

Diquaternary Salts of 1,5- and 1,8-Naphthyridines and the Structure of their Derived Pseudo-bases

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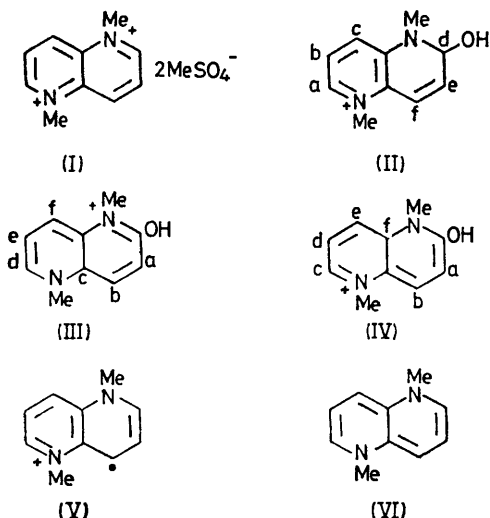
1,5-Naphthyridine and 1,8-naphthyridine react with dimethyl sulphate and with ethylene dibromide, respectively, to form 1,5-dimethyl-1,5-naphthyridinedi-ium dimethosulphate and 5,6-dihydroimidazo[1,2,3-*ij*][1,8]naphthyridinedi-ium dibromide. The salts readily form pseudo-bases. The salt from 1,5-naphthyridine is reduced by a one-electron transfer to give a relatively stable green radical cation.

As a result of our studies¹⁻³ of the relationship between chemical constitution and herbicidal activity in diquaternary salts of 2,2'- and 4,4'-bipyridyls we became interested in the chemistry of diquaternary salts of simple aromatic heterocyclic systems. When this investigation began diquaternary salts of pyrazine and pyrimidine were known⁴ but no diquaternary salt of a naphthyridine had been described. Recently, diquaternary salts of pyridazine have also been reported.⁵ We now report the preparation and some of the properties of diquaternary salts of 1,5- and 1,8-naphthyridines.⁶ Pokorny and Paudler have recently described⁷ diquaternary salts of naphthyridines, including those from 1,5- and 1,8-naphthyridines, but some of our results are not in complete accord with their conclusions.

1,5-Naphthyridine reacted with an excess of dimethyl sulphate to form 1,5-dimethyl-1,5-naphthyridinedi-ium dimethosulphate (I), the structure of which was confirmed by elemental analyses and by its n.m.r. spectrum. The salt (I) was hygroscopic. In aqueous solution it

nitrogen atom and neglect forms containing methylene groups. At pH values below about 5.0 the predominant form was the diquaternary salt (I), the u.v. spectrum in water at pH 0.8, for example, showing maxima at 270, 311, and 323 nm ($\log \epsilon$ 3.79, 3.91, and 4.11). At pH 8.0 the maxima were at 270 and 377 nm ($\log \epsilon$ 4.06 and 3.83). At intermediate pH values the spectrum showed the maxima of both species, which were present in equal amounts at pH 5.2. The n.m.r. spectrum in deuterium oxide containing sodium hydrogen carbonate corresponded to that of the pseudo-base. There was no evidence for the presence of more than one tautomer.

A study of the n.m.r. and u.v. spectra of the pseudo-base eliminated structure (IV) but did not permit a clear choice between structures (II) and (III). In the n.m.r. spectrum (see Experimental section) it was apparent from spin-decoupling experiments that the quartet at δ 6.68–6.94 (1H) was coupled with the doublets at δ 5.81–5.90 (1H) and 7.35–7.52 (1H). The quartet and doublets were not, however, coupled with the multiplet at δ 7.75–8.34, which corresponded to three associated protons. This result eliminates structure (IV), which comprises groups of two (a and b) and four protons (c–f). It is, however, consistent with either structure (II) or (III) which both contain two groups, each of three protons: downfield (II) a–c or (III) d–f, and upfield (II) d–f or (III) a–c. The band at 377 nm in the u.v. spectrum indicated the presence of strongly conjugated chromophores. This result is consistent with the fully conjugated structure (III). It does not, however, completely exclude structure (II). 1,2-Dihydro-1-methyl-1,5-naphthyridine, 1,2-dihydro-2-methoxy-1-methyl-1,5-naphthyridine, and 1,2-dihydro-2-hydroxy-1-methyl-1,5-naphthyridine, which are close relatives of structure (II) exhibit their longest wavelength absorptions at 335, 345, and 342 nm, respectively.⁸ In comparison with these three compounds, structure (II) could be expected to absorb at longer wavelength by virtue of the extra methyl group on the quaternary nitrogen, although the observed shift (30–40 nm) is perhaps more than would be expected (*cf.* ref. 9). Pokorny and Paudler⁷ consider the pseudo-base to have



was in reversible equilibrium with its pseudo-base, for which there are three possible tautomeric forms, (II)—(IV), if we assume complete separation on one

¹ J. E. Dickeson and L. A. Summers, *J. Sci. Food Agric.*, 1969, **20**, 74, and references cited therein.

² A. L. Black and L. A. Summers, *J. Chem. Soc. (C)*, 1971, 2271, and references cited therein.

³ A. L. Black and L. A. Summers, *J. Heterocyclic Chem.*, 1971, **8**, 29.

⁴ T. J. Curphey, *J. Amer. Chem. Soc.*, 1965, **87**, 2063.

⁵ T. J. Curphey and K. S. Prasad, *J. Org. Chem.*, 1972, **37**, 2259.

⁶ Preliminary communications, (a) L. A. Summers and J. E. Dickeson, *Chem. Comm.*, 1967, 1183; (b) I. F. Eckhard, R. Fielden, and L. A. Summers, *Chem. and Ind.*, 1973, 275.

⁷ D. J. Pokorny and W. W. Paudler, *Canad. J. Chem.*, 1973, **51**, 476.

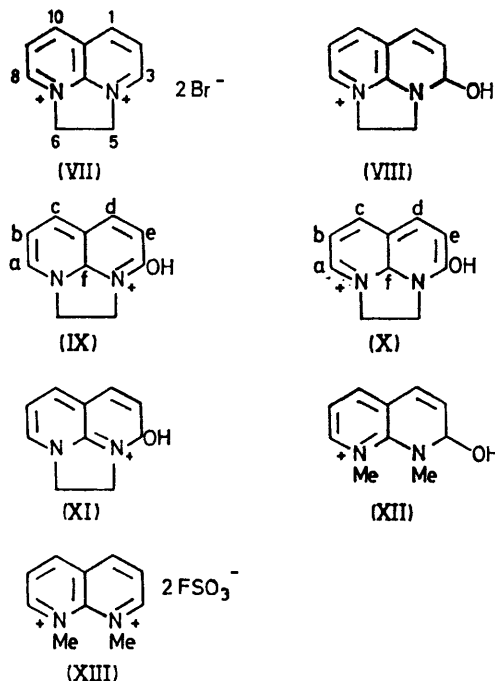
⁸ J. W. Bunting and W. G. Meathrel, *Canad. J. Chem.*, 1972, **50**, 917.

⁹ A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon, Oxford, 1964.

structure (II). However, other tautomers were apparently not considered.

Like planar diquatery salts of 2,2'- and 4,4'-bipyridyl,¹ an aqueous solution of the diquatery salt (I) was reduced by zinc powder with transfer of one electron to give a relatively stable green radical cation of which (V) is one canonical form. Since our preliminary communication,^{6a} the radical cation (V) has been generated from (I) electrolytically¹⁰ and its e.s.r. spectrum has been recorded.¹⁰ Polarography experiments in the pH range 2.7—4.3 confirmed that the reduction of the salt (I) involved one electron but not hydrogen (*cf.* ref. 11). It gave a symmetrical one electron reduction wave with a half-wave potential (E_0) of +0.02 V, independent of pH and concentration, due to the formation of (V). A second one-electron reduction wave was also obtained with E_0 *ca.* -0.35 V, presumably due to the formation of (VI). At higher pH values, the wave heights decreased in size and disappeared above pH 8.0. Simultaneously a reduction wave appeared at a much lower potential (*ca.* -0.80 V) due to the reduction of the pseudo-base. The radical cation (V) is stable for several minutes in the absence of air.

1,8-Naphthyridine formed a diquatery salt (VII) on reaction with 1,2-dibromoethane, but attempts to prepare a diquatery salt with dimethyl sulphate were unsuccessful, although a dimethyl diquatery salt of



1,8-naphthyridine has recently been prepared⁷ by use of methyl fluorosulphonate. The structure (VII) was confirmed by elemental analyses and by its n.m.r. spectrum in deuteriated trifluoroacetic acid. The imidazo[1,2,3-*ij*][1,8]naphthyridinium ring system has not been reported previously. The salt (VII) was even more unstable than the salt (I). In aqueous solution it was stable only at pH values below 1.5 (*cf.* ref. 7), the u.v.

spectrum in aqueous hydrobromic acid showing maxima at 259, 314, and 349 nm ($\log \epsilon$ 3.63, 3.68, and 3.74). At higher pH values it was in reversible equilibrium with the pseudo-base, which was the predominant form above pH 2.2, the u.v. spectrum in water at pH 5.6, for example, showing maxima at 257 and 351 nm ($\log \epsilon$ 3.68 and 3.78). There was no evidence from the u.v. spectrum for the presence of more than one form in the pH range 2.2—8.0. The pseudo-base can formally exist in four tautomeric or resonance hybrid forms, (VIII)—(XI), if we assume complete charge separation on one nitrogen atom. The structure was deduced from its n.m.r. spectrum in deuterium oxide containing sodium hydrogen carbonate. Apart from the signals due to the bridge methylene protons, which overlap with the residual water signal, the n.m.r. spectrum of the pseudo-base consisted of three groups of signals (each 2H). Two overlapping doublets appeared as a triplet at δ 7.82—8.10 and another two overlapping doublets formed a triplet at δ 6.90—7.16. A quartet at δ 6.08—6.37 and a singlet at δ 6.13 also overlapped. The presence of a singlet eliminates structures (VIII) and (XI). Spin-decoupling experiments showed that the quartet at δ 6.08—6.37 was coupled with the overlapping doublets at δ 6.90—7.16 and not with the more deshielded system at δ 7.82—8.10. This result eliminates structure (X), since in formula (X) proton b, which would give the only quartet signal, is coupled with the highly deshielded proton a, adjacent to the quaternary nitrogen atom. The result is consistent, however, with structure (IX), with the signals at δ 7.82—8.10 being assigned to protons d and e, the signals at δ 6.90—7.16 to a and c, the quartet at 6.08—6.37 to b, and the singlet at 6.13 to f. The pseudo-base therefore exists as structure (IX). The u.v. spectrum is in accord with this completely conjugated structure. In contrast, the pseudo-base (XII) from 1,8-dimethyl-1,8-naphthyridinedi-ium bisfluorosulphonate (XIII)⁷ absorbs in the u.v. at λ 273 and 336 nm ($\log \epsilon$ 3.74 and 3.98), which is in accord,⁸ along with n.m.r. evidence,⁷ with structure (XII). The difference in the structure of the pseudo-base (XII) as compared with (IX) is presumably due to the presence of the two methyl groups in the former structure, which sterically hinder the formation of the fully conjugated tautomer analogous to (IX).

Attempts to detect a radical cation from the reduction of the diquatery salt (VII) in aqueous or dilute acid solution with zinc dust were unsuccessful.

The salts (I) and (VII) were tested as post-emergent herbicides at 8 lb per acre against a number of flora but they were inactive. The lack of activity in (I) and (VII) compared with diquatery salts of 2,2'- and 4,4'-bipyridyls is in keeping with their instability at physiological pH values.

EXPERIMENTAL

Microanalyses were performed by the Australian Micro-analytical Service. Britton and Robinson and Sorenson

¹⁰ F. W. King, B.Sc. Thesis, Sydney University, 1968.

¹¹ E. Laviron and L. Roullier, *Compt. rend.*, 1972, **274C**, 1489.

buffers were used in the polarography experiments, which were conducted at 20° with a standard calomel electrode and 0.001M- and 0.0015M-solutions. Experimental error in the half-wave potentials was ± 0.02 V. U.v. absorption measurements were taken for 10^{-4} M-solutions in the same buffers or in dilute aqueous acid. N.m.r. spectra (60 MHz) were determined for 10% w/v solutions with sodium 3-trimethylsilylpropane-1-sulphonate as internal standard.

1,5-Dimethyl-1,5-naphthyridinedi-ium Dimethosulphate (I).—1,5-Naphthyridine (5.0 g) and redistilled dimethyl sulphate (75 ml) were heated under reflux for 1 h. After cooling, the mixture was poured into dry ethanol (250 ml). The grey solid which precipitated was crystallised from aqueous ethanol to afford the *salt*, m.p. 200° (decomp.) (33%) (Found: C, 37.9; H, 4.8; N, 7.2; S, 16.7. $C_{12}H_{18}N_2O_8S_2$ requires C, 37.8; H, 4.7; N, 7.3; S, 16.8%), λ_{\max} (pH 0.8) 270, 311, and 323 nm (log ϵ 3.79, 3.91, and 4.11), λ_{\max} (pH 8.0) 270 and 377 nm (log ϵ 4.06 and 3.83), δ (D_2O) (I) 3.70 (s, methosulphate CH_3), 4.98 (s, quaternary NCH_3), 8.70—8.96 (q, 3- and 7-protons), and 9.76—9.98 (t, 2-, 4-, 6-, and 8-protons), δ (D_2O - $NaHCO_3$) 3.35 (s NCH_3), 3.80 (s, methosulphate CH_3), 4.39 (s, quaternary NCH_3), 5.81—5.90 (1H, d), 6.68—6.94 (1H, q), 7.35—7.52 (1H, d), and 7.75—8.34 (3H, m).

5,6-Dihydroimidazo[1,2,3-ij][1,8]naphthyridinedi-ium Di-

bromide (VII).—Sublimed 1,8-naphthyridine (1 g) was added to boiling 1,2-dibromoethane (20 ml). The brown solid which formed rapidly was collected and was crystallised from ethanol containing a trace of aqueous hydrobromic acid to afford the *salt* (90%), m.p. $>320^\circ$ (Found: C, 37.8; H, 3.2; N, 8.5. $C_{10}H_{10}Br_2N_2$ requires C, 37.8; H, 3.2; N, 8.8%), λ_{\max} (pH 1.0) 259, 314, and 349 nm (log ϵ 3.63, 3.68, and 3.74), λ_{\max} (pH 5.6) 257 and 351 nm (log ϵ 3.68 and 3.78), δ ($CF_3 \cdot CO_2D$) (VII) 6.10 (s, CH_2), 8.61—8.85 (q, 2- and 9-protons), 9.59—9.74 (d, 1- and 10-protons), and 10.01—10.10 (d, 3- and 8-protons), δ (D_2O - $NaHCO_3$) (IX) *ca.* 4.10—4.94 (m, CH_2), 6.08—6.37 (q, H_b), 6.13 (s, H_f), 6.90—7.16 (t, H_a and H_c), and 7.82—8.10 (t, H_d and H_e).

1,8-Dimethyl-1,8-naphthyridinedi-ium bisfluorosulphonate (XIII) was prepared as described by Pokorny and Paudler.⁷ The m.p. and n.m.r. spectra agreed with those reported;⁷ λ_{\max} (pH 0.5) 285sh, 314, and 333sh nm (log ϵ 3.63, 3.78, and 3.73), λ_{\max} (pH 4.0) 273 and 336 nm (log ϵ 3.74 and 3.98).

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