Nitrogen Bridgehead Compounds. Part 70. Studies on Quinolizine Derivatives. Part 4 [1]. Ultraviolet-Visible Spectra and Chemical Properties of some Quinolizine Derivatives and their Monocyclic Tautomers

Angéla Schwartz, László Szabó*, Katalin Pusztay-Szabó

Institute of Organic Chemistry of the Semmelweis Medical University
H-1092 Budapest, Högyes E.u.7, Hungary

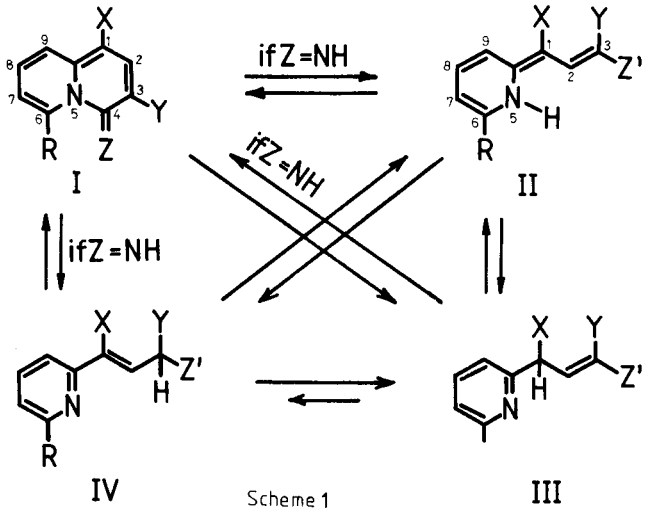
István Hermecz and Zoltán Mészáros

CHINOIN Pharmaceutical and Chemical Works Ltd.,
H-1045 Budapest, Tó u. 1-5, Hungary
Received July 22, 1986

Ultraviolet-visible spectra of 4-oxo **1** and 4-imino **2** quinolizines or their monocyclic tautomers **3**, **4** have been studied in neutral, acidic and basic ethanolic solution as well as in dimethyl sulfoxide and chloroform. Ring B of 4-oxo and 6-unsubstituted 4-imino compounds can be cleaved by sodium ethanolate more or less easily. Ring B of 6-methyl-4-iminoquinolizines is very unstable and they are present mainly in the monocyclic form which are partly dissociated in ethanol and dimethyl sulfoxide especially in higher dilution or in the presence of sodium ethanolate. In dilute acidic ethanol or chloroform, the dissociation is suppressed and in the latter solvent and in some cases, absorption bands can be observed due to a small amount of the 4-imino-6-methylquinolizines. In acidic solution of compounds **3B=C**, **3D**, **4E**, **4F=G** having simultaneously cyano and ethoxycarbonyl groups in 1 and 3 position, not simple reprotonation occurs but irreversible changes can be observed.

J. Heterocyclic Chem., **24**, 655 (1987).

In a previous paper, we reported [2] the synthesis and structure elucidation of 4-oxo-, and 4-iminoquinolizine derivatives. A comparative study of their ir and ^{1}H nmr spectra [1] showed that in the crystalline state as well as in solutions of relatively high concentration, the samples contain only one species corresponding either to formula I (*i.e.* to the bicyclic quinolizine structure) or one of the formulas **II-IV** (*i.e.* to a monocyclic pyridine structure) (Scheme 1). Several of the compounds have been previously described in the literature. In some cases, however, the structure assignments were not correct or appropriately supported by experimental data, moreover, in several cases, the spectroscopic data were missing [3,4,5,6,7]. The situation can be partly understood by the high sensitivity of some of the ultraviolet-visible spectra on pH, solvent or even on concentration. These facts prompted us to study the ultraviolet-visible spectra and behaviour of these compounds. The chemical properties of our sixteen compounds are shown in Scheme 2 [8]. Their ultraviolet-visible spectroscopic data are collected in Tables 1, 2 and 3.



Scheme 1

Bicyclic 4-Oxo Compounds.

The bicyclic 4-oxo compounds **1C**, **1D**, **1c**, **1d**, **1g**, **1h**, **1G** and **1H** form a homogeneous group. In the spectrum of their ethanolic solution, there are four distinct absorption bands between 200 nm and 500 nm having nearly the same position and intensity in the different compounds (Table 1). However, the absorption band of longest wavelength is at about 430 nm in the spectrum of the 6-methyl derivatives and at 400 nm in that of the 6-unsubstituted ones.

In acidic solution (hydrochloric acid in ethanol), the spectra do not change, but in basic solution (sodium ethanolate in ethanol), they are completely rearranged. In the 6-methyl-series, the products have been isolated and their uv-vis, ir and ^{1}H nmr spectra are in agreement with the proposed structure **5**. In their uv-vis spectrum, generally, two bands can be observed, only, depending on the substitution pattern of the side chain. The weak band appears at 245 nm, if C(3) has both a cyano and an ethoxycarbonyl group, and at 265 nm, if it has two ethoxycarbonyl groups. The strong band of long wavelength can be seen at 390-400 nm in compounds having a cyano group at C(1), and at 355-380 nm in those having an ethoxycarbonyl group in the same position. The band at 345-350 nm can not be ob-

Scheme 2

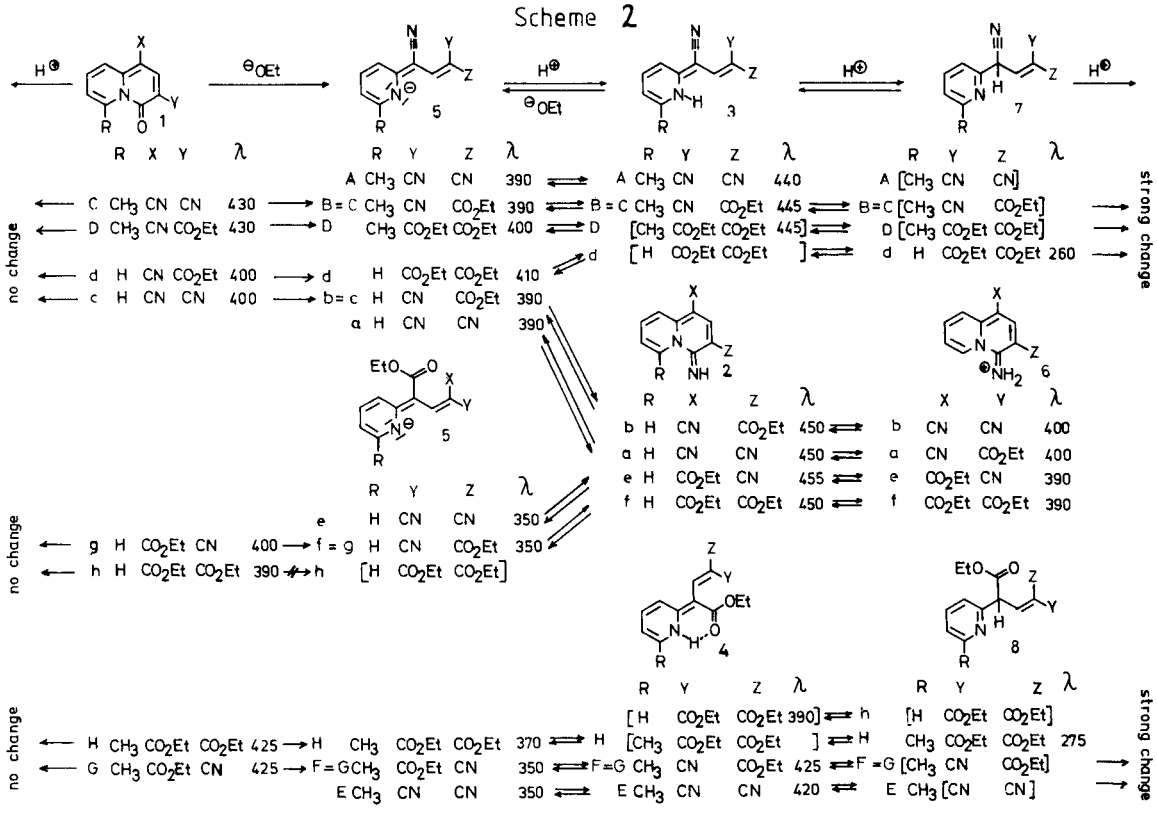


Table 1

Ultraviolet Visible Spectral Data of Bicyclic 4-Oxoquinolizine Derivatives

		λ max (nm) log ε											
1c	EtOH	215			265			345			400		
					4.11			3.75			4.03		
	⁻OEt		245			310					390		
			3.61			3.44					4.01		
1d	EtOH	215			265			345			400		
					4.20			3.90			4.19		
	⁻OEt	slight changes, only											
1g	EtOH	215			265			345			395		
		4.32			4.18			3.97			4.21		
	⁻OEt		245						355				
			4.04						4.44				
1h	EtOH	210			265			340			390		
		4.25			4.26			3.92			4.12		
	⁻OEt	slight changes, only											
1C	EtOH	215			270			350					435
		3.95			3.80			3.50					3.80
	⁻OEt		245			310					375		
			4.02			3.64					3.96		
1D	EtOH	215			270			350					430
		4.27			4.14			3.90					4.19
	⁻OEt				270						405		
					4.22						4.51		
1G	EtOH	220			270			350					425
		4.21			4.02			3.92					4.14
	⁻OEt		245						355				
			4.02						4.47				
1H	EtOH	220			270			350					425
		4.23			4.18			4.01					4.22
	⁻OEt				270				375				
					3.88				4.00				

Table 2

Ultraviolet Visible Spectral Data of Bicyclic 4-Iminoquinolizine Derivatives

		λ max (nm) log ε									
2a	EtOH	220		270				370		450	
		4.30		4.19				3.99		3.94	
	H^+	220		275		345			400		
				4.22		4.01			4.19		
	^-OEt			270	310			385			
				4.00	3.91			4.41			
	$CHCl_3$			270			365	380		455	
				3.44			3.11	3.12		3.18	
	DMSO			270 [d,b]			355	375 [a]	410	435 [d]	
				3.87			3.69	3.67	3.61	3.62	
2b	EtOH	220		270				375		455	
		4.36		4.25				3.96		4.03	
	H^+	220		275		345			405		
		4.52		4.09		3.94			4.12		
	^-OEt		245	270	320			390			
			3.80	4.47	3.90			4.52			
	$CHCl_3$			285			360	375		450	
				4.12			4.03	4.02		3.96	
	DMSO			275 [d,b]				375 [c]	410	455 [d]	
				4.18				4.00	3.97	3.95	
2e	EtOH	220		280				370		445	
		4.38		4.24				4.08		4.05	
	H^+	220		275		340			395		
		4.36		4.20		4.06			4.21		
	^-OEt			260			350				
				3.75			4.45				
	$CHCl_3$			280			360	375		450	
				4.17			4.06	4.12		4.03	
	DMSO			280			360	375		455	
				4.15			4.03	4.04		4.00	
2f	EtOH	220		280				370		445	
		4.07		3.94				3.82		3.80	
	H^+	220		270		340			392		
		3.84		3.86		3.75			3.91		
	^-OEt		245				355				
			4.04				4.44				
	$CHCl_3$			285			365	380		460 [e]	
				4.28			3.93	3.95		4.04	
	DMSO			285			365	370		450	
				3.82			3.77	3.79		3.67	

[a] Increasing for dilution and shifted to 390 nm. [b] Additional band for dilution at 320 nm. [c] Increasing for dilution and shifted to 400 nm. [d] Strong decreasing for dilution. [e] Some increasing for dilution.

served in any of the spectra. The reaction rate of ring cleavage is influenced by the substitutent at C(3) and C(6), *i.e.* simultaneous presence of 6-methyl and 3-cyano groups are favorable for it. **1d**, **1h** can be cleaved partially and under strong conditions, only, therefore their spectral data under these conditions can not be given in Table 1.

Acidification of the basic solutions results in different changes depending on the substituent at C(1) and C(3). Compound **5H** will be protonated at C(1) which is proved by two doublet at 4.53 δ ppm and 7.29 δ ppm, [1] respectively, as well as by the absorption band of longest wavelength at 280 nm. In spectra of those compounds which simultaneously have cyano and ethoxycarbonyl groups attached to C(1) and C(3), strong and irreversible changes can be observed which will be reported elsewhere. However, there is an exception to this rule, namely, in 6-unsubstituted compounds having a cyano group at C(3) **5c=b**, **5f=g**, the ring closure is faster and the spectra correspond to the protonated species of the 4-imino-derivatives **6b**, **6f** (see later).

Bicyclic 4-Imino-Compounds.

The 4-imino-6-unsubstituted compounds **2a**, **2b**, **2e**, **2f** also form a homogeneous group having four distinct ab-

Table 3

Ultraviolet Visible Spectral Data of Monocyclic Tautomers

		λ max (nm) log ε									
3A	EtOH	225		270		310	335		395		440
		3.48		3.32		3.42	3.44		3.90		3.76
	H^+			270 [a]			335				440
				3.41			3.72				4.12
	^-OEt	220		275		310			392		
		4.01		3.80		3.85			4.36		
	$CHCl_3$				285		350	370			440
					2.65		2.82	2.85			
	DMSO			275		310			395 [b]		440 [c]
				3.62		3.79			4.28		3.93
3B=C	EtOH	225		265	285		340		410		445
		3.78		3.16	2.95		3.94		4.22		4.33
	H^+	230		265	285		335				445
		3.79		3.62	3.58		3.97				4.37
	^-OEt		245	270		315			395		
			4.12	3.93		3.92			4.52		
	$CHCl_3$				290		350	370			450
					2.82		3.69	3.42			4.33
	DMSO			280		315			415 [b]		450 [c]
				3.62		3.76			4.02		3.58
4E	EtOH			270			340			420	
				3.89			4.26			3.87	
	H^+			270			340			425	
				3.67			4.02			3.66	
	^-OEt			260			350				
				3.79			4.40				
	$CHCl_3$			265	295		360			430	
					3.82		3.62			4.06	
	DMSO			270			340 [d]			420 [c]	
				3.80			4.25			3.77	
4F=G	EtOH	235		270			340			425	
		3.96		3.79			4.26			3.99	
	H^+	230		270			340			425	
		4.13		4.21			4.51			4.28	
	^-OEt		245				355				
			4.02				4.47				
	$CHCl_3$			265	300			365		435	
				3.67	4.16			3.92		440	
	DMSO			270			345 [d]			430 [c]	
				3.84			4.32			3.94	

[a] Additional band at 290 nm. [b] Increasing for dilution. [c] Decreasing for dilution. [d] Shift to 350 nm for dilution.

sorption maxima in ethanol between 200 and 450 nm (Table 2) which, in acidic solution, are shifted to wavelengths corresponding to those of the 4-oxo-6-unsubstituted compounds **1c**, **1d**, **1g**, **1h** indicating an increased interaction of N(5) with protonate C=NH group **6a**, **6b**, **6e**, **6f**. In basic solution, ring B is cleaved very easily and spectra are identical in shape and regularities to those of structures **5a**, **5b=c** and **5e**, **5f=g**.

The spectra in chloroform are similar to those recorded in ethanol. However, in dimethyl sulfoxide, the spectra of compounds **2a** and **2b** are changing in time, and becoming similar to those recorded in ethanol in the presence of sodium ethanolate. The intensity of the bands at 275 nm and 455 nm, respectively is reduced and the bands between 355 and 410 nm, merge into a single intensive absorption band at 400 nm. These changes become more intensive by dilution of the solution. It is now obvious, that in the case of these two compounds, ring opening and dissociation proceed simultaneously, the structure of the products obtained corresponds to that of **5a**, **5b=c** (it should be noted that the spectra recorded at different concentration clearly showed that, in concentration applied for recording the ^1H nmr spectra, the bicyclic species exist exclusively). With compounds **2e**, **2f**, the changes are negligible.

Acidification of the basic solutions produce spectra

identical to those recorded in acidic solution, proving ring closure and protonation.

Monocyclic Tautomers.

The compounds which are stabilized in the monocyclic tautomeric form **II** in crystalline state or in a concentrated solution necessary for ^{1}H nmr measurement [1], *i.e.* **3A**, **3B=C**, **4E** and **4F=G** can not be classified into any of the previous groups. Their ultraviolet-visible spectra are strongly different from those of the bicyclic quinolizine derivatives and depend on substituent at C(1).

The 1-cyano derivatives **3A**, **3B=C** show two strong bands between 390 nm and 450 nm, however, their intensities are mutually changing. In ethanolic hydrochloric acid, the band of longer wavelength, whereas in ethanolic sodium ethanolate, the band of shorter wavelength can be seen exclusively.

The spectra recorded under basic conditions are very similar to those of compounds **2a** and **2b** under the same conditions, and can be assigned to structures corresponding to formulas **5A** and **5B=C**, respectively. However, in slightly acidic solution, the spectra are significantly different of those of **2a** and **2b** under the same conditions. Whereas in the latter case, four bands of similar intensity can be seen, in slightly acidic solutions of **3A** and **3B=C**, one of high intensity, only. This is a common feature of the spectra recorded under either basic or acidic condition, consequently monocyclic tautomer **II** is present in acidic solution as well. As in neutral ethanol, the bands of both the acidic and basic solutions can be observed, it is evident that the monocyclic tautomer **II** is partially dissociated. Its pK_b estimated from the spectra is about 8-9 in agreement with the pK_b value of pyridine (8.85). In **3B=C**, under strongly acidic conditions, irreversible changes can be observed (see later).

Position of the dissociation equilibrium depends on solvent and concentration as well. In dimethyl sulfoxide, especially at low concentration, the spectra are becoming similar to those recorded under basic conditions, *i.e.* the intensity of the band at 440-450 nm is decreasing, that of the band at 390-400 nm increasing, with analogous changes at the weaker bands as well. However, in chloroform solution, disappearance of the band at 390-400 nm proves the complete suppression of the dissociation. Moreover, in this case, two new bands appear between 350 nm and 380 nm which are analogous, though much weaker, to those in spectra of **2a** and **2b** recorded in the same solvent. Consequently, in chloroform solutions of **3A** and **3B=C**, the monocyclic tautomer **II** is in equilibrium with the bicyclic tautomer **I**, though the concentration of this latter species remains low.

Ultraviolet-visible spectra of 1-ethoxycarbonyl-derivatives **4E**, **4F=G** have somewhat different characteristics. In ethanol, two large bands can be seen between 340 nm and 430 nm, but the band of longer wavelength is significantly weaker.

In ethanolic sodium ethanolate, this latter band disappears proving that it comes from the neutral monocyclic tautomer **II** and the band at about 340 nm undergoes a slightly bathochromic and hyperchromic shift, the spectra becomes very similar to those of compounds **2e** and **2f** recorded under the same conditions.

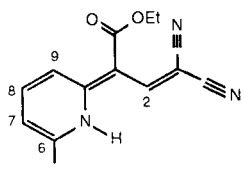
It can be concluded that in ethanolic solution of **4E** and **4F=G**, already under neutral conditions, the dissociation equilibrium lies well towards the deprotonated species. The phenomenon may be interpreted by the fact that one part of the negative charge formed after deprotonation can be more easily overtaken by the carbonyl oxygen of the 1-ethoxycarbonyl group near to the pyridine ring than by the nitrogen of the cyano group in the analogous 1-cyano derivatives. In slightly ethanolic hydrochloric acid, the spectra do not change at all. However, it should be noted, that the dissociation in ethanolic solution of **4E** and **4F=G** can not be suppressed by increasing the concentration of the acid because both compounds undergo rapid irreversible changes.

Position of the dissociation equilibrium depends again on solvent and concentration as well. In dimethyl sulfoxide, in particular at low concentration, the dissociation is increasing which is shown by the decrease of the intensity of the band at 420-430 nm, as well as by the slightly bathochromic and hyperchromic shift of the band at 340 nm, *i.e.* the shape of the spectrum is approaching to that recorded in basic solution. Again, in chloroform solution, important changes can be observed: the intensity of the band of longer wavelength is strongly increased and instead of the large band at 340 nm, one (in **4F=G**) or two (in **4E**) weak bands between 360 nm and 380 nm, as well as one weak but sharp band at 295-300 nm can be observed. These bands are analogous to those of the spectra of **2e** and **2f** in the same solvent. It can be concluded again that monocyclic tautomer **II** is in equilibrium with the bicyclic tautomer **I**, though the concentration of the latter is low in the equilibrium mixture.

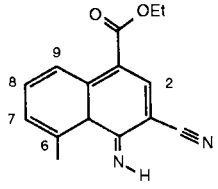
In the case of compound **4E**, the presence of the bicyclic tautomer **I** (**4I**) can have been demonstrated by ^{1}H nmr spectroscopy as well. If its chloroform solution is warmed, new signals appear in the spectrum, and among others, the new positions of the C(2) and C(9) protons which are close to those in the analogous **2e** compound (Table 4) clearly prove the ring closure. Moreover, the signal of the 6-methyl protons is shifted to a higher δ value which is characteristic to the bicyclic derivatives [1]. A weak and sharp band at 3280 cm^{-1} in the ir spectrum demonstrates the N=H group as well [1].

Table 4

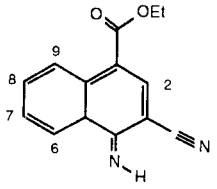
Characteristic ^{1}H NMR Data of Compounds **4E**, **4F**, and **2e** (in deuteriochloroform, TMS = 0 δ ppm)



4E



4F



2e

C(2)-H	7.85 (s)	8.14 (s)	8.21 (s)
C(6)-CH_3	2.66 (s)	2.89 (s)	
C(7)-H	6.95 (d)	6.88 (d)	7.24 (t)
C(8)-H	7.84 (t)	7.55 (t)	7.78 (t)
C(9)-H	7.24 (d)	8.95 (d)	9.18 (d)
OCH_2-	4.36 (q)	4.36 (q)	4.38 (q)
-CH_3	1.41 (t)	1.41 (t)	1.43 (t)

Finally, it should be noted that in strongly acidic ethanolic solution of the monocyclic compounds **3B=C**, **4E** and **4F=G**, or by strongly acidifying the basic ethanolic solutions of these compounds as well as that of **3D** *i.e.* in monocyclic species having simultaneously cyano and ethoxycarbonyl groups at C(1) and C(3), rapid and irreversible changes can be observed which will be reported later.

EXPERIMENTAL

The synthesis of the compounds have been published by us in an earlier paper [2].

The ultraviolet spectra were recorded on a Unicam SP 8-100 spectrophotometer.

The ultraviolet spectra of the compounds were taken in ethanolic solutions in 10^{-4} mole/l concentration. The spectra recorded in basic and acidic medium were taken in 10^{-2} mole/l sodium ethoxide and hydrochloric acid concentration, respectively. The substrate concentration was 5 x 10^{-5} mole/l. The spectra recorded in dimethyl sulfoxide and in chloroform were taken in 10^{-4} mole/l concentration. The spectroscopic data in Tables 1, 2 and 3 which are signed as "diluted" refer to the spectra of the solutions in 5 x 10^{-5}, and 2,5 x 10^{-5} mole/l concentration.

REFERENCES AND NOTES

[1] Part **3**. A. Schwartz, Z. Pál, L. Szabó. I. Hermecz and Z. Mészáros, *J. Heterocyclic Chem.*, **24**, 651 (1987).

[2] Part **2**. A. Schwartz, Z. Pál, L. Szabó, K. Simon, I. Hermecz and Z. Mészáros, *J. Heterocyclic Chem.*, **24**, 645 (1987).

[3] F. Bohlmann, N. Ottawa and R. Keller, *Ann. Chem.*, **584**, 162 (1954).

[4] T. R. Govindachari, S. Rajadurai, H. Submarian and B. S. Thyagarajan, *J. Chem. Soc.*, 3839 (1957).

[5] R. K. Hill, C. E. Glassick and E. S. Fliedner, *J. Am. Chem. Soc.*, **81**, 737 (1959).

[6] G. Kobayashi, Y. Matsuda, R. Natsuki, Y. Tominaga and C. Maseda, *Yakugaku Zasshi*, **94**, 44 (1974).

[7] K. Kurata, H. Awaya, C. Maseda, Y. Tominaga, Y. Matsuda and G. Kobayashi, *Yakugaku Zasshi*, **95**, 1431 (1975).

[8] For reason of clarity, the following rules have been applied in denoting the compounds: (1) numbering of the identical carbon and nitrogen atoms have been performed uniformly in bicyclic and monocyclic forms; (2) numbers **1**, **2**, *etc.* denote the type of compounds, capital letter refers to the 6-methyl series and lower case indicates the 6-unsubstituted series.