

Preparation and Structure Elucidation of
1,6,9,13-Tetraoxadispiro(4.2.4.2)tetradecane

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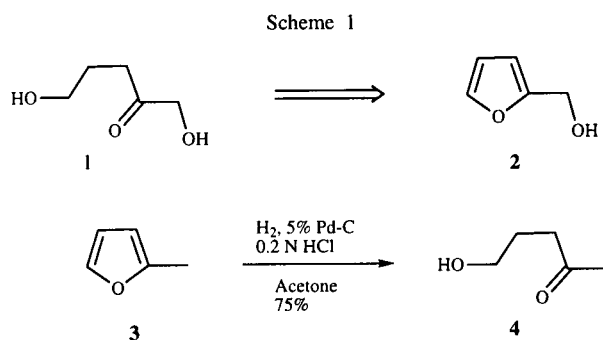
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The tricyclic title compound, a symmetrical dispiro oxygen heterocycle, was isolated as a byproduct in the hydrogenation of furfuryl alcohol in the presence of hydrochloric acid. NMR studies and single crystal X-ray analysis have established the relative stereochemistry of the two ketal carbons. Formation of the observed *trans* stereoisomer under equilibrating conditions is attributed to the anomeric effect.

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Introduction

In the course of a recent research project, the need arose to prepare the hitherto nearly unknown [1] 1,5-dihydroxy-2-pentanone (**1**) as a precursor to a substituted heterocycle. The synthesis was planned to proceed by reduction and hydrolysis of furfuryl alcohol (**2**), based on the reported[2] reduction of 2-methylfuran (**3**) to 1-hydroxy-4-pentanone (**4**) (Scheme 1).



Reduction of furfuryl alcohol in the presence of dilute hydrochloric acid did generate some of the desired ketonediol **1**, however, after distillation of the volatile products a solid product was observed in the distillation apparatus. Gas chromatographic analysis revealed that there was a considerable quantity of this byproduct present in the pot residue. Isolation and recrystallization of the white solid gave a product with a melting point of 95-98°C. A subsequent run of the reduction using less catalyst to minimize over-reduction gave a product mixture in which the previously observed product was the major component by gas chromatographic analysis. Workup, distillation of low boiling products and flash chromatography led to isolation of the solid product in 9% yield. Recrystallization from heptane gave a 5% yield of recrystallized product.

IR, NMR, and mass spectroscopic analysis led to the assignment of the backbone structure **5** to this product

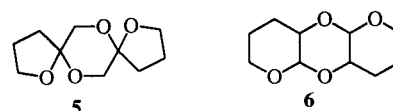


Figure 1

(Figure 1). CI-MS gave $(M + NH_4)^+ = 218$, indicating a molecular weight of 200. This product appeared to be a doubly dehydrated dimer of **1** ($118 + 118 - 2H_2O$). IR analysis showed that no carbonyl group was present. ¹H NMR analysis showed two distinct AB patterns at δ 3.4 - 4.2 and very complex multiplets at δ 1.6-2.2. The ¹³C NMR (DEPT) spectrum, on the other hand, showed only five signals, an unprotonated carbon at δ 102.4, and four methylene carbons at 67.7, 64.9, 33.6, and 23.3. The carbon spectrum showed that no olefin was present and that the dimer was highly symmetrical, with four methylene carbons bonded to oxygen and four bonded only to carbon.

A search of the literature for the molecular formula showed two earlier reports of structure **5**. Swadesh and Dunlop [3] reported a white solid isolated as a byproduct (0.8%) in the hydrogenation of furfuryl alcohol to tetrahydrofurfuryl alcohol without added acid. The solid had a melting point of 101-102°C and elemental composition and molecular weight leading to their assignment of structure **5** based on acid hydrolysis to a ketopentose. Their material was identical with a product isolated by another group [4] by a multistep procedure from glucose, however that work did not distinguish between structure **5** and structure **6** (Figure 1). It was clear from our NMR data that the first group was correct since no methine signals were observed.

The only structural question which remained was to distinguish between the RR, SS pair **5a** (*cis* with respect to A and C ring oxygen atoms) and the RS, SR **5b** (Figure 2,

only one isomer of **5a** shown; **5b** is a *meso* compound with *trans*-disposed A and C ring oxygen atoms). The degeneracy of the carbon signals from the two halves of the molecule in the ^{13}C NMR spectrum argued for structure **5b**, which has a center of inversion, over **5a**, which has no elements of symmetry when the six-membered ring is in a chair conformation.

Despite this NMR evidence, further consideration of possible conformations of **5a** revealed the possibility of non-chair conformations which could afford a simplified ^{13}C NMR spectrum due to symmetry. For example if **5a** were to exist in a boat or twist-boat conformation, the molecule would contain a C_2 axis (Figure 3).

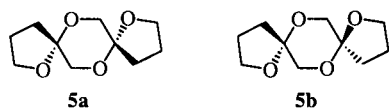


Figure 2

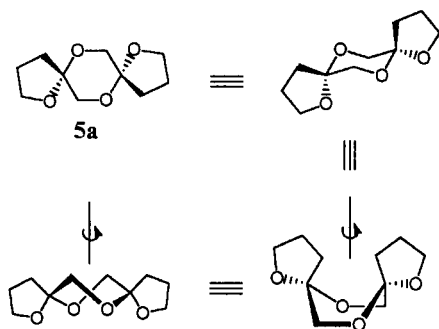


Figure 3

While we considered structure **5a** less likely for thermodynamic reasons, in order to establish the stereochemistry

Table 1
X-ray Structure Analysis

Formula	$\text{C}_{10}\text{H}_{16}\text{O}_4$
Molecular weight	200.23
Crystallization medium	heptanes
Color	Colorless
Cell dimensions	$a = 6.091(1)\text{\AA}$ $b = 8.812(2)\text{\AA}$ $c = 9.632(2)\text{\AA}$ $\beta = 100.242(3)^\circ$ $V = 508.7(1)\text{\AA}^3$
Space group	$\text{P2}_1/\text{c}$
Z	2
Density calcd.	1.307 g/cm^3
Linear absorption factor, mm^{-1}	1.00 cm^{-1}
Number of reflections	736
Observed reflections [$I > 3\sigma(I)$]	376
R	9.6
GOF	5.51

Table 2
Atomic Coordinates and Equivalent Isotropic Displacement Parameters

	x	y	z	B(eq)
O(1)	-0.120(1)	-0.0955(7)	0.3950(6)	6.3(1)
O(2)	0.225(1)	-0.1595(8)	0.6432(7)	6.8(2)
C(1)	0.050(1)	-0.052(1)	0.6416(8)	5.8(2)
C(2)	0.022(1)	-0.040(1)	0.7944(9)	6.4(2)
C(3)	0.258(2)	-0.069(1)	0.877(1)	7.8(3)
C(4)	0.366(2)	-0.155(2)	0.774(1)	9.0(3)
C(5)	-0.153(1)	-0.103(1)	0.5383(9)	5.8(2)

Table 3
Bond Lengths (\AA)

O(1)	C(1)	1.41(1)
O(1)	C(5)	1.43(1)
O(2)	C(1)	1.45(1)
O(2)	C(4)	1.46(2)
C(1)	C(2)	1.54(2)
C(1)	C(5)	1.48(2)
C(2)	C(3)	1.50(2)
C(3)	C(4)	1.50(2)

Table 4
Bond Angles ($^\circ$)

C(1)	O(1)	C(5)	114.2(8)
C(1)	O(2)	C(4)	109.3(9)
O(1)	C(1)	O(2)	108.1(8)
O(1)	C(1)	C(2)	108.2(9)
O(1)	C(1)	C(5)	112(1)
O(2)	C(1)	C(2)	103.4(9)
O(2)	C(1)	C(5)	108.0(9)
C(2)	C(1)	C(5)	117.0(9)
C(1)	C(2)	C(3)	104.1(9)
C(2)	C(3)	C(4)	105(1)
O(2)	C(4)	C(3)	107(1)
O(1)	C(5)	C(1)	112.4(9)

of **5a/b** single crystals were grown from mixed heptanes and analyzed by X-ray diffraction. The structure resulting from that analysis establishes the stereochemistry as *trans* with respect to the A and C ring oxygens (Figure 4). The molecule lies about an inversion center located in the center of the six-membered ring. The six-membered ring is a near perfect chair in the solid state. X-ray analysis details, non-hydrogen fractional atomic coordinates, bond lengths and angles are collected in Tables 1, 2, 3, and 4.

The formation of **5b** as the preferred isolable isomer in the dimerization of **1** can be rationalized as resulting from anomeric interactions.[5] In **5b** the oxygen atom of both five-membered rings occupies an axial position. While both **5a/b** may be kinetic products, rapid equilibration [6] to **5b** should occur under the acidic hydrogenation conditions. Such a configuration has also been established by X-ray crystallography for the closely related

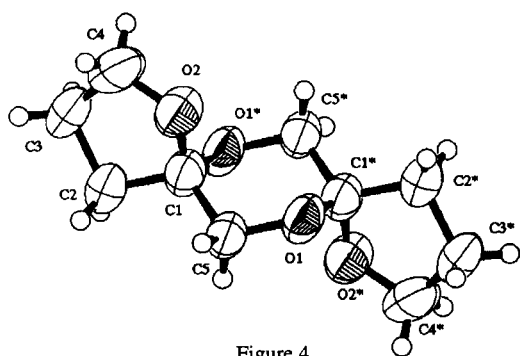


Figure 4

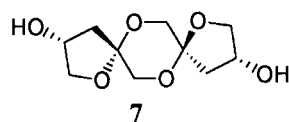


Figure 5

di-(3-deoxy-D-glycero-pentulose (Figure 5) [7].

The structure of the title compound, a dimeric byproduct from the hydrogenation of furfuryl alcohol, has been unambiguously established as **5b**.

EXPERIMENTAL

1,6,9,13-Tetraoxadispiro(4.2.4.2)tetradecane (**5b**).

A mixture of 25 g (0.255 moles) furfuryl alcohol, 7.5 ml 0.2N hydrochloric acid, 0.21 g 5% palladium on carbon, and 25 g acetone were hydrogenated on a Parr shaker apparatus at 40 psi for 2 hours and stopped after 110% of the theoretical amount of hydrogen was absorbed. The solution was neutralized to pH 7 with solid sodium carbonate and volatile solvents were removed by distillation. The residue was distilled at 1 Torr until solid was observed in the condenser. Flash chromatography

of the pot residue on silica gel eluted with 2:1 (v/v) heptane:ethyl acetate gave 2.40 g **5b**. Recrystallization from heptane gave 1.40 g **5b** with an uncorrected melting point of 95–98 °C. The crystal structure was determined on a Bruker SMART diffractometer by direct method using shelxs86 software.

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REFERENCES AND NOTES

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- [7a] Alfred D. French, George A. Jeffrey, Philip Pfeffer, Robert L. Dudley, Younghee Yeon, and Ernst Nitsch, *Carb. Res.*, **260**, 1 (1994). (b) E. Nitsch and B. Lotz, Eur. Pat. Appl. EP 432309 (1991), *Chem. Abst.* **116**:6917. It is of interest to note that the structure drawn in reference (7a), and subsequently abstracted into the *Chemical Abstracts* database, corresponds to **5a**. It does not agree with the X-ray crystal structure reported in the same paper, which corresponds to **5b**.