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A joint theoretical and experimental structural study of 5-carboxyethyl-3-(2′-furfurylmethyl) tetrahydro-2*H*-1,3,5-thiadiazine-2-thione

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Abstract—X-Ray analysis and semiempirical AM1 and ab initio HF/3-21G* and HF/6-31G* calculations reveal a favourable envelop conformation (A) for 3,5-disubstituted tetrahydro-2*H*-1,3,5-thiadiazines in which the N5 atom lies out of the main plane. NOE experiments show that this conformer (A) is also found in solution. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Compounds derived from tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones (TTT) (**1**) have received particular attention due to the pharmacological properties they display. It is well known that TTT present antibacterial,[1,2] antifungal,[3,4] antihelmintic[5] and antituberculous[6] activity. In this regard, we have previously reported the synthesis and antiprotozoan properties of new 2,5-disubstituted tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives[7] and described a study of their decomposition products and anti-cancer properties.[8] In addition, we have recently reported the first solid phase synthesis of 5-substituted 3-(5′-carboxypentyl)tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones from readily available starting materials.[9]

In this paper we present a structural study of 5-carboxyethyl-3-(2′-furfurylmethyl) tetrahydro-2*H*-1,3,5-thiadiazine-2-thione (**2**) by X-ray crystallographic analysis, determining the most stable conformation in the solid state, and by theoretical calculations to gain a better picture of the conformational profile of the given compound by means of the semiempirical AM1 method, as well as by ab initio calculations at Hartree–Fock level using the 3-21G* and 6-31G* basis sets. ^{1}H NOE experiments have also been carried out in order to obtain information about the conformational profile of compound **2** in solution (Fig. 1).

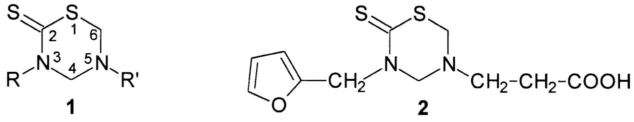

Figure 1. Tetrahydro-2*H*-1,3,5-thiadiazine-2-thiones (TTT) (**1**) and the TTT derivative (**2**) studied in this work.

2. Results and discussion

Compound **2** was synthesised by the reaction of furfurylamine (**3**) with carbon disulfide and potassium hydroxide, to give the dithiocarbamate potassium salt (**4**) (which was not isolated), followed by cyclocondensation with formaldehyde and β-alanine which provides the N5 of the thiadiazine ring (See Scheme 1), in a way similar to that reported for the general preparation of this saturated heterocyclic system.[7]

Compound **2** shows satisfactory analytical and spectroscopic data. Thus, in addition to the hydroxyl and carbonyl signals at 3386 (OH) and 1672 cm^{-1} (C=O) respectively, the FTIR spectrum shows the C=S signal at 1124 cm^{-1}. ^{1}H NMR spectrum shows two singlets corresponding to ring protons H4 and H6 at δ 4.50 and 4.51, respectively. The three protons of the furan ring appear as an overlapped ABX system and the signals at 2.35 and 2.79 ppm appear as triplets which are assigned to the methylene protons of

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Keywords: tetrahydro-2*H*-1,3,5-thiadiazines; X-ray analysis; theoretical calculations; structural study.

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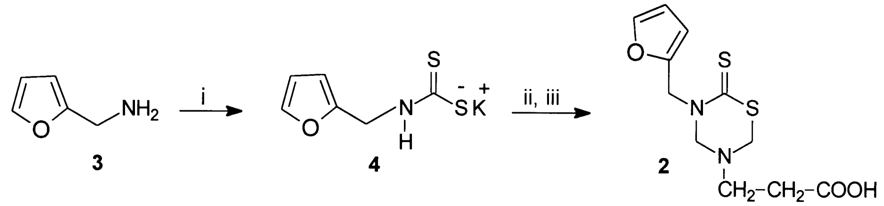

Scheme 1. (i) CS_2, KOH/H_2O 20%; (ii) HCOH, $H_2NCH_2CH_2COOH$; (iii) HCl (15%).

the aliphatic chain on N5. ^{13}C spectrum of compound **2** presents the carboxylic group at δ 173 and the thiocarbonyl group at 192 ppm. The assignment of all carbon atoms was carried out using DEPT-135°, HMQC and HMBC experiments (see Section 3).

Since thiadiazine-2-thiones **1** have not been subjected to experimental structure examination until now, the aim of this work is to obtain reliable structural information for this type of compounds by using theoretical calculations at the semiempirical AM1 quantum-chemical calculations and experimental X-ray analysis and NMR spectroscopic measurements. Also, ab initio Hartree–Fock calculations were performed taking into account the AM1 results.

The X-ray structure of compound **2** (Fig. 2) shows an envelop conformation for the thiadiazine-2-thione ring with a pseudo-mirror plane through C2, and puckering parameters[10] Q=0.507(3) Å, θ=126.6(3)° and ϕ=53.2(3)°. The weighted average bond distance within this ring is 1.590(1) Å. The C13 atom is positioned axial with respect to the N5 atom of the six-membered ring, whereas the S2 and C7 atoms are positioned in equatorial positions, respectively. The angle between the least-squares planes defined by this two rings is 71.6(2)°.

The crystal structure is stabilised forming dimers along the direction [010], by means of an intermolecular hydrogen bond [O17.O16 ($-x$, $-y-1$, $-z$)=2.646(3) Å, O17–H···O16=174°]. Intramolecular short contact interactions of the type C···O [C6···O12=3.415(3), C13···O17=2.828(3), C14···O12=3.394(4)], C···N [C13···N3=3.006(4)] and C···S [C7···S2=3.052(3)] Å help to keep the conformation of the molecule in the crystal. The unit cell contains no residual solvent accessible area (see Fig. 3)

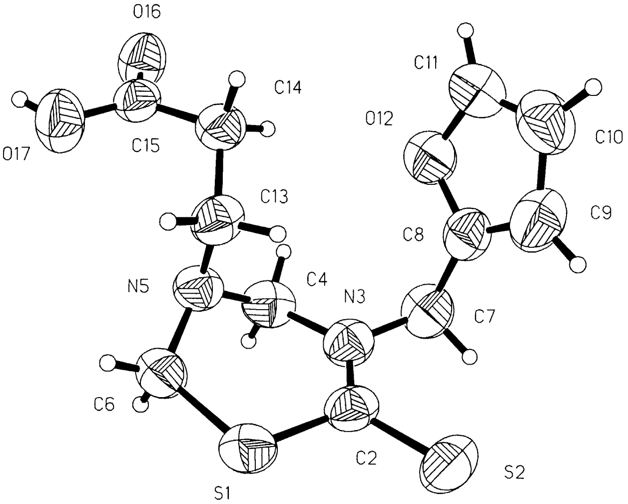

Figure 2. Plot showing the atomic numbering scheme for compound **2**. Displacement ellipsoids are drawn at 50% probability level for non-H atoms.

In compound **2**, the most important conformational changes that the given envelop conformation can undergo are concerned with ring inversion, where N5 can be either above or below the mean plane, as well as the N5 inversion (the umbrella inversion) which leads to a situation in which the substituent attached at N5 can be either in an axial or equatorial position. (see Fig. 4).

The relative stability of the four conformations shown in Fig. 4 was determined by using theoretical calculations at the semiempirical AM1 level. In all conformations the thiadiazine-2-thione ring shows an envelope conformation in which the N5 atom lies out of the plane while the rest of the atoms are almost coplanar. The calculated heats of formation (A, −49.2; B, −44.6; C, −48.3; D, −44.0 kcal mol^{-1}) reveal conformation A as the most stable one (see Fig. 5). This result is in agreement with the experimental conformation found in the crystal. Therefore, an axial substitution is preferred on the N5 atom. It is worth mentioning that although conformation A was found to be the most stable one, the presence of other conformations in solution can not be totally ruled out (see Fig. 5).

In order to gain further information on the conformational features of compound **2**, a potential energy scan was performed showing the conformational energy versus the torsion angle around the single bonds N3–C7, C7–C8, C14–C15, C13–C14 and N5–C13 (see numbering scheme in Fig. 2). In all cases the energy barrier was explored through a rotation of 360° with steps of 10°.

In conformation A, rotation around C8–C7–N3–C4, shows that at 180° the barrier rises up to 8 kcal mol^{-1}. In this conformation the furan ring eclipses the C=S (thione) bond. The diagram shows two local minima (see Fig. 6), one occurring near 80° (the most stable one) and the other occurring near −50°. In both cases, the furfuryl moety lies above or below the plane of the thiadiazine ring. The X-ray structure shows the C8–C7–N3–C4 torsion angle to be 90.7°, while theoretical calculations found 78.5° at the semi-empirical AM1 level, and ab initio calculations gave 85.0° for HF/3-21G* and 87.8° for HF/6-31G*.

The rotation around O12–C8–C7–N3 is shown in Fig. 7. The heat of formation vs the given torsion angle diagram suggests that furan ring can freely rotate around C8–C7 bond. Nevertheless, in the diagram two local minima are observed, one occurring at −80° and the other at 90°. In

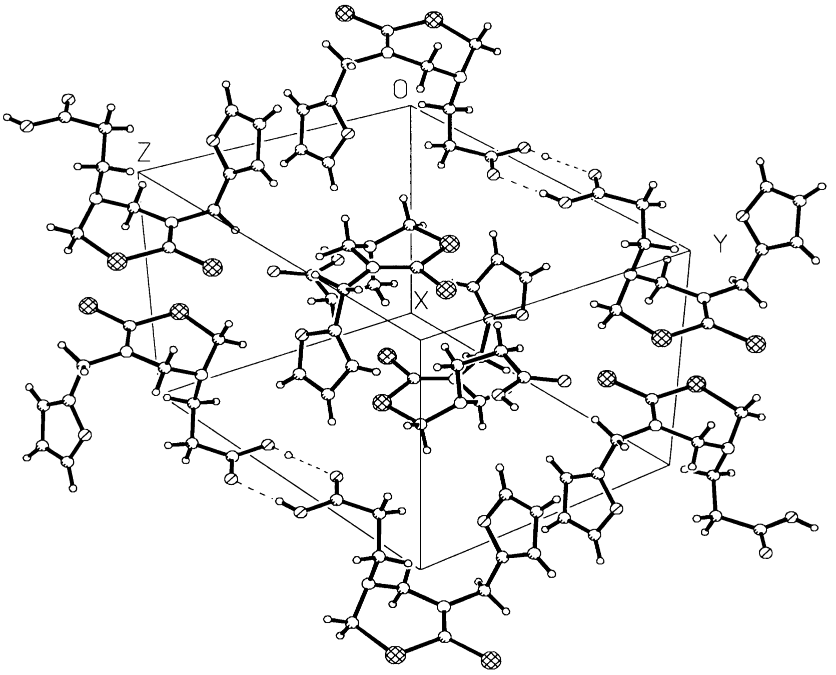

Figure 3. Packing of the molecules in the unit cell showing their dimeric associations by means of a strong hydrogen bond of the type OH···O.

both conformations, the plane containing the furan ring is perpendicular to the N3–C7 bond. The full optimised AM1 geometry found O12–C8–C7–N3=−80.1° (−81.5° by X-ray). In this case, ab initio calculations gave −77.9° and −78.5° for 3-21G* and 6-31G* basis set, respectively.

Rotations around N5–C13, C14–C15 and C13–C14 were found to have no barrier. These results suggest that the given moieties can freely rotate around their corresponding bonds.

For the most stable conformations A and C (see Fig. 5), was performed an ab initio geometry optimisation at Hartree–Fock level, using the 3-21G* and 6-31G* basis sets. This result points to conformation A to be also the most stable one. In this case HF/3-21G* method found conformation A to be 1.5 kcal mol^{-1} more stable than C, while HF/6-31G* method found A 0.4 kcal mol^{-1} more stable than C.

The geometrical features predicted by AM1, HF/3-21G* and HF/6-31G* calculations, and those determined by X-ray crystallography analysis are listed in Table 1, showing the most relevant bond distances, valence angles and dihedral angles of compound **2**. Although AM1 predicted values compare in general quite well with the experimental data, it is important to note some remarkable deviations, being the most significant in some bond distances and, specially, in those involving the sulphur atoms. More reliable results were obtained with the use of both, HF/3-21G* as well as HF/6-31G* methods. For instance, C2–S2 bond distance was found to be 1.669 Å in the crystal. Semiempirical

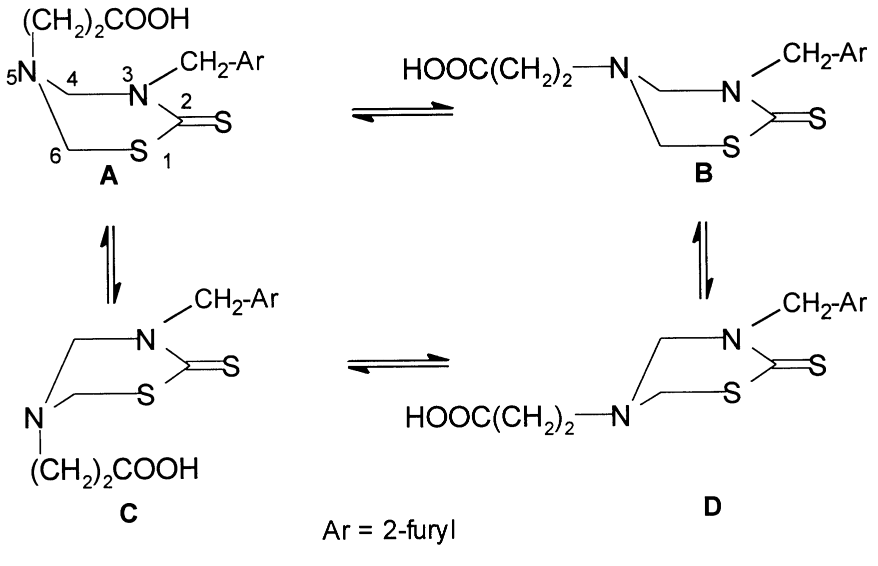

Figure 4. Different conformations for thiadiazine-2-thiones (**2**).

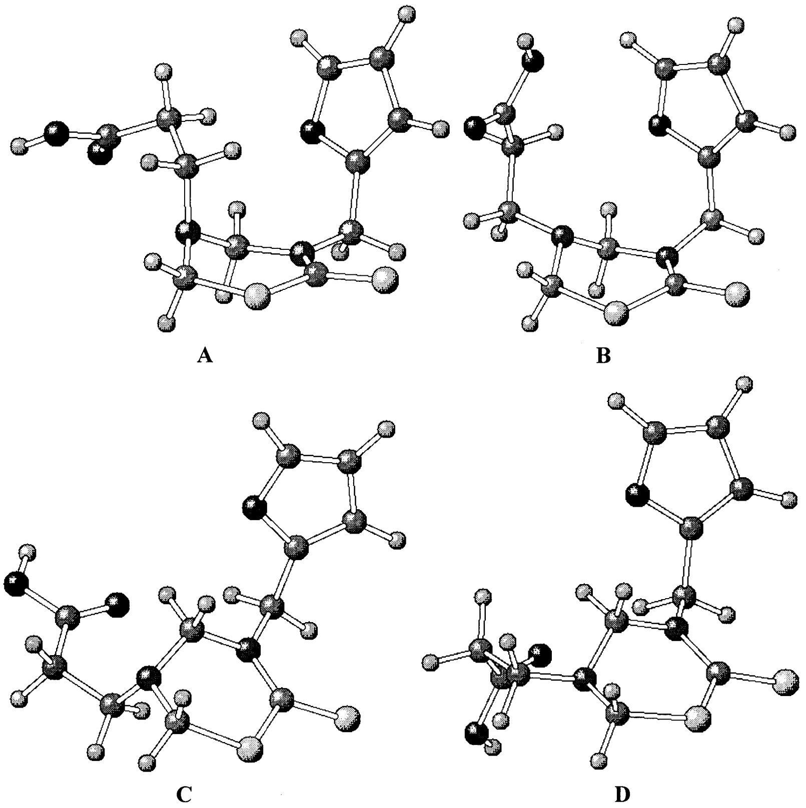

Figure 5. Four different conformations of compound **2** predicted by AM1 theoretical calculations. Conformation A is the energetically most favourable geometry.

AM1 predicts 1.579 Å, while using HF/3-21G* it is 1.673 Å and HF/6-31G* gives 1.672 Å.

Both calculated and experimental data found N3 to have an sp^2 hybridisation, according to the value of the angle C2–N3–C4 (calculated AM1: 123.2°, HF/3-21G*: 125.4° and HF/6-31G*: 125.1, observed X-ray: 124.0°). Atom N5 which is out of the plane is found to have sp^3 hybridisation with the angle C4–N5–C6 being 111.6° (AM1), 111.3° (HF/3-21G*), 110.7° (HF/6-31G*) and 109.9° in the crystal. The

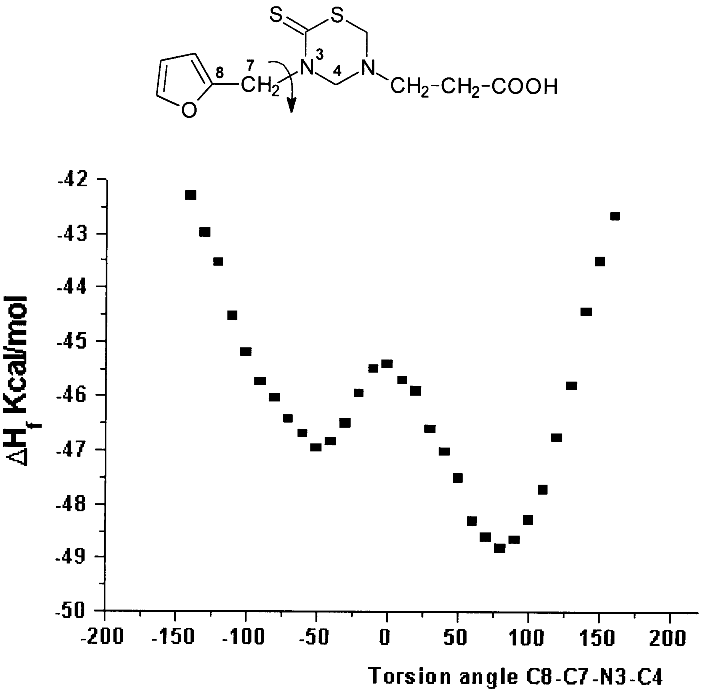

Figure 6. Energy dependence of compound **2** versus torsion angle C8–C7–N3–C4.

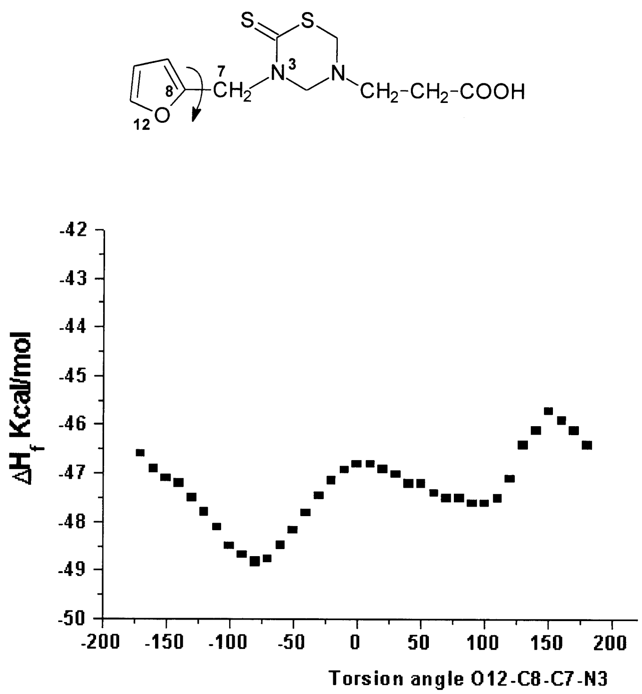

Figure 7. Energy dependence of compound **2** versus torsion angle O12–C8–C7–N3.

sp^2 hybridisation in N3 reduces the conformational flexibility in this centre in comparison to N5, in which the substituent can undergo axial or equatorial arrangement.

Substituents on nitrogens N3 and N5 are found at the same side of the envelop formed by the thiadiazine ring, C8–C7–N3–C4 being 75.0°, 85.0°, and 87.8° by AM1, HF/3-21G* and HF/6-31G* method, respectively, and 90.7° by X-ray analysis. The found values for C13–N5–C6–S1 were −83.8°, −72.9°, and −72.3° by AM1, HF/3-21G* and HF/6-31G*, respectively, and −71.3° by X-ray analysis.

It is important to note that the geometrical parameters calculated at the Hartree–Fock level with both 3-21G* and 6-31G* basis sets give essentially the same values for the geometrical data. Also AM1 is useful for predicting conformational features on this class of compounds.

In order to obtain information about the conformation of compound **2** in solution, NOE experiments were developed upon irradiation of the methylene groups in C4, C6, C7, C13 and C14. The NOEs observed indicate that conformer A can be also found in solution (see Table 2). Thus, as representative examples, irradiation of [CH_2]-4 showed a NOE effect on [CH_2]-7, [CH_2]-13 as well as on [CH_2]-14, and when [CH_2]-7 was irradiated, a strong NOE effect was observed on [CH_2]-4.

In summary, we have used semiempirical (AM1) and ab initio (HF/3-21G* and HF/6-31G*) theoretical calculations, as well as X-ray crystallographic analysis on a representative example of 3,5-disubustituted tetrahydro-2*H*-1,3,5-thiadiazine (**2**) to determine the most favourable conformation. A good agreement between the theoretical and experimental data has been found and it reveals that the favoured conformation A predicted by theoretical calculations is also found

Table 1. Most relevant bond distance, valence angles and dihedral angles for compound **2** (the numbering scheme is shown in Fig. 2). Bond distances are given in Å and angles in degrees (standard deviations in parenthesis)

	X-Ray	AM1	HF/3-21G*	HF/6-31G*
Bond distances				
S1–C2	1.743(3)	1.712	1.768	1.767
S1–C6	1.851(3)	1.761	1.841	1.835
S2–C2	1.669(3)	1.574	1.673	1.672
C2–N3	1.336(4)	1.375	1.332	1.330
N3–C4	1.488(4)	1.467	1.496	1.481
N3–C7	1.473(4)	1.448	1.481	1.470
C4–N5	1.437(4)	1.456	1.438	1.426
N5–C6	1.444(3)	1.440	1.448	1.431
N5–C13	1.466(3)	1.455	1.474	1.460
C7–C8	1.480(4)	1.484	1.488	1.493
C8–O12	1.360(4)	1.404	1.390	1.354
C11–O12	1.362(4)	1.394	1.387	1.347
Valence angles				
C2–S1–C6	104.3(1)	107.4	103.1	103.2
S1–C2–N3	120.7(2)	119.5	121.0	120.3
C2–N3–C4	124.0(2)	123.2	125.4	125.1
N3–C4–N5	114.2(2)	117.9	113.6	115.0
C4–N5–C6	109.9(2)	111.6	111.3	110.7
S1–C6–N5	113.0(2)	116.1	111.6	112.8
C2–N3–C7	120.7 (2)	120.6	120.7	120.7
C4–N3–C7	115.2 (2)	116.5	113.8	114.1
C4–N5–C13	114.6 (2)	116.3	117.4	116.1
C6–N5–C13	114.4 (2)	113.9	115.7	115.6
N3–C7–C8	112.9 (3)	114.7	112.2	113.6
C8–O12–C11	107.0(3)	106.4	107.1	107.3
Torsion angles				
C6–S1–C2–S2	178.3(2)	174.6	−179.7	−179.5
C6–S1–C2–N3	−1.1(3)	−6.9	0.8	1.5
C2–S1–C6–N5	−25.8(2)	−20.2	−31.6	−30.8
C2–S1–C6–H6A	95.5	100.3 (B)	89.6	90.8
C2–S1–C6–H6B	−147.1	−143.9 (A)	−152.5	−152.4
S1–C2–N3–C4	−4.8(4)	2.8	0.3	−2.1
S1–C2–N3–C7	177.1(2)	177.3	−177.9	−177.5
S2–C2–N3–C4	175.8(2)	−178.8	−179.1	179.0
S2–C2–N3–C7	−2.3(4)	−4.3	2.7	3.6
C2–N3–C4–N5	39.1(3)	30.1	29.9	32.5
O12–C8–C7–N3	−81.5(3)	−80.1	−77.9	−78.5
C14–C13–N5–C4	73.2 (3)	57.6	61.0	73.0
C14–C13–N5–C6	−158.6 (2)	−169.8	−164.3	−154.8
C2–N3–C4–H4A	160.7	153.0	151.9	154.5
C2–N3–C4–H4B	−82.4	−89.9	−91.1	−89.5
C7–N3–C4–N5	−142.8(2)	−144.7	−151.8	−151.8
C2–N3–C7–C8	−91.1(3)	−99.9	−96.3	−96.3
C8–C7–N3–C4	90.7(3)	75.0	85.0	87.8
N3–C4–N5–C6	−67.4(3)	−57.8	−64.3	−64.2
C4–N5–C6–S1	59.3(3)	50.7	64.5	62.4
N3–C7–C8–O12	−81.5(3)	−77.9	−77.9	−78.5
C13–N5–C6–S1	−71.3(3)	−83.8	−72.9	−72.3
C13–N5–C4–N3	63.0 (3)	75.4	72.3	70.3
C15–C14–C13–N5	60.5 (3)	47.0	46.0	50.9
O16–C15–C14–C13	−144.9 (3)	−97.3	−113.0	−122.1
O17–C15–C14–C13	37.5 (3)	83.6	66.1	58.6

Table 2. NOEs observed for compound **2** by irradiating to different protons

Proton	H4 (%)	H6 (%)	H7 (%)	H12 (%)	H13 (%)
H4	–	2	5	4.5	3.1
H6	1.9	–	–	3.8	2.7
H7	3.9	–	–	–	–
H13	4.5	–	–	–	6.1
H14	2.5	–	–	3.5	–

in the crystal. NOE experiments confirm the presence of conformation A in solution.

3. Experimental

3.1. General

The melting point was determined in a capillary tube in a Electrothermal C14500 apparatus and is uncorrected. The NMR spectrum was recorded on a Bruker AC spectrometer (250 MHz—^{1}H and 62.0 MHz—^{13}C) in DMSO-d$_6$. Chemical shifts are given as δ values against tetramethylsilane as the internal standard. The IR spectrum was measured with a Bruker IRS48 instrument as potassium bromide pellet. Mass spectra were obtained with a Hewlett–Packard 5989. Microanalysis was performed in a Perkin–Elmer 2400 CHN by the *Servicio de Microanálisis de la Universidad Complutense de Madrid*.

Semiempirical AM1[11] calculations were carried out using the MOPAC 6.0[12] program. The fully optimised ab initio geometries were obtained at the Hartree–Fock level using the 3-21G* and 6-31G* basis sets. Ab initio calculations were performed using the Gaussian 98 program[13] on an IBM RS/6000 workstation.

3.1.1. 5-Carboxyethyl-3-(2′-furfuryl)-tetrahydro-(2*H*)-1,3,5-thiazidine-2-thione (2). To a stirred solution of 0.9 ml (0.01 mol) of furfurylamine in 25 ml of water, 1.1 g (0.01 mol) of potassium hydroxide (as a 20% aqueous solution) and 0.6 ml (0.01 mol) of carbon disulfide were added at room temperature. The mixture was subsequently stirred for 4 h. Then 1.2 ml (0.02 mol) of formaldehyde solution (37%), was added and the stirring continued for 1 h. The mixture was filtered and the resulting solution added dropwise to a suspension of 8.9 g (0.01 mol) of β-alanine in 10 ml of a pH 7.8–8 phosphate buffer solution and stirred for an hour, filtered off and extracted with diethylether. The aqueous solution was cooled in an ice-bath and acidified to pH 2 by 15% hydrochloric acid. The precipitate was filtered and washed with a cool mixture of ethanol/water and then with cool ether. 65% yield (from cold water–ether) mp 131–132°C (d); $\nu_{\max}$/cm^{-1} 3386 (O–H), 1672 (C=O), 1500 (C=C), 1124 (C=S); ^{1}H NMR (DMSO-d$_6$) δ 12.24 (1H, br. s, OH), 7.61 (1H, m, H11), 6.44 (1H, d, J=3.42 Hz, H9), 6.43 (1H, d, J=3.42 Hz, H10), 5.30 (2H, s, H7), 4.51 (2H, s, H6), 4.50 (2H, s, H4), 2.79 (2H, t, J=2.79 Hz, H13), 2.35 (2H, t, J=6.96 Hz, H14); MS: *m*/*z* (%): 286 (M$^+$, 6), 139 (6), 115 (6), 109 (8), 81 (100), 76 (28), 53 (48). Anal. Calcd $C_{11}H_{14}N_2O_3S_2$ (286.96): C, 46.14; H, 4.93; N, 9.78. Found: C, 46.34; H, 4.98 N, 9.81.

3.2. X-Ray structure analysis

Crystals of **2** were grown by slow evaporation from ethanol.

3.2.1. Crystal data. $C_{11}H_{14}N_2O_3S_2$, M=286.96, Monoclinic, a=9.7875(5), b=12.1686(5), c=11.3742(6) Å, β=102.199(4)°, V=1324.1(1) Å^3 (by least-squares refinement on diffractometer angles for 44 automatically centred reflections with $10.68<\theta<28.01°$, λ=1.54178 Å, T=293(2) K), space group $P2_1/n$, Z=4, D$_c$=1.437(7) g cm^{-3}, μ=3.68 mm^{-1}. A prismatic colourless crystal (0.52×0.30×0.16 mm) was used for the analysis.

3.2.2. Data collection and processing. A Siemens P4 four-circle diffractometer with graphite monochromated CuKα radiation was used for data collection. The intensity data were collected using $\omega-2\theta$ scans, with ω scan width equal to the low range, plus the high range, plus the separation between the Kα_1 and Kα_2 positions; 3237 reflections measured ($3.71<\theta<69.15°$, $-1<h<10$, $-1<k$ 14, $-13<l<13$), 2363 unique (merging R=0.037) and $F^2\geq 2\sigma(F)^2$ for 2056 reflections which were retained in all calculations. Empirical absorption correction, via ψ scan was applied.[14] Three standard reflections were monitored every 100 reflections (intensity decay: none).

3.2.3. Structure solution and refinement. The structure was solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times *Ueq* of their parent atoms. Data collection: XSCANS.[15] Cell refinement: XSCANS.[15] Data reduction: XSCANS.[15] Program(s) used to solve structure: SHELXS97.[16] Program(s) used to refine structure: SHELXL97.[17] Molecular graphics: DIAMOND.[18] Software used to prepare material for publication: PLATON.[19] Detailed crystallographic data for compound **2** have been deposited at the Cambridge Crystallographic Data Centre (No. CCDC 147206) and are available on request.

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References

1. Zolnai, T. *Arzneim.-Forsch./Drug Res.* **1971**, *21*, 121–127.
2. Ertan, M.; Tayman, A. B.; Yulug, N. *Arch. Pharmacol.* **1996**, *323*, 605–609.
3. Ilhan, E.; Çapan, G.; Ergenç, N. *Il Farmaco* **1995**, *50*, 787–790.
4. Ertan, M.; Bilgin, A. A.; Palaska, E.; Yulug, N. *Arzneim.-Forsch./Drug Res.* **1992**, *42*, 160–163.
5. Schorr, M.; Dürckheimer, W.; Klatt, P.; Lämmler, G.; Nesemann, G.; Schrinner, E. *Arzneim.-Forsch./Drug Res.* **1969**, *19*, 1807–1819.
6. Aboul-Fadl, T.; Hassanin, K. *Pharmacie* **1999**, *54*, 244–247.
7. Ochoa, C.; Perez, E.; Perez, R.; Suárez, M.; Ochoa, E.; Rodríguez, H.; Gómez, A.; Muelas, S.; Nogal, J.; Matínez, R. *Arzneim.-Forsch./Drug Res.* **1999**, *49*, 764–769.
8. Perez, R.; Rodríguez, H.; Pérez, E.; Suárez, M.; Reyes, O.; González, L.; López, A.; Ezpeleta, O.; Pérez, C.; Ochoa, C. *Arzneim.-Forsch./Drug Res.* **2000**, *51*, 854–859.

9. Perez, R.; Reyes, O.; Suárez, M.; Garay, H.; Cruz, L.; Rodríguez, H.; Molero-Vilchez, M. D.; Ochoa, C. *Tetrahedron Lett.* **2000**, *41*, 613–616.
10. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.
11. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902–3909.
12. Stewart, J. J. P. *MOPAC*; QCPE No. 455.
13. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr., J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. GAUSSIAN 98; Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
14. North, A. C. T.; Phillips, D. C.; Mathews, F. S. *Acta Crystallogr.* **1968**, *A24*, 351–359.
15. X-ray Single Crystal Analysis System, Version 2.2; Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA, 1996.
16. Sheldrick, G.M. SHELXS97: Program for the solution of crystal structures; University of Göttingen: Germany, 1997.
17. Sheldrick, G.M. SHELXL97: Program for the refinement of crystal structures; University of Göttingen: Germany, 1997.
18. Bergerhoff, G. DIAMOND-Visual Crystal Structure Information System; Gerhard-Domagk-Str., 1, 53121 Bonn, Germany, 1996.
19. Spek, A. L. PLATON. *Acta Crystallogr.* **1990**, *A46*, C-34.