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Structure of Tetrahydro-*N*-methyl-2-(2-pyridinyl)-2-thiophenecarbothioamide* (Picartamide)

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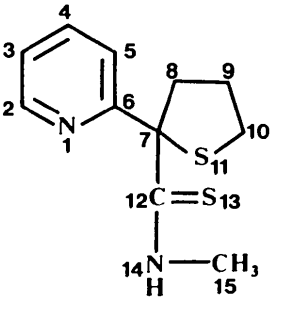
Abstract. $C_{11}H_{14}N_2S_2$, $M_r = 238{\cdot}37$, monoclinic, $P2_1/c$, $a = 8{\cdot}760\ (3)$, $b = 8{\cdot}732\ (2)$, $c = 16{\cdot}353\ (4)$ Å, $\beta = 112{\cdot}02\ (5)°$, $V = 1185{\cdot}3\ (5)$ Å^3, $Z = 4$, $D_m = 1{\cdot}334\ (2)$, $D_x = 1{\cdot}336$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 37{\cdot}53$ cm^{-1}, $F(000) = 504$, $T = 293$ K, $R = 0{\cdot}045$ for 1983 observed reflections. The tetrahydro-2-thiophene ring takes a β-envelope configuration and is linked with the thiocarboxamide group by an intramolecular N—H···S hydrogen bond. The NH group is intermolecularly hydrogen-bonded to the pyridine N atom, thus forming a 'cyclic' dimer structure between two centrosymmetrically related molecules.

Introduction. The regulation of gastric acid secretion is very useful for peptic ulcer therapy. H^+,K^+-ATPase inhibitors (ARIs) have been receiving increasing interest (Clissold & Campoli-Richards, 1986; Sachs, Carlsson, Lindberg & Wallmark, 1988), since the enzyme has been recognized as the acid pump involved in the terminal steps of the gastric acid secretory process.

Picartamide [*N*-methyl-2-(2-pyridyl)tetrahydro-2-thiophenethiocarboxamide] (1) could be considered to be a H^+,K^+-ATPase inhibitor inasmuch as it is a potent inhibitor of gastric acid secretion induced by histamide, pentagastric, carbachol and dibutyryl cyclic AMP in rats (Deregnaucourt & Hardy-Houis, 1982) and has no anticholinergic or antihistaminic property (Aloup, Bouchaudon, Farge, James, Deregnaucourt & Hardy-Houis, 1987).



(1)

In order to consider the relationship between the structures and activities of ARIs, it is of special importance to know their stable conformations. This paper deals with the crystal structure of picartamide.

Experimental. Cubic crystals of picartamide were grown from a chloroform/methylene dichloride mixture. Crystal density was measured by the flotation method using a CCl_4–C_6H_6 mixture. A well shaped crystal with approximate dimensions 0·2 × 0·2 × 0·3 mm was mounted on a Rigaku AFC-5 computer-controlled diffractometer with graphite-monochromated Cu $K\alpha$ radiation ($\lambda = 1{\cdot}5418$ Å). Unit-cell dimensions were determined by a least-squares fit of 2θ values of 25 reflections ($50 < 2\theta < 61°$). Intensities were measured by the ω–2θ scan technique

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with a scan rate of 3° min^{-1} in 2θ and a scan width of $\Delta(2\theta) = (1{\cdot}2 + 0{\cdot}15 \tan\theta)°$. Background intensities were measured for 5 s at each end of a scan. Four standard reflections (400, 040, 00$\bar{8}$, 33$\bar{6}$) monitored every 100 reflection intervals showed no significant variation in the intensities during data collection (within ±0·7%). 2027 independent reflections were collected within $2\theta = 130°$ [$(\sin\theta)/\lambda \leq 0{\cdot}588$ Å^{-1}]; index range of h −9 to 10, k 0 to 10, l −19 to 0. Corrections for Lorentz and polarization effects were applied to the intensity data; no absorption or extinction corrections were carried out.

The structure was solved by direct methods using *MULTAN*87 (Debaerdemaeker, Germain, Main, Tate & Woolfson, 1987). 1983 observed reflections [$|F_o| > 0{\cdot}0$] were used in the refinement; the function minimized was $\sum w(|F_o| - |F_c|)^2$. Positions of all H atoms were ideally calculated on the basis of stereochemical considerations, and were checked on a difference Fourier map calculated using the anisotropic non-H atoms. The structure was refined by the block-diagonal least-squares procedure with anisotropic temperature factors for non-H atoms and isotropic ones for H atoms. The weighting scheme used in the final refinement was $w = [\sigma(F_o)^2 + 0{\cdot}02531|F_o| - 0{\cdot}00027|F_o|^2]^{-1}$. The number of observations per refined parameter is 1983/193 = 10·27 and S is 1·583. The final R and wR values are 0·045 and 0·055, respectively. $(\Delta/\sigma)_{max}$ in the final refinement cycle was 0·22; $(\Delta\rho)_{max}$ and $(\Delta\rho)_{min}$ were 0·22 and −0·15 e Å^{-3}. The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). All crystallographic computations were performed on a MicroVAXII computer at the Computer Center, Osaka University of Pharmaceutical Sciences, using the *Universal Crystallographic Computing System–Osaka* (1979). The final atomic parameters are listed in Table 1.*

Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors* (Å^2) *for non*-H *atoms with e.s.d.'s in parentheses*

$B_{eq} = \frac{4}{3}\sum_i\sum_j \mathbf{a}_i\mathbf{a}_j B_{ij}$.

	x	y	z	B_{eq}
N(1)	−0·0872 (2)	0·1542 (2)	1·0998 (1)	2·82 (7)
C(2)	−0·2074 (3)	0·1505 (3)	1·1343 (2)	3·7 (1)
C(3)	−0·2073 (3)	0·2347 (4)	1·2046 (2)	4·4 (1)
C(4)	−0·0837 (3)	0·3302 (3)	1·2393 (2)	4·3 (1)
C(5)	0·0420 (3)	0·3367 (3)	1·2056 (2)	3·54 (9)
C(6)	0·0349 (2)	0·2488 (2)	1·1346 (1)	2·13 (7)
C(7)	0·1657 (2)	0·2515 (2)	1·0928 (1)	2·25 (7)
C(8)	0·2670 (3)	0·3989 (3)	1·1104 (2)	3·49 (9)
C(9)	0·3527 (3)	0·4019 (3)	1·0425 (2)	4·7 (1)
C(10)	0·2288 (4)	0·3761 (4)	0·9574 (2)	5·6 (1)
S(11)	0·07328 (7)	0·24865 (7)	0·97565 (4)	3·08 (2)
C(12)	0·2755 (2)	0·1120 (2)	1·1281 (1)	2·12 (7)
S(13)	0·39083 (7)	0·10499 (8)	1·23072 (4)	3·64 (2)
N(14)	0·2678 (2)	−0·0023 (2)	1·0739 (1)	2·58 (6)
C(15)	0·3576 (3)	−0·1447 (3)	1·0969 (2)	3·77 (9)

Table 2. *Bond lengths* (Å) *and angles* (°) *for non*-H *atoms with e.s.d.'s in parentheses*

N(1)—C(2)	1·344 (3)	C(7)—S(11)	1·827 (2)
N(1)—C(6)	1·327 (3)	C(7)—C(12)	1·545 (3)
C(2)—C(3)	1·365 (4)	C(8)—C(9)	1·527 (4)
C(3)—C(4)	1·340 (4)	C(9)—C(10)	1·483 (5)
C(4)—C(5)	1·381 (4)	C(10)—S(11)	1·856 (4)
C(5)—C(6)	1·376 (3)	C(12)—S(13)	1·660 (2)
C(6)—C(7)	1·510 (3)	C(12)—N(14)	1·323 (3)
C(7)—C(8)	1·537 (3)	N(14)—C(15)	1·456 (3)

C(2)—N(1)—C(6)	117·9 (2)	C(8)—C(7)—S(11)	104·1 (1)
N(1)—C(2)—C(3)	123·4 (2)	C(8)—C(7)—C(12)	109·7 (1)
C(2)—C(3)—C(4)	118·3 (2)	S(11)—C(7)—C(12)	113·3 (1)
C(3)—C(4)—C(5)	119·8 (2)	C(7)—C(8)—C(9)	105·5 (2)
C(4)—C(5)—C(6)	119·1 (2)	C(8)—C(9)—C(10)	107·3 (2)
N(1)—C(6)—C(5)	121·5 (1)	C(9)—C(10)—S(11)	107·2 (1)
N(1)—C(6)—C(7)	116·1 (1)	C(7)—S(11)—C(10)	93·3 (1)
C(5)—C(6)—C(7)	122·4 (1)	C(7)—C(12)—S(13)	120·8 (1)
C(6)—C(7)—C(8)	113·9 (1)	C(7)—C(12)—N(14)	116·9 (1)
C(6)—C(7)—S(11)	109·1 (1)	S(13)—C(12)—N(14)	122·3 (1)
C(6)—C(7)—C(12)	106·9 (1)	C(12)—N(14)—C(15)	124·3 (1)

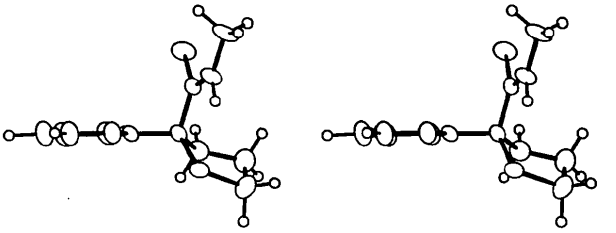

Fig. 1. A stereoscopic view of picartamide, viewed parallel to the pyridine ring.

Discussion. The bond lengths and angles are listed in Table 2. A stereoscopic view of picartamide, drawn by *ORTEP*II (Johnson, 1976) is presented in Fig. 1.

The bond lengths and angles all lie in a reasonable region, except for C(9)—C(10); this bond length is significantly shorter than the usual C—C single bond. The pyridine ring is essentially planar with deviations of −0·010 (3) to 0·009 (3) Å from its best-fit plane, and forms a dihedral angle of 79·5 (2)° to the thioamide group which takes the usual *trans* conformation [C(7)—C(12)—N(14)—C(15) = −177·5 (2)°]. As is obvious from Fig. 1, the thiophene ring takes a C(7)-*endo* envelope (C_s)-type configuration; torsion angles S(11)—C(7)—C(8)—C(9), C(7)—C(8)—C(9)—C(10), C(8)—C(9)—C(10)—S(11), C(9)—C(10)—S(11)—C(7) and C(8)—C(7)—S(11)—C(10) are −44·1 (2), 50·3 (2), −32·2 (2), 5·4 (2) and 22·3 (2)°, respectively, and the deviation of C(7) from the best plane consisting of C(8), C(9), C(10) and S(11) is 0·510 (4) Å. N(14) could participate in an intramolecular hydrogen bond with S(11),

* Lists of anisotropic temperature factors for non-H atoms, atomic parameters for H atoms and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52313 (13 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

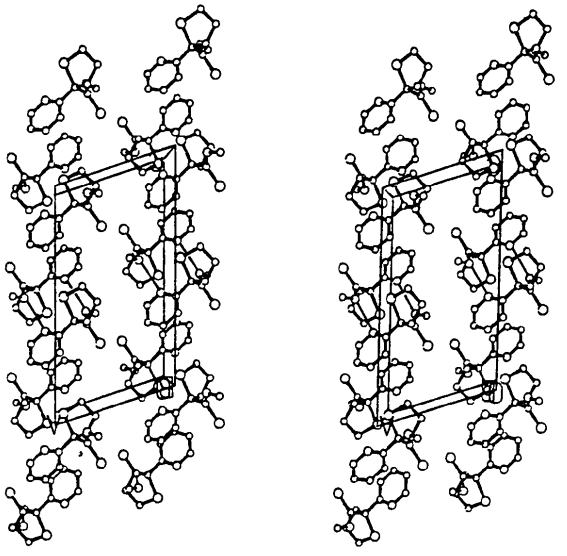

Fig. 2. A stereoscopic view of the crystal packing, viewed along the *b* axis. The hydrogen bonds forming cyclic dimers are shown by thin lines.

judging from its bonding parameters: N(14)···S(11) = 2·921 (2), H(14)···S(11) = 2·31 (3) Å and ∠N(14)—H(14)···S(11) = 117 (2)°. This interaction restricts the rotation around the C(7)—C(12) bond. Thus, the relative orientation of the thioamide group with respect to the pyridine ring appears to be highly fixed.

A stereoscopic view of the crystal packing is shown in Fig. 2. The molecules related by *c*-glide symmetry are arranged along the *c* axis and are stably held by normal van der Waals contacts among the neighboring molecules. N(14) participates in a hydrogen bond with the centrosymmetrically related N(1) [N(14)(x,y,z)···N(1)($-x$, $-y$, $2-z$) = 3·075 (3), H(14)···N(1) = 2·28 (3) Å and ∠N(14)—H(14)···N(1) = 133 (2)°], thus forming a cyclic dimer.

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Vernamycin B_α

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Abstract. 5-[4-(Dimethylamino)-*N*-methyl-L-phenylalanine]-virginiamycin S_1 monohydrate, 3-HyPic-Thr-D-Abu-Pro-MePheN$(CH_3)_2$-4-oxoPip-PhGly.-O—— H_2O, $C_{45}H_{54}N_8O_{10}.H_2O$, $M_r = 866{\cdot}94 + 18{\cdot}02$, orthorhombic, $C222_1$, $a = 22{\cdot}426\ (6)$, $b = 24{\cdot}043\ (6)$, $c = 19{\cdot}647\ (5)$ Å, $V = 10593{\cdot}4$ Å^3, $Z = 8$, $D_x = 1{\cdot}110$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}63$ mm^{-1}, $F(000) = 3760$, room temperature, $R(F) = 0{\cdot}050$ for 3631 reflections with $|F_o| > 3\sigma$ and 605 parameters refined. The peptide contains both a linear portion and a 19-atom depsipeptide ring with a junction at the threonine residue. The 19-atom backbone ring assumes a cup-like conformation folded around the 3-HyPic residue to form a globular entity with a predominantly hydrophobic surface. The conformation of the molecule is similar to that of virginiamycin (factor S) [Declercq, Germain, Van Meerssche, Hull & Irwin (1978). *Acta Cryst.* B**34**, 3644–3648].

Introduction. An unusual class of antibiotic peptides contains both a cyclic backbone and a linear peptide chain. Although these peptides occur naturally in diverse sources such as a Caribbean tunicate and various fungi, their common feature is a threonine

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