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2-Acetylpyridinium 4*N*-Phenylthiosemicarbazone Chloride 1.25-Hydrate†

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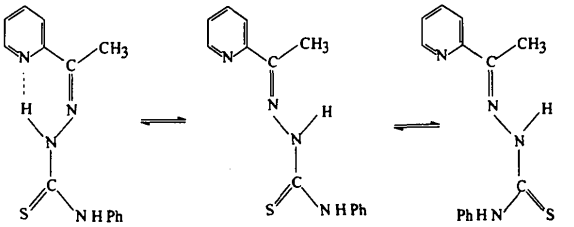
Abstract

Molecules of the title compound, $C_{14}H_{15}N_4S^+.Cl^-.1.25H_2O$, are linked through intra- and intermolecular hydrogen bonds to form a dimeric structure. The crystal structure of the dimer is stabilized by two intermolecular hydrogen bonds of the N—HN···S type and two intramolecular hydrogen bonds of the N—HN···Cl type. The inter- and intramolecular bonds form an eight-membered and a ten-membered ring, respectively.

Comment

Thiosemicarbazones (TSCs) have aroused considerable interest in chemistry and biology owing to their antibacterial, antimalarial, antineoplastic and antiviral activities (Liberta & West, 1992, and references therein). TSCs represent some of the most potent inhibitors of ribonucleoside diphosphate reductase known. The reductive conversion of ribonucleotides to their deoxyribonucleotide counterparts is a particularly critical step in the synthesis of DNA since deoxyribonucleotides are present at extremely low levels in mammalian cells and it has been argued that an inhibitor of ribonucleotide reductase could be more effective than an inhibitor of DNA polymerase in blocking DNA synthesis (Corey & Chiba, 1989; Liberta & West, 1992, and references therein).

*N*4-Monosubstituted and *N*4,*N*4-disubstituted thiosemicarbazones derived from 2-acetylpyridine were evaluated against leukemia P388 in the mouse. Significant antitumor activity (*T*/*C* > 125%) was observed for members of this class. A compound is considered active when the percentage increase in the median life span of the test group over the mean survival of the control group produces a percentage *T*/*C* (test/control) > 125. Enhancement of antitumor activity resulted from an increase in the size of the N4 substituent of the thiosemicarbazone moiety (Klayman, Scovill, Mason, Bartosevich, Bruce & Lin, 1983). In some cases, the highest *in vivo* activity is associated with a metal complex rather than the parent TSC (Levinson, 1980, and references therein). Structural studies of heterocyclic TSC derivatives with metal ions have been carried out (Kovala-Demertzi, Domopoulou, Demertzis, Raptopoulou & Terzis, 1994, and references therein; Kovala-Demertzi, Domopoulou, Demertzis, Valdez-Martinez, Hernandez-Ortega, Espinosa-Perez, West, Salberg, Bain & Bloom, 1996, and references therein) in order to obtain information on structure–activity relationships. Within the framework of these studies, we have undertaken the X-ray structural study of the title compound, $H_2Ac4NPh^+.Cl^-.1.25H_2O$, (1).



HAc4NPh

The crystals were found to contain hydrogen-bonded monoprotonated 2-acetylpyridine 4*N*-phenylthiosemicarbazone ($H_2Ac4NPh$) cations balanced by two hydrogen-bonded chloride anions. Selected hydrogen-bonding parameters are given in Table 3. The structure is best described as a polymeric chain. The intermolecular hydrogen-bonding network for (1) yields dimer units (Fig. 1). The structure is centrosymmetric with the halves of the dimer related by a crystallographic inversion centre located in the centre of the eight-membered $(SCNH)_2$ ring. Protonation of the pyridine N atom is likely to be influential in establishing the

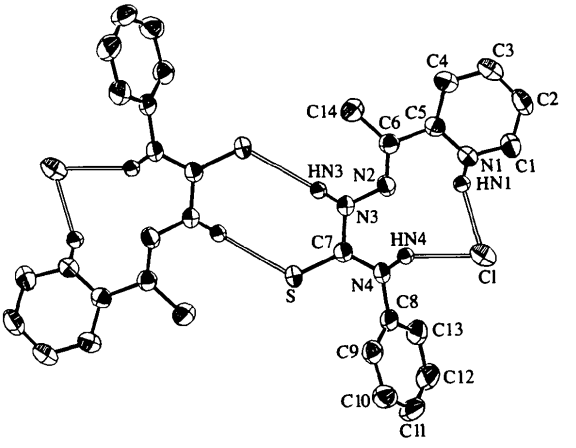


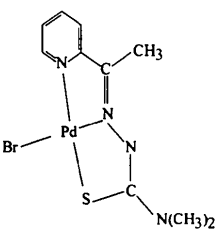
Fig. 1. A view of the dimeric structure of (1) showing the atomic labelling scheme. H atoms have been omitted for clarity; displacement ellipsoids are drawn at the 50% probability level.

† Alternative nomenclature: 2-[1-(4-phenylthiosemicarbazono)-ethyl]-pyridinium chloride 1.25-hydrate.

planarity of the dimer unit since it permits the formation of an additional ten-membered ring.

The observed N···S contact in (1) is connected to an approximately planar arrangement of the seven-atom fragment S═C7(N4)—N3—N2═C6—C5 and the pyridinium cation. The seven-atom fragment and the pyridinium cation form a plane, *A*; all deviations from the least-squares plane are less than 0.1 Å (0.095 Å for atom N4 and 0.066 Å for atom C4). This planar arrangement leads to enhanced possibilities for resonance. This is confirmed by a shortening of the N4—C7 bond to 1.330 (3) Å, an elongation of the N3—C7 bond to 1.376 (3) Å, a shortening of the N2—N3 bond to 1.363 (4) Å, an elongation of the N2—C6 bond to 1.284 (3) Å and a shortening of the C6—C5 bond to 1.474 (4) Å compared with the standard values of 1.355, 1.355, 1.401, 1.401, 1.279 and 1.490 Å, respectively (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). The planar N4 phenyl ring, *B*, appears to have rotated about the N4—C7 bond. The angle between planes *A* and *B* is 55.4 (3)°.

The protonated form (1) shows a *Z,E,Z* configuration about the C5—C6, C6—N2 and N3—C7 bonds for the donor centres N, N and S respectively. The same configuration (*Z,E,Z*) has been observed in the case of the complex [Pd(Ac4DM)Br]; Ac4DM represents the monodeprotonated form of 2-acetylpyridine 4*N*-dimethylthiosemicarbazone, HAc4DM (Kovala-Demertzi, Domopoulou, Demertzis, Valdez-Martinez, Hernandez-Ortega, Espinosa-Perez, West, Salberg, Bain & Bloom, 1996). In (1) the O atom of one molecule of water is at a distance of 3.086 (5) Å from the chloride ion [at $(-x, \frac{1}{2} - y, 1 + z)$] and 2.929 (5) Å from the O atom of the other water molecule [$O(2w)(y - \frac{1}{4}, \frac{1}{4} - x, \frac{5}{4} - z)$].



[Pd(Ac4DM)Br]

Experimental

2-Acetylpyridine 4*N*-phenylthiosemicarbazone (HAc4NPh) was prepared by reacting equimolar amounts of thiosemicarbazide dissolved in ethanol and 2-acetylpyridine (Klayman, Bartosevich, Griffin, Mason & Scovill, 1979). HAc4NPH behaves as a weak base and a weak monoprotic acid. Equilibrium in aqueous solutions is given by:

$$HAc4NPh + H_3O^+ \rightleftharpoons H_2Ac4NPh^+ + H_2O$$

$$Ac4NPh^- + H_3O^+ \rightleftharpoons HAc4NPh + H_2O.$$

The title compound (1), $H_2Ac4NPh^+.Cl^-.1.25H_2O$, was prepared by combining an aqueous solution of sodium tetrachloroplatinate in a 1:2 stoichiometric ratio with HAc4NPh in CH_3OH (H_2O:CH_3OH = 4:1). The solution was stirred for 24 h at room temperature and then filtered. Slow evaporation of the brownish filtrate gave clear brownish yellow crystals suitable for X-ray diffraction studies.

Crystal data

$C_{14}H_{15}N_4S^+.Cl^-.1.25H_2O$
M_r = 329.33
Tetragonal
$I4_1/a$
a = 32.41 (1) Å
c = 6.056 (3) Å
V = 6361.8 (1) Å^3
Z = 16
D_x = 1.376 Mg m^{-3}
D_m = 1.350 Mg m^{-3}
D_m measured by flotation in $CHCl_3$/petroleum ether solution
Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 25 reflections
θ = 5.5–11.5°
μ = 0.378 mm^{-1}
T = 298 K
Prism
0.50 × 0.20 × 0.20 mm
Brownish yellow

Data collection

Nicolet $P2_1$ diffractometer
$\theta/2\theta$ scans
Absorption correction: none
3217 measured reflections
2805 independent reflections
2021 observed reflections [$F_o > 6.0\sigma(F_o)$]
R_{int} = 0.0941
θ_{max} = 25°
h = 0 → 38
k = 0 → 38
l = 0 → 7
3 standard reflections monitored every 97 reflections
intensity decay: <3%

Refinement

Refinement on F
R = 0.0351
wR = 0.0350
S = 2.35
2648 reflections
251 parameters
Unit weights applied
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.253 e Å^{-3}
$\Delta\rho_{min}$ = −0.176 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	U_{eq}
S	0.06236 (2)	0.48528 (3)	−0.0113 (1)	0.0497
N1	0.00124 (8)	0.38842 (8)	0.8493 (4)	0.0460
N2	0.00680 (7)	0.43442 (7)	0.4906 (4)	0.0401
N3	0.01389 (7)	0.45555 (8)	0.2998 (4)	0.0433
N4	0.08215 (7)	0.44000 (8)	0.3420 (4)	0.0467
C1	0.0024 (1)	0.3646 (1)	1.0291 (6)	0.0564
C2	−0.0326 (1)	0.3581 (1)	1.1485 (6)	0.0577
C3	−0.0680 (1)	0.3766 (1)	1.0808 (6)	0.0540
C4	−0.0684 (1)	0.4015 (1)	0.8958 (5)	0.0473
C5	−0.03280 (8)	0.40746 (8)	0.7762 (5)	0.0387
C6	−0.02965 (8)	0.43220 (8)	0.5726 (6)	0.0386
C7	0.05353 (8)	0.45863 (8)	0.2203 (5)	0.0388
C8	0.12576 (8)	0.43978 (9)	0.3073 (5)	0.0435
C9	0.1430 (1)	0.42619 (9)	0.1128 (6)	0.0491
C10	0.1854 (1)	0.4230 (1)	0.0979 (7)	0.0613
C11	0.2102 (1)	0.4335 (1)	0.2724 (8)	0.0725
C12	0.1927 (1)	0.4476 (1)	0.4629 (8)	0.0726
C13	0.1505 (1)	0.4508 (1)	0.4841 (6)	0.0587

C14	−0.0681 (1)	0.4513 (1)	0.4815 (7)	0.0589
Cl	−0.11653 (2)	0.33708 (2)	−0.4435 (1)	0.0540
O(1*w*)	0.0472 (1)	0.2169 (1)	0.7526 (8)	0.1568
O(2*w*)	0	1/4	0.1250	0.2004

Table 2. *Selected geometric parameters (Å, °)*

S—C7	1.672 (3)	N4—C7	1.330 (3)
N2—N3	1.363 (4)	N4—C8	1.429 (3)
N2—C6	1.284 (3)	C5—C6	1.474 (4)
N3—C7	1.376 (3)	C6—C14	1.497 (4)
N3—N2—C6	120.8 (2)	C5—C6—C14	118.4 (3)
N2—N3—C7	119.4 (2)	S—C7—N3	119.4 (2)
C7—N4—C8	127.7 (2)	S—C7—N4	125.5 (2)
N1—C5—C6	118.0 (2)	N3—C7—N4	115.1 (2)
C4—C5—C6	125.0 (3)	N4—C8—C9	121.9 (3)
N2—C6—C5	114.7 (2)	N4—C8—C13	117.3 (3)
N2—C6—C14	126.9 (3)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*···*A*	*D*—H···*A*
N4—H···Cl^{i}	3.199 (3)	144 (3)
N1—H···Cl^{i}	3.023 (3)	150 (3)
N3—H···S^{ii}	3.584 (3)	175 (2)

Symmetry codes: (i) $y-\frac{1}{4}, \frac{1}{4}-x, \frac{1}{4}-z$; (ii) $-x, 1-y, z$.

Intensities were corrected for Lorentz and polarization effects. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1990). The structure refinement by full-matrix least-squares on *F* was carried out using *SHELX*76 (Sheldrick, 1976). All H atoms, except those of water molecules, were located by difference Fourier maps and refined isotropically. Non-H atoms were refined with anisotropic displacement parameters.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1047). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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(2*R*)-3-[(4*S*)-4-Benzyl-2-oxo-3-oxazolidinyl]-3-oxo-2-[(1*R*,2*S*)-2-vinylcyclohexyl]propionic Acid Methyl Ester and (2*R*)-3-[(4*S*)-4-Benzyl-2-oxo-3-oxazolidinyl]-3-oxo-2-[(1*R*,2*S*)-2-vinylcyclopentyl]propionic Acid Methyl Ester

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Abstract

Both the title structures, $C_{22}H_{27}NO_5$ and $C_{21}H_{25}NO_5$, exhibit similar conformations, as shown by a least-squares fit of the atoms common to both. The oxazolidine ring is intermediate between envelope and twist forms, with a slight dominance of the envelope in the former structure but the twist in the latter. Part of the oxazolidine ring of the former structure, however, shows high displacement parameters.

Comment

This work forms part of our studies on the synthesis of enantiopure *trans*-1,2-disubstituted cyclopentanes and cyclohexanes. These compounds are of special interest because of their frequent appearance as components of natural product molecules. They were easily obtained *via* an intramolecular allysilane addition of chiral alkylidene-1,3-dicarbonyl compounds. Further details of the reaction have been published elsewhere (Tietze & Schünke, 1995).

Both compounds (Figs. 1 and 2) have similar conformations. Fig. 3 shows a least-squares fit of both mol-