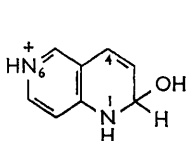
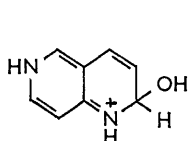
801. *Naphthyridines. Part II.*[1] *Covalent Hydration, Electron-deficiency, and Resonance Stabilisation in* 1,6-*Naphthyridines.*

By Adrien Albert and W. L. F. Armarego.

In aqueous solution, the cations of 3- and 8-nitro-1,6-naphthyridine, but not those of 4-nitroisoquinoline, 1,6-naphthyridine, and 3-nitro-1,5-naphthyridine, form covalent hydrates. The results support the hypothesis that both electron-deficiency and resonance stabilisation are necessary for covalent hydration in the cations of nitrogen-heteroaromatic compounds.

It has been shown that the cations of many nitrogen-heteroaromatic compounds undergo (reversible) covalent hydration in aqueous solution across a C=N bond. Hydrating cations commonly have (*a*) a high degree of electron-deficiency, and (*b*) a structure which, after the addition of water, has increased resonance possibilities.[2] The naphthyridine series appeared to offer opportunities to test the contribution made by these two factors, the relative importance of which has not yet been investigated.


(I)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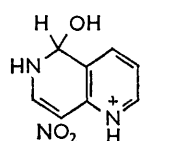
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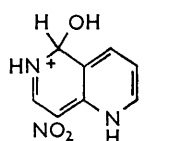

(IV)

No evidence of covalent hydration could be found in the cation of 1,6-naphthyridine,[1] although this species should be stabilised as the hydrate by resonance, *e.g.*, (I) ⟷ (II).

[1] Albert, *J.*, 1960, 1790 is Part I of this series.

[2] (*a*) Albert, *Chem. Soc. Special Publ.* No. 3, 1955, p. 125; (*b*) Perrin, *J.*, 1962, 645; (*c*) Albert, Armarego, and Spinner, *J.*, 1961, 2689, 5267; (*d*) Armarego, *J.*, 1963, in the press.

This has been designated the " 4-aminopyridinium-type " of resonance [3] because it is the one responsible for the high basic strength of 4-aminopyridine.[4] Hence it was decided to try to invoke covalent hydration by increasing the electron-deficiency of the molecule. This could be accomplished by inserting another ring-nitrogen atom to give, *e.g.*, 1,3,6-triazanaphthalene which is hydrated strongly [5] but with an amidinium-type resonance, and 1,4,6-triazanaphthalene which is hydrated strongly,[6] with a 4-aminopyridinium-type resonance. In the present work, however, we wished to increase electron-deficiency without leaving the naphthyridine series, and so investigated 3- and 8-nitro-1,6-naphthyridine. It will be shown that the cations of these two substances, which have both properties (*a*) and (*b*), readily undergo covalent hydration. For contrast, 3-nitro-1,5-naphthyridine was examined to observe the effect of electron-deficiency without the opportunity for resonance; and 4-nitroisoquinoline was compared with quinazoline with the same aim.

The desired reaction is an attack by the negatively charged region of a water molecule, *i.e.*, a nucleophilic attack, at an electron-deficient carbon atom. The purpose of choosing the 3- and the 8-position in 1,6-naphthyridine for insertion of nitro-groups was to reinforce the existing pattern of electron distribution, *i.e.*, one in which electron-deficiency is greatest in positions α- and γ- to the ring-nitrogen atom.[7]

Before examining the nitro-derivatives it was necessary to study the cation of 1,6-naphthyridine more carefully than in Part I.[1] The grounds on which this substance was thought not to form a hydrate were (i) the close similarity of the ultraviolet spectra in cyclohexane, and in water at pH 6·0 and at pH 1·0, and (ii) the pK_a value (3·78) which was not anomalous (cf. anomalous pK_a values of pteridine [2b] and quinazoline [2d]). These static methods cannot exclude a small percentage, *e.g.*, 10%, of hydrated cation. To clarify this point, an acid solution (pH 0·2) of 1,6-naphthyridine was rapidly (<1 sec.) neutralised with a buffer to give a final pH of 6·9, and examined for change in optical density at 320 mμ. No change was found, and it was concluded that deprotonation gave the anhydrous neutral species immediately, and hence hydration was absent in 1,6-naphthyridine cation.

The ionisation constants of 3- and 8-nitro-1,6-naphthyridines were found to be anomalous when compared with that of 3-nitro-1,5-naphthyridine (see Table). The ultraviolet spectra of the neutral species in water and in cyclohexane were closely similar, indicating the absence of hydration in this species (the crystalline solids, also, are anhydrous). On the other hand, the spectra of the cations of 3-nitro- and 8-nitro-1,6-naphthyridine showed, respectively, strong bathochromic shifts of the long-wavelength bands of 64 and 36 mμ with respect to the neutral species (see Table). The intensity of the long-wavelength band of the former cation (ε 1960) is much lower than that of the latter (ε 21,300), suggesting that if these bands are due to the hydrated cations then there must be less of the hydrated species in the 3-nitro-1,6-naphthyridine cation. By taking the spectra in sulphuric acid of increasing acidity, thereby decreasing the activity of water, the intensities of the bands at 361 and 348 mμ of 3- and 8-nitro-1,6-naphthyridine, respectively, were shown to decrease and finally disappear. The spectra obtained at high acidity were not very different from the spectra of the neutral species in water, solvent shifts being taken into account, and are the spectra of the anhydrous cations. This is true because the spectra in anhydrous dichloroacetic acid (Hammett acidity function H_0 −0·9),[2c] where only the anhydrous monocations of the nitronaphthyridines can exist, were almost identical with the spectra in sulphuric acid at H_0 −5·65. Moreover, addition of water (~10%) to the dichloroacetic acid solutions introduced bands at 360 and 350 mμ typical of the hydrated cations.

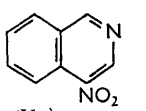
[3] Albert and Reich, *J.*, 1961, 127.
[4] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[5] Armarego, *J.*, 1962, 6094.
[6] Albert and Barlin, *J.*, 1963, in the press.
[7] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959, pp. 33, 37, 64, 67, 68.

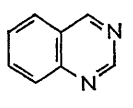
Physical properties of nitroazanaphthalenes.

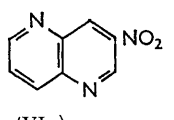
Naphthyridine	Ionisation in H_2O (20°)				Ultraviolet spectra [a] in H_2O (20°)			
	pK_a	Spread (±)	Concn. (10^{-4}M)	λ (mμ) [b]	Species [c]	$\lambda_{max.}$ (mμ)	log ε	pH or H_0
3-Nitro-1,6-	2·32	0·02	0·66	310	OA	248; 297 [d]	4·24; 3·87	7·0
					OA	247; 293	4·35; 3·88	— [e]
					+H	242 + *281* + *306* + *319*; 361	4·33 + *3·72* + *3·54* + *3·42*; 3·29	0·2
					+A	320	3·44	−0·9 [f]
8-Nitro-1,6-	2·59	0·01	0·40	350	OA	217; 276; *302* + 312 [d]	4·42; 3·59; *3·61* + 3·62	5·0
					OA	217; 259 + *263*; 304 + *312*	4·44; 3·61 + *3·60*; 3·45 + *3·42*	— [e]
					+H	280; 348	3·70; 4·33	−0·03
					+A	317	3·82	−0·9 [f]
1,6-Naphthyridine [g]	3·78	0·03	30	—	OA	222; 248; 303 + 314	4·34; 3·50; 3·50 + 3·45	6·0
					OA	221; 253; 304 + 315	4·47; 3·61; 3·47 + 3·38	— [e]
					+A	248 + *257* + *267*; 309 + *315*	3·50 + *3·40* + *3·23*; 3·65 + *3·63*	1·0
3-Nitro-1,5-	0·63	0·03	0·40	284	OA	234; 282; 312 [d]	4·33; 3·88; 3·77	6·0
					OA	233 + *243*; 275 + *277*; *298* + 311 + 323	4·51 + *4·38*; 4·02 + *4·01*; *3·62* + 3·69 + 3·61	— [e]
					+A	230; 273; 312 + 320	4·32; 3·78; 3·96 + 3·94	−2·5
4-Nitroisoquinoline	1·35 [h]				OA	208; 236; 346	4·46; 4·07; 3·49	7·0
					OA	233 + *241*; *311* + 329	4·27 + *4·17*; *3·52* + 3·59	— [e]
					+A	210; 235 + *257*; 353	4·49; 4·41 + *4·04*; 3·68	−1·12

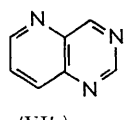
[a] Inflexions in italics. [b] Analytical wavelength. [c] O = neutral species, + = cation, A = anhydrous, H = hydrated. [d] These spectra were unaltered after standing at 20° for 24 hr. [e] Cyclohexane. [f] In anhydrous dichloroacetic acid, transparency limit ~305 mμ. [g] Physical properties from ref. 1. [h] Bryson, *J. Amer. Chem. Soc.*, 1960, **82**, 4871.

Final confirmation that these long-wavelength bands are due to the hydrated cations was obtained as follows: when an acid solution (pH 0·2) of 3-nitro-1,6-naphthyridine was rapidly neutralised (<1 sec.) with a buffer containing an equivalent of alkali to give a final pH of 6·93, the rate of decrease of optical density at 360 mμ followed first-order kinetics, and at 21° k_{obs} was $4·23 \times 10^{-2}$ sec.$^{-1}$ (half-life 16·4 sec.). Similarly with 8-nitro-1,6-naphthyridine at 350 mμ, 21°, and final pH 10·36, the first-order k_{obs} was $2·51 \times 10^{-3}$ sec.$^{-1}$ (half-life 4·6 min.). In both cases, after the optical density at infinite time was reached, the complete spectrum obtained was identical with that of the anhydrous neutral species. By analogy with previous work,[2b,c,d,5,8] rapid neutralisation gave the unstable hydrated neutral species and the observed rates refer to the dehydration–hydration process which is largely in favour of the anhydrous neutral species. The most likely structures for the hydrated cations of 3-nitro- and 8-nitro-1,6-naphthyridine are (I) ⟷ (II) (with a nitro-group in the 3-position) and (III) ⟷ (IV), respectively. Attack by water molecules


(Va)


(Vb)


(VIa)


(VIb)

in 8-nitro-1,6-naphthyridine cation most probably takes place on C-5, because it is the most electron-deficient carbon atom (compare C-4 in 1,3,8-triazanaphthalene [5]). The

[8] Armarego, *J.*, 1962, 561.

canonical form (IV) is less likely than (II) because of the *ortho*-quinonoid structure. However, hydration is an equilibrium reaction which involves very small free-energy changes,* so that the weak *ortho*-quinonoid form may be significant in stabilising (IV).

Similar experiments revealed that covalent hydration was absent in 4-nitroisoquinoline (Va) and 3-nitro-1,5-naphthyridine (VIa) [compare quinazoline [2c] (Vb) and 1,3,5-triazanaphthalene [7] (VIb) which are hydrated readily], but no resonance is possible from hydration across any C=N link in these two nitro-compounds. No unexpected differences in the spectra of the neutral species in cyclohexane and in water, and of the cation in water of 4-nitroisoquinoline were found. Further, rapid neutralisation of an acid solution (H_0 −0·18) to pH 8·0 showed no rate of change of optical density at 353 mμ, indicating absence of hydration in the cation. Like 4-nitroisoquinoline, 3-nitro-1,5-naphthyridine revealed no anomaly in its ultraviolet spectra, and rapid neutralisation of an acid solution showed no rate of change of optical density at 310 mμ.

It is thus shown that both electron-deficiency and resonance stabilisation are required for reversible covalent hydration in cations of nitrogen-heteroaromatic compounds.

Experimental

Microanalyses were by Dr. J. E. Fildes and her staff. Evaporations were carried out in a rotary evaporator at <40°/15 mm. The purity of substances was examined as before.[8] 4-Nitroisoquinoline was kindly supplied by Dr. A. Bryson.

4-Chloro-3-nitro-1,6-naphthyridine.—Ethyl 4-pyridylaminomethylenemalonate [9] was cyclised to ethyl 4-hydroxy-1,6-naphthyridine-3-carboxylate in diphenyl ether at 240—250°, under nitrogen. The average yield of purified ester from 20 experiments on a 9—36 g. scale was 55%. The ester was hydrolysed, decarboxylated, and nitrated to 4-hydroxy-3-nitro-1,6-naphthyridine as before,[10] but the nitro-compound was isolated by evaporating the nitration mixture to dryness. The hydroxynitronaphthyridine (4·2 g.) and phosphorus oxychloride (85 ml.) were refluxed for 2 hr. The solvent was removed *in vacuo*, and the residue was poured into ice-cold, saturated, aqueous sodium hydrogen carbonate and extracted with chloroform. The dried (Na_2SO_4) extract gave, on evaporation and recrystallisation from light petroleum (b. p. 60—80°), *4-chloro-3-nitro-1,6-naphthyridine* (3·0 g., 78%), m. p. 139—140° (Found: C, 45·5; H, 1·75; N, 17·0. $C_8H_4ClN_3O_2$ requires C, 45·8; H, 1·9; N, 16·9%). No loss of chlorine was observed after two recrystallisations from boiling ethanol.

3-Nitro-1,6-naphthyridine.—The above chloro-compound (2·1 g.) in chloroform (15 ml.), when mixed with a solution of toluene-*p*-sulphonhydrazide (1·86 g., 1 equiv.) in chloroform (15 ml.) and set aside at 20° for 3 days, deposited 3-nitro-4-(*N'*-toluene-*p*-sulphonylhydrazino)-1,6-naphthyridine hydrochloride (92%). The crude red hydrochloride (2·76 g.) and sodium carbonate (1·4 g.) were heated in water (60 ml.) and ethylene glycol (140 ml.) at 100° for 2 hr. with occasional shaking. The mixture was diluted with an equal volume of saturated aqueous sodium chloride and extracted with ether (6 × 70 ml.). The dried ($CaCl_2$) extract was evaporated and the residue was chromatographed in benzene on alumina (6″ × 1″; B.D.H.). Evaporation of the eluates and sublimation of the residue at 110°/0·2 mm., followed by recrystallisation from light petroleum (b. p. 60—80°), gave *3-nitro-1,6-naphthyridine* (10·6%) m. p. 159—160° (Found: C, 54·6; H, 3·0; N, 24·0. $C_8H_5N_3O_2$ requires C, 54·9; H, 2·9; N, 24·0%). No product was isolated when the reaction was carried out in 0·6N-sodium hydroxide.

Ethyl 3-Nitro-4-pyridylaminomethylenemalonate.—4-Amino-3-nitropyridine [11] (53 g., 1 mol.) and diethyl ethoxymethylenemalonate (88 g., 1 mol.) were heated at 120—130° for 48 hr. The crystals were extracted with hot light petroleum (b. p. 80—100°; 4 l.). The *product*, m. p.

* Whenever equilibrium quotients for hydrated and anhydrous species have been measured, the free-energy differences between hydrated and anhydrous species were less than 4 kcal. mole^{-1} (Dr. D. D. Perrin, personal communication).

[9] Hauser and Reynolds, *J. Org. Chem.*, 1950, **15**, 1224.
[10] Möller and Süs, *Annalen*, 1958, **612**, 153.
[11] Clark-Lewis and Singh, *J.*, 1962, 2379.

123—124° (101 g., 86%), that separated on cooling, was recrystallised from benzene–light petroleum (b. p. 40—60°) (Found: C, 50·3; H, 4·7; N, 13·6. $C_{13}H_{15}N_3O_6$ requires C, 50·5; H, 4·9; N, 13·6%).

Ethyl 4-Hydroxy-8-nitro-1,6-naphthyridine-3-carboxylate.—The preceding ester (5·0 g.) was added to diphenyl ether (50 ml.) at 180° and nitrogen passed through the solution. After 10 minutes' boiling, the mixture was cooled, the crystals were filtered off, and heating was repeated twice more. The three crops were combined, washed with light petroleum (b. p. 60—80°), and recrystallised from butan-1-ol (charcoal). The average yield of *naphthyridine ester*, m. p. 273—274° (decomp.) (Found: C, 50·4; H, 3·5; N, 15·7. $C_{11}H_9N_3O_5$ requires C, 50·2; H, 3·45; N, 16·0%), from 20 experiments was 30%. With larger quantities or longer heating the yields were considerably reduced.

4-Hydroxy-8-nitro-1,6-naphthyridine-3-carboxylic Acid.—The preceding ester (6·0 g.) in 2·5N-sodium hydroxide (96 ml.) was heated at 100° for 15 min.; the yellow solid dissolved and the red sodium salt crystallised. Water (96 ml.) was added and the solution heated for ⩾25 min. at 100°, then cooled in ice. Cold hydrochloric acid (20 ml.; *d* 1·18) was added and the buff precipitate was filtered off and washed with cold water. The *acid*, after one precipitation from 2·5N-sodium hydroxide with hydrochloric acid, had m. p. 283—284° (decomp.) (Found: C, 46·0; H, 2·15; N, 18·0. $C_9H_5N_3O_5$ requires C, 46·0; H, 2·1; N, 17·9%).

4-Hydroxy-8-nitro-1,6-naphthyridine.—The preceding acid (5·3 g.) and freshly distilled quinoline (110 ml.) were heated at 190° during 10 min., while stirred by bubbling nitrogen, and was then kept at 190—200° for 15 min. The solution was cooled and diluted with ether (260 ml.), and a small amount of tar filtered off through kieselguhr. The filtrate was diluted with light petroleum (b. p. 40—60°; 900 ml.) and the greenish-yellow *4-hydroxy-8-nitro-1,6-naphthyridine* that separated (3·3 g., 77%) was washed with light petroleum (b. p. 40—60°; 500 ml.). After recrystallisation from ethanol–light petroleum (b. p. 40—60°) it had m. p. 256—257° (decomp.) (Found: C, 50·0; H, 2·7; N, 21·8. $C_8H_5N_3O_3$ requires C, 50·3; H, 2·6; N, 22·0%).

4-Chloro-8-nitro-1,6-naphthyridine.—4-Hydroxy-8-nitro-1,6-naphthyridine (2·26 g.), phosphorus pentachloride (2·46 g., 1 equiv.), and phosphorus oxychloride (45 ml.) were refluxed for 1¼ hr. The solvent was removed *in vacuo*, and the residue was treated with saturated aqueous sodium hydrogen carbonate and extracted with chloroform. The residue from the dried (Na_2SO_4) extract was dissolved in benzene and passed through alumina (6″ × 1″). Evaporation of the eluates, followed by recrystallisation from light petroleum (b. p. 60—80°), gave *4-chloro-8-nitro-1,6-naphthyridine* (1·7 g., 68%), m. p. 182—183°, as colourless needles (Found: C, 45·7; H, 1·95; Cl, 16·9. $C_8H_4ClN_3O_2$ requires C, 45·8; H, 1·9; Cl, 16·9%).

8-Nitro-1,6-naphthyridine.—The preceding chloro-compound (1·64 g.) in chloroform (72 ml.), and toluene-*p*-sulphonhydrazide (1·46 g., 1 equiv.) in chloroform (40 ml.), when refluxed for 8 days, gave a 31% yield of the sparingly soluble hydrazinonaphthyridine hydrochloride. This salt (0·99 g.) and sodium carbonate (0·49 g.), in 70% aqueous ethylene glycol, were heated at 100° for 1 hr. and the mixture was worked up as for 3-nitro-1,6-naphthyridine. *8-Nitro-1,6-naphthyridine*, isolated in 23% yield, had m. p. 144—145° (from ethanol) [Found, for air-dried compound: C, 54·8; H, 3·4; N, 22·9. $C_8H_5N_3O_2,\frac{1}{4}C_2H_5{\cdot}OH$ requires C, 54·7; H, 3·5; N, 22·5%. Found, after drying at 65—75°/15 mm. for 1 hr. (KOH): C, 54·9; H, 3·0; N, 23·7. $C_8H_5N_3O_2$ requires C, 54·9; H, 2·9; N, 24·0%].

3-Nitro-1,5-naphthyridine.—Ethyl 3-pyridylaminomethylenemalonate [12] was cyclised to ethyl 4-hydroxy-1,5-naphthyridine-3-carboxylate in diphenyl ether.[12] The product was hydrolysed as before, but was decarboxylated in dry quinoline (80% yield) instead of in mineral oil.[13] 4-Hydroxy-1,5-naphthyridine, nitrated with fuming nitric acid as for the 1,6-isomer, gave 4-hydroxy-3-nitro-1,5-naphthyridine (71%), decomp. 325—330° [lit.,[14] 328—330° (decomp.)]. The nitro-compound was chlorinated, in the conditions for 4-hydroxy-8-nitro-1,6-naphthyridine, giving *4-chloro-3-nitro-1,5-naphthyridine* (53%) which, after recrystallisation from light petroleum (b. p. 60—80°), melted with darkening at 162—165° (softening at ~155°) (Found: C, 45·6; H, 1·9; Cl, 16·4. $C_8H_4ClN_3O_2$ requires C, 45·8; H, 1·9; Cl, 16·9%). With toluene-*p*-sulphonhydrazide in chloroform (24 hr. at 20°) a 52% yield of 3-nitro-4-(*N*′-toluene-*p*-sulphonylhydrazino)-1,5-naphthyridine hydrochloride was obtained. Decomposition of this

[12] Price and Roberts, *J. Amer. Chem. Soc.*, 1946, **68**, 1204.
[13] Adams, Bradsher, Amore, and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1317.
[14] Hart, *J.*, 1956, 212.

with dilute sodium carbonate in 70% aqueous ethylene glycol, as above, gave **3-*nitro*-1,5-*naphthyridine*** (33%), m. p. 183—184° (from ethanol) (Found: C, 55·2; H, 2·8; N, 24·1. $C_8H_5N_3O_2$ requires C, 54·9; H, 2·9; N, 24·0%).

Physical Properties.—The rapid neutralisations were carried out as before,[2b,d] and the ultraviolet spectra were measured with a Perkin-Elmer Spectracord, model 4000A, and the maxima checked with a Hilger Uvispek mark V manual instrument. Ionisation constants were determined by the method used in this Department.[15]

Nitrogen analyses of the nitronaphthyridines by the Dumas method gave consistently low results, and the Kjeldahl method, with glucose as reducing agent, gave better results.

We thank Mr. H. Satrapa for determining ionisation constants.

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[15] Albert and Serjeant, " Ionization Constants of Acids and Bases," Methuen, London, 1962.