304. *Interaction at a Distance in Conjugated Systems. Part I. The Basicities of (Amino- and Nitro-phenyl)-pyridines and -pyridine 1-Oxides.*

By A. R. Katritzky and P. Simmons.

The basicities of the compounds mentioned in the title indicate that nitro-groups attached to phenyl substituents in pyridine or pyridine 1-oxide interact only weakly with the heterocyclic ring, and by the inductive effect. A 4′-amino-group in the 2- or 4-phenylpyridinium ion gives some mesomeric stabilisation. The cationic heterocyclic rings (pyridinium ion)-2 and -4 behave as powerful electron-withdrawing substituents; the heterocyclic rings (pyridine 1-oxide)-2 and -4 behave as moderately electron-withdrawing substituents. The results support the conclusion [1] that phenylpyridines and their 1-oxides undergo nitration as the free bases.

Considerable interest has been shown in the interaction between two singly linked aromatic rings. For biphenyls, recent work on the dissociation constants of acids [2] and phenols,[3] the relative rate of halogenation and nitration of benzene, biphenyl, and nitrobiphenyls,[4] and the rates of desilylation [5] and hydrolysis of esters [6] has clarified the position: electronic effects are transmitted between the rings, but the effect is small and mainly inductive in nature. In particular, mesomeric interaction of a substituent in one ring with the other ring is very much weakened.

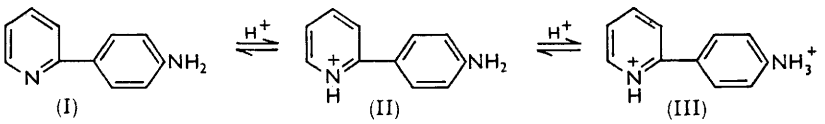
Little work has been done with heterocyclic analogues of biphenyl. Previously we showed [1] that 2- and 4-phenylpyridine 1-oxides are nitrated predominantly in the *meta*-position of the benzene ring, and gave tentative evidence that these compounds and 2- and 4-phenylpyridine are nitrated in the form of the free bases. Because these results indicated that strong interaction occurs between the rings in phenylpyridines we have made basicity and dipole-moment measurements which clarify the interactions between the benzene and pyridine rings and substituents in (amino- and nitro-phenyl)pyridines and their 1-oxides.

Preparation of Compounds.—The nitrophenylpyridines were prepared by nitration (cf. ref. 1), and converted into their *N*-oxides in the usual way. Catalytic hydrogenation of the nitrophenylpyridines afforded the amino-analogues. 2-*m*- and 2-*p*-Nitrophenylpyridine 1-oxides were selectively catalytically reduced to the corresponding amino-oxides, but this method failed in the 4-series; these results are in agreement with previous [7]

[1] Hands and Katritzky, *J.*, 1958, 1754.
[2] Berliner and Blommers, *J. Amer. Chem. Soc.*, 1951, **73**, 2479.
[3] Ketier, Bonner, and Eastman, *J. Amer. Chem. Soc.*, 1954, **76**, 5770.
[4] *Inter alia*, de la Mare and Hassan, *J.*, 1957, 3004; Mizuno and Simarmura, *J.*, 1958, 3875.
[5] Benkeser, Schroeder, and Thomas, *J. Amer. Chem. Soc.*, 1958, **80**, 2283.
[6] Berliner and Liu, *J. Amer. Chem. Soc.*, 1953, **75**, 2417.
[7] Katritzky and Monro, *J.*, 1958, 1263.

hydrogenations of pyridine 1-oxides which indicated that the *N*-oxide group in 2-substituted pyridine 1-oxides was sterically hindered and thus resisted reduction. 4-*p*-Aminophenylpyridine was converted into the 1-oxide by protecting the amino-group by ethoxycarbonylation (cf. ref. 8).

Results.—The pK_a values in Table 1 were determined by ultraviolet spectrometry in phosphate buffers (containing up to 2% of ethanol). Potentiometric titration could not be used because of solubility difficulties. The pK_a value of 3-*p*-nitrophenylpyridine could not readily be determined by the spectrophotometric method because the ultraviolet spectra of ion and conjugate base were not sufficiently different.



The aminophenylpyridine 1-oxides have two widely separated pK_a values, and the ultraviolet spectrum of the monoprotonated form shows [9] that the first proton adds to the amino-group, as would be expected. It could similarly be shown [9] that the first proton adds predominantly to the heterocyclic nitrogen atom in 2-*p*- and 4-*p*-aminophenyl pyridine [cf. (I) ⟶ (II) ⟶ (III)]. However, in contrast to the last two compounds,

TABLE 1. pK_a *Values.*

Compound	pK_a [a]	α [b]	Concn. (M × 10^4)	Wavelength (mμ)
4-Phenylpyridine	5·55	0·03	0·3	285
4-*p*-Nitrophenylpyridine	4·87	0·07	0·3	285
4-*m*-Nitrophenylpyridine	4·90	0·03	0·2	265
	6·26	0·02	0·3	350
4-*p*-Aminophenylpyridine	2·75	0·02	0·3	350
3-Phenylpyridine	4·80	0·06	0·6	245
2-Phenylpyridine	4·48	0·03	0·3	300
2-*p*-Nitrophenylpyridine	3·63	0·05	0·7	335
2-*m*-Nitrophenylpyridine	3·55	0·05	0·6	300
	5·70	0·04	0·5	350
2-*p*-Aminophenylpyridine	2·47	0·02	0·5	350
4-Phenylpyridine 1-oxide	0·83	0·10	0·3	290
4-*p*-Nitrophenylpyridine 1-oxide	0·58	0·03	0·3	230
4-*m*-Nitrophenylpyridine 1-oxide	0·58	0·03	0·2	295
4-*p*-Aminophenylpyridine 1-oxide	3·64	0·06	0·4	330
3-Phenylpyridine 1-oxide	0·74	0·03	0·2	250
3-*m*-Nitrophenylpyridine 1-oxide	0·47	0·03	0·2	260
2-Phenylpyridine 1-oxide	0·77	0·03	0·5	290
2-*p*-Nitrophenylpyridine 1-oxide	0·28	0·05	0·3	260
2-*m*-Nitrophenylpyridine 1-oxide	0·26	0·04	0·3	240
	3·82	0·10	0·6	310
2-*p*-Aminophenylpyridine 1-oxide	0·25	0·03	0·3	240
	3·92	0·15	0·3	250
2-*m*-Aminophenylpyridine 1-oxide	0·20	0·03	0·3	240

Measurements were made by the spectrophotometric method, at the wavelength and concentration indicated, in phosphate buffers containing up to 2% of ethanol.
[a] Arithmetical means of 6 values. [b] Standard deviations.

the potentiometric titration curves of 2- and 4-*m*-aminophenylpyridine showed no break at half-neutralisation; qualitatively this indicates that the two pK_a values for these compounds are much closer together (pK_1 being lower, and pK_2 higher) than for the *p*-aminophenyl-isomers.

The Basicity of the Pyridine Nitrogen Atom.—3- and 4-Phenyl groups respectively somewhat decrease and increase the pK_a of pyridine: the phenyl group is weakly electron-withdrawing by the inductive effect and can either withdraw or make electrons available

[8] Katritzky, *J.*, 1957, 191.
[9] Katritzky and Simmons, unpublished work.

TABLE 2. pK_a *Increments caused by amino-, nitro-, and ammonio-groups in phenylpyridines and their oxides.*

	Nitro		Amino	
	m	*p*	*m*	*p*
Pyridines				
4-Phenyl ...	−0·65	−0·68	<+0·7	+0·71
2-Phenyl ...	−0·93	−0·85	<+1·2	+1·22
Pyridine 1-oxides				
4-Phenyl...	−0·25	−0·25	—	—
3-Phenyl...	—	−0·27	—	—
2-Phenyl...	−0·51	−0·49	−0·57[a]	−0·52[a]

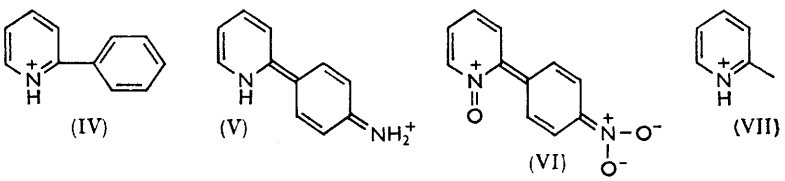
m and *p* refer to the phenyl rings. [a] Ammonio (NH_3^+) group.

by the mesomeric effect. By using the ρ constant for the basicities of pyridines (5·7),[10] the σ constants for *meta*- and *para*-phenyl groups (σ_m and σ_p) are calculated as −0·045 ± 0·01 and +0·085 ± 0·005 respectively, which are nearer to the σ values given by McDaniel and Brown [11] (−0·01 ± 0·05, +0·06 ± 0·05) than to the corresponding σ^+ values [13] (−0·18 and +0·11). Other work [10] also indicates that σ rather than σ^+ values give better correlation of pyridine basicities; this is surprising in view of the electron-demanding nature of the reaction.

A 2-phenyl group decreases the basicity of pyridine, probably because in the solvated ion (IV) the angle between the planes of the rings is larger than in the conjugate base; the ultraviolet spectra support this conclusion.[9]

A nitro-group in the *m*- or *p*-position of the phenyl group lowers the basicity in 2-, 3-, and 4-phenylpyridine (Table 2). The effect is somewhat larger in the 2-series, but *m*- and *p*-nitro-groups are equally effective (within experimental error), indicating that the basicity is weakened by the inductive effect of the nitro-group and that the mesomeric effect on the pyridine ring is not important. σ_p Constants for *p*-nitrophenyl and *m*-nitrophenyl groups are calculated as +0·074 and +0·068, respectively.

An amino-group in the *p*-position of the phenyl group increases the basicity of 2- and 4-phenylpyridine (Table 2); this effect, although comparatively weak (for, in pyridine itself, a *p*-amino-group increases the pK_a by 3·9 units [10]), must be largely due to mesomeric stabilisation of the cation [cf. (II) ⟷ (V)] because the basicity increase is much less in the corresponding *m*-aminophenyl compounds (see above). The σ_p constant for the *p*-aminophenyl group is −0·17.



These σ_p constants agree in sign, but are smaller in magnitude than those calculated by Berliner and his co-workers [6,14] of +0·17—+0·19 for *m*-nitrophenyl, +0·19—+0·27 for *p*-nitrophenyl, and −0·030 for *p*-aminophenyl.

The Basicity of the Pyridine Oxide Oxygen Atom.—The effects of phenyl groups on the basicity of pyridine 1-oxide, and of *m*- and *p*-nitro-groups in the phenyl rings on the basicity of 2-, 3-, and 4-phenylpyridine 1-oxide (Table 3) are in the same direction as in the pyridine series but smaller because the basic centre is further away (also, the difference between the amount of steric hindrance in the ion and conjugate base of 2-phenylpyridine 1-oxides is less). This indicates that, as in the pyridine series, only the inductive effect of the nitro-group is important and structures of type (VI) are not favoured. This conclusion is supported by the effect of ammonio-groups (NH_3^+) in the *m*- and *p*-positions, which is similar to that of *m*- and *p*-nitro-groups (Table 2). If ρ = 2·1 is used for the basicity of

[10] Jaffé and Doak, *J. Amer. Chem. Soc.*, 1955, **77**, 4441.
[11] McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420.

pyridine 1-oxides,[10] calculation gives the following σ_p constants: phenyl, —0·02; *p*-nitrophenyl, +0·10; *m*-nitrophenyl, +0·10: and σ_m constants: phenyl, +0·02; *p*-nitrophenyl, +0·15. These values are in reasonable agreement with those for the basicities of pyridines (see above).

TABLE 3. *Effect of heterocyclic substituents on the basicity of aniline.*

	Phenylpyridinium ion		Phenylpyridine 1-oxide	
	2	4	2	4
m-NH_2	—	—	—0·64	—
p-NH_2	—2·09	—1·81	—0·74	—0·92

Basicity of the Amino-group (Table 3).—The substitution of a 2- or 4-pyridyl 1-oxide group in the *meta*- or *para*-position of aniline (itself pK_a 4·56 [12]) has a base-weakening effect. The small difference between the effect in the *meta*- and the *para*-positions indicates that it is largely inductive in character. The 2- or 4-pyridinium group (cf. VII) has a still stronger base-weakening effect [here mesomeric interaction is probably involved because the effect is less in the *meta*-position (see above, and cf. ref. 1]. These results may be compared with the effect of the NMe_3^+ group which lowers the pK_a of aniline by 2·05 and 2·30 units respectively when it is in the *para*- and the *meta*-position.[15]

By using the ρ value for the basicity of anilines (2·77),[12] σ values can be calculated for these heterocyclic substituents (Table 4).

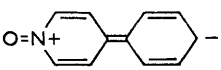
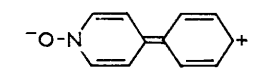
TABLE 4. *Hammett σ constants for heterocyclic rings as substituents.*

	Pyridinium ion		Pyridine 1-oxide	
	—2	—4	—2	—4
σ_m	—	—	0·23	—
σ_p	0·75	0·65	0·27	0·33

These values afford additional evidence that nitration of 2- and 4-phenyl-pyridine and -pyridine 1-oxides takes place on the free bases and not on the conjugate acids,[1] for groups that have σ_p constants greater than 0·6 are invariably strongly *meta*-directing.[11,12] The σ_p values for (1-hydroxypyridinium)-2- or 4- as a substituent are probably even higher than those of (pyridinium)-2- or 4- as a substituent; therefore nitration as cations should give very little *para*-substitution, which is contrary to experiment.[1]

Dipole Moments.—The dipole moments of 4-*p*-nitrophenyl, 4-*p*-aminophenyl-, and 4-phenyl-pyridine were determined as 1·90, 4·09, and 2·51 D respectively. That for 4-phenylpyridine 1-oxide was 4·52 D but those of the *p*-nitro- and *p*-amino-phenyl analogues could not be measured because of poor solubility in benzene. Compounds in other than the 4-*p*-series were not measured because of the difficulty in interpreting results.

The mesomeric moments for 4-phenylpyridine and its 1-oxide are therefore [16] 0·29 and 0·28 D, respectively, with the heterocyclic rings becoming negatively charged. This result shows that any contribution of a canonical form of type (VIII) in the oxide is just

(VIII)   (IX)

cancelled by the increased importance of form of type (IX) over the corresponding form in the pyridine. Introduction of a nitro-group into the *para*-position of 4-phenylpyridine changes the dipole moment by 4·41 D, *i.e.*, by the same amount as introduction of a 4-nitro-group into diphenyl; [17] the simplest explanation of this is that interaction between the nitro-group and the pyridine nitrogen atom is small.

[12] Jaffé, *Chem. Rev.*, 1953, **53**, 191.
[13] Brown, Okamote, and Inukai, *J. Amer. Chem. Soc.*, 1958, **80**, 4964.
[14] Berliner, Newman, and Riaboff, *J. Amer. Chem. Soc.*, 1955, **77**, 478.
[15] Roberts, Clement, and Drysdale, *J. Amer. Chem. Soc.*, 1951, **73**, 2181.
[16] Katritzky, Randall, and Sutton, *J.*, 1957, 1769.
[17] Everard and Sutton, *J.*, 1951, 2817.

Experimental

Nitrophenylpyridines.—2-Phenylpyridine [18] (31 g.) was added to sulphuric acid (100 c.c.) and nitric acid (*d* 1·50, 8·4 c.c.) at 20°. After 30 min. at 100°, water (450 c.c.) and then 5N-aqueous ammonia (200 c.c.) were added (A). The precipitate (14 g.) crystallised from ethanol to give 2-*p*-nitrophenylpyridine (12 g., 30%), m. p. 130—131° (lit.,[19] m. p. 130—131°). The aqueous liquors (from A) were basified with ammonia and extracted with chloroform. Solid from the solvents was twice recrystallised from 5N-nitric acid. The solid nitrate was basified with 10N-sodium hydroxide, extracted by chloroform, and the solid from the extracts recrystallised from ethanol to give 2-*m*-nitrophenylpyridine (9 g., 22%), m. p. 72—73° (lit.,[19] m. p. 73—74°).

3-Phenylpyridine was nitrated, and the reaction mixture basified, as above. Recrystallisation of the product from ethanol gave 3-*p*-nitrophenylpyridine (62%), m. p. 147—148° (lit.,[19] m. p. 148—149°).

4-Phenylpyridine was nitrated, and the reaction mixture basified, as above. Recrystallisation of the free bases from hydrochloric acid (5N) gave the solid *para*-hydrochloride which, after further recrystallisation (from HCl), was converted into 4-*p*-nitrophenylpyridine (35%); this after recrystallisation from ethanol had m. p. 124—125 (lit.,[19] m. p. 123—124°). The hydrochloric acid mother-liquors were basified, and the resulting solid was twice recrystallised from nitric acid (5N), then basified and recrystallised from ethanol to give 4-*m*-nitrophenylpyridine (29%), m. p. 109—110° (lit.,[19] m. p. 109—110°).

Nitrophenylpyridine Oxides.—2-*m*-Nitrophenylpyridine (5 g.), 30% aqueous hydrogen peroxide (8 c.c.), and acetic acid (16 c.c.) were heated for 24 hr. at 70°, more hydrogen peroxide (8 c.c.) being added after 12 hr. The whole was evaporated at 100°/12 mm., and the residue in chloroform digested with potassium carbonate. Evaporation of the chloroform layer and recrystallisation from ethanol gave the oxide (4·2 g., 78%), m. p. 175—177° (lit.,[1] m. p. 177—178°).

The following analogues were similarly prepared: 2-*p*-, (75%), m. p. 212—214°, from ethanol (lit.,[1] m. p. 216°); 3-*m*-, (65%), rods (from ethanol) changing at 148° to needles, m. p. 174—175° (Found: C, 60·6; H, 3·8; N, 13·1. $C_{11}H_8O_3N_2$ requires C, 61·1; H, 3·7; N, 13·0%); 4-*m*-, (53%), cubes, m. p. 208—209° from ethanol (Found: C, 61·2; H, 3·8%); 4-*p*-, (46%), rods, m. p. 221·5—223°, from ethanol (Found: C, 61·1; H, 3·8%).

Aminophenylpyridines.—2-*m*-Nitrophenylpyridine (1 g.) in ethanol (30 c.c.) was stirred over 5% palladium on charcoal (0·2 g.) under hydrogen for 40 min. Filtration and evaporation gave 2-*m*-aminophenylpyridine (0·6 g., 70%) as a new *polymorph*, needles m. p. 55—56°, from light petroleum (b. p. 40—60°) (Found: C, 77·6; H, 6·3. $C_{11}H_{10}N_2$ requires C, 77·6; H, 6·3%) (lit.,[20] m. p. 72—73°) [acetyl derivative, m. p. 141—143° (lit.,[21] m. p. 141—143°)].

The following analogues were similarly prepared: 2-*p*-, (62%), from light petroleum (b. p. 60—80°), m. p. 96—97·5° (lit.,[19] m. p. 97—98°); 3-*p*-, (70%), from aqueous ethanol, m. p. 118—119° (lit.,[19] m. p. 118—120°); 4-*m*-, (59%), from benzene, m. p. 165—166° (lit.,[21] 165—166°); 4-*p*-, (61%), from ethanol, m. p. 227—228° (lit.,[19] 232—234°).

Aminophenylpyridine 1-Oxides.—2-*m*-Nitrophenylpyridine 1-oxide (1 g.), ethanol (30 c.c.), and 5% palladised alumina (0·2 g.) were stirred under hydrogen for 80 min., 375 c.c. (6 equiv.) being absorbed. The solution was filtered and evaporated; the residue sublimed at 150°/1 mm., and the sublimate was crystallised from toluene to give 2-m-*aminophenylpyridine 1-oxide* (0·2 g., 25%) in plates, m. p. 172—173° (Found: C, 70·9; H, 5·5; N, 15·2. $C_{11}H_{10}ON_2$ requires C, 70·9; H, 5·4; N, 15·1%).

2-p-*Aminophenylpyridine 1-oxide* (20%) was similarly prepared; it formed plates, m. p. 195—200° (decomp.) from toluene (Found: C, 71·0; H, 5·5; N, 14·9%).

Ethyl chloroformate (1·4 c.c.) was added dropwise at 0° to 4-*p*-aminophenylpyridine (2 g.) under pyridine (4·5 c.c.). After 12 hr. water was added, to precipitate the crude product which was dried, dissolved in acetic acid (4 c.c.), and treated with 30% aqueous hydrogen peroxide (2·2 c.c.) at 70° for 12 hr. Volatile material was then removed at 100°/13 mm. A portion (0·2 g.) of the product was twice recrystallised from pyridine to give 4-p-*ethoxycarbonylaminophenylpyridine 1-oxide* (0·1 g.), m. p. 245—247° (Found: C, 65·0; H, 5·6; N, 11·4. $C_{14}H_{14}O_3N_2$

[18] Evans and Allen, *Org. Synth.*, 1956, Coll. Vol. II, p. 517.
[19] Forsyth and Pyman, *J.*, 1926, 2912.
[20] Cook, Heilbron, and Reed, *J.*, 1945, 182.
[21] Heilbron, Hey, and Lambert, *J.*, 1940, 1279.

requires C, 65·1; H, 5·5; H, 10·9%). The rest of the crude product was refluxed with concentrated hydrochloric acid (30 c.c.) for 3 days, the whole concentrated (to 5 c.c.) and basified with sodium hydroxide, and the resulting precipitate crystallised from ethanol to give 4-p-*aminophenylpyridine* 1-*oxide* (0·3 g., 18% overall) in plates, m. p. 270° (Found: C, 70·6; H, 5·3; N, 14·6%).

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