

Chemical Constitution and Activity of Bipyridylium Herbicides. Part VII.
6-Substituted Derivatives of 6,7-Dihydrodipyrido[1,2-a:2',1'-c]pyrazinediium
Dibromide (Diquat) and Dipyrido[1,2-a:2',1'-c]pyrazinediium Dibromide.

A. L. Black and L. A. Summers

Department of Chemistry, University of Newcastle Newcastle, N.S.W., Australia

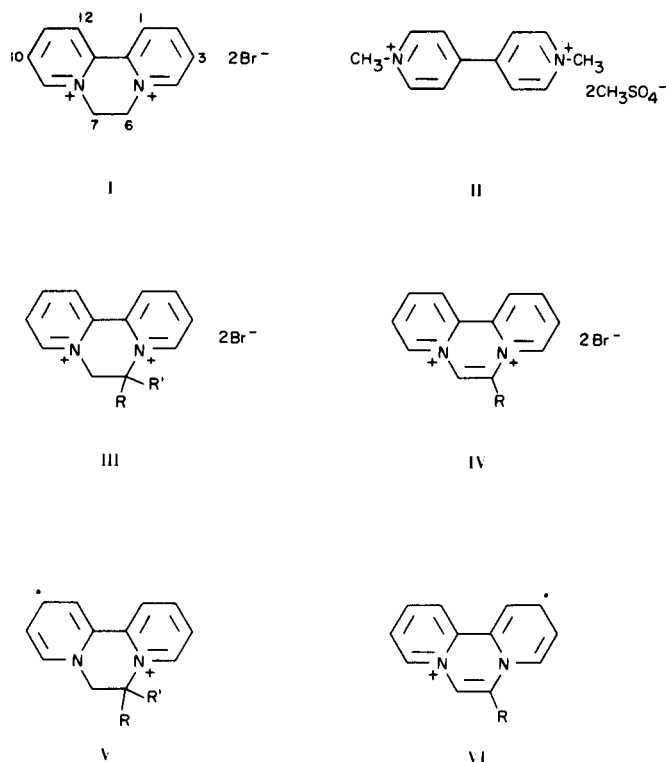
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6-Methyl, 6,6-dimethyl-, and 6-phenyl-6,7-dihydrodipyrido[1,2-a:2',1'-c]pyrazinediium dibromides are reversible one electron transfer systems with similar redox potentials to diquat dibromide. They are respectively about one-half, one-fourteenth and one-fiftieth as active as diquat as post-emergent herbicides and this finding illustrates the importance of molecular size in determining whether bipyridylium salts have outstanding phytotoxic activity. This conclusion is supported by a study of 6-methyl- and 6-phenyldipyrido[1,2-a:2',1'-c]pyrazinediium dibromides.

As a result of work reported (1) (2) in earlier papers of this series (3) and elsewhere (4-6) it is apparent that the introduction of substituents in the aromatic rings of the herbicides diquat (I) and paraquat (II) can considerably reduce their phytotoxic activity. This suggests *inter alia* that the dimensions of the molecule may play an important part in determining whether a compound possesses outstanding herbicidal properties. This idea is supported by the knowledge that the replacement of the methyl quaternising groups of paraquat by long alkyl groups greatly diminishes activity (4) (7). There has been little investigation of the effect on herbicidal activity of the presence of substituents on the ethylene bridge of diquat (I) although some diquaternary salts of this type (e.g. III; R=H; R'=CH₃) have been claimed to be herbicides in patents (8) (9). This paper reports the results of an investigation of three bridge substituted derivatives of diquat and two 6-substituted dipyrido[1,2-a:2',1'-c]pyrazinediium dibromides, the parent compound (IV; R=H) of which is known to be about one-eighth as active as diquat (2) (10) (11).

While 2,2'-bipyridine reacts readily with boiling 1,2-dibromoethane to give diquat (12) (13), the reaction of 2,2'-bipyridine with boiling 1,2-dibromopropane leads to considerable quantities of tars and to the formation of 2,2'-bipyridine hydrobromides *via* the elimination of hydrogen bromide from the secondary alkyl halide. Compound (III; R=H; R'=CH₃) was best prepared, albeit in low yield, by reacting 2,2'-bipyridine with 1,2-dibromopropane at 130° in 1-hexanol. The salts (III; R=R'=CH₃) (14) (15) and (III; R=H; R'=Ph) were obtained similarly. In our hands the methods of preparing (III; R=H; R'=CH₃) given in the patent literature (8) (9) were unsuccessful.

The salts (III; R=H; R'=CH₃), (III; R=R'=CH₃) and (III; R=H; R'=Ph) were stable in aqueous solution below



a pH of about 10.5, 9.0 and 7.5, respectively. The ultraviolet absorption spectra of the three salts closely resembled each other and that of diquat, λ_{max} 308-311 m μ (4), indicating that in each case the two pyridine rings are similarly conjugated.

The bipyridylium herbicides, diquat (I) and paraquat (II), are reduced in aqueous solution to give stable radical cations by a one electron transfer which is reversed by air (4). These redox properties are thought to be largely responsible for their herbicidal activity (7). Likewise the

salts (III; R=H; R'=CH₃), (III; R=R'=CH₃) and (III; R=H; R'=Ph) in aqueous solution on treatment with zinc dust immediately gave intensely green solutions due to the radical cations (V; R=H; R'=CH₃), (V; R=R'=CH₃) and (V; R=H; R'=Ph), respectively. When the reducing agent was removed and the solutions shaken in air, the green colour rapidly discharged. From NMR spectral evidence (*cf.* refs. 1,6,10) it was apparent that in each case the one electron transfer was completely reversible.

The uptake of one electron, but not hydrogen, was confirmed by polarography. In the pH range 2.5-9.0, the salts (III; R=H; R'=CH₃) and (III; R=R'=CH₃) each gave a typical one electron reduction wave with a half-wave potential of -0.35 volts against a normal hydrogen electrode independent of pH and concentration. A second reduction wave was also present in each case at about -0.70 volts although its potential was pH dependent (*cf.* ref. 1). Diquat dibromide (I) was included for comparison and it gave, as before (16), an E_o value of -0.36 volts. It is apparent from these results that the salts (III; R=H; R'=CH₃) and (III; R=R'=CH₃) are reversible one electron transfer systems with almost the same reduction potential as diquat. The phenyl substituted salt (III; R=H; R'=Ph) behaved similarly in the pH range 2.0-7.0. It had an E_o value of -0.29 volts.

The salts (IV; R=CH₃) and (IV; R=Ph) were prepared by literature methods (17) (18). They were stable in aqueous solution up to about pH 8.5 and 7.5, respectively (*cf.* ref. 10). Like the parent salt (IV; R=H) (10) (11), the salt (IV; R=CH₃) gave a deep brown solution on treatment with zinc dust due to the radical cation (VI; R=CH₃). When the zinc dust was removed and the solution shaken in air for about 2 minutes the brown colour changed to orange red. The NMR spectrum obtained then showed

that the diquatery salt (IV; R=CH₃) had been largely regenerated although small differences in the spectrum indicated that the one electron transfer was not quite completely reversible. This behaviour is analogous to that of (IV; R=H) (10) (11). The salt (IV; R=Ph) similarly gave a red-brown radical cation (VI; R=Ph). In this case the one electron transfer was essentially completely reversed by air (NMR evidence). On polarographic examination in the pH range 2.0-7.5 the salts (IV; R=CH₃) and (IV; R=Ph) gave a one electron reduction wave at potentials (E_o) of -0.30 and -0.27 volts, respectively. Above pH 4.0 a second wave was also evident for each salt at about -0.70 to -0.80 volts. It is apparent from these results that the salts (IV; R=CH₃) and (IV; R=Ph) are the oxidised forms of redox systems of similar potential to that of the parent salt (IV; R=H) which has an E_o value of -0.27 volts (10) (11).

The salts (III; R=H; R'=CH₃), (III; R=R'=CH₃), (III; R=H; R'=Ph), (IV; R=CH₃) and (IV; R=Ph) were tested as post-emergent herbicides at C.S.I.R.O., Division of Plant Industry, Canberra, against six plant species by methods previously described (2) and on mixed grass flora at Newcastle. Diquat dibromide (I) and (IV; R=H) were included for comparison. A summary of the results is given in Table I.

The methyl substituted salt (III; R=H; R'=CH₃) is only about half as active as diquat, while the dimethyl derivative (III; R=R'=CH₃) is less active still although both salts have essentially the same redox properties as diquat. The decrease in activity is almost certainly due to the increasing size of the di-cation. The results for the phenyl substituted salt (III; R=H; R'=Ph) confirm this trend although in this case the lower activity may be partly due to the higher redox potential of the salt.

TABLE I

Reduction Potentials and Post-emergent Herbicidal Activity of Bridge Substituted Derivatives of Diquat and Related Compounds.

Compound	Reduction Potential (E _o volts)	Colour of Radical Cation	Approximate Relative Activity (Diquat = 100)
(I)	-0.36	green	100
(III; R=H; R'=CH ₃)	-0.35	green	50
(III; R=R'=CH ₃)	-0.35	green	7.5
(III; R=H; R'=Ph)	-0.29	green	2.0
(IV; R=H)	-0.27	brown	12.5 (<i>cf.</i> ref. 2)
(IV; R=CH ₃)	-0.30	brown	2.0
(IV; R=Ph)	-0.27	red-brown	<1.0

The results from the fully aromatic salts (IV; R=CH₃) and (IV; R=Ph) support these findings. The methyl substituted compound is less active than the parent salt (IV; R=H) although the salts have similar redox properties while the phenyl derivative is less active still despite the fact that its redox potential is identical to that of (IV; R=H). These results provide compelling evidence that the overall dimensions of di-cations of this type are very important in determining whether they have high herbicidal activity. It has not escaped our notice that the methyl and phenyl substituents might be considered to confer greater lipid solubility on the substituted diquaternary salts. This might conceivably alter the distribution of the salts in plant tissue in such a way as to diminish their phytotoxic effects. We feel however that this factor is unlikely to cause the great differences in activity observed because of the high solubility of the salts in water.

EXPERIMENTAL

Polarography experiments, NMR spectra and microanalyses were carried out as described previously (6).

6,7-Dihydro-6-methyldipyrido[1,2-*a*:2',1'-*c*]pyrazinedium Dibromide (III; R=H; R'=CH₃).

A solution of 2,2'-bipyridine (10 g.) and 1,2-dibromopropane (20 ml.) in 1-hexanol (70 ml.) was heated in a stoppered flask at 130° for 50 hours. The crystalline product which formed was recrystallised from aqueous ethanol to give yellow crystals, m.p. 327° dec., yield 5%. The patent (9) gives neither m.p. nor analytical figures. The patent (8) gives m.p. ~300° but no analysis.

Anal. Calcd. for C₁₃H₁₄Br₂N₂: C, 43.6; H, 3.9; Br (total), 44.7; Br (ionic), 44.7; N, 7.8. Found: C, 43.6; H, 3.8; Br (total), 44.7; Br (ionic), 44.4; N, 7.7.

The NMR spectrum (deuterium oxide) showed a doublet at δ 1.68-1.79 (3 methyl H), a doublet at 5.38-5.43 (2 methylene H), a multiplet at 5.6-6.0 (1 methine H) and a complex multiplet at 8.35-9.45 p.p.m. (8 aromatic protons). The UV spectrum in water showed λ max 252 mμ (log ε 3.32), 260 (3.30), 313 (4.09) and 317 (4.07).

6,7-Dihydro-6,6-dimethyldipyrido[1,2-*a*:2',1'-*c*]pyrazinedium Dibromide (III; R=R'=CH₃).

A solution of 2,2'-bipyridine (5 g.) and 1,2-dibromo-2-methylpropane (10 ml.) in 1-hexanol (45 ml.) was heated in a stoppered flask at 130° for 5 days. The oil which formed solidified on cooling. The solid was crystallised from aqueous ethanol to give yellow green crystals of the hemihydrate, m.p. 293° dec. (lit. (14) (15) 280-285° dec.), yield 3%.

Anal. Calcd. for C₁₄H₁₆Br₂N₂·0.5H₂O: C, 44.1; H, 4.5; Br (total), 42.0; Br (ionic), 42.0; N, 7.3. Found: C, 44.0; H, 4.3; Br (total), 42.2; Br (ionic), 42.0; N, 7.1.

The NMR spectrum (deuterium oxide) showed a singlet at δ 1.93 (6 methyl H), a singlet at 5.35 (2 methylene H) and a multiplet at 8.38-9.60 p.p.m. (8 aromatic protons). The UV spectrum in water showed λ max 252 mμ (log ε 3.27), 260 (3.22), 313 (4.05) and 319 (4.02).

6,7-Dihydro-6-phenyldipyrido[1,2-*a*:2',1'-*c*]pyrazinedium Dibromide (III; R=H; R'=Ph).

A mixture of 2,2'-bipyridine (10 g.) and 1,2-dibromo-1-phenylethane (17 g.) was heated on a steam bath for 2 days. The solid which formed was washed with acetone and crystallised from a mixture of aqueous ethanol and acetone to give yellow-green crystals, m.p. 290° dec. (yield 11% of the dihydrate).

Anal. Calcd. for C₁₈H₁₆Br₂N₂·2H₂O: C, 47.4; H, 4.4; Br (total), 35.1; Br (ionic), 35.1; N, 6.1. Found: C, 47.5; H, 4.6; Br (total), 35.4; Br (ionic), 35.4; N, 5.8.

The NMR spectrum (deuterium oxide) showed a multiplet at δ 5.55-6.15 (2 methylene H), a quartet at 6.78-6.98 (1 methine H) and a complex multiplet at 7.36-9.34 p.p.m. (13 aromatic protons). The UV spectrum in water showed λ max 252 (log ε 3.64), 259 (3.62) and 314 (4.22).

6-Phenyldipyrido[1,2-*a*:2',1'-*c*]pyrazinedium Dibromide (IV; R=Ph).

This salt was prepared as described by Corr and Glover (17). It was crystallised from a mixture of acetone and aqueous hydrobromic acid to give green needles, m.p. 289-291° dec. with sintering at 212-214°. The literature (17) m.p. is 212-214°. The analysis corresponded to a monohydrate.

Anal. Calcd. for C₁₈H₁₄Br₂N₂·H₂O: C, 49.5; H, 3.7; Br, 36.8; N, 6.4. Found: C, 49.3; H, 3.75; Br, 36.8; N, 6.4.

The NMR spectrum (deuterium oxide) showed a singlet at δ 7.88 (5 phenyl protons) and a multiplet at 8.5-10.0 p.p.m. (9 aromatic protons).

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