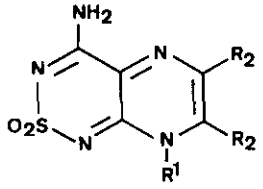
TAUTOMERISM IN PYRAZINO[2,3-c]-1,2,6-THIADIAZINE 2,2-DIOXIDES

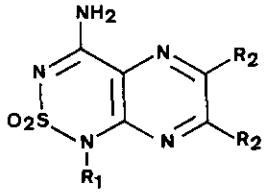
Pilar Goya, Angela Herrero, M.ª Luisa Jimeno
Carmen Ochoa,* and Juan Antonio Páez
Instituto de Química Médica (C.S.I.C.)
Juan de la Cierva, 3. 28006 Madrid, Spain

Félix Hernández Cano, Concepción Foces-Foces,
and Martín Martínez Ripoll
UEI de Cristalografía, Instituto Rocasolano (C.S.I.C.)
Serrano, 119. 28006 Madrid, Spain

Abstract-Tautomerism of pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxides has been studied, in solution, by uv, ^{13}C-, and natural abandance ^{15}N-nmr spectroscopies and in the solid state by X-ray crystallography. The 1-NH tatutomer is present in solid state and in the majority of solvents. Depending on the 6,7-substituent, the 8-NH tautomer is preferred in water solution. An improved synthesis of 6,7-diaryl substituted pyrazinothiadiazine derivatives is described.

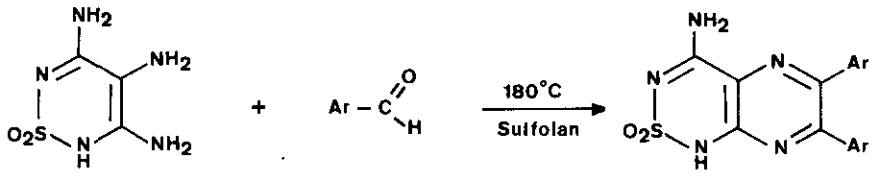
In previous work[1], we concluded that 4-aminopyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (**1**), and its 6,7-dimethyl (**2**) and 6,7-diphenyl (**6**) derivatives existed in water solution as the 8-NH tautomers. However, the ^{15}N-nmr spectra of compounds **2** and **6** suggest that the 1-NH tautomers are present in DMSO solution. In order to clarify the tautomerism of this kind of compounds, uv, ^{13}C- and ^{15}N-nmr spectroscopic studies on several 6,7-disubstituted pyrazinothiadiazine derivatives were carried out using different solvents. Compound **2** was analyzed by X-ray crystallography in order to verify which tautomer was present in solid state.
The syntheses of some of the compounds studied have been described elsewhere[1,2]. The 6,7-di(p-tolyl) derivative **7** was prepared using an improved method by which compound **8** was also synthesized.





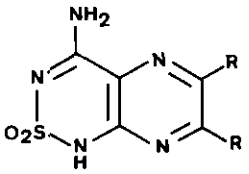
1	$R_1 = R_2 = H$	3	$R_1 = H$, R_2 = 2-thienyl
2	$R_1 = H$, $R_2 = Me$	4	$R_1 = H$, $R_2 = p-NO_2$-phenyl
6	$R_1 = H$, R_2 = phenyl	5	$R_1 = H$, $R_2 = p-Cl$-phenyl
7	$R_1 = H$, $R_2 = p$-tolyl	9	$R_1 = R_2 = Me$
8	$R_1 = H$, $R_2 = p$-MeO-phenyl	10	$R_1 = Me$, $R_2 = p-Cl$-phenyl
11	$R_1 = Me$, $R_2 = H$		
12	$R_1 = Me$, $R_2 = p-Cl$-phenyl		

Reaction of triamino derivative **13**[3] with suitable arylaldehydes in dry tetramethylenesulfone (sulfolan) at 180°C afforded the corresponding 6,7-diarylpyrazinothiadiazine derivatives. With respect to the procedure described before[2], the yield of pyrazinothiadiazine derivatives was increased from 50% to 80%. N-Methyl derivatives **10** and **12** were synthesized from compound **5** by reaction with dimethyl sulfate in alkali medium. This reaction afforded a mixture of 1-methyl and 8-methyl derivatives. Although the 8-methyl derivative was obtained in low yield, it could be isolated by flash chromatography. The 3-methyl derivative was not detected in the reaction mixture; its formation is not probable due to the steric hindrance of the 3-position.

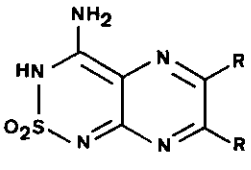


13

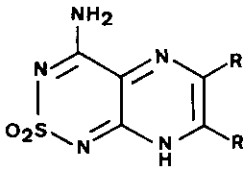
Concerning the annular tautomerism, three forms of 4-aminopyrazino 2,3-c -1,2,6-thiadiazine 2,2-dioxides, 1-NH (A), 3-NH (B) and 8-NH (C), are possible.



A



B



C

Concerning functional tautomerism, in which the NH_2 group is involved, there is a strong preference of the amino over the tautomeric iminodihydro structures, as found for most heterocyclic ring systems[4]. In fact, the 4-amino group appears as a primary amine in the ^{15}N-nmr spectra.

^1H-Nmr spectroscopy is not a useful tool to distinguish the proper structure among the three depicted tautomeric forms. However, ^{13}C- and ^{15}N-nmr are suitable techniques for this purpose, with the help of N-methyl derivatives **9**, **10**, **11** and **12**, used as suitable models to check the existence of 1-NH and 8-NH tautomers.

The ^{13}C-nmr data of the pyrazine and thiadiazine ring carbons of the compounds studied are gathered in Table 1. Assignments were based on reported data[2,5] and signal multiplicity.

TABLE 1

^{13}C-NMR DATA[a] OF PYRAZINOTHIADIAZINE RINGS

Compd.	C-4	C-4a	C-6	C-7	C-8a	N-Me (1)	N-Me (8)
2[b]	158.6	118.5	145.5	158.1	146.1	-	-
5[b]	158.3	120.2	144.2	154.8	147.1	-	-
5[c]	160.0	121.7	146.6	157.0	148.7	-	-
5[d]	159.5	121.4	146.0	156.4	148.4	-	-
7[b]	158.7	119.7	145.7	156.1	146.9	-	-
9[e]	158.7	119.7	144.9	158.1	147.0	27.8	-
10[b]	158.5	121.4	143.7	154.6	147.9 (q) ^3J=2.9	28.6	-
11[b]	156.0	127.7 (m)	125.4 (dd) ^1J=94.3 ^2J=5.4	138.3 d.d.q. ^1J=93.0 ^2J=13.7 ^3J=3.6	146.7	-	36.5
12[b]	156.3	125.9	130.0	145.7 (q) ^3J=3.6	145.8	-	36.6

[a] Chemical shifts in ppm and J in Hz. [b] In DMSO-d_6. [c] In MeOD. [d] In acetone-d_6. [e] Decoupled spectra in DMSO-d_6.

In ^{13}C-nmr, the major differences between the 1-methyl and 8-methyl derivatives were found in the chemical shifts of C-4a ($\simeq$ 6 ppm), C-6 and C-7 $\simeq$ 20 ppm). Comparison of the data of the NH compounds (**2**, **5** and **7**) with those of the N-methyl derivatives indicated that their 1-NH tautomers were present predominantly in DMSO, methanol and acetone solutions. The reported data[2] of compounds **3**, **4**, **6** and **8** were in agreement with the existence of those 1-NH tautomers in DMSO.

Moreover, from comparison of the ^{15}N-nmr data (Table 2) of compounds **2** and the 1-methyl derivative **9** it was possible to discard the existence of the 3-NH tautomer, since the N-3 chemical shift in compound **2** was shifted downfield. The difference of the N-3 chemical shifts in both compounds could be explained by a small participation of the iminodihydro tautomer **9**[6]. The difference of chemical shift between those N-1 was due to the effect of the methyl group[6].

TABLE 2

^{15}N-NMR DATA OF 4-AMINOPYRAZINOTHIADIAZINE DERIVATIVES[a]

Compd.	N-1	N-3	N-5	N-8	NH_2
2	251.5 (broad)	178.9	59.8	86.1 (broad)	284.0
6[b]	248.0	177.1	54.8	84.1	281.9 (t) ^{1}J=91.6
9	260.3	185.6	58.5	86.1	280.0

[a] DMSO as solvent, the nitrogen shielding values are reported with respect to external neat nitromethane, an increase in shielding being a positive increment.

[b] Coupled spectra.

^{15}N Assignments were straightforward, except for N-5 and N-8 that were assigned on the basis of the signal at 86.1 ppm. In compound **2**, this broadened signal appeared like those of N-1 (251.5 ppm) and this fact indicated that it corresponded to N-8. These broad signals were due to the existence of an equilibrium between the 1-NH and 8-NH tautomers, which, although strongly shifted towards the 1-NH tautomer was slow enough to show broad signals of the nitrogens involved.

Due to the little amount of the 8-methyl derivatives available and the lack of solubility of pyrazinothiadiazines it was not possible to record their ^{15}N-nmr spectra in other solvents than DMSO.

Uv spectra were measured in different solvents (H_2O, MeOH, $CHCl_3$ and DMSO) and the data are shown in Table 3.

TABLE 3

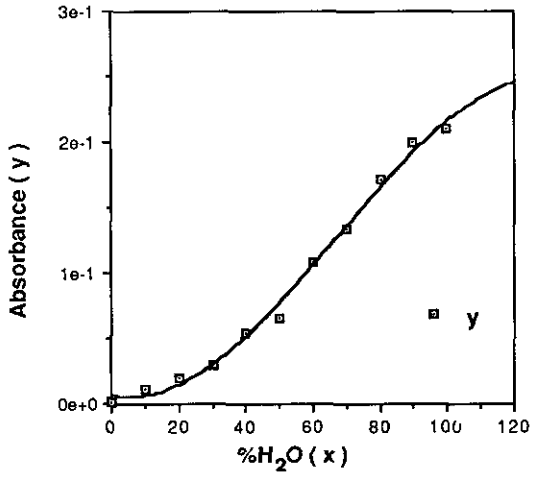
UV DATA OF PYRAZINO[2,3-c]-1,2,6-THIADIAZINE DERIVATIVES[a]

Comp.	Solvent	max (nm)				Molecular form	Tautomer isomer
1[1]	H_2O (pH=0)	246	336	-	401	(b)	NH-8
1[1]	H_2O (pH=7)	259	-	381	-	(c)	-
2[1]	H_2O (pH=1)	252	339	-	411	(b)	NH-8
2[1]	H_2O (pH=8)	263	-	382	-	(c)	-
2	MeOH (H^+)	248	340	-	-	(b)	NH-1
2	MeOH	249	341	(390)	-	(b)+(c)	NH-1
2	DMSO	267	355	-	-	(b)	NH-1
2	$HCCl_3$	250	348	-	-	(b)	NH-1
3	H_2O (pH=1)	290	395	-	-	(b)	NH-1
3	H_2O (pH=7)	280	-	418	-	(c)	-
4	H_2O (pH=1)	280	360	-	(420)	(b)	NH-1 > NH-8
5	H_2O (pH=1)	275	375	-	(420)	(b)	NH-1 > NH-8
5	H_2O (pH=7)	285	-	402	-	(b)	-
5	MeOH (H^+)	276	371	-	-	(b)	NH-1
5	MeOH	281	376	(403)	-	(b)+(c)	NH-1
5	DMSO	283	375	-	-	(b)	NH-1
5	$HCCl_3$	276	374	-	-	(b)	NH-1
6[1]	H_2O (pH=1)	276	369	-	441	(b)	NH-8
6[1]	H_2O (pH=6)	285	-	405	-	(c)	-
7	H_2O (pH=1)	280	378	-	440	(b)	NH-8
8	H_2O (pH=1)	288	390	-	445	(b)	NH-8
9[1]	H_2O (pH=7)	253	348	-	-	(b)	N-Me (1)
9	MeOH	255	348	-	-	(b)	N-Me (1)
10	MeOH	280	378	-	-	(b)	N-Me (1)
11[1]	H_2O (pH=7)	258	313	-	401	(b)	N-Me (8)
11	MeOH	260	324(sh)	-	410	(b)	N-Me (8)
12	MeOH	285	-	-	437	(b)	N-Me (8)

[a] The number in parentheses indicates low intensity bands.
(b) Neutral form.
(c) Monoanion.

The NH-derivatives studied had a strong acidic character reflected by the low pKa values[1] and in water solution, at neutral pH, were found in their anionic forms. They showed a typical absorption band between 381-418 nm depending on the substituents in the 6 and 7 positions. In methanol solution, the NH compounds were partly ionized and the band corresponding to the anionic form appeared with low intensity and disappeared on adding acid.

The 8-methyl derivatives **11** and **12** showed absorption bands at 410 and 437 nm respectively which were not present in 1-methyl derivatives **9** and **10**. Comparison of uv spectra of the NH derivatives with those of the corresponding methyl derivatives indicated that all the NH compounds existed as the 1-NH tautomer in chloroform, DMSO and methanol and as the 8-NH tautomer in water (pH≈1), except for compound **3** which existed as 1-NH, and **4** and **5** as a mixture of 1-NH and 8-NH tautomers in water. The strongly electron-withdrawing sulfone function caused the formation of the unusual cross-conjugated π-electron system in the 8-NH tautomer in water solution. This form resulted in a less acidic form and therefore more stable. When the 6 and 7 positions bear strong electron-withdrawing substituents (**3**, **4** and **5**), the equilibrium was shifted towards the 1-NH tautomer even in water solutions.



x	y
0	0.002
10	0.012
20	0.020
30	0.030
40	0.054
50	0.066
60	0.108
70	0.134
80	0.172
90	0.200
100	0.210

Fig.1. Plot of absorbance of 8-NH tautomer 'vs' $\%H_2O$

The uv spectra of compound **2** was measured in mixtures of water/methanol and the shift of the equilibrium of the 1-NH towards the 8-NH tautomers can be observed on changing the ratio of solvents from 100% methanol to 100% water solutions. The plot

of absorbance of the typical band of the 8-NH tautomers (411 nm) "versus" percentage of water is represented in Figure 1.

X-RAY DISCUSSION

The X-ray analysis of compound **2** demonstrated the existence of 1-NH tautomer in solid state. Figure 2 shows the structure of the molecule. Bond distances and angles reflected the usual bond type distribution (see Table 4). The thiadiazine ring adopted a distorted envelope conformation flapping at S1. The crystal is built up by an H-bonding network that associated molecules in dimers through N2...N7 bridges, establishes indefinite chains along the OZ direction through the N13...O15 interactions, and links these chains of dimers by means of N13...O14 contacts.

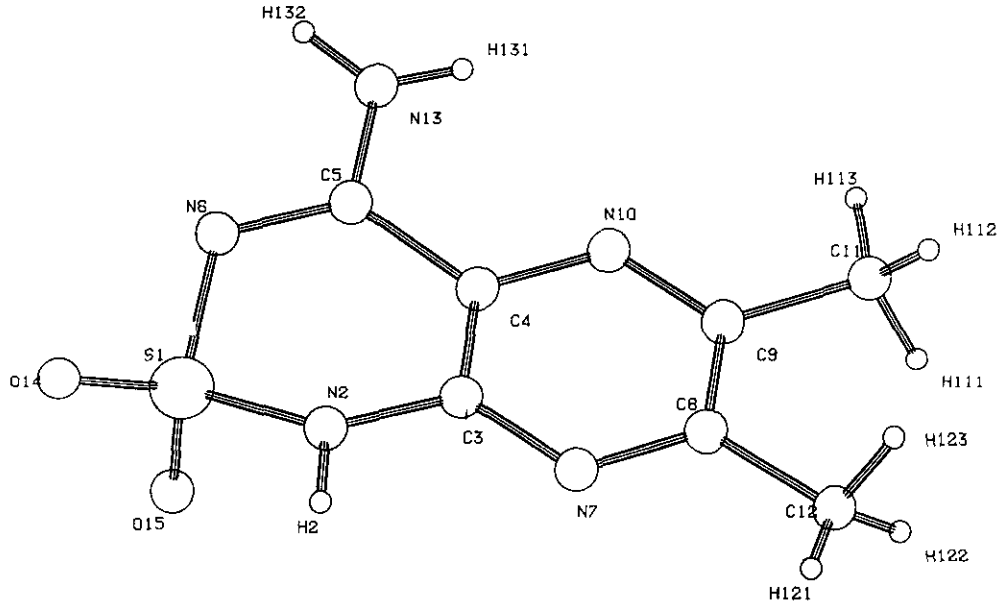


Fig. 2. A PLUTO view[11] of the molecular structure of compound **2** showing the atomic numbering used in the crystallographic work.

EXPERIMENTAL

Mps. were determined on a Köfler hot-stage apparatus and are uncorrected. Column chromatography was performed on Merck silica gel (60-230 mesh). Analytical tlc was

performed on aluminium sheets coated with 0.2 mm layer of silica gel 60 F_{254} (Merck).

^{1}H-Nmr spectra were recorded on Varian EM-390, Bruker AM-200 and Varian XL-300 spectrometers operating at 90, 200 and 300 MHz respectively, using TMS as internal standard. ^{13}C-Nmr spectra were recorded at 20.15 MHz on a Bruker WP-80 and at 50 MHz on a Bruker AM-200. The natural abundance ^{15}N-nmr spectra were obtained on a Varian XL 300 spectrometer operating at 30.41 MHz at 20°C, using 0.5-1.0 M solutions in a mixture of DMSO and 10% of DMSO-d_6 to provide the locking signal, and contained in 10 nm o.d. tubes.

Ir spectra were obtained on a Perkin Elmer 257 spectrophotometer and uv spectra were obtained on a Perkin Elmer 550 or on a Perkin Elmer 554 spectrophotometers.

X-Ray crystallography

The main characteristics of the X-ray analysis are given in Table 6. During the last cycles of refinement the H123 methyl hydrogen had to be kept fixed. The final atomic coordinates for the non-hydrogen atoms are given in Table 5 according to the numbering scheme displayed in Fig. 2. A list of structure factors, hydrogen parameters and thermal factors are available as supplementary material.

TABLE 4. SELECTED GEOMETRICAL PARAMETERS (A,°)

S1-N2	1.667(2)	S1-N6	1.588(2)
S1-O14	1.427(2)	S1-O15	1.439(2)
N2-C3	1.382(2)	C3-C4	1.393(2)
C3-N7	1.341(3)	C4-C5	1.468(3)
C4-N10	1.342(2)	C5-N6	1.318(2)
C5-N13	1.321(2)	N7-C8	1.332(2)
C8-C9	1.418(3)	C8-C12	1.490(4)
C9-N10	1.320(3)	C9-C11	1.496(3)
O14-S1-O15	116.4(1)	N2-S1-N6	104.2(1)
N6-S1-O15	110.2(1)	N6-S1-O14	109.6(1)
N2-S1-O15	108.5(1)	N2-S1-O14	107.2(1)
S1-N2-C3	117.3(1)	S1-N2-H2	119(2)
H2-N2-C3	117(2)	N2-C3-N7	118.0(2)
C5-C4-N10	118.1(2)	N7-C8-C12	117.2(2)
N10-C9-C11	117.9(2)	C5-N13-H132	119(2)
C5-N13-H131	119(2)	H131-N13-H132	122(3)
O15-S1-N6-C5	-77.8(2)	O14-S1-N6-C5	152.9(2)
C5-N6-S1-N2	38.5(2)	N6-S1-N2-C3	-42.8(2)
S1-N2-C3-C4	25.2(2)	N2-C3-C4-C5	2.1(3)
C3-C4-C5-N6	-7.5(3)	C4-C5-N6-S1	-17.0(3)
C4-C5-N13-H131	6(3)	C3-N7-C8-C12	178.3(2)
N7-C8-C9-C11	179.2(2)		
N2...N7i	3.295(2)	H2....N7i	2.43(3)
N13..O14ii	3.008(2)	H131..O14ii	2.37(3)
N13..O15iii	2.988(3)	H132..O15iii	2.15(4)
N2-H2.....N7i	173(3)	i: 1-x,	-y,1-z
N13-H131..O14ii	133(3)	ii: 1/2+x,1/2-y,1+z	
N13-H132..O15iii	159(3)	iii: x,	y,1+z

TABLE 5. ATOMIC PARAMETERS FOR $C_7H_9O_2N_5S$

THERMAL PARAMETERS AS:

$$Ueq=(1/3).\Sigma[U_{ij}.a_i^*.a_j^*.a_i.a_j.\cos(a_i,a_j)].10^4$$

Atom	x/a	y/b	z/c	Ueq
S1	0.39111(3)	0.21757(3)	0.78863(7)	202(2)
N2	0.4503 (1)	0.1051 (1)	0.7315 (3)	236(5)
C3	0.5586 (1)	0.0867 (1)	0.8490 (3)	193(5)
C4	0.6009 (1)	0.1329 (1)	1.0602 (3)	196(5)
C5	0.5296 (2)	0.1988 (1)	1.1639 (3)	201(5)
N6	0.4283 (1)	0.2267 (1)	1.0559 (3)	248(5)
N7	0.6194 (1)	0.0194 (1)	0.7584 (3)	240(5)
C8	0.7217 (2)	-0.0008 (2)	0.8803 (3)	257(5)
C9	0.7654 (2)	0.0465 (2)	1.0948 (3)	243(5)
N10	0.7040 (1)	0.1118 (1)	1.1820 (3)	228(5)
C11	0.8799 (2)	0.0224 (2)	1.2319 (4)	348(7)
C12	*0.7889 (2)*	*-0.0779 (2)*	*0.7845 (5)*	*459(8)*
N13	0.5689 (2)	0.2259 (1)	1.3777 (3)	266(5)
O14	0.2743 (1)	0.2021 (1)	0.7181 (3)	364(5)
O15	0.4351 (1)	0.3055 (1)	0.6867 (3)	356(5)

TABLE 6

CRYSTAL ANALYSIS PARAMETERS AT ROOM TEMPERATURE

Crystal data	
Formula	$C_7H_9O_2N_5S$
Crystal habit	Yellow cubic
Crystal size (mm)	0.33 x 0.37 x 0.30
Symmetry	Monoclinic, $P2_1/a$
Unit cell determination:	Least-squares fit from 49 reflexions ($\theta < 45°$)
Unit cell dimensions	12.4768(4), 12.5075(5), 6.1154(4) Å 90, 104.466(6), 90
Packing: $V(A^3)$, Z	924.07(8), 4
$Dc(g.cm^{-3})$, M, F(000)	1.633, 227.24, 472
$\mu(cm^{-1})$	30.03
Experimental data	
Technique	Four circle diffractometer: Philips PW1100 Bisecting geometry Graphite oriented monochromator: CuKα $\omega/2\theta$ scans, scan width: 1.5° Detector apertures 1 x 1°, up θ max. 65° 1 min./reflex.
Number of reflexions:	
Independent	1552
Observed	1540 [$3\sigma(I)$ criterion]
Standard reflexions:	2 reflexiones every 90 minutes Variation: none
Max-min transmission factors:	1.166-0.812
Solution and refinement	
Solution	Direct Methods
Refinement	L.s. on Fobs with 1 block
Parameters:	
Number of variables	168
Degrees of freedom	1336
Ratio of freedom	9.0
H atoms	Difference synthesis
Final shift/error	0.20
w-scheme	Empirical as to give no trends in $\langle w\,^2F\rangle$ vs. $\langle\|Fo\|\rangle$ and $\langle\sin\theta/\lambda\rangle$
Max. thermal value	$U22(C12)=0.057(15)A^2$
Final ΔF peaks	0.24 eA^{-3}
Final R and Rw	0.037, 0.039
Computer and programs	Vax11/750, XRAY76[7], MULTAN80[8], DIFABS[9]
Scattering factors	Int. Tables for X-Ray Crystallography[10].

4-Amino-6,7-di-(4'-tolyl)-8H-pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (7).

A stirred solution of 3,4,5-triamino-2H-1,2,6-thiadiazine 1,1-dioxide **(13)** (0.5 g, 2.8 mmol) in 5 ml of tetramethylenesulfone (sulfolan) was treated with p-toluylaldehyde (1.0 g, 8.3 mmol). The mixture was heated for 3 h at 180°C. The reaction solution was purified through silica gel column chromatography with chloroform-methanol (10:1) as eluent, to yield a yellow solid (0.87 g, 82%) which was recrystallized from methanol/water; mp > 350°C · Ir (nujol) ν : 3450-3100 (NH_2,NH), 1625 (C=N), 1310, 1165 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ: 7.25, 7.24 (4H, d, ^3J=8.1 Hz, H-m), 9.09 (2H, d, ^3J=8.1 Hz, H-o), 7.05 (2H, d, ^3J=8.1 Hz, H-o'), 7.00 (s, 2H, NH_2, deuterium oxide exchangeable), 2,30 (3H, s, CH_3), 2.26 (3H, s, CH_3). Anal. Calcd for $C_{19}H_{17}N_5O_2S$: C, 60.14; H, 4.52; N, 18.46; S, 8.45. Found: C, 60.24; H, 4.50; N, 18.21; S, 8.20.

4-Amino-1-methyl-6,7-di-(4'-chlorophenyl)pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (10)

Dimethyl sulfate (0.1 ml) was added dropwise to a solution of 0.21 g (0.5 mmol) of 5 in 25 ml of saturated sodium bicarbonate and 10 ml of ethanol. The reaction mixture was stirred at room temperature for 2 h and then 0.1 ml of dimethyl sulfate was added. The mixture was stirred at room temperature for 2 h more and the precipitate was removed by filtration. Its analytical (tlc) control showed a mixture of two reaction products (**10** and **12**) which were separated by chromatography on a silica gel column. Compound **10** was eluted with chloroform to yield 0.14 g (65%) of a yellow solid which was recrystallized from ethanol/water as yellow crystalline needles. Mp 194-195°C. Ir (KBr) ν : 3450-3200 (NH_2), 1640 (C=N), 1315, 1175 (SO_2) cm^{-1}. ^1H-Nmr (DMSO-d_6) δ : 9.00, 8.90 (2H, deuterium oxide exchangeable NH_2), 7.57, 7.54 (4H, d, ^3J=8.7 Hz, H-m), 7.49, 7.45 (4H, d, ^3J=8.7 Hz, H-o), 3.47 (s, 3H, CH_3-N). Anal. Calcd for $C_{18}N_{13}N_5O_2SCl_2$: C, 49.78; H, 3.02; N, 16.12; S, 7.38. Found: C, 49.83; H, 3.32; N, 15.85; S, 7.23.

4-Amino-8-methyl-6,7-di-(4'-chlorophenyl)pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (12)

From the above reaction mixture compound **12** was eluted with chloroform/methanol (50:1) to yield 0.05 g (23%) as a deep yellow solid which was recrystallized from ethanol/water. Mp 315-316°C. Ir (KBr) ν : 3400-3200 (NH_2), 1645 (C=N), 1290, 1140 (SO_2) cm^{-1}. ^1H-Nmr (DMSO-d_6) δ: 7.98, 7.95 (s, 2H, NH_2, deuterium oxide exchan-

geable), 7.60 (2H, d, ^3J=8.7 Hz, H-m), 7.55 (2H, d, ^3J=8.7 Hz, H-m'), 7.30 (2H, d, ^3J=8.7 Hz, H-o), 7.23 (2H, d, ^3J=8.7 Hz, H-o'), 3.37 (s, 3H, N-CH_3). Anal. Calcd. for $C_{18}H_{13}N_5O_2SCl_2$: C, 49.78; H, 3.02; N, 16.12; S, 7.38. Found: C, 49.88; H, 3.02; N, 16.14; S, 7.34.

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