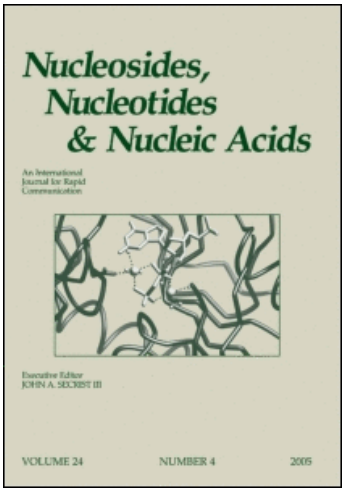

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Synthesis and Biological Evaluation of β-D-Pentofuranonucleoside Derivatives of 2-Azidoadenine and 6-Azidopurines

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ABSTRACT

β-D-pentofuranonucleoside derivatives of 2-azidoadenine and 6-azidopurines have been synthesized. The azido-tetrazolo tautomerism observed on such nucleoside analogues has been studied. The compounds were tested for their activity against HIV and HBV but they did not show significant antiviral effect.

Key Words: Nucleoside analogues; Azido-tetrazolo tautomerism.

INTRODUCTION

Some adenosine analogues substituted at the 2-position show interesting biological properties. For instance, 2-chloroadenosine derivatives exhibit potent antitumoral and antiviral activities as demonstrated with 2-chloro-2′-deoxyadenosine

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(Cladribine),[1] 2-chloro-2′,3′-dideoxyadenosine[2] and 2-chloro-2′,3′-dideoxy-2′,3′-didehydroadenosine,[2] respectively. In order to discover new nucleoside derivatives endowed with antiviral activity, modifications of the base and/or sugar moiety of natural nucleosides can be attempted. As a part of our ongoing research program on this topic, we have synthesized various β-D-pentofuranonucleoside derivatives bearing 2-azidoadenine as the base, most of them being hitherto unknown. Herein, we report on the synthesis of the ribo-, 2′-deoxy-, 2′,3′-dideoxy- and 2′,3′-dideoxy-2′,3′-didehydro-β-D-pentofuranonucleosides of 2-azidoadenine. The azido-tetrazolo tautomerism observed on 2-azidoadenine nucleoside analogues led us to synthesize the 6-azidopurine ribonucleoside counterparts in order to have a more thorough investigation on such tautomerism.

SYNTHESIS

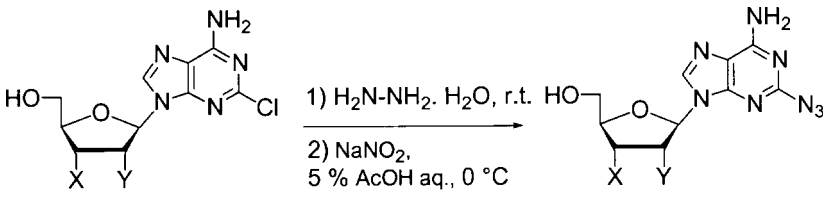
The preparation of the β-D-pentofuranonucleosides (**5**-**8**) of 2-azidoadenine (Sch. 1) was achieved from their corresponding 2-chloro-ribo- (**1**), -2′-deoxy- (**2**), -2′,3′-dideoxy- (**3**) and -2′,3′-dideoxy-2′,3′-didehydro- (**4**) β-D-pentofuranonucleoside counterparts via a methodology previously described in the case of 2-azidoadenosine.[3]

Additionally, the synthesis of the 6-azidopurine nucleoside derivatives (**11** and **12**) was carried out from their corresponding 6-chloro ribonucleoside counterparts by reaction of compound **9** with sodium azide in DMF or by treatment of compound **10** with hydrazine hydrate, followed by sodium nitrite in aqueous acetic acid at 0°C (Sch. 2).

Structural assignments for all the compounds were based on elemental analysis and physicochemical properties (melting point, ^{1}H NMR, ^{13}C NMR, UV, IR, mass spectra and optical rotation).

STUDIES ON THE AZIDO-TETRAZOLO TAUTOMERISM

Briefly, azido-substituted π-deficient nitrogen heterocycles may spontaneously cyclize to give a fused tetrazolo ring or, at least, an equilibrium mixture of both forms.



1 (X = OH, Y = OH)
2 (X = OH, Y = H)
3 (X = Y = H)
4 (X = Y = didehydro)

5 (X = OH, Y = OH)
6 (X = OH, Y = H)
7 (X = Y = H)
8 (X = Y = didehydro)

Scheme 1.

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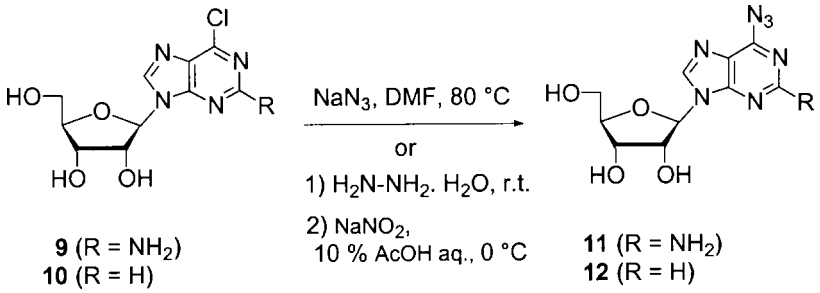
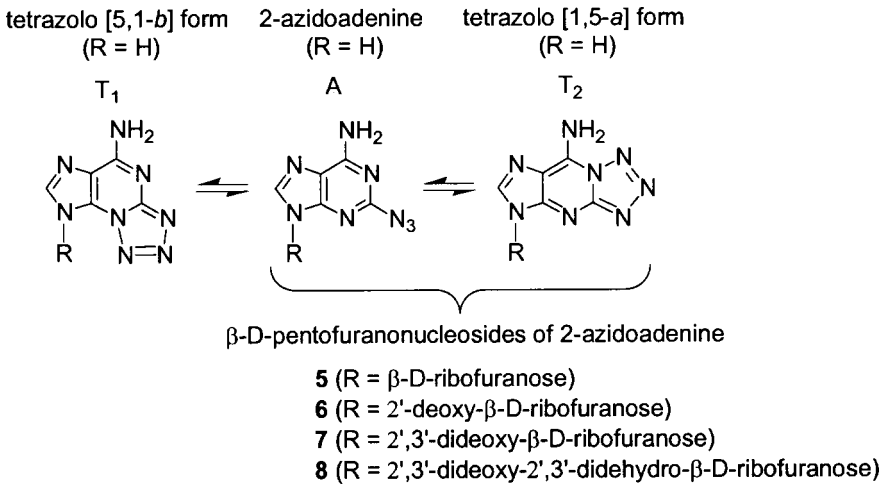


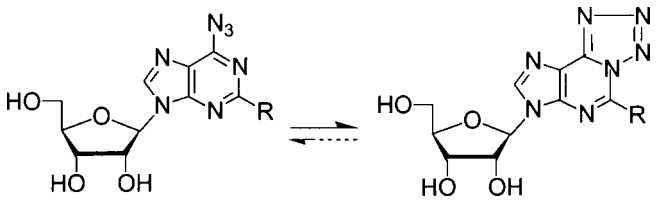
Scheme 2.

Such azido-tetrazolo tautomerism has been previously reported for the base 2-azidoadenine.[4] The latter has been shown to exist in DMSO solution under the azido form (A) in balance with the tetrazolo[5,1-*b*] and [1,5-*a*] form, T_1 and T_2 respectively (Sch. 3). The physico-chemical properties of the β-D-pentofuranonucleosides (**5-8**) of 2-azidoadenine showed that these compounds exist in balance between only two forms, the A and T_2 form. Furthermore, analysis of this equilibrium shown its temperature and solvent dependence. Our results are in accordance with those previously reported for compounds **5**[5] and **6**.[6]

Additionally, the azido-tetrazolo tautomerism on 6-azidopurine ribonucleoside derivatives (**11** and **12**) was also investigated by means of their physico-chemical properties. Our results clearly shown that compounds **11** and **12** exist only as their tetrazolo [5,1-*i*] forms (Sch. 4). These data are in agreement with those previously reported for compound **12**.[7]



Scheme 3.



11 (R = NH_2)
12 (R = H)

Scheme 4.

BIOLOGICAL EVALUATIONS

The β-D-pentofuranonucleoside derivatives of 2-azidoadenine (**5-8**) and 6-azidopurines (**11** and **12**) were tested for their in vitro inhibitory effects on the replication of HIV and HBV. None of these compounds showed significant antiviral activity.

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