

Structural Studies of 3- (1,2-O-Isopropylidene- α -D-xylosyl)-5-phenyl-1,2,4-oxadiazole

Ming Long ZHANG¹, Yu Xin CUI¹, Ling Tai MA¹, Li He Zhang^{1,*}
Yang LU², Bin ZHAO², Qi Tai ZHENG²

¹The National Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences,
Beijing Medical University, Beijing, 100083

²Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical
College, Beijing, 100050

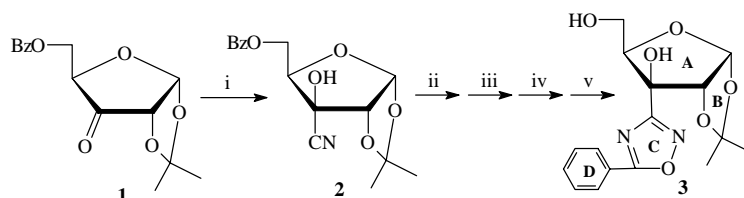
Abstract: 1,2-O-Isopropylidene-3-C-cyano-5-O-benzoyl- α -D-xylose **2** was prepared stereoselectively from 1,2-O-isopropylidene-3-oxo-5-O-benzoyl- α -D-xylose **1**. The structure of **2** was studied by two-dimensional NMR spectroscopy in conjunction with X-ray crystallography of its corresponding 5-phenyl-1,2,4-oxadiazole isocarbonucleoside derivative **3**. The absolute configurations of **2** and **3**, and conformation of **3** are described herein.

Keywords: 5-Phenyl-1,2,4-oxadiazole isocarbonucleoside; stereoselectivity; NMR spectroscopy; X-ray crystallography.

Our studies with isonucleosides and isocarbonucleoside have been carried out to search for anti-cancer and antiviral activities^{1,2,3}. Isocarbonucleoside is a new class of nucleoside analogues in which the nucleobase is linked to the position of ribose other than C_{1'} by carbon-carbon bond. The synthesis of carbonucleosides has been carried out successfully for several years^{4,5,6}. The synthesis of derivatives of 1,2,4-oxadiazole carbonucleoside bearing β -D-xylopyranosyl moiety has been reported^{7,8}. Some of them showed potent biological activities. Recently, a number of 5-aryl-1,2,4-oxadiazolines have been reported to possess anti-virus such as anti-HIV activities^{9,10,11}. In this paper, we report the synthesis and the structure of the isocarbonucleoside derivative 3- (1',2'-O-isopropylidene- α -D-xylosyl)-5-phenyl-1,2,4-oxadiazole **3**.

It has been found that only one isomer cyanohydrin **2** was obtained by a nucleophilic stereospecific addition of potassium cyanide to the ketose **1** in ether/water in 90% yield. When **2** was benzoylated and treated with hydroxyamine to provide amidoxime, then condensed with benzoyl chloride to form 5-phenyl-1,2,4-oxadiazole product, followed by debenzoylation to give the debenzoylated product **3**. In order to investigate the absolute configuration of **2**, we have studied on the structure of its corresponding derivative **3**, by two-dimensional NMR spectroscopy in conjunction with X-ray crystallography.

Scheme . (i) KCN/Et₂O/H₂O (ii) BzCl/Py (iii) NH₂OH/CH₃OH (iv) BzCl (v) CH₃ONa/CH₃OH



Experimental and Crystallography

The NMR spectra were recorded on Varian-INDVA-500 spectrometers with TMS as an internal standard. The X-ray crystal analysis sample was crystallized from an ethyl acetate-petroleum mixture in the form of colorless needle. The air dried crystal of **3** is a colorless transparent needle. The crystal size of the sample is 0.2 mm×0.2 mm×1 mm. Space group is P2₂1₂1. The crystal belongs to the orthorhombic system. The details of unit-cell parameters are: a=6.732 (2)Å, b=15.729 (1)Å, c=31.701 (1)Å. The volume of unit-cell is V= 3356.7 (3)Å³. Eight molecules are contained in one unit-cell Z=8.

The diffraction intensities of the crystal were collected on MAC DIP-2030K diffractometer. Radiation is done by graphite-monochromatized MoKα. The distance between the crystal and IP is 100 mm. The scan type is ω. The scan range is 0~180°, Δφ=5°, stationary count for 5° scan range. 36 pictures were taken for 8.5 minutes each. 3101 unique data were measured. Among them, 2974 are observable ($|F|^2 \geq 8\sigma|F|^2$).

All computations were performed on a computer with the direct method (SHELXS-86). 43 non-atom positions are obtained directly in E graph. The kinds of atoms are determined and corrected by full-matrix least-squares method. The locations of all hydrogen atoms are decided by geometry calculation method and difference Fourier synthesis. The final reliable factor: R=0.070, R_w=0.060 ($w=1/\sigma^2|F|$), (Δ/σ)_{max} =0.001, (Δρ)_{min} = -0.260 e/Å³, (Δρ)_{max} =0.240 e/Å³, S=2.732.

Result and Discussion

The X-ray crystal analysis of **3** shows that 1', 2'-oxygen of the xylofuranose (A) combined with acetone to form the isopropylidene ring (B). Both A and B are envelope conformation. The ¹H NMR spectrum: 1'-H, δ=6.00, J_{1',2'}}=3.5Hz; 2'-H, δ=4.77, J_{1',2'}}=3.5Hz, shows that the δ and J values quoted above were accurately determined from 2D GCOSY spectrum of **3**. The GNOESY spectrum of **3**, which indicates correlation of 1'-H with 2'-H, lends further support to the assignment of protons and the proposed conformation of **3** in solution. The correlations of both H_{1'} and H_{2'} with the H of methyl of isopropylidene agree the envelope conformation of A and B. The 3'-hydrogen of the xylofuranose is substituted by a 1,2,4-oxadiazole ring (C), and the 3-hydrogen of the 1,2,4-oxadiazole ring is substituted by a benzene (D). The C and D are in a plane conformation. The correlation of 3'-OH with 5'-OH expresses that both hydroxyl groups are in β side of the plane of xylofuranose (A), but B, C and D are in α side of the plane of A.

The result shows that the cyano group of **2** was introduced to C₃ from the α -face of furanose ring of **1**. This is probably due to the steric hindrance of the 5-benzoyl group on the β -face of furanose ring of **1**. Because **1** was prepared from D-xylose, the absolute configurations of C₁, C₂, C₄ of **1** are known the absolute configuration of C₃ of **2** is S.

The X-ray crystal analysis has found that an asymmetric unit contains both molecules with different conformations. It is clear that rotations of the bonds between 3'-C and 5-C make the conformations of the two molecules different. The dihedral angles between C and D are 5.0°, 6.4°. The torsion angles of 3'-O, 3'C, 5-C,4-N are 74.4° and -130.4°. There are intramolecular hydrogen bonds between oxygen of furan ring and 5'-O in the crystal. The intermolecular hydrogen bonds between 5'-O and 4'-O make the crystal stable. 5'-O \cdots 4'-O: 2.7355 Å (1+x,y,z), 2.7320 Å (1+x,y,z).

The molecular structure and atomic numbering **Scheme** of **3** as observed in the crystal structure are shown in **Figure 1**. **Figure 2** shows the crystal packing of **3** in projection on the a direction. **Figure 3** is the conformation comparison of two molecules with different conformations in an asymmetric unit of **3**.

Figure 1. crystal structure of **3**

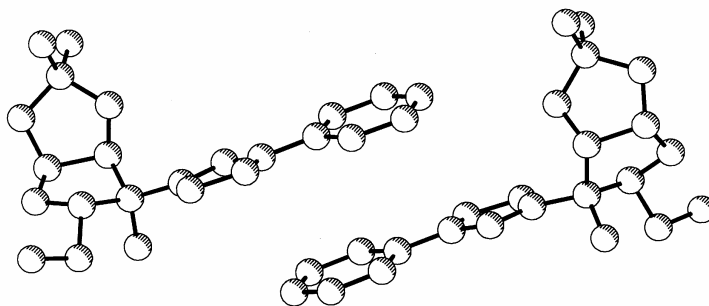


Figure 2. Crystal packing of **3** in projection on the a direction.

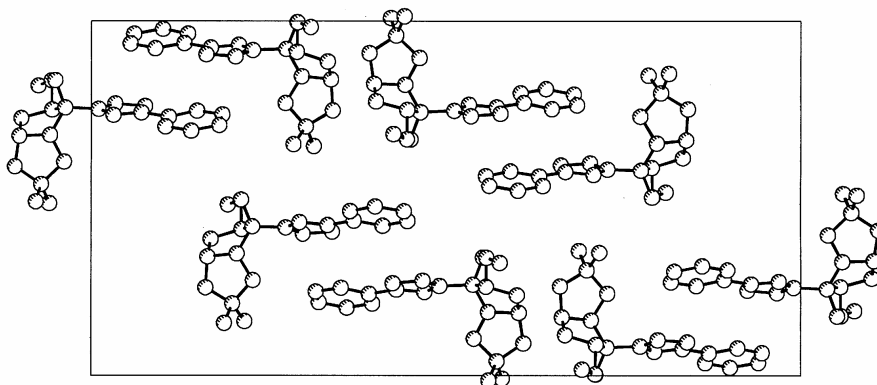
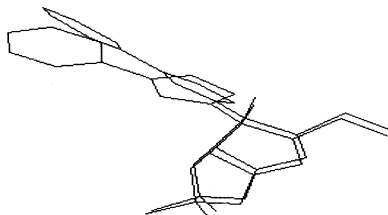


Figure 3. Conformation comparison of two molecules with different conformations in an asymmetric unit of **3**



Acknowledgments

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