

Nicotinothiazide

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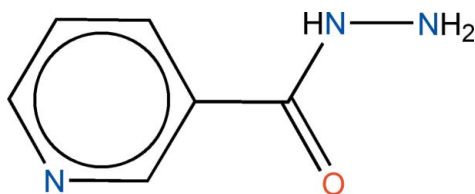
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Key indicators: single-crystal X-ray study; $T = 293$ K; mean $\sigma(\text{C}-\text{C}) = 0.002$ Å;
 R factor = 0.031; wR factor = 0.087; data-to-parameter ratio = 11.4.

The title molecule (alternative name: pyridine-3-carbohydrazide; $\text{C}_6\text{H}_7\text{N}_3\text{O}$) was obtained from the reaction of ethyl nicotinate with hydrazine hydrate in methanol. In the amide group, the C—N bond is relatively short, suggesting some degree of electronic delocalization in the molecule. The stabilized conformation may be compared with those of isomeric compounds picolinothiazide (pyridine-2-carbohydrazide) and isonicotinothiazide (pyridine-4-carbohydrazide). In the title isomer, the pyridine ring forms an angle of 33.79 (9°) with the plane of the non-H atoms of the hydrazide group. This lack of coplanarity between the hydrazide functionality and the pyridine ring is considerably greater than that observed in isonicotinothiazide (dihedral angle = 17.14°), while picolinothiazide is almost fully planar. The title isomer forms intermolecular N—H...O and N—H...N hydrogen bonds, which stabilize the crystal structure.

Related literature

The structure of the same compound has been determined independently and is reported in the following paper (Portalone & Colapietro, 2008). The structures of picolinothiazide (Zareef *et al.*, 2006) and isonicotinothiazide (Jensen, 1954; Bhat *et al.*, 1974) have been published. For related literature on the biological activity of these molecules, see: Ouellet *et al.* (2004); Zhao *et al.* (2007). For related literature, see: Bhat *et al.* (1974); Zareef *et al.* (2006).



Experimental

Crystal data

$\text{C}_6\text{H}_7\text{N}_3\text{O}$
 $M_r = 137.15$
 Orthorhombic, $P2_12_12_1$
 $a = 3.8855$ (7) Å
 $b = 10.5191$ (5) Å
 $c = 15.9058$ (9) Å

$V = 650.10$ (13) Å³
 $Z = 4$
 Mo $K\alpha$ radiation
 $\mu = 0.10$ mm⁻¹
 $T = 293$ (2) K
 $0.46 \times 0.30 \times 0.20$ mm

Data collection

Enraf–Nonius CAD-4
 diffractometer
 Absorption correction: none
 1534 measured reflections
 1051 independent reflections

866 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.015$
 3 standard reflections
 every 200 reflections
 intensity decay: $<1\%$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.031$
 $wR(F^2) = 0.087$
 $S = 1.09$
 1051 reflections

92 parameters
 H-atom parameters constrained
 $\Delta\rho_{\text{max}} = 0.18$ e Å⁻³
 $\Delta\rho_{\text{min}} = -0.15$ e Å⁻³

Table 1

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
$\text{N2}-\text{H2N}\cdots\text{N1}^{\text{i}}$	0.88	2.11	2.975 (2)	166
$\text{N3}-\text{H3NA}\cdots\text{O1}^{\text{ii}}$	0.87	2.22	3.045 (2)	157
$\text{N3}-\text{H3NB}\cdots\text{O1}^{\text{iii}}$	0.85	2.55	3.155 (2)	130

Symmetry codes: (i) $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $x+\frac{1}{2}, -y+\frac{3}{2}, -z+1$; (iii) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$.

Table 2

Selected bond lengths (Å) of nicotinothiazide (I), picolinic acid hydrazide (II) and isonicotinothiazide (III).

	(I)	(II)	(III)
$\text{N2}-\text{N3}$	1.418 (2)	1.422	1.429
$\text{C6}-\text{N2}$	1.335 (2)	1.334	1.346
$\text{C6}-\text{O1}$	1.231 (2)	1.235	1.235
$\text{C6}-\text{C2}$	1.503 (2)	1.507	1.513

Data collection: *CAD-4 EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD-4 EXPRESS*; data reduction: *HELENA* (Spek, 1996); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXL97*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: BH2145).

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supporting information

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Nicotinohydrazide

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S1. Comment

The importance of aromatic hydrazides is closely related to their biological activity and to the fact that they can be used for the syntheses of several other biologically active compounds. Nicotinohydrazide, (I), for example, is an efficient peroxidase-activated inhibitor of the POX activity of PGHS-2 (Ouelleta *et al.*, 2004). On the other hand, the isomer isonicotinohydrazide, (III, scheme 2), is not a potent inhibitor, with an IC_{50} of 129 mM against 15 mM for (I).

Structure also plays a major role in the activity of the anti-tuberculosis drug isonicotinohydrazide, which requires *Mycobacterium tuberculosis* catalase-peroxidase (KatG) activation to produce an acyl-NAD adduct (Zhao *et al.*, 2007). This adduct is of extreme importance since it is an inhibitor of the enoyl reductase (Mtb InhA), essential for the biosynthesis of acids present in mycobacterial cell walls. Picolinohydrazide, (II), and isonicotinohydrazide, (III), generate the hydrazide-NAD adduct in this system, while nicotinohydrazide, (I), does not. However, the yield of the (II)-NAD adduct is around 35% of that of the (III)-NAD adduct. As a result, (III) is a potent antituberculosis drug, while (I) and (II) are not.

In this context, studies of structural analogues of these biologically active compounds become fundamental and will be useful in elucidating the mechanism of action, which strongly depends on substrate selection and binding stoichiometry to the (III) binding site in KatG, which still has not been completely elucidated.

The crystal structures of picolinohydrazide, (II) (Zareef *et al.*, 2006), and isonicotinohydrazide, (III) (Jensen, 1954; Bhat *et al.*, 1974), have been previously reported and the structure of nicotinohydrazide (I) is here described. The three isomeric hydrazides are distinguished by just the position of the N atom in the pyridine ring with respect to hydrazide group (scheme 2). A selection of their structural parameters is shown in Table 2.

When the structural parameters of isomeric hydrazides are compared, some interesting aspects can be observed, which depend on the structural relation between the N atom in the ring and the hydrazide group. Indeed, while (II) crystallizes in the monoclinic system, isomers (I) and (III) crystallize in the orthorhombic system. The C6?O1 bond length in (I) and also in (II) and (III) are smaller than those usually observed in carboxylic acids (1.365 Å, Zareef *et al.*, 2006). Similarly, the C6—N2 bond distance observed in (I) is consistent with those reported for (II) and (III) hydrazides, suggesting a significant partial double-bond character; the bond lengths are consistent with resonance hybrids between a polar and a neutral form (Bhat *et al.*, 1974). Similar to the results reported (Bhat *et al.*, 1974) for isonicotinohydrazide, the N2—N3 and C2—C6 bonds of (II) have distances similar to their corresponding single bonds. In (I), the pyridine ring bond lengths are very similar to those obtained in related compounds and the ring lies in a plane which forms an angle of 33.79 (9)° with that of the non-H atoms in the hydrazide group. This lack of coplanarity between the hydrazide functionality and the pyridine ring is considerably greater than that observed in isonicotinohydrazide (-17.14°), while picolinohydrazide is almost fully planar, probably because in (II) N2 is in the same side and therefore closer to N1, favoring intramolecular N2—H···N1 hydrogen bond. Conversely, in the crystal structure of (I) N2 and N1 are on opposite sides of the molecule, and in this case only intermolecular hydrogen bonding takes place. The intermolecular hydrogen

bonds $\text{N3—H}\cdots\text{O1}$ and $\text{N2—H}\cdots\text{N1}$ (Table 1), which form a three-dimensional polymeric structure (Fig. 2) are fundamental for the stability of the crystal structure of (I).

S2. Experimental

Nicotinic acid hydrazine was synthesized by the reaction of ethyl nicotinate (43.9 mmol) and hydrazine hydrate 99% (27.5 mmol) in methanol. The reaction mixture was refluxed for 24 h., yielding a yellow solution. Upon cooling to 298 K, the product precipitated and it was washed with methanol and filtered. Colorless needle shaped crystals of (I) suitable for X-ray analysis were grown by recrystallization from a chloroform-methanol (9:1) solution by slow evaporation at room temperature.

S3. Refinement

All non-H atoms were refined with anisotropic displacement parameters. H atoms attached to C atoms were added at their calculated positions, with $\text{C—H} = 0.93 \text{ \AA}$ and $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{carrier C})$. H atoms of the hydrazide group were found in a difference map and treated with a riding model and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{carrier N})$. In the absence of significant anomalous scattering effects, no Friedel pairs were collected.

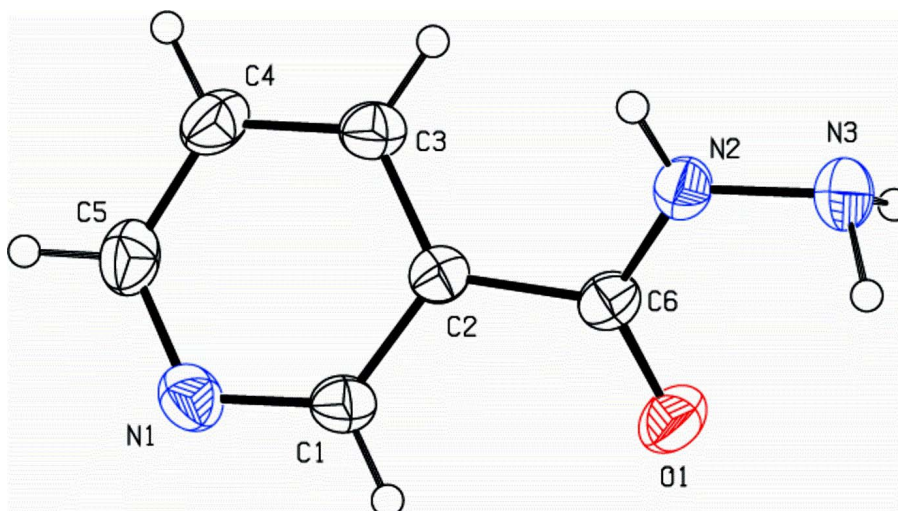


Figure 1

The molecular structure of (I) with labeling scheme. Displacement ellipsoids are shown at the 40% probability level.

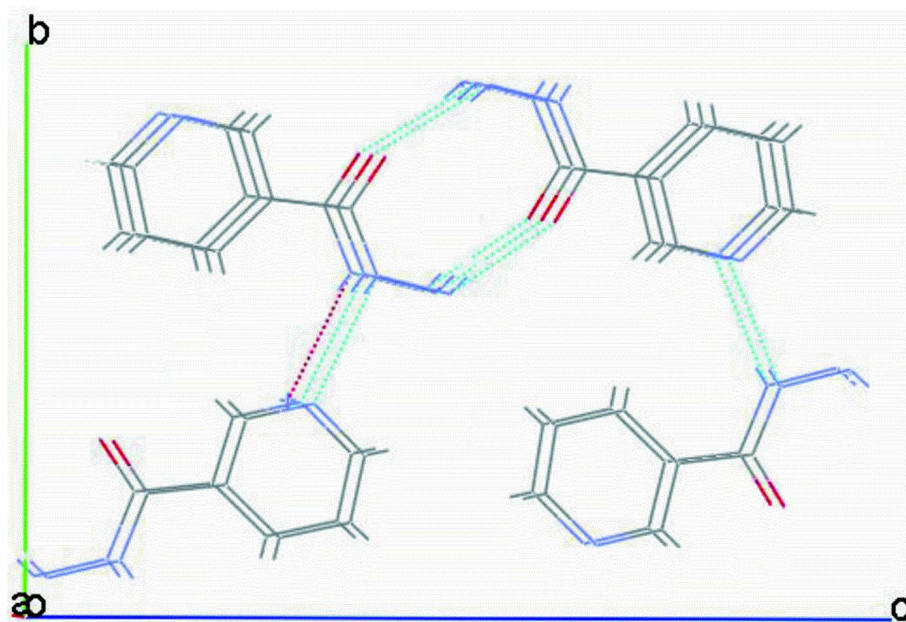


Figure 2

Packing of (I) showing the molecules connected through hydrogen bonds and stacked along [100].

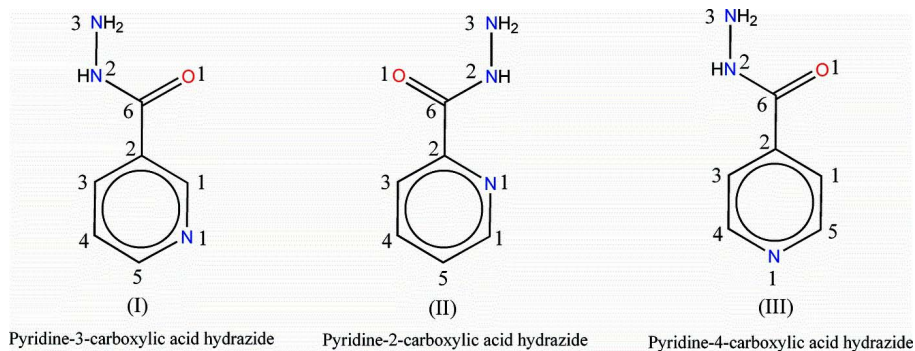


Figure 3

The structures of (I)–(III).

Pyridine-3-carbohydrazide

Crystal data

$C_6H_7N_3O$

$M_r = 137.15$

Orthorhombic, $P2_12_12_1$

Hall symbol: $P\ 2ac\ 2ab$

$a = 3.8855\ (7)\ \text{\AA}$

$b = 10.5191\ (5)\ \text{\AA}$

$c = 15.9058\ (9)\ \text{\AA}$

$V = 650.10\ (13)\ \text{\AA}^3$

$Z = 4$

$F(000) = 288$

$D_x = 1.401\ \text{Mg m}^{-3}$

Mo $K\alpha$ radiation, $\lambda = 0.71073\ \text{\AA}$

Cell parameters from 25 reflections

$\theta = 5.5\text{--}18.7^\circ$

$\mu = 0.10\ \text{mm}^{-1}$

$T = 293\ \text{K}$

Prismatic, colourless

$0.46 \times 0.30 \times 0.20\ \text{mm}$

Data collection

Enraf–Nonius CAD-4
diffractometer

Radiation source: fine-focus sealed tube

Graphite monochromator

ω – 2θ scans

1534 measured reflections

1051 independent reflections

866 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.015$

$\theta_{\text{max}} = 29.0^\circ$, $\theta_{\text{min}} = 2.3^\circ$

$h = -5 \rightarrow 2$

$k = -14 \rightarrow 0$

$l = -21 \rightarrow 0$

3 standard reflections every 200 reflections

intensity decay: <1%

Refinement

Refinement on F^2

Least-squares matrix: full

$R[F^2 > 2\sigma(F^2)] = 0.031$

$wR(F^2) = 0.087$

$S = 1.09$

1051 reflections

92 parameters

0 restraints

Primary atom site location: structure-invariant

direct methods

Secondary atom site location: difference Fourier
map

Hydrogen site location: inferred from
neighbouring sites

H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0344P)^2 + 0.1144P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} < 0.001$

$\Delta\rho_{\text{max}} = 0.18 \text{ e } \text{\AA}^{-3}$

$\Delta\rho_{\text{min}} = -0.15 \text{ e } \text{\AA}^{-3}$

Extinction correction: *SHELXL97* (Sheldrick,
1997), $F_c^* = kF_c[1 + 0.001x F_c^2 \lambda^3 / \sin(2\theta)]^{-1/4}$

Extinction coefficient: 0.040 (6)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters ($\text{\AA}^2$)

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{iso}}^*/U_{\text{eq}}$
C1	0.3825 (5)	0.84759 (16)	0.25136 (11)	0.0373 (4)
H1	0.4007	0.9092	0.2930	0.045*
C2	0.2298 (5)	0.73203 (14)	0.27215 (10)	0.0319 (4)
C3	0.2025 (5)	0.64013 (16)	0.20969 (10)	0.0382 (4)
H3	0.1029	0.5617	0.2212	0.046*
C4	0.3262 (6)	0.66735 (19)	0.12995 (11)	0.0455 (5)
H4	0.3114	0.6076	0.0870	0.055*
C5	0.4720 (7)	0.78517 (19)	0.11576 (11)	0.0472 (5)
H5	0.5524	0.8032	0.0620	0.057*
C6	0.0965 (5)	0.71648 (17)	0.36028 (10)	0.0344 (4)
N1	0.5043 (5)	0.87491 (14)	0.17489 (10)	0.0440 (4)
N2	0.1167 (5)	0.59906 (15)	0.39179 (9)	0.0405 (4)
H2N	0.2155	0.5365	0.3637	0.049*
N3	−0.0001 (5)	0.56759 (16)	0.47365 (9)	0.0472 (4)
H3NA	0.0877	0.6189	0.5112	0.057*
H3NB	−0.2101	0.5876	0.4784	0.057*
O1	−0.0227 (5)	0.80795 (12)	0.39876 (8)	0.0487 (4)

Atomic displacement parameters ($\text{\AA}^2$)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
C1	0.0405 (9)	0.0307 (7)	0.0405 (9)	0.0021 (8)	−0.0023 (8)	−0.0007 (6)
C2	0.0312 (8)	0.0314 (7)	0.0330 (7)	0.0041 (8)	−0.0025 (7)	−0.0001 (6)
C3	0.0445 (11)	0.0316 (8)	0.0384 (8)	0.0007 (8)	−0.0049 (8)	−0.0009 (7)

C4	0.0594 (14)	0.0442 (9)	0.0328 (8)	0.0060 (11)	−0.0039 (9)	−0.0057 (7)
C5	0.0550 (13)	0.0522 (10)	0.0345 (8)	0.0062 (11)	0.0050 (9)	0.0069 (8)
C6	0.0324 (9)	0.0367 (8)	0.0339 (7)	0.0012 (8)	−0.0035 (7)	−0.0040 (7)
N1	0.0481 (10)	0.0388 (7)	0.0451 (8)	0.0002 (8)	0.0019 (8)	0.0078 (6)
N2	0.0505 (10)	0.0373 (7)	0.0337 (7)	0.0027 (7)	0.0057 (7)	0.0007 (6)
N3	0.0557 (11)	0.0519 (9)	0.0338 (7)	−0.0021 (10)	0.0028 (8)	0.0045 (6)
O1	0.0604 (10)	0.0447 (7)	0.0409 (6)	0.0120 (7)	0.0060 (7)	−0.0060 (5)

Geometric parameters (Å, °)

C1—N1	1.336 (2)	C5—N1	1.338 (2)
C1—C2	1.392 (2)	C5—H5	0.9300
C1—H1	0.9300	C6—O1	1.231 (2)
C2—C3	1.390 (2)	C6—N2	1.335 (2)
C2—C6	1.503 (2)	N2—N3	1.418 (2)
C3—C4	1.386 (2)	N2—H2N	0.8830
C3—H3	0.9300	N3—H3NA	0.8746
C4—C5	1.381 (3)	N3—H3NB	0.8461
C4—H4	0.9300		
N1—C1—C2	123.70 (16)	N1—C5—H5	118.1
N1—C1—H1	118.2	C4—C5—H5	118.1
C2—C1—H1	118.2	O1—C6—N2	123.96 (16)
C3—C2—C1	118.02 (16)	O1—C6—C2	120.55 (16)
C3—C2—C6	124.35 (16)	N2—C6—C2	115.49 (15)
C1—C2—C6	117.60 (15)	C1—N1—C5	117.04 (16)
C4—C3—C2	118.93 (17)	C6—N2—N3	122.80 (15)
C4—C3—H3	120.5	C6—N2—H2N	121.7
C2—C3—H3	120.5	N3—N2—H2N	115.4
C5—C4—C3	118.49 (17)	N2—N3—H3NA	111.0
C5—C4—H4	120.8	N2—N3—H3NB	109.4
C3—C4—H4	120.8	H3NA—N3—H3NB	99.3
N1—C5—C4	123.81 (17)		

Hydrogen-bond geometry (Å, °)

<i>D</i> —H $\cdots$ <i>A</i>	<i>D</i> —H	H $\cdots$ <i>A</i>	<i>D</i> $\cdots$ <i>A</i>	<i>D</i> —H $\cdots$ <i>A</i>
N2—H2N $\cdots$ N1 ⁱ	0.88	2.11	2.975 (2)	166
N3—H3NA $\cdots$ O1 ⁱⁱ	0.87	2.22	3.045 (2)	157
N3—H3NB $\cdots$ O1 ⁱⁱⁱ	0.85	2.55	3.155 (2)	130

Symmetry codes: (i) $-x+1, y-1/2, -z+1/2$; (ii) $x+1/2, -y+3/2, -z+1$; (iii) $x-1/2, -y+3/2, -z+1$.