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SYNTHESIS OF 8-NITRO- AND 7-METHOXY-8-NITRO-1,2,4-TRIAZOLO [1,5-c]-PYRIMIDINES.

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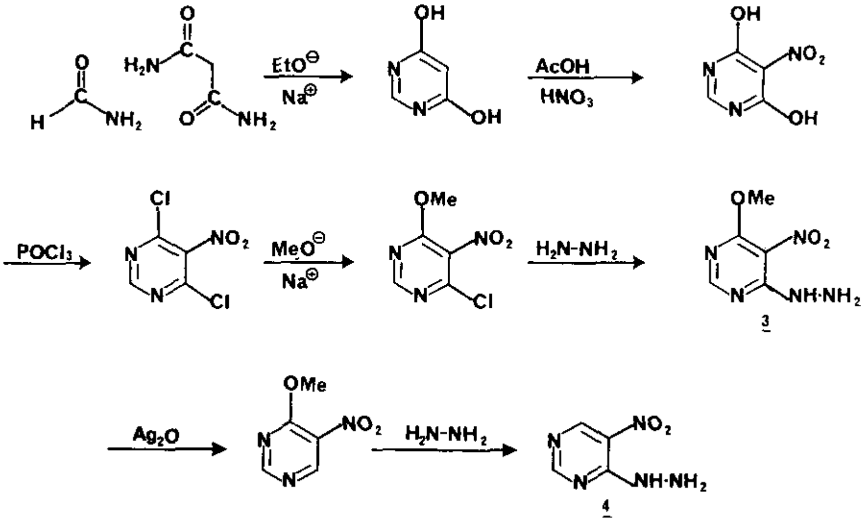
Abstract - 4-Hydrazino-5-nitropyrimidine and its 6-methoxy derivative were condensed under heating with ethyl orthoformate to afford the title compounds through the intermediacy of an imino ether. In both cases the first formed 1,2,4-triazolo[4,3-c]pyrimidines were not isolated and directly converted to their [1,5-c] isomer by a Dimroth rearrangement.

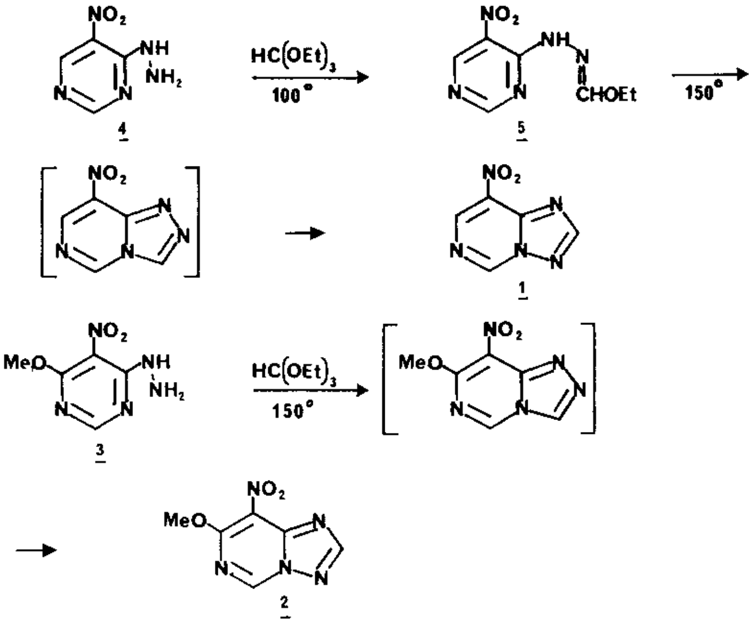
Previous work of our group on new heterocyclic phenols[1-4] has outlined the interest of such compounds in both fundamental[5-7] and pharmacological chemistry.[8] The analogy with the purine ring which is shown by fused heterocycles with a bridgehead nitrogen atom led us to synthesize some *analogues of C-nucleosides derived from 8-hydroxy-1,2,4-triazolo*[1,5-c]- *and* [4,3-c]-pyrimidines.[9] These compounds are related to the inosine structure by modification of the position of N-atoms. Since 2-β-D-ribofuranosyl-8-nitro-1,2,4-triazolo[1,5-a]pyridine has shown some cytotoxic and antiviral properties,[10] we have furthermore planned the synthesis of a pyrimidine analogue of this compound. The present report is concerned with the synthesis of the heterocyclic moiety of this analogue, i.e., 8-nitro-1,2,4-triazolo[1,5-c]pyrimidine (1) and its 7-methoxy derivative (2).

Since triazolopyrimidines can be conveniently prepared by condensation of hydrazinopyrimidines with orthoesters,[11] 4-hydrazino-5-nitropyrimidine (4) and its 6-methoxy derivative (3) appeared to be the promising starting materials for the planned synthesis. These compounds were prepared according to known procedures[12-16] which are summarized in the following Scheme.



As it was reported in our preceding publications,[4,9] the condensation of 5-alkoxy-4-hydrazinopyrimidines with orthoesters afforded generally in good yields the corresponding triazolopyrimidines. The latter compounds belong either to the [1,5-c] or the [4,3-c] series, depending not only on the temperature and the duration of the reaction, but also on the nature of the alkoxyl group and the orthoester used in the synthesis. Concerning the condensation of 4-hydrazino-5-nitropyrimidine with ethyl orthoformate, heating at 100°C (a temperature which was high enough to cause the expected cyclization in the above cases) resulted only in the isolation of the intermediate imino ether 5. Although intermediates of this type have been reported in other cases,[17] we could not isolate them during the course of our previous synthesis of 8-alkoxytriazolopyrimidines performed at this temperature. This difference may be explained in terms of electron-withdrawing effect of the nitro group which reduces the nucleophilicity of the N-3 atom, to a large extent, the cyclization being prevented at 100°C. Heating at 150°C of the intermediate 5 was necessary to achieve its cylization which led to 8-nitro-1,2,4-triazolo[1,5-c]pyrimidine (1). The initially formed [4,3-c] isomer could not be isolated and obviously it underwent a Dimroth rearrangement to the final compound 1 in the usual way of these series.

In the same manner 4-hydrazino-6-methoxy-5-nitropyrimidine led to 7-methoxy-8-nitro-1,2,4-triazolo[1,5-c] pyrimidine (2) when it was heated at 150°C in an excess of ethyl orthoformate.



All the products showed the expected spectral properties in uv, ir and nmr studies ; their structures were clearly established as follows.

In uv, the conjugation of the π-electrons of heterocycle with the NO_2 chromophore caused bathochromic shifts of the B-band and we observed a maximum at 335 nm (ϵ = 13290) for 1 and at 340 nm (ϵ= 14990) for 2. In ^1H nmr, the structure of intermediate N-(ethoxymethylene)-N'-(5-nitro-4-pyrimidinyl)hydrazine (5) was confirmed by the signals at 1.43 ppm and 4.43 ppm (J = 7 Hz) attributed respectively to the CH_3 triplet and CH_2 quartet. The ethylenic proton gave a signal at 7.21 ppm as a singlet. The other protons appeared in the 8.8-9.2 ppm region.

In cyclised compounds (1, 2), comparison with the described spectra of the fundamental heterocycle showed that the proton H-2 suffered the deshielding effect by the nitro group ($\Delta\delta$ = +0.29 ppm and 0.05 ppm respectively). In this latter case, we noticed the shielding effect by methoxy group.

These effects were observed equally for H-5 ($\Delta\delta$ = 0.44 and 0.18 ppm) and H-7 ($\Delta\delta$= 1 ppm) respectively for 1 and 2.

In conclusion, this work presents a first synthetic approach to desired 2-β-D-ribofuranosyl-8-nitro-1,2,4-triazolo [1,5-c] pyrimidine.

EXPERIMENTAL SECTION :

Elemental analyses were performed by the central service of CNRS ; all melting and boiling points are uncorrected. Infrared (ir) spectra were recorded on a Perkin-Elmer spectrophotometer 1420. ^{1}H Nmr spectra were obtained from a *WP60* or *WP80 Bruker spectrometer. Chemical shifts are* reported in parts per million (δ) downfield from tetramethylsilane used as internal standard in hexadeuterioacetone and hexadeuteriodimethyl sulfoxide. Mass spectra were taken on a R-10-10 Riber spectrometer under 70 ev.

7-Methoxy-8-nitro-1,2,4-triazolo [1,5-c] pyrimidine (2) : A solution of 4-hydrazino-6-methoxy-5-pyrimidine[16] (0.4 g, 2.16 mmol) in 4 ml (30 mmol) of ethyl orthoformate was heated with stirring to 110°C for 2 h then to 140°C for 1 h. After cooling, the resulting orange solid was collected by filtration yielding 0.2g of 2 (50 %) : mp 169-171°C (ethanol/hexane, 1/1) ; uv (ethanol, 10^{-4}M) λ_{max} nm (ε) ; 340 (14940) ; ^{1}H nmr (dimethyl sulfoxide-d_6) δ ppm : 4.20 (s, 3H, CH_3), 8.71 (s, 1H, H-2), 9.98 (s, 1H, H-5) ; mass spectrum m/z (relative abondance) : 195 ($M^{+\cdot}$, 100 %), 196 ($M^{+\cdot}$+1, 9.0 %), 165 (51.9 %). Anal. Calcd for $C_6H_5N_5O_3$: C, 36.92 ; H, 2.58 ; N, 35.89. Found : C, 37.3 ; H, 2.48 ; N, 35.18.

N-(Ethoxymethylene)-N'-(5-nitro-4-pyrimidinyl)hydrazine (5) : A solution of 4-hydrazino-5-nitropyrimidine (0.5 g, 3.23 mmol) in 1.5 ml (11.5 mmol) of ethyl orthoformate was heated with stirring to 100°C for 2 h. The reaction mixture was cooled to -20°C. After filtration and recristallization (ethanol), an orange solid was obtained (0.27 g, 40 %) : mp 149-151°C ; ir (KBr) νcm^{-1}: 3350 (NH) ; ^{1}H nmr (acetone-d_6) δ ppm : 1.43 (t, J=7Hz, 3H, CH_3), 4.43 (q, J=7Hz, 2H, CH_2), 7.21 (s, 1H, CH proton), 8.79 (s, 1H, H-6), 9.22 (s, 1H, H-2) ; mass spectrum m/z (relative abondance) : 211 ($M^{+\cdot}$, 31.7 %), 212 ($M^{+\cdot}$+1, 9.5 %), 166 (100 %). Anal. Calcd for $C_7H_9N_5O_3$: C, 39.81 ; H, 4.29; N, 33.31. Found : C, 39.62; H, 4.26 ; N, 33.26.

8-Nitro-1,2,4-triazolo [1,5-c] pyrimidine (1) : A solution of 4-hydrazino-5-nitropyrimidine (0.2 g, 1.29 mmol) in 1.5 ml (11.5 mmol) of ethyl orthoformate was heated at 100°C for 2 h then at 150°C for another 2 h. After cooling, the reaction mixture was filtered in order to eliminate tars ; addition of hexane caused the precipitation of the product 1. After filtration and recristallization (ethanol), a solid was obtained (0.064 g, 30 %) : mp 135°C (decomp.); uv (ethanol, 10^{-4}M) λ_{max} nm (ϵ): 355 (13290) ; ^{1}H nmr (dimethyl sulfoxide-d_6) δ ppm : 8.96 (s, 1H, H-2), 9.30 (s, 1H, H-7), 10.24 (s, 1H, H-5) ; mass spectrum m/z (relative abondance) : 165 ($M^{+\cdot}$, 100 %), 166 ($M^{+\cdot}$+1, 11.9 %), 135 (14.9 %). Anal. Calcd for $C_5H_3N_5O_2$: C, 36.37 ; H, 1.83 ; N, 42.42. Found : C, 36.32 ; H, 1.82 ; N, 42.45.

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