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The Crystal and Molecular Structure of N-t-Butyloxycarbonyl-L-thiazolidine-4-carboxylic Acid (C₉H₁₅NO₄S)

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The title compound ($C_9H_{15}NO_4S$) is orthorhombic with $a = 11 \cdot 937$ (12), $b = 12 \cdot 552$ (12), $c = 7 \cdot 836$ (8) Å, $Z = 4$, space group $P2_12_12_1$. 1186 independent reflexions were collected on an automatic diffractometer with Cu $K\alpha$ radiation. The structure was solved by direct methods and refined by full-matrix least squares to a final R of $0 \cdot 039$. Except for two of the methyl groups, the t-butyloxycarbonyl group is planar. The peptide unit and the thiazolidine ring conformation are similar to those found in thiazolidine-4-carboxylic acid. The packing of the molecules is governed by hydrogen bonding and van der Waals contacts.

Introduction

In a previous study of cyclo-glycyl-3-thiaprolyl (Haar, Fermandjian, Robert, Lefebvre-Soubeyran & Savrda, 1976) we have shown that the molecule adopts the same conformation as its analogue cyclo-L-prolyl-glycyl (Pettit, Von Dreele, Bollinger, Traxler & Brown, 1973; Von Dreele, 1975). It is interesting to know whether the diketopiperazine ring has any influence on the thiazolidine ring and to show that the substitution of an S atom does not disturb the proline ring conformation. The structure of the title compound was solved to compare it with cyclo-glycyl-3-thiaprolyl and with thiazolidine-4-carboxylic acid (Goodman, Niu & Su, 1970; Goodman, Chen, Benedetti, Pedone & Corradini, 1972; Loscalzo, Kallen & Voet, 1973) where the carboxyl group was found to have a zwitterionic structure.

Experimental

The crystals are colourless needles. The unit-cell dimensions were preliminarily determined from oscillation and Weissenberg photographs. The orthorhombic space group corresponding to the systematic absences is $P2_12_12_1$. For data collection a $0 \cdot 20 \times 0 \cdot 25 \times 0 \cdot 60$ mm crystal was mounted parallel to **a** on a CAD 3 Enraf–Nonius diffractometer. The measurement and least-squares refinement of ten high-Bragg-angle reflexions led to: $a = 11 \cdot 937$ (12), $b = 12 \cdot 552$ (12), $c = 7 \cdot 836$ (8) Å, $V = 1174$ Å³.

With $Z = 4$, $d_c = 1 \cdot 32$ which agrees with $d_o = 1 \cdot 31$ g cm⁻³. 1186 independent reflexions were collected with Cu $K\alpha$ ($\lambda = 1 \cdot 5418$ Å) Ni-filtered radiation in the θ–2θ scan mode up to $\theta = 66°$. The scan range varied according to $\Delta\theta = 1 \cdot 5 + 0 \cdot 4$ tg θ. Two standard reflexions were measured every 40 reflexions and showed no systematic variation. 88 reflexions with $I < 3\sigma(I)$ where $\sigma(I)$ is the standard deviation based on counting statistics were considered as unobserved and omitted from the refinement. The intensities were corrected for the Lorentz–polarization factor but not for absorption ($\mu = 25$ cm⁻¹). A Wilson plot gave the scale and overall temperature factor ($B = 3 \cdot 63$ Å²).

Structure determination and refinement

The structure was solved by direct methods. Normalized structure factors E_{hkl} were calculated and introduced in a *MULTAN* procedure (Germain, Main & Woolfson, 1971). 272 reflexions with $E > 1 \cdot 20$ were used to determine the starting sets. The E map computed from the most probable starting set gave the positions of all non-hydrogen atoms. A full-matrix least-squares refinement led to an R of $0 \cdot 130$ ($R = \sum w \lVert F_o \rvert - \lvert F_c \rVert / \sum w \lvert F_o \rvert$) which fell to $0 \cdot 067$ with anisotropic thermal parameters. At this stage a difference synthesis showed all the H atoms in their expected positions. In the last least-squares cycles all parameters were varied except the thermal parameters of the H atoms which were those of their attached atom. The function min-

Table 1. *Fractional atomic coordinates* ($\times 10^4$) *and thermal parameters* ($\times 10^4$) *in the form:*

$$T = exp\,[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$$

Estimated standard deviations ($\times 10^4$) are in parentheses.
B(in Å^2) is $\frac{4}{3}(\beta_{11}a^2 + \beta_{22}b^2 + \beta_{33}c^2 + 2\beta_{12}ab\cos\gamma + 2\beta_{13}ac\cos\beta + 2\beta_{23}bc\cos\alpha)$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	B
S	8264 (1)	705 (1)	−7743 (1)	97 (1)	51 (0)	197 (2)	−12 (1)	71 (1)	36 (1)	4·52
N	8423 (2)	2370 (2)	−9721 (3)	60 (2)	45 (2)	109 (4)	−11 (1)	−8 (2)	6 (2)	2·98
O(1)	10804 (2)	2678 (2)	−7017 (3)	56 (1)	109 (2)	126 (4)	12 (2)	−6 (2)	−40 (3)	4·41
O(2)	10673 (2)	2010 (2)	−9633 (3)	64 (2)	95 (2)	149 (5)	6 (2)	10 (2)	−49 (3)	4·42
O(3)	8009 (2)	2665 (2)	−12493 (3)	59 (1)	66 (2)	105 (3)	−15 (1)	−2 (2)	−11 (2)	3·35
O(4)	9024 (2)	3847 (2)	−10938 (2)	76 (2)	44 (1)	100 (3)	−13 (1)	−16 (2)	14 (2)	3·20
C(1)	8484 (3)	1995 (3)	−6769 (5)	73 (2)	66 (2)	126 (5)	2 (2)	15 (3)	18 (3)	3·81
C(2)	9025 (2)	2642 (2)	−8177 (4)	54 (2)	44 (2)	101 (5)	5 (2)	1 (2)	2 (3)	2·78
C(3)	8455 (2)	2944 (2)	−11161 (4)	43 (2)	47 (2)	114 (5)	−2 (2)	3 (3)	−0 (2)	2·74
C(4)	9124 (3)	4660 (2)	−12309 (4)	70 (2)	50 (2)	99 (5)	−7 (2)	1 (3)	13 (3)	3·20
C(5)	9741 (4)	4209 (4)	−13818 (5)	108 (4)	82 (3)	166 (7)	−22 (3)	49 (4)	−17 (4)	5·15
C(6)	9807 (4)	5511 (3)	−11457 (6)	119 (4)	52 (2)	169 (6)	−27 (3)	−3 (5)	1 (3)	4·75
C(7)	7968 (4)	5069 (4)	−12749 (7)	91 (3)	90 (3)	191 (8)	16 (3)	−7 (5)	54 (5)	5·19
C(8)	7883 (3)	1320 (3)	−9736 (5)	79 (3)	47 (2)	173 (6)	−17 (2)	−10 (4)	10 (3)	3·90
C(9)	10277 (2)	2396 (2)	−8384 (4)	54 (2)	45 (2)	103 (5)	3 (2)	3 (3)	0 (3)	2·81

imized was: $\sum w(|F_o| - |F_c|)^2$, where $w = (0·8 + 0·115F_o)^{-1}$. The final $R = 0·039$ and $R_w = 0·051$ where $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$.*

All calculations were performed on an IBM 370-168 computer with local versions of the following programs: *ORFLS* (Busing, Martin & Levy, 1963) for least-squares refinement; *GEST* (De Rango, Tsoucaris, Zelwer & Baudour, 1964) for Fourier synthesis; and NRC programs (Ahmed, Hall, Pippy & Huber, 1966) for geometrical calculations. Scattering factors were taken from *International Tables for X-ray Crystallography* (1962).

Description of the structure

Fractional coordinates and thermal parameters are listed in Tables 1 and 2. Figs. 1 and 2 give the bond lengths and angles.

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31686 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Hydrogen-atom coordinates* ($\times 10^3$) *and their e.s.d.'s in parentheses*

	x	y	z
H(1)	881 (3)	195 (3)	−577 (5)
H(1')	777 (5)	228 (5)	−669 (8)
H(2)	895 (2)	347 (3)	−795 (4)
H(5)	934 (4)	365 (4)	−1430 (7)
H(5')	1041 (4)	386 (2)	−1354 (6)
H(5'')	987 (5)	480 (4)	−1471 (7)
H(6)	1066 (5)	356 (4)	−1121 (8)
H(6')	986 (3)	612 (3)	−1230 (6)
H(6'')	951 (4)	572 (4)	−1042 (6)
H(7)	758 (5)	443 (4)	−1363 (7)
H(7')	755 (7)	513 (6)	−1165 (9)
H(7'')	792 (5)	567 (5)	−1344 (8)
H(8)	718 (4)	147 (4)	−990 (6)
H(8')	828 (4)	89 (3)	−72 (6)
HO(1)	1145 (4)	262 (3)	−717 (6)

The first noteworthy feature of the structure is the fact that of the 15 non-hydrogen atoms, eight [N, C(2), C(8), C(3), O(4), O(3), C(4), C(6)] lie in the same plane (Table 3). The deviations from this plane do not exceed 0·052 Å. The t-butyloxycarbonyl chain has the same conformation as in t-butyloxycarbonylazetidine-2-carboxylic acid (Cesari, D'Ilario, Giglio & Perego, 1975). C(5) and C(7) are *gauche* while C(6) is *trans* to the C(3)–O(4) bond. The torsion angles C(3)–O(4)–C(4)–X, where X = C(5), C(6), C(7), are respectively −63, 179, and 62°.
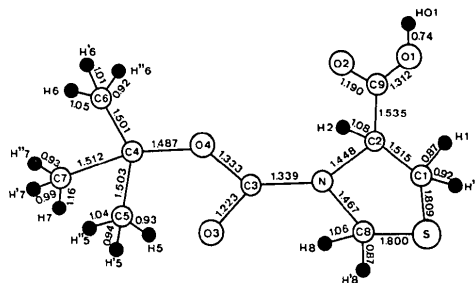

Fig. 1. Atomic numbering and bond distances. The estimated standard deviations are less than 0·004 Å for C–S, C–C, C–N, C–O bonds and 0·05 Å for C–H bonds.
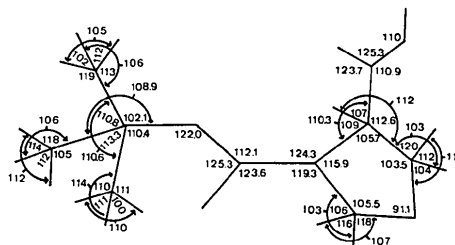

Fig. 2. Bond angles. The estimated standard deviations are about 0·3° for angles involving only non-hydrogen atoms and 5° for angles involving hydrogen atoms.
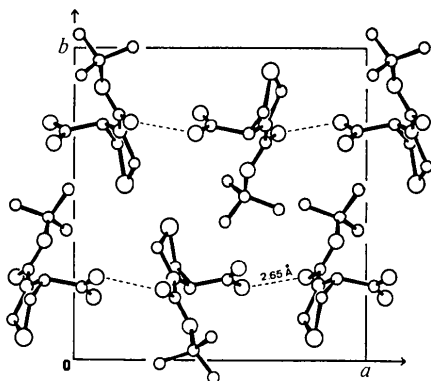
Fig. 3. Molecular packing projected along z. Dashed lines represent hydrogen bonds.

Table 3. *Equations of mean planes and deviations from these planes in* Å

The e.s.d.'s are in parentheses. The asterisk denotes and atom not included in the calculation of the plane.

Plane 1 $-0\cdot8385x + 0\cdot4535y - 0\cdot3021z + 9\cdot4356 = 0$

N	0·053 (3)	O(3)	−0·021 (2)
C(2)	−0·030 (3)	O(4)	0·003 (2)
C(8)	−0·009 (4)	C(4)	0·041 (3)
C(3)	0·005 (3)	C(6)	0·043 (5)

Plane 2 $-0\cdot8200x + 0\cdot5614y - 0\cdot1107z + 7\cdot5539 = 0$

C(1)	0·068 (4)	C(8)	0·076 (4)
C(2)	−0·128 (3)	S*	−0·710 (1)
N	0·136 (3)		

The thiazolidine ring has the same conformation as in thiazolidine-4-carboxylic acid. C(1), C(2), N, C(8) are nearly planar and the S atom lies 0·710 Å out of this plane, *endo* to the carboxyl group. The distances to the N atom are shorter than in thiazolidine-4-carboxylic acid, but are similar to those in t-butyloxycarbonyl-azetidine-2-carboxylic acid. This is due to the trigonal hybridization of the N atom; the sum of the three bond angles around N is 359·4°. The dissymmetry of the two C–O bonds reveals a strong double bond with O(2) (1·190 Å) and a single bond with O(1) (1·312 Å). The carboxyl group is planar and the N atom lies in the same plane; the dihedral angle N–C(2)–C(9)–O(2) is −1·8°. The intramolecular distance between N and O(2) is 2·724 Å. The peptide unit O(3), C(3), N, C(2), C(9), O(2) with C(8) instead of the H atom can be defined by the commonly designated angles φ, ψ, ω [here C(3)–N–C(2)–C(9), N–C(2)–C(9)–O(1) and O(4)–C(3)–N–C(2)] with respectives values −74·7, 177·5 and −6·0° (IUPAC–IUB Commission on Biochemical Nomenclature, 1970).

The packing is governed by van der Waals contacts and a strong hydrogen bond O(1)–HO(1)···O(3) of 2·653 Å. The hydrogen bond angle is 180°. Fig. 3 is a projection of the structure along z.

As already suggested by the X-ray analysis of related compounds such as thiazolidine-4-carboxylic acid, DL-proline hydrochloride (Mitsui, Tsuboi & Iitaka, 1969) and hydroxy-L-proline (Donohue & Trueblood, 1952) we find that the N atom lies in the same plane as the carboxyl group. The puckering of the S atom predicted by energy calculations and suggested by an NMR study (Torchia, 1971) is also observed. The sp^2 hybridization of the N atom restricts the puckering of the ring compared to thiazolidine-4-carboxylic acid where the S atom is 0·843 Å out of the plane. However for this latter compound the crystallized form is the zwitterionic form.

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