Stable Free Radicals.   Part II.[1]   Some Substituted Pyridinyls

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Cyano and methoxycarbonyl substituents at the 2- and 6-positions, unlike methyl groups, strongly stabilize pyridinyl radicals, particularly if the 4-position is blocked.   The structure–stability relationships in this series afford further evidence for the zwitterionic stabilization of radicals.

THE discovery by Kosower[2] of 1-ethyl-4-methoxy-carbonylpyridinyl (1) initiated studies on a new class of stable free radicals. Whereas 1-methylpyridinyl (2) dimerises at once,[3] the radical (1) is stable indefinitely in the absence of oxygen. Most structural modifications so far reported significantly reduce its stability: the

1-methyl homologue (3)[4] has a life of 2—3 days, and the introduction of other methyl groups into the ring has a marked destabilizing effect: compound (4) had a life of 10—20 min[4] and no radical (5) could be obtained.[4]

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[1] Part I, R. W. Baldock, P. Hudson, A. R. Katritzky, A. Smith, and F. Soti, preceding paper.

[2] E. M. Kosower and E. J. Poziomek, J. Amer. Chem. Soc., 1964, **86**, 5515.
[3] S. G. Mairanovskii, Trudy Chetvertogo Soveshchaniya Elektro-khim., Moscow, 1956, 223. (Chem. Abs., 1960, **54**, 9558i).
[4] M. Itoh and S. Nagakura, Tetrahedron Letters, 1965, 417; Bull. Chem. Soc. Japan, 1966, **39**, 369.

Electron-withdrawing groups other than methoxycarbonyl at the 4-position have been investigated, and also showed stabilization: the carbamoyl radical (6) had a life of 1—2 h [4] and the cyano-radical (7) a life of 7 days.[4] However, replacement of the ethyl group in (1) by an isopropyl group [5] or by a polymethylene chain linking two rings [6,7] gave stable radicals.

In formulae (1)—(22) all R = H except where otherwise indicated

R⁵⌇R⁴⌇R³ / R⁶⌇N⌇R² / R¹
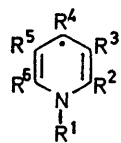
(1) R¹ = Et, R⁴ = CO₂Me
(2) R¹ = Me
(3) R¹ = Me, R⁴ = CO₂Me
(4) R¹ = R² = R⁶ = Me, R⁴ = CO₂Me
(5) R¹ = R³ = R⁵ = Me, R⁴ = CO₂Me
(6) R¹ = Me, R⁴ = CO·NH₂
(7) R¹ = Me, R⁴ = CN
(8) R¹ = Et, R⁴ = CN

The pyridinyls fit our proposed classification [1] of merostabilized radicals and, according to the considerations outlined in ref. 1, electron-withdrawing groups at the 2- and 6-positions should also stabilize pyridinyl
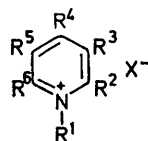
(9) R¹ = Et, R² = R⁶ = CN, X = BF₄⁻
(10) R¹ = Et, R² = R⁶ = CN, X = I⁻
(11) R¹ = Et, R² = OEt, R⁶ = CN, X = BF₄⁻
(12) R¹ = Me, R² = R⁶ = CO₂Me, X = CF₃SO₃⁻
(13) R¹ = Et, R² = R⁶ = CN, R⁴ = Me, X = BF₄⁻
(14) R¹ = Et, R² = R⁶ = CN, R⁴ = Me, X = I⁻
(15) R¹ = Et, R² = R⁶ = Me, R⁴ = CN, X = BF₄⁻
(16) R¹ = Et, R² = R⁶ = Me, R⁴ = CN, X = I⁻
(17) R¹ = OEt, R² = R⁶ = CN, X = BF₄⁻
(18) R¹ = Me, R⁴ = CN, X = CF₃·SO₃⁻

Preparation of Substituted Pyridinium Salts.— Attempted quaternization of 2,6-dicyanopyridine [8] failed with methyl iodide, but was successful with triethyloxonium fluoroborate. The 2,6-dicyano-1-ethylpyridinium fluoroborate (9) crystallized unchanged from acetonitrile–ethyl acetate, but on attempted recrystallization from ethanol–ether it was transformed into 6-cyano-2-ethoxy-1-ethylpyridinium fluoroborate (11). 2,6-Dicyano-1-ethylpyridinium fluoroborate with potassium iodide in acetonitrile gave the corresponding iodide (10).

Attempted quaternization of 2,6-bismethoxycarbonylpyridine [9] failed with triethyloxonium fluoroborate but succeeded with methyl trifluoromethanesulphonate to yield the salt (12). 2,6-Dicyano-4-methylpyridine [10] was transformed into its ethiodide (14) by quaternization with triethyloxonium fluoroborate followed by metathesis with potassium iodide. 4-Cyano-1-ethyl-2,6-dimethylpyridinium iodide (16) was prepared similarly.

2,6-Dicyanopyridine 1-oxide [10] was quaternized with triethyloxonium fluoroborate (not with dimethyl sulphate or methyl trifluoromethanesulphonate), but attempted conversion of the quaternary derivative (17) into 2,4,6-

tricyanopyridine with potassium cyanide [11] failed; attempted crystallization of (17) gave back the starting N-oxide.

Preparation of Known Free Radicals.—1-Ethyl-4-methoxycarbonylpyridinyl (1) was prepared from the pyridinium iodide according to the literature method; [2] it was stable indefinitely and its e.s.r. spectrum agreed with that reported.[2] 4-Cyano-1-ethylpyridinyl (8) [12] was prepared from the corresponding iodide by treatment with zinc; [2] it decomposed during 4 days in benzene solution. The e.s.r. spectrum of 170 lines (width 33·5 G) was too complex for interpretation.

4-Cyano-1-methylpyridinyl (7) [4] was prepared from the pyridinium trifluoromethanesulphonate (18) with zinc in acetonitrile in the presence of a catalytic amount of potassium iodide.[2] The complex e.s.r. spectrum (>220 lines) was 40·5 G wide. The radical decomposed completely in 24 h and was less stable than its 1-ethyl analogue (8), which is in keeping with Kosower's [5] observation that 4-methoxycarbonyl-1-methylpyridinyl is less stable than the 1-ethyl and 1-isopropyl analogues.

R⁴⌇ / R⁶⌇N⌇R² / R¹
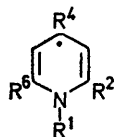
(19) R¹ = Et, R² = R⁶ = CN
(20) R¹ = Et, R² = R⁶ = CN, R⁴ = Me
(21) R¹ = Et, R² = R⁶ = Me, R⁴ = CN
(22) R¹ = Me, R² = R⁶ = CO₂Me

2,6-Dicyano-1-ethylpyridinyl (19).—Prepared [2] from the iodide (10) this radical decomposed immediately in the presence of air. The e.s.r. spectrum (Figure 1) is consistent with the following coupling constants: a_{H-4} 8·77; a_N 7·75; a_{H-3} 0·24; $a_{N(CN)}$ 1·41; $a_{N(CN)}$ 1·18; $a_{H(CH_2)}$ 4·27; $a_{H(CH_3)}$ 0·24 G. The intensities of the lines of the computed spectrum differ a little from those observed; in such a complex spectrum the shape is very sensitive to the magnitudes of the coupling constants and to the line width. The coupling constants suggest high spin density at the ring nitrogen atom and at C-4.

N≡C⌇N⌇C≡N⁻ / Et ⟷ N̄≡C⌇N⌇C≡N / Et

(23a)   (23b)
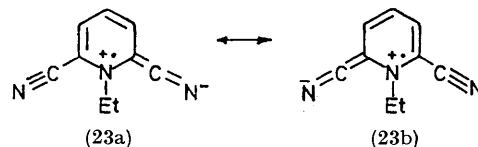
The high spin density on the nitrogen atom indicates the importance of zwitterionic forms, e.g. (23a and b).

[5] E. M. Kosower, personal communication.
[6] E. M. Kosower and Y. Ykegami, *J. Amer. Chem. Soc.*, 1967, 89, 461.
[7] M. Itoh and E. M. Kosower, *J. Amer. Chem. Soc.*, 1968, 90, 1843.
[8] R. Lukeš and M. Pergál, *Chem. listy*, 1958, 52, 68.
[9] N. E. Andersson and T. O. Soine, *J. Amer. Pharm. Assoc.*, 1950, 39, 460.

[10] M. Ishikawa, C. Kaneko, I. Yokoe, and S. Yamada, *Tetrahedron*, 1969, 25, 295.
[11] W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.*, 1959, 81, 4004.
[12] E. M. Kosower and J. L. Cotter, *J. Amer. Chem. Soc.*, 1964, 86, 5524.

However, the radical is destabilized because of the hydrogen atom at the high spin density C-4 and under nitrogen the radical decomposed completely in 3 days. To eliminate this destabilizing factor we synthesized the 4-methyl homologue.

2,6-*Dicyano*-1-*ethyl*-4-*methylpyridinyl* (20).—The iodide (14) gave the free radical (20) by treatment with zinc.[2] The pyridinyl (20) was completely stable in benzene at 20° in an oxygen-free atmosphere. The e.s.r. spectrum (Figure 2) showed the following coupling constants: $a_{H(CH_3)}$ 8·62; a_N 7·23; $a_{H(CH_3)}$ 4·05; $a_{N(CN)}$ 1·35 G; with better resolution further fine structure

presence of potassium iodide.[2] The e.s.r. spectrum (Figure 3) showed the following coupling constants: a_{H-4} 7·56; a_N 6·71; $a_{H(N-CH_3)}$ 5·16; a_{H-3} 2·06; $a_{H(O-CH_3)}$

(24)
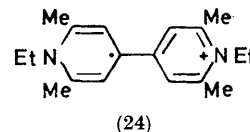
0·52 G. It decomposed completely in 5 h in benzene at room temperature. The instability is explained by the presence of the 4-hydrogen atom and the N-methyl
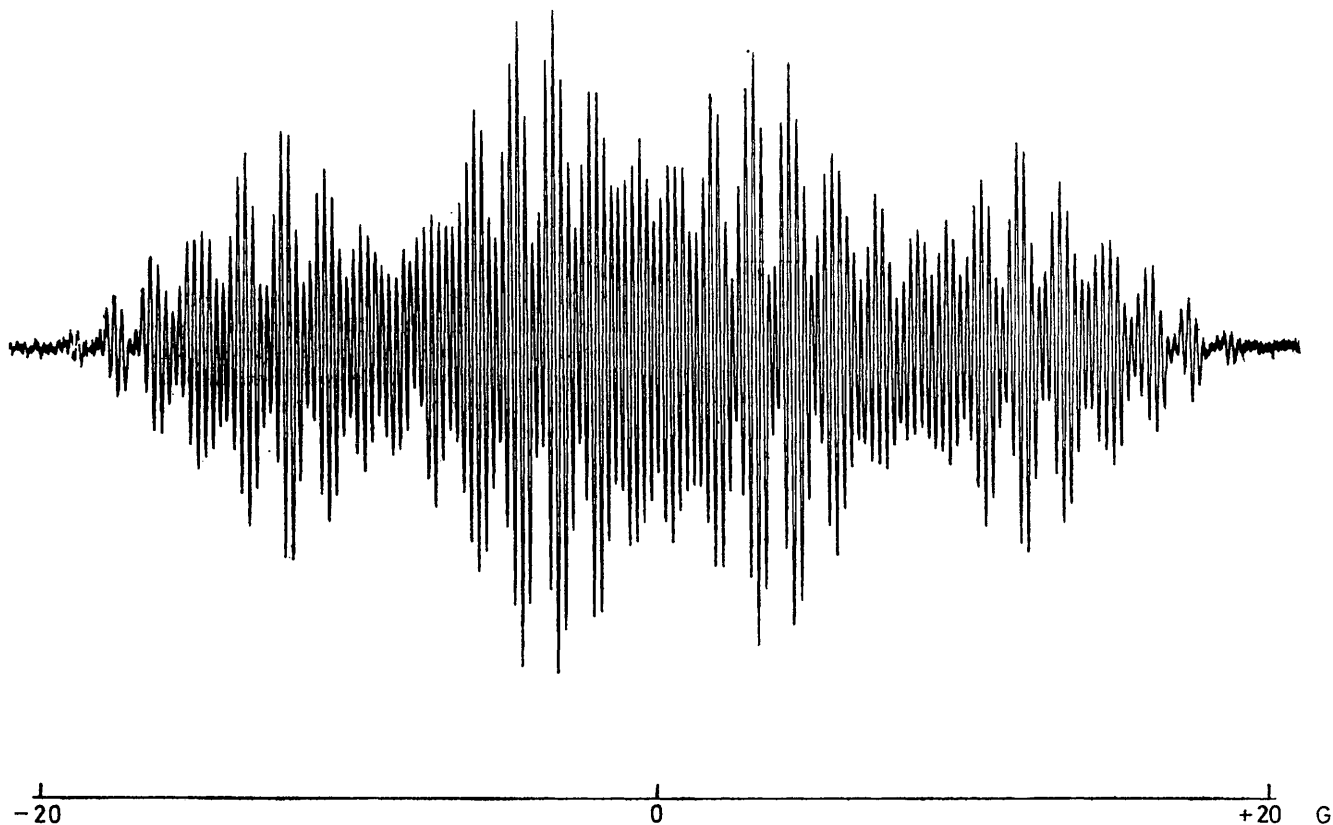

FIGURE 1   E.s.r. spectrum of 2,6-dicyano-1-ethylpyridinyl in benzene

was disclosed for the remaining hydrogen atoms of the ethyl group and H-3 and H-5 with coupling constants <0·25 G. This free radical is also very oxygen-sensitive; it decomposed at once in air to give a new free radical, the structure of which is under investigation.

4-*Cyano*-1-*ethyl*-2,6-*dimethylpyridinyl* (21).—Prepared from the iodide (16), this radical (21) was very unstable, decomposing completely in 2 h into a new, more stable radical, inert to oxygen and with an e.s.r. spectrum containing only an unresolved singlet. This new radical may be the viologen (24), by analogy with the decomposition of 4-cyano-1-methylpyridinyl.[12]

2,6-*Bismethoxycarbonyl*-1-*methylpyridinyl* (22).—The corresponding pyridinium trifluoromethanesulphonate (12) gave the free radical by treatment with zinc in the

group,[5] and the steric crowding of the N-methyl group [4] and the methoxycarbonyl groups.

General Discussion.—The stability of 2,6-dicyano-1-ethyl-4-methylpyridinyl (20) as compared with 2,6-dicyano-1-ethylpyridinyl (19) and 2,6-bismethoxycarbonyl-1-methylpyridinyl (22), which decomposed completely during 3 days and 5 h, respectively, is explained by the presence of the 4-hydrogen atom in (19) and (22). Under the same conditions 4-cyano-1-ethylpyridinyl (8) [12] and 4-cyano-1-methylpyridinyl (7) [4] decomposed completely during 4 days and 1 day, respectively, whereas 4-methoxycarbonyl-1-ethylpyridinyl (1) [2] was stable.

Substituents at the 2- and 6-positions inherently destabilize pyridinyl radicals; [4] hence the new radicals

with 2- and 6-cyano-groups should be compared with 4-cyano-1-ethyl-2,6-dimethylpyridinyl (21), which is very unstable, decomposing completely in 2 h.
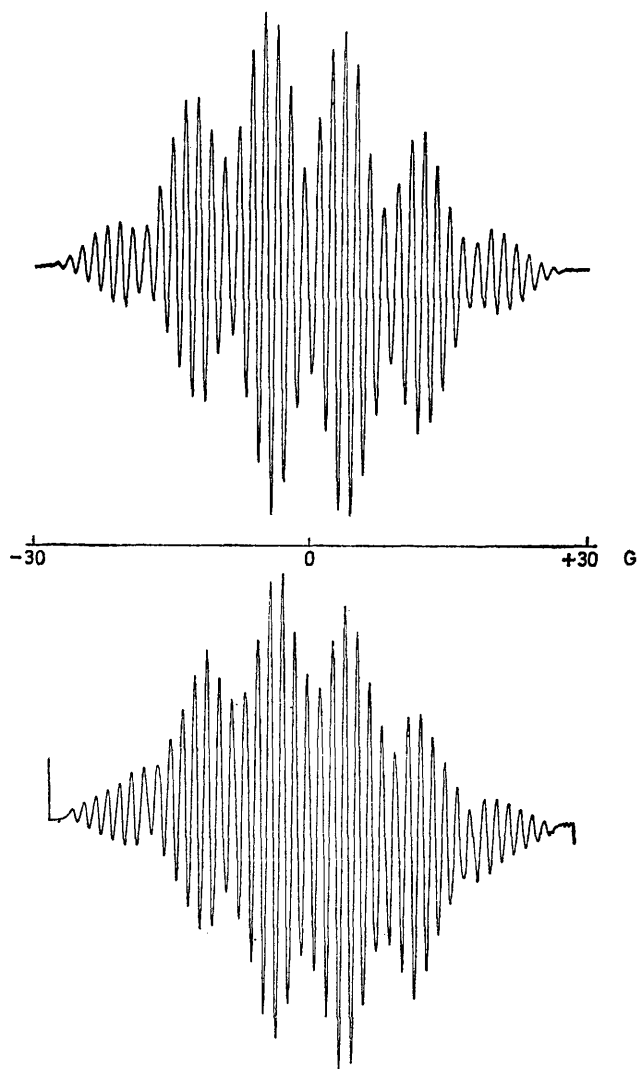

FIGURE 2 E.s.r. spectrum (top) of 2,6-dicyano-1-ethyl-4-methylpyridinyl in benzene. The computer simulation (bottom) is based on coupling constants given in the text. The line width was estimated to be 0·6 G and the line shape was considered to be a Lorentzian line

These experimental facts support the hypothesis [1] of zwitterionic stabilization of free radicals.

EXPERIMENTAL

M.p.s were determined on a Reichart hot-stage apparatus. N.m.r. spectra (Table) were recorded with a Perkin-Elmer R12 spectrometer and e.s.r. spectra with a Varian E-3 EPR spectrometer, respectively.

2,6-Dicyano-1-ethylpyridinium Fluoroborate (9).—2,6-Dicyanopyridine [8] (3·87 g, 0·03 mol) and triethyloxonium fluoroborate [13] (11·4 g, 0·06 mol) in dry 1,2-dichloroethane (50 ml) were kept at 20° for 50 h and then dry ether (50 ml) was added. The oily product which separated was taken up in dry acetonitrile (10 ml) and dry ethyl acetate (50 ml) was gradually added to give the *fluoroborate* as long needles (5·70 g, 78%), m.p. 172—174° (raised by recrystallization

from acetonitrile–ethyl acetate to 174—176·5°) (Found: C, 43·8; H, 2·6; N, 16·8. $C_9H_8BF_4N_3$ requires C, 44·1; H, 3·3; N, 17·2%).

2,6-Dicyano-1-ethylpyridinium Iodide (10).—2,6-Dicyano-1-ethylpyridinium fluoroborate (0·245 g, 0·001 mol) in dry acetonitrile (0·5 ml) was added to potassium iodide (0·166 g, 0·001 mol) in dry acetonitrile (10 ml) at 20°. After 15 h potassium fluoroborate (0·118 g, 94%) was filtered off and dry ethyl acetate (50 ml) was added gradually to give the *iodide* (0·206 g, 72%) as long red needles, m.p. 132—133·5° [raised by recrystallization from acetonitrile–ethyl acetate (1 : 5) to 134·5—135°] (Found: C, 38·0; H, 2·9; N, 14·8. $C_9H_8IN_3$ requires C, 37·9; H, 2·8; N, 14·7%).

6-Cyano-2-ethoxy-1-ethylpyridinium Fluoroborate (11).—2,6-Dicyano-1-ethylpyridinium fluoroborate (0·245 g, 0·001 mol) was heated under reflux in ethanol (10 ml) for 10 min. After cooling, dry ether (10 ml) was added to give the 2-*ethoxy fluoroborate* (0·129 g, 49%), as long needles, m.p. 79·5—82° [raised by recrystallisation from ethanol–ether (1 : 5) to 82—84°] (Found: C, 45·4; H, 4·9; N, 10·8. $C_{10}H_{13}BF_4N_2O$ requires C, 45·5; H, 5·0; N, 10·6%).

2,6-Bismethoxycarbonyl-1-methylpyridinium Trifluoro-methanesulphonate (12).—2,6-Bismethoxycarbonylpyridine [9] (0·195 g, 0·001 mol) and methyl trifluoromethanesulphon-ate [14] (0·164 g, 0·001 mol) were heated for 5 min at 60° and kept at 20° overnight. The crystalline precipitate was dissolved in acetonitrile (0·5 ml) and ether (5 ml) was added gradually to give the *trifluoromethanesulphonate* (0·229 g, 64%) as needles, m.p. 97—99° (changed by recrystallization from 1,2-dichloroethane to 97·5—99°) (Found: C, 36·2; H, 3·4; N, 3·6. $C_{11}H_{12}F_3NO_7S$ requires C, 36·8; H, 3·4; N, 3·9%).

2,6-Dicyano-1-ethyl-4-methylpyridinium Fluoroborate (13). —2,6-Dicyano-4-methylpyridine [10] (2·86 g, 0·02 mol) and triethyloxonium fluoroborate [13] (7·60 g, 0·04 mol) in dry 1,2-dichloroethane (40 ml) were kept at 20° for 50 h and then dry ether (40 ml) was added. The oily product was taken up in acetonitrile (10 ml) and ethyl acetate (100 ml) was added gradually to give the dicyano-4-*methyl fluoro-borate* (2·64 g, 51%) as prisms, m.p. 153·5—158·5° (Found: C, 46·1; H, 4·0; N, 16·0. $C_{10}H_{10}BF_4N_3$ requires C, 46·4; H, 3·9; N, 16·2%).

2,6-Dicyano-1-ethyl-4-methylpyridinium Iodide (14).—2,6-Dicyano-1-ethyl-4-methylpyridinium fluoroborate (0·518 g, 0·002 mol) in acetonitrile (2·5 ml) was added to potassium iodide (0·332 g, 0·002 mol) dissolved in acetonitrile (20 ml) at 20° and kept overnight. The separated potassium fluoroborate was filtered off and ethyl acetate (200 ml) was added gradually to the filtrate to give the dicyano-4-*methyl iodide* (0·339 g, 57%), as orange-yellow needles, m.p. 132—133° (decomp.) (Found: C, 40·4; H, 3·4; N, 13·5. $C_{10}H_{10}IN_3$ requires C, 40·2; H, 3·4; N, 14·1%).

4-Cyano-1-ethyl-2,6-dimethylpyridinium Fluoroborate (15). —2,6-Dimethyl-4-cyanopyridine [11] (0·528 g, 0·004 mol) and triethyloxonium fluoroborate [13] (1·90 g, 0·01 mol) in 1,2-dichloroethane (10 ml) were kept at 20° for 50 h. The precipitate was recrystallized from acetonitrile–ethyl acetate (1 : 6) to give the *fluoroborate* (0·704 g, 71%) as prisms, m.p. 147·5—151° (raised by recrystallization from aceto-nitrile–ethyl acetate to 150—152·5°) (Found: C, 47·2; H, 5·1; N, 11·3. $C_{10}H_{13}BF_4N_2$ requires C, 48·4; H, 5·3; N, 11·3%).

[13] H. Meerwein, Org. Synth., 1966, 46, 113.
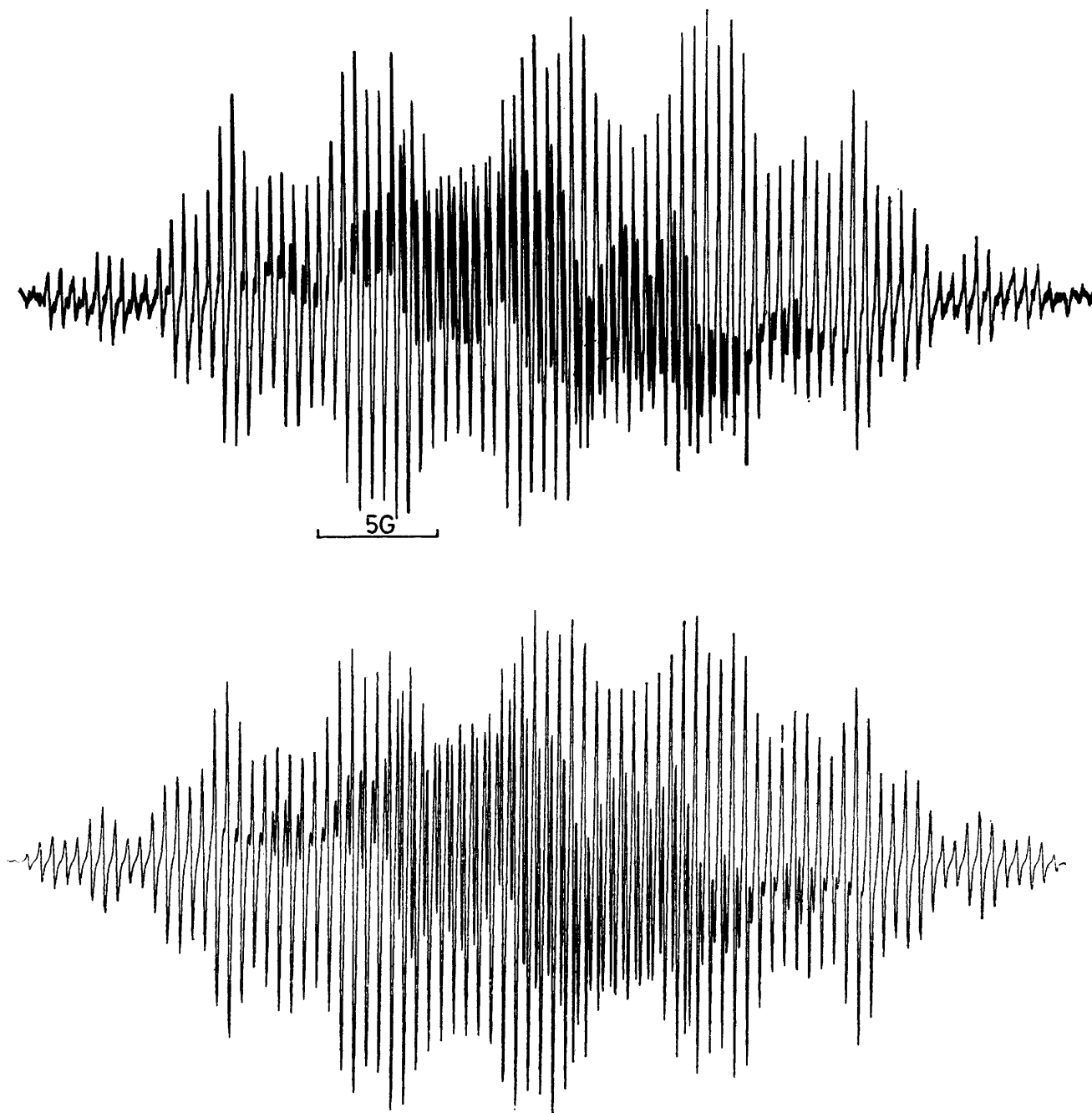[14] A. G. Burton, personal communication.

FIGURE 3 E.s.r. spectrum (top) of 2,6-bismethoxycarbonyl-1-methylpyridinyl in benzene. The computer simulation (bottom) is based on the coupling constants given in the text. The line width was estimated to be 0·7 G and the line shape was considered to be Lorentzian

N.m.r. spectra of substituted pyridinium salts: chemical shifts (τ values) and coupling constants (J/Hz)

| Compound | Aromatic protons | 1-Substituent | | | 2-Substituent | 4-Substituent | 6-Substituent | Anion | Solvent |
		CH_2	J	CH_3					
(9)	0·7—1·4	4·64	7·6	8·05	CN		CN	BF_4^-	$CF_3 \cdot CO_2H$
(10)	0·4—0·7	4·28	7·6	7·72	CN		CN	I^-	D_2O
(11)	1·2—1·6; 1·8—2·2	5·16	7·1	8·32	OEt: 5·16, 8·32 (J 7·1)		CN	BF_4^-	$CF_3 \cdot CO_2H$
(12)	1·0—1·5			5·29	CO_2Me: 5·77		CO_2Me: 5·77	$CF_3 \cdot SO_3^-$	$CF_3 \cdot CO_2H$
(13)	1·41	4·76	7·3	8·10	CN	Me: 7·10	CN	BF_4^-	$CF_3 \cdot CO_2H$
(14)	0·73	4·37	7·5	7·75	CN	Me: 6·73	CN	I^-	D_2O
(15)	1·90	5·22	7·5	8·33	Me: 6·97	CN	Me: 6·97	BF_4^-	$CF_3 \cdot CO_2H$
(16)	1·36	4·88	7·4	8·01	Me: 6·59	CN	Me: 6·59	I^-	D_2O
(17)	0·9—1·4	4·88	7·1	8·20	CN		CN	BF_4^-	$CF_3 \cdot CO_2H$
(18)	0·91 (J 6·0); 1·56			5·38		CN		$CF_3 \cdot SO_3^-$	$CF_3 \cdot CO_2H$

4-*Cyano*-1-*ethyl*-2,6-*dimethylpyridinium Iodide* (16).—4-Cyano-1-ethyl-2,6-dimethylpyridinium fluoroborate (0·620 g, 0·0025 mol) in acetonitrile (2 ml) was added to potassium iodide (0·415 g, 0·0025 mol) dissolved in acetonitrile (25 ml) at 20° and the mixture was kept overnight. The separated potassium fluoroborate was filtered off and ethyl acetate (200 ml) was added to the filtrate to give the *iodide* (0·490 g, 68%) as yellow needles, m.p. 212·5—214·5° (decomp.) (Found: C, 41·2; H, 4·6; N, 9·2. $C_{10}H_{13}IN_2$ requires C, 41·7; H, 4·6; N, 9·7%).

2,6-*Dicyano*-1-*ethoxypyridinium Fluoroborate* (17).—Triethyloxonium fluoroborate [13] (9·50 g, 0·05 mol) was added to 2,6-dicyanopyridine 1-oxide [10] (3·63 g, 0·025 mol) in 1,2-dichloroethane (25 ml) at 40° and the mixture was kept at 20° for 50 h. The 1-*ethoxy fluoroborate* (5·92 g, 91%) separated as needles, m.p. 134—139° (decomp.), which decomposed on attempted purification (Found: C, 40·9; H, 3·0; N, 16·0. $C_9H_8BF_4N_3O$ requires C, 41·4; H, 3·1; N, 16·1%).

Decomposition of 2,6-*Dicyano*-1-*ethoxypyridinium Fluoroborate.*—2,6-Dicyano-1-ethoxypyridinium fluoroborate (0·261 g, 0·001 mol) in ethanol (5 ml) was heated under reflux for 2 min and the solution was then kept overnight. 2,6-Dicyanopyridine 1-oxide (0·062 g, 43%) crystallised as prisms, m.p. and mixed m.p. with an authentic sample 187—189°.

4-*Cyano*-1-*methylpyridinium Trifluoromethanesulphonate* (18).—4-Cyanopyridine (Koch–Light; m.p. 80—82°) (0·104 g, 0·001 mol) and methyl trifluoromethanesulphonate [14] (0·164 g, 0·001 mol) were heated for 3 min at 60°. After cooling, the solid product was recrystallised twice from ethanol–chloroform (1 : 2) to give the *sulphonate* (0·118 g, 39%) as prisms, m.p. 136—140° (Found: C, 36·3; H, 2·7; N, 10·5. $C_8H_7F_3N_2O_3S$ requires C, 35·8; H, 2·6; N, 10·4%).

General Procedure for Preparation of Pyridinyl Radicals.—

Solvents were degassed by three freeze–pump cycles, then distilled on to molecular sieves (4A) (small pellets) which had been flame-dried under vacuum. The substituted pyridinium iodide (0·0001 mol) and zinc (0·00005 mol) were placed along with a Teflon-coated magnetic bar in the clean reaction flask of the apparatus shown in Figure 4. The system was connected to a vacuum line and evacuated
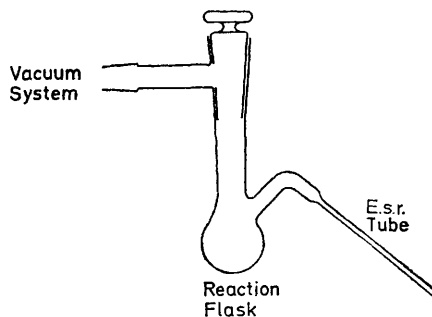

FIGURE 4 Reaction apparatus for the preparation and for the recording of the e.s.r. spectra of pyridinyl radicals

to 0·1 mmHg after careful flushing with nitrogen (oxygen-free). If a pyridinium salt other than the iodide was used, potassium iodide (0·00002 mol) was added to the reaction mixture. Acetonitrile (Spectrograde; 1 ml) was distilled into the reaction flask and the mixture was stirred for 1 h at 0°. The acetonitrile was distilled off and sodium-dried AnalaR benzene (2·5 ml) was distilled into the flask. After 20 min stirring at 20° the solution was transferred to the e.s.r. tube for measurement. No free radicals were obtained from the corresponding fluoroborate salts in the presence of potassium iodide by the same method.