Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides. Sulfur Dioxide Analogs of Pteridines

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Several pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide derivatives have been synthesized for the first time by condensation of suitable 4,5-diamino-1,2,6-thiadiazine 1,1-dioxides and symmetrical 1,2-dicarbonyl compounds. Structures of these compounds have been characterized by their elementary analyses, ^{1}H-nmr and uv spectra as well as their pK_a values. The most striking differences between this series and the corresponding pteridines are discussed.

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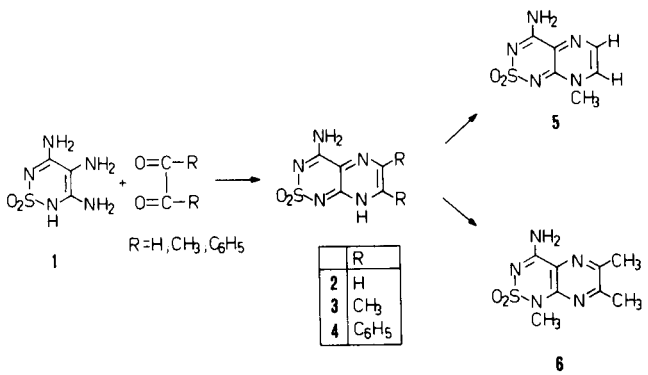
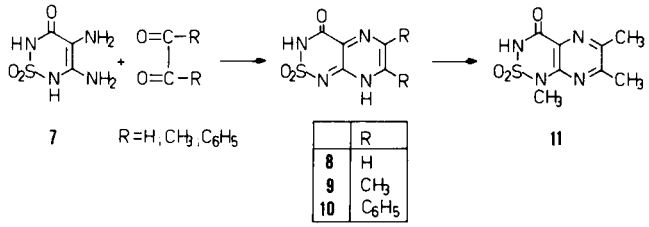
Our continuous interest in the chemistry of 1,2,6-thiadiazines and condensed systems required us to prepare pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides, which can be regarded as sulfur dioxide analogs of pteridines.

The syntheses of these compounds were carried out analogously to the Isay reaction [1], which consists of the condensation of a 4,5-diaminopyrimidine and a 1,2-dicarbonyl compound to form a pteridine. Thus, 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**1**) [2] was condensed with glyoxal, diacetyl and benzil yielding the corresponding 4-aminopyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides **2, 3** and **4**. These condensations can be achieved under neutral and slightly alkaline conditions respectively, but yields were higher using acid in water-ethanol mixtures. *N*-Methylation of **2** and **3** in alkaline solution with dimethyl sulfate led to monosubstitution at N-8 and N-1 yielding **5** and **6** respectively, whereas the 6,7-diphenyl derivative **4** failed to react from solubility reasons. Reaction in dimethyl formamide [3] was also unsuccessful.



Scheme 1

In a similar sequence of reactions lumazine analogs have been prepared condensing 4,5-diamino-6*H*-1,2,6-thiadiazine-3(2*H*)-one (**7**) [4] with glyoxal, diacetyl, and benzil respectively to yield **8, 9**, and **10** in reasonable yields. Treatment of **9** with dimethyl sulfate in weakly basic medium afforded again monosubstitution with formation of the 1-methyl derivative **11**.



Scheme 2

The structure elucidations of the newly synthesized compounds are based on various physical data. The empirical formulae are derived from C,H,N elementary analyses and mass spectra, whereas the various functional groups can be seen in the nmr spectra taken in DMSO-d_6. More detailed information about the fine structure of these molecules including tautomeric properties can best be depicted from the uv spectra based on the pK_a determinations (Table 1). From a comparison of the uv spectra of the isopterins (4-amino-2-oxo-1,2-dihydropteridines) [5] and the structurally analogous 4-aminopyrazino[2,3-*c*]-[1,2,6]thiadiazine 2,2-dioxides it can be concluded that the latter compounds exist in the neutral form as the 8-H tautomers due to the much closer spectral resemblance with the 8-substituted isopterins than the 1-H tautomers which absorb at much lower wavelengths (Figure 1).

The strongly acidifying *S*-dioxide function causes the formation of this unusual cross-conjugated π-electron system, which seems to be energetically more stable if the acidic hydrogen is localized at a more distant position forming a conjugated mesomeric sulfonamide function. The 4-oxopyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide derivatives **8-10** have to be regarded also as 8-H tautomers, since

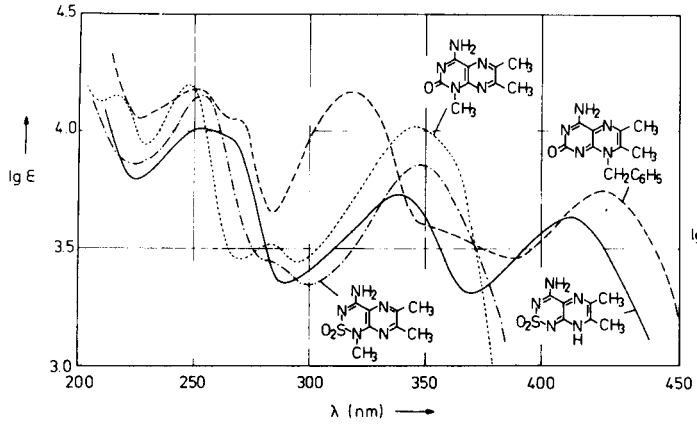


Figure 1. The uv absorption spectra of 4-amino-6,7-dimethyl-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (**3**) (*p*H 1) −, 4-amino-8-benzyl-6,7-dimethyl-2-oxo-2,8-dihydropteridine (*p*H 8.0) ---, 4-amino-1,6,7-trimethyl-2-oxo-1,2-dihydropteridine (*p*H 6.0) ... and 4-amino-1,6,7-trimethylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (**6**) (methanol) −·−·−·.

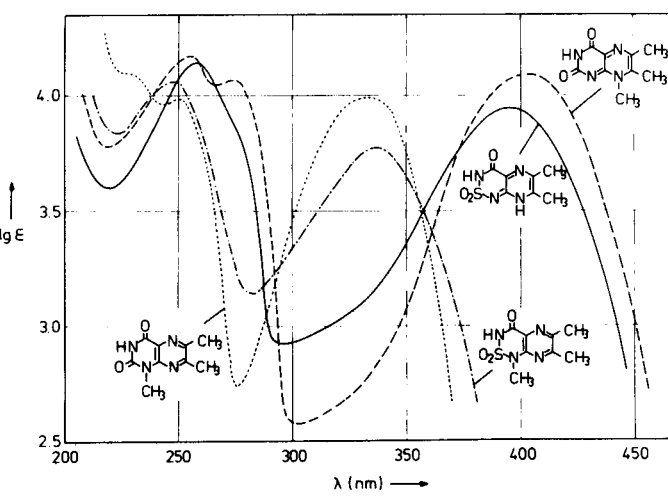


Figure 2. The uv absorption spectra of 6,7-dimethyl-4-oxo-3,4-dihydro-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (**9**) (*p*H 0.0) −, 6,7,8-trimethyllumazine (*p*H 7.0) ---, 1,6,7-trimethyllumazine (*p*H 5.0) ... and 1,6,7-trimethyl-4-oxo-3,4-dihydropyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide (*p*H 4.0) −·−·−·.

the spectral similarity to the 8-substituted lumazines [6] is very striking (Figure 2).

The strong acidic character of all compounds is reflected by the low lying pK_a values, which show an increase of acidity in comparison to the corresponding pteridines of about 6-7 units.

The structures of the *N*-methylated products **5**, **6** and **11** can also be determined from their uv spectra. Compound **5** has to be the 8-methyl derivative since its spectrum is very similar to **2**. Compounds **6** and **11** on the other hand, absorb at much lower wavelengths indicating that methyl-

Table 1

Physical Data of Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides

-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide		pK_a in water	UV Absorption Spectra λ max (nm)	UV Absorption Spectra log ε	pH	Molecular Form
4-Amino-8*H*-	(**2**)	3.54 ±0.1	246 336 401	3.95 3.66 3.47	0.0	[a]
			259 381	4.16 3.73	7.0	[b]
4-Amino-6,7-dimethyl-8*H*-	(**3**)	4.05 ±0.2	252 339 411	4.02 3.74 3.63	1.0	[a]
			263 382	4.17 3.83	8.0	[b]
4-Amino-6,7-diphenyl-8*H*-	(**4**)	3.51 ±0.1	276 369 441	4.26 3.97 3.45	1.0	[a]
			285 405	4.33 3.98	6.0	[b]
4-Amino-8-methyl-	(**5**)		258 313 401	3.98 3.18 3.76	7.0	[a]
			260 (324) 410	4.00 (3.23) 3.78	Methanol	[a]
4-Amino-1,6,7-trimethyl	(**6**)		253 348	4.15 3.89	7.0	[a]
			255 (286) 348	4.16 (3.38) 3.85	Methanol	[a]
4-Oxo-3,4-dihydro-8*H*-	(**8**)	1.20 ±0.1	255 386	4.15 3.79	−1.0	[a]
		5.50 ±0.04	240 332	3.99 3.62	3.0	[b]
			257 375	4.16 3.70	8.0	[c]
6,7-Dimethyl-4-oxo-3,4-dihydro-8*H*-	(**9**)	1.99 ±0.1	258 395	4.16 3.95	0.0	[a]
		6.25 ±0.07	244 335	4.04 3.79	4.0	[b]
			260 375	4.18 3.83	9.0	[c]
6,7-Diphenyl-4-oxo-3,4-dihydro-8*H*-	(**10**)	1.20 ±0.05	(222) 285 428	(4.27) 4.28 4.06	−1.0	[a]
		5.70 ±0.1	276 363	4.23 3.99	4.0	[b]
			238 285 396	4.19 4.31 3.98	10.0	[c]
1,6,7-Trimethyl-4-oxo-3,4-dihydro	(**11**)		248 338	4.09 3.81	4.0	[a]

[a] Neutral form. [b] Monoanion. [c] Dianion. Shoulder in parentheses ( ).

ation has not taken place at N-8 but more likely at N-1 due to the steric interaction of the adjacent 7-methyl group. The uv spectra are now in good agreement with those of 1,6,7-trimethylisopterin [5] (Figure 1) and 1,6,7-trimethyllumazine [7] (Figure 2) respectively. The different site of *N*-methylation in **5** and **6** can also be seen from the shift differences in the nmr spectra.

EXPERIMENTAL

Melting points are uncorrected. The uv spectra were recorded on a Carey Recording Spectrophotometer 118. Infrared spectra were measured on a Perkin-Elmer 257 or on an Infracord 137 E. The ^{1}H-nmr spectra were determined on a Varian XL-100 spectrometer with TMS as the internal standard.

4-Amino-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**2**).

A suspension of 1 g (5.6 mmoles) of 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**1**) in 6 ml of water, 25 ml of ethanol and 2 ml of 2*N* hydrochloric acid was treated with glyoxal (0.4 g, 5.6 mmoles) and refluxed for 10 hours. After cooling of the solution the yellow solid, which had appeared, was filtered off. Further concentration of the filtrate afforded more of the crude product. Recrystallization from water/ethanol gave 0.76 g (68%) pure **2** of mp 304-306°; ir (potassium bromide): 3500-3150 (NH_2, NH), 1665 (C=N), 1320, 1165 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.56 (d, 1H, =CH, J = 2.4 Hz), 8.5 (m, 2H, NH_2, deuterium oxide exchangeable), 8.33 (d, 1H, =CH, J = 2.4 Hz).

Anal. Calcd. for $C_5H_5N_5O_2S$ (199.1): C, 30.15; H, 2.51; N, 35.17; S, 16.08. Found: C, 30.28; H, 2.41; N, 35.53; S, 15.67.

4-Amino-6,7-dimethyl-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**3**).

This compound was prepared using the method described above for **2** starting from 1 g (5.6 mmoles) of **1** and diacetyl (0.5 g, 5.6 mmoles) in 5 ml of water, 20 ml of ethanol and 2 ml of 2*N* hydrochloric acid, yield 0.9 g (69%), mp 266-268°; ir (nujol): 3500-3150 (NH_2, NH), 1650 (C=N), 1315, 1165 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.2 (bs, 1H, NH_2, deuterium oxide exchangeable), 8.0 (bs, 1H, NH_2, deuterium oxide exchangeable), 2.5 (CH_3).

Anal. Calcd. for $C_7H_9N_5O_2S$ (227.2): C, 37.00; H, 3.96; N, 30.83; S, 14.09. Found: C, 37.01; H, 3.99; N, 30.57; S, 14.33.

4-Amino-6,7-diphenyl-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**4**).

This compound was prepared using the method described above for **2** starting from 0.5 g (2.8 mmoles) of **1** and benzil (0.58 g, 2.8 mmoles) in 30 ml of water, 30 ml of ethanol and 2 ml of 2*N* hydrochloric acid, yield 0.56 g (57%), mp 277-279°; ir (nujol): 3500-3100 (NH_2, NH), 1650 (C=N), 1315, 1150 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.6 (bs, 1H, NH_2, deuterium oxide exchangeable), 8.4 (bs, 1H, NH_2, deuterium oxide exchangeable), 7.5 (m, 10H, ArH).

Anal. Calcd. for $C_{17}H_{13}N_5O_2S$ (351.3): C, 58.11; H, 3.70; N, 19.94; S, 9.12. Found: C, 58.16; H, 3.68; N, 20.28; S, 9.50.

4-Amino-8-methylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**5**).

Dimethyl sulfate (0.2 ml) was added dropwise to a solution of 0.3 g (1.5 mmoles) of **2** in 20 ml of 0.1*N* sodium hydroxide and 5 ml of ethanol. The reaction mixture was stirred at room temperature for 3 hours and then 10 ml of 0.1*N* sodium hydroxide and 0.2 ml of dimethyl sulfate were added. After 4 hours stirring at room temperature the solution was cooled and the precipitate which had appeared was filtered and recrystallized from water to give 0.13 g (40%), mp >315°; ir (nujol): 3500-3200 (NH_2), 1640 (C=N), 1300, 1165 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.28 (d, 1H, =CH, J = 4.5 Hz), 7.85 (m, 2H, NH_2, deuterium oxide exchangeable), 7.73 (d, 1H, =CH, J = 4.5 Hz), 3.65 (s, 3H, NCH_3).

Anal. Calcd. for $C_6H_7N_5O_2S$ (213.2): C, 33.80; H, 3.28; N, 32.86; S, 15.02. Found: C, 33.83; H, 3.37; N, 33.04; S, 15.18.

4-Amino-1,6,7-trimethylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**6**).

Dimethyl sulfate (0.2 ml) was added dropwise to a solution of 0.28 g (1.2 mmoles) of **3** in 25 ml of 0.2 *M* sodium bicarbonate and 6 ml of ethanol. The reaction mixture was stirred at room temperature for 3 hours and then 0.2 ml of dimethyl sulfate was added. After 4 hours stirring at room temperature the solution was cooled and the precipitate which had appeared was filtered and recrystallized from water to give 0.15 g (57%), mp 244-246°; ir (nujol): 3500-3200 (NH_2), 1625 (C=N), 1305, 1165 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.65 (bs, 1H, NH_2, deuterium oxide exchangeable), 8.45 (bs, 1H, NH_2, deuterium oxide exchangeable), 3.35 (s, 3H, NCH_3), 2.55 (CH_3).

Anal. Calcd. for $C_8H_{11}N_5O_2S$ (241.2): C, 39.83; H, 4.56; N, 29.04; S, 13.27. Found: C, 39.94; H, 4.24; N, 29.31; S, 13.47.

4-Oxo-3,4-dihydro-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**8**).

This compound was prepared using the method described above for **2** starting from 0.5 g (2.5 mmoles) of 4,5-diamino-6*H*-1,2,6-thiadiazin-3(2*H*)-one 1,1-dioxide (**7**) and glyoxal (0.18 g, 2.5 mmoles) in 5 ml of water, 10 ml of ethanol and 1 ml of 2*N* hydrochloric acid, yield 0.18 g (32%), mp 244-246°; ir (nujol): 3500-3100 (NH), 1690 (C=O), 1620 (C=N), 1320, 1175 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 8.35 (d, 1H, =CH), 8.25 (d, 1H, =CH), 6.75 (m, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_5H_4N_4O_3S$ (200.1): C, 30.00; H, 2.00; N, 28.00; S, 16.00. Found: C, 29.87; H, 1.95; N, 28.01; S, 16.32.

6,7-Dimethyl-4-oxo-3,4-dihydro-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**9**).

This compound was prepared using the method described above for **2** starting from 0.4 g (2.2 mmoles) of **7** and diacetyl (0.58 g, 2.2 mmoles) in 5 ml of water, 15 ml of ethanol and 1.5 ml of 2*N* hydrochloric acid, yield 0.2 g (39%), mp 252-254°; ir (nujol): 3500-3100 (NH), 1675 (C=O), 1615 (C=N), 1325, 1175 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.5 (m, NH, deuterium oxide exchangeable), 2.45 (CH_3).

Anal. Calcd. for $C_7H_8N_4O_3S$ (228.2): C, 36.84; H, 3.51; N, 24.56; S, 14.03. Found: C, 36.85; H, 3.43; N, 24.44; S, 14.36.

6,7-Diphenyl-4-oxo-3,4-dihydro-8*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**10**).

This compound was prepared using the method described above for **2** starting from 0.5 g (2.8 mmoles) of **7** and benzil (0.6 g, 2.8 mmoles) in 20 ml of water, 10 ml of ethanol and 2 ml of 2*N* hydrochloric acid, yield 0.25 g (25%), mp 199-200°; ir (nujol): 3500-3100 (NH), 1680 (C=O), 1615 (C=N), 1325, 1165 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.3 (m, 10H, ArH), 7.1 (m, NH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{17}H_{12}N_4O_3S$ (352.3): C, 57.95; H, 3.41; N, 15.91; S, 9.09. Found: C, 57.60; H, 3.59; N, 16.15; S, 9.49.

1,6,7-Trimethyl-4-oxo-3,4-dihydropyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (**11**).

Dimethyl sulfate (0.2 ml) was added dropwise to a solution of 0.08 g (3.3 mmoles) of **9** in 6 ml 0.1 *M* of sodium bicarbonate and 3 ml of ethanol. The reaction mixture was stirred at room temperature for 3 hours and then 0.1 ml of dimethyl sulfate was added. After 4 hours stirring at room temperature, the solution was cooled and the precipitate which had appeared was filtered and recrystallized from water to give 54 mg (64%); ^{1}H-nmr (DMSO-d_6): δ 5.1 (m, NH, deuterium oxide exchangeable), 3.4 (s, 3H, NCH_3), 2.6 (s, CH_3).

Anal. Calcd. for $C_8H_{10}N_4O_3S\cdot\frac{1}{2}H_2O$: C, 38.24; H, 4.38; N, 22.31. Found: C, 37.96; H, 4.66; N, 22.58.

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