811. *Cinnolines. Part XXXV.* Studies of the Chloro- and Hydroxy-cinnolines.*

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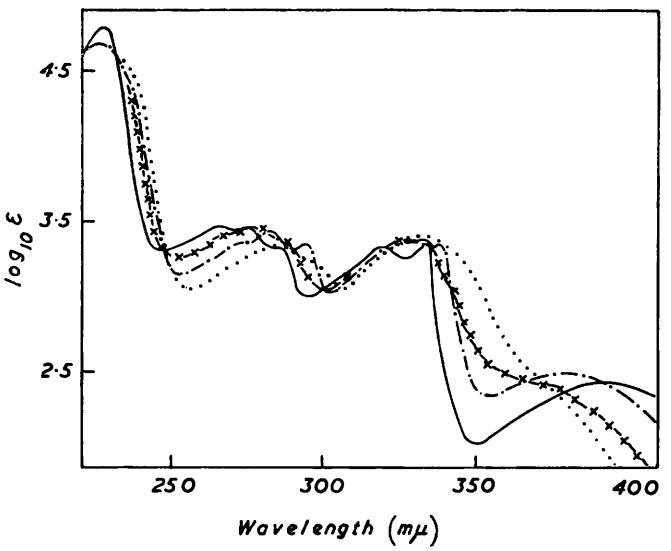
6-, 7-, and 8-Chlorocinnoline are described. The effect of chloro-substituents upon the cinnoline ultraviolet absorption spectrum, particularly the n–π^* band is discussed.

The ionisation constants of the hydroxycinnolines are reported and evidence for the importance of zwitterionic forms is discussed.

In studying the ultraviolet absorption spectra and basic strengths of the aminocinnolines (preceding paper) we found it desirable to examine other derivatives of this system, notably the chloro- and hydroxy-compounds.

(a) *Chlorocinnolines.*—In Figs. 1, 2, and 3 we give the ultraviolet extinction curves for 3-, 4-, 6-, 7-, and 8-chlorocinnoline in *cyclo*hexane and (except for the reactive 4-isomer)

Fig. 1. 3-*Chlorocinnoline* (*in* cyclo*hexane*) — . — . —; 3-*chlorocinnoline* (*in* EtOH) . . . . .; 7-*chlorocinnoline* (*in* cyclo*hexane*) ———; 7-*chlorocinnoline* (*in* EtOH) — × — × —.



in ethanol. Generally the band systems corresponding to those with $\lambda < 350$ mμ in the cinnoline spectrum [1] show bathochromic displacements as would be expected of bands produced by π–π^* transitions.

Tombácz [2] correlated the bands at about 300 mμ in the quinoline and *iso*quinoline spectra, and the band at 310 mμ in that of quinoxaline, with the naphthalene band at 308 mμ. All these bands were considered to arise from transitions polarised along the major axis of the molecules. Similarly the bands at 260—270 mμ for quinoline, *iso*quinoline, and quinoxaline, and at 275 mμ for naphthalene were related to transitions polarised along the minor axis. The π–π^* bands of the cinnoline absorption spectrum are very similar to those of *iso*quinoline, and the 322—317 and 308 mμ peaks in the former case may be related to those at about 300 and 260—270 mμ in the latter case.

The qualitative effects upon the positions of these bands of the substituents in the chlorocinnolines are only roughly in agreement with these assignments. Thus, the first long-wavelength π–π^* band suffers a bathochromic shift of 16, 11, 8, and 4 mμ in the

* Part XXXIV, *J.*, 1955, 2100.

[1] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[2] Tombácz, *Magyar Kém. Folyóirat*, 1950, **56**, 175.

3-, 7-, 8-, and 4-chloro-compounds respectively. The biggest shifts are produced by substituents at $C_{(3)}$ and $C_{(7)}$, as would be expected if the band is associated with a transition polarised along the major axis of the cinnoline nucleus. The effect of a 6-chloro-substituent in producing a very small hypsochromic shift is, in these terms, anomalous. With the medium-wavelength band, the effect of the substituent in 8-chlorocinnoline (bathochromic

FIG. 2. 4-*Chlorocinnoline* (*in* cyclo*hexane*) ———; 6-*chlorocinnoline* (*in* cyclo*hexane*) . . . . .; 6-*chlorocinnoline* (*in* EtOH) – – – – –.

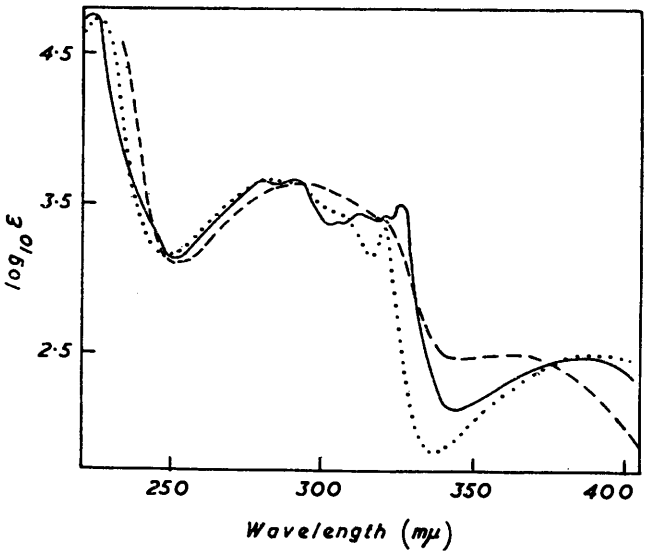
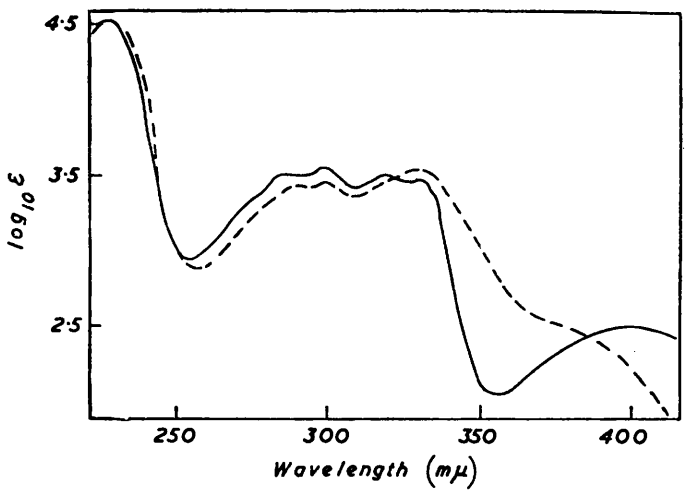


FIG. 3. 8-*Chlorocinnoline* (*in* cyclo*hexane*) ———; 8-*chlorocinnoline* (*in* EtOH) – – – – –



shift of 12 mμ) is to be expected if the band is connected with a transition polarised along the minor axis. However, the cases of 3-, 4-, 6-, and 7-chlorocinnoline (bathochromic shifts of 8, 6, 4, and 0 mμ respectively) are not simply related to such a picture. The strong interaction of the two nitrogen atoms presumably disturbs the situation. Examination of the extinction curves shows that those of the 3- and the 7-isomer are very similar, as are those of the 4- and the 6-compound. The curve for 8-chlorocinnoline is slightly different from those of the latter pair.

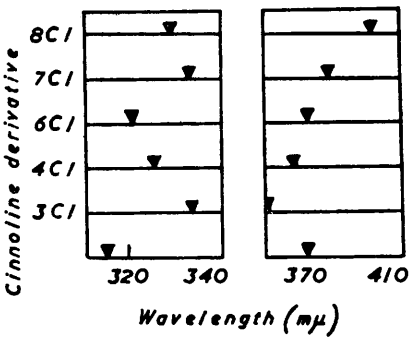
With regard to the intensities of the long-wavelength bands of the π–π^* spectra, application of the spectroscopic moments developed by Platt [3] would indicate an increase in the intensity ($\Delta\varepsilon$ +492) with 3- and 7-chlorocinnoline, and a decrease ($\Delta\varepsilon$ −192) with 4-, 5-, 6-, and 8-chlorocinnoline as compared with cinnoline. The observed changes in intensity ($\Delta\varepsilon$ +58, +871, +9, +211, and +871 for 3-, 4-, 6-, 7-, and 8-chlorocinnoline respectively) differ greatly from those predicted, but it is noteworthy that the 3-, 6-, and 7-isomers form a group, as do the 4- and 8-compounds. In the former group the resultant dipole falls more nearly along the short axis of the molecule, and in the latter group along the long axis.

The extinction curve of cinnoline in *cyclo*hexane [1] differs from those of related monoazanaphthalenes such as *iso*quinoline [4] most markedly in showing an additional low-intensity band (log $\varepsilon_{max.}$ 2·42) at 390 mμ. Hearn, Morton, and Simpson [1] remarked that this band " might well owe its origin to the presence of the –N=N– group in the molecule," and later authors [5,6] have identified it as arising from an n–π^* transition. Our observations on cinnoline support this assignment. Whilst the three main absorption bands (π–π^*) move slightly towards the red with change of solvent from *cyclo*hexane to water, that due to the n–π^* transition disappears (preceding paper) as would be expected.[7]

In studying the spectra of the diazines, Halverson and Hirt [8] observed that the introduction of chloro-substituents produced blue-shifts in the n–π^* band, and their results for the chloropyrazines have been discussed by Orgel.[9] He deduced that " substituents which can act as electron donors, but not as acceptors, should produce a blue-shift of the n–π^* spectra, since they stabilise the ground state more than the upper state."

With the extinction curves of 3-, 4-, 6-, 7-, and 8-chlorocinnoline it should first be noticed that again the change from non-polar to polar solvent produces the expected effect upon the n–π^* bands. In the diagram below we represent the effect of the change in

$\lambda_{max.}$ (mμ) *for* π–π^* *and* n–π^* *bands.*



position of the substituent upon the position of the n–π^* band and the longest-wavelength π–π^* band. In the cinnoline series the shifts in one band do not mirror those in the other as they do in the pyrazine series.[8] The n–π^* band undergoes a blue-shift with 3- and 4-chlorocinnoline, is unchanged with 6-chlorocinnoline, and shows a red-shift in 7- and 8-chlorocinnoline.

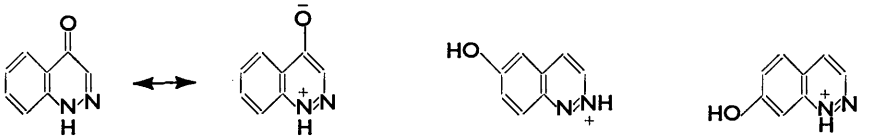
Clearly, in the bicyclic system the effect of the chloro-substituent upon the n–π^* band varies according to the position of the substituent. Qualitatively, this situation might be accounted for by recognising the dual character ($-I$, $+T$) of the chloro-substituent. The blue-shift caused by the 3- and 4-chloro-substituent could be caused by the strong $-I$ effect acting upon the $\sigma(n)$-electrons of the nitrogen atoms and increasing the strength of their binding. This influence will be in competition with the $+T$ effect of the substituent,

[3] Platt, *J. Chem. Phys.*, 1951, **19**, 263.
[4] Friedel and Orchin, " Ultra-violet Spectra of Aromatic Compounds," Wiley and Sons, New York, 1951, No. 271.
[5] Mason, " Recent Work on Naturally Occurring Nitrogen Heterocyclic Compounds," *Chem. Soc. Special Publ.* No. 3, 1955, p. 139.
[6] Badger and Walker, *J.*, 1956, 122.
[7] Kasha, *Discuss. Faraday Soc.*, 1950, **9**, 14.
[8] Halverson and Hirt, *J. Chem. Phys.*, 1951, **19**, 711.
[9] Orgel, *J.*, 1955, 121.

which by extending the conjugated system will lower the energy of the excited state. At some point this second effect will predominate over the first and produce a red-shift. This apparently happens in 7- and 8-chlorocinnoline, whilst a balance is attained in 6-chlorocinnoline.

This sort of situation does not appear to have been observed before, but will probably arise in other benzodiazines.

(b) *Hydroxycinnolines.*—Discussion of the dissociation constants of hydroxyl derivatives of heteroaromatic systems in terms of the electronic character of the hydroxyl group ($-I$, $+T$) is complicated by the possibilities of lactam–lactim tautomerism and zwitterion formation. With α- and γ-" hydroxy "-compounds these two terms are synonymous and in these cases the importance of tautomerism has long been recognised. In all such cases examined [10] the equilibrium greatly favours the lactam form (*e.g.*, I ⟷ II). In some



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

cases it is possible to write zwitterionic structures for monohydroxy-compounds which are not stabilised by resonance, and the work of Metzler and Snell [11] on 3-hydroxypyridine shows that zwitterion formation does not depend on such stabilisation. With the *Bz*-hydroxycinnolines zwitterions could be stabilised to some extent by resonance in every case. Both lactam–lactim tautomerism and zwitterion formation lead to apparent dissociation constants which make the heterocyclic hydroxy-compounds appear weaker, both as acids and as bases, than the true constants for the simple ionisation of the hydroxyl group and for cationisation of the neutral molecule would indicate. The figures for 3-hydroxypyridine [11] show this for the case of a zwitterion, and the weak basic and acidic characteristics of typical lactams are well known.

With these points in mind it is interesting to consider the observed pK_a values of the hydroxycinnolines recorded in Table 1. 4-Hydroxycinnoline is firmly established as a

TABLE 1.

	Basic pK_a *	Molar concn.	Acidic pK_a *	Molar concn.
Cinnoline	2·29	—	—	—
3-Hydroxycinnoline	0·21 ± 0·04 ‡	0·0001	8·61 ± 0·02	0·002
4- ,,	−0·35 ± 0·05 ‡	—	9·27	—
5- ,,	1·92 ± 0·06	0·002	7·40 ± 0·02	0·001
6- ,,	3·65 ± 0·01	,,	7·52 ± 0·01	0·002
7- ,,	3·31 ± 0·02	,,	7·56 ± 0·02	,,
8- ,, †	2·71 ± 0·00 ¶	—	8·17	,,

* In water at 20°.
† See refs. 12 and 15 for other determinations.
‡ Personal communication from Professor A. Albert.
¶ Spectroscopic determination. Titration (0·002M) gave 2·56 ± 0·06.

compound in which the lactam structure (I ⟷ II) is of predominating importance, and the available ionisation constants [12] enable the amide : enol ratio to be calculated [13] if the reasonable assumption be made that the tautomerism involves $N_{(1)}$ [as in (I)]. The ratio is about 3600 : 1, compared with 24,000 : 1 for 4-hydroxyquinoline.[13] Although the evidence is not complete it is most probable that 3-hydroxycinnoline also exists mainly in the lactam form.[14] The ionisation constants suggest that the amide : enol ratio is lower than with 4-hydroxycinnoline.

[10] For bibliography see Albert in ref. 5, p. 130.
[11] Metzler and Snell, *J. Amer. Chem. Soc.*, 1955, **77**, 2431.
[12] Albert and Hampton, *J.*, 1954, 505.
[13] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.
[14] Alford and Schofield, *J.*, 1953, 1811.

The acidic pK_a values show that, as would be expected, the *Bz*-hydroxycinnolines are stronger acids than phenol (pK_a 9·98) and the naphthols. The order of acid strengths (5 > 6 > 7 > 8) is not that to be expected from a simple consideration of the resonance stabilisation of the different anions. This is not surprising, for zwitterion formation probably occurs to a different degree in each case (see below) and the observed pK_a values are not the true constants for ionisation of the hydroxyl groups.

If the case of 5-hydroxycinnoline is disregarded, it will be seen that the order of basicities of the *Bz*-hydroxycinnolines is 6 > 7 > 8 (ΔpK_a values being 1·36, 1·02, and 0·42). This is the order found for the aminocinnolines, the corresponding ΔpK_a values being 2·75, 2·56, and 1·39. The amino-group, because of its greater $+T$ effect, should be more base-strengthening. As with the amines, the problem arises with the hydroxy-compounds of deciding which nitrogen atom is the basic centre in each case (the unlikely possibility that the oxygen atom accepts the proton is eliminated by the cationic ultraviolet absorption spectra). In this connection the relatively large ΔpK_a values found for 6- and 7-hydroxycinnoline indicate that, as in the related amines, the basic centres are here $N_{(2)}$ and $N_{(1)}$ respectively, giving the resonance-stabilised cations (III) and (IV).

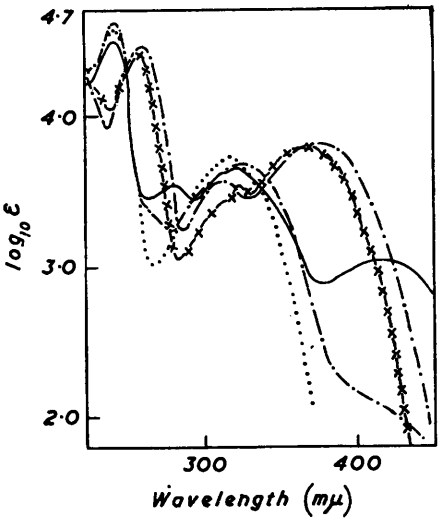


FIG. 4. *6-Hydroxycinnoline* (pH 5·43) ———; *6-hydroxycinnoline* (*in* EtOH) — · — · —; *6-hydroxycinnoline anion* (pH 10·0) – – · – – · – –; *6-hydroxycinnoline cation* (0·1N-HCl) — × — × —; *6-methoxycinnoline* (pH 7) . . . . .

The case of 8-hydroxycinnoline is not so clear-cut. Previously [15] it was tentatively represented as having its basic centre at $N_{(1)}$, but consideration of 8-aminocinnoline (preceding paper) suggests that in 8-hydroxycinnoline $N_{(2)}$ might be the main site of cationisation. However, the small value of ΔpK_a in this case, and the lack of information regarding the possible steric influence of the hydroxyl group, makes a choice impossible. Irving and Rossotti [16] suggested that the greater basic strength of 8-hydroxy-4-methylcinnoline (pK_a 3·28) than of 8-hydroxycinnoline pointed to $N_{(1)}$ as the more basic nitrogen atom in 8-hydroxy-4-methylcinnoline. This assignment is rendered uncertain by the factors just mentioned and lack of knowledge of the basic strength of 4-methylcinnoline.

The ultraviolet extinction curves of 6-, 7-, and 8-hydroxycinnoline in roughly "neutral" solution (Fig. 4 and Table 2) resemble fairly closely the curves of the related methoxy-compounds except that they show additional maxima above 400 mμ ($\lambda_{max.}$ 414, 449, and 452, $\log_{10}\varepsilon$ 3·03, 2·47, and 2·55 for the 6-, 7-, and 8-isomers respectively). With 6-hydroxycinnoline another maximum ($\log_{10}\varepsilon$ 3·54) also appears at 280 mμ. In each case the relatively small separations of the basic and acidic ionisation constants made it possible that these additional maxima arose from the presence in "neutral" solutions of small concentration of anions and cations. That this is not so is shown clearly from the spectra of the hydroxy-compounds in media sufficiently alkaline or acidic to ensure almost complete conversion

[15] Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009.
[16] Irving and Rossotti, *J.*, 1954, 2910.

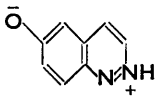
into the anion and cation respectively, and from the suppression of the additional maxima in alcohol solution. Clearly the subsidiary maxima must be ascribed to the presence in neutral solution not only of the uncharged molecule, but also of small concentrations of

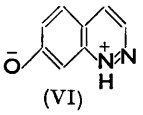
TABLE 2. *Ultraviolet absorption spectroscopy of the hydroxycinnolines.*[a]

Cinnoline deriv.	Solvent or pH	$\lambda_{max.}$ (mμ)	$\log_{10} \varepsilon_{max.}$
5-Hydroxy	−0·25	257, 310, *328*, 410	4·47, 3·16, *3·05*, 3·28
	4·52	245, *300*, 357	4·53, *3·06*, 3·39
	11·0	234, 262, 338, *385*, *425*	4·23, 4·42, 3·48, *3·19*, 3·11
5-Methoxy	7·0	245, *305*, 353	4·53, *3·15*, 3·44
6-Hydroxy	0·1N-HCl	255, *310*, 324, 367	4·42, *3·40*, 3·53, 3·80
	5·43	240, 280, *310*, 320, 414	4·50, 3·54, *3·60*, 3·66, 3·03
	10·0	259, 311, 376	4·45, 3·57, 3·82
	EtOH	240, *259*, *308*, 325, *340*, *423*	4·61, *3·41*, *3·61*, 3·68, *3·59*, *2·04*
6-Methoxy	7·0	240, 316	4·56, 3·72
7-Hydroxy	0·1N-HCl	250, 307, *325*, 388	4·55, 3·53, *2·93*, 3·44
	5·43	236, 267, 358, 449	4·58, 3·66, 3·47, 2·26
	10·0	253, 286, 402, *428*	4·62, 3·82, 3·54, 3·39
	EtOH	237, *264*, *284*, *296*, *306*, 358	4·63, *4·00*, *3·68*, *3·43*, *3·07*, 3·59
7-Methoxy	7·0	237, 269, 346	4·66, 3·46, 3·50
8-Hydroxy[b]	0·10	252, 306, *322*, 430	4·46, 3·16, *2·95*, 3·39
	5·25[c]	296, 360, 452	3·11, 3·36, 2·55

[a] Values in italics refer to shoulders or inflexions. [b] Cf. ref. 16. [c] This curve was not continued below 260 mμ. Curves at pH 0·10, 5·25, and 2·01 gave an isosbestic point (λ 388 mμ, $\log_{10} \varepsilon$ 3·12).

zwitterions (V), (VI), and (VII). The considerations outlined above render the site of the proton in (V) and (VI) fairly certain, but the structure (VII) is tentative. From the data available it is not possible to calculate the concentrations of the zwitterions in the different cases, but a consideration of the separation of the basic and acidic pK_a values in each case


(V)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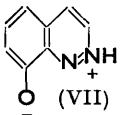
(VII)

suggests that the zwitterion concentration is greatest in the case of 6-hydroxycinnoline, a deduction which is supported by the relatively high intensity of the long-wavelength maximum in this case, and which conforms with the greater resonance stabilisation to be expected in the form (V).

5-Hydroxycinnoline appears to be slightly less basic than cinnoline. The significance of this fact is not at present clear. The wide separation of the two pK_a values for this compound, and the close similarity in neutral solution of the ultraviolet extinction curves of 5-hydroxy- and 5-methoxy-cinnoline make it very unlikely that appreciable zwitterion formation occurs in this case (insolubility makes the extension of the extinction curve difficult). The fact that the hydroxyl group is in the *peri*-position may result in a decrease in electromeric interaction with the nucleus, such as was observed with 5-aminocinnoline (preceding paper).

EXPERIMENTAL

6-Chlorocinnoline.—4 : 6-Dichlorocinnoline (2·1 g.), toluene-*p*-sulphonhydrazide (3·9 g.), and dry chloroform (60 c.c.) were heated under reflux for 4 hr. The solution reddened and a deep-red solid separated. The mixture was set aside overnight, the chloroform was evaporated, and the slightly sticky residue was added during 10 min. to anhydrous sodium carbonate (40 g.) in water (400 c.c.) at 95°. The solution was boiled under reflux for 1 hr. and then extracted with ether. The red solid recovered from the ether was extracted (Soxhlet) with light petroleum (b. p. 60—80°). The extract was filtered (charcoal) and concentrated, the almost pure product (1·07 g.) separating. 6-Chlorocinnoline formed pale yellow needles, m. p. 131—131·5° (Found : C, 58·6; H, 3·1. Calc. for $C_8H_5N_2Cl$: C, 58·4; H, 3·1%), from light petroleum (b. p. 60—80°). Schofield and Swain [17] gave m. p. 119—120° for an impure specimen.

[17] Schofield and Swain, *J.*, 1950, 392.

7-*Chlorocinnoline*.—In the same way 4 : 7-dichlorocinnoline (1·8 g.) gave 7-*chlorocinnoline* (0·55 g.), which formed felted pale yellow needles, m. p. 89—90° (Found : C, 58·9; H, 3·3%).

8-*Chlorocinnoline*.—4 : 8-Dichlorocinnoline (1·1 g.) appeared to react more slowly than its isomers, and refluxing was carried on for 6 hr. No solid separated, but removal of the chloroform gave a product which in the usual way provided 8-*chlorocinnoline* (0·53 g.). This formed pale yellow crystals, m. p. 88—89° (Found : C, 58·6; H, 3·2%). A mixture with 7-chlorocinnoline showed m. p. *ca.* 50°.

Ionisation Constants.—The hydroxy-compounds (0·001 or 0·002M) in 0·01M-perchloric acid were titrated at 20° ± 0·05° with 0·04M-sodium hydroxide from a semimicro-burette. Measurements of pH were made with a Cambridge instrument and a glass electrode.

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