Tetrahedron. Vol. 30, pp. 3839 to 3848. Pergamon Press 1974 Printed in Great Britain

MONOXIMES AND DIOXIMES OF 2,1,3-BENZOTHIADIAZOLE DIONES

A. S. ANGELONI, D. DAL MONTE,* S. POLLICINO, E. SANDRI and G. SCAPINI
Facolta' di Chimica Industriale dell'Universita' Viale Risorgimento, 4-40136 Bologna, Italy

(*Received in the UK* 2 *February* 1974; *Accepted for publication* 4 *March* 1974)

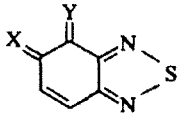
Abstract—NMR spectra, in organic solvents, and dissociation constants in water, have been determined for a series of monoximes, dioximes and mono-O-methyldioximes of 2,1,3-benzothiazole-4,5- and 4,7-dione. On the basis of NMR data "4 - hydroxy - 5 - nitroso-, 4 - hydroxy - 7 - nitroso- and 5 - hydroxy - 4 - nitroso - 2,1,3 - benzothiadiazole" exist predominantly in quinonemonoxime forms. Configurations were assigned to geometrical isomers. The 4,5- and 4,7 - di - O - methyldioximinobenzothiadiazoles were also investigated. Four and two geometrical isomers of the 4,5- and 4,7-derivatives, respectively, have been separated, and the physical and spectral properties of each isomer are described.

In connection with our studies on 2,1,3 - benzo - X - diazoles (X = O, S, N)[1-8] we were interested in obtaining data on the properties of hydroxynitroso derivatives and related compounds.

As the rearrangement of benzoxadiazole derivatives[8] could produce some complications in this study, we first examined benzothiadiazoles, which do not undergo an analogous reaction.

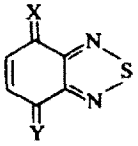
In this paper, the preparations and NMR studies on tautomerism and geometrical isomerism of 4 - nitroso - 5 - hydroxy - (**3**), 4 - hydroxy - 7 - nitroso - (**4**), 4 - hydroxy - 5 - nitroso - 2,1,3 - benzothiadiazole(**5**)† and related dioximino (**9**, **10**), mono - O - methyl and di - O - methyldioximino derivatives (**11–15**) are reported.

The p*Ka* values, in water at 25°, of 4,5- and 4,7 - dioximinobenzothiadiazole (**9**, **10**), their mono - O - methylethers (**13–15**) and hydroxynitrosobenzothiadiazoles (**3–5**) are also measured and the effect of the thiadiazole ring is discussed.



3: X = O; Y = NOH
5: X = NOH; Y = O
6: X = O; Y = NOMe
8: X = NOMe; Y = O

9: X = Y = NOH
11: X = Y = NOMe
13: X = NOH; Y = NOMe
14: X = NOMe; Y = NOH



4: X = O; Y = NOH
7: X = O; Y = NOMe
10: X = Y = NOH
12: X = Y = NOMe
15: X = NOMe; Y = NOH

†Formulas **5–5** represent the oxime tautomer.

RESULTS AND DISCUSSION

According to Pesin,[9] the nitrosation of 5-hydroxybenzothiadiazole (**1**) gave the 4-nitroso derivative (**3**). In a similar way, nitrosation of 4-hydroxybenzothiadiazole (**2**), which was reported to lead to the 7-nitroso derivative (**4**),[9] gave under conditions used previously, an approximately equimolecular mixture of 7-(**4**) and 5-nitroso isomer (**5**). Compounds **4** and **5** were separated and identified by reaction with hydroxylamine, the former yielding the known 4,7-dioxime (**10**),[8] the latter the same 4,5-dioxime (**9**) obtained from **3**. The 4,5- and 4,7 - mono - O - methyldioximes (**13–15**) were analogously obtained from **3–5** and methoxyamine; in this reaction, **3** yielded, in addition to 4 - oximono - 5 - O - methyloximinobenzothiadiazole (**14**), also [1,2,5] thiadiazole [3,4-e] 2,1,3 - benzoxadiazole (**21**).[10]

The 4- and 5 - O - methylmonoximes of benzothiadiazole - 4,5 - dione (**6**, **8**) and the 4 - O - methylmonoxime of benzothiadiazole - 4,7 - dione (**7**), models for quinonemonoxime tautomers, were prepared by standard methods and their structures were confirmed on the basis of the corresponding 4,5- and 4,7 - di - O - methyldioximes (**11** and **12** respectively).

For the unambiguous assignment of chemical shifts in **3** and **6**, the related 6-Me derivatives **16** and **17**, were also prepared.

The NMR spectra of most of the compounds examined (**3–17**) showed the presence of a mixture of geometrical isomers. The separation of di - O - methyldioximes **11** and **12**, from the crude mixtures was successful. Four (*anti*, *amphi-syn*, *syn*, and *amphi-anti*) and two (*syn-syn* and *syn-anti*) isomers, respectively were isolated in a pure form. (*vide infra*).

The NMR investigation was extended to include also hydroxy-(1, 2), hydroxyacetamidobenzothiadiazole (18–20) and [1.2.5] thiadiazolo - [3,4 - e]2,1,3 - benzoxadiazole (21).

The NMR spectra of 1–21 (Tables 1–3) were recorded in dioxan and dimethylsulphoxide; those of 3–17 were recorded also in pyridine. The chemical shifts for dioxan solutions were similar to those for dimethylsulphoxide, the closest analogy occurring in the 3–17 series [the solvent shift (τ_{dox}-τ_{Dmso}) never exceeded 0·2 ppm].*

The tautomerism of 3–5 may be discussed by comparing their spectral patterns with those of O-methylmonoximes 6–8 and on the basis of π-bond localisation.

Thus, in 2,1,3-benzothiadiazole[11] the *ortho*-coupling constant across the 6,7 bond (8·93 c/s) is significantly larger than that across the 5,6 bond (6·66 c/s); acetamido and/or OH groups tend to increase $J_{6,7}$ and $J_{5,6}$, which, however, in 1, 2, 18–20 attain the maximum value of 9·4 and 8·10 c/s, respectively (Table 1). The coupling constants $J_{6,7}$ and $J_{5,6}$ in O-methylmonoximes, dioximes, mono - O - methyl and di - O - methyldioximes (6–15) (Tables 2, 3) were higher than 10·1 c/s and similar to the *cis* coupling of the ethylene type. In 3–5 (Tables 2, 3) the *ortho*-coupling constants were $\geq$ 10·1 c/s; the high degree of π-bond localisation and the good agreement with the spectral patterns of O-methylmonoximes (6–8) showed that the oxime formulation correctly represents the structures of 3–5.

Configurations of the oxime derivatives were assigned mainly on the expectation of relative deshielding of the *syn*-proton coplanar with the oxime group and from pyridine-induced shifts (see Ref 8).

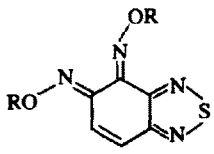
NMR spectra of 3 and 6 (Table 2) showed only one AB pattern and the configuration of =NOR in C-4 could not be assigned by the NMR criteria above reported. By comparing chemical shifts of H-6, H-7 with those of H-7 in 6-Me derivatives 16 and 17, the lower field signal was assigned to H-7. Only one isomer was detected in the spectrum of 5; the *syn* configuration (with respect to H-6) was attributed to the =NOH group in C-5 and the lower field signal was assigned to H-6 on account of the aromatic deshielding effect (pyridine). This assignment is supported by the general tendency for the α-hydrogen (H-6) to resonate at a lower field than the β-hydrogen (H-7) in an α,β-unsaturated oxime system.[12]

By comparison of the chemical shifts of 5 with those of the related O-methyl ether 8, the *syn* configuration could be tentatively assigned also to the latter compound.

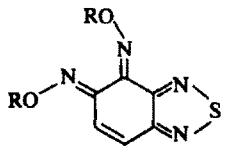
The 4,5-dioxime (9), its mono - O - methyl- and di - O - methyl ethers (13, 14, 11) have four possible isomers (A–D) depending on the orientation of the two oxime groups. The A and B isomers were found to prevail in all these compounds (Table 2).†

Syn or *anti* orientation of the =NOR groups in C-5 allows an unequivocal decision between A,B and C,D structures. Thus, the pyridine deshielding effect on H-6 of two isomers of 9 ruled out structures C,D. On similar grounds, two of three isomers of 4,5 - dioxime - 4 - mono - O - methyl ether (13) were assigned to A,B form and the third isomer to C,D; in agreement with the anisotropic effect of the oxime group, the H-6 proton of 13 resonates at a lower field in A,B isomers than in C or D. Assignment of A,B and C,D structures to four isomers of 4,5 - di - O - methyldioxime (11) were analogously deduced from the difference in chemical shifts of the H-6 proton. Also to the two isomers of 4,5 - dioxime - 5 - mono - O - methyl ether (14) the A,B configuration were assigned by comparison of chemical shifts with those of 9 and 11. The configuration of =NOR group in C-4 in A,B structures of 9, 11, 13 and 14 was tentatively assigned by taking account of the long range deshielding effect of the oximic group: in structure A, H-6 should resonate at a higher field than in structure B.§

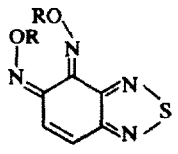
Where only one isomer C,D was detected (see 13), the configuration of the 4-NOMe was not assigned. Of the two isomers C,D of 11, the *syn* structure (C) could tentatively be assigned to the lower melting isomer: in this compound the difference between chemical shifts of H-6 and H-7 is smaller than in D isomer, according to A_2 pattern of the



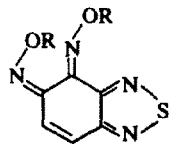
A
anti



B
amphi-syn‡



C
syn



D
amphi-anti‡

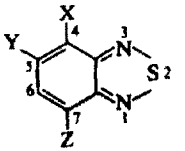
*The solvent shift is anomalous in 20.

†The NMR spectra of 11 were obtained from pure geometrical isomers, those of 9, 13 and 14 from a mixture of geometrical isomers.

‡*Syn* or *anti* with respect to H-6. *Syn* and *anti*, instead of Z and E configurational descriptors are used according to nomenclature employed for corresponding 4,7-dioximes.[8]

§The shielding of H-6 in A isomers relative to B isomers (0·03–0·1 ppm) agreed with that of H-4 in A and B isomers of bornane - 2,3 - dione dioxime (0·08 ppm),[13] and with the value of the long range anisotropic effect in *p*-benzoquinone dioxime (0·1 ppm).[14]

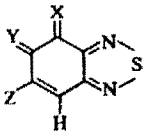
Table 1. Data of NMR spectra at 60 MHz in ppm (τ)[a]



Compounds															
No	X	Y	Z	*Solv*[b]	H-4	H-5	H-6	H-7	$COCH_3$	OH	NH	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
1[c]	H	OH	H	diox	2·87	—	2·75	2·14	—	1·43 (w ≃ 1)	—	2·35	0·66	—	—	9·36
				DMSO	2·76	—	2·59	2·05	—	−0·62 (w ≃ 7)	—	2·32	0·67	—	—	9·42
2[c]	OH	H	H	diox	—	3·15	2·53	2·49	—	0·97 (w ≃ 2)	—	—	—	7·14	1·14	8·99
				DMSO	—	3·04	2·43	2·48	—	−0·93 (w ≃ 5)	—	—	—	6·93	1·48	8·85
18	OH	NHAc	H	diox	—	—	2·53	1·99	7·80	0·31 (w ≃ 10)	1·37 (w ≃ 10)	—	—	—	—	9·30
				DMSO	—	—	2·46	2·15	7·77	−0·85 (w ≃ 4)	0·00 (w ≃ 6)	—	—	—	—	9·30
19	NHAc	OH	H	diox	—	—	2·61	2·29	7·62	−0·5 (w ≃ 5)	0·69 (w ≃ 12)	—	—	—	—	9·30
				DMSO	—	—	2·53	2·15	7·79	−0·25 (w ≃ 16)	0·00 (w ≃ 9)	—	—	—	—	9·30
20	OH	H	NHAc	diox	—	3·18	1·69	—	7·82	v.b.	1·13 (w ≃ 8)	—	—	8·00	—	—
				DMSO	—	3·10	1·99	—	7·79	−0·60 (w ≃ 6)	0·05 (w ≃ 5)	—	—	8·10		

[a] AB patterns unless specified otherwise. J in c/s; w, width at half height in c/s; v.b. very broad signal.
[b] Diox, dioxan; DMSO, dimethyl sulphoxide-d_6; Py, pyridine-d_5.
[c] ABC pattern analysed by LAOCOON III computer program, r.m.s. error less than 0·04 Hz.

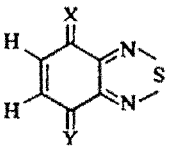
Table 2. Data of NMR spectra at 60 MHz in ppm (τ)[a]



Compounds					Z-6				H-7				NOMe				$J_{6,7}$			
No	X	Y	Z	Solv[a]	*syn*[b]		*anti*[b]		*syn*[b]		*anti*[b]		*syn*[b]		*anti*[b]		*syn*[b]		*anti*[b]	
				diox		3·34				2·22				—				10·25		
3	NOH	O	H	DMSO		3·29				2·08				—				10·20		
				Py		3·22				3·23				—				10·10		
				diox		3·39				2·29				*m*				10·35		
6	NOMe	O	H	DMSO		3·31				2·09				5·65				10·30		
				Py		3·34				2·31				5·71				10·20		
				diox		7·93[e]				2·36				—				1·35[h]		
16	NOH	O	Me	DMSO		8·04[e]				2·24				—				1·50[h]		
				Py		7·89[e]				2·43				—				1·50[h]		
				diox		7·93[e]				2·42				*m*				1·50[h]		
17	NOMe	O	Me	DMSO		i				i				i				i		
				Py		7·93[e]				2·47				5·68				1·50[h]		
				diox	2·50		—		2·80		—		—		—		10·50		—	
5	O	NOH	H	DMSO	2·50		—		2·71		—		—		—		10·50		—	
				Py	2·20		—		2·83		—		—		—		10·40		—	
				diox	2·61		—		2·79		—		*m*		—		10·40		—	
8	O	NOMe	H	DMSO	2·63[m]		—		2·63[m]		—		5·74		—		n		—	
				Py	2·62		—		2·79		—		5·83		—		10·35		—	
					A[c]	**B**[c]	**C**[c]	**D**[c]	**A**[c]	**B**[c]	**C**[c]	**D**[c]	**A**[c]	**B**[c]	**C**[c]	**D**[c]	**A**[c]	**B**[c]	**C**[c]	**D**[c]
				diox[d]	—	2·44	—	—	—	2·67	—	—	—	—	—	—	—	10·50	—	—
9[j]	NOH	NOH	H	DMSO	2·45	2·39	—	—	2·81	2·68	—	—	—	—	—	—	10·35	10·50	—	—
				Py	2·04	2·17	—	—	2·86	2·72	—	—	—	—	—	—	10·35	10·50	—	—
				diox	2·51	2·42	2·85		2·91	2·87	2·95		*m*	*m*	*m*		10·35	10·50	9·90	
13	NOMe	NOH	H	DMSO	2·49	2·39	2·69		2·82	2·79	2·94		5·82	5·80	5·76		10·40	10·50	10·00	
				Py	2·09	2·05	2·75		2·90	2·86	2·91		5·78	5·75	5·72		10·40	10·50	10·10	
				diox	2·59	2·55	—	—	2·89	2·68	—	—	*m*	*m*	—	—	10·40	10·40	—	—
14	NOH	NOMe	H	DMSO	2·59	2·51	—	—	2·75	2·68	—	—	5·92	5·86	—	—	10·35	10·50	—	—
				Py	2·49	2·42	—	—	2·72	2·85	—	—	5·94	5·88	—	—	10·35	10·50	—	—
				diox	2·54	2·51	2·91	2·91	2·90	2·88	3·07	3·13	*m*	*m*	*m*	*m*	10·40	10·50	10·2	10·1
11[j]	NOMe	NOMe	H	DMSO	2·60	2·53	2·77	2·79	2·75	2·72	2·91	3·05	5·81[e] 5·91[f]	5·80[e] 5·90[f]	5·81[e] 5·89[f]	5·80[e] 5·89[f]	10·35	10·50	10·2	10·2
				Py	2·57	2·40	2·91[n]	2·93	2·93	2·92	2·91[n]	3·05	5·78[e] 5·94[f]	5·77[e] 5·89[f]	5·82[e] 5·86[f]	5·73[e] 5·87[f]	10·35	10·50	*n*	10·2

[a] See footnotes *a* and *b* to Table 1; [b] *syn*, *anti* with respect to Z-6; [c] A, *anti*; B, *amphi–syn*; C, *syn*; D, *amphi–anti*; [d] **9** is sparingly soluble in dioxan and A isomer, if less than 15%, is undetectable. [e] 4-NOMe. [f] 5-NOMe. [g] τ_{Me}. [h] $J_{7,Me}$. [i] Insoluble. [j] *syn* (C) and *amphi-anti* (D) isomers are undetectable in the NMR spectrum of crude mixture. [m] Obscured by the solvent. [n] A_2 pattern.

Table 3. Data of NMR spectra at 60 MHz in ppm (τ)[a]



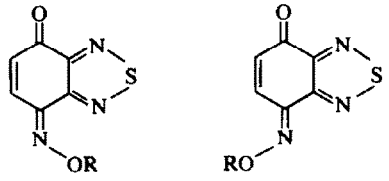
Compounds				H-5			H-6			NOH or NOMe			$J_{5,6}$		
No	X	Y	Solv	E[b]	F[b]		E[b]	F[b]		E[b]	F[b]		E[b]	F[b]	
			diox	3·29	3·29		2·53	1·96		v.b.	v.b.		10·60	10·50	
4	O	NOH	DMSO	3·24	3·24		2·33	1·92		−4·40	−4·20		10·60	10·40	
			Py	3·21	3·21		2·27	1·66		v.b.	v.b.		10·50	10·40	
			diox	3·31	3·31		2·58	2·08		*g*	*g*		10·50	10·50	
7	O	NOMe	DMSO	3·22	3·20		2·41	2·02		5·69	5·74		10·50	10·60	
			Py	3·23	3·26		2·53	2·14		5·74	5·84		10·50	10·50	
				F′[c]	G[c]	G′[c]	F′[c]	G[c]	G′[c]	F′[c]	G[c]	G′[c]	F′[c]	G[c]	G′[c]
10[d]	NOH	NOH	DMSO	2·48[h]	3·02		2·48[h]	2·61		−2·93	−3·12[e]		*h*	10·4	
											−2·70[f]				
			Py	2·09[h]	2·82		2·09[h]	2·18		v.b.	v.b.[e]		*h*	10·6	
											v.b.[f]				
			diox	2·66	2·71	3·14	2·51	3·11	2·58	*g*	*g*	*g*	10·7	10·6	10·5
15	NOMe	NOH	DMSO	2·67	2·78	3·12	2·47	2·97	2·58	5·84	5·84	5·82	10·6	10·5	10·5
			Py	2·57	2·65	3·04	2·16	2·84	2·09	5·86	5·86	5·78	10·6	10·5	10·5
			diox	2·62[h]	3·15		2·62[h]	2·69		*g*	*g*		*h*	10·5	
12[d]	NOMe	NOMe	DMSO	2·57[h]	3·03		2·57[h]	2·69		5·84	5·87[e]		*h*	10·6	
											5·81[f]				
			Py	2·58[h]	3·04		2·58[h]	2·63		5·85	5·85[e]		*h*	10·5	
											5·78[f]				

[a] See footnotes *a* and *b* to Table 1. [b] **E**, *anti*; **F**, *syn* with respect to H-6. [c] **F′**, 4-NOR and 7-NOR *syn* to H-5 and H-6; **G**, 4-NOR *syn* to H-5 and 7-NOR *anti* to H-6; **G′**, 4-NOR *anti* to H-5 and 7-NOR *syn* to H-6. [d] Insoluble in dioxan. Data for DMSO and Py, from Ref 8. [e] NOMe or NOH *syn* to H-6. [f] NOMe or NOH *anti* to H-6. [g] Obscured by the solvent. [h] A_2 pattern.

corresponding protons in [1.2.5] thiadiazolo [3.4-e] 2,1,3 - benzoxadiazole (**21**).*

An inspection of NMR data summarized in Table 2 for **A–D** isomers reveals a number of regularities: the change in chemical shifts of H-6, H-7, produced by substitution of 4-NOH and/or 5-NOH by NOMe is small, but in a distinct direction for **A** and **B** isomers; the 4-NOMe chemical shifts (τ 5·72–5·82) appear downfield with respect to 5-NOMe (τ 5·86–5·94); in **B** isomers is the trend for $J_{6,7}$ to be slightly higher than $J_{6,7}$ in **A,C** and **D** isomers, the more significantly difference being between $J_{6,7}$ of **A,B** and **C,D** isomers.

Both *syn* and *anti* isomers (**E** and **F**) were found in the spectrum of **4** and of its O-methyl ether **7**: the assignment given in Table 3 was made on the basis of the criteria above reported and requires no further discussion.



E *anti* **F** *syn*

R = H, Me

The 4,7-dioxime (**10**) and its di - O - methyl ether (**12**) (whose isomeric composition was previously investigated)[4] have three possible isomers (**E'**, **F'**, and **G**=**G'**) while 4,7 - mono - O - methyldioxime (**15**) have four (**E'**, **F'**, **G** and **G'**).

The spectral analysis of **15** showed the presence of three isomers, the undetectable form being the *anti–anti* (**E'**) as in **10** and **12**. In derivative **15** the structures **F'**, **G** and **G'** were assigned by comparison with the chemical shifts of *syn–syn* (**F'**) and *syn–anti* (**G**=**G'**) isomers of **10** and **12** (Table 3).

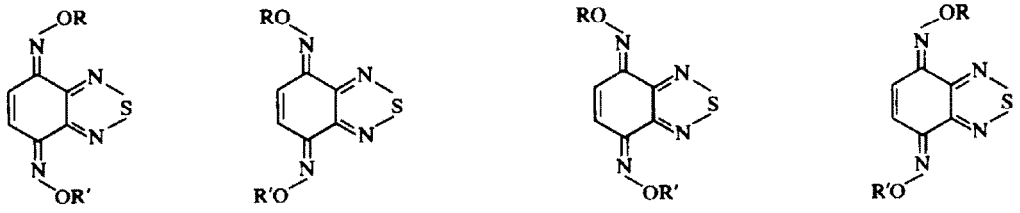
Ionisation constants. p*Ka* values, in water at 25°, of quinonemonoximes **3–5**, 4,5-dioxime (**9**), 4,7-dioxime (**10**) and their O-monomethyl ethers (**13–15**), measured by spectrophotometric method, are reported in Table 4.

The order of acid strength of quinonemonoximes **3–5** was the same as in hydroxynitrobenzothiadiazoles;[6] thus the 5 - oximino - 2,1,3 - benzothiadiazol - 4 - one (**5**) is a weaker acid than the 4 - oximino - 5 - one isomer (**3**) and both are stronger acids than 7 - oximino - 2,1,3 - benzothiadiazol - 4 - one (**4**).

The comparison of p*Ka* of **4** with that of 1,4 - benzoquinonemonoxime (p*Ka* 6·35)[15] indicates that the acidity of the former is lower than would be expected by considering the increase of acid strength by fusion of the thiadiazole ring.[6]

We believe that the apparent paradox can be explained in terms of the benzothiadiazole - 4,7 - dione type tautomer being relatively more stable than the benzoquinone type tautomer.† Indeed, the p*Ka* value of 4,7 - dioxime - O - monomethyl ether (**15**) is lower than that of the corresponding 1,4 - benzoquinone - dioximemono - O - methyl ether (p*Ka* 9·20);[15] this confirmed that, where the structure is the same, the benzothiadiazole compound is a stronger acid than the corresponding benzene derivative.

The 4,7-dioxime (**10**) is a di-basic acid and the



E' *anti–anti* **F'** *syn–syn* **G** *syn–anti* **G'** *syn–anti*

R and R' = H, Me

*Substitution of 4- and 5-NOMe groups by a furazan ring shifts the H-6, H-7 signals downfield with respect to those of **11** *syn* (**21**: A_2 pattern, τ_{dmso} 2·06; τ_{Dmso} 1·86).

†The weaker acidity of 4 - nitroso - 1 - naphthol with respect to 1,4 - benzoquinone monoxime was analogously explained.[16] NMR spectrum of 1,4 - benzoquinone monoxime (in dioxan soln) showed a detectable percentage of nitroso tautomer,[17] whereas this form did not appear in the spectrum of **4**.

‡See Experimental. The approximate p*Ka* value for the *anti* isomer is 8·8.

conjugate base of one oxime group is in conjugation with the other oxime group in the molecule; as a result, pKa_2 is higher than pKa_1 (K_1 and K_2 referring to the two successive ionisations of the oxime groups).

The 4,5-dioxime (**9**) is a monobasic acid in the investigated pH range (4–10) and its p*Ka* value is much lower than that of the 4,7-isomer.

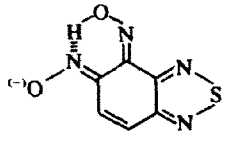
The stronger acidity of the 4,5-derivative can be explained by the prevailing *amphi-syn*‡ configuration of two oxime groups; in this configuration an

Table 4. Ionisation constants of oximinobenzo - 2,1,3 - thiadiazoles in water at 25°, I = 0·05 M

No	Subst	p*Ka*	
5	5-Oximino, 4-one	6·13 ± 0·02	
4	7-Oximino, 4-one	6·63 ± 0·03	
3	4-Oximino, 5-one	5·77 ± 0·01	
9	4,5-Dioximino	6·53 ± 0·02[a]	
10	4,7-Dioximino	8·38 ± 0·04[b]	10·07 ± 0·04[c]
13	4-O-Methyloximino, 5-oximino	8·88 ± 0·03	
14	4-Oximino, 5-O-methyloximino	8·81 ± 0·09	
15	4-Oximino-7-O-methyloximino	8·61 ± 0·03	

[a] This value is relative to 5-NOH group in *amphi–syn* form (*cf* text) and was obtained from potentiometric titration (*cf* Experimental).
[b] pKa_1.
[c] pKa_2.

intramolecular H-bond tends to stabilize the ion more than the acid and thus facilitates the dissociation of the proton (**9B**).



9B

In the absence of this H-bond, the p*Ka* values of both the oxime groups in an 4,5 - dioximinoderivative should be similar in magnitude to the p*Ka* of the 4,7-derivative. This is the case: p*Ka* values of 4,5 - dioxime - 4- and 5 - mono - O - methyl ethers (**13**, **14**), indeed, are close to that of 4,7 - dioximemono - O - methyl ether (**15**). In some aldoximes and ketoximes the p*Ka* values of the *anti* isomer were found to be higher than those of *syn* isomers[18] (Δ p*Ka* = 0·4–0·65); this suggests the supposition that the configuration of the oxime group could affect the acidity of geometrical isomers present as a mixture in the solutions of **4**, **10**, **13**, **15**. As we find that the prevailing oxime group orientation is *syn* to the homocyclic hydrogen (see Experimental), it would seem that the observed p*Ka* values are close to those of these forms.

EXPERIMENTAL

Light petroleum refers to the fraction of b.p. 30–50°; ligroin to the fraction of b.p. 80–120°.

The m.ps (Buchi–Tottoli apparatus) are uncorrected. Electronic spectra were determined on a Beckman DU-2 and NMR spectra on a Jeol C-60HL spectrometer; the chemical shifts are in ppm (τ) from internal TMS. Coupling constants (J) are in c/s (± 0·10).

5 - *Hydroxy* - 4 - *nitrosobenzothiadiazole* (**3**),* was obtained on nitrosation of **1**[19] according to a previously described method.[9] Yellow-green plates from $CHCl_3$–CCl_4 (1:1), m.p. 170–4° (dec); [lit[9]: 170–5° (dec)].

4 - *Hydroxy* - 7 - *nitroso* - (**4**) and 4 - *hydroxy* - 5 - *nitrosobenzothiadiazole* (**5**), obtained as a mixture in the nitrosation[9] of (**2**),[19] were separated in the following manner. The mixture (9 g) was suspended, under stirring, in Ac_2O (30 ml) and after 3 h at room temp, was filtered and washed with ether. The mixture obtained of the acetyl derivatives (9 g, 80%; m.p. 130–50°) was twice extracted with boiling CCl_4 (400 and 200 ml). The CCl_4-insoluble residue (4 g) was crystallised twice from benzene to give the acetyl derivative of **5**(**22**) at m.p. 178° (dec). (Found: C, 42·90; H, 2·31; N, 18·78. $C_8H_5N_3O_3S$ requires: C, 43·05; H, 2·26; N, 18·83%). **22** (2 g) was suspended in MeOH (100 ml) and conc HCl (5 ml) and the mixture was heated under reflux for 15 min. After removal of solvent the residue was diluted with water and the ppt collected. Crystallisation from AcOH yielded the pure **5**, m.p. 208–10° (dec). (Found: C, 39·70; H, 1·70; N, 23·20. $C_6H_3N_3O_2S$ requires: C, 39·77; H, 1·67; N, 23·20%). Removal of solvent from combined CCl_4 extracts yielded 4·2 g of acetyl derivative of **4** (**23**) in 85–90% purity, there being 10–15% of **22** present. Chromatography on Merck silica gel, using $CHCl_3$–MeOH (100:1) as eluent, gave **23** partially deacetylated; after treatment with Ac_2O, pure **23**, m.p. 145–6°, was obtained. (Found: C, 43·15; H, 2·17; N, 18·75. $C_8H_5N_3O_3S$ requires: C, 43·05; H, 2·26; N, 18·83%).

Hydrolysis of **23**, by the same procedure described for isomer **22**, followed by crystallisation from EtOH, yielded **4**, m.p. 243° (dec) [lit[9] 205–10° (dec)]. NMR spectrum in DMSO showed the *syn* (**4F**) and the *anti* (**4E**) isomers in a ratio 75:25.

4-*Methoxy*-5-*methyl*-1,2-*phenylenediamine* (**24**). 4-amino - 2 - methyl - 5 - nitroanisole[20] (7·3 g) in MeOH (400 ml) containing 10% Pd-C (1·0 g), hydrogenated at room temp and pressure, yielded 4 - methoxy - 5 - methyl - 1,2 - phenylenediamine as a violet product (5·5 g, 90%). Crystallisation from ligroin gave white needles melting at 107–8°. (Found: C, 63·10; H, 8·03; N, 18·36. $C_8H_{12}N_2O$ requires: C, 63·13; H, 7·95; N, 18·41%).

5 - *Methoxy* - 6 - *methylbenzothiadiazole* (**25**). To a soln of **24** (4·6 g) and triethylamine (14·6 g) in anhyd benzene (100 ml), was added dropwise with vigorous stirring, a benzene soln of $SOCl_2$ (6·2 g in 25 ml). The resulting mixture was heated under reflux for 2 h and then filtered. The benzene filtrate, after removal of solvent, gave the crude 5-methoxy-6-methyl benzothiadiazole (*ca* 3·0 g) which

*Nomenclature is irrespective of the structure of the compound.

was purified by crystallisation from ligroin; m.p. 110–11°. (Found: C, 53·26; H, 4·51; N, 15·60. $C_8H_8N_2OS$ requires: C, 53·32; H, 4·47; N, 15·55%).

5 - *Hydroxy* - 6 - *methylbenzothiadiazole* (**26**). Compound **25** (2·0 g) was heated und reflux for 40 min with 40 ml of HBr (48%). Cooling then gave the 4 - hydroxy - 6 - methylbenzothiadiazole (1·8 g, 72%), white needles (from toluene), m.p. 218–20°. (Found: C, 50·65; H, 3·68; N, 16·81. $C_7H_6N_2OS$ requires: C, 50·58; H, 3·64; N, 16·86%).

5 - *Hydroxy* - 6 - *methyl* - 4 - *nitroso benzothiadiazole* (**16**). A soln of **26** (1·7 g) in 0·4 N NaOH (25 ml) was acidified, with stirring, with 2N H_2SO_4 (10 ml). The resulting finely divided suspension of hydroxy compound was ice cooled (2–5°) and aqueous $NaNO_2$ (0·7 g in 25 ml) was added over 3 h; the mixture was stirred for 7 h at 5° and then filtered to give 5 - hydroxy - 6 - methyl - 4 - nitroso benzothiadiazole (1·5 g, 75%), m.p. 173° (dec) (from EtOH). (Found: C, 43·12; H, 2·63; N, 21·46. $C_7H_5N_3O_2S$ requires: C, 43·07; H, 2·58; N, 21·53%).

Benzothiadiazole - 4,5 - *dione* - 4 - *O* - *methylmonoxime* (**6**). $AgNO_3$ aq (2·4 g in 10 ml) was added to the aqueous K salt of **3** (2·8 g in 60 ml); [the salt was obtained by treatment of a 3% EtOH soln of **3** (120 ml) with 4% KOH–EtOH soln (20 ml)]. The dried Ag salt (3·4 g) was shaken with MeI (3·4 g) in dry ether (200 ml) in a stoppered bottle for 48 h. The soln was filtered, the ether removed and the residue crystallised repeatedly from n-heptane, yielded yellow-brown needles (0·8 g, 35%), m.p. 155°. (Found: C, 43·10; H, 2·63; N, 21·52. $C_7H_5N_3O_2S$ requires: C, 43·07; H, 2·58; N, 21·53%).

6 - *Methylbenzothiadiazole* - 4,5 - *dione* - 4 - *O* - *methylmonoxime* (**17**) and *benzothiadiazole* - 4,5 - *dione* - 5 - *O* - *methylmonoxime* (**8**) were obtained by the same procedure as described for **6**. **17** crystallised from n-heptane, m.p. 184–5° (yield, 45%). (Found: C, 45·85; H, 3·41; N, 20·03. $C_8H_7N_3O_2S$ requires: C, 45·92; H, 3·37; N, 20·09%). **8** crystallised from ligroin, m.p. 183–4° (yield, 12%). (Found: C, 43·02; H, 2·61; N, 21·46. $C_7H_5N_3O_2S$ requires: C, 43·07; H, 2·58; N, 21·53%).

Benzothiadiazole - 4,7 - *dione* - 7 - *O* - *methylmonoxime* (**7**). A mixture of benzothiadiazole - 4,7 - dione[8] (1·7 g), *O*-methylhydroxylamine hydrochloride (0·83 g) in MeOH (100 ml) was heated under reflux for 3 h. Removal of solvent and chromatography of residue on Merck silica gel, using ethyl ether-light petroleum (1:1) as eluent, gave benzothiadiazole - 4,7 - dione - 4 - O - methylmonoxime as a pale yellow solid which was crystallised from n-heptane, m.p. 171–6°. NMR spectrum in DMSO showed the *syn* (**7F**) and the *anti* (**7E**) isomers in a ratio 65:35. (Found: C, 43·15; H, 2·65; N, 21·51. $C_7H_5N_3O_2S$ requires: C, 43·07; H, 2·58; N, 21·53%).

Dioximino, mono - O - *methyl*- and *di* - O - *methyldioximinobenzothiadiazoles* (**9–15**), were obtained on heating under reflux during 3 h, equimolecular solns of the suitable quinonemonoximes (**3–8**) and hydroxylamine (or O-methylhydroxylamine) hydrochloride in MeOH, followed by removal of solvent. The starting quinonemonoxime, the obtained dioximino compound, its purification (or geometrical isomers separation), ratio of geometrical isomers (as determined from DMSO soln), m.p. and analytical data (or relevant literature) are reported below.

Compounds **3(5)**; **9**; crystallised from EtOH, *amphi–syn* (**9B**)/*anti* (**9A**) = 75/25; m.p. 199–200°. (Found: C, 36·53; H, 2·13; N, 28·54. $C_6H_4N_4O_2S$ requires: C, 36·73; H, 2·05; N, 28·56%).

Compound **4**; **10**; crystallised from EtOH–H_2O (1:1); *Syn–anti* (**10G, G'**)/*syn–syn* (**10F'**) = 24/76; m.p. 284°.[9]

Compound **3**; **14**; the crude residue (2·0 g), melting at 130–150°, was extracted 3 times with 120 ml of boiling n-heptane. Cooling of the n-heptane soln gave the [1.2.5] thiadiazolo [3.4-e] 2,1,3 - benzoxadiazole (**21**), m.p. 133–4°, identical with an authentic sample obtained as in Ref 10. The heptane-insoluble residue, crystallised from EtOH–H_2O (1:1) gave pure **14**; *amphi–syn* (**14B**)/*anti* (**14A**) = 56/44; m.p. 158–60° (Found: C, 39·76; H, 2·84; N, 26·90. $C_7H_6N_4O_2S$ requires: C, 40·00; H, 2·88; N, 26·65%).

Compounds **5(6)**; **13**; crystallised from EtOH–H_2O; *anti* (**13A**)/*amphi–syn* (**13B**)/*syn–syn* (**13C**) [or *amphi–anti* (**13D**)] = 50/42/8 (this ratio was determined on an uncrystallised product; the crystallised product gave: *amphi–syn*/*anti* = 55/45); m.p. 192–3°. (Found: C, 39·80; H, 2·96; N, 26·76. $C_7H_6N_4O_2S$ requires: C, 40·00; H, 2·88; N, 26·65%).

Compound **4**; **15**; crystallised from EtOH–H_2O (1:1); *syn–syn* (**15F'**)/*syn–anti* (**15G**)/*syn–anti* (**15G'**) = 49/19/32; m.p. 222–3°. (Found: C, 39·81; H, 2·95; N, 26·61. $C_7H_6N_4O_2S$ requires: C, 40·00; H, 2·88; N, 26·65%).

Compound **6**; **11**; crystallised from EtOH–H_2O (1:1); *amphi–syn* (**11B**)/*anti* (**11A**) = 40/60; m.p. 103–125°. (Found: C, 42·76; H, 3·62; N, 24·88. $C_8H_8N_4O_2S$ requires: C, 42·85; H, 3·69; N, 24·99%). Chromatography of the crude residue on Merck silica gel, using ethyl ether–light petroleum (1:1) as eluent, proved to be a means of separation of geometrical isomers. TLC was used to check the purity of each fraction and to determine R_f values (precoated Merck chromatoplates silica gel F_{254} and ethyl ether–light petroleum (1:1), as solvent were used). Four isomers were separated: *syn–syn* isomer (**11C**), m.p. 87–89° was fastest moving on TLC appearing at 0·46 R_f; UV: (EtOH) λ_{max} 231–3 (9550), 296–7 (15900) nm. *Amphi–anti* isomer (**11D**) appeared at 0·40 R_f and melted at 141–2° (from cyclohexane); UV: (EtOH) λ_{max} 234–5 (9550), 277–8 (15500), 319–28 (11200) nm. *Amphy–syn* isomer (**11B**) appeared at 0·37 R_f anol melted at 145–6° (from cyclohexane); UV: (EtOH) λ_{max} 283 (15500), 334–44 (9550) nm. *Anti* isomer (**11A**) was slowest moving on TLC, 0·29 R_f and melted at 138–9° (from cyclohexane); UV: (EtOH) λ_{max} 261–3 (12600), 337–44 (10000) nm. The isomers **11C** and **11D**, undetectable in the NMR spectrum of crude mixture, were isolated from a enriched mixture obtained from combined fastest moving fractions.

Compound **7**; **12**; the crude two components mixture [*syn–anti* (**12G, G'**)/*syn–syn* (**12F'**) = 35:65], m.p. 182–90°,[5] was crystallised from EtOH; the solid collected by cooling, m.p. 184–7° was the *syn–syn* isomer in about 90% purity, and the residue obtained after removal of solvent from ethanolic filtrate, m.p. 120–5°, was the *syn–anti* isomer in about 70% purity. Pure *syn–syn* isomer (**12F'**) was obtained by two crystallisations from EtOH: m.p. 193°; R_f 0·34 (determined on precoated Merck chromatoplates silica gel F_{254} with CH_2Cl_2 as solvent); UV: (EtOH) λ_{max} 329 (24·500) nm. Pure *syn–anti* isomer (**12G, G'**) was obtained on chromatography on Merck silica gel using CH_2Cl_2 as eluent (*syn–anti* isomer as slowest moving fraction, is obtained in about 85% purity, m.p. 130–6°) followed by two crystallisation from cyclohexane m.p. 141°; R_f 0·26 (determined as above); UV: (EtOH) λ_{max} 330 (28200) nm.

5 - *Acetamido* - 4 - *Hydroxybenzothiadiazole* (**18**). Compound **5** (0·9 g) was hydrogenated at room temp and pressure in 1% dioxan soln over 100% by weight of 10% Pd-C to yield 5 - amino - 4 - hydroxy - benzothiadiazole which was not isolated. Treatment of dioxan soln with

Table 5. Determination of ionisation constant of 4,5 - dioximinobenzothiadiazole (9)

Spectrophotometric det.		Potentiometric det.			
pH	p*Ka*	titrant 0·05 M ml	pH	p*Ka*[a]	p*KaC*[b]
5·97	6·69	0·0	4·58	—	—
6·18	6·74	0·5	5·76	6·71	6·53
6·36	6·82	1·0	6·13	6·73	6·53
6·57	6·81	1·5	6·41	6·78	6·53
6·76	6·94	2·0	6·67	6·85	6·55
6·97	7·04	2·5	6·93	6·93	6·53
7·16	7·12	3·0	7·29	7·11	6·52
7·53	7·35	3·5	7·85	7·48	—
7·70	7·48	4·0	8·48	7·87	8·78
8·00	7·71	4·5	9·19	8·24	8·88
8·25	7·84	5·0	10·08	—	—
8·43	7·96				
8·81	8·23				
9·20	8·35				

[a] p*Ka* calculated, by use of the Henderson equation $\left(pKa = pH - \frac{\log \text{salt}}{\log \text{acid}}\right)$ on 0·005 M solution.

[b] p*Ka* calculated on a mixture 0·0035 M of the *amphi–syn* form and 0·0015 M of the *anti*.

Ac_2O (2 ml) at room temp, overnight, followed by removal of solvent gave the crude **18** which was crystallised from toluene, m.p. 208–10°. (Found: C, 46·00; H, 3·31; N, 19·91. $C_8H_7N_3O_2S$ requires: C, 45·92; H, 3·37; N, 20·09%).

4 - *Acetamido* - 5 - *hydroxybenzothiadiazole* (**19**) and 7 - *acetamido* - 4 - *hydroxy* - *benzothiadiazole* (**20**) were obtained by the same procedure described under **18**. Compound **19** crystallised from ligroin m.p. 153–4°. (Found: C, 45·86; H, 3·42; N, 19·93. $C_8H_7N_3O_2S$ requires: C, 45·92; H, 3·37; N, 20·09%). Compound **20** crystallised from toluene; m.p. 205–6° (lit[9] 200–2°).

Dissociation constants were measured spectrophotometrically as described previously.[6]

Solns were 4×10^{-5} M in quinonemonoxime (**3–5**), 3×10^{-5} M in 4,7-dioximino derivative, 7×10^{-5} M in 4,5-dioximino derivative and were made up in buffer and salt at suitable pH at constant total I = 0·05 M.

Buffer used were: potassium dihydrogen phosphate-disodium hydrogen phosphate for the pH range 5·5–8, borate buffers for 8–10·2 and phosphate buffers for 10·5–11·5.

Optical density measurements, at λ_{max} for the appropriate anion, were made on a Beckman DU-2 spectrometer with a thermostated cell compartment. Measurements of pH were made on a Radiometer PHM26 pH-meter with a thermostated cell assembly. In all experiments the temperature was controlled to 25° ± 0·2.

The optical density of **14** solns varied on standing* (the change occurring quite rapidly above pH 8) and measurements were made on solns prepared freshly, mixing the stock soln of **14** with the suitable buffer soln immediately before use. The obtained dissociation constant is less precise (± 0·09) than those reported for other derivatives, which did not show the instability noted in **14**.

For the determination of pK_1 and pK_2 in 4,7-dioximinobenzothiadiazole (**10**), the spectrophotometric method modified for two ionisation constants which cause mutual interference was followed. This method, described by Albert and Serjant,[21] involves a series of successive approximations until constant pK_1 and pK_2 are obtained, and measurements at two wavelengths. For 4,7-dioximinobenzothiadiazole, data at one wavelength only (362 nm) were used and only one series of corrected values of optical density was calculated for obtaining constant results for pK_1 and pK_2.

4,5-Dioximinobenzothiadiazole (**9**): p*Ka* values (by spectrophotometry) showed an upward trend as the pH of the soln increased. Upon titrating with 0·05 M alkali an aqueous soln (0·005 M) of 4,5-dioxime, the same trend was observed as the titration progressed, and only one mol of alkali was required for neutralisation (Table 5). As the cause of the upward trend, could not be attributed to either the decomposition or a chemical irreversible transformation of 4,5-dioxime,† the presence of two isomers with significantly different ionisation constants, appeared the more reasonable hypothesis.

Considering a ratio *amphi–syn*/*anti*, in water, similar to that in organic solvents (about 70/30), the calculated p*Ka* for the *amphi–syn* form was 6·53 ± 0·02; this led to an approximate value of the p*Ka* of the *anti* isomer of 8·8 (Table 5).

*Owing to cyclisation of 4-oxime and 5 - O - methyloxime groups to furazane.

†4,5-Dioxime is stable to alkali and acids; preparative conditions corresponding to those used in spectrophotometric or potentiometric determination of p*Ka*, did not give cyclized compound, i.e., [1.2.5] thiadiazolo [3.4-e] 2,1,3 - benzoxadiazole (**21**).

Acknowledgments—The authors are indebted to professors A. R. Katritzky and A. J. Boulton for helpful discussions and suggestions and to the Consiglio Nazionale delle Richerche (Rome) for financial support.

REFERENCES

[1]D. Dal Monte and E. Sandri, *Ann. Chim. Italy* **53**, 1697 (1963)
[2]D. Dal Monte and E. Sandri, *Ibid.* **54**, 486 (1964)
[3]D. Dal Monte and E. Sandri, *Boll. Sci. Fac. Chim. Ind. Bologna* **22**, 33 (1964)
[4]D. Dal Monte and E. Sandri, *Ibid.* **26**, 127 (1968)
[5]D. Dal Monte, E. Sandri and S. Pollicino, *Ibid.* **26**, 153 (1968)
[6]D. Dal Monte, E. Sandri and W. Cere', *Ann. Chim. Italy* **60**, 801 (1970)
[7]D. Dal Monte, E. Sandri, L. Di Nunno, S. Florio and P. E. Todesco, *J. Chem. Soc.* (B) 2209 (1971)
[8]A. S. Angeloni, V. Cere', D. Dal Monte, E. Sandri and G. Scapini, *Tetrahedron* **28**, 303 (1972)
[9]V. G. Pesin, I. A. Belen'kaia-Lotsmanenko and A. M. Khaletskii, *Zh. Obshch. Khim.* **34**, 3753 (1964)
[10]P. B. Ghosh, *Tetrahedron Letters* No 32, 2999 (1971)
[11]A. J. Boulton, P. J. Halls and A. R. Katritzky, *Org. Magn. Resonance* **1**, 311 (1969)
[12]Y. L. Chow, C. J. Colon and D. W. L. Chang, *Canad. J. Chem.* **48**, 1664 (1970)
[13]A. Daniel and A. A. Pavia, *Tetrahedron Letters* 1145 (1967)
[14]H. Saito and K. Nukada, *J. Mol. Spec.* **18**, 355 (1965)
[15]M. J. Deschamps-Dutrieux and M. Chaillet, *Tetrahedron Letters* 1171 (1968)
[16]L. K. Creamer, A. Fischer, B. R. Mann, J. Packer, R. B. Richards and J. Vaughan, *J. Org. Chem.* **26**, 3148 (1961)
[17]R. K. Norris and S. Sternhell, *Aust. J. Chem.* **22**, 935 (1969)
[18]M. Charton and B. I. Charton, *J. Org. Chem.* **34**, 1871 (1969)
[19]A. M. Khaletskii, V. G. Pesin and I. A. Lotsmanenko, *U.S.S.R.* 145.243 Mar. 2 (1962)
[20]R. T. Arnold and J. C. McCool, *J. Am. Chem. Soc.* **64**, 1315 (1942)
[21]A. Albert and E. P. Serjeant, *Ionisation Constants of Acids and Bases* Ch. 4. Methuen, London (1962)