169. The Tautomerism of 1,3,4-Thiadiazol-2(3*H*)-ones. A ^{15}N-NMR-Study

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Summary

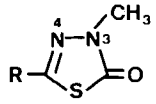
5-Substituted 1,3,4-thiadiazol-2(3*H*)-ones were shown to exist almost exclusively in the oxo tautomeric form with the aid of proton-coupled ^{15}N-NMR spectra using the corresponding 3-methyl-1,3,4-thiadiazol-2(3*H*)-ones and 5-substituted-2-methoxy-1,3,4-thiadiazoles as reference compounds.

Introduction. – We have reported [1] the synthesis and the ^{13}C-NMR data of 5-substituted 1,3,4-thiadiazol-2(3*H*)-ones and their *N*-methyl and *O*-methyl derivatives. The ^{13}C-NMR data indicated that the thiadiazolones exist predominantly in the oxo form. A quantitative estimation of the percentage of the oxo form was also made using the *N*-methyl and *O*-methyl derivatives as reference compounds for the oxo and hydroxy forms (see the *Scheme*) and correcting for the shift caused by the CH_3-groups. Because of the relatively large uncertainties of these CH_3-corrections and the high sensitivity of ^{15}N chemical shifts towards changes in the tautomeric equilibrium [2], the compounds were also studied by ^{15}N-NMR spectroscopy.

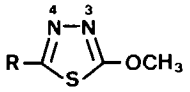
Scheme. *Compounds Investigated*

1a-e

	R
a	H
b	CH_3
c	CN
d	NH_2
e	OCH_3



2a-e



3a-d

Results. – The structures of the compounds investigated are given in the *Scheme*, the ^{15}N chemical shifts in *Table 1*. The signal assignments of all compounds except **3d** can be made on the basis of the chemical shifts. The assignments were corroborated for **3a** and **3b** by the N,H-coupling constants. The assignment in **3d** is based on the coupling of one of the pyridine-like N-atoms with the amino protons. This N-atom, therefore, occupies the 4-position, as only couplings over less than four bonds possess measurable values in these systems. Its chemical shift of 284.0 ppm is similar to that of 2,5-diamino-1,3,4-thiadiazole (294.1 ppm [3]). Furthermore, the data of **1d** correlate well with its thiocarbonyl analogue [3] if the downfield shift of thioamide N-atoms *vs.* amide N-atoms [4, p. 66] is taken into account.

The N,H-coupling constants are listed in *Table 2*. The one-bond coupling constant between N(3) and H–N(3) could only be observed in **1a** and **1d**. In **1b**, **1c** and **1e**, fast NH-exchange prevented observation. The relatively large value (102.6 Hz) of this coupling constant compares well with those recently reported for acyl hydrazines [5]. All other coupling constants show values expected from literature data [4] [6] as far as comparable compounds have been investigated.

Discussion. – *Position of the Tautomeric Equilibrium.* A comparison of the chemical shifts of the *N*-methyl derivatives **2** with the *O*-methyl derivatives **3** *(Table 1)* shows that the ^{15}N chemical shift of N(3) in **1** should be very sensitive to changes in the tautomeric equilibrium owing to the large chemical shift difference between pyrrole-like and pyridine-like N-atoms which ranges from 121.1 ppm for **2c/3c** to 134.9 ppm for **2d/3d**. For a quantitative analysis of the tautomeric equilibrium, however, a good model compound for the oxo form is necessary. The *N*-methyl compound would be a good approximation if reliable values for the chemical shift differences between NH and *N*-methyl compound were available. These methylation shifts are upfield shifts for amides, lactams, ureas and barbiturates (*cf.* [7] for a discussion of the values and the origin of the effect) and are somewhat dependent upon solvent and type of compounds. We obtained a methylation shift for 2-pyrrolidone and *N*-methyl-2-pyrrolidone of -4.7 ppm (upfield shift upon CH_3-substitution) in [D_6]DMSO (*cf. Exper. Part*), which is of the same magnitude as the chemical shift differences of N(3) in **2** and **1** (-5.5 to -6.7 ppm, *cf. Table 1*). In the azole series, a methylation shift of -5.6 ppm in [D_6]DMSO has been measured [8]. A correction for *O*-methylation in the model compounds for

Table 1. *^{15}N-Chemical Shifts[a]) in [D_6]DMSO at 298 K*

	R	1			2			3		
		N(3)	N(4)	N(R)	N(3)	N(4)	N(R)	N(3)	N(4)	N(R)
a	H	190.2	315.2	–	184.7	323.4	–	310.4	362.2	–
b	CH_3	187.5	304.3	–	181.2	312.9	–	310.5	352.7	–
b[b])	CH_3	183.8	300.0	–	180.4	311.7	–	307.4	349.6	–
c[c])	CN	200.3	339.4	266.4	194.4	345.0	267.6	315.5	388.4	269.5
d	NH_2	170.9	241.0	62.4	164.2	250.6	63.3	299.1	284.0	61.4
e	OCH_3	170.9	252.2	–	164.7	262.0	–	–	–	–

[a]) ±0.1 ppm at 40.55 MHz, external reference CH_3NO_2 ($\delta = 380.2$ ppm).
[b]) In $CDCl_3$ at 290 K.
[c]) In [D_6]DMSO at 300 K.

Table 2. *N,H-Coupling Constants*[a]) *in Hz*

Coupled nuclei	1			2			3
R	N(3), H–N(3)	N(4), H–N(3)	N(4), H–C(5) or N(4), H of substituent in the 5-position	N(3), CH_3–N(3)	N(4), CH_3–N(3)	N(4), H–C(5) or N(4), H of substituent in the 5-position	N(4), H–C(5) or N(4), H of substituent in the 5-position
a H[d])	102.6	8.2	12.7	1.5	2.2	13.0	11.0
b CH_3	b)	b)	3.6	1.3	2.5	3.5	3.1
c CN	b)	b)		1.2	2.4		
d NH_2[e])	102.6	c)	c)	1.6	2.6	≈2.6	≈2.5
e OCH_3	b)	b)		1.3	2.6		

a) ±0.2 Hz, in [D_6]DMSO, except **2b** and **3b** in $CDCl_3$.
b) Broad or *s* due to NH-exchange.
c) Broad signal $\Delta\nu$ ($^1/_2$) *ca.* 10 Hz.
d) ^3J between N(3) and H–C(5): **1a** 5.7, **2a** 6.3 and **3a** 3.3 Hz.
e) ^1J of the amino group: **1d** 85.7, **2d** 86.7 and **3d** *ca.* 86 Hz.

the hydroxy form **3** is expected to be small, as the change occurs in the γ-position to the N-atom (*cf.* 2-methylpyridine, 316.9 ppm *vs.* 2-ethylpyridine, 315.5 ppm [4]).

On the basis of these data, it can be concluded that the 1,3,4-thiadiazol-2(3*H*)-ones exist not predominantly [1] but almost exclusively in the oxo form. This result is corroborated by the proton-coupled spectra of **1a** and **1d** which indicate a very slow proton exchange, since coupling constants down to a few Hz can be resolved. It should be impossible to observe such coupling constants, if sizeable amounts of the hydroxy form were present and a rapid intermolecular proton exchange took place between oxo- and hydroxy-tautomers. The chemical shift differences of N(3) for **2a/1a** (−5.5 ppm) and **2d/1d** (−6.7 ppm) can be taken, therefore, as pure methylation shifts. As the shift differences of N(3) for **2b/1b**, **2c/1c** and **2e/1e** fall within that range, the presence of sizeable amounts of the hydroxy tautomer in the remaining compounds is also not probable. A dependence of the position of the tautomeric equilibrium on the nature of the substituent cannot be confirmed contrary to our earlier report. In the ^{13}C-NMR spectra [1], the methylation shift for C(5) is not only larger than that for C(4) in Δ^4-pyrrolin-2-one used for the CH_3-correction (−1.9 to −2.8 ppm as compared with −0.9 ppm), it is also dependent on the nature of the substituent in the 5-position, *i.e.* the upfield shift caused by the *N*-methyl group as compared with the NH-compound becomes larger with increasing electron demand of the substituent in the 5-position. The good correlation of the pK_a-values of **1** with the σ-values [1] can be explained with the better stabilization of the negative charge in the anion as the electron demand of the substituents increases.

Effects of the Substituents at C(5) on the Chemical Shifts of N(3) and N(4). The data are collected in *Table 3.* The effects for N(4) are analogous to those on β-C-atoms in C,C-double bonds but larger. To the best of our knowledge, no studies of substituent effects on pyridine-like N-atoms in five-membered heterocycles exist. Values for 2-substituted pyridines, however, are available [4] *(cf. Table 3).* The effects of an NH_2- and an CH_3O-group on N(4) are similar to those found in 2-substituted pyridines, whereas the effects of a CH_3- or a CN-group are much larger. The CH_3-group is obviously a – hyperconjugative – donor in the thiadiazolones and in methoxy-thiadiazole. The effects on N(3) are smaller than those on N(4) but possess the same sign indicating that they are also due to the donor/acceptor properties of the substituents.

Table 3. *Substituent Effects*[a]) *on the Chemical Shifts of N(3) and N(4) in* **1**, **2** *and* **3** *as Compared with those in 2-Substituted Pyridines*

	R	**1**		**2**		**3**		2-Substituted pyridines [4]
		N(3)	N(4)	N(3)	N(4)	N(3)	N(4)	
b	CH_3	−2.7	−10.9	−3.5	−10.5	0.1	−9.5	−0.4
c	CN	10.1	24.2	9.7	21.6	5.1	26.2	−0.9
d	NH_2	−19.3	−74.2	−20.5	−72.8	−11.3	−78.2	−51.5
e	OCH_3	−19.3	−63.0	−20.0	−61.4			−49.2

[a]) Difference between the chemical shifts of the compounds with R = X and R = H.

The chemical shifts of the nitrile and amino N-atoms are similar to those in the analogous phenyl compounds, *i.e.* benzonitrile (258.7 ppm) and aniline (56.5 ppm, $^1J = 82.6$ Hz) [4].

Experimental Part

The ^{15}N-NMR spectra were measured at 40.55 MHz with a *Bruker WM 400* spectrometer, using solutions of 1 g material in 3 ml [D_6]DMSO or $CDCl_3$. The chemical shifts were obtained from inverse-gated decoupled spectra with a pulse angle of *ca.* 70°, an acquisition time of 1.5 to 3 s (digital resolution of 0.3–0.7 Hz) and a delay of 20 s. The chemical shifts were measured with respect to external nitromethane and converted to the anh. liq. ammonia scale ($\delta_{CH_3NO_2} = 380.23$) [4] [9]. No correction for diamagnetic susceptibility differences was applied. Compounds **1a** and **1b** were also measured at a concentration of 200 mg/3 ml solution, but the chemical shifts observed differ only slightly (0.2 ppm) from those of the concentrated solutions. It is interesting to note that the N-atoms with double and triple bonds show higher intensities than those with single bonds only, probably owing to chemical shift anisotropy relaxation. The proton-coupled spectra were measured overnight with acquisition times between 2 and 6 s (digital resolution 0.3 Hz or better) and delays of 17–20 s.

^{15}N-NMR data of 2-pyrrolidone in [D_6]DMSO (*cf.* [10]): 114.2 ppm, $^1J = 92.1$ Hz, $^2J \approx {}^3J \approx 1.3$ Hz and of *N*-methyl-2-pyrrolidone: 109.5 ppm.

The synthesis and the physical properties of the compounds investigated are reported in [1].

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