Tautomeric Pyridines. Part XIV.[1] The Tautomerism of 2-Benzyl-, 2-Benzhydryl-, and 2-Anilino-pyridine

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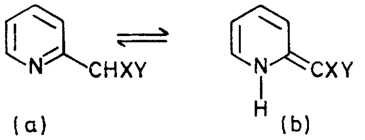
U.v. spectra of the pyridinoid title compounds and of models for the corresponding pyridonoid tautomers show that the pyridinoid tautomeric forms are greatly preferred in aqueous solutions. pK_a Measurements allow quantitative determinations of tautomeric equilibrium constants which are compared with data for various other systems; the latter data include new results for some enamine–imine equilibria. The aromatic character of the pyridonoid forms of the title compounds is discussed.

RECENT work[2] has shown that, in the equilibrium (1a) $\rightleftharpoons$ (1b), 2-picoline is favoured over the methide by log $K_u = 13{\cdot}3$. Similarly, 2-aminopyridine (4a) is favoured over the imine (4b) by log $K_u = 6{\cdot}2$; a result which revised earlier estimates of K_u for this equilibrium.[3] We now report results of an investigation of the tautomeric equilibria (2a) $\rightleftharpoons$ (2b), (3a) $\rightleftharpoons$ (3b), and (5a) $\rightleftharpoons$ (5b), designed to elucidate the effects of phenyl substitution on these tautomeric equilibria. Previous related work is fragmentary and inconclusive. Rud'ko *et al.*[4] concluded that some imino-form (5b) could be detected in the equilibrium (5a) $\rightleftharpoons$ (5b) by absorptions in the i.r. spectrum at *ca.* 1650 [ν(C=N)] and at 3220—3255 [bonded ν(N–H)] cm^{-1}. More recently, however, Mizuno *et al.*[5] attributed the complex ν(N–H) absorption to the two rotational isomers of the pyridinoid form and suggested, on the basis of i.r. data for related compounds and the invariance of the u.v. spectrum in various solvents, that anilinopyridines are 'not in tautomeric equilibria'.



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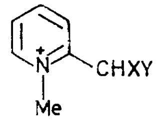
(2) X=H,Y=Ph
(3) X=Y=Ph



(6) X=H,Y=Ph
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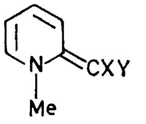

(8) X=H,Y=Ph
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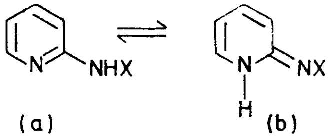

(4) X=H
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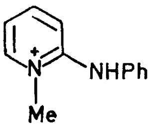

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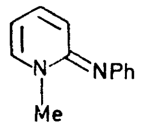

(11)

In the present quantitative study, spectral data and pK_a data for model compounds for the pyridonoid tautomers (2b), (3b), and (5b) were required. Accordingly, we prepared the methocations (6), (7), and (10) (see Experimental section); in basic solution these cations are deprotonated to yield (8), (9), and (11) respectively. Our interest in estimating aromatic

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[1] M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *Chem. Comm.*, 1971, 510 is considered as Part XIII.

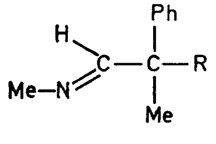
[2] (*a*) M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J.C.S. Perkin II*, 1972, 1295; (*b*) the pK_a for 1-methyl 2-pyridone methide and log $K_u = 14{\cdot}0$ for (10) $\rightleftharpoons$ (16) reported in ref. 2*a* have been refined after reappraisal of the H_- function used and the construction of the new function $H_{-(q)}$, M. J. Cook, A. R. Katritzky, P. Linda, and R. D. Tack, *J.C.S. Perkin II*, 1973, 1080.

[3] L. C. Anderson and N. V. Seeger, *J. Amer. Chem. Soc.*, 1949, **71**, 340 estimated the imino-form at $< 0{\cdot}1\%$ by u.v. spectroscopy; S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1952, 1461 obtained $\Delta G°$ of 7·3 kcal mol^{-1} from pK_a measurements, and N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Amer. Chem. Soc.*, 1970, **92**, 2929 derived $\Delta G°$ of 15 kcal mol^{-1} from theoretical calculations.

[4] A. P. Rud'ko, *Ukrain. khim. Zhur.*, 1968, **34**, 1275 (*Chem. Abs.*, 1969, **70**, 110,146*e*).

[5] T. Mizuno, M. Hirota, Y. Hamada, and Y. Ito, *Tetrahedron*, 1971, **27**, 6011.

resonance energies from tautomeric equilibria [1,2] (see later) prompted us to investigate some imine–enamine equilibria also, and we therefore prepared and measured the $\mathrm{p}K_{\mathrm{a}}$ values of the model compounds (12)—(15).



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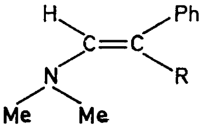

(14) R=H
(15) R=Ph

EXPERIMENTAL

M.p.s are uncorrected. N.m.r. spectra (60 MHz) were recorded at 35° on a Perkin-Elmer R12 spectrometer. U.v. spectra were recorded using a Unicam SP 800 spectrophotometer and $\mathrm{p}K_{\mathrm{a}}$ measurements for (2), (3), (5), (8), (9), and (11) were calculated [6] from spectrophotometric data obtained from spectra recorded on a Unicam SP 500 series 2 spectrophotometer. Buffer solutions for various pH ranges were prepared using hydrochloric acid (0·6—3·3), acetic acid–sodium hydroxide (3·6—5·6), dihydrogen potassium phosphate–sodium hydroxide (5·2—7·8), boric acid–sodium hydroxide (8·0—10·3), and sodium hydroxide (11·0—12·6). The H_0 acidity function [7] is used at acidities $<$ pH 0·5 and the $H_{-(\mathrm{q})}$ function [2b] is used at basicities $>$ pH 12·7. $\mathrm{p}K_{\mathrm{a}}$ Measurements for (12)—(15) were obtained by potentiometric titration in acetonitrile with perchloric acid, according to the method of Hall; [8] a plot of $E_{\frac{1}{2}}$ against $\mathrm{p}K_{\mathrm{a}}$ (aqueous phase) was set up for the reference bases aniline, 2,6-lutidine, piperidine, pyridine, benzylamine, and 1-methylpyridine, and the plot used to extrapolate aqueous phase $\mathrm{p}K_{\mathrm{a}}$ values for (12)—(15) from their $E_{\frac{1}{2}}$ values. The approach is expected to provide $\mathrm{p}K_{\mathrm{a}}$ values accurate to within 0·3 $\mathrm{p}K_{\mathrm{a}}$ units.[8]

2-Benzylpyridine (Koch–Light) had b.p. 75° at 0·3 mmHg (lit.,[9] b.p. 276·8—277·2° at 737 mmHg).

Preparation of Compounds.—The following were prepared by the literature methods quoted: 2-anilinopyridine [10] (62%), m.p. 108—109° (lit.,[10] 105—108°); 2-anilino-1-methylpyridinium iodide [11] (49%), m.p. 180·5—181·5° (lit.,[11] 176—179°), 2-benzyl-1-methylpyridinium iodide [12] (90%), m.p. 80—100° (decomp.) (lit.,[12] 116—117°) (Found: C, 50·2; H, 4·8; N, 4·2%. Calc. for $C_{13}H_{14}IN$: C, 50·2; H, 4·5; N, 4·5%); 2-benzhydrylpyridine [13] (66%), m.p. 58—59° (lit.,[13] 63°); 2-benzhydryl-1-methylpyridinium iodide [13] (90%), m.p. 236—239·5° (lit.,[13] 222—224°) (Found: C, 59·0; H, 4·6; N, 3·3. Calc. for $C_{19}H_{18}IN$: C, 58·9; H, 4·7; N, 3·6%); 2-dimethylamino-1,1-diphenylethylene [14] (88%), m.p. 76—80° (lit.,[14] 84°) (Found: C, 86·1; H, 7·6; N, 6·4. Calc. for $C_{16}H_{17}N$: C, 86·1; H, 7·6; N, 6·3%).

1-*Phenyl*-2-*dimethylaminoethylene* (14).—To phenylacetaldehyde (5 g) in dry ethanol (15 ml) was added anhydrous dimethylamine (5 ml) at room temperature. After 30 min, the solvent was removed and the residual liquid distilled to give the *amine* (14) (3 g, 49%) as a yellow liquid, b.p. 83° at 0·3 mmHg (Found: C, 81·7; H, 9·1; N, 9·3. $C_{10}H_{13}N$ requires C, 81·6; H, 8·8; N, 9·5%).

2,2-*Diphenylpropionaldehyde Methylimine* (13).—To 2,2-diphenylpropionaldehyde [15] (2 g) in ethanol (4 ml) was added methylamine in ethanol (33%, 3 ml). The solution was stirred at 60° during 1 h. After removal of the solvent, the residue was distilled to give the *methylimine* (13) (2 g, 94%) as a liquid, b.p. 103—104° at 0·35 mmHg (Found: C, 86·3; H, 7·9; N, 6·0. $C_{16}H_{17}N$ requires C, 86·1; H, 7·6; N, 6·3%).

2-*Methyl*-2-*phenylpropionaldehyde Methylimine* (12).—2-Methyl-2-phenylpropionaldehyde [16] (0·5 g) in ethanolic methylamine (33%, 4 ml) was stirred at 60° during 1 h. The solvent was evaporated off and the residual liquid distilled under vacuum in a microdistillation unit to give the *methylimine* (12) (0·5 g, 93%) as a liquid, b.p. 213° at atmospheric pressure (Found: C, 81·9; H, 9·2; N, 8·7. $C_{11}H_{15}N$ requires C, 82·0; H, 9·3; N, 8·7%).

DISCUSSION

U.v. Spectra and $\mathrm{p}K_{\mathrm{a}}$ *Data*.—The u.v. spectra of the neutral forms of the potentially tautomeric compounds [(2), (3), and (5)], are dissimilar from the u.v. spectra of the corresponding pyridonoid model structures [(8), (9), and (11), respectively] generated from the corresponding metho-cations (Table 1). Qualitatively, this substantiates expectations that each of the tautomeric equilibria lies well over to the pyridinoid form. Quantitative estimates of tautomeric equilibrium constants K_{u} are obtainable from the $\mathrm{p}K_{\mathrm{a}}$ of the mobile system and of one fixed form [17] provided that the cationic species generated are of similar structure. The u.v. absorptions of the cations of the mobile compounds (2) and (3) are very similar to those of the metho-cations (6) and (7) respectively. Although the cation of (5) exhibits a strong absorption at 243 nm which is less apparent in the u.v. spectrum of (10), both cations exhibit similar maxima at 315 nm. We conclude that each of the metho-cations [(6), (7), and (10)] provides a satisfactory model, although the relative stabilities of rotational isomers about the pyridine–CH_2Ph or –NHPh bonds will be affected by the spatial requirements of the atom or group bonded to the pyridine nitrogen.

The $\mathrm{p}K_{\mathrm{a}}$ data (Table 1) are compared in Table 2 with literature values for analogous compounds. Table 2 also illustrates the differential effects of phenyl substitution with those for acyl and sulphonyl substitution: the effect of the phenyl group is much the weakest, but qualitatively the trend of $\Delta\mathrm{p}K_{\mathrm{a}}$ over the four series for phenyl substitution is intermediate between those for RCO and RSO_2. For RCO, $\Delta\mathrm{p}K_{\mathrm{a}}$ is much greater for

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[6] A. Albert and E. P. Serjeant, 'The Determination of Ionization Constants,' Chapman and Hall, London, 1971, p. 44.

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[14] A. Seher, *Arch. Pharm.*, 1951, **284**, 380.

[15] A. McKenzie and R. Roger, *J. Chem. Soc.*, 1924, **125**, 2148, with modifications: the aldehyde was steam-distilled and purified *via* the semicarbazone.

[16] M. Tiffeneau and H. Dorlencourt, *Ann. Chim. Phys.* (*France*), 1909, **16**, 248, with modifications: the aldehyde was purified *via* the semicarbazone.

[17] A. R. Katritzky and J. M. Lagowski, *Adv. Heterocyclic Chem.*, 1963, **1**, 311.

TABLE 1

U.v. spectral maxima and pK_a data for 2-anilino-,2-benzyl-, and 2-benzhydryl pyridine

		U.v. spectra						Basicity determination			
		Cations			Neutral species						
Compound	Structure	$\lambda_{max.}$/ nm	$10^{-3}\varepsilon$		$\lambda_{max.}$/ nm	$10^{-3}\varepsilon$		pK_a[a]	Buffers	Analytical wavelength/ nm	10^5 Concentration/ M
2-Anilinopyridine	(5)	243 315	9·8 7·1	pH 2	269 310[b]	14·3 5·5	pH 10	5·84 ± 0·03	HOAC–NaOH KH_2PO_4–NaOH	270	4·4 (0·2% EtOH)
2-Anilino-1-methylpyridinium iodide	(10)	315	8·8	pH 7	273 348	9·4 6·3	pH 12	10·17 ± 0·02	HBO_3–NaOH NaOH	315	7·5
2-Benzylpyridine	(2)	265	7·3	pH 2	262 269[b]	4·5 3·4	pH 10	5·13 ± 0·02[d]	HOAc–NaOH KH_2PO_4–NaOH	268	9·5 (0·4% EtOH)
2-Benzyl-1-methylpyridinium iodide	(6)	267	7·1	pH 12	350	25·9[c]	$H_{-(q)}$[a]	17·01 ± 0·10		350	2·4
2-Benzhydrylpyridine	(3)	262	7·1	pH 2	260 270[b]	4·6 3·4	pH 8	4·51 ± 0·03	HCl HOAc–NaOH	275	4·4 (1·7% EtOH)
2-Benzhydryl-1-methylpyridinium iodide	(7)	265 275[b]	6·9 6·7	pH 12	370	15·2[c]	$H_{-(q)}$[a]	17·33 ± 0·10[e]	KH_2PO_4–NaOH	380	5·1

[a] pK_a Data were obtained spectrophotometrically.[6] Measurements on the $H_{-(q)}$ scale were obtained according to the method of ref. 2*b*. [b] Shoulder. [c] Extrapolated to zero time. [d] R. H. Linnell, *J. Org. Chem.*, 1960, **25**, 290, reports 5·13. [e] *Cf.* value of 12·5 determined by J. A. Berson, E. M. Evleth, jun., and Z. Hamlet, *J. Amer. Chem. Soc.*, 1965, **87**, 2887.

TABLE 2

pK_a Data for side-chain substituted 2-methyl and 2-aminopyridines and 1-methyl-2-pyridone methides and imines

Series									ΔpK_a[a]		
Parent	2-Subst.	X = H Y = H	X = Ph Y = H	X = Ph Y = Ph	X = COMe, Y = H	X = COPh, Y = H	X = SO_2Me, Y = H	X = SO_2Ph, Y = H	X = Ph Y = H	X = COPh, Y = H	X = SO_2R, Y = H
2-Methylpyridine	CHXY	5·97[b]	5·13[e]	4·51[e]		5·03[g]		2·54[g]	0·84	0·94	3·43[j]
1-Methyl-2-pyridone methide	CXY	19·25[c]	17·01[e]	17·33[e]		7·38[g]		10·45[g]	2·24	11·87	8·80[j]
2-Aminopyridine	NHX	6·86[d]	5·84[e]		2·01[f]	3·33[f]	1·10[h]		1·02	3·53	5·76[k]
1-Methyl-2-pyridone imine	NX	13·02[c]	10·17[e]		7·12[f]		−0·33[h]		2·85	~5[i]	13·35[k]

[a] pK_a (parent) − pK_a (substituted analogue). [b] H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723. [c] Ref. 2. [d] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 1948, 2240. [e] Present investigation. [f] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 1959, 1317. [g] S. Golding, A. R. Katritzky, and H. Z. Kucharska, *J. Chem. Soc.*, 1965, 3090; A. R. Katritzky, H. Z. Kucharska, and J. D. Rowe, *ibid.*, 1965, 3093. [h] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.*, 1961, 378. [i] Estimated after appraisal of other data in Table. [j] R = Ph. [k] R = Me.

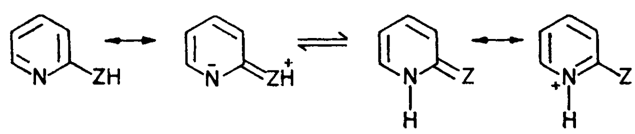
TABLE 3

Pyridinoid–pyridonoid resonance energy differences

Z	log K_u	$\Delta G°_u$/kcal mol^{-1}	pK_a (20a)	pK_a (20b)	log K_s	$\Delta G°_s$/kcal mol^{-1}	$A_{py} - A_X$
CH_2[a]	13·28	−18·2	9·43[d]	11·42[i]	1·99	−2·7	15·5
CHPh	11·88[b]	−16·3	6·18[e]	6·43[j]	0·25	−0·3	16·0
CPh_2	12·82[c]	−17·6	5·43[f]	5·98[k]	0·55	−0·8	16·8
NH[a]	6·16	−8·5	*g*	*g*	0	0	8·5
NPh	4·33	−5·9	9·25[h]	8·15[h]	−1·10	1·5	7·4

[a] Data for these compounds reported previously in ref. 2. [b] *Cf.* 11·5 estimated by S. F. Mason and C. F. Reynolds, unpublished data in K. Schofield, ' Heteroaromatic Nitrogen Compounds,' Butterworths, London, 1967, p. 325. [c] *Cf.* value of 11·7 estimated by S. F. Mason and C. F. Reynolds (see note *b*). [d] Value for cyclohexanone methylimine; M. Brezina and P. Zuman, *Chem. listy*, 1953, **47**, 975. [e] Value for (12); present investigation. [f] Value for (13); present investigation. [g] Assumed equal. [h] Values for 2-aminoindolenine (8·15) and 1,3,3-trimethyl-2-iminoindoline (9·25); ref. 18. [i] Value for 1,2-dimethyl-1,4,5,6-tetrahydropyridine; R. Adams and J. E. Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588. [j] Value for (14); present investigation. [k] Value for (15); present investigation.

the methide than for the pyridone imine whilst the opposite is true of RSO_2; an effect which can be explained in terms of the predominantly mesomeric effect of RCO, but inductive effect of RSO_2. The intermediate effect of the phenyl group may therefore reflect its interaction by both mesomeric and inductive mechanisms.



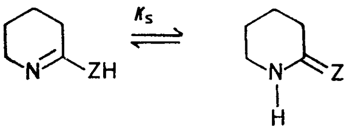
(16) (17) (18) (19)

Values of K_u for (2a) $\rightleftharpoons$ (2b), (3a) $\rightleftharpoons$ (3b), and (5a) $\rightleftharpoons$ (5b), calculated from the pK_a data, are reported in Table 3 together with data for (1a) $\rightleftharpoons$ (1b) and (4a) $\rightleftharpoons$ (4b) obtained earlier.[2] Variations in K_u for a series of 2-substituted pyridines can be rationalised by considering the relative stabilities of the contributing resonance canonical forms (16)—(19). In the aminopyridine series (Z = NH or NPh) delocalisation of the exocyclic nitrogen lone pair [(16) $\leftrightarrow$ (17)] should be marginally inhibited on replacing H by Ph whereas negative charge on the same nitrogen should be stabilised [(19)]. Data in Table 3 show that these factors reduce the heavy preponderance of the amino-form by a factor of 10^2 on substituting Ph for H. For the series Z = CH_2, CHPh, and CPh_2, the overriding factor affecting the equilibria is the stability of canonical forms of type (19). In each compound the equilibrium lies well in favour of the pyridinoid structure but the order of preference for the methide form is CHPh > CPh_2 > CH_2. This order demonstrates that one phenyl substituent more readily stabilises the formal negative charge than two; with two phenyl groups steric congestion causes non-coplanarity of the three rings bonded to the negative centre.

In previous work [2] we have used tautomeric equilibria to estimate differences in the aromatic resonance energies of pyridine and pyridonoid rings ($A_{py} - A_x$). In this approach the equilibrium constant K_u is compared with the corresponding equilibrium constant K_s for the saturated analogues (20a) $\rightleftharpoons$ (20b) and equation (1) may be derived.*

$$A_{py} - A_x = 1{\cdot}37\,(\log K_u - \log K_s) \qquad (1)$$

Neither K_s for (20a) $\rightleftharpoons$ (20b) (Z = NPh, CHPh, or CPh_2) nor pK_a data for the fixed models from which K_s values may be obtained are available. Tautomeric equilibrium constants and pK_a data are available or may be estimated, however, for compounds containing similar functional groups; thus the pK_a values of 2-aminoindolenine [19] and 1,3,3-trimethyl-2-iminoindoline [19] serve to provide an estimate of K_s for (20a) $\rightleftharpoons$ (20b) (Z = NPh) (Table 3). Data for imine–enamine equilibria analogous to (20a) $\rightleftharpoons$ (20b) for Z = CHPh and CPh_2 are scarce. Ahlbrecht *et al.*[20] used n.m.r. spectrometry to study the equilibrium PhMeCHCH=NMe $\rightleftharpoons$ PhMeC=CHNHMe and showed that K_s varied between 0·46 and 3 over a wide range of solvents. In the diphenyl series [21] the equilibrium favours the imine in ether but diphenylacetaldehyde imine tautomerises extensively to 2,2-diphenylvinylamine in ethanol.[22] We have now measured the pK_a values of the model compounds (12)—(15) using the potentiometric procedure (see Experimental section), and the data together with the derived tautomeric equilibrium constants and values of $A_{py} - A_x$ are presented in Table 3. Table 3 also contains the data obtained earlier for the unphenylated compounds. The variation in K_s on successive substitution of hydrogen by phenyl groups follows the same pattern as the variation in K_u and accordingly the values of $A_{py} - A_x$ are not substantially changed by the substituent group: as before [2a] we find that pyridone methides are considerably less aromatic than pyridone imines. In view of the limited number of examples and the expected errors in $A_{py} - A_x$, discussion of trends associated with phenyl substitution does not seem meaningful at this stage. The effect of stronger electron-withdrawing groups on the aromatic resonance energies of the methide and imino-structures is at present under investigation.



(a) (20) (b)

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* This equation is equivalent to equation (13) in reference 2*a*. The latter is one of five equations used to convert $\Delta G°$ values (obtained from K_T data) into $\Delta H°$ values required for the discussion of aromatic resonance energies. In the equation referred to, $\Delta G°$ is taken as providing a good approximation for ΔH_{int}.[18]

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