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Structural and spectral studies of thiosemicarbazones derived from 3- and 4-formylpyridine and 3- and 4-acetylpyridine

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Abstract

Crystal structures of thiosemicarbazones prepared from 3- and 4-formylpyridine and 3- and 4-acetylpyridine are included along with their UV spectra. 4-Formylpyridine thiosemicarbazone has the following structural properties: monoclinic, $P2_1/n$, $a = 7.2420(5)$, $b = 13.961(1)$, $c = 8.415(1)$ Å, $\beta = 90.90(1)°$, $V = 850.7(1)$ Å^3 and $Z = 4$; for 3-formylpyridine thiosemicarbazone: monoclinic, $C2/c$, $a = 13.661(2)$, $b = 7.1120(4)$, $c = 19.046(2)$ Å, $\beta = 107.71(1)°$, $V = 1762.8(3)$ Å^3 and $Z = 8$; for 4-acetylpyridine thiosemicarbazone: triclinic, P-1, $a = 8.104(3)$, $b = 8.512(2)$, $c = 8.708(3)$ Å, $\alpha = 83.85(0)$, $\beta = 66.66(0)$, $\gamma = 62.87(0)°$, $V = 488.9(3)$ Å^3 and $Z = 2$; for 3-acetylpyridine thiosemicarbazone monoclinic, $P2_1/a$, $a = 8.408(1)$, $b = 11.853(2)$, = $c = 9.777(3)$ Å, $\beta = 97.66(2)°$, $V = 985.7(4)$ Å^3 and $Z = 4$. Intramolecular and intermolecular hydrogen bonding are both present. There is a difference in the angles between the mean planes of the pyridine ring and thiosemicarbazone moiety in the two series.

Keywords: Heterocyclic thiosemicarbazones; 3-substituted; 4-substituted; Crystal structures

1. Introduction

Thiosemicarbazones, a class of compounds possessing a wide spectrum of potential medicinal applications, have been studied for their antitumor, antiviral, antibacterial, antimalarial, antifungal, anti-inflammatory and anti-HIV activities [1,2]. The 2-heterocyclic thiosemicarbazones have been the subject of extensive investigation [1, and references therein]. Changing the point of attachment of the thiosemicarbazone moiety to the 3- or 4- position on the heteroaromatic ring often causes a decrease in activity presumably due to a lesser ability for coordination [3]. Nevertheless, the literature contains examples of biologically important bidentate thiosemicarbazones: *p*-acetamidobenzaldehyde thiosemicarbazone, known as thiacetazone, is employed in the clinical treatment of tuberculosis [4,5]. Therefore, it is important to continue to prepare and characterize additional thiosemicarbazones. Here we report the UV spectra and crystal structures of 3-formyl- and 4-formylpyridine thiosemicarbazone, H3Fo4DH and H4Fo4DH, respectively, and 3-acetyl- and 4-acetylpyridine thiosemicarbazone, H3Ac4DH and H4Ac4DH, respectively (Fig. 1). A structural report of H4Fo4DH appeared some time ago [6] and our crystal structure

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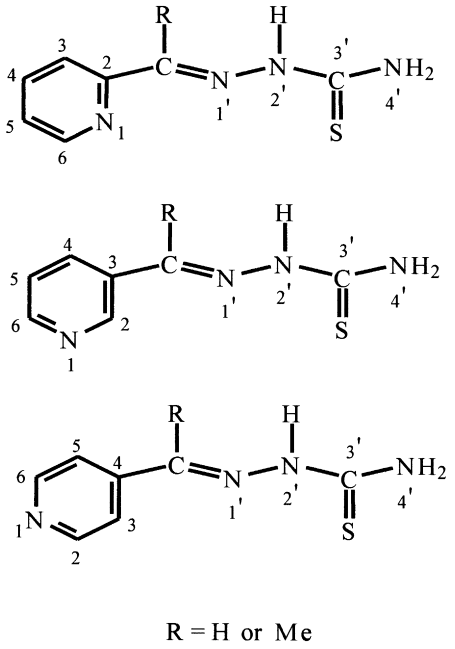

Fig. 1. Representations of the 3- and 4-formyl- and 3- and 4-acetyl-pyridine thiosemicarbazones.

results are in excellent agreement. The ^{1}H NMR and IR spectra of these thiosemicarbazones were reported recently [7,8].

2. Experimental

The thiosemicarbazones were prepared by refluxing a solution of the desired aldehyde or ketone with thiosemicarbazide (all starting materials were purchased from Aldrich) in ethanol. The crystals were obtained by slow evaporation of the preparative solutions. The melting points (°C) are as follows: H3Fo4DH: 237–238; H4Fo4DH: 253–254; H3Ac4DH: 219–221; H4Ac4DH: 194–196. UV spectra were recorded as DMSO solutions with a Hewlett–Packard 8453 spectrometer.

2.1. X-ray data collection, structure solution and refinement

Crystals were mounted on glass fibers and reflections were collected with a Siemens P4 diffractometer, MoK_α ($\lambda = 0.71073$ Å). The structures were solved

Table 1
Crystal data and structure refinement for H4Fo4DH, H3Fo4DH, H4Ac4DH and H3Ac4DH

Compound	H4Fo4DH	H3Fo4DH	H4Ac4DH	H3Ac4DH
Empirical formula	$C_7H_8N_4S$	$C_7H_8N_4S$	$C_8H_{10}N_4S$	$C_8H_{10}N_4S$
Color; habit	Yellow, prism	Yellow, prism	Yellow-orange, prism	Yellow-orange, prism
Crystal size (mm)	$0.40 \times 0.30 \times 0.10$	$0.35 \times 0.30 \times 0.15$	$0.40 \times 0.35 \times 0.15$	$0.45 \times 0.35 \times 0.10$
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/n$ (#14)	$C2/c$ (#15)	P-1 (#2)	$P2_1/a$ (#14)
Unit cell dimensions				
a (Å)	7.2420(5)	13.661(2)	8.104(3)	8.408(1)
b (Å)	13.961(1)	7.1120(4)	8.512(2)	11.853(2)
c (Å)	8.415(1)	19.046(2)	8.708(3)	9.777(3)
α (°)	90.00	90.00	83.85(0)	90.00
β (°)	90.90(1)	107.71(1)	66.66(0)	97.66(2)
γ (°)	90.00	90.00	62.87(0)	90.00
Volume (Å^3)	850.7(1)	1762.8(3)	488.9(3)	985.7(4)
Z	4	8	2	4
Formula weight	180.23	180.23	194.26	194.26
Density calculated (g/cm^3)	1.407	1.358	1.320	1.336
Absorption coefficient (mm^{-1})	0.327	0.316	0.290	0.294
F(000)	376	752	204	408
R	$R_1 = 0.0444$	$R_1 = 0.0413$	$R_1 = 0.0551$	$R_1 = 0.0519$
wR_2	0.0993	0.1042	0.1345	0.1094
Goodness-of-fit	2.183	1.110	2.416	1.522
Largest differential peak/hole (eÅ^{-3})	0.268/−0.425	0.192/−0.178	0.395/−0.428	0.305/−0.303

Table 2
Selected bond distances (Å) and angles (°) for H4Fo4DH, H3Fo4DH, H4Ac4DH and H3Ac4DH

Bond	H4Fo4DH	H3Fo4DH	H4Ac4DH	H3Ac4DH
C8–S	1.677(3)	1.693(2)	1.697(2)	1.697(2)
C7–N2	1.279(2)	1.278(2)	1.290(2)	1.284(3)
N2–N3	1.371(2)	1.367(2)	1.390(2)	1.384(3)
N3–C8	1.358(2)	1.357(3)	1.372(2)	1.354(3)
C8–N4	1.323(2)	1.311(3)	1.330(2)	1.311(3)
Angle				
C7–N2–N3	116.6(1)	116.5(2)	116.5(5)	118.2(2)
N2–N3–C8	118.6(1)	119.4(2)	118.6(1)	117.9(2)
N3–C8–N4	117.0(1)	117.0(2)	117.5(2)	117.9(2)
N3–C8–S	119.5(1)	119.1(2)	119.1(1)	119.2(2)
N4–C8–S	123.5(1)	123.9(2)	123.4(1)	122.9(2)

by direct methods [9] and subsequent difference Fourier maps, which revealed the position of all non-hydrogen atoms, and refined on F^2 by a full-matrix least-squares procedure using anisotropic displacement parameters [10]. Hydrogens on nitrogens were located by difference Fourier maps and refined isotropically and hydrogens attached to carbons were located in their calculated positions (C–H 0.93–0.97 Å) and refined using a riding model. Atomic scattering factors were taken from the International Table for X-ray Crystallography [11].

3. Results and discussion

3.1. Structural characterization

Table 1 has summaries of crystal data and X-ray data collection, data reduction and structure refinement results for H4Fo4DH, H3Fo4DH, H4Ac4DH and H3Ac4DH. Selected bond distances and angles for the four thiosemicarbazones are listed in Table 2. Perspective views for H4Fo4DH, H3Fo4DH, H4Ac4DH and H3Ac4DH are shown in Fig. 2a–d. Intramolecular and intermolecular hydrogen bonding parameters are presented in Table 3 and the mean plane data are compiled in Table 4.

As would be expected, there are not large differences in the bond distances of the thiosemicarbazone moieties. However, the imine C7–N2 and, possibly the N2–N3 bonds, would be expected to show a small difference in the two series; the average C7–N2 bond is 1.279(2) and 1.287(3) Å for the formylpyridine and acetylpyridine derivatives, respectively. The average N2–N3 bond is 1.369(2) Å for the formylpyridine thiosemicarbazones and 1.386(3) Å for the acetylpyridine thiosemicarbazones. The small differences are attributable to the different electronic effects of the aldehyde hydrogen and ketone methyl group.

The formylpyridine thiosemicarbazones have higher melting points compared to the corresponding acetyl analogues, probably due to the fact that the angle between the mean plane of the pyridine ring and the plane involving C(7)–N(2)–N(3)–C(8) is much smaller in the formylpyridine thiosemicarbazones (H3Fo4DH, 9.34(9)°; H4Fo4DH, 18.36(8)°) than in the corresponding acetylpyridine thiosemicarbazones (H3Ac4DH, 46.3(1)°; H4Ac4DH, 50.04(8)°). The smaller angle favors molecular stacking leading to higher density and melting point. In fact, the calculated densities (H3Fo4DH, 1.358 g/cm^3; H4Fo4DH, 1.407 g/cm^3; H3Ac4DH, 1.320 g/cm^3 and H4Ac4DH, 1.336 g/cm^3) are in agreement with closer packing for the formylpyridine thiosemicarbazones.

Table 3 contains the distances and angles for the hydrogen bonding of the four thiosemicarbazones. Three intermolecular hydrogen bonds are observed for H3Fo4DH, H4Ac4DH and H3Ac4DH and only two for H4Fo4DH. Taking into consideration the intermolecular hydrogen bonding, H3Fo4DH, H4Ac4DH and H3Ac4DH present each a N3–H3N…S bond and H4FoDH presents no such a bond, indicating that the melting points are not much affected by the presence of those interactions. Of note is the different mode of hydrogen bonding by the $N4H_2$ function in H3Fo4DH, which is the most planar of these four thiosemicarbazones.

3.2. Spectral characterization

The ^{1}H NMR spectra, reported previously [7,8], showed two signals for N4H_2 due to one hydrogen interacting with N2 in each of the compounds. N3*H* is found in the 11.65 region for the formylpyridine thiosemicarbazones, but at ca. $\delta = 10.35$ for the acetylpyridine thiosemicarbazones, which is consistent with hydrogen bonding to DMSO [12] in both cases.

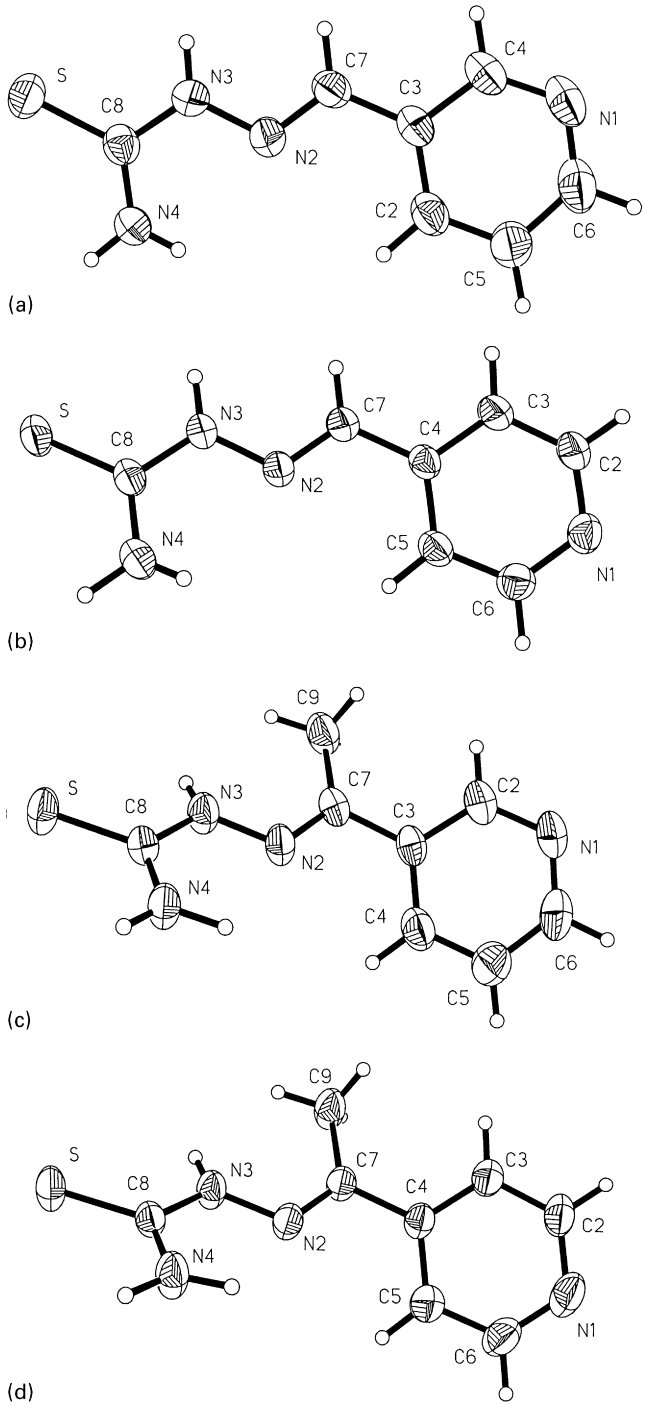

Fig. 2. Perspective view with atom numbering scheme and displacement ellipsoids at 50% probability level of (a) of H4Fo4DH; (b) H3Fo4DH; (c) H4Ac4DH; (d) H3Ac4DH.

Table 3
Hydrogen bonding interactions

Compound	D–H…A	*d*(D–H)	*d*(H…A)	*d*(D–H…A)	(D–H…A)
H4Fo4DH	N4–H4B–N2	0.77(2)	2.29(2)	2.615(2)	107(2)
	N4–H4B –N1	0.77(2)	3.064(6)	3.530(9)	122(2)
		0.963(6)	2.541(6)	3.495(7)	170(2)
	N4–H4A–S				
H3Fo4DH	N4–H4B–N2	0.83(3)	2.31(3)	2.624(2)	103(2)
	N4–H4A –N1	0.889(6)	2.052(5)	2.938(6)	174(2)
	N3–H3N– S	0.889(6)	2.522(6)	3.394(8)	167(2)
	N4–H4B–S	0.834(5)	2.792(7)	3.448(6)	137(1)
H4Ac4DH	N4–H4B–N2	0.95(3)	2.33(3)	2.656(2)	99(2)
	N4–H4B –N1	0.952(7)	2.138(6)	3.044(6)	158(2)
	N3–H3N– S	0.907(6)	2.631(8)	3.530(8)	171(2)
	N4–H4A–S	0.945(5)	2.557(6)	3.493(7)	171(1)
H3Ac4DH	N4–H4B–N2	0.99(3)	2.25(3)	2.618(3)	101(2)
	N4–H4B –N1	0.993(6)	2.011(6)	2.951(6)	157(2)
	N3–H3N– S	0.857(3)	2.815(7)	3.671(6)	177(1)
	N4–H4A–S	0.846(6)	2.630(3)	3.451(7)	164(2)

The lower field signal indicates a higher acidity for N(3)*H* in the formylpyridine thiosemicarbazones. This same effect has been observed in pyruvaldehyde bis(thiosemicarbazones), the ketone moiety having a significantly lower δ for the corresponding proton, ca. 9.9, than the aldehyde arm, ca. 11.1 [13].

The UV–visible spectra of all four thiosemicarbazones are very similar. An absorption at ca. 36 000 cm^{-1} is assigned to a ring $\pi-\pi^*$ transition and the bands in the 30 000–31 500 and 27 000–28 000 cm^{-1} ranges, are assigned to $n-\pi^*$ transitions within the thiosemicarbazone moiety, involving mainly C=N(1) and C=S, respectively [14]. The transition energies of the formyl thiosemicarbazones are lower than found for the corresponding acetyl analogues, probably due to a smaller angle between the thiosemicarbazone moiety and the pyridine ring which favors delocalization in the former (see Table 4).

Supplementary material: Crystallographic data (excluding structure factors) for the structures reported in this article have been deposited with Cambridge Crystallographic Data Centre as supplementary publications numbers 143285 to 143288. Copies of available material can be obtained on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Table 4
Mean plane deviations and angles between mean planes hydrogen bonding interactions

	Plane	Mean deviation	Largest deviation	Angle with previous plane
H4Fo4DH	N1–C2–C3–C4–C5–C6	0.0016	0.0025 (C6)	
	C7–N2–N3–C8–S–N4	0.0313	0.0569 (N3)	18.36(8)
H3Fo4DH	N1–C2–C3–C4–C5–C6	0.0059	0.0098 (C3)	
	C7–N2–N3–C8–S–N4	0.0115	0.0172 (N3)	9.34(9)
H4Ac4DH	N1–C2–C3–C4–C5–C6	0.0102	0.0145 (C4)	
	C7–N2–N3–C8–S–N4	0.0797	0.1566 (N2)	50.04(8)
H3Ac4DH	N1–C2–C3–C4–C5–C6	0.0037	0.0051 (C6)	
	C7–N2–N3–C8–S–N4	0.0625	0.1142 (N2)	46.3(1)

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