CONFIGURATION OF BENZOYLPYRIDINEOXIMES STUDIED BY ^1H AND ^{13}C NMR. EFFECT OF PROTONATION OF THE PYRIDINE NITROGEN ATOM

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A simple and convenient method is proposed for determining the configuration of E,Z-isomers of 2-, 3-, and 4-benzoylpyridines. The difference in chemical shifts (Δδ, ppm) in the system CCl_4–DMSO-D_6 and CCl_4–DMSO–CF_3COOD for the α-H atoms or the α, β-C atoms of the pyridine ring can be used to determine the configuration. The shift (Δδ) of the α-H signals to weak field is greater for the Z-isomers than for the E-isomers due to protonation of the pyridine nitrogen atom. The reverse dependence is seen in the ^{13}C NMR for the E,Z-isomers. The signals of the α-C atoms shift to stronger field after protonation.

The geometric configuration of oximes is usually found using multinuclear NMR (for example, see [1, 2]). Earlier [3] we determined the configuration of E- and Z-benzoylpyridineoximes and their esters using ^{13}C NMR data by considering the different shielding of C atoms in the γ-position relative to the hydroxyl (γ-effect). Shift reagents [4, 5], aromatic solvents [6], or protonation of the –C=N– nitrogen atom [7] have been used to assign accurately the configuration of oximes.

In the present work, the effect of protonation of the pyridine N atom on the chemical shifts of the H and C nuclei of the geometric E,Z-isomers of 2-, 3-, and 4-benzoylpyridineoximes (Ia, IIa-d, IIIa, b) is studied.

Z-I–Z-III E-I E-III

I, 2-pyridyl: a = H; II, 3-pyridyl: a R = H, b R = Br, c R = Cl, d R = F; III, 4-pyridyl: a R = Br, b R = OCH_3

The proton signals of all studied compounds shift to weak field (Table 1) on adding acid to CCl_4–DMSO-D_6. The pyridine H atoms exhibit the greatest change in chemical shifts. The change in chemical shifts of the benzene H atoms is insignificant. These changes are consistent with protonation of benzoylpyridineoximes at the pyridine N atom. Analogous shifts of proton signals are seen on protonation of pyridine and its derivatives [7, 8]. Adding a proton to the heterocyclic N atom deshields the H atoms in the β- and γ-positions and not those in the α-position of the pyridine. In the studied series of oximes I-III, the shift Δδ changes in the order $H_\gamma > H_\beta > H_\alpha$. In the series of oximes IIa-d, the greatest differences in the Δδ values for the E- and Z-isomers are seen for the proton in the 2-position. The shift Δδ for the Z-isomer is much greater (0.47-0.57 ppm) than for the E-isomer (0.27-0.28 ppm). For compounds III, the differences in Δδ values for the E- and Z-isomers are less than for the oximes II. However, the trends seen above persist. The possibility of forming an intramolecular H-bond in Ia affects the electron density distribution in the pyridine ring and consequently the chemical shifts of the heterocyclic protons. The greatest differences in the Δδ values of the E- and Z-isomers are seen for the proton in the 3-position.

A study of the effect of protonation on the chemical shifts in the ^{13}C NMR spectra demonstrated that the C atoms are more sensitive to a redistribution of electron density than the H atoms (Table 2). The chemical shifts depend on the CF_3COOD concentration in the system CCl_4–DMSO-D_6. The characteristic dependence on concentration of chemical shifts

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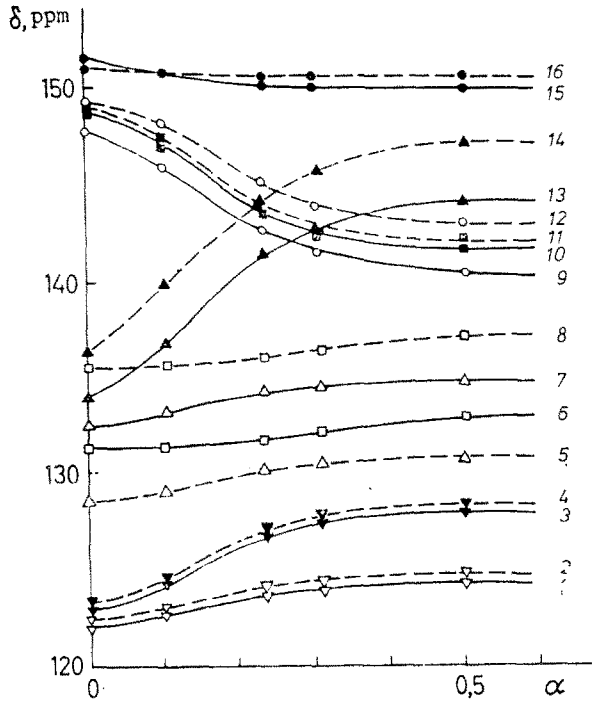

Fig. 1. ^{13}C chemical shifts, δ, of 3-(4-bromobenzoyl)pyridineoxime (IIb) as a function of α, where α = n ml CF_3COOD/(0.2 ml CCl_4 + 0.2 ml DMSO). Uneven numbers are the E-isomer; even numbers, the Z-isomer. Pyridine ring: $C_{(2)}$ (9, 12); $C_{(3)}$ (5, 7); $C_{(4)}$ (13, 14); $C_{(5)}$ (3, 4); $C_{(6)}$ (10, 11). Benzene ring: $C_{(1)}$ (6, 8); $C_{(4)}$ (1, 2). Atom $C_{(7)}$ (15, 16).

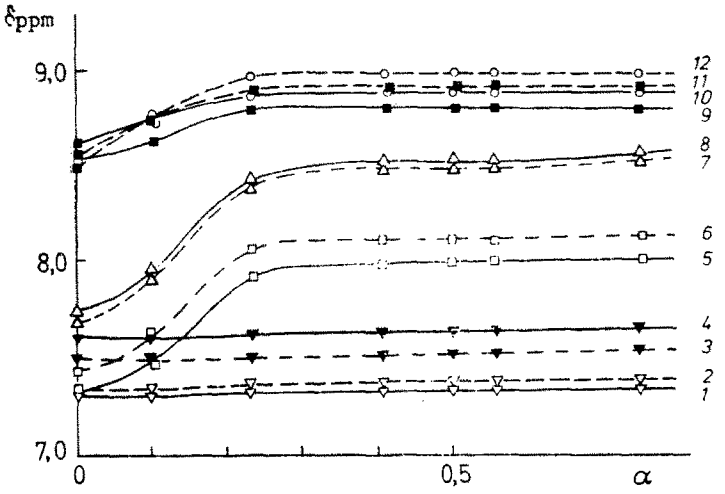

Fig. 2. ^1H chemical shifts, δ, of 3-(4-bromobenzoyl)pyridineoxime (IIb) as a function of α, where α = n ml CF_3COOD/(0.2 ml CCl_4 + 0.2 ml DMSO). Uneven numbers are the E-isomer; even numbers, the Z-isomer. Pyridine ring: 2-H (10, 12); 4-H (7, 8); 5-H (5, 6); 6-H (9, 11). Benzene ring: 2,2′-H (1, 2); 3,3′-H (3, 4).

of the C nuclei of the E- and Z-isomers of oxime IIb are presented in Fig. 1. The ^{13}C signals of configurational isomers in CCl_4–DMSO-D_6–CF_3COOD were assigned by using two-dimensional HC-correlation spectroscopy and by analyzing the ^1H–^{13}C SSCC. The analogous dependence of ^1H nuclei of the same oxime IIb are presented in Fig. 2. The shift of $^{13}C_{(α)}$ signals to strong field [7] and the increase in absolute SSCC values $^1J_{CH}$ by 10 Hz for the same C nuclei are consistent with addition of the proton to the pyridine N atom [9]. The shifts of the ^{13}C signals of the benzene ring are much less than Δδ for the ^{13}C signals of the pyridine. This also is consistent with the improbability of protonating the oxime N atom at this CF_3COOD concentration due to the significantly lower basicity of this atom. The lack of protonation of the oxime group is consistent with the data of [7] in which the shift of C signals of benzene to weak field on protonation of an oxime N atom, for example,

TABLE 1. Effect of Protonation on ^1H Chemical Shifts of Benzoylpyridineoximes

Compound	Isomer	$\Delta\delta=\delta(CCl_4-DMSO-CF_3COOD)-\delta(CCl_4-DMSO)$, ppm*							
		pyridine					benzene		
		2-H	3-H	4-H	5-H	6-H	2,2'-H	3,3'-H	4-H
I	E	—	−0,24	0,70	**	0,34	***	***	***
	Z	—	0,38	0,76	**	0,33	***	***	***
IIa	Z	0,57	—	0,80	0,69	0,40	0,05	0,05	—
IIb	E	0,29	—	0,72	0,60	0,30	0,03	0,03	—
	Z	0,48	—	0,71	0,65	0,35	0,01	0,01	—
IIc	E	0,29	—	0,66	0,60	0,34	0,10	0,10	—
	Z	0,47	—	0,67	0,62	0,38	0,06	0,08	—
IId	E	0,27	—	0,80	0,73	0,31	0,04	0,08	—
	Z	0,50	—	0,81	0,70	0,35	0,04	0,07	—
IIIa	E	0,22	0,63	—	0,63	0,22	0,01	0,03	—
	Z	0,31	0,72	—	0,72	0,31	−0,02	0,02	—
IIIb	E	0,21	0,64	—	0,64	0,21	0,05	−0,01	—
	Z	0,28	0,78	—	0,78	0,28	0,03	0,06	—

*The sign "+" denotes a shift to weak field on adding CF_3COOD.

**The chemical shift of 5-H was not determined due to overlap by signals of the benzene protons.

***The exact value $\Delta\delta$ was not determined due to overlap of the benzene multiplets, $\Delta\delta \approx$ 0.1 ppm.

TABLE 2. Effect of Protonation on ^{13}C Chemical Shifts of Benzoylpyridines*

Compound	Isomer	$\Delta\delta=\delta(CCl_4-DMSO-CF_3COOD)-\delta(CCl_4-DMSO)$, ppm**									
		pyridine					benzene				
		$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(1)}$	$C_{(2,2')}$	$C_{(3,3')}$	$C_{(4)}$	$C_{(7)}$
Ia	E	−6,85	5,21	11,07	3,95	−5,21	0,79	0,31	2,10	2,99	−5,67
	Z	−6,35	3,42	10,98	−0,83	−5,85	−0,25	2,41	1,56	3,00	−5,63
IIb	E	−7,55	2,00	10,04	5,01	−7,40	1,61	0,60	1,60	1,99	−1,77
	Z	−6,35	1,43	10,98	5,18	−6,82	1,90	0,92	1,53	1,90	−0,74
IId	E	−7,53	4,56	9,32	4,49	−7,42	1,34	0,60	1,13	1,25	−2,10
	Z	−6,33	2,77	10,24	4,49	−6,78	1,10	0,79	1,10	1,21	−2,36
IIIa	E	−7,69	2,89	9,41	2,89	−7,69	−1,54	0,05	0,96	−0,05	−0,57
	Z	−7,16	4,21	10,08	4,21	−7,16	−1,37	0,22	0,70	0,91	−1,11
IIIb	E	−7,43	3,08	9,51	3,08	−7,43	−1,17	0,47	0,81	1,72	−0,64
	Z	−6,90	4,37	10,13	4,37	−6,90	−0,97	0,63	0,64	0,57	−0,79

*^{13}C chemical shifts are determined under conditions where the ratio of solvent components is described by the formula α = [0.2 ml CF_3COOD/(0.2 ml CCl_4 + 0.2 ml DMSO)] = 0.5.

**The sign "−" denotes a shift to strong field on protonation of the pyridine N atom.

for the oxime of tolualdehyde, is 5.0-11.5 ppm. The signals of the remaining C atoms of oximes I-II shift to weak field. The greatest shift is seen for atom $C_{(4)}$ (9.3-11.1 ppm). The shift of the $C_{(7)}$ signal depends on the site of the oxyiminomethyl fragment on the pyridine ring and changes in the order 2 > 3 > 4. As for the PMR spectra, addition of acid to a solution of the oximes in CCl_4–DMSO-D_6 shifts the ^{13}C signals of the E- and Z-isomers to a different extent. This enables the ^{13}C spectra to be identified reliably. The shift of the pyridine $^{13}C_{(\alpha)}$ atom signals to strong field for the E-isomer is greater than for the Z-isomer. The $\Delta\delta$ of the $C_{(3)}$ signal can also be used to assign the Z- and E-isomers. This shift depends on the site of the oxime group on the pyridine ring. For compounds I and II, the shift of $C_{(3)}$ signal to weak field for the E-isomer is greater than for the Z-isomer. For oxime III, the reverse dependence is seen.

A linear dependence was found between the chemical shifts of the benzene $C_{(1)}$ atom of the E- and Z-isomers for the studied benzoylpyridineoximes I-III in CCl_4–DMSO-D_6–CF_3COOD. This was described by the equation:

TABLE 3. Difference in Chemical Shifts $\Delta\delta_{E-Z}$ of Quaternary C Atoms of E- and Z-Isomers of Benzoylpyridineoximes in CCl_4–DMSO-D_6 and CCl_4–DMSO-D_6–CF_3COOD

Compound	$\Delta\delta_{E-Z}$, ppm									
	benzene		pyridine							
	$C_{(1)}$		$C_{(2)}$		$C_{(3)}$		$C_{(4)}$		$C_{(=)}$	
	1*	2	1	2	1	2	1	2	1	2
I	−3,04	−2,00	2,63	2,13	—	—	—	—	0,88	0,84
IIb	−4,13	−4,42	—	—	3,69	4,27	—	—	0,17	−0,87
IIc	−3,85	−4,14	—	—	3,44	4,09	—	—	0,24	0,39
IId	−4,16	−4,40	—	—	3,62	4,41	—	—	0,64	0,90
IIIa	−3,59	−3,76	—	—	—	—	2,96	2,29	0,20	0,74
IIIb	−3,87	−4,07	—	—	—	—	2,91	2,29	0,20	0,35

*1) In CCl_4–DMSO; 2) in CCl_4–DMSO–CF_3COOD.

$$\delta^{Z}_{C_{(1)}} = 1.096\ \delta^{Z}_{C_{(1)}} - 16,521\ \ (r = 0.976;\ s = 0,121).$$

A satisfactory correlation was also found for the quaternary C atoms in the 2-, 3-, and 4-positions of the pyridine of the E- and Z-isomers of oximes I-III:

$$\delta^{E}_{C_{(Py)}} = 0.90\ \delta^{Z}_{C_{(Py)}} + 17,23\ \ (r = 0.999;\ s = 0,017).$$

A tendency is observed to decrease the difference in chemical shifts of the quaternary pyridine and benzene C atoms for the E- and Z-isomers (in the system CCl_4–DMSO-D_6 and CCl_4–DMSO-D_6–CF_3COOD) on going from 3- to 4- and 2-substituted pyridine (Table 3). Protonation of the oximes by a different method affects the value $\Delta\delta_{E-Z}$ of the quaternary C atoms. Thus, for oximes II and III, the difference $\Delta\delta_{E-Z}$ increases (in absolute value) on protonation, whereas that for oxime Ia decreases. A Beckmann rearrangement is not seen for the conditions under which the spectra were recorded (this was unambiguously determined by the constant set of ^1H and ^{13}C signals during acid addition). The oximes also did not isomerize [4-(p-bromobenzoyl)pyridineoxime only isomerized by about 20% on storage in an ampul for at least 1 month]. The effects are not simply interpreted. However, the stronger shift of ^1H signals to weak field for the Z-isomers can be explained as follows. Steric repulsion between the hydroxyl group and the pyridine ring drives the imino group out of the plane of conjugation. Due to this, the positive charge arising from protonation of the pyridine N atom is transferred less to the double bond.

Thus, the study of the ^1H and ^{13}C NMR spectra of benzoylpyridineoximes reveals their configuration based on the differences in the shift of the H and C atoms of the pyridine ring of the E- and Z-isomers on protonation of the pyridine N atom.

EXPERIMENTAL

The ^1H NMR spectra of 5% solutions in CCl_4–DMSO-D_6 and CCl_4–DMSO-D_6–CF_3COOD were taken on a Bruker AC-250 spectrometer with a TMS internal standard. The ^{13}C NMR and two-dimensional $^1H/^{13}C$ spectra of 15% solutions were obtained on an AC-250 spectrometer. For a number of oximes, $CDCl_3$ and acetone-D_6 were used as solvents. The programs POWGATE, GATEHET, and XHCORR of the standard Bruker package were used to record the ^{13}C resonance signals with full proton spin-spin decoupling, at high resolution, and in two-dimensional spectra, respectively.

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PECULIARITIES OF THE MASS-SPECTROMETRIC FRAGMENTATION OF (3-QUINUCLIDINYL)DIARYL(HETERYL)CARBINOLS

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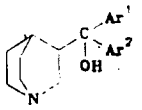
The principal pathways of the fragmentation of (3-quinuclidinyl)diaryl(heteryl)carbinols that involve cleavage of the quinuclidine–carbinol C–C bond and the bridge bond in the quinuclidine ring containing the substituent were studied. In addition to the indicated fragmentation pathways, fragmentation proceeding with opening of the bridge bond of quinuclidine that does not contain a substituent is observed. The rearrangement of the molecular ion that precedes fragmentation via the indicated pathway is examined.

The aim of the present research was to study the mass spectra of (3-quinuclidinyl)diaryl(heteryl)carbinols I-IX. A knowledge of the principles of the mass-spectrometric fragmentation of compounds of this series is important in connection with the study of their biotransformation in living organisms by mass spectrometry.* This research is also of independent interest from the point of view of mass-spectrometric behavior, since the presence of several charge-localization centers in the investigated molecules and the possibility of rearrangement of the molecular ions (M^+) prior to fragmentation make it possible to assume the realization of new specific fragmentation pathways.



I–IX

I, $Ar^1 = Ar^2$ = phenyl; II, $Ar^1 = Ar^2$ = 2-furyl; III, $Ar^1 = Ar^2$ =2-thienyl; IV, Ar^1 = 2-thienyl, Ar^2 = 2-furyl; V, $Ar^1 = Ar^2$ =o-tolyl; VI, Ar^1 = o-tolyl, Ar^2 = benzyl; VII, Ar^1 = phenyl, Ar^2 = 2-furyl; VIII, $Ar^1 = Ar^2$ =p-tolyl; IX, $Ar^1 = Ar^2$ =3-(o-xylyl).

Two principal fragmentation pathways are observed for most (3-quinuclidinyl)diaryl(heteryl)carbinols [1-4]. Fragmentation of the M^+ ion with the formation of F_1 and F_2 ions (Scheme 1) occurs as a result of the first pathway (A). It might be assumed that this process takes place from the open form of the M^+ ion via the mechanism described in [5, 6] for 3-substituted quinuclidines. This is indicated by both the one-step character of the formation of these ions directly from the M^+ ion, which was proved by direct analysis of the daughter ions (DADI), and by the similarity in the character of the fragmentation of the F_1 ion and the fragmentation of the analogous ions in the spectra of 3-quinuclidone and 3-acetoxyquinuclidine.

*Included among (3-quinuclidinyl)diaryl(heteryl)carbinols are the original antihistamine medicinal preparations fenkarol (I) and bikarfen (V), which are widely used in medical practice.

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