799. *Triazanaphthalenes. Part I.*[1] *Covalent Hydration in 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalene.*

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Syntheses of 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene are described. The overall ionization constants (K_a^{eq}) and ultraviolet spectra revealed a high degree of covalent hydration in the cations. The true ionization constants of the hydrated species of three triazanaphthalenes and of the hydrated species of the four mono(*Bz*)nitroquinazolines were measured and used to explain the apparently anomalous pK_a^{eq} values of the latter. The proportion of hydrated species in the neutral molecules of the triazanaphthalenes, and the position of protonation, are discussed.

Covalent hydration in the cations of the chloro-, methyl-, hydroxy-, methoxy-, and amino-quinazoline has been clearly demonstrated by ultraviolet spectra and by rapid reaction methods.[2] It was not, however, possible to demonstrate this for the mono(*Bz*-)-nitroquinazolines because the nitro-group made the spectra so complex that only small differences were observable between the neutral molecules and their cations. The overall ionization constants * for these nitroquinazolines (see Table 1) indicated, contrary to accepted rules, that the nitro-group was base-strengthening. It was therefore decided to study 1,3,*x*-triazanaphthalenes (where *x* is 5, 6, 7, and 8), in which each nitro-group in the quinazolines was replaced by a ring-nitrogen atom. In these new bases, the spectral complications of the nitro-group are absent and the electronic influences of the doubly bound nitrogen atom on the pyrimidine ring should be comparable [3] with those of the nitro-group in the nitroquinazolines. In addition, 1,2,3- and 1,3,4-triazanaphthalene were studied.

To establish the validity, in the present work, of equating the electronic influence of a doubly bound nitrogen atom with that of a nitro-group the ionization constants of the four mono(*Bz*)nitroquinolines and the four mono(*Bz*)nitroisoquinolines were determined and compared with the values available [4] for 1,5-, 1,6-, 1,7-, and 1,8-naphthyridine. The effect of a nitro-group in the benzene ring of quinoline or isoquinoline was to reduce the pK_a of the parent substance by about 2 units (see Table 1). The pK_a values of 1,6- and

* *I.e.*, the observed, time-dependent values which include both ionization and covalent hydration.

[1] Cf. Armarego, *Proc. Chem. Soc.*, 1961, 459.
[2] Armarego, *J.*, 1962, 561.
[3] Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford Univ. Press, 1942, p. 523.
[4] Albert, *J.*, 1960, 1790.

TABLE 1.

Ionization constants, in H_2O at 20°.

Substance	pK_a	Spread (±)	λ [a] (mμ)
Quinolines			
Quinoline	4·95 [b]	0·03	—
5-Nitro	2·73 [c]	0·03	230
6-Nitro	2·76 [c]	0·04	270
7-Nitro	2·44 [c]	0·03	279
8-Nitro	2·59 [c]	0·02	330
Isoquinolines			
Isoquinoline	5·40 [d]	—	—
5-Nitro	3·53 [c]	0·03	350
6-Nitro	3·47 [c]	0·04	223
7-Nitro	3·61 [c]	0·04	220
8-Nitro	3·59 [c]	0·03	355
Naphthyridines			
1,5-Naphthyridine	2·91 [e]	0·03	—
1,6-Naphthyridine	3·78 [e]	0·03	—
1,7-Naphthyridine	3·63 [e]	0·03	—
1,8-Naphthyridine	3·39 [e]	0·01	—
Triazanaphthalenes			
1,3,5-Triazanaphthalene	4·11 [g]	0·03	303
1,3,7-Triazanaphthalene	4·70 [g, h]	0·02	—
1,3,8-Triazanaphthalene	3·85 [g, h]	0·03	—
1,2,4-Triazanaphthalene	−0·82 [c]	0·05	244
4-Hydroxy-3,4-dihydro-1,3,5-	6·46	0·05	295
4-Hydroxy-3,4-dihydro-1,3,7-	6·35	0·05	295
4-Hydroxy-3,4-dihydro-1,3,8-	6·56	0·05	280
Quinazolines			
Quinazoline	3·51 [f, g]	0·05	—
5-Nitro	3·75 [f, g]	0·01	—
6-Nitro	4·18 [f, g]	0·01	—
7-Nitro	4·05 [f, g]	0·01	—
8-Nitro	4·00 [f, g]	0·02	—
3,4-Dihydro-4-hydroxy	7·77 [f]	0·04	290
3,4-Dihydro-4-hydroxy-5-nitro	6·43	0·05	300
3,4-Dihydro-4-hydroxy-6-nitro	7·02	0·05	320
3,4-Dihydro-4-hydroxy-7-nitro	6·15	0·05	340
3,4-Dihydro-4-hydroxy-8-nitro	6·00	0·05	360

[a] Analytical wavelength. [b] Albert, Goldacre, and Phillips, *J.*, 1948, 2240. [c] Thermodynamic. [d] Osborn, Schofield, and Short, *J.*, 1956, 4191. [e] Ref. 4. [f] Ref. 2. [g] These are pK_a^{eq} values. [h] Determined by potentiometric titration at 10^{-3}M-concentration as described by Albert and Phillips (*J.*, 1956, 1294).

TABLE 2.

Ultraviolet spectra,[a] in water at 20°.

Substance	Charge [b]	$\lambda_{max.}$	log ε	pH
1,3,5-Triazanaphthalene	0	251; 274 + 280 + 285 + 291 + 296 + 302	3·45; 3·21 + 3·32 + 3·40 + 3·55 + 3·50 + 3·61	7·0
	0	*236* + 244 + 251 + *261*; *271* + *276* + 281 + 286 + 292 + 298 + 305; 345	*3·53* + 3·56 + 3·54 + *3·40*; *3·24* + *3·34* + 3·47 + 3·54 + 3·68 + 3·63 + 3·80; 2·07	—[c]
	+	261 + 274	3·87 + 3·84	2·0
1,3,6-Triazanaphthalene	0	218; 263; *285* + *298*	4·42; 3·50; *3·35* + *3·16*	7·0
	0	216; 239; *247* + 258 + *269* + *298*; *330*	4·50; 3·43; *3·44* + 3·50 + *3·46* + *2·93*; *2·49*	—[c]
1,3,7-Triazanaphthalene	0	214; 249 + *259*; *305* + 314	4·36; 3·45 + *3·41*; *3·46* + 3·50	7·0
	0	214; *240* + 246 + *255* + *266*; *295* + 305 + 316	4·36; *3·45* + 3·49 + *3·42* + *3·20*; *3·35* + 3·46 + 3·48	—[c]
	+	254 + *261*; 278	3·94 + *3·92*; 3·69	2·6
1,3,8-Triazanaphthalene	0	*246* + 252 + *261*; 293 + *297* + 303	*3·50* + 3·51 + *3·41*; 3·73 + *3·72* + 3·72	6·0
	0	237 + 244 + *252* + *263*; 293 + 297 + 304	3·48 + 3·48 + *3·42* + *3·31*; 3·63 + 3·64 + 3·64	—[c]
	+	*250* + *259* + 281; 324	*3·63* + *3·64* + 3·91; 2·72	2·0
2-Aminopyridine-3-aldehyde	[d]	*214*; 257; 334	*3·80*; 3·76; 3·82	2·1
4-Aminopyridine-3-aldehyde	0 [e]	219; *253* + 258 + *265*; 312	4·42; *3·84* + 3·88 + 3·73; 3·54	7·2
	[d]	218; *261* + 263; 302	4·43; *4·03* + 4·04; 3·56	2·1
1,2,4-Triazanaphthalene	0	232; 307 + *340*; 415	4·49; 3·61 + *3·25*; 2·48	5·0
	+	243; 313; 387	4·44; 3·62; 3·14	−3·6 [f]
1,2,3-Triazanaphthalene 3-oxide	0 [e]	*239* + 266; 297; 375	*4·17* + 4·36; 3·82; 3·08	7·0
4-Methyl-1,2,3-triazanaphthalene 3-oxide	0 [e]	*242* + 255; 294 + *299*; 377	*4·30* + 4·40; 3·74 + *3·73*; 3·11	7·0

[a] Inflexions are in italics. [b] 0 and + represent neutral molecules and cations, respectively. [c] In cyclohexane. [d] Ionic species not known. [e] Neutral species are undoubtedly present at this pH. [f] H_0 value.

1,7-naphthyridine are also about 2 units below that of isoquinoline. In this case, N-6 and N-7 are protonated and the values should be compared with those for 5- and 8-nitroisoquinoline, respectively. Similarly, 1,5-naphthyridine (cf. 5-nitroquinoline) is a weaker base by 2 units than quinoline, but the pK_a value of the 1,8-isomer (cf. 8-nitroquinoline) is less by 1·55 units. The somewhat smaller difference in the last case is due to the *peri*-nitrogen atom which tends to increase the basic strength by hydrogen bonding. The nitro-group in the above azanaphthalenes is thus base-weakening and hence it should behave similarly in the nitroquinazolines. The base-strengthening effect in the nitroquinazolines suggests that covalent hydration is occurring.

Ultraviolet Spectra of the Neutral Molecules.—The I, II, and III bands of naphthalene (220, 275, and 312 mμ) can be distinguished in quinoline, isoquinoline,[5] naphthyridines,[4] and other azanaphthalenes,[5] whereas the spectra of mono(*Bz*)nitro-quinolines [6] and -isoquinolines [6,7] are more difficult to interpret. Similarly it has now been found that the spectra of 1,3,5-, 1,3,6-, 1,3,7- and 1,3,8-triazanaphthalene (Table 2) are also easier to interpret than those of the mono(*Bz*)nitroquinazolines.

The spectra of the neutral molecules of the four triazanaphthalenes in water have more detail than that of quinazoline. For the 1,3,6- and the 1,3,7-isomer the three main bands can be recognized whereas for the 1,3,5- and the 1,3,8-isomer the short-wavelength band I appears to have been displaced to much shorter wavelengths. The spectra of the neutral molecules in water and in cyclohexane are similar, indicating the absence of an appreciable amount of a hydrated species. The 1,3,5-isomer showed additional absorption in cyclohexane at 345 mμ due to an $n \longrightarrow \pi^*$ transition.

That 1,3,6-triazanaphthalene decomposed slowly at pH 7·17 (neutral molecule) was shown by a small change in spectrum observed after 3½ hr. (20°). The change was complete after about 2 weeks and the final spectrum was identical with that of 4-aminopyridine-3-aldehyde at pH 7·17. The neutral molecules of the other three triazanaphthalenes are very stable at this pH and the spectra were unchanged after 5 weeks. In stronger alkali (N-NaOH), however, decomposition was rapid.

Ultraviolet Spectra of the Cations.—When aqueous solutions of these four triazanaphthalenes were acidified, the spectra, taken 5—10 minutes after mixing, were found to be at shorter wavelengths than those of the corresponding neutral molecules (see Table 2). Hence these bases, as with quinazoline, are predominantly hydrated (>90%) as the cations. This conclusion was supported by rapidly neutralizing the acid solutions, whereupon the spectra of the cations altered only gradually (following first-order kinetics), but finally gave the spectra of the anhydrous neutral molecules. 1,3,8-Triazanaphthalene, in acid solution, has also a small absorption band at 324 mμ (ε 530) [in addition to the high-intensity band at 281 mμ (ε 8150)] which was first attributed to the presence of some anhydrous cation. This absorption was found to be due to the hydrated cation because when an alkaline solution was immediately acidified, in a rapid-reaction apparatus, the absorption at 324 mμ increased logarithmically with time. The rate of increase of absorption at 324 mμ and at 218 mμ were identical.

Unlike the neutral molecules the cations decomposed gradually at 20°. The times in Table 3 represent the times after mixing when the changes in the spectra were apparent. The spectra of 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene cations became steady after 5 weeks. No isosbestic points were observed during the changes, indicating that several reactions were taking place consecutively. The final spectrum of the cation of the 1,3,8-isomer was the same as the spectrum of 2-aminopyridine-3-aldehyde taken at the same pH. 1,3,6-Triazanaphthalene cation was the most unstable and decomposition at pH 2·07 began as soon as the solution was prepared and was nearly complete after 48 hr. The final spectrum obtained was identical with that of 4-aminopyridine-3-aldehyde at

[5] Osborn, Schofield, and Short, *J.*, 1956, 4191.
[6] Dewar and Maitlis, *J.*, 1957, 2521.
[7] Ochiai and Nakagome, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 497.

TABLE 3.

Substance	Propn. of hydrated to anhydrous [a] neutral species ($X_{max.}$)	*p*-$NO_2 \cdot C_6H_4 \cdot NH \cdot NH_2$ reaction [b] Colour of ppt.	Time	Time [b] at which UV spectra began to change at pH 2
4-Aminopyridine-3-aldehyde	—	Orange-red	1 min.	No change
Quinazoline	$0{\cdot}55 \times 10^{-4}$	No change	—	No change
1,3,5-Triazanaphthalene	$0{\cdot}45 \times 10^{-2}$	Rust	45 min.	50 min.
1,3,6-Triazanaphthalene	—	Yellow	3 min.	4 min.
1,3,7-Triazanaphthalene	$2{\cdot}3 \times 10^{-2}$	Rust	45 min.	50 min.
1,3,8-Triazanaphthalene	$0{\cdot}20 \times 10^{-2}$	Orange	60 min.	3 hr.
5-Nitroquinazoline	$0{\cdot}21 \times 10^{-2}$	—	—	40 min.[c]
6-Nitroquinazoline	$0{\cdot}15 \times 10^{-2}$	—	—	40 min.[c]
7-Nitroquinazoline	$0{\cdot}80 \times 10^{-2}$	—	—	No change
8-Nitroquinazoline	$1{\cdot}0 \times 10^{-2}$	—	—	35 min.[c]

[a] $K_a^B/(K_a^{eq} - K_a^B)$. [b] Approximate. [c] Small changes in intensities of the shorter-wavelength bands were observed.

pH 2·07. It was therefore not possible to measure the spectrum of this triazanaphthalene cation or the ionization constant. The final spectra of the decomposition products of the cations of 1,3,5- and 1,3,7-triazanaphthalene are taken to be, by analogy, those of 3-aminopyridine-2- and -4-aldehyde.

The spectrum of 1,2,4-triazanaphthalene at pH 5·0 has an $n \longrightarrow \pi^*$ transition band, and the difference in the position of the long-wavelength band for the cation and neutral molecule is probably due to the effect of protonation on this band, and not to hydration of the cation. The pK_a value of −0·82 (see Table 1) is compatible with the absence of covalent hydration.

1,2,3-Triazanaphthalene was not prepared because many observations [8] suggested that it would behave as an unstable diazonium compound. The 3-oxide has been examined and was found to decompose readily in acid solution. Similarly 4-methyl-1,2,3-triazanaphthalene 3-oxide decomposed in acid solution and the ionization constant could not be found. The product obtained by diazotization of *o*-aminobenzaldehyde oxime is 1,2,3-triazanaphthalene 3-oxide and not, as has been stated, the indazolone oxime [8] because its spectrum was similar to that of the product of diazotization of *o*-aminoacetophenone oxime (which is undoubtedly 4-methyl-1,2,3-triazanaphthalene 3-oxide [9]). Both spectra were determined at pH 7·17 where decomposition was negligible.

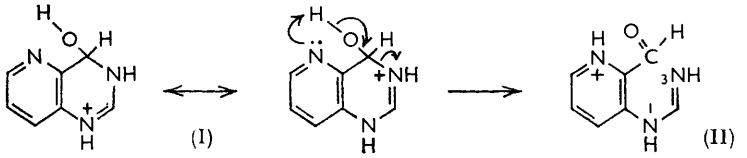
Position of Hydration.—The degradation of these triazanaphthalenes in acid solution to aminopyridinealdehydes excludes addition of water to the pyridine ring. Aldehyde reactions with *p*-nitrophenylhydrazine at pH 2 were performed and the times at which precipitation of the hydrazones occurred are given in Table 3. These times are in rough agreement with the spectral data (also in Table 3). This excludes the preliminary addition of water across the 1,2-double bond followed by ring opening, because only 3,4- or 1,4-addition of water followed by ring opening would lead to a positive aldehyde test. Mild oxidation with hydrogen peroxide (see ref. 1) was shown, by paper chromatography and ultraviolet spectroscopy, to yield in each case the corresponding 4-hydroxytriazanaphthalenes. Thus, as with quinazoline, hydration of 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene cations occurs at the 3,4- or 1,4-position. These two positions cannot be distinguished from one another in the cations because they are resonance-stabilized structures. For the neutral molecules, however, it is not possible to say whether 3,4- or 1,4-addition of water occurs. The former is the more likely because it would involve a fully conjugated system whereas 1,4-addition would produce a less stable system with an isolated (2,3-)double bond. In this paper the hydrated neutral species will be considered as having water covalently bound across positions 3,4.

The positive aldehyde tests indicate ring–chain tautomerism in the cations. In this, ring closure to (I) is favoured by any factor which places a positive charge on the aldehydic

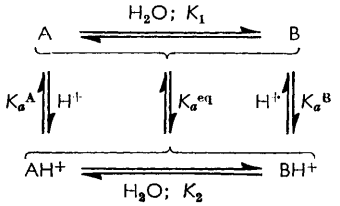
[8] Erickson, Wiley, and Wystrack, "The 1,2,3- and 1,2,4-triazines, tetrazines, and pentazines," New York, Wiley, 1956.

[9] Meisenheimer, Senn, and Zimmermann, *Ber.*, 1927, **60**, 1736.

carbon atom, and a negative charge on N-3 (and on N-1 with which it shares the charge because of resonance) in (II). But in 1,3,6-triazanaphthalene the aldehyde structure is favoured by the high proportion of positive charge which N-1 (and N-3) has to bear because of the well known 4-aminopyridine cation resonance.[10]



Ionization Constants (*Spectroscopic and Potentiometric*).—Like quinazoline, 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene are subject to the equilibria illustrated (ring opening, when it occurs, takes place through the hydrated cation), where A and B represent anhydrous and hydrated species, respectively. No difficulty was found in determining



the overall equilibrium pK_a values (pK_a^{eq}) for 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene because ring opening, which would upset this equilibrium, was inappreciable during the time (<30 min. see Table 3) in which the measurements were performed. The solution in each case was allowed to come to equilibrium before the readings were noted. The 1,3,6-isomer underwent ring opening too fast for the above equilibrium to be measured. In contrast with quinazoline the other three triazanaphthalenes showed fast but noticeable hysteresis during the measurements. The pK_a^{eq} values are, as in the mono(*Bz*)nitroquinazolines larger than that for quinazoline. These constants are meaningless for purpose of comparison because they depend on (i) K_a^A, (ii) K_a^B, and (iii) the ratio of anhydrous to hydrated species in the neutral molecules and in the cations.[11]

The kinetics of hydration–dehydration in the pH range 4—10 were slow enough to give reliable values of the pK_a of the hydrated species (*i.e.*, pK_a^B). This was done by immediately adjusting the pH of an acid solution to several values between 3 and 10 and measuring the rate of change of optical density at a particular wavelength. Extrapolation to zero time t_0 gave the optical density of the hydrated species at that wavelength. This gave reliable optical densities at t_0 because the half-lives of the hydrated neutral species were large (*e.g.*, for 1,3,8-triazanaphthalene k_{obs} $1{\cdot}23 \times 10^{-2}$ sec.$^{-1}$, half-life 56·3 sec., at 20° and pH 7·2). A plot of the extrapolated optical densities at the various pH values gave the typical curve in the Figure, and the pK_a^B values were calculated from the curve or from the optical densities at half the heights AB. The time required for one pK_a^B determination, which requires 10—13 runs, was less than 30 min.

It was not possible to apply the above treatment to the determination of the pK_a^A values for the anhydrous species. The whole curve in the Figure would, in this case, be displaced to much lower pH regions and would have to be obtained by extrapolation of rates which were too fast to give reliable values of the optical densities at t_0 (*e.g.*, for 1,3,8-triazanaphthalene k_{obs} at pH 2·7 and 20° is $5{\cdot}45 \times 10^{-1}$ sec.$^{-1}$ and the half-life 1·3 sec.). This is because hydration–dehydration is acid–base-catalyzed.

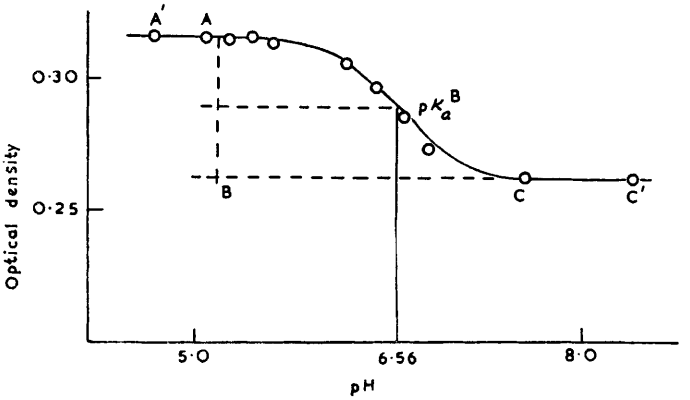
The pK_a^B values (the ionization constants for the 3,4-dihydro-4-hydroxy-compounds in Table 1) are about one unit less than that for hydrated quinazoline.[2] These constants

[10] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[11] Perrin and Inoue, *J. Phys. Chem.*, 1962, in the press.

involve only one species and its cation and can therefore be used for purposes of comparison. The base-weakening effect of the extra (pyridine) nitrogen atom is thus clearly demonstrated.

Thus electron-attracting substituents in the benzene ring of quinazoline do not decrease the ratio of hydrated to anhydrous species in the cations (see also ref. 1), and hence the cationic spectra of the four mono(*Bz*)nitroquinazolines can be taken to consist predominantly of the hydrated species. The presence of hydrated cations in the nitroquinazolines was shown by the ready formation of 4-hydroxynitroquinazolines on mild oxidation in acid solution.[2] By applying the above method the pK_a^B values for the four nitroquinazolines have been determined and they are all less than that of hydrated quinazoline (Table 1). It can therefore be concluded that no anomaly exists in the basic strengths of the mono(*Bz*-)nitroquinazolines and the triazanaphthalenes studied.

A knowledge of K_a^{eq} and K_a^{B} can be used to give an estimate of the possible limits for



Absorbancy–pH profile for $4{\cdot}04 \times 10^{-5}$M-3,4-dihydro-4-hydroxy-1,3,8-triazanaphthalene at 280 mμ and 20°.

the ratio of hydrated to anhydrous neutral molecules. Thus, from the above equilibrium diagram:

$$K_a^A = [H^+][A]/[AH^+] \quad \text{(i)}; \qquad K_a^B = [H^+][B]/[BH^+] \quad \text{(ii)}$$

and the overall equilibrium constant

$$K_a^{eq} = [H^+]([A] + [B])/\{[AH^+] + [BH^+]\} \quad \text{(iii)}$$

From (i), (ii), and (iii), the ratio of hydrated to anhydrous neutral species at equilibrium [12] is:

$$X = [B]_e/[A]_e = \{K_a^B/(K_a^{eq} - K_a^B)\}(1 - K_a^{eq}/K_a^A) \quad \text{(iv)}$$

The relation (iv) shows that X is independent of pH. Similarly it can be deduced that the ratio of hydrated to anhydrous cation at equilibrium [12] is $[BH^+]_e/[AH^+]_e = (K_a^A - K_a^{eq})/(K_a^{eq} - K_a^B)$, which is also independent of pH. When K_a^A is equal to K_a^{eq} the hydrated neutral species is absent from solution in the circumstances, and when $K_a^A \gg K_a^{eq}$ (*i.e.*, base strength is weaker), then:

$$X_{max.} = K_a^B/(K_a^{eq} - K_a^B) \quad \text{(v)}$$

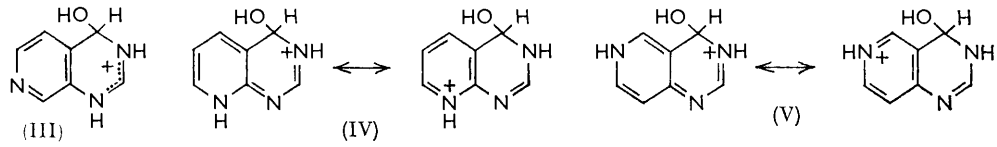
and (v) represents a maximum for the ratio of hydrated to anhydrous neutral species. Such values have been calculated for the nitroquinazolines and three triazanaphthalenes and are given in Table 3. They are of the order of 10^{-2}, which means that the percentage

[12] Inoue, personal communication.

of hydrated neutral species is ~1% at the most. In this property, the triazanaphthalenes fall between quinazoline (0·00005%) and pteridine (about 22%),[13] as would be expected.

Although the values of $X_{max.}$ calculated from the equation (v) show the upper limit of the relative amounts of the hydrated and the anhydrous neutral species present, the experimental results suggest strongly that these values are not far from the actual ratio. Thus the initial optical densities of the solutions made by rapidly mixing (<1 sec.) the alkaline solution of the base and different buffers did not vary to any significant extent at the pH region equal to $pK_a^{eq} - 0{\cdot}7$. This means that the pK_a^{A} values are at least 0·7 unit less than the pK_a^{eq} values. When the pK_a^{A} ($= pK_a^{eq} - 0{\cdot}7$) values are applied to equation (iv) the values of X calculated are not very different from the respective $X_{max.}$ given in Table 3.

Position of Protonation.—The addition of a proton to 1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-triazanaphthalene is not as complicated as might at first appear. Undoubtedly the anhydrous neutral molecules would be protonated in the pyridine rings if hydration did not occur in these compounds, and the hydrated species would be protonated in the pyrimidine ring to give the resonance-stabilized structures such as (III). It is reasonable to think



(III) (IV) (V)

that the electron-withdrawing influence of N-1 and N-3 on the pyridine-nitrogen atoms causes a decrease in basic strength of 4 pK_a units because the pK_a value [14] for 1,4,5-triazanaphthalene, which is not hydrated, is $1{\cdot}20 \pm 0{\cdot}02$. This would give a pK_a value of ~1 for the anhydrous species of these triazanaphthalenes. Since the cations were predominantly hydrated at pH 2—3 the proportion of anhydrous cations protonated in the pyridine ring at this pH is very small. At pH 2, protonation (an instantaneous process) on N-1 or N-3 in the hydrated species must upset the equilibrium K_1 (see equilibrium diagram) in favour of B, and finally a solution consisting predominantly of the hydrated cations (*e.g.*, III) is obtained. In one isomer protonation on the pyridine-nitrogen atom followed by hydration, to produce the resonance-stabilized cation (IV), could occur; but this is highly improbable at this pH, because the hydrated species of 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalene have similar basic strengths. Moreover, the structure (V) for the 1,3,6-isomer, which would confer a greater stabilizing effect, is not in agreement with the observed rapid decomposition of the hydrated cation.

Synthesis of Triazanaphthalenes.—Two routes were used for the preparation of triazanaphthalenes; (*a*) alkaline decomposition of the 4-*N*′-(toluene-*p*-sulphonylhydrazino)triazanaphthalene hydrochlorides, and (*b*) reaction of *o*-formamidopyridinealdehydes with methanolic ammonia. The intermediates for (*a*) were 4-chlorotriazanaphthalenes which were prepared by reaction of the respective 4-hydroxy-compounds with phosphorus pentachloride in phosphorus oxychloride. 4-Hydroxy-1,3,6-triazanaphthalene could not be obtained by the von Niementowski reaction with 4-aminonicotinic acid or its methyl ester whereas the other three hydroxy-compounds were readily obtained by this reaction. Methyl 4-aminonicotinate was converted into the amide and the latter cyclized with formamide to 4-hydroxy-1,3,6-triazanaphthalene. Toluene-*p*-sulphonylhydrazine reacted with the four 4-chloro-compounds to give the hydrazino-hydrochlorides in quantitative yields. Alkaline decomposition of these hydrochlorides was studied in detail and was most satisfactory when 2·2 mol. of sodium hydroxide in 70% ethylene glycol at 100° (1 hr.) was used. Thus 1,3,5- and 1,3,7-triazanaphthalene were obtained in 46 and 36% yield, respectively. The 1,3,8-isomer under similar conditions gave a 2 : 1 mixture of

[13] Perrin, *J.*, 1962, 645.
[14] Albert and Pedersen, *J.*, 1956, 4683.

1,3,8-triazanaphthalene and 2-aminopyridine-3-aldehyde from which the former was isolated by tedious chromatography. No 1,3,6-triazanaphthalene could be detected in a similar reaction, which is not surprising (see p. 4096).

1,3,6- and 1,3,8-Triazanaphthalenes were prepared by method (*b*). The synthesis was first tested with *o*-formamidobenzaldehyde which gave quinazoline in 88% yield. 2-Aminopyridine-3-aldehyde was formylated with acetic formic anhydride at room temperature and the formyl derivative gave 1,3,8-triazanaphthalene in 70% yield. 4-Aminopyridine-3-aldehyde was prepared analogously to 2-aminopyridine-3-aldehyde,[15] *i.e.*, by oxidation of 4-aminonicotinic *N'*-isopropylidenehydrazide with metaperiodate. Formylation of this aldehyde with acetic formic anhydride was successful only in the presence of anhydrous sodium formate and the yield of 4-formamidopyridine-3-aldehyde was never greater than 41%. This could be attributed to the difficulty in formylating the highly basic cation of 4-aminopyridine-3-aldehyde formed during the reaction. The formamido-compound gave 1,3,6-triazanaphthalene in 21% yield with methanolic ammonia.

Experimental

Microanalyses were by Dr. J. E. Fildes and her staff.

Evaporations were carried out in a rotary evaporator at 30—40°/15 mm., and the purity of materials was examined as before.[2] 5- and 7-Nitroquinoline,[16] 6- and 7-,[7] 5- and 8-nitroisoquinoline,[6] 2-aminopyridine-3-aldehyde,[15] 2-aminonicotinic acid,[17] cinchomeronic acid,[18] cinchomeronimide,[19] 4-hydroxy-1,3,5-,[15]-1,3,7-,[20] and -1,3,8-triazanaphthalene,[17] *o*-aminobenzaldehyde,[21] 1,2,3- and 4-methyl-1,2,3-triazanaphthalene 3-oxide,[9] and 1,2,4-triazanaphthalene [22] were prepared as described in the literature. 6- and 8-Nitroquinoline were available commercially.

4-*Aminonicotinic Acid*.—The synthesis described by Taylor and Corvetti [23] was used after some modification and on a considerably larger scale. 3-Picoline 1-oxide (60 g.) was added slowly to a cold mixture of nitric acid (165 ml.; *d* 1·5) and sulphuric acid (210 ml.; *d* 1·84) below 10°. The temperature was slowly raised to 100° and held there for 2½ hr. The mixture was poured into ice–water, the pH adjusted to 2—3 with sodium carbonate, and the product extracted with chloroform. The dried (Na_2SO_4) extract gave 4-nitro-3-picoline 1-oxide, m. p. 131—134° (lit.,[23] 136—138°), on evaporation. The average yield from 6 batches was 64%.

The nitro-oxide (125 g.) in glacial acetic acid (2500 ml.), under reflux, was heated at 100° on a steam-bath and iron filings (375 g.) were added slowly with stirring. Sometimes the reaction was vigorous and cold acetic acid was added to lower the temperature. When addition was complete heating and stirring were continued for 2 hr. As much acetic acid as possible was removed at 15 mm. and the residue treated with cold water (4 l.), the pH adjusted to 10—11 with 40% sodium hydroxide solution, and the product extracted with chloroform. The troublesome emulsion was filtered through liberal quantities of kieselguhr, the chloroform separated from the filtrate, and the aqueous layer saturated with sodium chloride and extracted further with chloroform. The dried (Na_2SO_4) extract gave 4-amino-3-picoline (60—70%), m. p. 107—109° (lit.,[19] 108—109°). This base (116 g.) was refluxed with acetic anhydride (350 ml.) for 30 min., the solvent was removed at 15 mm., and 4-acetamido-3-picoline (115 g., 72%) was collected at 150—160°/0·1—0·2 mm.; it solidified.

This acetyl derivative (115 g.) in water (17 l.) containing potassium permanganate (300 g.) was heated with stirring at 70—75° until the solution was decolorized (5—6 hr.). The manganese dioxide was filtered off (kieselguhr) and the aqueous solution evaporated to dryness at 15 mm. The residue was dissolved in water (400 ml.), acidified to pH 7, and then further with hydrochloric acid (100 ml.; *d* 1·18). The solution was refluxed for 1 hr., and 100 ml. of solvent were distilled off at 15 mm.; on cooling, the acid separated. Recrystallization from water

[15] Oakes, Pascoe, and Rydon, *J.*, 1956, 1045.
[16] Bradford, Elliott, and Rowe, *J.*, 1947, 442.
[17] Robins and Hitchings, *J. Amer. Chem. Soc.*, 1955, **77**, 2256.
[18] Armarego and Evans, *J. Appl. Chem.*, 1962, **12**, 45.
[19] Prepared as described for quinolinic imide by Sucharda, *Ber.*, 1925, **58**, 1727.
[20] Gabriel and Colman, *Ber.*, 1902, **35**, 2831.
[21] Kindly supplied by Dr. G. B. Barlin.
[22] Bischler, *Ber.*, 1889, **22**, 2801.
[23] Taylor and Corvetti, *J. Org. Chem.*, 1954, **19**, 1633.

gave 4-aminonicotinic acid (58 g., 55%), m. p. 335—336° (decomp.) [lit.,[23] 328° (decomp.)] (Found: C, 51·8; H, 4·4; N, 20·1. Calc. for $C_6H_6N_2O_2$: C, 52·2; H, 4·4; N, 20·3%).

Ethyl 4-*Aminonicotinate*.—4-Aminonicotinic acid (8·0 g.) in ethanol (16 ml.) was cooled while sulphuric acid (9·0 ml.; *d* 1·84) was added. The mixture was refluxed for 15 hr. on a steam-bath, poured into ice–water (75 ml.), neutralized with dilute aqueous ammonia, and extracted with chloroform. Evaporation of the extract gave the ethyl ester, m. p. 111—112° (5·6 g., 58%) [from benzene–light petroleum (b. p. 40—60°)] (lit.,[24] m. p. 109—111°) (Found: C, 57·8; H, 6·1; N, 16·9. Calc. for $C_8H_{10}N_2O_2$: C, 58·1; H, 5·9; N, 16·9%). The methyl ester was similarly prepared.

4-*Aminonicotinamide*.—The following is a modification of a previous method.[24] Methyl 4-aminonicotinate (12·4 g.) in methanol (100 ml.) and liquid ammonia (100 ml.) was heated under 100 atm. of nitrogen for 48 hr. at 60—70°, then a further quantity of ammonia (100 ml.) was added and the whole was kept at 100 atm. for 48 hr. at room temperature; yet more ammonia (100 ml.) was added and the whole was kept under the latter conditions for 60 hr. The solvent was evaporated and the residue digested with boiling chloroform (500 ml.) and filtered. Evaporation of the filtrate gave unchanged ester (3·3 g., 27%); and the insoluble 4-aminonicotinamide, m. p. 228—230° (lit.,[24] 229·5—230·5°), recrystallized from water (7·6 g., 69%).

4-*Hydroxy*-1,3,6-*triazanaphthalene*.—4-Aminonicotinamide (5·5 g.) and formamide (5·5 ml.) were heated at 165—175° for 2½ hr., cooled, treated with cold water (10 ml.), filtered, and washed with water and then ethanol. After recrystallization from water 4-*hydroxy*-1,3,6-*triazanaphthalene* (2·0 g., 34%) had m. p. 283—285° (decomp.) (Found: C, 57·1; H, 3·4; N, 28·3. $C_7H_5N_3O$ requires C, 57·1; H, 3·4; N, 28·6%). With boiling ethyl orthoformate and acetic anhydride the amide gave a similar yield of the hydroxy-compound but the product was always contaminated with a purple substance.

4-*Aminopyridine*-3-*aldehyde*.—Methyl 4-aminonicotinate (7·5 g.) and hydrazine hydrate (5·0 ml.) were heated at 100° for 1½ hr. The mixture was treated with water and 4-*amino-nicotinic hydrazide* was isolated and crystallized from butan-1-ol (6·5 g., 87%). It had m. p. 207—208° (Found: C, 47·7; H, 5·35; N, 36·5. $C_6H_8N_4O$ requires C, 47·4; H, 5·3; N, 36·8%). Ethyl 4-aminonicotinate gave the hydrazide in 70% yield.

The hydrazide (6·4 g.) was converted into its isopropylidene derivative by boiling " AnalaR " acetone (1 l.; 18 hr.). The crude hydrazone (8·1 g.) was oxidized to the aldehyde as follows: it was added in water (132 ml.) and ammonia (26 ml.; *d* 0·880) with shaking to a solution of sodium metaperiodate (14·5 g.) in water (200 ml.) containing ammonia (132 ml.; *d* 0·880) and shaken at room temperature for 30 min. The solution was treated with hydrated barium acetate (15 g.) in water (65 ml.), and the precipitate was filtered off (kieselguhr). The filtrate was adjusted to pH 7·0, saturated with sodium chloride, and extracted with chloroform. The dried (Na_2SO_4) extract gave, on evaporation, a low-melting solid which was sublimed at 110—120°/0·2 mm. Crystallization of the sublimate from benzene–light petroleum (b. p. 40—60°) gave 4-*aminopyridine*-3-*aldehyde* (1·4 g., 26%), m. p. 113—114° (Found: C, 59·2; H, 4·9; N, 23·1. $C_6H_6N_2O$ requires C, 59·0; H, 4·95; N, 22·9%).

4-*Chloro*-1,3,5-, -1,3,6-, -1,3,7-, *and* -1,3,8-*triazanaphthalene*.—These were obtained from the corresponding 4-hydroxy-compounds by the general method used for the preparation of 4-chloro-quinazolines.[2] The reaction times, which were critical, and the yields of purified materials were, respectively, as follows: 4 hr., 30%; [25] 1½ hr., 13%; 1 hr., 16%; and 1½ hr., 41%. The first two *compounds* are new and the m. p.s and analyses are given in Table 4.

2-*Formamidopyridine*-3-*aldehyde*.—2-Aminopyridine-3-aldehyde (20 g.) and freshly fractionated acetic formic anhydride [26] (10 ml.) were left at room temperature for 48 hr., then evaporated to dryness, and the residue sublimed at 120°/0·2 mm. The sublimate gave, on crystallization from methanol, 2-*formamidopyridine*-3-*aldehyde*, m. p. 124—125° (1·8 g., 73%) (Found: C, 56·2; H, 3·9; N, 18·45. $C_7H_6N_2O_2$ requires C, 56·0; H, 4·0; N, 18·7%).

4-*Formamidopyridine*-3-*aldehyde*.—4-Aminopyridine-3-aldehyde (1·5 g.) and finely ground anhydrous sodium formate (1·5 g.) in acetic formic anhydride (10 ml.) were kept at room temperature for 3 days. The solvent was removed *in vacuo* and the residue treated with cold saturated sodium hydrogen carbonate solution and extracted with chloroform. The dried (Na_2SO_4)

[24] Fox, *J. Org. Chem.*, 1952, **17**, 547.
[25] See, however, Price and Curtin, *J. Amer. Chem. Soc.*, 1946, **68**, 914.
[26] Béhal, *Compt. rend.*, 1889, **128**, 1460.

TABLE 4.

Triazanaphthalene	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
4-Chloro-1,3,5-	148—150° * [a]	50·7	2·5 [e]	—	$C_7H_4ClN_3$	50·8	2·4	—
4-Chloro-1,3,6-	82—83 [a, b]	50·6	2·3	24·8	,,	,,	,,	25·4
4-(*N'*-Toluene-*p*-sulphonyl-hydrazino)-1,3,8-	199—200 * [c]	47·6	3·9 [f]	—	$C_{14}H_{14}ClN_5O_2S$	47·8	4·0	—
1,3,5-	97—98 [a]	64·1	3·8	32·0	$C_7H_5N_3$	64·1	3·8	32·05
picrate	150—154 * [d]	40·3	2·9	21·6	$C_{13}H_8N_6O_7,1·5H_2O$	40·3	2·9	21·7
1,3,6-	131—132 [a]	64·2	3·8	31·8	$C_7H_5N_3$	64·1	3·8	32·05
1,3,7-	155—156 [a]	64·2	3·8	31·9	,,	,,	,,	,,
picrate	140 [d]	41·1	2·8	22·15	$C_{13}H_8N_6O_7,H_2O$	41·3	2·7	22·2
1,3,8-	107—108 [a]	64·1	3·9	31·7	$C_7H_5N_3$	64·1	3·8	32·05
picrate	152—153 [d]	41·3	2·7	21·8	$C_{13}H_8N_6O_7,H_2O$	41·3	2·7	22·2

* With decomp. [a] From light petroleum (b. p. 60—80°). [b] The colourless chloro-compound decomposed, when heated above 90°, to red needles which decomposed slowly above 150°. [c] From MeOH–Et_2O. [d] From H_2O. [e] Found: Cl, 21·1. Reqd.: Cl, 21·4%. [f] Found: S, 9·0. Reqd.: *S*, 9·1%.

extract gave, on evaporation and recrystallization of the residue from methanol, *4-formamidopyridine-3-aldehyde* (750 mg., 41%), m. p. 161—162° (Found: C, 56·2; H, 4·0; N, 18·9. $C_7H_6N_2O_2$ requires C, 56·0; H, 4·0; N, 18·7%).

Similarly *o-formamidobenzaldehyde*, m. p. 76—77° [from light petroleum (b. p. 60—80°)], was obtained in 85% yield (Found: C, 64·5; H, 4·6; N, 9·4. $C_8H_7NO_2$ requires C, 64·4; H, 4·7; N, 9·4%).

Triazanaphthalenes.—(*a*) *By alkaline decomposition of* 4-(N'-*toluene*-p-*sulphonylhydrazino*)-*triazanaphthalene hydrochlorides.* The hydrazino-hydrochlorides (5 mmoles) and a solution of sodium hydroxide (11 mmoles) in 70% ethylene glycol (60 ml.) were heated at 100° for 1 hr. 1,3,5- and 1,3,7-Triazanaphthalene were isolated as described previously for quinazolines.[2] 1,3,8-Triazanaphthalene which was isolated as a mixture was purified by gradient elution chromatography on alumina (8″ × 1″; B.D.H.) by using light petroleum (b. p. 40—60°)–benzene mixtures with increasing concentration of the latter. Three runs were necessary.

(*b*) *By ring closure.* *o*-Formamidopyridine-3-aldehyde (250 mg.) in saturated methanolic ammonia (15 ml.) was heated in a bomb at 100° for 2 hr. The solvent was removed *in vacuo*, the residue sublimed at 60—70°/0·2 mm., and the sublimate was recrystallized. The m. p.s and analytical figures for the triazanaphthalenes are given in Table 4.

Triazanaphthalene picrates were prepared in, and recrystallized from, water. 1,3,6-Triazanaphthalene gave a picrate which was obviously a mixture.

Physical Measurements.—Ionization and rate constants for the hydrated species were determined spectrophotometrically by the stop-flow technique and the details were as before.[11]

A solution of the heterocyclic base (10^{-4}—10^{-5}M) in dilute hydrochloric acid (to give pH ~2) was rapidly mixed in a modified " Chance " apparatus [13] with an equal volume of buffer, and the rate of change of optical density was observed. Extrapolation of the optical density to zero time gave the optical density plotted in the Figure. The buffers used were mixtures of 0·1M-succinic acid and 0·1M-sodium borate (for pH 3·6—6·9), 0·2M-potassium dihydrogen phosphate and 0·1M-sodium borate (pH range 6·3—9·2), 0·1M-sodium carbonate and 0·1M-sodium borate (pH range 9·5—10·2). In each buffer an equivalent quantity of alkali was added to neutralize the acid in the solution of the heterocyclic base. The necessary volume of 0·4M-sodium chloride was added to each buffer to give a constant ionic strength of 0·1. The ultraviolet spectra were measured with a Perkin–Elmer " Spectracord " model 4000 A, or a Shimadzu model RS 27 recording spectrophotometer, and the maxima checked with a Hilger Uvispek Mark V manual instrument.

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