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Research Article

Synthesis and Molecular Structure of *tert*-Butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate

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The compound *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate was synthesized as a cyclic amino acid ester from the corresponding ethyl 2-amino-4-(2-oxiranyl)butanoate HCl salt via an intramolecular lactonization reaction and was characterized by using ^{1}H NMR spectroscopy and high-resolution mass spectrometry. The product was then recrystallized from dichloromethane/diethyl ether and its structure was determined via single crystal X-ray diffraction analysis. The crystal was found to be of the monoclinic space group $P2_1/c$ (no. 14) with $a = 10.217(2)$ Å, $b = 11.676(3)$ Å, $c = 10.273(3)$ Å, $\beta = 114.186(13)^\circ$, and $D_{calc} = 1.350$ g/cm^3 at 123 K. The compound has bicyclo[2.2.2]octane structure including a lactone moiety and a piperidine ring, and the two diastereomers of the molecules are present in a 1 : 1 ratio in the crystal.

1. Introduction

The compound hydroxypipecolic acid (5-hydroxy-2-piperidinecarboxylic acid) is a six-membered homologue of 4-hydroxyproline. Hydroxypipecolic acid is found in some natural plants such as date and acacia trees, whereas 4-hydroxyproline is found in animals (collagen) [1, 2]. Several hydroxypipecolic acid derivatives have been synthesized via the intramolecular reactions of precursors functionalized with epoxide groups [3–5]. Generally, a diastereomeric mixture of *cis*- and *trans*-5-hydroxymethylpipecolic acids has been obtained. The formation of 5-hydroxymethylprolines along with the desired 5-hydroxypipecolic acids has also been noted [4–6]. The intramolecular reaction from epoxide precursor suffers the formation of both stereoisomers (*cis* and *trans*) and regioisomers (pipecolic acid and proline). The synthetic reports so far seem to be confused because of the formation of many products. The straightforward method to isolate this rare amino acid, hydroxypipecolic acid, is still desired with a clear compound characterization.

Previously, we synthesized a 4-hydroxyproline derivative from an amino acid bearing epoxide [7]. During this study, we observed that the *cis* isomer underwent intramolecular lactonization. Then, the product lactone, *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate, was isolated from the *trans* ester with ease. It was expected that *cis*-5-hydroxypipecolic acids would also undergo intramolecular lactonization, whereas the *trans* isomers would not. Indeed, when a mixture of *cis*- and *trans*-5-hydroxypipecolic acids derivatives reacted under acidic conditions, the *cis* isomer was successfully converted to the lactone, *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate, which was readily separated from the remaining *trans*-5-hydroxypipecolic acids using simple silica gel column chromatography.

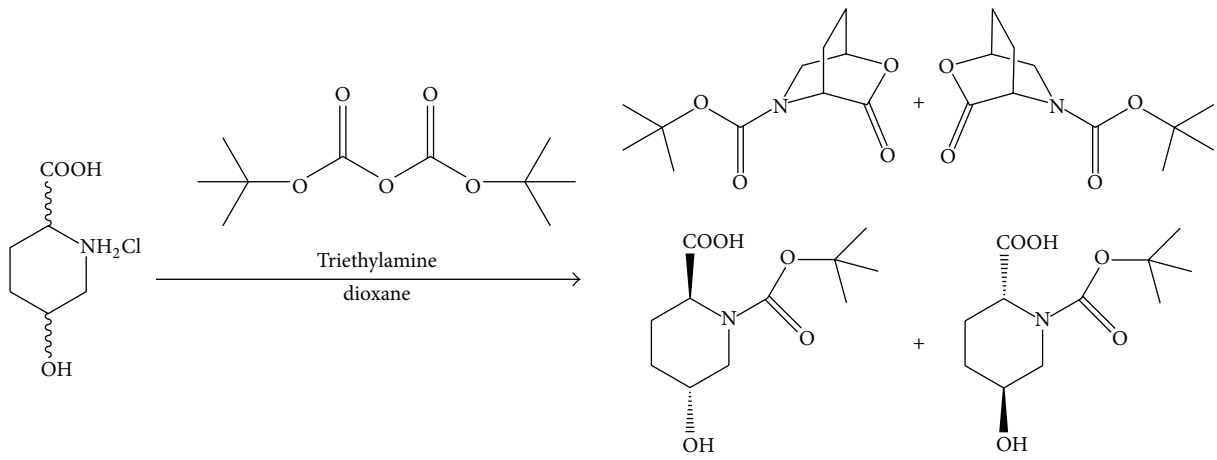

Figure 1: Synthesis of the starting material 5-hydroxypipecolic acid (left) and *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2, 2, 2]heptane-5-carboxylate (right).

2. Materials and Methods

All reagents and solvents were obtained from commercial sources and used as received.

The ^{1}H-NMR spectrum was recorded on a JEOL JNM α-500 spectrometer in $CDCl_3$ with tetramethylsilane (Me_4Si) as an internal reference. The positive fast atom bombardment (FAB) mass spectrum (MS) and high-resolution FAB mass spectrum of the compound were obtained on a JEOL JMS-SX102A spectrometer using nitrobenzyl alcohol (NBA) as the matrix and dichloromethane as the solvent. The instrument was operated in positive ion mode over an m/z range of 50–1000.

2.1. Synthesis of tert-Butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2] octane-5-carboxylate (Figure 1). Ethyl 2-amino-4-(2-oxiranyl)butanoate HCl salt was mixed with triethylamine (3.30 mL, 23.8 mmol) in dry dimethylformamide (48 mL) for 72 h. Subsequently, the solvent was evaporated and the residue was dissolved in 100 mL 1,4-dioxane. Di-*tert*-butyl dicarbonate (3.96 g, 18.1 mmol) and triethylamine (1.06 mL, 14.5 mmol) were added and stirred at room temperature for 18 h. After evaporation, the residue was dissolved in ethyl acetate, successively washed with 10% citric acid, 4% $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and then evaporated to give a mixture of the lactone and *tert*-butoxycarbonyl-*trans*-5-hydroxypipecolic acid ethyl ester as an oily mass. After silica gel column chromatography using chloroform as the eluent, the desired lactone *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate was obtained as white solid (0.67 g, 25% yield).

^{1}H NMR (500 MHz, $CDCl_3$) 1.47(s, 9H, *tert*-butyl H), 1.80(m, 1H, azabicyclo C–H), 2.00(m, 1H, azabicyclo C–H), 2.11(m, 1H, azabicyclo C–H), 2.22(br s, 1H, azabicyclo C–H), 3.45 (m, 1H, azabicyclo C–H), 3.63(m, 1H, azabicyclo C–H), 4.61–4.82(m, 2H, azabicyclo C–H). pos. FAB-MS: m/z 228 ($[M + H]^+$). HR-FAB-MS $[C_{11}H_{18}N_1O_4]^+$ ($[M + H]^+$): calculated = 228.12358, found = 228.1243.

Single crystals of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo [2.2.2]octane-5-carboxylate were obtained from a solution of dichloromethane/diethyl ether at room temperature. In principle, amino acids are moderately acid-sensitive and *tert*-butoxycarbonyl (Boc) group removal occurs in the presence of acidic air. Therefore, we carefully recrystallized the lactone from solution in absence of acidic air.

2.2. X-Ray Crystallography: Single-Crystal X-Ray Measurements and Structure Determination (Table 1). A colorless prismatic crystal of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate with the approximate dimensions 0.300 × 0.250 × 0.100 mm was mounted on a glass fiber. The data collection was performed on a Rigaku R-AXIS RAPID diffractometer using graphite monochromatized Cu–Kα-radiation (λ = 1.54187 Å) and a nominal crystal to area detector distance of 127.40 mm.

The data were collected at a temperature of 127 K to a maximum 2θ value of 136.4°. A total of 105 oscillation images were collected. Sweeps of the data were accomplished using ω scans from 50.0 to 260.0° in 10.0° steps, at χ = 50.0° and ϕ = 15.0°, χ = 50.0° and ϕ = 90.0°, χ = 50.0° and ϕ = 195.0°, χ = 50.0° and ϕ = 285.0°, and χ = 10.0° and ϕ = 60.0°. The exposure rate was 60.0 [sec/°] for all of the sweeps. Readout was performed in the 0.200 mm pixel mode.

Of the 13589 reflections that were collected, 2042 were unique (R_{int} = 0.0356); equivalent reflections were merged. The linear absorption coefficient, μ, for Cu–Kα radiation is 8.571 cm^{-1}.

An empirical absorption correction was applied that resulted in transmission factors ranging from 0.721 to 0.918. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods (SIR-97) [8], refined against F^2, and expanded using Fourier techniques. All nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms at carbon atoms were added geometrically and refined using a riding model (constrained).

The final cycle of full-matrix least-squares refinement (Least Squares function minimized: (SHELXL97): $\Sigma w (F_o^2 - F_c^2)^2$ where w = Least Squares weights) on F^2

Table 1: Crystallographic data.

Empirical formula	$C_{11}H_{17}N_1O_4$	
Formula weight	227.26	
Temperature	123 K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$ (no. 14)	
Unit cell dimensions	$a = 10.217(2)$ Å $b = 11.676(3)$ Å $c = 10.273(2)$ Å	$\beta = 114.186(13)^\circ$
Volume	1117.9(4) Å^3	
Z	4	
Density (calculated)	1.350 g/cm^3	
Absorption coefficient	0.857 mm^{-1}	
$F(000)$	488.00	
Crystal size	0.300 × 0.250 × 0.100 mm	
Theta range for data collection	3.79 to 68.26°	
Index ranges	$-12 \le h \le 12, -14 \le k \le 14, -12 \le l \le 12$	
Reflections collected	13589	
Independent reflections	2042 [R(int) = 0.0356]	
Reflections [$I > 2\sigma(I)$]	1845	
Completeness to theta = 68.26°	99.8%	
Absorption correction	Empirical	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2042/0/148	
Goodness-of-fit on F	1.195	
Final R_1 indices [$I > 2\sigma(I)$]	$R_1 = 0.0428$	
wR_2 indices (all data)	$wR_2 = 0.1266$	
Largest diff. peak and hole	0.30 and $-0.18e$Å^{-3}	

was based on 2042 observed reflections and 148 variable parameters and converged with unweighted and weighted agreement factors of $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.0428$ and $wR_2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma w(F_o^2)^2]^{1/2} = 0.1266$.

The standard deviation for an observation of unit weight (standard deviation of an observation of unit weight: $[\Sigma w(F_o^2 - F_c^2)^2/(N_o - N_v)]^{1/2}$ where N_o = number of observations, N_v = number of variables) was 1.20.

Neutral atom scattering factors were taken from Cromer and Waber [9]. Anomalous dispersion effects were included in Fcalc [10]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley [11]. The values for the mass attenuation coefficients were adopted from Creagh and Hubbell [12]. All calculations were performed using the CrystalStructure [13] crystallographic software package except for the refinement, which was performed using SHELXL-97 [14].

3. Results and Discussion

3.1. Synthesis of tert-Butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2] octane-5-carboxylate. The 5-hydroxypipecolic acid derivative *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate was synthesized from the mixture of *cis*- and *trans*-ethyl 2-amino-4-(2-oxiranyl)butanoate HCl salt via intramolecular lactonization. Under our experimental conditions, only the *cis*-isomer underwent lactonization to form a bicyclo[2.2.2]octane molecule probably during the workup. This lactone was nonpolar compared to the remaining *trans*-5-hydroxypipecolic acid derivative and thus it could be easily isolated as the mixture of (*S*, *S*) and (*R*, *R*) isomers.

No (*S*, *R*) and (*R*, *S*) isomers were obtained due to the structural properties of the starting compound.

3.2. Characterization of tert-Butyl 3-oxo-2-oxa-5-azabicyclo [2.2.2]octane-5-carboxylate. In the high resolution mass spectrum of the lactone, only two intensive signals with characteristic isotopic patterns for $[M + H]^+$ and $[M + Na]^+$ were detected. In the ^{1}H NMR spectrum, however, only several multiplets of proton signals corresponding to the methylene groups of the azabicyclo[2.2.2]octane ring were observed. Therefore, it was difficult to determine the exact structure of the molecule via ^{1}H NMR analysis.

A single-crystal X-ray diffraction study was thus performed on a crystal grown via the slow evaporation of a dichloromethane/diethyl ether (1 : 1) solution of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate. In general, amino acids are moderately acid-sensitive and Boc group removal occurs in the presence of acidic air. Therefore, we

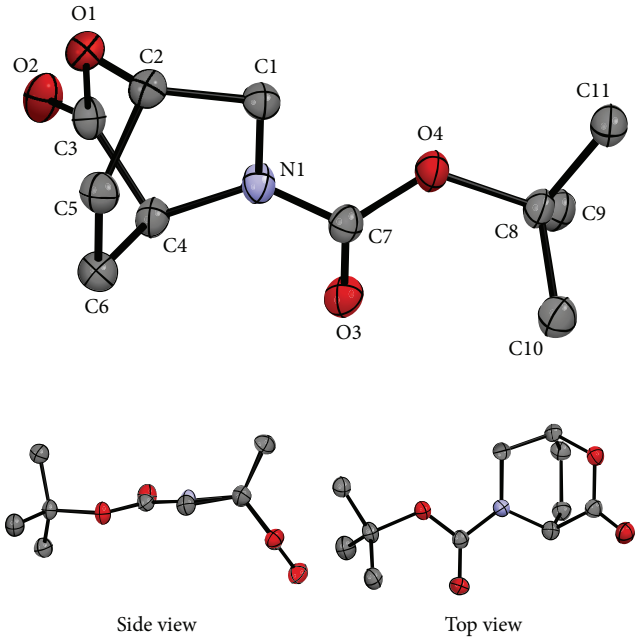

Figure 2: ORTEP view of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo [2.2.2]heptane-5-carboxylate. Hydrogen atoms are omitted for clarity. One of two isomers is only shown (below, side, and top view). Displacement ellipsoids are drawn at the 50% probability level. Blue and red ellipsoids show N and O atoms, respectively.

Table 2: Selected bond lengths (Å) and bond angles (°) for the compound.

O1–C2	1.475(3)	O1–C3	1.353(3)
O2–C3	1.203(3)	O3–C7	1.216(3)
O4–C7	1.3461(18)	O4–C8	1.479(3)
N1–C1	1.471(3)	N1–C4	1.464(2)
N1–C7	1.360(3)	C1–C2	1.520(3)
C2–C5	1.524(3)	C3–C4	1.526(3)
C4–C6	1.531(3)	C5–C6	1.548(3)
C8–C9	1.519(3)	C8–C10	1.516(3)
C8–C11	1.524(3)		
C2–O1–C3	112.77(16)	C7–O4–C8	121.03(14)
C1–N1–C4	114.75(15)	C1–N1–C7	124.37(13)
C4–N1–C7	120.84(14)	N1–C1–C2	105.57(12)
O1–C2–C1	107.49(13)	O1–C2–C5	108.06(13)
C1–C2–C5	112.44(18)	O1–C3–O2	120.66(19)
O1–C3–C4	112.23(15)	O2–C3–C4	127.08(17)
N1–C4–C3	107.03(14)	N1–C4–C6	109.67(14)
C3–C4–C6	106.59(16)	C2–C5–C6	108.73(14)
C4–C6–C5	107.62(13)	O3–C7–O4	126.41(18)
O3–C7–N1	124.16(15)	O4–C7–N1	109.43(15)
O4–C8–C9	109.35(13)	O4–C8–C10	111.30(16)
O4–C8–C11	102.20(15)	C9–C8–C10	111.35(16)
C9–C8–C11	111.06(16)	C10–C8–C11	111.23(13)

carefully recrystallized the lactone from solution in absence of acidic air. To the best of our knowledge, the exact structure of this lactone has not been characterized by X-ray analysis.

Molecular views of the compound were shown in Figure 2, and Table 2 lists selected bond lengths (Å) and bond angles (°) for the compound. Notably, the nitrogen atom N1 is located on the azabicyclo[2.2.2]octane ring. The local conformation of the piperidine ring on the azabicyclo[2.2.2]octane moiety is, on the other hand, fixed in the boat form exactly, by the lactone bridge linking the 2- and 4-positions of the piperidine ring.

The bicyclo[2.2.2]octane structure is slightly strained in the crystal lattice. The influence of crystal packing leads to a large increase in the bond length O1–C2 (1.475(3) Å) bond compared to that of the normal C–O bond (O4–C7 (1.3461(18) Å)). In addition, the shorter bond length of the N1–C7 (1.360(3) Å) is due to the effect of the π-conjugation in the C7–O3 double bond on the lone pair of N1. Furthermore, the bond lengths of the C–C single bonds in the bicyclo[2.2.2]octane framework are normal values at approximately 1.53 Å (Table 2) for each diastereomer. In the bicyclo[2.2.2]octane ring plane, the dihedral angle between C4–N1–C1–C2 and C2–O1–C3–C4 is 60.33°, between C2–O1–C3–C4 and C2–C5–C6–C4 is 61.55°, and between C4–N1–C1–C2 and C2–C6–C5–C4 is 58.16°. The difference in the dihedral angles can be explained by the greater length of the lactone bridge compared to that of the bridges of the piperidine ring.

The compound crystallizes in the space group $P2_1/c$ (no. 14) with two pairs of (*S*, *S*) and (*R*, *R*) diastereomers in the unit cell ($Z = 4$, Figure 3). No intra- and intermolecular hydrogen bonds exist in the crystal, but some intermolecular short contacts appear (Figure 4). The intermolecular short contacts are also listed in Table 3. In addition, no solvent molecules are included in the crystals.

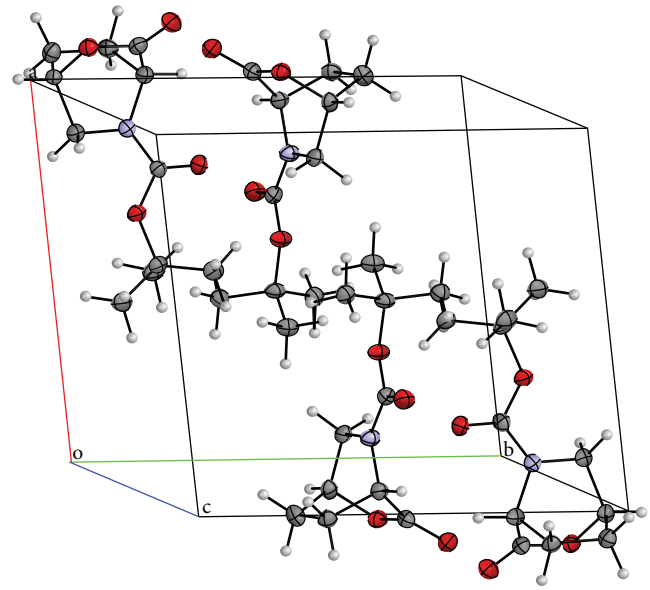

Figure 3: Crystal packing of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo [2.2.2]heptane-5-carboxylate. Blue and red ellipsoids show N and O atoms, respectively.

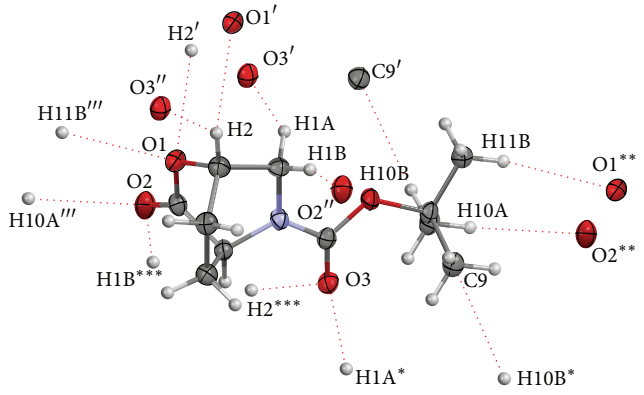

Figure 4: Intermolecular short contacts of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]heptane-5-carboxylate. Blue and red ellipsoids show N and O atoms, respectively.

Table 3: Intermolecular short contacts (Å) in the crystal.

O1–H2′	2.578	H2–O1′	2.578
O1–H11B‴	2.712	H2–O3″	2.612
O2–H10A‴	2.717	H1A–O3′	2.608
O2–H1B***	2.603	C9–H10B*	2.878
O3–H1A*	2.608	H10A–O2**	2.717
O3–H2***	2.612	H10B–C9′	2.878
H1B–O2″	2.603	H11B–O1**	2.712

Interestingly, the tricyclic moieties in the crystal exist along the crystallographic plane with a Miller index of (001). On the other hand, the Boc groups build up a two-dimensional hydrophobic domain along the crystallographic plane with a Miller index of (200).

Lechner et al. reported X-ray analysis of *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate [15]. The molecular structure of the azabicyclo[2.2.1] compound was highly strained because the compound includes a five-membered pyrrolidine ring moiety. Although the lactone having bicyclo[2.2.2] moiety which we reported in this paper was slightly strained, the distortion degree is very small compared to the azabicyclo[2.2.1] compound.

4. Conclusions

The lactone *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2] octane-5-carboxylate as a cyclic amino acid ester consisting of lactone and a piperidine group was synthesized and characterized by ^{1}H NMR spectroscopy, pos.FAB-MS, and high-resolution-MS. Its exact structure was determined via single crystal X-ray diffraction analysis. The 1 : 1 ratio of the (*S*, *S*) and (*R*, *R*) diastereomers of the compound is included in the centrosymmetric unit cell.

Additional Information

CCDC no. 991740 contains the supplementary crystallographic data for the compound *tert*-butyl 3-oxo-2-oxa-5-azabicyclo[2.2.2]octane-5-carboxylate (Supplementary Material available online at http://dx.doi.org/10.1155/2014/645079). The data can be obtained free of charge via http://www.ccdc.cam..ac.uk/data_request/cif by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallography Data Centre, 12 Union Road, Cambridge, CB2 IEZ, UK. Fax: +44(0) 1223-336033.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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