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EFFECT OF DIFFERENT SUBSTITUENTS ON AMINE–IMINE TAUTOMERISM OF 2-AMINO-4-METHYLTHIAZOLE DERIVATIVES

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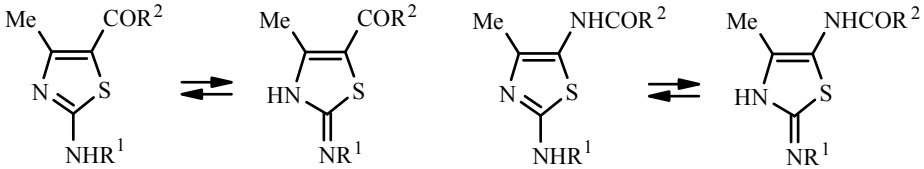
We have used ^{1}H NMR to study the amine–imine tautomerism of some esters and amides of 2-N-labeled 4-methylthiazole-5-carboxylic acids and 5-carbamic acids. We have shown that the nature of the substituents of the 2-NHR^1, 5-COR^2, or 5-NHCOR^2 groups affects that position of the tautomeric equilibrium.

Keywords: esters and amides of thiazole-5-carboxylic acid and thiazole-5-carbamic acid, amine–imine tautomerism.

Organic compounds containing an amidine group are potentially tautomeric systems. In this work, we used ^{1}H NMR to study the tautomeric equilibrium for some esters and amides of 2-N-substituted 4-methylthiazole-5-carboxylic acids (**1a-i**) and 5-carbamic acids **2a-i** (Table 1). The position of the double bond in thiazines and oxazines have a marked effect on the chemical shift of protons in the 4-CH_3 group of the heterocycle [1, 2], and so in this work we evaluated the tautomeric equilibrium of compounds **1** and **2** from the values of the chemical shift of the signal for this substituent.



1 a–i **2 a–i**

Since amine–imine conversions are "fast" on the NMR time scale [3, 4] and we observe only the averaged signals of the two tautomers in the proton spectra, a necessary condition for studying their equilibrium is to draw on model compounds with a fixed position for the double bond. As the model for the imine, we used the previously synthesized 3,4-dimethyl-2-thioxothiazolines **3a-e** (in all cases, the chemical shift of the 4-CH_3 group is equal to 2.7 ppm) and **4a,b** (the chemical shift for the 4-CH_3 group is respectively 2.22 ppm and 2.20 ppm) [5, 6], since for these compounds the anisotropy of the exocyclic and endocyclic double bond has the determining effect on the chemical shift of protons in the 4-CH_3 group. The inductive effect of the exocyclic heteroatom is much less pronounced due to the remoteness of the latter from this group.

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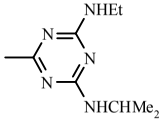
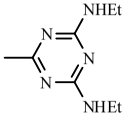
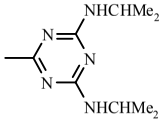
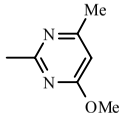
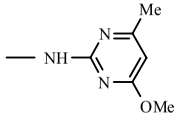
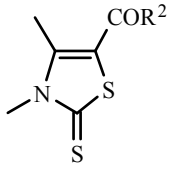
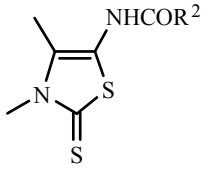
TABLE 1. Chemical Shifts of Signals for 4-CH_3 Groups of Compounds **1** and **2**

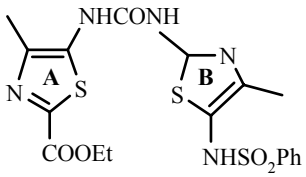
Compound	R^1	R^2	δ, ppm (4-CH_3)	Compound	R^1	R^2	δ, ppm (4-CH_3)
1a	Me	OCH_2COOMe	2.42	**2a**	SO_2Ph	OEt	2.0
1b	Me	OH	2.43	**2b**	SO_2Ph	$OCHMe_2$	1.98
1c	Me	OCH_2Ph	2.44	**2c**	SO_2Ph	OCH_2CH_2Cl	2.0
1d	$SO_2C_6H_4NHCOMe$	OEt	2.42	**2d**	SO_2Ph	$NHCMe_3$	1.98
1e	$SO_2C_6H_4NHCOMe$	NHPh	2.43	**2e**	SO_2Ph	$NHCH_2CH_2OPh$	2.0
1f		OEt	2.57	**2f**	SO_2Ph	$NHC_6H_3Cl_2$-*o,o*	2.1
1g		OEt	2.56	**2g**	$SO_2C_6H_4$-Me-*p*	NHC_6H_4Cl-*o*	2.08
1h		OEt	2.58	**2h**	$SO_2C_6H_4$-Me-*p*	$NHC_6H_3Cl_2$-*o,o*	2.08
1i		OEt	2.56	**2i**	SO_2Ph		2.15



3 a–e



4a,b



5

3 a R^2 = OMe, **b** R^2 = OCH_2Ph, **c** R^2 = OCH_2CH_2OPh, **d** R^2 = $OCH_2CH_2OC_6H_3Cl_2$-*o*,*o*, **e** R^2 = OCH_2COOMe; **4 a** R^2 = OCH_2CH_2Cl, **b** R^2 = $OCH_2CH_2NMe_2$

In the ^1H NMR spectra of compounds **1a-c**, the signal for the NCH_3 group has the shape of a doublet in the 2.85-2.90 ppm region, and the proton of the NH group in the 7.80-8.20 ppm region has the shape of a quadruplet with identical spin–spin coupling constants, and the integrated intensity of the quadruplet corresponds to a single proton. These data undoubtedly are evidence for the indicated compounds being found exclusively in the amino form, for which a singlet signal from the 4-CH_3 at 2.42-2.44 ppm is typical (Table 1). In the case of arylsulfonyl derivatives **1d,e**, the position of the latter is practically unchanged and so we may assume that they are also amines. In the spectra of compounds **1f-i**, in which the exocyclic nitrogen atom is directly bonded to the aromatic ring of the triazine or pyrimidine, the signal from the 4-CH_3 group is shifted downfield (2.56-2.58 ppm). Since in the case of compounds **3**, with an exocyclic double bond, the chemical shift of the protons in the 4-CH_3 group is equal to 2.70 ppm, the indicated change is probably connected with a shift of the tautomeric equilibrium toward the imino form.

The existence of compounds **1a-e** in the form of amines can be explained by the strong acceptor properties of the substituent on the 5 position of the thiazole, and also by the fact that in this form, due to rotation about the C–N bond, maximum overlap occurs between the unshared electron pair of the exocyclic nitrogen atom and the π-electrons of the C=N bond in the ring that are conjugated with the C=C and C=O bonds. Such a state is obviously energetically more favorable than the imino form. The latter, on the other hand, is possible for heteroaromatic derivatives **1f-i**, since in this case the π-electrons of the exocyclic C=N bond can interact with the π-electrons of the triazine or pyrimidine ring. The appearance of a new conjugated system probably compensates to some degree for the shortening of the conjugation chain in the thiazoline ring, and consequently the indicated compounds can be found in both the amine and the imine form.

In the ^1H NMR spectra of compounds **3a-e** and **4a,b**, the difference between the chemical shifts of the signals from the 4-CH_3 groups is 0.48-0.50 ppm, which probably is explained by the change in the properties of the substituent on the 5 position of the heterocycle.

Such a difference between the chemical shifts can also be expected for the similar compounds with an amine structure **1** and **2**. Consequently, absorption of the 4-CH_3 group in the 1.92-1.96 ppm region would correspond to compounds **2** in the amino form. Since in the spectra of **2a-e** the signals for this group are observed in the 1.98-2.00 ppm region, we can conclude that these compounds exist predominantly in the amine form. In the spectra of derivatives **2f-i**, we observe a downfield shift of the singlet for the 4-CH_3 group to 2.08-2.15 ppm (Table 1). Since the chemical shifts of the signals for these protons in the spectra of compounds **4a,b** are equal to 2.20-2.22 ppm, the observed pattern may be explained by a shift of the tautomeric equilibrium toward the imino form.

Thus based on our studies, we may conclude that the considered compounds may be found in both the amine and the imine forms, and that the substituents both on the exocyclic nitrogen atom and on the position 5 of the heterocycle affect the position of the tautomeric equilibrium. In fact, in the spectrum of compound **5** there are two singlet signals for the methyl substituents of heterocycles **A** and **B**. While the chemical shift of the first signal (2.03 ppm) is consistent with an amino structure for heterocycle **A**, the position of the second signal (2.52 ppm) indicates the presence in solution of some amount of the form with an imine structure for heterocycle **B**. Consequently, compound **5** is found in the form of a mixture of two tautomers, which may be explained by the acceptor properties of the bridging C=O bond.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Mercury Varian spectrometer (300 MHz) at 30°C, solvent DMSO-d_6, internal standard TMS. The compounds **1a-i, 2a-i, 3a-e, 4a,b** were described earlier in [5-7].

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