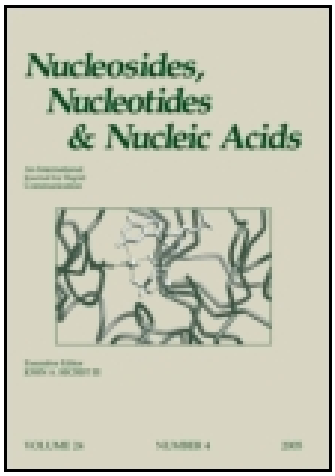

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3′-DEOXYRIBOFURANOSE DERIVATIVES OF 1-DEAZA AND 3-DEAZA-ADENOSINE AND THEIR ACTIVITY AS ADENOSINE DEAMINASE INHIBITORS

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ABSTRACT

2,6-Dichloro-1-deazapurine and 2,6-dichloro-3-deazapurine were coupled with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose. Deprotection of the obtained compounds and reaction with liquid ammonia gave the desired 2-chloroadenine nucleosides, which were dechlorinated to afford the corresponding 1-deaza and 3-deazaadenosine derivatives. Biological studies performed on ADA from calf intestine showed that these new nucleosides are inhibitors of the enzyme.

INTRODUCTION

Adenosine deaminase (ADA) is an important catabolic enzyme, which converts adenosine and deoxyadenosine to inosine and deoxyinosine, respectively. Moreover ADA is involved in the pathogenesis of the Severe Combined Immunodeficiency Disease (SCID) and is responsible for deamination of potentially useful drugs with a nucleosidic structure. Elevated serum ADA activity has been described in various autoimmune and inflammatory diseases, including Systemic Lupus Erythematosus (SLE) (1).

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Modifications of the purine moiety or/and substitution of the sugar moiety of adenosine with aliphatic chains led to derivatives with good ADA inhibitory activity (2). We reported in previous papers that 1-deazaadenosine analogues exhibit good inhibitory activity on ADA from several sources. In this research, we compared coupling of 2,6-dichloro-1-deazapurine or 3-deazapurine with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose and evaluated the obtained compounds as ADA inhibitors.

CHEMISTRY

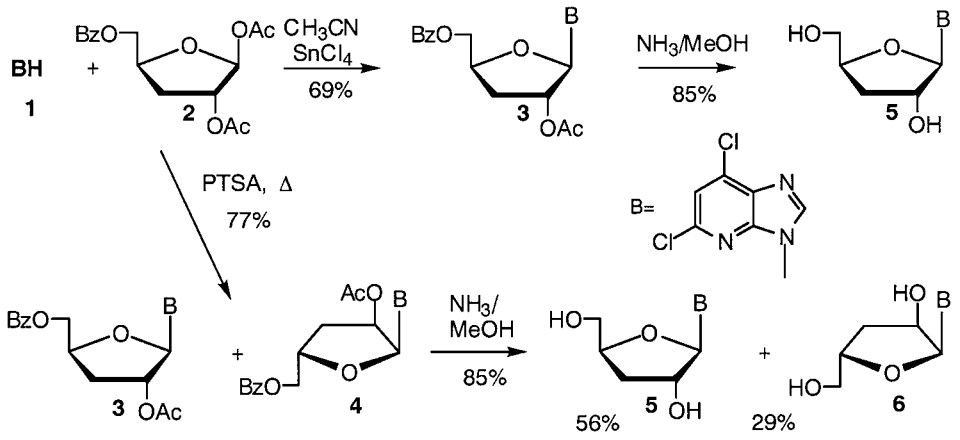
Coupling of 2,6-dichloro-1-deazapurine (**1**) with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy-β-D-ribofuranose (**2**), using tin tetrachloride as the acidic-catalyst, yielded only the β-anomer **3** (Scheme 1).

Deprotection with methanolic ammonia gave the the dichloro-1-deazanucleoside **5**. On the other hand, coupling of compounds **1** and **2** using the fusion method yielded a mixture of β- and α-anomers as shown in Scheme 1.

Room temperature standing of the protected compounds with methanolic ammonia gave the corresponding dichloro-1-deazanucleosides **5** and **6** (3,4).

In the case of 2,6-dichloro-3-deazapurine (**7**), coupling with sugar **2** in the presence of tin tetrachloride gave the β-anomer **8** in low yield. Deprotection with methanolic ammonia afforded the dichloro-1-deazanucleoside **12**. 2,6-Dichloro-3-deazapurine (**7**) was also coupled with **2** under fusion reaction conditions as shown in Scheme 2 (5).

The glycosylation site and the anomeric configuration were assigned on the basis of UV data and ^{1}H NMR spectra, including 1D ^{1}H NOE difference spectra, of the deprotected nucleosides **12**–**15**, obtained by treating compounds **8**–**11** with methanolic ammonia at room temperature. In a previous work we isolated,



Scheme 1.

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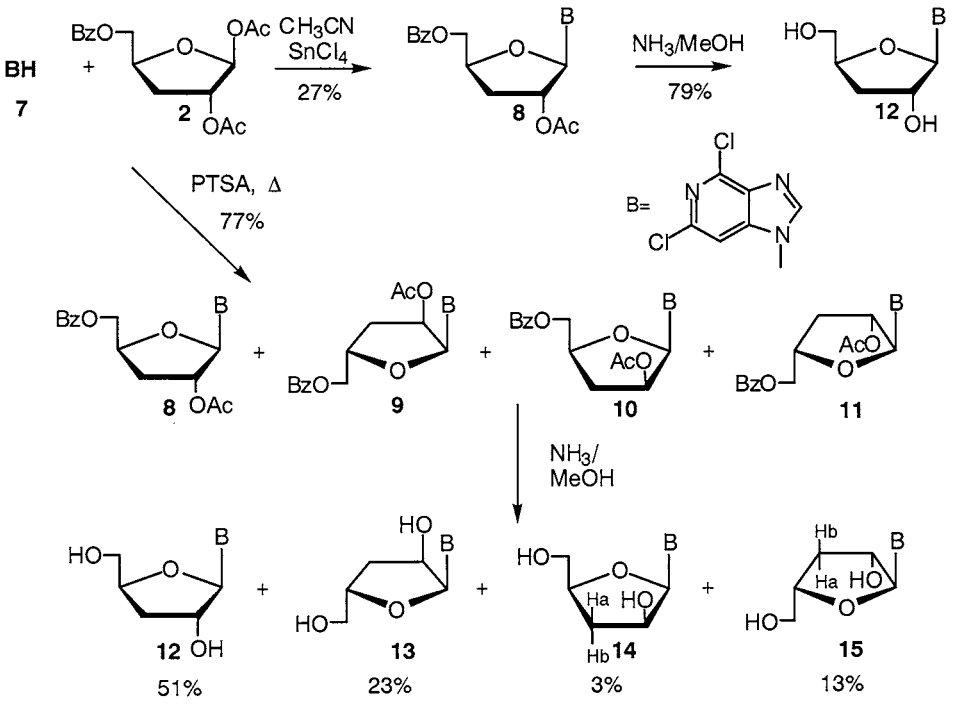
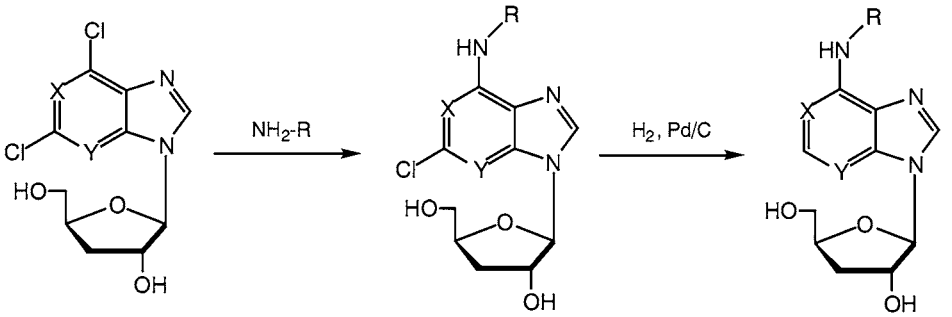


Scheme 2.

besides the N(9)-β- and the N(9)-α-3′-deoxyribonucleosides **12** and **13**, also the N(9)-α-3′-deoxyarabinonucleoside **15** (5). Now with further studies we also identified the N(9)-β-3′-deoxyarabino derivative **14**.

The UV spectra of the four nucleosides were practically identical. Saturation of H-C(1′) resulted in a NOE at the H-C(8) and H-C(3) signals in all four cases. The latter excludes without any doubt N(7) as glycosylation site. NOE at the H-C(4′) upon saturation of H-C(1′) of **12** established the β configuration. In the case of **14**, saturation of H-C(1′) gave a strong NOE at the H-C(2′) signal but not at the H-C(4′) one. This is probably due to the distortion induced in the sugar moiety by the different position of the OH-C(2′). NOE at the Ha-C(3′) upon saturation of H-C(1′) of **13** and **15** established the α configuration. The epimerization at C(2′) of nucleosides **14** and **15** has been demonstrated by the NOE observed at the H_b-C(3′) signal upon saturation of either H-C(2′) or H-C(4′). This result confirmed that the three protons are located on the same side of the sugar ring.

Reaction of compounds **5** and **12** with liquid ammonia at 130°C gave the nucleosides **16** and **18**, which were dechlorinated by catalytic hydrogenolysis to obtain the corresponding 3′-deoxy-1-deazaadenosine (**17**) and 3′-deoxy-3-deazaadenosine (**19**) as shown in Scheme 3. The same procedure could be utilized in order to introduce different amines in 6 position of these molecules.



5 X = CH, Y= N
12 X = N, Y = CH

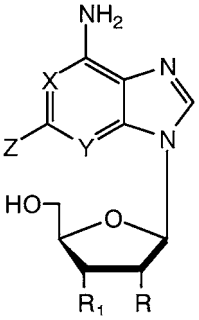
16 X = CH, Y= N, R = H
18 X = N, Y = CH, R = H

17 X = CH, Y= N, R = H
19 X = N, Y = CH, R = H

Scheme 3.

Table 1. ADA Inhibitory Activity of 1-deaza and 3-deaza Adenosines

Cpd.	X	Y	Z	R	R_1	K_i (μM)
Ia	CH	N	Cl	OH	OH	30
Ib	CH	N	H	OH	OH	0.38
Ic	CH	N	Cl	H	OH	23
Id	CH	N	H	H	OH	0.19
16	CH	N	Cl	OH	H	>100
17	CH	N	H	OH	H	2.5
IIa	N	CH	Cl	OH	OH	37
IIb	N	CH	H	OH	OH	400
IIc	N	CH	Cl	H	OH	61
18	N	CH	Cl	OH	H	152
19	N	CH	H	OH	H	411



RESULTS

The 3′-deoxy-1-deazaadenosines (**16** and **17**) and 3′-deoxy-3-deazaadenosines (**18** and **19**) were tested for their ability to inhibit calf intestine ADA (6). In Table 1 the activity of these compounds is compared to that of the corresponding ribose and 2′-deoxyribose derivatives.

2′-Deoxy-1-deazaadenosine (**Id**, $K_i = 0.19\ \mu$M) proved to be the most potent compound of the series, and it resulted more active than 1-deazaadenosine itself (**Ib**, $K_i = 0.38\ \mu$M). The 3-deaza derivatives are still inhibitors of the enzyme although always less potent than the corresponding 1-deaza analogues.

It is interesting to note that in the case of the 1-deaza nucleosides the presence of a chlorine atom on C(2) produces a decrease in the ADA inhibitory activity (**Ib**, $K_i = 0.38\ \mu$M *vs* **Ia**, $K_i = 30\ \mu$M), while in the case of the 3-deaza analogues the same substitution leads to more potent compounds (**IIb**, $K_i = 400\ \mu$M *vs* **IIa**, $K_i = 37\ \mu$M).

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