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(−)-ISOVALINE: CONFIRMATION OF ITS D-(=R)-CONFIGURATION BY X-RAY ANALYSIS OF ITS N-CHLOROACETYL DERIVATIVE

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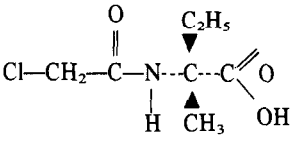
Abstract—The N-chloroacetyl derivative of (−)-isovaline **1** crystallizes in space group $P2_1$ with $Z = 4$ and $a = 10.675(6)$, $b = 7.698(4)$, $c = 11.739(2)$ Å and $\beta = 97.32(4)°$. The structure was solved by the heavy atom method and refined to $R = 0.0718$ and $R_G = 0.0991$ with 1890 independent reflexions ($F_0 > 0$). The absolute configuration of **1** was determined as *R* by application of the Hamilton test with two data sets (CuK_α and MoK_α-radiation). There are two independent molecules **1** showing flat backbone conformations, which include weak intramolecular bifurcated hydrogen bonds. Strong intermolecular hydrogen bonds determine the crystal packing, in which antiparallel chains of single molecules run along [010]. The (R)-assignment is in agreement with the order of elution (D before L) of enantiomers of N-trifluoroacetyl-DL-isovaline-n-propyl ester on glass capillaries coated with the chiral phase N-propionyl-L-valine-t-butylamide-polysiloxane.

Sterically hindered α-amino acids such as the dialkylated α-aminoisobutyric acid (Aib, 2-methylalanine) and isovaline (Iva, 2-ethylalanine) are constituents of naturally occuring peptide antibiotics.[1] The achiral 2-aminoisobutyric acid has been shown to have stabilizing effects on β-bends (type III) in tripeptides and to promote consecutive β-bends in Aib pentapeptides.[2] Recently we could demonstrate α-helix stabilizing effects of four α-aminoisobutyric acid residues incorporated in a helical undecapeptide model of alamethicin.[3-5] Isovaline may be even more interesting for conformational studies on peptides, because it is the simplest chiral α-dialkyl-α-amino acid. The incorporation of either (*R*)- or (*S*)-isovaline leads to diastereomers which may adopt different preferred conformations.

The determination of configuration of naturally-occuring isovaline has been obviously a problem also recently. Thus, in 1977 Pandey, Cook and Rinehart[6] made a wrong assignment (L instead of D) for isovaline in antiamoebins and emerimicins. As reported elsewhere[7] in detail the isovaline enantiomers could be resolved in our laboratory via N-trifluoro-acetyl-isovaline-n-propyl esters on glass capillary columns coated with the chiral phase Chirasil-Val (N-propionyl-L-valine-tert-butylamide-polysiloxane[8]). A base-line separation is obtained also chromatographing diasteromeric N-pentafluoropropionyl-DL-isovaline-(+)-3-methyl-2-butyl esters on glass capillaries coated with OV 17.[7] Both methods established clearly the natural occurence of D-isovaline in the antibiotics antiamoebin, emerimicin, trichotoxin A-40 and A-50, antibiotic Tü165 (CBS 382.62), stilbellin, samarosporin (emerimicin IV).[7] Rinehart *et al.* revised their earlier findings reporting recently D-isovaline for zervamicin[9] without comments. In the following we report on the X-ray structure of N-chloroacetyl-D-isovaline which was undertaken in view of the lack of X-ray data of isovaline and with respect to the various earlier attempts of configurational assignments based on its taste, on enzymatic hydrolysis of chloroacetyl-DL-isovaline by hog kidney acylase, and on the Clough–Lutz–Jirgensons rule.[10] (+)-Isovaline has been assigned the (*S*)-configuration by chemical correlation with (−)-quinic acid.[11,12] Interest in isovaline continues as shown in a recently published enantioselective synthesis of (*R*)-(−)-isovaline with 95% asymmetric induction.[13] The resolution of DL-isovaline via preferential crystallization of the diastereomeric menthyl esters[14] has been applied in order to obtain optically active samples for analytical work.[7] For the study described here we used the preparative resolution via enzymatic hydrolysis of N-chloroacetyl-DL-isovaline, which leaves the D-derivative unattacked.[10,15,16]

X-ray analysis of **1**



1

Clear colourless crystals of N-chloroacetyl-(−)-isovaline **1** could be grown as thin plates by slow evaporation of ethanolic solutions. Other solvents, like ethylacetate/hexane gave similar results and most of the crystals proved to be twinned by examination with a polarizing microscope and by Buerger precession photographs. After numerous attempts two crystals could be found, which were not too fragile, and which showed satisfactory diffraction quality.

The first crystal with approximate dimensions of $0.5 \times 0.5 \times 0.2\ mm^2$ was mounted on a NONIUS CAD 4 diffractometer (CuK_α, graphite monochromator). The following crystal data were obtained by accurate center-

ing of 22 high-angle reflexions:

a = 10.675(6) Å	M_r = 193.63 ($C_7H_{12}NO_3Cl$)
b = 7.698(4) Å	Space group: $P2_1$, Z = 4
c = 11.739(2) Å	μ = 3.19 mm^{-1} (CuK_α)
β = 97.32 (4)°	
V = 956.81 $Å^3$	

Intensity data were collected within a θ-range of 3–70° by ω/θ-scans of variable speed (maximum 40 s for weak reflections). Two periodically measured intensity control reflecions (115 and 4–12) showed a total intensity drop of about 10%; no attempt was made to correct this intensity decay, because the slight crystal decomposition was not linear and occured mainly in the second half of the data collection process. After the usual Lp-correction, 1890 independent reflexions with $F_0 > 0$ were used for the calculation of a sharpened Patterson map. Both chlorine atoms of the two molecules **1** in the asymmetric unit could be located, and the complete structure was developed stepwise by difference maps and least squares refinements. Most of the hydrogen atoms were located in a difference Fourier synthesis after refinement of the nonhydrogen atoms with anisotropic temperature factors. In the final least squares cycles, all methyl and methylene groups were refined as rigid groups with d(C–H) = 0.96 Å, and a common isotropic temperature factor for all hydrogen atoms of 0.10 $Å^2$ was used. In order to obtain a flat variance of $\Sigma\omega(F_o - F_c)^2$ vs $\sin\theta$ and $|F/F_{max}|$, a weighting scheme $\omega = 1/[\sigma^2(F_o) + gF_o^2]$ was introduced, in which g refined to 0.008. Convergence was obtained at R = 0.0718 and R_G = 0.0991 [$R_G = (\Sigma\omega\Delta^2/\Sigma\omega F_o^2)^{1/2}$]; a final difference Fourier synthesis showed only peaks with an electron density ≤ 0.27 $eÅ^{-3}$. The corresponding atomic coordinates are listed in Table 1 according to the numbering scheme given in Fig. 1.

Absolute configuration of **1**

In order to establish the absolute configuration of **1**, we applied the procedure proposed by Hamilton:[17] The final full matrix least squares cycles were carried out as described above, but with inverse atomic coordinates. The resulting R- and R_G-values of 0.0730 and 0.1022 showed, that the model with inverse configuration has to be rejected at a very high probability level. According to the tables given by Hamilton,[17,18] the significance level is ≤ 0.005. Recently Rogers[19] has communicated a formula, which allows the calculation of α-values below this limit. With the R_G-ratio of 0.1022/0.0991 = 1.0313 and N = 1640 (number of reflexions—number of refined parameters), α is calculated to 3×10^{-19}, whereas the R-ratio (0.0730/0.0718 = 1.017) leads to $\alpha = 4 \times 10^{-12}$. This extremely high probability, that the coordinates of Table 1 correspond to the correct configuration of **1** is in accordance with the configuration, which has been found independently by two glc methods.[7]

Although our X-ray and glc studies safely established the absolute configuration of **1**, we decided to collect a further data set with the second crystal and MoK_α-radiation on the following reasons: Firstly, with MoK_α-radiation the anomalous dispersion effects are much smaller, and we wanted to know, if the Hamilton test is applicable even with these small effects. Secondly, systematic errors by absorption and crystal decomposition are remarkably reduced by the use of MoK_α-radiation (μ = 0.32 mm^{-1}). With crystal dimensions of 0.35 × 0.30 × 0.16 mm^3 and experimental conditions similar to the data collection with CuK_α, 1701 symmetrically independent reflexions with $|F_0| > 0$ could be obtained. Analogous refinement with this data set resulted in R = 0.0567 and R_G = 0.0570, if the correct configuration was used, and in R = 0.0572 and R_G = 0.0573 with inverse coordinates. The R-factor ratios for R and R_G (1.0088 and 1.0053) together with N = 1451 led to $\alpha_1 = 8 \times 10^{-7}$ and $\alpha_2 = 9 \times 10^{-5}$. Obviously even in the case of very small differences in the R-factors, there is no contradiction to the results of the CuK_α-data set and both R and R_G-values are lower for the correct model.

The high significance levels α_1 and α_2 are a result of the dimensionality in the Hamilton test. In his original paper[17] Hamilton stated, that the dimension of the problem discussed here is b = 1. Rogers[19] has risen the question, whether the hypothesis is really one-dimensional. In this case, the probabilities for the correct assignments of configuration would be drastically reduced. However, according to our experience the Hamilton test has always given the correct configuration even in those cases, when C, N, O-structures afforded small R-factor differences (and the absolute configuration was known from synthesis, e.g. in peptides). Within the limits of error, the coordinates from the MoK_α-data refinement were the same as in Table 1, but the e.s.d.'s have been slightly better with the first data set.

Scattering factors for neutral atoms and anomalous dispersion terms were taken from tables of Cromer and Mann[20] and Cromer and Libermann.[21] All calculations were performed with SHELX (G. M. Sheldrick), PLUTO (S. Motherwell) and XANADU (P. Roberts and G. M. Sheldrick) on Telefunken TR 440 and UNIVAC 1100/80 computers at the Zentrum für Datenverarbeitung der Universität Tübingen.

DISCUSSION

Figure 1 shows a perspective view of the two independent single molecules. For a direct comparison, the orientation of the molecules has been changed and it does not correspond to the mutual orientation as it is found in the asymmetric unit.

The configuration at the C_α-atoms C3 and C10 is R according to the Cahn-Ingold-Prelog-conventions.[22] In terms of the usual description of the α-amino acids the isovaline derivative **1** is a L-alanine derivative in which the α-hydrogen is replaced by an ethyl substituent. The (D; *R*)(−)-isovaline has been found in all naturally occurring peptide antibiotics, which have been investigated by glc so far; antiamoebins, emerimicins, trichotoxins, suzukacillins, stilbellin, Tü 165 (CBS 382.62)[7] and also zervamycins.[9]

In Tables 2 and 3, bond lengths and angles are listed for both molecules of **1**.

Corresponding bond lengths in both molecules show differences in a range of 0 to 6σ with a mean value of 3.4σ. Similar differences (from 0 to 8σ, mean value 3.5σ) are observed for the bond angles. From a simple statistical point of view, most of the differences would be highly significant.[23] However, systematic errors from absorption and crystal decomposition certainly invalidates this conclusion. So, a final answer cannot be given as to whether the crystal packing leads to significant differences of bond lengths and angles in both molecules. Moreover, apparent differences in Tables 2 and 3 cannot be confirmed by the geometry resulting from the MoK_α data set.

Table 1

ATOM	X/A	Y/B	Z/C	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
CL1	0.8107 (1)	0.1664 (0)	0.5076 (1)	0.078(1)	0.062(1)	0.057(1)	-0.004(1)	-0.022(1)	0.003(1)
CL2	0.3087 (2)	0.1717 (3)	0.5044 (1)	0.092(1)	0.074(1)	0.056(1)	0.012(1)	-0.027(1)	-0.008(1)
N1	0.9869 (4)	0.3085 (6)	0.6993 (3)	0.054(2)	0.031(2)	0.035(2)	-0.002(2)	-0.005(2)	-0.001(2)
N2	0.4629 (4)	0.0214 (6)	0.7124 (3)	0.060(2)	0.025(2)	0.032(2)	0.000(1)	-0.002(2)	-0.000(2)
O1	1.0568 (4)	0.0459 (6)	0.7692 (3)	0.071(2)	0.029(2)	0.064(2)	0.004(2)	-0.008(2)	0.003(2)
O2	0.9478 (4)	0.6367 (5)	0.6640 (3)	0.072(2)	0.032(2)	0.047(2)	0.006(2)	-0.017(2)	0.006(2)
O3	1.0739 (4)	0.7201 (6)	0.8227 (3)	0.085(3)	0.028(2)	0.060(2)	-0.002(2)	-0.015(2)	-0.002(2)
O4	0.5101 (4)	0.2824 (5)	0.7908 (3)	0.081(2)	0.028(2)	0.045(2)	-0.003(1)	-0.018(2)	0.002(2)
O5	0.4405 (4)	-0.3062 (6)	0.6675 (3)	0.093(3)	0.032(2)	0.044(2)	0.000(2)	-0.015(2)	0.003(2)
O6	0.5155 (4)	-0.3918 (6)	0.8420 (3)	0.094(3)	0.031(2)	0.044(2)	0.001(2)	-0.018(2)	-0.001(2)
C1	0.9344 (5)	0.0478 (8)	0.5874 (4)	0.071(3)	0.036(3)	0.051(2)	-0.003(2)	-0.002(2)	-0.003(3)
C2	0.9957 (4)	0.1369 (7)	0.6935 (4)	0.049(2)	0.032(2)	0.042(2)	0.000(2)	-0.002(2)	0.000(2)
C3	1.0503 (4)	0.4194 (7)	0.7931 (3)	0.047(2)	0.028(2)	0.034(2)	0.000(2)	-0.005(2)	0.001(2)
C4	1.1932 (5)	0.3971 (8)	0.8069 (5)	0.048(2)	0.041(3)	0.072(3)	0.002(3)	-0.010(2)	0.004(2)
C5	0.9980 (5)	0.3868 (8)	0.9096 (4)	0.082(3)	0.046(3)	0.036(2)	0.004(2)	0.005(2)	0.004(3)
C6	0.8587 (7)	0.4147(14)	0.9014 (6)	0.098(5)	0.100(7)	0.096(5)	0.006(5)	0.060(4)	-0.002(5)
C7	1.0175 (5)	0.6041 (6)	0.7505 (4)	0.054(2)	0.026(2)	0.044(2)	-0.002(2)	0.008(2)	-0.002(2)
C8	0.4350 (5)	0.2748 (8)	0.5887 (4)	0.074(3)	0.038(3)	0.043(2)	0.008(2)	-0.007(2)	0.001(3)
C9	0.4708 (4)	0.1916 (8)	0.7067 (4)	0.048(2)	0.033(2)	0.038(2)	0.002(2)	-0.003(2)	0.002(2)
C10	0.4906 (4)	-0.0902 (6)	0.8127 (4)	0.046(2)	0.027(2)	0.037(2)	0.000(2)	-0.002(2)	0.000(2)
C11	0.3920 (5)	-0.0650 (9)	0.8960 (4)	0.065(3)	0.050(3)	0.039(2)	-0.004(2)	0.007(2)	0.004(3)
C12	0.6243 (4)	-0.0585 (7)	0.8737 (4)	0.056(2)	0.034(2)	0.039(2)	-0.002(2)	-0.007(2)	-0.001(2)
C13	0.7270 (5)	-0.0714(12)	0.7941 (6)	0.043(2)	0.077(5)	0.096(4)	0.003(4)	0.004(2)	-0.001(3)
C14	0.4808 (4)	-0.2744 (6)	0.7660 (3)	0.049(2)	0.030(2)	0.032(2)	-0.001(2)	-0.008(2)	-0.001(2)

The backbone angles at the Cα-atoms (N1–C3–C7 and N2–C10–C14) are definitively smaller than the usual value of 110°[24] (103.2(3) and 105.2(3)°). One could argue, that in the α,α-dialkyl-α-amino acids the alkyl groups lead to a compression of this angle. However, from X-ray studies of Aib-containing peptides,[2] such an arguement cannot be derived: in all cases the corresponding angles are near 110° and often larger than 110°. Probably, a reason for this fact is found in the unusual backbone-conformation: the torsional angles O2–C7–C3–N1 and O5-C14–C10–N2 (4.8 and −9.0°) demonstrate the nearly coplanar arrangement of the carboxycarbonyl groups C7–O2 resp. C14–O5 and the N–H groups in both molecules. Similarly, as shown in Fig. 1, the chloromethylene groups are also tilted towards these N–H groups (torsional angles Cl1–C1–C2–N1 resp. Cl2–C8–C9–N2 −22.6 and 36.3°). Such a backbone conformation clearly indicates, that the ac-

Table 2. Bond lengths (Å) with e.s.d.'s. in parentheses

	Molecule 1	Molecule 2	
Cl1 - C1	1.771(6)	C12 - C8	1.756(5)
C1 - C2	1.497(7)	C8 - C9	1.529(6)
C2 - O1	1.250(6)	C9 - O4	1.238(6)
C2 - N1	1.328(7)	C9 - N2	1.318(7)
N1 - C3	1.486(5)	N2 - C10	1.457(5)
C3 - C4	1.521(6)	C10 - C11	1.535(6)
C3 - C5	1.560(6)	C10 - C12	1.531(6)
C5 - C6	1.489(9)	C12 - C13	1.527(7)
C3 - C7	1.535(6)	C10 - C14	1.522(6)
C7 - O2	1.206(6)	C14 - O5	1.206(5)
C7 - O3	1.322(6)	C14 - O6	1.289(6)

Table 3. Bond angles with e.s.d.'s. in parentheses

	Molecule 1	Molecule 2	
Cl1- C1 - C2	114.9(4)	C12- C8 - C9	114.0(4)
C1 - C2 - O1	118.0(5)	C8 - C9 - O4	120.4(5)
C1 - C2 - N1	118.2(5)	C8 - C9 - N2	116.9(4)
O1 - C2 - N1	123.7(5)	O4 - C9 - N2	122.7(4)
C2 - N1 - C3	125.6(4)	C9 - N2 - C10	128.3(4)
N1 - C3 - C4	111.7(4)	N2 - C10- C11	110.8(4)
N1 - C3 - C5	112.1(4)	N2 - C10- C12	111.4(4)
N1 - C3 - C7	103.2(3)	N2 - C10- C14	105.2(3)
C3 - C5 - C6	112.6(4)	C10- C12- C13	113.6(4)
C5 - C3 - C7	110.0(4)	C12- C10- C14	109.5(4)
C4 - C3 - C7	108.9(4)	C11- C10- C14	109.0(4)
C3 - C7 - O2	123.9(4)	C10- C14- O5	122.2(4)
C3 - C7 - O3	110.6(4)	C10- C14- O6	113.8(3)
O2 - C7 - O3	125.5(5)	O5 - C14- O6	123.9(5)

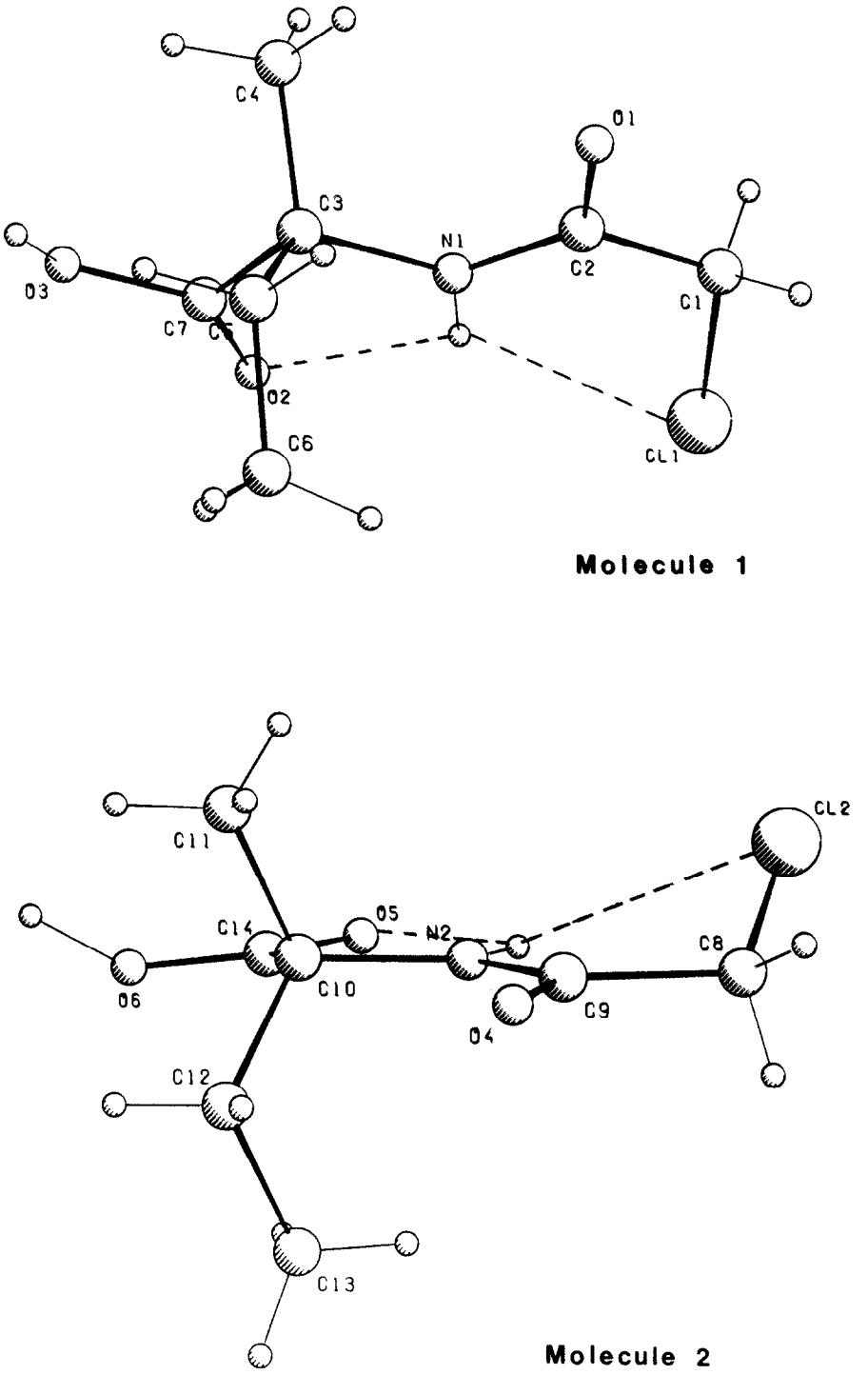


Fig. 1. Perspective of the two independent single molecules of N-chloroacetyl-(R)-isovaline (1).

ceptor atoms O2 resp. O5 and Cl1 resp. Cl2 are involved in intramolecular bifurcated hydrogen bonds, as depicted in Fig. 1 by dashed lines.

Hydrogen bonds in 5-membered rings (including hydrogen such as in 1) are rather weak,[25] because the lone pairs of the acceptor atoms occupy unfavourable positions, and the distances of the hydrogen atoms to these atoms are longer than in the more favourable six-membered ring systems. The distances H1...O2 resp. H2...O5 (2.11 resp. 2.10 Å) and H1...Cl1 resp. H2...Cl2 (2.44 resp. 2.43 Å) support this argument. Probably, besides the other reasons the before mentioned compression of the backbone Cα-angles is a consequence of this intramolecular hydrogen bonding.

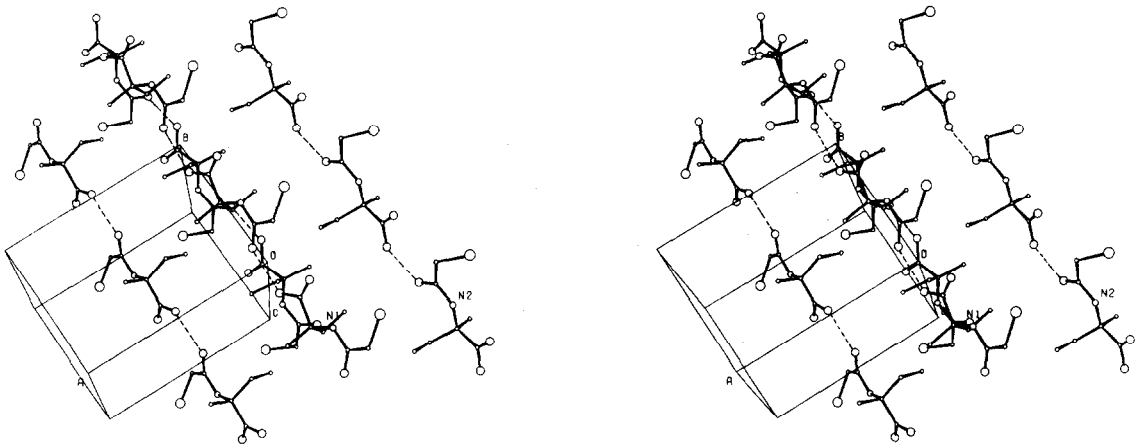


Fig. 2. Stereoscopic view of the crystal packing of N-chloroacetyl-(R)-isovaline (1).

Figure 2 shows a stereoscopic view of the crystal packing, in which the single molecules are connected by strong intermolecular hydrogen bonds to chains, running parallel to the b-axis. Particularly, molecules of type 1 and 2 form separate chains: the carboxy group O3–H link the acceptor atoms O1′ of the neighbouring molecules with symmetry translation x, 1+y, z (O3...O1′ = 2.588(6) Å), whereas the carboxy groups of molecules 2 (O6–H) connect the neighbouring molecules in the opposite direction with the acceptor atoms O4′, (O6...O4′ = 2.580(6) Å, symmetry translation on O4′: x, y−1, z). These antiparallel chains along [010] are held together by van der Waals forces.

EXPERIMENTAL

Preparation of N-chloroacetyl-DL-isovaline

DL-Isovaline has been prepared by the Strecker method from butanone.[15] It was characterized by ^{13}C-NMR (20.115 MHz) in ^{2}H-methanol, δ, ppm: 176.9 CO, 62.0 Cα, 30.2 Cβ (CH_2), 22.0 Cβ (CH_3), 7.4 Cγ, and ^{1}H-NMR (90 MHz) in ^{2}H-methanol, δ, ppm: 1.76 (m, β-CH_2), 1.44 (s, β-CH_3), 0.97 (t, γ-CH_3). Acetylation of isovaline yielded N-chloroacetyl-DL-isovaline,[15] which showed the following NMR-data: ^{13}C-NMR (20.115 MHz) in ^{2}H-chloroform/^{2}H-methanol (1:1), δ, ppm: 176.6 Iva-CO, 167.3 Cl-Ac-CO, 61.5 Cα, 43.1 Cl-CH_2, 29.8 Cβ (CH_2), 22.5 Cβ (CH_3), 8.5 Cγ; ^{1}H-NMR (90 MHz) in ^{2}H-methanol δ, ppm: 4.04 (s, Cl-CH_2), 2.00 (m, β-CH_2), 1.52 (s, β-CH_3), 0.86 (t, γ-CH_3). m.p. 163° uncorr. (Lit[15] 161.5–163° corr). Calc. C, 43.42; H, 6.25; N, 7.23; Cl, 18.31; Found: C, 43.91; H, 5.94; N, 7.15; Cl, 18.81%.

N-Chloroacetyl-D-isovaline **1**

The resolution of N-chloroacetyl-DL-isovaline was achieved by enzymatic digestion of the L-enantiomer with hog renal acylase as described by Baker *et al.*[15,16] The crystals of **1** were characterized as follows: mp 157.5° uncorrected (Lit[15] 158° corr); $[\alpha]_D^{25} = -9°$ (c = 2, ethanol), (Lit[15], $[\alpha]_D^{25} = -9.0°$ (c = 2, ethanol). Gas chromatography of the N-trifluoroacetyl-D-isovaline-isopropyl ester on a glass capillary column coated with Chirasil-Val[7,8] revealed no trace of the corresponding L-enantiomer.

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