Reactivity of 4-Amino-6,7-diphenyl-8*H*-pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide Towards Methylating Agents

Pilar Goya* and Juan Antonio Páez

Instituto de Química Médica (CSIC),
Juan de la Cierva, 3, 28006 Madrid, Spain

Wolfgang Pfleiderer

Fakultät für Chemie Universität Konstanz,
D7750 Konstanz, West Germany

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Reaction of the title compound with different methylating agents to give mono-, di- and trisubstituted derivatives has been studied.

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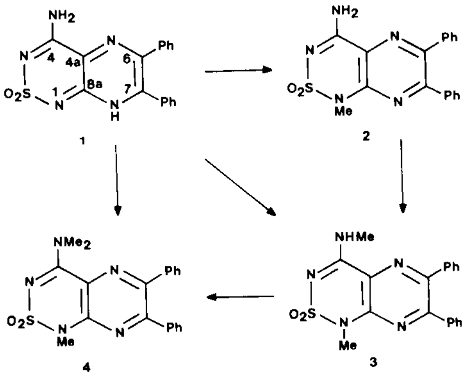
In relation with our ongoing work on heterocycles containing the N-SO_2-N moiety [1] we were interested in studying the methylation, under different conditions, of 4-amino-6,7-diphenyl-8*H*-pyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-dioxide (**1**) [2].

Attempts to methylate **1** in alkaline solution with dimethyl sulfate failed due to solubility reasons. However, treatment of **1** with excess methyl iodide in acetone afforded the mono-, di- and trimethyl derivatives **2**, **3** and **4** depending on whether one, two or three moles of potassium carbonate were used. Besides, selective methylation of **2** and **3** afforded **3** and **4** respectively.

Scheme 1



When methylation of **1** was carried out by treating its silyl derivative with methyl iodide following the procedure reported for 7-oxopyrazinothiadiazines [3], with or without base, only the N-1 monomethyl derivative **2** was obtained.

The structures of the compounds were established according to analytical and spectroscopic data (see Tables I and II). Monomethylation was clearly established at N-1 by comparison of the uv data of **2** with those of model compounds [4]. The fact that in **3** the second methylation had taken place at the exocyclic amino group was confirmed by the signal of the methyl in ^{1}H-nmr (a doublet which collapsed to a singlet on addition of deuterium oxide) and by the multiplicity of this methyl signal in ^{13}C-nmr.

Table I

Physical Data of 6,7-Diphenylpyrazino[2,3-*c*]-1,2,6-thiadiazines

Compound	UV (Methanol) λmax (nm)	^{1}H-NMR [a] N(1)-Me	N(4)-Me	Ph
2	220 275 375	3.53	-	7.3-7.6
3	221 276 376	3.65	3.18 J = 5.2 Hz	7.3-7.5
4	222 277 380	3.63	3.36, 3.73	7.3-7.6

[a] Compound **2** in DMSO-d_6; **3** and **4** in deuteriochloroform.

Table II

^{13}C-NMR Chemical Shifts (ppm) of 6, 7 Diphenylpyrazino [2,3-*c*]-1,2,6-thiadiazines

Compound	C-4	C-7	C-8a	C-6	C-4a	N(1)-Me	N(4)-Me	Ph			
1 [a]	159.1	156.6	147.6	146.1	120			137.1 128.5	130.1 128.4	128.9	
2 [b]	158.4	155.3	147.0	144.5	121.0	28.2		137.3 128.6	137.0 128.3	129.8 128.1	
3 [c]	156.4	156.2	147.4	144.7	120.6	28.5	28.1	137.2 128.8	137.0 128.4	129.9 128.3	129.4
4 [d]	156.6	153.0	147.8	143.2	122.9	28.4	42.0 41.0	136.9 128.9	136.5 128.3	129.6 128.0	129.5 127.9

[a] In DMSO-d_6 + 1% TFA. [b] In DMSO-d_6. [c] In deuteriochloroform.

The reaction course must involve subsequent removal of the relatively acid NH_2 protons since methylation in the absence of base afforded only the N-1 methyl derivative **2**. This behaviour contrasts with that of the structurally related pteridinamines in which direct alkylation of the amino group seems to be unknown. In those cases, indirect methods such as the Dimroth rearrangement have to be used in order to obtain exocyclic *N*-methylamino derivatives [5].

EXPERIMENTAL

Melting points are uncorrected. The uv spectra were recorded on a Perkin-Elmer 550-SE spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian EM-390 operating at 300 MHz and ^{13}C-nmr spectra on a Varian XL 300 operating at 75 MHz using TMS as internal standard. Mass spectra were obtained at 70 eV with a VG-12-250 spectrometer.

General Procedure for Methylation.

To a solution of compound **1** in acetone (40 ml) methyl iodide and potassium carbonate were added. The reaction was refluxed for 3 hours, evaporated to dryness and the residue treated with water. The precipitate was filtered and recrystallized.

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

This compound was prepared from **1**, 0.3 g (0.85 mmole) methyl iodide 4 ml and potassium carbonate 0.06 g (0.42 mmole) and recrystallized from water/methanol, 0.21 g (67%), mp 249-251°; ms: (m/e) 365 (M$^+$).

Anal. Calcd. for $C_{18}H_{15}N_5O_2S$ (365.4): C, 59.16; H, 4.14; N, 19.16; S, 8.77. Found: C, 59.03; H, 4.17; N, 18.96; S, 8.53.

4-Methylamino-1-methyl-6,7-diphenylpyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**3**).

This compound was prepared from **1**, 0.3 g (0.85 mmole), methyl iodide 4 ml and potassium carbonate 0.12 g (0.85 mmole) and recrystallized from ethanol, 0.22 g (68%), mp 250-252°; ms: (m/e) 379 (M$^+$).

Anal. Calcd. for $C_{19}H_{17}N_5O_2S$ (379.4): C, 60.14; H, 4.52; N, 18.46; S, 8.45. Found: C, 60.12; H, 4.61; N, 18.31; S, 8.38.

4-Dimethylamino-1-methyl-6,7-diphenylpyrazino[2,3-*c*]-1,2,6-thiadiazine 2,2-Dioxide (**4**).

This compound was prepared from **1**, 0.3 g (0.85 mmole), methyliodide 5 ml and potassium carbonate 0.18 g (1.3 mmole) and recrystallized from ethanol, 0.25 g (75%), mp 277-279°; ms: (m/e) 393 (M$^+$).

Anal. Calcd. for $C_{20}H_{19}N_5O_2S$ (393.5): C, 61.05; H, 4.87; N, 17.80; S, 8.15. Found: C, 60.76; H, 4.91; N, 17.57; S, 8.02.

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