1094. *Triazanaphthalenes. Part IV.*[1] *Covalent Hydration in 1,4,5-Triazanaphthalenes.*

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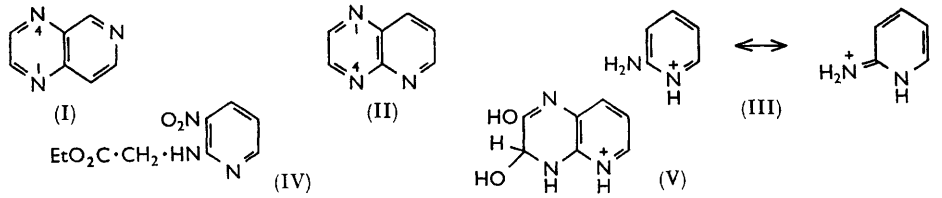
Syntheses, ionization constants, and ultraviolet spectra are presented for some 1,4,5-triazanaphthalenes. By rapid-reaction techniques, it is shown that the cation of the 2-hydroxy-derivative binds water covalently at the 3,4-bond. This is the first adduct found to be stabilized by a 2-amino-pyridinium type of resonance.

The cations of 1,4,6-triazanaphthalene (I) and its 3-hydroxy-derivative have been shown to add water readily across the 1,2-bond,[2] the product being stabilized by a 4-amino-pyridinium type of resonance, and the reaction has been studied kinetically.[1] It was

[1] Part III, Inoue and Perrin, *J.*, 1963, 5166.
[2] Albert and Barlin, *J.*, 1963, 5156.

decided to took for similar hydration in 1,4,5-triazanaphthalene (II) and its derivatives. It was realized that the only possible stabilization of hydration by resonance would be of the much weaker 2-aminopyridinium type (III). Formulæ (I) and (II) differ from that of pteridine by the omission from the latter of N-1 and N-3, respectively. We wished particularly to exmine 2-hydroxy-1,4,5-triazanaphthalene which is the 3-deaza-analogue of the strongly hydrated 6-hydroxypteridine.



Preparation of 1,4,5-*Triazanaphthalenes.*—1,4,5-Triazanaphthalene was made from commercial 2,3-diaminopyridine and glyoxal.[3] 3-Hydroxy-1,4,5-triazanaphthalene was prepared by condensing 2,3-diaminopyridine with ethyl mesoxalate, followed by hydrolysis and decarboxylation of the ethyl 3-hydroxy-1,4,5-triazanaphthalene-2-carboxylate.[4] Condensing 2,3-diaminopyridine with ethyl glyoxylate hemiacetal in alkali gave exclusively 2-hydroxy-1,4,5-triazanaphthalene, easily distinguishable from the 3-hydroxy-isomer by paper chromatography and prepared also by the following unequivocal route. 2-Chloro-3-nitropyridine [5] was condensed with ethyl aminoacetate to give ethyl 3-nitro-2-pyridylaminoacetate (IV), hydrogenation of which gave 3,4-dihydro-2-hydroxy-1,4,5-triazanaphthalene. This was readily oxidized by iodine to 2-hydroxy-1,4,5-triazanaphthalene. Oxidation of the latter, its dihydro-derivative, or 3-hydroxy-1,4,5-triazanaphthalene with potassium ferricyanide gave 2,3-dihydroxy-1,4,5-triazanaphthalene. This was also prepared from 2,3-diaminopyridine and diethyl oxalate.

6-Amino-1,4,5-triazanaphthalene was prepared as follows. 2,6-Diaminopyridine was coupled with diazotized aniline to give 2,6-diamino-3-phenylazopyridine (the previous preparation of which is poorly described [6]), which was hydrogenated to 2,3,6-triaminopyridine (more conveniently prepared thus than from the difficulty accessible 2,6-diamino-3-nitrosopyridine [7]). This triamine and glyoxal gave 6-amino-1,4,5-triazanaphthalene.[8]

Covalent Hydration.—No evidence of hydration could be found for 1,4,5-triazanaphthalene by the rapid methods described before.[1,2] Attempted oxidation with potassium permanganate was ineffective, but an excess of hydrogen peroxide gave the known [9] 6-hydroxy-1,4,5-triazanaphthalene.

2-Hydroxy-1,4,5-triazanaphthalene, a structural analogue of the strongly hydrated 6-hydroxypteridine, was found (by the stopped-flow technique [2]) to be hydrated in both the cation and the neutral species, but only the former hydrate was stable at equilibrium. The ratio of hydrated to anhydrous cation was calculated [10] to be 16 at equilibrium. The hydration apparently occurs at the 3,4-bond to give the cation (V), because gentle oxidation with potassium ferricyanide yielded 2,3-dihydroxy-1,4,5-triazanaphthalene. Dehyration, at 20°, of the neutral species followed first-order kinetics and was catalysed by hydrogen ions. The time of half-conversion was 6·2 min. at pH 6·69, but only 2·5 sec. at pH 4·25.

[3] Leese and Rydon, *J.*, 1955, 303.
[4] Clark-Lewis and Thompson, *J.*, 1957, 430.
[5] Ahmad and Hey, *J.*, 1954, 4516.
[6] Tschitschibabin and Seide, *J. Russ. Phys. Chem. Soc.*, 1918, **50**, 522 (*Chem. Zentr.*, 1923, III, 1022).
[7] Graboyes and Day, *J. Amer. Chem. Soc.*, 1957, **79**, 6421.
[8] Bernstein, Stearns, Shaw, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1151.
[9] Albert and Reich, *J.*, 1960, 1370.
[10] Perrin and Inoue, *Proc. Chem. Soc.*, 1960, 342.

Physical properties of 1,4,5-triazanaphthalenes.

1,4,5-Triazanaphthalene	Species *	Ionization (H_2O; 20°) pK_a	Spread (±)	Concn. (M)	A.w.l. †	Spectroscopy in water ‡‡ $\lambda_{max.}$ (mμ)	log ε	pH
(Unsubstituted)	o A ‡	—	—	—	—	258, 303 + 308 + 315, *335*	3·46, 3·98 + 4·00 + 4·11, *2·88*	7·0
	+ A ‡	1·20 §	—	—	—	*251* + 257 + *266*, 301 + 306 + 313, *342*	*3·50* + 3·53 + *3·42*, 4·05 + 4·06 + 4·16, *3·13*	−1·12
2-Hydroxy-3,4-dihydro	o	—	—	—	—	*270*, 319	*3·54*, 3·90	9·0
	+	5·28	0·04	10^{-4}	340	278, 325	3·66, 3·00	1·0
	—	12·11	0·04	10^{-4}	235	222, *278*, 319	4·34, *3·61*, 3·95	14·2
2-Hydroxy	o A ‡	—	—	—	—	222, 329, 341	4·31, 3·92, 3·94	5·0
	o H ¶	—	—	—	—	252—256, 307	3·67, 3·99	7·4
	+ A	2·74	0·05	10^{-5}	355	—	—	—
	+ Eq ¶	3·98	0·02	10^{-4}	330	*226*, 260, 319	*3·58*, 3·70, 4·06	0·0
	− A ‡	7·86	0·04	10^{-5}	235	230, *254*, 349	4·12, *3·74*, 3·97	10·0
3-Hydroxy	o	—	—	—	—	221, *260*, 327 + 336	4·34, *3·30*, 3·99 + 3·99	5·0
	+	0·12	0·03	10^{-4}	327	214, 328	4·37, 4·13	−2·3
	—	8·02	0·04	0·01	—	226, 348	4·47, 4·04	10·0
6-Hydroxy	o	—	—	—	—	217, 338 + 352	4·36, 4·20 + 4·10	7·0
	+	−1·20	0·04	10^{-5}	370	221, 355	4·17, 4·20	−3·3
	—	9·50	0·03	0·005	—	229, 360	4·33, 4·11	12·0
8-Hydroxy	o	—	—	—	—	246, 287, 351	4·31, 3·49, 3·83	5·0
	+	<1·3 **	—	—	—	—	—	—
	—	8·78 **	—	—	—	256, 308, 367	4·41, 3·46, 3·59 ††	12·0
2,3-Dihydroxy	o	—	—	—	—	220, 227, 241, 311, 323	3·87, 3·81, 3·60, 4·20, 4·13	5·0
	+	0·10	0·05	10^{-4}	290	220, 226, 255, 323	4·03, 3·97, 3·60, 4·32	−2·28
	—	8·45	0·05	10^{-5}	235	227, 256, 317, 328, 343	4·02, 3·61, 4·19, 4·28, 4·09	10·2
	— —	11·86	0·03	10^{-5}	240	224, 264, 333, 347	4·37, 3·62, 4·36, 3·32	14·2
6-Amino	o	—	—	—	—	229, *255*, 358	4·33, *3·69*, 4·09	7·0
	+	4·29	0·04	10^{-5}	230	220, 341, 356	440, 4·24, 4·13	1·0

* o Neutral species, + cation, − anion, − − dianion; A anhydrous (or substantially so), H hydrated, Eq equilibrium of anhydrous and hydrated species. † Analytical wavelength (mμ) for spectroscopic determination of pK_a; where there is no entry in this column, potentiometric titration was used. ‡ This is the more stable hydration form of this ionic species. § Albert and Pedersen, *J.*, 1956, 4683. ¶ 94% hydrated. ** Albert and Hampton, *J.*, 1952, 4985; 1954, 505. †† The reduced value of $\varepsilon_{max.}$ in the anion is compensated by broadening of the band. ‡‡ Shoulders and inflexions in italics.

The lower degree of hydration (94%) of the cation of 2-hydroxy-1,4,5-triazanaphthalene (at equilibrium) than of 3-hydroxy-1,4,6-triazanaphthalene [2] (~100%) may be explained by the lower stabilization available from a 2-amino- (III) than from the 4-aminopyridinium resonance (cf. the pK_a values of 2- and 4-aminopyridine, 6·86 and 9·17, respectively [11]).

As expected, hydration could not be detected for 3-, 6-, or 8-hydroxy-,[12] or 6-amino-1,4,5-triazanaphthalenes.

The ionization constants and ultraviolet spectra of substances mentioned in this paper are presented in the Table.

Experimental

The analyses were by Dr. Joyce Fildes and her staff. Details of methods for m. p.s., ultraviolet and infrared (KBr discs) spectra, ionization constants, paper chromatography, and calculation of yields have been given recently.[2]

3-Hydroxy-1,4,5-triazanaphthalene was prepared from 2,3-diaminopyridine and diethyl mesoxalate [4] (Found: C, 57·1; H, 3·4; N, 28·3. Calc. for $C_7H_5N_3O$: C, 57·1; H, 3·4; N, 28·6%); it had $\nu_{max.}$ 2800 (NH stretching), 1678 (C=O stretching) cm.$^{-1}$.

[11] Albert, Goldacre, and Phillips, *J.*, 1948, 2240.
[12] Albert and Hampton, *J.*, 1952, 4985.

2-*Hydroxy*-1,4,5-*triazanaphthalene*.—(*a*) 2,3-Diaminopyridine (1·1 g., 0·01 mole), 2N-sodium carbonate (10 ml.), and ethyl glyoxylate hemiacetal [13] (2·2 ml.) were refluxed for 1·5 hr., then adjusted to pH 5·2 with acetic acid and 10N-hydrochloric acid. The precipitate (1·23 g.) was recrystallized from 52 parts of water, giving 0·8 g. (53%) of 2-*hydroxy*-1,4,5-*triazanaphthalene* which darkens at 300° without melting (Found: C, 57·0; H, 3·4; N, 28·3%), $\nu_{max.}$ 2680 (NH stretching) 1702 (C=O stretching) cm.$^{-1}$. Paper chromatography in 3% aqueous ammonium chloride at 0° gave R_F 0·70, whereas the 3-hydroxy-isomer has R_F 0·60; none of the latter was formed in this reaction.

(*b*) 3,4-Dihydro-2-hydroxy-1,4,5-triazanaphthalene (see below) (0·1 g.) was heated to 100° in water (10 ml.) and cooled to 50°. Iodine (0·2 g.), dissolved in water (4 ml.) with potassium iodide, was added to the suspension which was then heated on a steam-bath for 5 min. The solution was adjusted to pH 4·8 with 2N-potassium carbonate and chilled. The 2-hydroxy-1,4,5-triazanaphthalene (65 mg.) was filtered off and recrystallized from water to give material identical with the above (Found: C, 57·25; H, 3·6; N, 28·9%).

Ethyl 3-*Nitro*-2-*pyridylaminoacetate* (IV).—10N-Sodium hydroxide (9·5 ml.) was added during 5 min. to a cooled, stirred suspension of ethyl aminoacetate hydrochloride (10 g.), water (5 ml.), and xylene (18 ml.), and stirring continued for 15 min. Potassium carbonate was added to form a paste. The xylene was decanted and the paste extracted with xylene (3 × 18 ml.). The extracts were dried (K_2CO_3) and added dropwise to a refluxing solution of 2-chloro-3-nitropyridine [5] (2 g.) in xylene (10 ml.), and refluxing was continued for 2 hr. (reactivity is slight at the temperature of boiling benzene). The precipitate from the chilled mixture was washed with xylene and discarded. The combined filtrates were evaporated and the yellow residue was chromatographed in benzene over alumina. The main yellow band was collected, and on fractionation gave *ethyl* 3-*nitro*-2-*pyridylaminoacetate* (2·3 g.), b. p. 143°/0·25 mm. (Found: C, 47·8; H, 4·8; N, 18·55. $C_9H_{11}N_3O_4$ requires C, 48·0; N, 4·9; N, 18·7%).

3,4-*Dihydro*-2-*hydroxy*-1,4,5-*triazanaphthalene*. A solution of stannous chloride dihydrate (6 g.) in 10N-hydrochloric acid (6 ml.) was added dropwise, during 10 min., to a stirred solution of the above ester (1 g.) in alcohol (20 ml.). The solution, which became hot, was stirred for 75 min. more, and chilled overnight. A solution of the precipitate in warm water (10 ml.) was adjusted to pH 3—3·5 with 5N-potassium hydroxide, then boiled and filtered from oxides of tin. The filtrate, when adjusted to pH 7 and chilled, deposited 3,4-*dihydro*-2-*hydroxy*-1,4,5-*triazanaphthalene* (0·75 g.). This gave colourless crystals (from ethanol), m. p. 287—289° (Found: C, 56·3; H, 5·0; N, 28·2. $C_7H_7N_3O$ requires C, 56·4; H, 4·7; N, 28·2%), infrared $\nu_{max.}$ 2830 (NH stretching) and 1683 (C=O stretching) cm.$^{-1}$.

2,3-*Dihydroxy*-1,4,5-*triazanaphthalene*.—(*a*) 2,3-Diaminopyridine (0·55 g.), N-hydrochloric acid (4 ml.), and diethyl oxalate (1·1 g.) were refluxed for 1 hr. The mixture was adjusted to pH 3·5 and chilled. The 2,3-*dihydroxy*-1,4,5-*triazanaphthalene* (0·5 g.) was filtered off and recrystallized from water. It melted above 310° (Found: C, 51·7; H, 3·2; N, 25·25. $C_7H_5N_3O$ requires C, 51·5; H, 3·1; N, 25·8%), $\nu_{max.}$ 3220 + 2720 (NH stretching), 1725 + 1679 (C=O stretching) cm.$^{-1}$, and was identical in R_F and infrared spectra with the products obtained as in (*b*), (*c*), and (*d*), below.

(*b*) Potassium ferricyanide (4 g.), dissolved in a little water was added to a solution of 3,4-dihydro-2-hydroxy-1,4,5-triazanaphthalene (0·25 g.) in 5N-potassium hydroxide (5 ml.). The mixture was set aside at 20° for 5 hr. and adjusted to pH 4·6. The 2,3-dihydroxy-1,4,5-triazanaphthalene (0·22 g.) was filtered off and recrystallized from water (Found: C, 51·3; H, 3·2; N, 25·5%).

(*c*) 2-Hydroxy-1,4,5-triazanaphthalene (0·1 g.), similarly oxidized, gave 2,3-dihydroxy-1,4,5-triazanaphthalene (65 mg.) (Found: C, 51·7; H, 3·2; N, 25·55%).

(*d*) 3-Hydroxy-1,4,5-triazanaphthalene (0·1 g.), similarly oxidized, gave 2,3-dihydroxy-1,4,5-triazanaphthalene (95 mg.) (Found: C, 51·7; H, 3·3; N, 25·6%).

2,3,6-*Triaminopyridine*.—A solution of sodium nitrite (7 g.) in water (30 ml.) was chilled and added to a stirred solution of aniline (8·6 g.) in 5N-hydrochloric acid at <10°. 2,6-Diaminopyridine (10 g.), suspended in water (40 ml.), was dissolved by dropwise addition of 10N-hydrochloric acid. To this solution, stirred and cooled to 5°, the solution of benzenediazonium chloride was added dropwise. Stirring was continued for 30 min. The solution was neutralized with sodium acetate. The yellow product was filtered off and, recrystallized

[13] Rigby, *J.*, 1950, 1907.

once from ethanol, gave 2,6-diamino-3-phenylazopyridine (12 g.), m. p. 130°. This substance (10 g.) was dissolved in ethanol (500 ml.), and hydrogenated over 5% palladium–charcoal catalyst (2 g.) at 20°/710 mm. 10N-Hydrochloric acid (40 ml.) was added, and the solution filtered. The catalyst was washed with water. The combined washings were evaporated to dryness, and the residue, recrystallized from 6N-hydrochloric acid, gave 2,3,6-triaminopyridine dihydrochloride (7 g.), m. p. 268° (lit.,[7] 270—271°).

6-*Amino*-1,4,5-*triazanaphthalene*, prepared from 2,3,6-triaminopyridine dihydrochloride and glyoxal, had m. p. 268—270° (lit.,[8] 267°) (Found: C, 57·7; H, 4·2; N, 38·4. Calc. for $C_7H_6N_4$: C, 57·5; H, 4·1; N, 38·3%).

Oxidation of 1,4,5-*Triazanaphthalene*.—Hydrogen peroxide (30% w/v; 0·6 ml., 4 equiv.), and 1,4,5-triazanaphthalene (0·2 g.) in 5N-sulphuric acid (2 ml.), were mixed and set aside at 20° for 24 hr. The solution was adjusted to pH 5·0 and evaporated to dryness. The residue, extracted with boiling ethanol, gave 6-hydroxy-1,4,5-triazanaphthalene (0·17 g.), m. p. 244° (lit.,[9] 246—248°) (Found: C, 57·3; H, 3·4; N, 28·1. Calc. for $C_7H_5N_3O$: C, 57·1; H, 3·4; N, 28·6%), $\nu_{max.}$ 2840 (NH stretching), 1692 + 1671 (C=O stretching) cm.$^{-1}$. The infrared spectrum was identical with that of an authentic specimen.[9]

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