

STUDY OF THE TAUTOMERISM OF 2-ETHOXYCARBONYL-3-OXO
DERIVATIVES OF QUINUCLIDINE AND BENZO[b]QUINUCLIDINE

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The tautomerism of 2-ethoxycarbonyl-3-oxoquinuclidine and 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine was investigated by means of IR and UV spectra and potentiometric titration. It was found that tautomeric equilibrium between the ketone, enol, and internally ionized forms is realized for 2-ethoxycarbonyl-3-oxoquinuclidine, and the position of the equilibrium is determined by the aggregate state of the substance and the nature of the solvent. The internally ionized form predominates in the crystals and in polar solvents (alcohol and water), while the ketone and enol forms are the primary ones in solvents of low polarity (chloroform and dioxane), and the percentage of the ketone form is always larger than that of the enol form. In contrast to this, 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine exists practically completely as the keto form in crystals and solutions.

Like other β -keto esters, 2-ethoxycarbonyl-3-oxo derivatives of quinuclidine and benzo[b]quinuclidine should have a capacity for keto-enol tautomerism. In fact, the literature contains data [1] indicating that 2-ethoxycarbonyl-3-oxoquinuclidine has the enol structure (Ib) in crystals but exists as the ketone form (Ia) (see the scheme below) in methylene chloride solution. However, no direct proof of the keto-enol tautomerism of this compound was presented, and the position of the tautomeric equilibrium as a function of the aggregate state and nature of the solvent was not studied. This problem was investigated in the present study as applied to 2-ethoxycarbonyl-3-oxoquinuclidine (I) and 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine (II).

Intense bands at 1728-1752 cm^{-1} and weak absorption at 1613-1616 cm^{-1} and 1650-1652 cm^{-1} are observed in the IR spectra of I in dioxane, chloroform, and carbon tetrachloride (see Table 1). These bands can apparently be assigned, respectively, to the stretching vibrations of the carbonyl groups of the ketone form and to the vibrations of the double bond and the ethoxy carbonyl group of the enol form with an intramolecular hydrogen bond [2-5].

The UV spectra of these solutions contain an absorption maximum at 245-260 nm (ϵ 2220-936, depending on the solvent), which should be associated with the presence of the enol form of I. In fact, the chelated enol forms of β -keto esters of the cyclohexane and piperidine series [4-6] have similar absorption at 250-258 nm, while the model compound of the ketone structure - 3-quinuclidone - has virtually no absorption above 220 nm [if the weak band at 308 nm (ϵ_{28}) is disregarded]. Thus, as assumed, according to the IR and UV spectra, I exists as a mixture of the ketone and enol tautomeric forms in the indicated solvents, and the position of the tautomeric equilibrium depends on the solvent (ϵ at 245-260 nm changes appreciably on passing from one solvent to another).

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TABLE 1. IR and UV Spectra of 2-Ethoxycarbonyl-3-oxo Derivatives of Quinuclidine and Benzo[b]quinuclidine

Com- pound	UV spectra		IR spectra					
	solvent	λ_{max} nm	ϵ	keto form		enol form		dipolar form
				$\nu_{C=O}$, cm^{-1}	$\nu_{C=C}$, cm^{-1}	$\nu_{C=O}$, cm^{-1}	$\nu_{C=C}$, cm^{-1}	
I	CCl ₄ CHCl ₃ Dioxane Water 96% Alcohol 100% Alcohol	259	2220	1752 s — 1730 s	1652 m	1616 w	1687 vs, 1640 w 1550 vs, b 1630 s 1560—1565s, vb 1640 w 1669—1575s, b 1635 m 1530—1500 vs 1642 s 1545s, b 1620 s	
		249	1640	1761s vs — 1728s	1652 w	1613 w		
		245	936	1745 vs	1660 w	1615 w		
		267	20000	1762 m — 1734 m	1677 m			
		266	13700	1720 w				
III	0.005 N NaOH† Water 96% Alcohol	267	14200	1737 s				
		267	92	1763m — 1737 s				
		267	148	1745m — 1727 s				
				1730 vs, b				
				1735—1732 vs, b				
II	Water** 99% H ₂ O + 1% C ₂ H ₅ OH 50% H ₂ O + 50% C ₂ H ₅ OH Alcohol Dioxane	264	865					
		264	761					
		264	639					
		264	486					
		265	500					

* The band corresponds to a carbonyl group involved in an intramolecular hydrogen bond.

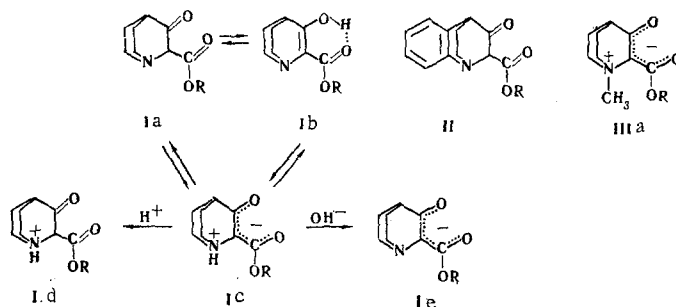
† Mineral oil paste.

‡ The UV spectrum of III also contains a maximum at 220–227 nm (ϵ 12,720–16,740), which is associated with the absorption of an iodide ion. Compound III is unstable in strong alkali solutions.

** The UV spectrum of II also contains a shoulder at 270 nm (ϵ 420) and a maximum of low intensity at 311 nm (ϵ 228), which is associated with the absorption of the keto group.

A different pattern is observed in the IR spectra of I in water and alcohol,* as well as in the IR spectra of crystals of I. The absorption maximum in the UV spectra is shifted to the long-wave region with a sharp increase in the extinction of λ_{max} (λ_{267} , ϵ 11,200–20,000). The intensity of the ketone bands ($1734\text{--}1752\text{ cm}^{-1}$ in $\text{C}_2\text{H}_5\text{OD}$ and 1720 cm^{-1} in KBr pellets) and enol bands ($1650\text{--}1677\text{ cm}^{-1}$) in the IR spectra decreases markedly, and a very intense absorption appears at $1545\text{--}1600\text{ cm}^{-1}$.

The appearance of the latter bands in the IR spectra and of intense absorption at 267 nm in the UV spectra should, in our opinion, be associated with the existence of I in the form of dipolar ion Ic under these conditions.



The following data speak in favor of this point of view.

1. The high-intensity band at $1545\text{--}1600\text{ cm}^{-1}$ is similar to the bands observed in carboxylic acid ions with an equalized system of $\text{O}=\text{C}=\text{O}$ bonds that is close in character to the system of bonds in Ic.
2. The similarity between the IR spectra of I (in D_2O in the region of the stretching vibrations of the double bonds) and the UV spectra of I in water and alcohol and the spectra of 2-ethoxycarbonyl-3-oxoquinuclidine methiodide (III) in aqueous sodium hydroxide. Under these conditions, III has the dipolar ion structure (IIIa) and is completely analogous to Ic in structure.
3. The data from the potentiometric titration of I in aqueous and alcoholic media. Two pK_a values were obtained during the determination of the ionization constants of I in water: pK_{a_1} 3.47 when I is titrated with acid ("proton addition") and pK_{a_2} 11.29 when I is titrated with alkali ("proton loss").

If the compound has structure Ia or Ib and is amphoteric, the pK_{a_1} value pertains to the basic group, while pK_{a_2} pertains to the acid group; for structure Ic, the titration processes are described by the equations $\text{Ic} \rightleftharpoons \text{Id}$ and $\text{Ic} \rightleftharpoons \text{Ie}$, and the pK_{a_1} value characterizes the acid group, and pK_{a_2} characterizes the basic group. The constants can be assigned on the basis of a change in the magnitude of pK_{a_1} on passing from water to a less polar solvent. In this case, the degree of dissociation should decrease; i.e., the pK_{a_1} value will increase if it characterizes the acid group and will correspondingly decrease if it characterizes the basic group. An increase in pK_{a_1} to 3.68 is observed for I in 80% (by volume) alcohol, which makes it possible to assign pK_{a_1} to the acid group and pK_{a_2} to the basic group (the groups are capable of mutual neutralization) and is evidence of the existence of I primarily in the form of a dipolar ion of the 3-hydroxypyridine or nicotinic acid type in water and alcohol solutions.

It should be noted that another possible explanation of the observed spectral data — the existence of I in the ionized form (as an anion) in water and alcohol — should be rejected. This follows from the high pK_a value for I during titration with alkali (11.29 in water). A very low degree of acid ionization ($\sim 0.0001\%$) corresponds to this pK_a value, which is in agreement with the practical absence of anions in aqueous solutions. The difference in the IR and UV spectra of I in water and alcohol from the spectra recorded from aqueous NaOD solutions, in which the compound is known to be present as anions, is also indicative of this.

The high-frequency region of the IR spectrum of crystals of I contains a distinct, intense band at 3080 cm^{-1} , which apparently should be assigned to the NH stretching vibrations in the dipolar ion. On deuteration, the band intensity decreases, and a new band appears in the spectrum at $2290\text{--}2310\text{ cm}^{-1}$. Another possible assignment of the band at 3080 cm^{-1} to ν_{CH} of the ketone form is excluded, since the band at 3080 cm^{-1} is absent in the spectrum of II, which has only the ketone structure in the crystalline state.

* The IR spectra of the compounds in D_2O and $\text{C}_2\text{H}_5\text{OD}$ were recorded in all cases.

Thus an examination of all of the data demonstrates that β -keto ester I in the crystalline state and in hydroxyl-containing solvents exists chiefly in the dipolar form (Ic with a certain percentage of enol Ib and ketone Ia; the dipolar form is absent in nonpolar solvents, and the compound is represented by an equilibrium mixture of the enol (Ib) and ketone (Ia) forms with predominance of the latter. The participation of the dipolar structure in the tautomeric equilibrium of I distinguishes the investigated system from the usual keto-enol systems.

It is possible that the unusual effect of solvents on the position of the tautomeric equilibrium previously observed for β -keto esters of the piperidine series [7] is also associated with the formation of a dipolar form for these compounds in hydroxyl-containing solvents rather than with the peculiarities of the solvation of a cyclic nitrogen atom, as proposed by Erastov and Ignat'eva.

In contrast to I, the tautomeric equilibrium for 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine (II) in the crystalline state and in solutions is practically completely shifted to favor the keto form. The IR spectrum of II contains intense absorption only at 1732-1735 cm^{-1} (in solutions) and 1730 cm^{-1} (in the crystalline state), which is characteristic for the stretching vibrations of the carbonyl group of the ketone form. According to potentiometric titration in water, pK_{a_1} is 2.52 and pK_{a_2} is 9.20, compared with pK_{a_1} 2.0 and pK_{a_2} 10.47 in 80% alcohol, which is evidence for the amphoteric character of II rather than for its dipolar form.

The presence of slight amounts of dipolar ions of II can be assumed only from the UV spectrum (an increase in the absorption at 264 nm as the percentage of water in the solvent increases). The shift in the equilibrium to favor the ketone form in the case of benzo[b]quinuclidine derivative II as compared with quinuclidine derivative I is apparently associated with the high strain of the cyclic system of the enol and dipolar forms of 2-ethoxycarbonyl-3-oxobenzo[b]quinuclidine. The decrease in the basicity of the cyclic nitrogen due to the inductive effect of the benzene ring should also be substantial in this respect for the latter form.

The conclusions regarding the tautomerism of I and II drawn in this study are in agreement with the results of PMR spectroscopy, which were examined in a special communication [8].

EXPERIMENTAL

The IR spectra of solutions and crystals (mineral oil pastes and KBr pellets) were recorded with a UR-10 spectrophotometer. The UV spectra of solutions were obtained with an EPS-3 spectrophotometer.

The basicity constants were calculated from the potentiometric titration curves of 0.01-0.001 M solutions of the substances in water and 80% alcohol. The titration was performed with glass and calomel electrodes with an RNM-22 potentiometer with an expander from the Radiometer company. The mean-square error in each determination did not exceed 0.03 pK units. The synthesis of 2-ethoxycarbonyl-3-oxoquinuclidine (I) has been previously described [9].

2-Ethoxycarbonyl-3-oxoquinuclidine Methiodide (III). A mixture of 1 g (5 mmole) of I and 0.73 g (5 mmole) of methyl iodide in 10 ml of anhydrous acetone was heated at 42-45°C for 5 h. The mixture was cooled to precipitate 1.52 g (88%) of the methiodide with mp 137-138° (dec.). Found: I 37.3; N 3.9%. $\text{C}_{11}\text{H}_{18}\text{INO}_3$. Calculated: I 37.4; N 4.1%.

2-Ethoxycarbonyl-3-oxobenzo[b]quinuclidine (II). Ethanol (42 ml) was added to 27 g (0.7 mmole) of potassium in 180 ml of absolute toluene, and the mixture was heated to 130-135° (bath temperature). A solution of 66 g (0.24 mmole) of 1-ethoxycarbonylmethyl-4-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline was added in the course of 2 h to the reaction mass at this temperature. The mixture was stirred and refluxed for 6 h and cooled, and the toluene solution was decanted. The residual caramel-like mass was treated with 415 ml of 10% acetic acid, the resulting solution was cooled with ice, and 48.8 g of anhydrous potassium carbonate was added to it. The mixture was then extracted with chloroform. The chloroform was removed, and the residue was vacuum fractionated to give 15.3 g (28%) of a product with bp 140-141° (0.6 mm). Found: C 68.8; H 6.2; N 5.9%. $\text{C}_{14}\text{H}_{15}\text{NO}_3$. Calculated: C 68.5; H 6.1; N 5.7%. The methiodide had mp 141-142° (from ethanol). Found: I 32.9; N 3.6%. $\text{C}_{15}\text{H}_{18}\text{INO}_3$. Calculated: I 32.8; N 3.6%.

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