**1093.** *Cyclic Quaternary Ammonium Salts. Part III.*[1] *The Synthesis of Dipyrido*[1,2-a : 2′,1′-c]*pyrazidi-inium Salts and their 6-Alkyl and 6-Aryl Derivatives*

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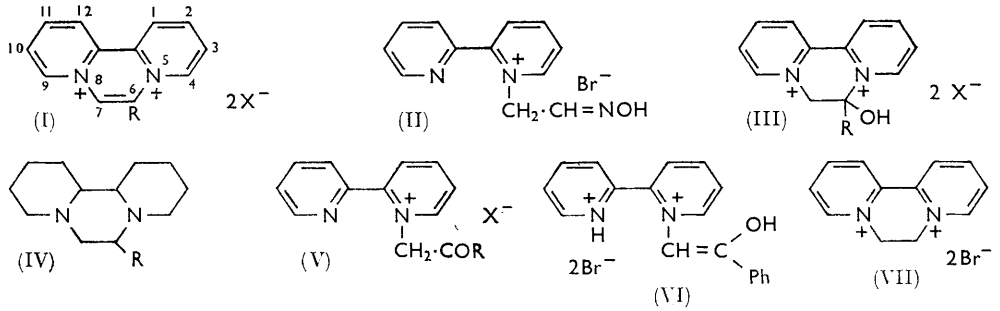
The synthesis and spectroscopic properties of the title compounds (I) are reported.

The weakness of pyrazine as a diacidic base is well known and is exemplified by its reluctance to form diquaternary salts. Phenazine is, however, a stronger base,[2] and diquaternary salts of phenazine have been reported.[3] The greater basic strength of phenazine compared with pyrazine is probably due to stabilisation of the cation and dication by increased charge distribution over the more extended π-electron system. It seemed likely, therefore, that the title compounds (I), in which both the nitrogen atoms of the central pyrazine ring are quaternary, would be stable and of interest as new aromatic systems. Consequently, their synthesis was undertaken.

Quaternisation of 2,2′-bipyridyl with bromoacetaldehyde oxime gave the monoquaternary salt (II) which was cyclised in good overall yield by heating in concentrated hydrobromic acid, the resulting hydroxy-dibromide [4] (III; R = H, X = Br) being precipitated with acetone. The structure of this compound was confirmed by its n.m.r. spectrum in $D_2O$, which showed a triplet centred at τ 3·0 corresponding to the proton on the hydroxylated carbon atom, a doublet centred at τ 4·5 corresponding to the methylenic protons, together with a collection of eight protons in the region τ 0·4—1·8. Hydrogenation of the dibromide in glacial acetic acid gave the dihydrobromide of the perhydro-base (IV; R = H). This sample, and its derived dipicrate, were identical with those obtained by the hydrogenation of the dihydro-compound (VII).[4,5] Treatment of the hydroxy-dibromide with boiling phosphorus tribromide gave the aromatic dibromide (I; R = H, X = Br). The n.m.r. spectrum of the aromatic dication in trifluoroacetic acid showed only a collection of ten protons in the region τ 0·4—1·8. Hydrogenation of the aromatic dibromide in methanol gave the dihydrobromide of the perhydro-base (IV; R = H), characterised as the dipicrate.[4]




Quaternisation of 2,2′-bipyridyl with bromoacetone and phenacyl bromide gave an adduct assumed to be the acetonyl quaternary salt (V; R = Me, X = Br) and the phenacyl quaternary salt (V; R = Ph, X = Br), respectively, both in high yield. However,

[1] E. E. Glover and G. H. Morris, *J.*, 1965, 3885.
[2] A. Albert, " Physical Methods in Heterocyclic Chemistry," Academic Press, London, 1963, vol. I, pp. 75 and 77.
[3] H. Hilleman, *Ber.*, 1938, **71**, *B*, 34.
[4] D. H. Corr and E. E. Glover, *Chem. and Ind.*, 1964, 2128; 1965, 847.
[5] R. C. Brian, R. F. Homer, and J. Stubbs, *Nature*, 1958, **181**, 446; R. F. Homer and T. E. Tomlinson, *J.*, 1960, 2498.

only the former could be cyclised in concentrated hydrobromic acid giving the methyl-hydroxy-dibromide [6] (III; R = Me, X = Br) in good yield. The n.m.r. spectrum of this dibromide in $D_2O$ showed singlets at $\tau$ 7·95 and 4·45 corresponding to the methyl and methylenic protons, respectively, together with a collection of eight protons in the region $\tau$ 0·3—1·7. Attempted cyclisation of the phenacyl quaternary salt (V; R = Ph, X = Br) with concentrated hydrobromic acid gave the enolic compound (VI). The infrared spectrum of this compound showed no absorption between 1620 $cm.^{-1}$ and a broad band in the region 2600—3100 $cm.^{-1}$. The n.m.r. spectrum of compound (VI) in $D_2O$ showed only a single proton peak, at $\tau$ 3·75, which slowly disappeared during 1½ hr., together with a collection of thirteen protons in the region $\tau$ 0·8—2·8. Treatment of the enolic compound (VI) with picric acid gave the monoquaternary picrate (V; R = Ph, X = picrate) confirming, that cyclisation of the phenacyl quaternary salt (V; R = Ph, X = Br) had not occurred on treatment with hydrobromic acid.

The methyl-hydroxy-compound (III; R = Me, X = Br) was dehydrated by boiling phosphorus tribromide, giving the 6-methyl aromatic dibromide [6] (I; R = Me, X = Br) in good yield. However, a more convenient route to this salt was by the cyclisation of the acetonyl quaternary salt (V; R = Me, X = Br) in boiling phosphorus tribromide. This procedure gave a higher overall yield, eliminated one stage and required a shorter reflux time with phosphorus tribromide. The n.m.r. spectrum of the 6-methyl dibromide in $D_2O$ showed a singlet at $\tau$ 6·8 corresponding to the methyl protons and a collection of nine protons in the region $\tau$ 0—1·4. Hydrogenation of this dibromide followed by basification gave the perhydro-base [6] (IV; R = Me).

Cyclisation of the phenacyl quaternary salt (V; R = Ph, X = Br) was achieved by boiling with phosphorus dibromide giving the 6-phenyl aromatic dibromide (I; R = Ph, X = Br) in good yield. The n.m.r. spectrum of this salt in trifluoroacetic acid showed a singlet at $\tau$ 2·6 corresponding to the phenyl protons and a collection of nine protons in the region $\tau$ 0—1·4. Hydrogenation of the 6-phenyl aromatic diquaternary salt and subsequent basification gave the 6-phenyl-perhydro-base (IV; R = Ph).

The infrared spectra of all three aromatic diquaternary salts (I; R = Me, Ph, or H, X = Br) showed a new band at 1680 $cm.^{-1}$.

## Experimental

Melting points were determined on a Kofler hot-stage apparatus and ultraviolet spectra on a Unicam S.P. 500 spectrophotometer.

Bromoacetaldehyde oxime was prepared using the method described by Kimber and Parham [7] for the preparation of the chloro-compound. Attempts to distil the bromo-oxime at atmospheric pressure resulted in its violent decomposition.

*6-Hydroxy-6,7-dihydrodipyrido* [1,2-a : 2′,1′-c[*pyrazidi-inium Dibromide* (III); R = H, X = Br).—A mixture of bipyridyl (1 g.) and bromoacetaldehyde oxime (1 g.) was warmed until homogeneous and set aside for 2 days. The resulting gum was washed with ether and dissolved in 48% hydrobromic acid (4 ml.). The solution was boiled for 2 min., cooled and acetone added. The precipitated *dibromide* [4] crystallised from methanol–ether as pale yellow prisms, m. p. 272—273° (decomp.) (0·89 g., 37%) (Found: C, 38·4; H, 3·7; N, 7·6. $C_{12}H_{12}Br_2N_2O,H_2O$ requires C, 38·1; H, 3·7; N, 7·4%).

The *dipicrate* [4] crystallised from water or nitromethane as yellow needles, m. p. 185—186° (Found: C, 44·1; H, 2·6; N, 17·7. $C_{24}H_{16}N_8O_{15}$ requires C, 43·9; H, 2·5; N, 17·1%).

*Dipyrido*[1,2-a : 2′,1′-c]*pyrazidi-inium Dibromide* (I; R = H, X = Br).—A suspension of the hydroxy-dibromide (III; R = H, X = Br) (1·58 g.) in phosphorus tribromide (15 ml.) was boiled under reflux for 1½ hr. The mixture was cooled and filtered. Crystallisation of the residue from methanol–ether gave the *dibromide* as yellow needles (1·02 g., 68%) which rapidly became paler on exposure to the atmosphere. The yellow colour was restored on drying *in vacuo*. The dibromide had m. p. >350° (Found: C, 40·3; H, 3·4; N, 7·77. $C_{12}H_{10}Br_2N_2,H_2O$ requires C, 40·0; H, 3·4; N, 7·8%); $\lambda_{max.}$ (in $H_2O$) 2150, 2240, 2390, 2650, 2720, 3100sh, 3220Å.

[6] I. C. Calder and W. H. F. Sasse, *Tetrahedron Letters*, 1964, 3871.
[7] R. W. L. Kimber and J. C. Parham, *J. Org. Chem.*, 1963, **28**, 3205.

($\log_{10}$ ε 4·13, 4·11, 4·19, 4·44, 4·58, 4·05, 4·15). The *dipicrate* crystallised from water as yellow needles, m. p. 265—269° (decomp.) (Found: C, 45·2; H, 2·1; N, 18·1. $C_{24}H_{14}N_8O_{14}$ requires C, 45·1; H, 2·2; N, 17·6%).

*Perhydrodipyrido*[1,2-a : 2′,1′-c]*pyrazine* (IV; R = H).—(i) A solution of the hydroxy-dibromide (III; R = H, X = Br) (0·34 g.) in glacial acetic acid (10 ml.) and water (2 ml.) was hydrogenated to completion over Adams catalyst at atmospheric temperature and pressure. The catalyst was filtered off and the solvent evaporated. The residue was crystallised from methanol ether giving the dihydrobromide [5] as colourless prisms, m. p. >350° (Quant.) (Found: C, 40·4; H, 7·0; N, 8·0. Calc. for $C_{12}H_{22}N_2$,2HBr: C, 40·4; H, 6·8; N, 7·9%). The *dipicrate* crystallised from water as yellow plates, m. p. 248—252° (decomp.) (Found: C, 44·1; H, 4·3; N, 17·35; $C_{12}H_{22}N_2$,$2C_6H_3N_3O_7$ requires C, 44·2; H, 4·3; N, 17·2%).

(ii) A solution of the aromatic dibromide was hydrogenated to completion over Adams catalyst at atmospheric temperature and pressure. The catalyst was filtered off and the solvent evaporated. The residue was converted into the *dipicrate* which crystallised from water as yellow plates identical with the sample described above, m. p. and mixed m. p. 248—252° (decomp.).

1-*Phenacyl*-2-(2-*pyridyl*)*pyridinium Bromide* (V; R = Ph, X = Br).—A mixture of bipyridyl (2 g.) and phenacyl bromide (2·64 g.) was warmed on a water-bath for 45 min. and set aside for 2 days. The solid product crystallised from ethanol–ether giving the *bromide* as colourless prisms, m. p. 174—176° (2·9 g., 64%) (Found: C, 60·4; H, 4·55; N, 8·1. $C_{18}H_{15}BrN_2O$ requires C, 60·85; H, 4·3; N, 7·9%). The *picrate* crystallised from nitromethane–isopropyl ether as yellow needles, m. p. 164—165° (Found: C, 57·3; H, 3·4; N, 13·6. $C_{24}H_{17}N_5O_8$ requires C, 57·25; H, 3·4; N, 13·9%). The *bromide hydrobromide*, obtained by dissolving the bromide in 48% hydrobromic acid and precipitating with acetone, crystallised from acetone–48% hydrobromic acid as yellow prisms, m. p. 136—138° (Found: C, 47·3; H, 4·15. $C_{18}H_{15}BrN_2$, HBr,$H_2O$ requires C, 47·6; H, 4·0%).

6-*Phenyldipyrido*[1,2-a : 2′,1′-c]*pyrazidi-inium Dibromide* (I; R = Ph, X = Br).—A suspension of the phenacyl monoquaternary salt (V; R = Ph, X = Br) (2·9 g.) in phosphorus tribromide (15 ml.) was boiled under reflux for 15 min. The mixture was cooled, filtered, and the black residue washed with ether. Crystallisaton from methanol–isopropyl ether gave a green solid (2·16 g., 58%). Recrystallisation from the same solvent gave the analytical sample of the *dibromide* as yellow prisms which rapidly became paler on exposure to the atmosphere. The yellow colour returned when the sample was dried *in vacuo*. The dibromide had m. p. 212—214° (Found: C, 47·6; H, 3·9; N, 6·8. $C_{18}H_{14}Br_2N_2$,$2H_2O$ requires C, 47·6; H, 4·0; N, 6·2%), $\lambda_{max.}$ (in $H_2O$) 2260, 2380, 2690, 2720, 2870sh, 3120, 3260Å ($\log_{10}$ ε 4·21, 4·24, 4·43, 4·43, 4·29, 4·12, 4·11). The *dipicrate* crystallised from water as yellow needles, m. p. 241—243° (decomp.) (Found: C, 50·2; H, 2·6; N, 15·9. $C_{30}H_{18}N_8O_{14}$ requires C, 50·4; H, 2·5; N, 15·7%).

6-*Phenylperhydrodipyrido*[1,2-a : 2′,1′-c]*pyrazine* (IV; R = Ph).—The aromatic dibromide (I; R = Ph, X = Br) was hydrogenated until uptake ceased, and the basic material obtained chromatographed in ether on an alumina column giving the colourless base (74%). The analytical sample was obtained by sublimation at 250°/0·5 mm., and had m. p. 110—115° (Found: C, 79·6; H, 9·8; N, 9·9. $C_{18}H_{26}N_2$ requires C, 80·0; H, 9·7; N, 10·4%). The *dipicrate* crystallised from nitromethane as yellow prisms, m. p. 215—217° (decomp.) (Found: C, 49·33; H, 4·25; N, 14·9. $C_{18}H_{26}N_2$,$2C_6H_3N_3O_7$ requires C, 49·45; H, 4·4; N, 15·4%).

1-*Acetonyl*-2-(2-*pyridyl*)*pyridinium Picrate* (V; R = Me, X = $C_6H_2N_3O_7$).—A mixture of 2,2′-bipyridyl (1·94 g.) and bromoacetone (1·71 g.) were warmed until homogeneous and set aside at room temperature for 3 weeks. The resulting solid was washed with ether giving a brown solid (2·84 g., 78%) which crystallised from ethanol–ether as very hygroscopic buff prisms, m. p. 162—164°. The *picrate* crystallised from water as yellow needles, m. p. 132—134° (Found: C, 51·9; H, 3·4; N, 16·2. $C_{19}H_{15}N_5O_8$ requires C, 51·7; H, 3·4; N, 15·9%).

6,7-*Dihydro*-6-*hydroxy*-6-*methyl*-*dipyrido*[1,2-a : 2′,1′-c]*pyrazidi-inium Dibromide* (III; R = Me, X = Br).—A solution of the above adduct (V; R = Me, X = Br) (0·77 g.) in 48% hydrobromic acid (4 ml.) was boiled for 2 min., cooled, and acetone added. The precipitated dibromide crystallised from acetone–48% hydrobromic acid as pale yellow prisms, m. p. 220—222° (decomp.) (lit.,[6] 220—225°) (0·75 g., 76%) (Found: C, 42·1; H, 3·9; N, 7·8. Calc. for $C_{13}H_{14}Br_2N_2O$: C, 41·7; H, 3·8; N, 7·5%). The *dipicrate* crystallised from water as yellow needles, m. p. 66—68° (Found: C, 43·9; H, 2·9; N, 16·5. $C_{25}H_{18}N_8O_{15}$,$H_2O$ requires C, 43·6; H, 2·9; N, 16·3%).

6-*Methyldipyrido*[1,2-a : 2′,1′-c]*pyrazidi-inium Dibromide* (I; R = Me, X = Br.)—(i) A suspension of the above adduct (V; R = Me, X = Br) (0·5 g.) in phosphorus tribromide (4 ml.) was boiled under reflux for 15 min. The mixture was filtered and the residue digested with hot ethanol. After filtration, the residue was crystallised from ethanol–ether giving the dibromide as yellow prisms m. p. >350° [lit.,[6] 300—305° (decomp.)] (0·366 g., 60%) (Found: C, 43·8; H, 3·6; N, 7·9. Calc. for $C_{13}H_{12}Br_2N_2$: C, 43·8; H, 3·4; N, 7·9%), $\lambda_{max.}$ (in $H_2O$) 2270, 2380, 2435, 2680, 2760, 3005sh, 3125, 3250, 3505Å ($\log_{10}$ ε 4·06, 4·12, 4·12, 4·51, 4·66, 3·89, 4·03, 4·11, 3·49).

(ii) Dehydration of the hydroxy-compound (III; R = Me, X = Br) with phosphorus tribromide gave the aromatic dibromide (60%) identical with the above sample.

6-*Methylperhydrodipyrido*[1,2-a : 2′,1′-c]*pyrazine* (IV; R = Me).—The aromatic dibromide (I; R = Me, X = Br) was hydrogenated to completion and the basic material obtained distilled from a bulb tube giving the free base,[6] b. p. 73—78° (bath temp.)/0·1 mm. (67%) (Found: C, 75·1; H, 11·4; N, 13·4. Calc. for $C_{13}H_{24}N_2$: C, 74·9; H, 11·6; N, 13·45%). The dipicrate crystallised from nitromethane as yellow prisms m. p. 267—268° (decomp.) (lit.,[6] 263—264°) (Found: C, 44·5; H, 4·5; N, 17·2. Calc. for $C_{25}H_{30}N_8O_{14}$: C, 45·0; H, 4·5; N, 16·8%).

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