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SYNTHESIS OF NEW HETEROCYCLIC PHENOLS : 8-HYDROXY-s-TRIAZOLO[1,5-c] AND [4,3-c] PYRIMIDINES

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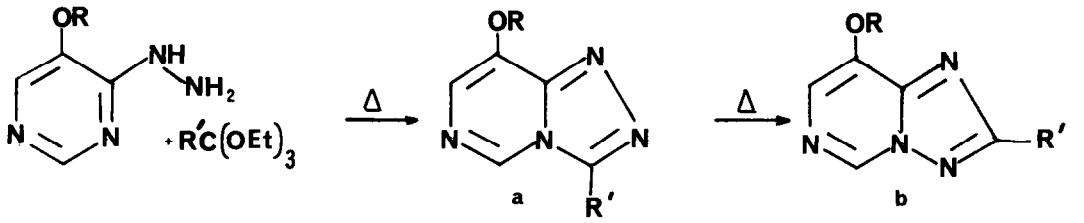
Summary : The unknown title phenols have been prepared by condensation of ethyl orthoformate with 5-benzyloxy-4-hydrazino-pyrimidine and subsequent hydrogenolysis of the protecting group.

C-nucleosides isosteres of natural purine nucleosides are expected to show potent biological activities[1]. So as part of our study on new heterocyclic phenols[2], we have undertaken the synthesis of 8-hydroxy-s-triazolo[4,3-c] and [1,5-c] pyrimidines 1 and 2, from which novel nucleosides analogues could be derived.

In this aim 5-alkoxy-4-hydrazino-pyrimidines 3 et 4, prepared according to Mac Omie et al[3], were condensed with orthoesters. As it is usually observed for condensation between hydrazino azines and orthoesters[4] the reaction with orthoacetate gave us the unrearranged products (i.e. the [4,3-c] isomers 5 and 7) which, upon heating at a higher temperature, suffered the Dimroth rearrangement to the [1,5-c] isomers 9 and 11. By contrast, coupling performed with ethyl orthoformate led directly to rearranged 8 in the case of the methyl ether 3, while both isomers 6 and 10 were obtained from the benzyl ether 4[5]. Subsequent hydrogenolysis of the benzyl protecting group provided the 8-hydroxy-s-triazolo [4,3-c] and [1,5-c] pyrimidines 1 and 2 which showed the expected spectral properties in IR, UV and ^{1}H NMR, and gave satisfactory mass spectrum and elemental analysis.

Structure elucidation of the above isomers was mainly based on the UV spectra which showed the differences observed in the literature[6] for the two series a and b in the 250-290 nm range. The assigned structures were further ascertained by the ^{1}H NMR data shown in the Table (δ ppm/TMS, DMSO-d_6) which are consistent with those of the parent fused heterocycles[6] (respectively 12 and 13) if one assumes shielding effects of substituents similar to those reported for benzene derivatives[7].

Further syntheses on progress, involving replacement of methyl group by an appropriate sugar and extension of the condensation to iminoethers and thioiminoethers are expected to afford C-nucleosides of these structures.



3 : R=CH_3
4 : R = $CH_2\phi$

1 : R=R'=H 5 : R=R'=H
R=$CH_2\phi$, 6 : R'=H ; 7 : R'=CH_3

2 : R=R'=H
R=CH_3, 8 : R'=H ; 9 : R'=CH_3
R=$CH_2\phi$, 10 : R'=H ; 11 : R'=CH_3

Compounds	H-2	H-3	H-5	H-7	R-8
12 : parent a	-	9.40	9.47	7.97	7.77
1 : a R=R'=H		9.37	8.99	7.37	OH = 5.8
5 : a R=R'=CH_3		Me=2.75	8.96	7.54	Me = 4.04
6 : a R=$CH_2\phi$, R'=H		9.43	9.15	7.69	*
7 : a R=$CH_2\phi$,R'=CH_3		Me=2.75	8.98	7.64	*
13: parent b	8.67	-	9.80	8.30	7.90
2 : b R=R'=H	8.6	-	9.35	7.75	OH = 4.5
8 : b R=CH_3 R'=H	8.65	-	9.50	7.98	Me = 4.09
9 : b R=R'=CH_3	Me=2.5	-	9.36	7.92	OMe= 4.05
10: b R=$CH_2\phi$,R'=H	8.65	-	9.50	8.07	*
11: b R=$CH_2\phi$,R'=CH_3	Me=2.52	-	9.37	8.02	*

* Benzyl group gave singlet at 5.4 ppm and multiplet at 7-7.5 ppm.

References and Notes

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