INVESTIGATION OF THE Z,E ISOMERISM OF N-(5-PYRIMIDYL)- AND N-(5-PYRIDYL) ACETAMIDINES

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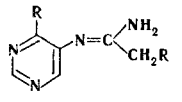
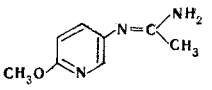
The processes of Z,E isomerization about the C = N bond and retardation of rotation about the C–N bond in N-(5-pyrimidyl)- and N-(5-pyridyl)-acetamidines were investigated on the basis of data on the temperature dependence of the PMR spectra. The effect of the type of heteroring, the volume of the ortho substituents, and the character of the solvents on the magnitude of the free energy of activation of Z,E isomerism was analyzed thoroughly. The possible mechanisms for the isomerization process are discussed.

In an investigation of 6-aminopyrimido[4,5-b]thiazines and 6-aminopyridothiazines it was observed that the reductive desulfuration of these compounds gives N-(5-pyrimidyl)- (I) and N-(5-pyridyl)acetamidines (II) [1].



I a-e



II

I a R=R'=H; b R=OCH$_3$, R'=H; c R=OCH$_3$, R'=C$_6$H$_5$; d R=NH$_2$, R'=H; e R=N(CH$_3$)$_2$, R'=H

The structure of the latter compounds was confirmed by the PMR and IR spectra: $\delta H_6 \sim 7.68$-8.24 ppm, $\delta CH_3 \sim 1.94$-2.01 ppm, $\delta NH_2 \sim 4.5$-4.7 ppm (Table 1, recording temperature above room temperature); νNH_2 3405-3533 cm^{-1}.

A peculiarity of the PMR spectra of Ia-e and II is the substantial temperature dependence of the form of the signals. At high temperatures ($\geq +70$°C) the signals corresponding to the individual protons or proton-containing groups are narrow; as the temperature is lowered, the signals become broader, after which they are split into doublets (Fig. 1). The intensities of the components of the low-temperature doublet differ for most of the cases. Thus the change in the form of the signals in the PMR spectra is apparently due to the existence of investigated compounds in two isomeric forms, and this may be associated with an equilibrium geometrical isomerism involving the N = C bond (A $\rightleftharpoons$ B), tautomeric transformations of the imine-amine type, or rotational isomerism about the C_{ar}–N single bond (A $\rightleftharpoons$ B).

The doubling of the signals of the CH_3 groups (Table 2), the NH_2 group (Table 5), and the H_2 proton* in the spectrum of Ia as the temperature is lowered makes it possible to exclude from consideration rotational isomerism about the C_{ar}–N bond (A $\rightleftharpoons$ C), inasmuch as such isomers are identical for it.

*The $\Delta \delta H_2$ value is 0.09 ppm at −31° in $CDCl_3$ solution.

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TABLE 1. Chemical Shifts for I and II (ppm)

Compound	t, °C	δCH_3 or δCH_2	δH_2	δH_3	δH_4	δH_5	δOCH_3 or $\delta N(CH_3)_2$	δNH_2	Solvent
Ia	+72	2,01	8,82	—	8,24		—	4,66	$CDCl_3$
Ib	+74	1,95	8,40	—	—	7,99	3,98	4,68	$CDCl_3$
Ic	+74	3,62	8,41	—	—	8,08	3,97	4,50	$CDCl_3$
Id	+110	1,94	8,97	—	—	7,91	—	—*	C_5D_5N
Ie	+100	1,88	8,43	—	—	7,82	3,06	—*	C_5D_5N
II	+74	1,97	—	6,64	7,10	7,68	3,89	4,54	$CDCl_3$

*The signals of the NH_2 protons are masked by the signals of the water in the solvent.

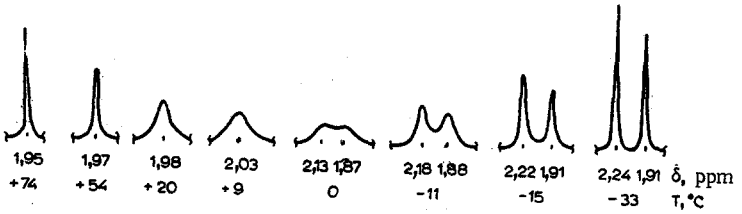
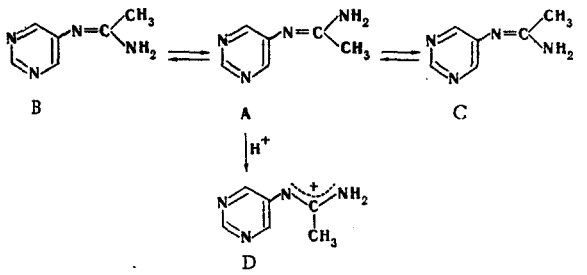


Fig. 1. Change in the form of the signals of the CH_3 group in Ib as the temperature changes (in $CDCl_3$ solution).



These facts also cannot be explained by tautomerism. First of all, it follows from the IR data that the heterylamidines in both the crystalline state and in solution exist only in a single-amine—tautomeric form: the intense ν_s and ν_{as} bands of NH_2 groups 3405-3425 and 3510-3533 cm^{-1} in $CHCl_3$) and the δ NH_2 band (1650-1690 cm^{-1} both in the crystal state and in solution in $CHCl_3$) are observed in the spectra. A further proof against tautomerism as a reason for the observed effects is the retention of the double set of signals of the compounds in CF_3COOH (Table 2), in which the compounds should exist only in the form of cation D.

The observed dependence of the form of the signals in the PMR spectra on the temperature is in good agreement only with the concept of equilibrium Z,E isomerism (A ⇌ B).* It follows from an analysis of the spectra that the maximum difference in the chemical shifts (during doubling of the signals) is observed for the CH_3 group (Table 2), NH_2 group (Table 5), and H_6,† which is natural for geometrical isomerism.

The signals of the CH_3 group of the two isomers are observed at 1.88-1.93 and 2.16-2.24 ppm in $CDCl_3$ solution) and at 1.93-2.01 and 2.31-2.32 ppm (in C_5D_5N solution in the PMR spectra of Ia,b,d,e and II (Table 2), and the weak-field signal is always more intense. An examination of molecular models of the amidines shows that the pyrimidine or pyridine ring and the amidine residue in the 5 position cannot exist in a single plane because of the presence of strong steric hindrance arising between the CH_3 (or NH_2) groups of the acetamidine chain and the H_6 and H_4 (or R) hydrogen atoms of the heteroaromatic ring. Elimination or weakening of the steric interaction may be achieved through rotation of the aromatic ring about the C_{ar}—N bond. This should cause an increase in the shielding of the cis-CH_3 group (E isomer) as compared with its shielding in the Z isomer, in which the heteroaramatic ring and the methyl group are trans-oriented relative to one another. Similar changes will also be observed for the signals of the protons of the NH_2 group in the investigated compounds: the cis-NH_2 group (Z isomer) should be more shielded than the trans-NH_2 group (the E isomer).

*Structure A is the syn isomer (E) and B is the anti isomer (Z).

†The difference in the chemical shifts for H_6 is 0.05-0.30 ppm for I and II.

TABLE 2. Data from the PMR Spectra and $\Delta G^{\neq}$ Values for Z,E Isomerization in I and II

Compound	Isomer	δCH_3, ppm	t*, °C	T_{coal}† °C	Percentage of isomers, %	$\Delta G^{\neq}$, kcal/mole	Solvent
Ia	E	1,93	−33	+50	42	16,4	$CDCl_3$
	Z	2,21			58	16.6	
	E	1,85	+20	+36	34	15.5	C_5D_5N
	Z	2,19			66	15,9	
	E	2,69	+25	+40	27	16,0	CF_3COOH
	Z	2,49			73	16,6	
Ib	E	1,91	−33	+9	45	14,1	$CDCl_3$
	Z	2,24			55	14,2	
	E	2,00	−35	+28	26	15,0	C_5D_5N
	Z	2,38			74	15,6	
	E	2,46	−22	+36	17	15,8	CF_3COOH
	Z	2,70			83	16,8	
Ic	E	3,49	−33	+25	25	15.0	$CDCl_3$
	Z	3,80			75	15,6	
Id	E	2,06	−31	~ +33	26	~ 15,5	C_5D_5N
	Z	2,31			74	~ 16,1	
Ie	E	1,86	−31	> +55	26	> 16,6	$CDCl_3$
	Z	2,16			74	> 17,2	
	E	2,01	−37	+65	23	17.1	C_5D_5N
	Z	2,32			77	17.9	
	E	2,38	+25	> +77	13	> 17,8	CF_3COOH
	Z	2,65			87	> 19,1	
II	E	1.88	−31	−9	22	13.2	$CDCl_3$
	Z	2.16			78	13.9	

*This is the temperature for which the chemical shifts of the methyl groups are given.

†The accuracy in the determination of the T_{coal} and $\Delta G^{\neq}$ values was ± 3° and ± 0.15 kcal/mole^{-1}, respectively.

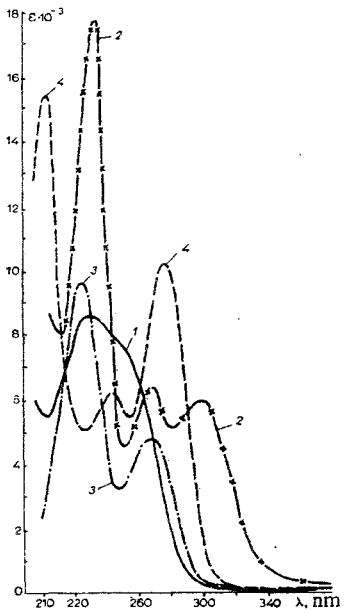


Fig. 2. UV spectra in dioxane; 1) N-(4-methoxy-5-pyrimidyl)acetamidine (Ib); 2) 4-methoxy-6-aminopyrimido[4,5-b]-1,4-thiazine (III); 3) 4-methoxy-5-aminopyrimidine (IV); 4) 4-methoxy-5-amino-6-methylthiopyrimidine (V).

Thus the strong-field signals of the CH_3 group (or of CH_2 in Ic) can be assigned to the E isomers, and the weak-field signals can be assigned to the Z isomers.* The assignment of the signals will be just the opposite for the NH_2 groups.

It might have been assumed that the higher intensity of the weak-field signals of the methyl groups is associated with the preferableness of the Z isomers, inasmuch as the NH_2 groups are smaller in volume than the CH_3 groups. This is confirmed by the fact that when the CH_3 group is replaced by the more bulky benzyl group (Ic), the difference in the intensities of the signals of the protons of the benzyl groups of the two isomers increases (the ratio of theE and Z forms in Ib and Ic are 45 : 55 and 25 : 75, respectively).

The difference in the chemical shifts of the signals of the methyl and benzyl groups in the E and Z isomers is ~ 0.26-0.32 ppm for the investigated compounds. Proceeding from these data and using the Johnson–Bovey Tables [4] we made an approximate evaluation of the angles of rotation of the aromatic ring relative to the plane of the double bond of the amidine residue (the ring currents of the pyrimidine ring were assumed to be equal to those of the benzene ring). It was found that the angle of rotation should be ~ 60-70°. Close values of the angle of rotation were also obtained on the basis of the chemical shifts of the NH_2 group. The agreement between the angles of rotation calculated from the chemical shifts of the CH_3, $CH_2C_6H_5$, and NH_2 groups makes it possible to speak of the close values of the ring currents of the pyrimidine and benzene rings.

*This assignment of the strong-field methyl signals to the cis groups is in agreement with the assignment of the signals made in [2, 3].

TABLE 3. $\Delta G^{\neq}_{corr}$ Values* for Ia, b, e and Their Salts and II (in kcal/mole^{-1})

Compound	$\Delta G^{\neq}$†		$\Delta G^{\neq}_{corr}$	
Base	$CDCl_3$	C_5D_5N	$CDCl_3$	C_5D_5N
Ia	16,6	15,9	16,6	15,9
Ib	14,2	15,6	12,8	14,2
Ie	>17,2	17,9	>15,6	16,3
II	13,9	—	13,4	—
Salts				
Ia	16,6		16,6	
Ib	16,8		15,4	
Ie	>19,1		>17,5	

*The $\Delta G^{\neq}_{corr}$ value is the difference in the free energy of activation without allowance for the electronic effect of the OCH_3 or $N(CH_3)_2$ groups (the value of the correction was taken from [3]).
† The $\Delta G^{\neq}$ values for the Z isomers are presented.

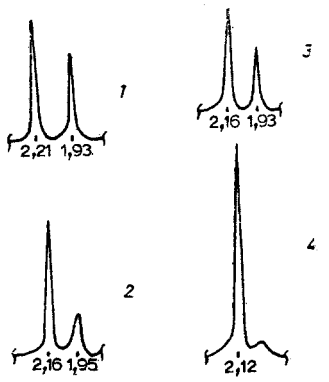
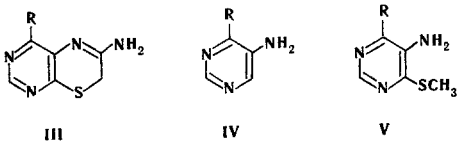


Fig. 3. Change in the intensity of the signals of the methyl group in the spectra of Ia: 1) in $CDCl_3$ solution; 2) in solution in $CDCl_3$ + CD_3OD; 3) in the sample in spectrum (2) to which more $CDCl_3$ has been added; 4) in CD_3OD solution (recording temperature −33°C).

It is natural to expect that an increase in the volume of the ortho substituent (R) in the heteroring should lead to an increase in the angle of rotation of the aromatic ring relative to the plane of the N = C bond, which may lead to an increase in the difference in the chemical shifts of the methyl groups of the isomeric forms. In fact, $\Delta\delta CH_3 = \delta_Z - \delta_E = 0.28$ and 0.20 ppm for Ia and its salt, respectively, while the $\Delta\delta CH_3$ values are 0.32 and 0.27 ppm for Ie and its salt, respectively. A similar increase in the $\Delta\delta CH_3$ values in the spectra of the E and Z isomers was previously observed in phenylimines and ketene aminals [2, 3].

When the heteroaromatic ring and the amidine system of bonds do not fit into a single plane, $\pi-\pi$ conjugation between them is disrupted, and conjugation of the free pair of electrons of the nitrogen atom of the amidine system with the π electrons of the pyrimidine ring appears; this should be reflected in the UV spectra. In fact, a comparison of the spectra of the amidines under investigation with the spectra of pyrimidothiazines III, which are model compounds with planar structures, and with substituted 5-aminopyrimidines IV and V,* in which there is only p−π conjugation with the amino group, confirms this point of view.



III IV V

III, IV R=OCH_3, NH_2, $N(CH_3)_2$

The UV spectra of the investigated amidines I and II differ appreciably from the spectra of III-V: only one broad absorption band, which is of low intensity and is shifted to lower wavelengths as compared with the longwave absorption of the model compounds (Fig. 2), is observed in them. The fact of the shift of the absorption bands to lower wavelengths as compared with the spectra of the models can be considered to be a confirmation of deviation of the amidine system from the plane of the heteroring, and owing to this, the considerable weakening of each type of conjugation.

It should be noted that solvents affect the ratios of the isomeric forms of the investigated acetamidines. For IIa in $CDCl_3$ solution the ratio of the Z and E forms is 58 : 42 at −33°, and the percentage of the E isomer decreases when CD_3OD is added; only 6% of the E isomer is present in methanol solution. These changes in the concentrations of the E and Z isomers are reversible: when the percentage of $CDCl_3$ in the alcohol is increased, the concentration of the E form increases (Fig. 3). The effect of perdeutero-N,N-dimethylformamide on the ratio of the E and Z isomers is similar to the effect of alcohol. This phenomenon is apparently associated either with the high probability of the formation of a solvent−amidine complex due to hydrogen bonds for the Z isomer, as compared with the E isomer, or with the fact that a polar solvent stabilizes the formation of the isomeric form with a large dipole moment.

*Substituted 5-amino-6-methylthiopyrimidines V were used for the evaluation of the effect of sulfur in the pyrimidothiazines on the UV spectra.

TABLE 4. Dependence of the $\Delta G^{\neq}$ Values for Ia on the Polarity of the Solvent

Solvent	ε	$\Delta G^{\neq}$, kcal/mole^{-1} *
Dioxane	2.2	16,8
Chloroform	4,7	16,6
Pyridine	12,5	15,9
Methanol	32.6	14,2
Dimethylformamide	36.7	13.7

*The $\Delta G^{\neq}$ values are given for the Z isomers.

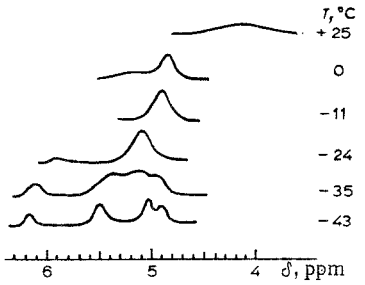


Fig. 4. Change in the form of the signals of the protons of the NH_2 group in the spectrum of Ic (in $CDCl_3$ solution) as the temperature changes.

It is known [3] that Z,E isomerization relative to the N = C bond for systems similar to those under investigation here may proceed both via a mechanism of rotational isomerization and by means of inversion of the imine nitrogen atom. It has been shown [3] that hindrance of the isomerization process as the size of the ortho substituents increases is characteristic for the rotational mechanism, while Z,E isomerization is facilitated in the case of an inversion mechanism. On the other hand, dependence of the the rate of the isomerization process on the polarity of the solvent is characteristic for a rotational mechanism of isomerization [5]; the more polar the solvent, the more rapidly the isomerization proceeds, whereas this dependence should not exist for the inversion mechanism. In this connection, we found the free energies of activation for the isomerization process ($\Delta G^{\neq}$) as a function of the presence of substituents in the ortho position of the pyrimidine ring and on the polarity of the solvent (Tables 2-4). The $\Delta G^{\neq}$ values were calculated from the formulas in [6].

It follows from an examination of the $\Delta G^{\neq}$ values that the pyridine ring facilitates Z,E isomerization as compared with the pyrimidine ring ($\Delta\Delta G^{\neq} = 3.2$ kcal/mole^{-1}) (Table 3).

Ortho substituents have a smaller effect, but one must take into account the fact that it is associated not only with the steric effect but also with the electronic effect of the substituting group. In order to isolate the steric effect in pure form we used data on the magnitude of the contribution of the electronic effect to the $\Delta G^{\neq}$ value of Z,E isomerization presented by Kessler and co-workers [3] for p-substituted tetraphenylguanidines. The corresponding $\Delta\Delta G^{\neq}$ values are 1.6 and 1.4 kcal/mole^{-1} for $N(CH_3)_2$ and OCH_3 groups, respectively.*

*It was assumed that the electronic effects of para and ortho substituents are equal in the systems under study [3].

TABLE 5. Chemical Shifts of the Protons of the NH_2 Groups and $\Delta G^{\neq}$ Values for Rotation about the C–N Bond in I and II

Compound	Isomer	δNH_2*, ppm	T_{coal}, °C	Percentage isomers, %	T†, °C	$\Delta G^{\neq}$, kcal/mole^{-1}
Ia	E	5.09 5.99	−11	42	−33	12,5
	Z	5.30 5.50	−35	58	−61	12.0
Ib	E	5.25 6.00	−11	45	−33	12,6
	Z	5.32 5,70	−35	55	−58	11,7
Ic	E	4.86 6,00	−11	25	−33	12,4
	Z	5.77 4,95	−35	75	−61	11.4
Ie	Z‡	5.08 5.47	−14	74	−31	12.8
II	Z‡	5,25 5,78	−31	78	−61	11.8

*In $CDCl_3$ solution.

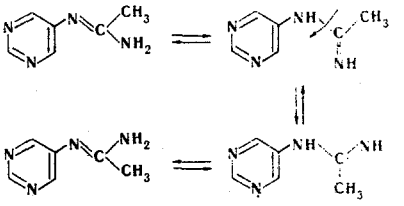
† This is the temperature for which the chemical shifts of the protons of the NH_2 group are given.

‡We were unable to estimate the $\Delta G^{\neq}$ values for the E isomers of Ie and II.

It follows from the data in Table 3 that a distinct dependence of the $\Delta G^{\neq}_{corr}$ value on the size of ortho substituents R is not observed either for salts Ia, b, e or for their bases, in contrast to the data in [3]. This makes it impossible to unambiguously assign the type of mechanism of the isomerization process in the investigated compounds.

The dependence of the $\Delta G^{\neq}$ values that we found (Ia) on the dielectric constant of the solvent (ε) is presented in Table 4. It follows from the data that the $\Delta G^{\neq}$ value decreases as the polarity of the solvent increases, and the isomerization at the N = C bond proceeds more readily. This sort of dependence is characteristic for rotational isomerization [5].

In addition to this, a different mechanism that includes a step involving tautomeric conversion can also be proposed for this class of compounds:



According to the IR spectral data presented above, I and II exist in the amino form. However, for the realization of isomerizational transition through a step involving tautomeric conversion it is sufficient to assume the presence in solution of a relatively low percentage of the imine forms (in which rotation also occurs) that is not detectable by IR spectroscopy.

A change in the form of the signals of the NH_2 protons, which indicates retardation of rotation of the NH_2 group about the C–N single bond, was detected for the investigated compounds when the temperature was lowered to −60° (Fig. 4). The certain increase in the barrier to rotation about this bond as compared with the C–N bond of amines is evidently due to the contribution of structure VI to the ground state, which is natural for amidine systems [7-9].

The differences in the free energies of activation of this process for both isomeric forms of I and II are presented in Table 5.

VI

It follows from these data that retardation of rotation is somewhat more pronounced (the $\Delta G^{\neq}$ values are higher) in the E isomers than in the corresponding Z isomers. This is in agreement with the literature data for tetramethylphenylguanidines [3].

EXPERIMENTAL METHOD

The PMR spectra were recorded with a JNM 4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra were obtained with a Perkin-Elmer 457 spectrometer. The UV spectra were recorded with an EPS-3 spectrophotometer.

LITERATURE CITED

1. T. S. Safonova, M. P. Nemeryuk, A. F. Keremov, N. I. Traven', and L. A. Myshkina, Khim. Geterotsikl. Soedin., 423 (1971).
2. D. Wurmb-Gerlich, F. Vögtle, A. Mannschreck, and H. A. Staab, Ann., 708, 36 (1967).
3. H. Kessler, P. F. Bley, and D. Leibfritz, Tetrahedron, 27, 1687 (1971).
4. C. E. Johnson and F. A. Bovey, J. Chem. Phys., 29, 1012 (1958).
5. H. Kessler, Chem. Ber., 103, 973 (1970).
6. H. Shanan-Atidi and K.-H Ber-Eli, J. Chem. Phys., 74, 961 (970).
7. R. C. Neuman and C. L. B. Joung, J. Chem. Phys., 69, 2570 (1965).
8. D. L. Harris and K. M. Wellman, Tetrahedron Lett., 50, 5225 (1968).
9. Z. Rappoport and R. Ta-Shma, Tetrahedron Lett., 52, 5281 (1972).