A NOVEL TETRACYCLIC SYSTEM CONTAINING THE 1,2,6-THIADIAZINE RING: SYNTHESIS, STRUCTURAL ASSIGNMENT AND TAUTOMERIC STUDIES

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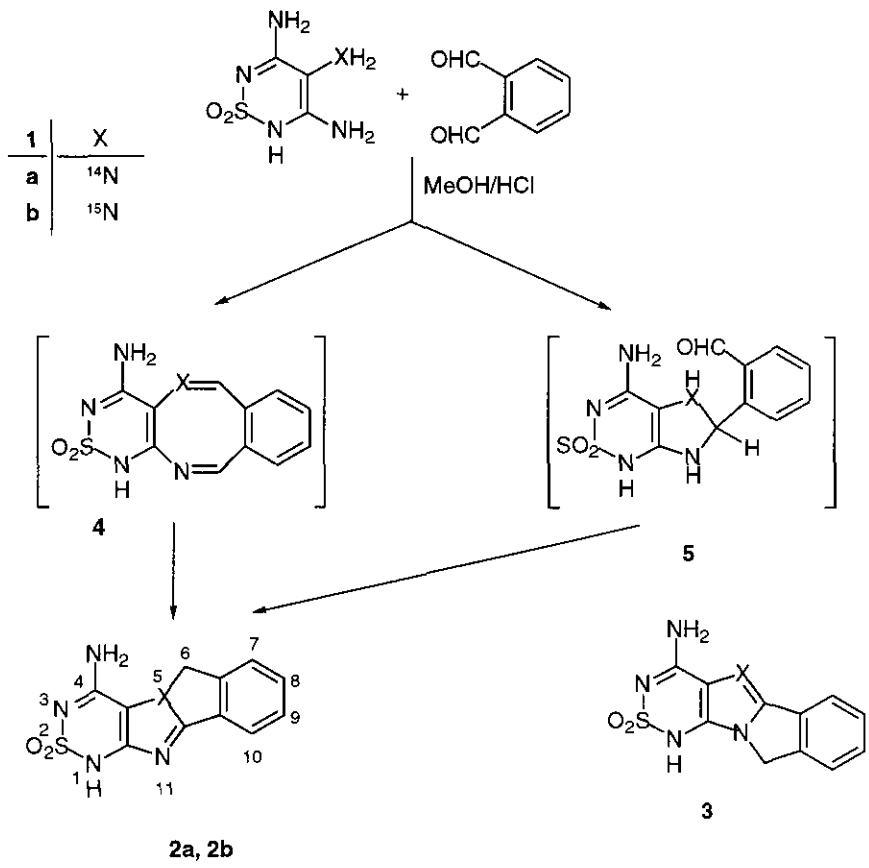
Abstract - Condensation of 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide with phthalaldehyde afforded a tetracyclic system of thiadiazino[3'4':4,5]imidazo-[2,1-*a*]isoindole 2,2-dioxide. In order to establish the correct structure it was necessary to use an ^{15}N-labelled thiadiazine derivative as starting material. *Ab initio* theoretical calculations and the Onsager model have been used to study annular tautomerism in this novel structure.

For quite some time, we have been interested in heterocycles containing the aminosulfonylamino, N-SO_2-N, group.[1] The interest in these compounds is due not only to their particular structural features but also to a variety of biological activities they have shown.[2,3] Within this context, we were interested in polycyclic derivatives incorporating the 1,2,6-thiadiazine 1,1-dioxide ring and so, we decided to study the reaction between the 3,4,5-triamino-1,2,6-thiadiazine (**1**) and phthalaldehyde.

The reaction of *o*-phenylenediamines with aromatic dicarbonyl compounds to give isoindolo[2,1-*a*]-benzimidazoles has been extensively explored.[4] In some cases, there has been some controversy on whether the final compound obtained could be the corresponding 1,4-benzodiazocine although mostly, the compounds have later been shown to be the imidazo[2,1-*a*]isoindole derivatives.[5]

In this paper, we want to report a more interesting case in which the starting diamino compound is thiadiazine (**1**) which can, in principle, give rise to both thiadiazinoimidazo[2,1-*a*]isoindoles (**2**) and (**3**). These isomers cannot be distinguished on the basis of NMR data, so it was necessary to use, as starting material, an ^{15}N labelled thiadiazine (**1b**) to definitely establish the structure as (**2**). A detailed study of the annular tautomerism of this novel structure by quantum mechanical *ab initio* calculations is also reported.

Reaction of 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**1a**)[6] with phthalaldehyde in methanol, at room temperature, afforded compound (**2a**). (Scheme 1).



Scheme 1

As mentioned above, in the reaction of triamino-2*H*-1,2,6-thiadiazine with phthalaldehyde two isomeric structures (**2** and **3**) are possible. However, in this case only one of the two possible isomers was obtained. The ^{1}H NMR, ^{13}C NMR (Table 1) and analytical data were compatible with both structures (**2a**) and (**3**) and it was not possible on these basis to distinguish between the two isomers.

Table 1. ^{13}C NMR spectral data (δ, *J* in Hz, DMSO-d_6)

Compd	C-11a	C-10b	C-4	C-4a	C-6	Other signals					
2a	154.8	154.5	152.7	102.9	50.6	143.6	129.3	128.6	127.7	124.0	120.6
		^{3}J = 1.3									
2b	154.7	154.6	152.7	102.9	50.5	143.5	129.3	128.5	127.6	124.0	120.6
6	155.7	155.6	152.2	102.8	50.6	143.6	129.3	128.7	127.4	123.9	120.0 29.3
	^{3}J = 3.0	^{3}J = 1.6		^{3}J = 4.5							

In order to definitely assign the structure of the isomer formed, an ^{15}N-labelled 3,4,5-triamino-2*H*-1,2,6-thiadiazine (**1b**) was prepared following the synthetic procedure described for (**1a**).[6] Thus, reaction of 3,5-diamino-4*H*-1,2,6-thiadiazine 1,1-dioxide[7] with Na $^{15}NO_2$ (5% enriched) in acetic acid solution and sodium dithionite afforded the triamino derivative (**1b**) unequivocally labelled at the 4-amino group. Reaction of **1b** with phthalaldehyde in the same conditions as above, afforded only one compound (**2b**). The isomeric structure was finally identified by ^{15}N NMR. The assignments of the chemical shifts of compound (**2a**) have been established by comparison with 1,2,6-thiadiazine derivatives.[8,9] Compounds (**2**) and (**3**) contain two types of nitrogen in the ring: the sp^2-type nitrogen which appears at lower field (δ = 154.8) and the sp^3-type nitrogen atom at higher field (δ = 292.1, 265.7 and 260.4) with a difference in chemical shift of about 100 ppm (Table 2). The ^{15}N NMR spectrum of the ^{15}N-labelled compound (**2b**) shows only one signal at δ = 259.0 corresponding to an sp^3-type nitrogen atom (N-5) and therefore, only compatible with structure (**2b**).

Table 2. ^{15}N NMR data for compounds (**2**)[a]

Compd	NH_2	N-1	N-5	N-11
2a[b]	292.1	265.7	260.4	154.8
2b			259.0	

[a] Shifts are in ppm and negative from external nitromethane in DMSO-d_6. [b] Due to the poor solubility of this compound in DMSO-d_6 it was not possible to record the signal corresponding to the N-3, which appears at δ = 150-180 in other 1,2,6-thiadiazine derivatives.[8,9]

In agreement with this fact, in the ^{13}C NMR coupled spectrum of compound (**2a**) the carbon atom whose chemical shift corresponds to C-11a appears as a singlet and the more shielded quaternary carbon atom C-4a as a triplet due to the coupling with hydrogens of the CH_2 group.

A definite mechanism for the formation of only compound (**2**) is difficult to propose. One possibility could be the rearrangement of a 1,4-bezodiazocine type intermediate such as **4** , that could end in both **2** or **3** . The other alternative could be a two-step sequence starting with the formation of the Schiff base between the proven more reactive amino group at position 4 of thiadiazine (**1**) and ring closure to the imidazolidine type ring (**5**). Finally, the second aldehyde function could close on one of the NH groups to give the isoindole derivatives (**2**) and (**3**). There is no significant evidence in favour of one or the other pathways although we have found that the type (**5**) thiadiazine structure, without the second aldehyde group, is readily oxidized in the reaction medium to the corresponding imidazo[4,5-*c*]-1,2,6-thiadiazine.[10] In any case, both pathways can give rise to both isomers, the conclusive evidence of this work lying on the final structural assignment and not on the mechanism which would be difficult to establish.

Tautomeric Studies

Compound **(2)** represents an interesting case of annular tautomerism, so we decided to study it both in solution and in the gas phase by *ab initio* calculations. In principle, compound **(2a)** can exist as four possible tautomers:

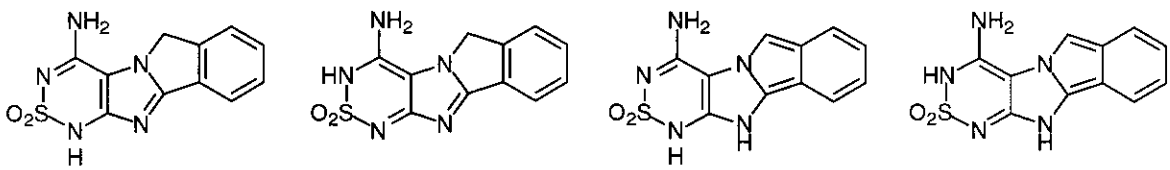


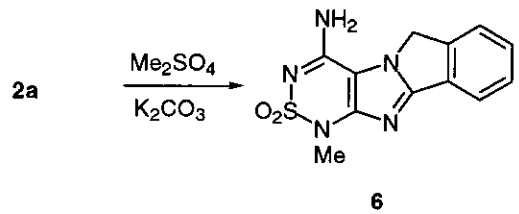
Figure 1. Tautomers **A-D** of compound **(2a)**.

In solution, information can be obtained from the uv spectra and pK_a value. Compound **(2a)** is an acid as reflected in its pK_a value which is comparable to other condensed systems containing the thiadiazine ring.[10,11] A comparison of the UV spectra of the neutral molecular form **(2a)** with its 1-methyl derivative **(6)** (Scheme 2), prepared by methylation of **(2a)** with dimethyl sulphate in a potassium carbonate solution, indicates that compound **(2a)** (Figure 1) exists in aqueous solution as the tautomer **A** (Table 3).

Table 3. Physical data of compounds **(2a)** and **(6)**.

		UV spectra in H_2O[a]									
	pK_a	λ_{max} (nm)				log ε				pH	Mol.
Compd	in H_2O form[b]										
		253	[276]	[299]	327	4.132	[3.814]	[3.773]	3.982	-3	+
	-0.03										
2a		244		[299]	335	4.146		[3.584]	3.996	2	o
	4.49										
		[244]	260		345	[4.154]	4.237		3.976	7	-
6[c]		[231]	254	[296]	330	—	—	—	—		o

[a] [ ]: Shoulder. [b] +: Cation; – : Monoanion; o : Neutral form. [c] Due to the poor solubility of this compound in water it was not possible to calculate the ε values.



Scheme 2

Tautomerism in this compound has also been studied by theoretical molecular orbital calculations. The problem with *ab initio* calculations in these large molecules with the aminosulphonyl group is which method to use. In this respect, a recent systematic study for heterocyclic compounds containing the SO_2 moiety has shown that the methods which include electron correlation provide a good geometric and electronic description.[12,13] Thus, the study was performed using a molecular orbital *ab initio* method at the Hartree-Fock level with the 6-31G*[14] basis set, and a local density functional method (LDF) which include electron correlation.[15,16]

The values of the calculated total and relative energies in the gas phase are collected in Table 4. The dipole moments of the four tautomers are also tabulated. The results obtained indicate that tautomers **A** and **B** are more stable (16-33 kcal.mol^{-1}) than non aromatic tautomers **C** and **D**. The relative low stability and lower dipole moments of tautomers **C** and **D** would make tautomers **A** and **B** more favoured in aqueous solution.

Table 4. Calculated energies (E, hartrees), relative energies (ΔE, kcal.mol^{-1}), and dipole moments (μ, Debye) of tautomers **A -D**.

	RHF/6-31G*			DMol		
	E	ΔE	μ	E	ΔE	μ
A	-1241.20125	0.0	12.26	-1239.10586	0.0	10.08
B	-1241.17902	13.9	13.64	-1239.08830	11.0	12.00
C	-1241.14768	33.6	6.74	-1239.08048	15.9	4.82
D	-1241.14882	32.9	7.22	-1239.08057	16.0	5.94

To study the relative stability of the different tautomers in aqueous solution the solvation effect has been considered via the self consistent reaction field (SCRF) method. This method is based on Onsager's reaction field theory[17,18] of electrostatic solvation. In this model the solvent is considered as a uniform dielectric with a given dielectric constant ε. The solute is situated in a spherical cavity of radius a_0 in the solvent medium. The permanent dipole of the solute induces a dipole in the surrounding medium, which in turn will interact with the solute dipole. This solute-solvent interaction is updated until self-consistency is

achieved. This interaction term is treated as a perturbation in the Hamiltonian of the isolated solute, and the solvation energy calculated through this scheme corresponds to the electrostatic contribution to the free energy of solvation.

Table 5. Calculated energies (E, hartrees) and relative energies (ΔE, kcal.mol^{-1}) in the SCRF model of tautomers **A** -**D**

	RHF/6-31G*		BLYP/6-31G*	
	E	ΔE	E	ΔE
A	-1241.21956	0	-1246.62092	0
B	-1241.20478	9.2	-1246.60235	11.6
C	-1241.15362	41.3	-1246.58386	15.9
D	-1241.15428	41.0	-1246.58807	15.9

The results obtained collected in Table 5, indicate that in the Onsager model with the molecular orbital method RHF/6-31G* and the density functional BLYP/6-31G*, tautomer **A** is more stable in water than tautomer **B** (9-12 kcal.mol^{-1})

The large stability difference of tautomer **A** in relation to the others indicate that only form **A** should be present in gas phase and water, this last result in good agreement with the experimental data obtained by UV spectrophotometry.

Experimental Section

General:

Melting points are measured on Reicher-Jung Thermovar micro melting point apparatus, without correction. NMR spectra were recorded on a Varian XL-300 and Varian Unity-500 (300 MHz and 125 MHz, for ^{1}H and ^{13}C, respectively). The signal of the solvent was used as reference. ^{15}N NMR were recorded on a Varian Unity-500 (50 MHz) spectrometer. The nitrogen shielding values are reported with respect to external nitromethane. The UV spectra were obtained on a Perkin Elmer Lambda 5 Spectrophotometer. MS spectra (electron impact, 70 eV) were obtained on a VG 12-250 (VG Masslab). Elemental analyses were performed on a Heraeus CHN-rapid analyzer.

Theoretical calculations:

All the structures were fully optimized without any symmetry restrictions in gas phase. The *ab initio* molecular orbital calculations were carried out with the Gaussian-94 program[19] at the RHF level of theory with the 6-31G* basis set. The minimization was performed using the Berny method. The default

parameters were used for the minimization convergence criteria. The LDF calculations were carried out using the DMol program[20] distributed by Biosym technologies. A double zeta numerical basis set with polarization functions in all the atoms and the Janak-Moruzzi-Williams (JMW) exchange correlation potential[21] were used. The geometry of the molecules was optimized until the gradient was smaller than 0.001 au.

The solvation effect has been studied using the self consistent reaction field (SCRF) method. This method is based on Onsager reaction theory of electrostatic solvation. In this model the water is considered as a uniform dielectric with a dielectric constant ε=78.5. The spherical cavity of radius a_0 has been calculated by the quantum mechanical approach proposed by Wong[22] which involves determining the 0.001 au electron density envelope and scaling this envelope by a factor of 1.33 to obtain the solute volume. An extra 0.5 Å is added to the resultant a_0 to account for the nearest approach of solvent molecules. The single point energies with the 6-31G* basis set at the HF level and with the BLYP functional were determined from the optimized geometries in gas phase

4-Amino-1H,6H-1,2,6-thiadiazino[3',4':4,5]imidazo[2,1-a]isoindole 2,2-dioxide (**2a**):

A suspension of 1.00 g (5.62 mmol) of **1** in 50 mL of methanol and 0.16 mL of concentrated hydrochloric acid was treated with 1.11 g (8.27 mmol) of phthalaldehyde and was stirred at rt for 2 h. The precipitate was filtered and recrystallized from water/ethanol to give 0.68 g of **2a** (44%); mp > 350 °C. ^{1}H NMR (DMSO-d_6) δ: 11.17 (br s, 1 H, NH), 7.81 (m, 1 H, Ph), 7.66 (m, 1 H, Ph), 7.52 (m, 2 H, Ph), 7.38 (br s, 2 H, NH_2), 5.38 (s, 2 H, CH_2). Anal. Calcd for $C_{11}H_9N_5O_2S$: C, 47.99; H, 3.30; N, 25.44; S, 11.65. Found: C, 47.81; H, 3.50; N, 25.31; S, 11.42.

4-Amino-1-methyl-6H-1,2,6-thiadiazino[3',4':4,5]imidazo[2,1-a]isoindole 2,2-dioxide (**3**):

A solution of 1.00 g of **2a** (3.63 mmol) in water and 1.50 g (10.85 mmol) of potassium carbonate was treated with 1.0 mL of dimethyl sulphate at rt for 4 h. The precipitate was filtered and recrystallized from acetic acid/water to give 0.40 g of **3** (40%); mp > 300 °C. ^{1}H NMR (DMSO-d_6) δ: 7.88 (m, 1 H, Ph), 7.70 (m, 1 H, Ph), 7.55 (m, 2 H, Ph), 7.53 (br s, 2 H, NH_2), 5.43 (s, 2 H, CH_2), 3.35 (s, 3 H, CH_3). MS (70 eV); *m/z* : 289 [M^+]. Anal. Calcd for $C_{12}H_{11}N_5O_2S$: C, 49.82; H, 3.83; N, 24.21; S, 11.08. Found: C, 49.73; H, 3.96; N, 23.84; S, 10.71.

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Dedicated to Professor W. Pfleiderer on the occasion of his 70th birthday.

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