On the Reactivity of 1*H*-Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide and Derivatives: Nucleophilic Substitution, Amination, Aldol-Type Condensation, Oxidation, and Hydrolysis

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This paper is dedicated to Professor *W. Pfleiderer* on the occasion of his 75th birthday
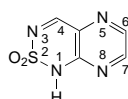
The reactivity of the 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide system, structurally related to pteridine, was studied, and a number of novel derivatives were synthesized. The chemical behaviors of these two related fused polyaza systems were compared.

Introduction. – The 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide system, first synthesized in our laboratory [1] and structurally related to pteridine, is of considerable pharmaceutical interest since some of its derivatives have shown interesting properties as diuretics, platelet aggregation inhibitors, and bronchodilator agents [2][3]. Particular structural features of this heterocycle are the lack of planarity, as shown by the three different X-ray structures of compounds incorporating this ring system (code CSD [4]: LICZOM [5], SAJWOP [6], WUNTON [7]) and the remarkable acidic character of H−N(1) with pKa values ranging from 1−4 [1][8]. Tautomerism is also an interesting aspect of this heterocycle that we have studied in solution and theoretically by *ab initio* calculations [9].

On several occasions, with the aim of optimizing some of the biological activities [10], we had to prepare many different derivatives, and, so, we have studied the reactivity of certain positions of the ring. Thus, we have previously described N(1) alkylation and transamination of the 4-amino group, and we have also studied regioselective syntheses of C(6)- and C(7)-substituted compounds [7][11][12].
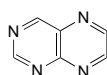

pteridine

1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine
2,2-dioxide

In this paper, we wish to report novel reactions of this particular heterocycle at the C(6) and C(7) positions, including S_N displacements of halogen atoms, amination, aldol-type condensations, and oxidation of Me groups. Also, hydrolysis of the amino group at C(4) to the corresponding 4-oxo group and conversion into the 4-thioxo compounds are described here for the first time.

Results and Discussion. – *Reactions with NH₃ and MeNH₂.* Nucleophilic attack of NH_3 and primary amines at 1-substituted 6-halopyrazinothiadiazine derivatives can occur at three different positions, affording the products of transamination at C(4), aminolysis at C(6), and amination at C(7). Thus, reaction of 6-chloro-1-methyl-7-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine (**1**) with NH_3, under pressure, afforded the corresponding aminolysis compound, 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine-4,6-diamine **3**. However, when the 6-chloro-1-ethyl derivative **2** [12][1]) reacted with $MeNH_2$ in equimolar amounts, the transamination product **4** was obtained. On working with an excess of $MeNH_2$, it was possible to obtain the 4,6-bis-methylamino compound **5** in which nucleophilic displacement had taken place concomitantly with transamination (*Scheme 1*).
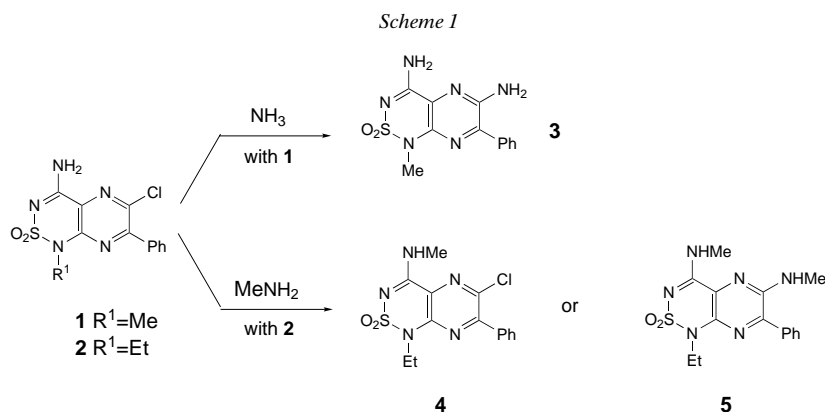
Scheme 1

The 6-bromo-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine **6** showed different behavior, and, thus, with NH_3, the 4,7-diamine derivative **7** was obtained, whereas, with $MeNH_2$, only the corresponding transamination product **8** could be isolated (*Scheme 2*).

Scheme 2

7 R¹=NH₂, R²=H
8 R¹=H, R²=Me
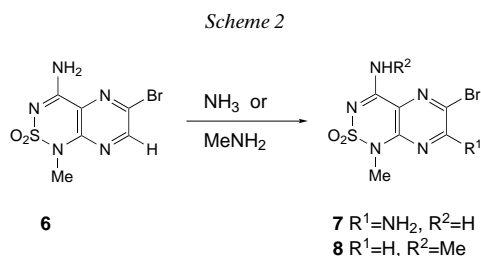
The starting methyl derivatives **1** and **6** and the ethyl derivative **2** [12] were obtained by reaction of the corresponding N(1)-unsubstituted 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazines with MeI or EtI, respectively, and Et_3N.

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[1]) In all previously studied reactions, we have shown that 1-methyl and 1-ethyl derivatives do not show any significant differences in their reactivity.

Synthesis of 7-Styrylpyrazinothiadiazines. These compounds were obtained by taking advantage of the acidic character of the 7-Me group of the 7-methyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazines, which can be conveniently deprotonated to afford the synthetically useful carbanions α to the aromatic pyrazine ring. Thus, 7-methyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazinamines **9a** [7], **9b** [1], and **9c** [12] reacted with benzaldehyde and 4-chlorobenzaldehyde in NaOH solution (EtOH/H$_2$O) to afford the corresponding 7-styryl derivatives **10a – c** in good yields (*Scheme 3*).
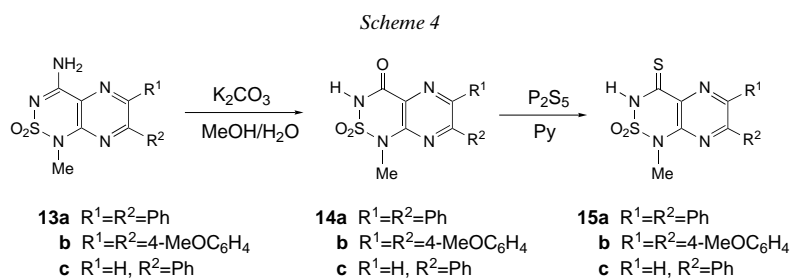
When this reaction was attempted with the corresponding 6-methyl isomer **9d** [7], only the starting material was recovered due to the less acidic character of the 6-Me group (as has also been observed in the case of pteridines [13]).

Scheme 3
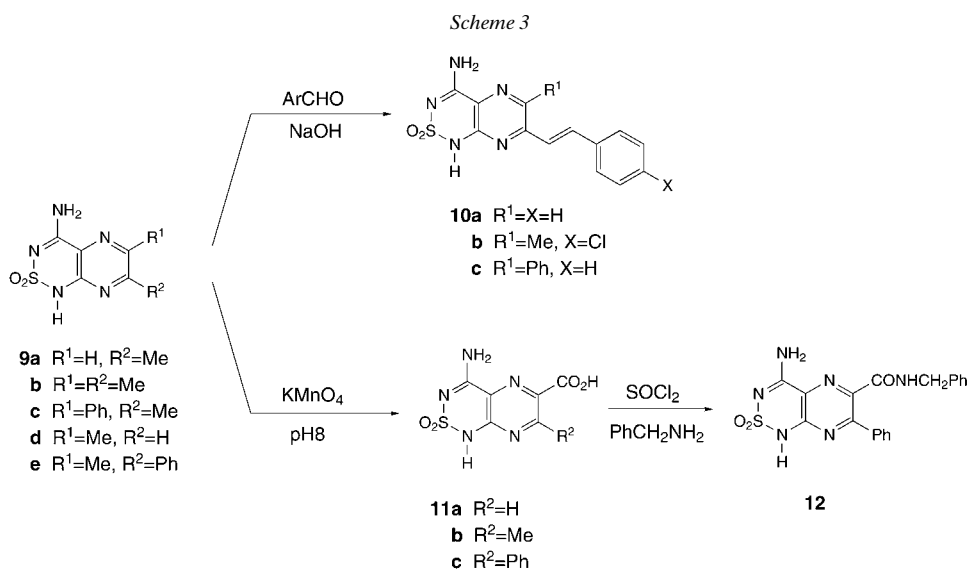
Oxidation Reactions. Another reaction that we studied in this particular heterocyclic system is oxidation of the Me group at position 6 to yield the corresponding 6-carboxylic acid derivatives, useful synthons for further syntheses.

Reaction of 6-methylpyrazinothiadiazinamines **9b** [1], **9d** [7], and **9e** [12] with KMnO$_4$ in aqueous basic medium, at pH 8, afforded the 6-carboxylic acids **11a – c**. These compounds can be used to prepare amides and thus, **11c** with SOCl$_2$ and PhCH$_2$NH$_2$ afforded **12** (*Scheme 3*). It is worth mentioning that, in the case of **9b**, the Me group at C(7) was not affected under these conditions.

Synthesis of Pyrazinothiadiazin-4-ones and -4-thiones. Hydrolysis of the 4-amino group provides an entry to the corresponding 4-oxo derivatives and so, the 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amines **13a** [14], **13b** [10], and **13c** [11] were readily converted to the 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-ones **14a – c** by reaction with K$_2$CO$_3$ in MeOH/H$_2$O (*Scheme 4*). It should be mentioned that the parent 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide system had previously been synthesized by us, by reaction of 4,5-diamino-2*H*-1,2,6-thiadiazin-3(6*H*)-one 1,1-dioxide and 1,2-dicarbonyl compounds [1]. However, the starting 4,5-diamino-2*H*-

Scheme 4

13a R^1=R^2=Ph   **14a** R^1=R^2=Ph   **15a** R^1=R^2=Ph
b R^1=R^2=4-MeOC$_6$H$_4$ **b** R^1=R^2=4-MeOC$_6$H$_4$ **b** R^1=R^2=4-MeOC$_6$H$_4$
c R^1=H, R^2=Ph   **c** R^1=H, R^2=Ph   **c** R^1=H, R^2=Ph

1,2,6-thiadiazin-3(6H)-one 1,1-dioxide [15] is difficult to prepare, and, so, this is a much more versatile method to obtain 4-oxo derivatives.

Finally, the 1H-pyrazino[2,3-c][1,2,6]thiadiazin-4(3H)-ones **14a**–**c** were converted to the hitherto unknown 4-thioxo derivatives **15a**–**c**, respectively, by reaction with P$_2$S$_5$ (*Scheme 4*).

The structures of all the newly synthesized compounds were established by analytical and spectroscopic data, including ^{1}H- and ^{13}C-NMR data (see *Tables 1* and *2*). The assignments of all compounds by their ^{13}C-NMR spectra was achieved by analysis of the chemical shifts and long-range-coupling constants and by comparison with other structures of these series.

Table 1. *Melting Points of 1*H-*Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides* **1**, **3**–**8**, **10**–**12**, **14**, *and* **15**

	R^1	R^2	R^3	R^4	M.p. [°]	Recryst. solvent
1	Cl	Ph	Me	NH$_2$	230–231	MeOH/H$_2$O
3	NH$_2$	Ph	Me	NH$_2$	310–312	–
4	Cl	Ph	Et	NHMe	250–252	EtOH/H$_2$O
5	NH Me	Ph	Et	NHMe	260–262	H$_2$O
6	Br	H	Me	NH$_2$	227–229	EtOH/H$_2$O
7	Br	NH$_2$	Me	NH$_2$	275–277	MeOH
8	Br	H	Me	NHMe	325–326	MeOH
10a	H	Ph–CH=CH	H	NH$_2$	>350	EtOH/H$_2$O
b	Me	4-ClC$_6$H$_4$–CH=CH	H	NH$_2$	310–312	MeOH/H$_2$O
c	Ph	Ph–CH=CH	H	NH$_2$	293–295	EtOH/H$_2$O
11a	COOH	H	H	NH$_2$	>350	EtOH/H$_2$O
b	COOH	Me	H	NH$_2$	>350	MeOH/H$_2$O
c	COOH	Ph	H	NH$_2$	244–246	EtOH/H$_2$O
12	CONHCH$_2$Ph	Ph	H	NH$_2$	>350	MeOH/H$_2$O
14a	Ph	Ph	Me	O	255–257	H$_2$O/MeOH
b	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	Me	O	260–261	H$_2$O/MeOH
c	H	Ph	Me	O	132–134	H$_2$O/MeOH
15a	Ph	Ph	Me	S	265–267	EtOH/H$_2$O
b	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	Me	S	258–259	MeOH/H$_2$O
c	H	Ph	Me	S	210–211	EtOH

Table 2. *^{13}C-NMR Spectral Data* ((D_6)DMSO) *for Compounds* **1**, **3** – **8**, **10** – **12**, **14**, *and* **15**. δ *in ppm.*

	C(4)	C(7)	C(8a)	C(6)	C(4a)	Other signals
1	157.3	155.6	147.0	136.5	121.0	135.2; 130.6; 129.7; 128.3; 38.3; 13.8
3	159.1	144.3	141.9	147.9	118.9	135.9; 130.1; 128.9; 128.5; 28.2
4	155.5	155.3	146.7	136.7	121.4	135.3; 130.8; 129.8; 128.5; 28.2; 38.5;13.9
5	157.7	148.2	146.0	140.0	119.1	135.3; 130.4; 129.2; 128.6; 37.8; 28.0; 37.8; 14.5
6	157.3	150.9	148.5	129.1	123.3	28.6
7	158.6	155.9	150.1	117.3	111.7	28.7
8	155.2	150.7	147.8	129.3	124.2	28.3; 28.7
10a	158.8	158.8	149.0	137.9	121.0	138.8; 123.8; 135.6; 130.4; 129.5; 128.3
b	158.6	151.0	147.7	145.6	120.2	138.0; 123.2; 136.5; 135.4; 129.8; 129.1; 128.9; 128.4; 127.6
c	158.6	152.1	147.1	145.4	119.9	137.2; 134.4; 134.2; 131.2; 129.8; 129.0; 122.9; 20.8
11a	157.5	149.2	151.4	132.6	120.2	163.8
b	157.3	160.0	148.9	132.1	118.8	165.6; 136.3; 130.3; 128.6; 128.3
c	157.5	157.1	148.8	136.7	119.2	163.9; 23.0
12	158.5	158.5	140.1	139.4	116.7	135.1; 133.9; 129.9; 129.6; 129.6; 129.2; 129.1;
						120.0; 128.7; 128.0; 127.8; 127.4; 127.1; 123.9
14a	163.5	153.9	147.7	145.1	124.1	133.5; 128.9; 128.2; 128.5; 137.8; 137.3; 127.8;
						129.5; 129.4; 128.1; 28.4
b	163.5	151.3	147.9	143.5	125.6	160.3; 159.8; 131.4; 113.9; 131.0; 55.4; 55.4
c	163.6	153.3	149.2	134.5	124.7	134.6; 131.4; 129.1; 126.7; 28.3
15a	162.7	152.5	147.7	145.0	124.0	129.5; 129.0; 128.4; 128.2; 28.3
b	161.1	155.2	147.0	145.9	119.9	160.9; 159.6; 130.6; 129.0; 113.5; 113.5; 55.3; 55.2; 28.5
c	162.7	152.8	149.0	133.7	125.2	134.6; 130.7; 128.7; 127.3; 27.9

In conclusion, we have studied the reactivity at different positions and of different substituents of a peculiar pteridine-like heterocycle, the 1*H*-pyrazino[2,3-*c*][1,2,6]thia-diazine 2,2-dioxide. In some cases, it behaves similarly to its structural analogue, isopterine, as for example in the reactivity of the 7-methyl group towards aldol-type condensations and of the 6-methyl group towards oxidating agents [16 – 18].

However, when not the reactivity of the substituents but that of the heterocycle itself is concerned, the pyrazino[2,3-*c*][1,2,6]thiadiazine system behaves differently and, for example, the direct amination at C(7) described here, or an unexpected alkoxylation with *N*-bromo- or *N*-chlorosuccinimide and alcohols that we have recently reported [19], are unprecedented in the pteridine series.

Experimental Part

General. Column chromatography (CC): silica gel (*Merck*, particle size 70 – 230 mesh). M.p.: *Reichert-Jung-Thermovar* micro-melting-point apparatus; uncorrected. ^{1}H- and ^{13}C-NMR Spectra: at 300 (^{1}H) and 75 MHz (^{13}C); *Gemini-* or *Varian-XL*-300 spectrometer; (D_6)DMSO solns.; δ in ppm, with the signal of the solvent as reference; *J* in Hz; δ(C) in *Table 2*. Mass spectra: EI, at 70 eV; *VG-12-250* spectrometer (*VG Masslab*). Elemental analyses: *Heraeus CHN-O-Rapid* analyzer.

*1-Methyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxides* **1** *and* **6**: *General Procedure.* To the corresponding 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-dioxide derivative in acetone and Et$_3$N, the alkyl halide was added. The mixture was refluxed and then evaporated. H$_2$O was added to the residue and the precipitate filtered and recrystallized from the appropriate solvent (see *Table 1*).

*6-Chloro-1-methyl-7-phenyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**1**). From 6-chloro-7-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-doxide (1.90 g, 16.1 mmol), acetone (80 ml), Et$_3$N (0.9 ml, 6.1 mmol), and MeI (1.9 ml, 33.5 mmol), reaction time 4 d: 1.68 g (86%) of **1**. ^{1}H-NMR: 3.41 (*t*, Me);

7.54 – 7.59 (*m*, 3 arom. H); 7.86 – 7.92 (*m*, 2 arom. H); 8.87 (br. *s*, 1 H, NH$_2$); 8.96 (br. *s*, 1 H, NH$_2$). Anal. calc. for C$_{12}$H$_{10}$ClN$_5$O$_2$S (323.73): C 46.22, H 3.58, Cl 10.49, N 20.73, S 9.49; found: C 46.50, H 3.43, Cl 10.35, N 20.88, S 9.30.

*1-Methyl-7-phenyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazine-4,6-diamine 2,2-Dioxide* (**3**). Compound **1** was treated with an excess of liquid NH$_3$ in a sealed tube at 80° for 6 d. Then, NH$_3$ was evaporated and the residue purified by CC (SiO$_2$, CH$_2$Cl$_2$/MeOH): 0.13 g (44%) of **3**. ^{1}H-NMR: 3.33 (*t*, Me); 6.16 (*s*, NH$_2$); 7.44 – 7.70 (*m*, 3 arom. H); 7.86 – 7.88 (*m*, 2 arom. H); 8.09 (br. *s*, 1 H, NH$_2$); 8.67 (br. *s*, 1 H, NH$_2$). Anal. calc. for C$_{12}$H$_{12}$N$_6$O$_2$S (303.33): C 49.82, H 3.83, N 24.20, S 11.08; found: C 49.47, H 4.04, N 23.97, S 11.17.

*6-Chloro-1-ethyl-*N^4*-methyl-7-phenyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**4**). From **2** (0.80 g, 2.4 mmol) in dry EtOH (80 ml) and MeNH$_2$ (33% in EtOH; 0.30 ml, 2.4 mmol) in a sealed tube at 80° for 48 h. The solvent was evaporated and the residue recrystallized from EtOH/H$_2$O: 0.48 g (60%) of **4**. ^{1}H-NMR: 1.32 (*t*, Me); 2.94 (*d*, Me); 4.06 (*q*, CH$_2$); 7.40 – 7.67 (*m*, 3 arom. H); 7.75 – 7.93 (*m*, 2 arom. H); 9.39 (*m*, NH). Anal. calc. for C$_{14}$H$_{14}$ClN$_5$O$_2$S (351.81): C 47.79, H 4.01, Cl 10.08, N 19.91, S 9.11; found: C 47.69, H 4.21, Cl 10.03, N 19.71, S 9.21.

*1-Ethyl-*N^4,N^6*-dimethyl-7-phenyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazine-4,6-diamine 2,2-Dioxide* (**5**). From **2** (0.50 g, 1.5 mmol) in dry EtOH (50 ml) and MeNH$_2$ (33% in EtOH; 1.80 ml, 2.4 mmol) in a sealed tube at 80° for 6 d. The solvent was evaporated and the residue recrystallized from H$_2$O: 0.27 g (54%) of **5**. ^{1}H-NMR: 1.26 (*m,* NH); 2.88 (*d*, Me); 2.95 (*s*, Me); 3.95 (*q*, CH$_2$); 6.60 (*m*, NH); 7.53 – 7.67 (*m*, 3 arom. H); 7.78 – 7.81 (*m*, 2 arom. H); 8.70 (br. *s*, NH). Anal. calc. for C$_{15}$H$_{18}$N$_6$O$_2$S (346.41): C 52.01, H 5.24, N 24.26, S 9.26; found: C 52.11, H 5.41, N 24.60, S 9.21.

*6-Bromo-1-methyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**6**). From 6-bromo-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-dioxide (3.00 g, 10.1 mmol), acetone (150 ml), Et$_3$N (1.4 ml, 10.1 mmol), and MeI (1.7 ml, 30.3 mmol), reaction time 24 h: 2.40 g (82%) of **6**. ^{1}H-NMR: 3.37 (*s*, Me); 8.86 (br. *s*, NH$_2$); 8.90 (br. *s*, 1 H, NH$_2$); 8.97 (br. *s*, 1 H, NH$_2$). Anal. calc. for C$_6$H$_6$BrN$_5$O$_2$S (292.11): C 24.67, H 2.07, Br 27.35, N 23.97, S 10.97; found: C 24.80, H 2.24, Br 27.12, N 24.06, S 11.85.

*6-Bromo-1-methyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4,7-diamine 2,2-Dioxide* (**7**). From **6** (0.60 g, 1.0 mmol) with an excess of liquid NH$_3$ in a sealed tube at r.t. for 10 d. NH$_3$ was evaporated and the residue recrystallized from H$_2$O/MeOH: 0.37 g (60%) of **7**. ^{1}H-NMR: 3.25 (*s*, Me); 8.10 (br. *s*, NH$_2$); 8.10 (*s*, H−C(7)); 8.26 (br. *s*). EI-MS: 306 (*M*$^{+\cdot}$). Anal. calc. for C$_6$H$_7$BrN$_5$O$_2$S (307.12): C 23.46, H 2.30, Br 26.02, N 27.36, S 10.44; found: C 23.40, H 2.49, Br 26.10, N 27.60, S 10.54.

*6-Bromo-*N^4,1*-dimethyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**8**). From **6** (0.30 g, 1.0 mmol) in dry EtOH (15 ml) and MeNH$_2$ (33% in EtOH; 0.4 ml, 3.0 mmol) in a sealed tube at r.t. for 48 h. The solvent was evaporated and the residue recrystallized from MeOH: 0.13 g (44%) of **8**. ^{1}H-NMR: 2.93 (br. *s*, Me); 3.29 (*s*, Me); 8.89 (*s*, H−C(7)); 9.39 (br. *s*, NH). EI-MS: 307 (*M*$^{+\cdot}$). Anal. calc. for C$_7$H$_8$BrN$_5$O$_2$S (306.14): C 27.46, H 2.63, Br 26.10, N 22.87, S 10.47; found: C 27.51, H 2.72, Br 26.44, N 22.67, S 10.21.

Compounds **10a – c**: *General Procedure.* To a soln. of the corresponding 7-methyl-1*H*-pyrazino-[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-dioxide **9a – c** (1.0 mmol) in H$_2$O (50 ml), benzaldehyde (2.0 mmol) and NaOH (2.0 mmol) in EtOH (10 ml) were added, and the mixture was refluxed for 72 h. The soln. was acidified with conc. HCl soln., and the precipitate was filtered and recrystallized from the appropriate solvent (*Table 1*).

*7-(2-Phenylethenyl)-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**10a**). From **9a** (0.50 g, 2.5 mmol), NaOH (0.19 g, 5.0 mmol), H$_2$O (125 ml), benzaldehyde (0.8 ml , 5.0 mmol), and EtOH (10.0 ml): 0.21 g (40%) of **10a**. ^{1}H-NMR: 7.39 – 7.47 (*m*, CH=C*H*, 1 arom. H); 7.39 – 7.47 (*m*, 2 arom. H); 7.70 – 7.73 (*m*, 2 arom. H); 7.86 (*d*, *J* = 16.2, C*H*=CH); 8.56 (*s*, H−C(6)); 8.57 (br. *s*, NH$_2$); 12.16 (br. *s*, NH). Anal. calc. for C$_{13}$H$_{11}$N$_5$O$_2$S (301.33): C 51.82, H 3.68, N 23.24, S 10.64; found: C 51.59, H 3.86, N 23.17, S 10.44.

*7-[2-(4-Chlorophenyl)ethenyl]-6-methyl-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**10b**). From **9b** (2.00 g, 8.8 mmol), NaOH (0.70 g, 17.6 mmol), H$_2$O (200 ml), 4-chlorobenzaldehyde (2.50 g, 17.6 mmol), and EtOH (20 ml): 1.52 g (50 %) of **10b**. ^{1}H-NMR: 2.67 (*s*, Me); 7.50 (*d*, 2 arom. H); 7.56 (*d*, *J* = 18.7, C*H*=CH,); 7.74 (*d*, CH=C*H*); 7.81 (*d*, 2 arom. H); 8.36 (br. *s*, 1 H, NH$_2$); 8.52 (br. *s*, 1 H, NH$_2$); 11.96 (br. *s*, 1 H, NH). Anal. calc. for C$_{14}$H$_{14}$ClN$_5$O$_2$S (349.79): C 48.07, H 3.46, Cl 10.14, N 20.02, S 9.17; found: C 48.03, H 3.75, Cl 10.22, N 20.12, S 9.21.

*6-Phenyl-7-(2-phenylethenyl)-1*H-*pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-Dioxide* (**10c**). From **9c** (0.40 g, 1.9 mmol) in NaOH (38 ml, 0.05N) and benzaldehyde (1.20 g, 7.6 mmol): 0.12 g (28%) of **10c**. ^{1}H-NMR: 7.24 (*d*, CH=C*H*, 1 arom. H); 7.39 – 7.42 (*m*, 3 arom. H); 7.53 – 7.56 (*m*, 5 arom. H); 7.70 – 7.76 (*m*, 2 arom. H); 7.85 (*d*, *J* = 14.8, C*H*=CH); 8.38 (br. *s*, 1 H, NH$_2$); 8.51 (br. *s*, 1 H, NH$_2$). Anal. calc. for C$_{19}$H$_{15}$N$_5$O$_2$S (377.00): C 60.46, H 4.00, N 18.55, S 8.49; found: C 60.31, H 3.95, N 18.31, S 8.32.

Compounds **11a – c**: *General Procedure.* To a soln. of the corresponding 6-methyl-1*H*-pyrazino[2,3-*c*]-[1,2,6]thiadiazine 2,2-dioxide derivative (1.0 mmol) in 0.05N aq. NaOH (140 ml), conc. HCl soln. was added until pH 8, followed by KMnO$_4$ (4.0 mmol). The mixture was refluxed for 24 h. After cooling, NaHSO$_3$ was added and the mixture stirred for 10 min. The precipitate was filtered and the soln. was acidified with conc. HCl soln. The precipitate was filtered and recrystallized from the appropriate solvent (*Table 1*): **11a – c**.

*4-Amino-1*H*-pyrazino[2,3-c][1,2,6]thiadiazine-6-carboxylic Acid 2,2-Dioxide* (**11a**). From **9d** (0.40 g, 1.9 mmol), in 0.05N aq. NaOH (38 ml) and KMnO$_4$ (1.20 g, 7.6 mmol): 0.12 g (28%) of **11a**. ^{1}H-NMR: 8.65 (br. *s*, 1 H, NH$_2$); 8.68 (br. *s*, 1 H, NH$_2$); 9.03 (*s*, H−C(7)). Anal. calc. for C$_6$H$_5$N$_5$O$_4$S (243.20): C 29.63, H 2.07, N 28.79, S 13.18; found: C 29.51, H 2.02, N 28.69, S 12.98.

*4-Amino-7-methyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazine-6-carboxylic Acid 2,2-Dioxide* (**11b**). From **9b** (0.40 g, 1.9 mmol), 0.05N aq. NaOH (38 ml), and KMnO$_4$ (1.20 g, 7.6 mmol): 0.12 g (28%) of **11b**. ^{1}H-NMR: 2.75 (*s*, Me); 8.60 (br. *s*, 1 H, NH$_2$); 8.83 (br. *s*, 1 H, NH$_2$). Anal. calc. for C$_7$H$_7$N$_5$O$_4$S (257.22): C 32.69, H 2.74, N 27.23, S 12.46; found: C 32.33, H 2.57, N 27.19, S 12.18.

*4-Amino-7-phenyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazine-6-carboxylic Acid 2,2-Dioxide* (**11c**). From **9e** (1.90 g, 6.6 mmol), 0.05N aq. NaOH (140 ml), and KMnO$_4$ (4.82 g, 24.4 mmol): 0.52 g (24%) of **11c**. ^{1}H-NMR: 7.51 – 7.66 (*m*, 5 arom. H); 8.75 (br. *s*, 1 H, NH$_2$); 8.79 (br. *s*, 1 H, NH$_2$). Anal. calc. for C$_{12}$H$_9$N$_5$O$_2$S (319.29): C 45.14, H 2.84, N 21.93, S 10.04; found: C 45.10, H 2.95, N 21.61, S 10.00.

*4-Amino-N^6-benzyl-7-phenyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazine-6-carboxamide 2,2-Dioxide* (**12**). A soln. of **9e** (0.50 g, 1.76 mmol) in SOCl$_2$ (3.2 ml, 44.0 mmol) was refluxed for 3 h. After careful removal of SOCl$_2$ *in vacuo*, the residue was treated with CHCl$_3$ (15 ml) and PhCH$_2$NH$_2$ (1.5 ml, 13.7 mmol), and the soln. was stirred at r.t. for 12 h. The soln. was neutralized with 2N HCl and the solvent evaporated. The residue was recrystallized from MeOH/H$_2$O: 0.30 g (41%) of **12**. ^{1}H-NMR: 4.38 (*d*, PhC*H*$_2$); 7.20 – 7.77 (*m*, 10 arom. H); 8.14 (br. *s*, NH$_2$); 9.33 (*m*, CONH). Anal. calc. for C$_{19}$H$_{16}$N$_6$O$_3$S (408.10): C 55.87, H 3.95, N 20.59, S 7.83; found: C 55.50, H 3.81, N 20.51, S 8.01.

*1*H*-Pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-one 2,2-Dioxides* **14a – c**: *General Procedure.* To a suspension of 1-methyl-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4-amine 2,2-dioxide **13** (1.1 mmol) in MeOH/H$_2$O 1:1 (40 ml), K$_2$CO$_3$ (0.5 g, 3.6 mmol) was added. The mixture was refluxed for 2 h, then MeOH was evaporated, and the soln. was acidified with conc. HCl soln. The precipitate was filtered and recrystallized from the appropriate solvent (see *Table 1*).

*1-Methyl-6,7-diphenyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-one 2,2-Dioxide* (**14a**). From **13a** (1.50 g, 3.5 mmol), MeOH/H$_2$O 1:1 (160 ml), and K$_2$CO$_3$ (1.60 g, 13.9 mmol): 1.30 g (90%) of **14a**. ^{1}H-NMR: 3.41 (*s*, Me); 7.33 – 7.46 (*m*, 10 arom. H). Anal. calc. for C$_{18}$H$_{14}$N$_4$O$_3$S · H$_2$O (366.40): C 56.24, H 4.19, N 14.57, S 8.34; found: C 56.62, H 4.39, N 14.92, S 8.21.

*6,7-Bis(4-methoxyphenyl)-1-methyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-one 2,2-Dioxide* (**14b**). From **13b** (1.50 g, 3.5 mmol), MeOH/H$_2$O 1:1 (100 ml), and K$_2$CO$_3$ (1.90 g, 11.9 mmol): 1.10 g (70%) of **14b**. ^{1}H-NMR: 3.31 (*s*, Me); 3.73 (*s*, 2 MeO); 7.32 – 7.54 (*m*, 4 arom. H); 7.30 – 7.41 (*m*, 4 arom. H). Anal. calc. for C$_{20}$H$_{18}$N$_4$O$_5$S (426.45): C 56.33, H 4.25, N 13.64, S 7.52; found: C 56.72, H 4.49, N 13.92, S 7.21.

*1-Methyl-7-phenyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-one 2,2-Dioxide* (**14c**). From **13c** (1.00 g, 3.5 mmol), MeOH/H$_2$O (120 ml), and K$_2$CO$_3$ (1.9 g, 11.9 mmol): 0.90 g (92%) of **14c**. 1 H-NMR: 3.49 (*s*, Me); 7.57 – 7.59 (*m*, 3 arom. H); 8.25 – 8.29 (*m*, 2 arom. H); 9.04 (*s*, H−C(6)). Anal. calc. for C$_{12}$H$_{10}$N$_4$O$_3$S (290.29): C 49.65, H 3.47, N 19.29, S 11.04; found: C 49.72, H 3.49, N 19.52, S 11.21.

*1*H*-Pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-thione 2,2-Dioxides* **15a – c**. *General Procedure.* A soln. of the 1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazin-4(3*H*)-one 2,2-dioxide **14** (1.0 mmol) in anh. pyridine (20 ml) was treated with P$_2$S$_5$ (2.5 mmol) and then refluxed for 48 h. The soln. was acidified with conc. HCl soln. and evaporated. The residue was dissolved in sat. NaHCO$_3$ soln. and then, conc. HCl soln. was added. The precipitate was filtered and recrystallized from the appropriate solvent (see *Table 1*).

*1-Methyl-6,7-diphenyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-thione 2,2-Dioxide* (**15a**). From **14a** (1.50 g, 4.2 mmol), pyridine (80 ml), and P$_2$S$_5$ (2.40 g, 10.5 mmol): 0.71 g (50%) of **15a**. ^{1}H-NMR: 3.47 (*s*, Me); 7.36 – 7.47 (*m*, 10 arom. H). Anal. calc. for C$_{18}$H$_{14}$N$_4$O$_2$S$_2$ (382.40): C 53.61, H 3.94, N 15.63, S 17.89; found: C 53.82, H 3.59, N 15.92, S 17.54.

*1-Methyl-6,7-bis(4-methoxyphenyl)-1*H*-pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-thione 2,2-Dioxide* (**15b**). From **14b** (1.00 g, 3.5 mmol), pyridine (60 ml), and P$_2$S$_5$ (2.00 g, 8.7 mmol): 0.40 g (42%) of **15b**. ^{1}H-NMR: 3.34 (*s*, Me); 3.78 (*s*, 2 MeO); 6.89 – 7.00 (*m*, 4 arom. H); 7.32 – 7.54 (*m*, 4 arom. H). Anal. calc. for C$_{20}$H$_{18}$N$_4$O$_5$S (442.45): C 58.52, H 4.42, N 13.65, S 15.62; found: C 58.77, H 4.59, N 13.92, S 15.21.

*1-Methyl-7-phenyl-1*H*-pyrazino[2,3-c][1,2,6]thiadiazin-4(3*H*)-thione 2,2-Dioxide* (**15c**). From **14c** (1.50 g, 6.0 mmol), pyridine (100 ml), and P$_2$S$_5$ (3.40 g, 15.0 mmol): 0.72 g (44%) of **15c**. ^{1}H-NMR: 3.71 (*s*, Me);

7.61 – 7.65 (*m,* 3 arom. H); 8.35 – 8.39 (*m,* 2 arom. H); 9.12 (*s,* H−C(6)). Anal. calc. for $C_{12}H_{10}N_4O_2S_2$ (306.36): C 47.05, H 3.29, N 18.29, S 20.93; found: C 47.20, H 3.51, N 18.63, S 20.60.

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