Chemistry of Natural Compounds and Bioorganic Chemistry

Transformations of β-D-xylofuranosyl nucleosides. Synthesis of 3′-azido-3′-deoxythymidine

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A modified synthesis of 3′-azido-3′-deoxythymidine starting from D-xylose is proposed.

Key words: nucleosides, D-xylose, 1-(5-*O*-benzoyl-2-deoxy-3-*O*-mesyl-β-D-xylofuranosyl)thymine, 3′-azido-3′-deoxythymidine.

The most well-known compound used in the chemotherapy of AIDS is 3′-azido-3′-deoxythymidine (**1**, AZT).[1,2] At present, numerous methods for the synthesis of this preparation exist (see, for example, Refs. 3—5). However, most of these methods are based on the use of natural thymidine, which is obtained by hydrolysis of DNA. Several procedures for the synthesis of AZT based on D-xylose are also known.[6—9] We propose a modified route for the synthesis of AZT; this route includes replacement of the 2′-OH group in 1-(5-*O*-benzoyl-3-*O*-mesyl-β-D-xylofuranosyl)thymine (**2**) (see Ref. 10) by chlorine (**2** → **3**) and subsequent reductive dehalogenation of chloride **3** upon treatment with Bu_3SnH in the presence of azobis(isobutyronitrile) to give 2′-deoxynucleoside **4**. Heating of compound **4** with 4 equiv. of NaN_3 in DMF at 150 °C affords 3′-azido-5′-*O*-benzoyl-3′-deoxythymidine (**5**) in 67% yield. The protective benzoyl group is removed by treatment with MeONa in MeOH. The overall yield of the target compound **1** based on D-xylose is 21%.

In the ^1H NMR spectrum of 2′-deoxynucleoside **4**, the signal for the H(1′) proton occurs at δ 6.33 as a doublet of doublets with spin-spin coupling constants ^3J = 3.32 and 8.03 Hz. On going to compound **5**, the signal for H(1′) transforms into a doublet of doublets with ^3J = 6.3 and 6.6 Hz (δ 6.2). The signal for the proton H(3′) (δ 4.40) shifts upfield (Δδ 0.98) in relation to that in the spectrum of compound **4** (δ 5.38). The protons H(2′) manifest themselves as two doublets of doublets at δ 2.40 and 2.56 with ^2J = −11.2 Hz. The ^1H and ^{13}C NMR data are fully consistent with the above-presented structures (Scheme 1).

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument operating at 300 and 75 MHz using $SiMe_4$ as the internal standard and $CDCl_3$ as the solvent. IR spectra were measured on a UR-20 instrument. Chromatography was performed on a column packed with silica gel LS 40/100 mm. The purity of the products was checked by TLC on Silufol UV 254 plates in the $CHCl_3$—MeOH (95 : 5) system.

The spectral parameters and the procedure for the synthesis of compound **2** were reported previously.[10]

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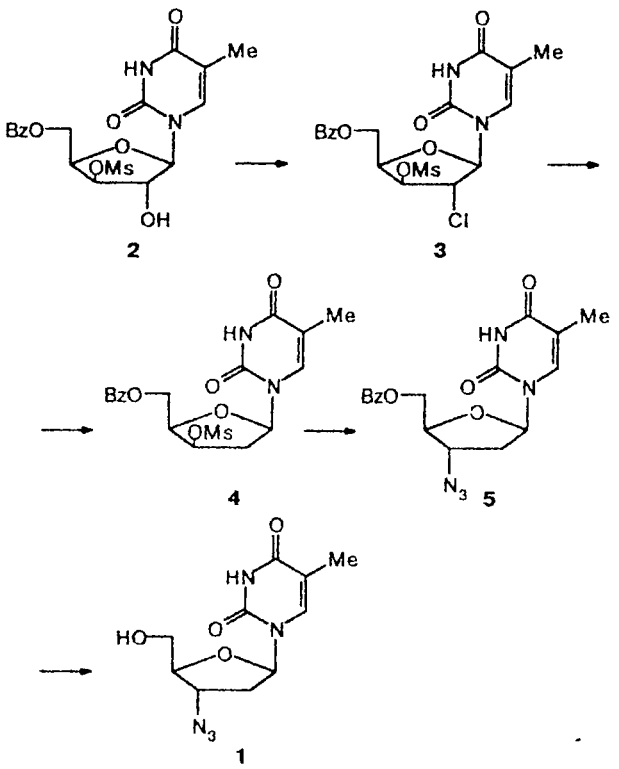
Scheme 1



1-(5-*O*-Benzoyl-2-chloro-2-deoxy-3-*O*-mesyl-β-D-xylofuranosyl)thymine (3). A solution of compound **2** (0.44 g, 1 mmol) and $SOCl_2$ (0.3 mL) in 4 mL of MeCN was refluxed for 3 h. The solvent was evaporated at 30 °C *in vacuo*, and the residue was distributed between ethyl acetate and water. The organic phase was separated, washed with a 5% solution of $NaHCO_3$ and water, dried with $MgSO_4$, and concentrated. The residue was dissolved in hot EtOH (7 mL), and the solution was refluxed with charcoal (0.2 g) and filtered. Evaporation of the EtOH gave 0.35 g (77%) of the product as a foam. R_f 0.36. ^{1}H NMR ($CDCl_3$), δ: 1.91 (d, 3 H, C(5)CH_3, J = 1.15 Hz); 3.12 (s, 3 H, CH_3SO_2); 4.62 (dd, 1 H, H(2′), $J_{2',3'}$ = 2.15 Hz, $J_{2',1'}$ = 2.71 Hz); 4.72 (dd, 1 H, H(5′b), $J_{5'b,4'}$ = 5.53 Hz, $J_{5'a,5'b}$ = −11.91 Hz); 4.78 (dd, 1 H, H(5′a), $J_{5'a,4'}$ = 5.60 Hz); 4.89 (m, 1 H, H(4′)); 5.29 (dd, H, H(3′), $J_{3',4'}$ = 3.68 Hz); 6.20 (d, 1 H, H(1′)); 7.67 (q, 1 H, H(6), J = 1.15 Hz); 7.47—8.08 (m, 5 H, Ar); 8.72 (s, 1 H, NH). Found (%): C, 46.82; H, 3.97; Cl, 7.32; N, 5.78. $C_{18}H_{19}ClN_2O_8S$. Calculated (%): C, 47.11; H, 4.14; Cl, 7.74; N, 6.11.

1-(5-*O*-Benzoyl-2-deoxy-3-*O*-mesyl-β-D-xylofuranosyl)thymine (4). A solution of Bu_3SnH (0.73 mmol) in 1 mL of toluene was added to a solution of compound **3** (0.28 g, 0.61 mmol) in 3 mL of dry toluene. The mixture was heated to 85 °C, azobis(isobutyronitrile) (10 mg) was added, and the mixture was stirred for 2 h at this temperature. The precipitate that formed after cooling of the solution was filtered off, washed with pentane, and dried in air. Yield 0.23 g (90%). R_f 0.30. ^{1}H NMR ($CDCl_3$), δ: 1.59 (s, 3 H, C(5)CH_3); 2.52 (ddd, 1 H, H(2′b), $J_{2'b,3'}$ = 1.0 Hz, $J_{2'a,2'b}$ = −13.6 Hz, $J_{2'b,1'}$ = 3.32 Hz); 2.70 (ddd, 1 H, H(2′a), $J_{2'a,3'}$ = 5.51 Hz, $J_{2'a,1'}$ = 8.03 Hz); 3.09 (s, 3 H, CH_3SO_2); 5.38 (ddd, 1 H, H(3′), $J_{3',4'}$ = 4.1 Hz); 4.51 (m, 2 H, H(5′a,b)); 4.41 (m, 1 H, H(4′)); 6.33 (dd, 1 H, H(1′)); 7.39 (s, 1 H, H(6)); 7.42—8.10 (m, 5 H, Ar); 8.21 (s, 1 H, NH). ^{13}C ($CDCl_3$, δ: 12.69 (C(5)CH_3); 38.72 (CH_3SO_2); 83.77 (C(1′)); 39.58 (C(2′)); 78.23 (C(3′)); 79.80 (C(4′)); 61.47 (C(5′)); 150.61 (C(2)); 163.75 (C(4)); 111.59 (C(5)); 128.63; 129.20; 129.76; 133.63 (C—Ar); 135.05(C(6)); 166.12 (PhC=O). Found (%): C, 50.68; H, 4.51; N, 6.43; S, 7.24. $C_{18}H_{20}N_2O_8S$. Calculated (%): C, 50.94; H, 4.72; N, 6.60; S, 7.55.

3′-Azido-5′-*O*-benzoyl-3′-deoxythymidine (5). A solution of compound **4** (0.43 g, 1 mmol) and NaN_3 (0.26 g, 4 mmol) in 5 mL of DMF was kept for 3 h at 150 °C. After cooling to room temperature, the reaction mixture was diluted with water, the product was extracted with ethyl acetate, and the organic layer was washed with water and dried with $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was chromatographed on a column with silica gel (8 g) to give 0.25 g (67%) of product **5**. R_f 0.37. IR, ν/cm^{-1}: 2112 (N_3). ^{1}H NMR ($CDCl_3$), δ: 1.61 (s, 3 H, C(5)CH_3); 2.40 (ddd, 1 H, H(2′a), $J_{2'a,3'}$ = 7.4 Hz, $J_{2'a,1'}$ = 6.6 Hz, $J_{2'a,2'b}$ = −11.2 Hz); 2.56 (ddd, 1 H, H(2′b), $J_{2'b,3'}$ = 4.7 Hz, $J_{2'b,1'}$ = 6.3 Hz); 4.22 (m, 1 H, H(4′)); 4.40 (ddd, 1 H, H(3′), $J_{3',4'}$ = 4.9 Hz); 4.59 (dd, 1 H, H(5′a), $J_{5'a,4'}$ = 3.7 Hz, $J_{5'a,5'b}$ = −12.2 Hz); 4.70 (dd, 1 H, H(5′b), $J_{5'b,4'}$ = 3.4 Hz); 6.20 (dd, 1 H, H(1′)); 7.40—8.05 (m, 6 H, H(6), Ar); 8.44 (s, 1 H, NH). Found (%): C, 54.96; H, 4.08; N, 18.47. $C_{17}H_{16}N_2O_5$. Calculated (%): C, 55.14; H, 4.32; N, 18.92.

3′-Azido-3′-deoxythymidine (1). Compound **5** (0.354 g, 1 mmol) was added to a 0.1 *M* solution of MeONa in MeOH (40 mL). The reaction mixture was kept for 24 h at room temperature and neutralized with the KU-2-08(H$^+$) cation-exchange resin. Then the cation exchanger was washed with MeOH, the combined filtrates were concentrated, and the residue was chromatographed on silica gel to give 0.238 g (95%) of product **1**. The physicochemical parameters of the compound obtained correspond to the published data.[4]

References

1. H. Mitsuya, K. J. Weinhold, P. A. Furman, M. H. St. Clair, S. Nusinoff-Lehrman, R. C. Gallo, D. Bolognesi, D. W. Barry, and S. Broder, *Proc. Natl. Acad. Sci. USA*, 1985, **82**, 7096.
2. E. De Clerq, *Antiviral Res.*, 1989, **12**, 1.
3. C. K. Chu, R. F. Shinazi, M. K. Ahn, G. V. Ullas, and Z. P. Gu, *J. Med. Chem.*, 1989, **32**, 612.
4. J. P. Horwits, J. Chua, and M. Noel, *J. Org. Chem.*, 1964, **29**, 2076.
5. R. P. Glinski, M. Sami Khan, and R. L. Kalamas, *J. Org. Chem.*, 1973, **38**, 4299.
6. H. Hrebanecky and A. Holy, *EP* 0301908: *Chem. Abstrs.*, 1989, **111**, 78550j.
7. N. B. Dyatkina and A. V. Azhayev, *Synthesis*, 1984, 961.
8. A. V. Rama Rao, M. K. Gurjar, and S. V. S. Lalitha, *J. Chem. Soc., Chem. Commun.*, 1994, 1255.
9. H. Meguro, H. Ozui, and A. Fujita, *JP* 01203399: *Chem. Abstrs.*, 1990, **112**, 77872z.
10. A. G. Mustafin, R. R. Gataullin, L. V. Spirikhin, I. B. Abdrakhmanov, and G. A. Tolstikov, *Zh. Org. Khim.*, 1996, **32**, 1842 [*Russ. J. Org. Chem.*, 1996, **32** (Engl. Transl.)].

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