SYNTHESIS OF CARBOCYCLIC OXETANOCIN ANALOGUES AS POTENTIAL ANTI-HIV AGENTS. PART 3

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Abstract ------Two new carbocyclic oxetanocin analogues have been prepared from 1-amino-3-methylenecyclobutane. The results of biological testing against HIV-1 in vitro are presented.

AZT\textsuperscript{2} is the only drug approved for clinical use against AIDS\textsuperscript{2} at the present time but this drug displays severe bone-marrow toxicity.\textsuperscript{3} Other 2',3'-dideoxynucleosides (dd-N) such as dd-cytidine, dd-adenosine, and dd-inosine are presently undergoing clinical trials against AIDS\textsuperscript{4} but their potential as future drugs might be limited due to the instability of their glycosidic bond.\textsuperscript{5} Carbocyclic nucleosides in which the carbohydrate moiety is replaced by a carbocyclic ring exhibit increased stability to enzymic and acid hydrolysis. Furthermore several members of this class of nucleoside analogues, including carbovir\textsuperscript{7} (1), iso-dd-adenosine\textsuperscript{6} (2), cyclobut-A\textsuperscript{8} (3), cyclobut-G\textsuperscript{8} (4) or SQ-32,829\textsuperscript{9} (5) have demonstrated potent antiviral activities against herpes viruses and HIV, along with low cytotoxicity. We report herein the synthesis of new carbocyclic analogues of oxetanocin A\textsuperscript{10} and oxetanocin G, namely 6 and 7.

\[
\begin{align*}
1 & \quad \text{Base} = G \\
2 & \quad \text{Base} = A \\
3 & \quad \text{Base} = A \\
4 & \quad \text{Base} = G; \quad R = \text{CH}_2\text{OH} \\
5 & \quad \text{Base} = G; \quad R = \text{OH} \\
6 & \quad \text{Base} = A \\
7 & \quad \text{Base} = G
\end{align*}
\]

The starting material 3-methylenecyclobutanoyl chloride (8) was synthesized from allene and acrylonitrile via 3-methylenecarbonitrile and the corresponding carboxylic acid as described.\textsuperscript{11} Upon heating with sodium azide, 8
Scheme 1

\[ R = \text{H} \]
\[ R = \text{NH}_2 \]

Scheme 2

\[ R = \text{H} \]
\[ R = \text{NH}_2 \]
was converted in one pot successively to the acid azide (9) and isocyanate (10) which was slowly transformed to the amine hydrochloride (11) (Scheme 1). All this sequence can be carried out in good overall yield (≥ 50%) providing that the hydrolysis of 10 by aqueous hydrochloric acid is performed in the cold to avoid any addition of acid to the double bond.

Adenine and guanine precursors (17) and (18) were then elaborated from 13 and 14 \(^{12}\) respectively by a known two step sequence. Osmium tetroxide dihydroxylation of 17 led to a mixture of the cis/trans isomers (19) and (21) in a 1:1 ratio according to Nmr data (in 63% yield after column chromatography on silica gel). In the same way osmium tetroxide dihydroxylation of 18 led to a 1:1 ratio of the cis/trans isomers (20) and (22) (in 52% yield after chromatography). In each case the cis isomers (19) and (20) (primary alcohol function in cis with respect to the base) could be crystallized from ethyl acetate in 18 and 21% yield respectively. The stereochemistry of the primary alcohol function in 19 and 20 was assigned on the basis of X-ray crystallographic analysis. \(^{14}\) Treatment of 19 with liquid ammonia gave 6 (90%) whereas hydrolysis of 20 in diluted aqueous hydrochloric acid under reflux gave the guanine derivative (7) (73%) (Scheme 2).

In antiviral tests using CEM cells \(^{13}\) 6 was inactive while 7 showed low activity: 59% inhibition of the cytopathogenic effect by HIV-1 at 400μM. In addition 7 exhibited a weak inhibition of HIV reverse transcriptase (≤ 50%) at 400μM.

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REFERENCES AND NOTES

2. Abbreviations used: HIV, human immunodeficiency virus; AZT, 3'-azido-3'-deoxy-thymidine; AIDS, Acquired Immunodeficiency Syndrome; A, adenine; G, guanine.
14. All compounds gave satisfactory analytical data.
15: mp 116 °C. Yield of 81% after extraction (CH₂Cl₂) and column chromatography (silica gel, CH₂Cl₂-EtOH : 98:2).

**Program for crystal structure solution.** Univ. of Göttingen, Federal Republic of Germany) and full-matrix least squares (Scheldrick, G. M. (1986). SHELX86. Program for crystal structure solution. Univ. of Göttingen, Federal Republic of Germany) and full-matrix least squares (Scheldrick, G. M. (1986). SHELX86. Program for crystal structure solution. Univ. of Cambridge, England) : C,N,O,Cl anisotropic, H isotropic refinement to R = 4.2 %. Weighting scheme w = [σ²(F) + 0.001 F²]⁻¹, σ from counting statistics.

**Crystal structure.** C₁₀H₁₂N₅O₂Cl, M = 269.6. Crystal dimensions 0.5 x 0.3 x 0.3 mm³. Monoclinic, P2₁/n, Z = 4. a = 7.843(3), b = 21.427(9), c = 6.549(3) Å and β = 92.38(5)°. V = 1100 Å³, dₓ = 1.54, μ = 2.9 cm⁻¹. ω/2θ scan mode (2θ < 56°), hkl < 1, ikl < 29, 1 < 9. The data collection gave 5303 reflexions in which 2082 were independent and > 3σ(I). Scan speed 0.04° s⁻¹, scan width 1.1°. Lorentz-polarization, no absorption corrections. Direct methods (Scheldrick, G. M. (1986). SHELX86. Program for crystal structure solution. Univ. of Cambridge, England) : C,N,O,Cl anisotropic, H isotropic refinement to R = 4.2 %. Weighting scheme w = [σ²(F) + 0.001 F²]⁻¹, σ from counting statistics.
6 : mp 229-231° C (EtOH). $^1$H-Nmr (100 MHz, DMSO-$d_6$) : δ 2.57-2.76(m, 4H, H-2', H-4'), 3.35(m, 2H, CH$_2$OH), 4.84(t, J=2.9 Hz, 1H, OH), 5.02-5.27(m, 1H, H-1'), 5.12(s, 1H, OH), 7.16(s, 2H, NH$_2$), 8.16(1s, 1H, H-2), 8.26(1s, 1H, H-8).

7 : mp > 260° C (EtOH-H$_2$O). $^1$H-Nmr (100 MHz, DMSO-$d_6$) : δ 2.40-2.70(m, 4H, H-2', H-4'), 3.40(br d, 2H, CH$_2$OH), 4.87-5.08(m, 3H, H-1', 2 x OH), 6.48(s, 2H, NH$_2$), 7.83(s, 1H, H-8), 10.53(br s, 1H, NH).

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