6. A. P. Shkumat, L. D. Patsenker, N. V. Adonina, V. K. Polyakov, and V. F. Lavrushkin, Zh. Khim. Zh., 53, No. 5, 529 (1987).

STRUCTURE AND DUAL REACTIVITY OF 2-PHENYLPEMOLINE

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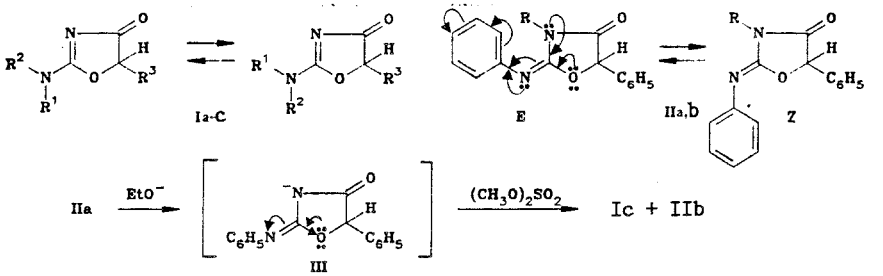
5-Phenyl-2-phenylimino-4-oxazolidinone exists in DMSO-D_6 in the form of a mixture of the E and Z isomers of the imino tautomer, but it crystallizes in the amino form. Parallelism between the basicity and nucleophilicity of the reaction centers of this mesomeric anion is observed when the alternative isomers (and the tautomers corresponding to them) differ significantly in stability. If this condition is not fulfilled, these parameters do not coincide, as is illustrated in the example of its methylation reaction.

2-Amino-4-oxazolinone (Ia) and 5-phenyl-2-amino-4-oxazolinone (pemoline, Ib) exist in solutions in the form of the amino tautomers [1, 2]. Their 2-methyl derivatives also have amino structures [3], while, the imino form predominates in the case of 5-phenyl-2-phenylimino-4-oxazolidinone (2-phenylpemoline, IIa), according to the data from UV spectroscopy in methanol [2]. The experience gained in the investigation of the structure of cyclic amidines [4] calls for the testing of this conclusion with the aid of PMR spectroscopy with the aid of model compounds Ic and IIb.



I a $R^1=R^2=R^3=H$; b $R^1=R^2=H$, $R^3=C_6H_5$; c $R^1=CH_3$, $R^2=R^3=C_6H_5$; II a R=H; b $R=CH_3$

In [1] only the singlet signal of the NH protons was discovered in the PMR spectrum of compound Ia in DMSO-D_6, but the signals of these protons were not detected at all in [2]. We found that in solutions of compounds Ia and Ib in DMSO-D_6, as in the case of 2-amino-4-thiazolinone [5], the NH protons have two signals of equal intensity, which are consistent with the amino structure and are attributable to automerization owing the hindered rotation around the partially double $C_{(2)}{=}{=}N_{(2')}$ bond [4, 5]. In the case of the thia analog, the addition of a phenyl ring to the exocyclic nitrogen atom results in "reversal" of the tautomeric equilibrium in solutions [4]. This is also true for compound IIa, as follows from a comparison of its PMR spectra in DMSO-D_6 with the spectra of methylated derivatives Ic and IIb, which simulate the amino and imino form of compound IIa, respectively.

The PMR spectrum of 2-methylphenyl derivative Ic attests to hindered rotation around the $C_{(2)}{=}{=}N_{(2')}$ bond and different populating of the conformers. The signal of the $C_{(5)}H$ proton is doubled, the low-field singlet (5.78 ppm) being approximately 5 times less intense

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then the signal at 5.72 ppm. Although the signal of the methyl protons at 3.44 ppm is not split, it has the asymmetric form characteristic of a coalescing "doublet" with a less intense high-field component. The aromatic absorption is displayed in the form of two comparatively narrow multiplets at 7.38 and 7.30 ppm.

The PMR spectrum of 3-methyl derivative IIb contains not only singlet signals for the CH_3, $C_{(5)}H$, and $C_{(5)}C_6H_5$ protons, but also a complex multiplet for the protons of the phenyl ring at the $N_{(2')}$ atom in the 6.95-7.32-ppm region, which corresponds to an AA'BB'C system. Like its thia analog [4], this compound exists in the form of the Z isomer due to the steric hindrances between the CH_3 and C_6H_5 groups.

The multiplet of the $N_{(2')}C_6H_5$ aromatic protons in potentially tautomeric compound IIa (6.95-7.70 ppm) is very reminiscent of the signal of the analogous protons in the PMR spectrum of its thia analog 2-phenylimino-4-thiazolidinone [4], being a "snapshot" of the dynamic system of the interconverting E and Z isomers of the imino tautomer. This absorption corresponds to the superposition of the AA'BB'C and DD'EE'F systems corresponding to the E and Z isomers, in which BB' is close to EE' (the m protons), and C is close to F (the p protons). The isomers are distinguished by the AA' and DD' signals of the o protons; the $N_{(2')}C_6H_5$ protons of the Z isomer of compound IIa resonate at the same position as the analogous protons of the Z isomer of compound IIb. In contrast to the thia analog, in the case of compound IIa, the E isomer is sterically more favorable than the Z isomer ([E]/[Z] ~ 4). This is unexpected in view of the van der Waals radii of the nitrogen and oxygen atoms [6]. The stability of the imino tautomer is due to the effects of the π-π and p-π conjugation with the participation of the phenyl ring at the exocyclic nitrogen atom $N_{(2')}C_6H_5$, the $C_{(2)}{=}N_{(2')}$ bond, and the $O_{(1)}$, $N_{(2')}$, and $N_{(3)}$ atoms [4].

In the crystalline state 2-phenylpemoline IIa exists in the amino form, demonstrating the complete analogy to 2-phenylimino-4-thiazolidinone [7]. This conclusion follows from a comparison of the $\nu_{C=O}$ and $\nu_{C=N}$ frequencies in the IR spectra of compounds IIa, Ic, and IIb, which are equal to 1720 and 1580, to 1740 and 1570, and to 1770 and 1680 cm^{-1}, respectively. The somewhat smaller value of $\nu_{C=O}$ for compound IIa in comparison to the value of $\nu_{C=O}$ for the model of the amino form (Ic) is attributed to the existence of an N–H···O hydrogen bond in its crystals [7].

The data on the methylation of the anion of 5-phenyl-2-methylamino-4-oxazolinone, which results in the formation of isomeric 2,2-dimethylamino and 3-methyl-2-methylimino derivatives in a 10:1 ratio [2], are closely related to the relative stability of the tautomers. Howell, Quinones, and Hardy [2] regarded these results as an example of compliance to "the principle of parallelism of nucleophilicity and basicity frequently observed in heterocyclic systems," although in reality there is no basis to raise this parallelism to the rank of a principle [8, 9].

We propose the following interpretation. If one of the isomeric methyl derivatives is richer in energy, and this is the case when the tautomers corresponding to them also differ in stability* (as is manifested by the difference between the basicities of the reaction centers in the mesomeric anion [10]), a scheme of charge and orbital control cannot be used to explain the positional selectivity of the process [11]. In such a case, the "nonintersection rule" [12], which underlies the evaluation of reactivity by perturbation theory, is not obeyed, and the use of the charges of the heteroatoms and the partial electron densities of the HOMO as static indices of the reactivity of the mesomeric anion of 5-phenyl-2-methylamino-4-oxazolinone cannot account for the $N_{(2')}$ vs. $N_{(3)}$ positional selectivity of its methylation [11]. The transition state leading to the energy-enriched reaction product, i.e., the 3-methyl derivative in the case under consideration, is "controlled by the reaction product" [13], i.e., is so high that this derivative does not manage to form in an appreciable amount due to the relatively fast occurrence of the competitive reaction. We note that Edwards' equation, which we modified for dual reactivity [14], is more prognostic in this case than is Klopman's equation [15], since the "basicity" term in Edwards' equation make it possible to take into account the relative stability of the reaction products, i.e., the factor which plays the main role in "control by the reaction product,"

*The stability of the tautomers is unquestionably symbatic to the stability of the alkyl derivatives corresponding to them, if the alkyl group does not create any significant steric hindrances to conjugation, etc. The amino tautomer of compound IIa is at least 17.4 kJ/mole more stable than the imino tautomer [10].

when the evaluation of the profile of the potential energy after the "product-like" transition state is important [11].

If the difference between the basicities of the alternative reaction centers of the mesomeric anion, i.e., the free energies of the tautomers and the methyl isomers corresponding to them, is small, the ratio between the isomeric products is explained by a scheme of charge and orbital control, which estimates the profile of the potential energy in the initial stage of the reaction, before the transition state [12], and it is not necessary to refer to the "parallelism between the nucleophilicity and the basicity" (especially in hydroxyl-containing media, where specific solvation of the anion centers is possible [8]), since the distribution of the charge in the mesomeric anion is not uniquely related to the position of the tautomeric equilibrium [8; 16, p. 157]. Consideration of the modified Edwards equation [14] leads to a similar conclusion: The smaller is the difference between the basicities of the reaction centers, the greater is the degree to which the positional selectivity is determined by the "polarizability" term, which usually increases as the basicity decreases. We encounter such a situation in the case of the methylation of the anion of 2-phenylpemoline IIa by dimethyl sulfate. According to the data in [2], only the 2-methyl isomer Ic forms in methanol, but, by carrying out the reaction in ethanol, we were able to also detect the 3-methyl derivative IIb with the aid of adsorption column chromatography. The ratio between exo- and endomethylation ($N_{(2')}$ vs. $N_{(3)}$) is above 3:1, whence it follows that the basicity and nucleophilicity of these atoms in the anion of compound IIa clearly do not coincide.

In order to obtain results on the methylation reaction in an acetonitrile medium which could be compared to the results for the thia analog [17, 18], we attempted to isolate the sodium salt of compound IIa in the solid state, but we were unsuccessful. For this reason, the kinetic investigation of the methylation reaction of compound IIa was carried out in acetonitrile containing 1 vol. % ethanol. Anion III was generated by adding a stoichiometric quantity of sodium ethoxide to a solution of compound IIa in acetonitrile. The parameters of the dissociation of the sodium salt of 2-phenylpemoline in acetonitrile containing 1% ethanol were found preliminarily by a conductometric method according to the techniques described in [19]: the dissociation constant $k_d^{25°C} = 2.11 \cdot 10^{-4}$, and the limiting equivalent conductivity $\lambda_0^{25°C} = 188.3$ cm$^2 \cdot \Omega^{-1} \cdot$mole^{-1}. The kinetic and positional characteristics of the reaction were determined according to the methods in [17, 18]. The rate constant of the methylation of the free anion $k_i^{25°C} = 1.77 \pm 0.10$ liter$\cdot$mole$^{-1}\cdot$sec^{-1}, and the ratio between the yields of the methyl isomers $N_{(2')}/N_{(3)} = 3.16 \pm 0.35$. The comparable data on the methylation of the anion of 2-phenylimino-4-thiazolidinone are as follows: $k_i^{25°C} = 6.51$ liter$\cdot$mole$^{-1}\cdot$sec^{-1} in acetonitrile [18], and $N_{(2')}/N_{(3)} = 0.50$ in acetonitrile containing 7% methanol [20]. The rate constant of the methylation reaction in acetonitrile containing 1% ethanol should not be significantly smaller than the rate constant in pure acetonitrile. Conversely, the positional selectivity $N_{(2')}/N_{(3)}$ even for such an insignificant ethanol content is comparable to the value of $N_{(2')}/N_{(3)}$ observed when the ethanol content is far greater [21], and, furthermore, the values of $N_{(2')}/N_{(3)}$ in pure ethanol and pure acetonitrile are of a single order [18, 22]. The decrease in the nucleophilicity of the heterocyclic anion and the simultaneous increase in the fraction of exomethylation at the $N_{(2')}$ atom upon the transition from the thia analog to the oxa analog is attributed to the stronger −I and +M effects of the O atom in comparison to the effects of the S atom [23, p. 165], which result, on the one hand, in a smaller negative charge density in the amidine fragment and, on the other hand, in greater mesomeric (electromeric) displacement of electron density to the exocyclic nitrogen atom of anion III.

While 2-phenylimino-4-thiazolidinone exists in the form of a mixture of amino and imino tautomers in methanol [24], in the case of oxa analog IIa, the amino form was not discovered in an ethanol solution [2]. Thus, the replacement of the $S_{(1)}$ heteroatom by $O_{(1)}$ results in stabilization of the imino form and simultaneously alters the ratio between the $N_{(2')}$ and $N_{(3)}$ isomers in favor of predominance of the $N_{(2')}$ isomer. The apparent contradiction expressed by the inconsistency between the basicity and nucleophilicity of the reaction centers of mesomeric ion III is observed for other tautomeric heterocycles, confirming the Hughes–Ingold rule [9, 16]. An explanation is provided by the kinetic control of the ratio between the methylation products and the thermodynamic control of the position of the tautomeric equilibrium. Already in the isolated (static) anion the distribution of the charge does not correspond to the stable tautomer form owing to its mesomeric delocalization [11]. The increase in the relative negative charge on the $N_{(2')}$ atom of anion III in comparison

to the thia analog as a result of p_π-π conjugation with the participation of the $O_{(1)}$ atom in the ring, even at the moment of reaction* [8], results in a change in the sign of the difference between the activation energies of the irreversible methylation reactions $E_a^{N_{(2')}} - E_a^{N_{(3)}}$, which is reflected in the change in the ratio between the $N_{(2')}$ and $N_{(3)}$ isomers in favor of exomethylation. It is also likely that a proton is added to the exocyclic nitrogen atom of anion III with a greater rate than to the cyclic nitrogen atom, i.e., $E_a^{amino} < E_a^{imino}$, but this does not influence the position of the tautomeric equilibrium, which is controlled by the difference between the free energies of the tautomers. The fact is that the p_π-π conjugation with the participation of the heteroatom of the ring in position 1 not only promotes the displacement of electron density to the $N_{(2')}$ atom in the anion, but also stabilizes the imino form of the neutral molecule. The greater is the capacity of the heteroatom in position 1 to participate in such conjugation, the higher is the fraction of exomethylation and the more stable is the imino form.

Our explanation demonstrates the groundlessness of the mechanistic interpretation of the inconsistency between the basicity and nucleophilicity of the $N_{(2')}$ and $N_{(3)}$ atoms in anion III given in [2], which was based on the assumption of initial (?) protonation of the anion at the $N_{(2')}$ atom followed by rapid isomerization (?) to the stable imino tautomer.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-497 C instrument (100 MHZ) with HMDS as an internal reference, the IR spectra were recorded on an ISK-29 spectrophotometer (tablets in KBr), and the UV spectra were recorded on an SF-16 spectrophotometer in ethanol. TLC was carried out on Silufol UV-254 plates; the eluent was a 1:10 ethanol–chloroform mixture. The methods used to carry out the conductometric measurements and to calculate the electrolytic dissociation parameters were described in [19], and the methods used to carry out the kinetic experiments and to determine the positional selectivity of the methylation reaction were described in [17, 18]. The data from the elemental analysis of compounds Ic and IIb for C, H, and N corresponded to the calculated data.

2-Amino-4-oxazolinone (Ia) was obtained according to the method in [25]. The yield was 31%. mp - 244°C (from 50% aqueous DMFA); according to the data in [26], mp = 246-247°C. PMR spectrum (in DMSO-D_6): 8.42, 8.20 (2H, NH_2); 4.48 ppm (2H, s, $C_{(5)}H_2$).

5-Phenyl-2-amino-4-oxazolinone (Ib) [26, 27]. The yield was 85%, mp = 257°C (from water; according to the data in [27]). mp = 255°C. PMR spectrum (in DMSO-D_6): 8.64, 8.40 (2H, NH_2); 7.16-7.30 (5H, m, C_6H_5); 5.56 ppm (1H, s, $C_{(5)}H$).

5-Phenyl-2-phenylimino-4-oxazolidinone (IIa) was obtained according to the method in [28]. The yield was 52%. mp = 211-213°C (from ethanol; according to the data in [28], mp = 207-211°C. IR spectrum: 3265, 3050 (NH), 1720 (C=O), 1636 (δ_{NH}), 1615 (C=C_{arom}), 1580 (C=N), 1515 cm^{-1} (C=C_{arom}). UV spectrum, λ_{max} (log ε): 254-255 nm (4.36). PMR spectrum (in DMSO-D_6): 6.95-7.70 (5H, m, $N_{(2')}C_6H_5$); 7.34 (5H, s, $C_{(5)}C_6H_5$); 5.80 ppm (1H, s, $C_{(5)}H$).

5-Phenyl-2-methylphenylamino-4-oxazolinone (Ic, $C_{16}H_{14}N_2O_2$) and 5-Phenyl-2-phenylimino-3-methyl-4-oxazolidinone (IIb, $C_{16}H_{14}N_2O_2$). A solution of sodium ethoxide obtained from 0.41 g (18 mmole) of sodium and 23 ml of ethanol was given an addition of 4.0 g (16 mmole) of compound IIa and 2.4 g (19 mmole) of dimethyl sulfate. The reaction mixture was boiled for 1.5 h, then given another addition of sodium ethoxide prepared from 0.20 g (9 mmole) of sodium and 10 ml of ethanol and an addition of 1.2 g (10 mmole) of dimethyl sulfate, boiled again for 1 h, and left to stand overnight. The precipitate of the sodium salt of methylsulfuric acid was filtered out, the filtrate was evaporated in a vacuum, the oily residue was treated with 50 ml of methylene chloride and 50 ml of 0.5 N NaOH, and the organic layer was dried by sodium sulfate overnight. The oil obtained after the evaporation of the methylene chloride in a vacuum was chromatographed in a 50 × 1 cm column filled with silica gel 100/160 μ (Silpearl, Czechoslovakia) in chloroform. The mixture was introduced in the form of a solution in 10 ml of chloroform mixed with an adsorbent. The eluent was chloroform. The contents of the 10-20-ml fractions were detected with the aid of TLC. The corresponding eluates were evaporated.

*The "polarizability" term is taken into account in the modified Edwards equation [14].

Compound Ic. The yield was 1.1 g (26%). mp = 106-107°C (from ethyl acetate); according to the data in [2], mp = 107-109°C. IR spectrum: 1740 (C=O), 1570 cm^{-1} (C=N). UV spectrum λ_{max} (log ε): 234-235 nm (4.34). PMR spectrum (in DMSO-D_6): 7.30-7.38 (10H, m, C_6H_5); 5.78, 5.72 (1H, $C_{(5)}H$); 3.44 ppm (3H, s, CH_3).

Compound IIb. The yield was 0.37 g (9%). mp = 92-94°C (from ethanol). According to the data in [2], mp = 90-92°C. IR spectrum: 1770 (C=O), 1680 cm^{-1} (C=N). UV spectrum, λ_{max} (log ε): 225 nm (4.05). PMR spectrum (in DMSO-D_6): 6.95-7.32 (5H, m, $N_{(2')}C_6H_5$); 7.36 (5H, s, $C_{(5)}C_6H_5$); 5.94 (1H, s, $C_{(5)}H$); 3.04 ppm (3H, s, CH_3). Compound IIb was identical to the compound obtained according to the method in [2].

LITERATURE CITED

1. G. Rapi, M. Ginanneschi, E. Belgodere, and M. Chelli, J. Heterocycl. Chem., 9, 285 (1972).
2. C. R. Howell, N. Q. Quinones, and R. A. Hardy, J. Org. Chem., 27, 1686 (1962).
3. C. F. Howell, W. Fulmor, N. Q. Quinones, and R. A. Hardy, J. Org. Chem., 29, 370 (1964).
4. S. M. Ramsh, N. A. Smorygo, E. S. Khrabrova, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 4, 544 (1986).
5. S. M. Ramsh, N. A. Smorygo, and A. I. Ginak, Khim. Geterotsikl. Soedin., No. 8, 1066 (1984).
6. L. Pauling and P. Pauling, Chemistry, Freeman, San Francisco (1975).
7. S. M. Ramsh, N. A. Smorygo, and E. S. Khrabrova, Khim. Geterotsikl. Soedin., No. 1, 32 (1985).
8. S. A. Shevelev, Usp. Khim., 39, 1773 (1970).
9. D. J. Cram, Fundamentals of Carbanion Chemistry, Academic Press, New York (1965).
10. S. M. Ramsh, A. I. Ginak, N. A. Smorygo, Yu. G. Basova, and E. G. Sochilin, Zh. Org. Khim., 14, 1327 (1978).
11. S. M. Ramsh, E. S. Khrabrova, A. I. Ginak, and G. B. Erusalimskii, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., 29, 33 (1986).
12. R. F. Hudson, "Nucleophilic reactivity," in: G. Klopman (ed.), Chemical Reactivity and Reaction Paths, Wiley, New York (1974), pp. 167-252.
13. B. C. Challis, J. N. Iley, and H. S. Rzepa, J. Chem. Soc., Perkin Trans II, No. 7, 1037 (1983).
14. S. M. Ramsh, A. I. Ginak, Yu. G. Basova, and L. P. Shamina, Zh. Org. Khim., 17, 846 (1981).
15. G. Klopman, "The generalized perturbation theory of chemical reactivity and its applications," in: G. Klopman (ed.), Chemical Reactivity and Reaction Paths, Wiley, New York (1974), pp. 55-165.
16. T. I. Temnikova and S. N. Semenova, Molecular Rearrangements in Organic Chemistry [in Russian], Khimiya, Leningrad (1983).
17. Yu. G. Basova, S. M. Ramsh, and A. I. Ginak, Zh. Org. Khim., 18, 2200 (1982).
18. Yu. G. Basova, S. M. Ramsh, A. I. Ginak, and A. E. Karpovich, Zh. Org. Khim., 18, 2205 (1982).
19. Yu. G. Basova, S. M. Ramsh, and A. I. Ginak, Zh. Org. Khim., 17, 663 (1981).
20. Yu. G. Basova, Dissertation for the degree of Candidate of Chemical Sciences, Leningrad (1980).
21. S. Shinkai, T. Fukunaga, O. Manabe, and T. Kunitake, J. Org. Chem., 44, 4990 (1979).
22. S. M. Ramsh, A. I. Ginak, Yu. G. Basova, and L. P. Shamina, Zh. Org. Khim., 17, 851 (1981).
23. General Organic Chemistry, Vol. 5, Phosphorus and Sulfur Compounds [in Russian], Khimiya, Moscow (1983).
24. S. M. Ramsh, N. A. Smorygo, A. I. Ginak, and E. G. Sochilin, Zh. Org. Khim., 15, 1506 (1979).
25. H. Aspelund, Acta Acad. Aboensis. Mat. Phys., 26, No. 8, 1 (1967).
26. W. Traube and R. Ascher, Berichte, 46, 2077 (1913).
27. C. F. Howell, N. Q. Quinones, and R. A. Hardy, J. Org. Chem., 27, 1679 (1962).
28. H. Aspelund, Acta Acad. Aboensis. Mat. Phys., 26, No. 11, 1 (1967).