131. *The Tautomerism of* N-*Heteroaromatic Hydroxy-compounds. Part III.*[1] *Ionisation Constants.*

By S. F. Mason.

Acidic and basic ionisation constants are reported for a number of *N*-heteroaromatic hydroxy-compounds and their *O*- and *N*-methyl derivatives. From the measured and from published values, tautomeric equilibrium constants (K_t = [NH form]/[OH form]) have been estimated for the mono-aza-compounds, and for the diaza-compounds with not more than one nitrogen atom conjugated with the hydroxyl group. For the diaza-compounds with a ring-nitrogen atom placed both *ortho* and *para* to the hydroxyl group, the equilibrium constant (K_{op} = [*ortho*-quinonoid NH form]/[*para*-quinonoid NH form]) has been similarly estimated. Such constants have been found to agree, to within an order of magnitude, with those determined spectrophotometrically.[1] The ionisation and tautomeric constants are shown to vary with the π-electron energies of the species in equilibrium.

THE equilibrium constant (K_t) of the tautomerism of *N*-heteroaromatic hydroxy-compounds (*e.g.*, I $\rightleftharpoons$ II) in aqueous solution to NH forms of a zwitterionic (*e.g.*, IIa) or an amide (*e.g.*, IIb) character may be measured spectrophotometrically[1] if the value of the constant lies in the range 10^2—10^{-2}. For larger or smaller values, K_t may be evaluated

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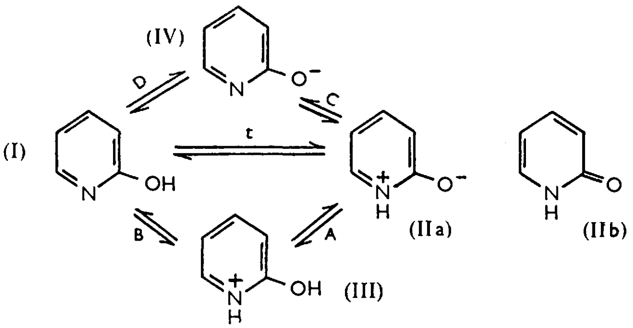
[1] Part II, Mason, *J.*, 1957, 5010.

by a more general method from the ionisation constants of a given compound and those of its *O*- and *N*-methyl derivatives,[2,3] as for amino-acids.[4] The empirical ionisation constants (K_1 and K_2) of a *N*-heteroaromatic hydroxy-compound are composite, and they are related



to the true constants of the NH- (K_A and K_C) and the OH-tautomer (K_B and K_D) by the expressions:

$$K_1 = K_A + K_B \quad \ldots\ldots\ldots \quad (1)$$

$$1/K_2 = 1/K_C + 1/K_D \quad \ldots\ldots\ldots \quad (2)$$

since the tautomers of a given compound (*e.g.*, I and II) form a common cation (*e.g.*, III) by displacement of the equilibria (A) and (B), and a common anion (*e.g.*, IV) by displacement of the equilibria (C) and (D). The basic ionisation constants of the NH- and OH-tautomers (K_A and K_B respectively) may be assumed to equal approximately the constants of the *N*-methyl (K_{NMe}) and the *O*-methyl derivative (K_{OMe}) respectively, so that the tautomeric constant (K_t) and the acidic ionisation constants of the tautomers (K_C and K_D respectively) may be calculated by means of equations (2) and (3):

$$K_t = [\text{NH-form}]/[\text{OH-form}] = K_A/K_B = K_D/K_C = K_{NMe}/K_{OMe} \quad . \quad (3)$$

If the basic ionisation constant of a *N*-heteroaromatic hydroxy-compound (K_1) and that of only one of its *O*- or *N*-methyl derivatives is known, K_t may be calculated by equations (4) or (5):

$$K_t = K_{OMe}/K_1 - 1 \quad \ldots\ldots\ldots \quad (4)$$

$$K_t = 1/(K_{NMe}/K_1 - 1) \quad \ldots\ldots\ldots \quad (5)$$

The ionisation constants of a number of *N*-heteroaromatic hydroxy-compounds and their *O*- and *N*-methyl derivatives have been measured in the present study, and the true ionisation constants of the tautomers (K_A, K_B, K_C, and K_D) and the tautomeric constant (K_t) have been calculated by means of the above equations, (3) being used wherever possible in calculating K_t (Tables 1 and 2). Hitherto, equation (4) has been used to afford the K_t values of *N*-heteroaromatic hydroxy-compounds from ionisation-constant data,[2,3] though equations (4) and (5) probably give less accurate values for K_t than does (3). The inductive, steric, and hyperconjugation effects of the methyl group on the ionisation constants of the *O*- and *N*-methyl derivatives of a given compound are probably of the same order in each derivative, and these effects will largely cancel out in calculations of a value for K_t according to equation (3), but not according to (4) and (5). The steric effect of the methyl group is important in the compounds with a hydroxyl group α to a ring nitrogen atom (Table 1, compounds 1, 4, and 11) for in these cases the parent substance, which is known spectroscopically to exist very largely in the NH-form,[1] is a stronger base

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[2] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.

[3] Albert and Phillips, *J.*, 1956, 1294.

[4] Cohn and Edsall, " Proteins, Amino-acids, and Peptides as Ions and Dipolar Ions," Reinhold, New York, 1943.

TABLE 1. *The ionisation* (K_1 *and* K_2) *and the tautomeric* (K_t = [NH-*form*]/[OH-*form*]) *constants of some monoaza-heteroaromatic hydroxy-compounds, and the ionisation constants of their* O- *and* N-*methyl derivatives* (K_{OMe} *and* K_{NMe} *respectively*) *in water at* 20°, *and the charge density at the position of the nuclear nitrogen atom* (q_n), *and the carbon atoms vicinal to the nitrogen atom* (q_c) *in the corresponding arylmethyl anion.*

						log K_t			
No.	Compound	pK_1	pK_2	pK_{OMe}	pK_{NMe}	I[d]	II[h]	q_n[k]	q_c
	Pyridines								
1	2-Hydroxy	0·75[a]	11·62[a]	3·28[a]	0·32[a]	2·96[e]	—	1·143	1·0
2	3-Hydroxy	4·86[a]	8·72[a]	4·88[a]	−4·96[a]	−0·08[e]	0·10	1·0	1·143
3	4-Hydroxy	3·27[a]	11·09[a]	6·62[a]	3·33[a]	3·29[e]	—	1·143	1·0
	Quinolines								
4	2-Hydroxy	−0·36[a]	11·74[a]	3·17[a]	--0·71[a]	3·88[e]	—	1·235	1·0
5	3-Hydroxy	4·30[a]	8·06	—	5·42 ± 0·02	−1·08[f]	−1·19	1·0	1·059
6	4-Hydroxy	2·27[a]	11·25[a]	6·65[a]	2·46[a]	4·19[e]	—	1·200	1·0
7	5-Hydroxy	5·20[a]	8·54[a]	—	6·12 ± 0·04	−0·86[f]	−1·27	1·050	1·0
8	6-Hydroxy	5·17[a]	8·88[a]	5·06 ± 0·05	7·15 ± 0·03	−2·09[e]	−1·85	1·0	1·059
9	7-Hydroxy	5·48[a]	8·85[a]	—	5·56 ± 0·02	0·69[f]	−0·37	1·059	1·0
10	8-Hydroxy	5·13[a]	9·89[a]	—	6·81 ± 0·02	−1·67[f]	−1·46	1·0	1·050
	iso*Quinolines*								
11	1-Hydroxy	−1·2[a]	—	3·05[a]	−1·8[a]	4·85[e]	—	1·200	1·0
12	4-Hydroxy	4·80 ± 0·03	8·68 ± 0·04	—	4·93 ± 0·03	0·46[f]	0·58	1·0	1·200
13	5-Hydroxy	5·40 ± 0·02	8·45 ± 0·03	—	6·90 ± 0·04	−1·45[f]	−1·42	1·0	1·050
14	6-Hydroxy	5·85 ± 0·03	9·15 ± 0·03	—	6·02 ± 0·03	0·32[f]	0·28	1·059	1·0
15	7-Hydroxy	5·70 ± 0·01	8·88 ± 0·02	—	7·09 ± 0·01	−1·37[f]	−1·42	1·0	1·059
16	8-Hydroxy	5·66 ± 0·01	8·40 ± 0·02	—	5·81 ± 0·02	0·38[f]	−0·06	1·050	1·0
	Acridines								
17	1-Hydroxy	4·18[b]	—	4·19[b]	—	−1·6[g]	−1·40[i]	1·0	1·024
18	2-Hydroxy	—	—	—	—	—	0·40[j]	1·118	1·0
19	3-Hydroxy	4·21,[b] 5·52	8·81[a]	4·27[b]	—	−0·8[g]	−1·82[i]	1·0	1·029
20	4-Hydroxy	—	—	—	—	—	−0·52[j]	1·095	1·0
21	5-Hydroxy	−0·32[a]	—	7[a]	—	7[a]	—	1·286	1·0
	Phenanthridine								
22	7-Hydroxy	4·39 ± 0·03[c]	8·68 ± 0·04[c]	—	—	—	<-1[i]	—	—

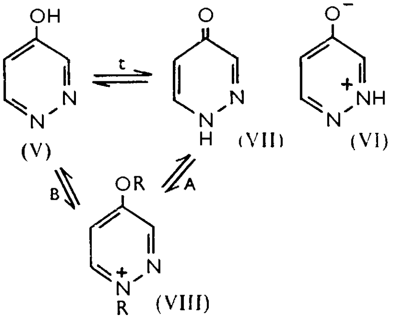
[a] Albert and Phillips, *J.*, 1956, 1294. [b] For 50% ethanol–water, from Albert, "The Acridines," Arnold, London, 1951, p. 114. [c] Determined spectroscopically at 5×10^{-4}M; analytical wavelengths 390 mμ and 385 mμ respectively. [d] Calc. from ionisation constants; present work. [e] Calc. by eqn. 3. [f] Calc. by eqn. 5. [g] For 50% ethanol–water, calc. by eqn. 4. [h] Determined spectroscopically; quoted from Part II. [i] For 1 : 9 ethanol–water. [j] For 1 : 4 ethanol–water. [k] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

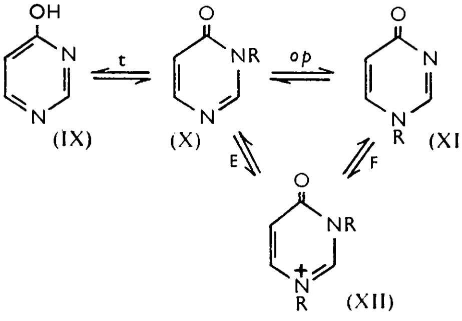
TABLE 2. *Ionisation constants of the* OH- (K_B *and* K_D) *and the* NH-*tautomers* (K_B *and* K_C) *tautomers of the monoaza-heteroaromatic hydroxy-compounds in water at* 20°, *calculated from the results of Table* 1 *and equations* (1), (2), *and* (3).

No.	Compound	pK_A	pK_B	pK_C	pK_D
1	2-Hydroxypyridine	0·75	3·71	11·62	8·66
2	3-Hydroxypyridine	5·12	5·22	8·46	8·36
3	4-Hydroxypyridine	3·27	6·56	11·09	7·80
4	2-Hydroxyquinoline	−0·31	3·57	11·74	7·86
5	3-Hydroxyquinoline	5·52	4·33	6·84	8·03
6	4-Hydroxyquinoline	2·27	6·46	11·25	7·06
7	5-Hydroxyquinoline	6·49	5·22	7·25	8·52
8	6-Hydroxyquinoline	7·03	5·18	7·02	8·87
9	7-Hydroxyquinoline	6·01	5·64	8·32	8·69
10	8-Hydroxyquinoline	6·60	5·14	8·42	9·88
11	1-Hydroxy*iso*quinoline	−1·2	3·6	—	—
12	4-Hydroxy*iso*quinoline	4·90	5·48	8·58	8·00
13	5-Hydroxy*iso*quinoline	6·84	5·42	7·01	8·43
14	6-Hydroxy*iso*quinoline	6·04	6·32	8·95	8·67
15	7-Hydroxy*iso*quinoline	7·14	5·72	7·44	8·86
16	8-Hydroxy*iso*quinoline	5·99	5·93	8·07	8·13
17	3-Hydroxyacridine	7·35	5·53	6·98	8·80
18	5-Hydroxyacridine	−0·32	7	—	—

than its *N*-methyl derivative, and the use of equation (5) gives a negative value for K_t. The superiority of equation (3) in general is illustrated by the cases in which K_t may be calculated by all three equations and evaluated spectroscopically (Table 1, compounds 2 and 8), as equation (3) gives the best agreement with the spectroscopic value.

Equations (3), (4), and (5) may be used to afford the tautomeric equilibrium constants of diaza-compounds (Table 3), provided that the OH- and the dominant NH-tautomer form a common cation. In such cases (*e.g.*, V) two different NH-tautomers are possible (*e.g.*, VI and VII) and three different cations. It has been demonstrated[1] that the predominant NH-tautomer of 4-hydroxypyridazine is (VII), and the ultraviolet spectra of the cationic forms of 4-hydroxy- and 4-methoxy-pyridazine, 1-methyl-4-pyridazone, and 4-hydroxy-2-methylpyridazinium chloride (Fig. 1) show that the predominant cationic structure is (VIII; R = H), as the first three compounds give almost identical absorption curves whilst the fourth has a quite different spectrum. Structure (VIII; R = H or Me) is the only one of the three possible cations which is common to 4-methoxypyridazine and 1-methyl-4-pyridazone, and exclusive of 4-hydroxy-2-methylpyridazinium chloride, so that the ratio of the ionisation constants of the first two compounds affords a measure of K_t by equation (3). The diaza-compounds listed in Table 3 with not more than one nitrogen atom in the ring carrying the hydroxyl group are known to exist largely in the OH-form,[1, 5] and since they are protonated and methylated on the same nitrogen atom, as the ultraviolet spectra of the cationic forms show (Table 3), a value for K_t may be calculated by equation (5) in these cases. The measured ionisation constants of the diaza-compounds and the calculated tautomeric constants are listed in Table 3.





In the diaza-compounds with nitrogen atoms placed both α and γ to the hydroxyl group (*e.g.*, IX) it has been shown spectroscopically that tautomerism occurs to two different NH-forms (*e.g.*, X and XI; R = H) with comparable stabilities.[6, 7, 8] In such cases K_t cannot be calculated from the ionisation constants of the *O*- and the *N*-methyl derivative by equation (3), as these derivatives do not possess a common cation.[7, 8] However, the parent substance (*e.g.*, IX) and its two *N*-methyl derivatives (*e.g.*, X and XI; R = Me) form cations with similar structures[7, 8] (*e.g.*, XII; R = H or Me), so that the constant of the equilibrium between the two NH-tautomers (K_{op}) may be calculated from the ionisation constants of the two *N*-methyl derivatives by equation (6):

$$K_{op} = [\textit{ortho}\text{-quinonoid NH-form}]/[\textit{para}\text{-quinonoid NH-form}]$$
$$= K_E/K_F = K_{o\text{-NMe}}/K_{p\text{-NMe}} \quad \ldots \ldots \ldots \ldots \quad (6)$$

where $K_{o\text{-NMe}}$ and $K_{p\text{-NMe}}$ are the ionisation constants of the *ortho*- and the *para*-quinonoid *N*-methyl derivative respectively (*e.g.*, X and XI; R = Me).

[5] Part I, Mason, *J.*, 1957, 4874.
[6] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[7] Brown, Hoerger, and Mason, *J.*, 1955, 211.
[8] Brown and Mason, *J.*, 1956, 3443.

TABLE 3. *Ionisation* (K_a) *and tautomeric* (K_t = [NH-]/[OH-*form*], *or* K_{op} = [ortho-*quinonoid* NH-*form*]/[para-*quinonoid* NH-*form*]) *constants of some di- and poly-aza-heteroaromatic compounds in water at* 20°; *the ultraviolet absorption spectra of their cationic forms and of those of their* O- *and* N-*methyl derivatives.* (*Values in italics refer to shoulders.*)

No.	Compound	pK_a	log K_t I[g]	log K_t II[k]	$\lambda_{max.}$ (mμ)	ε
1	3-Hydroxypyridazine ...	−1·8[a]	4·3[h]	—	265	2560
2	3-Methoxypyridazine	2·52[a]	—	—	269	2010
3	4-Hydroxypyridazine ...	1·07[a]	2·63[h]	—	245	8400
4	4-Methoxypyridazine	3·70[a]	—	—	247	10,320
5	1-Methyl-4-pyridazone ...	—	—	—	252[o]	10,650[o]
6	4-Hydroxy-2-methylpyridazinium chloride	1·74 ± 0·04	—	—	271; 233	4290; 3850
7	5-Hydroxypyrimidine......	1·87 ± 0·03	—	—	—	—
		6·78 ± 0·04	—	⩾−1·7		
8	8-Hydroxy-1 : 6-naphthyridine	4·08[b]	0·09	−0·05	328; 243	5660; 22,200
9	8-Hydroxy-6-methyl-1 : 6-naphthyridinium chloride	4·34[b]	—	—	332; 246	5750; 2300
10	8-Hydroxyquinazoline ...	3·41[b]	−3·85	—	*370*; 298; 257	*100*; 5480; 7000
11	8-Hydroxy-3-methylquinazolinium chloride	—	—	—	*370*; 300; 261	*86*; 6660; 6680
12	5-Hydroxyquinoxaline ...	0·9[b]	−4·8[i]	—	416; 338; 263	1110; 4770; 34,000
13	5-Hydroxy-1-methylquinoxalinium chloride	5·74[b]	—	—	426; 340; 264	1630; 5200; 32,000
14	1-Hydroxyphenazine	1·44[c]	−3·5[i]	—	—	—
15	5-Methyl-1-phenazone ...	4·9[c]	—	—	—	—
16	2-Hydroxyphenazine	2·6[d]	−0·2[i]	⩾−0·6	—	—
17	10-Methyl-2-phenazone ...	3·0[d]	—	—	—	—
			log K_{op} I[h]	log K_{op} II		
18	4-Hydroxypyrimidine......	1·85[a]	0·18[j]	0·40[l]	251; 224[p]	2970; 9840[p]
19	1-Methyl-4-pyrimidone ...	2·02 ± 0·04[e]	—	—	252; 229[p]	2640; 10,200[p]
20	3-Methyl-4-pyrimidone ...	1·84[e]	—	—	258; 226[p]	2940; 9080[p]
21	4-Hydroxyquinazoline ...	—	—	0·85[m]	—	—
22	4-Hydroxypteridine	−0·17[f]	1·72[j]	>1[n]	303; 257[q]	9120; 2690[q]
23	1-Methyl-4-pteridone	1·25[f]	—	—	305; 263[q]	10,720; 3090[q]
24	3-Methyl-4-pteridone	−0·47[f]	—	—	304; 265[q]	10,000; 2880[q]

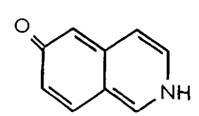
[a] Albert and Phillips, *J.*, 1956, 1294. [b] Albert and Hampton, *J.*, 1954, 505. [c] Michaelis, Hill, and Schubert, *Biochem. Z.*, 1932, **255**, 70. [d] Preisler and Hempelmann, *J. Amer. Chem. Soc.*, 1937, **59**, 141. [e] Measured spectroscopically at 5 × 10^{-5}M; analytical wavelengths, 240, 245, and 250 mμ. Brown and Mason, *J.*, 1956, 3443. [g] Calc. from ionisation constants: present work. [h] Calc. by eqn. 4. [i] Calc. by eqn. 5. [j] Calc. by eqn. 6. [k] Determined spectroscopically; from Part II. [l] Calc. from Fig. 2 of Brown, Hoerger, and Mason, *J.*, 1955, 211; analytical wavelength 240 mμ. [m] Calc. from the data of Hearn, Morton, and Simpson, *J.*, 1951, 3318. [n] Estimated from Fig. 2 of Brown and Mason, *J.*, 1956, 3443. [o] Staehelin, Eichenberger, and Druey, *Helv. Chim. Acta*, 1956, **39**, 1741. [p] Ref. 1. [q] Ref. *n*.

TABLE 4. *Charge density on the exocyclic atom* (q_x) *and the mobile bond order between the exocyclic atom and the nucleus* (p_{xy}) *of some arylmethyl anions.*

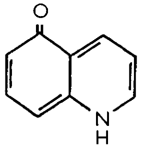
Aryl	q_x[a]	p_{xy}[b]	Aryl	q_x[a]	p_{xy}[b]
Phenyl	1·572	0·635	1-Naphthyl	1·450	0·688[c]
2-Naphthyl	1·529	0·649[c]	9-Anthryl......................	1·286	0·747
4-Diphenylyl	1·516	0·66[d]	*cyclo*Butadienyl	1·000	0·862

[a] Calc. by Longuet-Higgins's method (*J. Chem. Phys.*, 1950, **18**, 265). [b] Calc. by the Hückel method. [c] Wheland, *J. Amer. Chem. Soc.*, 1941, **63**, 2025. [d] Jacobs, *J.*, 1952, 292.

Values of K_{op} for three compounds have been calculated from equation (6) or from the spectra of the compounds, the values obtained by the two methods agreeing satisfactorily for 4-hydroxypyrimidine (Table 3). All the K_{op} values recorded are greater than unity, indicating that the *ortho*-quinonoid NH-forms (*e.g.*, X; R = H) are more stable than their *para*-quinonoid isomers (*e.g.*, XI; R = H) in aqueous solution. In non-polar solvents the *ortho*-quinonoid tautomer is similarly the more stable of the two forms.[5] The greater stability is not due to *ortho*-quinonoid resonance, for in the series of *N*-heteroaromatic hydroxy-compounds generally, the NH-tautomers with *para*-quinonoid resonance structures (*e.g.*, XIII) are more stable[1] relatively to the corresponding enol tautomer, than their isomers with *ortho*-quinonoid resonance structures (*e.g.*, XIV), provided that the oxygen and nitrogen atoms are not linked to the same carbon atom. The NH-tautomers with an oxygen atom α to a ring-nitrogen atom (*e.g.*, II; and X, R = H) contain an amide group, the resonance energy of which is probably greater than that of the vinylogous amide group of the NH-tautomers with an oxygen atom γ to a ring-nitrogen atom (*e.g.*, VII; and XI, R = H), as in the amide group the nitrogen and the oxygen atom enhance the electronegativity of the carbon atom between them, allowing that atom to form π-bonds more effectively with them. The greater energy of *para*-quinonoid resonance on the one hand and of amide resonance on the other nearly balance in determining the relative stabilities of compounds (X; R = H) and (XI; R = H), but on annelation and aza-substitution the aromatic π-electrons become progressively localised, so that the intrinsic amide group resonance becomes the more important factor. Thus in the series 4-hydroxypyrimidine, -quinazoline, and -pteridine the *ortho*-quinonoid form becomes increasingly the more stable of the two NH-tautomers (compounds 18, 21, 22, Table 3).



(XIII)



(XIV)

Fig. 1. *The ultraviolet spectra of the cationic forms,* (——) *4-hydroxypyridazine,* (– – – –) *4-methoxypyridazine,* (. . . .) *1-methyl-4-pyridazone, and* (— • —) *4-hydroxy-2-methylpyridazinium chloride.*

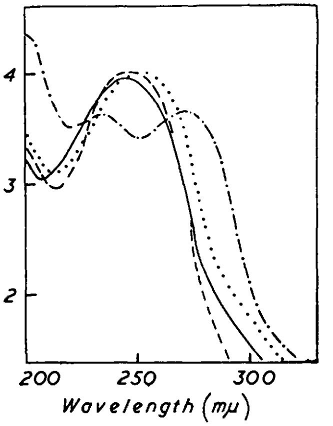
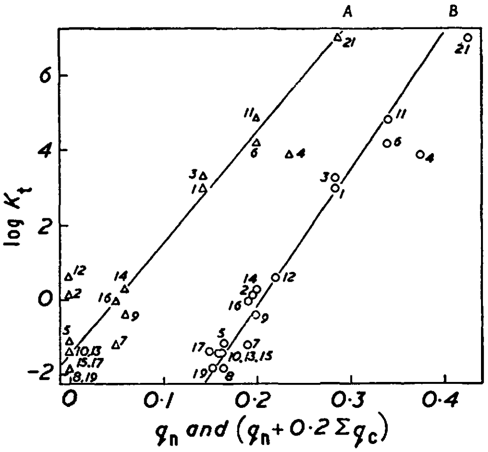


Fig. 2. (*A*) *Relation between* log K_t *and* q_n. (*B*) *Relation between* log K_t *and* (q_n + 0·2Σq_c)*:* 0·12 *of a unit has been added to the abscissa The numbers refer to the compounds in Table* 1.



In the monoaza-series of *N*-heteroaromatic hydroxy-compounds the tautomeric equilibrium constants vary widely, covering a range of 10^9 (Table 3). The ionisation constants of the NH-tautomers (K_A and K_C) also cover a wide range, whilst those of the OH-tautomers (K_B and K_D) show less variation (Table 2). The ionisation process governed by the constant, K_D (*e.g.*, I $\rightleftharpoons$ IV), is analogous to that of the aromatic phenols which show little variation of pK_a with the nature of the aromatic nucleus and the position at which the hydroxyl group is attached. Thus phenol, 1- and 2-naphthol, and 1- and 2-anthranol have the pK_a 9·96, 9·85, 9·93, 9·82, and 9·92 respectively.[9] A similar contrast

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[9] Lauer, *Ber.*, 1937, **70**, *B*, 1288; Schenkel, *Experientia*, 1948, **4**, 383.

has been noted[10] between the two series of ionisation constants of the aromatic and the *N*-heteroaromatic amines respectively. The large differences between the ionisation constants of the *N*-heteroaromatic amines, covering a range[11] of 10^6, have been ascribed[12] to the considerable variations in Coulombic energy, from one nuclear position to another, after protonation of a ring-nitrogen atom, whilst the small differences between the ionisation constants of the aromatic amines, covering only an order of magnitude, have been attributed[10] to the complementary variation of the Coulombic and the delocalisation energy in a series of such compounds.

Similar factors may be shown to govern the ionisation constants of aromatic and *N*-heteroaromatic hydroxy-compounds, and the tautomeric constants of the latter. In the aromatic phenols it is probable that the lone-pair electrons of the hydroxyl group are not extensively delocalised over the aromatic nucleus, owing to the large electronegativity difference between oxygen and carbon,[3] so that the Coulombic and the delocalisation energy do not vary greatly in the series. The π-electron energy of a phenol may be taken, approximately, to be that of the aromatic nucleus, whilst for the corresponding phenoxide ion there are two main additional π-energy terms, one due to the delocalisation of π-electrons into the Coulombic field of the oxygen atom and the other to the formation of the exocyclic π-bond. These terms vary in a series of phenoxide ions, the energy difference between a phenol and its anion, ΔE, being given by the relation:

$$\Delta E = q_x\alpha_O + 2p_{xy}\beta_{OO} + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where α_O is the increment in the Coulomb integral of a negatively charged oxygen atom relative to carbon, β_{CO} is the resonance integral between a carbon and a negatively charged oxygen atom, and, in the carbanion corresponding to the phenoxide ion, q_x is the charge density on the exocyclic atom and p_{xy} the mobile bond order between that atom and the nucleus. In a series of arylmethyl anions it may be expected that q_x and p_{xy} should be related, since the more electrons are delocalised from the exocyclic atom into the nucleus the smaller q_x and the larger p_{xy}. Empirically these two quantities are connected by the expression (Table 4)

$$p_{xy} = -0{\cdot}4q_x + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

Combining equations (7) and (8) gives:

$$\Delta E = q_x(\alpha_O - 0{\cdot}8\beta_{OO}) + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

Thus, if $\alpha_O \simeq 0{\cdot}8\beta_{CO}$, ΔE is approximately constant in the series of aromatic phenols, and no great variation of the ionisation constant of the phenol with the type of aromatic nucleus or with the position of substitution of the hydroxyl group is to be expected, as variations in the delocalisation energy of the anion are compensated by converse variations in the Coulombic energy.

In the *N*-heteroaromatic hydroxy-compounds there should be a similar complementary variation of the Coulombic and the delocalisation energy accompanying the transfer of a proton from the exocyclic oxygen atom, so that the Coulombic energy change after protonation of the ring-nitrogen atom remains the major variable π-energy term governing the relative values of the tautomeric constants in this series. If it is assumed that the lone-pair electrons of the oxygen atom are extensively delocalised over the nucleus in the NH-tautomer (*e.g.*, II) as in the phenoxide ion, but not in the OH-tautomer (*e.g.*, I) as in a phenol, the difference in π-electron energy between the tautomers is given by the term, $q_n\alpha_{NH}$, where α_{NH} is the difference between the Coulomb integrals of the carbon atom and the protonated nuclear nitrogen atom, and q_n is the charge density at the position of the latter atom in the corresponding arylmethyl anion. The relative tautomeric equilibrium

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[10] Hush, *J.*, 1953, 684.
[11] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[12] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.

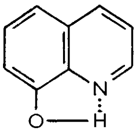
constants (K_t) in the series of *N*-heteroaromatic hydroxy-compounds should be governed, to a first approximation, by the variable π-energy term, $q_n\alpha_{NH}$, if the entropy change of the tautomerism is constant in the series.

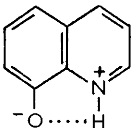
It has been shown [1] that the entropy change of the tautomerism at a given temperature is reasonably constant in three of the four cases studied, and as the major contribution to the entropy change is probably the increase in order resulting from the solvation of the zwitterionic NH-tautomer (*e.g.*, IIa) no great variation of that change in the series is likely. Thus the relative free energies of tautomerism in the series and the π-energies of the NH-tautomers should be related by the expression:

$$\boldsymbol{R}T \log K_t = q_n\alpha_{NH} + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

A plot of log K_t against q_n gives a fair straight line (Table 1, Fig. 2*A*) as equation (10) requires. The *ortho*- and *peri*-exceptions to the similar relation between q_n and the pK_a values of the *N*-heteroaromatic amines [12] have no analogues in the present series, owing to the self-cancellation of the inductive effect and hydrogen-bonding in the tautomerism of *N*-heteroaromatic hydroxy-compounds. In the case of 2-hydroxypyridine (I and II) the inductive effect of the nitrogen atom on the proton-releasing and -acepting properties of the oxygen atom should be of the same order as the reciprocal effect of the oxygen atom on the proton-donor and -acceptor properties of the nitrogen atom. Similarly, for 8-hydroxyquinoline both the OH-tautomer (XV) and the NH-tautomer (XVI) are intramolecularly hydrogen-bonded, so that the bonding has only a second-order effect [1] on the position of the tautomeric equilibrium (Table 1), whilst the pK_a value of 8-aminoquinoline is lowered considerably by hydrogen-bonding,[11] as only the uncharged species is bonded.

(XV)





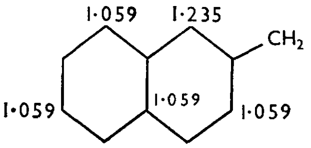
(XVI)

In the plot of log K_t against q_n (Fig. 2*A*) the "*meta*"-hydroxy-compounds, 3-hydroxypyridine and 4-hydroxy*iso*quinoline, though not 3-hydroxyquinoline, are anomalous, possessing larger K_t values than expected according to equation (10). These large K_t values have been ascribed to the inductive-electromeric effect.[1] When a nitrogen atom is substituted at an unconjugated (unstarred) position in the nucleus of an aromatic hydroxy-compound, both of the vicinal carbon atoms are in starred positions, bearing charge densities of greater than unity in the carbanion corresponding to the NH-tautomer. The electronegativity of such carbon atoms is increased inductively by the neutral nitrogen atom of the OH-tautomer and, more particularly, by the positively charged nitrogen atom of the NH-tautomer. Thus the carbon atoms vicinal to the nitrogen atom lower the energy of the NH-tautomer by a Coulombic contribution which varies with the position and the nucleus in which the nitrogen atom is substituted. The free energy of tautomerism may be related to this variable Coulombic energy term for the compounds in which the nitrogen atom is substituted in an unstarred position of the nucleus by the expression:

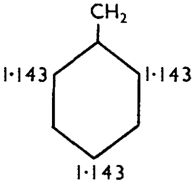
$$\boldsymbol{R}T \log K_t = \sum q_c\alpha_C + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

where q_c is the charge on the vicinal carbon atoms in the corresponding carbanion, and α_C the increment in the Coulomb integral of the carbon atom when it is placed adjacent to a positively charged nitrogen atom, the sum being taken over vicinal carbon atoms. The values of q_c for the arylmethyl anions corresponding to the three *meta*-hydroxy-*N*-heteroaromatic compounds considered are given in (XVII), (XVIII), and (XIX). The q_c values of the carbon atoms adjacent to a nitrogen atom substituted *meta* to the exocyclic group in

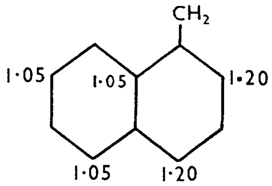
(XVIII) and (XIX) are large, so that, by equation (11), the Coulombic contributions to the stability of the corresponding NH-tautomers, those of 3-hydroxypyridine and 4-hydroxy-*iso*quinoline respectively, should be considerable. However, the charge densities on the carbon atoms vicinal to a nitrogen atom substituted at any unstarred secondary carbon atom position in (XVII) have the same small value, and the corresponding heteroanalogues, 3- and 6-hydroxyquinoline and 7-hydroxy*iso*quinoline, have tautomeric equilibrium constants of the same magnitude and smaller than those of 3-hydroxypyridine and 4-hydroxy*iso*quinoline (Table 1). The *N*-heteroaromatic hydroxy-compounds with the nitrogen atom substituted at an unstarred position in the nucleus are found to follow equation (11), log K_t correlating linearly with $\sum q_c$ in these cases, and giving from the gradient of the relation a value of about 10 kcal./mole for α_C (Table 1).



(XVII)



(XVIII)



(XIX)

When a nitrogen atom is substituted in a starred position of the nucleus of an aromatic hydroxy-compound the vicinal carbon atoms are unstarred, carrying in all cases charge densities of unity in the corresponding arylmethyl anion. Thus the lowering of the Coulombic π-energy of the tautomers, due to the enhanced electronegativity of the vicinal carbon atoms, is a constant in these cases. The main variable π-energy term is given by equation (10) when the nitrogen atom is substituted in a starred nuclear position, and by equation (11) when it is substituted in an unstarred position, the combination of the two, equation (12), governing the free energy of tautomerism of the complete series of *N*-heteroaromatic hydroxy-compounds:

$$\boldsymbol{R}T \log K_t = q_n\alpha_{NH} + \sum q_c\alpha_C + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad (12)$$

The Coulomb integral increment of a carbon atom adjacent to a positively charged nitrogen atom, α_C, should be proportional to the increment of the latter atom, α_{NH}, and empirically the experimental data may be best accommodated by the assumption that

$$\alpha_C = 0{\cdot}2\alpha_{NH} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

Combining equations (12) and (13) gives:

$$\boldsymbol{R}T \log K_t = \alpha_{NH}(q_n + 0{\cdot}2\sum q_c) + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad (14)$$

The plot of log K_t against $(q_n + 0{\cdot}2\sum q_c)$ gives a satisfactory straight line (Fig. 2*B*) over the range of K_t values from 10^{-2} to 10^3, covering the compounds with a nitrogen atom substituted both at a starred and an unstarred position. The compounds with K_t values $>10^3$ give points falling below the straight line (Fig. 2*B*), the NH-tautomers being less stable than expected according to equations (10) or (14). In these compounds the π-electron charge density on the nuclear nitrogen atom of the NH-tautomer, q_n, is large, so that this atom does not carry, even approximately, a net unit positive charge. Consequently the Coulomb integral increment, α_{NH}, in such cases is smaller than that of a nitrogen atom bearing a unit positive charge, thus accounting by equations (10) and (14) for the observed trend in K_t values when these are large. The slope of the line in Fig. 2*B* gives α_{NH} the value of about 50 kcal./mole and, by equation (13), α_C is equal to 10 kcal./mole, the latter agreeing with the value derived for α_C derived by equation (11).

The variation of the ionisation constants of the OH- and the NH-tautomer with the π-electron charge densities on the nuclear nitrogen atom, q_n, and the vicinal carbon atoms,

q_O (Table 2, Figs. 3 and 4) in the series of monoaza-heteroaromatic hydroxy-compounds supports further the assumption that lone-pair electrons are extensively delocalised over the nucleus from a negatively charged, but not from a neutral, exocyclic oxygen atom. The free energy of the ionisation process governed by the constant, K_A (*e.g.*, II $\rightleftharpoons$ III), may be equated to the right-hand side of equation (14), and a plot of log K_A against $(q_n + 0{\cdot}2\sum q_c)$ should give a straight line of slope $\alpha_{HN}/\boldsymbol{R}T$. A fair straight line is obtained (Fig. 3*A*) with a gradient giving α_{NH} the value of about 40 kcal./mole. The ionisation of the "*ortho*"-*N*-heteroaromatic hydroxy-compounds, unlike the tautomerism, is greatly influenced by the inductive effect and, for clarity, these compounds have been omitted from the plots of Figs. 3 and 4.

FIG. 3. (*A*) *Relation between* pK_A *and* $(q_n + 0{\cdot}2\Sigma q_c)$. (*B*) *Relation between* pK_B *and* $(q_n + 0{\cdot}2\Sigma q_c)$: 4 p$K$ *units have been added to the ordinate. The numbers refer to the compounds in Table* 2.

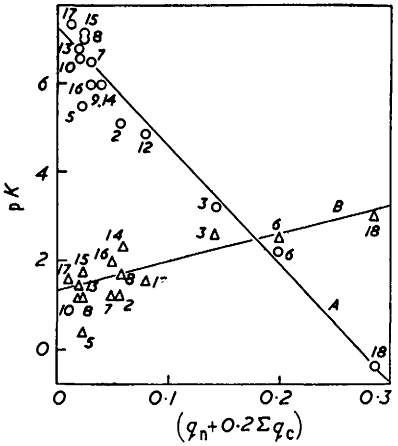
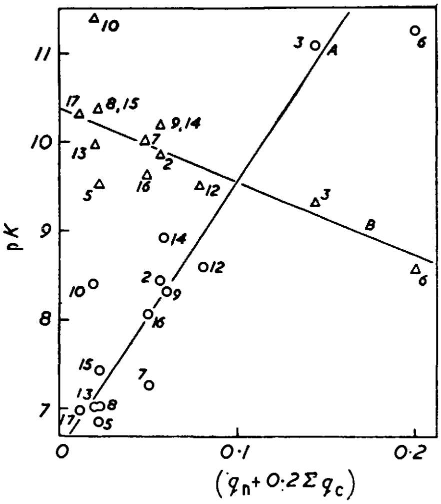


FIG. 4. (*A*) *Relation between* pK_O *and* $(q_n + 0{\cdot}2\Sigma q_c)$. (*B*) *Relation between* pK_D *and* $(q_n + 0{\cdot}2\Sigma q_c)$: 1·5 p$K$ *units have been substracted from the ordinate. The numbers refer to the compounds in Table* 2.



The free energy of the ionisation process governed by the constant, K_O (*e.g.*, II $\rightleftharpoons$ IV), should vary in the series according to equation (15):

$$\boldsymbol{R}T \log K_O = (\alpha_{NH} - \alpha_N)(q_n - 0{\cdot}2\sum q_c) + \text{Constant} \quad . \quad . \quad . \quad . \quad (15)$$

where α_N is the Coulomb integral increment of the neutral nitrogen atom. The relation between log K_O and $(q_n + 0{\cdot}2\sum q_c)$ is reasonably linear (Fig. 4*A*), the slope giving $(\alpha_{NH} - \alpha_N)$ a value of about 37 kcal./mole. The π-energy change in the ionisation process governed by the constant, K_B (*e.g.*, I $\rightleftharpoons$ III), should not vary in the series if the lone-pair electrons of the OH group are not delocalised at all, but the change may be equated to the right-hand side of equation (15) if these electrons are fully delocalised. The plot of log K_B against $(q_n + 0{\cdot}2\sum q_c)$ gives a line (Fig. 3*B*) with a slight slope, from which an apparent value of 8 kcal./mole may be obtained for the quantity $(\alpha_{NH} - \alpha_N)$. This value is too small, but the fact that it is non-zero indicates that the lone-pair electrons of the OH group are delocalised to a small degree. The constant, K_D, of the remaining ionisation process (*e.g.*, I $\rightleftharpoons$ IV) should be governed by equation (16):

$$\boldsymbol{R}T \log K_D = \alpha_N(q_n + 0{\cdot}2\sum q_c) + \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad (16)$$

The plot of log K_D against $(q_n + 0{\cdot}2\sum q_c)$ gives a fair straight line (Fig. 4*B*), from the slope of which a value of 12 kcal./mole for α_N may be obtained.

Expressed in terms of the Hückel carbon–carbon resonance integral, β, which has the thermochemical value [14] of about 20 kcal./mole, the Coulomb integral increments obtained in the present work are $\alpha_{NH} = 2{\cdot}5\beta$ (from Fig. 2*B*, and from Figs. 4*A* and 4*B*), $\alpha_N = 0{\cdot}6\beta$ (from Fig. 4*B*), and $\alpha_C = 0{\cdot}5\beta$ [from equation (11) and from (13) and (14)]. The value of $0{\cdot}6\beta$ for α_N has been shown to give approximately the correct dipole moment of pyridine,[15] and it is now widely used in molecular-orbital treatments of *N*-heterocyclic molecules.[16] Values of $0{\cdot}64\beta$ for α_N and $0{\cdot}58\beta$ for α_C have been derived from the variation of the ionisation constants of the aromatic amines and diamines with the delocalisation energy and charge density on the exocyclic atom of the corresponding arylmethyl anions,[10] both values agreeing with those obtained in the present work. A value of $1{\cdot}2\beta$ for $(\alpha_{NH} - \alpha_N)$ has been obtained from the relation between the ionisation constants of the *N*-heteroaromatic amines and the charge density at the position of the nuclear nitrogen atom in the corrresponding arylmethyl anion,[12] though no allowance was made for the effect of the enhanced electronegativity of the carbon atoms adjacent to a ring-nitrogen atom on the π-energy of the species in equilibrium. The effect is relatively important (compare the slopes of Figs. 2*A* and *B*), and if it is allowed for in the *N*-heteroaromatic amine series a value of $1{\cdot}85\beta$ for $(\alpha_{NH} - \alpha_N)$ is obtained,[17] in agreement with the value derived from Fig. 4*A*.

The ionisation constants, K_A, K_B, K_C, and K_D, when related to the π-energy differences between the species in equilibrium (Figs. 3 and 4), give less satisfactory linear plots than the tautomeric equilibrium constant, K_t (Fig. 2*B*). The inductive and hydrogen-bonding effects are self-cancelling in the latter equilibrium (see above), but not in the former, the magnitude of the observed deviations (Table 2, Figs. 3 and 4) providing a measure of these effects. In the case of 8-hydroxyquinoline, the constants K_A and K_B are not appreciably anomalous, suggesting that the cation is hydrogen-bonded intramolecularly to the same degree as both the NH- and the OH-tautomers (Fig. 3). The constants K_C and K_D, however, deviate by 1·4 and 1·1 units of p*K* respectively from the theoretical line (Figs. 4*A* and *B* respectively), indicating that the energy of the hydrogen bond is about 1·9 kcal./mole in the NH-tautomer and about 1·5 kcal./mole in the OH-tautomer of 8-hydroxyquinoline. From the K_t values of 6- and 8-hydroxyquinoline, the hydrogen bond of the NH-tautomer of 8-hydroxyquinoline has been calculated [1] to be 0·5 kcal./mole stronger than that of the OH-tautomer, in satisfactory agreement with these values. The "*meta*"-hydroxy-compounds, 3-hydroxy-pyridine and -quinoline and 4-hydroxy*iso*quinoline, are more acidic in the ionisation processes (A), (B), and (D), though not (C), than expected from the π-energy differences between the species in equilibrium (Figs. 3 and 4). An inductive effect between the oxygen and the nitrogen atom through two carbon atoms is probable in these compounds, distinct from the inductive-electromeric effect of the carbon atoms adjacent to the ring-nitrogen atom. The relative magnitudes of the deviations from one ionisation process to another of the "*meta*"-hydroxy-compounds suggest that the inductive effect of the heteroatoms depends upon their charge in the order, $^+NH > OH > N > O^-$, and the absence of marked deviations in the ionisation process (C) indicate that the negatively charged oxygen atom has an electronegativity not greatly different from that of an sp^2 hybridised carbon atom (Table 2, Figs. 3 and 4). The deviations of the "*ortho*"-hydroxy-compounds (Table 2) suggest an alternative order for the inductive effect of the heteroatoms, $OH > {}^+NH > O^- > N$, the last pair having apparent electronegativities less than that of an sp^2 hybridised carbon atom. In the "*meta*"-hydroxy-compounds the nitrogen atom is substituted at an unstarred position in the nucleus. and so it is formally neutral in the anion and carries a formal unit positive charge in the NH-tautomer, according to first order perturbation theory. However, in the "*ortho*"-hydroxy-compounds the nitrogen atom is substituted at a starred position, so that it is

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[13] Coulson and de Heer, *Trans. Faraday Soc.*, 1951, **47**, 681; *J.*, 1952, 483.
[14] Coulson, "Valence," Oxford Univ. Press, 1952.
[15] Chalvet and Sandorfy, *Compt. rend.*, 1949, **228**, 566; Lowdin, *J. Chem. Phys.*, 1951, **19**, 1323.
[16] Davies, *Trans. Faraday Soc.*, 1955, **51**, 449; Brown and Heffernan, *J.*, 1956, 4288.
[17] Unpublished result.

negatively charged in the anion (*e.g.*, IV) and carries less than a unit positive charge in the NH-tautomer (*e.g.*, II), according to the same approximation. The change in the order of the inductive effect of the heteroatoms on passing from the "*meta*"- to the "*ortho*"-hydroxy-compounds may be ascribed, therefore, to the reduced electronegativities of the nitrogen atoms in the anions and NH-tautomers of the "*ortho*"-compounds, owing to π-electron charge densities of greater than unity on those atoms.

EXPERIMENTAL

Materials were as in Part I.[5]

Absorption spectra were measured with a Hilger Uvispek H700/305 Quartz Spectrophotometer, and aqueous solutions with pH values two units less than the pK_1 value of the compound examined.

Ionisation constants were determined by potentiometric titration at 20° under nitrogen, a Cambridge pH meter being used with glass and calomel electrodes. The ionisation constants of the *N*-heteroaromatic hydroxy-compounds were measured at M/250 and those of the *O*- and *N*-methyl derivatives at M/100, each value recorded (Tables 1 and 2) being the average of nine determinations.

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