Kinetics and Mechanism of the Reactions of Primary Amines with Pyrylium Cations [1]

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The initial reaction of primary amines with pyrylium cations to give the ring-opened intermediate is fast for strongly basic amines and is base-catalysed for weak amines. Ring-closure of the intermediate to give the pyridinium derivative is subject to steric and electronic hindrance and is acid-catalysed. Solvent effects and the structure of the ring-opened intermediates are discussed.

WE have shown [2] by ^{13}C n.m.r. that n-butylamine, benzylamine, piperidine, and pyrrolidine all react with 2,4,6-triphenylpyrylium ion by fast ring-opening to vinylogous amides, which in the case of those from the primary amines (n-butylamine and benzylamine) undergo slow ring-closure to the 1-substituted-2,4,6-triphenylpyridinium cations. In view of the preparative importance of this type of reaction as the first stage of a two-step conversion of a primary amino-group into another functionality,[3] we have now investigated in detail the influence of amine and pyrylium structures and also of solvent, concentration, and temperature on the kinetics of this reaction. The results confirm and very considerably extend those obtained previously.

TABLE 1

U.v. absorption spectra: $\lambda_{max.}$/nm and ε/cm^2 mol^{-1}

									Vinylogous amide							
Pyrylium substituents [a]						Starting pyrylium [b]			c		d				Pyridinium [f]	
2	3	4	5	6	Anion	$\lambda_{max.}$	$10^{-3}\epsilon$	No.	$\lambda_{max.}$	$10^{-3}\epsilon$	Amine	$\lambda_{max.}$	$10^{-3}\epsilon$	λ [e]	$\lambda_{max.}$	$10^{-3}\epsilon$
Ph		Ph		Ph	ClO_4^-	418 369 282	24.2 33.9 16.9	(1)	444	19.1	Pr^i	444	18.5	444—305	305	27.1
Me		Ph		Ph	ClO_4^-	380 344 258	27.5 21.2 14.0	(8a)	444	8.5	PhCH$_2$	450	3.4	450	305	23.4
Bu^t		Ph		Ph	BF_4^-	392 370 257	24.9 20.4 12.9	(8b)	405	9.46	Pr^i	414	7.12	414	301	22.7
2,3-cyhex		Ph		Ph	BF_4^-	382 278	16.3 11.5		400	3.84	Pr^i	410	3.97	410	299	21.4
2,3-THN		Ph		Ph	BF_4^-	436 361 292	24.8 17.6 13.4	(12)	444	13.2	Pr^i	450	12.7	450	355	8.42
2T		Ph		Ph	ClO_4^-	455 370 320 296	23.8 31.0 7.5 7.5	(8c)	452	21.5	Pr^i	458	18.1	458	305	26.4
2T		Ph		2T	ClO_4^-	480 385 334 262	28.4 36.6 20.2 11.9		454	24.4	Pr^i	460	16.1	460	313	28.0
Ph	Ph		Ph	Ph	BF_4^-	434 312	17.6 22.2		393	21.6	Pr^i	398	16.6	398	322	10.4
Ph	Ph	Ph	Ph	Ph	Br^-	418 306	13.2 17.9		394	14.2	Pr^i	410	12.2	410	260	g

[a] 2T = 2-thienyl, 2,3-cyhex = 2,3-cyclohexeno, 2,3-THN = 2,3-tetrahydronaphtho[*b*]. [b] In CH_2Cl_2. [c] The spectra were taken after the addition of the amine (0.1 ml) to the CH_2Cl_2 (20 ml) pyrylium salt solution, see text. [d] In DMF, extrapolated to zero time, see text. [e] Analytical wavelength. [f] In DMF, extrapolated to infinite time. [g] Solvent absorption interferes with measurement of $\epsilon_{max.}$.

Very little previous kinetic work on pyryliums is available: their reactions with hydroxide anion [4] and with methoxide anion [5] have been studied and also the cyclisation of pent-2-ene-1,5-diones to pyryliums.[6] Moreover, the kinetics and mechanism of the reactions of hydroxide [7] and of piperidine [8] with *N*-phenylpyridiniums have been investigated.

Kinetic Method.—Reactions were followed by u.v. spectrometry: solutions of the pyrylium salt (6.1×10^{-3}M), with a measured quantity of amine, were prepared in a given solvent. Portions removed after known time intervals were diluted *ca.* 170 times with pure dimethylformamide (DMF) and the u.v. spectrum taken.

Table 1 records the u.v. spectra. Spectra for the pyrylium cations [*cf.* (1)] were recorded separately in dichloromethane and they are quite distinct from the spectra of the vinylogous amides [*cf.* (5)]. The spectral measurements of the vinylogous amide (5) were carried

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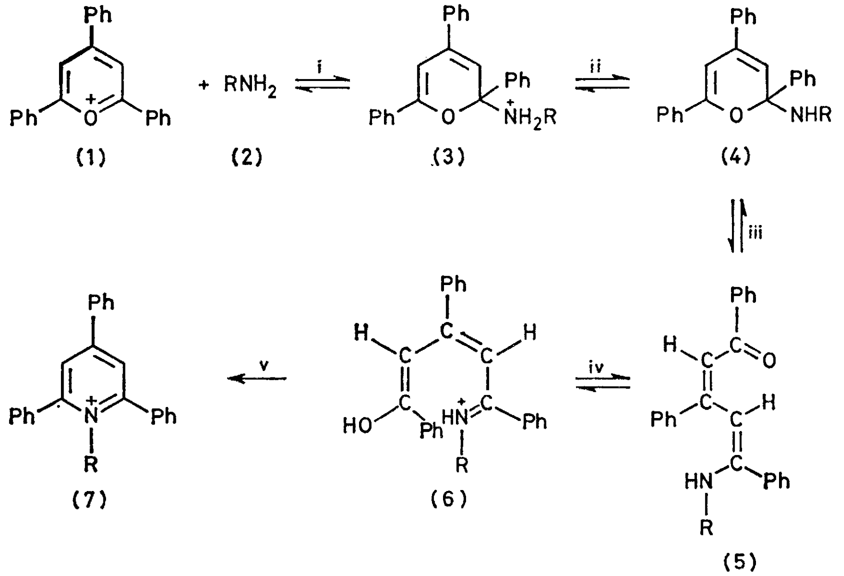
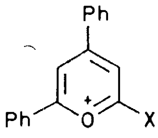
out under two sets of conditions. (a) Direct measurements were made of the spectra immediately after adding excess amine to a dilute dichloromethane solution of the pyrylium. (b) Excess of amine was added to a concentrated dichloromethane solution of the pyrylium, portions were then quenched with DMF at various time intervals, and the ε values were extrapolated back to zero time.

Small differences in $\lambda_{max.}$ were found for the two measurements, and larger ones for $\varepsilon_{max.}$ (see Table 1), reflecting the fast conversion rate of vinylogous amide (5) ⟶ pyridinium (7). Because of the first-order kinetics for the vinylogous amides ⟶ pyridinium conversion, errors in the magnitude of the ε value for the former do not affect the rate constants determined. Extrapolation to infinite time should give the spectra of the pyridinium cations in DMF (see Table 1): these were compared in many cases with independently determined u.v. spectra in EtOH and were in reasonable agreement. Table 1 also records the analytical wavelengths used.



(1) (2) (3) (4) (5) (6) (7)



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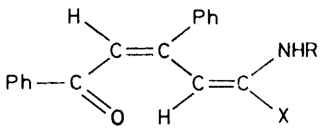

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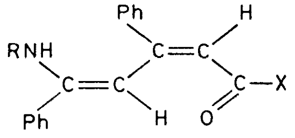

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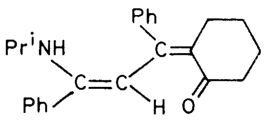

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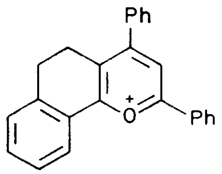

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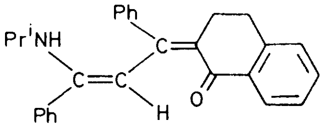

(13)

a, X = Me; b, X = Bu^t; c, X = 2-thienyl; d, X = Ph

Structure of Vinylogous Amides.—For the unsymmetrical pyryliums (8), amine attack could result in the formation of two different vinylogous amides, (9) or (10). The large difference in the $\lambda_{max.}$ for the vinylogous amide from (8b) ($\lambda_{max.}$ 405 nm) compared to that from (8d ≡ 1) (444 nm) (Table 1) indicates structure (10b) for the former. In (9b) the conjugation is extended, whereas that in (10b) is crossed; moreover, attack would be expected in (8b) away from the t-butyl group. The similarity of $\lambda_{max.}$ for the vinylogous amides from (1) and (8a) indicates that at least some (9a) is formed although the low $\varepsilon_{max.}$ suggests it may be mixed with (10a). (Williams found that 2-methyl-4,6-diphenylpyrylium is attacked by OH$^-$ at the 2-position.[4]) Analogously, the similarity of $\lambda_{max.}$ for the vinylogous amide from (8c) to that from the symmetrical dithienyl analogue indicates structure (10c) at least for a major part of the product.

The vinylogous amide (11) from the 2,3-cyclohexenopyrylium is assigned structure (11) as the $\lambda_{max.}$ is similar to (10b) and not to (9a). The tricyclic pyrylium (12) appears to give (13); in the isomeric vinylogous amide twisting of the amino-group is expected to give a hypsochromic shift. The $\lambda_{max.}$ for (13) is similar to that for (5) but the low $\varepsilon_{max.}$ may indicate that some of the other isomer is also formed.

Ring-opening of Pyrylium Cation to Vinylogous Amide.—Kinetics could be conveniently measured only when this first ring-opening step was fast. We found three sets of circumstances where this did *not* apply.

(i) In certain cases where less than 1.2 mol. equiv. of amine were used. Experiments with amine : pyrylium ratios of 1 and 0.9 showed that the complete conversion of (1) into (5) is not then obtained.

(ii) For reactions with amines of p$K_a < 8$, in the absence of a basic catalyst. In Figure 1, the time variation of the absorption at the $\lambda_{max.}$ for the pyrylium cation is shown for the reaction of aniline with triphenylpyrylium perchlorate in CH_2Cl_2 in the absence and presence of triethylamine. The reaction is very slow in the absence of NEt_3. The vinylogous amide formed rapidly in the presence of NEt_3 slowly cyclises; this cyclisation step is strongly catalysed by HOAc (see later) but HOAc does not help the initial reaction with aniline. We believe that this base catalysis is needed to remove the proton in the sub-step (ii) (3) $\longrightarrow$ (4).

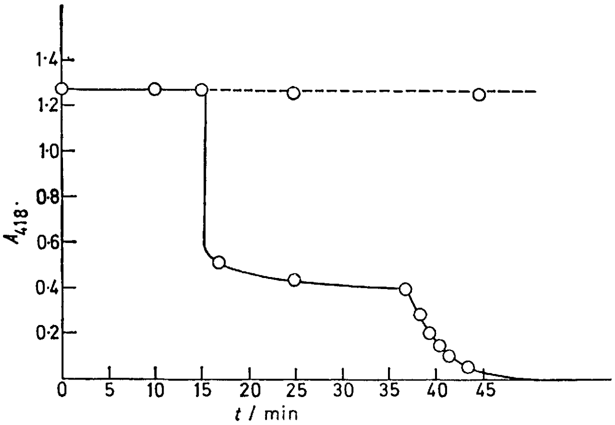

FIGURE 1 Plot of absorption at 418 nm of a dichloromethane solution of 2,4,6-triphenylpyrylium perchlorate (6.1×10^{-3}M) and aniline (12.2×10^{-3}M). The solid line shows the variation when triethylamine (to bring to 6.1×10^{-3}M) was added after 16 min and acetic acid (to bring to 2.46×10^{-2}M) was added after 37 min. The dotted line shows the unchanged absorbance in the absence of NEt_3 (acetic acid was added as before after 37 min)

(iii) When substantial quantities of a strong acid are added to the pre-formed vinylogous amide reversion to pyrylium cation occurs. As explained below, the vinylogous amide into pyridinium conversion is catalysed by acetic acid. We tested the effects of three different ratios of trifluoroacetic acid: (a) when 5 mol. equiv. CF_3CO_2H were added to the experiment with triphenylpyrylium perchlorate (1 mol) and n-butylamine (2 mol) in CH_2Cl_2, the u.v. spectrum of the aliquot portion indicated essentially complete re-formation of the pyrylium cation, which remained unchanged under these conditions. (b) Using 1.5 mol. equiv. CF_3CO_2H in this experiment gave pyrylium cation which was converted slowly, by almost zero-order kinetics to the pyridinium cation. Finally, (c) with 0.5 mol. equiv. CF_3CO_2H a similar rate-enhancing effect, with first-order kinetics, was observed as with the addition of acetic acid (see below).

In situation (a), essentially all the vinylogous amide (5) is reconverted into pyrylium cation (1). In situation (b), an equilibrium is set up in which a large quantity of (1) acts as a reservoir to constantly replenish the amount of (5), the concentration of which is then held nearly constant giving rise to the zero-order kinetics. Situation (c) is discussed below.

Ring-closure of Vinylogous Amides derived from n-Butylamine and Triphenylpyrylium Cation.—The reaction was followed both by the slow decrease in the concentration of the vinylogous amide (5) ($\lambda_{max.}$ 444 nm) and the increase in the concentration of the pyridinium cation (7; R = Bu^n) ($\lambda_{max.}$ 307 nm). Kinetic plots obtained in CH_2Cl_2 at 25 °C indicate (Table 2) that the reaction is approximately first order in pyrylium cation and zero order in Bu^nNH_2, suggesting unimolecular ring-closure of the vinylogous amide intermediate.

TABLE 2

Conversion of vinylogous amide from n-butylamine and 2,4,6-triphenylpyrylium tetrafluoroborate into 1-butyl-2,4,6-triphenylpyridinium in CH_2Cl_2 at 25 °C

10^3[Pyrylium]/M	6.11	6.11	6.11	3.05
$10^3[Bu^nNH_2]$/M	12.2	24.4	30.5	6.10
$10^3k_{obs.}/s^{-1}$	1.75	1.37	1.25	1.67

Small variations in rate were found for 2,4,6-triphenylpyryliums with different gegenions; rates relative to $ClO_4^- = 1$ were F^-, 1.8; BF_4^-, 1.6; and SCN^-, 1.1. This variation may be due to different amounts of ion association.

Using solutions that were 6.1×10^{-3}M in pyrylium (1) and 12.2×10^{-3}M in n-butylamine, the kinetic behaviour was found to be of similar type for a range of non-protic solvents: values of the first-order rate constants k show a general decrease with increasing solvent polarity (Table 3). This influence of solvent polarity may reflect the necessity for the vinylogous amide, which normally

TABLE 3

Reaction of 2,4,6-triphenylpyrylium perchlorate (1 mol) with n-butylamine (2 mol) plus triethylamine (1 mol)

Solvent	t/°C	Rate ($10^4k/s^{-1}$)	Relative rate	Dielectric constant
PhCl	25	4.56	22.8	5.6 [a]
$(CH_2Cl)_2$	25	3.12	15.6	10.4 [a]
$CHCl_3$	25	2.95	14.7	4.8 [a]
CH_2Cl_2	25	2.70	13.5	9.1 [a]
Me_2SO	50	1.43	1.65	46.6 [b]
MeCN	25 50	0.20 8.71	1.00	37.5 [a]
DMF	50	0.49	0.05	37.6 [c]

[a] Taken from J. A. Riddick and E. E. Toops, jun., eds., 'Organic Solvents,' 2nd edn., in the series, 'Technique of Organic Chemistry,' ed. A. Weissberger, Interscience, New York, 1955, vol. VII, pp. 271—274. [b] J. F. Coetzee and C. D. Ritchie, eds., 'Solute–Solvent Interactions,' Marcel Dekker, New York, 1969, p. 52. [c] Taken from J. Hine, 'Physical Organic Chemistry,' 2nd edn., McGraw-Hill, New York, 1962, p. 39.

adopts the extended configuration (5), to attain a 'curled up' configuration [*cf.* (6)] for ring-closure to occur. Toma and Balaban[9] also explained the increased tendency for pyridinium cyclisation to occur in non-polar compared with polar solvents by such arguments. We found a particularly low rate for DMF as solvent, probably because of its intrinsic basicity (see below).

The reaction of n-butylamine with 2,4,6-triphenylpyrylium in dimethyl sulphoxide was measured over the range 50—100 °C (Table 4): we found $\Delta H^{\ddagger}$ 15.8 ± 2.6 kcal mol^{-1} and $\Delta S^{\ddagger}_{323}$ −27.4 ± 4.5 cal mol^{-1} K^{-1}. The high negative entropy is in agreement with the mechanism postulated.

TABLE 4

Reaction of Bu^{n}NH$_2$ with 2,4,6-triphenylpyrylium perchlorate in dimethyl sulphoxide: variation of k/s^{-1} with temperature

T/K	323	348	373
10^3T^{-1}/K^{-1}	3.096	2.874	2.681
log k	−3.857	−3.102	−2.623

In protic solvents it was more difficult to obtain clean kinetics. Thus the reaction of 2,4,6-triphenylpyrylium with isopropylamine (catalysed by acetic acid, see later) in methanol was initially fast, but appeared to be inhibited to an increasing extent as the reaction progressed so that high conversion was not achieved.

Acid Catalysis of Ring-closure of Vinylogous Amides derived from Triphenylpyrylium and Various Amines.—Solutions of (5) were prepared from pyrylium (1) (6.1 × 10^{-3}M) and n-butylamine, isopropylamine, and aniline. The effect of adding various quantities of acetic acid on the rates of cyclisation (5) ⟶ (7) is recorded in Table 5 and Figure 2. The behaviour observed for the isopropylamine case, *i.e.* first rapid increase in rate for increasing amounts of AcOH, and then a levelling off, indicates a mechanism of the type of equation (1) where $k_{-a} \gg k_a, k_b$.

$$(5) + \mathrm{HOAc} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} (6) \xrightarrow{k_b} (7) \qquad (1)$$

We originally believed that this behaviour derived from a Michaelis–Menten like equation,[10] implying proportionality of $k_{obs.}$ with [AcOH] at low [AcOH], and independence of $k_{obs.}$ with [AcOH] at high [AcOH].

However recent work indicates that apparently first-order plots may possess considerable initial curvature, particularly where the ratio [amine + NEt$_3$] : [pyrylium + HOAc] falls below 1.5.[11]

Reaction of Amines with 2,4,6-Triphenylpyrylium: Rate Variation with Amine Structure.—Convenient rates (Table 6) were achieved at 25 °C in CH$_2$Cl$_2$ solution for the primary alkyl primary amine by the addition of 0.065 mol equiv. acetic acid but for the secondary alkyl primary amines and aryl primary amines only after the addition of 4.03 mol equiv. By examining the isopro-

TABLE 5

Ring-closure of the vinylogous amides (5) derived from n-butylamine, isopropylamine, and aniline in CH$_2$Cl$_2$ at 25 °C. Catalytic effect of acetic acid (AcOH) [a]

Isopropylamine		n-Butylamine		Aniline [b]	
10^4[AcOH]/M	$10^3k_{obs.}$/s^{-1}	10^4[AcOH]/M	$10^3k_{obs.}$/s^{-1}	10^4[AcOH]/M	$10^3k_{obs.}$/s^{-1}
24.6	0.644	0.976	5.45	0.0	0.13
49.2	1.48	1.95	6.08	24.6	1.63
74.0	2.20	3.90	7.84	49.2	2.30
123	3.83			148	5.21
246	5.39			246	5.67
345	5.52			330	5.90

[a] [Pyrylium] = 6.1 × 10^{-3}M, [amine] = 12.2 × 10^{-3}M. [b] 6.1 × 10^{-3}M-triethylamine was added.

TABLE 6

Relative rates for the reaction of 2,4,6-triphenylpyrylium perchlorate (1 mol) with amines (2 mol) in CH$_2$Cl$_2$ at 25 °C

	pK_a					
Amine	Value	Ref.	Acetic acid mol	Et$_3$N mol	Rate (10^3k/s^{-1})	Relative rate
(a) Unhindered amines						
EtNH$_2$	10.81	*a*	0.000 0.065		2.35 9.68	 102
Bu^{n}NH$_2$	10.77	*a*	0.00 0.065		1.73 7.84	 82.6
PhCH$_2$NH$_2$	9.33	*a*	0.065		6.04	63.6
(b) Hindered amines						
Pr^{i}NH$_2$	10.63	*b*	0.065 4.03		0.0949 5.39	1
Cyclopentylamine	10.65	*c*	4.03		3.02	0.561
Cyclohexylamine	10.64	*d*	4.03		3.75	0.696
1-Phenylethylamine	9.47	*e*	4.03		1.13	0.210
(c) Aromatic amines						
Aniline	4.63	*a*	4.03	1.00	8.86	1.64
m-Nitroaniline	2.47	*a*	4.03	1.00	0.303	0.056

[a] 'Handbook of Chemistry and Physics,' ed. R. C. Weast, C.R.C. Press, Cleveland, 1976—1977, 57th edn., p. D-147. [b] J. W Smith in 'The Chemistry of the Amino Group,' ed. S. Patai in the series 'The Chemistry of Functional Groups,' ed. S. Patai, Interscience, London, 1968, p. 174. [c] J. J. Christensen, R. M. Izatt, D. P. Wrathall, and L. D. Hansen, *J. Chem. Soc. A*, 1969, 1212. [d] Footnote *b*, p. 180. [e] G. Vexlearschi and P. Rumpf, *C. R. Acad. Sci.*, 1953, **236**, 939.

TABLE 7

Relative rates for the acetic-acid-catalysed reaction of pyrylium salts (1 mol) with benzylamine (2 mol) and with isopropylamine (2 mol) [a]

	Pyrylium cation substitution						Benzylamine + acetic acid (0.065 mol)		Isopropylamine + acetic acid (4.03 mol)		
Compound	2	3	4	5	6	Anion	$10^3k/s^{-1}$	Relative rate	$10^3k/s^{-1}$	Relative rate	$\frac{k_{PhCH_2NH_2}}{k_{Pr^iNH_2}}$
(1)	Ph		Ph		Ph	ClO_4^-	6.04	1.00	5.39	1.00	63.6
(1)	Ph		Ph		Ph	BF_4^-	5.85	0.97			
	Ph	Ph		Ph	Ph	BF_4^-	8.71	1.44	1.62	0.30	305
(8a)	Me		Ph		Ph	ClO_4^-	1.11	0.18	[b]		
	2,3-Cyclohexeno		Ph		Ph	BF_4^-	11.2	1.85	9.74	1.81	65.3
(8b)	Bu^t		Ph		Ph	BF_4^-	1.38	0.23	2.92	0.54	26.8
(8c)	2-Thienyl		Ph		Ph	ClO_4^-	1.80	0.30	0.527	0.10	194
	2-Thienyl		Ph		2-Thienyl	ClO_4^-	1.29	0.21	0.655	0.12	112
(12)	2,3-Tetrahydronaphtho-[b]		Ph		Ph	BF_4^-	2.05	0.34	3.25	0.60	35.8

[a] In dichloromethane at 25 °C. [b] Different reaction.

pylamine case under both sets of conditions, relative rates could be obtained.

Clearly, both steric and electronic effects are important: all the primary alkyl primary amines reacted *ca.* 100 times faster than the secondary alkyl primary amines. For the aromatic amines, the rate decreases with base strength.

Reaction of Amines with Pyryliums: Rate Variation with Pyrylium Cation Structure.—There is surprisingly little variation in the rates of ring-closure of the vinylogous amides with the structures of the pyryliums from which they were derived. Both for vinylogous amides derived from benzylamine, and for those from isopropylamine, the rates differed by hardly a factor of 10 (Table 7), and although the variations ran roughly parallel in the two series no clear correlation with structure is apparent. Effects of pyrylium structure will be investigated later in more detail.

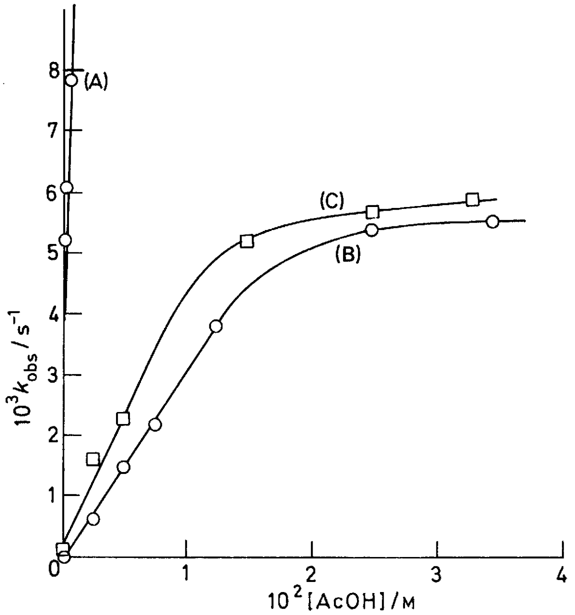

FIGURE 2 Variation of observed rate constants ($k_{1,obs.}$) for cyclisation of vinylogous amides (5) derived from 6.1 × 10^{-3}M-pyrylium (1) and 12.2 × 10^{-3}M-amine with quantity of acetic acid added (A) for n-butylamine, (B) for isopropylamine, (C) for aniline (in the presence of 6.1 × 10^{-3}M-triethylamine)

Conclusions.—This work illuminates the mechanism of the pyrylium ⟶ pyridinium interchange and should be helpful in choosing correct conditions to achieve high yields on a preparative scale under mild conditions.

EXPERIMENTAL

U.v. spectra were recorded on a Unicam SP 800A spectrophotometer. For quantitative absorbance measurements a Pye Unicam SP6-500 spectrophotometer was used.

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