Analogues of 8-Hydroxyquinoline having Additional Cyclic Nitrogen Atoms. Part II. Further Preparations, and Some Physico-chemical Properties.*

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Syntheses are described of 8-hydroxy-4-methyl-, 8-hydroxy-4-propyl- and 7-allyl-8-hydroxy-quinazoline. It is shown that acetic formic anhydride can formylate primary aromatic amines quantitatively at 5°.

Ionization constants and oil–water partition coefficients of thirteen analogues of 8-hydroxyquinoline have been determined and correlated with structure. The stability constants of the ferric, ferrous, cupric, and nickel complexes of these analogues are reported. The relative basic strength of the two nitrogen atoms in each of the following has been determined : 8-hydroxyquinazoline, 5-hydroxyquinoxaline, 4-hydroxy-1 : 5-naphthyridine, 8-hydroxy-1 : 6-naphthyridine, and 8-hydroxy-1 : 7-naphthyridine.

The acidic ionization constants of the monohydroxypyridines are reported and used in a discussion of the variations in acidic strength of nitrogenous heteroaromatic substances.

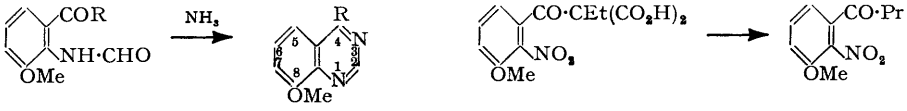
It is known that the outstanding antibacterial properties of 8-hydroxyquinoline (oxine) are due, not to oxine itself, but to the 1 : 1 complex which it forms with traces of iron in the medium (Albert, Gibson, and Rubbo, *Brit. J. Exp. Path.*, 1953, **34**, 119). Preliminary investigation of the analogues described in Part I* showed that the introduction of ring-nitrogen atoms had lowered the oil–water partition coefficient and, in proportion as this fell, the antibacterial action sharply decreased. In the expectation of restoring antibacterial action by raising the partition coefficient, small alkyl groups were inserted into the molecules of 8-hydroxycinnoline and 8-hydroxyquinazoline. This expectation was realized, supporting the hypothesis that the site of action of oxine is intracellular (Albert, Hampton, Selbie, and Simon, *Brit. J. Exp. Path.*, in the press). The present study reports the preparation of the alkyl-hydroxyquinazolines, also the determination of physical properties which shed light on the mode of action (particularly partition coefficients and the stability constants of the metal complexes).

8-Hydroxy-4-methylquinazoline was prepared by modifications of Bischler's general method (*Ber.*, 1891, **24**, 506; 1893, **26**, 1350) for the synthesis of quinazolines (*e.g.*, I⟶II). Attempts to prepare 2-formamido-3-methoxyacetophenone (I; R = CH_3) by heating 2-amino-3-methoxyacetophenone with formic acid under various conditions destroyed much of the amine. However, quantitative formylation occurred when the amine was shaken at 5° with acetic formic anhydride (cf. du Vigneaud and Meyer, *J. Biol. Chem.*, 1932, **98**, 295). Passing ammonia into a solution of (I; R = CH_3) in molten ammonium acetate (according to a general method of Schofield, Swain, and Theobald, *J.*, 1952, 1924) readily gave 8-methoxy-4-methylquinazoline (II; R = CH_3). Aluminium chloride converted this into 8-hydroxy-4-methylquinazoline.

3-Methoxy-2-nitrophenyl propyl ketone (IV), required for the synthesis of 8-hydroxy-4-propylquinazoline, was conveniently prepared by Bowman's method for the synthesis of ketones (*J.*, 1950, 325). Condensation of 3-methoxy-2-nitrobenzoyl chloride with dibenzyl sodioethylmalonate, followed by hydrogenolysis, gave the malonic acid (III), which

* Part I, *J.*, 1952, 4985.

yielded the desired ketone (IV) on being warmed. Reduction of (IV) with iron–acetic acid gave 2-amino-3-methoxyphenyl propyl ketone which was smoothly converted into the 2-formamido-ketone (I; R = Pr^n) with acetic formic anhydride. 8-Methoxy-4-propylquinazoline (II; R = Pr) was obtained (50% yield) therefrom by use of ammonia in molten ammonium acetate or, better, by the normal Bischler synthesis. Demethylation with aluminium chloride gave 8-hydroxy-4-propylquinazoline. Application of the general method of Brown and Murphy (*J. Amer. Chem. Soc.*, 1951, **73**, 3308) (treatment of the sodio-derivative of 8-methoxy-4-methylquinazoline in liquid ammonia with ethyl iodide) gave only a small yield of 8-methoxy-4-propylquinazoline.



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

8-Allyloxyquinazoline (prepared from 8-hydroxyquinazoline and allyl bromide) gave 7-allyl-8-hydroxyquinazoline by Claisen rearrangement.

TABLE 1. *Physical properties of analogues of 8-hydroxyquinoline.*

No.	Compound	Solubility (H_2O at 20°; M)	pK_a (in H_2O) * and concn. of determn. (20°) Basic pK_a	M	Acidic pK_a	M	Partition coeff. (20°) : oleyl alcohol–H_2O, pH 7·3
1	8-Hydroxyquinoline	0·0039	5·13 (± 0·02)	0·004	9·89 (± 0·03)	0·004	67
2	8-Hydroxycinnoline	0·0039	2·74 (± 0·02) [a]	0·005	8·20 (± 0·04)	0·003	5·6
3	8-Hydroxyquinazoline	0·0092	3·41 (± 0·01)	0·01	8·65 (± 0·02)	0·005	5·2
4	5-Hydroxyquinoxaline	0·045	0·9 (± 0·1) [e]	0·01	8·65 (± 0·04)	0·01	7·8
5	4-Hydroxy-1 : 5-naphthyridine	0·0057	2·85 (± 0·02)	0·01	10·01 (± 0·05)	0·005	<0·02
6	8-Hydroxy-1 : 6-naphthyridine	0·022	4·08 (± 0·02)	0·01	8·33 (± 0·02)	0·005	1·00
7	8-Hydroxy-1 : 7-naphthyridine	0·072	2·64 (± 0·04)	0·10	12·01 (± 0·05)	0·01	0·14
8	4-Hydroxypyridino(2′ : 3′-5 : 6)pyrimidine (IX)	0·0086	<2	0·01	8·95 (± 0·02)	0·009	<0·02
9	2′-Hydroxypyridino(3′ : 4′-2 : 3)pyrazine (VII)	0·065	<1·3	0·05	11·05 (± 0·05)	0·01	<0·02
10	4′-Hydroxypyridino(2′ : 3′-2 : 3)pyrazine (VIII)	0·028	<1·3	0·05	8·78 (± 0·03)	0·01	<0·02
11	8-Hydroxy-4-methylcinnoline	0·0021	3·18 (± 0·02)	0·005	8·34 (± 0·05)	0·002	16·3
12	8-Hydroxy-4-methylquinazoline	0·0025	2·90 (± 0·01)	0·005	8·75 (± 0·05)	0·002	16·5
13	8-Hydroxy-4-propylquinazoline	0·0012	[c]	—	8·82 (± 0·04)	0·001	135
14	7-Allyl-8-hydroxyquinazoline	0·00024	[c]	—	[c]	—	310
15	Cinnoline	—	2·70 [b]	0·007	—	—	—
16	Quinazoline	—	3·51 [b]	0·07	—	—	—
17	4-Methoxycinnoline	—	3·21 (± 0·08)	0·033	—	—	—
18	4-Methoxyquinazoline	—	3·13 (± 0·05)	0·033	—	—	—
19	4-Hydroxypteridine (VI)	0·03 [d]	<1·5 [d]	—	7·89 [d]	—	<0·02

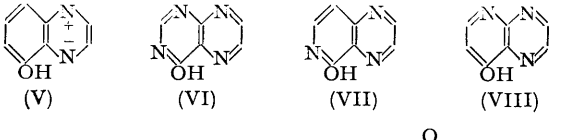
* pK_a = negative logarithm of the ionization constant.
[a] This, and similar low pK_a values, were determined by back-titration of an otherwise supersaturated solution. [b] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [c] Too insol. for accurate measurement (see text). [d] Albert, Brown, and Cheeseman, *J.*, 1951, 474. [e] Confirmed spectrometrically.

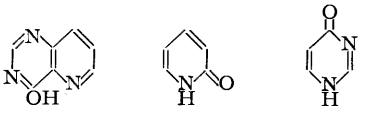
Ionization Constants.—These were determined potentiometrically as an essential preliminary to obtaining the stability constants of the metallic complexes. Table 1 shows that the introduction of one additional cyclic nitrogen atom into 8-hydroxyquinoline is invariably base-weakening. This effect, which varies in intensity with position and tends to be intensified if more than one nitrogen is introduced, is attributed to the electron-attracting property of the entering nitrogen atom (cf. Albert, Goldacre, and Phillips, *J.*, 1948, 2240). The positions where an extra ring-nitrogen atom is most base-weakening are 2-, 4-, 5-, and 7-. In these positions the resonance of the molecule can be strengthened, at the expense of the resonance of the ion, by dipolar structures involving two nitrogen

atoms, *e.g.*, (V) and its counterpart with the charges reversed (Table 1, Nos, 2, 4, 5, and 7). Considerations of valency debar this type of resonance when the second nitrogen is in the 3- or the 6-position (Nos. 3 and 6). The basic pK_a of 5-hydroxyquinoxaline, previously given as 2·15 (Freeman and Spoerri, *J. Org. Chem.*, 1951, **16**, 438), is now found to be 0·9 which agrees with a figure obtained spectrophotometrically (Irving and Rossotti, personal communication).

The basic pK_a of 8-hydroxy-4-methylcinnoline is almost 0·5 unit higher than that of 8-hydroxycinnoline, in accordance with the usual slight base-strengthening effect of methyl groups in heterocyclic compounds (Albert, Goldacre, and Phillips, *loc. cit.*). Nevertheless, 8-hydroxy-4-methylquinazoline is a weaker base than 8-hydroxyquinazoline. A similar contrast exists between 4-methoxy-cinnoline and -quinazoline (Table 1): the former is 0·5 pK_a unit stronger than cinnoline; but the latter is 0·4 unit weaker than quinazoline.

As expected, the nitrogenous analogues of 8-hydroxyquinoline are stronger acids than the parent substance. Exceptions are those analogues with a nitrogen atom replacing $C_{(7)}$, *viz.*, 8-hydroxy-1 : 7-naphthyridine and 2′-hydroxypyridino(3′ : 4′-2 : 3)pyrazine (VII). A nitrogen atom replacing $C_{(5)}$ is also slightly acid-weakening, as may be seen by comparing 4-hydroxy-1 : 5-naphthyridine with 8-hydroxyquinoline, and 4′-hydroxypyridino(2′ : 3′-2 : 3)pyrazine (VIII) with 5-hydroxyquinoxaline. However, when nitrogen


(V) (VI) (VII) (VIII)


(IX) (X) (XI)

atoms are introduced at both $C_{(5)}$ and $C_{(7)}$ in 8-hydroxyquinoline an increase in acidic strength results. Thus 4-hydroxypyridino(2′ : 3′-5 : 6)pyrimidine (IX) is stronger by 0·9 pK unit than 8-hydroxyquinoline, while 4-hydroxypteridine (VI) is 0·8 unit stronger than 5-hydroxyquinoxaline. These effects on the hydroxyl group, obviously connected with its attachment sometimes to an aromatic, sometimes to a heteroaromatic, ring, were clarified by determination of the pK values of the monohydroxypyridines, as tabulated.

Acidic pK_a *of hydroxypyridines and related compounds* (20°).

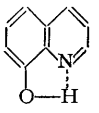
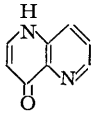
Compound	Phenol	2-Hydroxy-pyridine	3-Hydroxy-pyridine	4-Hydroxy-pyridine	2-Hydroxy-pyrimidine	4-Hydroxy-pyrimidine
Acidic pK_a (in H_2O at 20°)	9·98 [a]	11·62 (± 0·03)	8·72 (± 0·02)	11·09 (± 0·04)	9·17 [b]	8·59 [b]
Concn. at which determined	M/50	M/100	M/100	M/100	M/100	M/30

[a] Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058.
[b] Albert, Brown, and Cheeseman, *loc. cit.* 5-Hydroxypyrimidine is unknown.

The weak acidic strength of 2- and 4-hydroxypyridine relative to that of phenol is connected with the tendency of the un-ionized molecule to exist as a cyclic amide (X), or a vinylogue thereof. 3-Hydroxypyridine, which cannot form a cyclic amide, is not only more acidic than its isomers, but even more acidic than phenol because its nitrogen atom is electron attracting. 2- and 4-Hydroxypyrimidine can exist as cyclic amides, *e.g.*, (XI), but only one of the nitrogen atoms is involved whereas the other exerts an acid-strengthening effect. Hence they are stronger acids than either 2- or 4-hydroxypyridine. The variations in acidic pK_a among the analogues of 8-hydroxyquinoline can be explained similarly.

Oil–Water Partition Coefficients.—It has been shown that the distribution of a series of substances between water and various poorly miscible liquids always follows the same order, although the less water-soluble liquids give the greater spread of values (Collander, *Acta physiol. Scand.*, 1947, **13**, 363). Oleyl alcohol was used in preference to vegetable oils in the present studies because it is less viscous and more readily purified; in addition it is

representative of the fatty alcohols found in cytoplasmic membranes. Reference to Table 1 shows that, as expected, all the nitrogenous analogues of 8-hydroxyquinoline are considerably less lipophilic than the parent substance. Of the analogues with only one extra nitrogen atom, 4-hydroxy-1 : 5-naphthyridine and 8-hydroxy-1 : 7-naphthyridine have especially low partition coefficients. This is interpreted as follows: in aqueous solution at pH 7, 8-hydroxyquinoline is internally hydrogen-bonded, as (XII). Thus it has only one principal centre of hydration (the oxygen atom), whereas the above two naphthyridines, which are almost certainly cyclic amides, *e.g.*, (XIII), would possess three centres of hydration and hence be very much less lipophilic than 8-hydroxyquinoline. 4-Hydroxyquinoline, which is similar in structure to 4-hydroxy-1 : 5-naphthyridine (XIII), has been found to

(XII)   (XIII)

have an enol : amide ratio of 1 : 10,000 (Tucker and Irvin, *J. Amer. Chem. Soc.*, 1951, **73**, 1923). The infra-red spectra (as solids) of the other analogues having two nitrogen atoms showed no bands characteristic of carbonyl group absorption (Dr. L. N. Short, personal communication). The three analogues having three nitrogen atoms (Nos. 8—10) all have partition coefficients below the limit of measurement by our method (<0·02).

The insertion of small alkyl groups adjacent to one or other of the two centres of hydration (the oxygen atom and $N_{(3)}$) in 8-hydroxyquinazoline greatly increased the partition coefficient. The increase was 3-fold with a methyl group at $C_{(4)}$, 26-fold with a *n*-propyl group at $C_{(4)}$, and 60-fold with an allyl group at $C_{(7)}$. Nos. 2 and 11 show a similar relationship.

TABLE 2. *Stability constants of the metal complexes of analogues of* 8-*hydroxyquinoline* (*in* H_2O *at* 20°).

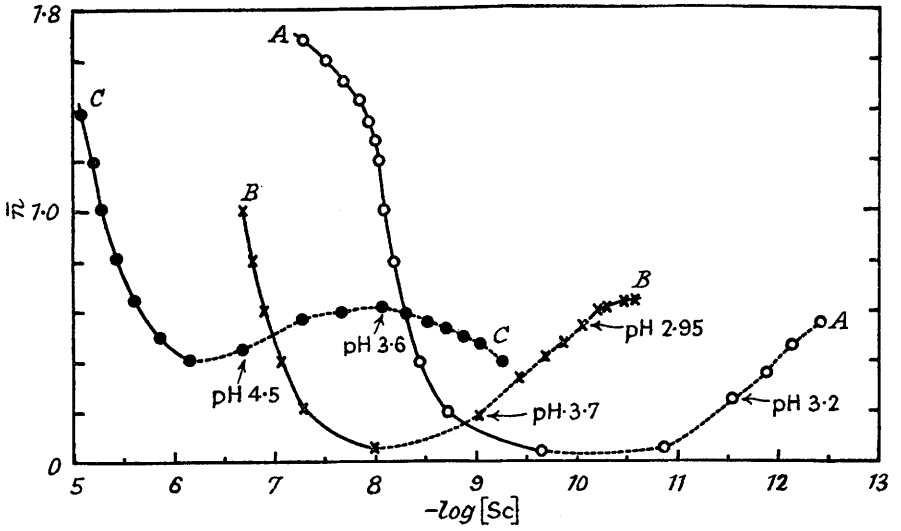
No.	Compound	Fe^{3+} complex log K'[b]	Fe^{3+} complex log K_s[d]	Cu complex log K'	Cu complex log K_s[h]	Ni complex log K'	Ni complex log K_s[h]	Fe^{2+} complex log K'	Fe^{2+} complex log K_s[h]
1	8-Hydroxyquinoline[a]	12·3	—	12·2	—	9·9	—	8·0	—
1*a*	8-Hydroxyquinoline-5-sulphonic acid[a]	12·0	33	12·5	23·1	10·0	18·1	8·4	15·1
2	8-Hydroxycinnoline	9·6	[g]	9·1	[g]	7·8[f]	14·9	6·7	[g]
11	8-Hydroxy-4-methylcinnoline	—	—	—	—	8·1	[g]	—	—
3	8-Hydroxyquinazoline	10·6	27·7	9·3	[g]	7·6[f]	14·4	6·6	12·2
12	8-Hydroxy-4-methylquinazoline	—	—	—	—	7·9	14·7	—	—
4	5-Hydroxyquinoxaline	9·3	25·8	[g]	[g]	7·6	[c]	6·8	[g]
5	4-Hydroxy-1 : 5-naphthyridine	11·0	27·8	6·9	13·4	5·8	10·5	5·8[f]	10·7
6	8-Hydroxy-1 : 6-naphthyridine	10·3	25·9		14·2	5·9[f]	10·9	5·9	10·5
7	8-Hydroxy-1 : 7-naphthyridine	12·2	[g]	8·3[f]	16·2	6·7	12·4	6·2	11·7
8	4-Hydroxypyridino(2′ : 3′-5 : 6)pyrimidine (IX) ...	—	—	—	—	6·1[f]	11·5	—	—
9	2′-Hydroxypyridino(3′ : 4′-2 : 3)pyrazine (VII)	11·0	[g]	7·5[f]	14·7	6·1[f]	11·3	5·4[f]	9·9
10	4′-Hydroxypyridino(2′ : 3′-2 : 3)pyrazine (VIII) ...	—	—	—	—	5·9[f]	11·0	—	—
19	4-Hydroxypteridine[a] (VI)	[c]	[c]	4·8[f]	9·5	4·4	7·8	3·4[f]	5·9

[a] Values taken from Albert, *Biochem. J.*, 1953, **54**, 646. [b] K' (the stability constant of the complex formed by addition of only one ligand molecule to one metallic cation) is given by $K' = \bar{n}/(1 - \bar{n})[Sc]$, where [Sc] is the concentration of the free chelating species (ligand anions) and $\bar{n}$ is the average number of molecules of ligand bound by one atom of metal. [c] No combination appeared to take place. [d] K_s (the overall stability constant) = $K' . K'' . K'''$. [g] Complex is too insol. for measurement. [f] Approx. value, the difference between log K' and log K'' being less than 1 unit (cf. Albert, *loc. cit.*). [g] Evaluation impossible, owing to simultaneous chelation by the zwitterionic species. [h] Calc. from $K_s = 1/[Sc]^2$ at $\bar{n} = 1$.

Stability Constants of Metal Complexes.—Some stability constants of the complexes of the analogues of 8-hydroxyquinoline with ferric, ferrous, cupric, and nickel ions are listed

in Table 2, together with the known constants for 8-hydroxyquinoline and 8-hydroxyquinoline-5-sulphonic acid (Albert, *Biochem. J.*, 1953, **54**, 646). (The K' values of this acid are almost identical with those for 8-hydroxyquinoline and hence it is likely that the K_s values of both substances are very close. Unfortunately the insolubility of the 1 : 2 complexes of 8-hydroxyquinoline interferes with measurement of K_s.)

It is seen from Table 2 that the analogues having one additional nitrogen atom, especially the hydroxynaphthyridines, have less avidity for metallic ions than 8-hydroxyquinoline has; this difference is most evident for the bivalent ions. The analogues with two additional nitrogen atoms have approximately the same chelating ability as the hydroxynaphthyridines, but chelate more readily than 4-hydroxypteridine (No. 19) which has three additional nitrogen atoms. Because of their poor solubility, it was not possible to determine all the ionization and stability constants of the allyl and propyl derivatives of 8-hydroxyquinazoline, but they should be similar to those of 4-methyl-8-hydroxyquinazoline (No. 12).



Formation curves of metal complexes :
A, Copper complex of 8-*hydroxy*-1 : 7-*naphthyridine.*
B, Copper complex of 4-*hydroxy*-1 : 5-*naphthyridine.*
C, Ferrous complex of 8-*hydroxy*-1 : 6-*naphthyridine.*
[Sc] *and* $\bar{n}$ *are defined in Table* 2.

The order of magnitude of the stability constants is in most cases $Cu^{2+} > Ni^{2+} > Fe^{2+}$. This order has been shown to hold for a wide variety of complex-forming agents (Mellor and Maley, *Nature*, 1948, **161**, 436; Irving and Williams, *ibid.*, 1948, **162**, 764; Albert, *Biochem. J.*, 1950, **47**, 531; 1952, **50**, 690). However the naphthyridines chelate with ferrous ions and nickel ions with comparable avidity.

As Table 2 indicates, the difference between the logarithms of the partial stability constants K' and K'' ($\log K'' = \log K_s - \log K'$) is rarely larger than one unit for the analogues of 8-hydroxyquinoline, whereas it is never less than 1·7 units for 8-hydroxyquinoline. Thus, the introduction of additional nitrogen atoms into 8-hydroxyquinoline diminishes the tendency for complex formation to proceed by the successive addition of ligand molecules to the metallic ion and a certain amount of simultaneous addition takes place.

The formation curves (Figure) of the complexes of the hydroxynaphthyridines differ from the formation curves of the remaining analogues by exhibiting an anomalous increase in the value of $\bar{n}$ (shown in the Figure by a broken line) at low values of [Sc]. This effect, which occurs only when the pH is less than 1 unit above the basic pK_a of the chelating agent, must be ascribed to complex formation by the cationic species of the molecule.

These cations, because of the electron-attracting property of their positively charged nitrogen atoms, are stronger acids than the corresponding neutral molecules, and hence can provide a given concentration of the chelating species (in this case a zwitterion) at a lower pH (cf. 8-hydroxy-1 : 6-naphthyridine methiodide in Table 3 as an example of this effect). It follows from the Figure that the basic centres of the three hydroxynaphthyridines (Nos. 5, 6, and 7) are respectively $N_{(5)}$, $N_{(6)}$, and $N_{(7)}$, because if in any instance the basic centre were $N_{(1)}$, the cationic species would be incapable of chelation

TABLE 3. *Chelation of quaternary analogues of 8-hydroxyquinoline with* Ni^{2+}.

Compound	Acidic pK_a (0·01M; 20°)	log K_s (20°)
8-Hydroxyquinazoline 3-methiodide	7·26 (± 0·03)	8·4
5-Hydroxyquinoxaline 1-methiodide	5·74 (± 0·02)	9·5
8-Hydroxy-1 : 6-naphthyridine 6-methiodide	4·34 (± 0·03)	*ca.* 11

It has frequently been suggested that the stability of metal complexes should increase when the basic strength of the nitrogen atom is increased, or when the acidic strength of the hydroxyl group is decreased (Phillips and Merritt, *J. Amer. Chem. Soc.*, 1949, **71**, 3984; Bjerrum, *Chem. Reviews*, 1950, **46**, 381). An attempt was made, therefore, to interpret differences in complex-forming ability among the simpler analogues of 8-hydroxyquinoline in terms of the pK_a values of the hydroxyl groups and of the nitrogen atoms involved in chelation. Location of the basic centre in each analogue was thus required. Preparation of the methiodides of 8-hydroxyquinazoline, 5-hydroxyquinoxaline, and 8-hydroxy-1 : 6-naphthyridine revealed that all these quaternary salts were able to form strongly bound nickel complexes (Table 3).

The basic centres of the compounds from which they were derived must therefore be $N_{(3)}$, $N_{(1)}$, snd $N_{(6)}$ respectively. Hence, a comparison of basic and acidic strength with chelating ability among the present series of analogues of 8-hydroxyquinoline would involve measurement of the lower basic pK_a of each analogue, and this has not yet been attempted. However, Tables 2 and 3 show that conversion of 5-hydroxyquinoxaline and 8-hydroxyquinazoline into quaternary salts causes a large reduction in the stability of the nickel complexes. This is consistent with the above hypothesis since in each case quaternization not only increases the acid strength of the hydroxyl group, but also must weaken the basic strength of $N_{(1)}$ by a coulombic effect.

Oil–Water Partition of Complexes.—It is interesting to know what relation exists between the lipoid-solubility of the analogues and that of the corresponding 1 : 2 complexes. The direct determination of the partition coefficients of these complexes is beset with difficulties. However, an approach to the problem was made by examining the percentage of analogue extracted from 0·0002M-aqueous solution by oleyl alcohol in the absence and presence of nickel ions. The total amount of analogue (combined and free) was estimated in the aqueous layer (spectrophotometrically as free analogue after liberation by dilution in 0·1N-hydrochloric acid). These extractions were repeated with 0·001M-solutions to make sure that saturation of the oleyl alcohol was not occurring.

TABLE 4. *Effect of metallic ions on the extraction of analogues of 8-hydroxyquinoline from aqueous solutions (25 ml.; 0·0002M) by oleyl alcohol (2 ml.) at 20° and* pH 5·6—6·6.

No.	Substance (as sodium salt)	Extraction (%) Ni^{2+} present (0·0001M)	Extraction (%) Ni^{2+} absent	Oil–water partition coeff. (from Table 1)
11	8-Hydroxy-4-methylcinnoline ...	87	56	16·3
2	8-Hydroxycinnoline	57	31	5·6
3	8-Hydroxyquinazoline	33	29	5·2
5	4-Hydroxy-1 : 5-naphthyridine	15	0	<0·02
6	8-Hydroxy-1 : 6-naphthyridine	20	7	1·0
7	8-Hydroxy-1 : 7-naphthyridine	10	1	0·14

Table 4 shows that the amount of analogue extracted in the presence of nickel always exceeds that extracted in its absence. A valid comparison between two substances can be made only where they have comparable pK_a values and comparable K_s values. Such a pair are Nos. 2 and 11. Here the presence of a methyl group has enhanced both extractions by roughly the same factor. Unfortunately it was not possible to examine more analogues by this method: the complexes of Nos. 8—10 and 19 were not appreciably

lipoid-soluble, whereas those of Nos. 1, 13, and 14 were so highly lipoid-soluble that a measurable amount could not be retained in the aqueous phase. Nevertheless, these findings provide some measure of support for the concept that the partition coefficients of metal-binding agents provide a guide to the lipoid-solubility of the complexes.

Experimental

Microanalyses were by Mr. P. R. W. Baker, Beckenham.

The solubility data in Table 1 were obtained by dilution of saturated aqueous solutions in 0·1N-sodium hydroxide and spectrometric comparison with standard solutions of the substances in sodium hydroxide of the same concentration.

Ionization constants were determined potentiometrically as described by Albert, Brown, and Cheeseman (*J.*, 1951, 474).

Stability Constants.—Titrations were carried out by adding 0·1N-potassium hydroxide (carbonate-free; 2·5 ml.) in ten equal portions to 0·0025M-aqueous solutions (100 ml.) of the analogues containing 1 equiv. of the appropriate metallic ion. Prior addition of hydrochloric acid (as much as 4 equivs.) was sometimes necessary to reveal the lower values of $\bar{n}$. Titrations with ferrous ions were carried out in boiled-out water under nitrogen. Calculations of the stability constants were carried out as described by Albert (*Biochem. J.*, 1950, **47**, 531; 1952, **50**, 690).

All the analogues formed red complexes with ferrous ions, and greenish- or reddish-black complexes with ferric ions (as in the case of 8-hydroxyquinoline), except that Nos. 5, 7, and 9 gave orange ferric complexes. Copper complexes were pale green, except those of Nos. 2, 3, and 4 which were yellow. Nickel complexes of Nos. 5, 7, and 8 were pale green, of No. 2 red, and of the remainder yellow.

Partition Coefficients.—Pure oleyl alcohol (b. p. 132°/0·03 mm., n_D^{20} 1·4608) was obtained by fractionating commercial oleyl alcohol in a 100-cm. Vigreux column (heated jacket), the reflux ratio being kept at about 5. The copious initial fractions (b. p. 105—125°/0·03 mm.) consisted mainly of cetyl alcohol.

A solution of each compound (10^{-3}M or $0·2 \times 10^{-3}$M) in M/20-phosphate buffer (pH 7·3; 3—25 ml.) was gently shaken until equilibrated (3 hr.) with a volume (2—20 ml.; measured by weight) of oleyl alcohol sufficient to extract 10—90% of the compound from the aqueous phase. After centrifugation, the upper layer of oleyl alcohol was sucked off, and residual droplets of oil were removed by pouring the aqueous solution through a small pad of cotton wool. The concentration of the compound in the aqueous phase before and after extraction was found spectroscopically by making suitable dilutions in 0·1N-sodium hydroxide. Each extraction was repeated at a 2- or 5-fold dilution; in every instance the value of the partition coefficient was in good agreement with the value obtained from the more concentrated solution. Those partition coefficients having a value greater than 1 should not be in error by more than ±5%.

3-Methoxy-2-nitroacetophenone.—Condensation of 3-methoxy-2-nitrobenzoyl chloride (Curd, Landquist, and Rose, *J.*, 1948, 1764) with ethoxymagnesiomalonic ester in benzene solution, followed by hydrolysis and decarboxylation of the resulting acylmalonic ester in boiling propionic acid (cf. Bowman, *J.*, 1950, 322), gave this ketone, m. p. 128°, in 95% yield.

2-Formamido-3-methoxyacetophenone (I; R = Me).—2-Amino-3-methoxyacetophenone (2·24 g.; Simpson, Atkinson, Schofield, and Stephenson, *J.*, 1945, 646) was added in portions, with shaking, during 15 min. to acetic formic anhydride (11 ml.; b. p. 29—32°/20 mm.; Béhal, *Compt. rend.*, 1889, **128**, 1460) at 0—5°. The solution was kept at 0—5° for a further 10 min., then poured on crushed ice. The pH was adjusted to 4 with 8N-ammonia, giving a white precipitate (1·31 g.) of *2-formamido-3-methoxyacetophenone*. An additional quantity (1·25 g.) was obtained by extracting the filtrate with chloroform (4 × 10 ml.), washing the extract with saturated aqueous sodium hydrogen carbonate (5 ml.), and evaporating the dried chloroform layer. The total yield was 97%. The compound formed colourless needles, m. p. 95°, from 600 parts of light petroleum (b. p. 60—80°) (Found: C, 62·2; H, 5·7; N, 7·3. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3%).

8-Methoxy-4-methylquinazoline (II; R = Me).—A stream of dry ammonia was passed for 3 hr. into a solution at 155—160° (bath-temp.) of the above formyl derivative (2 g.) in molten ammonium acetate (20 g.). Water (100 ml.) was added to the cooled mixture and the product (1·5 g., 83%; m. p. 129—130°) collected. Crystallization from water (50 parts) gave *8-methoxy-4-methylquinazoline* as colourless needles, m. p. 131° (Found, for material dried at 80°: C, 68·7; H, 5·5; N, 16·1. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%).

8-Hydroxy-4-methylquinazoline.—An intimate mixture of 8-methoxy-4-methylquinazoline (0·5 g.) and anhydrous aluminium chloride (1·5 g.) was heated at 100° (vigorous reaction !). The orange product was heated for 4 hr. at 130—135°, cooled, and dissolved in water (15 ml.). The solution was brought to pH 3—4 and extracted continuously with ether for 6 hr. The dried ethereal layer was evaporated and the gummy residue triturated with water (3 ml.), at pH 5, giving a yellow powder (0·30 g., 65%; m. p. 158—159°). Sublimation at 140—150°/25 mm., followed by crystallization from light petroleum (b. p. 60—80°; 65 ml.), gave cream-coloured needles (0·23 g.), m. p. 162°, of *8-hydroxy-4-methylquinazoline* (Found: C, 67·4; H, 5·0; N, 17·6. $C_9H_8ON_2$ requires C, 67·5; H, 5·0; N, 17·5%).

3-Methoxy-2-nitrophenyl Propyl Ketone.—A solution of 3-methoxy-2-nitrobenzoyl chloride (10·8 g., 0·05 mole) in benzene was slowly added, with shaking, to a benzene solution (20°) of dibenzyl sodioethylmalonate (0·05 mole; prepared from diethyl ethylmalonate by Bowman's method, *J.*, 1950, 325). The mixture was refluxed for 30 min., cooled, and poured into water containing a trace of sulphuric acid. The aqueous layer was separated and extracted with benzene (2 × 20 ml.). The benzene was washed with water (2 × 30 ml.), dried (Na_2SO_4), and evaporated under reduced pressure (finally at 100°/0·05 mm.), giving crude dibenzyl ethyl-(3-methoxy-2-nitrobenzoyl)malonate (24·1 g.) as a thick red gum. This was hydrogenated in ethyl acetate (100 ml.) over 10% palladium–strontium carbonate (2 g.; prepared according to Bowman, *loc. cit.*). The catalyst was filtered off, and the solution refluxed for 3 hr., cooled to 20°, and filtered from 3-methoxy-2-nitrobenzoic acid (0·7 g.). Removal of the ethyl acetate under reduced pressure and trituration of the residual gum with N-sodium hydroxide (100 ml.) gave a fawn-coloured solid, m. p. 73—78°. Crystallization of this from light petroleum (b. p. 60—80°; 200 ml.), then from methanol (4 ml.), yielded colourless prisms (2·8 g.), m. p. 82°, of *3-methoxy-2-nitrophenyl propyl ketone* (Found: C, 59·2; H, 5·7; N, 6·4. $C_{11}H_{13}O_4N$ requires C, 59·2; H, 5·9; N, 6·3%).

2-Formamido-3-methoxyphenyl Propyl Ketone (I; R = Pr^n).—Iron filings (3·25 g.) were added during 1 hr. to a stirred solution of the above ketone (2·6 g.) in acetic acid (12·5 ml.) on the steam-bath. Water (12·5 ml.) was added in 2·5-ml. portions at 15 min. intervals. The mixture was heated for 1 hr. more, then diluted with water (50 ml.) and extracted with ether (4 × 25 ml.). The ethereal layer was washed with 2N-sodium carbonate (20 ml.). Removal of the ether from the dried (Na_2SO_4) solution and distillation of the residue gave 2-amino-3-methoxyphenyl propyl ketone (2·15 g., 95%) as a yellow oil, b. p. 82—84°/0·02 mm. Reaction of this amine with acetic formic anhydride as described above gave 99% (m. p. 36°) of *2-formamido-3-methoxyphenyl propyl ketone* which formed colourless prisms, m. p. 37—37·5°, from 250 parts of light petroleum (b. p. 40—50°) (Found: C, 65·3; H, 6·6; N, 6·3. $C_{12}H_{15}O_3N$ requires C, 65·2; H, 6·8; N, 6·3%).

8-Methoxy-4-propylquinazoline (II; R = Pr^n).—This formyl derivative (0·2 g.) was heated for 8 hr. at 150—160° in a sealed tube with ethanolic ammonia (2 ml.; saturated at 0°). The alcohol was distilled off and 2N-sodium hydroxide (10 ml.) added to the residue. The mixture was extracted with light petroleum (b. p. 60—80°; 5 × 10 ml.), and the extract was washed with N-sodium hydroxide (10 ml.) and then evaporated, giving *8-methoxy-4-propylquinazoline* (0·17 g., 93%), m. p. 35—36°. The compound formed yellow needles, m. p. 38—39°, from light petroleum (b. p. 40—60°; 10 ml., concentrated to 2 ml.) (Found: C, 71·4; H, 6·9; N, 13·9. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 7·0; N, 13·9%).

8-Hydroxy-4-propylquinazoline.—8-Methoxy-4-propylquinazoline (0·45 g.) and anhydrous aluminium chloride (1·5 g.) were heated for 4 hr. at 130—135°. The cooled mixture was decomposed by the addition of water (15 ml.). An excess of 40% aqueous sodium hydroxide was added, and the yellow precipitate collected at 0°, washed with 2N-sodium hydroxide, and dissolved in water (30 ml.). The solution was adjusted to pH 7, giving a precipitate of *8-hydroxy-4-propylquinazoline* (0·27 g., 64%), m. p. 99—100°. Crystallization from light petroleum (b. p. 40—60°; 25 ml., concentrated to 3 ml.) gave pale yellow needles (0·25 g.), m. p. 100° (Found: C, 70·2; H, 6·5; N, 14·9. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%).

8-Allyloxyquinazoline.—Allyl bromide (1·7 g.) was added to a solution prepared from 8-hydroxyquinazoline (2 g.) and potassium (0·54 g.) in absolute methanol (10 ml.), and the mixture refluxed for 6 hr. After removal of the methanol, 2N-sodium hydroxide (10 ml.) was added and the mixture extracted with chloroform. The chloroform layer was dried (K_2CO_3) and evaporated under reduced pressure. Distillation of the residue gave an oil, b. p. 98—100°/0·04 mm., which on cooling formed colourless needles (1·67 g., 65%), m. p. 53—54°, of *8-allyloxyquinazoline*. When crystallized from 80 parts of light petroleum (b. p. 40—60°) the product melted at 55° (Found: C, 71·0; H, 5·4; N, 15·4. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

7-*Allyl*-8-*hydroxyquinazoline*.—8-Allyloxyquinazoline (0·6 g.) was heated for 10 min. at 195—200°. A solution of the product in N-sodium hydroxide (25 ml.) was extracted with benzene (2 × 10 ml.) (upper layer rejected), and adjusted to pH 6. The precipitate of fawn-coloured crystals (0·5 g., 83%), m. p. 108—109°, when crystallized from light petroleum (b. p. 60—80°; 20 parts) gave colourless plates (0·44 g.) of 7-*allyl*-8-*hydroxyquinazoline*, m. p. 109·5° (Found: C, 71·3; H, 5·5; N, 15·1. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·1%).

Methiodides.—8-Hydroxyquinazoline (0·5 g.) and methyl iodide (3 ml.) were heated at 100° for 3 hr. in a sealed tube. The product was washed with chloroform and crystallized from ethanol (25 ml.; concentrated to 10 ml.), giving colourless needles (0·51 g.), m. p. 192° (decomp.), of the *monoalcoholate* of 8-*hydroxyquinazoline* 3-*methiodide* (Found: C, 40·1; H, 4·5; N, 8·3; I, 37·3. $C_9H_9ON_2I,C_2H_6O$ requires C, 39·6; H, 4·5; N, 8·4; I, 38·0%). When heated at 100°, the product lost the alcohol.

Treatment of 5-hydroxyquinoxaline (0·25 g.) with methyl iodide as described above gave 5-*hydroxyquinoxaline* 1-*methiodide*, orange plates (0·40 g.), m. p. 177° (decomp.) [from *n*-propanol (22 ml.)] (Found, for material dried at 110°: C, 38·2; H, 3·2; N, 9·6. $C_9H_9ON_2I$ requires C, 37·5; H, 3·2; N, 9·7%).

A suspension of finely ground 8-hydroxy-1 : 6-naphthyridine (0·4 g.) in methyl iodide (8 ml.) was heated at 85° for 1 hr. The orange solid was washed with chloroform, crystallized from water (5 ml.) (charcoal), and dried in a vacuum over potassium hydroxide, giving the orange *monohydrate* (0·6 g.), m. p. 165—167° (decomp.), of 8-*hydroxy*-1 : 6-*naphthyridine* 6-*methiodide* (Found: C, 35·3; H, 3·7; N, 9·1. $C_9H_9ON_2I,H_2O$ requires C, 35·3; H, 3·6; N, 9·2%).

Other Materials.—4-Hydroxy-1 : 5-naphthyridine was prepared according to Klisiecki and Sucharda (*Roczn. Chem.*, 1927, **7**, 204; *Chem. Zentr.*, 1928, I, 2092). 4-Hydroxypyridino-(2′ : 3′ : 5 : 6)pyrimidine was prepared by Price and Curtin's method (*J. Amer. Chem. Soc.*, 1946, **68**, 914) in 70% yield.

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