TAUTOMERISM OF DERIVATIVES OF AZINES.

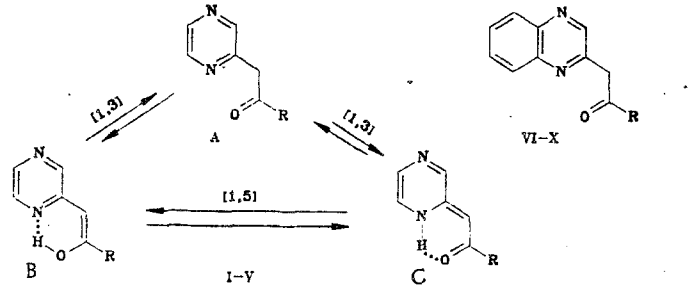
16.* TAUTOMERISM OF ACYLMETHYLPYRAZINES AND -QUINOXALINES

I. Ya. Mainagashev, V. V. Lapachev,
M. A. Fedotov, and V. P. Mamaev†

UDC 543.422.25:547.861:541.623

The tautomeric equilibria of acylmethylpyrazines and -quinoxalines in chloroform were studied by ^1H, ^{14}N, and ^{17}O NMR spectroscopy. It was shown that keto-enol tautomerism is realized in the acylmethylpyrazine series. Annelation leads to the development of an ylidene tautomer in the acylmethylquinoxaline series. A marked dependence of the position of the intrachelate equilibrium on the character of the solvent was observed.

We have previously obtained reliable data on the intrachelate [1,5]-sigmatropic tautomerism of acylmethylpyridines with the use of data from the ^{14}N and ^{17}O NMR spectra [2]. Within the framework of a systematic investigation of the tautomerism of derivatives of azines, in the present research we used ^1H, ^{14}N, and ^{17}O NMR spectroscopy to investigate the tautomerism of acylmethylpyrazines and the corresponding benzo analogs. For them, just as for acylmethylpyridines, two types of tautomeric transformations, viz., [1,3]- and [1,5]-sigmatropic tautomerism, can be realized in weakly polar solvents [3]. In the pyrazine series the first type of transformation is known in the case of pyrazinylmalononitriles [4], diacyl derivatives of methylpyrazine [5], and ethyl quinoxalinylpyruvate [6]. However, no reliable data on [1,5]-sigmatropic tautomerism of the B⇄C type in the pyrazine and quinoxaline series are available.



I, VI R=CF_3; II, VII R=C_6H_5; III, VIII R=p-$C_6H_4OCH_3$; IV, IX R=p-C_6H_4CN; V, X R=4-C_5H_4N

It is known that acylmethylpyrazines have chelate-forming properties [7], and information obtained regarding the structures of acylmethylpyrazines may prove to be useful in the search for complexing agents and in understanding the structures and reactivities of such compounds.

The aim of the present research consists in ascertaining the relative tendencies for the conversion of pyrazine derivatives to the NH form (C), as well as the effect of annelation and of the substituent in the side chain on the position of tautomeric equilibria of the [1, 5] type.

As subjects of the investigation we used acylmethylpyrazines I-V and -quinoxalines VI-X, which were synthesized by condensation of methylazines with esters of the corresponding acids in the presence of sodium hydride or sodium amide. For the three possible tautomers (aromatic keto form A, enol B, and ylidene C [6]) the equilibria of the A⇄B and A⇄C type are slow on the NMR time scale, and the percentage of aromatic keto form A is therefore readily determined by ^1H NMR spectroscopy [2, 6].

*See [1] for Communication 15.

†Deceased.

Novosibirsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk 630090. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1663-1667, December, 1987. Original article submitted July 11, 1986.

0009-3122/87/2312-1339$12.50

TABLE 1. PMR Spectroscopic Data for I-X (in $CDCl_3$ at 40°C)

Compound	Chemical shift, δ, ppm		[A]:[B + C], %	Compound	Chemical shift, δ, ppm		[A]:[B + C], %
	$-CH_2-$	=CH–			$-CH_2-$	=CH–	
I	4,24	6,04	5 : 95	VI	—	5,96	0 : 100
II	4,41	6,07	60 : 40	VII	4,64	6,14	22 : 78
III	4,37	6,01	80 : 20	VIII	4,71	6,19	37 : 63
IV	4,54	6,22	22 : 78	IX	5,14	6,24	10 : 90
V	4,49	6,24	15 : 85	X	—	6,22	0 : 100

TABLE 4. ^{14}N and ^{17}O NMR Spectral Characteristics and Tautomeric Compositions of Acylmethylazines I-X at 25°C in Chloroform

Compound	^{14}N NMR data		^{17}O NMR data		[A]:[B]:[C], %
	chemical shifts,* ppm	[B]:[C], %	chemical shifts, ppm	[B]:[C], %	
I			108	100 : 0	5 : 95 : 0
II	−40	100 : 0	109	100 : 0	60 : 40 : 0
III			105	100 : 0	80 : 20 : 0
IV			109	100 : 0	22 : 78 : 0
V			105	100 : 0	15 : 85 : 0
VI	−216	9 : 91	345	8 : 92	0 : 9 : 91
VII	−196	30 : 70	299	12 : 88	22 : 23 : 55
VIII	−210	15 : 85			37 : 9 : 54
X	−177	50 : 50	265	27 : 73	0 : 50 : 50

*The widths of the peaks at half the heights ($\Delta\nu_{1/2}$) were 400-600 Hz for the ^{14}H NMR spectra and 200-600 Hz for the ^{17}O NMR spectra. The accuracy in the determination of the chemical shifts was 2 ppm.

The results of an investigation of the tautomerism of acylmethylazines I-X by ^1H NMR spectroscopy are presented in Table 1, from which it is apparent that the percentage of tautomer A for acylmethylpyrazines I-V is substantially greater than in the case of the corresponding benzo analogs VI-X. The tautomeric equilibria of the pyrazine derivatives proved to be more sensitive to the substituents attached to the carbonyl group than for the corresponding quinozaline derivatives. For I-X we observed a decrease in the percentage of the A form in the mixture with an increase in the acceptor character of substituent R in the side chain. A similar fact was also previously observed for aceylmethylpyridines [2, 8].

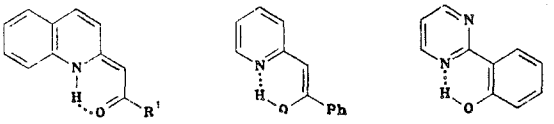
Fast equilibria of the B⇄C type were evaluated by ^{17}O and ^{14}N NMR spectroscopy from the positions of the averaged signals of the B and C forms relative to the signals of model compounds. The principles of modeling of tautomers of the B and C type and the accuracy of the determination were previously discussed in [2].

The results of an investigation of the [1,5]-sigmatropic tautomerism of the acylmethylazines I-X are presented in Table 2. The ^{14}N NMR spectrum of phenacylpyrazine contains only a broad signal at ∿−40 ppm. Judging from this value, the B⇄C intrachelate equilibrium is shifted markedly to favor the enol form, and ^{17}O NMR spectroscopy is more informative in this case [2]. In the ^{17}O NMR spectra of acylmethylpyrazines I-V the range of change in the ^{17}O chemical shifts of the averaged signal of the oxygen atoms of the B and C forms is rather narrow (5 ppm) and virtually borders on the experimental error (Δδ = ±2 ppm). The ^{17}O chemical shifts of I-V lie in the range of the ^{17}O chemical shifts of compounds of the enol and phenol type with an intramolecular hydrogen bond [9]. A comparison with model compounds (Table 2) clearly indicates a complete shift of the intrachelate equilibrium of acylmethylpyrazines I-V to favor enol tautomer B. The UV spectra of I-V, in which the long-wave maximum at 400 nm that is characteristic for ylidene structures [10] is absent, are in good agreement with the total absence of ylidene tautomer C.

Thus an equilibrium of A⇄B type (keto-enol tautomerism) is realized for acylmethylpyrazines I-V in weakly polar solvents. One's attention is directed to the high stability of the ^{17}O chemical shift of the OH group, which is virtually independent of the form of substituent

R. This makes it possible to use the data obtained to study fast equilibria of the B⇄C type also in the case of other acylmethylazines.

It has been previously shown [2] that in the case of acylmethylpyridines the introduction of an acceptor substituent into the side fragment stabilizes NH form C. For example, the transition from acetonylpyridine to trifluoroacetonylpyridine leads to the development of a significant amount of the ylidene tautomer [2]. The corresponding trifluoroacetonylpyrazine (I) does not give an NH form, i.e., in the acylmethylpyrazine series the introduction of a CF_3 group is clearly insufficient for stabilization of the ylidene tautomer in $CHCl_3$. Annelation of the heterorings may serve as another factor in stabilization of the ylidene form of acylmethylazines. Thus, for phenacylpyridine the B⇄C intrachelate equilibrium is shifted to favor enol B, while for phenacylquinoline it is shifted to favor ylidene tautomer C [2, 6]. A similar effect is also manifested on passing from I-V to their annelated analogs VI-X. Thus the UV spectra of phenacylquinoline and quinoxaline VII contain long-wave maxima of the NH form at ~400 nm (see [6]). The forms and positions of the absorption bands for these two compounds are similar in many respects, and this indicates the presence of substantial amounts of the ylidene form in the tautomeric mixture of quinoxaline VII. The signals in the ^{14}N NMR spectra in the region characteristic for the NH forms of azinylmethanes [10] confirm the existence of intrachelate [1,5]-tautomerism in the series of acylmethylquinoxalines VI-VIII and X (Table 2). The ^{17}O NMR data are in good agreement with this conclusion. Using the ^{14}N and ^{17}O chemical shifts of I-V and XI-XIV as models, one can determine the position of the intrachelate equilibrium (Table 2).



XI, XII XIII XIV

XI R^1=Ph; XII R^1=CH_3; $-\delta_{^{14}N}$, ppm · XI 224 [2, 11], XIII 130 [2], XIV 130 [12]; $\delta_{^{17}O}$, ppm: XI 326 [2, 11], XII 365 [2, 11]

In the case of VII, VIII, and X one can see the character of the effect of substituents that are capable of conjugation effects. An increase in the electron-donor capacity of the substituent on passing from phenacylquinoxaline VII to methoxy analog VIII is accompanied by appreciable stabilization of the ylidene tautomer, while the introduction of an acceptor substituent (X) is accompanied by appreciable stabilization of the enol tautomer. In the first case energetically favorable conjugation of the donor (OCH_3) and acceptor (C=O) groups of ylidene tautomer C is evidently important. On the other hand, for pyridyl derivative X conjugation of the two electron-acceptor centers in tautomer X(C) (the pyridyl fragments and the carbonyl group) is energically unfavorable.

Thus the data obtained on the intrachelate [1,5]-sigmatropic tautomerism of acylmethylquinoxalines showed that annelation markedly stabilizes the NH form. In the pyrazine series annelation has a stronger effect than varying substituent R in the side chain.

Considering the substantial rearrangement of the structures of the tautomers in transitions of the B⇄C type one might expect that the energies of solvation of the tautomers would differ substantially. In fact, we observed a strong effect of the solvent on tautomerism of the [1,5] type in the series of acylmethylazines. For acylmethylazines that form one of the chelate forms of the B or C type we were able to observe the development of another chelate tautomer. Thus, according to the preliminary data obtained by means of UV spectroscopy, the transition from solutions of trifluoroacetonylpyrazine in $CHCl_3$ to solutions in methanol is accompanied by the appearance in the intrachelate equilibrium of a new tautomer of the C type (λ_{max} 365 nm). The reverse effect — shifting of the intrachelate equilibrium to favor the enol tautomer — was observed in the case of phenacylquinoline on passing from solutions in $CHCl_3$ to solutions in heptane; the intensity of the long-wave band of the NH form (λ_{max} 420-433 nm) decreases, and the absorption of the enol form at λ_{max} 393 nm increases in this case. The effect of solvents on intrachelate [1,5]-sigmatropic tautomerism is of general interest and will be investigated in greater detail.

EXPERIMENTAL

The UV spectra of solutions of the compounds ($c = 10^{-4}$ M) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 5% solutions in $CDCl_3$ at 40°C were recorded

TABLE 3. Characteristics of I, IV, IX, and X

Compound	T_{mp}, °C	Recrystallization solvent	Found, %			Empirical formula	Calc., %		
			C	H	N (F)		C	H	N (F)
I	115—117	Alcohol	44,4	3,0	(29,9)	$C_7H_5F_3N_2O$	44,2	2,6	(30,0)
IV	140—142	Benzene—petroleum ether (1:3)	69,6	3,9	18,6	$C_{13}H_9N_3O$	69,9	4,0	18,8
IX	213—215	Chloroform—alcohol (3:1)	74,8	4,2	15,6	$C_{17}H_{11}N_3O$	74,7	4,0	15,4
X	192—194	Alcohol—water (5:1)	72,0	4,5	16,9	$C_{15}H_{11}N_3O$	72,3	4,4	16,9

with a Varian A-56/60 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The ^{14}N and ^{17}O NMR spectra for the natural percentages of the isotopes were obtained from 10-15% solutions in chloroform at 25°C with a Bruker CXP-300 spectrometer at 40.69 MHz for the oxygen nuclei and at 21.68 MHz for the nitrogen nuclei. Saturated solutions were used for IV and X, which are only slightly soluble in $CHCl_3$. The chemical shifts are presented relative to the external standards CH_3NO_2 (^{14}N NMR) and H_2O (^{17}O NMR). Positive signs correspond to a weak-field shift (deshielding).

Compounds II, III, and V were synthesized by the method in [13], VII and VIII were synthesized by the method in [15], and I, IV, IX, and X were obtained by the method in [14, 15].

General Method for the Acylation of Methyl Azines. A 35-mmole sample of NaH was added in an atmosphere of dry argon to a solution of 7 mmole of the 2-methyl azine and 8.4 mmole of the ethyl ester of the corresponding acid in 40-50 ml of absolute monoglyme, and the mixture was refluxed with stirring for 5 h. The mixture was then cooled, and the unchanged NaH was decomposed cautiously with alcohol; 50 ml of water was then added. The mixture was made slightly acidic with 10% HCl, and the aqueous part was extracted with ethyl acetate. The organic extracts were combined and dried with anhydrous $MgSO_4$, the solvent was removed by distillation, and the crude substance was purified by column chromatography on silica gel (40-100 μm); the height of the column was 70 cm, the diameter was 2 cm, and the eluent was chloroform. The characteristics of the new compounds are presented in Table 3.

LITERATURE CITED

1. O. P. Petrenko and V. V. Lapachev, Zh. Org. Khim. (in press).
2. V. V. Lapachev, S. A. Stekhova, I. Ya, Mainagashev, M. A. Fedotov, V. E. Hall, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 6, 802 (1986).
3. N. S. Zefirov and S. S. Trach, Zh. Org. Khim., 12, 697 (1976).
4. B. Pilarsky, H. Foks, K. Osmialowski, and R. Kaliszan, Monatsh. Chem., 115, 179 (1984).
5. S. K. Chakrabartty and R. Levine, J. Heterocycl. Chem., 4, 109 (1967).
6. R. Mondelly and L. Merlini, Tetrahedron, 22, 3253 (1966).
7. J. S. England and J. C. Guyon, Microchim. Acta, No. 6, 935 (1973).
8. M. I. Kabachnik, Zh. Vsesoyuzn. Khim. Obshchestva, 7, 263 (1962).
9. V. V. Lapachev, I. Ya. Mainagashev, S. A. Stekhova, M. A. Fedotov, V. P. Krivopalov, and V. P. Mamaev, Chem. Commun., No. 8, 494 (1985).
10. V. P. Mamaev and V. V. Lapachev, in: Soviet Scientific Reviews, Section B, Vol. 7, edited by N. K. Kochetkov and M. E. Vol'pin, Harwood Acad. Publ., New York—London (1985), p. 1.
11. S. A. Stekhova, V. V. Lapachev, O. P. Petrenko, and V. P. Mamaev, in: The IX International Congress of Heterocyclic Chemistry. Abstracts, edited by T. Kametani, Hoshi University, Tokyo (1983), p. 423.
12. S. A. Stekhova, V. V. Lapachev, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 7, 994 (1981).
13. J. D. Behun and R. Levine, J. Am. Chem. Soc., 81, 5157 (1959).
14. J. F. Wolfe, D. E. Portlock, and D. J. Feuerbach, J. Org. Chem., 39, 2006 (1974).
15. E. H. Sund and D. L. Callender, J. Chem. Eng. Data, 25, 189 (1980).