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22. *Quinoxalines and Related Compounds. Part IV.* The Fine Structure of the 2- and 3-Hydroxyquinoxalines and 2-Amino- and 2-Mercapto-quinoxaline.*

By G. W. H. Cheeseman.

Ultraviolet absorption and ionisation properties indicate that 2- and 3-hydroxyquinoxalines exist in solution largely in the amide form. It is probable that in solution 2-aminoquinoxaline exists predominantly in the amino-form and 2-mercaptoquinoxaline in the thioamide form.

Little is known about the ultraviolet absorption and ionisation properties of quinoxalines. In the present investigation the structures of the potentially tautomeric hydroxy-, amino-, and mercapto-quinoxalines have been studied by comparison of their ultraviolet spectra and ionisation constants with those of their fixed methylated tautomers.

The ultraviolet spectrum of the neutral molecule of 2-hydroxyquinoxaline was closely similar to that of its *N*-methyl derivative (I; R = Me, R_1 = H), but dissimilar from that of 2-methoxyquinoxaline (II; R = H) (Table, Fig. 1). This indicated that the hydroxy-compound existed largely in the amide form (I; R = R_1 = H). The cations of 2-hydroxyquinoxaline and its *N*-methyl derivative also showed similar ultraviolet absorption; these spectra differed from the spectrum of the cation of 2-methoxyquinoxaline (Table, Fig. 2).

* Part III, *J.*, 1957, 3236.

Analogous relations were observed between the spectra of 2-hydroxy-3-methylquinoxaline and its *N*- and *O*-methyl derivatives both as neutral molecules and as cations (Table).

The relative basicities of these hydroxyquinoxalines and their *N*- and *O*-methyl derivatives (Table) also suggested that the hydroxy-compounds existed predominantly in the amide form. Thus the hydroxy-compounds were bases of similar strength to their *N*-methyl derivatives but appreciably weaker bases than their *O*-methyl derivatives. The

FIG. 1. *Neutral molecules of 2-hydroxy-* (——) *2-methoxy-* (. . . .), *and 1 : 2-dihydro-1-methyl-2-oxoquinoxaline* (– – – –).

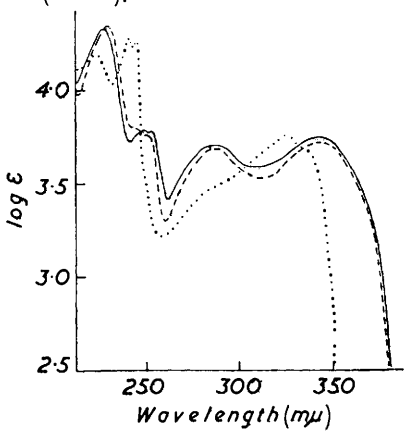
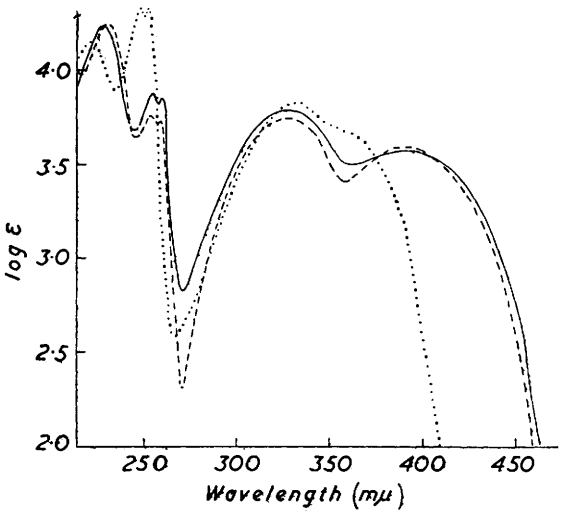
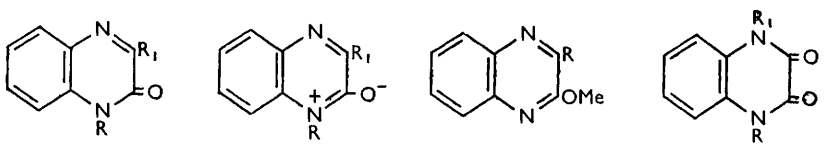


FIG. 2. *Cations of 2-hydroxy-* (——), *2-methoxy-* (. . . .), *and 1 : 2-dihydro-1-methyl-2-oxo-quinoxaline* (– – – –).



basic constants of 2-hydroxypyrazine (pK_a −0·1), its *N*-methyl derivative (pK_a −0·04), and 2-methoxypyrazine (pK_a 0·75) follow a similar pattern, and further examples may be cited.[1] The neutral molecules of the hydroxyquinoxalines and their *N*-methyl derivatives are stabilised by structures such as (Ia). There are however no similar resonance possibilities for base-weakening to stabilise the neutral molecules of the corresponding methoxyquinoxalines.



Oakes, Pascoe, and Rydon [2] compared the spectrum in ethanol of both 2 : 4-dihydroxy-1 : 3 : 5- and 2 : 4-dihydroxy-1 : 3 : 8-triaza-naphthalene with those of the *OO'*- and *NN'*-dimethyl derivatives. They concluded tentatively that these hydroxyazanaphthalenes exist as true hydroxy-compounds, but the *ON*-dimethyl derivatives were not available for comparison. It was therefore of interest to compare the spectrum of the neutral molecule of 2 : 3-dihydroxyquinoxaline with those of its *NN'*-, *ON*-, and *OO'*-dimethyl derivatives, (III; R = R_1 = Me), (I; R = Me, R_1 = OMe), and (II; R = OMe). The spectrum of the dihydroxy-compound most closely resembled that of its *NN*-dimethyl derivative (Table, Fig. 3), indicating that it must exist predominantly in the diamide form (III;

[1] Albert and Phillips, *J.*, 1956, 1294.
[2] Oakes, Pascoe, and Rydon, *J.*, 1956, 1045.

Quinoxaline	Ionisation [a] (in H_2O) pK_a	Spread (±)	Concn. (10^{-5}M)	$\lambda_{analyt.}$ (mμ) [b]	Solv.[c]	Spectroscopy $\lambda_{max.}$, mμ ($\log_{10}\varepsilon$)
Parent	—	—	—	—	C_6H_{12} [d]	367(2·40) + 360(2·61) + 353(2·74) + 346(2·81) + 339(2·84); 316(3·80) + 310(3·69) + 304(3·74) + 298[e](3·63) + 293[e](3·59); 235(4·40) + 232(4·51) + 230—229[e](4·41)
2-Methyl-	—	—	—	—	,,	317(3·77) + 309—308(3·74) + 297[e](3·61); 238(4·38) + 234(4·48) + 231[e](4·38)
2-Chloro-	—	—	—	—	,,	329(3·68) + 319(3·795) + 311[e](3·73); 242(4·44) + 238(4·51) + 236—235[e](4·42)
2-Hydroxy-	—	—	—	—	H_2O 4·0 [f]	343(3·74); 287(3·70); 254(3·78) + 250(3·79); 228(4·32)
anion	9·12 [g]	0·03	250	—	H_2O 12·8	350(3·80); 288(3·31) + 282(3·30); 237(4·41)
cation	−1·38 [h]	0·01	6	390	H_2O −3·5	395—385(3·57—3·58); 326(3·79); 259(3·85) + 254(3·87); 228(4·25)
2-Methoxy-	—	—	—	—	C_6H_{12}	336(3·74) + 328(3·68) + 322(3·79) + 315(3·68) + 309(3·63); 278(3·49); 244(4·33) + 241(4·31); 225(4·28)
					EtOH	336(3·73) + 324(3·79) + 314(3·725); 288(3·55); 242(4·22); 223(4·22)
					H_2O 4·5	333[e](3·69) + 326(3·75); 245(4·25) + 241(4·26); 223(4·19)
cation	0·28	0·07	5	356	H_2O −3·3	353[e](3·70) + 331(3·84); 252(4·31) + 248(4·31); 222(4·14)
1 : 2-Dihydro-1-methyl-2-oxo-	—	—	—	—	C_6H_{12}	362—361(3·51) + 351(3·71) + 345(3·71) + 336(3·71) + 331[e](3·67) + 323[e](3·57); 290(3·60) + 286(3·55) + 279(3·73) + 270(3·61); 232(4·45)
					EtOH [i]	346(3·73) + 336(3·71); 282(3·73); 252[e](3·64) + 231(4·40)
					H_2O 4·5	345(3·715); 287(3·68); 252(3·76) + 245[e](3·80); 230(4·34)
cation	−1·15	0·04	6	391	H_2O −3·0	395—386(3·59—3·58); 326(3·74); 258(3·73) + 254(3·76); 231(4·24)
2-Hydroxy-3-methyl-	—	—	—	—	H_2O 4·0 [j]	340—330(3·83—3·84); 285(3·71); 254(3·79) + 250(3·79); 228(4·26)
anion	9·88	0·03	250	—	H_2O 12·8	343(3·90); 290(3·32); 238(4·40)
cation	0·48	0·04	5	375	H_2O −1·8	378—368(3·74); 320(3·795); 260(3·81) + 255(3·80); 230(4·23)
2-Methoxy-3-methyl-	—	—	—	—	C_6H_{12}	331(3·83) + 317(3·87) + 309(3·74); 244(4·30) + 240(4·29); 223[e](4·20)
					H_2O 5·1	332(3·81) + 319(3·88); 246(4·24) + 242—241(4·26); 223(4·17)
cation	1·38	0·01	5	350	H_2O −1·0	339(3·90); 252(4·305) + 248(4·27); 222(3·995)
1 : 2-Dihydro-1 : 3-dimethyl-2-oxo- [k]	—	—	—	—	C_6H_{12}	352[e](3·59) + 341(3·83) + 327—326(3·82); 288(3·66) + 277(3·81) + 270[e](3·75); 231 (4·48)
					H_2O 4·8	340—334(3·82—3·81); 285(3·71); 253(3·80) + 245[e](3·82); 228(4·30)
cation	0·51	0·09	5	375	H_2O −1·8	377—369(3·74); 316(3·77); 260(3·77) + 254(3·75); 231(4·22)
2 : 3-Dihydroxy- [l]	—	—	—	—	H_2O 5·1 [f]	342[e](3·68) + 326(4·00) + 312(4·07); 262[e](3·63) + 258(3·655); 236(3·90) + 229(4·00)
2 : 3-Dimethoxy-	—	—	—	—	C_6H_{12}	325(4·11) + 317(3·94) + 310(4·11) + 304(3·90) + 298—297(3·85) + 292—291(3·65) + 286(3·55) + 280(3·43) + 274(3·39); 243(4·26); 223[e](4·31)
					H_2O 5·1	325(3·91) + 311(3·99) + 301[e](3·81); 244(4·18); 222[e](4·21)
cation	−1·15	0·06	5	340	H_2O −3·3	336[e](3·99) + 329(4·01); 255(4·11) + 250(4·11); 225(4·06)
1 : 2-Dihydro-3-methoxy-1-methyl-2-oxo-	—	—	—	—	C_6H_{12}	334(3·73) + 322(3·97) + 310—309(3·92) + 290(3·66); 277(3·69) + 268—267(3·70) + 259(3·69); 230—229(4·28)
					H_2O 5·1	319(3·99) + 312[e](3·97); 252[e](3·87) + 248(3·88); 227(4·20)
1 : 2 : 3 : 4-Tetrahydro-1 : 4-dimethyl-2 : 3-dioxo-	—	—	—	—	H_2O 5·05	340[e](3·67); 325(3·99) + 313(4·05); 259[e](3·73) + 254(3·765); 238(4·01) + 232(4·06)
1 : 2-Dihydro-3-hydroxy-1-methyl-2-oxo-	—	—	—	—	EtOH	339[e](3·63) + 324(3·99) + 311(4·07) + 300[e](3·98); 259(3·71); 239(3·98) + 232—231 (4·025)
					H_2O 5·2	341[e](3·65) + 325(3·98) + 312(4·05); 261[e](3·66) + 256(3·695); 236[e](3·94) + 230(4·02)
anion	9·74	0·03	500	—	H_2O 12·8	338[e](3·90) + 325(4·11) + 314(4·07); 238(4·11)
2-Amino-	—	—	—	—	H_2O 7·2	353(3·80) + 310—290[e](3·39); 240(4·33)
cation	3·90 [m]	0·04	1000	—	H_2O 1·0	352—348(3·84) + 326—310[e](3·76); 257(4·07) + 252(4·05); 231(4·25)
2-Methylamino-	—	—	—	—	H_2O 7·2	363(3·79); 296—286[e](3·24—3·25); 248(4·43)
cation	4·10	0·05	1000	—	H_2O 1·0	354—350(3·855) + 312—304[e](3·74); 259(4·055) + 253(4·07) + 237(4·29)
2-Dimethylamino-	—	—	—	—	H_2O 7·2	382(3·845); 304—296[e](3·16—3·18); 254(4·40)
cation	3·72 [n]	0·02	1000	—	H_2O 1·0	368(3·93) + 320—314(3·72); 253[e](4·15) + 241(4·29)
2-Mercapto-	—	—	—	—	H_2O 3·8	405—395(4·04) + 329[e](3·37); 279(4·255)
anion	7·72 [o]	0·02	500		H_2O 11·65	382(3·92); 279(4·24); 217(4·23)
cation	−1·11	0·04	5	476	H_2O −3·3	480—476(3·86) + 400—360[e](3·36); 289(4·37)
2-Methylthio-	—	—	—	—	H_2O 4·9	356(3·94); 266(4·175); 240(4·16)
cation	0·26	0·06	5	391	H_2O −1·8	392(3·93); 257(4·20)

R = R_1 = H). The spectrum of the neutral molecule of 1 : 2-dihydro-3-hydroxy-1-methyl-2-oxoquinoxaline (I; R = Me, R_1 = OH) was closer to that of (III; R = R_1 = Me), its *N*-methyl derivative, than to that of (I; R = Me, R_1 = OMe), its *O*-methyl derivative (Table). Thus in common with other compounds with hydroxy-groups α to ring nitrogen atoms, the equilibrium for the tautomerism of the 2- and 3-hydroxyquinoxalines in solution is such that only small amounts of the enol form are present.[3]

Comparison of the spectra of the neutral molecules of 2-amino-, 2-methylamino-, and 2-dimethylamino-quinoxaline showed the expected bathochromic shifts of absorption bands associated with the substitution of a methyl group for the hydrogen atom of an amino-group (Table, Fig. 4).[4] The similarity in the spectra and ionisation constants of

FIG. 3. *Neutral molecules of* 2 : 3-*dihydroxy-* (——), 2 : 3-*dimethoxy-* (. . . .), 1 : 2-*dihydro*-3-*methoxy*-1-*methyl*-2-*oxo-* (— · — · —) *and* 1 : 2 : 3 : 4-*tetrahydro*-1 : 4-*dimethyl*-2 : 3-*dioxo-quinoxaline* (– – – –).

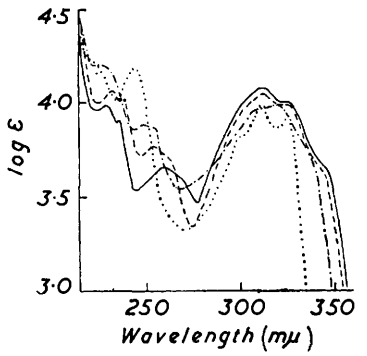
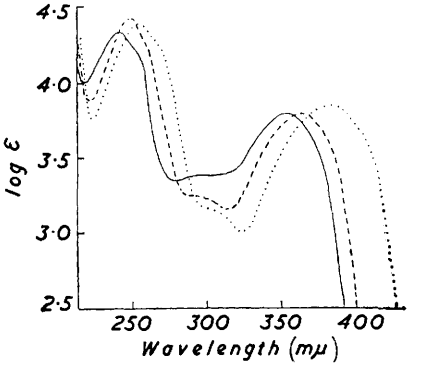


FIG. 4. *Neutral molecules of* 2-*amino-* (——), 2-*methylamino-* (– – – –), *and* 2-*dimethylamino-quinoxaline* (. . . .).



the 2-amino- and 2-dimethylamino-compounds suggested that 2-aminoquinoxaline existed predominantly in the amino- rather than the imino-form. This was to be expected, as related α-amino-*N*-heteroaromatic compounds have also been shown to exist mainly in the amino-form.[3] The evidence was incomplete as the corresponding nuclear *N*-methyl derivative of 2-aminoquinoxaline was not available for comparison. The change in spectrum which occurred when these aminoquinoxalines were dissolved in solutions sufficiently acid to convert them into mono-cations, indicated that it was a ring nitrogen, rather than the extranuclear nitrogen atom, that accepted the proton. However, Schofield and Osborn [5] have shown that 5-aminoquinoxaline accepts the first proton on the amino-group.

Footnotes to Table:

[a] Potentiometric determinations of p*K* were carried out at 25°, and spectroscopic determinations at room temperature, which varied from 15° to 25°. [b] An entry in this column indicates that the ionisation constant was determined spectroscopically. [c] Where the solvent was water the entry is followed by the pH of the solution. [d] Mason (*Chem. Soc. Special Publ.* No. 3, 1955, p. 139) gave $\lambda_{max.}$ 340 ($\log_{10}\varepsilon$ 2·76) and 312 (3·70). These values were taken from the smooth curve drawn through the vibrational fine structure of the *n*–π and first π–π bands. [e] Shoulder or inflection. [f] Spectrum in 0·1N-hydrochloric acid (Landquist, *J.*, 1953, 2830) showed similar $\lambda_{max.}$ and $\varepsilon_{max.}$ values. [g] Albert, Brown, and Cheeseman (*J.*, 1952, 1620) obtained 9·08 at 20°. [h] Albert and Phillips (*J.*, 1956, 1294) gave −1·37. [i] For spectrum in 96% ethanol, Clark-Lewis (*J.*, 1957, 422) gave $\lambda_{max.}$ 346 ($\log\varepsilon$ 3·72), 282 (3·72), and 230 (4·31). [j] Extinction curve by Lanning and Cohen (*J. Biol. Chem.*, 1951, **189**, 109) showed $\lambda_{max.}$ at *ca.* 335, 285, and 250 mμ. [k] For spectrum in ethanol, Dawson, Newbold, and Spring (*J.*, 1949, 2579) gave $\lambda_{max.}$ 336·5 ($\log_{10}\varepsilon$ 3·85), 280·5 (3·75), and 229 (4·33). [l] Albert and Phillips (*loc. cit.*) gave 9·52 for the acidic pK_a at 20°. [m] Albert, Goldacre, and Phillips (*J.*, 1948, 2240) obtained 3·96 at 20°. [n] In 10% ethanol. [o] In 50% ethanol.

[3] Albert, *Chem. Soc. Special Publ.* No. 3, 1955, p. 124.
[4] Brown and Short, *J.*, 1953, 331.
[5] Osborn and Schofield, *J.*, 1956, 4191.

The differences in the ultraviolet absorption spectra of the neutral molecules of 2-mercapto- and 2-methylthio-quinoxaline (Table, Fig. 5) suggested that the mercapto-compound existed mainly in the thioamide rather than the thiol form. There were also differences in the light absorption of the cations derived from these compounds (Table, Fig. 6). 2-Mercaptoquinoxaline proved to be a weaker base than its *S*-methyl derivative (Table). This again suggested a predominantly thioamide structure for 2-mercaptoquinoxaline, but more conclusive evidence must await measurements on the *N*-methyl derivative.

Quinoxalines, because of the 1 : 4-arrangement of their ring nitrogen atoms, are only weakly basic.[6] Methyl substitution has a base-strengthening effect, [*e.g.*, parent compound

FIG. 5. *Neutral molecules of 2-mercapto-* (——) *and 2-methylthio-quinoxaline* (. . . .).

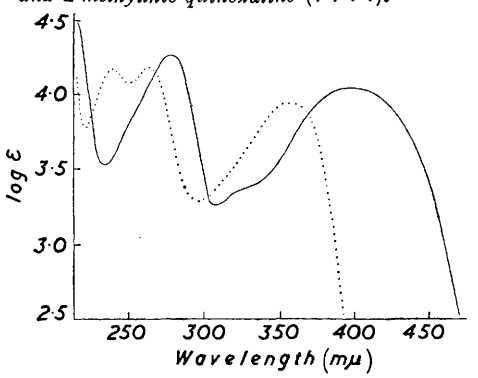


FIG. 6. *Cations of 2-mercapto-* (——) *and 2-methylthio-quinoxaline* . . . .).

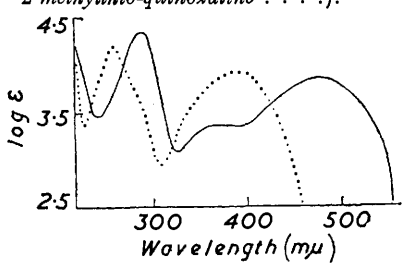
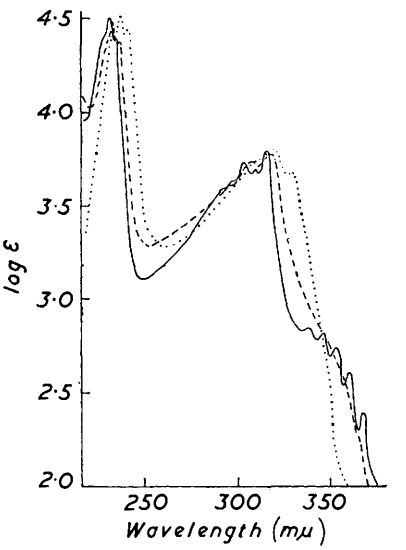


FIG. 7. *Spectrum of quinoxaline* (——), *2-methylquinoxaline* (– – –), *and 2-chloroquinoxaline* (. . . .) *in* cyclo*hexane*.



(pK_a 0·56), 2-methylquinoxaline (pK_a 0·95) [7]. 2-Hydroxy-3-methylquinoxaline has now been found to be a stronger base than 2-hydroxyquinoxaline; the quinoxalines (I; R = R_1 = Me) and (II; R = Me) were similarly stronger bases than the corresponding demethyl compounds (I; R = Me, R_1 = H) and (II; R = H). Methoxyl substitution had a base-weakening effect, thus. 2 : 3-dimethoxyquinoxaline was a weaker base than 2-methoxyquinoxaline, itself a weaker base than the parent compound. As expected 2-mercaptoquinoxaline was a stronger acid, and 3-methyl-2-hydroxyquinoxaline a weaker acid than 2-hydroxyquinoxaline.

The spectrum of quinoxaline in *cyclo*hexane (Table, Fig. 7) shows bands attributable to n–π and π–π transitions.[8a] In water [9] or methanol [10] the less intense n–π band is

[6] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[7] Albert, Brown, and Wood, *J.*, 1954, 3832.
[8] Mason, (*a*) *Chem. Soc. Special. Publ.* No. 3, 1955, p. 139; (*b*) *J.*, 1955, 2336.
[9] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[10] Bohlmann, *Chem. Ber.*, 1951, **84**, 860.

obscured by the long-wave π–π band, since change from non-polar to polar solvent causes *n*–π bands to shift to shorter wavelengths, whereas π–π bands are not greatly affected by change of solvent.

Substitution in the quinoxaline nucleus at position 2 produces bathochromic shifts in the π–π bands. This increases in the order Me < Cl < OMe < SMe < NMe_2 (Table, Fig. 7). These substituents produce similar bathochromic effects on the 260 mμ band of the benzene spectrum and the 300 mμ band of the pteridine spectrum.[8b] By analogy with the spectra of the chloropyrazines[11] and chloropteridines,[8b] a chloro-substituent should exert a hypsochromic effect on the *n*–π band of the quinoxaline spectrum. This effect was not observed in the spectrum of 2-chloroquinoxaline in *cyclo*hexane (Table, Fig. 7) because the *n*–π band was obscured by the more intense π–π band. A comparison of the spectra of 2-methoxy-, 2-methoxy-3-methyl-, and 2 : 3-dimethoxy-quinoxaline in water or *cyclo*hexane indicated that the long-wave band of the disubstituted quinoxalines was of increased intensity but at slightly shorter wavelengths.

The anomalous features in the spectrum of the neutral molecule of 6-hydroxypteridine, the pteridine analogue of 2-hydroxyquinoxaline, are due to the formation of a hydrate, the molecule of water being added across the 7 : 8-carbon–nitrogen double bond.[12] No similar anomalies were observed in the spectrum of the neutral molecule of 2-hydroxyquinoxaline. On anionisation a bathochromic shift characteristic of the hydroxyazanaphthalenes was observed (Table).[12] The spectrum of the anion of 2-hydroxyquinoxaline resembled that of the neutral molecule of 2-aminoquinoxaline, as is general for phenoxide ions and the corresponding aromatic amines.[13]

Experimental

Materials.—Quinoxaline and 2-methylquinoxaline were prepared by Jones and McLaughlin's method.[14] The sources of other quinoxalines were given in earlier papers.[15]

Physical Measurements.—Ultraviolet measurements were made with a Unicam S.P. 500 instrument. Measurements of pH were made with a Cambridge bench-type pH meter, standardised with buffer solutions of pH 4·00 and 9·19 at 25°, prepared from Cambridge buffer tablets. A Doran Alkacid sealed glass electrode and a Cambridge calomel electrode were used. Glycine, acetate, and phosphate buffers (0·01M) were used; solutions of lower pH were prepared from standard solutions of either hydrochloric or sulphuric [16] acid. Ionisation constants were determined either potentiometrically or spectroscopically in the usual manner.[1] The limits quoted in the table define the spread in the calculated pK_a values over the range 30—70% neutralisation.

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[11] Halverson and Hirt, *J. Chem. Phys.*, 1951, **19**, 711.
[12] Brown and Mason, *J.*, 1956, 3443.
[13] Jones, *J. Amer. Chem. Soc.*, 1945, **67**, 2127.
[14] Jones and McLaughlin, *Org. Synth.*, 1950, **30**, 86.
[15] Cheeseman, (*a*) *J.*, 1955, 1804; (*b*) *J.*, 1957, 3236.
[16] Michaelis and Granick, *J. Amer. Chem. Soc.*, 1942, **64**, 1861.