Abstract: (S)-1-Methyl-2-oxoimidazolidine-4-carboxylic acid 1 is an analog of (S)-pyroglutamic acid, a key component of naturally occurring peptide hormones and synthetic pharmaceutical candidates. The reaction of (S)-2-amino-3-(methylamino)propionic acid with COCl₂ and aqueous NaHCO₃ followed by ion exchange afforded 1, which was recrystallized from acetonitrile and then characterized by IR, ¹H NMR, ¹³C NMR, polarimetry, elemental microanalysis, high-resolution mass spectrometry and single-crystal X-ray diffraction. The acid 1 crystallized in the orthorhombic chiral space group P₂₁2₁2₁ with cell constants a = 6.2275(4) Å, b = 8.3963(5) Å, c = 24.9490(14) Å. The X-ray crystal structure revealed that two distinct conformers of 1 occur at alternating positions within helices which are supported by hydrogen bonds. Each molecule of 1 is linked to its two neighbors in the helix by a total of three hydrogen bonds, and four molecules of 1 are contained within each turn of the helix. The pattern of hydrogen bonds illustrates a preference for the carboxylic acid group to act as a hydrogen bond donor and for the urea unit to be a hydrogen bond acceptor.

Keywords: X-ray structure; imidazolidine-2-one; amino acid; urea; phosgene

1. Introduction

The heterocyclic amino acid derivative (S)-1-methyl-2-oxoimidazolidine-4-carboxylic acid 1 (Figure 1) is a structural analogue of naturally occurring (S)-pyroglutamic acid 2, which forms the N-termini of several biologically active peptides, including thyrotropin-releasing hormone (TRH) and luteinizing hormone releasing hormone (LH-RH) [1,2]. 1 is both a precursor to, and a metabolite of, the angiotensin converting enzyme (ACE) inhibitor imidapril 3, which is used for the treatment of hypertension [3–5]. Furthermore, the incorporation of 1 into synthetic drug candidates has been reported in recent patents that are related to a range of conditions, including pain [6], cancer [7] and hepatitis C [8].

Previously, 1 has been prepared by the deprotection of the corresponding alkyl esters [8], which can be made in several steps from asparagine derivatives, using Hofmann degradation chemistry to modify the amide side chain [3]. Racemic 1 has also been formed in situ via a reaction of rac-2-amino-3-(methylamino)propionic acid hydrochloride 4 with
phosgene under alkaline conditions but was further transformed into its methyl ester without being isolated [9]. Only limited characterization data (e.g., $^1$H NMR and low-resolution mass spectra) are available for 1. In particular, the crystal structure of 1 appears not to have been determined, despite the interesting possibilities for hydrogen bonding and polymorphism that exist in similar compounds, as exemplified by the reversible thermostalience (jumping when placed on a heated surface) of (S)-pyroglutamic acid 2 crystals [10].

Here, we report the preparation, isolation, characterization, and X-ray structure determination of (S)-1 formed in one synthetic step (Scheme 1), starting with (S)-2-amino-3-(methylamino)propionic acid (BMAA) hydrochloride 4, an amino acid salt that is commercially available from Merck and other suppliers of fine chemicals.

![Scheme 1. Preparation of (S)-1-methyl-2-oxoimidazolidine-4-carboxylic acid 1 from (S)-2-amino-3-(methylamino)propionic acid hydrochloride 4.](image)

2. Results

(S)-1-Methyl-2-oxoimidazolidine-4-carboxylic acid 1 was prepared via the reaction of amino acid 4 with phosgene in the presence of excess sodium hydrogencarbonate (Scheme 1). The cyclized product 1 was water-soluble, so the aqueous solution was passed through a column of Dowex 50WX2-100 strongly acidic ion-exchange resin in the $H^+$ form to convert the sodium salt into the free carboxylic acid species, which was recrystallized from hot acetonitrile after lyophilization to remove water. The acid 1 was characterized by elemental analysis, infrared, $^1$H NMR (Supplementary Materials, Figure S1) and $^{13}$C NMR data (Figure S2) and high-resolution mass spectrometry (Figure S3), which are consistent with the free acid obtained with >99% purity. The melting point and NMR data for acid 1 matched those of a sample that we prepared from $N$-benzyloxy carbonyl-L-asparagine in four steps according to the method of Lemieux et al. [7]. Crystals of 1 were heated on a hot-stage microscope from an ambient temperature to their melting point of 183 °C; thermostalience was not observed under these conditions, whereas it did occur for (S)-2.

A single-crystal X-ray diffraction study (Figure 2) confirmed the structure of 1, in which all molecules have the same enantiomeric form and occupy the chiral space group $P2_12_12_1$; a CIF report for this crystal structure is available in the Supplementary Materials associated with this paper.

Two crystallographically independent conformers of (S)-1 were present within the unit cell of 1. Both conformers adopt flattened half-chair conformations to accommodate trigonal planar geometry at the urea carbonyl carbon atoms; in one of the conformers, the carboxylic acid substituent is pseudo-equatorial with respect to the heterocyclic ring, whereas in the other conformer, the carboxylic acid is pseudo-axial. These differences are illustrated by the observed $C_{\text{urea}}{}\text{N}\cdots C-C_{\text{carboxyl}}$ torsion angles of 145.9° and 109.0° in the two conformers. The molecules of 1 each possess two potential hydrogen bond donor groups (urea N-H and carboxylic acid O-H) and two potential hydrogen bond acceptors (urea C=O and carboxylic acid C=O). The crystal structure of 1 contains helical assemblies of 1’s molecules linked by hydrogen bonds in which the two conformers alternate, with each turn of the helix comprising four molecules of 1 (Figure 3). Each molecule of 1 participates in a total of three hydrogen bonds that connect it to two neighbors within a helical chain. Every carboxylic acid O-H forms a hydrogen bond to the urea C=O of its neighbor (O-H···O distances 2.51 and 2.53 Å, angles 167.3° and 165.2°, respectively, depending on the role of each conformer). Additional hydrogen bonds are formed by
using the urea N-H of one conformer to create a link with the acid C=O of the other conformer (N–H···O distance = 2.88 Å, angle = 151.6°). Half of the acid C=O groups and half of the urea N-H groups are thus not used for hydrogen bonding, showing a preference for the carboxylic acid groups to act as hydrogen bond donors and for the urea units to act as hydrogen bond acceptors, in accordance with the greater electronegativity of oxygen compared with nitrogen.

Figure 2. ORTEP representation of the X-ray crystal structure of the acid 1. Key: C dark grey, H pale grey, O red, N blue. Thermal ellipsoids are shown at the 50% probability level. The unit cell contains two crystallographically independent conformers of (S)-1.

Figure 3. Ball and stick representations of helical assemblies formed by hydrogen bonding (cyan and red) within the crystal structure of acid 1. Key: C dark grey, H pale grey, O red, N blue. Viewed (a) perpendicular to helix axis and (b) approximately parallel to helix axis.
3. Experimental

3.1. General Experimental Details

Unless otherwise stated, all commercially available solvents and reagents were used without further purification. Melting points were measured using a hot-stage microscope (Reichert). IR spectra were obtained by attenuated total reflection (ATR) using a Perkin-Elmer Spectrum 65 FT-IR spectrometer. NMR spectra were recorded using a Bruker AVIII 400 spectrometer. Elemental microanalysis was performed by Medac Ltd., Chobham, Surrey, UK. Mass spectra were obtained by the EPSRC NMSF, Swansea, UK.

3.2. Synthesis of (S)-1-Methyl-2-oxoimidazolidine-4-carboxylic Acid 1

A stirred solution of 4 (154.6 mg, 1.00 mmol) in water (10 mL) was cooled in an ice bath and treated with NaHCO₃ (840 mg, 10.0 mmol), followed by 20% (w/w) phosgene in toluene (1.6 mL, 3.5 mmol). The bath was allowed to attain room temperature; after 22 h, the aqueous phase of the reaction mixture was passed through a column of Dowex 50WX2-100 ion exchange resin (H⁺ form) and eluted with water. The combined filtrate and washings were lyophilized and recrystallized from hot acetonitrile to present title compound 1 (100.7 mg, 70%) as colorless needles, mp 183–185 °C. Found: C, 41.83; H, 5.61; N, 19.62. C₅H₇N₂O₃ requires C, 41.67; H, 5.59; N, 19.43%. [α]D²4 –9.4 (c 1.02 in H₂O); IR νmax/cm⁻¹ (ATR) 3170, 1708, 1516, 1452, 1242; ¹H NMR δH (400 MHz, D₂O) 2.63 (3H, s, NMe), 3.50 (1 H, dd, J = 9.7, 5.2 Hz, H-5), 3.72 (1 H, apparent t, J = 10.0 Hz, H-5), 4.27 (1 H, dd, J = 10.3, 5.2 Hz, H-4); ¹³C NMR δC (100.6 MHz, D₂O) 29.5 (NMe), 49.9 (C-5), 51.2 (C-4), 163.5 (C-2), 175.6 (CO₂H); high-resolution mass spectrum m/z (ESI−) found: 143.0458; C₅H₇N₂O₃⁻ ([M−H]⁻) requires 143.0462.

3.3. X-ray Structure Determination of 1

Single-crystal X-ray diffraction was carried out at the Queen Mary University of London using the KAPPA APEX ii DUO diffractometer (Bruker UK Ltd., Coventry, UK), with MoKα radiation (λ = 0.71073 Å). X-ray crystal structures were solved and refined using the Bruker SHELXXL version 2018/2 software package.

A translucent colorless needle-like specimen of C₅H₇N₂O₃, approximate dimensions 0.080 mm × 0.090 mm × 0.300 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data were measured. A total of 5961 frames were collected. The total exposure time was 16.56 h. The frames were integrated with the Bruker SAINT V8.18C software package using a narrow-frame algorithm. The integration of the data using the Bruker SHELXTL version 2018/2 software package.

The final anisotropic full-matrix least-squares refinement on F² with 185 variables converged at R1 = 2.44%, for the observed data and wR2 = 6.58% for all data. The goodness of fit was 1.087. The largest peak in the final electron density synthesis was 0.156 e⁻/Å³, and the largest hole was −0.186 e⁻/Å³, with an RMS deviation of 0.037 e⁻/Å³. On the basis of the final model, the calculated density was 1.468 g/cm³ and F(000), 608 e⁻.

Supplementary Materials: CIF report for the crystal structure of 1, Figure S1: ¹H NMR spectrum of 1 (400 MHz, D₂O); Figure S2: ¹³C NMR spectrum of 1 (100.6 MHz, D₂O); Figure S3: ESI mass spectrum of 1.
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Data Availability Statement: Crystallographic data (excluding structure factors) for the acid 1 are available in the Supplementary Materials of this paper and were deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1549794. Copies of the data can be obtained, free of charge, upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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References

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