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Structure of (6*S*,13*bR*)-1,2,3,5,6,13*b*-Hexahydro-6-isopropyl-8*H*-pyrrolo[1',2':1,2]pyrazino[3,4-*b*]quinazoline-5,8-dione

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Abstract. C₁₇H₁₉N₃O₂, monoclinic, *P*2₁, *a* = 5.382 (1), *b* = 17.534 (4), *c* = 8.198 (1) Å, β = 100.46 (1)°, *Z* = 2, *d*_m = 1.323, *d*_c = 1.299 Mg m⁻³, *F*(000) = 316, μ(Cu Kα) = 0.618 mm⁻¹. *R* = 0.052 for 1284 significant reflections. The proline-containing *cis*-peptide unit which forms part of a six-membered ring deviates from perfect planarity. The torsion angle about the peptide bond is 3.0 (5)° and the peptide bond length is 1.313 (5) Å. The conformation of the proline ring is *C*_s-*C*^β-*endo*. The crystal structure is stabilized by C—H...O interactions.

Introduction. The proline ring plays an important role in the bend regions of protein chains. The title compound (Fig. 1) with a dipeptide-like fragment with prolyl and valyl residues affords a possibility of studying the conformations of these two side chains. NMR studies had indicated (Rajappa & Advani, 1973) an axial conformation of the valyl side chain.

In the present compound, there are no proton donors of type O—H or N—H. The only possible proton donor is the C—H group. C—H...O and C—H...N interactions have been previously observed in crystal structures (Sutor, 1962; Leiserowitz, 1976). Evidence

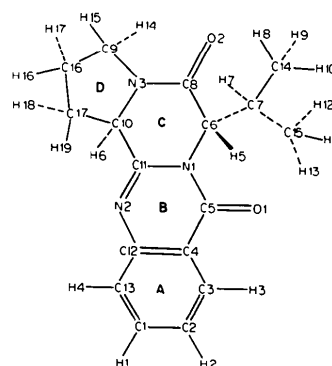


Fig. 1. The atomic numbering.

for significant C—H...O interactions has been obtained from an X-ray powder diffraction study of the neutral-ionic phase transition in tetrathiafulvalene-chloranil (Batail, La Placa, Mayerle & Torrence, 1981). It is of interest to look for similar interactions in the present situation.

The title compound, a tetracyclic quinazolone, was derived from *cyclo*(-L-Val-L-Pro-), but during its synthesis, the proline centre epimerized, so that the product has the *S* configuration at the valine and the *R*

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configuration at the proline centres (Rajappa & Advani, 1973). It was crystallized from ether/hexane solutions. Intensity data were collected on a Nonius CAD-4 diffractometer in the ω - 2θ scan mode with monochromated Cu $K\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$) from a crystal of dimensions $0.5 \times 0.2 \times 0.1 \text{ mm}$. Of the 1436 reflections measured up to $\theta = 70^\circ$, 1284 were considered significant [$|F| > 2\sigma(|F|)$]. No correction was made for absorption ($\mu r \approx 0.12$).

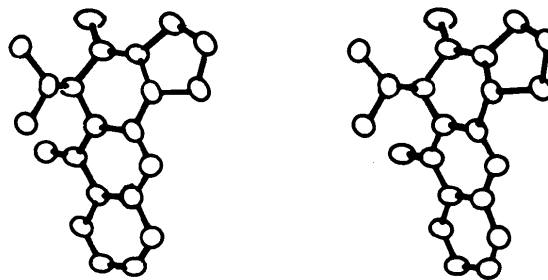


Fig. 2. A stereoview of the molecule.

Table 1. Fractional coordinates ($\times 10^4$) and equivalent isotropic temperature factors for the non-H atoms with *e.s.d.*'s in parentheses

$$U_{eq} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i \cdot a_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{eq} (\text{\AA}^2)$
O(1)	9573 (5)	5977	5246 (3)	0.071 (1)
O(2)	10200 (4)	8553 (2)	6319 (3)	0.075 (1)
N(1)	6711 (4)	6948 (2)	4661 (3)	0.043 (1)
N(2)	3215 (5)	6890 (2)	2477 (3)	0.049 (1)
N(3)	6400 (5)	8492 (2)	4612 (3)	0.052 (1)
C(1)	2805 (9)	4950 (2)	775 (5)	0.070 (2)
C(2)	5058 (7)	4635 (2)	1589 (4)	0.063 (2)
C(3)	6661 (8)	5052 (2)	2712 (4)	0.054 (2)
C(4)	6039 (6)	5800 (2)	3074 (3)	0.046 (1)
C(5)	7663 (6)	6218 (2)	4387 (4)	0.049 (2)
C(6)	7898 (6)	7380 (2)	6144 (4)	0.047 (2)
C(7)	6406 (6)	7304 (2)	7584 (4)	0.056 (2)
C(8)	8259 (7)	8202 (2)	5693 (5)	0.054 (2)
C(9)	6354 (8)	9276 (3)	3940 (6)	0.070 (2)
C(10)	4080 (6)	8075 (2)	3940 (6)	0.046 (2)
C(11)	4636 (6)	7251 (2)	3634 (3)	0.041 (1)
C(12)	3827 (6)	6132 (2)	2223 (3)	0.043 (1)
C(13)	2187 (7)	5687 (2)	1072 (4)	0.061 (2)
C(14)	7973 (11)	7632 (3)	9179 (5)	0.059 (2)
C(15)	5649 (12)	6486 (3)	7864 (6)	0.081 (3)
C(16)	3704 (9)	9355 (2)	2935 (5)	0.071 (2)
C(17)	2927 (10)	8537 (2)	2412 (5)	0.067 (2)

Table 2. Fractional coordinates ($\times 10^4$) and isotropic temperature factors for the H atoms

	<i>x</i>	<i>y</i>	<i>z</i>	$U (\text{\AA}^2)$
H(1)	1674 (75)	4682 (24)	-40 (48)	0.078 (11)
H(2)	5685 (68)	4114 (21)	1429 (38)	0.065 (9)
H(3)	8086 (67)	4907 (17)	3376 (39)	0.055 (9)
H(4)	654 (74)	5976 (20)	475 (45)	0.073 (11)
H(5)	9397 (59)	7207 (16)	6465 (32)	0.036 (7)
H(6)	2990 (61)	8082 (15)	4743 (37)	0.050 (8)
H(7)	4655 (67)	7601 (16)	7357 (39)	0.060 (9)
H(8)	8188 (95)	8180 (28)	8837 (53)	0.104 (15)
H(9)	6977 (86)	7605 (25)	10070 (61)	0.094 (15)
H(10)	9424 (77)	7355 (21)	9422 (45)	0.071 (12)
H(11)	7244 (97)	6243 (27)	8111 (58)	0.096 (16)
H(12)	4787 (107)	6447 (29)	9045 (68)	0.126 (16)
H(13)	4419 (124)	6313 (28)	6762 (75)	0.123 (16)
H(14)	6541 (76)	9598 (28)	4702 (49)	0.081 (13)
H(15)	7751 (69)	9340 (19)	3173 (43)	0.071 (10)
H(16)	3643 (76)	9710 (25)	1846 (49)	0.091 (11)
H(17)	2422 (78)	9561 (24)	3633 (47)	0.088 (12)
H(18)	1216 (94)	8478 (25)	2183 (55)	0.089 (15)
H(19)	3868 (98)	8401 (25)	1605 (55)	0.096 (14)

The structure was solved by direct methods with *SHELX* (Sheldrick, 1976). The non-hydrogen atoms were refined by least squares to $R = 0.126$ with anisotropic thermal parameters. At this stage all the H atoms were located from a difference map. R converged to 0.052 by including in the refinement the H atoms with isotropic thermal parameters. The weighting scheme was $w = 1/\sigma^2(|F|)$. Final parameters of the non-H and H atoms are listed in Tables 1 and 2 respectively.* A stereoview of the molecule is shown in Fig. 2.

Discussion. The bond lengths (Table 3) and angles (Table 4) of the peptide unit are in good agreement with those quoted for the *cis*-peptide unit (Ramachandran & Sasisekharan, 1968). The peptide unit is not quite planar, with ω , θ_N and θ_C (Ramachandran, Lakshminarayanan & Kolaskar, 1973) being $3.0 (5)$, $-1.0 (7)$ and $0.4 (6)^\circ$ respectively.

Rings *A* and *B* are essentially planar whereas ring *C* (Fig. 1) is significantly non-planar. The average deviations of the six atoms from their mean planes are

* Lists of structure factors, anisotropic thermal parameters, torsion angles, bond lengths and angles involving H atoms and intermolecular contacts have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36825 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. Bond lengths (\AA) involving non-H atoms

O(1)-C(5)	1.211 (4)	C(3)-C(4)	1.399 (5)
O(2)-C(8)	1.240 (5)	C(4)-C(5)	1.455 (4)
N(1)-C(5)	1.413 (5)	C(4)-C(12)	1.393 (4)
N(1)-C(6)	1.476 (4)	C(6)-C(7)	1.549 (5)
N(1)-C(11)	1.377 (4)	C(6)-C(8)	1.509 (5)
N(2)-C(11)	1.274 (4)	C(7)-C(14)	1.533 (6)
N(2)-C(12)	1.394 (5)	C(7)-C(15)	1.522 (6)
N(3)-C(8)	1.313 (5)	C(9)-C(16)	1.518 (7)
N(3)-C(9)	1.480 (6)	C(10)-C(11)	1.506 (5)
N(3)-C(10)	1.465 (4)	C(10)-C(17)	1.526 (5)
C(1)-C(2)	1.388 (6)	C(12)-C(13)	1.406 (5)
C(1)-C(13)	1.367 (5)	C(16)-C(17)	1.533 (5)
C(2)-C(3)	1.356 (5)		

Table 4. Bond angles (°) involving non-H atoms

C(5)–N(1)–C(6)	118.8 (3)	C(6)–C(7)–C(14)	109.7 (3)
C(5)–N(1)–C(11)	122.0 (3)	C(6)–C(7)–C(15)	112.7 (3)
C(6)–N(1)–C(11)	119.2 (3)	C(14)–C(7)–C(15)	110.3 (4)
C(11)–N(2)–C(12)	117.3 (3)	O(2)–C(8)–N(3)	124.7 (4)
C(8)–N(3)–C(9)	124.8 (3)	O(2)–C(8)–C(6)	120.6 (3)
C(8)–N(3)–C(10)	123.6 (3)	N(3)–C(8)–C(6)	114.8 (3)
C(9)–N(3)–C(10)	111.6 (3)	N(3)–C(9)–C(16)	103.7 (4)
C(2)–C(1)–C(13)	120.7 (4)	N(3)–C(10)–C(11)	111.1 (3)
C(1)–C(2)–C(3)	120.3 (4)	N(3)–C(10)–C(17)	103.6 (3)
C(2)–C(3)–C(4)	120.2 (3)	C(11)–C(10)–C(17)	115.9 (3)
C(3)–C(4)–C(5)	119.6 (3)	N(1)–C(11)–N(2)	125.0 (3)
C(3)–C(4)–C(12)	120.1 (3)	N(1)–C(11)–C(10)	115.6 (3)
C(5)–C(4)–C(12)	120.3 (3)	N(2)–C(11)–C(10)	119.4 (4)
O(1)–C(5)–N(1)	121.1 (3)	N(2)–C(12)–C(4)	121.8 (3)
O(1)–C(5)–C(4)	126.0 (3)	N(2)–C(12)–C(13)	119.5 (3)
N(1)–C(5)–C(4)	112.8 (3)	C(4)–C(12)–C(13)	118.7 (3)
N(1)–C(6)–C(7)	112.1 (3)	C(1)–C(13)–C(12)	120.1 (3)
N(1)–C(6)–C(8)	110.1 (3)	C(9)–C(16)–C(17)	104.4 (4)
C(7)–C(6)–C(8)	112.1 (3)	C(10)–C(17)–C(16)	102.6 (3)

Table 5. Torsion angles (°) involving the valyl C^β atom

C(11)–N(1)–C(6)–C(7)	78.6 (4)
C(5)–N(1)–C(6)–C(7)	–98.1 (3)
O(2)–C(8)–C(6)–C(7)	93.6 (4)
N(3)–C(8)–C(6)–C(7)	–86.8 (4)

0.01, 0.03 and 0.19 Å for the rings A, B and C respectively.

The C^β atom of the valyl residue is in the axial position (Table 5), as has been predicted from NMR studies (Rajappa & Advani, 1973). The axial geometry is preferred to the equatorial in order to avoid an unfavourable interaction between C^β and O(1).

The torsion angles of the valyl side chain are $\chi^1 = \text{N}(1)\text{--C}(6)\text{--C}(7)\text{--C}(14) = 169.3 (3)$ and $\chi^2 = \text{N}(1)\text{--C}(6)\text{--C}(7)\text{--C}(15) = 46.0 (4)^\circ$.

The bond lengths and bond angles of the prolyl residue agree well with the average values given by Ashida & Kakudo (1974). The torsion angles θ , χ^1 , χ^2 , χ^3 and χ^4 (Balasubramanian, Lakshminarayanan, Sabesan, Tegoni, Venkatesan & Ramachandran, 1971) which define the conformation of the pyrrolidine ring are shown in Fig. 3. The atoms C(17) (C^β) and C(11) (C') are on the same side of the mean plane through the pyrrolidine ring whereas C(16) (C^γ) is on the other side. The deviations of C^β and C^γ from the plane through C^α, N and C^δ are 0.442 (5) and –0.156 (4) Å respectively. This geometry is intermediate between the C_s–C^β–endo and C₂–C^β–endo conformations as defined by Ashida & Kakudo (1974). It is closer to C_s–C^β–endo puckering. A similar conformation has been observed for one of the prolyl residues in the crystal structure of *o*-bromobenzyl-oxycarbonyl-Gly-Pro-Leu-Gly-Pro (Ueki, Bando, Ashida & Kakudo, 1971).

The crystal structure (Fig. 4) is stabilized by two C–H...O intermolecular hydrogen bonds: C(10)–

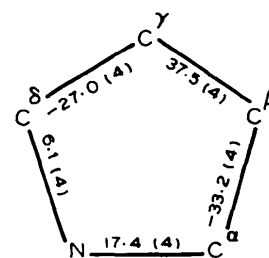


Fig. 3. Torsion angles (°) in the pyrrolidine ring.

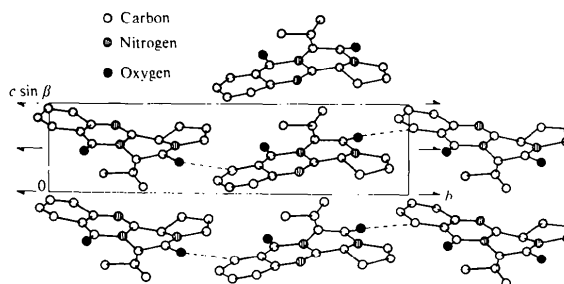


Fig. 4. Packing of the molecules as viewed along a.

H(6)...O(2) and C(3)–H(3)...O(2) with C...O = 3.216 (4) and 3.317 (4) Å, H...O = 2.30 (3) and 2.54 (3) Å, and $\angle\text{C–H}\cdots\text{O} = 159 (3)$ and $126 (3)^\circ$ respectively.

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