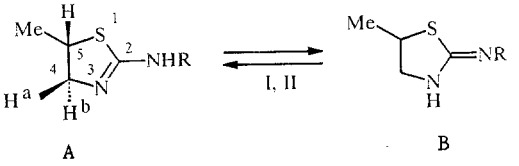
STRUCTURE OF 2-AMINO-5-METHYLTHIAZOLINE AND ITS N-METHYL DERIVATIVES

N. A. Martem'yanova, Yu. M. Chunaev,*
N. M. Przhiyalgovskaya, L. N. Kurkovskaya,
O. S. Filipenko, and S. M. Aldoshin

As indicated by PMR spectroscopic data, 2-amino-5-methylthiazoline and 2-methylamino-5-methylthiazoline exist in the imine form in the temperature interval from +20° to −100°C. Interaction of the 2-amino-5-methylthiazoline with methyl iodide results in alkylation at the endocyclic nitrogen atom.

Amine–imine tautomerism of alkyl- and aryl-substituted 2-aminothiazolines has attracted the attention of researchers from the end of the last century up to the present time [1, 2]. Such long-term interest in this prototropic conversion is understandable if we consider that, even though many studies of such tautomerism have employed modern physicochemical methods, the actual structure of the tautomers remains an open question. A large volume of experimental material has been accumulated on the spectral properties of 2-aminothiazoline derivatives that exist in the amine or imine form, and this information is being used to establish the structure of the tautomers of 2-alkyl(aryl)aminothiazolines. However, we do not yet have any unambiguous criteria for assigning tautomers to one structure or the other.

In the methylation of 2-amino-5-methylthiazoline (I), we encountered a problem in establishing the structure of not only the original base, for which amine–imine tautomerism is possible (A ⇄ B), but also its N-methyl derivatives. As far back as 1889, on the basis of chemical evidence, the imine structure B was postulated for 2-amino-5-methylthiazoline [1]. The basis for this assignment was the recovery and identification of 2-methylamino-1-methylethanesulfonic acid in the reaction mixture obtained by oxidizing the product of methylation of compound I. An analogous conclusion was drawn in [2] from studies of the IR spectra of 2-amino-5-methylthiazoline (I) and 2-methylamino-5-methylthiazoline (II). The basic criterion for determining the structure of these compounds was the frequency of stretching vibrations of the C=N group, which for the exocyclic double bond (structure B) was 20-40 cm^{-1} higher than for the C=N bond in the ring (structure A), amounting to approximately 1640 and 1610 cm^{-1}, respectively. In [3, 4], however, an exactly opposite interpretation was given for the IR spectra of substituted aminothiazolines.



A B

I R = H, II R = Me

Furthermore, in [5, 6], on the basis of ^1H and ^{13}C NMR spectra, the thiazoline II was assigned the amine structure A; but in [7], on the basis of mass spectra of this substance, the decision favored the imine form B. Such contradictory data compelled us to return once more to the investigation of the structure of compounds I and II.

*Deceased.

D. I. Mendeleev Moscow Chemical Technology Institute, Moscow 125190. Branch of the Institute of Chemical Physics, Russian Academy of Sciences, Chernogolovka 142432. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 415-419, March, 1993. Original article submitted October 20, 1992.

 0009-3122/93/2903-0352$12.50

TABLE 1. PMR Spectra of Compounds I-III and V

Compound	Solvent	T, °C	Chemical shifts, δ, ppm[1]*						
			=NH	NH	$=NCH_3$	NCH_3	4-H[a], 4-H[b]	5-H	5-CH_3
I	$CDCl_3$	+20	5,57		—	—	3,60,~4,0	~4,0	1,38
		-20	5,96		—	—	3,61,~4,0	~4,0	1,38
		-50	6,32		—	—	3,64,~4,0	~4,0	1,39
	$CDCl_3$—CD_2Cl_2, 1 : 1	-80	~7,7	~5,0	—	—	3,66,~4,0	~4,0	1,38
		-95	8,34	4,98	—	—	3,66,~4,0	~4,0	1,37
		-100	8,41	4,96	—	—	3,66,~4,0	~4,0	1,37
II	$CDCl_3$	+20	—	~4,0[2*]	2,92	—	3,67, 4,03	3,94	1,39
		-20	—	4,30	2,89	—	3,65, 4,03	3,96	1,35
		-50	—	4,80	2,89	—	3,65, 4,03	3,96	1,35
III	$CDCl_3$	+20	5,67	—	—	2,92	3,22, 3,63	3,75	1,43
V[3*]	$CDCl_3$	+20	—	—	3,01	2,84	—	—	1,39

*For compounds I and II, $J_{CH3,5\text{-}H}$ = 6.4 ± 0.3 Hz; $J_{4\text{-}H^a,5\text{-}H}$ = 3.8 ± 0.3 Hz; $J_{4\text{-}H^b,5\text{-}H}$ = 7.1 ± 0.4 Hz; $J_{4\text{-}H^a,4\text{-}H^b}$ = 11.9 ± 0.3 Hz; for compound III, $J_{CH3,5\text{-}H}$ = 6.6 Hz; $J_{4\text{-}H^a,5\text{-}H}$ = 6.0 Hz; $J_{4\text{-}H^b,5\text{-}H}$ = 12.4 Hz; $J_{4\text{-}H^a,4\text{-}H^b}$ = 9.5 Hz.

*Exchange with a small quantity of water.

*Values listed are for spectrum of reaction mixture obtained upon treatment of I with methyl iodide; blanks indicate that signals are overlapped by signals of compounds I and III.

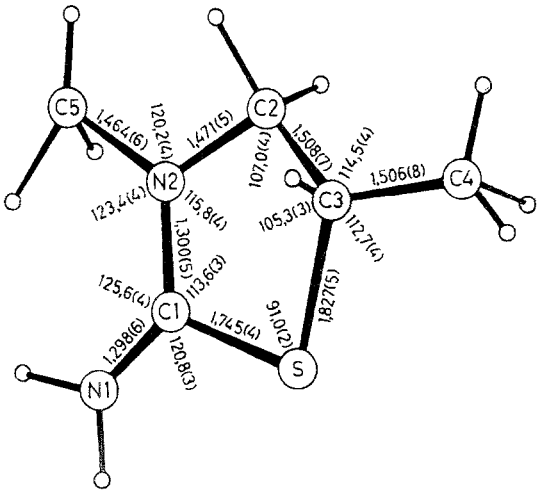


Fig. 1. Structure of cation IV.

We obtained 2-amino-5-methylthiazoline (I) as described in [1], by cyclization of allylthiourea in the presence of concentrated hydrochloric acid. We obtained 2-methylamino-5-methylthiazoline (II) as described in [8],* by cyclization of N-methyl-N′-2-hydroxypropylthiourea in the presence of phosphoric hexaethyltriamide.

In the PMR spectrum of the base II at room temperature, J_{NH,CH_3} is absent, as was also noted in [2]. However, this does not necessarily mean that compound II exists in the imino form B, since the absence of this particular constant at room temperature may be due to intermolecular proton exchange. As the temperature is lowered, the signal of the $N-CH_3$ group narrows rapidly. Here, we do not observe any splitting of the signal of the N-methyl group due to interaction of protons of the NH and CH_3 groups. This result indicates that 2-methylamino-5-methylthiazoline II, the same as compound I, exists in the imino form B at low temperatures.

*This compound has arbitrarily been assigned the imine structure in accordance with [9].

TABLE 2. Coordinates of Nonhydrogen Atoms ($\times 10^4$) and Hydrogen Atoms ($\times 10^3$), and Temperature Corrections U(iso) and U(eq) ($\times 10^3$) for Compound IV

Atom	x	y	z	U(iso)/U(eq)
$I_{(1)}$	2814(0)	997(0)	1197(1)	559
$S_{(1)}$	-457(1)	2663(1)	5411(2)	616
$N_{(1)}$	435(3)	4105(4)	2434(6)	587
$N_{(2)}$	1453(3)	3574(3)	4697(5)	427
$C_{(1)}$	575(3)	3548(4)	4008(6)	426
$C_{(2)}$	1472(4)	2751(4)	6353(6)	518
$C_{(3)}$	306(4)	2491(5)	7350(6)	606
$C_{(4)}$	126(5)	1286(5)	8363(8)	908
$C_{(5)}$	2440(4)	4218(4)	3725(6)	512
$H_{(1)}$	2895(9)	2750(9)	1318(9)	519(9)
$H_{(1)}$	909(9)	4613(9)	1595(9)	317(9)
$H_{(1,1)}$	4836(9)	861(9)	2068(9)	193(9)
$H_{(2)}$	2060(9)	3241(9)	6830(9)	318(9)
$H_{(2,1)}$	1824(9)	2116(9)	5763(9)	344(9)
$H_{(3)}$	83(9)	3112(9)	8686(9)	515(9)
$H_{(4)}$	-585(9)	1177(9)	9092(9)	597(9)
$H_{(4,1)}$	594(9)	1218(9)	9352(9)	581(9)
$H_{(4,2)}$	223(9)	617(9)	7325(9)	689(9)
$H_{(5)}$	2842(9)	4266(9)	4843(9)	610(9)
$H_{(5,1)}$	2575(9)	3780(9)	2245(9)	437(9)
$H_{(5,2)}$	2103(9)	4693(9)	2444(9)	842(9)

We investigated compounds I and II by means of PMR in $CDCl_3$ or in a mixture of $CDCl_3$ and CD_2Cl_2, at temperatures from +20° to −100°C (Table 1). At room temperature, the signals of the protons attgached to the nitrogen atom of the base I are observed in the form of a common exchange signal (corresponding in intensity to two protons) in the 5.57 ppm region. As the temperature is lowered, this signal is shifted downfield and is gradually broadened; at −80°C it is separated into two broad signals that become narrower as the temperature is further lowered. At −100°C, two narrow, equal-intensity singlets are observed (δ 4.96 and 8.41 ppm). The absence of splitting (i.e., a geminal SSCC in the NH_2 group) is evidence in favor of the view that the protons are located on different nitrogen atoms. On the basis of our results, we can conclude that compound I, at low temperatures, has the structure of 2-imino-5-methylthiazolidine B.

In establishing the structure of compounds I and II at room temperature (where exchange of mobile protons in NH groups is possible, making the chemical shifts and multiplicity of their signals noncharacteristic), we used the chemical shifts of the signals from protons of the methylene group 4-CH_2. It is known that the presence of a double bond in the five-membered ring (amine structure A) leads to deshielding of protons of the 4-CH_2 group by some 0.3-0.6 ppm in comparison with the imine structure B [2]. The chemical shifts of the 4-CH_2 protons of compounds I and II at low temperatures are hardly any different from those at +20°C (Table 1), suggesting that compounds I and II exist primarily in the imino form B at room temperature.

Having established the structure of the base I, we investigated the product of its methylation, since this reaction can take place at either the endocyclic or the exocyclic nitrogen atom, forming the isomeric compounds II and III [10]. The synthesis was performed by the method described in [1]. As the methylating agent we used methyl iodide. The product yield, after separation and purification, was 60%.

III, V IV

III R = H, V R = Me

A comparison of the PMR spectra of the methylated product and the previously obtained 2-methylimino-5-methylthiazolidine II [8] showed that these compounds are not identical. The most important differences in their spectra are in the chemical shifts of the protons of the $CHCH_2$ fragment (Table 1), so we have grounds for ascribing the structure III to the product of the methylation reaction. The correctness of this conclusion is supported by the results obtained in an x-ray

structural study of 2-imino-3,5-dimethylthiazolidine hydroiodide (IV). The structure of this compound is illustrated in Fig. 1. It will be seen that the methyl group is actually located on the endocyclic nitrogen atom.

In order to obtain a more profound understanding of the interaction of the base I with methyl iodide, we used PMR to investigate the reaction mixture. In addition to 2-imino-3,5-dimethylthiazolidine III, this mixture contains the original base I and a product of dimethylation (V) (Table 1). These substances are present in a 15:4:1 ratio, according to the integral intensities of the proton signals of $N-CH_3$. We could not find any product with the structure of II that would be obtained by monomethylation at the exocyclic nitrogen atom. Thus, the reaction of 2-imino-5-methylthiazolidine I with methyl iodide proceeds at the endocyclic nitrogen atom and leads to the formation of 2-imino-3,5-dimethylthiazolidine III. Methylation of III gives 2-methylimino-3,5-dimethylthiazolidine V.

We believe that our results have brought some clarity to the question of the structure of 2-amino-5-methylthiazoline and its N-methyl derivatives.

We wish to express our profound appreciation to V. Yu. Kovtun and L. I. Mizrakh for valuable discussion of the results of this work.

EXPERIMENTAL

The PMR spectra were recorded in a Bruker WP-200-SY NMR spectrometer, with TMS as an internal standard.

For the x-ray structure study, we grew transparent, prismatic crystals of the iodide IV, which had the following crystallographic indexes: a = 12.620(4), b = 11.123(4), c = 6.917(2) Å, β = 77.15(3)°, V = 946.70 Å^3, d = 2.681 g/cm^3, Z = 4. $[C_5H_{11}N_2]^+I^-$, space group $P2_1/a$. The intensities of 700 independent reflections with $I > 2\sigma(I)$ were measured in a KM-4 automatic four-circle diffractometer (Mo Kα radiation, graphite monochromator, $\Theta/2\Theta$ scanning to $\Theta_{max} = 10°$). The structure was deciphered by the direct method, using the SHELXS-86 program [11]. The coordinates of the hydrogen atoms were determined objectively from a Fourier difference synthesis; the coordinates were refined by the full-matrix least-squares method in the anisotropic approximation for the nonhydrogen atoms and the isotropic approximation for the hydrogen atoms. The coordinates listed in Table 2 correspond to final values of the divergence factors R = 0.028 and R_ω = 0.31.*

REFERENCES

1. S. Gabriel, Ber. Dtsch. Chem. Ges., **22,** 2984 (1889).
2. T. M. Ivanova, K. L. Burshtein, L. I. Mizrakh, A. M. Vasil'ev, and A. N. Gvozdetskii, Khim. Geterotsikl. Soedin., No. 7, 981 (1989).
3. E. M. Peresleni and Yu. N. Sheinker, Zh. Fiz. Khim., **38,** 2152 (1964).
4. P. Sohar and L. Toldy, Acta Chim. Acad. Sci. Hung., **75,** 99 (1984).
5. S. T. Cholpankulova, L. A. Tsoi, A. D. Salimbaeva, G. A. Ryskieva, N. N. Alekseeva, and L. T. Kalkabaeva, Izv. Akad. Nauk KazSSR, Ser. Khim., No. 6, 75 (1984).
6. V. V. Negrebetskii, N. N. Vorob'eva, L. V. Razvodovskaya, A. F. Grapov, and N. N. Mel'nikov, Zh. Obshch. Khim., **57,** 2310 (1987).
7. A. E. Lyuts, V. V. Zamkova, and L. A. Tsoi, Tr. Inst. Khim. Nauk, Akad. Nauk KazSSR, **53,** 140 (1980)
8. L. I. Mizrakh, L. Yu. Polonskaya, A. N. Gvozdetskii, A. M. Vasil'ev, and L. B. Karpunina, Zh. Obshch. Khim., **58,** 2246 (1988).
9. L. I. Mizrakh, L. Yu. Polonskaya, A. N. Gvozdetskii, and A. M. Vasil'ev, Zh. Obshch. Khim., **56,** 73 (1986).
10. L. I. Mizrakh, L. Yu. Polonskaya, A. N. Gvozdetskii, T. M. Ivanova, and L. B. Karpunina, Khim. Geterotsikl. Soedin., No. 4, 563 (1990).
11. G. M. Sheldrick, SHELXS-86: Programme for Crystal Structure Determination, Cambridge University Press (1986).

* As in Russian original; possibly intended as 0.031 — Translator.