Pyridiniums as Potential Synthetic Substitutes for Nitrogen Mustards

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Dialkylamino-alkyl primary amines **1b** and **2b** are converted by pyrylium salts into the corresponding pyridinium derivatives. The pyridinium salts act as aminoalkylating agents for representative *O*-, *S*-, *N*-, and *C*-nucleophiles and are potentially safe substitutes for nitrogen mustards in the reactions.

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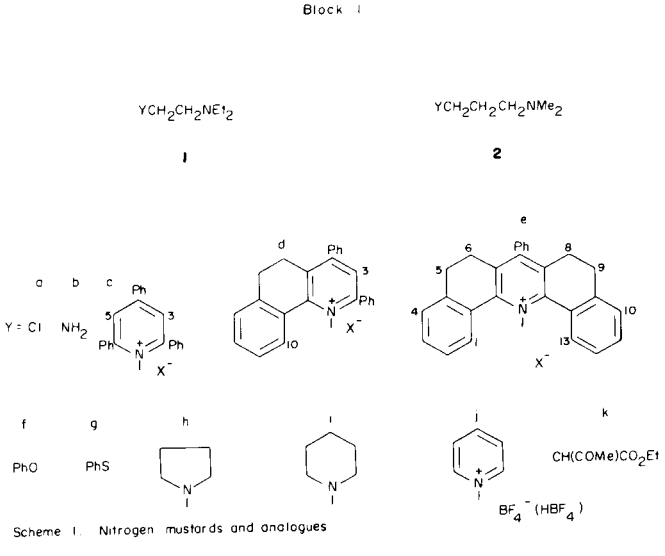
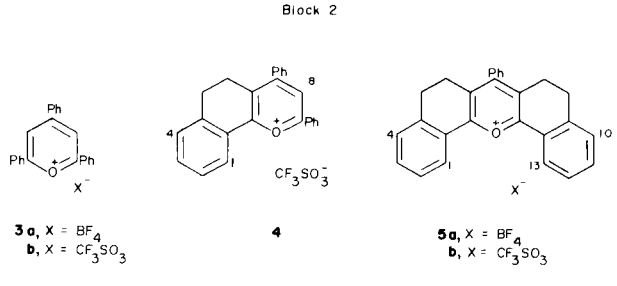
Chloroalkylamines such as **1a** and **2a** have been extensively used for aminoalkylation, and many useful pharmaceuticals have been prepared in this way (2). However, haloalkylamines are often highly toxic, particularly the "nitrogen-mustard", bis (β-chloroethyl)amine (3). We therefore utilised our method of activating amino groups by reaction with a pyrylium salt to form pyridinium salts of the diamines **1b** and **2b**.



Scheme 1. Nitrogen mustards and analogues

Preparation of Pyridinium Salts.

Triphenylpyrylium **3**, and the tricyclic **4** and pentacyclic **5** analogues were each reacted with *N,N*-diethylethylenediamine **1b** and *N,N*-dimethyl-1,3-propylenediamine **2b** to give the corresponding pyridiniums **1c-e** and **2c-e**, often as trifluoromethanesulfonates, and sometimes as tetrafluoroborates (Table 1). Within each series, **c, d,** and **e** are successively more reactive (4). The *N*-(2-aminoethyl)acridinium **1e** could not be prepared at *ca.* 25°: a low temperature modification was developed as a consequence of kinetic studies (*vide infra*) on the other *N*-(2-aminoethyl) systems **1c** and **1d** which indicated that acridinium **1e** might be unstable at ambient temperatures.



Proton nmr spectral data for the pyridiniums are recorded in Table 2. In general, $^{+}NCH_2$ resonate between δ 4.4-5.4, increasing from **c** to **e** due to decreasing

Table 1

Preparations of Dialkylaminoalkylazacycloniums (**1c-e, 2c-e**)

Compound No.	Anion	Method	Yield (%)	Recrystallisation solvent (a)	Melting point (°C)	Formula	Analysis (%) Found C	H	N	Required C	H	N
1c	BF_4	A	53	Ethanol	137-138	$C_{29}H_{31}BF_4N_2$	70.5	6.5	5.6	70.5	6.3	5.7
1c	CF_3SO_3	A	72	Ethanol	126-127	$C_{30}H_{31}F_3N_2O_3S$	64.7	5.6	4.9	64.7	5.6	5.0
1d	CF_3SO_3	A	58	(b)	110 (c)	$C_{32}H_{33}F_3N_2O_3S$	65.5	5.8	4.8	65.9	5.7	4.8
1e	CF_3SO_3	C	56	(b)	208 (c)	$C_{34}H_{35}F_3N_2O_3S$	66.7	5.7	4.6	67.1	5.7	4.6
2c	BF_4	B	63	Ethanol	177-178	$C_{28}H_{29}BF_4N_2$	69.6	6.1	5.7	70.0	6.1	5.8
2c	CF_3SO_3	B	51	Methanol (d)	123-124	$C_{29}H_{29}F_3N_2O_3S$	64.2	5.3	5.2	64.2	5.4	5.2
2d	CF_3SO_3	B	42	Ethanol	137-138	$C_{31}H_{31}F_3N_2O_3S$	65.3	5.5	4.8	65.5	5.5	4.9
2e	BF_4	B	52	(b)	181 (c)	$C_{32}H_{33}BF_4N_2$	72.8	6.4	5.1	72.3	6.3	5.4
2e	CF_3SO_3	B	77	(b)	110-112	$C_{33}H_{33}F_3N_2O_3S$	66.3	5.9	4.7	66.4	5.6	4.7

(a) Needles unless otherwise indicated. (b) Too labile for recrystallisation. (c) With decomposition. (d) Plates.

Table 2

^{1}H-NMR Data (a) for the Dialkylaminoalkylazacycloniums (**1c-e, 2c-e**)

Compound No.	*N*-Substituent						Leaving Group			
	N^+-C*H*$_2$	CH_2-C*H*$_2$-C	CH_2-C*H*$_2$-N	N-C*H*$_3$	N-C*H*$_2$-Me	CH_2-C*H*$_3$	3,5-H (b) or 8-H (c)	1-H (c) or 1,13H (d)	C_2H_4	Other aromatic
	2H, t	2H, m	2H, t	6H, s	4H, q	6H, t	m	m	m	m
	δ J	δ	δ J	δ	δ J	δ J	δ H	δ H	δ H	δ H
1c	4.5 6	-	2.4 6	-	1.9 6	0.5 6	7.8 2	- -	- -	7.4-8.0 15
1d	5.2 6	-	2.3 7	-	2.0 7	0.9 7	7.9 1	8.5 1	2.9 4	7.2-8.0 13
1e (e)	5.6 6	-	2.3 6	-	2.0 7	0.6 7	- -	8.5 2	2.7 8	7.0-7.9 11
2c	4.4 6	1.6	1.6 (f)	1.6	- -	- -	7.7 2	- -	- -	7.4-8.0 15
2d	5.1 8	1.7	1.7 (f)	1.7	- -	- -	7.8 1	8.2 1	2.9 4	7.3-7.6 13
2e	5.4 6	1.8 (f)	1.8 (f)	1.8	- -	- -	- -	8.2 2	2.9 8	7.3-7.6 11

(a) δ Chemical shift value in ppm for deuteriochloroform as the solvent, TMS as the internal standard; J = 3-bond coupling constant in Hz; [s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet]. (b) Of the pyridinium nucleus. (c) Of the quinolinium nucleus. (d) Of the acridinium nucleus (e) In $(CD_3)_2SO$. (f) Obscured by singals in same region.

shielding effect of the flanking phenyls, maximum in **c** and least in **e**. Shielding by these phenyls also moves the terminal C*H*$_3$ resonance upfield to δ 0.5-0.9 for **1c-e**. The remaining aliphatics generally are at δ 1.4-2.8. The aromatic resonances are as previously described (5), notably pyridinium 3,5*H* in **1c** appear at δ 7.8 singlet, 1,13*H* in **1e, 2e** at *ca.* δ 8.5 multiplet and the rest of the aromatic *H* at δ 7.1-7.9.

Kinetic Studies.

Extensive work from our group has shown that *N*-alkylpyridiniums react with neutral nucleophiles in chlorobenzene solution by S_N1 and/or S_N2 mechanisms with clean kinetics (6). Reactions with piperidine monitored by uv spectroscopy form a useful guide to reactivity. We accordingly investigated the kinetics of reactions of **1c-e** and **2c-e** under our standard conditions. Ultraviolet data are recorded in Table 3. Plots of k_{obs} values *vs* concentration of piperidine (Table 4) gave straight lines (7) from which the unimolecular (k_1) and bimolecular (k_2) rate constants were calculated (Table 5). For **1c-e**, in the absence of nucleophile, slightly lower k_{obs} (a factor of *ca.* 10%) are observed (Table 4). Possibly this is due to "internal return" of the aminoalkyl cation back to the pyridine from a "tight ion pair" (8).

Table 3

Ultraviolet Data for the Dialkylaminoalkylazacycloniums (**1c-e, 2c-e**)

Compound No.	Solvent	λ observed (nm)	ϵ_1 (substrate)	ϵ_2 (leaving group)
1c	Chlorobenzene	312	22,300	6,000
1d	Chlorobenzene	348	12,000	1,704
1e	Chlorobenzene	391	(a)	0
2c	Ethanol/2% chlorobenzene	303	27,700	6,500
2d	Ethanol/2% chlorobenzene	348	15,600	3,200
2e	Chlorobenzene	391	19,800	0

(a) This compound has a half life of *ca.* 0.5 hour at 30°, ϵ_1 was not determined.

For the β-diethylaminoethyl derivatives **1c-e** the reactions occur overwhelmingly by the S_N1 mechanism, whereas reaction occurs by both S_N1 and S_N2 mechanisms for the 3-dimethylaminopropyl compounds **2c-e**. See Table 5.

Aminoalkylation Reactions.

On heating in inert solvents, all the pyridiniums (**1c-e** and **2c-e**) expel the leaving group and give polymeric products, presumably **6** and **7**, which are found to be highly insoluble in organic solvents and showed broadened ^{1}H nmr signals in the aliphatic (δ 2-3.5) region. The best analysis for **6** is given in the Experimental. Haloalkylamines have similarly been shown to polymerize (9).

Block 3

6 **7**

The triphenylpyridiniums **1c** and **2c** were used to alkylate oxygen, sulfur, nitrogen and carbon nucleophiles. Thus sodium phenoxide gave **1f** and **2f**, sodium thiophenate gave **1g** and **2g**, the corresponding amine yielded **1h, 2i, 1j** and **2j**, and sodio acetoacetate afforded **1k**. Due to ready decomposition of some of the products, sometimes satisfactory analyses were not obtained. In these cases (**1i** and **2i**), ^{13}C nmr and mass spectral evidence is given. See Experimental. Table 6 reports ^{1}H nmr data of the dialkylaminoalkylated products.

Reactions using **1d,e** and **2d,e** with superior (4) pyridine leaving groups led to lower yields of dialkylaminoalkylated products contaminated with polymeric

Table 4

Observed Rate Constants for Reaction of Dialkylaminoalkylazacycloniums (**1c-e, 2c-e**) with Piperidine in Chlorobenzene

Compound No.	$10^3 \times$ [Nu] (mol l^{-1})	$10^5 \times k_{obs}$ (sec^{-1})	r	Compound No.	$10^3 \times$ [Nu] (mol l^{-1})	$10^5 \times k_{obs}$ (sec^{-1})	r
1c (50°)	0 (a)	0.47	0.9988	**2c** (100°)	7	0.73	0.9973
	14	0.38	0.9988		10	0.74	0.9992
	27 (a)	0.54	0.9994		316	1.38	0.9974
	41	0.41	0.9998		422	1.57	0.9996
	55 (a)	0.53	0.9979		556	1.68	0.9994
	68	0.42	0.9986		660	1.63	0.9900
	82 (a)	0.55	0.9998				
	95	0.45	0.9997				
1d (30°)	0 (a)	1.89	0.9998	**2d** (100°)	228	50.5	0.9987
	23	1.82	0.9994		313	52.5	0.9996
	46	1.85	0.9996		393	52.8	0.9991
	65 (a)	2.65	0.9993		469	56.8	0.9979
	68	1.89	0.9998				
	130 (a)	2.76	0.9997				
	195	2.77	0.9999				
1e (30°)	0 (a)	26.2	0.9974	**2e** (50°)	0	0.96	0.9963
	0	35.7	0.9998		24	1.08	0.9928
	32 (a)	32.0	0.9976		121	1.68	0.9986
	65	48.8	0.9981		242	2.18	0.9922
	97 (a)	32.3	0.9985		276	2.62	0.9970
	129	49.0	0.9992		362	2.78	0.9931
	162 (a)	32.5	0.9989				
	194	49.5	0.9995				

(a) Measured simultaneously as a set of four; other runs also another set of four.

Table 5

Results of the Kinetic Studies of Dialkylaminoalkylazacycloniums (**1c-e, 2c-e**) in Chlorobenzene with Piperidine

Compound No.	Temperature (°C)	No. of Experiments	$10^5 \times k_1$ (sec^{-1}) First order	$10^5 \times k_2$ (1 mol^{-1} sec^{-1}) Second order
1c	50	8	0.45 ± 0.09	(0.4 ± 1.5)
1d	30	7	1.8 ± 0.4	(5.6 ± 3.7)
1e	30	8	39 ± 7	(-0.07 ± 0.01)
2c	100	6	0.8 ± 0.2	1.5 ± 0.4
2d	100	4	45 ± 7	24 ± 6
2e	50	6	1.0 ± 0.2	5.2 ± 0.8

material (**6** or **7**). These pyridiniums are highly activated whereas the 2,4,6-triphenylpyridiniums **1c,2c** are potentially safe analogues of haloalkylamines.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin Elmer 257 grating spectrometer and the ^1H nmr spectra were run on a Perkin Elmer (60 MHz) R12 permanent magnet instrument. The ^{13}C nmr data were collected on a JEOL FX-100 spectrometer operating at 25.05 MHz. An SP-800A spectrophotometer was used to record the ultraviolet spectra whilst the fixed wavelength optical density measurements were made on an SP6-500 digital display spectrophotometer. Melting points were recorded on a Reichert microscope hot stage apparatus and are uncorrected.

Preparation of Pyryliums.

The following pyryliums were prepared by literature procedures: 2,4,6-triphenylpyrylium tetrafluoroborate, mp 258-260° (lit (10) mp 253-255°) and trifluoromethanesulfonate, mp 247-248° (lit (5) mp 257-259°); 5,6-dihydro-2,4-diphenylbenzo[*h*]chromenylium trifluoromethanesulfonate, mp 266-268° (lit (5) mp 271-272°); 5,6,8,9-tetrahydro-7-phenyldibenzo[*c,h*]xanthylium tetrafluoroborate, mp 265-266° (lit (11) mp 265°) and trifluoromethanesulfonate, mp 312-313° (lit (5) mp 304°).

General Methods for Syntheses of Dialkylaminoalkylazacycloniums.

Table 6

^{1}H-NMR Data (a) for the Dialkylaminoalkylated Products (**1f,g,h,j,k; 2f,g,i,j**)

Compound No.	Solvent	Dialkylaminoalkyl-						Nucleophile (Nu)-					
		Nu-CH_2	CH_2-CH_2-CH_2	CH_2-CH_2-N	N-CH_3	N-CH_2-Me	CH_2-CH_3	Aromatic				Aliphatic	
		2H, t	2H, m	2H, t	6H, s	4H, q	6H, t						
		δ J	δ	δ J	δ	δ J	δ J	δ	H	M	J	δ	H	M	J
1f	$CDCl_3$	4.0 6	-	2.8 6	-	2.5 7	1.0 7	6.8-7.4	5	m	-		-		
1g	CCl_4	2.9 (b)	-	2.8 (b)	-	2.5 7	1.0 7	7.3	5	m	-		-		
1h (c)	$CDCl_3$	2.6 (d)	-	2.6 (d)	-	2.6 (d)	1.0 8					1.8	4	m	-
												2.6	4	m	-
1j (e)	$(CD_3)_2SO$	5.1 7	-	3.7 8	-	3.4 7	1.3 7	8.2	2	t	6		-		
								8.7	1	m	-				
								9.1	2	d	6				
1k	$CDCl_3$	2.4 (d)	-	2.4 (d)	-	2.4 (d)	1.1 (d)					1.1	3	t	(d)
												2.5	3	s	-
												4.2	2	q	7
2f	$CDCl_3$	4.0 6	2.0	2.4 6	2.2	-	-	6.8-7.4	5	m	-		-		
2g	CCl_4	2.5 7	1.9	3.1 6	2.3	-	-	7.4	5	m	-		-		
2i (e)	$CDCl_3$	2.3 (d)	1.6	2.3 (d)	2.2	-	-		-			1.5	6	m	-
												2.3	4	m	-
2j (e)	$(CD_3)_2SO$	4.6 7	2.4	3.1 8	2.8	-	-	8.2	2	d	6		-		
								8.6	1	m	-				
								9.1	2	d	6				

(a) δ Chemical shift values in ppm relative to TMS; J = 3-bond coupling constant in Hz; s = singlet, d = doublet, t = triplet, q = quartet, M = multiplicity. (b) Second order splitting. (c) The ^{13}C-nmr are reported in the Experimental. (d) Obscured by other CH_2 signals in same region. (e) Fluoroborate salts.

Method A.

The pyrylium (10 mmoles) was suspended in dichloromethane (5 ml), the amine (15 mmoles) was added and the solution stirred for 40 minutes. Acetic acid (0.1 ml) was added and, after stirring for a further 2 hours, the mixture was poured into ether (200 ml) and stirred. The resulting crystals were removed by filtration and washed, first with water then with ether.

Method B.

The same procedure as for Method A was used except with amine (10.01 mmoles) and triethylamine (5 mmoles).

Method C.

The pyrylium (10 mmoles) was suspended in dichloromethane (20 ml) and the mixture under nitrogen was cooled, using a 2-propanol/solid carbon dioxide bath, to *ca.* -55°; the amine (15 mmoles) was added and the mixture stirred at this temperatue for 1 hour. Acetic acid (0.1 ml) was added and the solution warmed to *ca.* 25° over a period of *ca.* 30 minutes. The mixture was poured into ether (200 ml) and worked up as in Method A.

Polymerization Reactions.

The following procedure is illustrative. The dialkylaminoalkylazacyclonium **1e** (10 mmoles) was refluxed in dichloromethane (50 ml) for 4 hours. A solid precipitated, was collected by filtration and washed with dichloromethane, mp 245-255°.

Anal. Calcd. for $(C_7H_{14}F_3N_2SO_3)_n$: C, 33.7; H, 5.7; N, 5.6. Found: C, 35.2; H, 5.6; N, 5.6.

N,N-Diethyl-2-phenoxyethylamine (**1f**).

Compound **1c** (X = trifluoromethanesulfonate) (1 g, 1.8 mmoles) and sodium phenoxide (0.5 g, 5.3 mmoles) in toluene (150 ml) were kept at 111° for 2 hours. Extraction with aqueous hydrochloric acid (1 *M*, 20 ml × 6) was followed by treatment with potassium hydroxide (16 g). The amine was extracted into ether (20 ml × 3), dried (magnesium sulfate) and distilled at 68-70°/1 mm to give product **1f** (0.2 g, 57%) (lit (12) bp 114-116°/5 mm); ^{13}C nmr δ 11.9 (q), 47.9 (t), 51.8 (t), 66.4 (t), 114.4 (d), 120.5 (d) and 129.3 (d).

Anal. Calcd. for $C_{12}H_{19}NO$: C, 74.6; H, 9.9; N, 7.2. Found: C, 74.6; H, 10.1; N, 7.2.

N,N-Dimethyl-3-phenoxypropylamine (**2f**).

This compound was prepared (37%) similarly using compound **2c** (X = trifluoromethanesulfonate) and 6 hours reaction time. The product had bp 62-63°/1 mm (lit (13) bp 115°/15 mm); ^{13}C nmr δ 27.6 (t), 45.5 (q), 56.4 (t), 66.0 (t), 114.4 (d), 120.5 (d) and 129.3 (d).

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.7; H, 9.6; N, 7.8. Found: C, 73.8; H, 10.1; N, 8.0.

N,N-Diethyl-2-phenylthioethylamine (**1g**).

Compound **1c** (X = trifluoromethanesulfonate) (1 g, 1.8 mmoles) and sodium thiophenate (1 g, 5.9 mmoles) in toluene (50 ml) were refluxed for 50 minutes. The solution was cooled to *ca.* 25°, filtered and then the amine was extracted into hydrochloric acid (1 *M*, 5 × 20 ml). Potassium hydroxide (5 g) was added and the product extracted into ether (5 × 20 ml). The ethereal layer was dried (magnesium sulfate) and the amine (0.25 g, 67%) remaining on removal of the solvent at *ca.* 20°/25 mm, was distilled, bp 100-102°/1 mm (lit (14) bp 156-158°/22 mm); ^{13}C nmr δ 11.9 (q), 31.2 (t), 47.0 (t), 52.1 (t), 125.6 (d), 128.8 (d) and 136.6 (s); m/e 209 (m^+) and 100 (m^+-SPh).

N,N-Dimethyl-3-phenylthiopropylamine (**2g**).

This compound was prepared (56%) similarly from **2c** (X = trifluoromethanesulfonate) and a 2 hours reaction time, and characterised as the hydrochloride (formed by passing dry hydrochloric acid through an ethereal solution), prisms, mp 118-120°.

Anal. Calcd. for $C_{11}H_{18}ClNS$: C, 57.0; H, 7.8; N, 6.0. Found: C, 56.7; H, 7.6; N, 5.8.

N,N-Diethyl-2-pyrrolidinoethylamine (**1h**).

Compound **1c** (X = trifluoromethanesulfonate) (1 g, 1.8 mmoles) was heated in pyrrolidine (2 ml) and ethanol (10 ml) at *ca.* 80° for 8 hours.

The mixture was kept at *ca.* 4° for 24 hours and then 2,4,6-triphenylpyridine (0.47 g, 85%) filtered off. The solvent was removed at *ca.* 20°/25 mm, potassium hydroxide (8% aqueous, 20 ml) added and the amine was extracted into ether (5 × 20 ml). Removal of the ether at *ca.* 20°/25 mm and distillation at 54-58°/1 mm gave the amine (0.18 g, 58%) (lit (15) bp 56-58°/3 mm); m/e 170 (m^+); ^{13}C nmr δ 10.3 (q), 21.9 (t), 48.0 (t), 50.3 (t) and 53.1 (t).

N,N-Dimethyl-3-piperidinopropylamine (**2i**).

Compound **2c** (X = trifluoromethanesulfonate) (1 g, 1.8 mmoles) was heated at *ca.* 108° in piperidine (10 ml) for 10.5 hours. Ethanol (20 ml) was added and the mixture kept at *ca.* 4° for 24 hours. Work-up as for compound **1g** gave the amine (0.16 g, 50%), bp 54-58°/1 mm ^{13}C nmr δ 19.1 (q), 19.7 (t), 22.5 (t), 31.7 (q), 51.2 (t), 52.0 (t) and 52.6 (t); m/e 170 (m^+).

1-(2-Diethylammonium)pyridinium bis-tetrafluoroborate (**1j**).

Compound **1c** (X = fluoroborate) (1 g, 2.0 mmoles) was heated at *ca.* 111° in pyridine (15 ml) for 5 hours. Cooling and addition to ether (100 ml) gave an oil which was dissolved in ethanol (20 ml) and fluoroboric acid (45% aqueous, 1.5 ml). On standing at 4°, compound **1j** (0.06 g, 10%) crystallised as needles, mp 116-117°.

Anal. Calcd. for $C_{11}H_{20}B_2F_8N_2$: C, 37.3; H, 5.7; N, 7.9. Found: C, 37.2; H, 5.9; N, 7.8.

1-(3-Dimethylammonium)pyridinium bis-Tetrafluoroborate (**2j**).

This compound (9%) was prepared similarly [from compound **2c** (X = fluoroborate)] as needles (from acetone-ethanol), mp 99-100°.

Anal. Calcd. for $C_{10}H_{18}B_2F_8N_2$: C, 35.5; H, 5.3; N, 8.2. Found: C, 35.5; H, 5.3; N, 8.1.

3-Ethoxycarbonyl-*N,N*-diethyl-4-oxopentylamine (**1k**).

Compound **1c** (X = trifluoromethanesulfonate) (1 g, 1.8 mmoles) was heated at *ca.* 80° for 8 hours with the sodio derivative from ethyl acetoacetate (0.25 g, 1.8 mmoles) and sodium (0.043 g, 1.8 mmoles) in ethanol (15 ml). After 24 hours at 4° the precipitated 2,4,6-triphenylpyridine (0.53 g, 95%) was filtered off. Removal of solvent and distillation gave compound **1k** (0.074 g, 18%), bp 84-86°/3 mm (lit (16) bp 115-120°/5 mm).

Anal. Calcd. for $C_{12}H_{23}NO_3$: C, 62.9; H, 10.1; N, 6.1. Found: C, 63.3; H, 10.3; N, 5.7.

Kinetic Measurements.

Reactions were followed spectrophotometrically under pseudo first order conditions by the previously established (17) method.

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