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Short Communication

SHORT COMMUNICATION

Synthesis, characterization and crystal structure of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride

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Abstract: The synthesis of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride is reported here. The compound was characterized by elemental analysis, infrared, and ^{1}H- and ^{13}C-NMR spectroscopy. The structure of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride was confirmed by single-crystal X-ray analysis.

Keywords: asymmetric ligand; infrared; ^{1}H- and ^{13}C-NMR spectroscopy; X-ray analysis.

INTRODUCTION

Six-membered cyclic urethanes and their derivatives are an important class of compounds that can serve as small building blocks for the synthesis of pharmaceutical compounds[1] or 1,3-amino alcohols.[2] The preparation, spectral characterization and crystal structure of (2*S*)-2-(2-oxo-1,3-oxazinan-3-yl)propanoic acid, as a six-membered cyclic urethane, was previously described.[3] After opening the cyclic form of this compound, the obtained derivatives could be used as suitable precursors for the synthesis of numerous asymmetric ligands. In this paper, the preparation and characterization of the (2*S*)-2-(2-oxo-1,3-oxazinan-3--yl)propanoic acid derivative, *i.e.*, *N*-(3-chloropropyl)-(2*S*)-alaninate, are

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reported. Furthermore, the single crystal X-ray structure determination of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride is reported.

EXPERIMENTAL

Reagents and instruments

The commercially available chemicals were used without further purification except that 1-butanol was dried according to a standard laboratory method. (2*S*)-2-(2-Oxo-1,3-oxazinan--3-yl)propanoic acid was prepared as previously described.[3]

Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer using the KBr pellet technique (4000–400 cm^{-1}). The ^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini-2000 (200 MHz) spectrometer in D_2O using tetramethylsilane as the internal standard. Elemental microanalyses for C, H and N were performed by standard methods using a Vario EL III C, H, N elemental analyzer.

Preparation of butyl N-*(3-chloropropyl)-(2*S*)-alaninate hydrochloride*

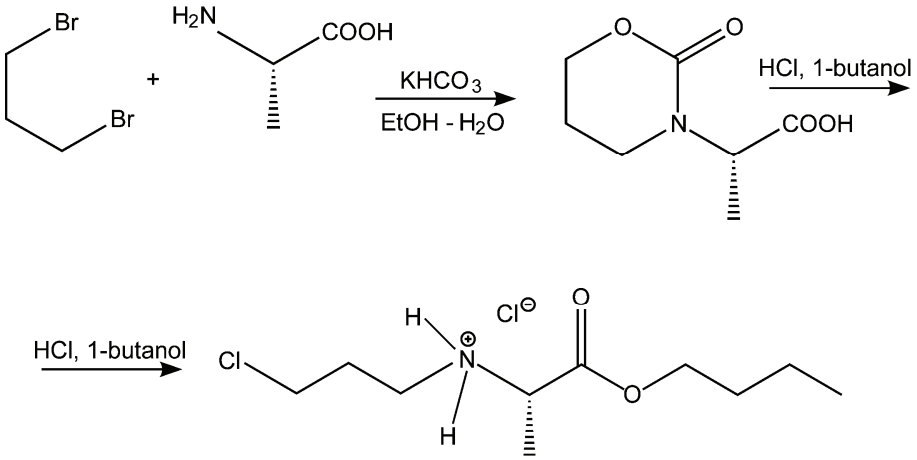
To 50 mL of dry 1-butanol saturated with gaseous HCl, 1.50 g (8.7 mmol) of (2*S*)-2--(2-oxo-1,3-oxazinan-3-yl)propanoic acid was added and the mixture was refluxed for 12 h. The mixture was allowed to reach room temperature, filtered off and the filtrate was left in refrigerator for two days. The obtained white powder was filtered off and washed with diethyl ether.

X-ray data collection

Appropriate crystals for X-ray crystal structure determination were collected after recrystallization of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride from water. Data were collected at room temperature on an Oxford Diffraction Xcalibur Gemini S diffractometer equipped with CuK_α radiation (λ = 1.54184 Å).

RESULTS AND DISCUSSION

The synthesis route of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride is given in Scheme 1.



Scheme 1. Synthesis of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride.

Analytic and spectroscopic measurements

Butyl N-*(3-chloropropyl)-(2*S*)-alaninate hydrochloride*. Yield: 1.515 g (67.45 %); Anal. Calcd. for $C_{10}H_{21}Cl_2NO_2$ (FW: 258.178): C, 46.52; H, 8.20; N, 5.34 %. Found: C, 45.92; H, 8.95; N, 5.43 %. IR (KBr, cm^{-1}): 3435, 2938, 1743, 1447, 1315, 1207, 1112, 1087, 960, 839, 735. ^{1}H-NMR (200 MHz, D_2O, δ / / ppm): 0.91 (3H, *t*, ^3J = 7.01 Hz, C^5H_3), 1.37 (2H, *m*, C^4H_2), 1.57 (3H, *d*, ^3J = = 6.96 Hz, C^7H_2), 1.68 (2H, *m*, C^3H_2), 2.22 (2H, *m*, C^9H_2), 2.89 (2H, *t*, ^3J = 7.12 Hz, C^8H_2), 3.29 (2H, *t*, ^3J = 6.96 Hz, $C^{10}H_2$), 3.71 (2H, *t*, ^3J = 6.51 Hz, C^2H_2), 3.29 (1H, *q*, ^3J = 6.96 Hz, C^6H). 13C-NMR (50 MHz, D_2O, δ / ppm): 16 (C_5H_3), 17 (C_7H_3), 21 (C_4H_2), 31 (C_3H_2), 33 (C_9H_2), 44 ($C_{10}H_2$), 47 (C_8H_2), 59 (C_6H), 70 (C_2H_2), 173 (C1OOBu).

The microanalysis results confirmed the composition of the titled compound. The proposed structure based on its infrared and NMR (^{1}H and ^{13}C) spectra is given in Fig. 1. This structure was confirmed by crystal structure analysis.

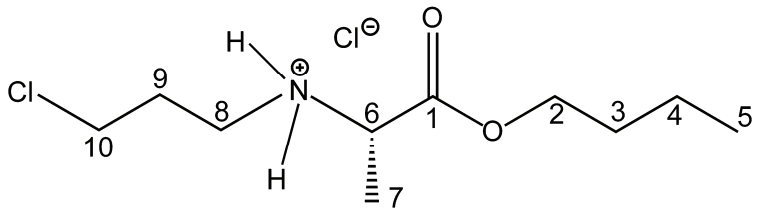


Fig. 1. Numbering of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride used for the NMR data.

Thus, in the IR spectrum of the compound, the absorption band for secondary ammonium group $\nu(R_2NH_2^+)$ was observed at 3435 cm^{-1}. The absorption band at 1743 cm^{-1} is characteristic for an ester group,[4] while the bands at 1207 and 2938 cm^{-1} arise from C–O and methyl groups, respectively.

The expected resonances were found in ^{1}H-NMR spectrum. The chemical shift for methyl protons was found at 0.91 ppm. In the ^{13}C-NMR spectrum of the title compound, the ester carbon resonance was found as expected at around 173 ppm.[5]

Crystal structure of butyl N-*(3-chloropropyl)-(2*S*)-alaninate hydrochloride*

Data for X-ray crystal structure determination were processed with CrysAlis software[6] and corrected for absorption by an analytical numeric method.[7] The crystal structure was solved by direct methods, using Sir2002[8] and refined using SHELXL.[9]

H atoms bonded to C atoms were placed at the geometrically calculated positions with C–H distances fixed to 0.97 and 0.96 Å and isotropic displacement parameters equal to $1.2U_{eq}$ and $1.5U_{eq}$ of the parent methylene and methyl C

atoms, respectively. H atoms bonded to the N atom were located in the difference Fourier map and refined isotropically. The correct absolute structure of the compound was confirmed by the Flack parameter[10] of 0.01(3). A summary of crystallographic data is given in Table I. The software used for the preparation of the material for publication were WinGX,[11] PLATON,[12] PARST[13] and ORTEP.[14]

TABLE I. Crystal data and structure refinement for butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride

Empirical formula	$C_{10}H_{21}Cl_2NO_2$
Formula weight	258.18
Temperature / K	293(2)
Wavelength / Å	1.54184
Crystal system	Orthorhombic
Space group	$P2_12_12$
Unit cell dimensions	
a /Å	7.2650(4)
b / Å	14.8864(7)
c / Å	13.308(1)
V / Å^3	1439.3(2)
Z	4
μ / mm^{-1}	3.939
F(000)	552
D_{calc} / g cm^{-3}	1.191
Crystal size / mm^3	0.19 × 0.06 × 0.04
θ range for data collection / °	3.32−67.5
Reflections collected	8742
Independent reflections	2903
Flack parameter[10]	0.01 (3)
Goodness-of-fit on F^2	1.075
R_{int}	0.0361
R_1, wR_2 [$I > 2\sigma$(I)]	0.0492, 0.1436

The title compound crystallizes in the orthorhombic space group $P2_12_12$. The asymmetric unit contains one ester molecule protonated on the N atom, which is neutralized by the chloride anion (Fig. 2). The bond lengths and angles (Table II) are comparable to those of R_2edda-type esters (R refers to the isopropyl[4] or cyclopentyl[5] group), which comprise similar CH_2–CH_2–NH_2^+–$CH(CH_3)$–COO fragments and also crystallize as hydrochloride salts. In the present compound, the torsion angles within the long, heteroatomic chain vary from 173.2(3) to 178.8(3)°, which describes a fully extended conformation. The backbone of the molecule is therefore approximately planar with the R.M.S. deviation for all non-H atoms, except the alaninate methyl C, of 0.09 Å. This is unlike the above mentioned R_2edda derivatives,[4,5] in which the ester group significantly deviates from the rest of the aliphatic chain. Namely, in two previously reported examples, the dihedral angle between the best plane of the

–COO fragment and the plane passing through the rest of non-H atoms of the chain exceeds 50°. In the present compound, the corresponding dihedral angle has the value of 5.2(7)°. This difference in orientation of ester group can be related with the fact that the extended *n*-butyl ester moiety points away from the rest of the molecule and, in contrast to the bulky isopropyl ester and cyclopentyl ester fragments, can avoid possible steric hindrance. It could also be suggested that the *n*-butyl ester moiety better complies with all the *trans*-conformation of the aliphatic chain, resulting in an extended molecule with more efficient crystal packing.

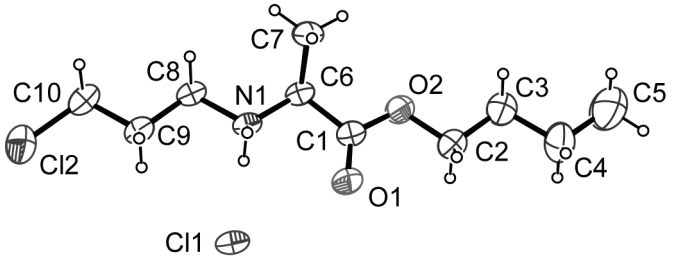


Fig. 2. Molecular structure of butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride. Displacement ellipsoids are drawn at the 40 % probability level.

TABLE II. Selected bond lengths (Å) and angles (°)

Bonds		Angles	
Cl2−C10	1.773(5)	C9−C10−Cl2	112.5(3)
O1−C1	1.194(4)	O1−C1−O2	124.7(3)
O2−C1	1.313(5)	C1−O2−C2	116.2 (3)
O2−C2	1.462(5)	O2−C2−C3	109.1 (4)
N1−C6	1.483 (5)	N1−C6−C1	107.2(3)
N1−C8	1.497(4)	N1−C6−C7	112.2 (3)
C6−C7	1.523(5)	N1−C8−C9	110.9(3)

The crystal packing is dominated by two N1−H···Cl1 hydrogen bonds formed between the protonated amino group and the Cl anion (Table III). These rather strong interactions with nearly linear interaction angles connect the screw-related molecules into a zigzag chain parallel to the *a* axis (Fig. 3). The *n*-butyl ester and chloropropyl moieties of the adjusted molecules point to the same side of the chain, giving rise to a secondary, weak C10−H10a···O1 interaction. The

TABLE III. Geometry of the hydrogen bonds (Å, °); symmetry codes: *i*) *x*, *y*, *z*; *ii*) *x*–1/2, –*y*+1/2, –*z*+1; *iii*) *x*+1/2, –*y*+1/2, –*z*+1

D−H···A	D−H	D···A	H···A	D−H···A
N1−H1a···Cl1$^{i)}$	0.94(4)	3.150(3)	2.21(4)	177(3)
N1−H1b···Cl1$^{ii)}$	0.92(4)	3.114(3)	2.20(4)	172(3)
C10−H10a···O1$^{iii)}$	0.97	3.200(5)	2.50	129

chains of the molecules can be considered as principal packing motifs of this crystal structure. The further molecular arrangement is mostly based on van der Waals interactions. In contrast to the chloride anion, which represents the most important hydrogen bonding acceptor site, the Cl atom of the chloropropyl moiety plays no role in intermolecular interactions. The closest donor, the butyl ester C2–H2b fragment, is placed at a distance of 3.08 Å.

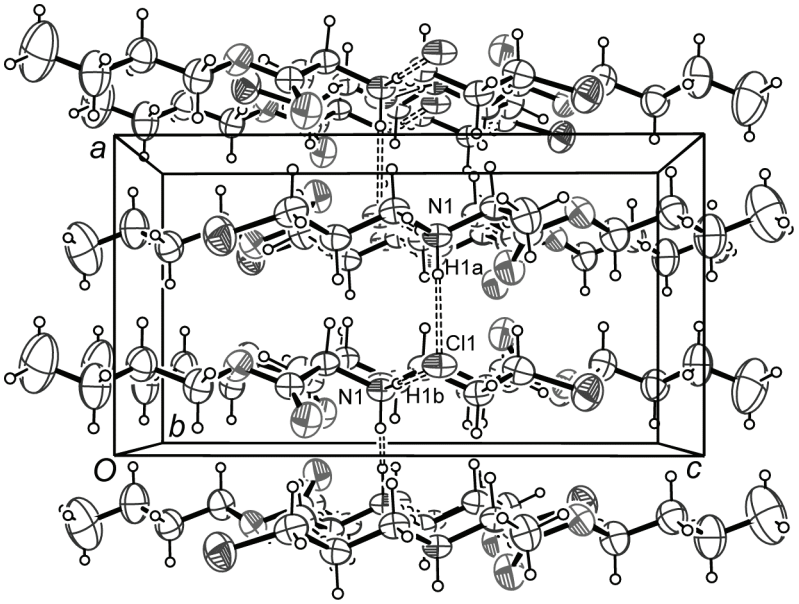


Fig. 3. Segment of crystal packing as viewed down the *b* axis. The strongest N−H···Cl hydrogen bonds are represented as dashed lines.

CONCLUSIONS

In reaction of (2*S*)-2-(2-oxo-1,3-oxazinan-3-yl)propanoic acid and dry 1-butanol saturated with gaseous HCl, butyl *N*-(3-chloropropyl)-(2*S*)-alaninate hydrochloride was prepared. The compound was characterized by NMR spectroscopy, IR spectroscopy and elemental analysis. The compound crystallizes in the orthorhombic space group $P2_12_12$. In the crystal packing, the molecules of *N*-(3--chloropropyl)-(2*S*)-alaninate hydrochloride are linked into chains by two strong N−H···Cl hydrogen bonds. The molecules further interact by means of weak van der Waals interactions.

SUPPLEMENTARY DATA

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre CCDC No. 891442. The data are available free of charge *via* www.ccdc.cam.ac.uk/data_request/cif (or from the CCDC,

12 Union Road, Cambridge CB2 1EZ, UK; +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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И З В О Д

СИНТЕЗА, КАРАКТЕРИЗАЦИЈА И КРИСТАЛНА СТРУКТУРА БУТИЛ-*N*-(3-ХЛОРПРОПИЛ)-(2*S*)-АЛАНИНАТ-ХИДРОХЛОРИДА

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У раду је описана синтеза бутил-*N*-(3-хлорпропил)-(2*S*)-аланинат-хидрохлорида. Једињење је окарактерисано елементалном анализом, инфрацрвеном, ^{1}H- и ^{13}C-NMR спектроскопијом. Структура *N*-(3-хлорпропил)-(2*S*)-аланинат-хидрохлорида је потврђена рендгенском структурном анализом.

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