in the conjugated tetrazole system.

We thus attempted the same transformation on compound 5. This afforded the desired product 6, of which an X-Ray structure was easily obtained (scheme 2)[6], confirming the rearrangement.



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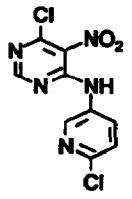
Scheme 1



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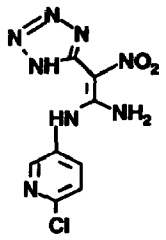

6

Scheme 2

Our work brought to light and gives further evidence for this rearrangement which seems quite general in this family and can be used for the synthesis of potentially insecticidal and antiviral compounds. Moreover, we have shown that it takes place in very mild conditions which, for example, do not alter the isopropylidene group or the nucleoside linkage.

REFERENCES AND NOTES

1. Kubo, I. ; Kim, M. ; Wood, W.F. ; Naoki, H. *Tetrahedron. Lett.* **1986**, *27*, 4277 - 4280.
2. Kamikawa, T. ; Fujie, S. ; Yamagiwa, U. ; Kim, M. ; Kawaguchi, H. *J.Chem.Soc.Chem.Comm;* **1988**, 195 - 196.
3. Sodium azide (13.8 mmol) was added to a solution of chloropyrimidine 2 (11.52 mmol) in DMF (12 ml). The reaction warmed slightly and NaCl precipitated. After stirring for 10 min at 20-25°, the reaction was poured onto 120 ml of water. After filtration of the slight precipitate and extraction with diisopropyl ether, the aqueous phase was just saturated with sodium chloride. After one week, the precipitate was filtered from this aqueous solution, washed with water and dried under vacuum. Yield was 73 % mp : 148°C ; IR (ν_{max} cm^{-1}, nujol) : 3000-3800, 1644, 1592. NMR (^1H 400 MHz, DMSO-d_6) δ = 1.32 and 1.48 (3H, s, CH_3, isopropylidene) ; 3.42 and 3.51 (2H, m, $\underline{CH_2}$ - OH) ; 4.24 (1H, t, CH_2-$\underline{CH}$-0) ; 5.63 (1H, s after D_20, N-$\underline{CH}$-0) ; 8.84 and 9.71 (2H, NH_2) ; 10.71 (1H, d, $\underline{NH}$-CH) ; 15.92 (1H, s, NH). NMR(^{13}C 75 MHz,DMSO-d_6) δ = 24.6 ; 26.4 ; 61.7 ; 82 ; 85.3 ; 86.1 ; 87.8 ; 101.6 ; 149.8 ; 155.9. UV (EtOH) λ_{max} (ϵ) = 228 (13900) ; 241 (13400) ; 331 (15900). MS (FD) M^+ = 343. anal. for$C_{11}H_{17}N_7O_6$ (requires) C, 38.48 ; H, 4.99 ; N, 28.56 (found) C, 38.0 ; H, 5.0 ; N, 28.6.
4. Butler, R.N. ; *Advances in Heterocyclic Chemistry* **1977**, *21*, 408 - 412.
5. Temple, C. ; Kussner, C.L. ; Montgomery, J.A. *J. Org. Chem*, **1968**, *33*, 2086 - 2089.
6. Thanks are due to Pr. Baert F. (Lille University, France) for providing us X-Ray spectra. Space group $P\bar{1}$; a = 14.15, b = 6.90, c = 6.21, α = 85.58, β = 97.38, γ = 97.33. Full details will be published elsewhere.

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