Short Communication

Potential Anti-HIV Active Pyranoid Analogs of AZT

Zbigniew Kaluza,[a] Erik B. Pedersen,[a,*] Carsten M. Nielsen[b] and Marek Chmielewski[c]

[a]Department of Chemistry, Odense University, DK-5230 Odense M, Denmark, [b]Retrovirus Laboratory, Enterovirus Department, Statens Seruminstitut, Amager Boulevard 80, DK-2300 Copenhagen, Denmark and [c]Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland

Kaluza, Z., Pedersen, E. B., Nielsen, C. M. and Chmielewski, M., 1990. Potential Anti-HIV Active Pyranoid Analogs of AZT. – Acta Chem. Scand. 44: 294–296.

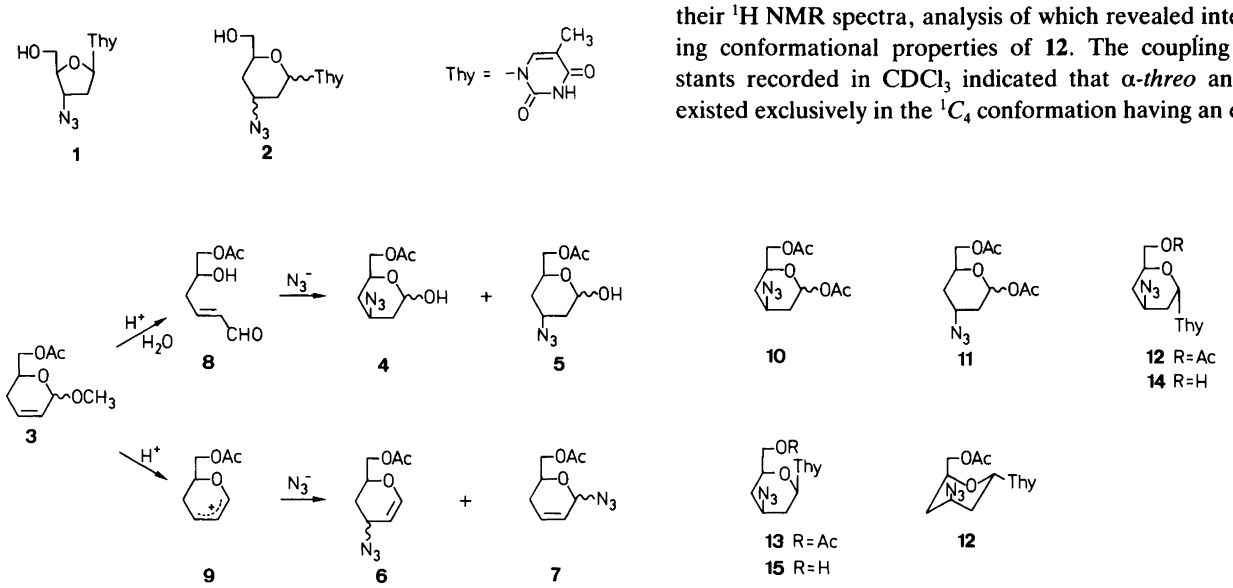
3′-Azido-3′-deoxythymidine (**1**; AZT) is a powerful and selective agent active against acquired immune deficiency syndrome (AIDS).[1] An essential step in the replicative cycle is the synthesis of DNA from viral RNA which is accomplished by using the viral enzyme, reverse transcriptase. Since AZT lacks the 3′-OH group of the natural substrates, DNA chain elongation is precluded. Several other dideoxynucleoside analogoues[2] show a selectivity index comparable to that of AZT and therefore it was of interest to investigate the synthesis of structurally related compounds. In this paper we explore a simple pathway leading to diastereomeric compounds **2** which are pyranoid analogs of AZT (**1**) and therefore offer potential anti-viral activity.

As the substrate we selected readily available racemic compound **3**.[3] The acetate **3** upon treatment with 80% aqueous acetic acid and sodium azide, at room temperature, for 7 days (Scheme 1) yielded a mixture of *threo* **4** (41%) and *erythro* compound **5** (30%) which was separated into pure components by silica chromatography. Diastereomers **4** and **5** were accompanied by an inseparable mixture of the glycal **6** and its regioisomer **7** (12%).

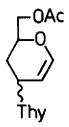
The structure and conformation of compounds **4–7** were assigned on the basis of ^1H and ^{13}C NMR spectra (see the Experimental). Integration of appropriate signals in the ^{13}C NMR spectra of **4** and **5** made it possible to determine the α,β anomeric composition of both mixtures.

On the basis of literature data[4] it is obvious that the formation of **4** and **5** via the hydrolysis of **3** to the α,β-unsaturated aldehyde **8** followed by a Michael addition of hydrazoic acid to the double bond in **8** and rapid formation of the hemiacetal ring. This way leads to a considerable quantity of *threo* isomer.[4,5] In contrast **6** and **7** are the result of a parallel reaction, involving the formation of cation **9**, followed by the preferred axial attack of the entering nucleophile.

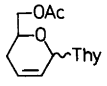
Acetylation of **4** and **5** with acetic anhydride and pyridine afforded, after silica chromatography, the 1-*O*-acetates **10** and **11**, respectively; α and β anomers of **10** and **11** were not separated. Reaction of *threo* acetates **10** with silylated thymine in a acetonitrile–1,2-dichloroethane mixture (4:3) in the presence of trimethylsilyl triflate at ca. 0 °C, for 4 min followed by silica chromatography gave two products **12** and **13** in 10 and 36% yield, respectively. Deduction of the configuration of **12** and **13** was based on interpretation of their ^1H NMR spectra, analysis of which revealed interesting conformational properties of **12**. The coupling constants recorded in $CDCl_3$ indicated that α-*threo* anomer existed exclusively in the $^1C_4$ conformation having an equa-



Scheme 1.



16



17

torial thymine residue. Deacetylation of **12** and **13** in a standard manner with ammonia in methanol afforded the stable, water soluble nucleosides **14** and **15**.

Reaction of *erythro* acetates **11** with silylated thymine under the same conditions proceeded in a more complicated way. The axial position of the azido group in **11** enables the ready elimination of hydrazoic acid and the formation, in very low yield, of a mixture of products which was not separated. Examination of ^1H and ^{13}C NMR spectra of this mixture showed presence of the glycal **16** and its regioisomer **17**.

In anti-HIV studies we used the HIV strain HTLV-IIIB and the MT-4 cell line. Compounds **13** and **15** did not show anti-HIV activity at 333 μM whereas compound **14** was toxic at 130 μM to MT-4 cells, but showed no significant anti-HIV activity.

Experimental

NMR Spectra. **4**: *NMR ($CDCl_3$) from the mixture of α and β-anomers (1:5).* α-anomer: ^1H NMR (250 MHz) selected data: δ = 1.42 (q, 1 H, H-4a, $J_{4a4e} \approx J_{4a5} \approx J_{4a3} \approx 12$ Hz), 1.59 (br t, 1 H, H-2a, $J_{23} \approx J_{2a2e} \approx 11.8$ Hz), 1.85–2.3 (m, 2 H, H-2e, H-4e), 3.94 (m, 1 H, H-3, $\Sigma|J| \approx 32.6$ Hz), 5.45 (brs s, 1 H, H-1). ^{13}C NMR (63 MHz): δ = 20.56 (CH_3), 33.05 (C-4), 37.84 (C-2), 52.26 (C-3), 65.65 (C-6), 66.26 (C-5), 91.63 (C-1), 170.78 (C=O).

β-anomer: ^1H NMR (250 MHz) selected data: δ = 3.57 (m, 1 H, H-3, $\Sigma|J| = 33.5$ Hz), 4.78 (br d, 1 H, H-1, $J_{12a} = 8$ Hz). ^{13}C NMR: δ = 32.35 (C-4), 37.84 (C-2), 55.3 (C-3), 65.81 (C-6), 70.5 (C-5), 94.25 (C-1).

5: *NMR ($CDCl_3$) from the mixture of α and β-anomers (2:5).* (Assignment as α or β may be interchanged). α-anomer: ^1H NMR (250 MHz) selected data: δ = 4.42 (m, 1 H, H-5, $\Sigma|J| = 18.6$ Hz), 5.31 (br s, 1 H, H-1). ^{13}C NMR δ = 30.64 (C-4), 32.64 (C-2), 53.29 (C-3), 61.56 (C-5), 66.21 (C-6), 90.84 (C-1).

β-anomer: ^1H NMR (250 KHz) selected data: δ = 5.08 (d, 1 H, H-1, $J_{12a} = 9.1$ Hz). ^{13}C NMR (63 MHz): δ = 30.57 (C-4), 35.68 (C-2), 55.38 (C-3), 66.00 (C-5), 91.92 (C-1).

NMR ($CDCl_3$) from the mixture of erythro *and* threo *isomers (3:1) of* **6** *and α and β (8:1) of* **7**. (Assignments as *threo* or *erythro* and α or β may be interchanged). **6**: *threo* isomer: ^1H NMR (250 MHz) selected data: δ = 4.80 (br t, 1 H, H-2), 6.51 (dd, 1 H, H-1, $J_{12} = 6.2$ Hz, $J_{13} \approx 0.8$ Hz). ^{13}C NMR: δ = 29.97 (C-4), 51.93 (C-3), 65.38 (C-6), 72.06 (C-5), 99.82 (C-2), 146.00 (C-1).

6: *erythro* isomer: ^1H NMR (250 MHz) selected data: δ = 4.96 (t, 1 H, H-2, $J_{23} = 6.1$ Hz), 6.65 (d, 1 H, H-1, J = 6.1 Hz). ^{13}C NMR (63 MHz): δ = 30.41 (C-4), 50.16 (C-3), 65.46 (C-6), 69.28 (C-5), 97.09 (C-2), 147.68 (C-1).

7: α-anomer: ^1H NMR (250 MHz) selected data: δ = 5.54 (br s, 1 H, H-1), 5.70 (m, 1 H, H-2), 6.09 (m, 1 H, H-3).^{13}C NMR (63 MHz): δ = 25.80 (C-4), 65.55 (C-5), 66.52 (C-6), 84.54 (C-1), 123.87 (C-2), 128.16 (C-3).

7: β-anomer: ^{13}C NMR (63 MHz) selected data: δ = 84.88 (C-1), 124.83 (C-3), 130.57 (C-2).

10: *NMR ($CDCl_3$) from the mixture of α and β-anomers (1:4).* ^1H NMR (250 MHz) selected data of α-anomer: δ = 1.50 (br q, 1 H, H-4a, $J_{4a4e} \approx J_{4a5} \approx J_{4a3} \approx 11.9$ Hz), 1.72 (dt, 1 H, H-2a, $J_{2a2e} \approx J_{2a3} \approx 12.5$, $J_{2a1} = 3.3$ Hz), 6.30 (br s, 1 H, H-1). ^{13}C NMR (63 MHz): δ = 32.57 (C-4), 34.05 (C-2), 52.37 (C-3), 65.66 (C-6), 67.96 (C-5), 91.44 (C-1).

^1H NMR (250 MHz) selected data of β-anomer: δ = 5.69 (dd, 1 H, H-1, $J_{12a} = 10$ Hz, $J_{12e} \approx 0.3$ Hz). ^{13}C NMR (63 MHz): δ = 32.19 (C-4), 35.21 (C-2), 55.02 (C-3), 65.40 (C-6), 71.42 (C-5), 92.00 (C-1).

11: *NMR ($CDCl_3$) from the mixture of α and β-anomers (1:10).* (Assignment as α or β may be interchanged). ^1H NMR (250 MHz) selected data of α-anomer: δ = 6.2 (br s, 1 H, H-1). ^{13}C NMR (63 MHz): δ = 29.86 (C-2), 51.57 (C-3), 65.83 and 65.42 (C-5, C-6), 90.29 (C-1).

^1H NMR (250 MHz) selected data of β-anomers: δ = 5.98 (dd, 1 H, H-1, $J_{12a} = 8.8$ Hz, $J_{12e} = 2.3$ Hz). ^{13}C NMR (63 MHz): δ = 30.53 (C-4), 33.58 (C-2), 54.63 (C-3), 65.55 (C-6), 69.69 (C-5), 90.60 (C-1).

12: *NMR ($CDCl_3$) selected data.* ^1H NMR (500 MHz): δ = 1.79 (dt, 1 H, H-4a, $J_{4ae} = 14.4$ Hz, $J_{4a5} \approx J_{4a3} \approx 4.6$ Hz), 2.10 (ddd, 1 H, H-4e, $J_{4e5} = 4.6$ Hz, $J_{4e3} = 5.8$ Hz), 2.16 (ddd, 1 H, H-2a, $J_{2a2e} = 13.7$ Hz, $J_{2a3} = 4.0$ Hz), 4.15 (dd, 1 H, H-6, $J_{65} = 4$ Hz), 4.20 (m, 1 H, H-3, $\Sigma|J| = 18.2$ Hz), 4.29 (m, 1 H, H-5, $\Sigma|J| = 22.6$ Hz), 4.58 (dd, 1 H, H-6, J_{66} = 12.2 Hz, $J_{65} = 8.4$ Hz), 5.97 (dd, 1 H, H-1, $J_{12a} = 8.8$ Hz, $J_{12e} = 3.6$ Hz). ^{13}C NMR (63 MHz): δ = 29.37 (C-4), 33.18 (C-2), 53.9 (C-3), 63.79 (C-6), 71.06 (C-5), 76.40 (C-1).

13: *NMR ($CDCl_3$) selected data.* ^1H NMR (250 MHz): δ = 1.41 (q, 1 H, H-4a, $J_{4a4e} \approx J_{4a5a} \approx J_{4a3} \approx 12.2$ Hz), 1.55 (q, 1 H, H-2a, $J_{2a1} \approx J_{2a2e} \approx J_{2a3} \approx 11.6$ Hz), 1.8–2.3 (m, 2 H, H-2e, H-4e), 3.7–4.0 (m, 2 H, H-5, H-3), 4.20 (m, 2 H, H-6), 5.75 (d, 1 H, H-1, $J_{12a} = 11.6$ Hz), 7.2 (s, 1 H, H–C=C), 9.78 (s, 1 H, NH). ^{13}C NMR (63 MHz): δ = 32.44 (C-4), 36.89 (C-2), 55.41 (C-3), 65.49 (C-6), 73.37 (C-5), 79.55 (C-1).

15: *NMR (CD_3OD) selected data.* ^1H NMR (250 MHz): δ = 1.35 (q, 1 H, H-4a, $J_{4a4e} \approx J_{4a5} \approx J_{4a3} \approx 12$ Hz), 1.56 (q, 1 H, H-2a, $J_{2a2e} \approx J_{2a1} \approx J_{2a3} \approx 11.6$ Hz), 1.85–2.1 (m, 2 H, H-2e,

H-4e), 5.60 (dd, 1 H, H-1, J_{12e} = 2.2 Hz). ^{13}C NMR (63 MHz): δ = 33.15 (C-4), 36.58 (C-2), 57.37 (C-3), 65.39 (C-6), 77.63 (C-5), 81.43 (C-1).

16: *^1H NMR selected data. threo:* 6.0 (br d, 1 H, H-1), 5.03 (m, 1 H, H-2). *erythro:* 6.0 (br d, 1 H, H-1), 4.75 (t, 1 H, H-2).

17: *^1H NMR selected data.* 6.55 (br s, 1 H, H-1), 6.3 (m, 1 H, H-3), 5.6 (m, 1 H, H-2).

Acknowledgements. The Danish Natural Science Research Council is gratefully acknowledged for their support.

References

1. Mitsuya, H., Weinhold, K. J., Furman, P. A., St. Clair, M. H., Lehrman, S. N., Gallo, R. C., Bolognesi, D., Barry, D. W. and Broder, S. *Proc. Natl. Acad. Sci. USA 82* (1985) 7096.
2. Horwitz, J. P. *Invest. New Drugs 7* (1989) 51.
3. Jurczak, J., Konowal, A. and Zamojski, A. *Rocz. Chem. 44* (1970) 1587; *Chem. Abstr. 74* (1971) 12938c.
4. Chmielewski, M., Jurczak, J. and Zamojski, A. *Tetrahedron 34* (1978) 2977.
5. Chmielewski, M. *Pol. J. Chem. 54* (1980) 1197.

Received October 2, 1989.