Tautomerism of Benzo- and Cyclopenta-[1,2,6]thiadiazine *S,S*-Dioxides

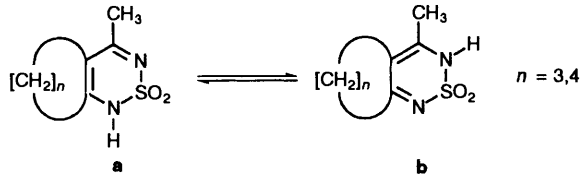
Ana Castro and Ana Martínez *
Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain

The synthesis and spectroscopic characterization of fused 1,2,6-thiadiazine *S,S*-dioxides **1–6** have been carried out. The tautomerism of this heterocyclic system has been studied by means of experimental and theoretical techniques.

Prototropic tautomerism is one of the most interesting problems in heterocyclic chemistry and has been the subject of many studies.[1] Additionally, tautomerism can be decisive regarding biological action, as has been shown for nucleic acids.[2]

Continuing our research into this problem,[3] we report here the tautomerism of dioxides of thiadiazines **1–6**, compounds which show interesting muscular relaxant properties *in vitro*.[4]

This kind of compound can exist in two tautomeric forms, **a** and **b**. With the aim of determining which form predominates,



a **b**

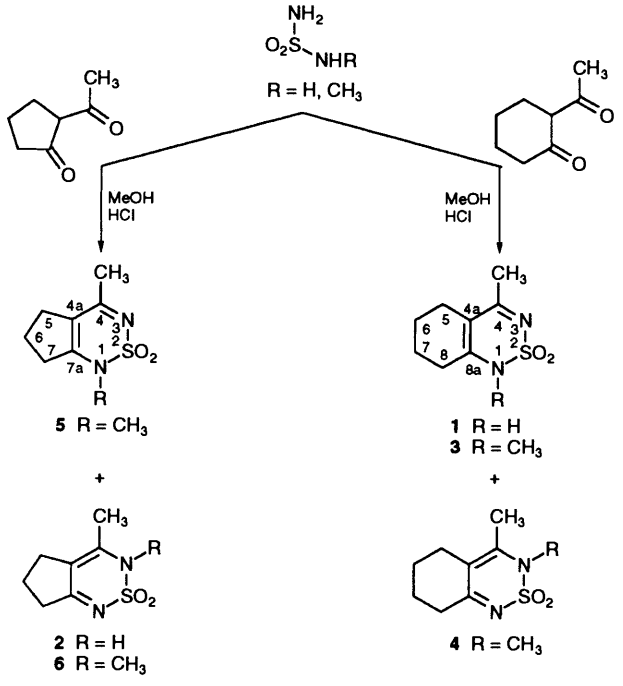
and in order to investigate whether the size of the ring (n = 3 or 4) influences the prototropic exchange, a detailed experimental study in solution and the solid state, and a theoretical one corresponding to the gas phase, have been carried out.

Results and Discussion

Synthesis.—Thiadiazines (**1** and **2**) and their corresponding *N*-CH_3 derivatives (**3–6**) were obtained by condensation of sulfamide and *N*-methylsulfamide with 2-acetylcycloalkanones in methanol saturated with hydrogen chloride (Scheme 1). Compound **1** had previously been described by Wright,[5] but only analytical data were reported. *N*-Methylsulfamide was synthesized following an efficient procedure described in our laboratory[6] in 95% overall yield. The condensation of this sulfamide with 2-acetylcycloalkanones afforded mixtures of two different isomers whose ratios were estimated by ^{1}H NMR of the crude reaction mixture. These were 45:55 and 33:67 for derivatives **3**:**4** and **5**:**6**, respectively. The isomers were separated by silica gel column chromatography.

NMR (^{1}H and ^{13}C) spectroscopic data for compounds **1–6** are collected in Tables 1 and 2. The substitution patterns were determined by means of NOE experiments. Thus, selective irradiation of the signal corresponding to the NCH_3 protons resulted in a positive NOE effect on the signal corresponding to the CCH_3 group when the isomer was N-3 substituted, or on the signal corresponding to the methylene group nearest to the heterocyclic nitrogen when the isomer was N-1 substituted.

In order to unequivocally assign all the NMR signals (^{1}H and ^{13}C), COSY and HETCOR experiments were performed on compounds **3** and **6**. Quaternary heterocyclic carbon atoms directly linked to nitrogen atoms (C-4 and C-7a or C-8a) were assigned by selective irradiation and by recording the ^{1}H–^{13}C coupled spectra. These experiments were carried out on compounds **3–6**. By irradiation at CCH_3, the coupling between



Scheme 1

CCH_3 and C-4 (the quaternary carbon directly bonded) disappeared; thus, C-4 and C-7a or C-8a could be unequivocally assigned.

As a result of the complete assignment, it is noted that CCH_3 is shielded by around 7 ppm upon substitution at N-3, a fact which can be used for future elucidations.

Tautomerism in Solution.—The ^{13}C NMR data of the thiadiazines synthesized can be used to assign the tautomeric structures present in solution. By comparison of the chemical shifts of **1** and **2** (see Table 2) with those of model compounds **3–6** in which the prototropy is blocked, it can be concluded that in $CDCl_3$ and [$^2H_6$]DMSO solutions, thiadiazine **1** exists mainly as tautomer **a**, while derivative **2** exists mainly as tautomer **b**.

However, the spectra showed significant peak broadening for the quaternary carbons directly linked to nitrogen atoms. This observation can be explained assuming a low rate of prototropic exchange between the two nitrogens. The kinetics of the prototropic exchange is greatly dependent on the solvents' nature. In [$^2H_6$]DMSO at 298 K, exchange is so slow that the signals corresponding to these atoms are not observed. When spectra were recorded in [$^2H_8$]THF (THF = tetrahydrofuran) at 173 K, no modifications of the shapes of the signals could be observed, showing again that in the case of dioxides of thiadiazines, prototropy is not very sensitive to temperature.[7] On the other hand, a scalar relaxation of the second kind may operate on these carbon atoms, and so an appreciable line

Table 1 ^{1}H NMR data of compounds **1–6** in $CDCl_3$

Compound	δ_H (multiplicity)[a] 5-H	6-H	7-H	8-H	CCH_3	NR	J/Hz
1	2.82 (m)	1.73 (m)		2.50 (m)	2.25 (s)	8.87 (s)	
2	2.63 (t)	2.01 (q)	2.76 (t)	—	2.18 (t)	9.20 (s)	$J_{5\text{-H},6\text{-H}}$ 8 $J_{6\text{-H},7\text{-H}}$ 8
3	2.37 (t)	1.79 (m)	1.70 (m)	2.52 (t)	2.25 (s)	3.40 (s)	$J_{5\text{-H},6\text{-H}}$ 6 $J_{6\text{-H},7\text{-H}}$ 6 $J_{7\text{-H},8\text{-H}}$ 6
4	2.37 (t)	1.70 (m)		2.58 (t)	2.18 (s)	3.44 (s)	$J_{5\text{-H},6\text{-H}}$ 6 $J_{7\text{-H},8\text{-H}}$ 6
5	2.69 (t)	2.16 (q)	2.91 (t)	—	2.20 (s)	3.44 (s)	$J_{5\text{-H},6\text{-H}}$ 7 $J_{6\text{-H},7\text{-H}}$ 7
6	2.60 (t)	1.98 (q)	2.62 (t)	—	2.15 (s)	3.49 (s)	$J_{5\text{-H},6\text{-H}}$ 8 $J_{6\text{-H},7\text{-H}}$ 8

[a] q = quintet.

Table 2 ^{13}C NMR data (δ_c) of compounds **1–6**

Compound	Solvent	C-4	C-4a	C-5	C-6	C-7	C-7a	C-8	C-8a	CCH_3	NCH_3
1	[$^2H_6$]DMSO[a]	*b*	106.51	23.17	21.93	20.74	—	28.80	*b*	22.24	—
	$CDCl_3$[c]	175.15	108.06	23.92	22.25	21.04	—	28.90	152.32	23.91	—
	$CDCl_3$–CF_3CO_2H	174.44	110.63	24.19	22.20	21.05	—	30.21	161.51	22.80	—
	CP/MAS	175.34	106.10	23.97	22.76	21.28	—	29.10	154.51	23.97	—
2	[$^2H_6$]DMSO[a]	*b*	109.86	21.28	26.55	34.65	*b*	—	—	19.06	—
	$CDCl_3$[d]	150.01	111.38	21.39	26.28	35.36	181.75	—	—	19.38	—
	$CDCl_3$–CF_3CO_2H	156.52	113.58	21.38	26.97	35.32	180.39	—	—	19.37	—
	CP/MAS	150.72	111.93	21.42	26.86	35.77	184.54	—	—	19.44	—
3	$CDCl_3$[e]	173.76	109.78	24.78	21.19	21.46	—	27.47	154.28	23.89	30.43
4	$CDCl_3$[f]	153.89	109.14	25.68	21.46	22.49	—	34.39	173.64	16.31	32.02
5	$CDCl_3$	170.48	112.47	29.66	21.60	33.23	163.26	—	—	24.20	32.98
6	$CDCl_3$	152.90	112.27	28.15	21.52	36.01	180.20	—	—	17.60	31.41

[a] DMSO = dimethylsulfoxide. [b] Not observed. [c] $^1J_{CH_3} = {}^1J_{C\text{-}5} = {}^1J_{C\text{-}6} = {}^1J_{C\text{-}7} = {}^1J_{C\text{-}8} = 136$ Hz. [d] $^1J_{CH_3} = {}^1J_{C\text{-}5} = {}^1J_{C\text{-}6} = {}^1J_{C\text{-}7} = 147$ Hz. [e] $^1J_{C\text{-}5} = {}^1J_{C\text{-}8} = 124$ Hz; $^1J_{C\text{-}6} = {}^1J_{C\text{-}7} = 113$ Hz; $^1J_{CCH_3} = 129$ Hz; $^1J_{NCH_3} = 124$; $^3J_{C\text{-}6} = {}^3J_{C\text{-}7} = 43$ Hz. [f] $^1J_{C\text{-}5} = {}^1J_{C\text{-}8} = 128$ Hz; $^1J_{C\text{-}6} = {}^1J_{C\text{-}7} = 124$ Hz; $^1J_{CCH_3} = 130$ Hz; $^1J_{NCH_3} = 142$.

broadening can be observed.[8] When a few drops of trifluoroacetic acid were added, the prototropic exchange becomes catalysed, and consequently all the carbon atoms were observed as narrow signals. This addition of acid does not produce any shift of the spectral peaks, which proves that compound protonation can be discounted.

Tautomerism in the Solid State.—The ^{13}C CP/MAS spectra of derivatives **1** and **2** (Table 2) indicate that in the solid state both compounds exist as single tautomers since each carbon appears as a unique signal. By comparison of the chemical shifts of **1** and **2** in the solid state with those found in solution, it can be concluded that thiadiazine **1** exists as tautomer **a** in the solid state, while derivative **2** exists as tautomer **b**.

Theoretical Calculations of the Tautomerism of Thiadiazines **1** *and* **2**.—Tautomerism in heterocycles can also be studied by quantum-chemical calculations since the relative stability of two tautomers depends on the difference between their lowest energies.[9] In the present case, two different semiempirical methods were chosen AM1,[10] which has proved useful for the study of tautomeric equilibria,[11] and PM3,[12] which has been recently shown to give good results in this type of study.[13] AM1 calculations were carried out with the AMPAC program package[14] and PM3 calculations with the MOPAC V5.0.[15] In all cases, the ChemQM interface of the molecular modelling program ChemX[16] was used and full geometry optimizations with the Fletcher–Powell algorithm[17] were carried out. The input geometries were the standard ones within ChemX, taking into account the X-ray data for the N–SO_2–N moiety.[18]

The heats of formation (ΔH_f°) and the populations of each tautomer calculated by a Boltzmann distribution at 298 K (n) are gathered in Table 3. As can be seen, the more abundant tautomer is the one that places the proton at N-1 (tautomer **a**) in the case of the 6-membered ring (compound **1**). However, if the ring size is smaller (compound **2**), the tautomeric equilibrium is strongly shifted to the form that locates the proton on N-3 (tautomer **b**). These results are in good agreement with those found in solution and solid state.

Conclusions.—Thiadiazines **1** and **2** exist as tautomers **1a** and **2b**. This fact can be explained if one considers the possibility of the existence of a Mills–Nixon effect in this kind of heterocycle, which produces a fixation of the π-electron system. Thus, the Mills–Nixon effect may operate on compound **2**, stabilizing the tautomer with a single bond along the ring-fusion.

Although from the beginning of this century[19] to our days,[20] there has been some controversy about the existence of this effect, more recent theoretical studies are clearly in favour of this kind of electronic fixation.[21] We have recently shown[22] that the Mills–Nixon effect operates in the fused pyrazole heterocyclic system. Considering the parallelism found between pyrazoles and thiadiazines,[23] we might extrapolate these results to provide an explanation for the tautomerism found in dioxides of fused thiadiazines. There is, however, one important structural difference between these two heterocyclic series, *viz.* aromaticity. The thiadiazine ring is non-planar (the SO_2 group is found out of the plane defined by the other ring atoms) and so the ring cannot be aromatic.[24] For this reason, tautomerism in dioxides of fused thiadiazines is probably controlled not only

Table 3 Calculated heats of formation and relative populations at 298 K for compounds **1** and **2**

Compound	Method	Tautomer	ΔH_f°/ kcal mol^{-1} [a]	ΔH_f°(a) − ΔH_f°(b)/ kcal mol^{-1} [a]	n (%)
1	AM1	**a**	−55.243	−0.272	61
		b	−54.971		39
	PM3	**a**	−69.729	−0.188	58
		b	−69.541		42
2	AM1	**a**	−45.766	1.266	10
		b	−47.032		90
	PM3	**a**	−63.997	1.227	10
		b	−65.224		90

[a] 1 cal = 4.184 J.

by electronic effects, but by structural ones as bending effects, proton–proton interactions near the ring fusion site and possible strain due to the fusion of the five-membered ring.

Experimental

Melting points were determined with a Reichert-Jung Thermovar and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrometer. Column chromatography was performed on Merck silica gel 60 (70–230 mesh). ^{1}H NMR spectra were obtained at 298 K using tetramethylsilane as internal standard on Varian-Gemini 200 and Varian XL-300 spectrometers, operating at 200 and 300 MHz, respectively. ^{13}C NMR spectra were recorded on Varian-Gemini 200 and Bruker AM-200 spectrometers, operating at 50 MHz and using tetramethylsilane as internal reference. ^{13}C CP/MAS-NMR spectra were recorded with a TOSS sequence on a Bruker-CXP-400 instrument operating at 100 MHz, under the following conditions: spinning rate 4.1 kHz; spectral width 50.0 kHz; acquisition time 5.0 s.

*4-Methyl-5,6,7,8-tetrahydro-*1H*-2,1,3-benzothiadiazine* 2,2-*Dioxide* (**1**).—A solution of sulfamide (6.0 g, 0.06 mol) and 2-acetylcyclohexanone (8.4 g, 0.06 mol) in methanol (50 cm^3) was cooled to 0 °C and saturated with hydrogen chloride. The reaction mixture was stirred at room temperature for 1 h. The solid was collected by filtration and recrystallized from water–methanol to yield **1** (9.6 g, 74%), m.p. 178–179 °C (lit.,[5] 180–181 °C).

4-Methyl-3,5,6,7-tetrahydrocyclopenta[c][1,2,6]*thiadiazine* 2,2-*Dioxide* (**2**).—2-Acetylcyclopentanone (7.6 g, 0.06 mol) was added to a solution of sulfamide (6.0 g, 0.06 mol) in methanol (50 cm^3). The reaction mixture was saturated with hydrogen chloride at 0 °C and stirred at room temperature for 3 h. The solvent was evaporated *in vacuo* and the residue recrystallized from water to yield **2** (5.0 g, 43%), m.p. 142 °C (Found: C, 45.2; H, 5.6; N, 15.3; S, 17.1. $C_7H_{10}N_2O_2S$ requires C, 45.17; H, 5.37; N, 15.04; S, 17.22%); ν_{max}(KBr)/cm^{-1} 3150 (N–H), 1310 and 1120 (SO_2).

*1,4-Dimethyl-5,6,7,8-tetrahydro-*1H*-2,1,3-benzothiadiazine* 2,2-*Dioxide* (**3**) *and* *3,4-Dimethyl-5,6,7,8-tetrahydro-*3H*-2,1,3-benzothiadiazine* 2,2-*Dioxide* (**4**).—A solution of methylsulfamide[6] (1 g, 9 mmol) and 2-acetylcyclohexanone (1.2 g, 9 mmol) in methanol (25 cm^3) was saturated with hydrogen chloride at 0 °C and the mixture stirred at room temperature for 1 h. The solvent was evaporated under reduced pressure and the residue, which was a mixture of two isomers, was chromatographed on a silica gel column using ethyl acetate–hexane (1 : 1) as eluent.

From the first fraction was isolated **3** (0.81 g, 41%), m.p. 110–112 °C (Found: C, 50.4; H, 6.8; N, 13.2; S, 14.8. $C_9H_{14}N_2O_2S$ requires C, 50.48: H, 6.53; N, 13.07; S, 14.97%); ν_{max}(KBr)/cm^{-1} 1400 and 1150 (SO_2).

From the second column fraction was isolated compound **4** (0.90 g, 47%), m.p. 63–65 °C (Found: C, 50.7; H, 6.8; N, 12.9; S, 14.6. $C_9H_{14}N_2O_2S$ requires C, 50.48; H, 6.53; N, 13.07; S, 14.97%); ν_{max}(KBr)/cm^{-1} 1410 and 1160 (SO_2).

1,4-Dimethyl-1,5,6,7-tetrahydrocyclopenta[c][1,2,6]*thiadiazine* 2,2-*Dioxide* (**5**) *and* *3,4-Dimethyl-3,5,6,7-tetrahydrocyclopenta*[c][1,2,6]*thiadiazine* 2,2-*Dioxide* (**6**).—A mixture of methylsulfamide (1 g, 9 mmol) and 2-acetylcyclopentanone (1.1 g, 9 mmol) in methanol (25 cm^3) was saturated with hydrogen chloride at 0 °C and stirred at room temperature for 5 days. The solvent was evaporated *in vacuo* and the residue was chromatographed on a silica gel column using diethyl ether as eluent.

From the first fraction was isolated derivative **5** (0.12 g, 7%), m.p. 93–95 °C (Found: C, 47.75; H, 6.3; N, 14.0; S, 15.9. $C_8H_{12}N_2O_2S$ requires C, 48.01; H, 5.99; N, 13.99; S, 16.02%); ν_{max}(KBr)/cm^{-1} 1320 and 1160 (SO_2).

From the second fraction was isolated compound **6** (0.26 g, 15%), m.p. 110 °C (Found: C, 47.7; H, 6.3; N, 14.15; S, 16.0. $C_9H_{14}N_2O_2S$ requires C, 48.01; H, 5.99; N, 13.99; S, 16.02%); ν_{max}(KBr)/cm^{-1} 1300 and 1160 (SO_2).

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