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TAUTOMERISM AND SPATIAL ISOMERISM IN THE 2-PHENYLAMINOTHIAZOLIN-4-ONE SERIES

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UDC 543.422.25.4.6:541.62:547.789.5

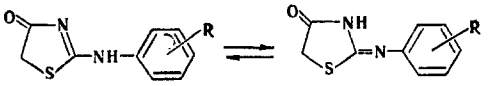
The existence of amine—imine tautomerism in 2-phenylaminothiazolin-4-ones was confirmed by comparison of the IR and UV spectra of these compounds with N-methyl model compounds with amine and imine structures. It is shown that the temperature changes in the PMR spectra are associated with syn—anti isomerization relative to the exocyclic CN bond. The kinetic parameters of this isomerization were calculated, and it was established that it is realized in the imine form via an inversion mechanism.

A pronounced dependence of the form and position of the signals of the phenyl protons on the temperature is observed in the PMR spectra of p-substituted 2-phenylaminothiazolin-4-ones (solutions in deuterodimethylformamide, deuteropyridine, and deuteroacetone). At high temperatures the signals of these protons correspond to the four-spin AA'BB' system (Fig. 1, spectrum a). As the temperature is lowered, the doublet of the ortho protons becomes broader, a coalescence stage occurs (Fig. 1, spectrum b), and the doublet is split into two doublets (Fig. 1, spectra c and d). At low temperatures the nonequivalence of the meta protons is also manifested (Fig. 1, spectrum d). For the investigated series of compounds this is also accompanied by splitting of the signals of the CH_2 group of the thiazoline ring into a doublet.

The temperature changes in the spectra indicate the existence in the investigated substances of two molecular forms in equilibrium with one another; the rate of conversion from one form to the other increases appreciably as the temperature is raised. In the case under consideration the appearance of different molecular forms may be due to tautomerism, syn—anti isomerism, or conformation isomerism due to retarded rotation of the phenyl group about the N—C_6H_5 bond.

The amine—imine tautomerism (IA—IB) of 2-arylamino derivatives of thiazolin-4-one was previously detected by means of the IR spectra [1, 2] and an examination of the dependence of the pK_a values on the σ^o values [3].

In the present research we made a more detailed study of the tautomerism of these compounds by means of model compounds (II-V):



IA IB

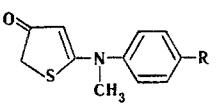
S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 190-195, February, 1978. Original article submitted March 1, 1977.

 0009-3122/78/1402-0148$07.50

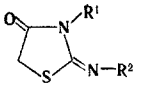
TABLE 1. Data from the IR and UV Spectra of I-V

Compound	R	IR spectra				UV spectra (dioxane)	
		crystals		$CHCl_3$			
		$\nu_{C=O}$	$\nu_{C=N}$	$\nu_{C=O}$	$\nu_{C=N}$	λ_{max}	ε
Ia	*p*-$N(CH_3)_2$	1691 s	1520 s	1690 m ‡ 1725 m	1525 s br‡ 1635 sh	272 308	10350 12300
Ib	*p*-OCH_3	1668 s (1700 w sh)	1490—1510 vs br 1635 s	1690 s 1725 m	1525 s br 1640 s	283	10340
Ic	*p*-CH_3	1675 s	1490—1520 vs br 1636 s	1700 s 1737 s-m	1543 s 1650 s	274	9660
Id	H	1676 s	1500 vs br 1638 s	1700 m 1740 s	1542 s 1650 s br	270	8600
Ie	*p*-Br	1697 s 1720 m	1567 s 1638 m	1740 m‡	1649 s‡	274	11200
If	*p*-Cl	1697 s 1720 s	1570 s 1635 m	1740 m‡	1650 m‡	274	9660
Ig	*m*-Cl	1700 s 1728 s-m	1570 s — 1585 s 1637 s	1700 w sh – 1725 m – 1743 s	1583 m 1655 vs	272	7420
Ih	*p*-NO_2	1688 s 1705 m sh	1510 vs br 1632 s-m	1738 m‡	1650 s‡	316	13720
IIb	*p*-OCH_3	1690 s	1530 vs br	1690 s	1535 vs	255	1900
IIc	*p*-CH_3	1698 s	1545 vs br	1695 s	1535 vs	256	19160
IId	H	1690 s	1538 vs br	1688 s	1530 vs br	256	17940
III	H	1728 s	1636 vs	—	—	272	8200
IV	$C_6H_4CH_3$-*m*	—	—	1727 s*	1634* vs br	274	6620
V	$CH_2C_6H_5$	1714	1645 vs	1724 s†	1645 vs†	—	

*In dimethyl sulfoxide.
†In dioxane.
‡The spectra were of low quality because of the low solubilities of the compounds.



II



III-V

I a R=*p*-$N(CH_3)_2$; b R=*p*-OCH_3; c R=*p*-CH_3; d R=H; e R=*p*-Br; f R=*p*-Cl; g R=*m*-Cl; h R=*p*-NO_2; i R=*o*-OCH_3; j R=*o*-CH_3; III $R^1=CH_3$, $R^2=C_6H_5$; IV $R^1=R^2=C_6H_4CH_3$-*m*; V $R^1=R^2=CH_2-C_6H_5$

In the case of model compounds with an amine structure (II) an appreciable decrease in the ν_{CO} (1688-1698 cm^{-1}) and $\nu_{C=N}$ (1525-1545 cm^{-1}) bands is observed in the spectra as compared with imine models III-V ($\nu_{C=O}$ 1728 and $\nu_{C=N}$ 1636 cm^{-1}) because of the presence in the ring of a conjugated $-\overset{\overset{O}{\|}}{C}-N=C$ grouping.

Two groups of ν_{CO} and $\nu_{C=N}$ bands corresponding to the amine and imine tautomeric forms are observed in the IR spectra of most of the investigated thiazolidones, and the intensities of these bands vary as a function of the solvent and the substituent in the phenyl ring (Table 1). An examination of these data shows that most of the investigated compounds are mixtures of two tautomeric forms. As compared with the solutions of the compounds, in the case of crystalline substances the equilibrium is shifted to favor the amine forms. The imine form predominates in nonpolar solvents (dioxane and chloroform). The introduction of electron-acceptor substituents in the phenyl ring leads to an increase in the intensities of the $\nu_{C=O}$ and $\nu_{C=N}$ bands corresponding to the imine form.

In the UV spectra of the amine models the absorption maximum is observed in the shorter-wave region [λ 256 nm (ε 18,000-19,000)] and with a higher extinction than in the case of imine models III and IV [λ 272 nm (ε 8200)].

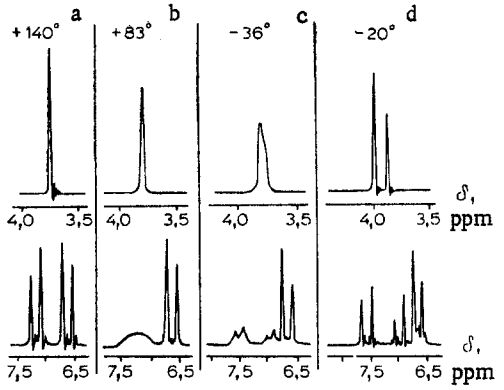


Fig. 1. Change in the signals of the CH_2 group and the phenyl protons of Ia as a function of the temperature in deuterodimethyl sulfoxide.

TABLE 2. Kinetic Parameters of the Syn—Anti Isomerization of I

Comp.	R	Δν, Hz	k, syn/anti	T_f, °C	$\Delta G^{\neq}_{c\to a}$, kcal/mole	$\Delta G^{\neq}_{a\to c}$, kcal/mole	$\lg k^{25°}_{c\to a}$	$\lg k^{25°}_{a\to c}$	σ
a	*p*-$N(CH_3)_2$	33,0	1,5	+83	18,2	17,9	−0,62	−0,410	−0,60
b	*p*-OCH_3	41,3	1,4	+74	17,5	17,3	−0,119	+0,051	−0,27
i	*o*-OCH_3	4,5	1,5	+8	15,4	15,1	+1,487	+1,652	
c	*p*-CH_3	46,0	1,4	+70	17,3	17,0	+0,089	+0,258	−0,17
j	*o*-CH_3	10,7	6,5	+18	16,2	15,2			
e	*p*-Br	50,1	1,1	+60	16,5	16,4	+0,649	+0,695	+0,232
f	*p*-Cl	50,0	1,1	+56	16,3	16,2	+0,800	+0,845	+0,227
f	*p*-Cl*	50,0	1,1	+56	16,3	16,2			+0,227
h	*p*-NO_2	48,7	0,77	+35	15,2	15,4	+1,613	+1,495	+0,778

*By the method of complete analysis of the form of the line (CAFL).

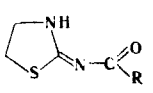
TABLE 3. Results of Elementary Analysis and Melting Points of 2-Aryliminothiazolin-4-one Derivatives

Compound	mp, °C	Found, %		Empirical formula	Calculated, %	
		C	H		C	H
Ia	230	56,60	5,62	$C_{11}H_{13}N_3OS$	56,17	5,53
Ib	184	54,08	4,39	$C_{10}H_{10}N_2O_2S$	54,05	4,50
Ic	183	58,20	4,94	$C_{10}H_{10}N_2OS$	58,25	4,85
Id	178	56,13	3,94	$C_9H_8N_2OS$	56,25	4,16
Ie	225	39,62	2,34	$C_9H_7BrN_2OS$	39,87	2,58
If	206	47,49	3,02	$C_9H_7ClN_2OS$	47,68	3,09
Ig	180	47,69	3,22	$C_9H_7ClN_2OS$	46,68	3,09
Ih	250	45,40	3,21	$C_9H_7N_3O_3S$	45,57	2,95
Ii	149	54,20	4,71	$C_{10}H_{10}N_2O_2S$	54,05	4,50
IIb	143,5	55,41	3,31	$C_{11}H_{12}N_2O_2S$	55,93	3,08
IIc	125	60,78	6,22	$C_{11}H_{12}N_2OS$	60,54	5,92
IId	55	58,51	5,03	$C_{10}H_{10}N_2OS$	58,25	4,85
IIId	125	58,70	5,21	$C_{10}H_{10}N_2OS$	58,25	4,85
IV	128	68,73	5,34	$C_{17}H_{16}N_2OS$	68,92	5,40
V	86	68,56	5,11	$C_{17}H_{16}N_2OS$	68,92	5,40

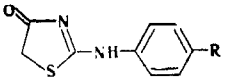
Depending on the solvent, a change in the spectra corresponding to a shift in the tautomeric equilibrium is observed for all of the investigated compounds. Thus an increase in the extinction of the absorption maximum and a shift of the maximum of the shorter-wave region are observed for alcohol and water solutions as compared with dioxane solutions for most of the compounds.

The character of the change in the spectrum on passing from dioxane to alcohol and a mixture of 95% H_2O and 5% alcohol also changes as a function of the substituent in the phenyl ring. The spectra of the nitro derivative in all solvents (95% H_2O + 5% alcohol, 97% alcohol + 3% H_2O, and dioxane) are similar. The spectra of Ic,d in dioxane are similar to the spectra of imine model III. Thus the UV spectral data are in agreement with the results of IR spectroscopy and make it possible to assume that the investigated compounds are mixtures of two forms. The imine form predominates in dioxane (90% of the imine form for Id*), and a considerable amount of the amine form is present in water and alcohol. The nitro derivative evidently has an imine structure in all of the solvents.

At first glance, the shift of the tautomeric equilibrium to favor the amine form in polar solvents is not in agreement with the available data on the tautomerism of 2-acrylaminothiazolines [4] (A), for which an increase in the percentage of the amine form was observed in nonpolar solvents.



A



B

However, one should bear in mind that in both cases an increase in the polarity of the medium should lead to stabilization of the form in which the C=O and C=N bonds are in a conjugated position and substantial polarization of the molecules takes place. For this reason, the opposite effects of the solvent of the tautomeric equilibrium constants of B and 2-acylaminothiazolines are completely explicable and are due to the fact that for the latter the indicated orientation of the bonds is realized in the imine form, whereas for the corresponding 2-phenylaminothiazolin-4-ones it is realized in the amine form.

Thus, the IR and UV spectral data confirm the presence of amine—imine tautomerism in the series of investigated compounds.

However, a number of facts indicate that tautomerism is not the reason for the change in the character of the signals in the PMR spectra as the temperature changes. Thus there is no correlation between the ratios of the intensities of the signals corresponding to the different isomeric forms (at low temperatures) and the percentages of the tautomers in the mixture. For example, the p-nitro derivative, which exists almost completely in the imine form, gives a distinct picture of splitting of the signals of the ortho protons into doublets with approximately equal intensities when it is cooled.

Furthermore, over the indicated temperature range one could not have expected the pronounced slowing down of amine—imine tautomerism that is observed in the PMR spectra.

In a preliminary study of some 2-phenylaminothiazolinones in deuterodimethylformamide we made the assumption that the observed changes in the PMR spectra are due to the retarded rotation about the N—C_6H_5 bond [5]. However, during a subsequent study of these compounds in other solvents (deuteropyridine and deuteroacetone), as well as in p-dimethylaminophenyl and benzyl derivatives, it was found that different intensities of the components of the signals, as well as broadening and splitting of the signal of the ring CH_2 group, are observed in their PMR spectra as the temperature is lowered. This could not be due to rotational isomerism relative to the N—C_6H_5 bond. Subsequently, during a complete analysis of the form of the line (CAFL) it was found that the signals of the aromatic protons in the low-temperature PMR spectra correspond to superimposition of the CC'DD' and EE'FF' systems when DD' is close to FF' (meta protons), whereas an ABCD system should have been expected in the case of rotational isomerism. All of the regularities observed in the spectra can be explained by spatial isomerization relative to the exocyclic CN bond. The presence of syn and anti isomers for the imine form (or of rotational isomers relative to the C—N bonds in the amine forms) should be in good agreement with the observed character of the change in the signals with the temperature (the transition from the AA'BB' system to CC'DD' and EE'FF' systems, doubling of the signals of the ring CH_2 groups, and the different intensities of the components of the signals corresponding to the two isomers). The tautomerism and rotation of the phenyl ring about the N—C_6H_5 bond evidently take place at a high rate over the investigated temperature range. Each of the two signals corresponding to the syn and anti

*Imine models were not available for the other compounds, and we were therefore unable to make a quantitative estimate of the percentages of the tautomeric forms.

structures is therefore the average of the signals of the amine and imine forms. The mechanism of the isomerization of the investigated compounds was determined on the basis of a study of the effect of the character and position of the substituents in the phenyl ring on the magnitude of the energy barrier of the syn–anti transformation [6].

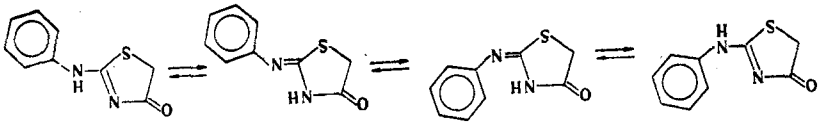
The free energies of activation ($\Delta G^{\neq}$) were calculated from the Eyring equation. The τ value for one of the compounds (If) was calculated from the signals of the ortho protons both by the method of complete analysis of the form of the line (CAFL) with a computer* and from approximate formula (1) [7]

$$P_A - P_B = \left[\frac{\tau^2(2\pi\Delta\nu)^2 - 2}{3}\right]^{1/2} \cdot \frac{1}{2\pi\Delta\nu\tau}, \quad (1)$$

where $\Delta\nu$ is the difference in the chemical shifts of the signals of the two isomers in the absence of exchange, and P_A and P_B are the mole fractions of the two states. Since the results of the computer calculation were in agreement with the results of calculation from the approximate equation, the kinetic parameters of spatial isomerization of all of the remaining I were calculated from formula (1). The results of the calculation are presented in Table 2. It follows from the results that the introduction of ortho substituents into the phenyl ring leads to a decrease in the energy barrier to isomerization. This constitutes evidence in favor of an inversion transformation, which can occur only in the imine form [6].

Good correlation (γ = 0.997) between the logarithms of the isomerization rate constants calculated for t = 25°C† with the Hammett substituent σ-constants is observed for the investigated 2-phenylaminothiazolin-4-ones. The reaction constants (ρ) calculated from this dependence (1.38 and 1.63) are close to the corresponding ρ values of imines in which syn–anti isomerization is realized at the C=N bond via an inversion mechanism [6]. This constitutes yet another confirmation of an inversion mechanism for the isomerization of 2-phenylaminothiazolines.

Thus the results make it possible to conclude that syn–anti isomerization in 2-phenylaminothiazolin-4-ones is realized in the imine form and that the subsequent establishment of the isomerization equilibrium takes place through amine-imine tautomerism.



tautomerism syn–anti isomerization tautomerism

EXPERIMENTAL

The IR spectra of mineral oil pastes and $CHCl_3$, dioxane, and DMSO solutions of the compounds were recorded with a Perkin–Elmer 457 spectrophotometer. The UV spectra of solutions of the compounds in alcohol, 95% H_2O + 5% alcohol, and dioxane were obtained with an EPS-3 spectrophotometer. The PMR spectra were recorded with a Jeol C-60-HL spectrometer with tetramethylsilane as the internal standard.

Compounds I, IV, and V were synthesized by the method described in [8] by reaction of monoaryl- or symmetrical diarylthioureas with chloroacetic acid.

The model N-methyl derivatives were obtained by methylation of the corresponding sodium salts of 2-arylaminothiazolidin-4-ones with methyl iodide in a sealed tube by the method in [9].

The results of elementary analysis and the melting points of the investigated compounds are presented in Table 3.

*The authors thank G. V. Lagodzinskaya and co-workers for performing the calculations by the method of complete analysis of the form of the line.
†In this case the entropy of activation was assumed to be zero ($\Delta S^{\neq} = 0$) [6].

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3-NITRO-5-CHLOROMETHYLSALICYLALDEHYDE IN THE SYNTHESIS OF PHOTOCHROMIC SPIROCHROMENES OF THE INDOLINE SERIES

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UDC 541.145:547.752'814.1.07:543.422.6

The nitration of 5-chloromethylsalicylaldehyde leads to 3-nitro-5-chloromethylsalicylaldehyde, the chlorine atom in which is smoothly replaced by a hydroxy or acetoxy group. The salicylaldehydes obtained condense with 1,3,3-trimethyl-2-methyleneindoline to give the corresponding photochromic indolinespirochromenes. The spectral-kinetics of the photochromic transformations of the spirochromenes are discussed.

The introduction of a chloromethyl group in the 3 position of 5-nitrosalicylaldehyde has made it possible to carry out the synthesis of a number of interesting indolinespirochromenes that have photochromic properties [1]; other chloromethylnitrosalicylaldehydes have not been described in the literature.

In an attempt to carry out the nitration of 5-chloromethylsalicylaldehyde (I)[2] by the action of nitric acid in glacial acetic acid or acetic anhydride or by means of copper nitrate in acetic anhydride under conditions of treatment of the reaction mixture that permit contact with water, instead of the expected 3-nitro-5-chloromethylsalicylaldehyde (II) we isolated its hydrolysis product — 3-nitro-5-hydroxymethylsalicylaldehyde (III); aldehyde II was isolated in satisfactory yield when treatment with water was excluded. The reaction of 3-nitro-5-hydroxymethylsalicylaldehyde III with thionyl chloride in the presence of dimethylaniline in chloroform also led to aldehyde II.

The lability of the halogen atom in the chloromethylnitrosalicylaldehyde (II) molecule is illustrated by its easy replacement by an acetoxy group on reaction with anhydrous sodium acetate in acetic acid, which leads to 3-nitro-5-acetoxymethylsalicylaldehyde (IV).

Aldehydes III and IV react with 1,3,3-trimethyl-2-methyleneindoline to give the corresponding indolinespirochromenes Va,b. We were unable to obtain a spirochromene from aldehyde II via a similar reaction; only pronounced resinification of the reaction mixture was observed.

For comparison, by reaction of 1,3,3-trimethyl-2-methyleneindoline with 3-nitro-5-methylsalicylaldehyde [3] we obtained the corresponding methyl-substituted spirochromene Vc.

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow 103787. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 196-199, February, 1978. Original article submitted March 21, 1977.

0009-3122/78/1402-0153$07.50