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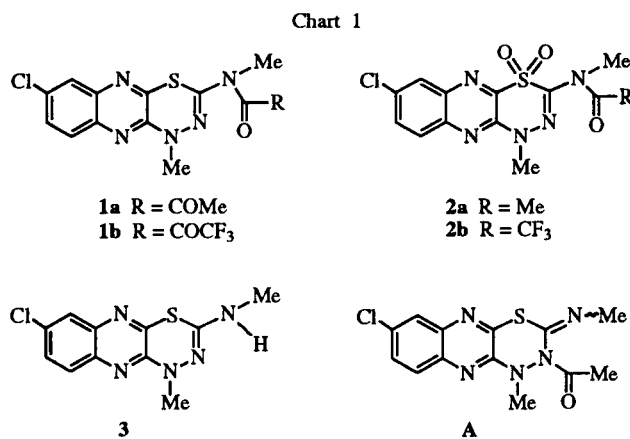
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The carbon signals of the 2-acylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines **1a,b**, 2-acylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1,1-dioxides **2a,b**, and 2-amino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **3** in deuteriodimethyl sulfoxide and in deuteriotrifluoroacetic acid were assigned by the nmr (HMBC, HMQC) spectroscopy. The comparison of the carbon chemical shifts in deuteriodimethyl sulfoxide with those in deuteriotrifluoroacetic acid clarified that compounds **1a**, **1b**, and **3** were deuterized at the N₅-position in deuteriotrifluoroacetic acid, while the 1,1-dioxides **2a,b** did not undergo the N₅-deuteration in deuteriotrifluoroacetic acid.

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In the past several decades, numerous ¹³C-nmr studies on organic compounds have been reported by many research groups, and the assignment for the carbon signals of various heterocyclic compounds have been accumulated and provided in journals and nmr spectral data books. Among the heterocyclic compounds, 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines have been synthesized by several research groups [1-3], but the systematic assignment for the carbon signals of 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxalines have seldom been reported. Recently, we have also synthesized 2-(*N*-acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **1a**, 8-chloro-4-methyl-2-(*N*-trifluoroacetyl)methylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **1b**, 2-(*N*-acetyl)methylamino-8-chloro-4-methyl-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1,1-dioxide **2a**, 8-chloro-4-methyl-2-(*N*-trifluoroacetyl)methylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline 1,1-dioxide **2b**, and 8-chloro-4-methyl-2-methylamino-4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline **3** (Chart 1) [4], wherein the detailed inspection of the nmr spectral data for compound **1a** excluded the 2-imino structure A (Chart 1). In continuation of the above study, we have accomplished the assignment for all carbons of compounds 1-3 from the HMBC and HMQC spectral data in the nmr spectroscopy. Consequently, the comparison of the carbon chemical shifts in deuteriodimethyl sulfoxide (DMSO-*d*₆) with those in deuteriotrifluoroacetic acid (TFA-*d*₁) provided evidence for the deuteration site of compounds 1 and 3 in deuteriotrifluoroacetic acid. This paper describes the assignment for all the carbons of compounds 1-3 in deuteriodimethyl sulfoxide and in deuteriotrifluoroacetic acid together with the deuterized structure of compounds 1 and 3 in deuteriotrifluoroacetic acid.



All carbon signals of compounds **1a,b**, **2a,b**, and **3** in deuteriodimethyl sulfoxide and in deuteriotrifluoroacetic acid are shown in Tables 1 and 2, respectively, wherein the signals are assigned by the HMBC and HMQC spectral data. The respective carbon chemical shifts composing the 4*H*-1,3,4-thiadiazino[5,6-*b*]quinoxaline ring were similar between the *N*-acetyl **1a** and *N*-trifluoroacetyl **1b** derivatives and between the *N*-acetyl *S*-dioxide **2a** and *N*-trifluoroacetyl *S*-dioxide **2b** derivatives, except for the slightly different C₂ carbon chemical shifts between the *S*-dioxides **2a** and **2b**.

When the respective carbon chemical shifts of compound **1a** in deuteriodimethyl sulfoxide were compared with those in deuteriotrifluoroacetic acid, a considerable deshielding of the C₂ (13.2 ppm) and C_{10a} (12.8 ppm) carbons was observed together with a deshielding of the C_{9a} (5.8 ppm) carbon (Chart 2). In contrast, an eminent

Table 1

Carbon Chemical Shifts for Compounds **1a**, **b**, **2a**, **b**, and **3** in Deuteriodimethyl Sulfoxide

Carbon	Chemical Shift (δ ppm)				
	1a	1b	2a	2b	3
C ₂	133.5	132.8	134.5	130.3	139.8
C _{4a}	144.9	143.8	144.0	143.4	144.9
C _{5a}	139.1	139.0	140.9	141.0	139.7
C ₆	128.2	128.5	129.8	129.9	127.4
C ₇	130.2	131.0	135.3	135.6	129.5
C ₈	139.4	139.4	138.7	139.0	137.9
C ₉	125.9	126.0	127.9	127.8	125.6
C _{9a}	130.0	130.5	134.5	135.2	128.5
C _{10a}	136.0	132.8	139.7	139.1	144.1
N ₄ -Me	39.3	39.4	41.4	41.4	39.1
C ₂ -NMe	35.4	34.7	36.5	38.6	29.2
C=O	172.0	156.6	171.0	157.3	---
Me	22.7	---	21.6	---	---
CF ₃	---	115.6	---	115.5	---

Table 2

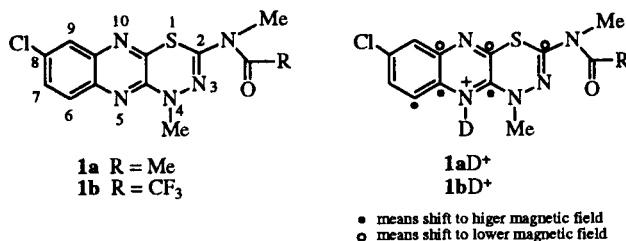
Carbon Chemical Shifts for Compounds **1a**, **b**, **2a**, **b**, and **3** in Deuteriotrifluoroacetic Acid

Carbon	Chemical Shift (δ ppm)				
	1a	1b	2a	2b	3
C ₂	146.7	145.9	131.5	129.2	147.8
C _{4a}	138.0	138.2	143.2	143.0	135.2
C _{5a}	126.5	126.5	141.3	142.3	126.8
C ₆	118.9	119.2	129.6	129.6	117.8
C ₇	133.2	133.6	136.6	136.5	132.6
C ₈	137.1	137.5	138.4	138.4	133.1
C ₉	127.2	127.5	127.2	127.2	126.7
C _{9a}	135.8	136.3	139.8	139.9	135.3
C _{10a}	148.8	146.8	137.7	137.0	146.8
N ₄ -Me	41.3	41.3	40.8	40.7	41.6
C ₂ -NMe	35.3	34.6	37.0	38.1	28.3
C=O	177.9	159.8	177.7	161.3	---
Me	22.1	---	20.0	---	---
CF ₃	---	115.4	---	115.7	---

shielding of the C_{5a} (12.6 ppm) and C₆ (9.3 ppm) carbons was observed together with a shielding of the C_{4a} (6.9 ppm) carbon. Such a tendency was also observed in compound **1b** (Chart 2).

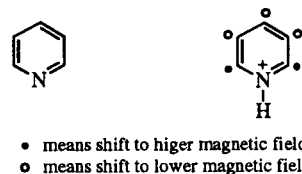
The above deshielding and shielding data suggested a structural change such as a ring *N*-deuteration in the deuteriotrifluoroacetic acid solution of compounds **1a** and **1b**. Namely, it is well known that the α -carbons (C₂ and C₆) of protonated pyridine (Chart 3) are shielded (7.8 ppm) in comparison with those of pyridine, while the β -carbon (C₃ and C₅) and γ -carbon (C₄) of protonated pyridine are deshielded [β -carbons (5.1 ppm), γ -carbon (12.4 ppm)] when compared with those of pyridine [5]. A similar shielding of the α -carbons was further observed in the nmr spectra of 2,6-dichloroquinoxaline [6] when compared the respective carbon chemical shifts in deuteriodimethyl sulfoxide with those in deuteriotrifluoroacetic acid (Chart 4) [7]. The C₅ atom was also shielded in deuterized

Chart 2



Compound	Carbon	Chemical Shift (δ)		Difference in δ
		in DMSO- <i>d</i> ₆	in TFA- <i>d</i> ₁	
1a	C ₂	133.5	146.7	13.2
	C _{4a}	144.9	138.0	6.9
	C _{5a}	139.1	126.5	12.6
	C ₆	128.2	126.5	9.3
	C _{9a}	130.0	135.8	5.8
	C _{10a}	136.0	148.8	12.8
1b	C ₂	132.8	145.9	13.1
	C _{4a}	143.8	138.2	5.6
	C _{5a}	139.0	126.5	12.5
	C ₆	128.5	119.2	9.3
	C _{9a}	130.5	136.3	5.8
	C _{10a}	132.8	146.8	14.0

Chart 3

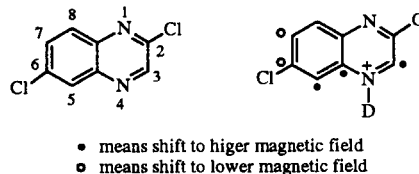


Carbon	Chemical Shift (δ) [a]		Difference in δ
	Pyridine	Pyridinium	
C ₂ , C ₆	150.2	142.4	7.8
C ₃ , C ₅	123.9	129.0	5.1
C ₄	135.9	148.3	12.4

[a] Reference No. 5

2,6-dichloroquinoxaline [7]. From the shielding and deshielding data in Charts 2-4, the deuteration site of compounds **1a** and **1b** in deuteriotrifluoroacetic acid was interpreted as the N₅ atom.

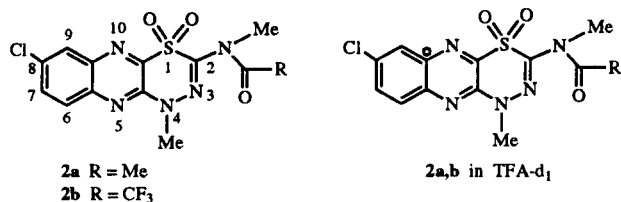
Chart 4



Carbon	Chemical Shift (δ)		Difference in δ
	in DMSO- <i>d</i> ₆	in TFA- <i>d</i> ₁	
C ₂	147.3	148.4	1.1
C ₃	146.6	141.1	5.5
C _{4a}	140.8	133.7	7.1
C ₅	127.8	122.7	5.1
C ₆	134.9	141.8	6.9
C ₇	132.1	135.8	3.7
C ₈	130.1	129.1	1.0
C _{8a}	139.9	141.9	2.0

When the respective carbon chemical shifts of the *S*-dioxides **2a** and **2b** in deuteriodimethyl sulfoxide were compared with those in deuteriotrifluoroacetic acid, most of carbon signals were not so shifted except for a deshielding of only the C_{9a} carbon (4.7-5.3 ppm) (Chart 5). A prominent shielding was not observed in these cases, suggesting the absence of the N₅-deuteration presumably due to a decrease in the basicity of the N₅ atom by the electron-withdrawing *S*-dioxide moiety. Such a decrease in the electron density by the *S*-dioxide moiety would be supported by the following data.

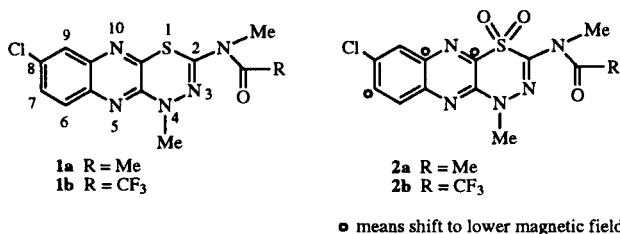
Chart 5



Compound	Carbon	Chemical Shift (δ) in DMSO-d ₆	Chemical Shift (δ) in TFA-d ₁	Difference in δ
2a	C _{9a}	134.5	139.8	5.3
2b	C _{9a}	135.2	139.9	4.7

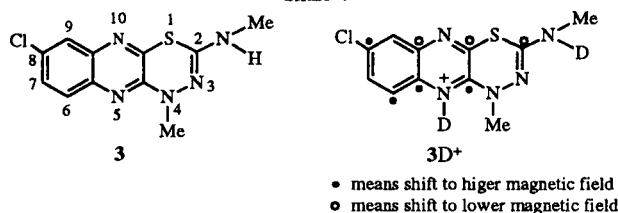
Namely, when the respective carbon chemical shifts of compound **1a** in deuteriodimethyl sulfoxide were compared with those of the *S*-dioxide **2a** in deuteriodimethyl sulfoxide, the C₇, C_{9a}, and C_{10a} carbons of the *S*-dioxide **2a** were deshielded (3.7-5.1 ppm) (Chart 6). A similar tendency was observed between compound **1b** and the *S*-dioxide **2b** in deuteriodimethyl sulfoxide (Chart 6).

Chart 6



Carbon	Chemical Shift (δ)		Difference in δ
	1a in DMSO-d ₆	2a in DMSO-d ₆	
C ₇	130.2	135.3	5.1
C _{9a}	130.0	134.5	4.5
C _{10a}	136.0	139.7	3.7
1b in DMSO-d ₆ 2b in DMSO-d ₆			
C ₇	131.0	135.6	4.6
C _{9a}	130.5	135.2	4.7
C _{10a}	132.8	139.1	6.3

Chart 7



Carbon	Chemical Shift (δ)		Difference in δ
	in DMSO-d ₆	in TFA-d ₁	
C ₂	139.8	147.8	8.0
C _{4a}	144.9	135.2	9.7
C _{5a}	139.7	126.8	12.9
C ₆	127.4	117.8	9.6
C ₈	137.9	133.1	4.8
C _{9a}	128.5	135.3	6.8
C _{10a}	144.1	146.8	2.7

When the respective carbon chemical shifts of compound **3** in deuteriodimethyl sulfoxide were compared with those in deuteriotrifluoroacetic acid (Chart 7), compound **3** was also suggested to be deuterated at the N₅ atom from the data on a remarkable shielding of the C_{4a} (9.7 ppm), C_{5a} (12.9 ppm), and C₆ (9.6 ppm) carbons. A shielding of the C₈ carbon (4.8 ppm) and a deshielding of the C_{10a} carbon (2.7 ppm) in compound **3** were different in degree from those in compounds **1a,b** [C₈ carbon (1.9-2.3 ppm), C_{10a} carbon (12.8-14.0 ppm)], which might be due to the absence or presence of the acyl group in the side chain.

EXPERIMENTAL

The nmr (HMBC and HMQC) spectra of compounds **1a,b**, **2a,b**, **3**, and 2,6-dichloroquinoxaline were measured at 30° with a Varian XL-400 spectrometer at 400 MHz.

Acknowledgement.

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REFERENCES AND NOTES

- [1] A. J. Elliot, *J. Heterocyclic Chem.*, **18**, 799 (1981).
- [2] A. J. Elliot, U. S. Patent 4025510, 1977.
- [3] A. J. Elliot and M. S. Gibson, *J. Org. Chem.*, **45**, 3677 (1980).
- [4] Y. Kurasawa, M. Sekine, H. S. Kim, and Y. Okamoto, *J. Heterocyclic Chem.*, **33**, 1859 (1996).
- [5] Carbon-13 Nuclear Magnetic Resonance Spectroscopy for Organic Chemists, G. C. Levy and G. L. Nelson, eds, Wiley-Interscience, a Division of John Wiley and Sons, Inc., New York, London, Sydney, and Toronto, 1972, p 140 and references cited therein.
- [6] G. Sakata and K. Makino, *Chem. Letters*, 323 (1984).
- [7] The N₄-deuteration, but not N₁-deuteration, is reasonable in the deuteriotrifluoroacetic acid solution of 2,6-dichloroquinoxaline because of the presence of the C₂-chlorine atom.