STUDY OF THE TAUTOMERISM OF 2-ETHOXYCARBONYL-3-OXOQUINUCLIDINE AND -BENZO[b]QUINUCLIDINE BY PMR SPECTROSCOPY

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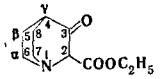
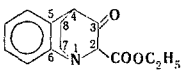
The tautomeric equilibrium of 2-ethoxycarbonyl-3-oxoquinuclidine in various media was studied by PMR spectroscopy. The conclusion of the predominance of the keto form in nonpolar and dipolar forms in hydroxyl-containing solvents was confirmed. The lifetime of the forms was estimated to be ~0.03 sec in CD_3OD at 75°C. In all of the investigated solvents, 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine exists as a mixture of two diastereomeric keto forms, the ratio between which depends on the solvent. The time required to establish equilibrium between the diastereomers at room temperature is no more than 5 min. The proton in the 2 position is exchanged by deuterium in deuterohydroxyl solvents; the half-exchange period is ~2 min in CD_3OD at −24°, and the activation energy of deuterium exchange is ~8 kcal/mole.

In [1], IR and UV spectra and potentiometric titration methods were used to demonstrate the existence of a characteristic tautomeric equilibrium for 2-ethoxycarbonyl-3-oxoquinuclidine (I), in which an intraionized form participates in addition to the ketone and enol forms, and the position of the tautomeric equilibrium depends substantially on the solvent. The equilibrium for 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine (II) in all of the investigated solvents was shifted almost entirely to favor the ketone form.

In the present paper we report the results of an investigation of the tautomerism of the indicated compounds in various solvents by PMR spectroscopy.



I



II

The compact multiplet at strong field (Table 1) in the spectrum of I in $CDCl_3$ is affiliated with the four β protons of the quinuclidine ring. The quintet of the γ proton is situated at weaker field. The signal at 3.99 ppm is a doublet with a spin−spin coupling constant (SSCC) [4] J = 1.5 Hz and apparently should be assigned to the 2-H proton, which interacts with one of the 6-H protons [2,3] (Fig. 1). The intensity of this signal is approximately one proton unit (p.e.), which indicates predominance of the ketone tautomer in the equilibrium (no less than 90%). The signals of the α protons for 6- and 7-H lie at 2.7-3.5 and are observed as three partially overlapped multiplets.

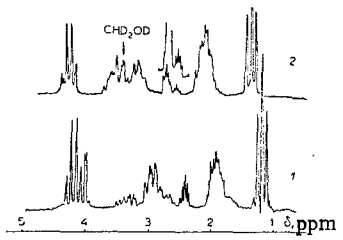


Fig. 1. PMR spectra of I: 1) in $CDCl_3$; 2) in CD_3OD.

The PMR spectra of I in CH_2Cl_2, CH_3NO_2, $C_6H_5NO_2$, and C_6H_5Cl have a similar appearance.

The spectrum of I in CD_3OD differs substantially from the spectra examined above. Thus two quintets with a relative intensity of 4:1, which

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TABLE 1. Chemical Shifts of the Protons of I and Ia + Ib in Various Solvents (δ, ppm)*

Solvent	Temp., °C	Form†	Conc., %	2-H	4-H	syn-6-H	anti-6-H	syn-7-H	anti-7-H	5,8-H	$CH_2(C_2H_5)$	$CH_3(C_2H_5)$
$CDCl_3$	20	ket	>90	3,99	2,42	3,35	2,75	2,97		1,93	4,18	1,22
CD_3OD	25	ket	20		2,45					2,02	4,22	1,28
		sym	80		2,63	3,07	3,42	3,07	3,42	2,02	4,17	1,28
CD_3OD	75	ket	25		2,48					2,05	4,18	1,30
		sym	75		2,65					2,05	4,18	1,30
CD_3OD+0,5 *M* CD_3ONa	20	an			2,37	2,65	2,85	2,60	2,85	1,71	4,11	1,25
CD_3COOCD_3	−8	ket	80		2,45							
		sym	20		2,65							
Furfural	−8				2,87		3,30—3,70			2,20	4,82	1,32
	75				2,60		2,96—3,42			2,12	4,29	

*The PMR spectra were obtained with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz. The internal standard was tetramethylsilane.

†Abbreviations: ket is ketone, sym is symmetrical, and an is anionic form.

TABLE 2. Relative Concentration of the Symmetrical Form in Various Solvents

Indexes	Solvent							
	chloroform	methyl acetate	chlorobenzene	isopropyl alcohol	methyl alcohol	nitrobenzene	nitromethane	furfural
Dielectric permeability, ε	5	7	10	26	36	36	38	42
Conc. of symmetrical form, %	<10	25	<10	50	80	<10	<10	60

TABLE 3. Chemical Shifts of the Protons of syn-II, anti-II, and IIc in Various Solvents

Solvent	Temp., °C	Form	Conc., %	2-H	4-H	syn-7-H	anti-7-H	syn-8-H	anti-8-H	H (aryl)	$CH_2(C_2H_5)$	$CH_3(C_2H_5)$
$CDCl_3$	20	II syn-	72	4,23	3,79	2,95	3,33	2,1	2,4	7,1—7,3	4,06	1,06
		II anti	28	3,90	3,76	2,8	3,8				4,33	1,28
CD_3OD	20	II syn-	78	4,60*	3,76	2,87	3,43	2,1	2,4	7,3	4,00	1,09
		II anti	22	4,12*	3,76						4,28	1,33
CD_3OD+0,05 *M* CD_3ONa	20	II syn-	55		3,76					7,3	4,00	1,09
		II anti	15		3,76						4,28	1,33
		II c	30		3,57						4,13	1,26

*Determined at −51°.

correspond to the signals of this proton in two forms, are observed in the region of chemical shifts characteristic for 4-H. Two sets of signals with the same relative intensity are also affiliated with the ethyl groups of the substituents. The signal of the proton in the 2 position of keto form I is not observed, apparently as a consequence of exchange of 2-H with a labile deuteron of the solvent. The addition of chloroform to a solution of I in CD_3OD causes an increase in the relative intensity of the signals of the form present in the lesser amount, which is consequently the ketone form, since the ketone predominates in pure chloroform.

In addition to the indicated signals of the γ proton and substituent, the spectrum of the form that predominates in CD_3OD contains a compact multiplet of β protons at strong field and two multiplets, which are affiliated with the α protons, at weaker field. The structures of these multiplets are evidence that the α

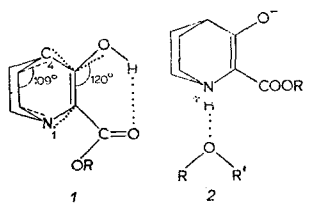
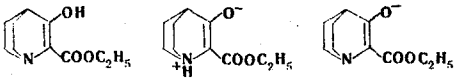


Fig. 2. Hydrogen bonds in Ia and Ib: 1) intramolecular; 2) intermolecular.

protons of the quinuclidine ring of the form that predominates in CD_3OD are equivalent in pairs and are consequently affiliated with a molecule that is symmetrical relative to the plane of the $C_2-C_3-C_4$ atoms.*

Both enol Ia and dipolar ion Ib, which was proposed in [1] as the predominant component of the tautomeric equilibrium of I in CD_3OD, are symmetrical forms of this sort. A mixture of forms Ia and Ib will also give a spectrum that corresponds to the symmetrical form when they rapidly interconvert.

In analogy with bicyclo[2.2.2]octene or quinuclidine derivatives with an endocyclic double bond [4,5], the multiplet at weakest field (centered at 3.42) was assigned to the signals of the α protons in the anti orientation relative to the N−C=C−C link.



Ia Ib Ic

The spectrum of a mixture of the two tautomeric forms – symmetrical and ketone – is also observed at room temperature in deuterated isopropyl alcohol [$(CD_3)_2CDOD$]. The ratio of the forms in this solvent is about 1:1 (Table 2).

Proton-magnetic-resonance spectra that are typical for "slow" exchange between the forms [6] were observed in all of the cases considered above. Exchange accelerated on heating. The signals of the 4-H protons of the various forms are markedly broadened in the spectrum of I in CD_3OD at 75°, while the signals of the protons of the ethyl group merged as a consequence of the exchange. Using the data in Table 1 for the 4-H and CH_2 (in C_2H_5) signals, it can be demonstrated that the lifetime of the forms at this temperature is included in the interval 0.05 sec > T > 0.01 sec.

The spectrum that corresponds to this sort of "intermediate" exchange [6] between the forms was observed at room temperature in deuterated methyl acetate (CD_3COOCD_3). We were able to slow down the exchange on lowering the temperature to −10° and −35° and observe separately the signals of the 4-H protons in the ketone and symmetrical forms.

Exchange occurs even more rapidly between the ketone and symmetrical forms in furfural. In this solvent, a change in the temperature has a marked effect on the relative concentrations of the tautomeric forms, which leads to a dependence of the observed chemical shift of the 6-H, 7-H, and 4-H protons on the temperature.

Exchange between the forms is accelerated by CD_3O^- ions. Thus only one set of signals with averaged chemical shifts is observed in the spectrum of I in CD_3OD + 0.005 M CD_3ONa. The lifetime of each of the forms in this solvent does not exceed 0.05 sec.

Turning to the problem of the structure of the symmetrical form, we will examine the changes in the chemical shift of the protons of the quinuclidine ring as the state of the ionized groups of molecules changes. As follows from Table 1, transition from the symmetrical forms (in CD_3OD) to anion Ic (in CD_3OD + 0.5 M CD_3ONa) is accompanied by a shift in the signals of all of the protons of the quinuclidine ring to strong field. In this case, the maximum effect is observed for the signals of the α protons – $\Delta\delta_\alpha$ = 0.5 ppm (average value) – and the minimum effect is observed for the γ proton – $\Delta\delta_\gamma$ = 0.26 ppm. It can therefore be assumed that the charge on the nitrogen atom changes on passing from neutral methanol to alkaline methanol. Consequently, dipolar ion Ib is the predominant form in neutral methanol. This conclusion is in agreement with the data obtained in [1].

The relative concentration of symmetrical form Ia + Ib in various solvents is presented in Table 2.

It follows from Table 2 that the relative concentration of the symmetrical forms does not correlate with a characteristic of the solvent such as the dielectric permeability (ε). However, solvents whose molecules contain an oxygen atom with an unshared pair of electrons in the p or sp^3 orbitals stand out notice-

*The paired equivalence of the β protons is less appreciable because of merging of the signals of these protons into one multiplet.

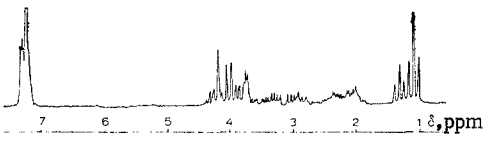


Fig. 3. PMR spectrum of a mixture of diastereomers syn-II and anti-II in $CDCl_3$.

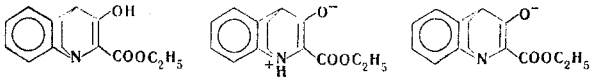
ably with respect to the percentage of the symmetrical form. It can therefore be assumed that an intermolecular hydrogen bond, in which the O atoms of the solvent and the $N-H^+$ group of the dipolar ion participate (Fig. 2, structure 1), is more favorable in the bicyclic system under consideration than intramolecular hydrogen bonding in the enol form (Fig. 2, structure 2).

The reason for this may be the decrease in the energy of the intramolecular hydrogen bond in Ia because of steric effects.

For undistorted angles and bond lengths, the distance between the cis-oriented N and 4-C atoms in the $N-C=C-C$ fragment (taken as being isolated) exceeds the same distance in the $N-C-C-C$ fragment by 0.5 Å. The $\angle C_4C_3C_2$ and $\angle C_3C_2N$ angles in a real molecule of quinuclidine with an endocyclic double bond (for example, in Ia, Ib, or Ic) are reduced as compared with the values of these angles in an isolated $N-C=C-C$ fragment. Reduction of the $\angle C_4C_3C_2$ and $\angle C_3C_2N$ angles will induce an increase in the remaining angles of this fragment, including $\angle C(OOR)C_2C_3$ and $\angle C_2C_3O(H)$, which will lead to an increase in the $(C=)O\cdots H(-O)$ distance (Fig. 2, structure 2) and weakening of the intramolecular hydrogen bond.

Turning to II, it should first be noted that the appearance of a second asymmetrical 4-C center in II leads to the possibility of the existence of two diastereomeric keto forms with syn or anti orientations of the substituent relative to the benzene ring. The PMR spectra of II are the spectra of mixtures of the indicated diastereomers. Of the signals of the protons of the quinuclidine ring, two singlets of different intensity, which are apparently affiliated with the 2-H protons of the two diastereomeric keto forms (Table 3), are found at weakest field. The singlet at relatively stronger field was assigned to the proton of the diastereomer that contains the indicated proton in the syn orientation (and the $COOC_2H_5$ substituent in the anti orientation) relative to the benzene ring [7]. The two (and only two) sets of signals of the protons of the ethyl groups of the substituent in the 2 position also attest to the presence of a mixture of diastereomers in solution.

Thus the signals of enol form IIa or dipolar ion IIb were not detected in the PMR spectra of any of the investigated solvents; on the basis of this, it can be asserted that the concentration of these forms did not exceed 3-5%.



IIa IIb IIc

Exchange exists between the keto forms, since a difference in the relative concentrations of the diastereomers of II is observed in different solvents. The exchange can be characterized as "slow," since the signals corresponding to the two diastereomeric keto forms are narrow at room temperature (and even at 90°).*

The conversion of one diastereomer of II into the other is associated with detachment of a 2-H proton. Replacement of a 2-H proton by a deuteron therefore occurs in solvents that contain labile deuterons [CD_3OD and $(CD_3)_2CDOD$], and this is accompanied by disappearance of the signal of this proton in the PMR spectra of the keto forms. At room temperature deuterium exchange occurs at such a rate that the 2-H signal cannot be observed in the PMR spectra of II in the indicated solvents. Solutions of IIc in CD_3OD were prepared and studied at low (−51 and −24°) temperatures in order to investigate the deuteration kinetics. The deuterium-exchange rate constants (K) at −24 and −51° and the half-exchange times (τ) at these temperatures were found from the dependence of the relative intensity of the 2-H signals on time, and the deuterium-exchange activation energy (E) was also estimated.†

* "Intermediate" exchange between syn-II and anti-II is observed only on heating (to 75°) in CD_3OD in the presence of CD_3ONa.

† The values indicated below pertain to the kinetics of deuterium exchange in the predominant diastereomer, which is characterized by a syn orientation of the substituent relative to the benzene ring. The corresponding constants for the second isomer have the same order of magnitude.

°C	K, min^{-1}	$\tau = 0.695/K$, min	E, kcal/mole
−24	0.34	2	
−51	0.046	16	8

Thus the deuterium-exchange activation energy, i.e., the energy for detachment of 2-H in II, is low, which is in agreement with the previously indicated low rate of exchange between the two diastereomeric keto forms at 90°.

The data on the equilibrium of tautomeric forms of I and II in the same solvent – CD_3OD (Tables 1 and 3) – demonstrate that the relative concentration of the symmetrical form of 2-ethoxycarbonyl-3-oxoquinuclidine exceeds the relative concentration of the corresponding form of 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine by a factor of at least 80. This is possibly due to the great rigidity of the benzo[b]quinuclidine molecule, as a consequence of which the above-mentioned difference in the distances between the N and 4-C atoms for the $N-C=C-C$ and $N-C_7-C_8-C_4$ fragments in IIa or IIb can be compensated exclusively through distortion of the valence angles (or bond lengths) and is associated with a considerable increase in the energy of the molecule.

In addition, it can be assumed that the shift of the equilibrium to favor the keto form of II over I is associated with the lower basicity of the nitrogen of the quinuclidine ring of benzo[b]quinuclidine. The formation of dipolar ion IIb for the keto ester of benzo[b]quinuclidine therefore proves to be less favorable than the formation of Ib for the keto ester of quinuclidine.

A form with sp^2-hybridized 2-C and 3-C atoms in II was observed only in methanol in the presence of sodium methoxide. In this medium, signals of anion IIc, the molar concentration of which approximately corresponds to the Na^+ molar concentration in solution, are present along with the signals of the two diastereomeric keto forms. The magnitudes of the chemical shifts of the protons of the C_2H_5 group of anion IIc are intermediate between the corresponding values in keto forms II, as should have been expected from the geometry of the IIc molecule and the anisotropic effect of the benzene ring on the shifts of the protons of the C_2H_5 groups.

LITERATURE CITED

1. Yu. N. Sheinker, E. M. Peresleni, I. V. Persianova, E. E. Mikhlina, V. Ya. Vorob'eva, A. D. Yanina, and L. N. Yakhontov, Khim. Geterotsikl. Soedin., 229 (1972).
2. N. Bhacca and D. Williams, Applications of Nuclear Magnetic Resonance in Organic Chemistry [Russian translation], Mir, Moscow (1966), p. 150.
3. V. F. Bystrov and A. U. Stepanyants, J. Mol. Spectr., 21, 241 (1966).
4. K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H. Tanida, Can. J. Chem., 42, 926 (1964).
5. E. E. Mikhlina, V. Ya. Vorob'eva, K. F. Turchin, and M. V. Rubstsov, Khim. Geterotsikl. Soedin., 1083 (1968).
6. J. Pople, V. Schneider, and G. Bernstein, High Resolution Nuclear Magnetic Resonance, McGraw-Hill (1959).
7. K. F. Turchin, E. B. Mikhlina, A. D. Yanina, V. Ya. Vorob'eva, L. N. Yakhontov, and Yu. N. Sheinker, Khim., Geterotsikl. Soedin., 981 (1971).