SYNTHESIS AND E/Z STEREOISOMERISM OF 6-CARBALDOXIME DERIVATIVES OF PYRAZINO[2,3-c]-1,2,6-THIADIAZINE 2,2-DIOXIDE

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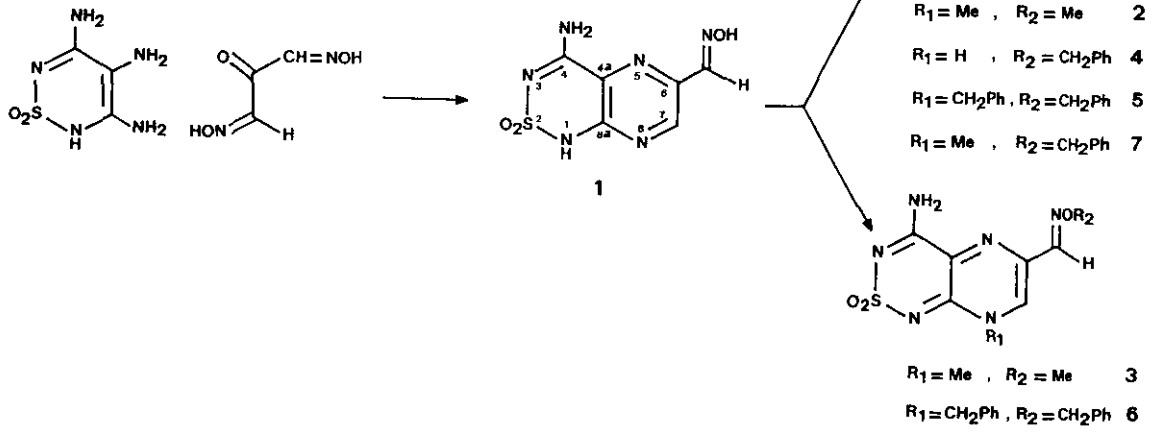
Abstract- The synthesis of 6-carbaldoxime derivatives of pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide is reported. Tautomerism and E/Z stereoisomerism are discussed on the basis of uv and nmr spectral data.

The synthesis, biological activity and physico-chemical properties of heterocycles containing the $-N-SO_2-N-$ moiety have interested us for some time.[1] In connection with a project dealing with the functionalization of the SO_2 analogue of pteridine, namely pyrazino-[2,3-c]-1,2,6-thiadiazine 2,2-dioxide, it became necessary to obtain the corresponding 6-carbaldoxime compound (**1**) and some of its derivatives. These oximes showed interesting configurational problems which were worth a more detailed nmr study. Thus, in this paper, we report the first synthesis of pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxides bearing the hydroxyiminomethyl function together with ^{13}C and ^1H nmr study of their configurational equilibria. Tautomeric aspects and pK_a values are also discussed on the basis of uv spectral data.



The parent compound 4-amino-6-[(hydroxyimino)methyl]-1H-pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (**1**) was obtained from 3,4,5-triamino-2H-1,2,6-thiadiazine 1,1-dioxide[2] and propanetrione-1,3-dioxime (following a modification of the procedure used for related pteridines).[3] Alkylation of this compound with dimethyl sulfate afforded a mixture from which it was possible to separate the corresponding dimethyl derivatives (**2**) and (**3**). Treatment of **1** with benzyl bromide in a basic aqueous solution afforded the (benzyloxyimino)methyl derivative (**4**), which precipitated from the reaction medium. Further benzylation of **4** in acetone yielded a mixture from which it was possible to separate both the N-1 and N-8 benzyl isomers (**5**) and (**6**). The corresponding N-1 methyl derivative (**7**) was prepared from **4** and methyl iodide under standard conditions.

The structures of the newly synthesized compounds were established on the basis of analytical and spectroscopic data (Tables 1, 2 and 3). The site of alkylation was assigned by uv and ^{13}C nmr spectral data in comparison with previously reported related structures.[5]

For the N'-unsubstituted compounds (**1**) and (**4**) information of the predominant molecular species in solution can be deduced from the uv spectra and the spectrophotometrically determined pK_a values (Table 1). The site of the tautomeric equilibria can be depicted from the two uv absorption bands of the neutral species since the longest band at 400 nm is characteristic for the N(8)-H tautomer whereas the second band at 350 nm indicates the presence of N(1)-H isomer. This assignment which has been proved in related compounds[5] indicates that the neutral species of the N'-unsubstituted derivatives (**1**) and (**4**) exist, in water, as a mixture of the N(1)-H and N(8)-H tautomers.

Table 1
Uv-Absorption spectra of 6-carbaldoxime derivatives of pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxides

Compd	pK_a in H_2O	λ_{max} (nm)				log ε				Solvent	Mol[a] form
1	2.97±0.02	216	276	359	426	3.39	4.29	3.71	3.39	H_2O(pH=1)	0
	10.53±0.02	220	284	[296]	401	3.94	4.30	[4.26]	3.82	H_2O(PH=5)	-
		218		305	416	3.92		4.39	3.81	H_2O(pH=13)	--
2		221	280	364		3.93	4.20	3.68		MeOH	0
3		[220]	297	382	439	[3.79]	4.22	3.47	3.60	MeOH	0
4	3.07±0.07		285	360	428		4.33	3.70	3.43	H_2O(pH=1)	0
		[228]	[294]	300	399	[4.02]	[4.30]	4.30	3.84	H_2O(pH=6)	-
5		[221]	285	362		4.12	4.30	3.78		MeOH	0
6		[228]	297	378	437	4.22	4.46	4.15	3.75	MeOH	0
7		216	282	363		4.02	4.21	3.70		MeOH	0

[a] 0, neutral form; -, anion; --, dianion.

The ^1H nmr spectra of these oximes, gathered in Table 2, showed double signals for some of the protons due to the presence of both the E and Z isomers, their ratio being time-dependent.

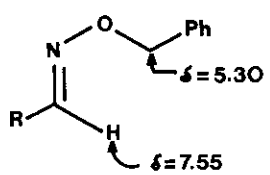
The spectra of recently prepared samples indicated a predominance of the Z isomers. After equilibration the Z isomer is predominant in DMSO, except in the case of compound (**7**), whereas in $CDCl_3$ the major isomer is E.

Table 2
^{1}H Nmr data, in DMSO-d_6, of 6-carbaldoxime derivatives of pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxides

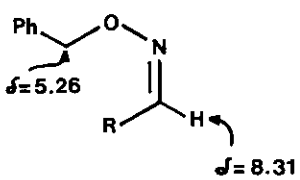
Compd	Isomer	H-7[a]	CH=NO[a]	O-CH_2[a]	N-CH_2[a]	Others[b]	Z/E ratio[c]
1	Z	8.95	8.08			8.71, 8.54 (br s, 2H,	79/21[d]
	E	9.46	7.49			NH_2)	
2	Z	9.02	8.18	3.99	3.41	8.95, 8.82 (br s, 2H,	64/36[d] 26/74[e]
	E	9.44	7.55	4.03	3.42	NH_2)	
3	Z	8.71	8.03	3.92	3.68	8.00, 7.82 (br s, 2H,	53/47[d]
	E	9.08	7.37	3.99	3.68	NH_2)	
4	Z	8.91	8.21	5.26		8.64, 8.44 (br s, 2H,	55/45[d]
	E	9.33	7.55	5.30		NH_2), 7.40 (m, 5H, Ph)	
5	Z	9.01	8.23	5.24	5.22	9.05, 8.82 (br s, 2H,	71/29[d] 26/74[e]
	E	9.41	7.60	5.28	5.22	NH_2), 7.35 (m, 10H, Ph)	
6	Z	8.68	8.10	5.37	5.18	8.08, 7.88 (br s, 2H,	91/9[d]
	E	9.00	7.40[f]	5.33	5.15	NH_2), 7.40 (m, 10H, Ph)	
7	Z	9.03	8.26	5.28	3.31	8.79 (br s, 2H, NH_2),	13/87[d] 25/75[e]
	E	9.48	7.61	5.32	3.31	7.42 (m, 5H, Ph)	

[a] Singlets. [b] These signals correspond to both isomers. [c] In the equilibrium. [d] In DMSO-d_6. [e] In $CDCl_3$. [f] Together with the Ph signals.

The assignment of the configuration was done on the basis of NOE experiments carried out in compound (**7**). Irradiation of the signals corresponding to the protons of the aldoxime and of the methylene group of the benzyl rest showed an NOE effect only on the signals appearing at 7.55 and 5.30 ppm, which were thus assigned to the E isomer. To the best of our knowledge, this is the first time that this method has been used to establish the configuration in O-substituted oximes.[6]



E



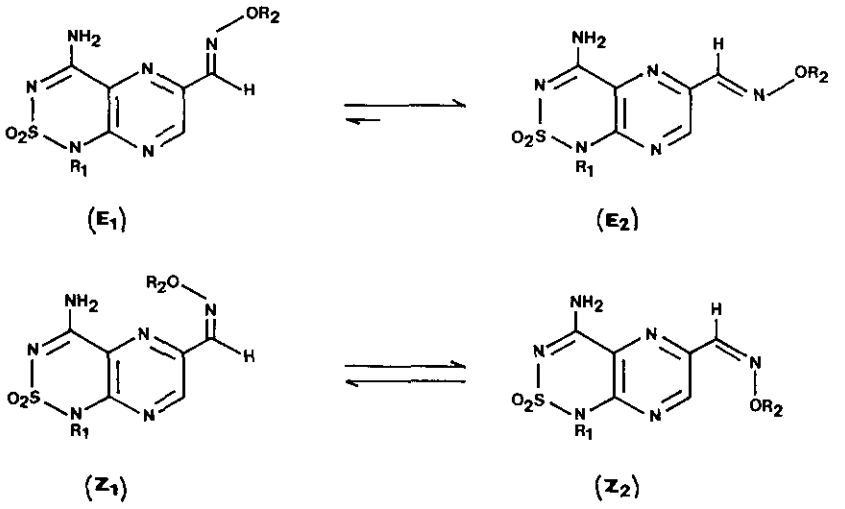
Z

The ^{13}C nmr spectra of these compounds (Table 3) can be used to obtain information about the preferred conformation about the C_6-C_9 bond. The predominance of conformation (E_2) in the E isomer can be deduced from the value of the coupling constant $^3J_{C-7,H-9}$=5.8 Hz since in aromatic systems the fact that ^3J (cis) < ^3J (trans) can be used for assignment purposes.[7]

Table 3
^{13}C Nmr data, in DMSO-d_6, of 6-carbaldoxime derivatives of pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxides

Compd	Isomer	C-4	C-7	C-8a	C-6	C-4a	CH=NO	OCH_2	NCH_2
1	Z	158.1	145.9 J=187.8, ^{3}J=4.0	148.5	140.7	121.0	145.9 J=170.2	-	-
3	Z	155.6	136.9 J=190.0, ^{3}J=4.1	145.7	127.8	126.4	145.5 J=169.4	61.3	39.8
4	Z	157.9	146.2 J=187.9, ^{3}J=4.0	148.8	139.3	121.2	146.7 J=170.5	76.3 J=145.9	-
5	Z	158.2	145.9 J=189.2, ^{3}J=3.7	148.5	139.0	122.6	146.5 J=170.8	76.4 J=146.0	45.6 J=142.0
	E	158.0	150.1	147.8	136.3	123.2	143.4	76.7	45.6
6	Z	155.6	135.3 J=189.4, ^{3}J=3.8	145.2	128.0	127.9	146.1 J=170.2	75.9 J=144.3	53.8 J=144.5
7	Z	157.9	145.9 J=188.6, ^{3}J=3.8	148.9	138.5	122.5	146.6 J=170.6	76.5 J=142.9	28.7 J=143.0
	E	157.6	150.2 J=191.8, ^{3}J=5.8	148.1	136.1	123.0	143.5 J=181.7	76.9 J=143.0	28.8 J=143.0

This conformational preference in the E isomer (E_2) of a situation similar to that found in bipyridine can be explained taking into account the repulsion of the lone pairs of both nitrogens that occurs in the other conformation (E_1). On the other hand, the value of this coupling constant ($^3J_{C-7,H-8}$ 4 Hz) of the Z isomer indicates that this form is probably a mixture of both conformers (Z_1) and (Z_2).



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EXPERIMENTAL

Melting points were determined with a Reichert-Jung Thermovar apparatus and are uncorrected. The uv spectra were recorded with a Perkin-Elmer Lambda 5 spectrophotometer. The ^1H nmr spectra were recorded with a Varian XL-300 (300 MHz) and the ^{13}C nmr were recorded with a Varian XL-300 (75 MHz).

4-Amino-6-[(hidroxyimino)methyl]-1H-pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (1)
A mixture of 3,4,5-triamino-2H-1,2,6-thiadiazine 1,1-dioxide (1.0 g, 5.56 mmol) and propanetrione-1,3-dioxime (1.0 g, 8.62 mmol) in water (25 ml) and concentrated hydrochloric acid was stirred for 10 h at room temperature. The precipitated solid was filtered and recrystallized from water to give 0.79 g (58%) of **1**, mp 265-267°C (decomp). Anal. Calcd for $C_6H_6N_6O_3S$: C, 29.75; H, 2.49; N, 34.70; S, 13.24. Found: C, 29.78; H, 2.62; N, 34.46; S, 12.98.

4-Amino-1-methyl-6-[(methyloxyimino)methyl]pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (2) and 4-amino-8-methyl-6-[(methyloxyimino)methyl]pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (3)
To a solution of **1** (2.0 g, 8.3 mmol) in 0.4 N sodium hydroxide (25 ml), dimethyl sulfate (2 ml) was added. The reaction mixture was stirred at room temperature for 4 h and the precipitate was filtered, washed with 0.5 N potassium carbonate (25 ml) and treated with chloroform. The insoluble material once recrystallized from water afforded 1.3 g (58%) of **3**, mp >300°C. Anal. Calcd for $C_8H_{10}N_6O_3S$: C, 35.55; H, 3,73; N, 31.09. Found: C, 35.65; H, 3.67; N, 31.00.
The chloroform solution was evaporated to dryness and the residue was recrystallized from methanol/water to give 0.12 g (5%) of **2**, mp 275-277°C. Anal. Calcd for $C_8H_{10}N_6O_3S$: C, 35.55; H, 3,73; N, 31.09. Found: C, 35.84; H, 3.93; N, 30.88.

4-Amino-6-[(benzyloxyimino)methyl]-1H-pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (4)
Benzyl bromide (2.1 g, 12.3 mmol) was added to a solution of **1** (2.0 g, 8.3 mmol) in 0.25 N sodium hydroxide (100 ml) and methanol (70 ml). The mixture was stirred at room temperature for 4 h and the methanol removed "in vacuo". The solution was acidified with 35% hydrochloric acid and the precipitate was filtered, washed with chloroform and recrystallized from ethanol/water to give 1.35 g (49%) of **4**, mp 233-235°C. Anal. Calcd for $C_{13}H_{12}N_6O_3S$: C, 46.98; H, 3.64; N, 25.29. Found: C, 46.94; H, 3.66; N, 24.99.

4-Amino-1-benzyl-6-[(benzyloxyimino)methyl]pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (5) and 4-amino-8-benzyl-6-[(benzyloxyimino)methyl]pyrazino[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (6)

A solution of **4** (0.5 g, 1.5 mmol) and benzyl bromide (0.5 g, 2.9 mmol) in acetone (25 ml) with potassium carbonate (0.1 g, 0.75 mmol) was refluxed for 4 h. The solvent was removed "in vacuo" and the residue was separated on a silica gel column (70-230 mesh) using chloroform/methanol (50:1) as eluent.

The first fraction corresponding to **5** was recrystallized from ethanol to give 0.29 g (46%), mp 168-170°C. Anal. Calcd for $C_{20}H_{18}N_6O_3S$: C, 56.86; H, 4.29; N, 19.89. Found: C, 56.74; H, 4.44; N, 19.69.

The second fraction was identified as **6** and recrystallized from ethanol/methanol to give 0.12 g (19%), mp 263-265°C. Anal. Calcd for $C_{20}H_{18}N_6O_3S$: C, 56.86; H, 4.29; N, 19.89. Found: C, 56.85; H, 4.36; N, 19.64.

4-Amino-1-methyl-6-[(benzyloxyimino)methyl]pyrazino-[2,3-c]-1,2,6-thiadiazine 2,2-dioxide (7)

To a suspended solution of **4** (1.5 g, 4.7 mmol) and potassium carbonate (0.32 g, 2.4 mmol) in acetone (100 ml) an excess of methyl iodide was added and the mixture was refluxed for 4 h. The solvent was removed "in vacuo" and 0.5 N potassium carbonate (100 ml) was added. The precipitated solid was filtered and recrystallized from ethanol/methanol to give 0.8 g (51%) of **7**, mp 193-195°. Anal. Calcd for $C_{14}H_{14}N_6O_3S$: C, 48.55; H, 4.07; N, 24.26. Found: C, 48.83; H, 4.24; N, 23.99.

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