A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part 12.[1] A General Synthesis of 2-Chloropyridines and 2-Pyridones

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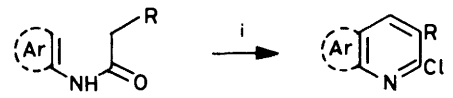
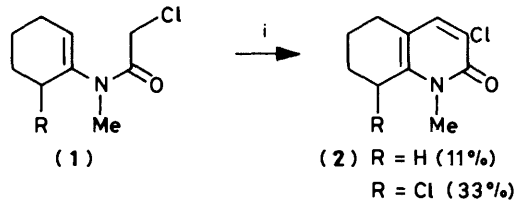
The Vilsmeier formylation of tertiary and secondary enamides leads to 2-pyridones and 2-chloropyridines, respectively. The reaction appears to be quite general allowing substitution in the 1-, 3-, 5-, or 6-position or combinations of these. The major limitation arises with enamides which are unsymmetrically substituted on the double bond with alkyl groups, when mixtures can result. Attempts to introduce a 4-substitutent by a variation of the Vilsmeier reagent had limited success.

In earlier papers we have described the synthesis of quinolines[2] and thienopyridines[3] by the cyclisation of *N*-acylarylamines under Vilsmeier conditions (Scheme 1). In principle, this reaction should be applicable to the synthesis of pyridines by the use of enamides. Indeed, during the course of our work chemists at Monsanto reported,[4] albeit in poor yield and with severe structural limitations, the cyclisation of chloroacetylenamides [*e.g.* (**1**)] to the tetrahydroquinolines (**2**). The chloroacetyl group was claimed to be essential for the reaction to succeed. We have already shown that enamidines are easily transformed into 6-chloro-2-iminopyridine.[1] We herein show that enamides with a wide variety of substitution patterns efficiently cyclise to give 2-pyridones or 2-chloropyridines.

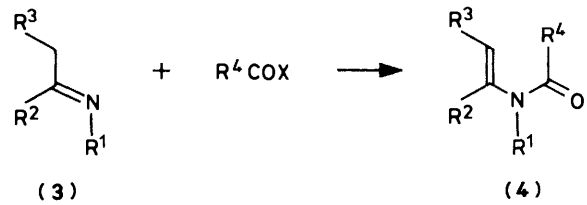


Scheme 1. *Reagents:* i, DMF, $POCl_3$



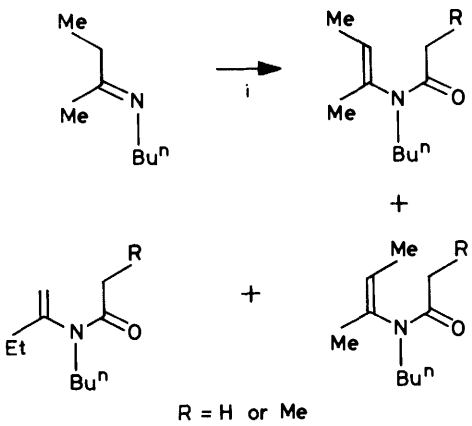
(**1**) (**2**) R = H (11%), R = Cl (33%)

Reagents: i, DMF, $POCl_3$, CH_2Cl_2



(**3**) (**4**)

Scheme 2.



Scheme 3. *Reagents:* i, $(RCH_2CO)_2O$

The Synthesis of the Enamides.—The simplest general route to *N*-substituted enamides involves the acylation of an iminoaldehyde or -ketone (Scheme 2). In agreement with the findings of Breederveld[5] we found that acetic and propionic anhydrides proved efficient while lower yields were obtained with acid chlorides. The enamides recorded in Table 1 were prepared in this way. Aldehyde imines were readily obtained using the base-catalysed method of Campbell and co-workers.[6] The ketone derivatives were made using the acid-catalysed conditions of Norton's groups (Table 2).[7] The enamides (**4**) derived from iminoketones showed several types of isomerism. Thus, while acetophenone *N*-(n-butyl)imine (**3x**) gave only one product on acetylation, the related imines of butan-2-one (**3t**) and (**3u**) gave a mixture of the *E*- and *Z*-isomers of *N*-butyl-*N*-(1-methylprop-1-enyl)acetamide as well as lesser amounts of *N*-butyl-*N*-(1-methylenepropyl)acetamide (Scheme 3), as indicated by ^1H and ^{13}C n.m.r. spectroscopy. This picture was often further complicated by rotameric isomerism about the amide CO–N bond, a feature noted in most of the enamides. This isomerism was noted with the enamides of all the unsymmetrical aliphatic ketones (**4m**—**w**).

Secondary enamides are not as trivially available as their tertiary analogues, as witnessed by the variety of methods reported for their synthesis. We found that Barton's method[8] involving the action of, for example, acetic anhydride on cyclohexanone oxime (Scheme 4) gave the reported yield of a product containing the enamide (**5**) admixed with unknown inseparable impurities (by ^1H n.m.r.) despite being one-spot pure on t.l.c. in several systems. We also had little success with Corey's method[9] involving cyclohexane oxime and acetic anhydride in dimethylformamide, catalysed by titanium(III) acetate. However, the simple method of Ben-Ishai and Zehavi,[10] in which the ketone (*e.g.* cyclohexanone) was condensed with a primary amide (*e.g.* acetamide or propionamide) in toluene with toluene-*p*-sulphonic acid catalysis was effective.

The Conversion of Enamides into 2-Pyridones and Pyridines.—In order first to optimise the cyclisation conditions we closely

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Table 1. Enamides (4) prepared by the action of R^4COX on an imine (3) (Scheme 2)

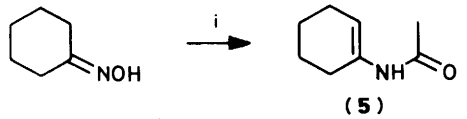
Imine (3)				Enamide (4)	Yield
R^1	R^2	R^1	R^2COX	R^4	(%)
a; Bu^n	$(CH_2)_4$		Ac_2O	Me	79
b; Bu^n	$(CH_2)_4$		$(EtCO)_2O$	Et	71
c; Bu^n	$(CH_2)_4$		Pr^nCOCl	Pr^n	41
d; Bu^n	$(CH_2)_4$		$ClCH_2COCl$	CH_2Cl	57
e; Bu^n	$(CH_2)_4$		$CH(CH_2)_2COCl$	$(CH_2)_2Cl$	10
f; Bu^n	$(CH_2)_4$		$Cl(CH_2)_3COCl$	$(CH_2)_3Cl$	19
g; Bu^n	$(CH_2)_4$		$PhOCH_2COCl$	CH_2OPh	32
h; Bu^n	$(CH_2)_4$		MeCH=CHCOCl	CH=CHMe	53
i; Bu^n	$(CH_2)_4$		PhCH=CHCOCl	CH=CHPh	30
j; Pr^n	H	H	Ac_2O	Me	63
k; Pr^n	H	H	$(EtCO)_2O$	Et	45
l; $PhCH_2$	H	H	Ac_2O	Me	55
m; Pr^n	H	Me	Ac_2O	Me	43
n; Pr^n	H	Me	$(EtCO)_2O$	Et	37
o; Bu^n	H	Me	Ac_2O	Me	43
p; Bu^n	H	Me	$(EtCO)_2O$	Et	53
q; $PhCH_2$	H	Me	Ac_2O	Me	61
r; Pr^n	H	Et	Ac_2O	Me	41
s; Pr^n	H	Et	$(EtCO)_2O$	Et	28
t; Pr^n	Me	Me	$(EtCO)_2O$	*a*	21
u; Bu^n	Me	Me	Ac_2O	*a*	31
v; Pr^n	Me	Et	Ac_2O	*a*	41
w; Bu^n	Me	Pr^i	Ac_2O	*a*	32
x; Bu^n	Ph	H	Ac_2O	Me	50

[a] Mixture, see text.

Table 2. Imines (3) prepared as described in the text

Imine	B.p. (°C) at 760 mmHg	Lit. b.p. (°C) at 760 mmHg	Yield (%)	Ref.
(3j)	73.5—78	74	78	*i*
(3l)	94—99[a]	94[b]	59	*i*
(3m)	94—102	101	62	*i*
(3o)	119—127	118—127	79	*j*
(3q)	100—102[c]	101[c]	83	*i*
(3; $R^1 = PhCH_2$, $R^2 = H$, $R^3 = Me$)	136—137	—	75	—
(3s)	120—125	125	77	*i*
(3; $R^1 = Bu^n$, $R^2 = Me$, $R^3 = H$)	126—134	129—131[e]	52	*k*
(3t)	118—126	129	53	*i*
(3u)	144—150	45—46[f]	70	*l*
(3v)	145—154	140	35	*m*
(3; $R^1 = Bu^n$, $R^2 = Me$, $R^3 = Bu^i$)	178—180	81[g]	47	*n*
(3; $R^1 = Bu^n$, $R^2 = Me$, $R^3 = Ph$)	94—95[d]	83—84[h]	50	*p*

[a] At 22 mmHg. [b] At 21 mmHg. [c] At 16 mmHg. [d] At 4 mmHg. [e] At 740 mmHg. [f] At 12 mmHg. [g] At 15mm Hg. [h] At 0.4 mmHg. [i] R. Tiollais, *Bull. Soc. Chim. Fr.*, 1947, 708. [j] Ref. 6. [k] E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, 1963, **28**, 692. [l] F. Asinger, M. Thiel, and G. Lipfert, *Liebigs Ann. Chem.*, 1959, **627**, 195. [m] G. Bianchetti, P. D. Groce, D. Pocar, and G. G. Gallo, *Rend. Ist. Lamb. Sci. Lett., A*, 1965, **99**, 296 (*Chem. Abstr.*, 1966, **65**, 15366f). [n] J.-C. Gautier, S. Risse, and J. Wiemann, *Ann. Chim. (Paris)*, 1970, **5**, 435. [p] F. Asinger and K. Halcour, *Monatsh. Chem.*, 1963, **94**, 1029.

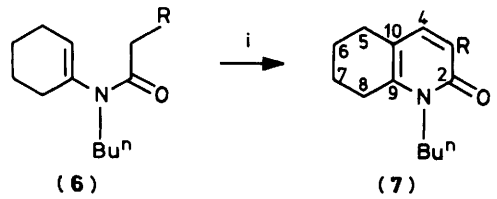


(5)

Scheme 4. *Reagents:* i, Ac_2O, pyridine, 48 h, heat

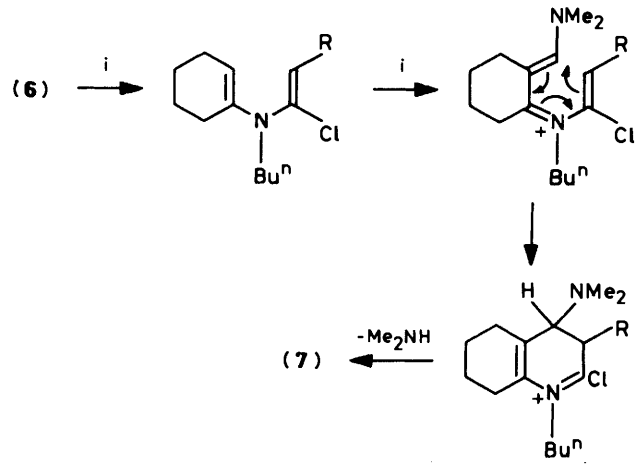
studied the cyclohexanone-based enamides, similar to those reported earlier.[4] Using Chupp's conditions[4] [*i.e.* an excess of dimethylformamide (DMF) with phosphoryl chloride in refluxing methylene dichloride] very poor yields indeed were obtained of the desired tetrahydroquinoline. This was improved by replacing the solvent with chloroform. However, when phosphoryl chloride (7 mol) was used as solvent with a DMF to enamide ratio of 3:1 mol (conditions we had earlier found to be optimum for quinoline synthesis[2a]) the enamides cyclised efficiently and in fair yield (Scheme 5).

Complex mixtures of products were obtained when 3-chloropropanol or 4-chlorobutanol derivatives were similarly treated. Unlike the quinoline synthesis, no formation of the 3-aldehyde (**7**; R = CHO) was observed in the case of the acetylenamide (**6**; R = H), indicating that the reaction proceeded by formylation of the cyclohexane ring, this being the more nucleophilic of the two potential enamide sites (Scheme 6). Subsequent cyclisation is clearly faster in these cases than a second formulation (a process available with acetamidothiophens in which, depending upon the amount of DMF available, unformylated or formylated products are generated at will[3]). To our surprise the crotonyl enamide (**6**; R = CH_3CH=) gave 1-butyl-5,6,7,8-tetrahydroquinolin-2(1*H*)-one (**7**; R = H) in 31% yield. No identifiable product was isolated from the cinnamoyl analogue (**6**; R = PhCH=).

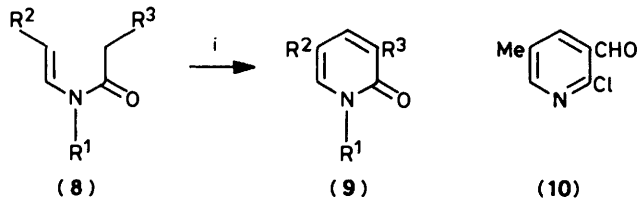


R	Yield of (7) (%)
H	32
Cl	53
Me	77
Et	52
OPh	60

Scheme 5. *Reagents:* i, DMF (3 mol), $POCl_3$ (7 mol); 2 h, 20 °C then 4 h, 75 °C



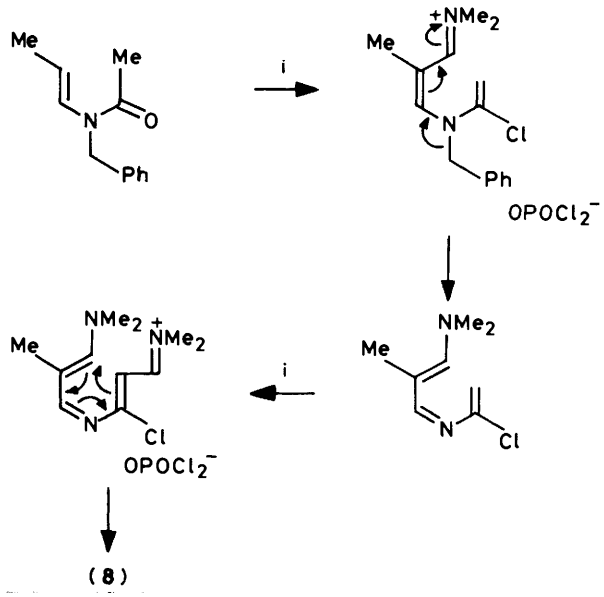
Scheme 6. *Reagents:* i, DMF, $POCl_3$



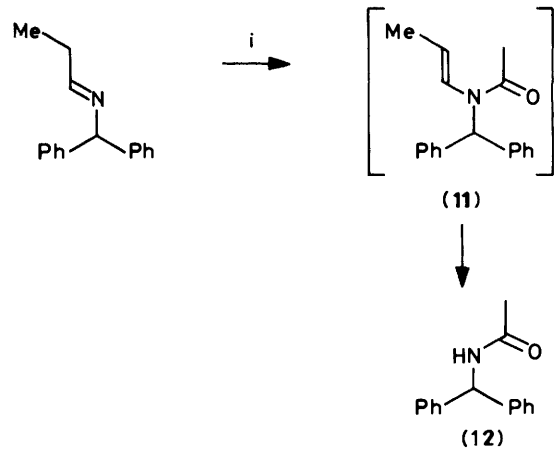
	R^1	R^2	R^3	Yield of (9) (%)
a;	Pr^n	Me	H	52
b;	Pr^n	Me	CHO	14
c;	Bu^n	Me	H	55
d;	Bu^n	Me	CHO	17
e;	Bu^n	Me	Me	62
f;	Pr^n	Et	H	58
g;	Pr^n	Et	CHO	13
h;	Pr^n	Et	Me	69
i;	$PhCH_2$	Me	H	44

Scheme 7. *Reagents:* DMF, $POCl_3$

Aldehyde-derived enamides were next studied, cyclisation of these allowing the synthesis of 5-substituted or 3,5-disubstituted 2-pyridones. Indeed, under the optimised conditions, good yields of pyridones were again obtained (Scheme 7). Acetyl enamides in every case gave 5-substituted pyridones together with the easily separated 5-substituted 3-formylpyridone in a *ca.*



Scheme 8. *Reagent:* i, Vilsmeier reagent

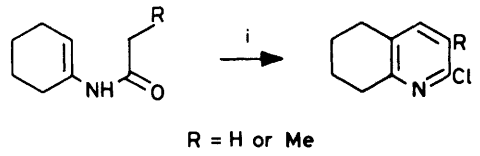


Reagents: i, Ac_2O, Et_3N

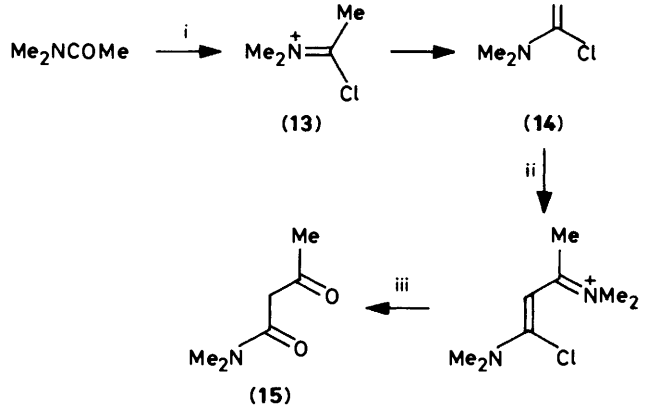
4:1 ratio. Varying the reaction conditions did not materially alter this ratio or allow the aldehyde to become the major product. This suggested that, unlike the more rigid cyclohexane-based intermediates, the rate of the second formylation is competitive with cyclisation. Interestingly, the 1-(*N*-acetyl-*N*-benzylamino)propene gave the expected 1-benzyl-5-methyl-2-pyridone (**9i**) (44%) together with 2-chloro-5-methylpyridine-3-carbaldehyde (**10**) (12%), formed, as shown in Scheme 8, by formylation, debenzylation, and subsequent formylation and cyclisation. With a view to optimising this potentially valuable synthesis we endeavoured to prepare the benzhydryl enamide (**11**) containing a better leaving group on nitrogen. Unfortunately, only *N*-benzhydrylacetamide (**12**) was formed.

The acetaldehyde-derived enamides (**8**; R^3 = H) did not yield pyridines on formylation, probably because of the unfavoured *E* geometry of the formylated enamide. Thus the *N*-benzyl-*N*-acetylaminoethane (**8**; $R^1 = PhCH_2$, $R^2 = R^3$ = H) gave β-dimethylaminoacrylaldehyde (17%) and *N*-benzylacetamide (30%) as the only recognisable products.

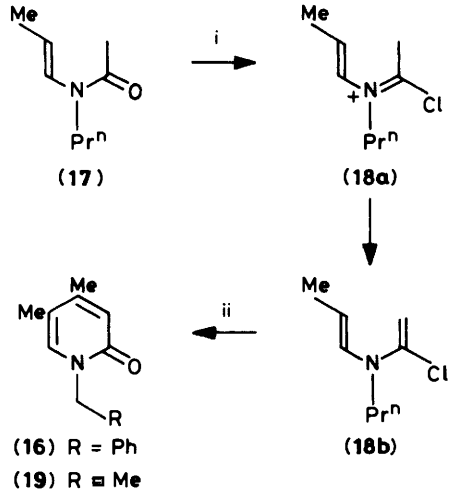
The mixtures of enamides derived from unsymmetrical ketones (Scheme 3) were next studied. Thus, formylation of *N*-butylacetamidostyrene (**4x**) gave solely 1-butyl-6-phenyl-2-pyridone (68%), the corresponding enamide mixture (Scheme 3,



Scheme 9. *Reagents:* i, Vilsmeier reagent



Scheme 10. *Reagents:* i, $POCl_3$; ii, (**13**); iii, H_2O



Reagents: i, $POCl_3$; ii, (**18a**)

R = H) from methyl ethyl ketone gave only 1-butyl-5,6-dimethyl-2-pyridone (43%), and the methyl isobutyl ketone enamide (**4w**) gave just 1-butyl-6-isobutyl-2-pyridone (19%). However, the methyl n-propyl ketone enamide (**4v**) gave a mixture of 1,6-dipropyl-2-pyridone (13%) and 5-ethyl-6-methyl-1-(n-propyl)-2-pyridone (29%).

Finally, we examined the cyclisation of secondary enamides, which were transformed efficiently into 2-chloropyridines on formylation. Thus 1-acetamido- (**5**) and 1-propionamido-cyclohexene gave 2-chloro-4,5,6,7-tetrahydroquinoline and its 3-methyl derivative in 62 and 45% respectively (Scheme 9).

By this means we have been able to prepare 2-pyridones specifically substituted in the 3-, 5-, or 6-position, or in any combination of these. In principle, 4-substituents could be introduced by use of acylating agents other than DMF–$POCl_3$. The higher alkyl homologues of the Vilsmeier reagent [*e.g.* (**13**)] suffer since they tend to generate an enamide [*e.g.* (**14**)] capable of self-condensation (*e.g.* Scheme 10). However, since such a chloroenamide might be less reactive than our enamides, we subjected one (**4p**) to the action of dimethylacetamide in $POCl_3$ and obtained 1-benzyl-4,5-dimethyl-2-pyridone (**16**) in 18% yield together with acetyl-*N*,*N*-dimethylacetamide (**15**) (24%). However, the parent enamide [*e.g.* (**17**)] may be viewed as a source of both a Vilsmeier-type reagent (**18a**) and a chloroenamide (**18b**) by the action of $POCl_3$. We were thus gratified to isolate 4,5-dimethyl-1-(n-propyl)-2-pyridone (**19**) in a surprisingly good yield (59%) by treating the enamide (**17**) with $POCl_3$ and a catalytic trace of DMF. Not surprisingly, when we attempted to acylate the same enamide (**17**) with acylating agents such as acetyl and benzoyl chlorides, the same pyridone (**19**) was the sole isolable product, in low yield, and the acylating agents were not incorporated at all.

Experimental

The general conditions are as described in the preceding paper.[1] Ether refers to diethyl ether.

The Synthesis of the Enamides.—(*a*) *By acylation of imines.* The aldehyde imines were prepared as follows.[6] To the neat primary amine (0.5M) was added, dropwise, the aldehyde (0.5M) at 5—8 °C during 2 h with stirring. After the addition, the mixture was warmed to room temperature and several potassium hydroxide pellets added. After 30 min the lower aqueous layer was removed and the crude imine stored overnight over further pellets prior to distillation at atmospheric pressure. The ketone imines were prepared thus:[7] to a mixture of the primary amine (0.5M) and the ketone (0.5M) were added 2—3 drops of concentrated hydrochloric acid. The exothermic reaction soon subsided and the mixture was left for 24 h at room temperature. Potassium hydroxide pellets were then added and after a short period the water layer was separated and treated as above.

General methods.[5] (i) To a solution of the imine (0.5 mol) and triethylamine (0.5 mol) in dry benzene (200 ml) was added acetic anhydride or propionic anhydride (0.5 mol) at 5—8 °C with stirring. After the addition, the mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed and the residue was distilled. The product-containing fraction was taken up in ether and washed with water, dried, and evaporated.

(ii) The imine (0.1 mol) in dry ether (150 ml) and triethylamine (10.0 g, 0.1 mol) were cooled in an ice-bath. The acid chloride (0.1 mol) was added dropwise with stirring at 0—10 °C. After a further 30 min at room temperature, the precipitated hydrochloride was filtered off, the solvent removed, and the residue distilled. The products so formed are collected in Tables 1 and 3.

(*b*) *By acetylation of cyclohexane oxime.*[8] (i) Cyclohexanone oxime (11.3 g, 0.1 mol), dry pyridine (60 ml), and acetic anhydride (40 ml) were refluxed for 48 h under nitrogen. After removal of the pyridine under reduced pressure, the black residue was dissolved in ether and washed with sodium carbonate solution (100 ml, 10% w/v). The two-phase mixture was filtered through Celite and the organic layer separated, dried ($MgSO_4$), and evaporated to give a yellow oil. This was absorbed onto alumina and, after 1 h, was eluted with light petroleum admixed with ether. The product although showing only one spot on t.l.c. appeared to contain at least three isomers showing three acetyl methyl singlets (2.01, 2.10, and 2.17 p.p.m.) and three olefinic CH signals (5.15, 6.05, and 6.70 p.p.m.).

(ii) To cyclohexanone oxime[9] (2.28 g, 0.02 mol) in acetic anhydride (10 ml) and dimethylformamide (20 ml) was added with stirring freshly prepared titanium(III) acetate [from sodium acetate and titanium(III) chloride] (15.0 g, 0.67 mol).

Table 3. Properties of the enamides (**4**)*

Enamide	B.p. (°C) mmHg	$\nu_{max.}$ (cm^{-1})	^{1}H N.m.r. ($CDCl_3$) δ(p.p.m.)	^{13}C N.m.r. ($CDCl_3$) δ(p.p.m.)	Mass spectrum *m/z* (assignment, %)
(**4a**)	122—125/5[a]	1 655, 1 640, 1 440 1 400, 920	2.00s (Me), 0.80—2.40m (15 H), 3.73t (CH_2), (olefinic H)		
(**4b**)	126—130/5	1 655, 1 640, 1 455, 1 435, 1 400, 920	1.09t (Me), 0.71—2.51m (17 H), 3.40t (CH_2), 5.60s (olefinic H)	9.03q, 12.81q, 19.16t, 20.69t, 21.97t, 23.81t, 25.81t, 27.10t, 29.41t, 44.32t 126.04d, 137.94s, 171.87s	209[e] (M^+, 98%), 194 (M − Me, 8%), 180 (M − Et, 54%), 152 (M − C_3H_5O, 100%)
(**4c**)	134—138/3	1 655, 1 640, 1 440, 1 400, 920	0.75—2.40m (22 H), 3.40t (CH_2), 5.65s (olefinic H)	12.82q, 18.19t, 19.16t, 20.68t, 21.96t, 23.80t 27.33t, 29.41t, 34.43t, 44.30t, 126.07d, 138.00s 170.89s	
(**4d**)	158—160/5		0.80—2.40m (15 H), 3.42t (CH_2), 4.12s (CH_2Cl), 5.65s (olefinic H)	12.90q, 1916t, 20.62t, 21.85t, 23.92t, 26.85t, 28.96t, 41.00t, 44.72t, 127.42d, 136.98s, 164.63s	
(**4e**)	149—151/3	1 660, 1 640, 1 435, 14 400, 920	0.70—2.50m (15 H), 2.80t (CH_2), 3.40t (CH_2), 3.80t (CH_2Cl), 5.65s (olefinic H)	13.53q, 19.87t, 21.34t, 22.58t, 24.59t, 27.93t, 30.00t, 36.44t, 40.25t, 45.21t, 127.78s, 138.15s, 168.43s	
(**4f**)	160—164/3	1 645, 1 635, 1 440, 1 400, 920	0.80—2.60m (19 H), 3.40t (CH_2), 3.60t (CH_2Cl), 5.60s (olefinic H)	13.57q, 19.84t, 21.32t, 22.64t, 24.59t, 27.88t, 28.19t, 28.37t, 30.08t, 44.63t, 45.15t, 127.27d 138.35s, 170.71s	
(**4g**)	212—218/7	1 665, 1 645, 1 600, 1 580, 1 490, 1 440, 1 410, 1 220, 1075, 920, 750	0.70—2.25m (15 H), 3.40t (CH_2), 4.55s (CH_2), 5.60s (olefinic H), 6.70—7.60m (5 H, Ph)	13.48q, 19.83t, 21.30, 22.53t, 24.60t, 27.44t, 29.73t, 45.22t, 66.46t, 114.57d, 121.04d, 127.17d, 129.22d, 137.41s, 158.28s, 166.82s	
(**4h**)	129—131/3	1 665, 1 645, 1 620, 1 435, 1 390, 1 225, 960	1.83dd (CH*Me*), 0.70—2.40m (15 H, 3.40t (CH_2), 5.55s (olefinic H), 6.15dd (COCH), 6.63—7.20dq (CHMe)	12.85q, 16.91q, 19.26t, 20.75t, 21.97t, 23.92t, 27.68t, 29.52t, 44.57t, 122.31d, 126.33d, 137.69, 138.67d, 166.17s	
(**4i**)	180—185/2	1 655, 1 640, 1 620, 1 450, 1 400, 1 230, 1 130, 980, 920, 760, 700	0.70—2.40m (15 H), 3.50t (CH_2), 5.65s (olefinic H), 6.76d (COCH), 7.00—7.50m (5 H, Ph), 7.68 (CHPh)	13.16q, 19.51t, 21.08t, 2.22t, 24.16t, 28.02t, 29.73t, 44.92t, 118.73d, 126.58d, 126.90d, 128.01, 128.51d, 134.98s, 137.80s, 140.10d, 164.0s	
(**4j**)	75—81/14[b]	1 675, 1 625, 1 430, 1 390, 1 225, 1 155, 1 050, 1 030, 960, 840	0.93t (Me), 1.60m (CH_2), 2.25 (Me), 3.60t (CH_2), 4.25—4.65dd (CH_2), 6.63—7.05dd (CH_2)		
(**4k**)	92—94/16	1 680, 1 625, 1 430, 1 385, 1 225, 1 155 1 050, 1 030, 960, 840	0.90t (Me), 1.40t (Me), 1.55m (CH_2), 2.46q (CH_2), 3.55t (CH_2), 4.10—4.55dd (CH_2), 6.55—7.10dd (CH)		

Table 3. (*cont.*)

Enamide	B.p. (°C) mmHg	$\nu_{max.}$ (cm^{-1})	^{1}H N.m.r. ($CDCl_3$) δ(p.p.m.)	^{13}C N.m.r. ($CDCl_3$) δ(p.p.m.)	Mass spectrum *m/z* (assignment, %)
(4l)	144—150/10	3 050, 1 680, 1 630, 1 430, 1 390, 1 350, 1 225, 1 030, 990, 850, 730, 700	2.28s (Me), 4.20—4.55d (CH_2), 4.82d (CH_2), 6.65—7.10dd (CH), 7.20s (Ph). Peaks from rotamer at 2.10s, 4.70s		
(4m)	92—96/14[c]	1 675, 1 650, 1 400, 1 220, 1 145, 1 040, 930	0.87t (Me), 1.20—1.80m (CH_2), 1.70dd (Me), 2.15s (Me), 3.55t (CH_2), 4.80—5.30dq (olefinic H), 6.45dd (olefinic H)		141 (M^+), 126 (M − Me), 70 (100%)
(4n)	104—112/15	1 675, 1 650, 1 410, 1 220, 1 135, 1 070, 935	0.90t (Me), 1.18t (Me), 1.20—1.80m (CH_2), 1.72dd (Me), 2.48q (CH_2), 3.57t (CH_2), 4.90—5.40dq (olefinic H), 6.50dd (olefinic H)		
(4o)	113—115/16	1 675, 1 650, 1 405, 1 380, 1 210, 1 150, 1 042, 935	0.88m (Me), 1.10—1.70m (CH_2,CH_2), 1.74dd (Me), 2.14s (Me), 3.57t (CH_2), 4.85—5.35dq (olefinic H), 6.50dd (olefinic H)		155 (M^+), 140 (M − Me), 126 (M − Et), 70 (100%)
(4p)	125—129/15	1 665, 1 640, 1 410, 1 370, 1 200, 1 130, 1 065, 945	0.92t (Me), 1.14t (Me), 1.20—1.70m (CH_2CH_2), 1.73dd (Me), 2.43q (CH_2), 3.57t (CH_2), 2.80—5.30dq (olefinic H), 6.47dd (olefinic H)	8.66q, 13.15q, 14.86q, 19.67t, 26.51t, 28.61t, 42.59t, 107.14d, 127.48d, 1714.s	
(4q)	165—167/14	1 680, 1 650, 1 400, 1 210, 990, 735, 690	1.65dd (Me), 2.27s (Me), 4.83s (CH_2), 4.80—5.20q (olefinic H), 6.53dd (olefinic H), 7.23s (Ph). Peaks from rotamer at 2.12s and 4.70s	14.60q, 21.29q, 45.98t, 108.35d, 124.83d, 126.083d, 126.69d, 127.69, 138.69s, 168.29s	
(4r)	106—107/14[d]	1 675, 1 645, 1 410, 1 225, 1 155, 1 050, 935	0.92t (Me), 1.05t (Me, 1.20—1.85 (CH_2), 2.08q (CH_2), 2.20s (Me), 3.59t (CH_2), 4.80—5.31dt (olefinic H), 6.52d (olefinic H)		155 (M^+), 126 (M − Et), 98 and 84 (100%)
(4s)	114—117/15	1 680, 1 650, 1 465, 1 410, 1 220, 1 140, 1 075, 935	0.90t (Me), 1.03t (Me, 1.15t (Me), 1.20—1.80m (CH_2), 2.05q (CH_2), 2.46q (CH_2), 3.59t (CH_2), 4.80—5.35dt (olefinic H), 6.53d (olefinic H)		169 (M^+), 140 (M − Et), 98 (100%)
(4t)	105—115/15	1 650br, 1 440, 1 390, 1 300, 1 280	(a) 1.55d (Me, 1.75 (Me), 5.38q (C*H*Me). (b) 4.97d. Other complex overlapping peaks not assigned	(a) 45.45t, 46.00t, 121.83,d 123.43d; 134.71s, 135.26s; 171.14s, 17256s (*cis* and *trans* pairs). (b) 39.56t, 110.98t, 148.32s, 173.82s	
(4u)	117—121/15	1 670, 1 655, 1 440, 1 400, 1 300, 1 215	0.87t (Me), 1.10—1.70m (CH_2CH_2), 1.53d (Me), 1.79s (Me), 2.00s (Me), 3.38t (CH_2), 5.41q (olefinic H). Contains *cis*- and *trans*-1-methyl-prop-1-enyl isomers and small signals for *N*-(n-butyl)-*N*-1-methylene-propyl)acetamide. 5.00d (olefinic CH_2)	43.84t, 44.05t; 122.17d, 123.88d; 135.60s, 136.01s; 168.27s (*cis* and *trans* isomeric pairs)	
(4v)	100—100/13	1 650, 1 440, 1 390, 1 300, 1 280	(q) 3.35t (NCH_2), 5.33t (olefinic H). (b) 3.25t (NCH_2), 5.003 (olefinic H). (q) is 1-methylbut-1-enyl (b) 1-methylene-butyl isomer in the ratio 3:1		196 (M^+, 6%), 154 (M − Me, 5), 140 (M − Et, 66), 126 M − 43, 10), 57 (100)

(4w)	128—131/15	1 645, 1 390, 1 290	(a) 1.79d, 1.85d (*Me*CH), 2.00s (MeCO), 5.12dd (olefinic H), (*E*)- and (*Z*)-1,3-dimethylbut-1-enyl isomers. (b) 2.08s (MeCO), 4.98d (olefinic CH_2); 3-methyl-1-methylenebutyl isomer	(a) 132.62s, 132.98, 134.55d, 136.41d, 167.50s; (b) 112.25t, 146.25s, 167.50s
(4x)	108—109/2	1 660, 1 635, 1 610, 1 580, 1 440, 1 390, 1 300, 1 225, 900, 780, 710	0.87t (Me), 1.10—1.75m (CH), 1.06s (Me), 3.48t (CH_2), 5.47d (olefinic CH_2), 7.40s (Ph)	

[a] Lit.,[11] b.p. 120 °C/5 mmH. [b] Lit.,[5] b.p. 77—78 °C/14 mmHg. [c] Lit.,[5] b.p. 92—93 °C/14 mmHg. [d] Lit.,[5] 106—107 °C/14 mmHg. [e] 209.1777. $C_{13}H_{23}NO$ requires 209.1778.
* Some of the liquid enamides prepared in this paper were used without purification to analytical standards, this being impractical owing to the nature of the compounds. However, full spectra data are given in every case.

Table 4. 2-Pyridones and pyridines from the Vilsmeier formylation of the enamides (**4**)

Enamide	Product R	Yield (%)	M.p. or (b.p./mmHg) (°C)	$\nu_{max.}$(cm^{-1})	^{1}H N.m.r. ($CDCl_3$) δ(p.p.m.	^{13}C N.m.r. ($CDCl_3$)* δ_C(p.p.m.)	Molecular formula	Analysis (%) Found (Required) C	H	N	Mass spectrum† *m/z*
(**6**)	(**7**) H	32	(120/0.05)	2 940, 1 660, 1 585, 1 540, 820	7.05d (4-H), 6.35d (3-H), 4.00t (CH_2), 2.85—2.35m (2 CH_2), 2.10—0.80m (11 H), $J_{3,4}$ 9 Hz	161.7s (C-2), 141.8s (C-9), 140.0d (C-4), 116.5d (C-3), 113.3s (C-10), 42.1t (C-11), 29.6t (C-8), 26.5t (C-5), 25.6t (C-12), 21.5t (C-7), 20.8t (C-6), 19.3t (C-13), 12.7q (C-14)	$C_{13}H_{19}NO$				205, 188, 176, 163, *149*
(**6**)	(**7**) Cl	53	136—137	1 640, 1 590, 1 535, 1 220	7.25s (4-H), 4.00t (CH_2), 2.85—2.35m (2 CH_2), 2.00—0.80m (11 H)	158.3s (C-2), 141.4 (C-9), 138.6d (C-4), 122.2s (C-3), 113.6s (C-10), 44.1t (C-11), 29.9t C-8), 27.0t (C-5), 26.2t (C-12), 21.9t (C-7), 21.2t (C-6), 19.8t (C-13), 13.2q (C-14)	$C_{13}H_{18}ClNO$	64.9 (65.1)	7.6 (7.6)	5.8 (5.8)	241, 239, 224, 222, 212, 210, 199, 197, 185, *183*
(**6**)	(**7**) Me	77	96.5—97.5	1 645, 1 590, 1 560, 1 240, 1 100	6.92s (4-H), 4.02t (CH_2), 2.85—2.35m (2 CH_2), 2.10s (Me), 1.95—0.80m (11 H)	162.2s (C-2), 139.0s (C-9), 138.1d (C-4), 125.2s (C-3), 113.0s (C-10), 42.8t (C-11), 30.0t (C-8), 26.8t (C-5), 25.8t (C-12), 22.0t (C-7), 21.3t (C-6), 19.7t (C-13), 16.2q (Me), 13.0q (C-14)	$C_{14}H_{21}NO$	76.45 (76.65)	9.9 (9.7)	6.4 (6.4)	219, 202, 190, 177, *163*
(**6**)	(**7**) Et	52	(155/0.03)	1 645, 1 600, 1 560, 1 450, 1 230, 920	6.86s (4-H), 3.98t (CH_2), 2.80—2.30m (6 H), 1.90—1.40m (8 H), 1.15t (Me), 0.95m (Me)	162.0s (C-2), 139.0s (C-9), 136.4d (C-4), 131.0s (C-3), 113.1s (C-10), 42.9t (C-11), 30.1t (C-8), 27.1t (C-5), 26.0t (C-12), 22.9t (C-15), 22.2t (C-15), 22.2t (C-17), 21.5t (C-6), 19.9t (C-13), 13.2q (C-14)	$C_{15}H_{23}NO$	76.1 (77.2)	9.9 (9.9)	6.4 (6.0)	219, 202, 190, 177, *163*

Table 4. (*cont.*)

Enamide	Product R	Yield (%)	M.p. or (b.p./mmHg) (°C)	$\nu_{max.}$(cm $^{-1}$)	^{1}H N.m.r. ($CDCl_3$) δ(p.p.m.	^{13}C N.m.r. ($CDCl_3$)* δ_C(p.p.m.)	Molecular formula	Analysis (%) Found (Required) C	H	N	Mass spectrum† *m/z*
(6)	(7) OPh	60	Low m.p.	1 655, 1 610, 1 590, 1 550, 1 450, 1 400, 750, 685	7.50—6.90m (Ph), 6.78s (4-H), 4.07t (CH_2), 2.80—2.25 (4 H), 1.95—0.80m (11 H)	157.4s (C-2), 156.4s (C-1′), 142.9s (C-3), 137.1s (C-9), 128.8d (C-2′6′), 126.0d (C-4), 122.1d (C-4′), 116.8d (C-3′,5′), 112.3s (C-10), 43.1 (C-11), 29.9t (C-8), 27.0t (C-5), 25.7t (C-12), 21.8t (C-7), 21.1t (C-6), 19.6t (C-3), 13.0q (C-14)	$C_{19}H_{23}NO_2$				*297*, 280, 268, 255, 241 M^+ 297.1726 (297.1728 required)
(4h)	(7) H	31	See above				$C_{13}H_{19}NO$				
(8a)	**(9a)**	52	(115—120/0.1)	1 670, 1 600, 1 535, 1 460, 1 375, 1 260, 825	7.20dd (4-H), 7.08s (6-H), 6.47dd (3-H), 3.87t (CH_2), 2.10s (Me), 2.10—1.30m (CH_2), 0.90t (Me), $J_{3.4}$ 9; $J_{3.6}$ 1; $J_{4.6}$ 2 Hz		$C_9H_{13}NO$				151, 150, 136, 128, *109* M^+ 151.0952 (151.0953 required)
	(9b)	14	(160—165/0.1) 101—102	1 680, 1 650, 1 585, 1 530, 720	10.20s (CHO), 7.73 (4-H), 7.30d (6-H), 3.88t (CH_2), 2.15s (Me), 2.10—1.59m (CH_2), 0.97t (Me), $J_{4.6}$ 2 Hz		$C_{10}H_{13}NO_2$	67.4 (67.0)	7.1 (7.3)	7.9 (7.8)	180, 179, 164, *151*, 136, 109
(8c)	**(9c)**	55	(120—125/0.1)	1 675, 1 600, 1 540, 1 460, 1 380, 1 265, 825	7.19dd (4-H), 7.10s (6-H), 6.46dd (3-H), 3.90t (CH_2), 2.05s (Me), 1.90—1.15m (2 CH_2), 0.92t (Me), $J_{3.4}$ 9; $J_{3.6}$ 1; $J_{4.6}$ 2 Hz		$C_{10}H_{15}NO$				165, 148, 136, 123, *109* M^+ 165.1152 (165.1153 required)
	(9d)	17	(120—125/0.1) 68—69	1 685, 1 655, 1 595, 1 540, 935, 775, 720	10.40s (CHO), 7.88d (4-H), 7.40d (6-H), 4.00t (CH_2), 2.26s (Me), 2.05—1.10m (2 CH_2), 0.95t (Me), $J_{4.6}$ 2 Hz		$C_{11}H_{15}NO_2$	68.5 (68.4)	7.8 (7.8)	7.3 (7.25)	193, 178, *165*, 151, 109
(8e)	**(9e)**	62	(120/0.03)	1 655, 1 600, 1 560, 1 240, 760	7.05s (4-H), 6.96s (6-H), 3.90t (CH_2), 2.12s (Me), 2.04s (Me), 1.95—1.05m (2 CH_2), 0.93t (Me)		$C_{11}H_{17}NO$				179, 162, 150, 136, *123* M^+ 179, 1309 (179.1309 required)
(8f)	**(9f)**	58	(115—117/0.1)	1 660, 1 600, 1 540, 1 150, 830	7.23dd (4-H), 7.08s (6-H), 6.48d (3-H), 3.87t (CH_2), 2.40q (CH_2), 2.00—1.40m (CH_2), 1.13t (Me), 0.93t (Me), $J_{3.4}$ 9; $J_{4.6}$ 2 Hz		$C_{10}H_{15}NO$				165, 150, 123, *108* M^+ 165.1152 (165.1153 required)
	(9g)	13	(120—125/0.1) 91—92.5	1 680, 1 665, 1 600, 1 540, 1 240, 960, 775	10.40s (CHO), 7.97d (4-H), 7.42d (6-H), 3.95t (CH_2), 2.50q (CH_2), 2.10—1.50m (CH_2), 1.20t (Me), 100t (Me), $J_{4.6}$ 3 Hz		$C_{11}H_{15}NO_2$	68.7 (68.4)	7.9 (7.8)	7.3 (7.25)	193, 178, *165*, 150, 123, 108

(**8h**)	(**9h**)	69	(123—126/0.05)	1 665, 1 610, 1 570, 1 465, 1 380, 1 240, 770	7.07s (4-H), 6.95s (6-H), 3.87t (CH_2), 2.37q (CH_2), 2.14s (Me), 1.80m (CH_2), 1.14t (Me), 0.94t (Me)		$C_{11}H_{17}NO$				179, 164, 137, *122* M^+ 179, 1309 (179.1309 required)
(**8i**)	(**9i**)	44	(160—170/0.1) 80—81	1 665, 1 595, 710	7.30s (Ph), 7.15d (4-H), 7.05s (6-H), 6.53d (3-H), 5.10s (CH_2), 2.02s (Me), $J_{3,4}$ 9 Hz		$C_{13}H_{13}NO$	78.7 (78.4)	6.8 (6.6)	7.0 (7.0)	199, *91*
	(**10**)	12	(120—125/0.1) 114—115	1 685, 1 600, 1 565, 750, 730	10.47s (CHO), 8.49d (6-H), 8.05d (4-H), 2.42s (Me), $J_{4,6}$ 2 Hz		C_7H_6ClNO	54.1 (54.0)	4.0 (3.9)	9.0 (9.0)	157, 156, *155*, 154, 128, 126, 119, 91
(**4v**)	1,6-Di(n-propyl)-2-pyridone†	13	(140—143/0.1)	1 660, 1 590, 1 540, 830	7.25dd (4-H), 6.40 (3-H), 6.00d, (5-H), 4.00t (CH_2), 2.36t (CH_2), 2.00—1.40m 1.30—0.80m (2 Me)		$C_{11}H_{17}NO$				179, 164, 137, *122* M^+ 179, 1310 (179.1310 required)
	5-Ethyl-6-methyl-1-(n-propyl)-2-pyridone	29			7.16d (4-H), 6.40d (3-H), 4.05t (CH_2), 2.54q (CH_2), 2.33s (Me), 2.00—1.40m (CH_2), 1.30—0.80m (2 Me), $J_{3,4}$ 9 Hz		$C_{11}H_{17}NO$				
(**4w**)	1-(n-Butyl)-6-iso-butyl-2-pyridone	19	(140—145/0.05)	1 660, 1 590, 1 465, 790	7.21dd (4-H), 6.40dd (3-H), 5.97dd (5-H), 4.02t (CH_2), 2.46dd (CH_2), 2.00—0.80m (14 H), $J_{3,4}$ 9; $J_{4,5}$ 7; $J_{3,5}$ 1.5 Hz		$C_{13}H_{21}NO$				207, 912, 190, *150*, *109* M^+ 207.1601 (207.1601 required)
(**4x**)	1-(n-Butyl)-6-phenyl-2-pyridone	68	Oil	1 660, 1 605, 1 590, 1 550, 1 500, 1 160, 1 130, 810, 770, 720, 705	7.65—7.20m (Ph and (4-H), 6.60dd (3-H), 6.04dd (5-H), 3.91t (CH_2), 1.80—0.90m 2 CH_2), 0.70t (Me), $J_{3,4}$ 9; $J_{4,5}$ 7; $J_{3,5}$ 1.5 Hz		$C_{11}H_{25}NO$				277, 210, 184, *171* M^+ 227.1310 (227.1310 required)
(**6**; R = H)	2-Chloro-5,6,7,8-tetrahydro-quinoline	62	Oil	15 580, 1 565, 1 445, 1 420, 1 195, 1 135, 1 100, 990, 860, 810	7.32d (4-H), 7.00d (3-H), 3.10—2.60m (2 CH_2), 2.00—1.65m (2 CH_2), $J_{3,4}$ 8.5 Hz	157.5s (C-2), 147.1 (C-9), 138.8d (C-4), 130.4s (C-10), 120.5d (C-3), 31.7t (C-8), 27.4t (C-5), 221.t, 21.9t (C-6 and C-7)					169, *167*, 141, 149, 132, 104
(**6**; R = Me)	2-Chloro-3-methyl-5,6,7,8-tetrahydro-quinoline	45	Oil	1 595, 1 555, 1 450, 1 425, 1 385, 1 380, 1 175, 1 160, 1 030, 720, 710	7.20s (4-H), 3.00—2.65m (2 CH_2), 2.28s (Me), 2.00—1.60m (2 CH_2)	154.0s (C-2), 146.6s (C-9), 139.0d (C-4), 130.1s (C-10), 127.7s (C-3), 30.7t (C-8), 26.8t (C-5), 21.8t, 21.4t (C-6 and C-7), 17.8q (C-11)					183, *181*, 168, 1688, 155, 153, 146

* The multiplicity in the off-resonance spectrum is indicated after the chemical shift. † Base peak in italics. ‡ Hydrogen in place of Bu^n.

After 5 h at room temperature a dark green solution was obtained, and the solvent was removed under reduced pressure. The white gum was treated with aqueous sodium carbonate (50 ml, 10% w/v) and extracted with ethyl acetate. The dried extract was evaporated to give a yellow oil (1.20 g) which proved to be a complex mixture.

(*b*) *Condensation of acetamide and cyclohexanone.* A solution of acetamide (10.8 g, 0.1 mol), cyclohexanone (39.2 g, 0.4 mol), and toluene-*p*-sulphonic acid (0.1 g) in toluene (200 ml) was refluxed under a Dean and Stark water separator. After removal of the required 3.6 ml of water (24 h) the solution was cooled and washed with aqueous sodium hydrogencarbonate (2 × 50 ml, 10% w/v) and then aqueous sodium bisulphate (2 × 150 ml). The toluene solution was then dried ($MgSO_4$) and evaporated to give a yellow oil (12.0 g). This was absorbed onto alumina and eluted with light petroleum–chloroform to give *N*-cyclohex-1-enylacetamide (**5**) as a pale yellow solid, m.p. 62—64 °C (lit.,[12] m.p. 65—66 °C). In a similar manner from propionamide was obtained *N*-cyclohex-1-enylpropionamide (46%), m.p. 92—94 °C, which was used without further purification; $\nu_{max.}$(Nujol mull) 3 280, 1 660, 1 640, 1 540, 1 240, and 730 cm^{-1}; $\delta(CDCl_3)$ 1.15 (t, Me), 1.35—1.80 (m, CH_2CH_2), 1.90—2.50 (m, $CH_2CH_2CH_2$), 6.05 (s, olefinic H), and 6.60—7.05 (br, NH).

Conversion of the Enamides into 2-Pyridones and Pyridines.—General method. To phosphoryl chloride (21.75 g, 0.14 mol) was added dropwise, at 0—5 °C with magnetic stirring, dimethylformamide (4.40 g, 0.06 mol) followed by the enamide (0.02 mol). After being stirred for 2 h at ambient temperature, the mixture was heated at 75 °C for a further 4 h. This dark red solution was poured into ice–water (300 ml) to give a clear orange solution which was basified with aqueous sodium hydroxide (40%), extracted with chloroform, and the extract dried ($MgSO_4$) and evaporated. The residue was chromatographed on alumina using varying mixtures of ethyl acetate and light petroleum as eluant. The products were then either recrystallised or distilled using a Kugelröhr apparatus and are collected in Table 4.

4,5-*Dimethyl*-1-(*n-propyl*)-2-*pyridone* (**19**). *N*-(n-Propyl)-*N*-prop-1-enylacetamide (**17**) (2.82 g, 0.02 mol) in phosphoryl chloride (21.75 g, 0.14 mol) containing 2 drops of dimethylformamide was heated at 75 °C for 4 h. After work-up as above, with elution through alumina using ethyl acetate–light petroleum, the title product was obtained as a yellow oil (59%); $\nu_{max.}$(liquid film) 1 665, 1 590, 1 455, and 1 435 cm^{-1}; $\delta(CDCl_3)$ 7.00 (s, 6-H), 6.38 (s, 3-H), 3.85 (t, CH_2), 2.10 (s, Me), 1.99 (s, Me), 1.90—1.35 (m, CH_2), and 0.93 (t, Me); *m/z* 165, 164, 137, and 123 (100%); M^+, 165.1152 ($C_{10}H_{15}NO$ requires *M*, 165.1153).

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