## 824. *Covalent Hydration in* 1,4,5,8-*Tetra-azanaphthalenes.*

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In aqueous solution 1,4,5,8-tetra-azanaphthalene and its 2-methyl and 2,3-dimethyl derivatives are covalently hydrated as the cations. However, their neutral molecules, and the neutral molecules and cations of the 2,3,6-trimethyl and 2,3,6,7-tetramethyl derivatives, are predominantly anhydrous. The structures (VIII; R = R′ = H; R = Me, R′ = H; and R = R′ = Me, respectively) are assigned to the hydrated cations.

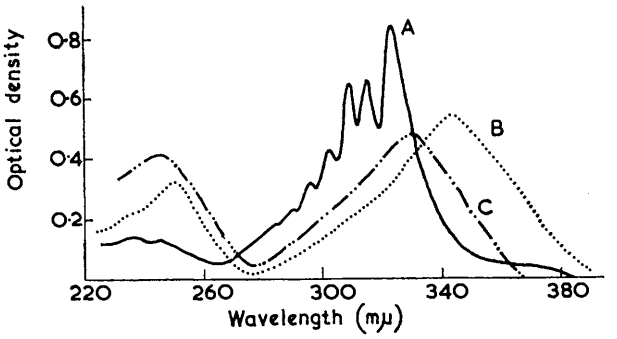
Covalent hydration has been demonstrated in the cations of a number of condensed pyrimidine heterocycles. These include quinazoline (5,6-benzopyrimidine),[1] 1,3,5-, 1,3,7-, and 1,3,8-triazanaphthalenes (pyridopyrimidines),[2] and pteridines (pyrazinopyrimidines).[3] An extension of this work is to find out if water can be added across the carbon–nitrogen double bond in condensed pyrazine nuclei which are unsubstituted, *e.g.*, in quinoxaline, 1,4,5- and 1,4,6-triazanaphthalene, and 1,4,5,8-tetra-azanaphthalene.

The neutral molecule of quinoxaline in water is anhydrous, for the ultraviolet spectra in water and in cyclohexane are closely similar.[4] In the present work it is shown that the cation also is anhydrous, because the spectra in aqueous acid and in anhydrous dichloroacetic acid are similar. The observed low p$K_a$ value of quinoxaline (0·56) [5] is compatible with its anhydrous nature because hydration would make one of the nitrogen atoms more strongly basic. 1,4,6-Triazanaphthalene has been shown to be covalently hydrated, though only in the cation,[6] and this hydration takes place in the pyrazine ring.[7] The neutral molecule and cation of 1,4,5-triazanaphthalene in water are anhydrous.[7]

[1] Albert, Armarego, and Spinner, *J.*, 1961, 2689, 5267.
[2] Armarego, *J.*, 1962, 4094.
[3] Perrin, *J.*, 1962, 645.
[4] Hirt, King, and Cavagnol, *J. Chem. Phys.*, 1956, **25**, 574.
[5] Albert and Phillips, *J.*, 1956, 1294.
[6] Inoue and Perrin, *Proc. Chem. Soc.*, 1960, 342.
[7] Albert and Barlin, *J.*, 1963, in the press.

The aim of the present investigation was to increase the electron deficiency on the carbon atoms in the last-named substance in order to facilitate water addition, *e.g.*, by introducing another nitrogen atom in the pyridine ring.[8] The results obtained with such a substance, 1,4,5,8 tetra-azanaphthalene (pyrazinopyrazine), will now be described.

1,4,5,8-*Tetra-azanaphthalene.*—The ultraviolet absorption spectrum of 1,4,5,8-tetra-azanaphthalene in water at pH 7·0 has two main bands. The band at the longer wavelength has much fine structure (see Figure). In addition, there is a weak band with a




Ultraviolet spectra (in water) of 1,4,5,8-tetra-azanaphthalene: (A) neutral species (pH 7·0); (B) hydrated cation (pH 0·5); (C) hydrated neutral species (pH 8·1).

flat maximum at 375 mμ which is due to the $n \rightarrow \pi^*$ transition. This characteristic spectrum was unchanged at 20° for 5 days, and it was almost unchanged in cyclohexane; hence, because the neutral species is anhydrous in the solid state, it must also be so in water. In aqueous acid, all the fine structure disappears and the long-wavelength band moves further (20 mμ) towards the visible region.

During spectrophotometric determination of the ionisation constant, the optical density readings at 344 mμ reached a steady value rapidly at low pH values but took progressively longer as the pH was increased. Thus, at pH 3·26, about 18 hours was

TABLE 1.

Ionisation constants in $H_2O$ at 20°.

| Substance | p$K_a$ | Spread (±) | Concn. ($10^{-4}$M) | λ * (mμ) |
|---|---|---|---|---|
| 1,4,5,8-Tetra-azanaphthalene | 2·51 † | 0·03 | 0·25 | 344 |
| 2-Methyl- | 1·14 † | 0·03 | 0·50 | 350 |
| 2,3-Dimethyl- | −0·25 | 0·03 | 0·20 | 329 |
| 2,3,6-Trimethyl- | −0·53 | 0·04 | 0·20 | 345 |
| 2,3,6,7-Tetramethyl- | −0·02 | 0·03 | 0·40 | 374 |
| Pyrazines | | | | |
| 2-Amino-5,6-dimethyl- | 3·89 | 0·01 | 0·40 | 350 |
| 2,3-Diamino- | 4·88 ‡ | 0·04 | 0·80 | 255 |
| | 0·76 § | 0·10 | 0·80 | 255 |
| 2-Amino-3-dimethylamino- | 4·29 | 0·02 | 0·40 | 375 |
| | −0·24 § | 0·05 | 0·40 | 375 |
| 2,3-Diamino-5,6-dimethyl | 5·36 | 0·02 | 0·40 | 375 |
| | 1·23 § | 0·05 | 0·40 | 375 |
| 2-Amino-3-dimethylamino-5,6-dimethyl- | 4·88 | 0·02 | 0·25 | 370 |
| | −0·18 § | 0·05 | 0·25 | 400 |

* Analytical wavelength. † Equilm. readings taken after 24 hr. ‡ Cf. 2-aminopyrazine 2·93 (Cheeseman, *J.*, 1962, 242). § Hammett functions at which 50% of base is protonated.

necessary to obtain a steady reading. [The equilibrium figures gave a p$K_a$ value of 2·51 (see Table 1).] That no degradation had occurred during the measurement was shown when the original spectrum of the neutral species was obtained by adjusting an acid

[8] Albert, " Heterocyclic Compounds," Athlone Press, London, 1959, p. 40.

solution, which had been kept for 24 hr. at 20°, from pH 0·0 to pH 6·0 and then setting it aside for 6 days. The anomalous nature of the cation, as revealed by the slow equilibration, suggested that either covalent hydration or ring opening had occurred.

When an acid solution of the anomalous cation was immediately mixed (within 1 second) with a buffer solution containing an equivalent of alkali to give a final pH of 8·1, the spectrum of a new substance (shown later to be the hydrated neutral molecule, see Figure) was obtained. It was similar to that of the anomalous cation but displaced to shorter wavelengths. At this high pH, the spectrum altered only slowly, but after 16 days at 20° it had completely changed to the characteristic spectrum of the anhydrous neutral molecule. By observing the rate of change of optical density at 309 mμ after rapid neutralisation at 23·8°, it was found that the decomposition of the new substance followed first-order kinetics. When the final buffers had pH 0·21, 0·98, and 2·05 the first-order constants observed were 0·385, 0·073, and 0·0106 sec.$^{-1}$ and the half-lives were 1·9, 9·5, and 65 sec., respectively. The conversion of the anomalous into the anhydrous neutral species is thus acid-catalysed, which explains the drifts during the establishment of equilibrium in the above p$K_a$ determination.

That water was involved in the formation of the anomalous cation was shown by examining the spectrum of 1,4,5,8-tetra-azanaphthalene in anhydrous dichloroacetic acid ($H_0$ — 0·9);[1] except for small solvent shifts, it was similar to that of the anhydrous neutral molecule. The anhydrous cation of 1,4,5,8-tetra-azanaphthalene (predicted p$K_a$ —2·7, see below) should not be formed in anhydrous or aqueous dichloroacetic acid. However, gradual addition of water to the acid solution of the base caused appearance of the band at 348 mμ, due to the anomalous cation, and a corresponding decrease in the optical densities of the peaks at 324, 317, and 310 mμ. At a concentration of 1·5% by weight of water in dichloroacetic acid, 50% of the anomalous cation was formed. The other bands

TABLE 2.

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

| Substituents | Species[b] | $\lambda_{max.}$ (mμ) | log ε | pH or $H_0$ |
|---|---|---|---|---|
| | | 1,4,5,8-*Tetra-azanaphthalenes* | | |
| Unsubst. | ANM | *224* + *230* + 237 + 245; *278* + *238* + 290 + 296 + 302 + 308 + 315 + 322; 375[c] | *3·38* + *3·31* + 3·30 + 3·15; *3·39* + *3·57* + 3·70 + 3·85 + 3·98 + 4·16 + 4·15 + 4·26; 2·33 | 7·0 |
| | ANM | *224* + 232 + 239 + 247; *273* + *278* + 283 + 289 + 295 + 301 + 307 + 314 + 321; 402[c] | *3·40* + 3·33 + 3·26 + 3·22; *3·08* + *3·29* + 3·51 + 3·71 + 3·86 + 3·96 + 4·11 + 4·08 + 4·27; 2·36[c] | — |
| | ANM | 310 + 317 + 324; *350* | 4·04 + 4·05 + 4·16; *3·26* | −0·9 |
| | HC | 250; 342 | 4·02; 3·79 | 0·5 |
| | HNM[g] | 244; 331 | 3·92; 3·97 | 8·1 |
| 2-Methyl- | ANM | *224* + *238* + *247*; *288* + *294* + 300 + 306 + 313 + 320 + 327; *360* | *3·48* + *3·22* + *3·04*; *3·65* + *3·73* + 3·90 + 4·03 + 4·19 + 4·18 + 4·28; *2·49* | 7·0 |
| | ANM | *240* + *248*; *275* + *281* + *287* + 292·5 + 298·5 + 304·5 + 311·5 + 318 + 325; 401 | *3·24* + *3·08*; *3·12* + *3·36* + *3·58* + 3·74 + 3·90 + 3·99 + 4·16 + 4·13 + 4·27; 2·17 | —[h] |
| | ANM | *308* + 316 + 322 + 330 | *3·69* + 3·85 + 3·87 + 3·99 | −0·9[f] |
| | HC | 246; 365 | 3·81; 4·12 | −2·0 |
| 2,3-Dimethyl- | ANM | *225* + *240* + *248*; *295* + *303* + *309* + 315·5 + 322 + 329; *362* | *3·51* + *3·25* + *3·12*; *3·70* + *3·94* + *4·07* + 4·24 + 4·21 + 4·30; *2·67* | 7·0 |
| | ANM | *227* + *233* + 241·5 + 249·5; *283* + *289* + 294 + 300 + 306·5 + 313 + 320 + 327; 390 | *3·48* + *3·34* + 3·14 + 3·04; 3·47 + 3·61 + 3·75 + 3·90 + 4·01 + 4·19 + 4·16 + 4·27; 2·25 | —[d] |
| | ANM | *312* + *320* + 324 + 333 | *3·97* + *4·11* + 4·12 + 4·18 | −0·9[f] |
| | HC | 246; 378 + *394* | 3·88; 4·09 + *4·02* | −2·28 |

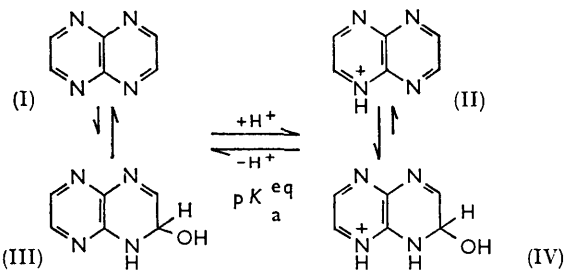
TABLE 2. (*Continued.*)

| Substituents | Species [b] | $\lambda_{max.}$ (mμ) | log ε | pH or $H_0$ |
|---|---|---|---|---|
| 2,3,6-Trimethyl- | ANM | 208 + *226*; *283* + *299* + *307* + *313* + 320 + 326·5 + 334·5 | 4·24 + *3·61*; *3·42* + *3·72* + *3·97* + *4·09* + 4·26 + 4·24 + 4·33 | 7·0 |
| | ANM | *226*; *280* + *286* + 292 + 297 + 303·5 + 310 + 317 + 324 + 331·5; 390 | *3·61*; *3·28* + *3·53* + 3·68 + 3·80 + 3·94 + 4·07 + 4·25 + 4·23 + 4·33; 2·35 | —[d] |
| | AC | *331* + 340; 387 | *4·18* + 4·21; 2·98 | −0·9[f] |
| | AC [i] | 212 + *234*; *332* + 343; 373 + *401* | 3·98 + *3·63*; *4·10* + 4·18; 3·71 + *3·51* | −2·76 |
| 2,3,6,7-Tetramethyl- | ANM | 209 + 241 + *230*; 280 + *308* + 322 + 329 + 337 | 4·22 + 4·20 + *3·60*; 3·35 + *4·00* + 4·29 + 4·26 + 4·34 | 7·0 |
| | ANM | *235* + *250*; *288* + 293 + 299·5 + 306 + 313 + 319 + 326 + 334; 378 | *3·57* + *3·11*; *3·57* + 3·67 + 3·76 + 3·96 + 4·09 + 4·27 + 4·24 + 4·36; 2·52 | —[h] |
| | AC | *336* + 347 | *4·26* + 4·29 | −0·9 |
| | AC | 215 + *235*; *335* + 346 | 4·10 + *3·52*; *4·29* + 4·34 | −2·3 |
| | | *Quinoxaline* [j] (for comparison) | | |
| | AC | 242 + *244* + 331 | 4·40 + *4·38*; 3·85 | −2·1 |
| | AC | 333 | 3·90 | 0·9[f] |
| | | *Pyrazines* | | |
| 2-Amino-5,6-dimethyl- | NM | 232; *284* + 322 | 4·02; *3·21* + 3·81 | 7·0 |
| | C | 234; 345 | 4·06; 3·91 | 1·0 |
| 2,3-Diamino- | NM | 239; 321 | 3·95; 3·90 | 7·0 |
| | MC | 245; 331 | 3·99; 3·96 | 2·8 |
| | DC | 242; 341 | 3·97; 3·99 | −1·38 |
| 2-Amino-3-dimethyl-amino- | NM | 250; 327 | 3·81; 3·88 | 7·0 |
| | MC | 260; 345 | 3·80; 3·91 | 2·0 |
| | DC | 258; 363 | 3·96; 3·99 | −2·28 |
| 2,3-Diamino-5,6-dimethyl- | NM | 237; 335 | 3·98; 3·96 | 8·0 |
| | MC | 244; 352 | 3·92; 4·01 | 3·3 |
| | DC | 242; 366 + *380* | 4·03; 4·14 + *3·97* | −1·12 |
| 2-Amino-3-dimethyl-amino-5,6-dimethyl- | NM | 245; 339 | 3·87; 3·93 | 7·0 |
| | MC | 249; 358 | 3·83; 3·99 | 2·5 |
| | DC | 259; 390 | 3·95; 4·06 | −2·28 |

[a] Inflexions are in italics. [b] NM = neutral molecule, ANM = anhydrous neutral molecule, HNM = hydrated neutral molecule, AC = anhydrous cation, HC = hydrated cation, MC = monocation, and DC = dication. [c] Flat maximum. [d] In cyclohexane. [e] This $n \rightarrow \pi^*$ band is from Mason (*J.*, 1962, 493). [f] In anhydrous dichloroacetic acid. [g] This spectrum was obtained by rapidly neutralising a solution of the hydrated cation in a buffer at pH 8·1. [h] In a 0·1% solution of chloroform in cyclohexane. [i] This contains a trace of hydrated cation. [j] The $pK_a$ is 0·56 ± 0·04 (cf. ref. 5).

at lower wavelengths could not be observed because the transparency limit of dichloroacetic acid is *ca.* 300 mμ.

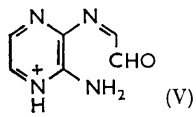
The observed value of 2·51 is an equilibrium $pK_a$ ($pK_a^{eq}$) which includes protonation and covalent hydration, as shown in the equilibria between (I), (II), (III), and (IV):

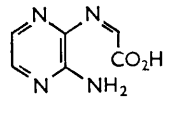



Similar equilibria occur with quinazolines,[9] pteridines,[3] and some triazanaphthalenes.[2]

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

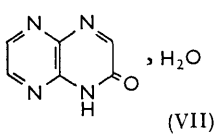
It is, however, also conceivable, that formation of the hydrated cation is very fast at all pH values and is followed by a slow rate-determining ring-opening of the cation (IV) to give the aldehyde (V) by a simple prototropic shift. The second possibility was excluded on the following grounds: (*a*) Acid solutions of 1,4,5,8-tetra-azanaphthalene, mixed with buffered solutions of *p*-nitrophenylhydrazine to give finally pH 2·5, 1·0, and 0·0, were unchanged at 20° for 2 hr. Controls with glyoxal, glyoxal diethyl monoacetal, and *o*-aminobenzaldehyde gave immediate precipitates, or colours, of the hydrazones. (*b*) One equivalent of hydrogen peroxide at 20° converted 1,4,5,8-tetra-azanaphthalene in N-sulphuric acid in 3 days into a highly insoluble material which, after filtration and drying in air (in order to avoid the possibility of ring closure by heat), had the formula $C_6H_4N_4O_2,\frac{1}{4}H_2O$. Its infrared spectrum was identical with that of 2,3-dihydroxy-1,4,5,8-tetra-azanaphthalene (except for the 2500—3300 cm.$^{-1}$ water region) and included strong carbonyl bands at 1720 and 1680 cm.$^{-1}$. The authentic dihydroxy-compound was prepared by condensing 2,3-diaminopyrazine with diethyl oxalate and heating the product at 230° for 3 hr. to complete ring closure. This evidence, therefore, supports the structure (IV) for the anomalous cation, and consequently (III) for the anomalous neutral molecule, because the ring-opened structure (V) would have oxidised

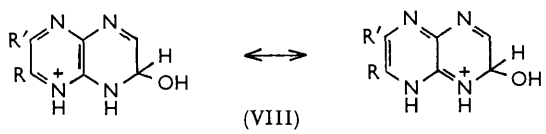

(V)


(VI)

to the acid (VI) under these conditions. (*c*) A detailed kinetic study [10] of the hydration-dehydration process in azaheterocycles has shown it to be acid- and base-catalysed, to follow first-order kinetics when one water molecule is involved, and to be measurably slow in the pH region 1·0—11.

Although the dihydroxy-compound was the only product isolated from the mother-liquors of the above oxidation, it seems that oxidation of the hydrated cation gave 2-hydroxytetra-azanaphthalene (itself readily hydrated across the 3,4-double bond) and was followed by further rapid oxidation to the dihydroxy-compound. This is not unlikely because 2-hydroxy-1,4,5-triazanaphthalene is known to be hydrated [7] (in the cation) to a small extent. An attempt was thus made to prepare 2-hydroxy-1,4,5,8-tetra-azanaphthalene by condensing 2,3-diaminopyrazine with ethyl glyoxylate hemiethyl acetal. The slightly soluble product gave analytical figures for $C_6H_6N_4O_2$, indicating that it had formula (VI) or (VII). It gave one carbonyl band, at 1700 cm.$^{-1}$, and the structure (VI) was excluded on the evidence that the infrared spectrum was unchanged (except for the 2500—3300 cm.$^{-1}$ region) after 1½ hours' heating at 180°. Oxidation at 20° with hydrogen peroxide in 2N-sulphuric acid gave only 2,3-dihydroxy-1,4,5,8-tetra-azanaphthalene, in 50% yield.


(VII)


(VIII)

The anomalous cation of 1,4,5,8-tetra-azanaphthalene can therefore be written as the covalently hydrated cation (VIII; R = R′ = H) which is stabilised by a 2-amino-pyridine type of resonance. The cation of 1,4,5-triazanaphthalene, however, is anhydrous although a similar resonance is possible. The reason for hydration in 1,4,5,8-tetra-azanaphthalene may well be due to the higher content of doubly bound nitrogen atoms which cause a sufficiently strong electron-deficiency at the carbon atoms. Since hydration is a slow equilibrium process, the 2-aminopyridine type of resonance, although

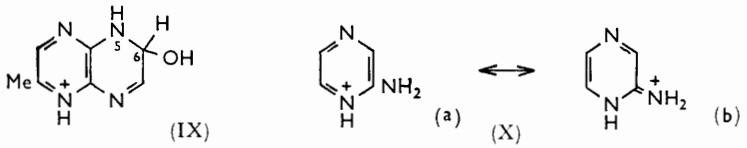
[10] Inoue and Perrin, *J. Phys. Chem.*, 1962, **66**, 1689; *J.*, 1962, 2600; and personal communication.

involving little energy change, must play a significant part. Hydration in 1,4,5,8-tetra-azanaphthalene is thus intermediate between those of pteridine [3] (which is hydrated to the extent of ~22% in the neutral molecule, and almost completely in the cation which slowly undergoes ring opening) and 1,4,5-triazanaphthalene.

*C-Methyl derivatives of* 1,4,5,8-*Tetra-azanaphthalene.*—The replacement of a hydrogen atom by a methyl group, on the carbon atom that undergoes attack by $OH^-$ or water molecules in the hydration of azaheterocycles, has been shown to inhibit hydration to a large degree.[1,3,10,11] This effect can be demonstrated in the 1,4,5,8-tetra-azanaphthalenes. 2,3,6,7-Tetramethyl-1,4,5,8-tetra-azanaphthalene is a weak base ($pK_a$ −0·02; see Table 1) and its neutral molecule is anhydrous, as shown by the similarity of the spectra in water and in cyclohexane. Its cation in water shows small bathochromy (9 mμ) when compared with the neutral molecule. The spectrum in dichloroacetic acid, where 90% of the molecules are protonated, is identical with that in aqueous acid (see Table 2) and addition of water does not alter the spectrum. With this compound as the standard for this series, and 0·8 * and 0·3 $pK_a$ unit as the base-strengthening effect of a methyl group when in the protonated and the unprotonated ring, respectively, the $pK_a$ values predicted for 2,3,6-trimethyl-, 2,3-dimethyl-, 2-methyl-, and unsubstituted 1,4,5,8-tetra-azanaphthalene become about −0·8, −1·1, −1·9, and −2·7, respectively.

By this method, it was shown that the neutral molecules of the trimethyl; 2,3-dimethyl; and monomethyl-1,4,5,8-tetra-azanaphthalene were anhydrous. The cation of the 2,3,6-trimethyl compound was almost fully anhydrous. 2,3-Dimethyl-1,4,5,8-tetra-azanaphthalene cation was predominantly hydrated since in dichloroacetic acid, where ~80% of cation should be present if the $pK_a$ (Table 1) refers to the anhydrous cation, the spectrum was essentially that of the anhydrous neutral molecule. Similarly, the cation of the 2-methyl derivative was predominantly hydrated in aqueous solution. In both cases addition of water to the dichloroacetic acid solutions caused the appearance of the bands, at ~380 and 360 mμ, respectively, corresponding to the hydrated cations. These results are in agreement with the ionisation constants. Whereas the $pK_a$ value of the trimethyl derivative differs but little from the predicted value, the difference is large in the di- and the mono-methyl derivatives. This apparently base-weakening effect of *C*-methyl groups has been found also in the 2-aminopteridine series.[11]

The structure (VIII; R = R′ = Me) for the hydrated cation of 2,3-dimethyl-1,4,5,8-tetra-azanaphthalene is derived from its analogy with the parent substance, and the two available positions (*i.e.*, 2 and 3) for hydration are equivalent. The case is somewhat different with the 2-methyl-1,4,5,8-tetra-azanaphthalene cation because there are two possibilities. 7,8-Addition is favoured because the resonance-stabilised cation (VIII; R = Me, R′ = H) is formed. No such stabilisation is possible if the 5,6-position is hydrated (*i.e.*, IX).




(IX) (X)

*Aminopyrazines.*—The physical properties of five aminopyrazines have been determined and are given in Tables 1 and 2. The basic strength of 2-aminopyrazines increases on introduction of a second amino-group in position 3. However, the first dissociation of 2,3-diaminopyrazines decreases when two methyl groups are introduced into one of the amino-groups. Cheeseman [12] has shown that in 2-aminopyrazine, protonation occurs

* Compare the $pK_a$ values of 0·6, 1·4, and 3·7 for pyrazine, 2-methylpyrazine, and 2,3,5,6-tetramethylpyrazine (ref. 8, p. 345).

[11] Albert, Howell, and Spinner, *J.*, 1962, 2595.
[12] Cheeseman, *J.*, 1962, 242.

on N-1 and, as with 2-aminopyridine, the resonance structure (X) can be written for the cation. The base-weakening effect in 2-amino-3-dimethylaminopyrazines can be attributed to the lack of significant contribution from (X; b) on account of steric hindrance. The ultraviolet spectra show two bands in all three species. The long-wavelength band moves progressively towards the visible region on going from neutral molecule to monocation and then to dication.

## 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.[9]

2,3-*Diaminopyrazine*.—Diethylmalonate (400 g.) was nitrosated as described previously,[13] but it was necessary to wash the nitroso-compound with 20% urea solution. The undistilled product, in half its volume of ethanol, was hydrogenated with 5% palladium–charcoal (15 g.) at 100—50 atm. below 40° and reduction required 8—10 hr. No hydrogen uptake occurred at atmospheric pressure of hydrogen (cf. ref. 12). Ethyl aminomalonate was obtained in 74% overall yield and had b. p. 108°/1·4 mm.; it was converted to aminomalondiamide as described.[12] Attempts to convert the diamide into 2-hydroxypyrazine-3-carboxamide by the method of Muehlmann and Day [14] were unsatisfactory but Jones's method,[15] on a 50-g. scale, gave 79% of the hydroxy-amide. This was degraded with potassium hypobromite,[16] on a 40-g. scale, to give a 74—84% yield of 2-amino-3-hydroxypyrazine, m. p. 290—295° (decomp.) [lit.,[16] 292—298° (decomp.)]. 2-Amino-3-chloropyrazine (40—70% yield), m. p. 168—169° (lit.,[16] 168°), was prepared from the hydroxy-compound (5 g.) and phosphorus oxychloride (20 ml.) (the recommended addition of water [14] was found inadvisable) in a sealed tube at 118° for 6 hr.

2-Amino-3-chloropyrazine (8 g.), aqueous ammonia (*d* 0·880; 80 ml.), liquid ammonia (80 ml.), and a trace of copper bronze were heated in a steel tube at 135° for 24 hr. The solution in water (100-ml. portions) was repeatedly evaporated to dryness. The residue was boiled with ethyl acetate (50 ml.), and the mixture was filtered; the insoluble 2,3-diaminopyrazine (70—80%), m. p. 195—200° (lit.,[14,16] 203°), was used in the subsequent condensations.

2,3-*Diamino*-5,6-*dimethylpyrazine*.—2-Amino-5,6-dimethylpyrazine-3-carboxylic acid [17] (13 g.) and diphenyl ether (40 ml.) were heated at 210—217° for 15 min., cooled, diluted with chloroform (200 ml.), boiled with charcoal, and filtered, and the chloroform was removed *in vacuo*. The residue was diluted with light petroleum (b. p. 40—60°); 2-amino-5,6-dimethylpyrazine (8·3 g., 80%) was filtered off and, after recrystallisation from benzene–light petroleum (b. p. 40—60°), had m. p. 147—148° (lit., 151° and 140—144°, where carbitol acetate [18] and sulphuric acid,[19] respectively, were used for decarboxylation) (Found: C, 58·5; H, 7·35; N, 33·7. Calc. for $C_6H_9N_3$: C, 58·5; H, 7·4; N, 34·1%). This amine was brominated and aminated as before.[17]

2-*Amino*-3-*dimethylaminopyrazine*.—2-Amino-3-chloropyrazine (1 g.), 30% aqueous dimethylamine (8 ml.), and a trace of copper bronze were heated in a sealed tube at 120—130° for 24 hr. 2-*Amino*-3-*dimethylaminopyrazine* (0·75 g., 75%) separated on cooling, sublimed at 100°/0·02 mm., and after recrystallisation from light petroleum (b. p. 60—80°) had m. p. 110—111° (Found: C, 52·3; H, 7·3; N, 40·8. $C_6H_{10}N_4$ requires C, 52·15; H, 7·3; N, 40·55%).

2-*Amino*-3-*dimethylamino*-5,6-*dimethylpyrazine*.—This *base* was obtained in 98% yield from 2-amino-3-bromo-5,6-dimethylpyrazine by the above method and had m. p. 108—109° (Found: C, 58·0; H, 8·6; N, 33·7. $C_8H_{14}N_4$ requires C, 57·8; H, 8·5; N, 33·7%).

1,4,5,8-*Tetra-azanaphthalene* (by H. T. Openshaw and G. K. Ruffell).—2,3-Diaminopyrazine (0·7 g.), dissolved in a mixture of 50% w/w aqueous glyoxal (1·35 g.) and water (10 ml.), was heated on a steam-bath for 5 min.; the yellow crystals (0·65 g.) were collected, sublimed at 170°/0·75 mm., and recrystallised from water, giving 1,4,5,8-*tetra-azanaphthalene*, decomp.

[13] Day and Schipper, *J. Amer. Chem. Soc.*, 1952, **74**, 350.
[14] Muehlmann and Day, *J. Amer. Chem. Soc.*, 1956, **78**, 242.
[15] Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 78.
[16] McDonald and Ellingson, *J. Amer. Chem. Soc.*, 1947, **69**, 1034.
[17] Weijlard, Tishler, and Erickson, *J. Amer. Chem. Soc.*, 1945, **67**, 802.
[18] Ellingson and Henry, *J. Amer. Chem. Soc.*, 1948, **70**, 1257.
[19] Albert and Pedersen, *J.*, 1956, 4683.

>270° (Found: C, 54·6; H, 3·0; N, 42·5. $C_6H_4N_4$ requires C, 54·5; H, 3·05; N, 42·4%). The present author finds this method satisfactory also with larger quantities.

2-*Methyl*-1,4,5,8-*tetra-azanaphthalene*.—2,3-Diaminopyrazine (0·25 g., 1 mol.) in ethanol (5 ml.), and a solution of 25% aqueous methylglyoxal (0·64 ml.; 1·3 equiv.), gave yellow needles after 24 hr. at 20°. Paper chromatography showed the reaction to be incomplete in 3 hr. Sublimation at 120—130°/0·02 mm. and recrystallisation from ethanol gave 2-*methyl*-1,4,5,8-*tetra-azanaphthalene*, m. p. 196—197° after change of colour to orange at ~170° (Found: C, 57·5; H, 4·2; N, 38·6. $C_7H_6N_4$ requires C, 57·5; H, 4·1; N, 38·3%).

2,3-*Dimethyl*-1,4,5,8-*tetra-azanaphthalene*.—The preparation reported [18] gave very poor yields and the following is an application of the method used for 1,4,6-triazanaphthalene.[19] 2,3-Diamino-5,6-dimethylpyrazine (0·5 g., 1 mol.) in ethanol (10 ml.), and glyoxal monohydrate (0·32 g., 1·15 equiv.) were refluxed for 1 hr., filtered, and cooled. 2,3-Dimethyl-1,4,5,8-tetra-azanaphthalene (0·35 g., 60%) separated as yellow needles and, after sublimation at 130—140°/0·02 mm. and recrystallisation from ethanol had m. p. 215—216° (lit.,[18] 216°) (Found: C, 60·0; H, 5·0; N, 34·9. Calc. for $C_8H_8N_4$: C, 60·0; H, 5·0; N, 35·0%).

2,3,6-*Trimethyl*-1,4,5,8-*tetra-azanaphthalene*.—2,3-Diamino-5,6-dimethylpyrazine (0·5 g., 1 mol.) in ethanol (10 ml.) and 25% aqueous methylglyoxal (1·25 ml., 1·2 equiv.) were set aside at room temperature for 4 days. The dark solution was evaporated, and the residue was dissolved in benzene, boiled with charcoal, filtered, and evaporated. The benzene solution was passed through an alumina column (6 × ½ in.; B.D.H.) which was eluted with benzene. The yellow eluates were evaporated; the residue, sublimed at 120—130°/0·3 mm. and recrystallised from benzene–light petroleum (b. p. 40—60°), gave 2,3,6-*trimethyl*-1,4,5,8-*tetra-azanaphthalene* (0·29 g., 46%), m. p. 152—153° (Found: C, 62·15; H, 5·75; N, 32·1. $C_9H_{10}N_4$ requires C, 62·05; H, 5·8; N, 32·2%).

2,3,6,7-*Tetramethyl*-1,4,5,8-*tetra-azanaphthalene*.—The following is a modification of an earlier preparation.[18] 2,3-Diamino-5,6-dimethylpyrazine (0·5 g.) and diacetyl (0·5 ml.) in water (40 ml.) were refluxed for 25 min. No solid separated on cooling, so boiling was continued for 30 min. and the solution evaporated. The residue in benzene gave the tetramethyl compound (0·36 g., 53%) on addition of light petroleum (b. p. 40—60°); after sublimation at 130—140°/0·3 mm. and recrystallisation from benzene–light petroleum (b. p. 40—60°), this had m. p. 254—256° (darkening) [lit.,[18] 260—261° (decomp.)] (Found: C, 64·0; H, 6·3; N, 29·9. Calc. for $C_{10}H_{12}N_4$: C, 63·8; H, 6·4; N, 29·8%).

2,3-*Dihydroxy*-1,4,5,8-*tetra-azanaphthalene*.—2,3-Diaminopyrazine (0·25 g.) and ethyl oxalate (5 ml.) were refluxed for 3 hr. (reaction was incomplete in 10 min.), then cooled, and the crystals were collected, suspended in 0·5N-hydrochloric acid (60 ml.), and filtered off. After 3 hours' heating at 230° and recrystallisation from dimethylformamide, 2,3-*dihydroxy*-1,4,5,8-*tetra-azanaphthalene* (0·2 g., 54%) had m. p. >360° (Found: C, 44·2; H, 2·5; N, 34·0. $C_6H_4N_4O_2$ requires C, 43·9; H, 2·5; N, 34·1%), $\nu_{max.}$ 1720vs, 1680vs, 1580m, 1485m, 1445ms, 1425w, 1385s, 1330w, 1275m, 1200s, 960w, 885mw, 742m, and 659m cm.$^{-1}$ (KBr disc).

*Oxidation of* 1,4,5,8-*Tetra-azanaphthalene*.—1,4,5,8-Tetra-azanaphthalene (27·4 mg.) in N-sulphuric acid (0·5 ml.) and 30% hydrogen peroxide (0·024 ml., 1 equiv.) were kept at 20° for 3 days. The light brown solid, m. p. >360°, that separated was collected (9·6 mg., 28%), washed with water, and dried in air. A similar experiment with 2 equiv. of hydrogen peroxide gave the same substance (13 mg., 32%) (Found: C, 42·6; H, 2·4; N, 33·3. $C_6H_4N_4O_2,\frac{1}{4}H_2O$ requires C, 42·7; H, 2·7; N, 33·2%).

2-*Hydroxy*-1,4,5,8-*tetra-azanaphthalene*.—2,3-Diaminopyrazine (125 mg.) in N-sulphuric acid (1·2 ml.) and ethyl glyoxylate ethyl hemiacetal (0·22 g., 1·3 ml.) were warmed to dissolve the diamine sulphate and set aside at 20° for 4 days. Sodium citrate (0·12 g.) and water (10 ml.) were added, and the red solid was washed with boiling water and alcohol and collected (142 mg., 75%). It decomposed above 200° (Found: C, 43·7; H, 3·8; N, 33·9. $C_6H_4N_4O,H_2O$ requires C, 43·4; H, 3·6; N, 33·7%), had $\nu_{max.}$ 1700s, 1492ms, 1465s, 1375m, 1285mw, 1220m, 1203s, 1110w, 1070w, 840w cm.$^{-1}$ (KBr disc), and was insoluble in most solvents. After 1½ hours' heating at 180° the infrared spectrum was unaltered except for the 2500—3300 cm.$^{-1}$ region. When 20 mg. of the hydrate were suspended in 2N-sulphuric acid (0·4 ml.) and treated with 30% hydrogen peroxide (0·048 ml., 2 equiv.) the solid that was collected after 2 days at 20° (9·5 mg., 49%) had an infrared spectrum identical with that of 2,3-dihydroxy-1,4,5,8-tetra-azanaphthalene.

Anhydrous dichloroacetic acid for the spectroscopic work was prepared by fractionating

B.D.H. laboratory reagent acid at 720 mm. through a helix-packed, vacuum-jacketed, column (30 × ½ in.), redistilling it, and cooling it at 2° until *ca.* 70% crystallised. The liquid was decanted, the solid liquefied, and the crystallisation repeated. The crystalline product was stored in a desiccator over calcium chloride.

*Physical Properties.*—The rapid reactions were carried out as described [3] but with a Shimadzu model RS 27 recording spectrophotometer, and the rate of change of optical density at a fixed wavelength was measured directly. The ultraviolet spectra were measured on a Perkin-Elmer " Spectracord " model 4000A, and the maxima checked with a Hilger Uvispek mark V manual, instrument; infrared spectra were taken with a Perkin-Elmer 21 double-beam spectrophotometer. Ionisation constants were determined spectrophotometrically by the method used in this Department.[20]

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[20] Albert and Serjeant, " Ionization Constants," Methuen, London, 1962.