401. *Ionization Constants of Heterocyclic Substances. Part VI.*[1] *Some Substituted Pyridines.*

By G. B. Barlin.

Ionization constants and ultraviolet spectra are reported for amino- and hydroxy-pyridines made earlier.[2,3]

2-(and particularly 4-)Aminopyridines owe their high basic strength to an excess of resonance in the cation over what is possible in the neutral molecule.[4] It was interesting to determine whether a nitro-group placed *ortho* to the amino-group would exert an

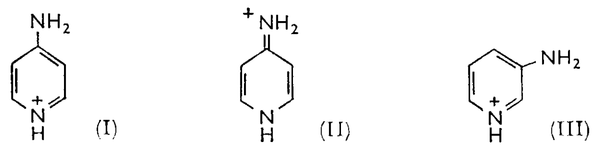
[1] Part V, Albert and Barlin, *J.*, 1962, 3129.
[2] Albert and Barlin, *J.*, 1963, 5156.
[3] Albert and Barlin, *J.*, 1963, 5737.
[4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.

unusually great base-weakening effect owing to either a cross-resonance, or steric interference with the position of the amino-group which must be co-planar in the cation if maximum resonance is to occur. The effect of a nitro-group on the basic and acidic ionizations of 2- and 4-hydroxypyridines was also studied because resonance plays a part in stabilizing at least the neutral molecule of these substances.[5]

It was found that a 3-nitro-group exerts a strong base-weakening effect (3·32—4·75 p*K* units) in all the compounds examined, *viz.*, 2- and 4-amino-3-nitro-, 4-methylamino-3-nitro-, 2-chloro-3-nitro-, 4-ethoxy-3-nitro-, and 2- and 4-hydroxy-3-nitro-pyridine (see Table, where constants of substances lacking the nitro-group are also given for comparison). This result is of the same order as the base-weakening effect of the 3-nitro-group on pyridine (4·42 p*K* units), and it is concluded that principally inductive (—*I*) influences are being exerted in all cases. Again the 3-nitro-group strengthens the acidic ionization of 2- and 4-hydroxypyridine by a similar amount (3·10—3·44 units).

Similarly a 2-chloro-group, which lowers the basic strength of pyridine by 4·51 p*K* units through mainly (—*I*) influence,[6] exerts no greater effect (*viz.*, 3·37—4·35 units) in 4,5-diamino-2-chloro-, 2,3-diamino-6-chloro-, and 2-chloro-3-nitro-pyridine. The presence of two chlorine atoms in 5-amino-2,4-dichloropyridine causes little further diminution than observed above, and the pK_a value is reduced to a figure 5·25 units below that of 3-aminopyridine.

In the monoaminopyridines, addition of a proton to the resonance stabilized 4-(and 2-)-aminopyridinium cations (I ↔ II), where both nitrogen atoms carry some charge, is more difficult than to the uncharged extranuclear amino-group of the 3-aminopyridinium cation



(I) (II) (III)

(III) and the differences in the pK_a values of the two cations of 2-, 3-, and 4-aminopyridine are, respectively, 14·46, 7·48, and 15·47. 2,3-(and 3,4-)Diaminopyridines show a first basic pK_a of the order of the more basic 2-(and 4-)aminopyridine, which signifies protonation and resonance as in 2- and 4-aminopyridine. However the second pK_a is of the order found for 3-aminopyridine, signifying that the second protonation is on the 3-amino-group.

Electron release by an extranuclear *N*-methyl group in 3-amino-4-methylamino-, 4-amino-3-methylamino-, and 4-methylamino-3-nitro-pyridine results in the usual small base-strengthening effect, *viz.*, 0·15—0·43 unit.

Ultraviolet Spectra.—In accordance with R. N. Jones's rule,[7] the ultraviolet spectra of the anion of 2- and 4-hydroxy-3-nitropyridine are similar to those of the neutral molecules of 2- and 4-amino-3-nitropyridine, respectively.

Conversion of the neutral molecules of 2,3- and 3,4-diamino-, and 3-amino-4-methylamino- and 4-amino-3-methylamino-pyridine to the monocation produces a bathochromic shift as is observed in 2-, 3-, and 4-aminopyridine,[8] where protonation is known to take place on the ring nitrogen atom; addition of a second proton produces an hypsochromic shift as is observed in 3-aminopyridine cation [9] and signifies that the second proton adds to the 3-amino- or 3-methylamino-group.

Replacement of a hydrogen atom by a methyl group on an extranuclear amino-group is seen to have the customary small bathochromic effect on the spectrum of the cations of 3,4-diamino- and 4-amino-3-nitro-pyridine, but little effect on that of the neutral species.

[5] Albert and Phillips, *J.*, 1956, 1294.
[6] McDaniel and Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 3756.
[7] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[8] Mason, *J.*, 1960, 219.
[9] Albert, *J.*, 1960, 1020.

Physical properties.

		Ionization (H_2O; 20°)				Spectroscopy in water [p]		
Pyridine	Species [a]	pK_a	Spread (±)	Concn. (M)	A.w.l [b]	$\lambda_{max.}$ (mμ)	log ε	pH
Pyridine	+	9·23 [c]	—	—	—	—	—	—
2-Amino-3-nitro-	0	—	—	—	—	217·5, *238*, *260*, 389	4·30, *3·80*, *3,57*, 3·82	5·0
	+	2·38 [d]	—	—	—	<210, 264, 360	>4·26, 3·66, 3·85	0·4
4-Amino-3-nitro-	o	—	—	—	—	230·5, 269, 362	4·27, 3·56, 3·64	8·0
	+	5·04	0·03	0·00004	260	227, 259, *265*, 331	4·27, 3·98, *3·92*, 3·57	2·0
2-Amino-	+	6·86 [c]	—	—	—	—	—	—
	++	−7·6 [e]	—	—	—	—	—	—
3-Amino-	+	5·98 [c]	—	—	—	—	—	—
	++	−1·5 [f]	—	—	—	—	—	—
4-Amino-	+	9·17 [c]	—	—	—	—	—	—
	++	−6·3 [e]	—	—	—	—	—	—
4-Methylamino-	o	—	—	—	—	237, *272*, 386	4·28, *3·55*, 3·71	8·0
3-nitro-	+	5·19	0·05	0·00004	270	231, 267, 350	4·21, 4·08, 3·59	2·0
4-Methylamino-	+	9·66 [g]	—	—	—	—	—	—
2-Chloro-3-nitro-	o	—	—	—	—	209, *240*, 281	4·12, *3·56*, 3·45	7·0
	+	−2·6 [h]	—	—	—	239, 278	3·66, 3·76	−4·9
2-Chloro-	+	0·72 [i]	—	—	—	—	—	—
4-Ethoxy-3-nitro-	o	—	—	—	—	213, 252, 294	4·23, 3·67, 3·41	7·0
	+	2·67	0·04	0·0013	310	221, *239*, 277, *332*	4·28, *3·95*, 3·35, *2·45*	0·0
4-Ethoxy-	+	6·67 [j]	—	—	—	—	—	—
2-Hydroxy-3-nitro- [k]	o	—	—	—	—	257, 362	3·40, 3·85	5·0
	+	−4·00	—	—	—	240, 303	3·54, 3·87	17·5M-H_2SO_4
	—	8·52	—	—	—	216·5, 260, 392	4·23, 3·53, 3·82	12·0
2-Hydroxy-	+	0·75 [l]	—	—	—	—	—	—
	—	11·62 [m]	—	—	—	—	—	—
4-Hydroxy-3-nitro-	o	—	—	—	—	224·5, 249, *257*, 326	4·22, 3·90, *3·81*, 3·54	4·0
	+	−0·70	0·05	0·00005	254	217·5, 279, *335*	4·34, 3·33, *2·30*	−2·8
	—	7·65	0·04	0·00005	254	227·5, 265, 361	4·25, 3·50, 3·61	10·0
4-Hydroxy-	+	3·27 [l]	—	—	—	—	—	—
	—	11·09 [m]	—	—	—	—	—	—
3-Nitro-	+	0·81 [n]	—	—	—	—	—	—
4,5-Diamino-	o	—	—	—	—	217·5, 249, 290	4·46, 3·81, 3·54	7·0
2-chloro-	+	4·79	0·03	0·000025	235	233, 290·5	4·40, 3·88	2·5
	++	0·08	0·05	0·000025	235	218, *224*, 265	4·17, *4·08*, 4·20	−2·28
2,3-Diamino-	o	—	—	—	—	246, 311	3·85, 3·84	7·0
6-chloro-	+	3·02	0·04	0·0001	350	231·5, 258, 312, *325*	3·82, 3·46, 3·71, *3·69*	1·0
	++	−0·91	0·04	0·0001	350	233, 317	3·92, 3·94	−3·0
2,4-Dichloro-	o	—	—	—	—	209, 244·5, 305	4·41, 4·01, 3·50	7·0
5-amino-	+	0·73	0·04	0·00004	266	228, 264, 336	4·37, 3·83, 3·59	−1·38
2,3-Diamino-	o	—	—	—	—	238, 301	3·78, 3·77	10·0
	+	7·00	0·02	0·00004	330	249, 318	3·66, 3·91	3·5
	++	−0·01	0·05	0·00004	330	227, 305	3·94, 3·80	−2·3
3,4-Diamino-	o	—	—	—	—	245, 283	3·80, 3·57	12·0
	+	9·14 [o]	0·03	0·00004	244	225, 286	4·28, 3·93	5·0
	++	0·49	0·04	0·00004	260	207·5, 262	4·13, 4·19	−1·85
3-Amino-	o	—	—	—	—	214, 258, *280*	4·35, 3·90, *3·72*	12·0
4-methylamino-	+	9·57	0·03	0·00004	300	226, 291	4·19, 4·08	5·0
	++	0·38	0·04	0·00004	300	210, *216*, 271	4·00, 3·85, 4·23	−2·28
4-Amino-	o	—	—	—	—	216, 252, 284	4·36, 3·74, 3·58	12·0
3-methylamino-	+	9·37	0·04	0·00004	310	228, 294	4·35, 3·85	5·0
	++	0·12	0·04	0·00004	310	208, 262	4·12, 4·19	−2·3
2-Ethoxycarbonyl-	o	—	—	—	—	221, 264, 400	4·32, 3·67, 3·84	7·0
methylamino-3-nitro-	+	0·53	0·05	0·0001	280	211, 269, 365	4·29, 3·85, 3·80	−1·85

[a] o Neutral species, + cation, ++ dication, — anion. [b] Analytical wavelength (mμ) for spectroscopic determinations of pK_a. [c] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [d] Personal communication from Dr. D. J. Brown. [e] Bender and Chow, *J. Amer. Chem. Soc.*, 1959, **81**, 3929. [f] Albert, *J.*, 1960, 1020. [g] Essery and Schofield, *J.*, 1961, 3939. [h] Personal communication from Dr. R. Willette. [i] Brown and McDaniel, *J. Amer. Chem. Soc.*, 1955, **77**, 3752. [j] Clarke and Rothwell, *J.*, 1960, 1885. [k] Personal communication from Drs. E. Spinner and J. White. [l] Albert and Phillips, *J.*, 1956, 1294. [m] Albert and Hampton, *J.*, 1954, 505. [n] Bryson, *J. Amer. Chem. Soc.*, **1960**, **82**, 4871. [o] Cf. Albert and Pedersen, *J.*, 1956, 4683 who give 9·08 (potentiometric). [p] Shoulders and inflexions in italics.

Experimental

Ionization constants were determined by methods developed in this Department.[10] Ultra-violet spectra were measured first on a Shimadzu model RS27 recording spectrophotometer and then the $\lambda_{max.}$ and ε values were checked on a Hilger " Uvispek " manual instrument.

The compounds used were prepared as previously.[2,3] 2-Amino-3-nitropyridine was supplied by Dr. D. J. Brown.

I thank Professor A. Albert for valuable discussion, and Messrs, H. Satrapa, C. Arandjelovic, and K. Tratt for experimental assistance.

Department of Medical Chemistry, Institute of Advanced Studies,
Australian National University,
Canberra, A.C.T., Australia. [*Received, September* **24*th*, 1963**.]

[10] Albert and Serjeant, " Ionization Constants of Acids and Bases," Methuen, London, 1962.