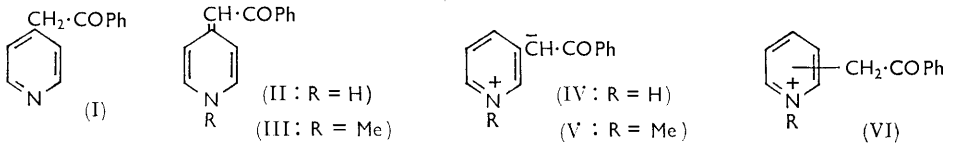
568. *Potentially Tautomeric Pyridines. Part VI.*[1] 2-, 3-, *and* 4-*Phenacylpyridines*

By A. R. Katritzky, H. Z. Kucharska, and J. D. Rowe

Basicity and spectral measurements of the phenacylpyridines and the corresponding *N*-alkylated anhydro-bases indicate that, although the former exist mainly as such in aqueous solutions, appreciable amounts of the tautomers are also present. In some polar solvents, 3- and 4-phenacylpyridine exist essentially as ketones but, for the 2-isomer, appreciable amounts of chelated enol occur. The present results are related to those for other potentially tautomeric pyridines.

The present Paper reports the tautomerism of the phenacylpyridines (I) ⇌ (II) and discusses the results together with those of the isomeric acylamino-,[2] sulphonylamino-,[3] and phenylsulphonylmethyl-pyridines.



Preparation of Compounds.—2-, 3-, and 4-Phenacylpyridines were prepared by literature methods [4-6] and converted into their respective methiodides in methanol. The anhydro-bases were prepared by ion-exchange techniques except that the 3-isomer could only be obtained as an ethanolic solution.

Basicity Measurements (Table 1).—Making the usual assumption that an *N*-methyl group will not appreciably affect the basicity, the results show that the picolyl ketone

TABLE 1

p*K* Values

Compound	Concn. (10^{-3}M)	Wavelength (mμ)	pK_a	Standard deviation
2-Phenacylpyridine (proton addn.)	3·61	262	5·03	±0·04
,, (proton loss)	4·32	350	13·27	±0·02
2-Phenacylpyridine methiodide	1000	—	7·38 *	±0·02
3-Phenacylpyridine (proton addn.)	1000	—	4·87 *	±0·03
,, (proton loss)	5·68	343	13·71	±0·05
3-Phenacylpyridine methiodide	3·42	354	11·18	±0·05
4-Phenacylpyridine (proton addn.)	1000	—	4·93 *	±0·03
,, (proton loss)	4·96	353	12·46	±0·03
4-Phenacylpyridine methiodide	1000	—	7·58 *	±0·02

* The determination was done by potentiometric titration using an E.I.L. model 23A direct-reading pH meter. Other results were obtained on a Unicam S.P. 500 spectrophotometer with 0·1M-potassium dihydrogen phosphate–dipotassium hydrogen phosphate buffer for proton addition to 2-phenacylpyridine, and in standard sodium hydroxide for the other compounds.

predominates in aqueous solution for all the potentially tautomeric compounds, and that the K_T are 220, 2,000,000, and 450 for the 2-, 3-, and 4-series, respectively. The phenacylpyridines are all somewhat weaker as bases than pyridine (pK_a = 5·21), reflecting the

[1] Part V, S. Golding, A. R. Katritzky, and H. Z. Kucharska, preceding Paper.
[2] Part II, R. A. Jones and A. R. Katritzky, *J.*, 1959, 1317.
[3] Part III, R. A. Jones and A. R. Katritzky, *J.*, 1961, 378.
[4] C. Osuch and R. Levine, *J. Org. Chem.*, 1956, **21**, 1099.
[5] A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Amer. Chem. Soc.*, 1956, **78**, 674.
[6] C. Osuch and R. Levine, *J. Org. Chem.*, 1957, **22**, 939.

electron-withdrawing inductive effect of the CH_2COPh group. However, this effect is much less than that for the CH_2SO_2Ph group.[1]

Ultraviolet Spectra (Table 2).—The spectra of the phenacylpyridines are similar to those of the corresponding anhydro-bases in aqueous acid, indicating that cations of type (VI) are found in all cases. The phenacylpyridine neutral species in aqueous solution give spectra that are quite distinct to those of the anhydro-bases, which show strong absorption in the 400 mμ region. However, in the 2- and 4-series, weak absorption is shown in this region (cf. Figure 1). On the reasonable assumption that the *N*-methyl group does not greatly affect the ultraviolet spectra, the results indicate K_T of 560 and 260 for the 2- and 4-series, respectively, in aqueous solution. The agreement between these results and those from the pK values is good in view of the assumptions made.

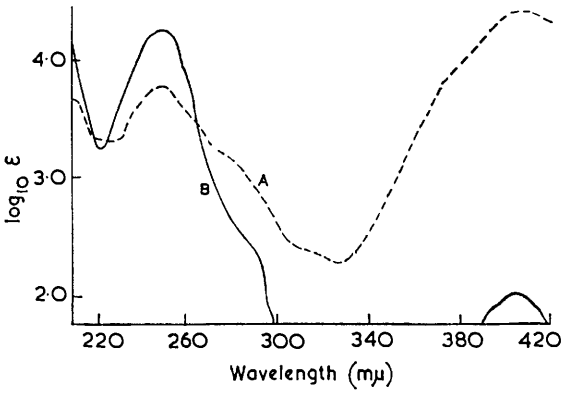


FIGURE 1. Ultraviolet spectra of (A) 4-(benzoylmethylene)-1,4-dihydro-1-methylpyridine in aqueous solution, pH 10·2, (B) 4-phenacylpyridine in aqueous solution, pH 6·8

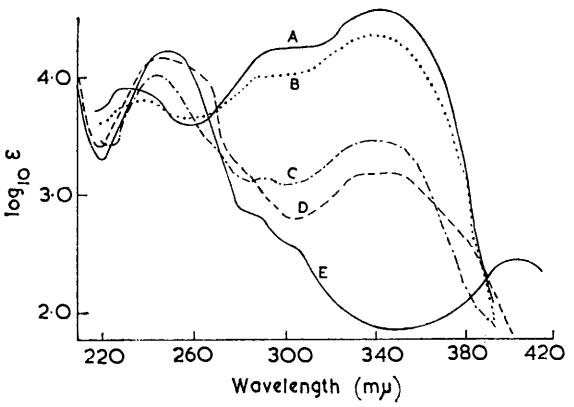


FIGURE 2. Ultraviolet spectra of 2-phenacylpyridine in (A) cyclohexane, (B) ether, (C) methanol–ether, (D) methanol, and (E) aqueous solution, pH 6·8

The spectrum of 3-phenacylpyridine is similar in solvents of low polarity to that in aqueous solutions showing that it exists in all these media essentially completely in the phenacyl form. The spectrum of 4-phenacylpyridine loses the long-wavelength absorption in non-polar solvents, indicating that the small proportion of the benzoylmethylene form present in aqueous solution decreases still further in these media. However, the spectrum of 2-phenacylpyridine shows drastic changes (Figure 2): this is due to its occurrence in the chelated enolic form (VII) in non-polar media. Similar ultraviolet spectra have been previously obtained for 2-phenacylpyridine by Branch, Beckett, and Cowell[7] (see also

[7] R. F. Branch, A. H. Beckett, and D. B. Cowell, *Tetrahedron*, 1963, **19**, 401.

TABLE 2

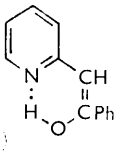
Ultraviolet spectral maxima (mμ)

Compound	Cation		Neutral				Anion			
	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$	λ	$10^{-3}\varepsilon$
2-Phenacylpyridine	262	16·2	255	16·2	400	0·14	259	11·9	350	9·55
anhydro-base	263	20·0	250	10·55	325 410	10·5 24·9	—	—	—	—
3-Phenacylpyridine	255	17·1	251	15·6	—	—	232	10·4	343	15·2
methiodide	249	15·9	245 *	18·2	354	25·2	—	—	—	—
zwitterion derivative †	251	—	245	—	354	—	—	—	—	—
4-Phenacylpyridine	250	17·7	247	17·0	403	0·10	235	9·35	353	22·1
anhydro-base	252	20·0	249	13·4	408	38·6	—	—	—	—

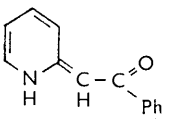
* Shoulder. † Obtainable only in solution.

Spectra of cations were determined in N-sulphuric acid for 2-, 3-, and 4-phenacylpyridine, and 0·01N-sulphuric acid for the other compounds except the 3-zwitterion derivative which was in buffer at pH 4·5. Neutral species were measured in buffer, pH 6·8, for 2-, 3-, and 4-phenacylpyridine, in buffer, pH 10, for the 2- and 4-anhydro-bases and N-sodium hydroxide for the 3-methiodide and zwitterion derivative. Anionic species were measured in N-sodium hydroxide. Spectra were obtained on a Perkin-Elmer Ultracord 137 recording spectrophotometer, and a Unicam S.P. 500 spectrophotometer.

refs. 8 and 9) who have made an intensive infrared and ultraviolet spectroscopic study of the tautomerism of 2-phenacylpyridine and many of its substituted derivatives. Our results confirm theirs, and extend them by defining the contribution of the NH form (VIII).



(VII)



(VIII)

Infrared Spectra.—The spectra of chloroform solutions and Nujol mulls of 3- and 4-phenacylpyridine showed the characteristic bands for the 3- and 4-substituted pyridine rings and for the phenacyl groups.* This demonstrates the predominant occurrence of the phenacyl forms in these media. The infrared spectra of 2-phenacylpyridine and its substituted derivatives were studied by Branch and his co-workers [7-9] who showed that such compounds mostly exist in the enolic form (VII) in the solid state, and as mixtures of this with some keto-form in solution in chloroform and other solvents. Our results are in agreement with their conclusions.

Conclusions and Discussion.—The above results show clearly that 3-phenacylpyridine exists mainly as such in all media. 4-Phenacylpyridine also exists mainly in this form, although in aqueous solution a detectable amount of the benzoylmethylene form occurs. 2-Phenacylpyridine occurs as the enol in non-polar media and in the solid state, but in aqueous solution it exists principally in the phenacyl form, together with some as the benzoylmethylene dihydropyridine derivative.

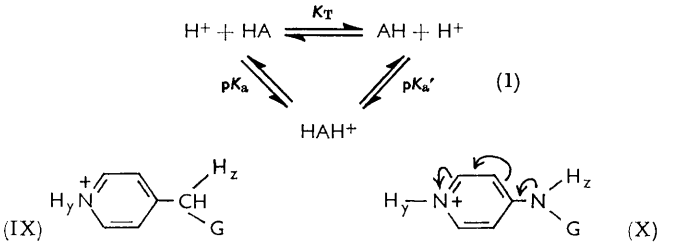
It is now possible to compare the results for the tautomerism of pyridine derivatives containing the groups $NHCOCH_3$, $NHSO_2CH_3$, CH_2COPh, and CH_2SO_2Ph. For the 4-substituted pyridine derivatives, the logarithmic tautomerism constants are 5·2, −1·7, 2·65, and 7·6, respectively. The different effect in passing from a carbonyl to a sulphonyl derivative in the NHX and CH_2X series is due to the occurrence of the lone electron-pair on nitrogen in the NHX derivatives, as previously suggested.[2] The differences in the tautomeric constants depend (cf. equation 1) on the variations in the acidity of

* Details and assignments will be published later.

[8] R. F. Branch, *Nature*, 1956, **177**, 671.
[9] R. F. Branch, *Nature*, 1957, **179**, 42.

the two alternative protons (H_y and H_z) which can be lost in the mesomeric cations (IX) and (X).

In cation (IX), changing G from COPh to SO_2Ph increases the acidity of H_y by 1·16 pK units, reflecting the much stronger inductive effect of SO_2Ph than COPh (mesomeric effects play no part here). However, in cation (X), changing G from COPh to SO_2Ph has essentially no effect on the acidity of H_y. The expected acid-strengthening inductive effect of SO_2Ph is balanced by the greater mesomeric effect of COPh. This mesomeric effect draws on the lone pair of electrons on the nitrogen atom and lessens the electron shift shown by curved arrows in formula (X).



The effect of similar changes on the acidity of H_z may be studied in the compounds in which H_y is replaced by a methyl group. In cation (X) the change to SO_2Ph increases the acidity of H_y by 6·4 pK units. This is due to (i) the greater inductive effect of SO_2Ph and (ii) the fact that the *d*-orbitals of the SO_2Ph group can conjugate with both the mutually perpendicular pairs of electrons on the nitrogen atom, whereas there can be no increase in conjugation in the COPh compound. By contrast, the change of COPh to SO_2Ph in (IX) *decreases* the acidity by 3·8 pK units, undoubtedly due to the fact that the developing electron pair on carbon can be so much more effectively delocalised on a carbonyl than on sulphonyl.

Experimental

2-, 3-, and 4-Phenacylpyridines (prepared by literature methods and with m. p.s in agreement with those quoted) were refluxed with an excess of methyl iodide and methanol for 15—18 hr. Evaporation to dryness and recrystallisation from methanol–ether afforded 1-*methyl*-2- (78%), plates, m. p. 182—184° (decomp.) (Found: C, 49·7; H, 4·1; N, 4·2. $C_{14}H_4INO$ requires C, 49·5; H, 4·1; N, 4·1%); 1-*methyl*-3- (88%), plates, m. p. 117—119° (decomp.) (Found: C, 49·6; H, 4·1; N, 4·2%); and 1-*methyl*-4-*phenacylpyridinium iodide* (60%), plates, m. p. 178—180° (decomp.) (Found: C, 49·3; H, 4·1; N, 4·1%).

The Anhydro-bases.—The methiodides, in ethanol, were passed through Amberlite IRA-400 resin (OH^- form) to afford 2-(*benzoylmethylene*)-1,2-*dihydro*-1-*methylpyridine* (47·5%), needles, m. p. 117—119° [from ethyl acetate–light petroleum (b. p. 60—80°)] (Found: N, 6·9. $C_{14}H_{13}NO$ requires N, 6·6%); anhydro-1-methyl-3-phenacylpyridine hydroxide as a red ethanolic solution (the compound was not isolated); 4-(*benzoylmethylene*)-1,4-*dihydro*-1-*methylpyridine* (38%), needles, m. p. 124—126° [from ethylacetate–light petroleum (b. p. 60—80°)] (Found: N, 6·7%).

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