SYNTHESIS OF CARBOCYCLIC OXETANOCIN ANALOGUES AS POTENTIAL ANTI-HIV AGENTS. PART 3[1]

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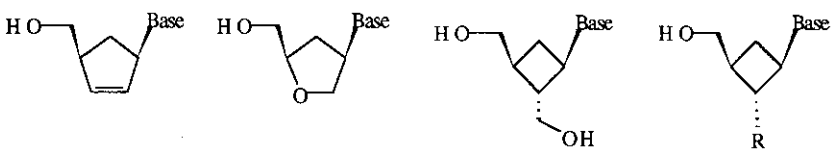
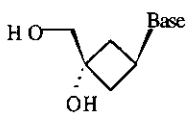
Abstract --------Two new carbocyclic oxetanocin analogues have been prepared from 1-amino-3-methylenecyclobutane. The results of biological testing against HIV-1[2] in vitro are presented.

AZT[2] is the only drug approved for clinical use against AIDS[2] at the present time but this drug displays severe bone-marrow toxicity.[3] Other 2',3'-dideoxynucleosides (dd-N) such as dd-cytidine, dd-adenosine, and dd-inosine are presently undergoing clinical trials against AIDS[4] but their potential as future drugs might be limited due to the instability of their glycosidic bond.[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[7] (**1**), iso-dd-adenosine[6] (**2**), cyclobut-A[8] (**3**), cyclobut-G[8] (**4**) or SQ-32,829[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[10] and oxetanocin G, namely **6** and **7**.



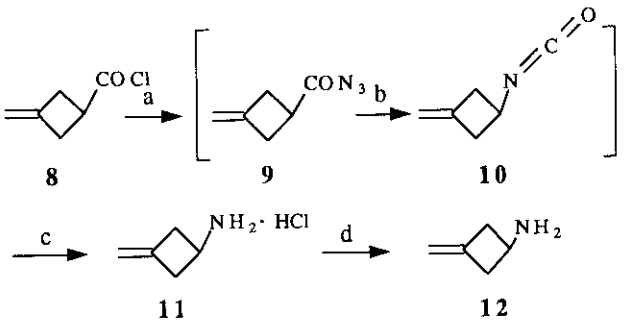
1 Base = G **2** Base = A **3** Base = A **4** Base = G; R = CH_2OH **5** Base = G; R = OH



6 Base = A

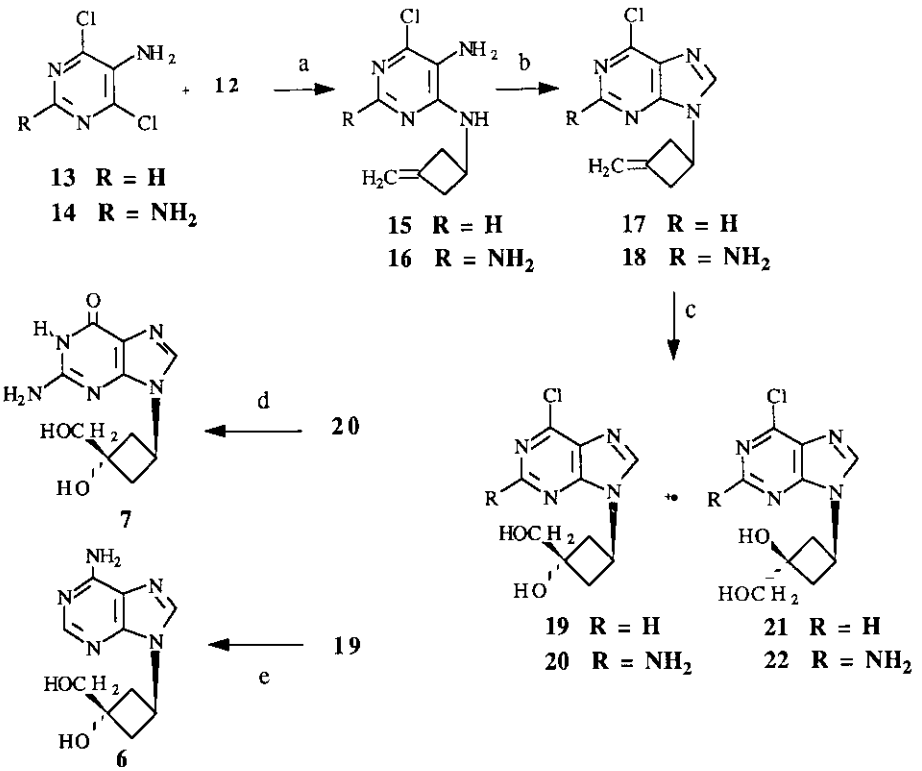
7 Base = G

The starting material 3-methylenecyclobutanoyl chloride (**8**) was synthesized from allene and acrylonitrile *via* 3-methylenecarbonitrile and the corresponding carboxylic acid as described.[11] Upon heating with sodium azide, **8**



a) : NaN_3, MeCOMe, H_2O, 0°C, 0.5 h; b) : 60°C, 1 h; c) : 2N HCl (1.5 equiv.), 0°C,2 h ; d) : KOH in excess, H_2O, distn. over KOH twice

Scheme 1



a) : n-BuOH, NEt_3, 100°C,48 h; b) : $HC(OEt)_3$, MeCN, cat. HCl, room temperature, 24 h; c) : OsO_4, N-methylmorpholine- N-oxide, t-BuOH, 85°C /N_2, 2.5 h ; d) 1 N HCl reflux, 6 h; e) : NH_3 , MeOH, room temperature, 24 h

Scheme 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.

ACKNOWLEDGMENTS

Financial support from the ANRS (Agence Nationale de Recherche sur le SIDA) is acknowledged. We are indebted to Marc Lemaitre, Rhône Poulenc Rorer, Vitry-sur-Seine for biological assays.

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2. Abbreviations used : HIV, human immunodeficiency virus ; AZT, 3'-azido-3'-deoxy-thymidine ; AIDS, Acquired Immunodeficiency Syndrome ; A, adenine ; G, guanine.
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14. All compounds gave satisfactory analytical data .

12 : bp 108°C. ^{1}H-Nmr (100MHz,DMSO-d_6) : δ 1.96(br s, 2H, NH_2), 2.24-2.55(m, 2H, H-2, H-4), 2.65-2.96(m, 2H, H-2, H-4), 3.38(q, J=5.5 Hz, 1H, H-1), 4.76(m, 2H, CH_2 =).

15 : mp 116° C. Yield of 81 % after extraction (CH_2Cl_2) and column chromatography (silica gel, CH_2Cl_2-EtOH : 98-2). ^{1}H-Nmr (100 MHz,$CDCl_3$) : δ 2.5-2.78(m, 2H, H-2', H-4'), 3.25-3.31(m, 2H, H-2', H-4'), 3.48(br s, 2H, NH_2), 4.57(q, J=6.8 Hz, 1H, H-1'), 4.90(m, 2H, CH_2=), 5.19(br d, J = 6 Hz, 1H, NH), 8.07(s, 1H, H-2).

16 : mp 147° C. Yield of 72 % after column chromatography (silica gel ,CH_2Cl_2-EtOH : 95-5). ^{1}H-Nmr (100 MHz, $CDCl_3$) : δ 1.72(br s, 2H, NH_2), 2.74(m, 2H, H-2', H-4'), 3.07(m, 2H, H-2', H-4'), 4.42-4.64(m, 3H, H-1', NH_2), 4.87(m, 2H, CH_2=), 5.57(br d, 1H, NH).

17 : mp 94° C (H_2O). (95 % yield). ^{1}H-Nmr (100 MHz, $CDCl_3$) : δ 3.28-3.48(m, 4H, H-2', H-4'), 5.08(m, 2H, CH_2 =), 5.16(q, J=7.8 Hz, 1H, H-1'), 8.24(s, 1H, H-2), 8.76(s, 1H, H-8).

18 : mp 136-137° C (EtOH) . Yield of 89 % after column chromatography (silica gel, CH_2Cl_2-EtOH : 98-2). ^{1}H-Nmr (100 MHz, $CDCl_3$) : δ 3.29-3.38(m, 4H, H-2', H-4'), 4.95(q, J=7.8 Hz, 1H, H-1'), 5.03(m, 4H, CH_2 = , NH_2), 7.91(s, 1H, H-8).

19 : mp 156-157° C ($CHCl_3$). ^{1}H-Nmr (100 MHz, DMSO-d_6) : δ 2.52(m, 2H, H-2', H-4'), 2.82(m, 2H, H-2', H-4'), 3.29-3.39(t, J=5.7 Hz, 2H, CH_2OH), 4.83(m, 1H, OH), 5.28(m, 2H, H-1', OH), 8.79(s, 1H, H-8), 8.81(s, 1H, H-2). Crystal structure. $C_{10}H_{11}N_4O_2Cl$, M = 254.6. Crystal dimensions 0.6 x 0.3 x 0.3 mm^3. Automatic, graphite monochromated (λ = 0.7107 Å) 4-circle Philips diffractometer. Monoclinic, $P2_1/n$, Z = 4. **a** = 7.843(3), **b** = 21.427(9), **c** = 6.549(3) Å and β = 92.38(5)°. V = 1100 Å^3, d_x = 1.54, μ = 2.9 cm^{-1}. ω/2θ scan mode (2θ < 56°), |h| < 11, |k| < 29, l < 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). SHELXS86. Program for crystal structure solution. Univ. of Göttigen, Federal Republic of Germany) and full-matrix least squares (Scheldrick, G. M. (1976). SHELX76. Program for crystal structure determination. Univ. of Cambridge, England) : C,N,O,Cl anisotropic, H isotropic refinement to R = 4,2 %. Weighting scheme w = $[\sigma^2(F) + 0.001\ F^2]^{-1}$, σ from counting statistics.

20 : mp 209-212°C (AcOEt). ^{1}H-Nmr (100 MHz, DMSO-d_6) : δ 2.10-2.82 (m, 4H, 2CH_2), 3.34(m, 2H, CH_2OH), 4.83(t, J=2.9 Hz, 1H, OH), 5.05-5.14(m, 2H, H-1', OH), 6.84(br s, 2H, NH_2), 8.26(s, 1H, H-8). Crystal structure. $C_{10}H_{12}N_5O_2Cl$, M = 269.6. Crystal dimensions 0.5 x 0.3 x 0.3 mm^3. Monoclinic, space group C2/c, Z = 8, a = 15.277(7), b = 8.022(4), c = 19.692(9) Å, and β = 105.59(8)°. V = 2325 Å^3, d_x = 1.54, μ = 2.8 cm^{-1}. 2θ < 64°, |h| < 21, |k| < 11, l < 29. The data collection gave 8049 measured data, in which 2675 were unique and > 3σ(I). Scan speed 0.045°s^{-1}, scan width 1.3°. Final R = 4.2 %, w = $[\sigma^2(F) + 0.003\ F^2]^{-1}$. Unmentioned data identical to that of **19**.

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, C$\underline{H}_2$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_2O). ^{1}H-Nmr (100 MHz, DMSO-d_6) : δ 2.40-2.70(m, 4H, H-2', H-4'), 3.40(br d, 2H, C$\underline{H}_2$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).

Received, 25th March, 1991