264. *Ionization Constants of Heterocyclic Substances. Part II.* Hydroxy-derivatives of Nitrogenous Six-membered Ring-compounds.*

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Acidic and basic ionization constants are reported for 87 hydroxy(and related)-derivatives of nitrogenous six-membered heterocyclic compounds. The significance of the relative magnitudes of the values is discussed, and some useful generalizations are obtained.

The tautomeric equilibria between enol and amide in α- and γ-hydroxy-derivatives are shown greatly to favour the amide form, and in several cases the ratio has been calculated. The conclusions are supported by determination of some dipole moments.

WHEREAS the strengths of many heterocyclic bases and their amino-derivatives have been determined and discussed (Part I), little is known about the acidic and basic strengths of the hydroxy-derivatives. A number of such determinations are now reported (Tables 1 and 4; low values correspond to strong acids and weak bases). For monofunctional substances such as phenol and pyridine, " proton lost " corresponds to the acidic function and " proton gained " to the basic function but this simple correlation is not observed by all difunctional substances. The potentiometric method was used because of its convenience, but the more laborious spectrometric method was adopted in cases where (*a*) the solubility was too low (10^{-3}M is usually the lower limit of accuracy for potentiometric titration), (*b*) the constant was extreme (*e.g.*, potentiometry loses in accuracy when the pK is less than the logarithm of the dilution), or (*c*) the substance was too hygroscopic. Thus the results are presented at various dilutions, the effect of which on the pK of acids can be approximately calculated from the equation :

$$pK_a \text{ (thermodynamic)} = pK_a \text{ (as determined)} + 0{\cdot}5\sqrt{I}$$

where I is the ionic strength at half-neutralization. Thus an acid titrated at the following molarities should have the quantity in parentheses added to the pK_a values recorded here : 0·05M (0·08); 0·02M (0·05); 0·01M (0·03); 0·002M (0·02); 0·0005M (0·01). For bases, these quantities should be subtracted.

Certain of the basic constants in Table 1 turn out to be lower than had been supposed in the literature, so that ultraviolet spectra, measured at pH 2 in the belief that they were those of the cation, turn out to be those of the neutral molecule (*e.g.*, Nos. 2, 14, 16, and 27).[1]

Hydroxypyridines.—(a) *The* pK_a' *values* (*representing protons gained*). A preliminary discussion of the electronic effects of methoxyl and hydroxyl groups in a simple aromatic system is desirable to clarify the more complex situations found in the pyridine series which is, in turn, a model for the remaining series in Tables 1 and 4. The pK's of aniline and *o*-, *m*-, and *p*-methoxyaniline are [2] respectively 4·58, 4·49, 4·20, and 5·29. In *m*-methoxyaniline, only the inductive effect ($-I$) is possible, and it is base-weakening. The other isomers show the opposed influences of the $-I$ and the (base-strengthening) mesomeric effect ($+M$). The pK's of *o*-, *m*- and *p*-hydroxyaniline are [3] respectively 4·72, 4·17 and 5·50. Comparison of the *m*-derivatives shows that the inductive effect of methoxyl and hydroxyl is identical and this has been demonstrated also with acids,[4] *e.g.*, 4·09 and 4·08 respectively for *m*-methoxy- and *m*-hydroxy-benzoic acid. Inspection of the values for the *o*- and *p*-isomers reveals that the $+M$ effects of methoxyl and hydroxyl are similar, that of hydroxyl being somewhat greater.

3-Methoxypyridine (No. 8) is subject only to a ($-I$) effect and hence should be a slightly weaker base than pyridine, as is seen to be the case. Moreover, as would be predicted,

* *J.*, 1948, 2240 is regarded as Part I.

[1] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.
[2] Hall and Sprinkle, *ibid.*, 1932, **54**, 3469.
[3] Kuhn, *Helv. Chim. Acta*, 1928, **11**, 7.
[4] Dippy, *Chem. Rev.*, 1939, **25**, 151.

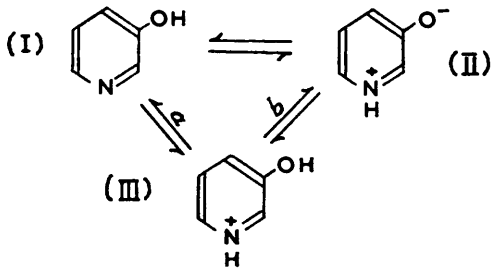
TABLE 1. *Ionization of substances having only one hetero-atom (in water at 20°).*

No.	Substance	Protons lost: pK_a	Spread [h] (±)	Concn.[h] (M)	Protons gained: pK_a'	Spread [h] (±)	Concn.[h] (M)	Analytical wavelength (μ)
1	Pyridine	—	—	—	5·23 [i]	—	—	—
2	2-Hydroxy	11·62 [a]	—	—	0·75 [j]	0·01	0·0001	296
3	3-Hydroxy	8·72 [a,b]	—	—	4·86 [k]	0·01	0·05	—
4	4-Hydroxy	11·09 [a]	—	—	3·27	0·02	0·05	—
5	2 : 4-Dihydroxy	6·50	0·01	0·02	1·37	0·03	0·05	—
		13	—	0·02				
6	2 : 4 : 6-Trihydroxy	4·6 [c]	—	0·02	—	—	—	—
		9·0	—	0·02				
		13	—	0·02				
7	2-Methoxy	—	—	—	3·28	0·06	0·01	—
8	3-Methoxy	—	—	—	4·88	0·03	0·0002	295
9	4-Methoxy	—	—	—	6·62	0·02	0·02	—
10	3-Hydroxypyridine methochloride	4·96 [d]	0·02	0·03	—	—	—	—
11	1-Methyl-2-pyridone	—	—	—	0·32	0·02	0·0001	297
12	1-Methyl-4-pyridone	—	—	—	3·33	0·02	0·02	—
13	Quinoline	—	—	—	4·93	0·02	0·0002	309
14	2-Hydroxy	11·74	0·02	0·005	−0·31 [l]	0·06	0·0005	254 (pK_a')
15	3-Hydroxy	8·06	0·03	0·005	4·30	0·05	0·005	—
16	4-Hydroxy	11·25	0·03	0·01	2·27 [m]	0·02	0·02	—
17	5-Hydroxy	8·54 [e]	0·02	0·0025	5·20	0·01	0·0025	—
18	6-Hydroxy	8·88	0·01	0·005	5·17	0·01	0·005	—
19	7-Hydroxy	8·85 [e]	0·01	0·0025	5·48	0·03	0·0025	—
20	8-Hydroxy	9·89 [a]	—	—	5·13 [a]	—	—	—
21	2 : 4-Dihydroxy	5·86	0·02	0·0001	0·76	0·05	0·00005	292 (pK_a) / 312 (pK_a')
22	2-Methoxy	—	—	—	3·17	0·03	0·001	—
23	4-Methoxy	—	—	—	6·65 [n]	—	—	—
24	1-Methyl-2-quinolone	—	—	—	−0·71	0·1	0·0002	254
25	1-Methyl-4-quinolone	—	—	—	2·46 [n]	—	—	—
26	*iso*Quinoline	—	—	—	5·46	0·02	0·002	332
27	1-Hydroxy	— [f]	—	—	−1·2	0·2	0·0002	272
28	1-Methoxy	—	—	—	3·05	0·02	0·0001	331
29	2-Methyl*iso*quinolone	—	—	—	−1·8	0·1	0·0001	276
30	Acridine	—	—	—	5·62	0·02	0·0002	403
31	3-Hydroxy	8·81	0·03	0·00002	5·52	0·02	0·00002	432 (pK_a) / 362 (pK_a')
32	5-Hydroxy (acridone)	— [f]	—	—	−0·32	0·08	0·00002	322
33	5-Methoxy	—	—	—	7 [g]	—	—	—
34	Phenanthridine	—	—	—	4·65	0·02	0·0001	315
35	2-Hydroxy	8·79	0·04	0·00005	4·82	0·03	0·00005	383 (pK_a) / 318 (pK_a')
36	6-Hydroxy	8·43	0·03	0·00005	5·35	0·02	0·00005	331 (pK_a) / 333 (pK_a')
37	9-Hydroxy (phenanthridone)	— [f]	—	—	< −1·5	—	0·00001	336, 322, 297
38	9-Methoxy	—	—	—	2·38	0·04	0·00002	345

[a] Albert and Hampton, *J.*, 1954, 505. [b] Cf. 8·6, Shaw, *J. Amer. Chem. Soc.*, 1949, **71**, 67 (no details); 8·60 ± 0·08, Metzler and Snell, *ibid.*, 1955, **77**, 2421 (spectrometric). [c] Unstable (oxidizes), hence values only approximate; no basic properties evident. [d] No other pK below 12·5. [e] 5- and 7-Hydroxyquinoline methiodide, titrated with alkali, give 6·12 and 5·56 respectively (Dr. S. F. Mason, unpublished work). [f] Very weak acid, insol. in N-sodium or -potassium hydroxide. [g] Hydrolyses too fast for an exact determination. [h] These results are given only for new determinations. [i] From Part I; cf. 5·16 (25°), thermodynamic, Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26. [j] Cf. 1·28, Swain and Brown, *J. Amer. Chem. Soc.*, 1952, **74**, 2538 (from one measurement only); 1·23, Stiller, Kerestezy, and Stevens, *ibid.*, 1939, **61**, 1237; both authors used potentiometry which is unsuitable for so low a value. The value 5·03 (25°) for " α-hydroxy-β-ethylpyridine " (Hall and Sprinkle, *ibid.*, 1932, **54**, 3469) must refer to 2-ethyl-3-hydroxypyridine. [k] Cf. 4·76, Stiller *et al.* (ref. *j*); 5·10 ± 0·16, Metzler and Snell (ref. *b*). [l] Cf. 5·5, Veley, *J.*, 1908, **93**, 2138 (methyl-orange method). [m] Cf. 2·34 (and 11·06), Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923 (potentiometric, 30°). [n] From Tucker and Irvin (ref. *m*), corrected from 30° to 20°. [o] An entry in this column signifies that the determination was spectrometric (otherwise potentiometric).

3-hydroxypyridine (No. 3) gives the same pK on adding acid as does 3-methoxypyridine but here there is a complicating factor. The addition of alkali to 3-hydroxypyridine methochloride (No. 10) gives a pK of 4·96, similar to that obtained by adding acid to No. 3,

although it arises by the loss of a proton from the 3-hydroxy-group of No. 10. Thus the pK of 4·86 in 3-hydroxypyridine must correspond to two distinct processes (*a*) and (*b*), and this substance must be present in aqueous solution both as the neutral molecule (I) and the dipolar ion (II). Metzler and Snell [5] recently reached this conclusion from spectrometric evidence: 3-hydroxypyridine has two peaks above 250 mμ; that at 313 μ agrees with the sole peak of the methochloride, the other (at 277 μ) agrees with that of 3-methoxypyridine. This enabled them to estimate that approximately equal amounts of the forms (I) and (II) are present in neutral aqueous solution. The addition of a little alcohol causes the peak of the dipolar form (313 μ) to vanish.[5] Also the dipole moment of 3-hydroxypyridine in benzene and dioxan (Table 3) shows that the neutral molecule is the principal species in such solvents, because the dipole moment of (II) would be of the order of 16 D.



The high proportion of the dipolar ion in aqueous solutions of 3-hydroxypyridine is due to the mutual inductive effect of the two groups: the cation strengthens the acid group, and the anion strengthens the basic group. This effect should therefore fall off with distance and be quite small in such substances as 6-hydroxyquinoline (No. 18), where 5·17 may be taken as the basic, and 8·88 as the acidic value. But in 3-hydroxypyridine, 4·86 is compounded of the basic constant of (I) (*i.e.*, addition of proton to nitrogen) and the acidic constant of (III) [*i.e.*, loss of proton to give the oxygen-anion (II)]. In the present case, where roughly equal amounts of (I) and (II) are present, these constants are equal, and may be calculated [5] to be 5·2 (a ten-fold decrease in the amount of dipolar ion would make the observed constant and the true basic constant, as defined here, practically identical). The observed pK_a of 8·72 for 3-hydroxypyridine is similarly compounded of two constants, each of which is 8·42. Thus 3-hydroxypyridine is intermediate between nicotinic acid * (which is about 95% dipolar in neutral solution [6]) and *p*-aminobenzoic acid (where the groups hardly interact). An analogy from aliphatic chemistry is provided by cysteine where two constants are shared almost equally by the mercapto- and the ammonium groups.[7]

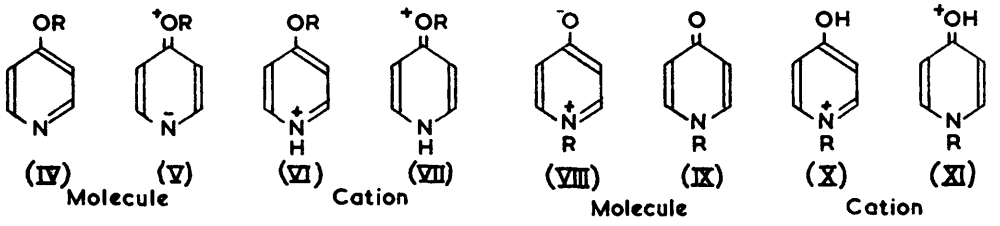
The 2- and 4-derivatives of pyridine, because of tautomeric possibilities, present a more complex picture which was clarified by preliminary study of the *O*- and the *N*-methyl derivatives. In 2- and 4-methoxypyridine (Nos. 7 and 9), the inductive effect of the methoxy-group is modified by a mesomeric effect. In the neutral molecule, resonance between forms such as (IV) and (V; R = Me) should be slight because *both* the oxygen and the nitrogen in the latter bear charges in opposition to the natural order of electronegativities. On the other hand, the cations (VI) and (VII) are capable of a moderate degree of resonance, a base-strengthening effect which overcomes the base-weakening inductive effect more successfully in the 4- than in the 2-derivative, as would be expected.

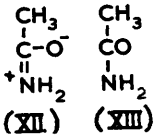
The *N*-methyl derivatives of 2- and 4-hydroxypyridine (Nos. 11 and 12) have a very different distribution of electrons from their *O*-methyl isomers. Admittedly the resonance of the cations is similar for *O*- and *N*-derivatives [*i.e.*, the pair (X) ⟷ (XI), differs from

* The values [6] are 2·09 (carboxyl) and 4·77 (nitrogen), evidence of less interaction than in 3-hydroxypyridine because of a smaller inductive effect. Here, as in other comparisons in this paper, the simplifying and reasonable assumption is made that the degree of hydration is of the same order of magnitude.

[5] Metzler and Snell, *J. Amer. Chem. Soc.*, 1955, **77**, 2431.
[6] Jaffé, *ibid.*, p. 4445.
[7] Grafius and Neilands, *ibid.*, p. 3389.

the pair (VI) ⟷ (VII) only by substitution of methyl for hydrogen]. On the other hand, the resonance of the neutral form, *i.e.*, between (VIII) and (IX), must be much greater in the *N*-methyl derivatives because the oxygen and the nitrogen atoms bear charges in accordance with their relative positions in the electronegativity scale [contrast (VIII) with (V)].* Dipole-moment measurements confirm that the neutral molecules of the *N*-methyl isomers are more highly polar than those of the *O*-methyl isomers (Table 3).





Accordingly it is not surprising to find that the *N*-methyl derivatives are much weaker bases than their *O*-methyl isomers. Of these *N*-methyl derivatives, the α-isomer (No. 11) is weaker than the γ-isomer (No. 12) because the close approach of the groups in No. 11 increases the ion–dipole interaction whereby the positively charged nitrogen atom hinders approach of a proton to the oxygen atom. It is not a steric effect because 2-*tert.*-butylpyridine is not appreciably weaker than 2-methylpyridine.[8]

2- and 4-Hydroxypyridine can now be discussed. Table 1 shows that their affinity for protons is similar to that of their *N*-methyl (and far below that of their *O*-methyl) derivatives. Thus the enolic tautomer, such as (IV; R = H), must play an exceedingly small part in the equilibrium state of these substances, whereas the strong resonance between the dipolar ion and the amide (VIII and IX; R = H) predominates. (The argument has been simplified by omitting minor contributions to resonance hybrids, especially forms with a charge upon carbon, which, although significant for pyridine itself, should become less so when two polarizable atoms are present.) These two hydroxypyridines may be compared with acetamide where the low [9] pK_a (−0·5) is a consequence of resonance [10] (21 kcal./mole) between (XII) and (XIII). In effect, α-hydroxypyridine is a cyclic amide, and 4-hydroxypyridine is a vinylogous [11] amide.

Results in Table 1 permit calculation [12] of the ratio of amide to enol tautomers [*i.e.*, the ratio of the hybrid (VIII) ⟷ (IX) to (IV) (R = H in all cases)] in the hydroxy-derivatives at equilibrium in aqueous solution, by using the equation

$$\log R = \mathrm{p}K_{\mathrm{OMe}} - \mathrm{p}K_{\mathrm{OH}}$$

where R is the ratio of amide to enol tautomers, and pK_{OMe} and pK_{OH} are the observed values for the addition of a proton to corresponding methoxy- and hydroxy-compounds. This method assumes that the intrinsic basic constant for, say, (IV; R = H) would differ little from that of (IV; R = Me) (that this is a reasonable assumption may be gauged by reference to the values of the methoxy- and hydroxy-anilines, above). The results are

* The relation between this resonance hybrid and the small amount of enol (*e.g.*, IV, where R = H) with which it is in equilibrium is discussed below. The example of 3-hydroxypyridine (above) showed that the tendency to form dipolar ions, *e.g.*, (II), is strong even when these are not stabilized by resonance, as (VIII) is.

[8] Brown and Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723.
[9] Hall, *ibid.*, 1930, **52**, 5115.
[10] Pauling, "Nature of the Chemical Bond," Cornell Univ. Press, Ithaca, 1942, p. 138.
[11] Fuson, *Chem. Revs.*, 1935, **16**, 1.
[12] Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923; cf. Edsall and Blanchard, *ibid.*, 1933, **55**, 2337.

given in Table 2 and show a wide range of values. Although a vanishingly small amount of the enolic form is present in 5-hydroxyacridine, chlorination (to 5-chloroacridine) by phosphorus oxychloride occurs no less readily than with 2-hydroxypyridine, doubtless

TABLE 2. *Approximate ratio of amide to enol tautomers* [i.e., *of the hybrid* (VIII) ⟷ (IX) *to* (IV) (R = H *in all cases*)] *in neutral aqueous solution at* 20°.

2-Hydroxypyridine ...	340	2-Hydroxyquinoline ...	3000	5-Hydroxyacridine	10,000,000
4-Hydroxypyridine ...	2200	4-Hydroxyquinoline ...	24,000 [a]	9-Hydroxyphenanthridine	8000
		1-Hydroxy*iso*quinoline	18,000	4-Hydroxycinnoline	3600

[a] Cf. 12,900 at 30°, Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923.

because the enolic form is produced as fast as it is consumed; also the proportion of enol would be favoured by a low dielectric constant. The ratios in Table 2 may conceivably explain why diazomethane produces only 2-methoxypyridine from 2-hydroxypyridine, whereas the *N*-methyl derivative is the main product from 4-hydroxypyridine.[13]

The conclusion that 2- and 4-hydroxypyridine are highly dipolar resonance hybrids is supported by dipole-moment measurements. It is clear from Table 3 that these substances are considerably more polar than their *O*-methyl derivatives. Unfortunately, no fine analysis of the results is practicable because of the sensitivity of moments to slight changes in structure, such as valency angles and (for the 2-derivatives) freedom of rotation.

TABLE 3. *Dipole moments* (μ; *in* D) *of pyridine derivatives in benzene at* 25°.

Substance	2-	3-	4-
Hydroxypyridine	1·95 [a]	2·00 [b]	(5·3) [d]
O-Methyl derivative	1·15	2·75	3·00
N-Methyl derivative	4·15	— [c]	6·9

[a] 2·95 in dioxan. [b] 2·95 in dioxan. [c] Too insoluble for determination. [d] Too insoluble in benzene for direct determination, the figure being calculated from the value in dioxan (6·30; cf. 6·0, Curran and Leis, *J. Amer. Chem. Soc.*, 1952, **74**, 4584).

(b) *The* pK_a *values* (*representing protons lost*). Table 1 shows that 2- and 4-hydroxypyridine are much weaker acids than the 3-isomer [this is a simpler approach than that of concentrating attention solely on the dipolar ion (VIII; R = H) by referring to, say, 2-hydroxypyridine as an acid of pK 0·75, comparable in strength with mineral acids]. The weakness of these acids is understandable by analogy with acetamide [14] (pK = 15·1) which has a strong resonance between the neutral forms (XII) and (XIII) resulting in great acid-weakening. Thus 4-hydroxypyridine is weakened as an acid by the high resonance stabilization of the neutral forms, (VIII and IX; R = H), which was discussed above.

Because very little enol (IV; R = H) is present in the neutral molecule, these constants accurately represent the ionization of the hybrid (VIII) ⟷ (IX) (R = H). However, the following equation enables a value (pK_E) to be calculated [5] for the ionization of an enol:

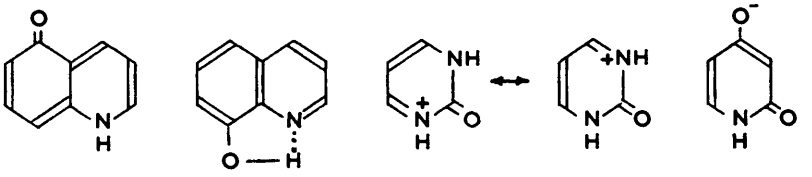
$$pK_E = pK_a - \log (R + 1)$$

(where pK_a is the value as determined and R is the ratio of tautomers from Table 2). This gives pK_E values for 2- and 4-hydroxypyridine of 9·09 and 7·74 respectively, to be compared with 8·72 for the 3-isomer (or, more correctly, 8·42, corrected for 50% dipolar ion by the above equation). These figures may be compared with the values for phenol [15] and its *o*-, *m*- and *p*-nitro-derivatives,[16] respectively 9·98, 7·25, 8·28, and 7·21; all nitrophenols show the inductive effect ($-I$) of the nitro-group, the *o*- and *p*-isomers also show a mesomeric effect ($-M$), both of which are acid-strengthening, and the *o*-isomer also has an *ortho*-effect which is acid-weakening. Qualitatively the same influences seem to be present in the hydroxypyridine enols, and, on the evidence of 3-hydroxypyridine, the

[13] Mosher in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, p. 534; Meyer, *Monatsh.*, 1905, **26**, 1311.
[14] Branch and Clayton, *J. Amer. Chem. Soc.*, 1928, **50**, 1680.
[15] Bordwell and Cooper, *ibid.*, 1952, **74**, 1058.
[16] Wheland, "The Theory of Resonance," Wiley, New York, 1944, p. 172; Martin and Butler, *J.*, 1939, 1366.

inductive effect of an uncharged ring-nitrogen atom is quantitatively similar to that of a nitro-group.

General Discussion.—It is now possible to apply these generalizations to the remaining substances in Tables 1 and 4. The pK_a and pK_a' values of 2-, 3-, and 4-hydroxyquinoline (Nos. 14—16) and their *O*- and *N*-methyl derivatives resemble those of the corresponding pyridines and are explicable similarly. 5-, 6-, and 7-Hydroxyquinoline appear to be normal phenols and it is interesting that the values for 5-hydroxyquinoline (No. 19) do not suggest any great content of the transannular tautomer (XIV). 8-Hydroxyquinoline is a



(XIV) (XV) (XVI) (XVII) (XVIII)

weaker acid than these, the bonding of the ionizable hydrogen atom between oxygen and hydrogen, as (XV), making it less mobile.

The interpretation of α- and γ-hydroxypyridine, existing in aqueous solution mainly as amides rather than as enols, can be applied not only to the quinolines (see above) but also (among the one-nitrogen systems) to the *iso*quinoline, phenanthridine, and acridine series (see Table 1). Table 4 shows that it can also be applied to the pyridazine, pyrimidine, and pyrazine series (among two-nitrogen monocyclic systems), to the cinnoline, phthalazine, quinazoline, quinoxaline, and naphthyridine series (among two-nitrogen bicyclic systems), and also in more complex series. 2-Hydroxypyrimidine (No. 47) is an unusual example of an α-hydroxy-group's not depressing the basic strength of the parent substance, because the symmetrical structure of the cation of the amide form makes possible an unusual base-strengthening resonance (XVI) ⟷ (XVII).

That α- and γ-hydroxy-compounds exist mainly in the amide form *in the solid state* has been established by *X*-ray crystallography for 2-hydroxypyridine,[17] 2 : 4-dihydroxypyrimidine [18] and 2 : 4 : 6-trihydroxy-1 : 3 : 5-triazine,[19] and by infrared spectrometry for 2- and 4-hydroxypyrimidine ; [20] *in aqueous solution* by ultraviolet spectrometric comparison with *O*- and *N*-methyl derivatives for 2- and 4-hydroxypyridine,[21] 2-hydroxyquinoline,[22] 5-hydroxyacridine,[23] 2- and 4-hydroxypyrimidine [20] and their *C*-alkyl-derivatives,[24] 2 : 4-dihydroxypyrimidine,[24] 4-hydroxyquinazoline,[25] and 4-hydroxycinnoline [25] (also, but not adequately, for 4-hydroxyquinoline, 1-hydroxy*iso*quinoline, 3-hydroxypyridazine, 3-hydroxycinnoline, and 2-hydroxypyrazine [26]). None of these methods can detect even 1% of a minor constituent and hence cannot furnish the information on ratios presented above ; however, their confirmation that the amide is the major product is welcome.

It is, in general, not desirable to extend to rings containing two or more nitrogen atoms the calculations of amide : enol ratios used for the one-nitrogen rings, for it cannot be assumed with any certainty that the same nitrogen is protonated in the pair of compounds being contrasted. However in such cases as 4-hydroxycinnoline, where only one of the nitrogen atoms can take part in the tautomerism, the calculation can be used with some confidence.

The polyhydroxy-pyridines and -quinolines (Nos. 5, 6, 21) lose the first proton at a

[17] Penfold, *Acta Cryst.*, 1953, **6**, 591.
[18] Parry, *ibid.*, 1954, **7**, 313.
[19] Newman and Badger, *J. Amer. Chem. Soc.*, 1952, **74**, 3545.
[20] Brown, Hoerger, and Mason, *J.*, 1955, 211 ; Brown and Short, *J.*, 1953, 331.
[21] Specker and Gawrosch, *Ber.*, 1942, **75**, 1338.
[22] Ley and Specker, *ibid.*, 1939, **72**, 192 ; Ault, Hirst, and Morton, *J.*, 1935, 653.
[23] Acheson, Burstall, Jefford, and Sansom, *J.*, 1954, 3742.
[24] Marshall and Walker, *J.*, 1951, 1004.
[25] Hearn, Morton, and Simpson, *J.*, 1951, 3318.
[26] Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181 ; Alford and Schofield, *J.*, 1953, 1811 ; Dutcher, *J. Biol. Chem.*, 1947, **171**, 321 ; Eichenberger, Rometsch, and Druey, *Helv. Chim. Acta*, 1954, **37**, 1298.

much lower pH than their monohydroxy-analogues. This seems to be due to action of one of the hydroxy-groups as a normal aromatic phenol whilst the other is engaged in the amide resonance. An acid-strengthening resonance, involving (XVIII) and a similar anion with the charge on the other oxygen atom, is also possible but it makes only a minor contribution here because symmetrically equivalent structures are not involved. There is no acid-strengthening in the monoanion of 2 : 4-dihydroxypyrimidine where both hydroxyl groups

TABLE 4. *Ionization of substances having two hetero-atoms, in water at* 20°.

		Protons lost			Protons gained			
No.	Substance	pK_a	Spread (±)	Concn. (M)	pK_a'	Spread (±)	Concn. (M)	Analytical wavelength (μ)
39	Pyridazine	—	—	—	2·33 [g]	—	—	—
40	3-Hydroxy	10·46	0·03	0·02	−1·8	0·3	0·0002	285 (pK_a')
41	4-Hydroxy	8·68	0·01	0·02	1·07	0·03	0·00005	262 (pK_a')
42	3 : 6-Dihydroxy	5·67 13	0·01	0·02	−2·2	0·4	0·0002	300 (pK_a')
43	3-Methoxy	—	—	—	2·52	0·01	0·02	—
44	4-Methoxy	—	—	—	3·70	0·02	0·02	—
45	3 : 6-Dimethoxy	—	—	—	1·61 [f]	0·01	0·02	—
46	Pyrimidine	—	—	—	1·30 [g]	—	—	—
47	2-Hydroxy	9·17 [a]	—	—	2·24 [a]	—	—	—
48	4-Hydroxy	8·59 [b]	—	—	1·85 [b]	—	—	—
49	2 : 4-Dihydroxy (Uracil)	9·38 [c] 12	0·06	0·01	—	—	—	—
50	4 : 5-Dihydroxy	7·48 11·61	0·01 0·07	0·02 0·02	1·99 [f]	0·03	0·05	—
51	4 : 6-Dihydroxy	5·4 [d]	—	0·02	—	—	—	—
52	2 : 4 : 5-Trihydroxy (*iso*Barbituric acid)	8·11 [e] 11·48 [f]	0·02 0·03	0·01 0·01	—	—	—	—
53	2 : 4 : 6-Trihydroxy (Barbituric acid)	3·9 [g] 12·5	—	—	—	—	—	—
54	2 : 4 : 5 : 6-Tetrahydroxy (Dialuric acid)	2·83 [h] 11	—	—	—	—	—	—
55	2-Methoxy	—	—	—	<1	—	0·02	—
56	4-Methoxy	—	—	—	2·5 [r]	—	—	—
57	4-Hydroxy-5-methoxy	8·60	0·02	0·02	1·75 [f]	0·04	0·02	—
58	1-Methyl-2-pyrimidone	—	—	—	2·50	0·04	0·03	—
59	1-Methyl-4-pyrimidone	—	—	—	1·8 [s]	—	0·05	—
60	3-Methyl-4-pyrimidone	—	—	—	1·84	0·03	0·03	—
61	Pyrazine	—	—	—	0·6 [q]	—	—	—
62	2-Hydroxy	8·23 [i]	—	—	−0·1 [i]	0·08	0·0005	360, 275
63	2-Methoxy	—	—	—	0·75 [f]	0·04	0·05	—
64	1-Methyl-2-pyrazone	—	—	—	−0·04	0·06	0·0001	350
65	Cinnoline	—	—	—	2·29 [k]	—	—	—
66	3-Hydroxy	8·64	—	—	0·21	0·04	0·0002	395
67	4-Hydroxy	9·27	0·03	0·01	−0·35	0·05	0·00005	337
68	5-Hydroxy	7·40 [k]	—	—	1·92 [k]	—	—	—
69	6-Hydroxy	7·52 [k]	—	—	3·65 [k]	—	—	—
70	7-Hydroxy	7·56 [k]	—	—	3·31 [k]	—	—	—
71	8-Hydroxy	8·20 [l]	—	—	2·74	—	—	—
72	4-Methoxy	—	—	—	3·21 [l]	—	—	—
73	Phthalazine	—	—	—	3·47 [q]	—	—	—
74	1-Hydroxy	11·99 [f]	0·02	0·01	−2	—	0·0002	308
75	Quinazoline	—	—	—	3·51 [q]	—	—	—
76	2-Hydroxy	10·69	0·03	0·0002	1·30	0·02	0·0002	360 (pK_a) 390 (pK_a')
77	4-Hydroxy	9·81	0·02	0·033	2·12	0·05	0·033	—
78	6-Hydroxy	8·19	0·01	0·005	3·12	0·03	0·005	—
79	8-Hydroxy	8·65 [t]	—	—	3·41 [t]	—	—	—
80	3-methiodide	7·26 [t]	—	—	—	—	—	—
81	2 : 4-Dihydroxy	9·78	0·03	0·0005	2·5 [u]	—	0·0005	—
82	2-Methoxy	—	—	—	1·31 [f]	0·08	0·02	—
83	4-Methoxy	—	—	—	3·13 [t]	—	—	—
84	Quinoxaline	—	—	—	0·56 [v]	0·04	0·0005	362
85	2-Hydroxy	9·08 [t]	—	—	−1·37	0·07	0·003	400 (pK_a')
86	5-Hydroxy	8·65 [t]	—	—	0·9 [t]	—	—	—
87	1-methiodide	5·74 [t]	—	—	—	—	—	—
88	6-Hydroxy	7·92	0·02	0·002	1·40	0·02	0·0002	400 (pK_a')
89	2 : 3-Dihydroxy	9·52	0·04	0·001	—	—	—	—
90	1 : 5-Naphthyridine	—	—	—	2·91	0·03	0·05	—
91	4-Hydroxy-	10·01 [l]	—	—	2·85 [l]	—	—	—

TABLE 4. (*Continued.*)

No.	Substance	Protons lost: pK_a	Spread (±)	Concn. (M)	Protons gained: pK_a'	Spread (±)	Concn. (M)	Analytical wavelength (μ)
92	Phenazine	—	—	—	1·23 [q]	—	—	—
93	1-Hydroxy	8·5 [m]	—	—	1·44 [w]	—	—	—
94	2-Hydroxy	7·5 [n]	—	—	2·6 [n]	—	—	—
95	5-Methyl-1-phenazone	—	—	—	4·9 [w]	—	—	—
96	10-Methyl-2-phenazone	—	—	—	3·0 [n]	—	—	—
	Substances with three hetero-atoms							
97	1 : 3 : 5-Triazine	— [o]	—	—	—	—	—	—
98	2 : 4-Dihydroxy	6·5 [p]	—	0·02	—	—	—	—
99	1 : 4 : 5-Triazanaphthalene	—	—	—	1·20 [f]	0·03	0·05	—
100	8-Hydroxy	8·76 [t]	—	—	0·60 [t]	0·03	0·0002	280
101	1 : 4 : 6-Triazanaphthalene	—	—	—	2·5 [s]	—	0·05	—
102	5-Hydroxy	11·05 [t]	—	—	−0·78 [t]	0·03	0·0002	400

[a] Brown, *Nature*, 1950, **165**, 1010. [b] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [c] Cf. 9·3 (and >13), Shugar and Fox, *Biochim. Biophys. Acta*, 1952, **9**, 199 (spectrometric); 9·45, Levene, Bass, and Simms, *J. Biol. Chem.*, 1926, **70**, 229 (potentiometric, 25°). [d] Unstable to alkali (slow decomposition). [e] Cf. 8·4 (approx.), Wood, *J.*, 1906, **89**, 1831 (hydrolysis of ethyl acetate). [f] Thermodynamic value obtained by correction for the mean ionic activity with Davies's coefficient (*J.*, 1938, 2093); this reduces the large spread encountered in potentiometry when pK's lie outside the range 3—11. [g] From Fox and Shugar, *Bull. Soc. chim. belges*, 1952, **61**, 44 (spectrometric). [h] From Richardson and Cannan, *Biochem. J.*, 1929, **23**, 68 (potentiometric, H_2 electrode, 30°). [i] Albert, Brown, and Cheeseman, *J.*, 1952, 1620. [j] From Alford and Schofield, *J.*, 1953, 1811 (potentiometry). [k] Unpublished values determined by Dr. K. Schofield (Exeter) on material synthesized in his laboratory, and quoted here by kind permission. [l] Albert and Hampton, *J.*, 1954, 505 (see this also for 8-hydroxy-1 : 6- and -1 : 7-naphthyridine). [m] From Muller, *J. Biol. Chem.*, 1942, **145**, 425. [n] From Preisler and Hempelmann, *J. Amer. Chem. Soc.*, 1937, **59**, 141. [o] This very weak base was almost instantly destroyed by water and no value could be obtained. [p] Slowly hydrolysed by alkali during titration. [q] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [r] Brown and Short, *J.*, 1953, 311. [s] Unstable (hydrolysis). [t] Kindly determined by Dr. S. F. Mason. [u] Back-titration. [v] Albert, Brown, and Wood (*J.*, 1954, 3832) obtained 0·72 ± 0·1 (potentiometrically at 0·1M, a method now considered not sufficiently accurate for so low a value). [w] From Michaelis, Hill, and Schubert, *Biochem. Z.*, 1932, **255**, 70.

are engaged in amide resonances (cf. Nos. 48 and 49; also Nos. 77 and 81). 4 : 5- and 4 : 6-Dihydroxypyrimidine (Nos. 50 and 51) are stronger acids because only one hydroxyl group can tautomerize to an amide (restriction by valency). Of these, the 4 : 6-isomer is yet stronger because the anion can form a resonance hybrid from symmetrical structures. Because barbituric acid (No. 53) and its *NN'*-dimethyl derivative have similar spectra and acidities, Fox and Shugar [27] concluded that the same group is ionizing in both at about pH 4, but they are not necessarily correct in attributing this to the methylene group rather than a truly phenolic 6-hydroxy-group. True, inserting two ethyl groups in the 5-position raises the pK to 7·8, but such acid-weakening would be expected in the non-aromatic structure thus produced.

Finally, the effect of a second nitrogen atom on an α- or γ-hydroxyl substituent is to increase the acidic strength greatly. The general inductive effect of the additional nitrogen atom disturbs the acid-weakening (amide) resonance by drawing upon electrons necessary for its operation (compare Nos. 41 and 48 with No. 4, and Nos. 47 and 62 with No. 2). Three ring-nitrogen atoms intensify this effect (No. 98).

In addition to the constants given in Tables 1 and 4, those of a number of hydroxypteridines [28] and hydroxypurines [29] are available.

EXPERIMENTAL

Potentiometric Titrations.—0·0005 Mole of the dried specimen was dissolved in air-free water and titrated under nitrogen, a Cambridge pH set being used with glass and calomel electrodes (standardized to pH 4·00 with 0·05M-potassium hydrogen phthalate and 9·20 with 0·05M-borax at 20°). Agreement on restandardization of this instrument after a titration was ±0·01 unit. 0·9 Equivalent of hydrochloric acid, or of carbon dioxide-free potassium hydroxide, was added

[27] Fox and Shugar, *Bull. Soc. chim. belges*, 1952, **61**, 44.
[28] Albert, Brown, and Cheeseman, *J.*, 1951, 474; 1952, 1620. Albert and Brown, *J.*, 1953, 74.
[29] Albert and Brown, *J.*, 1954, 2060.

in nine equal portions. The nine pK values for each pH reading were calculated (when acid was the titrant) from the formula :

$$pK_a = pH - \log ([B] + [H^+]/[BH^+] - [H^+])$$

where $[BH^+]$ and [B] are the concentration of the molecule, protonated and non-protonated respectively, if hydrolysis corrections (taken care of by the rest of the formula) are neglected; and (when alkali was the titrant) from :

$$pK_a = pH + \log ([AH] - [H^+]/[A^-] + [H^+])$$

The nine pK values were converted into antilogarithms before averaging. The small spreads encountered gave additional confirmation of the purity of the substance. Solutions of the substance were made as concentrated (but not above 0·05M) as solubility permitted to keep the hydrolysis corrections low. The strength of the titrant was 0·1N (added from a burette), or N (from a micrometer syringe) for the more concentrated solutions.

Spectrometric Determinations of pK.—Solutions were made in a series of buffers, standardized with a glass electrode. This series decreased in pH down to values where the change in spectrum, corresponding to the step of ionization under study, ceased; and similarly it increased towards the alkaline direction. Buffers (0·01M) of low ultraviolet absorption (glycine, borate, phosphate, acetate, and formate) were used, and for low values the hydrogen-ion exponent solutions (sulphuric acid) of Hammett and Paul.[30] Measurements were made in the Hilger " Uvispek " ultraviolet spectrophotometer (1 cm. cells). Buffer solutions of the same strength were used as controls. At wavelengths selected because of marked differences found between the extinction coefficients of the neutral molecule (ε_M) and that of the protonated form (ε_{MH^+}), the extinction coefficients of the sum of the two species (ε) were measured at such pH values as were found, during the course of the determinations, to correspond to the range from 15 to 85% protonation in 8 equal steps. The pK's were determined from the following formula :

$$pK_a = pH - \log [(\varepsilon_{MH^+} - \varepsilon)/(\varepsilon - \varepsilon_M)]$$

converted into antilogarithms, and averaged. No hydrolysis correction is required in this method, but the usual activity corrections apply.[31]

Dipole Moments.—A conventional apparatus of improved design [32] was used. The benzene was dried (Na) and freshly distilled, the dioxan was first refluxed with sodium for 8 hr. The *O*- and *N*-methyl derivatives were dried (NaOH) and refractionated immediately before use; 2-hydroxypyridine was dried (P_2O_5) at 20°/20 mm. for 24 hr., 3-hydroxypyridine for 1 hr. in air at 110°, 4-hydroxypyridine first as for the 2-isomer, then at 100°/0·01 mm. for 1 hr. All substances are hygroscopic and were handled expeditiously. The moments were calculated from the approximate relation proposed by Smith.[33] The reported values are the mean of 5—7 determinations at different concentrations. The values agreed within ±0·05 D.

Preparations (Analyses by Mr. P. R. W. Baker, Beckenham).—Many of the substances are well known and were purchased or made by well-established methods. They were purified to the constants given in the literature and in addition examined for extraneous material by paper-chromatography in aqueous ammonium chloride (3%) and in butanol–acetic acid. α- and γ-Methoxy-compounds were made only by the action of sodium methoxide on the corresponding chloro-compounds, and not by direct methylation, so as to avoid contamination with the *N*-methyl isomers. They were fractionated under reduced pressure and measured immediately after preparation, because of their tendency to isomerize. After measurement, it was confirmed spectrometrically that only 5-methoxyacridine had undergone any acid-catalysed hydrolysis.

3-Methoxypyridine was made from 3-hydroxypyridine (m. p. 126°) and diazomethane by a method used for 3-methoxy-5-methylpyridine.[34]

3-Hydroxypyridine methochloride. Methyl iodide (0·62 ml., 1 equiv.) was refluxed for 1 hr. with 3-hydroxypyridine (0·95 g.) in benzene (60 ml.). The crystals were washed with boiling benzene, dissolved in water (5 ml.), and shaken with silver oxide (1, then 0·1, equiv.). The filtrate (pH 8·5) was extracted with ether (50 + 50 ml., discarded) to remove any 3-methoxypyridine, acidified to pH 2 with hydrochloric acid, and allowed to crystallize in a desiccator

[30] Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 827; Hammett, " Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 268.
[31] Herington, *Discuss. Faraday Soc.*, 1950, **9**, 26.
[32] Few, Smith, and Witten, *Trans. Faraday Soc.*, 1952, **48**, 211.
[33] Smith, *ibid.*, 1950, **46**, 394 (equation 9).
[34] Marion and Cockburn, *J. Amer. Chem. Soc.*, 1949, **71**, 3402.

(Found: C, 49·9; H, 5·55; N, 9·65; Cl, 24·15. Calc. for C_6H_8ONCl: C, 49·5; H, 5·55; N, 9·6; Cl, 24·35%).

3-*Hydroxyquinoline* (with Dr. J. H. LISTER). The published method gives poor yields because of self-coupling.[35] The solid diazonium chloride [36] from 3-aminoquinoline (3·7 g.) was added slowly to boiling water (80 ml.). After 30 minutes' further boiling, the solution was treated with charcoal, then cooled, and an excess of sodium hydrogen carbonate was added. The base was filtered off and recrystallized from dilute ethanol (yield, 48%; m. p. 198°).

1-*Hydroxy*iso*quinoline*. *iso*Quinoline (6·5 g.), acetic acid (15 ml.), and 30% hydrogen peroxide (4·5 ml.) were heated for 3 hr. at 70°. Further hydrogen peroxide (4·5 ml.) was added and heating continued for 3 hr. More hydrogen peroxide (4·5 ml.) was added again and the mixture evaporated in a vacuum at 70°. 2N-Sodium carbonate was added to the residue (until alkaline), which was shaken with chloroform (4 × 50 ml.). The chloroform layer was dried (K_2CO_3) and taken to dryness. The residue was ground under ether, filtered, and dried, giving 5 g. of *iso*quinoline *N*-oxide dihydrate, m. p. 98° (cf. Ochiai *et al.*[37] who used perphthalic acid). The oxide was refluxed with 10 parts of acetic anhydride for 4 hr. The volatile material was removed *in vacuo* and the residue refluxed with 5 parts of N-sodium hydroxide for 15 min., more alkali being added until the pH ceased to fall below 10. The suspension was then brought below pH 10 with acetic acid, refrigerated, filtered, and dried, giving 3·4 g. of crude 1-hydroxy*iso*quinoline. This was recrystallized from 130 parts of boiling water, giving colourless crystals (m. p. 208°) identical with material prepared by older methods.

2-*Methyl*-1-iso*quinolone* (1 : 2-*dihydro*-2-*methyl*-1-*oxo*iso*quinoline*). This was prepared from *iso*quinoline methiodide by Decker's method; [38] it was distilled at 0·1 mm. and recrystallized from light petroleum; it melted at 57° (lit., 38—40°).

1-*Methoxy*iso*quinoline* (Dr. J. H. LISTER). Fernau [39] obtained an oil, b. p. about 240°, from the silver salt of 1-hydroxy*iso*quinoline and methyl iodide and described it as 1-methoxy*iso*quinoline, the only mention in the literature. Sodium methoxide [1 equiv., from sodium (1·05 g.) in methanol (12 ml.)] and 1-chloro*iso*quinoline (6·4 g.) were refluxed for 4 hr. After chilling, sodium chloride was filtered off and washed with methanol. The filtrates were evaporated and the residue was extracted with ether. The extract was dried (KOH) and the ether recovered. The residual oil was fractionated, giving 1-methoxy*iso*quinoline (88%) as a colourless oil, b. p. 135—136°/21 mm. (Found: C, 75·2; H, 5·8; N, 9·1. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·7; N, 8·8%).

Phenanthridines. The 2- and 4-hydroxy- and 9-methoxy-phenanthridines were kindly presented by Drs. C. L. Arcus and M. M. Coombs,[40] and 9-hydroxyphenanthridine by Dr. L. Walls.

Pyridazines. These were all kindly supplied by Dr. J. Druey.[41]

2 : 4 : 5-*Trihydroxypyrimidine* (Dr. D. J. BROWN). This was made by simultaneous reduction and hydrolysis [42] of 5-nitrouracil, and recrystallized thrice from water (60 parts), giving white needles (Found, after drying at 120°/0·01 mm.: C, 37·15; H, 3·2; N, 21·8. Calc. for $C_4H_4O_3N_2$: C, 37·5; H, 3·15; N, 21·85%). The *O*- and *N*-methylated pyrimidines were supplied by Dr. Brown also.[20] We thank Dr. J. F. W. McOmie for a gift of 4 : 5-dihydroxy- and 4-hydroxy-5-methoxy-pyrimidine.

2-*Methoxypyrazine* (Dr. J. LISTER). 2-Hydroxypyrazine [43] (5 g.) was heated at 100° with phosphorus oxychloride (30 ml.) for 40 min. The reagent was removed *in vacuo* (20 mm.) and the residue stirred into crushed ice. The recovered oxychloride was treated similarly, as some product had volatilized, and both aqueous solutions were extracted with ether (extracts dried over Na_2SO_4). The ether was recovered and the residue fractionated, giving 2-chloropyrazine, b. p. 60—61°/28 mm., in 85% yield (published yield: 58%).[43] This oil (3 g.) and methanol (3 ml.) were chilled to 0° and added to a chilled solution of sodium methoxide (1 equiv., 0·7 g. of sodium in 10 ml. of methanol). The mixture was refluxed at 120° for 2 hr. and cooled. The precipitated salt was washed with methanol, and the combined filtrates were evaporated (at

[35] Mills and Watson, *J.*, 1910, **97**, 753.
[36] Abramovitch, *J.*, 1954, 3839.
[37] Ochiai, Ishihara, and Zai-Ren, *J. Pharm. Soc. Japan*, 1944, **64**, 72; *Chem. Abs.*, 1951, **45**, 8526.
[38] Decker, *J. prakt. Chem.*, 1893, **47**, 37.
[39] Fernau, *Monatsh.*, 1893, **14**, 66.
[40] Arcus and Coombs, *J.*, 1954, 4319.
[41] Druey, Meier, and Eichenberger, *Helv. Chim. Acta*, 1954, **37**, 121; Schmidt and Druey, *ibid.*, p. 134; Eichenberger, Rometsch, and Druey, *ibid.*, p. 1298.
[42] Davidson and Baudisch, *Ber.*, 1925, **58**, 1685.
[43] Erickson and Spoerri, *J. Amer. Chem. Soc.*, 1946, **68**, 400.

760 mm.). The residue was dissolved in a little water and extracted with ether (extracts dried over Na_2SO_4). The ether was recovered and the 2-*methoxypyrazine* (40%) distilled (b. p. 60—61°/29 mm.) (Found: C, 54·9; H, 5·4; N, 24·9. $C_5H_6ON_2$ requires C, 54·55; H, 5·5; N, 25·45%). 1-Methyl-2-pyrazone [44] was recrystallized from light petroleum after sublimation.

1-Hydroxyphthalazine was kindly presented by Dr. N. B. Chapman, and 4-methoxycinnoline by the late Dr. J. Simpson.

2-*Hydroxyquinazoline.* This substance is poorly described in the literature. Prof. B. E. Christensen kindly supplied a specimen prepared from 2-aminobenzaldehyde and urea.[45] This was purified through the hydrochloride. Part of it was converted through 2-chloro- into 2-methoxy-quinazoline,[46] and the latter was refluxed with 0·5N-alcoholic sodium hydroxide for 4 hr. The solution was neutralized, evaporated, and extracted with ether, and then with cold water. The residue, a poorly soluble white powder, was chromatographically identical with the starting material. When boiled with 200 parts of water, both specimens dissolved in 2 hr. and deposited nothing on concentration to 20 parts and chilling. This behaviour is suggestive of ring-opening because evaporation in the presence of a trace of acid regenerated the original poorly soluble material. For determination of pK, it was dissolved in acid, and the solution diluted with the requisite buffers.

1 : 5-Naphthyridine [47] and 1 : 4 : 5-triazanaphthalene [48] and the 1 : 4 : 6-isomer [49] were purified by sublimation (all prepared by Mr. C. Pedersen).

1 : 3 : 5-Triazine [50] was kindly presented by Dr. C. Grundmann. 2 : 4-Dihydroxytriazine was prepared by the oxidation of uric acid.[51]

We thank Dr. J. W. Smith for advice on the determination of dipole moments; also our colleagues: Dr. S. F. Mason for helpful discussions, Dr. D. J. Brown, Dr. J. H. Lister, and Mr. C. Pedersen for carrying out the preparations to which their names are attached; also Mr. K. Tratt for general assistance. All pK values not otherwise indicated were determined by the Department's head technician, Mr. E. P. Serjeant, to whom our best thanks are offered.

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[*Received, November 22nd,* 1955.]

[44] Dutcher, *J. Biol. Chem.*, 1947, **171**, 321.
[45] Gabriel and Stelzner, *Ber.*, 1896, **29**, 1300.
[46] Bogert and May, *J. Amer. Chem. Soc.*, 1909, **31**, 512.
[47] Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081.
[48] Leese and Rydon, *J.*, 1955, 303.
[49] Koenigs, Bueren, and Jung, *Ber.*, 1936, **69**, 2690.
[50] Grundmann and Kreutzberger, *J. Amer. Chem. Soc.*, 1954, **76**, 5646.
[51] Brandenberger and Brandenberger, *Helv. Chim. Acta*, 1954, **37**, 2207.