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

S. Costanzi , C. Lambertucci , R. Volpini , S. Vittori , G. Lupidi <sup>a</sup> & G. Cristalli

<sup>a</sup> Dipartimento di Biologia M.C.A. , University of Camerino , Camerino, I-62032, Italy

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 20(4-7), 1037-1041 (2001)

## **3'-DEOXYRIBOFURANOSE DERIVATIVES OF 1-DEAZA AND 3-DEAZA-ADENOSINE AND THEIR ACTIVITY AS ADENOSINE DEAMINASE INHIBITORS**

**S. Costanzi,<sup>1</sup> C. Lambertucci,<sup>1</sup> R. Volpini,<sup>1</sup> S. Vittori,<sup>1</sup>  
G. Lupidi,<sup>2</sup> and G. Cristalli<sup>1,\*</sup>**

<sup>1</sup>Dipartimento di Scienze Chimiche, via S. Agostino 1, Italy

<sup>2</sup>Dipartimento di Biologia M.C.A., University of Camerino,  
I-62032, Camerino, Italy

### **ABSTRACT**

2,6-Dichloro-1-deazapurine and 2,6-dichloro-3-deazapurine were coupled with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy- $\beta$ -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 Immuno-deficiency 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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\*Corresponding author.

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-dezaadenosine 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- $\beta$ -D-ribofuranose and evaluated the obtained compounds as ADA inhibitors.

## CHEMISTRY

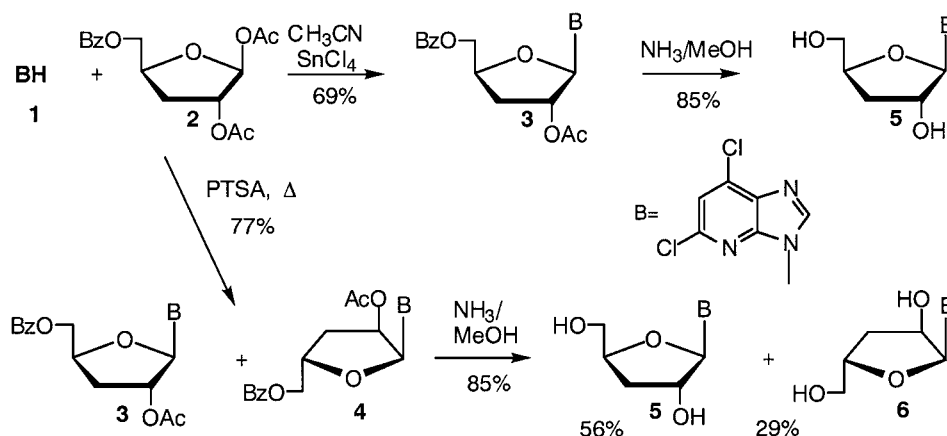
Coupling of 2,6-dichloro-1-deazapurine (**1**) with 1,2-*O*-diacetyl-5-*O*-benzoyl-3-deoxy- $\beta$ -D-ribofuranose (**2**), using tin tetrachloride as the acidic-catalyst, yielded only the  $\beta$ -anomer **3** (Scheme 1).

Deprotection with methanolic ammonia gave the dichloro-1-deazanucleoside **5**. On the other hand, coupling of compounds **1** and **2** using the fusion method yielded a mixture of  $\beta$ - and  $\alpha$ -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).

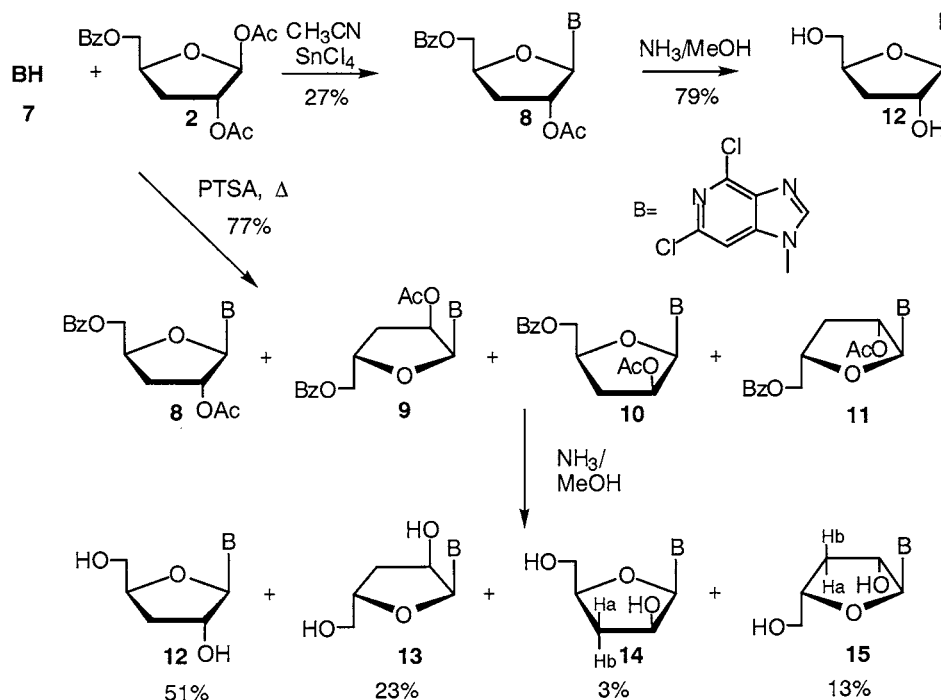
In the case of 2,6-dichloro-3-deazapurine (**7**), coupling with sugar **2** in the presence of tin tetrachloride gave the  $\beta$ -anomer **8** in low yield. Deprotection with methanolic ammonia afforded the dichloro-1-deazanucleoside **12**. 2,6-Dichloro-3-deazapurine (**7**) was also coupled with **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  $^1\text{H}$  NMR spectra, including 1D  $^1\text{H}$  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.





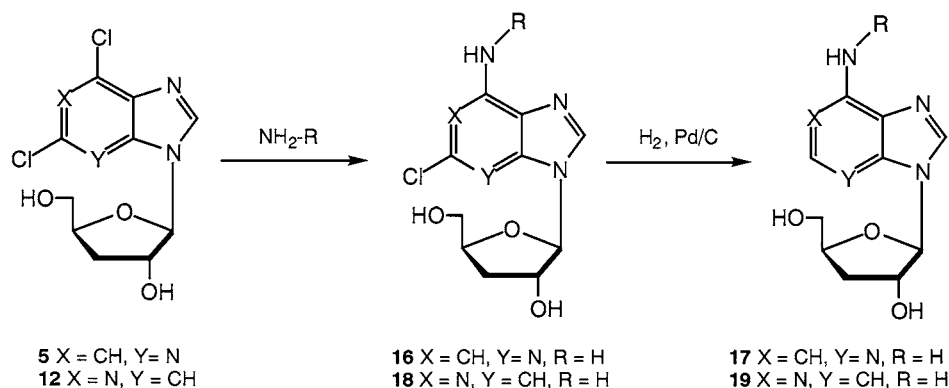
Scheme 2.

besides the N(9)- $\beta$ - and the N(9)- $\alpha$ -3'-deoxyribonucleosides **12** and **13**, also the N(9)- $\alpha$ -3'-deoxyarabinonucleoside **15** (5). Now with further studies we also identified the N(9)- $\beta$ -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  $\beta$  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  $\alpha$  configuration. The epimerization at C(2') of nucleosides **14** and **15** has been demonstrated by the NOE observed at the H<sub>b</sub>-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.





Scheme 3.

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

| Cpd.       | X  | Y  | Z  | R  | R <sub>1</sub> | K <sub>i</sub> (μM) |  |
|------------|----|----|----|----|----------------|---------------------|--|
| <b>Ia</b>  | CH | N  | Cl | OH | OH             | 30                  |  |
| <b>Ib</b>  | CH | N  | H  | OH | OH             | 0.38                |  |
| <b>Ic</b>  | CH | N  | Cl | H  | OH             | 23                  |  |
| <b>Id</b>  | CH | N  | H  | H  | OH             | 0.19                |  |
| <b>16</b>  | CH | N  | Cl | OH | H              | >100                |  |
| <b>17</b>  | CH | N  | H  | OH | H              | 2.5                 |  |
| <b>IIa</b> | N  | CH | Cl | OH | OH             | 37                  |  |
| <b>IIb</b> | N  | CH | H  | OH | OH             | 400                 |  |
| <b>IIc</b> | N  | CH | Cl | H  | OH             | 61                  |  |
| <b>18</b>  | N  | CH | Cl | OH | H              | 152                 |  |
| <b>19</b>  | 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<sub>i</sub> = 0.19 μM) proved to be the most potent compound of the series, and it resulted more active than 1-deazaadenosine itself (**Ib**, K<sub>i</sub> = 0.38 μM). 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<sub>i</sub> = 0.38 μM vs **Ia**, K<sub>i</sub> = 30 μM), while in the case of the 3-deaza analogues the same substitution leads to more potent compounds (**IIb**, K<sub>i</sub> = 400 μM vs **IIa**, K<sub>i</sub> = 37 μM).

### ACKNOWLEDGMENTS

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