1002. *The Tautomerism of* N-*Heteroaromatic Hydroxy-compounds. Part II.* Ultraviolet Spectra.*

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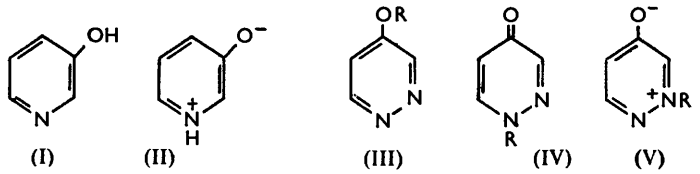
The ultraviolet spectra of a number of *N*-heteroaromatic hydroxy-compounds and their *O*- and *N*-methyl derivatives with fixed structures have been measured. By comparing spectra, it is found that tautomerism from O–H (*e.g.*, I) to N–H (*e.g.*, II) forms is general amongst the monoaza- and some diaza-heterocyclic hydroxy-compounds. Equilibrium constants (K_t = [N–H form]/[O–H form]) have been estimated from the spectra, and they have been found to increase with conjugation between the oxygen and the nitrogen atom, and with the addition of fused benzene rings, and to decrease with aza-substitution, with a rise in temperature, and with a fall in the dielectric constant of the solvent.

THE ultraviolet spectra of a number of heteroaromatic compounds with a hydroxyl group α or γ to a ring-nitrogen atom have been shown to resemble those of the corresponding *N*-methyl derivatives and to differ from those of the corresponding *O*-methyl derivatives, in alcohol or aqueous solution, establishing that these compounds tautomerise predominantly to amide forms.[1] Other *N*-heteroaromatic hydroxy-compounds have been less extensively studied. From the ultraviolet spectra in alcohol and in aqueous solutions of arbitrary pH, it has been concluded that the hydroxy-quinolines and -*iso*quinolines with a hydroxyl group neither α nor γ to a ring-nitrogen atom are essentially phenolic.[2] However, 2- and 4-hydroxyacridine [3] and 2-hydroxyphenazine,[4,5] on passing from non-aqueous to aqueous-alcohol or water solutions, undergo marked spectral changes which have been attributed to tautomerism from O–H to N–H forms,[3,4,5] and 3-hydroxypyridine has been shown by ultraviolet spectroscopy to exist equally as enol (I) and zwitterionic (II) forms in neutral aqueous solution.[6]



(I) (II) (III) (IV) (V)

In the present work the ultraviolet spectra of a wide range of *N*-heteroaromatic hydroxy-compounds have been examined in organic solvents and in aqueous solutions buffered to the isoelectric pH values of the compounds. For comparison, the spectra of the corresponding *N*-methyl and, where available, the *O*-methyl derivatives have been measured. The results show (Table 1) that the compounds with a hydroxyl group α or γ to a ring-nitrogen atom have a spectrum similar to that of their *N*-methyl derivative and different from that of their *O*-methyl derivative both in organic and in aqueous solvents, indicating that they tautomerise predominantly to the amide form under these conditions. The diaza-compounds with one nitrogen atom α or γ to the hydroxyl group and the other in a non-conjugated position may tautomerise from an enol (*e.g.*, III; R = H) to an amide (*e.g.*, IV; R = H) or a zwitterion (*e.g.*, V; R = H) form. In these cases too the amide

* Part I, *J.*, 1957, 4874.

[1] Specker and Gawrosch, *Ber.*, 1942, **75**, 1338; Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923; Hearn, Morton, and Simpson, *J.*, 1951, 3318; Brown, Hoerger, and Mason, *J.*, 1955, 211; Brown, and Mason, *J.*, 1956, 3443; Den Hertog and Buurman, *Rec. Trav. chim.*, 1956, **75**, 257.

[2] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

[3] Albert and Short, *J.*, 1945, 760.

[4] Badger, Pearce, and Petit, *J.*, 1951, 3204.

[5] Perkampus, *Z. phys. Chem.* (*Frankfurt*), 1956, **6**, 18.

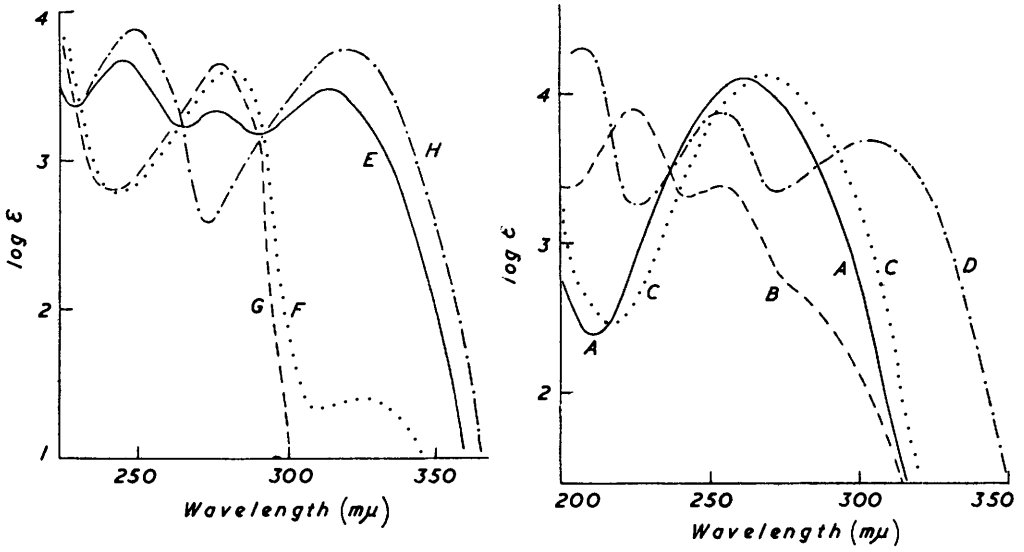
[6] Metzler and Snell, *J. Amer. Chem. Soc.*, 1955, **77**, 2431.

form is preferred, as the spectrum of 4-hydroxypyridazine resembles that of its 1-methyl (IV; R = Me) but not that of its 2-methyl (V; R = Me) or its *O*-methyl (III; R = Me) derivative (Fig. 1, Table 1).

The monoaza- and some diaza-compounds with a hydroxyl group neither α nor γ to a ring-nitrogen atom show a change of spectrum on passage from an organic solvent to an aqueous solution at the isoelectric pH (Fig. 2, Table 1). The spectrum of a given compound in alcohol solution resembles closely that of the *O*-methyl derivative, but in aqueous solution new bands appear with positions corresponding to those observed in the spectrum of the *N*-methyl derivative. A continuous change of spectrum with solvent composition is observed in alcohol–water and dioxan–water mixtures, the bands in the same positions

FIG. 1. *Absorption spectra of* (*A*) 4-*hydroxypyridazine* (*neutral molecule*) (pH 4·8), (*B*) 4-*methoxypyridazine* (*neutral molecule*) (pH 7·0), (*C*) 1-*methyl*-4-*pyridazone* (*neutral molecule*), *and* (*D*) 4-*hydroxypyridazine* 2-*methochloride* (*zwitterion*) (pH 7·0).

FIG. 2*a*. *Absorption spectra of* (*E*) 3-*hydroxypyridine in aqueous buffer* (pH 6·90), (*F*) 3-*hydroxypyridine in alcohol*, (*G*) 3-*methoxypyridine* (*neutral molecule*), *and* (*H*) 3-*hydroxypyridine methochloride* (*zwitterion*) (pH 7·0).

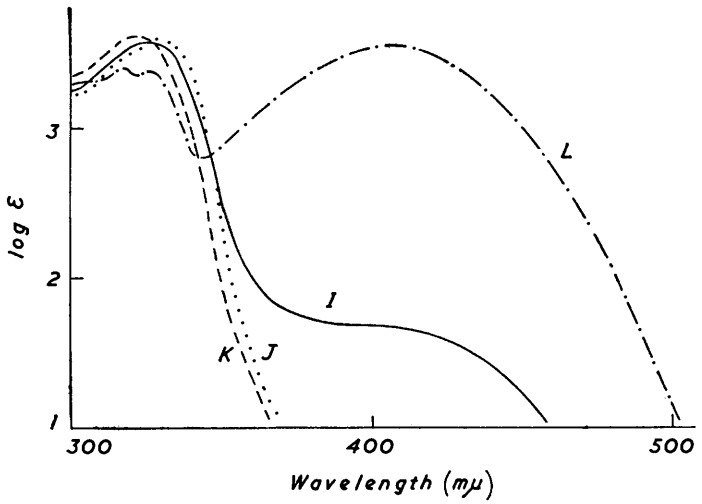


as those of the *N*-methyl derivative falling, and those at the same wavelength as the bands of the *O*-methyl derivative rising, in intensity as the dielectric constant decreases. The absorption curves in such mixtures show a single set of isosbestic points, indicating that the spectral changes are due to the displacement of a single equilibrium process with change of solvent. In general, therefore, both enol (*e.g.*, I and VI) and zwitterionic (*e.g.*, II and VII) forms exist in equilibrium in solvents of high dielectric constant.

The *N*-methyl derivative of a given compound invariably absorbs radiation at a longer wavelength than the *O*-methyl derivative (Fig. 2, Table 1), and a particular feature of the change of spectrum with solvent shown by the parent hydroxy-compound is the appearance of a band in aqueous solution beyond the long-wavelength limit of absorption in alcohol solution. The intensity of this band, which is due to the absorption of the zwitterionic form alone, thus affords a measure of the tautomeric equilibrium. Methyl groups, for the most part, exert only second-order effects on the position and intensity of allowed electronic transitions ($\varepsilon > 1000$), and accordingly the spectrum of an *N*-methyl derivative may be taken as a good model for the absorption characteristics of the zwitterionic tautomer of the parent hydroxy-compound. On this assumption the relative amounts of the enol and zwitterionic forms of a given *N*-heteroaromatic hydroxy-compound at the isoelectric pH may be calculated from the intensities of the bands of longest wavelength in the spectra

of the compound and its *N*-methyl derivative. Values of the calculated tautomeric equilibrium constants (K_t = [N–H form]/[O–H form]) are listed in Table 1. In some diaza- and some tricyclic cases the spectra of the corresponding *N*-methyl derivatives were not available. However, the spectra of analogous monoaza- or dicyclic *N*-methyl derivatives allow lower or upper limits respectively to be calculated for K_t, as the intensity of the long-wavelength band in the spectrum of a given *N*-methyl compound, in general, decreases on aza-substitution and increases with the addition of a fused benzene ring (cf. compounds 6, 16, 22, 33, and 44; 29 and 60; 24 and 64; Table 1).

FIG. 2*b*. *Absorption spectra of* (*I*) 6-*hydroxyquinoline in aqueous buffer* (pH 7·02), (*J*) 6-*hydroxyquinoline in alcohol*, (*K*) 6-*methoxyquinoline* (*neutral molecule*) (pH 7·5), *and* (*L*) 6-*hydroxyquinoline methochloride* (*zwitterion*) (pH 10).



The value of K_t varies widely in the range of compounds studied, being often large when the hydroxyl group is conjugated with a ring nitrogen atom or is β to such an atom. Conjugation allows dipolar resonance forms (*e.g.*, VIa) to contribute with the neutral form (*e.g.*, VIb) to the structure of the enol, and neutral transannular amide forms (*e.g.*, VIIa) to contribute with the dipolar form (*e.g.*, VIIb) to the structure of the zwitterion. These types of resonance may be expected to favour the N–H tautomer at the expense of the O–H tautomer. The values for K_t show that transannular "*para-para*-quinonoid" structures (*e.g.*, VIII) are more effective in this respect than "*ortho-para*-quinonoid" structures (*e.g.*, VIIa), which in turn are more effective than "*ortho-ortho*-quinonoid" structures (*e.g.*, IX). The addition of a fused benzene ring to a compound with a given type of conjugation usually enhances K_t (cf. compounds 23 and 63; 28 and 59), presumably because the entire benzenoid resonance is replaced by quinonoid resonance in the dicyclic cases (*e.g.*, VIIa), whilst only two-thirds of the benzenoid resonance is so replaced in the corresponding tricyclic cases (*e.g.*, X). 2-Hydroxyphenanthridine has a lower K_t value than its dicyclic analogue, 7-hydroxyquinoline, but here the benzenoid resonance of all three rings must be replaced by quinonoid resonance in the transannular amide form (XI).

The β-hydroxy-compounds, 3-hydroxypyridine and 4-hydroxy*iso*quinoline, but not 3-hydroxyquinoline, possess much larger K_t values than any other compound in which the nitrogen and oxygen atoms are not conjugated (Table 1). In such compounds the carbon atoms vicinal to the ring-nitrogen atom are conjugated to the oxygen atom, and their electronegativity is greatly enhanced by the adjacent positively charged nitrogen atom in the zwitterionic N–H tautomer. Thus *o*- and *p*-quinonoid structures with negative

TABLE 1. *The absorption spectra of* N-*heterocyclic hydroxy-compounds and their* O- *and* N-*methyl derivatives in the visible and ultraviolet regions, and the values of their tautomeric constants,* K_t = [Zwitterion]/[Enol], *calculated from the spectra.* (*Wavelengths and molecular extinctions in italics refer to shoulders or inflexions.*)

No.	Compound	pK_a (H_2O; 20°)	Solvent *	$\lambda_{max.}$ (mμ)	ε	K_t
1	2-Hydroxypyridine	0·75 [c]; 11·62 [c]	pH 6, CH	293; 224 298; 230	5890; 7230 4540; 8880	*k*
2	2-Methoxypyridine	3·28 [c]	pH 7	269	3230	
3	1-Methyl-2-pyridone	0·32 [c]	pH 5	297; 226	5700; 6100	
4	3-Hydroxypyridine	4·86 [c]; 8·72 [c]	pH 6·80	315; 278; 246; 211	3060; 2320; 5120; 15,800	1·27
			EtOH	279; 215	4440; 6480	
5	3-Methoxypyridine	4·88 [c]	pH 7·0	276; 216	3960; 8320	
6	3-Hydroxypyridine methochloride	4·96 [c]	pH 7·0	320; 249; 213	5810; 8120; 24,640	
7	2-Hydroxypyrazine	−0·1 [c]; 8·23 [c]	pH 4·5 EtOH	317; 221 321; 224	5520; 8820 5490; 8950	*k*
8	2-Methoxypyrazine	0·75 [c]	pH 7·0	290; 209	5240; 9600	
9	1-Methyl-2-pyrazone	−0·04 [c]	pH 7·0	323; 223	5610; 9370	
10	3-Hydroxypyridazine	−1·8 [c]; 10·46 [c]	pH 6·0 EtOH	281; 220 290; 222	2790; 3160 2700; 3600	*k*
11	3-Methoxypyridazine	2·52 [c]	pH 6·0	265	2330	
12	2-Methyl-3-pyridazone [a]	— [c]	EtOH	295; 223	3100; 3100	
13	4-Hydroxypyridazine	1·07 ; 8·68 [c]	pH 4·8 EtOH	262 266	12,740 13,100	*k*
14	4-Methoxypyridazine	3·70 [c]	pH 7·0	254; 224	2570; 8240	
15	1-Methyl-4-pyridazone [b]	—	EtOH	269	14,800	
16	4-Hydroxypyridazine 2-methochloride	1·74 [d]	pH 7·0	302; 254; 207	4840; 8240; 22,120	
17	5-Hydroxypyrimidine	1·87 [d]; 6·78 [d]	pH 4·32 EtOH	*325*; 271; 214 276; 218	107; 4750; 9720 5330; 9970	⩾0·02 [1]
18	2-Hydroxyquinoline	−0·31 [c]; 11·74 [c]	pH 5·5	324; 270; 245; 224	6300; 6550; 8520; 26,720	*k*
19	2-Methoxyquinoline	3·17 [c]	pH 6·8	318; 307; 267; *260*	2200; 2070; 2000; *1990*	
20	1-Methyl-2-quinolone	−0·71 [c]	pH 7·0	325; 272; 245; 228	6500; 6900; 10,250; 34,100	
21	3-Hydroxyquinoline	4·30 [c]; 8·06 [c]	pH 6·18	365; 330 + 321; *270*	430; 4080 + 4100; *3060*	0·064
			EtOH	334 + 324; 278 + 267	4800 + 4850; 3000 + 3080	
22	3-Hydroxyquinoline methochloride	5·42 [d]	pH 10	384; 320 + 308; 255	7140; 1700 + 1680; 14,600	
23	5-Hydroxyquinoline	5·20 [c]; 8·54 [c]	pH 6·87	450; 312; *268*; 240	193; 2870; *3290*; 37,400	0·054
			EtOH	323; 242	3400; 56,000	
24	5-Hydroxyquinoline methochloride	6·12 [d]	pH 8·5	462; 332 + 318; 273	3800; 1150 + 1240; 33,100	
25	6-Hydroxyquinoline	5·17 [c]; 8·88 [c]	pH 7·02	*400*; 325; 272; 225	*49*; 3860; 3060; 30,500	0·014
			EtOH	331; 274; 227	4100; 2800; 32,100	
26	6-Methoxyquinoline	5·06 [d]	pH 7·5	325; 268; 223	3900; 2940; 32,400	
27	6-Hydroxyquinoline methochloride	7·15 [d]	pH 10	408; 325 + 316; 270	3500; 3950 + 4000; 26,800	
28	7-Hydroxyquinoline	5·48 [c]; 8·85 [c]	pH 7·16	402; 327; 258; 225	3030; 3810; 12,800; 26,700	0·43
			EtOH	333; 263; 227	5250; 2910; 37,400	
29	7-Hydroxyquinoline methochloride	5·56 [d]	pH 8	406; 311; 261	10,000; 1550; 32,500	
30	8-Hydroxyquinoline	5·13 [c]; 9·89 [c]	pH 7·51	430; 303; *270*; 240	51; 2100; *2290*; 17,200	0·035
			EtOH	305: 242		
31	8-Hydroxyquinoline methochloride	6·81 [d]	pH 10	442; 346 + 334; 273	1520; 1310 + 1200; 37,000	
32	4-Hydroxy*iso*quinoline	4·80 [d]; 8·68 [d]	pH 6·74 EtOH	359; *320*; *240* 330; 295; 230	7640; *4260*; 8800 4860; 3950; 16,100	3·76
33	4-Hydroxy*iso*quinoline methochloride	4·93 [d]	pH 8·5	364; *320*; 248	9660; 3670; 9180	

TABLE 1. (*Continued.*)

No.	Compound	pK_a (H_2O; 20°)	Solvent *	$\lambda_{max.}$ (mμ)	ε	K_t
34	5-Hydroxy*iso*quinoline	5·40 [d]; 8·45 [d]	pH 6·92	*400*; 330; 296; 230	*135*; 4400; 3570; 22,800	0·038
			EtOH	326; 302; 235	5200; 5260; 30,600	
35	5-Hydroxy*iso*quinoline methochloride	6·90 [d]	pH 10·0	408; 349; 269; 233	3720; 6120; 21,000; 16,800	
36	6-Hydroxy*iso*quinoline	5·85 [d]; 9·15 [d]	pH 7·50	353; 263; 229	8040; 17,200; 43,600	1·92
			CH	319; 280; 225	694; 2160; 25,600	
37	6-Hydroxy*iso*quinoline methochloride	6·02 [d]	pH 10·0	358; 267; 230	12,220; 22,900, 34,400	
38	7-Hydroxy*iso*quinoline	5·70 [d]; 8·88 [d]	pH 7·29	400; 338; 257; 221	*110*; 3060; 6550; 49,000	0·038
			EtOH	338; 259; 225	3460; 5510; 52,500	
39	7-Hydroxy*iso*quinoline methochloride	7·09 [d]	pH 10·0	408; 298; 261	2970; 8200; 50,400	
40	8-Hydroxy*iso*quinoline	5·66 [d]; 8·40 [d]	pH 7·03	430; 328; *247*	2700; 4340; *15,500*	0·87
			EtOH	380; 333; 233	1860; 4050; 28,000	
41	8-Hydroxy*iso*quinoline methochloride	5·81 [d]	pH 10·0	400; 334; 257	5820; 4950; 20,000	
42	4-Hydroxy-1 : 5-naphthyridine	2·85 [e]; 10·01 [e]	pH 6·5	323; 240	9600; 25,120	*k*
			EtOH	328; 242	9370; 26,300	
43	8-Hydroxy-1 : 6-naphthyridine	4·08 [e]; 8·33 [e]	pH 6·20	368; 325; 257; 239	2160; 3110; 12,000; 14,480	0·90
			EtOH	327; 241	3700; 27,920	
44	8-Hydroxy-1 : 6-naphthyridine 6-methochloride	4·34 [e]	pH 7·0	362; 260	4550; 9600	
45	8-Hydroxy-1 : 7-naphthyridine	2·64 [e]; 12·01 [e]	pH 7·32	325; 283; 239	3470; 5620; 12,080	*k*
			EtOH	331; 285; 240	3440; 5670; 13,100	
46	5-Hydroxycinnoline	1·92 [f]; 7·40 [f]	pH 4·66	356; *305*; 244	2480; *1190*; 32,480	*k*
			EtOH	359; *305*; 245	2430; *1200*; 33,100	
47	6-Hydroxycinnoline	3·65 [f]; 7·52 [f]	pH 5·58	402; 320; 281; 238	1200; 4720; 3750; 24,000	⩾0·1 [m]
			EtOH	326; 241	4850; 40,500	
48	7-Hydroxycinnoline	3·31 [f]; 7·56 [f]	pH 5·44	448; 354; 267; 235	282; 2970; 5140; 42,600	⩾0·03 [n]
			EtOH	355; *275*; 237	3970; *6100*; 47,600	
49	8-Hydroxycinnoline	2·74 [c]; 8·20 [c]	pH 5·47	525; 359; 296; 242	21; 2610; 1240; 32,200	⩾0·004
			EtOH	362; 303; 246	2700; 1110; 34,000	
50	6-Hydroxyphthalazine	3·94 [d]; 7·95 [d]	pH 5·95	*375*; 325 + 313; 275	*1540*; 3070 + 3110; 5950	⩾0·1 [m]
			EtOH	317; 279; 228	3140; 6680; 38,200	
51	6-Hydroxyquinazoline	3·12 [c]; 8·19 [c]	pH 5·65	336; 264; 231	3270; 3290; 31,600	*k*
			EtOH	342; 265; 233	3700; 3690; 45,000	
52	8-Hydroxyquinazoline	3·41 [e]; 8·65 [e]	pH 6·03	324; 239	2550; 28,080	*k*
			EtOH	329; 241	2670; 29,100	
53	8-Hydroxyquinazoline 3-methochloride	7·26 [e]	pH 10·5	443; 328 + 317; 275	174; 5150 + 5470; 6210	
54	5-Hydroxyquinoxaline	0·9 [e]; 8·65 [e]	pH ·380	*355*; 325; 250	*1460*; 2860; 30,280	*k*
			EtOH	*363*; 326; 252	*1520*; 2900; 30,000	
55	5-Hydroxyquinoxaline 1-methochloride	5·74 [e]	pH 10	550; 335; 288; 237	2440; 1780; 28,400; 9100	
56	6-Hydroxyquinoxaline	1·40 [c]; 7·92 [c]	pH 4·66	342; 244	5880; 20,400	*k*
			EtOH	350; 245	5950; 21,000	
57	1-Hydroxyacridine	4·18 [g]; 10·7 [g]	10% EtOH–H_2O	*550*; 386; 358	*42*; 3450; 3670	0·036
			EtOH [h]	392; 360	3550; 3550	
58	1-Hydroxyacridine methochloride	—	pH 9—10 [i]	550; 380	1200; 3600	
59	2-Hydroxyacridine	4·86 [g]; 9·9 [g]	20% EtOH–H_2O [h]	466; 363; 351	10,000; 16,000; 12,500	2·5
			90% Et_2O–EtOH [h]	391; 351	5600; 8000	
60	2-Hydroxyacridine methochloride	—	pH 9—10 [i]	470; 350	14,000; 12,000	
61	3-Hydroxyacridine	5·52 [c]; 8·81 [c]	10% EtOH–H_2O	*500*; 380; 355	*60*; 4470; 6300	0·015
			EtOH [h]	396; 354	5000; 7000	

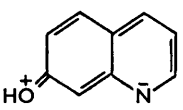
TABLE 1. (*Continued.*)

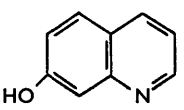
No.	Compound	pK_a (H_2O; 20°)	Solvent *	$\lambda_{max.}$ (mμ)	ε	K_t
62	3-Hydroxyacridine methochloride	—	pH 9—10 [i]	500; 370	4000; 10,000	
63	4-Hydroxyacridine	4·45 [g]; 9·4 [g]	20% EtOH–H_2O [h]	570; 398; 360	1000; 2800; 5000	0·33
			EtOH [h]	400; 358	2800; 4500	
64	4-Hydroxyacridine methochloride	—	pH 9—10 [i]	570; 360	4000; 4500	
65	2-Hydroxyphenanthridine	4·82 [c]; 8·79 [c]	pH 6·80	*450*; 360 + 347; 253	*17*; 2270 + 2240; 45,200	⩽0·001 [n]
			EtOH	365 + 351; 254	2400 + 2460; 43,600	
66	6-Hydroxyphenanthridine	5·35 [c]; 8·43 [c]	pH 6·89	377; 328; 299; 251	10,400; 3500; 8000; 43,600	⩽5 [n]
			Dioxan	328; 297; 254	1360; 13,600; 50,000	
67	7-Hydroxyphenanthridine	4·39 [d]; 8·68 [d]	10% EtOH–H_2O	*395*; 361 + 347; 301	*315*; 2300 + 2310; 4680	⩽0·1 [q]
			EtOH	364 + 349; 303; 253	2550 + 2510; 4060; 44,100	
68	2-Hydroxyphenazine	2·6 [c]; 7·5 [c]	H_2O [j]	490; 410; 365	2800; 4200; 9000	⩾0·25 [r]
			EtOH [j]	410; 355	6500; 9000	

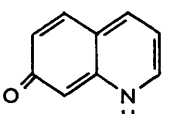
* H_2O unless otherwise stated; CH = *cyclo*hexane.

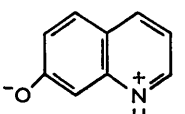
[a] Quoted from Druey, Eichenberger, and Rometsch, *Helv. Chim. Acta*, 1954, **37**, 1298. [b] Unpublished values kindly provided by Drs. J. Druey and P. Schmidt. [c] pK_a values quoted from Albert and Phillips, *J.*, 1956, 1294. [d] pK_a values quoted from Part III. [e] pK_a values quoted from Albert and Hampton, *J.*, 1954, 505. [f] pK_a values quoted from Osborn and Schofield, *J.*, 1956, 4207. [g] pK_a values for 50% alcohol quoted from Albert, "The Acridines," Arnold, London, 1951, p. 114. [h] Spectra quoted from Albert and Short, *J.*, 1945, 760. [i] Spectra quoted from Nitzsche, *Ber.*, 1944, **77**, 337. [j] Spectra quoted from Badger, Pearce, and Petit, *J.*, 1951, 3204. [k] Not measurable spectroscopically. [l] Based on the extinction of the 320 mμ band of compound 6. [m] Based on the extinction of the 358 mμ band of compound 37. [n] Based on the extinction of the 406 mμ band of compound 29. [p] Based on the extinction of the 440 mμ band of compound 41. [q] Based on the extinction of the 408 mμ band of compound 39. [r] Based on the extinction of the 470 mμ band of compound 60.

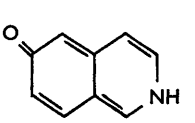
charge on one or the other of the vicinal carbon atoms (*e.g.*, XII, XIII, and XIV) should make relatively important contributions to the stability of the N–H tautomer in these cases. The effectiveness of the structures may be expected to have the order (XIV) > (XII) > (XIII), for in (XIII) the benzenoid resonance of both rings is replaced by quinonoid resonance, whilst in (XIV) the benzenoid resonance of only one ring is lost.

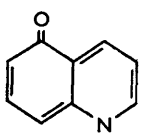

(VIa)

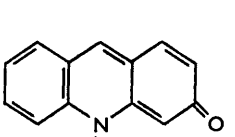

(VIb)

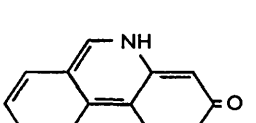

(VIIa)


(VIIb)


(VIII)

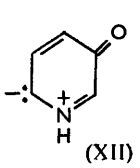

(IX)

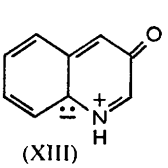

(X)

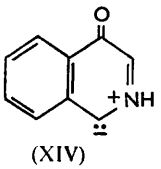

(XI)

Thus the K_t value of 4-hydroxy*iso*quinoline is larger than that of 3-hydroxypyridine, whilst that of 3-hydroxyquinoline is smaller (Table 1). The K_t values of the other hydroxy-quinolines and -*iso*quinolines in which the nitrogen and oxygen atoms are not formally conjugated are of the same magnitude as that of 3-hydroxyquinoline (Table 1), and in these compounds too the benzenoid resonance of both aromatic rings is replaced by quinonoid resonance in the structure analogous to (XIII) contributing to the resonance hybrid of the zwitterionic N–H tautomer.

The diaza-compounds have smaller K_t values than their monoaza-analogues (Table 1), since a second nuclear nitrogen atom reduces the proton-accepting property of the first more than it enhances the proton-releasing property of the oxygen atom. Thus the ionisation constants of 4-hydroxy*iso*quinoline are separated by 3·88 pK_a units, whilst those of 8-hydroxy-1 : 6-naphthyridine are separated by 4·25 units, and the tautomeric constant of the former compound is four times as large as that of the latter. In the latter compound, where the two nitrogen atoms are substituted in different rings, the decrease in K_t is smaller than in the cases (compounds 46—49, Table 1) where they are substituted in the same ring. The proton-accepting capacity of a nitrogen atom is lowered more by another nitrogen atom substituted in the same ring than in the condensed ring (Table 1), as such an atom reduces the π-electron density of the ring in which it is substituted more than that of the condensed ring.[7]


(XII)


(XIII)


(XIV)

7-Hydroxycinnoline has a larger K_t value than the 8-isomer, yet their zwitterionic forms may both resonate with neutral "*ortho-para*-quinonoid" amide forms; among their monoaza-analogues, 7-hydroxyquinoline and 8-hydroxy*iso*quinoline have K_t values of the same order (Table 1). In 8-hydroxycinnoline intramolecular hydrogen-bonding favours the enol tautomer, as a zwitterion stabilised by resonance with a neutral form requires the breaking of the hydrogen bond and the union of the tautomeric proton with the 2-nitrogen atom. In 8-hydroxyquinoline, on the other hand, intramolecular hydrogen-bonding favours the zwitterion form, as its K_t value is larger than that of the 6-isomer, whilst 5- and 7-hydroxy*iso*quinoline, which are analogous in that the hydroxyl group is not substituted in the same ring as the nitrogen atom and is not conjugated to it, have the same K_t values (Table 1). Thus $^+$N–H···O$^-$ hydrogen-bonding is stronger than comparable O–H···N bonding. The standard free-energy change of the tautomeric equilibrium at 20° is 500 cal. larger in 8- than in 6-hydroxyquinoline, and the strengths of these types of hydrogen bond differ to approximately the same degree if the standard entropy changes of the two equilibria are similar.

The tautomerism of *N*-heteroaromatic hydroxy-compounds to zwitterionic forms is repressed in solvents of low dielectric constant. The variation of the classical tautomeric constant of 6-hydroxy*iso*quinoline with dielectric constant has been determined from the molar extinction of the 353 mμ band of this compound in dioxan–water mixtures of varied compositions at 20°. The constant falls by a factor of 800 as the dielectric constant is reduced from 80 to 2·1 (Table 2), and since the activity coefficient of the neutral enol form is probably not greatly affected by a change of solvent, the fall must be due principally to an increase in the activity coefficient of the zwitterionic N–H form with the decrease in dielectric constant. A plot of the logarithm of the tautomeric constant (log K_t) against the logarithm of the dielectric constant (log D) does not give a straight line (Table 2), the curve obtained suggesting that log K_t is proportional to $D^{0\cdot3}$ in the region of high dielectric constant and to $D^{0\cdot7}$ in the region of low dielectric constant.

An increase in temperature also represses the tautomerism of *N*-heteroaromatic hydroxy-compounds to zwitterionic forms, showing that the tautomerism is exothermic. The thermal variation of the tautomeric constants of four compounds, representing the type of no conjugation and the three types of transannular *o*- and *p*-quinonoid conjugation between the nitrogen and the oxygen atom, have been measured from the change of their

[7] Coulson and Longuet-Higgins, *J.*, 1949, 971.

absorption spectra with temperature over the range 15—85°. From the observed constants, the standard heat content and entropy changes of the tautomerism at 20° and 80° have been calculated (Table 3), the values obtained being accurate to within about 10%. The results (Table 3) show that, at a given temperature, the variation of the change in standard free energy of tautomerism from compound to compound is due mainly to the

TABLE 2. *The tautomeric equilibrium constant* (K_t = [N–H form]/[O–H form]) *of 6-hydroxy*isoquinoline *in dioxan–water at* 20°.

Dioxan (%) ...	0	10	20	30	40	50	60	70	80	90	100
Dielectric constant [a]	80	71	62	53	44	32	27	18	11	5·7	2·1
log K_t	0·29	0·11	−0·15	−0·38	−0·66	−0·93	−0·98	−1·26	−1·59	−2·01	−2·62

[a] Quoted from Åkerlof and Short, *J. Amer. Chem. Soc.*, 1936, **58**, 1241.

variation of the heat-content change. The standard entropy change of the tautomerism, at a given temperature, is approximately constant for 3-hydroxypyridine and 6- and 8-hydroxy*iso*quinoline, though not for 5-hydroxyquinoline. The anomalous entropy change in the tautomerism of 5-hydroxyquinoline cannot be due to the steric effect of a C–H group *peri* to the hydroxyl group, as the hydroxyl group in 8-hydroxy*iso*quinoline is also *peri* to a C–H group. The most important factor contributing to the standard entropy change of the tautomerism of a *N*-heteroaromatic hydroxy-compound may be expected to be the increase in order resulting from the solvation of the zwitterion. The solvation of a zwitterion at a given temperature, and the decrease of that solvation with an increase in temperature, are not likely to vary widely from one compound to another in the present series, so that an approximately constant standard entropy change of tautomerism is to be expected at a given temperature for the compounds studied.

TABLE 3. *Variation of the tautomeric equilibrium constant* (K_t = [N–H form]/[O–H form]) *with temperature, and the standard heat content* (ΔH) *and entropy* (ΔS) *changes at* 20° *and* 80°.

	log K_t				$-\Delta H$ (kcal./mole)		$-\Delta S$ (cal./mole/°c)	
	20°	40°	60°	80°	20°	80°	20°	80°
6-Hydroxy*iso*quinoline ...	0·29	0·16	0·03	−0·16	2·6	6·0	7·3	17·7
3-Hydroxypyridine	0·10	−0·05	−0·22	−0·40	2·5	5·7	7·8	17·9
8-Hydroxy*iso*quinoline ...	−0·06	−0·17	−0·30	−0·50	2·1	5·3	7·5	17·3
5-Hydroxyquinoline	−1·28	−1·36	−1·44	−1·54	1·6	3·0	11·0	15·6

EXPERIMENTAL

Sources of Materials.—These were as in Part I (preceding paper).

Absorption Spectra.—These were measured with a Hilger Uvispek H700/305 quartz spectrophotometer, in the solvent listed in Table 1. The buffer solutions were 0·01M-acetate (for pH 3·8—5·7), 0·01M-phosphate (for pH 6·0—7·9, and 10·3—11·3), and 0·01M-borate (for pH 8·2—10·0). The variations of the spectra with temperature were measured by means of a water-jacketed cell-holder maintained at a constant temperature (±0·05°) with water circulated from a thermostat.

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