287. *The Chemistry of Simple Heterocyclic Systems. Part IV. Basic Strengths of Some 4-Substituted Cinnolines, Quinazolines, and Quinolines.*

By J. R. KENEFORD, J. S. MORLEY, J. C. E. SIMPSON, and P. H. WRIGHT.

The basic strengths have been determined potentiometrically for a series of quinoline, quinazoline, and cinnoline derivatives containing various 4-substituents. For the parent bases, and for compounds containing the groups OH, Cl, OPh, and OMe, the order of basicity is quinoline > quinazoline > cinnoline, which is the reverse of the observed order of strengths, as acids, of the hydroxy-compounds. For amino- and anilino-compounds, however, the order is quinoline > cinnoline > quinazoline, and chemical evidence indicates that the transposition is the result of abnormally low values for the quinazoline derivatives.

For each heterocyclic type, basicity diminishes in the order 4-NH_2 > NHPh > 6-NO_2-4-NH_2 > 4-OMe > OPh > Cl > OH. The effect of methoxyl is base-strengthening in the quinoline and cinnoline series (compared with the unsubstituted compounds), but is base-weakening in the quinazoline nucleus.

THE determination of the pK_a values of some 4-amino-cinnolines, -quinazolines, and -quinolines (Morley and Simpson, this vol., p. 1014) disclosed the interesting fact that the order of basicity of the 6-nitro-4-amino-derivatives, namely, quinoline > cinnoline > quinazoline, is not the reverse of the presumed order of strengths, as acids, of 4-hydroxy-compounds, *viz.*, cinnoline > quinazoline > quinoline, as judged by qualitative observations. The pK_a determinations recorded below were made partly in order to investigate this apparent anomaly, and partly in order to compare certain reactions (unpublished) of 4-substituted cinnolines, quinazolines, and quinolines with their strengths as bases or acids.

The values given in Tables I and II were all obtained in 50% aqueous alcohol by the potentiometric method, using the conditions already described (*loc. cit.*). The equation previously referred to (*loc. cit.*) was used in order to make the method applicable to weak bases, and three independent determinations were made on the weakest base (4-hydroxycinnoline, Table I) in order to form some idea of the degree of uncertainty involved in such cases. Of numerous determinations by different workers, the only values for a single compound which differed significantly from each other were those for 4-methoxyquinazoline, and we are unable to account for the exceptional behaviour of this compound. Table I gives values for a complete set of bases of the triple heterocyclic series, and Table II shows values for some miscellaneous quinoline and cinnoline compounds. The values given in Table III were obtained by titrating the hydroxy-compounds in 50% aqueous alcohol with sodium hydroxide, applying (to the value for 4-hydroxyquinoline) the corresponding correction for a weak acid.

TABLE I.

Basic strengths of 4-substituted quinolines, quinazolines, and cinnolines in 50% aqueous alcohol.

pK_a values and concentrations. [c = (mols./litre) × 10^3].

	Quinoline.		Quinazoline.		Cinnoline.	
Substituent.	pK_a.	c.	pK_a.	c.	pK_a.	c.
4-OH	2·41	4·96	2·07	4·93	1·77	4·93
					1·66 (*a*)	4·93
					1·72 (*a*)	4·93
4-Cl	2·59	5·26	2·10 (*e*)	5·62	2·08	5·47
4-OPh	4·42 (*b*)	5·16	2·44 (*e*)	4·08	2·27	4·05
H	5·0 (*c*)	—	3·26 (*d*)	6·96	2·51 (*f*)	14·59 6·18 4·96
			2·49 (*b*)	3·62		
4-OMe	5·35 (*b*)	5·16	2·73	6·61	2·71	3·62
			2·91	7·89		
6-NO$_2$-4-NH$_2$	6·41 (*e*)	4·45	3·71 (*e*)	2·94	5·08 (*e*)	3·60
4-NHPh	7·52	5·00	4·65	5·00	5·31	5·00
4-NH$_2$	8·47	6·58	5·17 (*e*)	6·44	6·26 (*e*)	4·72

Determinations were made at 21—22° unless otherwise stated.

(*a*) At 15°. (*b*) At 18—19°. (*c*) Pouterman and Girardet, *Experientia*, 1947, **3**, 28. (*d*) Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405, give 3·2 in 50% aqueous alcohol at 27°. (*e*) At 25°. (*f*) Titration of free base gave 2·50; titration of hydrochloride with sodium hydroxide gave 2·52.

TABLE II.

Basic strengths of 4-substituted quinolines and cinnolines in 50% aqueous alcohol.

pK_a values and concentrations at 25° ± 2°.

	Quinoline.		Cinnoline.	
Substituent.	pK_a.	c.	pK_a.	c.
4-Cl-6-NO$_2$	2·13	3·66	—	—
4-Cl-8-NO$_2$	2·64	3·90	—	—
8-NO$_2$-4-OPh	2·94	2·10	2·49	2·07
6-NO$_2$-4-OPh	3·25	2·09	3·15	2·14
8-NO$_2$-4-NH$_2$	6·63	3·92	—	—
4 : 6-(NH$_2$)$_2$	—	—	6·86 (*a*)	4·10

(*a*) Titration of hydrochloride with sodium hydroxide.

TABLE III.

Acid strengths of 4-hydroxy-compounds in 50% aqueous alcohol.

pK_a values and concentrations at 21°.

Quinoline.		Quinazoline.		Cinnoline.	
pK_a.	c.	pK_a.	c.	pK_a.	c.
12·43	6·21	9·98	6·16	9·53	6·16

Examination of these results leads to the following conclusions.

(i) For a given arrangement of substituents, the quinoline is invariably (in both Tables I and II) a stronger base than the cinnoline derivative.

(ii) Broadly speaking, the difference between the pK_a value of a quinoline and that of the analogous quinazoline or cinnoline increases as the pK_a values themselves increase. This effect, however, is only qualitative; that is to say, a smooth curve is not obtained if, for example, values for ($pK_{a(\text{quinoline})}$–$pK_{a(\text{cinnoline})}$) are plotted against $pK_{a(\text{quinoline})}$.

(iii) For 4-hydroxy-, 4-chloro-, 4-phenoxy-, and 4-methoxy-compounds, as well as for the unsubstituted bases, the relative order of basicity is quinoline > quinazoline > cinnoline [*i.e.*, the reverse of that shown by the hydroxy-compounds as acids (Table III)], but for the amino- and anilino-compounds the order is quinoline > cinnoline > quinazoline (Table I). It thus follows that the replacement of one of the " normal " groups (OH, Cl, OPh, OMe) by an " abnormal " group (NH_2, NHPh) has imposed a significant fine-structural change on either the cinnoline or the quinazoline derivatives. We have observed (unpublished results) that, among 4-amino- and 4-substituted-amino-derivatives of each type, the quinazoline compounds alone are hydrolysed in acid solution to the hydroxy-compounds; the fine-structural change in question may, therefore, be associated with the aminoquinazolines.

(iv) The order of effectiveness in promoting basicity of the various 4-substituents, *viz.*, 4-NH_2 > NHPh > 6-NO_2-4-NH_2 > 4-OMe > OPh > Cl > OH, is the same in each of the three heterocyclic series, but the effect of a methoxyl group, relative to that of a hydrogen atom, is different in the three series, 4-methoxy-quinoline and -cinnoline being stronger, and 4-methoxyquinazoline weaker, bases than the unsubstituted compounds. The base-weakening effect of a 4-methoxyl group attached to a quinazoline nucleus is also apparent if the pK_a value of 8-aminoquinazoline (2·49) is compared with that of 8-amino-4-methoxyquinazoline (2·31) (Elderfield, Williamson, Gensler, and Kremer, *J. Org. Chem.*, 1947, **12**, 405). However, the differences involved are too small to justify discussion of their possible significance.

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WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY,
LIVERPOOL SCHOOL OF TROPICAL MEDICINE.

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