Ultraviolet Spectra of N-Heterocyclic Systems. II. The Spectra of 5~8-Hydroxyisoquinolines and Related Compounds*

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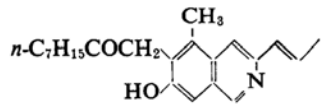
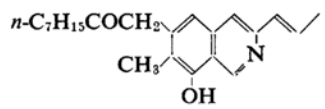
The mold pigment, monascorubrin, when treated with ammonia gives monascamine, which in turn, when reacted with, zinc affords monascaminone, a key degradation product for structural studies[1,2]. Preliminary spectroscopic measurements showed it to be an isoquinoline derivative hydroxylated at the 5-, 6-, 7- or 8-position. The four hydroxyisoquinolines have accordingly been synthesized and the ultraviolet spectra of the free hydroxy compounds, the methoxylated compounds, and the methiodides have been measured in neutral, acid, and basic methanol solutions; these curves have been compared with the curves of the corresponding derivatives prepared from the natural monascaminone in order to determine, if possible, which of the two alternative structures I, II is more appropriate[3].



(I)



(II)

The spectra of hydroxyisoquinolines, hydroxyquinolines, and their derivatives have been compared under a variety of conditions in the present paper so that there may be deduced general qualitative characteristics useful in structural studies. The azanaphthalenes with the hydroxyl group either at the α- or γ-position with respect to the ring nitrogen atom exist predominantly in the amide form in solvents of low dielectric constant[4-7], a behavior which is similar to the well known 2-hydroxy- and 4-hydroxypyridines[8-10]. These hydroxyazanaphthalenes have been omitted from the present paper; only those in which the hydroxy group is not placed α or γ to the ring nitrogen atom will be considered.

The spectra of the compounds measured are shown in Table I and Figs. 1—9; the peaks reported previously by Mason for 8-hydroxyisoquinoline[7] do not seem to be correct. The measurements were undertaken under limiting conditions, i. e., conditions in which the presence of a tautomeric mixture or an equilibrium between species with different net charge need not be taken into consideration. For example, in methanol, unlike in water of the isoelectric pH value, the parent compounds exist solely as one species and not as a tautomeric mixture. On the other hand, the methiodide of 7-hydroxyisoquinoline in methanol shows a complex absorption of seven peaks, which was shown to be due to the presence of a mixture

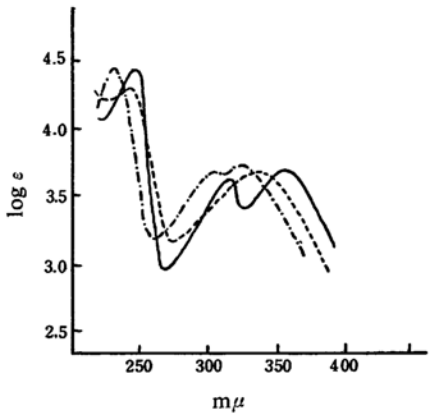


Fig. 1. Ultraviolet spectra of 5-hydroxyisoquinoline.
———: in 0.1 N HCl-MeOH
·—·—: in MeOH
------: in 0.1 N NaOH-MeOH

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Part I, K.Nakanishi, N. Suzuki and F. Yamazaki, This Bulletin, **34**, 53 (1961).

1) M. Ohashi, S. Kumasaki, S. Yamamura, K. Nakanishi and H. Koike, *J. Am. Chem. Soc.*, **81**, 6339 (1959).

2) B. C. Fielding, F. J. Haws, J. S. E. Holker, A. D. G. Powell, A. Robertson, D. N. Stanway and W. B. Whalley, *Tetrahedron Letters*. No. 5, 24 (1960).

3) To be published soon. NMR spectroscopy could not clearly differentiate between the two alternative structures: M. Ohashi, A. Terahara and K. Nakanishi, This Bulletin, **33**, 1311 (1960).

4) G. W. Ewing and E. A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946).

5) G. F. Tucker and J. L. Irvin, ibid., **73**, 1923 (1951).

6) A. Albert and J. N. Phillips, *J. Chem. Soc.*, **1956**, 1294.

7) S. Mason, ibid., **1957**, 5010.

8) A. Albert, *Chem. Soc. Spec. Publ.*, No. 3, 124 (1955).

9) A. Albert and E. Spinner, *J. Chem. Soc.*, **1960**, 1221.

10) E. Spinner, ibid., **1960**, 1226, 1232.

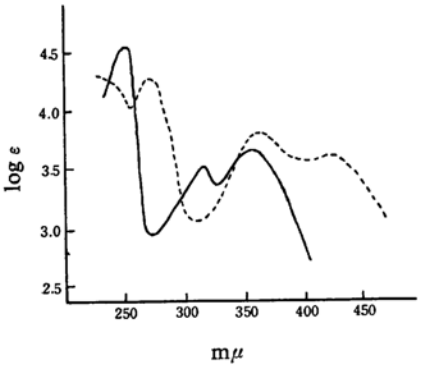

Fig. 2. Ultraviolet spectra of 5-hydroxyisoquinoline methiodide.
———: in 0.1 N HCl-MeOH
------: in 0.1 N NaOH-MeOH

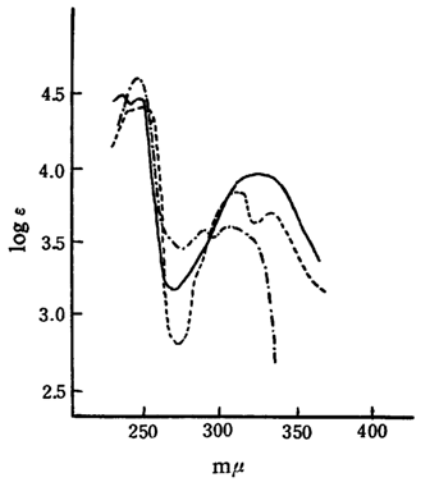

Fig. 3. Ultraviolet spectra of 6-hydroxyisoquinoline.
———: in 0.1 N HCl-MeOH
·—·—·: in MeOH
------: in 0.1 N NaOH-MeOH

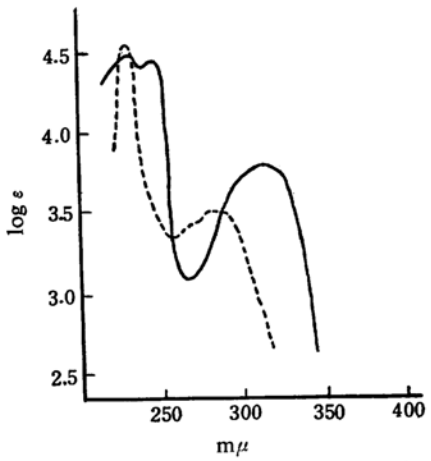

Fig. 4. Ultraviolet spectra of 6-methoxyisoquinoline.
———: in 0.1 N HCl-MeOH
------: in 0.1 N NaOH-MeOH

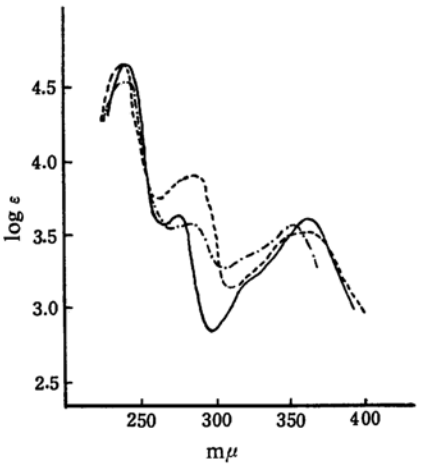

Fig. 5. Ultraviolet spectra of 7-hydroxyisoquinoline.
———: in 0.1 N HCl-MeOH
·—·—·: in MeOH
------: in 0.1 N NaOH-MeOH

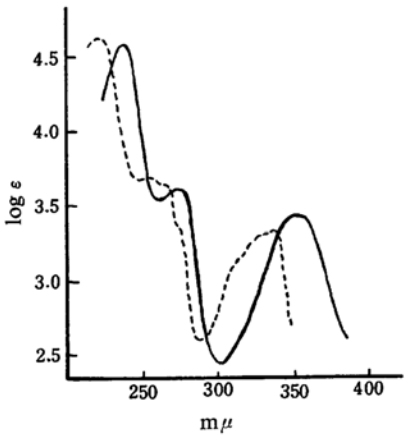

Fig. 6. Ultraviolet spectra of 7-methoxyisoquinoline.
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------: in 0.1 N NaOH-MeOH

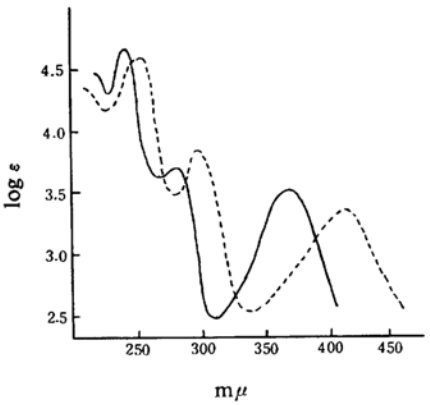


Fig. 7. Ultraviolet spectra of 7-hydroxyisoquinoline methiodide.
———: in 0.1 N HCl-MeOH
------: in 0.1 N NaOH-MeOH

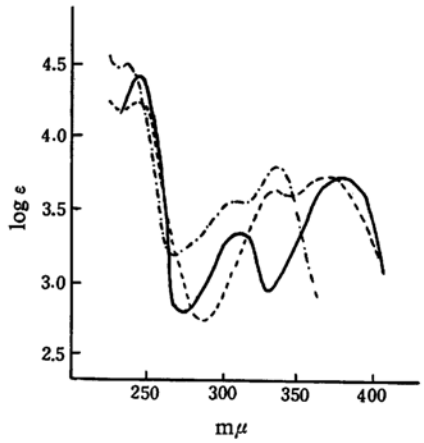


Fig. 8. Ultraviolet spectra of 8-hydroxyisoquinoline.
———: in 0.1 N HCl-MeOH
·—·—: in MeOH
------: in 0.1 N NaOH-MeOH

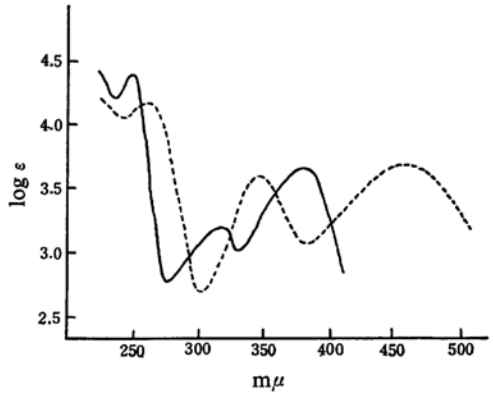


Fig. 9. Ultraviolet spectra of 8-hydroxyisoquinoline methiodide.
———: in 0.1 N HCl-MeOH
------: in 0.1 N NaOH-MeOH

of neutral (zero net charge, No. 17) and cationic (No. 16) species. Thus in comparing spectra of compounds capable of existing as mixtures, the conditions should be chosen so that complicating factors are not called into play. The spectra of other hydroxyazanaphthalenes[4,7] are also considered in the following discussion, but those of 6-hydroxyisoquinoline and derivatives (Nos. 6—10) seem to constitute a special type and will be mentioned later. Figs. 1—9 and the data published so far show that, excepting the 6-hydroxyisoquinoline derivatives (Figs. 3 and 4), all curves are roughly made up from three major absorptions; the peaks of monoazanaphthalenes are known to

TABLE I. SPECTRA OF 5~8-HYDROXYISOQUINOLINES AND DERIVATIVES

No.	Comp.	Solv.	λ_{max}	log ε	Fig.	Ionic species	Type
1	5-OH	N	234/303 328	4.45/3.65 3.70	1	a	π_3/π_2 π_1
2	〃	A	251/318 367	4.47/3.63 3.70	1	b	〃
3	〃	B	248/340	4.28/3.81	1	c	〃
4	5-OH, CH_3I	A	255/322 368	4.51/3.46 3.66	2	f	〃
5	〃	B	245(sh) 274/362 430	4.22 4.26/3.87 3.52	2	g	〃
6	6-OH	N	229/266+286+300	4.65/3.62+3.65+3.63	3	a	π_3 π_2/π_1
7	〃	A	228+247/321	4.55+4.51/3.84	3	b	〃
8	〃	B	241+253/276(sh) 308 332	4.46+4.40/3.20 3.87 3.65	3	c	〃
9	6-OCH_3	A	230+247/311	4.49+4.45/3.76	4	d	π_3 π_2/π_1
10	〃	B	231/266+280+290	4.65/3.40+3.49+3.50	4	e	π_3/π_2 π_1
11	7-OH	N	224 260+268+273/301(sh) 333	4.55 3.59+3.59+3.42/ 3.31 3.58	5	a	π_3 π_2/π_1
12	〃	A	241 278/318(sh) 362	4.64 3.65/3.16 3.63	5	b	〃
13	〃	B	238 282+289/360	4.64 3.85+3.88/3.51	5	c	〃
14	7-OCH_3	A	241 268+275/354	4.58 3.58+3.61/3.46	6	d	〃
15	〃	B	233 255+263/326+337	4.67 3.69+3.66/3.32+3.33	6	e	〃
16	7-OH, CH_3I	A	217 243 280/367	4.48 4.71 3.72/3.54	7	f	〃
17	〃	B	217 265 308/424	4.39 4.64 3.86/3.38	7	g	〃
18	8-OH	N	233/304+334	4.47/3.57+3.79	8	a	π_3/π_2 π_1
19	〃	A	245/310 378	4.47/3.39 3.72	8	b	〃
20	〃	B	247/328 370	4.28/3.66 3.78	8	c	〃
21	8-OH, CH_3I	A	217 250/315 378	4.48 4.31/3.22 3.68	9	f	〃
22	〃	B	263/347 460	4.21/3.59 3.69	9	g	〃

N; MeOH, A; 0.1 N HCl-MeOH, B; 0.1 N NaOH-MeOH
/; location of the lowest trough,
+; multiplets, sh: shoulder

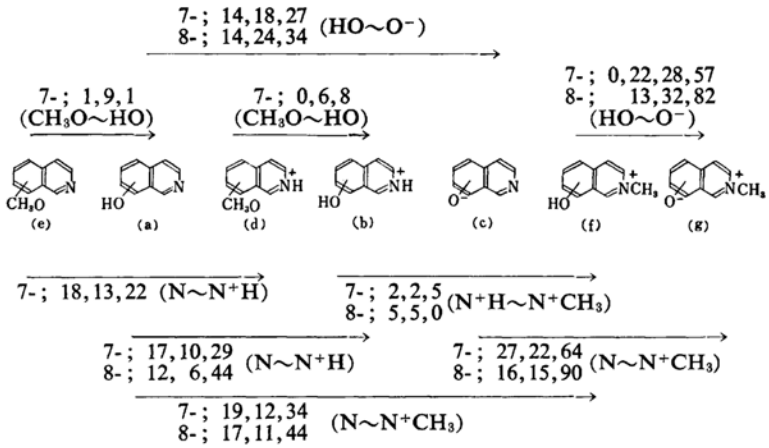


Plate 1. $\Delta\lambda_{max}$ between the ionic species of 7- and 8-hydroxyisoquinolines in methanol. (Figures denote $\Delta\lambda_{max}$ of π_3 π_2 and π_1 bands; for multiplets. the middle peak or the mean wavelength is taken.)

be $\pi\rightarrow\pi^*$ bands[11], and they will hereafter be abbreviated as π_1, π_2 and π_3-bands (in order of decreasing wavelengths).

The shifts of the bands accompanying change in media and derivatives parallel those observed for 3-hydroxypyridine[7,12-14], and the main species as shown in Plate 1 account consistently for these shifts. The species (a—g) are arranged in the order of increasing wavelengths of the peaks (from left to right).

The following common trends are apparent: (a) ionization of the phenolic group causes a red shift, a vs. c, f vs. g, (b) methylation of the phenolic group causes a slight blue shift, a vs. e, b vs. d; (c) *N*-protonation causes a red shift, e vs. d, a vs. b, (d) the change $N\rightarrow N^+CH_3$ causes a red shift larger than that due to *N*-protonation, c vs. g, a vs. f, compare also b vs. f, (e) in general, the shift for the π_1-band ($\Delta\pi_1$) is the largest, and $\Delta\pi_2 > \Delta\pi_3$ for ionization of the phenolic group, while $\Delta\pi_3 > \Delta\pi_2$ for changes involving *N*-protonation or *N*-quaternarization, (f) published data show that this general tendency is also observable in other hydroxyquinolines and hydroxyisoquinolines[4,7]. In addition to this generalization the compounds fall broadly into the α-naphthol or the β-naphthol' type as already noted by Ewing and Steck[4], which can be further refined into the form as summarized in Table II. This general classification may be observed in all of the simple hydroxylated monoazanaphthalenes (excepting 6-hydroxyisoquinoline). Full data for the methoxy and *N*-methyl compounds are missing but since the general aspects of the curves are not greatly altered by the changes of $OH\sim OCH_3$ and $N^+H\sim N^+CH_3$, excepting roughly parallel shifts of the entire curve, it can be presumed that the same relation holds for these derivatives also. Indeed, this is seen in the limited examples shown in Figs. 5, 6 and 7. The most apparent distinction between the α- and β-naphthol series is that in the former the lowest trough in the curve is located between the π_3 and π_2 bands, whereas in the latter, with the exception of the cation of the isoquinolines, the trough lies between the π_2 and π_1 bands. The exceptional behavior of the β-naphthol type quinoline cations is

TABLE II. CLASSIFICATION OF THE ULTRAVIOLET SPECTRA OF HYDROXYQUINOLINES AND HYDROXYISOQUINOLINES IN METHANOL

α-Naphthol type

5- and 8-Hydroxy-Q, 5- and 8-hydroxy-isoQ

Neutral (a, e)	;	$\pi_3/\pi_2+\pi_1$
Cation (b, d, f) Q	;	π_3/π_2(doublet) π_1
iso Q	;	π_3/π_2 π_1
Anion (c)		$\pi_3/\pi_2+\pi_1$

β-Naphthol type

3-, 6- and 7-Hydroxy-Q[4], 7-hydroxy-isoQ (6-hydroxy-isoQ)

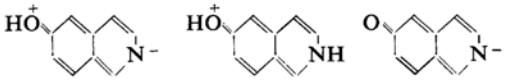
Neutral (a, e)	;	$\pi_3\pi_2$(multiplet)/π_1
Cation (b, d, f) Q	;	π_3/π_2 π_1
iso Q	;	π_3 π_2/π_1
Anion (c)	;	π_3 π_2/π_1

Q; Quinoline
/; Location of lowest trough
+; Poorly resolved or coalesced bands
( ); Alphabets in parentheses denote species shown in Plate 1.

11) S. F. Mason, *Chem. Soc. Spec. Publ.*, **No. 3**, 139 (1955).
12) D. E. Metzler and E. E. Snell, *J. Am. Chem. Soc.*, **77**, 2431 (1955).
13) K. Nakamoto and A. E. Martell, ibid., **81**, 5857 (1959).
14) S. F. Mason, *J. Chem. Soc.*, **1959**, 1253.

caused by the fact that upon *N*-protonation the shift of the π_2-band is much larger (35～50 mμ) than those of the π_1- or π_3-bands (0～20 mμ) (see Figs. 9—11 in Ref. 4).

The spectra of 6-hydroxyisoquinolines (Nos. 6—10, Figs. 3 and 4) do not fall into the general differentiation described in Table II, although the shifts accompanying changes in the species fall in line with the sequence shown in Plate 1. This could possibly be due to the fact that the nitrogen and oxygen functions are located in positions favorable for the contribution of "para-para-quinonoid" canonical structures[7] such as:



Neutral Cation Anion

However, it can be stated that these canonical structures do not make a major contribution since if this were the case, they would rather behave like pyridones or quinolones (e. g., 4-hydroxyquinoline[5]) which do not fall into the pattern outlined in Plate 1. It is interesting to note, that whereas the K_t constant (K_t= [N-H form]/[O-H form]) of other hydroxyazanaphthalenes in aqueous solutions buffered to the isoelectric pH are much less than the unity, those of 6-hydroxyisoquinoline and 4-hydroxyisoquinoline are exceptionally high (1.92 and 3.76, respectively)[7]. In view of the high value of 3.76 for 4-hydroxyisoquinoline, the spectra of this compound might also fail to agree with the generalizations of Table II. The theoretical implications of these trends are still not clear, but it is hoped that the empirical generalizations shown in Plate 1 and Table II will be of assistance in structural studies of natural products.

Experimental

Materials.—The hydroxyisoquinolines and their methyl ethers were prepared according to following literatures:

5-Hydroxyisoquinoline; R. A. Robinson, *J. Am. Chem. Soc.* **69**, 1942 (1947):
6-Hydroxyisoquinoline and 6-methoxyisoquinoline; idem., ibid., **69**, 1936, 1944 (1947):
7-Hydroxyisoquinoline and 7-methoxyisoquinoline; R. D. Woodward and W. E. Doering, ibid., **67**, 868 (1945):
8-Hydroxyisoquinoline; R. A. Robinson, ibid., **69**, 1944 (1947).

The methiodides were prepared by treating a solution of 100 mg. of the hydroxyisoquinoline in 10 ml. of 1 : 1 acetone-benzene with 3 ml. of methyl iodide, refluxing for 1 hr., collecting the precipitate after cooling, and recrystallizing from ethanol. The 5-, 7-, and 8-hydroxyisoquinoline methiodides melted at 235～237°C, 218～220°C and 217～219°C, respectively.

Measurement of Spectra.—The absorption spectra were measured with a Beckman DK-2 and a Hitachi Model EP-2 spectrophotometer in the solvents listed in Table I.

Summary

The spectra of monohydroxymonoazanaphthalenes in which the hydroxyl group is neither α nor γ to the ring nitrogen atom have been compared under various conditions. Shifts of peaks accompanying changes in the species involved have been generalized and a distinction between the spectra of the α- and β-naphthol type hydroxyazanaphthalenes has been made.

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