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Synthesis and Crystal Structure of Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene *exo,exo*-2,3-dicarboxylate

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Abstract Dimethyl-7-oxabicyclo[2.2.1]hept-5-ene *exo*, *exo*-2,3-dicarboxylate (1) was prepared by Fisher esterification of 7-oxabicyclo[2.2.1]-hept-5-ene *exo*-2,3-dicarboxylic anhydride (2) in methanol. The colorless plates obtained were characterized by FT-IR, ¹H- and ¹³C-NMR, TGA-DSC, and single crystal X-ray diffraction. The material crystallizes in space group P_{2_1}/c , with a = 9.2375(14) Å, b = 12.8757(18) Å, c = 9.4608(15) Å, $\beta = 115.327(3)^\circ$, V = 1017.1(3) Å³, and Z = 4. Chains of hydrogen-bonded molecules along the *c*-axis interact in the *b* direction to form layers parallel to the *bc* plane.

Keywords Oxanorbornene derivatives · 2D-NMR · Crystal structure · Thermal analysis

Introduction

As part of the undergraduate chemistry curriculum, the students in the organic chemistry laboratories are required

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Centro de Química, Instituto Venezolano de Investigaciones Científicas, Caracas, Venezuela to carry out projects, which involve common organic chemistry reactions. Over the years, we have encountered interesting results such as new polymorphs of previously reported compounds [1].

One of these projects involved the synthesis of a 7oxanorbornene derivative dimethyl-7-oxabicyclo[2.2.1] hept-5-ene *exo,exo*-2,3-dicarboxylate (*exo-diester*) (1) following an easy two-step procedure described in the literature [2]. Compound 1 was thus prepared by Fisher esterification of the adduct 7-oxabicyclo[2.2.1]-hept-5-ene *exo*-2,3-dicarboxylic anhydride (*exo-anhydride*) (2) which was prepared as described before [3].

It is interesting to note that the *endo*-diester is also produced in the synthesis following the procedure of France et al., as demonstrated by ¹H-NMR. However, only the *exo*-diester crystallized from the reaction mixture. A complete study by ¹H- and ¹³C-NMR is being carried out and will be published elsewhere.

These compounds, along with their endo counterparts, may be useful as starting materials for the synthesis of diastereomerically pure compounds [4, 5], and for the regioselective control of reactions of asymmetrical dienes and dienophiles [6]. They may also serve as monomers in ring-opening metathesis polymerizations (ROMP) [5], among other synthetic applications. In fact, the trans (exo, endo) isomer of 1 (Compound 3) was obtained as part of the synthesis of 1,4-anhydro- β -D-galactopyranose, a carbasugar analogue which has been proposed as an intermediate in the reaction catalyzed by uridine diphosphate-α-D-galactopyranose mutase (UDP-Galp mutase) [7]. This enzyme is essential for the survival of Mycobacterium tuberculosis and therefore is a possible target for antituberculosis agents.



Experimental

Synthesis and Preliminary Characterization

The compound dimethyl-7-oxabicyclo[2.2.1]hept-5-ene exo, exo-2,3-dicarboxylate (1) was prepared in two steps. The first step involves the Diels–Alder reaction between furan and maleic anhydride at room temperature to yield 7-oxabicyclo[2.2.1]hept-5-ene exo-2,3-dicarboxylic anhydride (2). The second step involves converting the anhydride to the diester in refluxing methanol by drop wise addition of concentrated HCl. The product was then recrystallized in hot methanol producing colorless plates upon cooling.

The IR spectra were recorded from KBr discs, using a PE-1600 FTIR Spectrometer with IRDM software. IR (cm⁻¹): λ (C–H sp² symmetric) 3098; λ (C–H sp² asymmetric) 3032; λ (C–H bridge head) 2290; λ (C–H sp ring) 2948; λ

(C=O) 1748 and 1732; λ (C=C tension) 1634; λ (C–O ester vibration) 1254.

The ¹H-NMR spectra were obtained on a Bruker Avance DRX 400. ¹H-NMR:(400 MHz; CDCl₃; $\delta_{\rm H}$, ppm); (2H (Csp²), s) 6.44; (2H (C bridge head), s) 5.25; (6H (2 methoxy groups), s) 3.68; (2H (H2 and H7), s) 2.81.

The ¹³C-NMR spectra were obtained on a Bruker Avance DRX 400. ¹³C-NMR: (100.13 MHz; CDCl₃; $\delta_{\rm C}$, ppm); (2C (C=O), s) 171.8; (C (Csp²), d) 136.5; (C (C bridge head), d) 80.3; (C (C methoxilic), q) 52.1; (C (α), d) 46.9.

Thermogravimetric analysis (TGA and DTG) and differential scanning calorimetry measurements (DSC) were performed in a Perkin-Elmer TGA7 thermal analyzer and a Perkin-Elmer DSC7 cell, under a dynamic dry nitrogen atmosphere at a heating rate of 10 °C min⁻¹. TGA (temperature range 25–500 °C): weight loss to only step 129.991–167.294 °C; DSC (temperature range 25– 125 °C): 119.2 °C, endo.

Single Crystal X-ray Data Collection and Structure Determination

Single crystal X-ray intensity data were collected on a Rigaku AFC7S diffractometer operating at 50 kV and 30 mA, with a Mercury CCD area detector, using MoK_{α} radiation $(\lambda = 0.71069 \text{ Å})$, and a graphite monochromator. A total of 235 images were collected in five sets of data with 2θ = -10.0858° , $\omega = 0^{\circ}$, and ϕ/χ values of $0^{\circ}/0^{\circ}$, $0^{\circ}/90^{\circ}$, $90^{\circ}/90^{\circ}$, $180^{\circ}/90^{\circ}$, and $270^{\circ}/90^{\circ}$. The image width was 2.00° in ω and the exposure time was 40 s. The crystal to detector distance was optimized at 41.168 mm. Unit cell parameters were determined from 1490 reflections in the range $2.90^{\circ} \leq \theta$ $\leq 28.10^{\circ}$ and were refined by least-squares [8]. Absorption, form, scale factor, among other corrections, were done by a multi-scan technique using a form function based on spherical harmonics [8]. The structure was solved by Direct methods with SHELXS [9]. Full matrix least-squares structure refinement was carried out with SHELXL [10]. Positions and anisotropic thermal parameters were refined for all non-hydrogen atoms. Hydrogen atoms were placed in calculated positions and were refined using a riding model with their U_{iso} equal to 1.2 times (1.3 for the methyl hydrogens) the U_{eq} of the carbon atom to which they are attached.

Results and Discussion

Characterization by Thermal and Spectroscopic Techniques

Compound (1) was characterized by FT-IR, ¹H-NMR, ¹³C-NMR, and thermogravimetric analysis (TGA-DSC). The FT-IR spectrum (Fig. 1) showed the characteristic



absorptions for this type of material. The ¹H-NMR experiment (Fig. 2) showed only four signals, indicating that the molecule is symmetrical in solution. There should be a plane bisecting the molecule through O1 and the C4–C5 and C2–C7 bonds. However, from this experiment it is not possible to determine the *endo* or *exo* conformation of the H2 and H7 protons, attached to C2 and C7, respectively. A NOESY (Nuclear Overhauser Effect Spectroscopy) would show the spatial relationships between the different protons in the molecule. The main evidence would be the interaction between the protons α with respect to the carbonyl carbon and the olefinic protons. The NOESY experiment, indeed, confirmed the *exo* configuration since the signal at 2.81 ppm, which corresponds to the H2 and H7 protons, interacts with the signal at 6.44 ppm which corresponds to the H4 and H5 protons, attached to the olefinic carbons C4 and C5.

From the structure of the *exo*-anhydride adduct (2) [3], the average distances H2 to H4 and H5 to H7 is approximately 2.97 Å. These distances are analogous to the H2 to

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H4 and H5 to H7 distances in the *exo*-diester (1), which are in average 2.88 Å. Since structural data on the related *endo* compounds is not available, the corresponding distances can be calculated based on the expected geometry of the compounds, using programs such CS ChemOffice Version 9.0 [CambridgeSoft, Cambridge, MA, USA]. The calculations are summarized in Table 1.

From these calculations, the distances between the protons under consideration in the *endo* adduct differ by 1.17 Å (4.17–3.00 Å) with respect to the *exo* diastereomer. Therefore, an experimental value of 4.05 Å (2.88 + 1.17 Å) would be expected for the *endo*-diester. This is in agreement with the NMR-NOESY experiment, where a distance of approximately 3.00 Å between the protons results in a medium– strong interaction whereas distances greater than 4.00 Å would produce weak interactions, which would be outside the detection limit of the experiment.

 Table 1 Distances between hydrogens involved in the NOESY interactions

	exo-anhydride		exo-diester	
	exo (Å)	endo (Å)	exo (Å)	endo (Å)
Theoretical	3.15	4.20	3.00	4.17
Experimental	2.97	-	2.88	-

The results of the TGA/DSC analysis of compound (1) is shown in Fig. 3. As evident from Fig. 3a, the material begins to suffer decomposition at 130 °C with peak temperature of 151.34 °C. The DSC, Fig. 3b, shows an endotherm with peak temperature of 119.20 °C, corresponding to a ΔH of 104.48 J/g. This transition corresponds to melting of the compound since it is not associated with a weight loss.



Fig. 3 (a) TGA and (b) DSC curves for dimethyl-7-oxabicyclo[2.2.1]hept-5-ene *exo,exo*-2,3-dicarboxylate (1)

Analysis of the Crystal Structure

Crystal data, experimental parameters and summary of refinement parameters are presented in Table 2. Table 3 contains relevant bond lengths and angles. Figure 4, obtained with Diamond [11], shows the molecular conformation with the atom numbering scheme. In the solid state the molecule is not completely symmetrical. The orientation of the carbonyl groups (C1–O2 and C8–O5) with respect to the six-member ring is different. The torsion angle O2–C1–C2–C3 is only –0.7(2)° while the C6–C7–C8–O5 torsion angle is 46.7(2)°. This may be due to the difference in hydrogen bonding and contact patterns for O2 and O5. O5 participates in only one long contact with the H6 atom of a molecule with symmetry operation 1-x, -y, 1-z [O5…H6–C6, O5…H6 2.637 Å, O5…C6 3.603(2) Å, angle 169.80°]. On the other hand, O2 participates in a chain

Table 2 Crystallographic data for Compound 1

	1	
CCDC deposit no.	CCDC 633223	
Color/shape	Colorless/plates	
Formula	$C_{10}H_{12}O_5$	
Formula weight	212.20	
Crystal size (mm)	$0.16 \times 0.24 \times 0.34$	
Crystal system	Monoclinic	
Space group	<i>P</i> 2 ₁ /c	
Unit cell dimensions		
a (Å)	9.238(1)	
<i>b</i> (Å)	12.876(2)	
<i>c</i> (Å)	9.461(2)	
β (°)	115.327(3)	
V (Å ³)	1017.1(3)	
Ζ	4	
$D_{\rm c}~({\rm g~cm^{-1}})$	1.386	
<i>F</i> (000)	448	
<i>T</i> (K)	290	
$\mu (MoK_{\alpha}) (mm^{-1})$	0.112	
θ range (°)	2.9; 28.1	
Limiting indices	$-11 \leq h \leq 11,$	
	$-14 \leq k \leq 14,$	
Absorption connection	$-9 \le l \le 11$	
Absorption correction	wuuu-scan	
In dependent reflections [1 (2 0=())]	11310/2017	
Independent reflections $[I (2.06(I))]$	$\frac{1099}{\Gamma}$	
Remement method	Full-matrix least-squares on F	
Einel Diadine [L(20 c(D)]	2017/0/136 D 0.0546 D 0.1407	
Final <i>R</i> indices $[I (2.0\sigma(I))]$	K_1 , 0.0546; WK_2 , 0.140/	
<i>R</i> indices (all data)	K_1 , 0.0008; WK_2 , 0.148/	
Goof	1.12	
Largest diff. peak and hole ($e A^{-3}$)	0.22 and -0.22	

 Table 3 Selected bond distances (Å) and angles (°) for Compound (1)

O1–C3	1.470(2)	C1–C2	1.481(3)
O1–C6	1.432(2)	C2–C3	1.518(3)
O2C1	1.209(2)	C2–C7	1.573(2)
O3-C1	1.322(2)	C3–C4	1.499(3)
O3-C10	1.422(3)	C4–C5	1.315(3)
O4–C8	1.335(2)	C5–C6	1.505(3)
O4–C9	1.424(3)	C6–C7	1.544(3)
O5–C8	1.220(2)	C7–C8	1.491(3)
C3O1C6	94.63(12)	O1-C6-C5	102.90(15)
C1-O3-C10	113.29(18)	O1-C6-C7	102.39(13)
C8–O4–C9	113.98(16)	C5–C6–C7	102.54(14)
O2C1O3	123.96(19)	C2-C7-C6	100.97(13)
O2C1C2	127.17(18)	C2–C7–C8	114.71(14)
O3-C1-C2	108.87(14)	C6–C7–C8	109.18(14)
C1C2C3	109.96(14)	O4–C8-O5	124.17(19)
C1C2C7	114.17(15)	O4–C8–C7	109.10(14)
C3–C2–C7	100.07(13)	O5–C8–C7	126.72(17)
O1-C3-C2	102.34(14)	С7-С2-Н2	111.00
O1-C3-C4	103.30(14)	С5-С4-Н4	128.00
C2-C3-C4	104.78(14)	C4-C5-H5	127.00
C3–C4–C5	104.99(17)	С2-С7-Н7	111.00
C4C5C6	106.61(17)		

hydrogen bond with H2–C2 from a molecule at *x*, $\frac{1}{2}-y$, $\frac{1}{2}+z$ [O2…H2 2.501 Å, O2…C2 3.480(2) Å, angle 178.00°]. This hydrogen bond can be described with the first order graph set symbol N₁ = C(4). The chains run parallel to the *c*-axis with the molecules alternating on both sides of the chains producing a sort of square-wave pattern (Fig. 5). They interact along the *b*-axis with another chain related by the *c*-glide plane to produce sheets almost par-



Fig. 4 Molecular structure of dimethyl-7-oxabicyclo[2.2.1]hept-5ene *exo,exo*-2,3-dicarboxylate (1) (Ellipsoids drawn at the 50% probability level)



Fig. 5 View of the structure of dimethyl-7-oxabicyclo[2.2.1]hept-5ene exo,exo-2,3-dicarboxylate (1) down the a axis

allel to the bc plane. These sheets stack along the *a*-axis and interact only through van der Waals contacts.

In contrast, the structure of the *exo,endo* isomer (3) [7] has a different hydrogen bonding pattern. The calculations performed using the data retrieved from the *Cambridge Structural Database*, Version 5.28 [12] for 3 (REFCODE VEBTOM) indicated that there is an intramolecular hydrogen bond between the carbonyl oxygen of the *exo* substituent (O2) and the β hydrogen atom (H3). This hydrogen bond [O2...H3–C3, O2...H3–2.43 Å, O2...C3 2.9147(16) Å, angle 109°] is described by the graph set

symbol S(5). Additionally, the bridge oxygen (O1) participates in a long contact with the bridge-head proton H6 of a molecule with symmetry operation -x, 1-y, -z [O1…H6– C6, O1…H6 2.60 Å, O1…C6 3.3709(17) Å, angle 134°]. It is interesting to note that the *endo* methyl ester group and the *endo* proton (H7) do not participate in intramolecular or intermolecular contacts of importance.

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