Synthesis and Physicochemical Properties of 1,2,6-Thiadiazine 1,1-Dioxides. A Comparative Study with Pyrazoles

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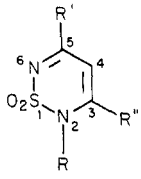
The chemical and structural properties of 18 1,2,6-thiadiazine 1,1-dioxides have been studied. By comparison with the corresponding pyrazoles it could be established that there are some analogies between pyrazoles and thiadiazine 1,1-dioxides, but because of the great difference in aromaticity, both series of heterocycles behave quite differently in other cases. However, a rough parallelism is observed in the tautomeric equilibrium, the ^{13}C chemical shifts, and the reactivity of the 4-position. As a consequence, the hypothesis will be made that these similarities are general and could be extended to a whole variety of heterocyclic and alicyclic structures.

Although derivatives of the 2*H*-1,2,6-thiadiazine 1,1-dioxide ring bearing functional groups are well-known (see, for instance, ref 1-4), there are few publications dealing with simple derivatives,[5-8] of 1, and the parent compound, **1a**, has never been described.



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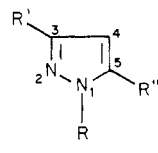
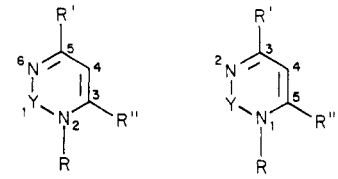


2

	a	b	c	d	e	f	g	h	i
R	H	Me	Bz	H	Me	Bz	Me	Bz	H
R′	H	H	H	Me	Me	Me	H	H	Me
R″	H	H	H	H	H	H	Me	Me	Me
	j	k	l	m	n	o	p	q	r
R	Me	Bz	H	Me	Bz	Me	Bz	H	Me
R′	Me	Me	Ph	Ph	Ph	Me	Me	NH_2	NH_2
R″	Me	Me	Me	Me	Me	Ph	Ph	H	H

In order to compare their physicochemical behavior and tautomerism with the related pyrazole derivatives **2**, we have prepared the compounds shown above. From these, only compounds **1c**[7], **1i**,[5-8] **1j**,[7,8] **1k**,[7] **1l**,[8] **1m**,[8] and **1q**[9] were already known; the rest, including **1a**, are here reported for the first time. In the following structures we emphasize the analogies and differences between both series. Note, particularly, that carbon atoms C_3 and C_5 in one series correspond to C_5 and C_3 in the other one, and thus $J_{3,4}$ in thiadiazines is equivalent to $J_{4,5}$ in pyrazoles.

Synthesis. Reaction of Sulfamides with 1,3-dicarbonyl compounds (or their acetal derivatives) is the general procedure for the preparation of thiadiazine 1,1-dioxides **1**. With *N*-substituted sulfamides two isomers can be obtained when R′ ≠ R″. The same isomers, but in different proportions, are formed by N-alkylation of the unsubstituted compounds (mixtures of tautomers I and II in Scheme I).



1, Y = SO_2 2, Y = directly bonded

Pyrazoles **2** are prepared in an analogous way. With the assumption for step A that the nucleophilic addition is rate and product determining (which is generally accepted for pyrazoles[10a]), the main difference between both series is that the activation energy is lower in the case of pyrazole formation since hydrazine is a more powerful nucleophile than sulfamide. It is worth mentioning that the relative amounts of isomers III and IV are comparable only in series **n** (Table I). In cyclization step A, the ratio of III/IV depends on the reactivity of both carbonyl groups and, in series **f**, on the rate of hydrolysis of the acetal (for pyrazoles[11]). This last fact could explain the differences observed between thiadiazine 1,1-dioxides and pyrazoles for the **f** series (Table I).

In most cases, path B gives preferentially the less hindered pyrazole;[10b] in the case of the 3(5)-phenyl-5(3)-methyl derivative **1**, the less hindered **m** isomer is obtained in comparable amounts in both series, but in the case of the 3(5)-methyl derivative **d**, the amount of the less hindered **e** isomer is larger in thiadiazine 1,1-dioxide **1e** than in pyrazole **2e** because the SO_2 group contributes to the steric hindrance around the N_6 nitrogen atom. In the case of the 3(5)-amino derivative **1q**, we have obtained only the 5-substituted isomer **1r** (the N-butylation of 3(5)-aminopyrazole **2q** gives 75% of the isomer **2r**[13]).

(1) García-Muñoz, G.; Ochoa, C.; Stud, M. *J. Heterocycl. Chem.* **1977**, *14*, 431.
(2) Ochoa, C.; Stud, M. *J. Heterocycl. Chem.* **1978**, *15*, 221.
(3) Goya, P.; Molina, C.; Ochoa, C.; Stud, M. *Heterocycles* **1981**, *16*, 5.
(4) Goya, P.; Martínez, P.; Ochoa, C.; Stud, M. *J. Heterocycl. Chem.* **1981**, *18*, 459.
(5) Degering, E. F.; Wilson, J. E. *J. Org. Chem.* **1952**, *17*, 339.
(6) Wright, J. B. *J. Org. Chem.* **1964**, *29*, 1905.
(7) Roe, A. M.; Harbridge, J. B. *Chem. Ind. (London)* **1965**, 182.
(8) Pagani, G. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2050.
(9) Albrecht, H. A.; Blout, J. F.; Konzelmann, F. M.; Plati, J. T. *J. Org. Chem.* **1979**, *44*, 4191.
(10) (a) Coispeau, G.; Elguero, J. *Bull. Soc. Chim. Fr.* **1970**, 2717. (b) Elguero, J.; Jacquier, R. *Ibid.* **1966**, 2832.
(11) Lazaro, R.; Mathieu, D.; Phan Tan Luu, R.; Elguero, J. *Bull. Soc. Chim. Fr.* **1977**, 1163.
(12) Auwers, K. V.; Stuhlmann, H. *Ber.* **1926**, *59*, 1043.

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Table I. Relative Amounts of Isomer III Obtained by Steps A and B

compd	% yield (compd no.)			
	step A ($H_2NYNHBz$)		step B [XMe]	
	R′ = Ph, R″ = Me	R′ = Me, R″ = H	R′ = Me, R″ = H	R′ = Ph, R″ = Me
thiadiazine 1,1-dioxides	70 (1f)	90 (1n)	80 (1e) [IMe], 80 (1e) [SO_4Me_2]	70 (1m) [IMe]
pyrazoles	55 (2f)[a,c]	95 (2n)[b,c]	60 (2e) [IMe], 65 (2e) [SO_4Me_2][d,c]	75 (2m) [IMe][e]

[a] This work (benzylhydrazine dihydrochloride and β-oxobutyraldehyde dimethyl acetal). [b] This work (benzylhydrazine dihydrochloride and benzoylacetone). [c] Proportions of isomers III and IV determined by ^1H NMR on the crude reaction mixture. [d] This work (methylation with dimethyl sulfate in basic medium). [e] Reference 12.

Table II. Proton NMR Results

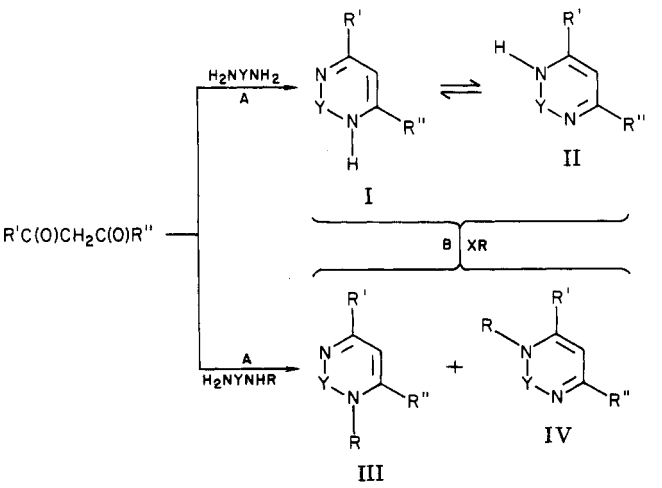
no.	R	R′	R″	solvent	shift, δ H-2	H-3	H-4	H-5	coupling constants, Hz
1a	H	H	H	Me_2SO-d_6	~8.8	7.88	5.94	7.88	$J_{3,4} = J_{4,5} = 5.65$
1b	Me	H	H	C_6D_6	2.54	5.60	4.68	7.15	
				$CDCl_3$	3.54	7.28	5.85	7.94	
				Me_2SO-d_6	3.46	7.79	5.95	8.05	$J_{3,4} = 7.05, J_{4,5} = 4.65, J_{3,5} = 2.55$ $J_{H_3,Me} = 0.75$
				HMPT[a]		8.16	5.96	8.16	
1c	Bz	H	H	C_6D_6	4.42, 7.10	6.30	4.95	7.28	
				$CDCl_3$	4.97, 7.44	7.10	5.78	7.90	
				Me_2SO-d_6	5.03, 7.42	7.92	6.03	8.10	$J_{3,4} = 7.10, J_{4,5} = 4.54, J_{3,5} = 2.38$
				HMPT[a]	5.00, 7.30	8.25	5.99	8.25	
1d	H	Me	H	Me_2SO-d_6	~9.1	7.71	5.85	2.18	$J_{3,4} = 6.25$
1e	Me	Me	H	Me_2SO-d_6	3.43	7.62	5.91	2.22	$J_{3,4} = 7.36$
1f	Bz	Me	H	Me_2SO-d_6	5.00, 7.40	7.73	5.95	2.23	$J_{3,4} = 7.35$
1g	Me	H	Me	Me_2SO-d_6	3.45	2.34	5.96	7.89	$J_{4,5} = 4.86, J_{H_4,Me} = 0.52$
1h	Bz	H	Me	Me_2SO-d_6	5.15, 7.33	2.16	6.06	8.02	$J_{4,5} = 4.85, J_{H_4,Me} = 0.57$
1i	H	Me	Me	Me_2SO-d_6	~10.5	2.11	5.81	2.11	
1j	Me	Me	Me	C_6D_6	2.81	1.30	5.03	1.78	$J_{H_4,Me} = 0.60$
				$CDCl_3$	3.45	2.23	5.76	2.20	$J_{H_4,Me} = 0.60$
				Me_2SO-d_6	3.38	2.27	5.92	2.15	$J_{H_4,Me} = 0.54$
1k	Bz	Me	Me	Me_2SO-d_6	5.19, 7.33	2.21	6.05	2.14	$J_{H_4,Me} = 0.50$
1l	H	Ph	Me	Me_2SO-d_6	~10.1	2.29	6.57	7.5-8.1	$J_{H_4,Me} = 0.52$
1m	Me	Ph	Me	C_6D_6	2.89	1.47	5.99	7.2-8.1	
				Me_2SO-d_6	3.54	2.49	6.86	7.6-8.2	$J_{H_4,Me} = 0.56$
1n	Bz	Ph	Me	C_6D_6	4.70, 7.23	1.36	5.81	7.1-7.8	$J_{H_4,Me} = 0.56$
				$CDCl_3$	5.18, 7.35	2.25	6.42	7.4-8.0	$J_{H_4,Me} = 0.55$
				Me_2SO-d_6	5.36, 7.33	2.39	7.03	7.5-8.2	
1o	Me	Me	Ph	C_6D_6	2.96	7.32	5.47	1.89	
				Me_2SO-d_6	3.43	7.80	6.43	2.50	
1p	Bz	Me	Ph	Me_2SO-d_6	4.93[b]	b	6.30	2.30	
1q	H	NH_2	H	Me_2SO-d_6	~10.8[c]	7.12[c]	5.25[c]	7.32[c]	$J_{3,4} = 8$[c]
					11.1	7.23	5.33	7.62, 7.77	$J_{3,4} = 7.47$
1r	Me	NH_2	H	Me_2SO-d_6	3.27	7.38	5.49	7.49, 7.67	$J_{3,4} = 7.91$

[a] HMPT = hexamethylphosphorotriamide. [b] Both phenyls between 7.1 and 7.5 ppm. [c] Albrecht's values.[9]

Chemical Reactivity. Except for the N-alkylation, we have not studied the reactivity of thiadiazine 1,1-dioxides (that of pyrazoles is well documented[14]). However, a few facts could be summarized as follows. Electrophilic substitution always takes place in position 4 for thiadiazines[8] and pyrazoles.[14a] For N-unsubstituted derivatives, nucleophilic substitution takes place on the NH, for instance, in the addition to formaldehyde (thiadiazines[7] and pyrazoles[14b]). In both series, ring reduction is achieved by catalytic hydrogenation: formation of the pentahydro derivatives from thiadiazines (this paper and ref 6) and formation of pyrazolidines from pyrazoles.[14c]

The main difference between the two series is that thiadiazine 1,1-dioxides are less basic and more acidic (when R = H) than pyrazoles. Due to the high solubility of the thiadiazine 1,1-dioxide sodium salts in water it is not possible to carry out N-alkylations under liquid–liquid phase-transfer catalysis conditions (see Experimental

Scheme I



(13) González, E.; Faure, R.; Vincent, E. J.; Espada, M.; Elguero, J. *Org. Magn. Reson.* **1979**, *12*, 587.

(14) (a) Schofield, K.; Grimmett, M. R.; Keene, B. R. T. "The Azoles"; Cambridge University Press: Cambridge England, 1976; p 31; (b) p 203; (c) p 152.

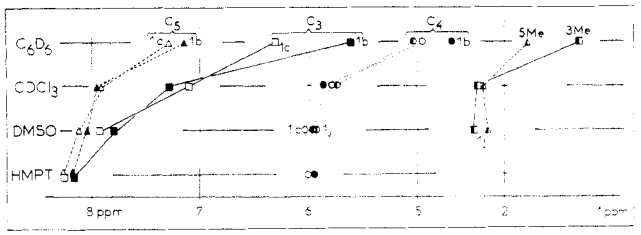


Figure 1. Solvent effects on the proton chemical shifts of compounds **1b,c,j**.

Section), a method that gives excellent results for the preparation of *N*-alkylpyrazoles.[15]

Physicochemical Properties. Proton Magnetic Resonance Studies. The chemical shifts and coupling constants (AX and ABX spectra) of compounds 1 are gathered in Table II. The coupling constants have been measured very carefully several times, and the error can be estimated to ±0.05 Hz. The assignments are based on four criteria: intercomparison, coupling constants, solvent effects, and *C*-phenyl signal multiplicity.

As a consequence of the prototropic exchange, positions 3 and 5 became equivalent and could not be differentiated by proton NMR. Thus, the chemical shifts and coupling constants of N-unsubstituted thiadiazine 1,1-dioxides **1a,d,i,l,q** are mean values (this point will be further discussed under tautomerism). In N-substituted derivatives, $J_{3,4}$ is always larger than $J_{4,5}$, $J_{H,H}$, and $J_{H,Me}$. In the pyrazole series, with N substituents like methyl or benzyl, $J_{3,4} \simeq J_{4,5}$, and only when the substituent on the nitrogen is a powerful electron-withdrawing group (like COMe, SO_2Ph, or 2,4-dinitrophenyl)[16] does $J_{4,5}$ becomes larger than $J_{3,4}$. A first conclusion is that the π system appears more localized in thiadiazine 1,1-dioxides than in pyrazoles, unless the fixation of the pyrrolic lone pair prevents its π delocalization. As in azoles,[17] but with larger values, we have observed a ^4J coupling between the *N*-methyl group and the proton at position 3($^4J_{H,Me}$ = 0.75 Hz, compound **1b**).

Solvent effects provide a useful criterion to assign substituents, proton or methyl, at positions 3 and 5 of N–R pyrazoles.[18] A parallel study of compounds **1b,c,j** has been carried out. Figure 1 resembles the figures obtained for pyrazoles:[18] in both series, the signal corresponding to the substituent (H or Me) contiguous to the NR group is the most sensitive to solvent effects. This method has been applied to **1n**, in order to assign its isomeric structure from the *C*-methyl signal. The value in C_6D_6 (1.36 ppm) is characteristic of a methyl at position 3.

When the C substituent is a phenyl group, the above criteria cannot be applied. Fortunately, the appearance of the phenyl signal at position 5 (two multiplets, H_o and H_m + H_p) is very different from that of the phenyl at position 3 (a singlet, due to the steric hindrance of NR). This method has often been used in *C*-phenylpyrazole derivatives,[16,19,20] and it remains valid for thiadiazine 1,1-dioxides; for instance, the isomers obtained by methylation of **1l** are easily identified by the appearance of the phenyl signal (Me_2SO-d_6 as solvent): **1m**, 7.6–8.2 ppm (phenyl at position 5); **1o**, 7.80 ppm (singlet, phenyl at position 3).

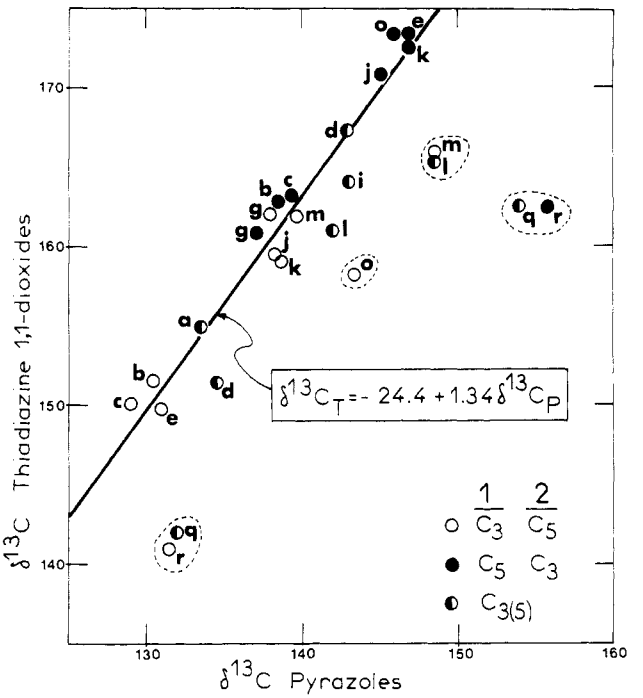


Figure 2. Carbon-13 chemical shifts: thiadiazine 1,1-dioxides vs. pyrazoles.

A remarkable fact is observed in the spectra of the 5-amino compounds **1q** and **1r** in Me_2SO: the amino signal is split into two peaks. the anisochrony of the NH protons is probably due to restricted rotation around the C_5–NH_2 bond accompanied by slow proton exchange, a situation rather common in amides[21] but very unusual in amino heterocycles.

Carbon-13 Magnetic Resonance Studies. Table III contains carbon chemical shifts and Table IV some coupling constants (first-order analysis) of thiadiazine 1,1-dioxides. Carbon-13 chemical shifts provide a very efficient method to identify pairs of isomers. For instance, when position 3 is unsubstituted, the NMe signal appears at about 35 ppm (**1b,e**); the presence of a substituent at position 3 shifts the signal to ~31 ppm (steric effect, **1g,j,m**). Another signal characteristic of the structure is the CMe signal: at position 5 it appears at ~24.5 ppm (**1e,f,j,k,o,p**) and at 3 at ~20 ppm (**1g,h,j,k,m,n**).

The N-unsubstituted derivatives show mean signals due to the prototropic tautomerism. In one case, **1i**, the signal belonging to carbons 3 and 5 appears as a broad peak (Bruker WP-80 at 20 MHz). An increase of the insert temperature (up to 70 °C) produces a considerable narrowing of the peak. For pyrazoles, it is often necessary to cool the sample to observe broad signals.[22,23] However, an experiment carried out under the conditions described by Chenon et al.[22] (HMPT at −17 °C) on product **1d** did not give the expected result (observation of narrow signals corresponding to each tautomer, I and II). At 20 °C in HMPT (Cameca 250 at 62.5 MHz) the product shows signals at 23.2 (Me), 98.8 (C_4), 167.0 (C_3), and 151.6 ppm (C_5), the two last ones being considerably broadened. The spectra registered at −10, −20, and −40 °C show only the

(15) Elguero, J.; Espada, M.; Mathieu, D.; Phan Tan Luu, R. *An. Quim.* **1979**, *75*, 729.
(16) Elguero, J.; Jacquier, R; Tien Duc, H. C. N. *Bull Soc. Chim. Fr.* **1966**, 3727.
(17) Elguero, J.; Fruchier, A.; Könnecke, A. *Monatsh. Chem.* **1980**, *111*, 775.
(18) Elguero, J.; Jacquier, R. *J. Chim. Phys. Phys.-Chim. Biol.* **1966** *63*, 1242.
(19) Lynch, B. M.; Hung, Y. Y. *Can. J. Chem.* **1964**, *42*, 1605.
(20) Tensmeyer, L. G.; Ainsworth, C. *J. Org. Chem.* **1966**, *31*, 1878.
(21) Jackman, L. M. In "Dynamic Nuclear Magnetic Resonance Spectroscopy"; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; p 215.
(22) Chenon, M. T.; Coupry, C.; Grant, D. M.; Pugmire, R. *J. Org. Chem.* **1977**, *42*, 659.
(23) Claramunt, R. M.; Elguero, J.; Marzin, C.; Seita, J. *An. Quim.* **1979**. *75*, 701.

Table III. Carbon-13 Chemical Shifts[a]

no.	R	R'	R''	shift, δ C-2	C-3	C-4	C-5
1a	H	H	H		155.0	98.7	155.0
1b	Me	H	H	36.4	151.4	99.1	162.8
1c	Bz	H	H	52.4 (CH_2), 135.3 (C_i), 127.6 (C_o), 128.3 (C_m), 127.9 (C_p)	150.1	100.3	163.2
1d	H	Me	H		151.4	98.7	167.3, 22.9 (Me)
1e	Me	Me	H	35.8	149.7	99.6	173.6, 24.7 (Me)
1f	Bz	Me	H	52.0 (CH_2), 135.8 (C_i), 128.0 (C_o), 128.6 (C_m), 128.0 (C_p)	148.5	101.2	174.2, 24.8 (Me)
1g	Me	H	Me	31.1	162.0, 20.1 (Me)	100.4	160.8
1h	Bz	H	Me	48.2 (CH_2), 135.5 (C_i), 126.5 (C_o), 128.7 (C_m), 127.7 (C_p)	162.2, 20.1 (Me)	102.2	161.2
1i	H	Me	Me		164.1,[b] 22.2 (Me)	98.8	164.1,[b] 22.2 (Me)
1j	Me	Me	Me	30.6	159.6, 20.0 (Me)	101.0	171.4, 24.6 (Me)
1k	Bz	Me	Me	47.8 (CH_2), 135.8 (C_i), 126.6 (C_o), 128.7 (C_m), 127.6 (C_p)	159.8, 20.0 (Me)	103.1	172.8, 24.7 (Me)
1l	H	Ph	Me		161.0, 20.8 (Me)	96.3	165.4, 134.7 (C_i), 127.6 (C_o), 128.9 (C_m), 132.3 (C_p)
1m	Me	Ph	Me	31.0	162.0, 20.6 (Me)	98.0	166.1, 134.8 (C_i), 127.6 (C_o), 128.9 (C_m), 132.4 (C_p)
1n	Bz	Ph	Me	48.8 (CH_2), 135.3 (C_i), 126.3 (C_o), 128.5 (C_m), 127.4 (C_p)	160.8, 20.4 (Me)	99.6	166.5, 134.1 (C_i), 127.5 (C_o), 128.6 (C_m), 132.4 (C_p)
1o	Me	Me	Ph	34.3	158.2, 137.2 (C_i), 128.2 (C_o), 128.8 (C_m), 131.0 (C_p)	104.3	173.5, 24.7 (Me)
1p	Bz	Me	Ph	50.3 (CH_2), 135.7 (C_i), 126.4 (C_o), 128.7 (C_m), 127.3 (C_p)	157.4, C_i,[c] 128.1 (C_o), 128.0 (C_m), 131.1 (C_p)	107.1	174.4, 24.7 (Me)
1q	H	NH_2	H		142.1	90.4	162.4
1r	Me	NH_2	H	34.8	140.9	90.5	162.5

[a] Hexadeuteriodimethyl sulfoxide as solvent. See structure 1 for numbering. [b] Broad signal; when the sample is heated (70 °C) the signal becomes narrow. [c] Nonassigned.

Table IV. ^1H-^{13}C Coupling Constants

no.	R[a]	coupling constant, Hz C-2	C-3	C-4	C-5
1a	H		^1J = 180.9, ^2J = 4.8, ^3J = 7.1	^1J = 173.7, ^2J = 5.0	^1J = 180.9, ^2J = 4.8, ^3J = 7.1
1b	Me	^1J = 142.7, ^3J = 4.0	^1J = 184.7	^1J = 176.2, ^2J = 1.8, ^3J = 7.2	^1J = 183.3, ^2J = 3.7, ^3J = 8.4
1c	Bz	^1J = 144.3 (CH_2)	^1J = 183.9, ^2J = 5.0, ^3J = 6.5	^1J = 175.8, ^2J = 1.5, ^3J = 7.1	^1J = 183.4, ^2J = 3.6, ^3J = 8.3

[a] R' = R'' = H.

signals at 23.2 and 98.8 ppm; the peaks corresponding to C_3 and C_5 are lost in the base line.

There are two ways to discuss the chemical shifts of Table III: to make a comparison with homologous pyrazoles (Figure 2) or by use of total charge densities (Figure 3). In order to compare carbons C_3 and C_5 (C_4 is almost insensitive to substituents) in series **1** and **2**, we have been compelled to measure some pyrazole derivatives whose chemical shifts in Me_2SO-d_6 were not known.[24]

Clearly, amino derivatives (**q** and **r**) and carbons bearing a phenyl substituent in compounds **l**, **m**, and **o** deviate from the other 19 points. From these last values a correlation could be established (eq 1), introducing twice the values of the equivalent signals of compounds **a** and **i**.

$$\delta(^{13}C_T) = -\delta\ 24.4 + 1.34\delta(^{13}C_P),\ n = 21,\ CC^2 = 0.92 \quad (1)$$

For the deviation of the *C*-phenyl carbons in compounds **l**, **m**, and **o**, two explanations are possible. First, the dihedral angle between the phenyl ring and the heterocycle changes from pyrazole to thiadiazine 1,1-dioxide (six-membered rings are "larger" than five-membered rings), and this modification influences the chemical shift of the *C*-phenyl carbon. Second, the SCS (substituent chemical shift) produced by a phenyl group is different when it is conjugated with an aromatic ring (pyrazole) than when it is conjugated with an unsaturated ring (thiadiazine 1,1-dioxide). Since all the carbons, and not only those bearing an amino group, of compounds **q** and **r** deviate markedly (see Figure 2), a different explanation, which shall be discussed in connection with tautomerism, ought to be postulated.

(24) Carbon chemical shifts (δ) of pyrazoles in Me_2SO-d_6: **2a**;[13] **2b**;[13] **2c**;[25] **2d**, 11.7 (Me), 106.0 (C_4), 134.6 (C_5), 142.7 (C_3); **2e**;[13] **2g**;[13] **2i**, 11.9 (Me), 103.3 (C_4), 143.0 (C_3 and C_5); **2j**;[13] **2k**, 10.8 (Me_5), 13.3 (Me_3), 52.3 (CH_2), 138.7 (C_5), 146.9 (C_3); **2l**, 11.3 (Me), 101.2 (C_4), 142.0 (CMe), 148.5 (CPh); **2m**, 10.7 (CMe), 35.9 (NMe), 102.0 (C_4), 139.6 (C_5), 148.3 (C_3); **2o**, 13.2 (CMe), 36.1 (NMe), 105.1 (C_4), 143.4 (C_5) 146.1 (C_3); 2q;[13] 2r.[13]

(25) Elguero, J.; Espada, M. *An. Quim.* **1979**, *12*, 771.

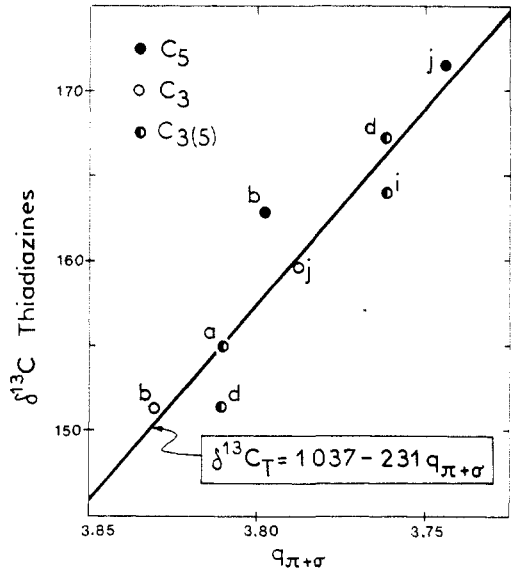


Figure 3. Thiadiazine 1,1-dioxides: carbon-13 chemical shifts vs. total charge densities.

Table V. Experimental and Calculated Dipole Moments of Thiadiazine 1,1-Dioxides

no.	expl (dioxane)	calcd (CNDO/2)	vectorial calcd
1a		7.96	6.25
1b		7.82	6.25
1c	6.22		6.25
1d	6.42	8.62 [3Me (I)]	6.24
		8.64 [5Me (II)]	6.52
1e		7.71[a]	6.24
1f			6.24
1g			6.52
1h			6.52
1i	6.71	9.17, 8.55[a]	6.50
1j	6.70	9.02	6.50
1k	6.64		6.50
1q	7.18	9.07, 8.58[a] [3NH_2 (I)]	6.19
		9.48 [5NH_2 (II)]	7.21

[a] Experimental geometry.

Total charge densities, calculated by the CNDO/2 method by using ideal geometries[26] for compounds **1a,b,d,i,j**,[28] have been compared with the experimental ^{13}C chemical shifts (Figure 3): there is a rough correlation (eq 2).

$$\delta(^{13}C_T) = 1037 - 231\ q_{\pi+\sigma},\ CC^2 = 0.884 \qquad (2)$$

Combining eq 1 and 2, we found a third correlation (eq 3) clearly related to one of the different equations found in pyrazoles[27] (eq 4).

$$\delta(^{13}C_P) = 792 - 172 q_{\pi+\sigma} \qquad (3)$$

$$\delta(^{13}C_P) = 800 - 171 q_{\pi+\sigma} \qquad (4)$$

Dipole Moments. The experimental values for six thiadiazine 1,1-dioxides have been determined in dioxane (Table V). In heteroaromatic compounds, the CNDO/2 calculated dipole moments are in good agreement (±0.3 D) with the experimental ones.[29,30] In this case, the calculated values are over evaluated, either by using ideal or experimental geometries. Presumably the lone-pair repulsions between the N_6 nitrogen atom and the SO_2 group are ill-described by the CNDO/2 method, a problem we have already observed in other sulfur compounds.[31] Vectorial calculations, on the other hand, give quite satisfactory results. The vectorial moment for the SO_2 group (μ_{SO_2} = 5 D) has been calculated[32] from the value of ν_{SO_2} = 1150 cm^{-1} in the infrared spectra (Nujol) of compound

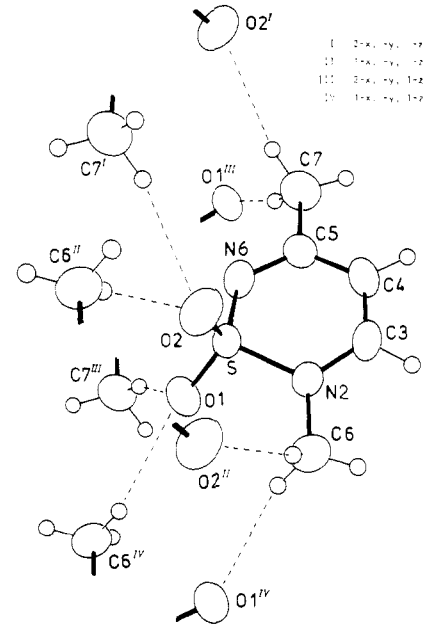


Figure 4. Perpective drawing of the crystal structure of compound **1e**. Some symmetrically related atoms are also shown. Dashed lines represent intermolecular contacts.

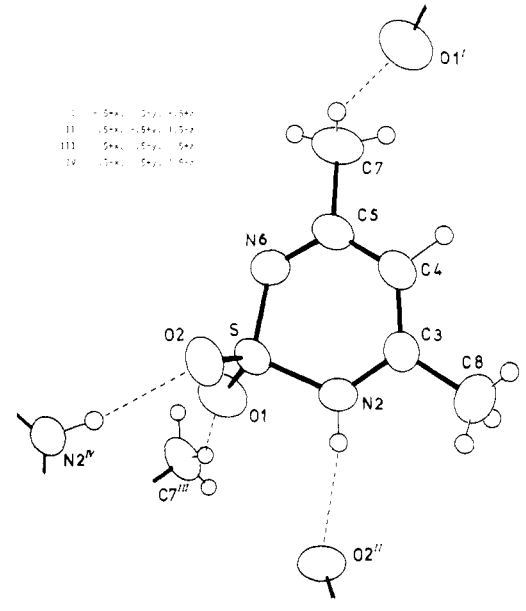


Figure 5. Perspective drawing of the crystal structure of compound **1i**. Some symmetrically related atoms are also shown. Dashed lines represent hydrogen bonds and other intermolecular contacts.

(26) We have shown, in a systematic study of ^{13}C chemical shifts vs. total charge densities,[27] that the use of experimental geometries do not improve the correlation.

(27) Fayet, J. P.; Vertut, M. C.; Fruchier, A.; Tjiou, E. M.; Elguero, J. *Org. Magn. Reson.* **1978**, *11*, 234.

(28) ^{13}C NMR [compound, assignment (δ value)]: **1a**, C_3 (3.8218), C_5 (3.7961), mean value (50:50 mixture) 3.8090; **1b**, C_3 (3.8305), C_5 (3.7968); **1d** (3-methyl tautomer), C_3 (3.7790), C_5 (3.7926); **1d** (5-methyl tautomer), C_3 (3.8208), C_5 (3.7475), mean values (58:42 mixture; see under tautomerism) *C*-methyl (3.7607), CH (3.8090); **1i**, C_3 (3.7794), C_5 (3.7431), mean value (50:50 mixture) 3.7612; **1j**, C_3 (3.7874), C_5 (3.7429).

(29) Mauret, P.; Fayet, J. P.; Fabre, M. *Bull. Soc. Chim. Fr.* **1975**, 1675.

(30) Fayet, J. P.; Vertut, M. C.; Mauret, P.; Claramunt, R. M.; Elguero, J.; Alcalde, A. *Bull. Soc. Chim. Belg.* **1978**, *87*, 189.

(31) Faure, R.; Galy, J. P.; Vincent, E. J.; Elguero, J.; Fayet, J. P.; Mauret, P.; Vertut, M. C. *Bull. Soc. Chim. Fr.* **1977**, 288.

(32) Fayet, J. P.; Robinet, G.; Mauret, P.; Labarre, J. P. *J. Chim. Phys.* **1971**, *68*, 1192.

Table VI. Bond Lengths (Å)

atoms	compds 1e	1i
S-O(1)	1.421 (2)	1.426 (3)
S-O(2)	1.419 (2)	1.426 (3)
S-N(2)	1.672 (2)	1.640 (3)
S-N(6)	1.583 (2)	1.591 (3)
N(2)-C(3)	1.346 (3)	1.358 (4)
N(2)-H		0.82 (4)
N(2)-C(6)	1.471 (4)	
N(6)-C(5)	1.310 (3)	1.310 (4)
C(3)-C(4)	1.356 (4)	1.355 (3)
C(3)-H	0.97 (3)	
C(3)-C(8)		1.488 (4)
C(4)-C(5)	1.404 (3)	1.407 (3)
C(4)-H	0.95 (4)	1.02 (4)
C(5)-C(7)	1.496 (4)	1.502 (5)
C(6)-H(1)	0.96 (3)	
C(6)-H(2)	0.97 (5)	
C(6)-H(3)	0.90 (5)	
C(7)-H(1)	1.05 (5)	0.97 (6)
C(7)-H(2)	0.96 (5)	0.91 (6)
C(7)-H(3)	0.94 (7)	0.99 (5)
C(8)-H(1)		0.94 (5)
C(8)-H(2)		0.82 (6)
C(8)-H(3)		0.90 (6)

1i; the other vectorial moments are literature values.[33]

X-ray Structure Determinations. A single-crystal X-ray analysis was undertaken in order to establish the structure of compounds **1e** and **1i**. Figures 4 and 5 show partial views of the crystal structures of both compounds, the interatomic distances being very similar (Table VI) to the main differences located at the bonds S–N_2, S–N_6, and N_2–C_3. The length S–N_2 of 1.640 Å for compound **1i** is close to the value for a single bond.[34] The somewhat lengthened value of 1.672 Å for this bond in compound **1e** is probably due to the presence of the methyl substituent on N_2. The distances S–N_6 are much closer in both compounds (1.591 and 1.583 Å, respectively). The S–O bond lengths are typical for most thiadiazine 1,1-dioxides carrying functional groups.[9,35,36]

The calculated atomic deviations[37] from the best least-squares planes are listed in Table VII. Both molecular rings can be described as envelopes, the S atoms being at the flaps. This molecular conformation, more or less distorted, seems to be the general rule for most thiadiazine 1,1-dioxide rings, functionalized[9,35,36] or not (this paper).

Some aspects of the crystal packing can be deduced from Figures 4 and 5, where the shortest intermolecular approaches are shown as dashed lines. All these contacts are of the van der Waals type, except in compound **1i** (Figure 5) whose molecules are also held together through hydrogen bonds of the type N_2–H···O_2, implying distances N_2···O_2 = 2.904 Å and H···O_2 = 2.09 Å with an angle at the H atom to 171°.

It is interesting to compare the experimental bond lengths and the bond orders calculated by the CNDO/2 method by using the experimental geometries.

From Table VIII, the relationships shown in eq 5–8 could be calculated.

$$d_{SO}\ (Å) = 2.48 - 0.50p_{SO},\ CC^2 = 1 \quad (5)$$

$$d_{SN}\ (Å) = 1.95 - 0.27p_{SN},\ CC^2 = 0.893 \quad (6)$$

$$d_{CN}\ (Å) = 1.50 - 0.12p_{CN},\ CC^2 = 0.980 \quad (7)$$

$$d_{CC}\ (Å) = 1.55 - 0.12p_{CC},\ CC^2 = 0.894 \quad (8)$$

The two last ones are comparable to those previously established for benzazoles by using likewise similar crystal bond lengths[38] (eq 9 and 10).

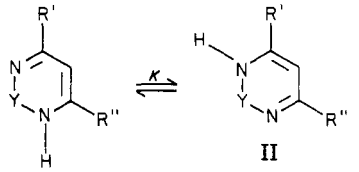
$$d_{CN}\ (Å) = 1.45 - 0.18p_{CN} \quad (9)$$

$$d_{CC}\ (Å) = 1.51 - 0.18p_{CC} \quad (10)$$

It is also interesting to compare the N–C and C–C bond lengths, determined by X-ray crystallography, for thiadiazine 1,1-dioxide and pyrazole rings. In thiadiazine 1,1-dioxides (Table VIII) there are differences between "single" and "double" bonds (single to double bond ratio about 1.035) whereas in pyrazole[39] there is no significant difference.

Aromaticity. Several times we have encountered problems related to the "aromaticity" of thiadiazine 1,1-dioxides: proton–proton coupling constants indicating a π localization, bond lengths and bond orders showing an alternance of "single" and "double" bonds, nonplanarity of the ring. As a consequence of the presence of the SO_2 bridge between the nitrogen atoms the "pyrazolic aromaticity"[40] is suppressed, but the N_2—C_3=C_4—C_5=N_6 system is clearly conjugated.

Tautomerism. The tautomerism of thiadiazine 1,1-dioxides is at the core of this study in relation with the tautomerism of pyrazoles.[13,41a]



I II

$$K = [I]/[II]$$

Being unable to sufficiently slow down the tautomeric rate to measure directly by NMR the equilibrium constant (as Grant did for pyrazoles),[22] we must use interpolation methods.[41b] The percentage of tautomer I when R′ = Me and R″ = H is given by the eq 11. P_d is the property of

$$\%\ \text{I (5-methyl tautomer)} = \frac{(P_d + \Delta P) - P_g}{P_e - P_g} \times 100 \quad (11)$$

compound **1d**, ΔP is the effect of the *N*-methyl group on *P* (calculated from **1b** and **1a** or **1j** and **1i**), and P_e and P_g are the properties of the fixed derivatives III (**1e**) and IV (**1g**). The method works well when $\Delta P/P_e - P_g$) is small.

Usually proton chemical shifts are unsuitable for tautomeric studies,[41c] and proton–proton coupling constants ought to be preferred. Carbon-13 NMR gives better re-

(33) To the pyrrolic fragment, C–NH–C, has been assigned the experimental value of pyrrole itself (1.80 D) along the N–H bond, as has been the C–NMe–C fragment (1.90 D). To the pyridinic fragment, C–N–C, has been assigned the moment (2.20 D) of pyridine itself, oriented from the nitrogen atom toward the lone pair.[29]

(34) Gillespie, R. J.; Ireland, P. R.; Wekris, J. E. *Can. J. Chem.* **1975**, *53*, 3147.

(35) Esteban-Calderon, C.; Martinez-Ripoll, M.; Garcia-Blanco, S. *Acta. Crystallogr., Sect. B* **1979**, *B35*, 2795.

(36) Cabezuelo, M. D.; Cano, F. H.; Foces-Foces, C.; García-Blanco, S. *Acta Crystallogr., Sect.* B **1977**, *B33*, 3588 and references cited therein.

(37) Nardelli, M.; Musatti, A.; Domiano, P.; Andreatti, G. *Ric. Sci.* **1965**, 807.

(38) Escande, A.; Lapasset, J.; Faure, R.; Vincent, E. J.; Elguero, J. *Tetrahedron* **1974**, *30*, 2903.

(39) Berthou, J.; Elguero, J.; Rérat, C. *Acta Crystallogr., Sect. B* **1970**, *B26*, 1880.

(40) Cook, M. J.; Katritzky, A. R.; Linda, P. *Adv. Heterocycl. Chem.* **1974**, *17*, 299.

(41) (a) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. "The Tautomerism of Heterocycles"; Academic Press: New York, 1976; p 269; (b) p 29; (c) p 42; (d) p 47; (e) p 33; (f) p 423; (g) p 272; (h) p 291.

Table VII. Atomic Deviations (Å) from Least-Squares Planes[a]

	compd			compd	
plane 1[b]	1e	1i	plane 2[b]	1e	1i
C(3)	−0.016 (3)	−0.015 (3)	S	0.000 (1)	−0.000 (1)
C(4)	0.030 (3)	0.042 (3)	O(1)	0.000 (2)	−0.000 (3)
C(5)	−0.020 (2)	−0.038 (3)	O(2)	−0.000 (2)	−0.000 (3)
N(2)	0.001 (2)	−0.002 (3)			
N(6)	0.009 (2)	0.017 (3)			
S*	0.328 (1)	0.405 (1)			
O(1)*	−0.578 (2)	−0.382 (3)			
O(2)*	1.707 (2)	1.815 (3)			
C(6)*	−0.113 (3)				
C(7)*	−0.148 (4)	−0.230 (5)			
C(8)*		−0.175 (5)			

[a] Asterisked atoms are not included in the plane calculations. [b] Angles between planes 1 and 2: **1e**, 89.63°; **1i**, 90.48°.

Table VIII. Bond Lengths (d) and Bond Orders (p) of Thiadiazine 1,1-Dioxides 1e and 1i

	S-O		S-N		C-N		C-C	
compd	d, Å	p	d, Å	p	d, Å	p	d, Å	p
1e	1.421	2.12	1.672 (N_2)	1.09	1.346 (N_2-C_3)	1.21	1.356 (C_3-C_4)	1.63
			1.583 (N_6)	1.34	1.310 (N_6-C_5)	1.55	1.404 (C_4-C_5)	1.18
1i	1.426	2.11	1.640 (N_2)	1.09	1.358 (N_2-C_3)	1.18	1.355 (C_3-C_4)	1.57
			1.591 (N_6)	1.35	1.310 (N_6-C_5)	1.53	1.407 (C_4-C_5)	1.19

Table IX. Study of the Tautomerism of Compound 1d

	compd						
	1a	1b[a]	1i	1j[a]	1d	1e	1g
$^3J_{HH}$, Hz	5.65	5.85			6.25	7.36	4.86
δ ^{13}Me			22.2	22.3	22.9	24.7	20.1
δ ^{13}CMe			164.1	165.5	167.3	173.6	162.0
δ ^{13}CH	155.0	157.1			151.4	149.7	160.8
μ[c]					6.42	6.24[b]	6.52[b]

ΔP, Hz	$\lvert P_e - P_g \rvert$, Hz	$\Delta P/(P_e - P_g)$	% I (5-Me tautomer)
0.20	2.5	0.08	64
0.1	4.6	0.02	63
1.4	11.6	0.12	58
2.1	11.1	0.19	66, 36

[a] Mean value (50:50 mixture). [b] Vectorially calculated dipole moment for the NH tautomer. [c] Dipole moment in debyes.

sults.[41d] In the case of compound **1d**, three carbon atoms can be used: the *C*-methyl carbon and carbons C_3 and C_5.

The results obtained by the four methods (Table IX) give 60–65% of tautomer I (R′ = CH_3, R″ = H) for compound **1d** in Me_2SO-d_6. The ratios $\Delta P/(P_e - P_g)$ are comparable; remarkably enough is the result obtained with $^3J_{H,H}$ [$\Delta P/(P_e - P_g) = 0.08$], a consequence of the localization of the π system. In the pyrazole series[16] ($\Delta P = 0.25$ Hz and $J_e - J_g = 0.3$ Hz) the ratio (0.83) reveals the impossibility to apply this method to pyrazoles.

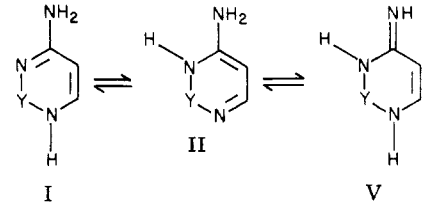
Dipole moments (using $P = \mu^2$)[41e] are often used in tautomeric studies. In Table IX we have compared the experimental value for compound **1d** (6.42^2 D^2) with the vectorially calculated values for both tautomers (6.24^2, 6.52^2 D^2). The result, 36%, is probably not significant because $|P_e - P_g|$ (3.6 D^2) is too small. An experimental error less than 0.1 D on μ (**1d**; 6.34 instead of 6.42 D) gives 64% of tautomer I; an error of the same order of magnitude in the calculated values completely modifies the percentage.

In the case of thiadiazine 1,1-dioxide **1l**, it is unnecessary to carry out interpolation calculations since the Me, CMe, and CPh chemical shifts of compounds **1l** and **1m** are almost identical and quite different from the chemical shifts of the other fixed derivative **1o**. Thus the tautomeric equilibrium between the I (3-methyl 5-phenyl) and II (3-phenyl 5-methyl) thiadiazine 1,1-dioxides is largely shifted toward I.

All these results justify a posteriori the direct comparison between ^{13}C chemical shifts of N-unsubstituted derivatives **1d–2d** and **1m–2m**.

Finally, the more complicated problem of the amino derivative **1q** is discussed.

Comparison of ^{13}C NMR spectra of **1q** and **1r** shows a close analogy. Presumably in Me_2SO-d_6, the tautomer II (eq 12) represents only a small contribution. In the solid



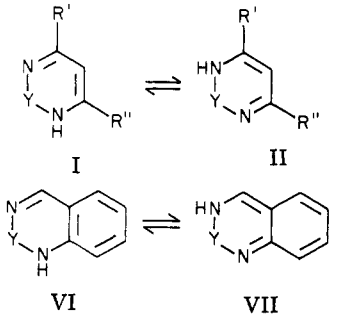
I II V (12)

state, Albrecht[9] has shown inequivocably (X-ray structure) that the isomer I is the only present in the crystal (localization of the three N–H protons). The $^3J_{H,H}$ coupling constant (7.47 Hz) is also in agreement with structure I, by comparison with **1r** ($^3J_{H,H}$ = 7.91 Hz) even if we do not know the value for the 2-methyl 3-amino derivative. However, there is a series of anomalies in this case: both **1q** and **1r** behave anormally in Figure 2, the vectorially calculated moment for tautomer I differs greatly with the experimental value (6.19 instead of 7.18 D), and the cal-

culated charge densities do not correlate with ^{13}C chemical shifts. All these facts can be explained taking into account the imino tautomer V. Normally, in amino derivatives of heterocycles, the amino tautomer predominates largely (that is the case for pyrazoles),[41f] but this is valid only when the heterocycle is "aromatic". The "nonaromaticity" of thiadiazine 1,1-dioxides justifies the relative stability of tautomer V. So our conclusion is that compound **1q** is a mixture of tautomers I and V.

It is now possible to make some comparisons between thiadiazine 1,1-dioxides 1 and pyrazoles 2 with regard to tautomerism.

For R′ = Me and R″ = H, the proportion of tautomer I rose to 60–65% for the thiadiazine and only 46% for the pyrazole; the small difference between both equilibrium constants ($\Delta\Delta G_{25} \simeq 0.3$ kcal mol^{-1}) can be related to the fact that the value for 1 has been determined in Me_2SO at 28 °C, and those for 2 were determined in HMPT at −17 °C.[42] For R′ = Ph and R″ = Me, in both series there is more than 80% of tautomer I (for 2, see ref 41g). For R′ = NH_2 and R″ = H (putting aside the problem of the existence of the imino tautomer V in the case of the thiadiazine), the equilibrium I ⇌ II lies strongly on the side of tautomer I (for 2, see ref 41f). Finally, in the case of the benzologues, tautomer VI (eq 13) is the most stable both for thiadiazines[43] and for pyrazoles.[41h]

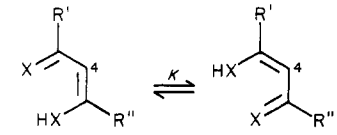


I II

VI VII (13)

Conclusion

The analogies and differences between thiadiazine 1,1-dioxides and pyrazoles are one example of the more general case where Y is any bridge between the two nitrogen atoms: o-C_6H_4, benzodiazepines, CH_2CH_2, diazepines, CH_2, dihydropyrimidines, CO, pyrimidones, etc. The breaking of the π loop destroys the "aromaticity", but our heuristic hypothesis is that the reactivity of position 4 will remain unchanged, the ^{13}C chemical shifts will be proportional, and the tautomeric equilibrium constants will be almost unchanged. The conclusion concerning tautomerism is probably valid for the influence of the nature of R′ and R″ on the equilibrium constant in alicyclic compounds (eq 14) like β-diketones, β-keto esters, β-keto amides, and their



(14)

X = O, NR, S

thio and amino derivatives. If this is true, then the conclusion concerning the annular tautomerism of pyrazoles[13] is valid for a whole series of compounds (eq 15).

$$\log K/K_0 = a\Delta\sigma_I + b\Delta\sigma_R \text{ with } a > 0,\ b < 0, \text{ and } |a| > |b| \quad (15)$$

(42) Grant's[22] results in HMPT at −17 °C (direct determination by ^{13}C NMR, integrated intensities of the methyl signals).
(43) Pews, R. G. *J. Heterocycl. Chem.* **1979**, *16*, 1069.

Experimental Section

General Methods. Melting points were determined in a Kofler apparatus and are uncorrected. Proton NMR spectra were recorded at 90 MHz on a Varian EM-390 spectrometer or at 250 MHz on a Cameca 250 spectrometer. Carbon-13 NMR spectra were recorded at 15.1 MHz on a Bruker WP-60-DS or at 25 MHz on a Varian XL-100 spectrometer. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The electrical dipole moments were measured in dioxane at 25 °C. The Debye formula was used as the Halverstadt and Kumler extrapolation method[44] for the calculations of total polarization. The ring geometry used in CNDO/2 calculations is as follows: SO, 1.435 Å; C=N, 1.43 Å; CC and CN, 1.47 Å; NH, 0.89 Å; CH, 1.00 Å; O–S–O, 115.1°; N–S–N, 105.6° (for the methyl substituents: CH, 1.10 Å; C–Me, 1.52 Å; N–Me, 1.48 Å).

Compound **1e** ($C_5H_8N_2O_2S$) crystallizes in the space group $P2_1/c$ with four molecules in a cell of dimensions a = 9.390 (1) Å, b = 10.452 (1) Å, c = 7.3152 (4) Å, and β = 94.64 (1)°. The molecular weight is 160.21 g mol^{-1}, and the calculated density is 1.49 g cm^{-3}. Compound **1i** ($C_5H_8N_2O_2S$) crystallizes in the space group $P2_1/n$ with four molecules in a cell of dimensions a = 12.699 (1) Å, b = 7.227 (1) Å, c = 7.923 (1) Å, and β = 92.42 (1)°. The molecular weight is the same as in compound **1e**, and the calculated density is 1.46 g cm^{-3}. The intensities of 2073 (for **1e**) and 2127 (for **1i**) independent reflexions up to θ = 30° were measured on a computer-controlled four-circle diffractometer. Graphite-monochromated Mo Kα radiation (λ = 0.710 69 Å) and the $\omega/2\theta$ scan technique were used. No crystal decomposition was observed during the data collection process. The data were corrected for absorption[45] effects (μ = 3.85 cm^{-1} for **1e** and 3.79 cm^{-1} for **1i**). After correction for Lorentz and polarization factors, 1332 (**1e**) and 1036 (**1i**) reflections were considered as observed with the criterion $I > 4\sigma(I)$ and were used in the subsequent calculations. Scattering factors for neutral atoms and anomalous dispersion corrections for S were taken from the literature.[46] Both crystal structures were solved by using the multisolution tangent formula approach with the program MULTAN.[47] Most of remaining calculations were performed with the X-ray 70 System.[48] The structures were first refined anisotropically with unit weights. The hydrogen atoms were located on a difference map with those reflexions within sin $\theta/\lambda < 0.5$ Å^{-1}. A convenient weighting scheme[49] was selected to prevent bias in $\langle w\Delta^2F\rangle$ vs. $\langle \sin\theta/\lambda\rangle$ and vs. $\langle F_o\rangle$. Several cycles of weighted anisotropic refinement (fixed isotropic thermal parameters for H atoms) gave the following unweighted and weighted discrepancy indices: R = 0.033 and R_w = 0.038 for compound **1e** and R = 0.041 and R_w = 0.047 for compound **1i**.

Reactions between Sulfamide or Benzylsulfamide and β-Dicarbonyl Compounds. Dry hydrogen chloride was bubled for 15 min through a solution of the sulfamide (50 mmol) and the corresponding β-dicarbonyl compound (50 mmol) in 50 mL of absolute ethanol. The reaction mixture was refluxed for 6 h and the solvent evaporated to dryness under reduced pressure.

(i) Sulfamide and Malonaldehyde Tetramethyl Acetal. The syrup thus obtained could not be purified by column chromatography to give an analytical sample of 2*H*-1,2,6-thiadiazine 1,1-dioxide (**1a**): IR (Nujol) 3200, 1640, 1340, 1160 cm^{-1}. However, its ^1H and ^{13}C NMR spectra showed only the signals expected for **1a**. Furthermore, this sample was made to react with methyl iodide to afford exclusively compound **1b**.

(44) Halverstadt, I. F.; Kumler, W. D. *J. Am. Chem. Soc.* **1942**, *64*, 2988.
(45) Schwarzenbach, D. "ORABS Program"; Technische Hochschule University of Zürich, 1972.
(46) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 72–98.
(47) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declercq, J. P. "MULTAN"; Physics Department, University of York: York, England 1977.
(48) Stewart, J. M.; Kundell, F. A.; Baldwin, J. C. "The X-ray 70 System"; Computer Science Center, University of Maryland: College Park, MD, 1970.
(49) Martínez-Ripoll, M.; Cano, F. H. "PESOS Program"; Instituto Rocasolano, CSIC: Madrid, Spain, 1975.

(ii) Sulfamide and β-Oxobutyraldehyde Dimethyl Acetal. The residue was recrystallized from ethyl acetate–hexane to give 5.4 g (75%) of 5-methyl-2*H*-1,2,6-thiadiazine 1,1-dioxide (**1d**) as white needless: mp 97 °C; IR (Nujol) 3250, 1625, 1310, 1150 cm^{-1}.

Anal. Calcd for $C_4H_6N_2O_2S$: C, 32.87; H, 4.10; N, 19.17. Found: C, 32.94; H, 3.80; N, 18.85.

(iii) Benzylsulfamide and β-Oxobutyraldehyde Dimethyl Acetal. The ^1H NMR spectrum of the residue showed the signals corresponding to a mixture of 2-benzyl-5-methyl-1,2,6-thiadiazine 1,1-dioxide (**1f**, 72%) and 2-benzyl-3-methyl-1,2,6-thiadiazine 1,1-dioxide (**1h**, 28%). The mixture was crystallized from ethanol to give 5.2 g (40%) of pure **1f** as white needless: mp 104 °C; IR (Nujol) 1610, 1335, 1175 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.68; H, 5.08; N, 11.65.

By fractioned crystallization of the residue from ethanol, 0.9 g (7%) of **1h** was obtained as white plates: mp 98–99 °C; IR (Nujol) 1600, 1325, 1175 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.08; N, 11.86. Found: C, 55.87; H, 5.23; N, 12.01.

(iv) Benzylsulfamide and Benzoylacetone. In this case the reaction mixture had to be refluxed for 24 h to yield a mixture of 2-benzyl-3-phenyl-5-methyl-1,2,6-thiadiazine 1,1-dioxide (**1p**, 10%) and 2-benzyl-5-phenyl-3-methyl-1,2,6-thiadiazine 1,1-dioxide (**1n**, 90%) as shown by its ^1H NMR spectrum. Crystallization of the mixture from ethanol afforded 9.7 g (60%) of pure **1n** as white rods: mp 119–120 °C; IR (Nujol) 1610, 1340, 1175 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.33; H, 5.33; N, 9.28.

Compound **1p** was isolated pure from the residue after crystallization of **1n** by TLC (silica gel, 4:1 hexane–ethyl acetate as eluent, two runs): R_f of **1n** 0.13, R_f of **1p** 0.24; mp 85 °C (ethanol); IR (Nujol) 1595, 1365, 1180 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.42; H, 4.98; N, 9.20.

Alkylation Reactions. (i) With Diazomethane. To a solution of the corresponding thiadiazine (10 mmol) in 100 mL of ethyl acetate was added an excess of ethereal solution of diazomethane. After 3 h the solution was evaporated to dryness.

(ii) With Methyl Iodide. A stirred solution of the thiadiazine (10 mmol) in acetone (70 mL) was treated with potassium carbonate (5 g) and methyl iodide (30 mmol). The mixture was refluxed for 4 h and then evaporated to dryness after the precipitate was filtered off.

(iii) With Dimethyl Sulfate. To a stirred solution of the thiadiazine (10 mmol) in 1 N sodium hydroxide (50 mL) was added dimethyl sulfate (1.5 mL, 15 mmol) dropwise. The mixture was stirred for 6 h and then extracted with ethyl acetate (2 × 50 mL). The extract was dried over sodium sulfate and evaporated to dryness.

(iv) With Benzyl Chloride. To a solution of the thiadiazine (10 mmol) in 50 mL of 1 N sodium hydroxide was added benzyl chloride (10 mmol). The mixture was stirred at room temperature for 12 h, and no reaction was observed. Thus more benzyl chloride (10 mmol) was added, and the mixture was refluxed for 12 h. The organic compounds were extracted from the aqueous medium with ethyl acetate. The extracts were dried over sodium sulfate, and the solvent was evaporated.

(v) With Benzyl Chloride by Using Phase-Transfer Catalysis. To a solution of sodium hydroxide (20 g) in water (20 g) were added the thiadiazine (30 mmol) and tetrabutylammonium bromide (4 mg). This mixture was treated with a solution of benzyl chloride (30 mmol) in 150 mL of dry toluene. The mixture was vigorously stirred and refluxed for 6 h. The organic layer was separated from the mixture and dried over sodium sulfate. The solvent was evaporated.

Reaction of 1a with Methyl Iodide. The syrup obtained was purified by TLC (silica gel, 9:1 chloroform–ethanol as eluent) and the product crystallized from ethanol to give 1 g (70%) of 2-methyl-1,2,6-thiadiazine 1,1-dioxide (**1b**): mp 76–77 °C; IR (Nujol) 1615, 1330, 1185 cm^{-1}.

Anal. Calcd for $C_4H_6N_2O_2S$: C, 32.87; H, 4.10; N, 19.17. Found: C, 32.77; H, 4.39; N, 19.45.

Reactions of 1d. (i) With Diazomethane. A mixture of 2,5-dimethyl-1,2,6-thiadiazine 1,1-dioxide (**1e**, 66%) and 2,3-dimethyl-1,2,6-thiadiazine 1,1-dioxide (**1g**, 34%) was obtained; the relative amounts of both isomers were measured by ^1H NMR spectroscopy. The mixture was crystallized from ethanol to yield 0.8 g (50%) of pure **1e**: mp 109 °C; IR (Nujol) 1625, 1340, 1180 cm^{-1}.

Anal. Calcd for $C_5H_8N_2O_2S$: C, 37.50; H, 5.00; N, 17.50. Found: C, 37.27; H, 5.09; N, 17.34.

Compound **1g** has not been isolated pure.

(ii) With Methyl Iodide. A mixture of **1e** (82%) and **1g** (18%) was obtained. From this mixture 1 g (64%) of **1e** was isolated by crystallization from ethanol. The compound was identical in all respects with the one obtained above.

(iii) With Dimethyl Sulfate. A mixture of **1e** (79%) and **1g** (21%) was obtained. From this mixture **1e** was isolated as above.

Reaction of 3-Methyl-5-phenyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (11)[8] with Methyl Iodide. A mixture of 2,3-dimethyl-5-phenyl-1,2,6-thiadiazine 1,1-dioxide (**1m**, 70%) and 2,5-dimethyl-3-phenyl-1,2,6-thiadiazine 1,1-dioxide (**1o**, 30%) was obtained. The relative amounts of both isomers were measured as above. Crystallization of this mixture afforded pure **1m**: mp 146 °C (ethanol), (lit.[8] mp 147 °C); IR (Nujol) 1570, 1320, 1175 cm^{-1}.

Compound **1o** was isolated pure from the residue after crystallization of **1m** by TLC (silica gel, 2:1 hexane–ethyl acetate as eluent): R_f of **1m** 0.16, R_f of **1o** 0.42; mp 130 °C; IR (Nujol) 1590, 1340, 1170 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.08; N, 11.86. Found: C, 56.08; H, 4.97; N, 11.60.

Reaction of 5-Amino-2*H*-thiadiazine 1,1-Dioxide (1q)[9] with Methyl Iodide. In the reaction residue, only the 2-methyl-5-amino isomer was present. Upon crystallization from ethanol, 1.35 g (84%) of 2-methyl-5-amino-1,2,6-thiadiazine 1,1-dioxide (**1r**) was isolated as yellow needless: mp 205–207 °C; IR (Nujol) 3460, 3400, 3340, 3240, 1640, 1350, 1140 cm^{-1}.

Anal. Calcd for $C_4H_7N_3O_2S$: C, 29.81; H, 4.34; N, 26.08. Found: C, 29.98; H, 4.44; N, 25.88.

Benzylation of 3,5-Dimethyl-2*H*-1,2,6-thiadiazine 1,1-Dioxide (1i).[5] Attempts to benzylate compound **1i** by both methods described above were unsuccessful.

Catalytic Hydrogenation of 2-Benzyl-1,2,6-thiadiazine 1,1-Dioxide (1c).[7] A solution of **1c** (10 mmol) in 50 mL of ethanol was hydrogenated with 30 psi of hydrogen in the presence of platinum oxide catalyst at 60 °C. After 3 h the catalyst was filtered off and the solvent evaporated to dryness. The residue was recrystallized from ethyl acetate–cyclohexane to yield 1.20 g (80%) of 2,3,4,5,6-pentahydro-1,2,6-thiadiazine 1,1-dioxide as white needless: mp 115 °C; IR (Nujol) 3300, 3150, 1340, 1175 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.3–1.7 (m, 2 H), 3.2–3.5 (m, 4 H), 6.4 (br s, 2 H, NH).

Anal. Calcd for $C_3H_8N_2O_2S$: C, 26.47; H, 5.92; N, 20.58. Found: C, 26.49; H, 5.96; N, 20.65.

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Registry No. **1a**, 61403-64-3; **1b**, 79991-28-9; **1c**, 717-41-9; **1d**, 79991-29-0; **1e**, 79991-30-3; **1f**, 79991-31-4; **1g**, 79991-32-5; **1h**, 79991-33-6; **1i**, 697-44-9; **1j**, 79991-34-7; **1k**, 723-40-0; **1l**, 4475-62-1; **1m**, 54696-86-5; **1n**, 79991-35-8; **1o**, 54696-45-6; **1p**, 79991-36-9; **1q**, 71565-67-8; **1r**, 79991-37-0; **2e**, 694-48-4; **2f**, 73882-45-8; **2n**, 79991-38-1; 2,3,4,5,6-pentahydro-1,2,6-thiadiazine 1,1-dioxide, 67104-89-6; sulfamide, 7803-58-9; malonaldehyde tetramethyl acetal, 102-52-3; β-oxobutyraldehyde dimethyl acetal, 5436-21-5; benzylsulfanide, 14101-58-7; benzoylacetone, 93-91-4; benzylhydrazine dihydrochloride, 20570-96-1.

Supplementary Material Available: Listings of atomic coordinates, anisotropic thermal parameters, bond angles, torsion angles, intermolecular contacts, and experimental dipole moments calculations (9 pages). Ordering information is given on any current masthead page.