Nitrogen Bridgehead Compounds. Part 69. Studies on Quinolizine Derivatives. Part 3 [1]. Infrared and ^{1}H NMR Spectroscopic Studies of Quinolizine Derivatives and Their Monocyclic Tautomers

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Infrared and ^{1}H nmr spectra of 4-oxo, **1**, and 4-imino, **2**, quinolizine derivatives or their monocyclic tautomers **3**, **4** have been comparatively studied. The number of ethoxycarbonyl groups, the signals of the hetero proton, the C(9)-H, and the C(6)-CH_3 group in the ^{1}H nmr spectrum, moreover the N-H stretching vibration bands proved to be diagnostically important for monocyclic or bicyclic as well as for 4-oxo or 4-imino structures. A weak intramolecular hydrogen bridge in compounds **2b** and **2f**, a strong chelate type hydrogen bridge in **4E** and **4F=G** could have been demonstrated as well.

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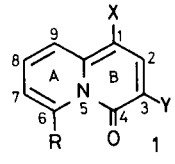
Earlier [1], we reported the synthesis of a series of compounds [2] (Scheme 1) prepared by reacting 2-pyridinacetic acid derivatives with ethoxymethylenemalonic acid derivatives and proved that they have either a bicyclic quinolizine structure like **1** or **2** or a monocyclic tautomeric form like **3** or **4**. The compounds **1c, d, g, h, 1H, 2b, 2f, 3A, 3B=F** and **4E** have been previously prepared by others [3-10], too, however, ir spectral data for **1c, 1d, 1h, 2b, 2f, 3A, 3B=C** and **4E** [3,6,8,4,10], ^{1}H nmr spectral data for **1c, d, g, h, 3A** and **3B=C** [6,10] have been given, only. Moreover, contradictory structures have been attributed to some of them owing, at least partially, to the lack of comparable spectroscopic data [1]. Even existing data are not free from contradictions. In the ^{1}H-nmr spectra of **1g** and **1h**, the signals at 9.40 and 9.46 δ ppm respectively have been correctly assigned to C(9)-H [6]. This relatively high chemical shift can be explained by the anisotropic effect of the 1-ethoxycarbonyl group [1]. Had compound **4E** and its analogous methyl ester and 8-methyl derivative a bicyclic structure suggested by Kurata *et al* [10], they should have a similar signal in the ^{1}H nmr spectrum. However, no such signals have been reported. As we have proved that compound **3A** and **4E** are monocyclic derivatives, the above mentioned two analogues should presumably have a monocyclic structure as well. In this paper, we give a systematic analysis of the infrared and ^{1}H nmr spectra of the compounds prepared by us. This analysis can contribute not only to completion of the spectroscopic data, and to elimination of the contradictions mentioned above, but can render possible a detailed spectroscopic study of this family of derivatives as well.



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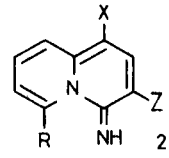
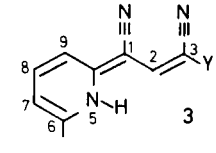


2

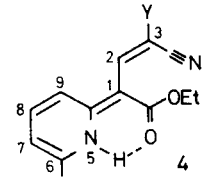
	R	X	Y
1c	H	CN	CN
1d	H	CN	CO_2Et
1g	H	CO_2Et	CN
1h	H	CO_2Et	CO_2Et
1c	CH_3	CN	CN
1D	CH_3	CN	CO_2Et
1G	CH_3	CO_2Et	CN
1H	CH_3	CO_2Et	CO_2Et

	R	X	Z
2a	H	CN	CN
2b	H	CN	CO_2Et
2e	H	CO_2Et	CN
2f	H	CO_2Et	CO_2Et



3

Y	
3A	CN
3B=C	CO_2Et



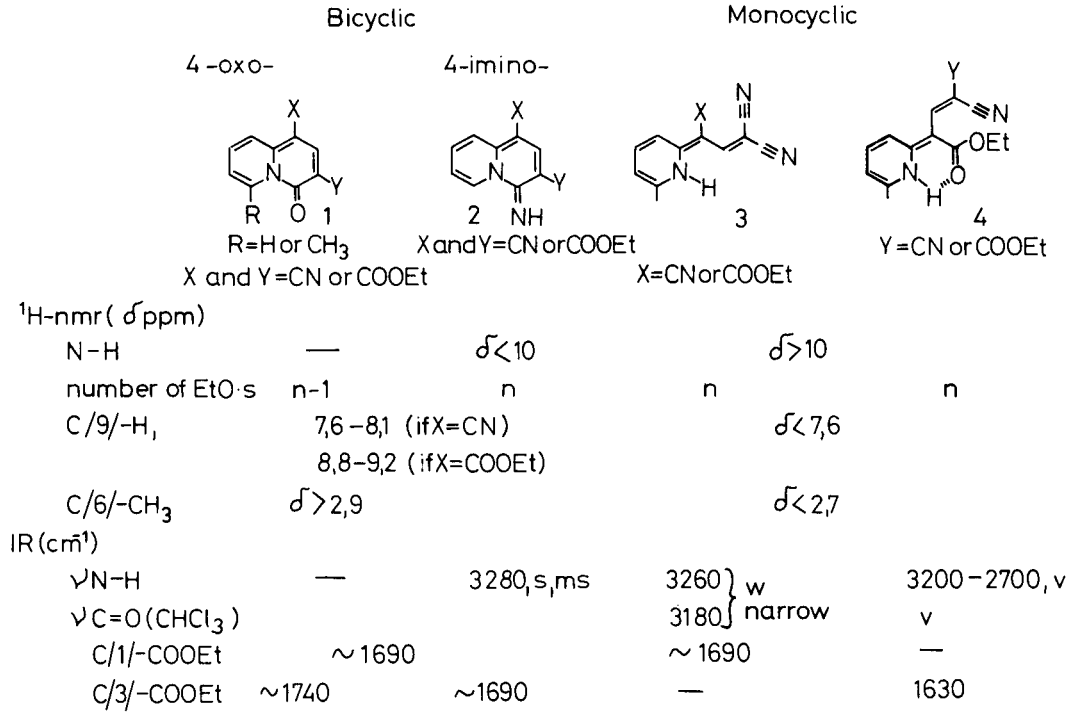
4

Y	
4E	CN
4G=F	CO_2Et

Scheme 1

Infrared Spectra.

The most characteristic infrared absorption bands (in



Scheme 2

Table 1

Characteristic Infrared Spectroscopic Data of Compounds **1c, d, g, h, 1C, D, G, H, 2a, b, e, f, 3A, B=C, 4E, G=F** (cm^{-1}) in Potassium Bromide pellets.

Compound	1 CN	3 CN	1 COOEt	3 COOEt	4 CO	3 COOEt + 4 CO	imino	amino
1c	2220	2210			1700			
1d	2220					1740 + 1700 [a]		
1g		2215	1700		1670			
1h			1690			1740 + 1690 [b]		
1C	2220	2220			1700			
1D	2215					1730 [a] + 1680		
1G		2215	1710		1675			
1H			1690			1740 [b] + 1690		
2a	2215	2205					3260	
2b	2210			1690			3260	
2e		2205		1690			3260	
2f				1680			3260	
3A	2210	2190					3300-3000	
3B=C	2210	2195		1690			3300-3000	
4E		2205	1620				3200-2700	
4G=F		2190	1630	1690			3200-2700	

[a] Stronger band. [b] Much stronger band.

potassium bromide pellet) of the compounds are collected in Table 1. In compounds **2a, b, e, f**, a sharp band of medium intensity can be found at 3260 cm^{-1} in the crystalline state as well as in solution, the latter revealing no concentration dependence. This band is characteristic of a C(=)NH group and it proves the formation of the 4-iminoquinolizine ring. In **3A, B=C** and **4E, G=F** compounds this band is missing. In the ir spectra of **3A** and **3B=C** a

weak, slightly broadened band between 3000 and 3200 cm^{-1} can be observed which is characteristic of secondary amines, whereas in those of compounds **4E** and **4G=F**, there is a broad, weak band fading into the base-line between 3200 and 2500 cm^{-1}. The shape and the intensity of this band remains unchanged in solution suggesting a strong intramolecular hydrogen bond. The C≡N stretching band is found between 2190 and 2220 cm^{-1} in the monocyclic compounds **3A**, **3B=C**, **4E**, **4G=F** and at somewhat higher frequencies in the bicyclic ones **2a**, **b**, **e**, **f**. The carbonyl stretching band of the 1-ethoxycarbonyl group in the bicyclic compounds **1g**, **h**, **1G**, **H**, **2e**, **f** and that of the 3-ethoxycarbonyl group in the monocyclic **3B=C**, **4G=E**, and 4-iminobicyclic compounds **2b**, **2f** are found in the region characteristic of the conjugated esters 1710-1680 cm^{-1}, in the latter cases also providing evidence for that the carbonyl group is not involved in a strong hydrogen bond. In the monocyclic compounds **4E**, **G=F**, however, the carbonyl stretching band of the 1-ethoxycarbonyl group appears at a very low frequency, and shows no solvent dependence indicating again a strong intramolecular hydrogen bond (hydrogen chelate).

If the ethoxycarbonyl group is in the position 3 of the quinolizin-4-one ring (**1d**, **1h**, **1D**, **1H**) in solid phase spectrum a carbonyl frequency coupling has been observed between the lactam carbonyl group and the ester carbonyl groups. This type of frequency coupling has been studied in details in the analogous 1-azaquinolizin-4-ones (4*H*-pyrido[1,2-*a*]pyrimidin-4-ones) by Horváth *et al.* [11]. The carbonyl stretching band of the ethoxycarbonyl group is separated from that of the 4-oxo group and the intensities of the two bands are significantly different: in the 6-methyl derivatives the band of higher frequency is more intensive, whereas in the 6-unsubstituted derivatives, the ratio is reversed. The occurrence of the frequency coupling indicates an *O-cis* configuration of the two carbonyl groups. In the solution spectrum of **1H**, the intensities of the two bands tend to be equal, thus, in solution, the *O*-trans configuration predominates. Interestingly, the position of the 4-oxo band is affected by the C(1)-substituent: in the presence of a 1-cyano group (**1c**, **1C**) it appears at 1700 cm^{-1}, in the presence of 1-ethoxycarbonyl group (**1g**, **1G**) at 1670, and 1675 cm^{-1}, respectively. In the bicyclic 4-imino compounds, the C=N stretching band is overlapped by the skeletal vibration bands of the ring system.

^{1}H NMR Spectra.

The ^{1}H nmr spectroscopic data of the compounds are collected in Table 2. Unfortunately, the compound **2a** was not sufficiently soluble in dimethyl sulfoxide, therefore the spectrum was recorded in trifluoroacetic acid, and its data cannot be compared to those of the other compounds.

In all compounds, the C-H signals of ring A appear in the aromatic region indicating a considerable extent of cyclic delocalization. The signal of C(6)-H atom adjacent to the heteroatom is, as expected, shifted more downfield than the others. In the bicyclic compounds, the replacement of the cyano by ethoxycarbonyl group in positions C(1) or C(3) influences the chemical shifts of the hydrogens of ring A in two cases only. On the one hand, compounds **2b**, **2f** in which the 3-ethoxycarbonyl group can enter into an intramolecular hydrogen bond with the 4-imino group, a slight paramagnetic shift can be observed on the signal of C(6)-H atom. On the other hand, in all bicyclic pair of compounds, the replacement of the 1-cyano group by an ethoxycarbonyl group gives rise to at least 1 δ ppm paramagnetic shift on the signal of C(9)-H due to the anisotropic effect of the ethoxycarbonyl group.

In monocyclic compounds, replacement of the 3-cyano group by an ethoxycarbonyl group exerts no effect on the chemical shift of the protons or ring A. However, replacement of the 1-cyano group by a 1-ethoxycarbonyl group shifts slightly but significantly all the proton signals of ring A paramagnetically (**3A** → **4E**), (**3B=C** → **4G=F**). Considering the electronegativies of the cyano and ethoxycarbonyl groups, an opposite effect would be expected, but the formation of a strong intramolecular hydrogen bond between the 1-ethoxycarbonyl and the pyridine NH apparently overcompensate this effect.

The signal of C(2)-H of all compounds appears at high chemical shift, and its position is sensitive to the substituents at C(1) and C(3). The fact can be explained on the one hand by the electronic properties of the substituents, on the other hand by the paramagnetic anisotropic effect of the ethoxycarbonyl group, though this latter is significantly smaller in the case of C(2)-H than in that of C(9)-H.

Table 2
Characteristic ^{1}H NMR Data of Compounds **1c**, **d**, **g**, **h**, **1C**, **D**, **G**, **H**, **2a**, **b**, **e**, **f**, **3A**, **B=C**, **4E**, **G=F**
(δ ppm, δ TMS = 0)

Compound	Solvent	NH	2 - H	6 - CH_3	7 - H	8 - H	9 - H
2a	TFA		8.77	9.30	8.25	8.60	8.76
3A	DMSO-d_6		7.91		7.19	8.02	7.43
2b	DMSO-d_6	9.72 [a]	8.20	9.55	7.57	8.15	7.86
3B=C	DMSO-d_6	11.47 [a]	8.16		7.10	7.95	7.37
1c	DMSO-d_6		8.74	9.32	7.76	8.23	8.08
1C	DMSO-d_6		8.47		7.36	7.99	7.82
1d	DMSO-d_6		8.47	9.22	7.64	8.17	7.96
1D	DMSO-d_6		8.28		7.31	7.90	7.71
2e	DMSO-d_6	7.57 [a]	8.12	9.41	7.49	8.02	8.96
4E	DMSO-d_6	14.30 [a]	7.51		7.58	8.22	7.58
2f	DMSO-d_6	9.61 [a]	8.51	9.57	7.45	7.99	9.00
4G=F	DMSO-d_6	14.20 [a]	8.19		7.52	8.17	7.56
1g	DMSO-d_6		8.55	9.22	7.66	8.15	9.08
1G	DMSO-d_6		8.45		7.32	7.90	8.92
1h	DMSO-d_6		8.81	9.30	7.63	8.14	9.18
1H	DMSO-d_6		8.67		7.28	7.87	8.87

[a] In deuteriochloroform.

Replacement of 4-oxo by 4-imino group (**1c** → **2a**, **1d** → **2b**, **1G** → **2e**, **1h** → **2f**) shifts as expected the signal of C(2)-H considerably, those of C(7)-H, C(8)-H and C(9)-H slightly diamagnetically. In contrast to it and in spite of the electronegativities of the functional groups, the signal of C(6)-H is shifted slightly paramagnetically, presumably due to stronger anisotropic effect of the imino group, compared to that of the oxo group.

In the bicyclic compounds, substitution of hydrogen by methyl (H → CH_3) in position 6 (**1c** → **1C**, **1d** → **1D**, **1g** → **1G**, **1h** → **1H**) gives rise to a relatively large diamagnetic shift on the A ring protons. Since in aromatic compounds, the methyl groups have only a weak influence on the chemical shift, the observed difference can be explained by a steric strain between the methyl and carbonyl groups involving a longer bond between C(4) and N(5), therefore the carbonyl group exerts a smaller influence on the ring protons. A similar bond elongation has been observed by Simon *et al.* [12] in ethyl 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate.

The signal of 6-methyl group of bicyclic compounds appears always at higher δ ppm value than that of the monocyclic compounds due to the higher electronegativity of the ring nitrogen atom, and to the anisotropic effect of the 4-oxo moiety.

The largest differences in the chemical shifts as well as the shapes of proton signals can be observed at (N)-H atoms. In the spectra of the bicyclic 4-imino derivatives **2b**, **2e**, **2f**, the signal is relatively sharp and appears below 10 δ ppm, namely, in those of **2b** and **2f** at a position which is 2 δ ppm higher than in that of **2e** owing to a weak intramolecular hydrogen bond in the former compounds. In the spectra of the monocyclic compounds **3A**, **4E**, **4G=F**, the significantly broadened (N)-H signals appears well over 10 δ ppm, namely in these of **4E** and **4G=F** in a position which is 3 δ ppm higher than in that of **3A** proving once again a very strong intramolecular hydrogen bond in the former compounds. This (N)-H proton can be exchanged to deuterium very slowly, only.

Conclusions.

The conclusions of the infrared and ^{1}H nmr spectral data are summarized in Scheme 2. These data rendered possible to establish if a given compound produced in the reaction of a 2-pyridineacetic acid derivative with an ethoxymethylene malonic acid derivative has a monocyclic or a bicyclic, moreover in the latter case, a 4-oxo or 4-imino structure. Of the three possible monocyclic tautomers having the hydrogen atom at C(1), C(3), or N(5), only this letter one (**3** and **4**) could be detected under the conditions studied by us.

EXPERIMENTAL

The synthesis of the compounds are described in our previous paper [1]. The ir spectra were recorded on a Unicam SP 1200 instrument in potassium bromide pellets, and/or in chloroform solution 1 or 2%. The ^{1}H nmr spectra were recorded on a JEOL JNM PS 100 instrument using 2×10^{-1} *M*/l solutions.

Acknowledgement.

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* Author to whom correspondence should be addressed.

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[2] 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.

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