Deethoxycarbonylation of 2-(Ethoxycarbonyl)pyridinium Salts with Primary Amines and Competing $S_NANRORC$ Reactions

Alan R. Katritzky,* Radi Awartani, and Ranjan C. Patel

Department of Chemistry, University of Florida, Gainesville, Florida 32611, and School of Chemical Sciences, University of East Anglia, Norwich, England

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2-(Ethoxycarbonyl)pyridinium salts with primary amines undergo competing $S_NANRORC$ and deethoxycarbonylation reactions. Proportions vary: methylamine gives only the former but *tert*-butylamine only the latter reaction. α-Unsubstituted pyridiniums thus become readily available.

Further studies[1] of pyridinium salts derived from pyryliums and amines require α-unsubstitued 2,4-diphenylpyridinium derivatives. We now report a novel method for their preparation since they cannot readily be obtained directly from 2,4-diphenylpyrylium salts.[2] 2-(Ethoxycarbonyl)-4,6-diphenylpyrylium (**3**) with amines gave 1-substitued 2-(ethoxycarbonyl)-4,6-diphenylpyridinium salts (cf. ref 2), which are deethoxycarbonylated with *tert*-butylamine (Scheme I): the ethoxycarbonyl group is transformed to leave an intermediate ylide. Methyl-, ethyl-, benzyl-, and isopropylamines with 2-(ethoxycarbonyl)pyridiniums gave $S_NANRORC$[3] and/or deethoxycarbonylation products.

Preparation of Pyrylium Salts. 2-(Ethoxycarbonyl)-4,6-diphenylpyrylium (**3**) tetrafluoroborate[4] and triflate[5] have been prepared previously from **1** with ethyl pyruvate. Analogously, **2** yielded the 6-*tert*-butyl analogue **4**, and **5** was obtained from benzylidene-α-tetralone. Ester exchange of **3** formed the methyl ester **6**.

Reactions of Pyrylium Salts with Ammonia and Amines. Pyrylium salts **4** and **5** on treatment with ammonium acetate gave the expected pyridines. Pyryliums **3–5** reacted smoothly in CH_2Cl_2 with aniline and 4-methyl- and 4-chloroaniline to give high yields of pyridiniums **7–9**, respectively. Similarly, the 2-(methoxycarbonyl)pyrylium **6** with aniline gave the corresponding pyridinium **10** (see Table I and Chart I).

Hydrolysis of Pyridinium-2-carboxylic Esters. Basic hydrolysis of **7a** and **8a** with aqueous NaOH gave the corresponding betaines **11** and **12**, both too hygroscopic for analysis and therefore characterized spectroscopically (CO_2^- at 1650 cm^{-1}; characteristic NMR signals; see Experimental Section).

Decarboxylation Reactions. Of various acid- or base-catalyzed procedures applied to the decarboxylation of the betaines **11**, the most successful was reflux with $HI–H_2O$ which gave the iodide **13**, I^- (90%); this method has been used to prepare further 1-aryl-2,4-diphenylpyridinium iodides.[5]

However, a better procedure for the conversion of **7a** → **13a** was found to be refluxing with *tert*-butylamine in ethanol: **13a** was obtained as the triflate (97%). Similarly, pyridinium salts **7b,c** were converted into the deethoxycarbonylated products **13b,c** in high yield (Table II). The IR spectrum showed loss of CO_2Et (at ca. 1750 cm^{-1}), and the ^1H NMR (Table III) spectrum showed the C(2) H signal as a downfield doublet at δ 8.5. The 6-*tert*-butylpyridiniums **8a–c** and the tricyclic pyridiniums **9a–c** react similarly to give the corresponding 2-unsubstituted pyridiniums.

As the reaction worked equally well with the methyl ester **10**, the mechanism probably involves attack of the *tert*-butylamine at the C=O group and elimination of *t*-$BuNHCO_2Et$ from intermediates of type **16**, an elimi-

Scheme I

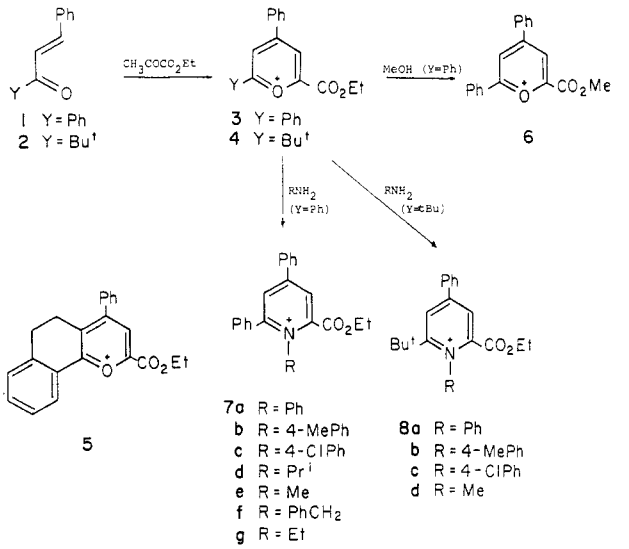
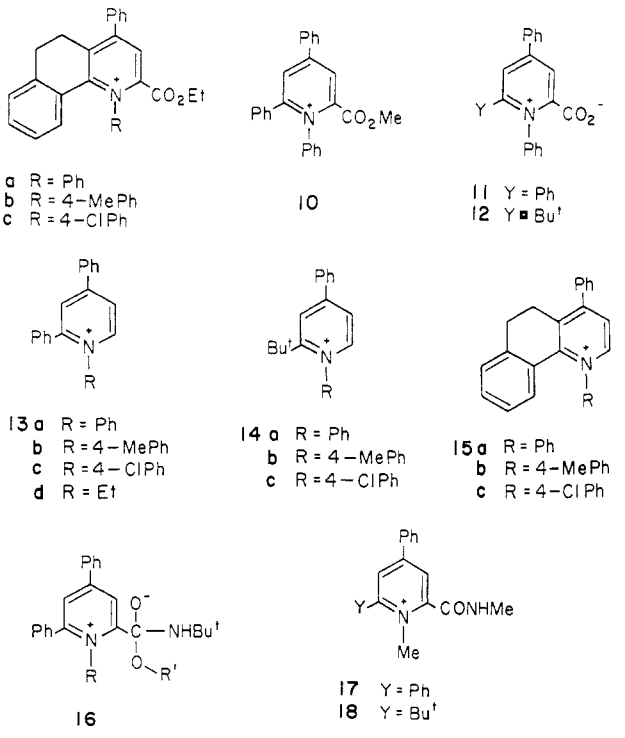


Chart I



* To whom correspondence should be addressed at the University of Florida.

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Table I. Preparation of 2-(Alkoxycarbonyl)pyridinium Salts[a,b]

compd	N substituent	anion	time, h	yield, %	mp, °C (form[c])
8a	Ph	BF_4	96	87	188-189 (N)
8b	*p*-MePH	BF_4	72	89	162-163 (Pl)
8c	*p*-ClPh	BF_4	72	91	225-227 (Pr, Pl)
8d	Me	BF_4	10	96	173-175 (N)
7a	Ph	BF_4	3	95	185-186[d] (N)
7a	Ph	CF_3SO_3	6	93	148-150[e] (N)
7b	*p*-MePh	BF_4	8	96	202-204[f] (N)
7c	*p*-ClPh	BF_4	4	95	182-184[g] (N)
10	Ph	CF_3SO_3	6	94	193-194[h] (Pr)
9a	Ph	BF_4	10	85	170-172 (N)
9b	*p*-MePh	BF_4	12	92	172-173 (Mi)
9c	*p*-ClPh	BF_4	8	90	188-190[i] (N)

[a] All reactions were conducted in CH_2Cl_2 at 25 °C. [b] C, H, and N analyses within 0.4% were obtained for all new compounds. [c] Crystal form: N = needles, Pr = prisms, Pl = plates, Mi = microcrystals. [d] Lit.[2] mp 185-187 °C. [e] Sample prepared by Cozens[5] has a melting point of 160 °C. [f] mp[5] = 203 °C. [g] mp[5] = 186 °C. [h] S found, 6.3% (required 6.2%). [i] Cl found, 6.7% (required 6.7%).

Table II. Products of Deethoxycarbonylation, S_NANRORC Reactions, and/or Amide Formation from the Reaction of 2-(Ethoxycarbonyl)-1,4,6-triphenylpyridinium Salts with Amines[a]

substrate	anion	amine	product	method	time, h	yield, %	mp, °C (form[b])
7a	CF_3SO_3	*t*-$BuNH_2$	13a	B	12	97	138 (N)
7a	BF_4	*t*-$BuNH_2$	13a	B	12	95	235 (Pl)
7a	CF_3SO_3	$MeNH_2$	17	A	3.5	90	167-168 (N)
7a	CF_3SO_3	$MeNH_2$	7e	A	4	95	115-118 (N)
7a	BF_4	$MeNH_2$	7e	A	4	93	173-175 (N)
7a	CF_3SO_3	$PhCH_2NH_2$	7f	A	5	89	158-160 (N)
7a	BF_4	*i*-$PrNH_2$	7d	A	12	95	130-132 (N)
7b	BF_4	*t*-$BuNH_2$	13b	B	12	94	215-217 (N)
7c	BF_4	*t*-$BuNH_2$	13c	B	12	94	194-195 (N)
8a	BF_4	*t*-$BuNH_2$	14a	B	24	85	224-226 (N)
8b	BF_4	*t*-$BuNH_2$	14b	B	24	80	239-240 (Pr)
8c	BF_4	*t*-$BuNH_2$	14c	B	18	80	232-235 (Pl)
9a	BF_4	*t*-$BuNH_2$	15a	B	24	90	237-239 (Pr)
9b	BF_4	*t*-$BuNH_2$	15b	B	24	85	270-272 (Pr)
9c	BF_4	*t*-$BuNH_2$	15c	B	12	90	245-246 (Pl)

[a] See footnote *b* in Table I. [b] See footnote *c* in Table I.

nation which is possibly helped by the buttressing effect of the 6-phenyl groups on the N substituent.

tert-Butylamine failed to react with **7a** in CH_2Cl_2 at 25 °C (12 h) or at reflux (36 h) or in CCl_4, benzene, or THF as solvents. The need for the alcoholic solvent supports a highly polar intermediate such as **16** for this reaction.

ANRORC Reactions. We tried the reactions of *N*-phenyl-2-(ethoxycarbonyl)pyridinium **7a** with $MeNH_2$, $EtNH_2$, and *i*-$PrNH_2$ and found that one or more of four different types of products could be produced (cf. Table IV): (i) simple deethoxycarbonylation to **13a**; (ii) simple ANRORC reaction to give, e.g., **7d–f**; (iii) ANRORC reaction combined with deethoxycarbonylation to give, e.g., **13d**; (iv) ANRORC reaction combined with conversion of the ester to amide to give, e.g., **17**.

Reaction of **7a** with excess methylamine gave the *N*-methyl amide **17** (Table V), with 1 mol of $MeNH_2$ **7a** yielded the *N*-methyl ester **7e** (95%), indicating that the S_NANRORC[3] reaction (cf. Zincke reaction[6]) is preferred to the ester–amide interchange. Reaction of **8a** with $MeNH_2$ similarly given mainly the *N*-methyl compound **8d**: pyrylium **4** with excess $MeNH_2$ afforded the amide **18**.

Ethylamine with **7a** at 25 °C in CH_2Cl_2 gave a mixture. In refluxing ethanol, 1-ethyl- (**13d**) and 1-phenyl-2,4-diphenylpyridinium (**13a**) in the ratio 80:20 (as deduced by ^1H NMR) were obtained, the former via S_NANRORC and elimination reactions and the latter from elimination of CO_2Et only. The ANRORC reaction does not necessarily preceed the elimination as **13a** reacted with $EtNH_2$ in CH_2Cl_2 at 20 °C to give the ANRORC product **13d**.

At 25 °C in CH_2Cl_2, isopropylamine with **7a** gave only the S_NANRORC product, 1-isopropyl-2-(ethoxycarbonyl)-4,6-diphenylpyridinium (**7d**, 95%). However, in the refluxing EtOH, the elimination product **13a** was obtained.

^1H NMR Spectra. The structures of all the foregoing products are supported by their ^1H NMR spectra. For derivatives retaining a 2-substituent (Table III) the C(3)H and C(5)H signals appear as finely split doublets near δ 8.0 and 8.3 for both the 6-phenyl and the 6-*tert*-butyl series, whereas the C(3)H signal appears as a singlet for the tricyclic series. In the *N*-aryl compound, the CH_2 and CH_3 of CO_2Et occur near δ 4.0 and 1.0, respectively; both these signals are shifted down field by ca. 0.5 ppm in the *N*-alkyl derivatives, reflecting the shielding effect of the *N*-aryl ring.

In the compounds which have lost the 2-substituent (Table V), the ring protons form a characteristic pattern: C(2)H, C(3)H, and C(5)H show respectively, a d (J = 7 Hz)

(2) 2,4-Disubstituted pyryliums react readily with primary amines to give ring opening, but reclosure of the vinylogous amide to the pyridinium occurs in low yield if at all. Agha, B. Ph.D. Thesis, University of East Anglia, 1981. Chermprapai, A. Ph.D. Thesis, University of East Anglia, 1981.

(3) Nucleophilic substitution by addition of nucleophile, ring opening, and ring closure. Cf.: van der Plas, H. C. *Acc. Chem. Res.* **1978**, *11*(12), 462.

(4) Katritzky, A. R., Chermprapai, A.; Patel, R. C.; Tarraga-Tomas, A. *J. Org. Chem.*, in press.

(5) Cozens, A., unpublished work.

(6) Zincke, T. *Justus Liebigs Ann. Chem.* **1903**, *330*, 361; **1904**, *333*, 296.

Table III. ^{1}H NMR (100 MHz) Spectral Data of 2-RCO_2-Substituted Pyridiniums[a]

	C subst[h]			N		2-subst				δ(C(3) H)[b]	δ(C(5) H)[b]		aromatic multiplets		1-subst		
compd	2	5	6	subst	anion	δ	mult	H's	J			δ(t-Bu)	δ	H's	δ	mult	H's
8a	CO_2Et	H	t-Bu	Ph	BF_4	1.04	t	3	8	8.14	8.46	1.40	7.40-8.00	10	c		
						4.05	q	2	8								
8b	CO_2Et	H	t-Bu	p-MePh	BF_4	1.04	t	3	8	8.10	8.42	1.36	7.10-7.90	9	2.3	s	3
						4.06	q	2	8								
8c	CO_2Et	H	t-Bu	p-ClPh	BF_4	1.06	t	3	8	8.09	8.38	1.34	7.50-7.90	9	c		
						4.06	q	2	8								
11	CO_2	H	Ph	Ph						8.10	8.32		7.10-7.40	10	7.50-7.70	m	3
															7.80-7.94	m	2
10	CO_2Me	H	Ph	Ph	CF_3SO_3	3.66	s	3		8.25	8.50		7.20-7.60	13	c		
													7.84-7.98	2			
17	CONHMe	H	Ph	Ph	CF_3SO_3	3.03	d	3	4.5	7.80	7.98		7.40-7.80	10	4.02	s	3
						8.90	m	1									
17	CONHMe	H	Ph	Ph	BF_4	3.10	d	3	4.5	7.95	8.08		7.40-7.80	10	4.01	s	3
						8.90	m	1									
7e	CO_2Et	H	Ph	Me	CF_3SO_3	1.48	t	3	8	8.12	8.52		7.50-7.90	10	4.20	s	3
						4.25	d	2	8								
7e	CO_2Et	H	t-Bu	Me	BF_4	1.50	t	3	8	8.40	8.27		7.50-7.90	5	4.50	s	3
						4.63	q	2	8								
7d	CO_2Et	H	Ph	i-Pr	BF_4	1.52	t	3	7	8.06	8.22		7.00-8.00	10	1.70	d	6[d]
						4.63	q	2	7						5.14	m	1
7f	CO_2Et	H	Ph	$PhCH_2$	CF_3SO_3	1.22	t	3	8	8.10	8.55		7.20-8.00	15	6.00	s	2
						4.50	q	2	8								
9a[e]	CO_2Et	C_8H_8[f]		Ph	BF_4	1.02	t	3	7	7.98[g]			7.20-7.60	14	c		
						4.10	q	2	7								
9b[e]	CO_2Et	C_8H_8[f]		p-MePh	BF_4	1.04	t	3	7	7.94[g]			6.80-7.60	13	c		
						4.14	q	3	7								
9c	CO_2Et	C_8H_8[f]		p-ClPh	BF_4	1.06	t	3	7	8.06[g]			6.82-7.70	13			
						4.15	q	2	7								

[a] $CDCl_3$/TFA solvent; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; coupling constants in hertz. [b] One H, doublet, $J_{3,5}$ = 2 Hz. [c] Signals for protons are hidden within those for the other aromatic protons. [d] J = 8 Hz. [e] CH_2CH_2 group gives a 4-H multiplet at δ 2.8-3.20. [f] C_8H_8 = dihydronaphtho. [g] Singlet. [h] The C-3 substituent is H and the C-4 substituent is Ph in all cases.

Table IV. Reactions of 2-(Ethoxycarbonyl)-1,4,6-triphenylpyridinium Tetrafluoroborate with Primary Amines

		% yield (product)			
amine[a]	method[b]	$S_NANRORC$ ester	$S_NANRORC$ amide	$S_NANRORC$ dethoxy-carbonylation	deethoxy-carbonylation
$MeNH_2$	A		94 (17)		
	B		92 (17)		
$EtNH_2$	A	d (7g)	d		
	B			80 (13d)	20 (13a)
i-$PrNH_2$	A	95 (7d)			
	B				95 (13a)
t-$BuNH_2$	A	none			
	B				94 (13a)

[a] Amines were used in excess (3-5 mol of amine/1 mol of pyridinium). [b] Method A involves the reaction of pyridinium with excess amine at room temperature in CH_2Cl_2, while method B involves the reaction of the pyridinium with amine in refluxing ethanol. [c] Whenever mixtures were involved, yields were deduced from ^{1}H NMR spectra. [d] Difficult to assign yields by ^{1}H NMR integration.

Table V. ^{1}H NMR Spectral Data of Deethoxycarbonylated Pyridinium Salts

compd[a]	C_6	N subst	anion	δ(C(2) H)[b]	δ(C(3) H)[c]	δ(C(5) H)[d]	δ(t-Bu)	aromatic multiplets δ	aromatic multiplets H	1-subst δ	1-subst mult	1-subst H
13a	Ph	Ph	CF_3SO_3	8.85	8.38	8.24		7.26-7.56	10	7.66-7.74	m	3
										7.80-8.00	m	2
13a	Ph	Ph	BF_4	8.70	8.36	8.18		7.20-7.44	10	7.56-7.74	m	3
										7.80-7.96	m	2
13a	Ph	Ph	I	9.30	8.48	8.10		7.20-8.00	15	e		
										7.63	dd	2
13b	Ph	p-MePh	BF_4	8.75	8.30	8.20		7.00-7.50	10	7.94	dd	2[f]
										2.38	s	3
13c	Ph	p-ClPh	BF_4	8.74	8.30	8.18		7.20-7.50	10	7.60	dd	2[f]
										7.90	dd	2
14a	t-Bu	Ph	BF_4	8.34	8.00	8.24	1.34	7.40-8.40	10	e		
14b	t-Bu	p-MePh	BF_4	8.34	8.02	8.27	1.38	7.36-7.90	9	e		
										2.46	s	3
14c	t-Bu	p-ClPh	BF_4	8.30	8.00	8.23	1.33	7.40-8.00	9	e		
13d	Ph	Et	BF_4									
15a	C_8H_8[b]	Ph	BF_4	8.60	7.90			6.80-7.80	15	e		
15b	C_8H_8[b]	p-MePh	BF_4	8.62	7.90			6.90-7.60	14	e		
										2.46	s	3
15c	C_8H_8[b]	p-ClPh	BF_4	8.60	7.94			6.90-7.60	19	e		

[a] C(2) H, C(3) H, C(4) Ph, C(5) H. [b] 1 H, d, J^o = 7 Hz. [c] 1 H, dd, J^o = 7 Hz, J^m = 2 Hz. [d] 1 H, J^m = 2 Hz. [e] Signals for the protons are hidden within those for the other aromatic multiplets. [f] J^o = 6.5 Hz, J^m = 2.5 Hz.

near δ 9, a dd (J = 2, 7) near δ 8.3, and a d (J = 2 Hz) near δ 8.2.

Conclusion. From the above results it is clear that as the size of the alkyl group of the primary amine increases, the tendency for an $S_NANRORC$ reaction to occur lessens: 2-CO_2Et elimination is the only reaction with *tert*-butylamine.

These deethoxycarbonylation reactions result in readily available pyridiniums with unsubstituted α-positions which are not easily obtained from the corresponding pyryliums.

Experimental Section

^{1}H NMR Spectra were recorded with Varian HA-100 and Varian A-60 A spectrometers using internal Me_4Si as a standard. IR spectra were obtained on a Perkin-Elmer 297 spectrophotometer. Melting points were recorded on a Reichert hot-stage microscope and are uncorrected.

The following compounds were prepared by using literature methods: 2-(ethoxycarbonyl)-4,6-diphenylpyrylium tetrafluoroborate [mp 157–158 °C (lit.[4] mp 154 °C) and trifluoromethanesulfonate [mp 184–186 °C (lit.[5] mp 194–196 °C)].

2-(Ethoxycarbonyl)-4-phenyl-6-*tert*-butylpyrylium Tetrafluoroborate (4). Benzalpinacolone[7] (2; 8 g, 68 mmol), ethyl pyruvate (2.5 g, 22 mmol), and BF_3·OEt_2 (45%, 6.5 mL, 24.0 mmol) were stirred at 40 °C for 12 h. The resulting dark red crystalline mass was triturated with ether (100 mL). The pale yellow crystals were filtered off and recrystallized from acetone to give the pyrylium 4: 2.7 g (34.0%); needles; mp 221–222 °C; IR ($CHBr_3$) 1740 (s), 1615 (s), 1040 (br) cm^{-1}; NMR ($CDCl_3$/TFA) δ 1.44 (t, 3 H), 1.56 (s, 9 H), 4.55 (9, 2 H), 7.4–7.8 (m, 3 H), 8.0–8.10 (m, 2 H), 8.34 (d, 1 H, J = 2 Hz), 8.75 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{18}H_{21}O_3BF_4$: C, 58.21; H, 5.7. Found: C, 58.2; H, 5.4.

5,6-Dihydro-2-(ethoxycarbonyl)-4-phenylbenzo[*h*]chromenylium Tetrafluoroborate (5). Benzylidene-α-tetralone[8] (2 g, 8.5 mmol), ethyl pyruvate (1.2 g, 10.4 mmol), and BF_3·OEt_2 (45%, 2.4 g, 17.1 mmol) were heated at 100 °C for 0.5 h. The resulting red oil was added dropwise to vigorously stirred ether (100 mL). The precipitated pink solid was crystallized from absolute EtOH to give yellow needles of the chromenylium: 0.5 g (14%); mp 170–172 °C; IR ($CHBr_3$) 1745 (s), 1620 (s), 1050 (br) cm^{-1}; NMR ($CDCl_3$/TFA) δ 1.38 (t, 3 H, J = 7 Hz), 2.90–3.10 (m, 2 H), 3.18–3.28 (m, 2 H), 4.46 (q, 2 H, J = 7 Hz), 7.20–7.70 (m, 9 H). Anal. Calcd for $C_{22}H_{19}O_3BF_4$: C, 63.2; H, 4.6. Found: C, 63.5; H, 4.6.

2-(Methoxycarbonyl)-4,6-diphenylpyrylium Trifluoromethanesulfonate (6). 2-(Ethoxycarbonyl)-4,6-diphenylpyrylium trifluoromethanesulfonate[5] (3; 1 g, 2.2 mmol) was refluxed in anhydrous MeOH (10 mL) for 24 h. The reaction mixture was concentrated in vacuo (25 mmHg) to ca. 2 mL. Addition of Et_2O (20 mL) gave yellow needles of the 2-(methoxycarbonyl)pyrylium trifluoromethanesulfonate[5]: 0.9 g (95%); mp 202–204 °C; IR ($CHBr_3$) 1750 (s), 1630 (s), 1270 (br), 1030 (s) cm^{-1}; NMR ($CDCl_3$/TFA) δ 4.12 (s, 3 H), 7.5–7.8 (m, 6 H), 8.12 and 8.20 (dd, 2 H, J = 2 Hz, J = 8 Hz), 8.32 and 8.40 (dd, 2 H, J = 2 Hz, J = 8 Hz), 8.75 (d, 1 H, J = 2 Hz), 8.90 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{20}H_{15}F_3O_6S$: C, 54.6; H, 3.4; S. 7.3. Found: C, 54.9; H, 3.3; S. 7.2.

General Method for Reaction of Pyrylium Salts 3–6 with Amines. To a suspension of the pyrylium salt (3 mmol) in CH_2Cl_2 (30 mL) at 25 °C was added the amine (3.3 mmol). The red solution was stirred at 25 °C for an appropriate time (Table I). After concentration of the yellow mixture in vacuo (25 mmHg), the residue was triturated with ether (50 mL) to give after filtration white crystals of the pyridinium which were recrystallized from absolute EtOH. See Table I for the physical data and Table II for ^{1}H NMR details.

2-(Ethoxycarbonyl)-4-phenyl-6-*tert*-butylpyridine. A mixture of the pyrylium tetrafluoroborate 4 (0.2 g, 0.54 mmol) and ammonium acetate (0.04 g, 0.55 mmol) was refluxed in absolute EtOH for 36 h. Dilution with water afforded the pyridine (0.16 g, 88%) as microcrystals (difficult to recrystallize): mp 56–58 °C; IR ($CHBr_3$) 1705 (s), 1590 (s), 1385 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.38 (t, 3 H, J = 7 Hz), 1.40 (s, 9 H), 4.40 (q, 2 H, J = 7 Hz), 7.20–7.60 (m, 5 H), 7.62 (d, 1 H, J = 2 Hz), 8.04 (d, 1 H, J = 2 Hz). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.4; N, 5.0. Found: C, 76.1; H, 7.8; N, 4.7.

5,6-Dihydro-2-(ethoxycarbonyl)-4-phenylbenzo[*h*]quinoline. This compound was prepared as above after 4 h of reflux and gave on dilution with water the quinoline as microcrystals: 0.18 g (92%); mp 87–89 °C; IR ($CHBr_3$) 1710 (s), 1605 (s), 1355 (s) cm^{-1}; NMR ($CDCl_3$) 1.45 (t, 3 H, J = 7 Hz), 2.70–3.10 (m, 4 H), 4.46 (q, 2 H, J = 2 Hz), 7.00–7.70 (m, 7 H), 7.90 (s, 1 H), 8.40–8.50 (m, 2 H). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.8; N, 4.3. Found: C, 79.9; H, 6.4; N, 3.9.

1,4-Diphenyl-6-*tert*-butylpyridinium-2-carboxylate (12). 1,4-Diphenyl-2-(ethoxycarbonyl)-6-*tert*-butylpyridinium tetrafluoroborate (**7a**; 2.0 g, 4.5 mmol) was stirred at 25 °C as a suspension in aqueous NaOH (0.5 N, 12 mL, 6 mmol) for 5 days. The solvent was removed in vacuo, and then residue was extracted with CH_2Cl_2 (25 mL) and precipitated with ether (100 mL) to give

(7) Hill, G. A.; Spear, C. S.; Lachowiz, J. S. *J. Am. Chem. Soc.* **1923**, *45*, 1557.
(8) Rapson, W. S.; Shuttleworth, R. G. *J. Chem. Soc.* **1940**, 636.

the hygroscopic betaine (1.2 g, 80%), which decomposes on attempted recrystallization: IR ($CHBr_3$) 1650 (s), 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 9 H), 7.6–8.4 (m, 10 H), 8.8 (d, 1 H, J = 2 Hz), 8.95 (d, 1 H, J = 2 Hz).

1,4,6-Triphenylpyridinium-2-carboxylate (11). 2-(Ethoxycarbonyl)-1,4,6-triphenylpyridinium tetrafluoroborate (**8a**; 5 g, 10.7 mmol) was stirred at 25 °C as a suspension in aqueous NaOH (0.5 N, 25 mL, 12.5 mmol) for 24 h. The white solid was filtered off and washed with water (500 mL) and ether (50 mL) to give the betaine as microcrystals: 3.2 g (85%); mp 150 °C dec (satisfactory analysis not obtained due to decomposition on attempted recrystallization); IR ($CHBr_3$) 1650 (s), 1618 (s) cm^{-1}; NMR ($CDCl_3$/TFA) δ 7.5–7.9 (m, 15 H), 8.10 (d, 1 H, J = 2 Hz), 8.38 (d, 1 H, J = 2 Hz).

1,2,4-Triphenylpyridinium iodide (13) was obtained by refluxing 1,4,6-triphenylpyridinium-2-carboxylate (11) (2 g, 5.7 mmol) with aqueous HI (65%, 1.20 g, 6.1 mmol) in THF (50 mL) for 4 h to yield yellow crystals (washed with ether). Recrystallization from absolute EtOH gave yellow needles: 2.1 g (85%); mp 273–274 °C; IR ($CHBr_3$) 1630 cm^{-1}; NMR ($CDCl_3$/TFA) δ 7.6–7.9 (m, 15 H), 8.10 (d, 1 H, J^m = 2 Hz), 8.43 and 8.5 (dd, 1 H, J^m = 2 Hz, J^o = 7 Hz), 9.38 (d, 1 H, J^o = 7 Hz). Anal. Calcd for $C_{23}H_{18}NI$: C, 63.5; H, 4.1; N, 3.2; I, 29.2. Found: C, 63.1; H, 4.1; N, 3.2; I, 29.4.

ANRORC Reaction. Method A. The 2-(ethoxycarbonyl)-pyridinium salt (2 mmol) was stirred in CH_2Cl_2 (10 mL) for 12 h with the amine (3–6 mmol) at 25 °C. The yellow solution was concentrated in vacuo (25 mmHg) and triturated with Et_2O.

Deethoxycarbonylation with Amines. Method B. The 2-(ethoxycarbonyl)pyridinium salt (2 mmol) refluxed in EtOH (5 mL) with *tert*-butylamine (6 mmol) for 12 h. The resulting red solution was concentrated in vacuo (25 mmHg) and residue triturated with Et_2O to give a white solid which was recrystallized from ethanol.

Reaction of Maleimides and Ethyl 3-Aminocrotonates. A Reinvestigation Leading to an Improved Synthesis of Pyrrolo[3,4-*c*]pyridines[1]

Kanhaiya R. Shah and C. DeWitt Blanton, Jr.*

Department of Medicinal Chemistry, School of Pharmacy, University of Georgia, Athens, Georgia 30602

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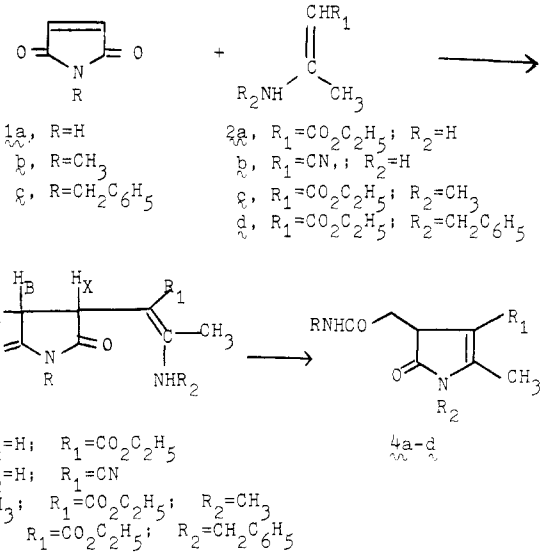
Conditions employed for the reaction between maleimides and ethyl aminocrotonates were shown to yield pyrrolo[3,4-*c*]pyridines rather than the previously reported pyrrolo[2,3-*b*]pyrroles.

The condensation of maleimide (**1a**) and 3-aminocrotonates or 3-aminocrotonitrile in a Nenitzescu-type reaction[2] has been reported[3] to give adducts **3** and **4** (Scheme I). Cyclization under basic conditions was claimed[3] to yield pyrrolo[2,3-*b*]pyrroles, which were converted to various derivatives (e.g., **5–7**).[4] During the preparation of additional derivatives,[5] several observations raised doubts about the structural assignments for compounds **5–7**, and data are presented to account for these observations and the new structural assignment.

Scheme I



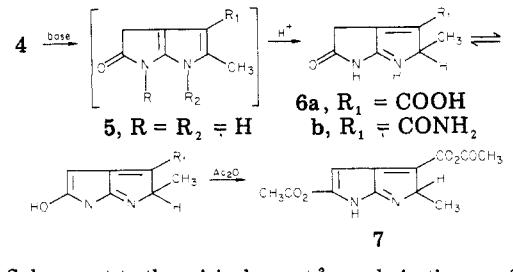
When *N*-methylmaleimide (**1b**, R = CH_3) was treated with ethyl 3-(methylamino)crotonate (**2c**; R_1 = $CO_2C_2H_5$, R_2 = CH_3), an adduct, ethyl 3-(methylamino)-2-(1-methyl-2,5-dioxopyrrolidin-3-yl)crotonate (**3c**; R = R_2 = CH_3, R_1 = $CO_2C_2H_5$) was isolated and characterized. The NMR spectrum of the product obtained upon cyclization[3]

(1) Taken in part from the Ph.D. Dissertation of K.R.S., University of Georgia, Dec 1979.

(2) (a) C. D. Nenitzescu, *Bull. Sci. Chim. Rom.*, 11, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930); (b) M. T. Weiss, G. R. Allen, Jr., G. J. Gibs, C. Pidacks, J. F. Poletto, and W. A. Remers, *Top. Heterocycl. Chem.*, 178 (1969).

(3) C. D. Blanton, Jr., J. F. Whidby, and F. H. Briggs, *J. Org. Chem.*, **25**, 3929 (1971).

(4) The original pyrrolo[2,3-*b*]pyrrole structural assignment[3] was based on elemental analysis, NMR and IR spectroscopy, and the preparation of several derivatives (e.g., **7**):



(5) Subsequent to the original report,[3] one derivative was found to possess marginal antineoplastic activity, and further studies were suggested in an effort to exploit this potential lead. Compound **7** (structure reassigned as **12a**) had T/C (test/control) ratios of 133 and 126 at 200 mg/kg in the 3PS31 (P388 lymphocytic leukemia) system and, therefore, met the criterion for activity (T/C = 125). This compound was also active in the 9KB5 (human epidermoid carcinoma of the nasopharynx) cell culture system, but it was inactive against 3B131 (B16 melanocarcinoma), 3CD72 ($CD8F_1$ mammary tumor), 3C872 (colon 38), 3LE21 (L1210 lymphoid leukemia), 3LL39 (Lewis lung carcinoma), 3C2G5 (CX-1 colon xenograft), and 3MBG5 (MX-1 breast xenograft), according to the standard protocol of the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.[6]

(6) (a) R. I. Geran, N. H. Greenberg, M. M. MacDonald, A. M. Schumacher, and B. J. Abbott, *Cancer Chemother. Rep.*, **3**(2), 1, 1972; (b) "Instruction Booklet 14, Screening Data Summary Interpretation", Drug Research and Development, Chemotherapy, National Cancer Institute: Bethesda, MD, 1972.

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