Synthesis, Polarography and Herbicidal Activity of Quaternary Salts of 2-(4-Pyridyl)-1,3,5-Triazines, 5-(4-Pyridyl)pyrimidine, 2-(4-Pyridyl)pyrimidine and Related Compounds

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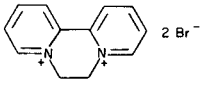
Received August 29, 1979

2-(4-Pyridyl)-1,3,5-triazine, 2-(4-pyridyl)-4-methyl-1,3,5-triazine, 2-(4-pyridyl)-4,6-dimethyl-1,3,5-triazine and 2-(4-pyridyl)pyrimidine have been prepared by modification of established triazine and pyrimidine syntheses. These compounds and some of their relatives have been converted to quaternary pyridinium salts. The polarographic reduction potentials of the salts in aqueous solution are *p*H dependent. The activity of the salts as post-emergent herbicides is reported.

J. Heterocyclic Chem., **17**, 333 (1980).

The mode of action of the bipyridinium herbicides diquat (I) and paraquat (II) is connected with their ability to be rapidly reduced in aqueous solution to a stable radical cation (*e.g.*, III) at a potential (E_0) of about -0.35 to -0.45 V by a one electron transfer, not involving hydrogen, which is rapidly and quantitatively reversed by oxygen (1-3). We recently showed that the diquaternary salt 2,4-bis-(4-methyl-4-pyridinio)-1,3,5-triazinediium dichloride (IV) is likewise an effective post-emergent herbicide (4). It too is reduced to a stable radical cation in aqueous solution at a potential (E_0) of about -0.44 V by a one electron transfer which is rapidly and quantitatively reversed by oxygen.

Block 1



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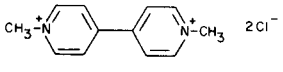

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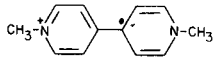

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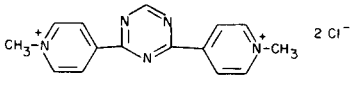

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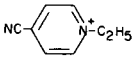

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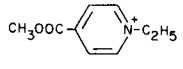
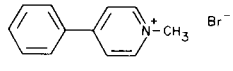


VI

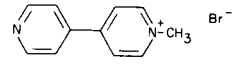
Some time ago it was reported that certain monoquaternary salts of pyridine containing strong electronegative groups in the *para* position, such as 4-cyano-1-ethylpyridinium (V) salts, are reduced polarographically in aqueous alkaline solution to a free radical by a one electron transfer not involving hydrogen (5). The E_0 value obtained with the salt (V) was -0.61 V. Other similar quaternary salts of pyridine, however, for example the salt (VI) were reduced in aqueous solution by a process involving hydrogen. In non-aqueous media the salts (V) and (VI) were both reduced to radicals by a one electron transfer not involving hydrogen.

Since the salt (IV) can also be considered to be a pyridine monoquaternary salt containing a strong electronegative group in the *para* position we have prepared and examined polarographically in aqueous solution a number of new monoquaternary salts of pyridine containing a triazine substituent or related heterocyclic ring system in the *para* position with a view to establishing whether these salts are reduced in aqueous solution to a stable radical. The quaternary salts have also been evaluated for herbicidal activity. Related monoquaternary salts are known to have some herbicidal activity. For example, 1-methyl-4-phenylpyridinium salts (VII), known as cyperquat, are effective in nutsedge control (*e.g.*, 6-12) and 1-methyl-4,4'-bipyridinium salts (VIII) are claimed to be herbicides (13).

Block 2



VII



VIII

2-(4-Pyridyl-1,3,5-triazine (IX) was synthesised by reacting the iminomethyl ether obtained from 4-cyanopyridine with excess formamidine in alkaline medium. The triazine (IX) was converted into the pyridine quaternary salts

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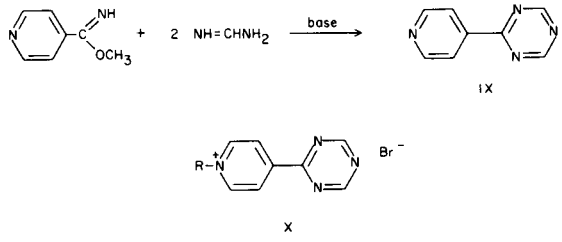
Block 3



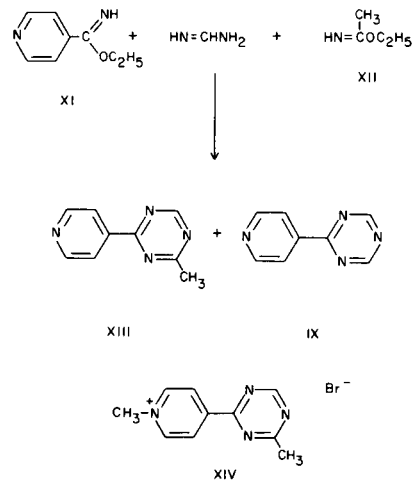
IX

X

(X, R = CH_3), (X, R = C_2H_5), (X, R = C_3H_7), (X, R = $CH_2.CH=CH_2$) and (X, R = $CH_2.COOC_2H_5$) by reaction with the appropriate alkyl bromide.

2-(4-Pyridyl)-4-methyl-1,3,5-triazine (XIII) was prepared by condensing ethyl isonicotylimidate (XI) (14) with ethyl acetimidate (XII) (15) and formamidine. It was separated from the co-product, 2-(4-pyridyl)-1,3,5-triazine (IX) by

Block 4



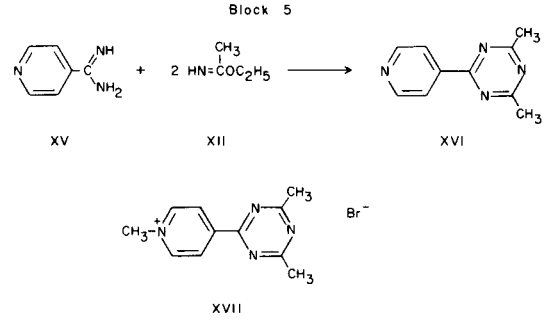
XI XII

XIII IX

XIV

ether extraction and repeated recrystallisation. It was converted to the salt (XIV) with methyl bromide.

Block 5



XV XII XVI

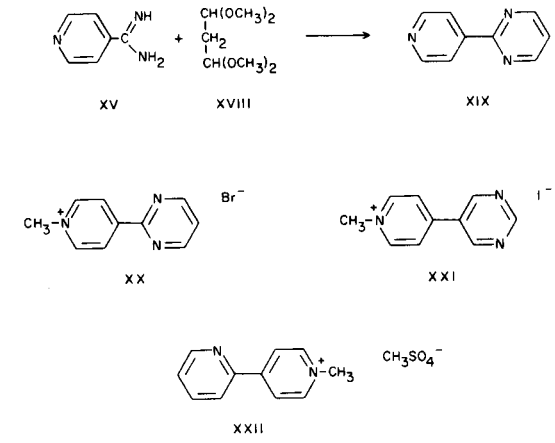
XVII

2-(4-Pyridyl)-4,6-dimethyl-1,3,5-triazine (XVI) was similarly prepared from isonicotinamidine (XV) and ethyl acetimidate (XII). It was converted to the quaternary salt (XVII) with methyl bromide.

2-(4-Pyridyl)-pyrimidine (XIX) was synthesised by condensing isonicotinamidine (XV) with 1,1,3,3-tetramethoxypropane (XVIII). It gave the pyridinium salt (XX) on reaction with methyl bromide.

5-(4-Pyridyl)-pyrimidine (17) was converted to the quaternary salt (XXI) by reaction with methyl iodide, while 2,4′-bipyridine gave the salt (XXII) on reaction with dimethyl sulfate.

Block 6



XV XVIII XIX

XX XXI

XXII

The salt, 1-methyl-4,4′-bipyridinium bromide (VIII) was prepared from 4,4′-bipyridine and methyl bromide. The salt (VII) was obtained by a literature method (18).

The twelve quaternary salts (X, R = CH_3), (X, R = C_2H_5), (X, R = C_3H_7), (X, R = $CH_2.CH=CH_2$), (X, R = $CH_2.COOC_2H_5$), (XIV), (XVII), (XX), (XXI), (XXII), (VIII) and (VII) were examined polarographically in aqueous solution in the *p*H range 3.3-10.1. The results are given in Table 1. It is evident that the strongly electronegative triazine substituted salts are more easily reduced than the pyrimidine, pyridine or phenyl substituted salts, which often gave no clear reduction wave. There was no evidence, however, that the salts which gave reduction waves were reduced to a stable radical even in alkaline solution. The reduction waves were all *p*H dependent.

As expected, in view of these results, the salts were all very much less active as herbicides than diquat and paraquat. The more easily reduced triazine substituted salts (X, R=$CH_2.CH=CH_2$) and (X, R=$CH_2.COOC_2H_5$), however, showed good post-emergent herbicidal activity at 4 kg./ha against several plant species (19) and were more active than salts which were weaker electron acceptors. Their mode of herbicidal action is almost certainly different from that of diquat and paraquat (20).

EXPERIMENTAL

Sorenson or Britton and Robinson buffers were used in the polarography experiments which were conducted at 20° with a standard calomel electrode and 0.001 *M* solutions. The half-wave potentials are

Table 1

Polarographic Reduction Potentials (E_0) of Quaternary Pyridine Salts

Salt	E_0 (volts) pH 10.1	9.1	8.1	7.0	6.0	5.0	4.1	3.3
X, R = CH_3	(a)	-0.50	-0.45	-0.42	-0.37	-0.29	-0.25	-0.20
X, R = C_2H_5	(a)	(a)	-0.44	-0.40	-0.33	-0.30	-0.23	-0.17
X, R = C_3H_7	(a)	(a)	-0.45	-0.40	-0.35	-0.27	-0.23	-0.20
X, R = CH_2•$CH{=}CH_2$	-0.47	-0.45	-0.43	-0.35	-0.32	-0.27	-0.23	-0.17
X, R = CH_2•$COOC_2H_5$	-0.50	-0.45	-0.39	-0.33	-0.30	-0.25	-0.21	(a)
XIV	-0.55	-0.53	-0.48	-0.43	-0.38	-0.33	-0.28	-0.25
XVII	-0.58	-0.55	-0.51	-0.47	-0.42	-0.37	-0.33	(a)
XX	-0.85	-0.80	-0.75	-0.67	-0.61	-0.55	-0.50	-0.45
XXI	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)
XXII	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)
VIII	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)
VII	(a)	(a)	(a)	(a)	(a)	(a)	(a)	(a)

(a) No clear reduction wave.

given as E_0 values and were calculated by adding 0.25 volts to the $E_{1/2}$ values.

2-(4-Pyridyl)-1,3,5-triazine (IX).

To a solution of sodium (1 g., 0.04 mole) in methanol (500 ml.) there was added 4-cyanopyridine (104 g., 1.0 mole). The mixture was stirred for 6 hours at room temperature. Sodium methoxide (162 g., 3.0 moles) and formamidine hydrochloride (240 g., 3.0 moles) in dimethylformamide (500 ml.) were added slowly. After stirring for 16 hours at 28° the mixture was heated for 6 hours at 100°. After cooling, the solvent was evaporated. Excess water was added and the precipitate was collected and washed with water. The precipitate was crystallised from tetrahydrofuran to afford 2-(4-pyridyl)-1,3,5-triazine, m.p. 189-191° (yield 77%). The nmr spectrum (deuteriochloroform) consisted of a doublet at δ 8.3-8.4 (2H), a doublet at 8.8-8.9 (2H) and a singlet at 9.35 ppm (2H, triazine protons).

Anal. Calcd. for $C_8H_6N_4$: C, 60.75; H, 3.8; N, 35.4. Found: C, 60.6; H, 3.55; N, 35.5.

1-Methyl-4-(2-*sym*-triazinyl)pyridinium Bromide (X, R = CH_3).

2-(4-Pyridyl)-1,3,5-triazine (IX) (14.2 g.) and methyl bromide (11.4 g.) were heated to 80° in dimethylformamide (100 ml.) in an autoclave. After cooling the precipitate was filtered, washed with acetone and dried *in vacuo*. The product had m.p. 276-278° (yield 82%). The nmr spectrum (deuterium oxide) consisted of a singlet at δ 4.5 (3H, methyl), a multiplet at 8.8-9.15 (4H, pyridine protons) and a singlet at 9.5 ppm (2H, triazine protons).

Anal. Calcd. for $C_9H_9BrN_4$: C, 42.7; H, 3.6; N, 22.1; Br, 31.6. Found: C, 42.6; H, 3.6; N, 22.0; Br, 31.5.

1-Ethyl-4-(2-*sym*-triazinyl)pyridinium Bromide (X, R = C_2H_5).

2-(4-Pyridyl)-1,3,5-triazine (0.1 mole) and ethyl bromide (0.17 mole) in dimethylformamide (150 ml.) were stirred at 100° for 6 hours. After removal of the solvent the residue was treated with acetone and the precipitate filtered off. The product was washed with acetone and dried. It had m.p. 223-224° and was very hygroscopic (yield 85%). The analysis indicated the presence of a small amount of water. The nmr spectrum (deuterium oxide) consisted of a triplet at δ 1.45-1.75 (3H, methyl), a quartet at ∿ 4.5-4.9 (2H, methylene), a multiplet at 8.8-9.15 (4H, pyridine protons) and a singlet at 9.45 ppm (2H, triazine protons).

Anal. Calcd. for $C_{10}H_{11}BrN_4$ with 1.3% H_2O: C, 44.4; H, 4.2; N, 20.7. Br, 29.5; H_2O, 1.3. Found: C, 44.6; H, 4.5; N, 20.6; Br, 29.8; H_2O, 1.3.

1-Propyl-4-(2-*sym*-triazinyl)pyridinium Bromide (X, R = C_3H_7).

This salt was prepared similarly using bromopropane as quaternising agent. It had m.p. 180-182° and was hygroscopic.

Anal. Calcd. for $C_{11}H_{13}BrN_4$ with 0.7% H_2O: C, 46.7; H, 4.7; N, 19.8; Br, 28.2; H_2O, 0.7. Found: C, 46.7; H, 4.7; N, 19.8; Br, 28.5; H_2O, 0.7.

1-Allyl-4-(2-*sym*-triazinyl)pyridinium Bromide (X, R = CH_2•$CH{=}CH_2$).

This salt was prepared similarly using allyl bromide in boiling chloroform. It had m.p. 170-172° and was hygroscopic.

Anal. Calcd. for $C_{11}H_{11}BrN_4$ with 0.7% H_2O: C, 47.0; H, 4.0; N, 19.9; Br, 28.4; H_2O, 0.7. Found: C, 46.8; H, 4.1; N, 19.8; Br, 28.5; H_2O, 0.7.

1-Ethoxycarbonylmethyl-4-(2-*sym*-triazinyl)pyridinium Bromide (X, R = CH_2•$COOC_2H_5$).

This salt was prepared likewise using ethyl bromoacetate in boiling ethyl alcohol. It had m.p. 193-195° and was hygroscopic.

Anal. Calcd. for $C_{12}H_{13}BrO_2N_4$ with 0.8% H_2O: C, 44.0; H, 4.1; N, 17.0; Br, 24.4; O, 10.5; H_2O, 0.8. Found: C, 44.2; H, 4.1; N, 16.6; Br, 24.4; O, 10.5; H_2O, 0.8.

2-(4-Pyridyl)-4-methyl-1,3,5-triazine (XIII).

Ethyl isonicotylimidate (XI) (14) (0.1 mole), ethyl acetimidate (XII) (15) (0.1 mole) and formamidine hydrochloride (0.1 mole) were stirred at 55° for 5 hours. After cooling the mixture was diluted with water and the precipitate of the co-product 2-(4-pyridyl)-1,3,5-triazine (IX) was filtered off and washed with water. The filtrate was extracted with ether. The ethereal layer was dried and the solvent removed. The residue was crystallised several times from hexane to afford 2-(4-pyridyl)-4-methyl-1,3,5-triazine, m.p. 99-102° (yield 16%). The nmr spectrum (deuteriochloroform) consisted of a singlet at δ 2.8 (3H, methyl), a doublet at 8.3-8.4 (2H), a doublet at 8.8-8.9 (2H) and a singlet at 9.25 ppm (1H; triazine proton).

Anal. Calcd. for $C_9H_8N_4$: C, 62.8; H, 4.7; N, 32.5. Found: C, 62.9; H, 4.75; N, 32.35.

1-Methyl-4-(4-methyl-2-*sym*-triazinyl)pyridinium Bromide (XIV).

This salt was prepared from 2-(4-pyridyl)-4-methyl-1,3,5-triazine (XIII) and methyl bromide in chloroform at 90° in an autoclave. It had m.p. 194-196° and was hygroscopic (yield 30%). The nmr spectrum (deuterium oxide) consisted of a singlet at δ 2.85 (3H, triazine methyl), a singlet at 4.55 (3H, quaternary methyl), a multiplet at 8.9-9.2 (4H, pyridine protons) and a singlet at 9.4 ppm (1H, triazine proton).

Anal. Calcd. for $C_{10}H_{11}BrN_4$ with 1.7% H_2O: C, 44.2; H, 4.3; N, 20.6; Br, 29.4; H_2O, 1.7. Found: C, 43.9; H, 4.15; N, 20.25; Br, 29.9; H_2O, 1.7.

2-(4-Pyridyl)-4,6-dimethyl-1,3,5-triazine (XVI).

Isonicotinamidine hydrochloride (0.15 mole) was mixed with ethyl

acetamidate (0.45 mole) and the mixture heated to 58°. The exothermic reaction was completed in 15 minutes. The mixture was cooled and the precipitate collected and washed with acetonitrile. The filtrate was diluted with water and extracted with ether. The ether extracts were dried and the solvent removed. The residue was crystallised from hexane to afford 2-(4-pyridyl)-4,6-dimethyl-1,3,5-triazine, m.p. 72-74° (yield 74%). Yanagiya, *et al.*, gave m.p. 72° (16). The nmr spectrum (deuteriochloroform) consisted of a singlet δ 2.65 (6H, methyl), a doublet at 8.15-8.25 (2H) and a doublet at 8.65-8.75 ppm (2H).

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.6; H, 5.5; N, 29.9.

1-Methyl-4-(4,6-dimethyl-2-*sym*-triazinyl)pyridinium Bromide (XVII).

This salt was prepared by reaction of 2-(4-pyridyl)-4,6-dimethyl-1,3,5-triazine (XVI) with methyl bromide in dichloromethane at 80° in an autoclave. It had m.p. 272-273° (with decomposition). The nmr spectrum (deuterium oxide) consisted of a singlet at δ 2.9 (6H, triazine methyl), a singlet at 4.6 (3H, quaternary methyl) and a multiplet at 8.85-9.2 ppm (4H, pyridine protons).

Anal. Calcd. for $C_{11}H_{13}BrN_4$: C, 47.0; H, 4.7; N, 19.9; Br, 28.4. Found: C, 46.8; H, 4.6; N, 19.5; Br, 28.15.

2-(4-Pyridyl)pyrimidine (XIX).

Isonicotinamidine hydrochloride (0.6 mole) and 1,1,3,3-tetramethoxypropane (0.99 mole) were heated to 130° and water (1 ml.) was added. After 16 hours agitation the mixture was cooled and the black mass was then diluted with water and extracted with chloroform. After drying the solvent was evaporated to afford a residue which was twice distilled at 89°/0.07 mm to give 2-(4-pyridyl)-pyrimidine m.p. 79-81° (yield 31%). The nmr spectrum (deuteriochloroform) consisted of a triplet at δ 7.2-7.35 (1H, pyrimidine proton at position 5), a doublet at 8.2-8.3 (2H) and a multiplet at 8.7-8.9 (4H).

Anal. Calcd. for $C_9H_7N_3$: C, 68.8; H, 4.5; N, 26.7. Found: C, 68.5; H, 4.7; N, 26.5.

1-Methyl-4-(2-pyrimidyl)pyridinium Bromide (XX).

This salt was prepared from 2-(4-pyridyl)pyrimidine (XIX) and methyl bromide in dry dimethyl-formamide by heating for 16 hours at 80° in an autoclave. After cooling, the precipitate was filtered, washed with acetone and dried. It had m.p. 284-287° (with decomposition) and was hygroscopic. The nmr spectrum (deuterium oxide) consisted of a singlet at δ 4.4 (3H, quaternary methyl), a triplet at 7.5-7.65 (1H, pyrimidine proton at position 5) and a multiplet at 8.6-8.9 ppm (6H).

Anal. Calcd. for $C_{10}H_{10}BrN_3$ with 1.7% H_2O: C, 46.8; H, 4.0; N, 16.4; Br, 31.15. Found: C, 47.0; H, 4.0; N, 16.3; Br, 31.1.

1-Methyl-4-(5-pyrimidyl)pyridinium Iodide (XXI).

This salt was obtained by reacting 5-(4-pyridyl)pyrimidine (17) with methyl iodide in boiling methanol for 16 hours. After cooling it was obtained in 85% yield. The m.p. was > 250°.

Anal. Calcd. for $C_{10}H_{10}IN_3$: C, 40.15; H, 3.35; N, 14.05; I, 42.4. Found: C, 40.1; H, 3.4; N, 14.0; I, 42.8.

1-Methyl-2',4-bipyridinium Methylsulfate (XXII).

2,4'-Bipyridine (0.16 mole) and dimethyl sulfate (0.16 mole) were dissolved in chloroform (100 ml.) and the mixture refluxed for 3 hours. The crystals which formed were collected, washed with chloroform and dried. They had m.p. 146° (yield 84%).

Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.1; N, 9.9; S, 11.4. Found: C, 50.75; H, 5.0; N, 9.8; S, 11.3.

1-Methyl-4,4'-bipyridinium Bromide (VIII).

4,4'-Bipyridine (0.05 mole) and methyl bromide (0.05 mole) were dissolved in methanol (100 ml.) and heated in an autoclave for 16 hours at 70°. On cooling 1,1'-dimethyl-4,4'-bipyridinium dibromide (7.4 g.) was separated by filtration. The filtrate was concentrated and treated with acetone. The white precipitate was crystallised thrice from methanol/acetone to afford 1-methyl-4,4'-bipyridinium bromide (3.2 g.) as the monohydrate, m.p. 232-234°. The nmr spectrum (deuterium oxide) consisted of a singlet at δ 4.55 (3H, methyl), a doublet at 7.85-7.95 (2H), a doublet at 8.35-8.45 (2H), a doublet at 8.7-8.8 (2H) and a doublet at 8.9-9.0 ppm (2H).

Anal. Calcd. for $C_{11}H_{11}BrN_2 \cdot H_2O$: C, 49.05; H, 4.9; N, 10.4; Br, 29.7. Found: C, 48.9; H, 4.85; N, 10.5; Br, 29.9.

1-Methyl-4-phenylpyridinium Bromide (VII).

This salt was prepared as described by Hedrich (18). It had m.p. 168-169°.

Acknowledgement.

We thank Dr. W. Leuchtenberger, DEGUSSA Wolfgang, Hanau FR6, for a supply of 1-methyl-2',4-bipyridinium methylsulfate.

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