355. *Naphthyridines: Ionization Constants and Spectra of Four Parent Substances.*

By Adrien Albert.

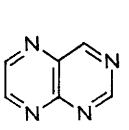
Ionization constants and ultraviolet spectra of the four unsubstituted naphthyridines have been measured and compared with those of related heteroaromatic substances.

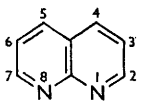
The surprisingly high basic strength [1] of pteridine (I) ($pK_a = 4{\cdot}12$) suggested this study of certain naphthyridines, *e.g.*, 1,8-naphthyridine (II) to see if any abnormalities occur. Each of the four naphthyridines is derivable from pteridine by the loss of one nitrogen atom from each ring. No unsubstituted naphthyridine was known until 1927 when the 1,8- [2] and the 1,5-isomer [3,4] were prepared. 1,5-Naphthyridine can be readily made by the Skraup reaction from 3-aminopyridine,[3,4] and the possibility that it may be the 1,7-isomer has been carefully eliminated.[4,5] As 2- and 4-aminopyridine do not take part in Skraup reactions, but can be converted into α- or γ-hydroxynaphthyridines, it seemed expedient to replace the hydroxy-group in these by chlorine and the latter by hydrogen. Attempted removal of chlorine by hydrogenation has led to difficultly separable mixtures of naphthyridine, hydronaphthyridines, and starting material.[2] It has now been found better to replace the chlorine by the hydrazine-group, which is later oxidized to the required naphthyridine with copper sulphate, a method found useful in the pyridine series.[6] In this way, 1,6- and 1,7-naphthyridine were obtained in good yield from their

[1] Albert, Brown, and Cheeseman, *J.*, 1951, 474.
[2] Koller, *Ber.*, 1927, **60**, 1918.
[3] Bobranski and Sucharda, *Ber.*, 1927, **60**, 1081.
[4] Hart, *J.*, 1954, 1879.
[5] Klisiecki and Sucharda, *Roczniki Chem.*, 1927, **7**, 204; *Chem. Abs.*, 1928, **22**, 777.
[6] Thielepape and Spreckelsen, *Ber.*, 1922, **55**, 2929.

4-hydroxy-derivatives. To prevent formation of the 1,5-isomer, the preparation of 4-hydroxy-1,7-naphthyridine commenced with 3-aminopyridine 1-oxide, and the orientation of 4-hydroxy-1,7-naphthyridine so produced has been carefully established.[7] The low-melting form (55°) of 1,5-naphthyridine, obtained in two ways by Miyaki,[8] was not encountered.

Ionization.—The basic strengths of the naphthyridines (see Table) are lower than those of quinoline and isoquinoline, as would be expected from the relayed inductive effect of a


(I)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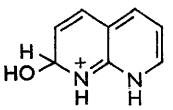
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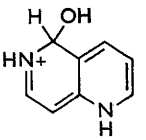

(IV)

second doubly bonded nitrogen atom. The basic strength of 1,8-naphthyridine appears to be raised by hydrogen bonding, in the cation, not possible in other isomers. Mesomeric effects, which would weaken the 1,7- and the 1,5-isomer, are evidently small. The greater strength of the 1,6- and the 1,7-isomer suggests that a high proportion of their cations have the proton on the 6(7)- rather than on the 1-nitrogen atom (cf. the pK's of quinoline and isoquinoline in the Table). Yet variations in pK_a between these four isomers are much less than in those diazanaphthalenes having both nitrogen atoms in the one ring (*viz.*, cinnoline [9] 2·3, phthalazine [10] 3·5, quinazoline [10] 3·5, quinoxaline [11] 0·7). No connexion is evident between the pK and electron distribution as calculated from molecular-orbital theory.[12]

Thus the pK_a values of those diazanaphthalenes having nitrogen atoms in the positions found in pteridine (I), taken in conjunction with the pK_a of 1,4,5-triazanaphthalene (1·20),[13] confirm the impression that the pK of pteridine [1] (4·12) is anomalously high. Increased resonance in the cation is the most likely cause of this strengthening.

Spectra.—It is evident from the Table, that the spectra of the naphthyridines (neutral molecules in water) strongly resemble one another. Only 1,5-naphthyridine gave appreciably more detail in a hydrocarbon solvent than in water. The I, II, and III bands of naphthalene (220, 275, and 312 mμ) can be distinguished just as in the spectra of quinoline and isoquinoline which those of the naphthyridines resemble (see Figure). The lack of a large hypsochromic shift when 1,6- and 1,8-naphthyridine are made into cations contrasts with the hypsochromic shift of 47 mμ in quinazoline [9] for which a resonance-strengthened, hydrated cation has been postulated.[14] Valency would permit resonance stabilization of a hydrated cation for these two naphthyridines also, but only through the canonical forms (III) and (IV) where all high-energy structures (Kekulé and *para*-quinonoid) have been lost. In view of the spectral similarity between each neutral naphthyridine molecule and its cation, and the resolution into distinct II and III bands, such hydration seems quite unlikely.

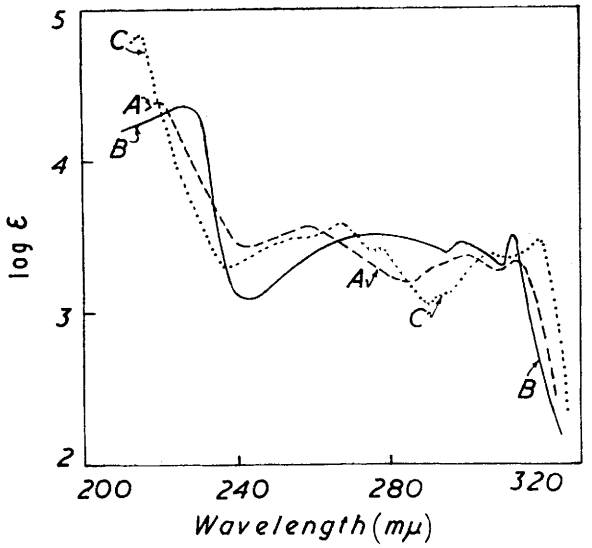
Since this work was completed, I have learnt of Ikekawa's syntheses [15] of 1,6- and 1,7-naphthyridine, m. p. 25—27° (not analysed) and 57—60° respectively, *viz.*, 6·5—7° below those found here.

[7] Murray and Hauser, *J. Org. Chem.*, 1954, **19**, 2008.
[8] Miyaki, *J. Pharm. Soc. Japan*, 1942, **62**, 257.
[9] Osborn and Schofield, *J.*, 1956, 4191.
[10] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[11] Albert, Brown, and Wood, *J.*, 1954, 3832.
[12] Longuet-Higgins and Coulson, *J.*, 1949, 971.
[13] Albert and Pedersen, *J.*, 1956, 4683.
[14] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959, p. 121.
[15] Ikekawa, *Chem. Pharm. Bull.* (*Japan*), 1958, **6**, 263, 401.

Physical constants of naphthyridines.

Substance	Ionization in water at 20° pK_a	Spread	Concn. (M)	Ultraviolet spectra (shoulders in italics) $\lambda_{max.}$ (mμ)	log ε	pH
In water						
1,5-Naphthyridine ...				249,[c] *297* + 303 + 310	3·65, *3·75* + 3·81 + 3·79	5·0
Cation	2·91	±0·03	0·05	268,[c] 305 + 313	3·54, 3·99 + 4·04	0·1
1,6-Naphthyridine ...				222, 248, 303 + 314	4·34, 3·50, 3·50 + 3·45	6·0
Cation	3·78	±0·03	0·003	248[c] +*257* + *267*, 309	*3·50* + *3·40* + *3·23*, 3·65	1·0
1,7-Naphthyridine ...				220, 260, 301 + 313	4·40, 3·57, 3·37 + 3·35	6·0
Cation	3·63	±0·03	0·005	217, 266, 302 + 313	4·58, 3·61, 3·53 + 3·48	1·0
1,8-Naphthyridine ...				260,[c] 301 + 309	3·62, 3·80 + 3·81	6·0
Cation	3·39	±0·01	0·01	302[c] + 309	4·02 + 4·01	1·0
Quinoline				226, 275, 299 + 312[d]	4·36, 3·51, 3·46 + 3·52	
Cation	4·94[a]			233, 313[d]	4·50, 3·80	
Isoquinoline				267[c] + 278, 306 + 319[b]	3·57 + 3·41, 3·38 + 3·47	
Cation	5·40[b]			227, 266 + 273, 332[b]	4·66, 3·30 + 3·30, 3·63	
In cyclohexane						
1,5-Naphthyridine				249 + 257 + 267 284 + 290 + 296 + 302 + 308	3·65 + 3·65 + 3·49 3·40 + 3·54 + 3·71 + 3·69 + 3·81	
1,6-Naphthyridine ...				221, 253, 304 + 315	4·47, 3·61, 3·47 + 3·38	
1,7-Naphthyridine ...				220, 260, 303 + 314	4·38, 3·52, 3·23 + 3·15	

[a] Ref. 10. Ref. 9. [c] Another peak <220. [d] Ref. 1.



Ultraviolet spectra in water of the neutral molecules of (A) 1,7-naphthyridine, (B) quinoline, and (C) isoquinoline.

Experimental

Analyses are by Dr. J. E. Fildes and her staff. Ionization constants and spectra were determined as before.[16]

1,5-*Naphthyridine*.—The Skraup reaction of 3-aminopyridine with arsenic oxide [4] (which gives 36% of material, m. p. 72°) was improved as follows. 3-Aminopyridine (7·5 g.), sodium *m*-nitrobenzenesulphonate (35 g.), water (45 ml.), glycerol (25 ml.), and sulphuric acid (82 g.) were heated at 135° with stirring for 4 hr. Water (100 ml.) was added and the mixture made alkaline with sodium hydroxide and steam-distilled as long as the condensate gave a precipitate with picric acid. The distillate was made alkaline and continuously extracted with ether. The extract was dried (Na_2SO_4) and the ether removed. The residue was recrystallized from

[16] Albert and Phillips, *J.*, 1956, 1294.

light petroleum (b. p. 60—70°), and sublimed at 40°/0·005 mm. to colourless needles (50%), m. p. 75° (lit.,[3,5] 75°).

1,6-*Naphthyridine*.—4-Hydroxy-1,6-naphthyridine was prepared [17] by hydrolysing and decarboxylating the 3-ethoxycarbonyl derivative. In preparing the latter from 4-aminopyridine and ethyl ethoxymethylenemalonate,[18] it was found essential to recrystallize the diethyl 1-*p*-aminopyridylethylidenemalonate to m. p. 74° before ring-closure. It was necessary also to purify the 4-hydroxy-1,6-naphthyridine-3-carboxylic acid from alkali before the decarboxylation, for which the quinoline must be freshly distilled and dry. 4-Hydroxy-1,6-naphthyridine (1 g.; m. p. 303—304°; lit.,[17] 297—299°) and phosphorus oxychloride (15 ml.) were refluxed for 1 hr. The volatile material was removed at 100 mm., and the residue added to ice and water, which was then extracted with chloroform (3 × 20 ml.). The extract was dried (Na_2SO_4) and evaporated. The residue, recrystallized from light petroleum (b. p. 60—70°), gave colourless 4-*chloro*-1,6-*naphthyridine* (50%), m. p. 90° (Found, for material dried at 20° over KOH and shredded paraffin: N, 16·65. $C_8H_5N_2Cl$ requires N, 17·0%). Attempted sublimation at 70° led to loss through dimerization.

4-Chloro-1,6-naphthyridine (1 g.), alcohol (12 ml.), and hydrazine hydrate (1·25 g., 2 equiv.) were set aside at 20° for 4 days. The alcohol was recovered below 40° and the residue recrystallized from 5 parts of water, giving 90% of 4-*hydrazino*-1,6-*naphthyridine* as orange crystals which slowly evolved vapours above 230° and melted about 270° (Found, for material dried at 20° over $CaCl_2$: C, 60·0; H, 5·15; N, 34·65. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%).

To 4-hydrazino-1,6-naphthyridine (0·82 g.) and kieselguhr (1 g.) in boiling water (35 ml.), was added copper sulphate (2·5 g.) in boiling water (11 ml.), and the slurry was refluxed for 15 min., made alkaline with 10N-sodium hydroxide (nitrogen evolved), and filtered. The cake was refluxed with water (7 ml.) and filtered. The combined filtrates were shaken with methylene chloride (3 × 40 ml.), which was then dried (Na_2SO_4) and recovered below 40° The crystalline residue was sublimed at 20°/0·005 mm., giving 60% of colourless 1,6-*naphthyridine*, m. p. 31·5°, having a powerful mouse-like odour (Found: C, 73·8; H, 4·5; N, 21·7. $C_8H_6N_2$ requires C, 73·8; H, 4·6; N, 21·5%).

1,7-*Naphthyridine*.—3-Aminopyridine 1-oxide [7] was purified by heating it for 0·5 hr. at 60°/0·5 mm., and extracting the residue (Soxhlet) with chloroform (the oxide crystallized in the flask). The ester, obtained by condensation with ethyl ethoxymethylenemalonate, cyclized well only when quite pure. The product was reduced with sodium dithionite,[19] which proved better than iron,[7] and decarboxylated in pure, dry quinoline (the earlier method [7] proving better than the later one [19]). The resulting 4-hydroxy-1,7-naphthyridine was recrystallized from water (8 parts) until it gave only one spot on paper chromatography (3% aqueous ammonium chloride) (Found: C, 66·0; H, 4·2; N, 19·1. Calc. for $C_8H_6ON_2$: C, 65·8; H, 4·1; N, 19·2%).

This was converted through 4-chloro- [7] into 4-*hydrazino*-1,7-*naphthyridine*, as for the above isomer, except that it was refluxed for 3 hr. and not set aside. This gave 90% of pale yellow crystals (from 50 parts of water) which effervesced at 234° (Found: C, 59·6; H, 5·3; N, 35·6. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%). This hydrazine, when oxidized as the above isomer, gave 60% of 1,7-*naphthyridine*, which sublimed at 40°/0·005 mm. as colourless crystals, m. p. 64°. The odour is faint, as with the 1,5-isomer (Found: C, 74·5; H, 4·5; N, 21·5%).

1,8-*Naphthyridine*, m. p. 98°, was prepared from methyl 2,4-dihydroxy-1,8-naphthyridine-3-carboxylate, through 2,4-dichloro-1,8-naphthyridine which was hydrogenated and fractionated.[2]

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[17] Möller and Süs, *Annalen*, 1958, **612**, 153.
[18] Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224.
[19] Süs and Möller, *Annalen*, 1956, **599**, 233.