Reactions of 1-Alkoxycarbonylpyridinium Salts with Nucleophiles: Stereoelectronic Restrictions on Carbonyl Activation of α-Nucleophilic Attack

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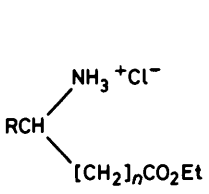
The lack of reactivity of *N*-(α-ethoxycarbonylalkyl)-2,4,6-tri-substituted pyridinium salts toward nucleophilic displacement of the *N*-substituent is ascribed to stereoelectronic effects. Although such esters undergo ready base hydrolysis to give the corresponding acids, they are highly resistant to attack by other nucleophiles at the C=O function; this behaviour is rationalised.

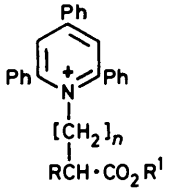
As part of our investigation of the transformation of primary amino-groups into other functionalities mediated by pyrylium salts,[1] we have now studied the esters of amino-acids. Several reports deal with the reaction of amino-acids with 2,4,6-trimethylpyrylium salts [2] but 2,4,6-trimethylpyridine is a poor leaving group. The insolubility of amino-acids in nonpolar solvents hinders their reaction with pyrylium salts which form pyridinium salts containing better leaving groups. In view of these considerations the corresponding esters of the amino-acids seemed more appropriate for the reaction, although previous work on their reactions with pyrylium salts is sparse. Ethyl glycinate has, however, been found to react successfully with 2,4,6-triphenylpyrylium salt.[2d]

Preparation of Pyridinium Salts.—The amino-ester hydrochlorides (1a—c) were converted into the corresponding 2,4,6-triphenylpyridinium salts and into the other 1-ethoxycarbonylpyridinium salts (7a)—(10a) (Table 1) in the usual way. The pyridinium salts (2) and (7a)—(10a) were characterised by ^{1}H n.m.r. spectroscopy (Table 2) which show a 2 H singlet for the pyridine ring protons together with peaks characteristic for the alkyl group.

Attempted Nucleophilic Displacement Reaction of the Pyridinium Salts (2).—A halogen atom α to an ethoxycarbonyl group is activated towards nucleophilic substitution.[3] It was, therefore, expected that nucleophilic displacement reactions, previously reported for *N*-alkyl-2,4,6-triphenylpyridinium salts,[1] would take place readily with compound (2). This is not so: thiourea gave mixtures [4] (contrast ref. 5), and semi-quantitative kinetic measurements with piperidine in chlorobenzene [4] indicated rates much less than, for example, the *N*-benzyl analogue.[6]



(1)



(2)

a; R = H, n = 1
b; R = Me, n = 0
c; R = $PhCH_2$, n = 0

a; R = H, n = 0, R^1 = Et
b; R = H, n = 1, R^1 = Et
c; R = Me, n = 0, R^1 = Et
d; R = $PhCH_2$, n = 0, R^1 = Et
e; R = H, n = 0, R^1 = Me

Under forcing conditions with pyridine as nucleophile unexpected results were obtained: compound (2c) gave the 1-ethyl-2,4,6-triphenylpyridinium salt (4) presumably by the mechanism of type (3) ⟶ (4). The pyridinium salt (2b) gave triphenylpyridine, probably by reverse Michael elimination to give ethyl acrylate.

We believe that the compounds (2b—d) are unreactive towards nucleophilic displacement for stereoelectronic

TABLE 1

Preparation of *N*-alkoxycarbonylalkyl-substituted pyridinium salts

Compd.	Anion	Cryst. solvent	Cryst. form	Yield (%)	M.p. (°C)	Found (%) C	Found (%) H	Found (%) N	Molecular formula	Required (%) C	Required (%) H	Required (%) N
(2a)	BF_4	EtOH	Needles	66	201—203 [a]	67.5	4.9	2.9	$C_{27}H_{24}NO_2BF_4$	67.4	5.0	2.9
(2b)	BF_4	EtOH	Needles	64	265—268	68.0	5.2	2.8	$C_{28}H_{26}NO_2BF_4$	67.9	5.3	2.8
(2c)	BF_4	Me_2CO–Et_2O	Prisms	41	115—117	67.6	5.6	2.7	$C_{28}H_{26}NO_2BF_4$ 0.4 Me_2CO [c]	67.6	5.5	2.7
(2d)	BF_4	EtOH–H_2O	Prisms	15	196—199	71.4	2.4	5.1	$C_{34}H_{30}NO_2BF_4$	71.5	2.5	5.3
(2e)	BF_4	MeOH	Rhombs	51	191—193	66.7	4.6	3.0	$C_{26}H_{22}NO_2BF_4$	66.8	4.8	3.0
(10a)	BF_4	EtOH	Needles	62	145—146	67.8	5.5	2.6	$C_{29}H_{26}NO_2BF_4$ 0.5 C_2H_5OH	67.9	5.5	2.6
(9a)	CF_3SO_3	EtOH	Prisms	50	154	59.7	5.0	2.7	$C_{26}H_{26}NO_2CF_3SO_3$	59.8	5.0	2.7
(7a)	BF_4	CH_2Cl_2	Prisms	61	270 (decomp.)	65.0	6.1	3.0	$C_{25}H_{28}NO_2BF_4$	65.1	6.1	3.0
(8a)	BF_4	EtOH–Et_2O	Needles	25	89—90 [b]	48.6	6.2	4.8	$C_{12}H_{18}NO_2BF_4$	48.8	6.2	4.8

[a] *J. Gen. Chem. U.S.S.R.*, 1963, 2357, (ClO_4^-), m.p. 143—144 °C. [b] *J. Gen. Chem. U.S.S.R.*, 1963, 2357, (ClO_4^-), m.p. 93—94 °C. [c] Confirmed by ^{1}H n.m.r. and i.r. spectra.

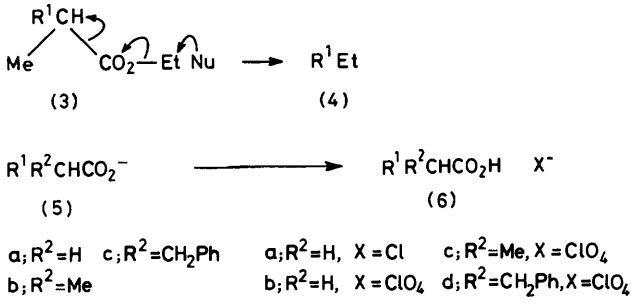
TABLE 2

^{1}H N.m.r. data [a] of *N*-alkoxycarbonylalkyl-substituted pyridinium salts

Compd.	Pyridine (3,5) (s, 2 H)	Phenyl (m, 15 H)	CO_2CH_2 δ	(q) J_{12}	$CO_2CH_2CH_3$ δ	(t) J_{12}	N-CH (R)	Others
(2a)	7.95	7.65	4.00	8	1.00	8	5.10 (s, 2 H)	
(2b)	7.80	7.60	3.90	8	1.10	8	4.75 (t, 2 H, J_{12} 8)	2.50 (t, 2 H, J_{12} 8)
(2c)	7.90	7.65	4.15	8	1.15	8	5.55 (q, 1 H, J_{12} 8)	1.45 (d, 3 H, J_{12} 8)
(2d)	7.86	7.86—7.34 7.10—6.66 (m, 5 H)	4.05	6	1.10	6	5.50 (dd, 1 H, J_{12} 8 and 4)	3.35 (dd, 1 H, J_{12} 4, J_{11} 14) 2.15 (dd, 1 H, J_{12} 8, J_{11} 14)
(2e)	7.94	7.60	—	—	—	—	5.07 (s, 2 H)	3.53 (s, 3 H)
(10a)	7.50 (m, 15 H)		3.95	7	1.00	7	5.45 (s, 2 H)	2.90 (s, 4 H)
(9a)	7.55 (m, 11 H)		4.25	6	1.20	6	5.30 (s, 2 H)	2.95 (m, 4 H),
	8.44 (d, 1 H, J_{13} 2)	8.00 (m, 2 H)	4.04	7	1.08	7	5.64 (s, 2 H)	1.90 (m, 4 H) 1.72 (s, 9 H)
(7a)	8.15 (d, 1 H, J_{13} 2)	7.57 (m, 8 H)						
(8a)	7.60		4.25	7	1.25	7	5.25 (s, 2 H)	2.65 (s, 6 H) 2.50 (s, 3 H)

[a] δ Values, *J* in Hz, solution in $CDCl_3$.

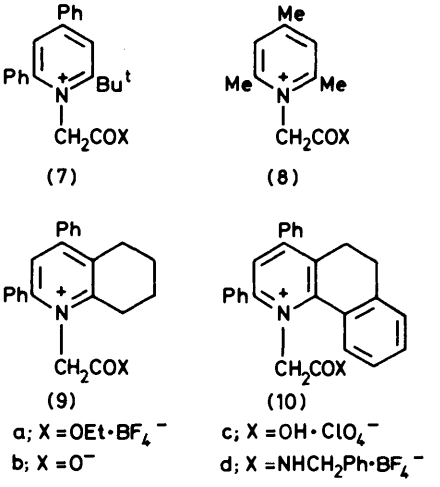
reasons. Activation by the ethoxycarbonyl group is believed to involve overlap of an approaching nucleophile with the C=O π* orbital.[7] Examination of models shows that the ethoxycarbonyl group is constrained by the 2,6-diphenyl groups so that the C=O π-orbital is orthoganol to the N–CH_2 δ-orbital. Hence an approaching nucleophile cannot interact simultaneously with the δ-N–C and π* C=O orbitals.



Reaction of Nucleophiles with the Pyridinium Salts (2) *at the Ester Group*.—The salt (2a) with two equivalents of ethanolic potassium hydroxide at 20 °C for 2 h gave the betaine (5) (59%). However, hydrolysis of the salt (2a) under acid conditions to give the salt (6a) required much more vigorous conditions: 20 h reflux in HOAc–H_2O–HCl.

The contrast between the difficulties of nucleophilic displacement of the pyridine ring and the very mild base-catalysed hydrolysis suggested that other suitable nucleophiles should react selectively with (2a) at the ester group. However, (2a) proved extraordinarily unreactive towards nucleophiles as evidenced by the following.

(a) Fusion with 2-aminopyridine at 170 °C for 8 h gave recovered starting material (after 29 h at 190 °C, 2,4,6-triphenylpyridine formed). (b) Heated in aniline at 100 °C for 18 h—no reaction. (c) Refluxed with benzylamine in toluene—95% starting material recovered. (d) No transesterification on refluxing in methanol for 4 h. (e) No reaction on refluxing 24 h with hydroxylamine in ethanol.



Reactions of N-*Ethoxycarbonylpyridinium Salts* (7a)—(10a) *with Nucleophiles*.—As for compound (2), the esters (7a), (8a), and (10a) were readily hydrolysed by potassium hydroxide–ethanol at 20 °C to give the corresponding betaines (7b), (8b), and (10b) (Table 3). They are all highly hygroscopic and could not be completely freed from water without decarboxylation; they could, however, be characterised by ^{1}H n.m.r. and i.r. spectroscopy (Table 4). With perchloric acid the corresponding salts (7c), (8c), and (10c) (Table 5) were obtained.

However, the ester (9a) reacted quite differently on attempted base hydrolysis: instead of the expected compound (9b), the cyclised product (11) was isolated (89%). Evidently compound (11) is formed *via* the anhydrobase (12) (intermolecular acylations of which are known [8]). The easy formation of compound (11) is explained by the favourable conformation of the anhy-

TABLE 3

Preparation [a] of pyridinium betaines

Compd.	Time (h)	Yield (%)	Found (%) C	H	N	Molecular formula	Required (%) C	H	N
(5a)	2	59	77.5	5.1	3.4	$C_{25}H_{19}NO_2$ (1.3 H_2O) [b]	77.2	5.6	3.6
(10b)	1¾	70	79.9	5.5	3.5	$C_{27}H_{21}NO_2$ (0.8 H_2O) [b]	79.9	5.6	3.5
(7b)	2	75	77.4	6.5	3.9	$C_{23}H_{23}NO_2$ (0.6 H_2O) [b]	77.5	6.9	3.9
(5b)	2	58	77.0	5.6	3.5	$C_{26}H_{21}NO_2$ (1.5 H_2O) [b]	76.8	6.0	3.5
(5c)	2	55	82.3	5.7	2.9	$C_{32}H_{25}NO_2$ (0.6 H_2O) [b]	82.4	5.7	3.0

[a] At 25 °C. [b] Confirmed by i.r. spectroscopy.

TABLE 4

^{1}H N.m.r. data of pyridinium betaines [b]

Compd.	Aromatic	^{1}H N.m.r.[a] N-CH_2	Others
(5a)	7.82 (s, 2 H) 7.60 (m, 15 H)	4.62 (s, 2 H) 5.33 (d, 1 H, J_{11} 16)	
(10b)	8.5—7.3 (m, 15 H)	4.82 (d, 1 H, J_{11} 16) 5.38 (d, 1 H, J_{11} 16)	2.85 (s, 4 H)
(7b)	8.1—7.1 (m, 12 H)	4.90 (d, 1 H, J_{11} 16)	1.70 (s, 9 H)
(5b)	8.4—7.3 (m, 17 H)	5.51 (q, 1 H, J_{12} 8)	1.18 (d, 3 H, J_{12} 8) 3.50 (dd, 1 H, J_{11} 16, J_{12} 4)
(5c)	8.4—6.2 (m, 22 H)	5.66 (dd, 1 H, J_{12} = 4 and 12)	2.62 (dd, 1 H, J_{11} 16, J_{12} 12)

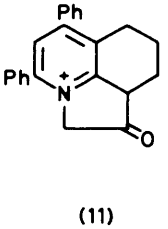
[a] Solution in $CDCl_3$, δ values, J in Hz. [b] C=O band at *ca.* 1 640 cm^{-1}.

TABLE 5

Chemical analysis of pyridinium acids [a]

Pyridinium acids	Decomp. temp. (°C)	Found (%) C	H	N	Mol. formula	Required (%) C	H	N
(6b)	133	64.7	4.1	3.0	$C_{25}H_{20}NO_2ClO_4$	64.4	4.3	3.0
(10c)	145	65.9	4.7	2.8	$C_{27}H_{22}NO_2ClO_4$	65.9	4.5	2.9
(7c)	230	61.4	5.3	3.1	$C_{23}H_{24}NO_2ClO_4$ (0.2 H_2O)	61.4	5.5	3.1
(6c)	197	63.5	4.8	2.8	$C_{26}H_{22}NO_2ClO_4$ (0.7 H_2O)	63.4	4.8	2.8
(6d)	137	67.8	5.1	2.6	$C_{32}H_{26}NO_2ClO_4$ (0.6 H_2O)	67.8	4.8	2.5

[a] They all show a broad carbonyl peak at *ca.* 1 750 cm^{-1}



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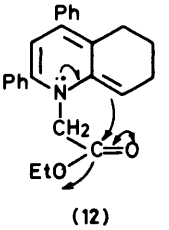

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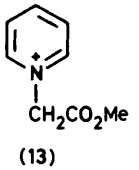
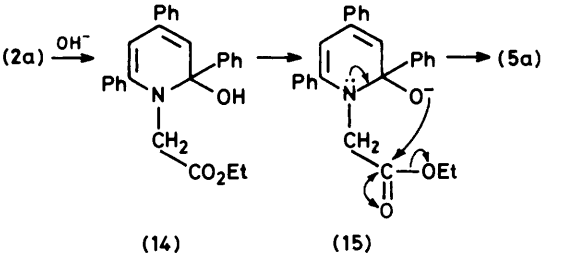


(13)

drobase (12) for the intramolecular attack at the C=O bond.

The reactivity of the esters (7a), (8a), and (10a) to benzylamine was compared with that of (2a). In refluxing toluene compound (7a) did not react, compound (10a) formed the amide (10d) slowly (50% conversion *ca.* 20 h) and compound (8a) formed (8d) somewhat faster (50% conversion *ca.* 12 h). By contrast, the 1-methoxycarbonylmethylpyridinium salt (13) gives the amide readily with benzylamine in refluxing ethanol.[9] The reactivity order (13) ≫ (8a) > (10a) ≫ (7a), (2a) clearly indicates steric hindrance.

The steric hindrance caused by *ortho* alkyl groups to



(14) (15)

SCHEME

nucleophilic attack at the carbonyl group of benzoic esters is well known: it reaches severe proportions in the *O,O'*-di-t-butyl derivative.[10] However, in the benzoic ester series hydrolysis, *i.e.* nucleophilic attack by OH^-, is also affected. The unique sensitivity of (2a) and similar compounds towards OH^- suggest a special mechanism: possibly intermediates of type (14) are involved (see Scheme), alternatively ring opening could occur.

EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus, and are uncorrected. I.r. spectra were run using NaCl plates on a Perkin-Elmer 357 grating spectrophotometer as solutions in $CHBr_3$. ^1H N.m.r. spectra were obtained on a Perkin-Elmer 60 MHz R-12 spectrometer.

Compounds prepared by Literature Methods.—2,4,6-Triphenylpyrylium tetrafluoroborate [11] (35%), m.p. 250—253 °C (lit.,[11] m.p. 253—255 °C); 7,9-diphenyl-5,6-dihydrobenzochromenylium tetrafluoroborate [12] (78%), m.p. 265 °C (lit.,[12] m.p. 270 °C); 2,4-diphenyl-5,6,7,8-tetrahydrochromenylium trifluoromethanesulphonate [5] (51%), m.p. 185—187 °C (lit.,[8] m.p. 187 °C); 2-t-butyl-4,6-diphenylpyrylium tetrafluoroborate [13] (36%), m.p. 230 °C [lit.,[13] m.p. 224—225 °C (decomp.)], 2,4,6-trimethylpyrylium tetrafluoroborate [14] (44%), m.p. 223 °C (decomp). [lit.,[14] m.p. 224—226 °C (decomp)].

General Procedure for preparing 1-*Alkoxycarbonylalkylpyridinium Salts.*—The pyrylium salt (1g) was stirred with the amino-ester hydrochloride (1 mol equiv.) and triethylamine (2 mol equiv.) in dichloromethane (10 ml) at 20 °C for 2 h. Acetic acid (2 mol equiv.) was added to the mixture and stirring was continued for 2 h. The solvent was removed at 100 °C/0.5 mmHg. The red oily residue was triturated with diethyl ether and water to give the pyridinium salts (Table 1).

General Procedure for preparing Pyridinium Betaines.—Potassium hydroxide (10%, 2 mol equiv.) was added to a suspension of pyridinium salt (1 g) in ethanol (10 ml). The purple solution was stirred at 20 °C for 2 h. After filtration, solvent was removed at 100 °C/0.5 mmHg to give a gum which when triturated with diethyl ether formed the pyridinium betaine.

[2/021 *Received, 7th January,* 1982]

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