455. *The Strength of Heterocyclic Bases.*

By Adrien Albert, Reginald Goldacre, and John Phillips.

The relative strength of heterocyclic bases constitutes a comparatively unexplored territory. Ionisation constants are now recorded for 120 heterocyclic bases belonging to 30 different, completely unsaturated, ring systems.

The principle of *additional ionic resonance*, which is known to be responsible for the enhanced basic strength of 2- and 5-aminoacridines, is shown to operate in many other nuclei.

The insertion of a further nitrogen into a pyridine ring (as in phenazine or quinoxaline) is shown to cause a marked lowering of basic strength, whereas the insertion of a further nitrogen into a pyrrole ring (as in indazole or benziminazole) creates definite basic properties where none was demonstrable before.

The addition of a benzene ring to a heterocyclic base, so that two carbon atoms are shared, usually affects the basic strength to only a relatively small extent.

The strength of *saturated* heterocylic bases is known to be approximately that of the corresponding aliphatic amines (*ca.* pK_a 10). However, little exact information is available concerning the strength of *unsaturated* heterocyclic bases. Of these, the acridine series has been most thoroughly explored and a survey of 115 acridines (Albert and Goldacre, *J.*, 1943, 454; *J.*, 1946, 706) has facilitated the prediction of approximate pK values in this series, an important consideration in chemotherapy because the kationic species is by far the most antibacterial.

The strengths of bases derived from 30 other heterocyclic systems have now been surveyed and interpreted from the following standpoint. The ionisation constants of these heterocyclic systems differ qualitatively from those of saturated systems through having a component not found in the latter. This component comes from the change (upon ionisation) in the energetics of the resonating system of π electrons, in which system the basic centre is intimately concerned. Hence the ionisation constant, as the measure of the free-energy change on ionisation, must carry a term closely related to the change in resonance energy upon adding a proton to the nitrogen. If it were possible to calculate this resonance change and to estimate the ionisation entropy change, the results reported here could be discussed in terms of fundamental thermodynamics. However, such calculations are not yet possible and hence the plan followed has been to deal with the more striking features of the new data in terms of the qualitative resonance energy ideas used in interpreting our acridine work.

The most important of these is the " additional ionic resonance effect " conveniently illustrated as follows. Acridine itself is a fairly weak base of pK_a 5·6 (cf. Table II). The strength rises slightly when an amino-group is inserted in the 3- or 4-position (normal amino-derivatives) and is distinctly weakened if this group is in the 1-position (*ortho*-effect). However, an amino-group in the 2- or 5-position adds greatly to the basic strength because it brings about a resonance in the ions [through the pairs of canonical structures (VI, *a* and *b*) and (VII, *a* and b)] additional to that provided by the non-ionised molecule (Albert and Goldacre, *loc. cit.*). The

case of 2-aminoacridine suggests that the loss of a Kekulé ring can be largely compensated for by the type of *p*-quinonoid structure shown (VII, *b*). On the other hand, an *o*-quinonoid structure, of the type of (VIII), although a possible contributor to the ion of 4-aminoacridine, is of little value for this purpose.

As this " additional ionic resonance effect " furnished the strongest aminoacridine bases, it was decided to pay particular attention to it in other heterocyclic series. Before investigating these, it was thought advisable to consider those open-chain compounds which show this effect in its simplest form.

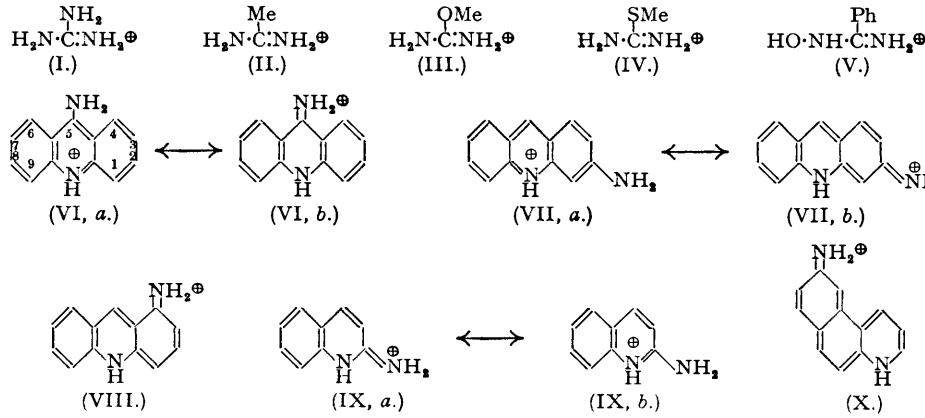
TABLE I.

Ionisation of open-chain bases having additional ionic resonance, determined in water at 20°.

No.	Substance.	pK_a.*	Dilution (1/M.).	Mode of preparation.	M. p.
1	[Guanidine (I)] †	13·71	0·5	—	—
2	Acetylguanidine	8·33	20	A	142°
3	[Phenylguanidine] ‡	10·88	30	—	—
4	[Acetamidine (II)] §	12·52	25	—	—
5	Benzamidine	11·6	10	B	80
6	[*O*-Methyl*iso*urea (III)] ‖	9·80	50	—	—
7	[*N*-Phenyl-*O*-methyl*iso*urea] ¶	7·3	—	—	—
8	*S*-Methyl*iso*thiourea (IV)	9·83	40	C	—
9	*N*-Phenyl-*S*-methyl*iso*thiourea	7·14	160	D	71
10	Benzamidoxime (V)	4·82	160	E	78

* pK_a is the negative logarithm of the acidity constant $[B][H^+]/[BH^+]$.
† Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3469.
‡ Davis and Elderfield, *J. Amer. Chem. Soc.*, 1932, **54**, 1499.
§ Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162.
‖ Zief and Edsall, *J. Amer. Chem. Soc.*, 1937, **59**, 2245.
¶ Bruce, *ibid.*, 1904, **26**, 419 (conductimetry).
A Korndörfer, *Arch. Pharm.*, 1903, **241**, 467.
B Pinner and Klein, *Ber.*, 1878, **11**, 6.
C The sulphate (Shildneck and Windus, *Org. Synth.*, 1932, **12**, 52) was titrated with alkali.
D Bertram, *Ber.*, 1892, **25**, 49.
E Tiemann and Kruger, *Ber.*, 1884, **17**, 1865.

It will be seen from Table I that guanidine (I) is the strongest base of the series. Its ion has three equivalent structures in which each NH_2 in turn carries the kationic charge and the double bond, making for a higher degree of resonance than exists in the non-ionised molecule and thus accounting for the extraordinarily high basic strength (cf. Pauling, " The Nature of the Chemical Bond ", Cornell, 1942, p. 213; Branch and Calvin, " The Theory of Organic Chemistry ", Prentice-Hall, 1941, p. 194). The case of acetamidine (II) is similar, but the fact that there are only two equivalent structures contributing to the ion has led to a loss of basic strength, partly compensated by the electron-donating properties of the methyl group. In *O*-methyl*iso*urea (III) and *S*-methyl*iso*thiourea (IV), the electron-donating methyl group has been replaced by



electron-attracting groups, with some loss of basic strength. Nos. 2, 3, 5, 7, and 9 were included in this comparison, to help assess the effects of electron-attracting groups on these values, which

are subject to similar influences in heterocyclic nuclei. The resultant pK_a values may be compared with those of 5-aminoacridine (9·99), which is a vinylogous amidine and 2 : 5-diaminoacridine (11·49), which is a vinylogous guanidine. We shall see that when not one, but two, hetero-atoms of these open-chain bases form part of a heterocyclic ring, cross-resonances seriously reduce the base-strengthening features of their structure [cf. acetamidine and pyrimidine (No. 79); guanidine and 2-aminopyrimidine (No. 80); *S*-methyl*iso*thiourea and 2-aminothiazole (No. 129)]. Benzamidoxime (V), the ion of which has no equivalent resonance structures and is electronegatively substituted, is seen to be a weak base.

Quinoline and Pyridine compared with Acridine.—Table II lists the pK_a values of pyridine and quinoline and all their monoamino-derivatives. Some of these values have been reported in brief (Albert and Goldacre, *Nature*, 1944, **153**, 467) but they have now been more accurately established by repeated titrations averaging 6—10 points on the curve. Acridine compounds substituted in analogous positions have been placed opposite the corresponding pyridine and quinoline compounds to facilitate comparison. The lower solubility in water of the acridines necessitated a higher dilution [see Experimental Section for the (small) effect of concentration on pK].

It may be seen from Table II that the removal of one or two benzene rings from acridine and the aminoacridines has affected most of the pK values, but not profoundly. Acridine is the strongest and quinoline the weakest of the unsubstituted bases, but the differences are small. Nos. 13, 17, 19, and 20 would be classed as normal amino-derivatives (as defined above for Nos. 27 and 28); they show a small elevation in pK_a (0·01—1·4 units). No. 22 (8-aminoquinoline) shows an *ortho*-effect (depression of pK_a) comparable to that of its acridine analogue (No. 30).

TABLE II.

The ionisation of heterocyclic bases (1 *nitrogen atom in ring*) (*determined in water at* 20°).

No.	Pyridine series.	pK_a.	Dilution (1/M.).	M. p.
11	Pyridine	5·23 *	60	—
12	2-Amino-	6·86 †	60	57°
13	3-Amino-	5·98 †	60	64
14	4-Amino-	9·17 ‡	45	158

No.	Quinoline series.	pK_a.	Dilution (1/M.).	M. p.
15	Quinoline	4·94 *	60	—
16	2-Amino-	7·34	60	131°
17	3-Amino-	4·95	60	94
18	4-Amino-	9·17	60	154
19	5-Amino-	5·46	60	110
20	6-Amino-	5·63	60	117
21	7-Amino-	6·65	60	94
22	8-Amino-	3·99	60	65
23	4-Amino-2-methyl-	9·44	240	164
24	2 : 4-Diamino-	9·45	40	197—198

No.	Acridine series.	pK_a.§	Dilution (1/M.).
25	Acridine	5·60	2500
—	(no analogue)	—	—
—	(no analogue)	—	—
26	5-Amino-	9·99	2500
27	4-Amino-	6·04	6000
28	3-Amino-	5·88	6000
29	2-Amino-	8·04	5000
30	1-Amino-	4·40	3000

* These values are in good accord with numerous other determinations in the literature.

† Tropsch, *Monatsh.*, 1914, **35**, 777, obtained 7·2 for the 2-isomeride and 6·6 for the 3-isomeride (conductimetry).

‡ Tropsch (*loc. cit.*) obtained 9·2 (conductimetry).

§ Taken from Albert and Goldacre, *J.*, 1946, 706.

The remaining compounds might reasonably be expected to show some evidence of additional ionic resonance. Nos. 14, 18, and 26 (which have an ion of the VI, *a* and *b* type) all show this to a high degree. The case of 4-aminopyridine illustrates the approximately equivalent resonance energy of a nucleus consisting of a Kekulé ring and one consisting of a *p*-quinonoid structure of the type (VI, *b*), because the partial destruction of a Kekulé ring, in forming the ion, has not cancelled a large additional ionic resonance. However, additional ionic resonance is not so marked in No. 21 as in No. 29, presumably because in No. 21 one *p*-quinonoid structure (of the type VII, *b*) replaces two Kekulé rings, whereas in No. 29, one *p*-quinonoid and one Kekulé ring replace two Kekulé rings. 2-Aminopyridine and particularly 2-aminoquinoline (Nos. 12 and 16) show an additional ionic resonance effect involving an *o*-quinonoid structure (*e.g.*, IX, *a* and *b*) which is actually a cyclic amidine and has no analogue in the acridine series. 2 : 4-Diaminoquinoline (No. 24) does not show much elevation of pK_a above No. 18.

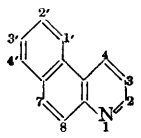
The insertion of a methyl group usually gives rise to a base-strengthening effect (0·3—1·0 pK unit) in the pyridine, quinoline, and acridine series (Constam and White, *Amer. Chem. J.*, 1903, **29**, 46; Felsing and Biggs, *J. Amer. Chem. Soc.*, 1933, **55**, 3624; Albert and Goldacre, 1946, *loc. cit.*), particularly if it is in the α- or γ-position. 4-Amino-2-methylquinoline (No. 23) is the

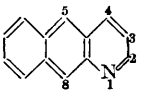
first of several fresh examples of this effect encountered in the present work (see also Tables III and V).

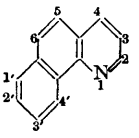
TABLE III.

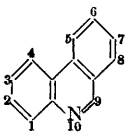
The ionisation of heterocyclic bases (1 *nitrogen atom in ring*) (*continued*).

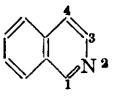
(Determined in water, except for values in parentheses which were determined in 50% alcohol, all at 20°.)


5 : 6-Benzquinoline.


6 : 7-Benzquinoline.


7 : 8-Benzquinoline.


Phenanthridine.


*iso*Quinoline.

No.	Substance.	pK_a.	ΔpK_a, water — alcohol.	Dilution (1/M.).	Source.	M. p.
31	5 : 6-Benzquinoline	5·15 (3·90)	1·25	10,000 (40)	F	94°
32	4-Amino-	(7·99)	—	(60)	G	150—151
33	4-Amino-2-methyl-	(8·45)	—	(120)	G	161
34	2-Methyl-	(4·44)	—	(160)	I	83
35	2-Amino-4-methyl-	7·14 (6·51)	0·63	100,000 (200)	G	224—225
36	4′-Amino-	5·20 (4·10)	1·10	(40)	J	175
37	3′-Amino-	(4·02)	—	(80)	H	222—224
38	1′-Amino-	5·03	—	10,000	H	156—157
39	2′ : 4′-Diamino-	(4·91)	—	(60)	J	249
40	6 : 7-Benzquinoline	5·05 (3·84)	1·21	7,000 (120)	G	116·5
41	4-Amino-	(8·75)	—	(300)	G	233 (sealed)
42	4-Amino-2-methyl-	(9·45)	—	(160)	G	180
43	4-Amino-2-methyl-8-chloro-	(5·95)	—	(300)	G	179—180
44	8-Chloro-	(2·5)	—	(160)	K	142
45	3 : 4-Diamino-	(8·15)	—	(320)	G	212 (dec.)
46	3-Amino-	4·78 (3·73)	1·05	10,000 (400)	G	240—241
47	7 : 8-Benzquinoline	4·25 (3·15)	1·10	10,000 (40)	L	52
48	4-Amino-	(7·68)	—	(120)	G	173—174
49	4-Amino-2-methyl-	(7·96)	—	(60)	G	149—150
50	2-Amino-4-methyl-	6·74 (6·02)	0·72	20,000 (240)	G	133—134
51	6-Amino-2-methyl-	(5·23)	—	(160)	G	128—129
52	1′-Amino-2-methyl-	(4·75)	—	(160)	G	141·5
53	Phenanthridine	(3·30)	—	(60)	G	107—108
54	9-Amino-	7·31 (6·75)	0·56	13,000 (120)	M	195
55	2-Amino-9-methyl-	(5·66)	—	(160)	N	173
56	7-Amino-9-methyl-	(5·23)	—	(160)	N	232
57	2 : 7-Diamino-9-methyl-	(6·26)	—	(160)	N	265
58	2 : 7 : 9-Triamino-	(8·06)	—	(160)	G	200
59	[*iso*Quinoline]	5·14 *	—	—	—	—
60	1-Amino-	7·62	—	160	O	123

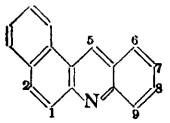
* Determined by Kolthoff, *Biochem. Z.*, 1925, **162**, 289.
F Knueppel, *Ber.*, 1896, **29**, 708.
G Albert, Brown, and Duewell, this vol., p. 1284.
H A specimen was kindly presented by Prof. C. Hamilton of the University of Nebraska.
I Eastman-Kodak, recrystallised.
J Clem and Hamilton, *J. Amer. Chem. Soc.*, 1940, **62**, 2349.
K Clemo and Driver, *J.*, 1945, 829.
L Haid, *Monatsh.*, 1906, **27**, 318.
M Morgan and Walls, *J.*, 1932, 2225.
N A specimen was kindly presented by Dr. L. Walls of the Wellcome Chemical Research Laboratories.
O Chichibabin and Oparina, *J. Russ. Phys. Chem. Soc.*, 1920, **50**, 543.

Benzquinolines, Phenanthridines, and Benzacridines.—Tables III and IV record the pK_a values of some representative members of 8 other heterocyclic series having one ring-nitrogen. Unfortunately, the very sparing solubility of these substances (particularly the primary amines) in water and, in some cases, the lack of a decided colour-change upon ionisation, often necessitated carrying out potentiometric titrations in aqueous alcohol. However, 12 of the compounds were examined in water (colorimetrically in a series of buffers) and if these compounds may be taken as representative, the ΔpK values (depressions of pK_a due to alcohol)

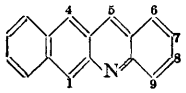
TABLE IV.

The ionisation of heterocyclic bases (1 *nitrogen atom in ring*) (*concluded*).

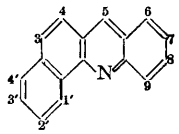
(Determined as in Table III.)



3 : 4-Benzacridine.



2 : 3-Benzacridine.



1 : 2-Benzacridine.

No.	Substance.	pK_a.	ΔpK_a, water — alcohol.	Dilution (1/M.).	Source.	M. p.
61	3 : 4-Benzacridine	4·70 (4·16)	0·54	* (160)	P	132°
62	5-Amino-	(8·41)	—	(240)	G	236—237
63	7-Amino-	(5·03)	—	(170)	G	237—238
64	8-Amino-	7·42 (6·51)	0·91	33,000 (300)	Q	264—265
65	8-Acetamido-	(4·48)	—	(320)	Q	269
66	8-Dimethylamino-	7·31 (6·99)	0·32	48,000 (240)	R	184
67	2 : 3-Benzacridine	(4·52)	—	(480)	G	223
68	5-Amino-	(9·72)	—	(120)	G	231—232
69	5-Acetamido-	(4·56)	—	(640)	G	*ca.* 230 (dec.)
70	7-Amino-	(5·38)	—	(320)	G	285—286
71	5-Amino-6 : 7 : 8 : 9-tetrahydro-	(9·66)	—	(60)	G	236—238
72	1 : 2-Benzacridine	(3·45)	—	(160)	S	108
73	5-Amino-	(8·13)	—	(320)	G	196—197
74	7-Amino-	(4·05)	—	(160)	G	165
75	8-Amino-	6·72 (5·97)	0·75	40,000 (240)	Q	200
76	4′ : 5-Diamino-	(8·44)	—	(200)	G	225—226

* The pK in water was determined by extrapolation from titrations in 50, 40, 30, and 20% alcohol to 0% alcohol.

G As in Table III.

P Baezner, *Ber.*, 1904, **37**, 3077.

Q Albert, this vol., p. 1225.

R Ullmann and Marić, *Ber.*, 1901, **34**, 4318. A sample was kindly presented by Drs. L. Small and L. Sargent through the Anti-Malarial Survey.

S Ullmann and La Torre, *Ber.*, 1904, **37**, 2922.

cover much the same range as that found in the acridine series. The nature of the connexion between the value of this depression and the molecular structure has been discussed (Albert and Goldacre, *loc. cit.*, 1946), and the extreme values known are zero (4-aminoquinoline) and 1·49 pK units (acridine) but most of them lie between 0·5 and 0·8. In any given series, the members with additional ionic resonance usually have the smallest ΔpK's.

It is seen from the tables that the parent substances (Nos. 31, 40, 47, 53, 61, 67, and 72) have pK's close to those of quinoline and pyridine. The 7 : 8-benzquinolines and 1 : 2-benzacridines, which share a structural feature, are weaker bases than their isomerides. The following are classified as normal amino-derivatives, as defined above for 3- and 4-aminoacridines, and it will be seen that the elevation of pK is of the same order as in the quinoline and acridine series (cf. Table II) : Nos. 36, 37, 38, 39, 46, 51, 52, 56, 63, 70, and 74.

An elevation of pK derived from an additional ionic resonance of the type (VI, *a*, *b*) is seen in Nos. 32, 33, 41, 42, 45, 48, 49, 62, 68, 71, 73, and 76 and is of the same size as in 4-aminoquinoline and 5-aminoacridine (*i.e.*, *ca.* 5·0 units).

Elevations of pK similarly derived from the ionic resonance (VII, *a* and *b*) occur in Nos. 64, 66, 75, and possibly 55, and are of the same size as in 2-aminoacridine. Further elevations similarly derived (from IX, *a* and *b*) are found in Nos. 35, 50, 54, 58, and 60 and are of the same size as in 2-aminoquinoline. Because phenanthridine may be regarded as benzo*iso*quinoline, the relevant *iso*quinolines (Nos. 59 and 60) have been included for comparison.

Small but definite elevations due to a methyl group appear quite consistently, as in the quinoline and acridine series and the usual examples of depression due to *N*-acetylation or *C*-chlorination were found (Nos. 65, 69, 43, and 44). No. 45, compared with No. 41, appears to show an *ortho*-effect comparable with that of *o*-phenylenediamine.

The angular series in Tables III and IV have three Kekulé rings and all the nuclear stability

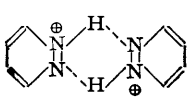
that goes with this structure. However, the formation of ions of the types (VI), (VII), and (IX) does not destroy any more Kekulé structures in the benzquinoline and benzacridine series than in the quinoline or acridine series. On the other hand, it is not expected that structures (such as X) which entirely destroy the Kekulé structure could give rise to additional ionic resonance : the low pK's of Nos. 36 and 39 support this.

Six-membered Rings with Two Nitrogen Atoms.—Reference to Table V shows that the introduction of a second nitrogen into a six-membered ring already containing a nitrogen atom greatly reduces the basic strength, often by as much as 4 pK units. Pyridine (No. 11) may be compared with pyridazine, pyrimidine, and pyrazine (Nos. 77, 79, 88), quinoline (No. 15) with cinnoline, phthalazine, quinazoline, and quinoxaline (Nos. 90, 92, 94, and 99), and acridine (No. 25) with phenazine (No. 104).

A small loss of basic strength upon the introduction of a second nitrogen is seen even in saturated compounds, *e.g.*, the pK_a of ammonia, 9·3, falls to 8·5 in hydrazine (Bredig, *Z. physikal. Chem.*, 1894, **13**, 289) and that of piperidine, 11·6, falls to 10·3 in piperazine (Kolthoff, *Biochem. Z.*, 1925, **162**, 289). However, the loss is greater in the present series because several factors are involved. In the first place, the second nitrogen atom is electron-attracting and hence base-weakening. Then, in several cases there are opportunities for the formation of *exactly equivalent* dipolar structures in the non-ionised molecule (*e.g.*, XII) and these may strengthen the resonance of this species at the expense of the ion. The particularly low pK_a values of pyrazine, quinoxaline, and phenazine (Nos. 88, 99, and 104) are cases in point. These substances are vinylogues of azobenzene, which is a very weak base for a similar reason (cf. also molecular nitrogen in this connexion). However, pyridazine, cinnoline, and phthalazine (Nos. 77, 90, and 92), which have adjacent nitrogens and hence appear more clearly to resemble azobenzene, are capable of forming hydrogen-bonded pairs of ions (*e.g.*, XIII) which have extra resonance relative to the non-ionised molecule. This is not possible in *trans*-azobenzene for steric reasons.


(XI.)


(XII.)


(XIII.)

It is of interest that cinnoline was described as a " strong base " (Busch and Rast, *Ber.*, 1897, **30**, 521) although the pK_a is now found to be only 2·70. Several other instances have come to light where a writer has been misled as to the strength of bases by relying on criteria other than an actual pK measurement.

Table V contains a few examples of normal amino-derivatives of the type of 3-aminoacridine, *viz.*, Nos. 82, 97, and 105, and, as expected, the pK is not increased by more than 2 units. No. 98 shows the *ortho*-effect, but Nos. 101 and 105 do not because in the latter both nitrogens are equivalent. The remainder of the amino-derivatives would be expected to show additional ionic resonance due to one or other of the types (VI), (VII), or (IX) discussed above. With one exception (2-aminoquinazoline, No. 95) the expected increment of over 2 pK units is found. Table V also contains some polyamino-compounds in which each amino-group separately has been shown to introduce additional ionic resonance (Nos. 85, 86, 103, 108, and 109). These compounds would bear the same relation to the corresponding monoamino-derivatives which guanidines bear to amidines were it not for the many possibilities for cross-resonances. 2 : 4-Diaminopyrimidine (No. 85) exemplifies mutual reinforcement of basic strength but 2 : 4 : 6-triaminopyrimidine (No. 86) is weaker, a curious fact which we have carefully confirmed (cf. also Nos. 106 and 109).

The usual slight base-strengthening properties of the methyl group are seen again in Nos. 87, 83, and 84, the last two examples being of interest because of the sulphonamide drugs derived from them.

The effect of inserting more than two nitrogens into a six-membered ring should, by extrapolation, be very base-weakening. Unfortunately, such compounds are unstable. Although no synthesis of 1 : 3 : 5-triazine has been recorded, two of its amino-derivatives are listed in Table VI (Nos. 110 and 111). It will be seen that they are about 1·5 units weaker than the corresponding pyrimidines (Nos. 84 and 86).

A small selection of phenanthrolines has also been included in Table VI to represent heterocyclic compounds with two nitrogens in *different* rings. The pK_a values of Nos. 112—114 are approximately equal to those of the corresponding benzacridines (Table III) and hence form a contrast to phenazine (No. 104) with which they are isomeric.

TABLE V.

The ionisation of heterocyclic bases (2 nitrogen atoms in a six-membered ring).

(Determined as in Table III.)

No.	Substance.	pK_a.	Dilution (1/M.).	Source.	M. p.	B. p.
77	Pyridazine	2·33	10	T	—	205—206°/760 mm.
78	[3-Amino-]	5·19 *	—	—	—	—
79	Pyrimidine	1·30	15	U	—	123/760 mm.
80	2-Amino-	3·54	10	V	127—128°	—
81	4-Amino-	5·71	200	W	151—152	—
82	[5-Amino-]	2·83 *	—	—	—	—
83	2-Amino-4-methyl-	4·15	60	X	159—160	—
84	2-Amino-4 : 6-dimethyl-	4·85	160	X	153	—
85	2 : 4-Diamino-	7·26	160	W	144—145	—
86	2 : 4 : 6-Triamino-	6·84	160	Y	245—246	—
87	4-Methyl-	1·98	20	U	—	—
88	Pyrazine	0·6	10	Z	—	118/760 mm.
89	2-Amino-	3·14	20	AA	117—119	—
90	Cinnoline	2·70	150	BB	37—38	—
91	4-Amino-	6·84	160	CC	210	—
92	Phthalazine	3·47	80	DD	91—92	—
93	1-Amino-	6·60	150	EE	210—211	—
94	Quinazoline	3·51 (3·2) †	15 (50) (27°)	FF	—	241/760 mm.; 133/23 mm.
95	2-Amino-	4·43	150	GG	206	—
96	4-Amino-	5·73	150	GG	272	—
97	[6-Amino-]	(3·2) †	(50) (27°)	—	—	—
98	[8-Amino-]	(2·4) †	(50) (27°)	—	—	—
99	Quinoxaline	~0·8	10	HH	28	228—229/760 mm.
100	2-Amino-	3·96	150	II	155—156	—
101	5-Amino-	2·62	150	JJ	94—95	—
102	6-Amino-	2·95	160	KK	158—159	—
103	2 : 3-Diamino-	4·70	240	KK	(dec.)	—
104	Phenazine ‡	1·23±0·10	3000	LL	173—174	—
105	1-Amino-	(2·6)	(300)	MM	175—176	—
106	2-Amino-	4·75 (3·46)	12,000 (120)	NN —	279 —	— —
107	1 : 3-Diamino-	(5·64)	(240)	MM	274—275	—
108	2 : 3-Diamino-	(4·74)	(130)	OO	(dec.)	—
109	2 : 7-Diamino-	4·63 (3·9)	8000 (160)	PP —	(dec.) —	—

* Unpublished value kindly communicated to us by Dr. R. O. Roblin, of The American Cyanamid Co.'s Laboratory, Stamford.

† These results are reproduced from Elderfield, Williamson, Gensler, and Kremer (*J. Org. Chem.*, 1947, **12**, 405).

‡ Phenazine proved to be photosensitive, hence its solution was prepared in the light of a 5-watt red lamp. By fairly rapid working, consecutive readings on the absorptiometer (violet glass filter) agreed well.

T Evans and Wiselogle, *J. Amer. Chem. Soc.*, 1945, **67**, 60. A specimen was kindly presented by Dr. Wiselogle.

U Gabriel and Colman, *Ber.*, 1899, **32**, 1534.

V A quantity was kindly presented by Monsanto, Ltd., and was recrystallised.

W The corresponding chloro-compound was heated with alcoholic ammonia at *ca.* 180° for 8 hours (K. F. Baker, unpublished).

X Benary, *Ber.*, 1930, **63**, 2601; Combes and Combes, *Bull. Soc. chim.*, 1892, **7**, 791. Samples were kindly presented by Prof. A. K. Macbeth of Adelaide.

Y A quantity was kindly presented by Dr. G. M. Dyson and recrystallised.

Z A quantity was kindly presented by Dr. R. O. Roblin and refractionated.

AA Ellingson, Henry, and McDonald, *J. Amer. Chem. Soc.*, 1945, **67**, 1711; Weijlard, Tishler, and Erickson, *ibid.*, p. 802.

BB Jacobs, Winstein, Henderson, and Spaeth, *ibid.*, 1946, **68**, 1310. A quantity of the hydrochloride, m. p. 160—162°, was kindly presented by Prof. Jacobs. The base was titrated immediately after fractionation.

CC Baker, this vol., p. 1713.

DD Gabriel and Müller, *Ber.*, 1895, **28**, 1830.

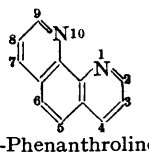
EE A specimen was kindly supplied by Prof. A. K. Macbeth and Mr. H. Rodda of Adelaide (unpublished preparation).

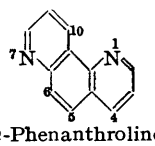
FF Riedel, D.R.-P., 174,941, 1905 (Friedl., **8**, 1238).
GG Macbeth and Rodda, *Nature*, 1945, **156**, 207.
HH Hinsberg, *Ber.*, 1884, **17**, 318.
II Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1944, **66**, 1957.
JJ Platt and Sharp, *J.*, in the press.
KK Specimens were kindly presented by Merck & Co., Inc., Rahway, recrystallised and analysed.
LL Kehrman and Havas, *Ber.*, 1913, **46**, 342.
MM Albert and Duewell, *J. Soc. Chem. Ind.*, 1947, **66**, 11.
NN Wohl and Lange, *Ber.*, 1910, **43**, 2187.
OO Fischer and Hepp, *Ber.*, 1889, **22**, 356 (analysed).
PP D.R.-P. 148,113, 1902 (Friedl., **7**, 341). A specimen was kindly presented by Dr. W. M. Clark through the Anti-Malarial Survey (analysed).

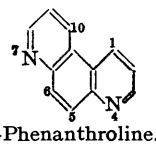
TABLE VI.

Ionisation of heterocyclic bases (3 *nitrogen atoms in a six-membered ring*; *or* 1 *nitrogen atom in each of two six-membered rings*).

(Determined as in Table III.)


o-Phenanthroline.


m-Phenanthroline.


p-Phenanthroline.

No.	Substance.	pK_a.	Dilution (1/M.).	Source.	M. p.
110	2-Amino-4 : 6-dimethyl-1 : 3 : 5-triazine	3·60	60	QQ	171—172°
111	Melamine (2 : 4 : 6-triamino-1 : 3 : 5-triazine)	5·16 *	160	RR	—
112	*o*-Phenanthroline	(4·27)	(40)	SS	117 (anhydrous)
113	*m*-Phenanthroline	(3·11)	(40)	TT	78
114	*p*-Phenanthroline	(3·12)	(40)	TT	177
115	1-Amino-	*ca.* 7·3	110	G	204
		(7·29)	(320)		
116	1 : 10-Diamino-3 : 8-dimethyl-	(8·76 & 6·31)	(160)	UU	324 (dec.)
117	2 : 2′-Dipyridyl	4·23	160	VV	69

* This compares with the values, 5·1 (spectroscopy) and 5·0 (titration), obtained by Dixon, Woodberry, and Costa, *J. Amer. Chem. Soc.*, 1947, **69**, 599.

QQ Tscherven-Iwanow, *J. pr. Chem.*, 1892, **46**, 147.
RR A specimen, kindly presented by Dr. C. Gibian of Timbrol, Ltd., Sydney, was recrystallised and analysed (C, H, and N).
SS G. F. Smith Chemical Co., Columbus, Ohio, recrystallised.
TT Specimens, kindly presented by Prof. W. O. Kermack, were recrystallised.
UU Jacini, *Gazzetta*, 1939, **69**, 111; 1940, **70**, 621.
VV British Drug Houses, recrystallised.

The increased basic strength of *o*-phenanthroline, compared with its isomerides, is ascribed to the simultaneous union of one proton to both nitrogens (by electrovalent and hydrogen bonds, respectively). This effect is not evident in the somewhat similarly constituted 2 : 2′-dipyridyl (No. 117) doubtless because of its free rotation around the 2 : 2′-bond.

1-Amino-*p*-phenanthroline (No. 115) does not give a titration curve of theoretical slope in water, in which it forms a somewhat viscous solution. An ion–base association, stronger than those described in the acridine series (Albert and Goldacre, *loc. cit.*, 1946), is indicated. The conditions are favourable because, in the mono-ion, one ring nitrogen will carry a formal negative charge and the other an ionic positive charge. The titration curve in 50% alcohol is almost regular. No. 116 is an interesting case of two (almost) independent additional ionic resonances in the one molecule (contrast 2 : 5-diaminoacridine, Albert and Goldacre, *loc. cit.*).

Heterocyclic Five-membered Rings.—Five-membered rings containing only one nitrogen are well known to be weak bases; for example, the pK_a of 0·4 has been calculated for pyrrole (Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5123), and indole is apparently no stronger. It is generally agreed (cf. Sidgwick, " Organic Chemistry of Nitrogen ", Oxford 1937, p. 490) that this effect is ascribable to a base-weakening resonance in which the nitrogen of the non-ionised molecule becomes positive and quaternary, somewhat as in aniline.

It has been known for some time that in at least three cases (pyrazole, glyoxaline, and

TABLE VII.

The ionisation of heterocyclic bases (five-membered rings).

(Determined as in Table III.)

No.	Substance.	Basic pK_a.	Dilution (1/M.).	Source.	M. p.	Acidic pK_a.
(a) *Two nitrogens in ring*						
118	[Pyrazole]	2·53 *	—	—	—	—
119	[Glyoxaline]	7·03 †	10 to 100	—	—	—
120	Indazole	1·3±0·2	100	WW	147—148°	—
121	3-Amino-	3·15	100	XX	154	—
122	6-Amino-	(3·66)	(160)	WW	206	—
123	Benziminazole	5·53 ‡	40	YY	170	12·3
124	2-Amino-	7·54	160	VV	222	—
(b) *More than two nitrogens in ring*						
125	[1 : 2 : 4-Triazole]	2·55 *	—	—	—	—
126	Benztriazole	1·6	20	ZZ	99	8·57 §
127	5-Aminotetrazole	6·03 ‖	80	AAA	200	1·80
		(6·77)	(160)	—	—	(2·55)
(c) *Two different hetero-atoms*						
128	Thiazole	2·53	10	BBB	(b. p. 117)	—
129	2-Amino-	5·39	130	V	90	—
130	Benzthiazole	(1·2±0·1)	(10)	CCC	(b. p. 231/760 mm.)	—
131	2-Amino-	4·51	160	DDD	129	—
132	Benzoxazole	(decomp.)	160	EEE	(b. p. 93/18 mm.)	—
133	2-Amino-	3·73	100	DDD	130	—

* Dedichen, *Ber.*, 1906, **39**, 183 (rate of hydrolysis of ethyl formate).
† Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146 (potentiometry).
‡ Schwarzenbach and Lutz (*Helv. Chim. Acta*, 1940, **23**, 1162) obtained 5·60 (potentiometry).
§ Schwarzenbach and Lutz, *loc. cit.*, obtained pK_a 8·44.
‖ Baur (*Z. physikal. Chem.*, 1897, **23**, 411) obtained pK_a 6·21 (conductimetry).

WW Noelting, *Ber.*, 1904, **37**, 2584. The published m. p. of 210° (Witt, Noelting, and Grandmougin, *Ber.*, 1890, **23**, 3635; Kwartler and Lucas, *loc. cit.*) appears to be corrected because 206° was the highest m. p. obtainable in spite of repeated recrystallisation with change of solvents. 6-Nitroindazole was also reduced in turn with hydrogen and Raney nickel (Kwartler and Lucas, *loc. cit.*), ammonium bisulphide (Witt *et al.*, *loc. cit.*), and tin and hydrochloric acid (Gabriel and Stelzner, *Ber.*, 1896, **29**, 307), always with the same result (Found : C, 62·8 H, 5·3; N, 31·5. Calc. for $C_7H_7N_3$: C, 63·1; H, 5·3; N, 31·6%).
XX Kwartler and Lucas, *J. Amer. Chem. Soc.*, 1943, **65**, 1804.
YY Wagner and Millett, *Org. Synth.*, 1939, **19**, 12.
ZZ Ladenburg, *Ber.*, 1876, **9**, 222.
AAA Thiele, *Annalen*, 1892, **270**, 45.
BBB McLean and Muir, *J.*, 1942, 383.
CCC Mills, *J.*, 1922, **121**, 460.
DDD Skraup, *Annalen*, 1919, **419**, 66.
EEE von Niementowski, *Ber.*, 1897, **30**, 3064.

benziminazole, Nos. 118, 119, and 123; Table VII) the insertion of another nitrogen in the ring is base-strengthening, and this has now been shown to be so for indazole also (No. 120). The base-strengthening effect of the second nitrogen, an effect which contrasts so sharply with what has been demonstrated in six-membered rings (Table V), must be ascribed to additional resonance (*e.g.*, between XIV, *a* and *b*) in the ions of each of the four compounds. From this, a base-weakening effect must be subtracted in those compounds which have adjacent nitrogens (Nos. 118 and 120) owing to hydrogen bonding of the non-ionised molecules (*e.g.*, XV; cf. Hunter, *J.*, 1941, 1). Additional ionic resonance effects, corresponding to 2-aminoquinoline, are demonstrated in some amino-derivatives (Nos. 121 and 124 and, possibly, 122). It is interesting to see 6-aminoindazole described in the literature as a strong base (Witt, Noelting, and Grandmougin, *Ber.*, 1890, **23**, 3635).

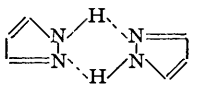
The effect of three nitrogens in a five-membered ring is shown in 1 : 2 : 4-triazole (No. 125) and benztriazole (No. 126); the base-weakening effect of the third nitrogen can be large [*e.g.*, $\Delta pK = -4{\cdot}4$ in passing from glyoxaline (No. 119) to 1 : 2 : 4-triazole].

5-Aminotetrazole is strongly acid to litmus (the pH of an M/80-solution is 4·1). It appears to be zwitterionic in nature, using the criterion afforded by titration both in alcohol and in water, *i.e.*, a rise in both pK_a values in 50% alcohol (cf. Albert and Goldacre, *loc. cit.*, 1946). The fact that the loss of a proton would make all nitrogens equivalent brings about a strong additional

resonance in the anion, hence the acidic pK is low. The electron-repelling effect of a stable anion acts as a further base-strengthening factor here.


(XIV, *a*.)


(XIV, *b*.)


(XV.)

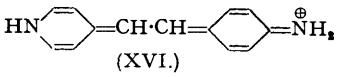

(XVI.)

Table VII concludes with a few five-membered ring systems containing two hetero-atoms. Benzoxazole was found to be decomposed to 2-formamidophenol too rapidly by acid to give a reliable titration figure. Thiazole and benzthiazole are seen to be much weaker bases than pyridine and quinoline. Additional ionic resonance is demonstrated for their amino-derivatives (Nos. 129 and 131) which are cyclic *iso*thioureas.

The following order of (increasing) basic strength was predicted by Brooker, Sprague, and Cressman (*J. Amer. Chem. Soc.*, 1945, **67**, 1889) for several compounds which have now been measured: indole, benzthiazole, quinoline, thiazole, 5 : 6-benzquinoline, pyridine, and benziminazole. These authors used an indirect, qualitative method (comparing the spectra of cyanine dyes of which these substances were constituents), but it will be seen from Tables II—VII that thiazole was not correctly placed.

Effect of adding a Benzene Ring.—The foregoing tables contain a number of examples of substances differing from one another by a benzene ring, added in such a way that two carbons are shared by two rings. This has not produced any dramatic change in pK values which have, in general, shifted by only $\pm 0{\cdot}5$—1 pK unit. The extreme examples of this effect are pyrimidine to quinazoline ($+2{\cdot}2$) and glyoxaline to benziminazole ($-1{\cdot}5$ pK unit).

Styryl Derivatives.—Some styryl compounds were examined for signs of a base-strengthening resonance derived from possible contributions to the ion of a structure such as (XVI). This seemed a remote possibility because it implied the loss of two Kekulé rings; moreover, the corresponding aminostyryl-acridines had proved to be weak bases (Albert and Goldacre, *loc. cit.*, 1943). Actually, the pK_a values of 4-(*p*-aminostyryl)- and 2 : 6-bis-(*p*-aminostyryl)-pyridine (Royer, *J.*, 1947, 560) were found to be 6·25 and 5·97 respectively (M/100,000; H_2O) and, as expected, these show little enhancement above the value for pyridine (5·23).

Experimental.

Potentiometric titration was used to obtain those pK values where the concentration is shown as M/500 or greater; in other cases absorptiometry in buffers of a series of pH values was used. Both techniques were carried out exactly as previously described (Albert and Goldacre, *loc. cit.*, 1946).

In this work the policy has been followed of carrying out potentiometric titrations at concentrations as high as solubility permitted in order to keep the hydrolysis corrections low. The effect of the various dilutions on the "classical" pK_a values, as determined, can be eliminated by transforming them into thermodynamic pK_a values by adding the following corrections, M/10, 0·23; M/50, 0·10; M/200, 0·05; M/600, 0·03.

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