Tetrahedron Vol. 35, pp. 2151 to 2153
Pergamon Press Ltd., 1979. Printed in Great Britain

THE STRUCTURE OF 1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES

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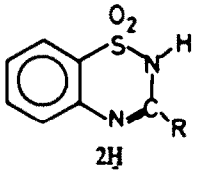
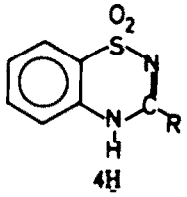
(*Received in UK 1 March 1979*)

Abstract—The structure of N-unsubstituted 1,2,4-Benzothiadiazine-1,1-dioxides has been investigated by means of NMR spectroscopy. ^{13}C NMR spectra obtained in DMSO-d_6 solution show the actual tautomeric form to be the 4H tautomer.

Substituted 1,2,4-benzothiadiazine-1,1-dioxides have been extensively investigated due to their pharmacological activity[1-7] e.g. *diazoxide* as antihypertensive agent and *chlorothiazide* as diuretic agent. In spite of these investigations there still exists some controversy concerning the structure of compounds with the possibility of existence as a 2H or a 4H tautomer.



2H



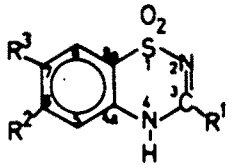
4H

Novello *et al.*[1] tentatively concluded that the tautomeric form present in ethanol solution was the 4H tautomer on basis of UV measurements. Also UV measurements by Yudis[4] indicated the 4H tautomer to be the dominant form, but Topliss and Yudis[4] preferred to retain the hitherto used 2H-nomenclature, although they used the formulas for the 4H tautomer. MO-calculations[3] also indicated the 4H tautomer as being the dominant form. In spite of these investigations recent work on mass spectrometry and structure-activity relationship[5-7] only mention the compounds as 2H tautomers.

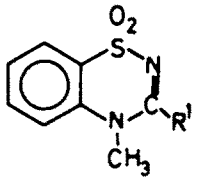
In view of our interest in sulphonylated formamidines and formamidrazones,[8,9] especially those with the possibility of existence in tautomeric forms, we have carried out an NMR investigation on some representative 1,2,4-benzothiadiazine-1,1-dioxides, which can be regarded as cyclic sulphonylformamidines.

As especially ^{13}C NMR spectra have proved valuable for estimating the actual tautomeric form present in solution,[8] these spectra were recorded for compounds **1a–d** with the possibility of tautomerism, compounds **2a–b** as models for the 4H tautomer and compounds **3a–b** as models for the 2H tautomer. The spectra were obtained for all compounds in DMSO-d_6 solution and for some of them in methanol-d_4 solution. As the methanol spectra showed no difference from the DMSO spectra, DMSO was preferred as solvent due to better solubility.

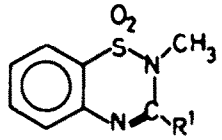
The assignment which appears from Table 1 was made by help of model compounds and by shielding effects for the substituents on the benzene ring. Chemical shift values for aromatic systems can be calculated by use of the shielding effects of the substituents.[10] This type of calculations give reasonable results provided the substituents are *meta* or *para*. For the compounds examined here we might expect an extra effect from the *ortho* substitution and an additional effect due to the "ring formation". ^{13}C NMR shift values have been reported for some sulphonamide drugs[11] but no *ortho*-substituted sulphonamides were investigated. We therefore recorded the ^{13}C NMR spectra of 2-aminobenzenesulphonamide and 2-N-methylaminobenzenesulphonamide to obtain information about the influence of *o*- substitution in sulphonamides. The results (in the experimental part) show that the actual shift values are in agreement with the calculated values, indicating that the *ortho* substitution do not have great influence in this system. To get reasonable shielding effects for the benzothiadiazine-1,1-dioxide system the shift values from the open chain sulphonylformamidines[8] were used.



(Compound; R^1, R^2, R^3): **1a**; H,H,H. **1b**; H,Cl,SO_2NH_2. **1c**; CH_3,H,H. **1d**; CH_3,H,Cl.



2a, R^1 = H. **2b**, R^1 = CH_3



3a, R^1 = H. **3b**, R^1 = CH_3

The distinction between the signals from C atoms 4a and 8a could not be made with certainty from calculated assignments because of unknown influence of the "ring formation". From an undecoupled spectrum of **2a** showing the "three bond couplings", it was possible to make the assignment. The signal from C atom 8a was found at 123.8 ppm as two doublets while C atom 4a was found as a multiplet at 136.8 ppm.

From Table 1 it appears that the signal from C 4a for the 2H tautomer models are found around 143 ppm, while for the 4H tautomer model and for compounds **1** it was found from 135.2 to 138.8 ppm. The signal for C 8a in compounds **1** and **2** are in the area 121–124 ppm, while it is found at a slightly lower field for compounds **3**. The

Table 1. ^{13}C NMR chemical shift values (DMSO-d_6) in ppm (rel. TMS)

Compound	C3	C4a	C5	C6	C7	C8	C8a	N-$\underline{C}H_3$	C-$\underline{C}H_3$
1a	148.7	135.7	118.6	134.1	124.7	127.7	123.6		
1b	149.7	135.6	121.5	139.0	139.9	126.2	121.4		
1c	158.2	136.2	118.2	134.0	124.4	127.1	122.0		23.6
1d	158.5	135.2	120.7	134.4	130.3	123.8	123.1		23.7
2a	152.2	136.8	117.5	134.3	125.1	127.9	123.8	39.0	
2b	161.8	138.8	117.7	134.1	124.6	127.0	124.1	36.9	25.4
3a	149.0	143.8	122.5	135.1	128.6	128.6	126.8	31.7	
3b	156.6	143.1	122.0	134.9	127.6	128.0	125.7	30.0	24.0

Table 2. ^1H NMR chemical shift values [a] in DMSO-d_6 solution

Compound	C3 - $\underline{H}$	C3 - $C\underline{H}_3$	N - $C\underline{H}_3$	N - $\underline{H}$	Arom. $\underline{H}$
1a	8.05 (s)			11 - 13	7.2 - 8.0 (m)
1b[b]	8.10 (s)			11 - 13	8.26 (s), 7.51 (s)
1c		2.38 (s)		7 - 10	7.1 - 7.9 (m)
1d		2.38 (s)			7.2 - 7.8 (m)
2a	8.05 (s)		3.65 (s)		7.3 - 8.0 (m)
2b		2.53 (s)	3.65 (s)		7.3 - 8.0 (m)
3a	7.85 (s)		3.50 (s)		7.3 - 8.0 (m)
3b		2.51 (s)	3.48 (s)		7.3 - 8.0 (m)

[a] Multiplicity given in paranthesis. [b] The $SO_2N\underline{H}_2$ protons were found at δ 7.88 ppm.

signal pattern for C atoms 5–8 closely resembles each other for compounds 1a,1c,2a and 2b, while compounds 3a and 3b show differences especially for C 5.

These data strongly indicate that the actual tautomeric form in solution is the 4H tautomer, and as only one set of signals was present the existence of "greater amounts" of 2H tautomer can be ruled out.

The ^1H NMR spectra (Table 2) were of less conclusive value regarding the estimation of the actual tautomeric form present. All compounds showed only one set of signals at room temperature. For chlorothiazide 1c NMR spectra were obtained in acetone-d_6 down to −50°, but no doubling of signals or couplings were observed. The C3–H signal position for compounds 1a,1b,2a and 3a indicate that 1a,1b and 2a exist in the same tautomeric form, while no conclusions could be drawn from the C3–CH_3 signals for compounds 1c,1d,2b and 3b, probably because the distance between the methyl group and the heterocyclic ring is too long.

Conclusively the compounds 1a–d exist predominantly as one tautomer in solution, as only one set of signals were observed both in ^1H and ^{13}C spectra. Furthermore this tautomeric form is the 4H tautomer as proved by the ^{13}C NMR measurements. It therefore seems reasonable to use both the formula and the name for the 4H tautomer for the benzothiadiazine-1,1-dioxides with the possibility of tautomerism as the actual position of the "tautomeric" hydrogen may be of importance in, e.g. structure-activity relationship and other pharmacological studies.

EXPERIMENTAL

The compounds investigated were prepared by previously published procedures.[2,12] ^1H NMR spectra were obtained on a Jeol JNM MH 60/II instrument. ^{13}C NMR spectra were obtained on a Bruker WH 90 instrument.

2-Aminobenzenesulphonamide. ^{13}C NMR (DMSO-d_6) ppm: C1, 125.7; C2, 147.0; C3, 116.6; C4, 134.5; C5, 118.3; C6, 129.4. Calc.: C1, 129.5; C2, 150.8; C3, 120.5; C4, 138.2; C5, 122.1; C6, 133.2.

2-N-*Methylaminobenzenesulphonamide*. ^{13}C NMR (DMSO-d_6) ppm: C1, 126.0; C2, 146.8; C3, 112.4; C4, 134.6; C5, 115.7; C6, 129.1. Calc.: C1, 130.2; C2, 151.0; C3, 116.6; C4, 138.8; C5, 119.9; C6, 133.5. Calculated shift values: Coumpound 2a. C4a, 136; C5, 120; C6, 132; C7, 125; C8, 126; C8a, 134. Compound 3a. C4a, 147; C5, 122; C6, 136; C7, 126; C8, 128; C8a, 130.

Acknowledgements—We are indepted to Statens Naturvidenskabelige Forskningsråd for ^1H and ^{13}C NMR facilities. A gift of chlorothiazide from Merck Sharp, Dohme and of diazoxide from Essex Pharma A/S is greatfully acknowledged.

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