Z-, *E*-Isomers of 1,2:4,5-di-*O*-cyclohexylidene-β-D-*erythro*-hexo-2,3-diulopyranose oxime

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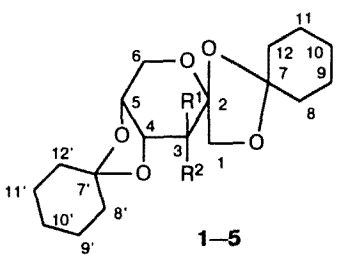
The syntheses of 1,2:4,5-di-*O*-cyclohexylidene-β-D-fructopyranose and 1,2:4,5-di-*O*-cyclohexylidene-β-D-*erythro*-hexo-2,3-diulopyranose were improved. A method for the separation of isomeric oximes of diulose was developed, and their structures were established by ^{13}C NMR spectroscopy. 3-Amino-3-deoxy-1,2:4,5-di-*O*-cyclohexylidene-β-D-psycopyranose was obtained.

Key words: D-*erythro*-hexo-2,3-diulopyranose oxime, geometrical isomers, aminodeoxy sugars.

Many aminodeoxy sugars are known to possess high biological activities and exhibit, *e.g.*, antimicrobial, antiviral, and antitumor effects.[1] Therefore, syntheses of new representatives of aminodeoxy sugars from ulose oximes are of interest.

This paper deals with the improvement of the syntheses of 1,2:4,5-di-*O*-cyclohexylidene-β-D-fructopyranose (**1**) and 1,2:4,5-di-*O*-cyclohexylidene-β-D-*erythro*-hexo-2,3-diulopyranose (**2**).



1—5

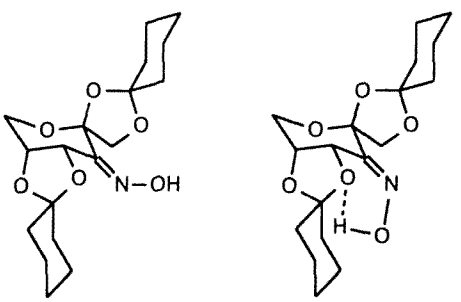
1: R^1 = OH, R^2 = H

2: R^1, R^2 = O

3, 4: R^1, R^2 = NOH

5: R^1 = H, R^2 = NH_2

The treatment of D-fructose with a large excess of cyclohexanone using sulfuric acid as a catalyst resulted in an increase in the yield of 1,2:4,5-di-*O*-cyclohexylidene-β-D-fructopyranose **1** by 23 % as compared with the reported procedure.[2] The oxidation of **1** with pyridinium dichromate (PDC) gave diulose **2** in a yield 10 % higher than that upon the oxidation with DMSO.[2] The treatment of diulose **2** with hydroxylamine yielded isomeric oximes that could not be separated earlier.[1,2] We pioneered in separating this mixture into the individual *Z*- (**3**) and *E*-isomers (**4**) of 1,2:4,5-di-*O*-cyclohexylidene-β-D-*erythro*-hexo-2,3-diulopyranose oxime by fractional crystallization and column chromatography. The reduction of both oxime **3** and oxime **4** resulted in the same product (**5**). The reduction of diulose **2** is known[2] to give the product of *ribo*-configuration. This suggests that compound **5** is 3-amino-3-deoxy-1,2:4,5-di-*O*-cyclohexylidene-β-D-psycopyranose.



Z-isomer (**3**) *E*-isomer (**4**)

The previous papers did not report the methods for the establishment of the configurations of these isomers. Therefore, we examined their ^1H and ^{13}C NMR spectra in details. ^1H NMR spectra of the isomers under study were found to have no marked difference and thus were not suitable for the assignment of configuration. However, ^{13}C NMR spectra of these substances have characteristic differences (Table 1). The signal for C(3) of the *Z*-isomer is shifted downfield by 3.2 ppm relative to that for the *E*-isomer that corresponds to the common rule.[3] As there is a hydrogen bond between the hydrogen atom of the oxime fragment and the oxygen atom at C(4) in the *E*-isomer, the rotation around the N—O bond is hindered, and the compound becomes more stable (the yield of the *E*-isomer is more than fourfold higher than that of the *Z*-isomer). At the same time, the

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nucleus of C(4) is somewhat shielded. It should also be mentioned that the signal of C(2) of the *Z*-isomer is shifted downfield by 2.6 ppm relative to that of the *E*-isomer.

Experimental

All reagents and solvents used were purified according to the known procedures. Melting points were measured on an MP-S3 (Japan) instrument. Elemental analyses were performed on an MT-3 (Japan) automatic analyzer. Optical rotations were measured on a Perkin Elmer-241 MC polarimeter. NMR spectra were recorded on a Bruker AC-80 (80 MHz for ^1H and 20.1 MHz for ^{13}C) spectrometer in $CDCl_3$ with $SiMe_4$ as the internal standard. IR spectra were recorded on a Perkin Elmer-PE-325 spectrophotometer. Column chromatography was performed on silica gel 100/200 μm (P. R. China) using the following eluents: (**A**) benzene—dioxane, 3 : 1; (**B**) benzene—methanol—diethyl ether, 8 : 1 : 1; (**C**) light petroleum—acetone, 10 : 1; and (**D**) light petroleum—acetone, 15 : 1. Solutions were concentrated *in vacuo* at a temperature not higher than 45 °C.

1,2:4,5-Di-*O*-cyclohexylidene-β-D-fructopyranose (1). Powdered dry D-fructose (18 g) was added to anhydrous cyclohexanone (160 mL) with stirring and cooling to 10 °C, and strong H_2SO_4 (2.8 mL) was added dropwise. The reaction mixture was stirred for 7 h, neutralized with $NaHCO_3$, and concentrated to give a residue that crystallized on storage. It was recrystallized from methanol to give (**1**) (18.8 g, 55 %) as white crystals, m.p. 144—145 °C, $[\alpha]_D^{22}$ −133.7° (*c* 1.0, $CHCl_3$) (lit.[2]: m.p. 145—146 °C, $[\alpha]_D^{20}$ −133.5° (*c* 1.0, $CHCl_3$)). R_f 0.58 (**A**), 0.73 (**B**).

1,2:4,5-Di-*O*-cyclohexylidene-β-D-*erythro*-hexo-2,3-diulopyranose (2). Acetic anhydride (13.6 mL) was added dropwise to a solution of pyridinium dichromate[4] (13.6 g) in anhydrous dichloromethane (100 mL) with vigorous stirring. Then a solution of compound **1** (17.0 g, 50 mmol) in dichloromethane (50 mL) was added, and the reaction mixture was refluxed for 1.5 h (TLC monitoring). The mixture was cooled, diluted with anhydrous diethyl ether (100 mL), and filtered. The filtrate was concentrated, and the residue was chromatographed on a column with silica gel (eluent **C**) to give diulose **2** (12.6 g, 75 %) as white crystals, m.p. 150—151 °C, $[\alpha]_D^{22}$ −91.1° (*c* 1.0, $CHCl_3$) (lit.[2]: m.p. 152—153 °C, $[\alpha]_D^{20}$ −90.0° (*c* 1.0, $CHCl_3$)). R_f 0.76 (**A**), 0.92 (**B**). Found (%): C, 64.10; H, 7.80. $C_{18}H_{26}O_6$. Calculated (%): C, 63.89; H, 7.74. IR, ν/cm^{-1}: 1730 (C=O).

***Z*- and *E*-Oximes of 1,2:4,5-di-*O*-cyclohexylidene-β-D-*erythro*-hexo-2,3-diulopyranose (3, 4).** A 10% aqueous solution of NaOH (230 mL) was added to a solution of $NH_2OH \cdot HCl$ (57.4 g) in 230 mL of water. A solution of **2** (18 g, 53 mmol) in methanol (500 mL) was added over 2 h with heating to 65 °C and stirring. The mixture was then cooled and concentrated *in vacuo*. The residue was dissolved in a minimum volume of methanol and cooled to give mainly crystals of *E*-isomer **4**. The crystals were filtered off, and the filtrate was concentrated to turbidity and kept to give mainly crystals of *Z*-isomer **3**. Each fraction was chromatographed on a column with silica gel using eluent **D** for the isolation of the *E*-isomer and eluent **C** for the isolation of the *Z*-isomer. ***Z*-Isomer**: yield 2 g (10.7 %), m.p. 159—169 °C, $[\alpha]_D^{20}$ −18° (*c* 1.0, $CHCl_3$), R_f 0.58 (**B**). Found (%): C, 61.8; H, 7.7; N, 3.9. $C_{18}H_{27}NO_6$. Calculated (%): C, 61.17; H, 7.70; N, 3.96. ^1H NMR, δ: 1.7 (m, 20 H, cyclohexylidene); 3.9—4.8 (m, 6 H, carbohydrate); 5.7 (s, N—OH). ***E*-Isomer**: yield 14.5 g (77 %), m.p. 188—189 °C, $[\alpha]_D^{20}$ −7° (*c* 1.0, $CHCl_3$), R_f 0.47 (**B**). Found (%): C, 61.80; H, 7.52; N, 4.11. ^1H NMR, δ: 1.7 (m, 20 H, cyclohexylidene); 3.9—4.8 (m, 6 H, carbohydrate); 5.5 (s, N—OH).

Table 1. Chemical shifts (δ) in ^{13}C NMR spectra of *Z*- and *E*-oximes **3** and **4**

Atom	*Z*-	*E*-	Atom	*Z*-, *E*-
C(1)	73.4	73.6	C(7)	103.7
C(2)	113.5	110.9	C(7′)	101.6
C(3)	151.7	148.5	C(8), C(12),	35.4—36.2
C(4)	73.6	75.4	C(8′), C(12′)	
C(5)	73.3	73.4	C(9)—C(11),	23.8—25.0
C(6)	64.4	64.5	C(9′)—C(11′)	

Table 2. Chemical shifts (δ) in ^{13}C NMR spectrum of aminosugar **5**

Atom	δ	Atom	δ
C(1)	69.5	C(7)	98.7
C(2)	101.5	C(7′)	96.1
C(3)	53.8	C(8), C(12),	30.4—32.2
C(4)	70.8	C(8′), C(12′)	
C(5)	69.3	C(9)—C(11),	20.1—22.2
C(6)	60.1	C(9′)—C(11′)	

3-Amino-3-deoxy-1,2:4,5-di-*O*-cyclohexylidene-β-D-psyco-pyranose (5). A solution of $LiAlH_4$ (3.4 g) in anhydrous THF (125 mL) was added dropwise to a solution of **3** (2.0 g, 5.66 mmol) in anhydrous THF (65 mL) with stirring. The mixture was stirred for 7.5 h and cooled to 5 °C. The excess of $LiAlH_4$ was slowly decomposed with water. The precipitate of inorganic salts was filtered off and washed with THF (3×20 mL), and the filtrate was dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give **5** (1.88 g, 98 %) as a syrup, $[\alpha]_D^{20}$ +38° (*c* 3.0, $CHCl_3$), R_f 0.65 (**B**). Found (%): C, 64.01; H, 8.41; N, 4.20. $C_{18}H_{29}NO_5$. Calculated (%): C, 63.69; H, 8.61; N, 4.13. IR, ν/cm^{-1}: 3329, 3400 (NH_2). Compound **5** (98 %, syrup) was also obtained from **4** in the same way, $[\alpha]_D^{20}$ +39° (*c* 3.0, $CHCl_3$), R_f 0.65 (**B**). Found (%): C, 64.03; H, 8.39; N, 4.19. IR, ν/cm^{-1}: 3329, 3400 (NH_2). ^{13}C NMR data is given in Table 2.

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References

1. W. Sowa, *Can. J. Chem.*, 1968, **46**, 1586.
2. K. James, A. R. Tatchell, and P. K. Ray, *J. Chem. Soc., C*, 1967, **24**, 2681.
3. Shen′ Chifan, *^{13}C Nuclear Magnetic Resonance Spectra*, P. R. China, Beijing University Press, 1988, 99 pp.
4. E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 1979, 399.

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