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A Novel Synthesis of Oxanosine and 1-Thiaguanosine[1]

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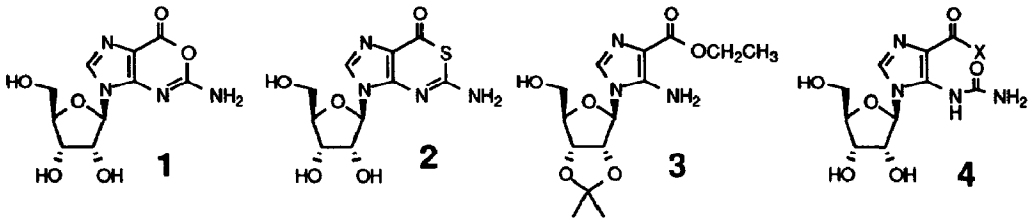
Abstract: A novel total synthesis of oxanosine has been developed. The key heterocycle forming reaction of this synthesis is the carbodiimide mediated dehydration and cyclization of an urea-acid derived from AICA-riboside. The same procedure was also applied to the synthesis of 1-thiaguanosine.

Oxanosine (**1**) is a nucleoside antibiotic isolated from *Streptomyces capreolus* MG265-CF3,[2] with antimicrobial and carcinostatic activities.[3,4,5,6] Its structure was determined by single crystal X-ray analysis.[7] The reported ability of oxanosine to revert cells expressing the activated *ras* oncogene back to normal suggests that oxanosine maybe useful as an antitumor agent. This activity suggests that 1-thiaguanosine (**2**) might also be of biological interest. Although **2** is unknown when we started this work, an unsuccessful attempt to synthesize an analog of **2** has been reported.[8]

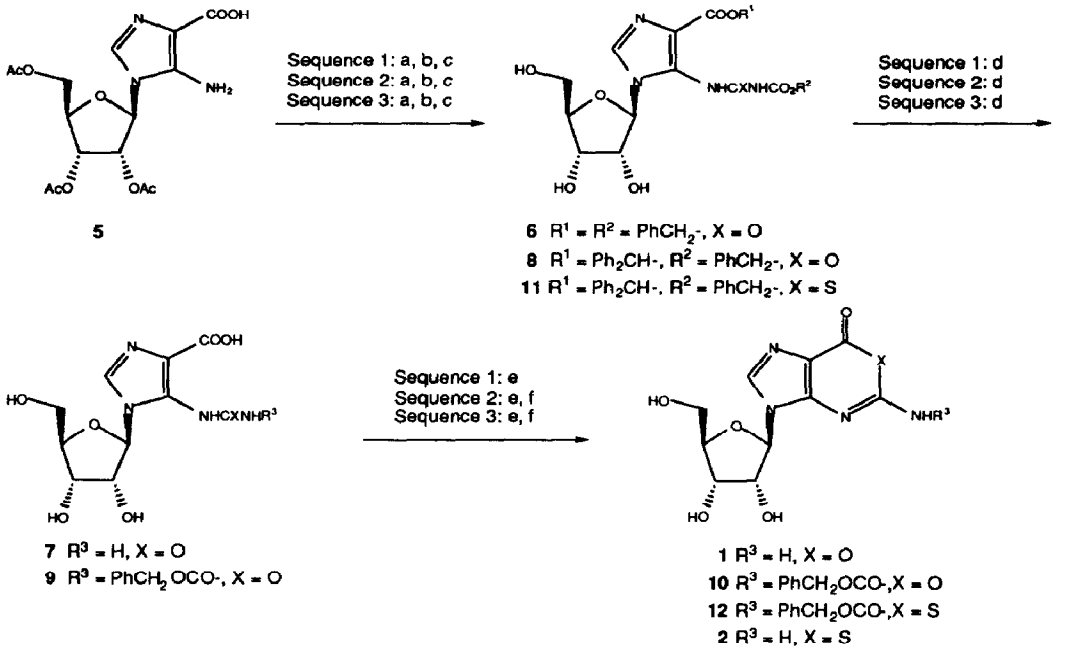
We decided to prepare a sample of oxanosine to further explore this possibility. A total synthesis of oxanosine (**1**) which utilizes intermediate **3** has been reported.[9,10] The literature procedure requires tedious chromatography, and the penultimate step (19% yield) in the synthesis requires harsh conditions which result in a low overall yield of oxanosine (7% from **3**, in our experience the yields were substantially lower). Furthermore, **3** is not commercially available and its preparation requires a lengthy synthesis.[11] We now report an alternate route for the synthesis of oxanosine (**1**) that offers significant improvements over the earlier route. This new synthesis of **1** also suggested a possible route for the preparation of **2**.



We envisaged the key step in our synthesis as an intramolecular dehydration - cyclization reaction occurring between the activated carboxylic acid and the urea moiety in **4**. It was felt that activation of the carboxylic acid could be achieved under very mild conditions, and since the cyclization is intramolecular to form a 6-membered ring, no protection for the alcohols would be required.

Compound **5** is readily obtainable from the commercially available AICA-riboside in two steps *via* a known procedure.[12] The direct condensation of **5**, as either the free acid or its silyl ester, with isocyanate to form the desired urea afforded complex reaction mixtures. However, protection of **5** as the benzyl ester first, followed by condensation with benzyloxycarbonyl isocyanate[13] and deacetylation gave **6**[14] in moderate yield

(Scheme 1, Sequence 1). Compound **6** was hydrogenated to give the free acid-urea **7**, which set the stage for testing the key ring-formation reaction. When **7** was treated with an excess of water soluble carbodiimide, oxanosine was obtained in excellent yield. Thus, this approach reproducibly afforded **1** in a 5% overall yield from commercially available AICA-riboside.



Scheme 1. Synthesis of Oxanosine *via* Carboxylic Acid/Urea Cyclodehydration

Sequence 1: a) $PhCH_2Br$, $nBuN^+I^-$, K_2CO_3, DMF (48%); b) $PhCH_2OCONCO$, $ClCH_2CH_2Cl$ (100%); c) NH_3, CH_3OH (44%); d) H_2, 10% Pd/C, EtOH (75%); e) $(CH_3)_2N(CH_2)_3NCNC_2H_5 \cdot HCl$, CH_3OH, H_2O (89%).

Sequence 2: a) Ph_2CN_2, CH_2Cl_2 (87%); b) $PhCH_2OCONCO$, $ClCH_2CH_2Cl$ (100%); c) KOH, CH_3OH (100%); d) TFA, $C_6H_5OCH_3$, CH_2Cl_2; e) DCC, DMF (33% for d) and e)); f) H_2, 10% Pd/C, DMF (75%).

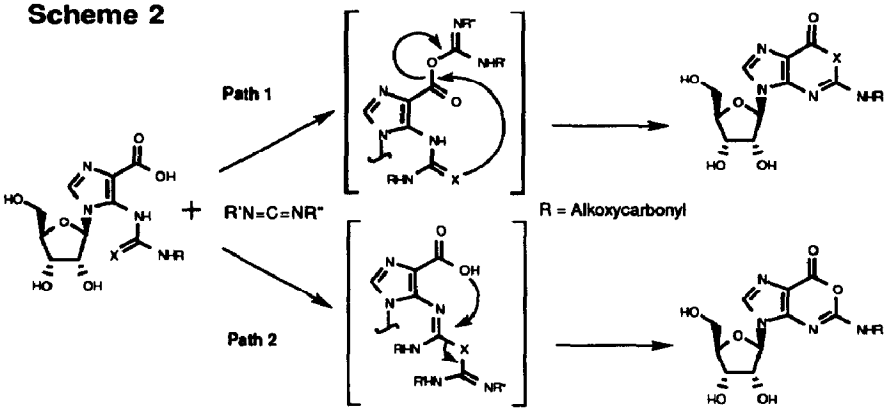
Sequence 3: a) Ph_2CN_2, CH_2Cl_2 (87%); b) $PhCH_2OCONCS$, $ClCH_2CH_2Cl$ (98%); c) KOH, 2-PrOH, dioxane, H_2O (79%); d) TFA, $C_6H_5OCH_3$, CH_2Cl_2; e) DCC, DMF (64% for d) and e)); f) H_2, 10% Pd/C, DMF (53%).

The two major drawbacks to the above route were the benzylation step and the hydrolysis of the acetyl groups, each of which proceeded in less than 50% yield. To circumvent these problems, **5** was converted in excellent yield to its diphenylmethyl ester with diphenyldiazomethane (Scheme 1, Sequence 2). Urea formation followed by ester hydrolysis with potassium hydroxide gave **8** in almost quantitative yield. Selective acid catalyzed removal of the diphenylmethyl group provided the free acid **9**, which was cyclized with DCC to furnish the benzyloxycarbonyl protected form of oxanosine, **10**, in moderate yield. Compound **10** could be hydrogenated to give **1** in 8% overall yield from AICA-riboside. Although this route produced only a marginally better yield than the first one, it provided a selectively protected form of oxanosine, namely **10**, which could be useful in preparing other derivatives. If the formation of **10** is not needed, **8** could be directly hydrogenated to give **7** in 73% yield, which could then be converted to oxanosine as in the first route, giving oxanosine in 21% overall yield from AICA-riboside.

By employing the dehydration - cyclization methodology developed for the synthesis of **1**, but substituting isothiocyanate for isocyanate, one should be able to obtain **2** if, as depicted in Scheme 2, Path 1 (X = S), the dehydration reaction proceeds *via* an activated carboxylic acid. On the other hand, if the reaction proceeds *via* activation of the thiourea (Scheme 2, Path 2), oxanosine (**1**) would result. In the synthesis involving the use of isocyanate (X = O), either reaction pathway would lead to oxanosine (**1**). Although carbodiimide activation of carboxylic acids is well known, activation of the type shown in Path 2 has also been documented.[15] In order to ascertain which of these mechanisms is operable, and also determine whether this dehydration - cyclization procedure is a viable route to **2**, the chemistry outlined in Scheme 1, Sequence 3, was performed.

Compound **5** was esterified with diphenyl diazomethane, acylated with benzyloxycarbonyl isothiocyanate ($PhCH_2OCONCS$)[16] and deacetylated to afford **11** in excellent yield. When **11** was treated with acid to selectively hydrolyze the diphenylmethyl ester, and the resultant acid was reacted with dicyclohexylcarbodiimide (DCC), **12** was isolated in 64% yield after chromatography. The oxygen analog **10**, which is chromatographically distinct from **12**, was not detectable in the reaction mixture by thin layer chromatography (TLC). At least in the sulfur analog, these results support the mechanism shown in Scheme 2, Path 1, and rule out the possibility that the reaction proceeds via Path 2. Hydrogenolysis of **12** then completed the synthesis of 1-thiaguanosine (**2**) in 23% yield from **5**, and 9% from commercially available AICA-riboside.

Scheme 2



Thus, by using the dehydration and cyclization methodology, we have developed a novel synthesis of oxanosine (**1**), and 1-thiaguanosine (**2**). These reaction sequences should also be applicable to the preparation of other N^9-substituted oxanosine and 1-thiaguanine analogs. The synthetic oxanosine showed the expected antimicrobial activity which was reversed by guanosine.[17] It is gratifying to note that 1-thiaguanosine (**2**) is also a moderately active anti-microbial, although slightly less potent than oxanosine, and its activity against *E. coli* 257 was completely reversed by guanosine. The detailed biological activity of **2** will be reported elsewhere.

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