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Effect of π-Electron Delocalization on Tautomeric Equilibria – Benzoannulated 2-Phenacylpyridines

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Most benzoannulated 2-methylpyridines react with phenyllithium and substituted alkyl benzoates to give the corresponding 2-phenacylpyridines. 3-Methylisoquinoline is transformed into 2-benzoyl-3-methyl-1-phenyl-1,2-dihydroisoquinoline under these conditions, but replacement of phenyllithium with lithium isopropylcyclohexylamide is effective for production of 3-phenacylisoquinolines. Except in the cases of some substituted 6-phenacylphenanthridines, tautomeric mixtures of benzoannulated 2-phenacylpyridines in chloroform solution always contain the ketimine forms. (*Z*)-2-(2-Hydroxy-2-phenylvinyl)pyridine (enolimine) forms also contribute if the pyridine ring is not benzoannulated or if such annulation is at positions 4,5. On the other hand, (*Z*)-2-benzoylmethylene-1,2-dihydropyridine (enaminone) forms exist in equilibrium with the ketimine tautomers if the pyridine ring is benzoannulated at positions 3,4 or 5,6, or at both of these locations. As well as the effectiveness of π-electron delocalization, other effects, such as the strength of the intramolecular hydrogen bonding, should also be considered in order to infer the tautomeric preferences. Strongly electron-donating substituents were found to stabilize the ketimine forms in each series.

Introduction

According to the concept of resonance,[1] π-electron delocalization is a very powerful phenomenon in suitably substituted, and especially in benzoannulated, molecules. This effect is a very important factor affecting the physical and chemical properties of compounds, such as the stabilities of tautomeric species.[2] Experimentally determined tautomeric constants indicate that benzoannulation at positions 3,4 or 5,6 increases the stabilities of 2-pyridone (1*H*-pyridine-2-one) forms, whereas annulation at positions 4,5 shifts tautomeric equilibria towards the 2-hydroxypyridine forms.[3] In solution, *o*-nitrosophenol exists in equilibrium with its *o*-quinone monooxime tautomer.[4,5] On the other hand, only the oxime tautomers of *o*-nitrosonaphthols were found to be present in the gas phase and in solution.[6] The same form [i.e., (benzo)-*o*-quinone monooxime] is present in the solid state.[6–8]

Benzoannulation at positions 5,6 favors *N*-salicylideneamine (solutions in chloroform and acetonitrile) over its NH tautomer [i.e., aminomethylene-1*H*-naphthalene-2-one (2-oxo-1,2-dihydro-naphthylidene-1-amine)].[9] These compounds and some tautomers of 2-acylmethylpyridines contain structurally similar fragments. 2-Phenacylpyridines (**1K**, Scheme 1) and their 5,6-benzo derivatives (**3K**) do not usually appear in the solid (crystal) state,[10,11] while more stable tautomers [i.e., (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines (**1O**) and (*Z*)-2-benzoyl-methylene-1,2-dihydropyridines (**3E**)], are observed there.[10,11] In chloroform solution 2-phenacylpyridines (ketimines) substituted in the benzene ring exist in equilibrium with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines (enolimines) stabilized by the intramolecular hydrogen bond.[10]

NMR studies show that 2-phenacylquinolines (ketimines) coexist in chloroform with similarly stabilized (*Z*)-2-benzoylmethylene-1,2-dihydroquinolines (this enaminone tautomer prevails independently of substitution present in the benzoyl moiety).[11] DMSO solution contains exclusively (*Z*)-6-(*p*-nitrobenzoyl)-methylene-5,6-dihydrophenanthridine [no 6-(*p*-nitrophenacyl)phenanthridine (**5K**, $R^7 = NO_2$) was detected].[12] 3-(*p*-Methylphenacyl)isoquinoline (ketimine) definitely predominates over (*Z*)-3-(2-hydroxy-2-phenylvinyl)isoquinoline (enolimine) in chloroform solution.[13] In DMSO solution, 1-(*p*-methylphenacyl)isoquino-

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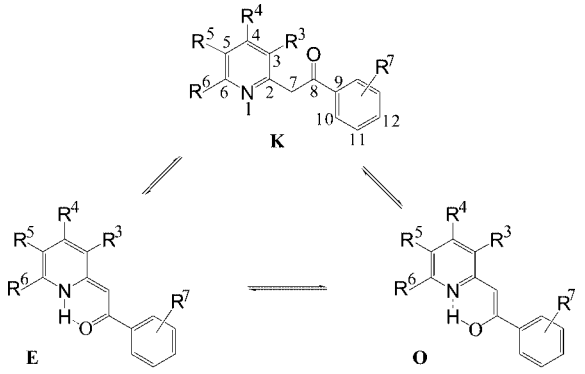


Series	R^3	R^4	R^5	R^6
1	H	H	H	H
2	H	benzo		H
3	H	H	benzo	
4	benzo		H	H
5	benzo		benzo	

R^7 = *p*-N(CH$_2$)$_4$, *p*-NMe$_2$, *p*-OCH$_3$, *p*-CH$_3$, H, *p*-Cl, *p*-Br, *m*-F, *p*-CF$_3$,

Scheme 1.

line (**4K**, R^7 = Me) was found to exist in tautomeric equilibrium with (*Z*)-1-(*p*-methylbenzoylmethylene)-1,2-dihydroisoquinoline (**4E**, R^7 = Me), previously erroneously formulated as (*Z*)-1-(2-hydroxy-2-*p*-methylphenylvinyl)isoquinoline (**4O**, R^7 = Me).[14] It is also known that (1*Z*,3*Z*)-1,4-bis(pyridin-2-yl)buta-1,3-diene-2,3-diol (enediol) coexists with (3*Z*)-3-hydroxy-1,4-bis(pyridin-2-yl)but-3-en-2-one (ketimine-enolimine)[15] but dibenzoannulation is responsible for the exclusive presence of (3*Z*)-3-hydroxy-1,4-bis(quinolin-2-yl)but-3-en-2-one in chloroform solution.[16] Although these observations show that benzoannulation of 2-(acylmethyl)pyridines affects the tautomerism, the relative stabilities of different tautomers present in solution are not known. This prompted us to study the tautomeric equilibria of phenacyl derivatives of pyridine, quinoline, isoquinoline, and phenanthridine, and to find out how the presence and location of benzene ring(s) in the molecules affects the populations of the various tautomeric species of 2-phenacylpyridines.

Results and Discussion

Low energy barrier rearrangements (reversible processes) enable different isomeric species (e.g., tautomers) to exist in equilibrium. This dynamics may involve only two species, but very often the number of interconverting compounds is higher. Although there should be no doubt about high contributions of more stable isomers, there are no definite known rules to evaluate their stability. Different effects such as steric and electronic (inductive and resonance) interactions have to be considered when looking for the labile tautomers. 2-Phenacylpyridines exist in equilibrium (solution in chloroform) with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines, the corresponding enolimine forms.[10] Benzoannulation of the pyridine ring in these compounds affects the tautomeric equilibria both qualitatively and quantitatively.[11] For the latter compounds a question arises regarding the contribution of electron delocalization to increased stability of the (*Z*)-2-benzoylmethylene-1,2-dihydroquinolines, the enaminone tautomers of 2-phenacylquinolines.[10,11] To discover whether the resonance effect is really responsible for this increased stability of the enaminone forms (and their increased contributions to the tautomeric mixtures), different benzoannulated 2-phenacylpyridines were studied.

Synthesis and Identification of Tautomers

Naming of compounds exhibiting tautomerism can be somewhat problematic. Substituted (*Z*)-2-benzoylmethylene-1,2-dihydroquinolines **3E** are the only species present in the crystalline state,[11] whereas 2-phenacylpyridines **1K** and (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines **1O** have been detected when strongly electron-donating or electron-withdrawing substituents, respectively, are present in the molecule.[10] Since no X-ray results are available for the solid phenacyl derivatives of phenanthridine and isoquinoline (the tautomer appearing in the solid product is not known), double names (i.e., these of the potential tautomers) are used in this paper for the solid reaction products. The species present in solution were identified, so they are named properly.

2-Phenacylpyridines/(*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines and 2-phenacylquinolines/(*Z*)-2-benzoylmethylene-1,2-dihydroquinolines were prepared by treatment of picolyllithium (2-lithio-methylpyridine) or quinaldyllithium (2-lithiomethylquinoline) with substituted ethyl or methyl benzoates.[10,11] 1-Phenacylisoquinolines/(*Z*)-1-benzoylmethylene-1,2-dihydroisoquinolines, 3-phenacylisoquinolines/(*Z*)-3-(2-hydroxy-2-phenylvinyl)isoquinolines, and 6-phenacylphenanthridines/(*Z*)-6-benzoylmethylene-5,6-dihydrophenanthridines were obtained in a similar manner (see Exp. Sect. and Table 1 for details). It is noteworthy that other synthetic methods for these compounds are also known: 1-phenacylisoquinoline can be prepared by treating 1-methylsulfonylisoquinoline[17] or 1-chloroisoquinoline[18] with sodium amide and acetophenone, as well as by addition of water to 1-ethynylisoquinoline.[19] Reductive debenzoylation of 2-benzoyl-1-phenacyl-1,2-dihydroisoquinoline also affords 1-phenacylisoquinoline.[20] Some of its substituted derivatives can also be obtained from 1-methylisoquinoline when treated with phenyllithium and substituted benzonitrile,[14] with *p*-nitrobenzoyl cyanide[12] or with aryl- or alkyllithium and substituted alkyl benzoates.[21] 3-Phenacylisoquinoline can be prepared by addition of water to 3-ethynylisoquinoline.[19,22] 3-Methylisoquinoline can also be transformed into 3-phenacylisoquinoline by treatment with lithium isopropylcyclohexylamide and benzonitrile,[13] while 6-(*p*-nitrophenacyl)phenanthridine has been obtained from 6-methylphenanthridine and *p*-nitrobenzoyl cyanide.[12]

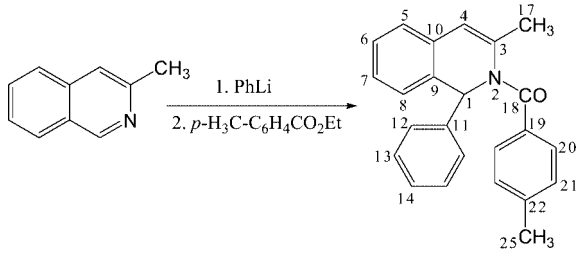
Table 1. Synthetic and physical data.

Series/R^7	Alkyl[a]	Method[b]	Yield (%)	M.p. (°C)
2*l*/*p*-$N(CH_2)_4$	Et	–	12	248–250
2*l*/*p*-CH_3	Et	–	22	120–122[c]
4*l*/*p*-$N(CH_2)_4$	Et	B	69	169–170
4*l*/*p*-NMe_2	Et	B	62	131–133
4*l*/*p*-CH_3	Et	A	8	98–100
4*l*/*p*-Br	Et	A	21.5	147–149[d]
4*l*/*p*-CF_3	Me	A	16.5	153–155
5*l*/*p*-$N(CH_2)_4$	Et	–	80	235–237
5*l*/*p*-NMe_2	Et	–	10.5	204–210
5*l*/*p*-OCH_3	Et	–	76	245–247
5*l*/*p*-CH_3	Et	–	13	97–99
5*l*/H	Et	–	12.5	131–134
5*l*/*p*-Cl	Me	–	12.5	153–159
5*l*/*m*-F	Et	–	12	167–172
5*l*/*p*-CF_3	Me	–	14	200–202

[a] In substrate, i.e. *p*-substituted alkyl benzoate (see Exp. Sect.). [b] See Exp. Sect. for details. [c] Literature m.p. 106–110 °C.[13] [d] Yellow oil, according to Gnichtel and Möller.[14]

The general synthetic strategy for 1-methylisoquinoline (for use in syntheses of 1-phenacylisoquinolines) was in principle that of Schlittler and Müller.[23] 1-Phenylethylamine was condensed with dimethoxyacetaldehyde [$(MeO)_2$-CHCHO; originally diethoxyacetaldehyde was used],[23] and the obtained (2,2-dimethoxyethylidene)-(1-phenylethyl)-amine [Ph–$CH(CH_3)$N=$CHCH(OMe)_2$] was cyclized under acidic conditions.

Successive treatment of 3-methylisoquinoline with phenyllithium and ethyl *p*-methylbenzoate gave 3-methyl-2-(*p*-methylbenzoyl)-1-phenyl-1,2-dihydroquinoline (Scheme 2 and Exp. Sect.). The molecular structure of this unexpected reaction product was confirmed by NMR and X-ray crystallography.[24] It is known that similar treatment of 3-methylisoquinoline with lithium isopropylcyclohexylamide and *p*-toluonitrile gives 3-(*p*-methylphenacyl)isoquinoline in low yield.[13]



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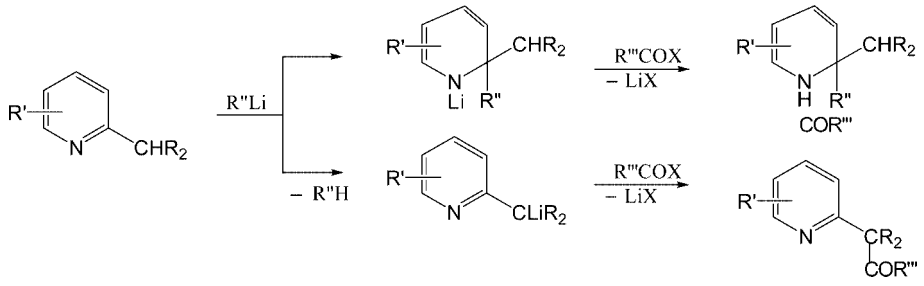
Scheme 2.

The formation of different products in these reactions had also been observed previously. Organolithium compounds can add to the azomethine linkages in pyridine or its benzo derivatives[25] and substitution of the lithium atom in the reaction product allows 2-substituted 1,2-dihydropyridines to be prepared.[25] Although 2-alkylpyridines may undergo similar reactions, lithiation may also take place at the alkyl group,[25] so in 2-alkylpyridines there is competition between lithiation at the ring nitrogen or at the *exo* carbon atom.[25] In consequence, acylation of the lithium byproducts produces 1-acyl-1,2-dihydro- and 2-(acylmethyl)pyridines, respectively (Scheme 3).[25]

The ability of a methyl group to react with an organolithium compound (R–CH_3 + R′Li → R–CH_2Li + R′H) is governed by the acidity of the methyl hydrogen atoms.[25a] It is well known that 2-methylpyridine, 2-methylquinoline, 1-methylisoquinoline, and 6-methylphenathridine undergo *C*-lithiation.[11,25–27] 1-Aryl-2-benzoyl-1,2-dihydroisoquinolines (Reissert-type compounds) can be obtained by treatment of isoquinoline with arylmagnesium halide and benzoyl chloride[28] or, in some special cases, of 2-arylbenzoylisoquinolinium salts with *N*,*N*-dialkylanilines.[29,13] The activity of the methyl group in 3-methylisoquinoline when treated with lithium isopropylcyclohexylamide and *p*-toluonitrile has been demonstrated through the formation of 3-(*p*-methylphenacyl)isoquinoline in low yield.[13] It should be mentioned, however, that a different acylmethyl derivative of this type, 2-isoquinolin-3-ylindan-1,3-dione, was obtained through the action of phthalic anhydride on 3-methylisoquinoline itself.[30]

Effect of Substituents and Temperature on the Contents of Tautomeric Mixtures

The integrated intensities of 7-H signals in the ^{1}H NMR spectra were used to calculate the contents of the different forms in solution.[10,11] As can be seen in Table 2, the tautomeric mixtures, except in the cases of some congeners in series **5**, always contain the **K** forms, which coexist with the **O** forms if the pyridine rings are not benzoannulated (series **1**) or if such annulation is at positions 4,5 (series **2**). On the other hand, the **E** forms exist in equilibrium with the **K** tautomers if the pyridine rings are 3,4- (series **4**) or



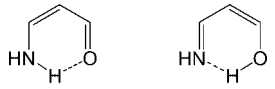
Scheme 3.

5,6-benzoannulated (series **3**), or if benzoannulation is present at both of these positions (series **5**). One should keep in mind that 6-phenacylphenanthridine, owing to the presence of two nonequivalent benzene rings in its system, has structural fragments similar to both benzoannulated 2-phenacylquinoline and 1-phenacylisoquinoline. There is a question as to how the benzene ring(s) in the molecule influence(s) the contributions of different species in solution. π-Electron delocalization has been found to be responsible for tautomeric preferences in numerous cases,[2] but other effects, such as strengths of intramolecular hydrogen bonds, should also be taken into account. Theoretical calculations[32] indicate that the hydrogen bond in **7O** (Scheme 4) is considerably stronger than that in **7E**, so the strength of this bond is responsible for the higher stability of **1O** and **2O** relative to **1E** and **2E**.

Table 2. **K** form contents (%)[a] (solutions in chloroform, 303 K).

R^7	Series **1** [b,c]	**2**[b]	**3**[d,e]	**4** [d]	**5** [d]
p-$N(CH_2)_4$	99.0	≥ 99	39.3[f]	48.2	4.0
p-NMe_2	95.7	–	33.0	26.3	2.0
p-NH_2	90.8	–	24.6	–	–
p-OMe	84.8	–	11.1	–	1.2
p-Me	72.5	60.7[g]	6.7	5.2	0.0
m-Me	64.4	–	4.8	–	–
H	58.1	–	4.7	–	0.0
p-F	56.8	–	4.2	–	–
p-Br	50.6	–	2.1	2.5	–
p-Cl	45.5	–	2.2	–	0.0
m-F	34.0	–	1.8	–	0.0
m-Br	32.5	–	1.5	–	–
p-CF_3	18.6	–	1.0	1.5	0.0
p-NO_2	7.8	–	–	–	–

[a] Based on integral intensities of 7-H signals in the ^{1}H NMR spectrum, accuracy: ±0.5%. [b] Another tautomer present: **O**. [c] Ref.[10] [d] Another tautomer present: **E**. [e] Ref.[11] [f] Ref.[31] [g] 60.6% based on intensities of 6-H signals.



7E **7O**

Scheme 4.

On the other hand, although intramolecular hydrogen bonding in **3E**, **4E**, and **5E** is much weaker than in the corresponding enolimine tautomers, π-electron delocalization in these molecules is very effective. Electron-withdrawing substituents increase the acidic character of methylene hydrogen atoms in the **K** forms and in consequence their transfer to the *aza* atoms in these compounds is easier. If the pyridine ring is not annulated in the correct position (series **3**–**5**), the formed tautomer **O** is not very stable and it is transformed into **E**.

It can be seen (Table 2) that the dependence of **K** (%) (content of the **K** form) on substitution is of the same nature in each series: electron-withdrawing substituents decrease the amount of ketimine form in the tautomeric mixtures. In general, the populations of this tautomer are lower for quinolin-2-yl and isoquinolin-1-yl derivatives than for pyridin-2-yl and isoquinolin-3-yl derivatives and are exceptionally low for dibenzoannulated (i.e., phenanthridin-6-yl) derivatives (these compounds are both benzoannulated quinolin-2-yl and isoquinolin-1-yl derivatives).

When dissolved in chloroform, 2-phenacylpyridines exist in equilibrium with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines.[10] The character of the substituent on the benzene ring significantly affects the tautomeric equilibrium [the amounts of the enolimine forms stabilized by intramolecular hydrogen bonding are 1% for R = *p*-$N(CH_2)_4$ and 92% for *p*-NO_2]. The negative logarithm of the tautomeric equilibrium constant (K_T) is linearly dependent on the Hammett σ substituent constants;[10] the dependence of K_T on temperature is exponential: the more electron-withdrawing the substituent, the more distinct is the influence of temperature.[10] The reaction **K** → **O** is exothermic for all pyridin-2-yl derivatives except for those bearing strongly electron-donating substituents.[10]

NMR studies (Table 3) show that 2-phenacylquinolines coexist in chloroform solutions with the (*Z*)-enaminone forms, stabilized by intramolecular hydrogen bonding (these tautomers prevail for all substituents studied).[11] Electron-donating substituents in the phenacyl part of the molecule increase the amount of the ketimine form (Table 2).[11,31] Variable-temperature ^{1}H NMR measurements show that higher temperatures have the same effect.[11] The negative logarithm values of the equilibrium constants (pK_T) were found to be linearly dependent on Hammett σ substituent constants for these equilibria; pK_T vs. temperature correlation has linear character.[11] In general, strongly electron-withdrawing substituents cause transformation from the ketimine to enaminone forms to become more exothermic, but the values of the heats of reaction for the 2-phenacylquinolines studied are not linearly dependent on σ.[11]

The data collected in Table 4 show that reductions in the temperatures of chloroform solutions of 1-phenacylisoquinolines decrease the **K** form contents, so this temperature effect on the contribution of the ketimine tautomer **K** is of the same type as that observed for solutions of 2-phenacylpyridines bearing electron-donating substituents.[10] On the other hand, the amounts of the **K** forms increase with reductions in temperature both for solutions of 2-phenacylpyridines bearing electron-withdrawing substituents[10] and for 2-phenacylquinolines.[11]

It is noteworthy that the "non-aromatic" tautomer **E** (Scheme 5) would not be expected to be preferred for isoquinolin-3-yl derivatives (and indeed, this form was not detected in chloroform solution).

The contributions of different tautomeric forms (**K**, **O**, and **E**) can be evaluated by comparing the integrated intensities of their H7 signals in the ^{1}H NMR spectra of the tautomeric mixtures (Table 4). These numbers enable the calculation of the relative experimental energies of the tautomers.[10,11] For the **K** form in series **4** the following results were obtained: 8.4, 8.7, 16.5, and 21.6 kJ mol^{-1} for R^7 = 4-$N(CH_2)_4$, 4-NMe_2, 4-Me, and 4-Br, respectively (energy with respect to form **4E**), so it can be seen that the **K** form

Table 3. Selected ^{1}H, ^{13}C, and ^{15}N NMR chemical shifts (δ) of 1-phenacylisoquinolines, 3-phenacylisoquinolines, 6-phenacylphenanthridines, and their tautomers for 0.1–0.2 M solutions in $CDCl_3$ at 303 K.[a]

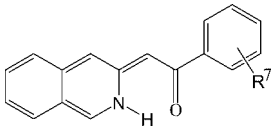
Tautomer	N**H** or O**H**	7-H	7-C	8-C	1-N
2K/*p*-N$(CH_2)_4$	–	4.55	47.59	195.15	–69.2
2K/*p*-Me	–	4.60	48.01	196.89	–73.1
2O/*p*-Me	14.41	6.20	95.10	160.07	–105.6
4K/*p*-N$(CH_2)_4$	–	4.90	46.64	194.23	–72.6
4E/*p*-N$(CH_2)_4$	15.99	6.71	83.58	184.64	–234.2
4K/*p*-NMe_2	–	4.90	46.55	194.29	–72.7
4E/*p*-NMe_2	16.02	6.74	83.61	184.35	–233.7
4K/*p*-Me	–	4.97	46.50	[b]	–72.1
4E/*p*-Me	16.19	6.75	84.62	184.29	–229.3
4K/*p*-Br	–	5.00	[b]	[b]	[b]
4E/*p*-Br	16.31	6.75	85.22	182.18	–226.4
4K/*p*-CF_3	–	4.97	[b]	[b]	[b]
4E/*p*-CF_3	16.21	6.69	84.57	182.73	–228.2
5K/*p*-N$(CH_2)_4$	–	5.00	[b]	[b]	–73.7
5E/*p*-N$(CH_2)_4$	15.63	6.77	84.4	186.89	–250.5
5K/*p*-NMe_2	–	4.98	[b]	[b]	–73.5
5E/*p*-NMe_2	15.65	6.76	84.54	186.78	–250.1
5K/*p*-OMe	–	4.99	[b]	[b]	[b]
5E/*p*-OMe	15.67	6.69[c]	84.66	186.20	–247.8
5E/*p*-Me	15.83	6.80[c]	85.14[d]	187.06	–246.9
5E/H	15.87	6.81[c]	85.34	187.11	–246.2
5E/*p*-CF_3	15.93	6.75	85.43	184.95	–243.9
5E/*p*-Cl	15.89	6.77	85.05	185.55	–245.4
5E/*m*-F	15.88	6.76	85.22	185.24	–244.9

[a] See refs.[10,11] respectively, for the corresponding chemical shifts in the series **1** and **3**. [b] These signals were not found due to low amounts of the tautomeric form in question. [c] There is a very weak signal for 7-H in the **K** form at about 5 ppm. [d] There is a very weak signal for 7-C in the **K** form at about 45 ppm.

Table 4. 1-Phenacylisoquinoline **4K** contents (%)[a] in chloroform solutions at different temperatures.

Temp. (K)	*p*-N$(CH_2)_4$	*p*-NMe_2	*p*-Me	*p*-Br
303	48.2	26.3	5.2	–
293	44.6	23.9	4.2	2.5
283	42.2	20.7	3.4	1.9
273	38.7	18.4	2.5	1.4
263	35.6	16.3	1.8	0.9
253	31.9	13.1	1.2	0.6
243	31.6	10.7	0.7	–

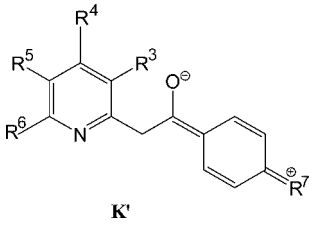
[a] Based on integral intensities of 7-H signals in ^{1}H NMR spectrum. Accuracy: ±0.5%.



Scheme 5.

is only slightly less stable than the **E** form for strongly electron-donating substituents in this series (experimental results confirm this conclusion). Since lower temperatures favor the **E** form, reaction **K** → **E** has an exothermic character. Insignificant effects of temperature on the ^{1}H NMR spectra show that **5E** is much more stable than **5K** (not the case in other series).

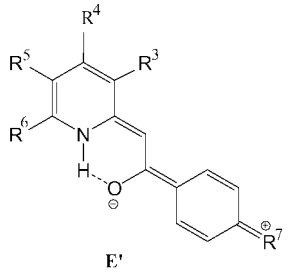
It can be seen (Table 2) that the presence of electron-donating substituents in the phenacyl part of the molecule favors the **K** form (Scheme 6). The pyridine ring in this tautomer still has an aromatic character.



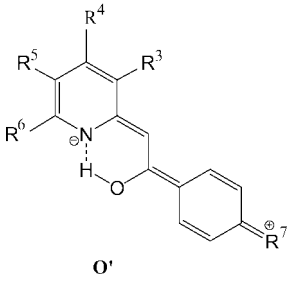
K'

Scheme 6.

Notwithstanding that the forms **E** and **O** are stabilized by intramolecular hydrogen bonds, those carrying electron-donating substituents are not stable because neither the pyridine nor the benzene rings in these molecules are aromatic (Scheme 7).



E'



O'

Scheme 7.

Conclusions

Benzoannulation affects the prototropic tautomerism of 2-phenacylpyridines. Except in the cases of some substituted 6-phenacylphenanthridines, tautomeric mixtures of benzoannulated 2-phenacylpyridines in chloroform solutions always contain the ketimine forms, coexisting with (*Z*)-2-(2-hydroxy-2-phenylvinyl)pyridines (enolimine forms) if the pyridine ring is not benzoannulated or if such annulation is at positions 4,5. On the other hand, (*Z*)-2-benzoylmethylene-1,2-dihydropyridines exist in equilibrium with ketimine forms if the pyridine ring is annulated at positions 3,4 or 5,6, or at both of these positions. Besides π-electron delocalization in these molecules, other contributions, such as the strengths of intramolecular hydrogen

bonds, should also be considered in order to infer tautomeric preferences. The dependence of the ketimine form content on substitution is of the same nature in each series: electron-withdrawing substituents decrease the amount of ketimine forms in the tautomeric mixtures. On the other hand, strongly electron-donating substituents stabilize the ketimine forms. In general, the contributions of this tautomer are lower for quinolin-2-yl and isoquinolin-1-yl derivatives than for pyridin-2-yl and isoquinolin-3-yl derivatives and are the lowest for dibenzoannulated (i.e., phenanthridin-6-yl) derivatives. The transformation of the ketimine into the enaminone form is exothermic in character and strongly electron-withdrawing substituents enhance this effect. Electron-withdrawing substituents increase the acidic character of the methylene hydrogen atoms in the ketimine forms and facilitate their transfer to the aza atoms.

Experimental Section

Syntheses

Ethyl *p*-(Pyrrolidino)benzoate: A solution of ethyl *p*-fluorobenzoate (3.36 g, 20 mmol) and pyrrolidine (4.26 g, 60 mmol) in DMSO (35 mL) was stirred at 95 °C for 24 h and then poured into water (700 mL). The product was extracted with ethyl ether, the extract was dried (K_2CO_3), and the solvent was evaporated to provide the solid, which after crystallization from ethanol melts at 114–116 °C (literature m.p. 103–104 °C).[33] Yield 3.81 g (87%).

(2,2-Dimethoxyethylidene)-(1-phenylethyl)amine: Toluene (200 mL) and 1-phenylethylamine (50 mL, 47.00 g, 0.39 mol) were added to a solution of dimethoxyacetaldehyde in water (60%, 67 mL, 77.05 g, 0.44 mol, Aldrich) and the obtained mixture was heated under nitrogen in a flask fitted with a Dean–Stark trap until 37 mL of water had been collected, after which 73.70 g (92%) of a product boiling at 135–145 °C/1 Torr was collected. $C_{12}H_{17}NO_2$ (207.27): calcd. C 69.53, H 8.27, N 6.76; found C 69.31, H 8.49, N 6.54.

1-Methylisoquinoline: Concd. sulfuric acid (168.6 mL) was added dropwise at 0 °C to (2,2-dimethoxyethylidene)(1-phenylethyl)amine (32.60 g, 0.16 mol), the contents of the flask (fitted with a reflux condenser) being stirred magnetically during addition. At the beginning the reaction mixture was so viscous that stirring was not efficient and shaking of the flask by hand was necessary. More acid (281 mL) was then added in one portion at room temperature and the flask was heated until the temperature of the reaction mixture reached 160 °C. After two more minutes at this temperature the contents of the flask were poured into crushed ice (400 g), made basic with concd. aqueous sodium hydroxide, and steam distilled. The distillate was extracted with ethyl ether and dried (Na_2CO_3) to provide 1-methylisoquinoline (13.74 g, 61%, b.p. 114–115 °C/8 Torr, literature b.p. 81 °C/1 Torr)[34,35] after evaporation of the solvent and distillation of the residue.

6-Methylphenanthridine: A known synthetic method was used.[36] After recrystallization from heptane the product melted at 82–83 °C (literature m.p. 84 °C).[36]

3-Phenacylisoquinolines/(*Z*)-3-(2-Hydroxy-2-phenylvinyl)isoquinolines (2): A solution of 3-methylisoquinoline (1.0 g, 7.0 mmol, Aldrich) in dry ether (40 mL) was added slowly at –78 °C under nitrogen to a freshly prepared solution of lithium isopropylcyclohexylamide (from 1.18 mL, 1.02 g, 7.30 mmol of distilled isopropylcyclohexylamine in 50 mL of dry ether and 1.8 mL of a 2 M solution of *n*-butyllithium in *n*-hexane). After 1 h the substituted alkyl benzoate (7.2 mmol) was added to the flask and the reaction mixture was allowed to warm to room temperature overnight. It was then worked up by addition of water (60 mL) and extraction with ether. The extracts were dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by column chromatography [silica gel (230–400 mesh), eluent: *n*-hexane/ethyl acetate, 3:1] and recrystallized from ethanol.

p-N(CH$_2$)$_4$: $C_{21}H_{20}N_2O$ (316.39): calcd. C 79.71, H 6.37, N 8.86; found C 79.41, H 6.49, N 8.99.

p-CH$_3$: $C_{18}H_{15}NO$ (261.31): calcd. C 82.73, H 5.79, N 5.36; found C 82.63, H 5.59, N 5.24.

1-Phenacylisoquinolines/(*Z*)-1-Benzoylmethylene-1,2-dihydroisoquinolines (4). Method A: Phenyllithium was obtained by heating a magnetically stirred reaction mixture containing lithium (0.1 g, 13 mmol) and freshly distilled bromobenzene (1.0 g, 6.5 mmol) at reflux in absolute diethyl ether (40 mL, standard procedure: the reflux condenser was equipped with a $CaCl_2$ tube and the reaction was usually initiated by addition of 1–2 crystals of iodine). The obtained solution was treated dropwise with 1-methylisoquinoline (0.83 g, 5.8 mmol) and heated at reflux for ca. 1 h to provide 1-methylisoquinolyllithium (1-methyllithioisoquinoline). The substituted alkyl benzoate (5.8 mmol) diluted with absolute ethyl ether (5 mL) was then added to the reaction vessel and the obtained mixture was heated at reflux for 1 h. The reaction was quenched by addition of water (20 mL), the product was extracted from the water layer with ether, the combined extracts were dried (K_2CO_3), and the ether was evaporated to provide the solid, which was usually recrystallized twice from ethanol.

Method B: A solution of *n*-butyllithium in *n*-hexane (2 M, 4.0 mL, 8.0 mmol) was added (by syringe) to a stirred solution of 1-methylisoquinoline (1.02 g, 7.2 mmol) in dry ethyl ether (45–50 mL) under nitrogen atmosphere (the reaction mixture was cooled with an ice/salt bath during addition). After 30 min a saturated solution of the substituted alkyl benzoate (7.2 mmol) in dry ethyl ether was added dropwise to the flask. The cooling bath was removed after 1 h and the contents of the flask were stirred for another 2–3 h. Water (50 mL) was then slowly added to the reaction mixture with stirring. The organic layer was then combined with the ether extract of the aqueous phase and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by column chromatography [silica gel (230–400 mesh), toluene/acetone (10:1) or hexane/ethyl acetate (9:1)] and recrystallized from ethanol.

p-N(CH$_2$)$_4$: $C_{21}H_{20}N_2O$ (316.39): calcd. C 79.71, H 6.37, N 8.86; found C 79.69, H 6.47, N 8.59.

p-NMe$_2$: $C_{19}H_{18}N_2O$ (290.35): calcd. C 78.59, H 6.25, N 9.65; found C 78.31, H 5.99, N 9.56.

p-CH$_3$: $C_{18}H_{15}NO$ (261.31): calcd. C 82.73, H 5.79, N 5.36; found C 82.53, H 5.50, N 5.16.

p-Br: $C_{17}H_{12}BrNO$ (326.20): calcd. C 62.59, H 3.71, N 4.29; found C 62.72, H 3.90, N 4.01.

p-CF$_3$: $C_{18}H_{12}F_3NO$ (315.20): calcd. C 68.59, H 3.81, N 4.44; found C 68.68, H 3.81, N 4.66.

6-Phenacylphenanthridines/(*Z*)-6-Benzoylmethylene-5,6-dihydrophenathridines (5): These compounds were prepared similarly to 1-phenacylisoquinolines (Method A; 6-methylphenathridine was used instead of 1-methylisoquinoline). The product was extracted from the water layer with chloroform, the combined extracts (diethyl ether + chloroform) were dried with Na_2SO_4, and the solvents

were evaporated to provide the solid, which was usually recrystallized twice from ethanol.

p-N(CH$_2$)$_4$: $C_{25}H_{22}N_2O$ (366.45): calcd. C 81.93, H 6.05, N 7.65; found C 81.66, H 5.83, N 7.38.

p-NMe$_2$: $C_{23}H_{20}N_2O$ (340.43): calcd. C 81.14, H 5.92, N 8.23; found C 80.91, H 6.17, N 8.02.

p-OCH$_3$: $C_{22}H_{17}NO_2$ (327.37): calcd. C 80.71, H 5.24, N 4.28; found C 80.60, H 5.25, N 4.49.

p-CH$_3$: $C_{22}H_{17}NO$ (311.37): calcd. C 84.86, H 5.50, N 4.50; found C 84.63, H 5.45, N 4.74.

H: $C_{21}H_{18}NO$ (300.36): calcd. C 83.97, H 6.04, N 4.66; found C 83.69, H 6.29, N 4.63.

p-Cl: $C_{21}H_{14}ClNO$ (331.79): calcd. C 76.01, H 4.25, N 4.22; found C 76.12, H 4.03, N 4.01.

m-F: $C_{21}H_{14}FNO$ (315.33): calcd. C 79.98, H 4.47, N 4.44; found C 79.89, H 4.26, N 4.22.

p-CF$_3$: $C_{22}H_{14}F_3NO$ (365.34): calcd. C 72.32, H 3.86, N 3.83; found C 72.52, H 3.94, N 3.63.

3-Methyl-2-(*p*-methylbenzoyl)-1-phenyl-1,2-dihydroisoquinoline (6): A solution of 3-methylisoquinoline (Aldrich, 7.0 mmol) in absolute ethyl ether (10 mL) was added dropwise with stirring to a solution of phenyllithium [obtained by a standard method from freshly distilled bromobenzene (1.57 g, 10 mmol), absolute diethyl ether (50 mL), and lithium (0.14 g, 20 mmol)]. The reaction mixture was stirred at room temperature for an additional 2 h. Ethyl benzoate (7.0 mmol) diluted with absolute ethyl ether (5 mL) was then added to the reaction vessel and the obtained mixture was heated at reflux for 2 h. The reaction was quenched by addition of water (20 mL), the product was extracted from the water layer with ether, the combined extracts were dried (K_2CO_3), and the ether was evaporated to provide the crude solid product. This was purified by column chromatography [silica gel (230–400 mesh), toluene/ethyl acetate (20:1)] and recrystallized from the eluent. Yield 0.16 g (11%), m.p. 170–172 °C. ^{1}H NMR ($CDCl_3$): δ = 7.53 (t, 1 H, 14-H), 7.20–7.35 (m, 12 H, 5-H, 6-H, 7-H, 8-H, 12-H, 13-H, 20-H, 21-H), 6.79 (s, 1 H, 1-H), 6.07 (s, 1 H, 4-H), 2.39 (s, 3 H, 17-H), 1.62 (s, 1 H, 25-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 169.80 (18-C), 141.40 (22-C), 140.39 (11-C), 135.68 (3-C), 133.98 (19-C), 132.93 (10-C), 131.69 (9-C), 129.02 (21-C), 128.38 (20-C), 128.05 (12-C), 127.87 (14-C), 127.12 (13-C), 127.23, 126.96, 126.80 (6-C, 7-C, 8-C), 124.65 (5-C), 115.88 (4-C), 58.88 (1-C), 22.64 (17-C), 21.47 (25-C) ppm. ^{15}N NMR ($CDCl_3$): δ = –240.7 (2-N) ppm. $C_{24}H_{21}NO$ (339.42): calcd. C 84.92, H 6.24, N 4.13; found C 84.63, H 5.99, N 4.34.

NMR Spectroscopy

^{1}H, ^{13}C, and PFG ^{1}H,^{13}C HMQC and HMBC spectra were recorded with dilute $CDCl_3$ solutions in a 5-mm sample tube at 30 °C on a Bruker Avance DRX 500 spectrometer fitted with an inverse detection probehead and *z*-gradient accessory working at 500.13 MHz and 125.77 MHz, respectively.

In ^{1}H NMR experiments the number of data points was 64 K, giving a spectral resolution of 0.05 Hz, the number of scans was 8, and the flip angle was 30°. An exponential window function of the spectral resolution was used prior to FT. The ^{1}H NMR chemical shifts are referenced to the signal of residual [D$_5$]DMSO (δ = 2.50 ppm from TMS).

In ^{13}C experiments the number of data points was 32 K, giving a spectral resolution of 0.5 Hz, the number of scans varied between 1000–10000 depending on the case, and the flip angle was 30°. A composite pulse decoupling (Waltz-16) was used to remove proton couplings. An exponential window function of the spectral resolution was used prior to FT. The ^{13}C NMR chemical shifts are referenced to the central peak of the solvent [D$_6$]DMSO (δ = 39.50 ppm from TMS).

The number of data points in PFG ^{1}H,^{13}C HMQC and HMBC measurements was 1024 (f_2) × 256 (f_1). This matrix was zero-filled to 2048 × 512 and apodized by a shifted sine bell window function along both axes prior to FT.

In PFG ^{1}H,^{15}N HMBC experiments a 100 ms delay was used for evolution of long-range couplings. The number of data points was 1024 (f_2) × 512 (f_1: ^{15}N). This matrix was zero-filled to 2048 × 1024 and apodized by a shifted sine bell window function along both axes prior to FT.

^{15}N NMR chemical shifts are referenced to the signal of external CH_3NO_2 (δ = 0.0 ppm) in a capillary (1 mm diameter) inserted coaxially within an NMR tube with 5 mm diameter. All acquisition and processing parameters are available from E. K. on request.

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