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Novel Route for Synthesis of (*S*)-1-Benzyl-6-oxopiperidine-2-carboxylic Acid and its Crystal Structure

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A piperidine carboxylic acid was synthesized and the structure of compound was confirmed by spectral methods and the X-ray diffraction experiment was employed to investigate the crystal structure of (*S*)-1-benzyl-6-oxopiperidine-2-carboxylic acid. In the crystal structure of the title compound **5**, $C_{13}H_{15}NO_3$, one molecule creates independent part of the unit cell. The compound crystallizes in the orthorhombic space group $P2_12_12_1$with a = 8.1384(3), b = 10.5953(3), c = 14.1104(3) Å and α = β = γ = 90º. The piperidine ring exhibits a chair conformation. The mean plane of the piperidine ring makes a dihedral angle of 61.10(9)º with the planar benzyl ring. The crystal structure packing of the compound is controlled by strong intermolecular O-H···O hydrogen bonds and weak C-H···O intramolecular interactions.

Keywords: Synthesis, Oxopiperidine-carboxylic acid, Single-crystal X-ray study, R factor = 0.0296.

INTRODUCTION

The presence of a piperidine ring is a characteristic feature of antihistaminic agents, oral anesthetics, narcotic analgesics, tranquillizers and hypotensive agents[1]. Many piperidine derivatives also form the skeleton of several alkaloids[2]. A large variety of 4-piperidones with different substituents in the 1, 2, 3, 5 and 6 positions with further substitutions in the 2- and 6-substituent phenyl rings have been reported elsewhere[3-9]. Derivative of the oxopiperidine carboxylic acid are an important class of compounds, which can be used as starting materials for several classes of synthetic drugs, such as enzyme inhibitors[10], immuno suppressors[11], antibiotics[12] and mycotoxic agents[13]. Nitrogen heterocycles, in particular piperidone alkaloids, occur in both plants and animals and some of them possess a variety of biological activity, including cytotoxic and anticancer properties[14-17]. As part of our studies on the substituent effects on the structures we present here the results of the X-ray crystallographic analyses of compound **5**. A view of the independent molecule with the atom-numbering schemes is shown in Fig. 1.

In continuation with our ongoing program of synthesis of novel benzoanalogue (**1**) (**Scheme-I**) of the alkaloid cryptopleurine (**2**) we have recently been concerned with the development of viable procedures for the preparation of optically pure *N*-thienylheterbenzyl-6-oxopiperidine carboxylic acids (**5**).

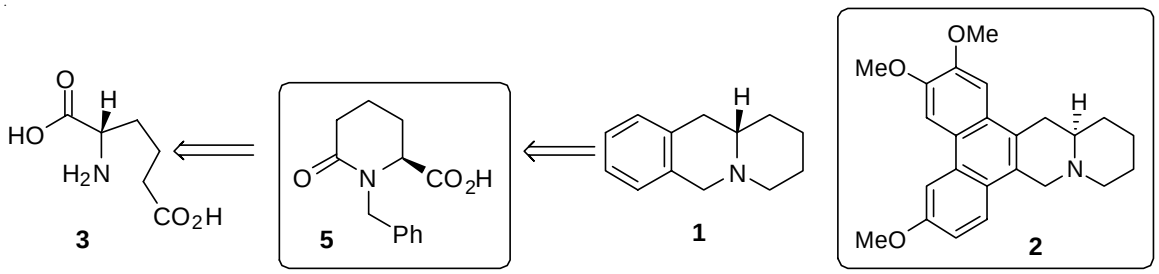
The procedure which was used is similar to that which we have published for the similar *N*-thienylmethyl-6-oxopiperidine-2-carboxylic acids[18].

As highlighted in the (**Scheme-II**), synthesis of (**5**) began with condensation of the disodium salt (*S*)-2-aminoadipic acid (**3**) and benzaldehyde to form the expected Schiff base. A subsequent *in situ* reduction of the formed imine intermediate with sodium borohydride took 3.5 h at 0 °C followed by treatment with concentrated hydrochloric acid at the same temperature gave the crude product (4) in two steps. Finally, cyclization of this crude product by reflux in water for 8 h afforded compound **5** in good yield (73 %).

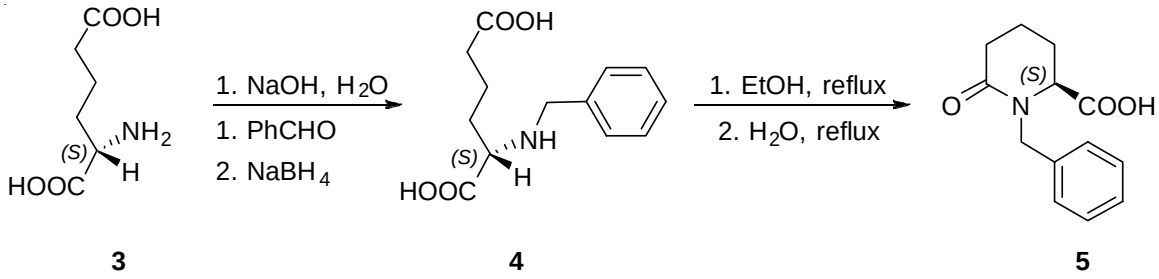
The structure of the compound **5** was established by spectral methods, mainly by ^{1}H- and ^{13}C NMR methods (HMBC, HSQC, COSY and TOCSY) and HRMS analysis. The molecular and crystal structure of (*S*)-1-benzyl-6-oxopiperidine-2-carboxylic acid (**5**) was also determined.

EXPERIMENTAL

Synthesis and crystallization: Melting points were determined with the Stuart SMP-30 melting-point apparatus. Optical rotations were measured with a P-2000 Polarimeter (PTC-203,



Scheme-I



Scheme-II

Jasco) in water-jacketed 10 cm cell at the wavelength of the sodium D line (λ = 589 nm). Specific rotations are given in units of 10^{-1} deg cm^2/g and concentrations are given in mg/mL. The optical purity of the present compound was assesed by NMR analysis of the diastereomeric salt. The salt the obtained by the reaction of (**5**) with (R)-(+)-α-methylbenzylamine directly in the NMR tube. The IR spectra was recorded with a Nicolet 5700 FT-IR spectrometer of KBr discs. ^1H and ^{13}C NMR spectra was recorded with Inova 600 Varian spectrometers in CD_3OD. Solvent and chemical shift (δ) is quoted in ppm and is referenced to TMS as an internal standard.

Preparation of (*S*)-1-benzyl-6-oxopiperidine-2-carboxylic acid (5): (*S*)-2-Aminoadipiic acid (**3**) (8.06 g, 50 mmol) was added at room temperature to a freshly prepared solution of NaOH (2 M, 45 mL) and EtOH (10 mL). To the resulting mixture was added dropwise a solution of freshly distilled benzaldehyde (5.84 g, 55 mmol) in EtOH (18 mL) over 10 h and the reaction mixture was then stirred for 72 h. Then, sodium borohydride (2.28 g, 60 mmol) was added at 0 °C in small portions and the mixture stirred for 3.5 h allowing the temperature to rise to room temperature. The resulting clear solution was extracted with ether (3 × 50 mL). The aqueous layer was acidified to pH 3 at 0-5 °C with HCl (1:1). The crystalline precipitate was collected, washed carefully with cooled water (10 mL) and dried to give a solid. The suspension of crude (*S*)-2-(benzylamino)adipiic acid (**4**) (11.13 g, 88.6 mmol) in water (250 mL) was refluxed for 8 h and then cooled to 0 °C for 5 h. The precipitate formed was collected, washed with cold water to give acid (**5**) (8,51 g, 73 %) as colourless crystals; m.p. 148.1-149.2 °C (**Scheme-II**), R_f = 0.12 (CH_2Cl_2-acetone 1:1), $[\alpha]_D^{22}$ =+ 98.9° (*c* = 1.04, MeOH); IR (KBr, ν_{max}, cm^{-1}): 2951, 2887, 2459, 1735, 1570, 1489, 1456, 1431, 1407, 1365, 1331, 1286, 1260, 1192, 1158, 1105, 1076, 1058, 1034, 995, 954, 890, 812, 791, 755, 706, 649, 622, 514, 475, 451; ^1H NMR (CD_3OD): δ 7.46-7.10 (m, 1H), 5.25 (t, 1H, *J* = 17.5 Hz), 3.94 (dd, 1H, *J* = 5.6 and 3.0 Hz), 3.61 (t, 1H, *J* = 17.5 Hz), 2.54-2.47 (m, 1H), 2.34 (td, 1H, *J* = 10.0 and 6.8 Hz), 2.09-1.83 (m, 1H), 1.78-1.56 (m, 1H). ^{13}C NMR (CD_3OD): δ 173.0 (s), 169.1 (s), 137.3 (s, C-1´, Ar), 128.4 (d, C-3´, 5´, Ar), 127.5 (d, C-2´,6´, Ar), 127.1 (d, C-4´, Ar), 58.4 (d, C-2), 48.5 (t, CH_2-N), 31.2 (t, C-5), 25.9 (t, C-3), 18.2 (t, C-4). HRMS calcd for $C_{13}H_{15}NO_3$ (233, 27) $[M + 1]^+$: 234, 1052, found 234, 1044.

TABLE-1
CRYSTAL AND STRUCTURE REFINEMENT DATA FOR THE TITLE COMPOUND **5**[a]

Empirical formula	$C_{13}H_{15}NO_3$
Formula weight	233.26
Temperature, K	298(2)
Crystal system, space group	Orthorhombic,$P2_12_12_1$
a, Å	8.1384(3)
b, Å	10.5953(3)
c, Å	14.1104(3)
α = β = γ, °	90
Volume, $Å^3$	1216.72(6)
Z	4
ρ_{calc}, Mg m^{-3}	1.273
μ, mm^{-1}	0.091
Absorption correction	Analytical
Transmission, T_{min}, T_{max}	0.961, 0.983
Detector resolution, pixels mm^{-1}	5.2170
F(000)	496.0
Crystal shape, size, mm	needle, 0.53 × 0.26 × 0.19
Crystal colour	colourless
Radiation	MoK_α (λ = 0.7107)
2Θ range for data collection, °	4.808 to 50.684
Index range of hkl	$-9 \le h \le 9$, $-12 \le k \le 12$, $-17 \le l \le 17$
Reflections collected	17788
Independent reflections	2227, R_{int} = 0.0174
Parameters, restraints, constraints	158, 0, 0
Goodness-of-fit on F^2	1.055
Final R indexes, $I \ge 2\sigma(I)$	R_1 = 0.0296, wR_2 = 0.0823
Final R indexes, all data	R_1 = 0.0313, wR_2 = 0.0840
Highest peak, deepest hole, e Å-3	0.11, -0.12
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.0470P)^2 + 0.1114P]$ where $P = (F_o^2 + 2F_c^2)/3$
Extinction correction	none
Absolute configuration	syn
Flack parameter	-

[a]CCDC 971918 contains the crystallographic data

X-Ray structure determination

Refinement: Hydrogen atoms were placed in calculated positions with C-H distances in the range of 0.93-0.98 Å and constrained to ride on their parent atom (s). The U_{iso}(H) values were set at 1.2 U_{eq} (C) for the compound **5**, hydrogen atom for O-H group was refined independently with O-H distance 0.91(4) Å.

Computing details: Data collection: CrysAlis CCD; cell refinement: CrysAlis CCD; data reduction: CrysAlis RED (Oxford Diffraction, 2009); program (s) used to solve structure: SHELXS97[19], Sir2014[20]; program (s) used to refine structure: SHELXL97[19]; molecular graphics: DIAMOND[21]; software used to prepare material for publication: SHELXL97[19], ShelXle[22], WinGX[23], PLATON[24], PARST[25] and OLEX2[26].

RESULTS AND DISCUSSION

The title compound **5** crystallizes in the crystal system orthorhombic, space group $P2_12_12_1$, Z = 4. The molecular structure of the present compound **5** and the non-H atoms labelling scheme is shown in Fig. 1. The absolute configuration of the title compound **5** was established by the synthesis of the compound containing the chiral reference molecule of known absolute configuration. The benzyl ring is planar, one neighbouring atom adopts displacement: C6 = 0.028(2) Å and the central six-membered *N*-heterocyclic ring is not planar and adopts a chair conformation with a Cremer-Pople[27] puckering amplitude (Q) = 0.447(3) Å and orientation angles θ = 42.3(4)º, φ = 118.7(5)º. A calculation of least-squares planes shows that this ring is puckered in such a manner that the four atoms adopt displacement: C1 = -0.085(2), C2 = 0.177(3), C4 = -0.180(3) and C5 = 0.095(2) Å, two atoms are displaced from this plane on opposite sides, with out-of-plane displacement: C3 = -0.525(4) and N1 = 0.265(2) Å, three neighbouring atoms adopt displacement: C6 = 0.708(2), C13 = -1.557 (2) and O1 = 0.257(2) Å from this central six-membered *N*-heterocyclic ring (mean plane). Atom N1 is sp^2-hybridized, as evidenced by the sum of the valence angles around atom N1: 359.8 (2)º. These data are consistent with conjugation of the lone-pair electrons on nitrogen atom with the adjacent carbonyl, similar to what is observed for amides. Table-2 summarizes the selected geometrical parameters of the title compound. There are weak intramolecular C6-H6B···O1 interactions in the molecular structure which generates an S(5)[28] (Fig. 1). Strong intermolecular O2-H2···O1 hydrogen bonds, involving the carboxylate group at the 2-position as H-atom donor and the carbonyl group at the 6-position as H-atom acceptor, link the molecules into the infinite C(7) zigzag chains of molecules along the c axis[28] (Fig. 2). The bond length of the carbonyl group C5 = O1: 1.240(3) Å is somewhat longer than typical carbonyl bond. This may be due to the fact that atom O1 participates in intermolecular hydrogen bond. Hydrogen bonds play a significant role in a construction of crystal structure, in such a manner, Table-3 and Fig. 2 show the hydrogen bonds. The dihedral angle between the mean plane of the central piperidine ring and the plane of the benzyl ring is 61.10(9)º.

Conclusion

Six-membered *N*-heterocycles are involved in a wide range of biologically important chemical reactions in living

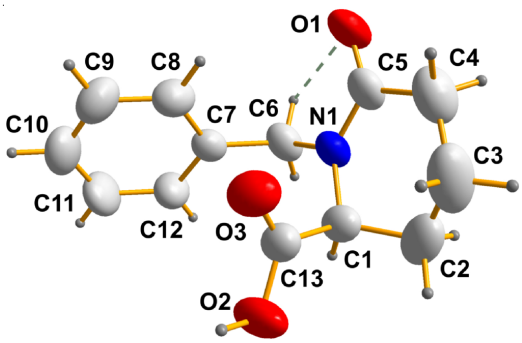


Fig. 1. Molecular structure of the title compound with the non-H atomic numbering scheme. Displacement ellipsoids of the molecule are drawn at the 50 % probability level. The intramolecular hydrogen bond is shown as a dashed line

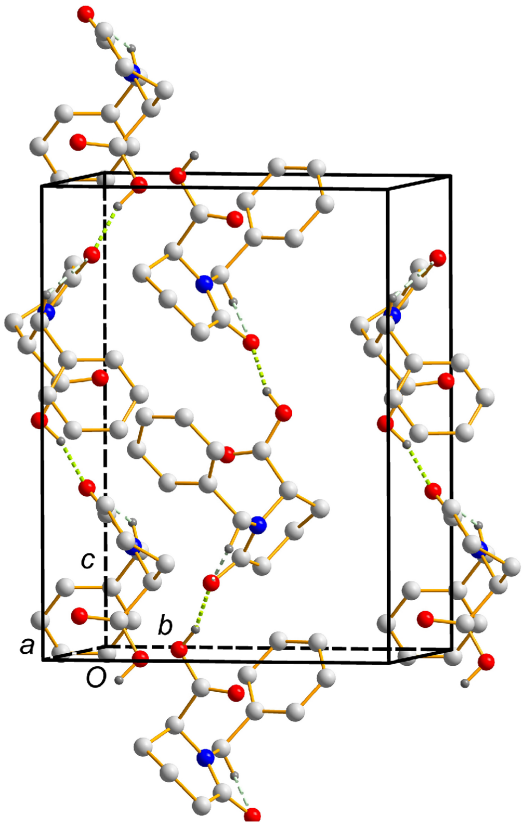


Fig. 2. Molecular packing view of the title compound **5** in the crystal structure. Molecular links along c-axis are generated by O-H···O hydrogen bonds shown by dashed lines. The rest of H atoms have been omitted for clarity

TABLE-2
SELECTED INTRAMOLECULAR BOND DISTANCES (Å), VALENCE ANGLES AND TORSION ANGLES (°) OF THE TITLE COMPOUND **5**

C1-N1	1.460 (2)	C5-N1-C1	123.5 (2)
C5-N1	1.335 (2)	O2-C13-C1	111.1 (2)
C6-N1	1.466 (3)	C5-N1-C6	119.9(2)
C1-C2	1.513 (3)	C13-O2-H2	107.0(2)
C1-C13	1.530 (2)	N1-C5-O1	120.4(2)
C1-H1	0.980	O2-C13-O3	124.9(2)
O2-H2	0.91 (4)	N1-C6-C7	114.9(2)
O3-C13	1.194(2)	C1-N1-C6	116.4(2)
O1-C5	1.240(3)	O1-C5-N1-C1	-171.1(2)
C6-C7	1.509(3)	O1-C5-N1-C6	3.0(2)
C7-C8	1.388(3)	C1-C13-O2-H2	177.3(2)
C7-C12	1.371(3)	N1-C1-C13-O2	149.6(2)

TABLE-3
GEOMETRY OF THE HYDROGEN BONDS (Å, deg) IN CRYSTAL AND MOLECULAR STRUCTURE OF THE TITLE COMPOUND (**5**)

D-H···A	Symmetry code	D···H	H···A	D···A	D-H···A
O2-H2···O1	1.5-x, 1-y, 0.5 + z	0.906 (38)	1.696 (39)	2.574 (2)	162.39 (3.68)
C6-H6B···O1	x, y, z	0.970 (2)	2.314 (2)	2.700 (2)	102.78 (12)

organisms and therefore they form one of the most important and well investigated classes of organic compounds. (*S*)-1-benzyl-6-oxopiperidine-2-carboxylic acid was prepared in good yield starting from (*S*)-2-aminoadipoic acid. The crystal and the molecular structure of the title compound in solid state were studied by X-ray structure analysis. The molecules are linked by a combination of strong intermolecular O-H···O hydrogen bonds and weak C-H···O intramolecular interactions, resulting in a one-dimensional chains in the crystal structure.

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