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Electro-organic Reactions Part 35. Efficient Carbon - Oxygen Bond Formation in the Anodic Coupling of Pyridopyrimidine Derivatives.

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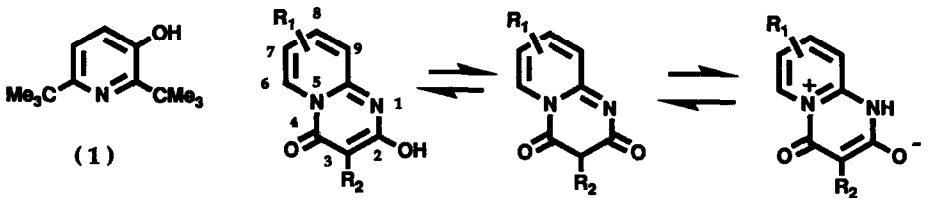
Abstract. 4-H-Pyrido[1,2-a]pyrimidine-2,4-diones (Chichibabin) derivatives, formed by condensation of 2-aminopyridines with substituted dialkylmalonates, are electroactive. In solution in CH_2Cl_2/CF_3CO_2H mixtures they are smoothly and selectively anodically coupled in high yield. The products are novel and unexpected; radical coupling at the C-3 and O-4 positions is involved and the proposed mechanism is analogous to that of oxidative phenolic coupling.

There is a need for better methods for direct 3-substitution in pyridine. Nucleophilic and radical substitution can be efficient but reaction is predominantly at the 2- and 4-positions. Electrophilic substitution, at the 3-position, is bedevilled not only by the intrinsic deactivation of the pyridine ring but also by initial attachment of electrophilic reagents to the ring nitrogen atom; this further deactivates the molecule to be substituted.

In our hands attempts[1] at direct anodic trifluoroacetoxylation of substituted pyridines, using methods similar to those developed by Eberson et al[2a] and by Miller et al[2b], gave interesting but preparatively impractical results. Where there was severe steric hindrance at nitrogen a modest (16%) yield of the 3-hydroxyl derivative (**1**) was obtained after aqueous work-up. In less hindered cases substitution was at the nitrogen to give after work-up the corresponding N-oxide, often in good yield.

An alternative approach is to derivatise pyridine prior to electrolysis so that the nucleophilicity of the ring nitrogen is lessened. This paper describes the results of an exploration of this approach. The Chichibabin derivatives (**2**) are relatively easily formed[3] from 2-aminopyridines, which may after further reaction be recovered by hydrolysis if neccessary. The correct structural representation of these derivatives is problematical but should (**2a**) and (**2b**) be substantial contributors to the correct description then it implies a lessening of the aromaticity of the pyridine ring and of the nitrogen (N-5) nucleophilicity.



(1) (2a) (2b) (2c)

RESULTS AND DISCUSSION:

The Chichibabin derivatives (4H-pyrido[1,2-a]pyrimidine-2,4-diones) : Two routes have been used. Route A is the original one[3] in which a suitably substituted dialkylmalonate is condensed with 2-aminopyridines by reaction at 160-200°C for several hours with continuous removal of the alcohol. In route B chloroarylmalonate esters are used which are more reactive in the condensation reaction which consequently proceeds rapidly at modest temperatures[4].

The derivatives prepared by these routes are given in Table 1 which also displays yields and melting points. Many of the compounds listed in Table 1 are new and their characterisation is described in the experimental section. Of immediate and practical importance is the solubility of these derivatives; the high melting points are a reflection of their polarity and also in keeping with this is the low solublity in organic solvents of all but those substituted with lipophilic alkyl groups. The parent compound (3) is insoluble in all organic solvents tried including DMSO, MeCN, DMF, and alcohols. The 3-hexyl (5) and 3-octyl (6) compounds are more soluble; the 3-octyl (6) derivative, for instance, is significantly soluble in CH_2Cl_2 > $CHCl_3$ > MeCN. The most soluble derivatives are those with alkyl substitution at C-3 and at one of the ring positions (C-7, C-8 or C-9) and it is these which feature largely in the electrochemical experiments. All of the derivatives are soluble in mixtures of CF_3CO_2H(TFA)/CH_2Cl_2, in which they are presumably protonated.

Voltammetry and coulometry : Single sweep cyclic voltammetry revealed irreversible oxidation at a platinum bead anode in both acetonitrile and mixtures of trifluoroacetic acid and dichloromethane. Plots of i_p *vs* $v^{1/2}$ are linear, as expected for uncomplicated diffusion-controlled behaviour. The Chichibabin derivatives are much more soluble in the acidic solvent and are oxidised at *ca.* 0.4V more anodic than in neutral solution (MeCN); this is consistent with protonation of the derivatives to give less easily oxidised positively charged species. In later experiments we have chosen to use a constant boiling mixture (1:3) of trifluoroacetic acid and dichloromethane with triethylammonium trifluoroacetate (TEATFA) as supporting electrolyte. This is a very convenient electrolyte system which is not significantly oxidised at up to 2.6V (*vs* Ag/Ag^+).

Table 1. 4H-Pyrido[1,2-a]pyrimidine-2,4-diones

Compound No.	R_1	R_2	Route[a]	Yield (%)	m.p. (°C)
(3)	H	H	A	96	296 (d)
(3)	H	H	B1	83	296 (d)
(3)	H	H	B2	98	296 (d)
(4)	H	C_4H_9	B1	92	232-35
(4)	H	C_4H_9	B2	88	232-35
(5)	H	C_6H_{13}	A	88	185-87
(6)	H	C_8H_{17}	A	90	204-5
(6)	H	C_8H_{17}	B1	83	204-5
6)	H	C_8H_{17}	B2	79	204-5
(7)	8-Me	H	A	89	280-85 (d)
(7)	8-Me	H	B1	82	280-85 (d)
(7)	8-Me	H	B2	88	280-85 (d)
(8)	7-Me	H	A	92	306-8 (d)
(8)	7-Me	H	B1	78	306-8 (d)
(8)	7-Me	H	B2	82	306-8 (d)
(9)	6-Me	H	B1	74	190-94
(10)	8-Me	Me	A	81	310 (d)
(11)	7-Me	Me	A	94	315 (d)
(12)	8-Me	C_4H_9	A	93	239-41
(12)	8-Me	C_4H_9	B1	88	239-41
(12)	8-Me	C_4H_9	B2	83	239-41
(13)	7-Me	C_4H_9	A	89	260-62
(13)	7-Me	C_4H_9	B1	93	260-62
(14)	6-Me	C_4H_9	B1	83	220-22
(14)	6-Me	C_4H_9	B2	81	220-22
(15)	9-Me	C_8H_{17}	A	90	127-29
(16)	8-Me	C_8H_{17}	A	92	213-14
(16)	8-Me	C_8H_{17}	B1	83	213-14
(16)	8-Me	C_8H_{17}	B2	81	213-14
(17)	7-Me	C_8H_{17}	A	86	226-27
(17)	7-Me	C_8H_{17}	B1	86	226-27
(18)	6-Me	C_8H_{17}	B1	79	178-80

[a] See experimental section

The results of the cyclic voltammetric experiments are summarised in Table 2; the first nine entries are set out to allow a comparison of the effect of substitution at the 3- and the nuclear (6, 7, 8, 9) positions. Clearly the solvent and electrolyte has a marked effect upon the oxidation

potential; the gross effects may reflect the extent of protonation but in the absence of information concerning the basicities of the substrates and the acidity of the TFA/CH_2Cl_2 mixtures little can be said about small changes. However, it is clear that alkyl substitution at C-3 results in significant cathodic shifts in $E_{p,a}$ whereas the effect of nuclear substitution is very much smaller. A noteworthy exception concerns compound (18) ; in this case the combination of 3-octyl and 6-methyl substitution causes (18) to be the most easily oxidised substrate in TFA/CH_2Cl_2 - cf. entries for compounds (17) and (16).

Table 2. Cyclic Voltammetry: 4H-Pyrido[1,2-a]pyrimidine-2,4-diones

Compound	R_1	R_2	Anodic peak potential ($E_{p,a}$)[a]		
			MeCN/TBAF[b]	TFA/CH_2Cl_2/ TBAF	TFA/CH_2Cl_2 TEATFA[d]
(3)	H	H	-[e]	1.82	1.76
(6)	H	C_8H_{17}	0.80	1.20	1.56
(9)	6-Me	H	-	-	1.74
(18)	6-Me	C_8H_{17}	-	-	1.24
(8)	7-Me	H	-	-	1.86
(17)	7-Me	C_8H_{17}	0.80	1.23	1.44
(7)	8-Me	H	-	-	1.80
(16)	8-Me	C_8H_{17}	0.83	1.26	1.46
(15)	9-Me	C_8H_{17}	0.85	1.25	-
(4)	H	C_4H_9	-	-	1.54
(5)	H	C_6H_{13}	0.78	1.24	-
(12)	8-Me	C_4H_9	0.87	1.30	1.54
(13)	7-Me	C_4H_9	0.90	1.27	1.50
(14)	6-Me	C_4H_9	-	-	1.46

[a] V *vs* Ag/Ag^+ at $0.3Vs^{-1}$; [b] Bu_4NBF_4 (TBAF) at 0.1M;
[c] CF_3CO_2H/CH_2Cl_2 (1:2), TBAF (0.1M);
[d] CF_3CO_2H/CH_2Cl_2 (1:3), $Et_3NHO_2CCF_3$ (TEATFA) at 0.1M;
[e] insoluble.

A controlled potential coulometric experiment was performed, on a preparative scale, for the anodic oxidation at the peak potential of 3-octyl-4H-pyrido[1,2-a]pyrimidine-2,4-dione (6) at a platinum anode in TFA/CH_2Cl_2(1:2) with TBAF(0.1M). The cyclic voltammetric behaviour of compound (6) was typical of the range of derivatives studied. The current-charge profile displayed in Figure 1 illustrates the smooth electrolysis also found for other derivatives; the electrolysis can be seen to be effectively a $1Fmol^{-1}$ process.

Controlled Potential Electrolysis : Electrolyses, typically at 1.3 - 1.6V (*vs* Ag/Ag^+), were carried out in TFA/CH_2Cl_2 mixtures at a platinum disc anode. In early experiments TBAF (0.1M) was the supporting electrolyte but latterly the more convenient $Et_3NHO_2CCF_3$ (TEATFA) has been used ; work-up from this solvent/electrolyte system is especially convenient (see experimental section).

The electrolyses proceeded smoothly to 1.0 $Fmol^{-1}$ and apparently single products were isolated in 60 - 88% yield. The structure of these products could not at first be unambiguously determined from spectroscopic data, although subsequently this information was found to be entirely consistent with the structure determined by X-ray crystallography. For those compounds with nuclear methyl substitution and with alkyl substitution at C-3 it was possible to recrystallise the products from a variety of solvents. Consequently the product of controlled potential anodic oxidation of compound (**12**) was determined by X-ray crystallography to be (**20**, R_1=8-Me, R_2=C_4H_9)) - see Figure 2. By analogy, confirmed by the n.m.r. and mass spectrometric data, similar coupling products are obtained from the compounds listed in Table 3 which summarises the results of controlled potential electrolyses of the type shown in Scheme 1. In some cases it proved possible to isolate the product prior to decarboxylation (**19**), and work-up from methanol gave the corresponding methyl ester (**21**).

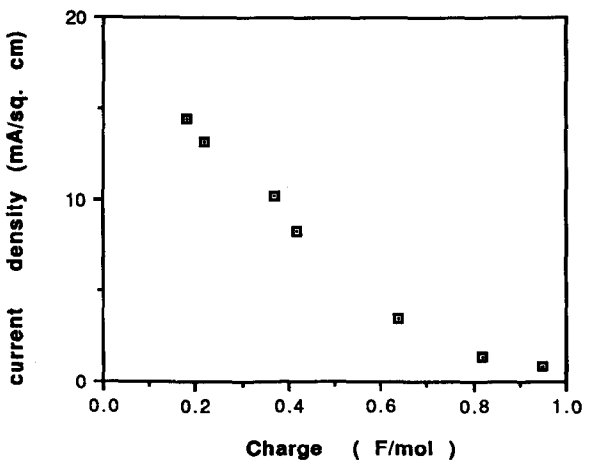
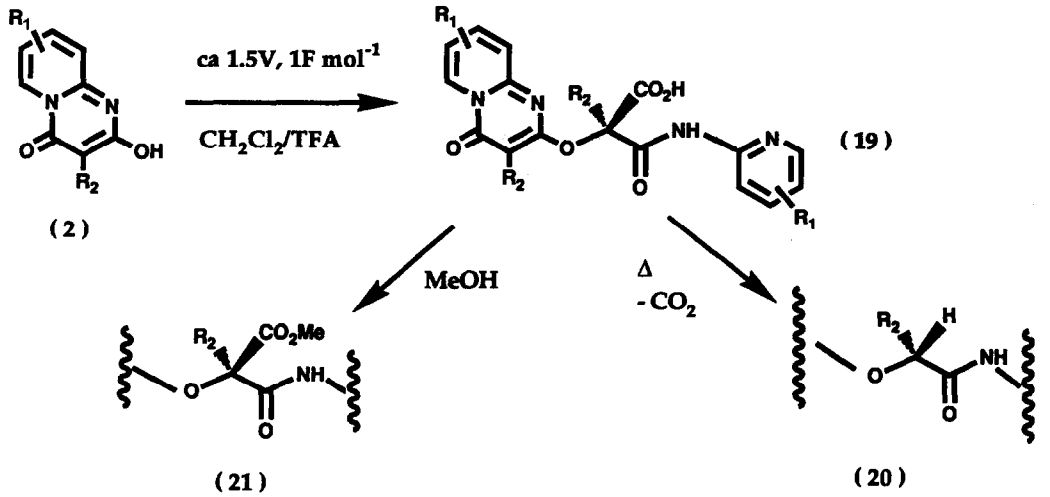


Figure 1 Controlled potential electrolysis of (6)



SCHEME 1

Table 3. Controlled potential electrolysis[a] (see Scheme 1)

Compound	R_1	R_2	Product type [Yield %]		
			(19)	(20)	(21)
(6)	H	C_8H_{17}	81[b]	3	-
(12)	8-Me	C_4H_9	-	88[c]; 72	40[d]
(13)	7-Me	C_4H_9	-	75	-
(15)	9-Me	C_8H_{17}	-	73	-
(16)	8-Me	C_8H_{17}	-	65	-
(17)	7-Me	C_8H_{17}	-	68	-

[a] Unless otherwise states: Pt anode; 1.3-1.6V (*vs* Ag/Ag^+); 1 F mol^{-1}; CH_2Cl_2/TFA (2:1); Bu_4NBF_4 (0.1M).

[b] As (a) but CH_2Cl_2/TFA (3:1) with $Et_3NHO_2CCF_3$ (0.1M) and cold, aqueous, work-up.

[c] As (b) but neturalisation with $(NH_4)_2CO_3$ prior to work-up.

[d] Methyl ester of (19) - work-up with MeOH.

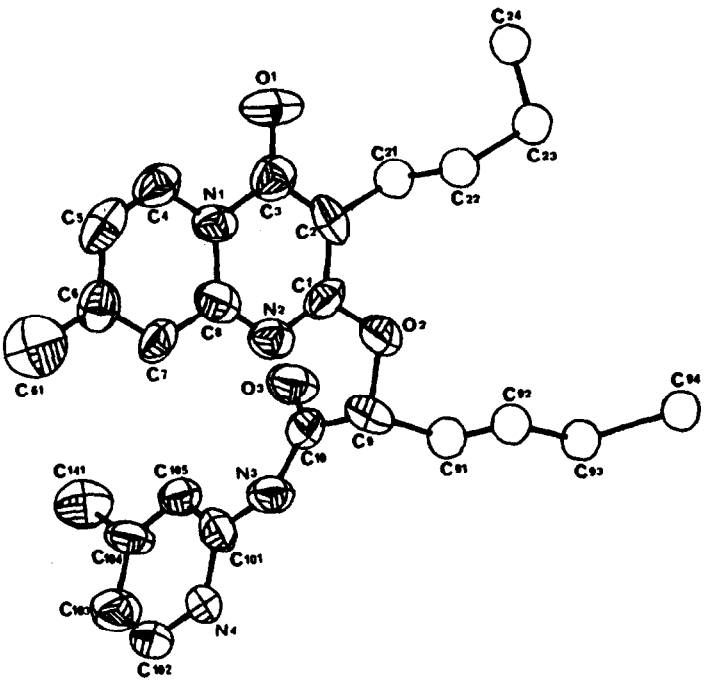
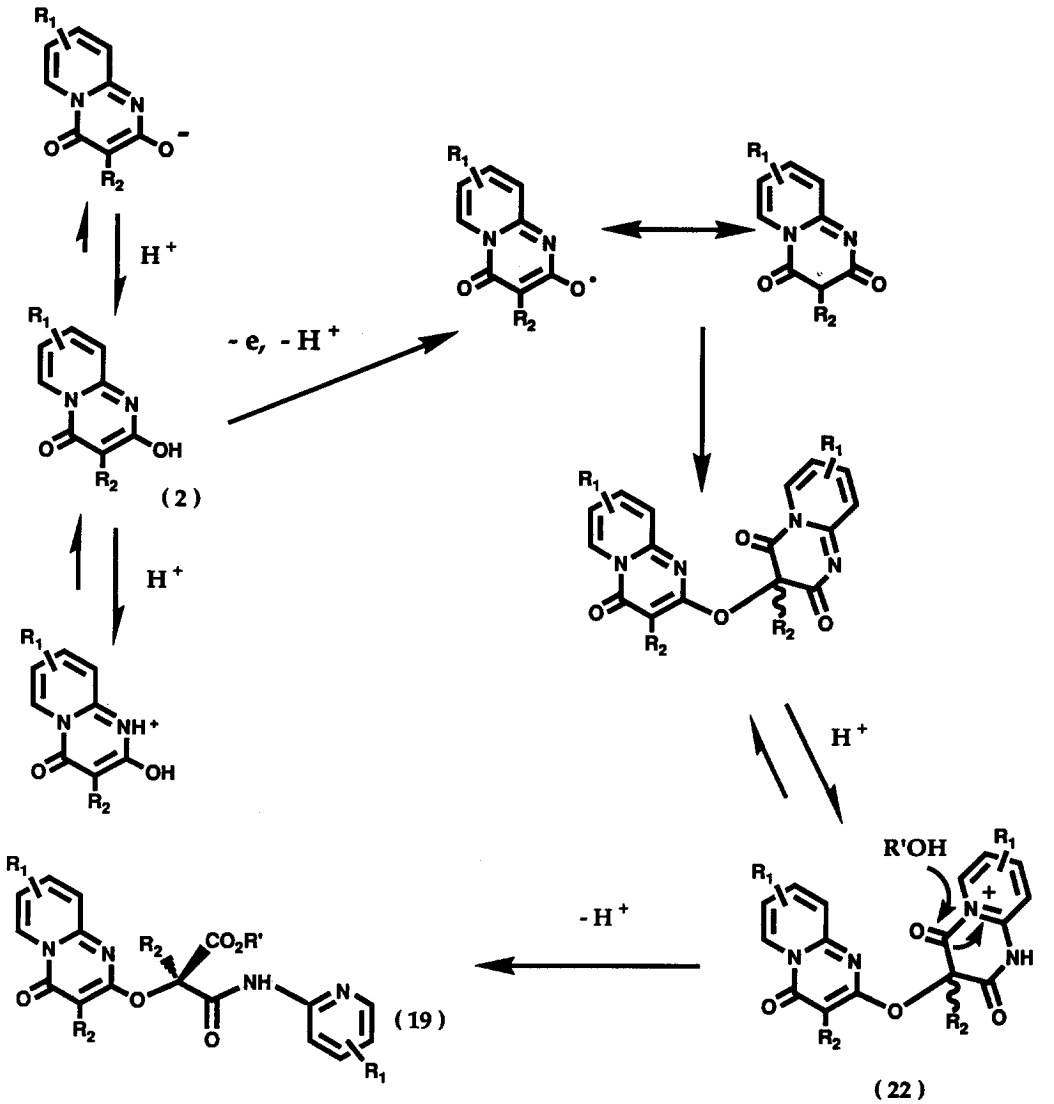


Figure 2. Structure of (20) as determined by X-ray crystallography

Mechanistic rationalisation :

The mechanism proposed in Scheme 2 is consistent with the key experimental observations. It accounts for the products of type (20) and the intermediacy of the easily decarboxylated compounds of type (19). Formation of the last has been confirmed by isolation in one case and by *in situ* conversion into a methyl ester in another. The role of the acidic medium is not only to enhance solubility but also to protonate the first-formed coupled product to give an N-acylpyridinium species (22) which is the most likely route to ring opening.

The difficulty of correctly representing the structure of the starting materials has been alluded to. In Schemes 1 and 2 an enolic structure is assumed which is consistent with the oxidative coupling being analogous to phenolic coupling. The shifts in oxidation potential with acidity are also common to the pyridopyrimidones and phenols[5]; for convenience it is assumed in Scheme 2 that by analogy with phenols in acidic media it is the neutral form which is oxidised. A mechanism could be devised which involved coupling of radical-cations after oxidation of the protonated form and loss of one proton. In the absence of evidence in favour of this the simpler explanation is preferred.



SCHEME 2

There is no evidence of C-C or of O-O coupling. Perhaps the last is not surprising as the peroxy species resulting would readily fragment back to the parent radical. One possible explanation for the lack of C-C coupling is that products from this would either be strained or subject to considerable repulsive coulombic interaction between the carbonyl groups.

Experimental.

Solvents and supporting electrolytes. *Acetonitrile* (Aldrich 99%) was refluxed over calcium hydride (1g/100ml) for two days then, after filtration, over P_2O_5 (0.5g/100ml) for 5h followed by slow fractional distillation through an efficient column. It was stored in the dark, under N_2 and over fresh molecular seive (4A). *Dichloromethane* (BDH) was shaken with concentrated H_2SO_4 and after washing with water and dilute sodium bicarbonate it was dried ($CaCl_2$) and distilled from calcium hydroxide. *Trifluoroacetic acid* (Aldrich) was used as received. *Tetra-n-butylammonium tetrafluoroborate* (TBAF, Fluka) was crystallised from methanol and dried under high vacuum (<0.1 mm). *Triethylammonium trifluoroacetate* (TEATFA) in CH_2Cl_2/TFA was prepared *in situ* by the addition of a weighed amount of twice-distilled triethylamine to CH_2Cl_2/TFA (3:1) to give an 0.1M solution.

4-H-Pyrido[1,2-a]pyrimidine-2,4-diones (see Table 1).

Method A. The appropriate 2-aminopyridine (0.015 mol) and the substituted diethylmalonate (0.01 mol) were mixed to a slurry with ethanol (5 ml) and heated for 2-4h at 160-180°C with provision for the continuous removal by distillation of ethanol. After cooling the residue was mixed with ethanol, filtered,and the solid product washed with ethanol. Several of the alkyl-substituted compounds could be crystallised from $CHCl_3$ or CH_3CN.

Method B1. The 2-aminopyridine (0.006 mol) and the appropriate bis-(2,4,6-trichlorophenyl)malonate (0.005 mol) were dissolved in acetone (*ca* . 10 ml) and triethylamine (0.01 mol) added. After several minutes of vigorous stirring a yellow solid separated which after filtration and washing was sufficiently pure for further use.

Method B2, was as for B1 but with the ommission of the triethylamine and with heating under reflux.

The compounds listed in Table 1 form a closely related series and the m.s., i.r. and n.m.r. spectroscopic data show relatively small compound-to-compound differences. Satisfactory microanalytical results were obtained for new compounds and for the rest melting points agreed well with published values; these are included in Table 1. A representative rather than exhaustive list of physical data is here presented; the compounds described are chosen to represent the main structural features of the substrates for electrolysis.

3-Hexyl-4H-pyrido[1,2-a]pyrimidine-2,4-dione: (**5**) : n (Nujol), 3140, 2700-2000(b), 1685, 1650, 1608, 1585, 1505, 1255, 1150, 1025, 775 cm^{-1}. ^1H n.m.r., d ($CDCl_3$), 0.86(t, 3H, CH_3), 1.31(m, 8H, $[CH_2]_4$), 2.67(t, 2H, CH_2), 7.24(t, 1H, J=7HZ, H-7), 7.59(d, 1H, J=7Hz, H-8), 9.18(d, 1H, J=7Hz, H-6). m.s., *m/z* 246.139(M^+, $C_{14}H_{18}N_2O_2$ requires 246.136), 189.1(10%), 176(33.6%), 174.9(100%), 121.1(39%), 38.1(32%), 55.2(20.8%). Found[Required](%): C, 68.35[68.25]; H, 7.29[7.31]; N, 11.21[11.38]; O, 13.15[13.00].

8-Methyl-4H-pyrido[1,2-a]pyrimidine-2,4-dione (**7**) : n (Nujol), 2700-2000(b), 1670, 1625, 1585, 1515, 1355, 1315, 1280, 795 cm^{-1}. ^1H n.m.r., d ($CDCl_3$), 2.50(s, 3H, 8-CH_3), 4.90(s, 1H, H-3), 7.03(d, 1H, J=8Hz, H-7), 7.70(s, 1H, H-9), 9.02(d, 1H, J=8Hz, H-6). m.s., *m/z* 176.058[83.3%](M^+, $C_9H_8N_2O_2$ requires 176.058), 148.0(21.1%), 135.0(100.0%), 92.2(61.4%), 80.1(14.9%), 69.1(47.7%), 65.2(32.7%), 60.2(10.2%), 52.3(17.2%).

3-n-Butyl-8-methyl-4H-pyrido[1,2-a]pyrimidine-2,4-dione (**12**) : n (Nujol), 1680, 1650, 1625, 1590, 1510, 1400, 1265, 1160, 935, 815, 785, 760 cm^{-1}. ^1H n.m.r., d ($CDCl_3$), 0.96(m, 3H, CH_3), 1.58(m, 4H, $[CH_2]_2$), 2.56(s, 3H, 8-CH_3), 2.66(t, 2H, J=8Hz, 3-$[CH_2]$) 7.06(d, 1H, J=8Hz, H-7), 7.38(s, 1H, H-9), 9.04(d, 1H, J=8HZ, H-6). m.s., *m/z* 232.122[15.7%](M^+, $C_{13}H_{16}N_2O_2$ requires 232.121), 203.0(26%), 189.0(100.0%), 135.1(34.2%), 92.1(43.8%), 65.1(23.2%), 55.2(16.4%).

3-n-Octyl-7-methyl-4H-pyrido[1,2-a]pyrimidine-2,4-dione (**17**) : n (Nujol), 3000-2800, 1675, 1650, 1610, 1585, 1520, 1205, 1150, 815, 720 cm^{-1}. ^1H n.m.r., d ($CDCl_3$), 0.86(m, 3H, CH_3), 1.32(m, 12H, $[CH_2]_6$), 2.45(s, 3H, 7-CH_3), 2.70(t, 2H, J=7Hz, 3-$[CH_2]$), 7.52(d, 1H, J=8Hz, H-9), 7.76(d, 1H, J=8Hz, H-8), 8.98(s, 1H, H-6). m.s., m/z 288.184[33.9%](M^+, $C_{17}H_{24}N_2O_2$ requires 288.183), 190.1(39.6%), 189.2(100%), 135.0(28.6%), 92.1(24.9%) 65.1(10.5%), 55.2(13.2%). Found[Required](%): C,70.71[70.83], H,8.23[8.33], N,9.90[9.72], O,11.17[11.11].

Electrochemical experiments. The controlled potential electrolyses were carried out in a water-jacketted two-compartment glass cell. The anode compartment, of 100 cm^3 volume, was equipped with a platinum disc

electrode (area *ca* 10.5 cm^2); the separator was medium porosity sintered glass and a carbon rod secondary electrode was used. The reference electrode consisted of a sealed sinter-tipped glass tube containing a silver wire and an 0.1M solution of silver nitrate in acetonitrile. The procedures described below are typical of those used in this work.

Controlled potential oxidation of (12) : Compound (**12**) [1.50g, 0.0065 mol] was dissolved in 100ml of CH_2Cl_2/TFA(2:1) with TBAF(0.1M). The solution was electrolysed at a platinum anode at 1.50V (Ag/Ag^+) until 1.29 $Fmol^{-1}$ had been consumed. The initial and final current densities were 17.39 and 2.82 $mAcm^{-2}$ respectively. The anolyte was concentrated by rotary evaporation, diluted with water (30-50 ml) and the product extracted with several portions of diethyl ether (15-20 ml). The ether extracts were combined, washed (H_2O), dried ($MgSO_4$) and concentrated to ca 10ml. Gradual addition of petroleum ether (60-80°C) caused the product (**20**, R_1=8-Me, R_2=C_4H_9)) to precipitate. It was recrystallised from acetonitrile and obtained in 72% isolated yield. In an alternative work-up the anolyte was concentrated carefully to near dryness and dry methanol (20 ml) added. The methanol was removed at a rotary evaporator and the process repeated for a total of four times. Conventional work-up with water and ether extraction allowed isolation of the ester product (**21**) which was purified by column chromatography (silica type H, Merck, ether/petroleum ether(60-80°C, 1:1, and then methanol/ether[2:3]).

Controlled potential oxidation of (6) : Freshly distilled triethylamine (0.7 ml) was added dropwise to a mixture of trifluoroacetic acid (12 ml) and dichloromethane (33 ml). At up to 2.3V, in the cell described above, only a small background current was evident (<5 mA). Compound (**6**) [1.4g, 0.005 mol] was dissolved in this anolyte and electrolysed at 1.50V until 1.4 $Fmol^{-1}$ had been consumed and the background current had fallen from 90 mA to 3 mA. The anolyte was removed and evaporated to dryness under reduced pressure at room temperature. Cold water was added to the residue and the solid product extracted into dichloromethane; the extract was washed with portions of cold water, dried ($MgSO_4$) , and carefully evaporated to give an almost pure sample of the carboxylic acid product (**19**) in 81% yield. Neutralisation of the anolyte residue with ammonium carbonate prior to work-up gives the decarboxylated product - e.g. similar electrolysis of (**12**) with such work-up gave (**20**, R_1=8-Me, R_2=C_4H_9) in 88% yield.

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