Stereoselective Syntheses of Substituted 5,6-Dihydro-2(1*H*)-pyridinones in Polyphosphate Media

Charles M. Marson,* Urszula Grabowska, and Asad Fallah

Department of Chemistry, The University, Sheffield S3 7HF, U.K.

Timothy Walsgrove

SmithKline Beecham, Chemical Development, Old Powder Mills, nr. Leigh, Tonbridge, Kent TN11 9AN, U.K.

Drake S. Eggleston and Paul W. Baures

SmithKline Beecham Pharmaceuticals, Research and Development Division, Box 1539, L-950, King of Prussia, Pennsylvania 19406

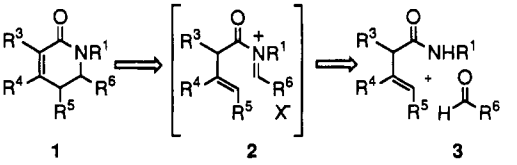
Received August 2, 1993®

δ-Lactams have been synthesized with excellent stereocontrol of substituents by condensing 3-alkenamides with aryl aldehydes in polyphosphoric ester. The scope of the condensation of 3-alkenamides with aryl aldehydes in several phosphate media is examined, and a rationale is proposed regarding γ-lactam *versus* δ-lactam formation.

The 5,6-dihydro-2(1*H*)-pyridinone ring system **1**[1,2] has considerable potential in synthesis, since it could act as a precursor of a wide variety of substituted piperidines,[3] piperidones, pyridines,[3] and pyridones; it has been used to prepare α-substituted amines,[4] of which the piperidine alkaloids,[3] *e.g.* andrachine **4**,[5] pipermethystine **5**,[6] anatabine **6**,[7] and piplartine[8] typify this important class. Additionally, access to quinolizidine[9] and indolizidine[9,10] alkaloids of pharmaceutical activity could also be gained *via* the 5,6-dihydro-2(1*H*)pyridinone ring system which has been employed as a key intermediate **7** in the synthesis of ipecacuanha alkaloids including emetine,[11] and whose versatility is exemplified by its ability to undergo epoxidation,[1] bromination,[1] and [2 + 2] cycloaddition of the C=C double bond;[12] cuprates effect 1,4-addition,[13] and Michael additions[14] occur with esters.

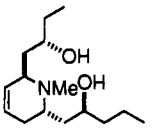
Methods of preparing 5,6-dihydro-2(1*H*)-pyridinones[1-3] are typically nongeneral,[2] require forcing conditions, and

Scheme 1

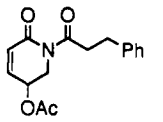


1 2 3

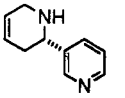
5,6-Dihydro-2(1*H*)-pyridinones *via* [5+1] Component Condensations



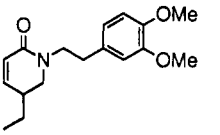
Andrachine **4**



Pipermethystine **5**



Anatabine **6**



7

do not afford stereocontrolled placement of substituents. We envisaged a convenient route to the pyridinones **1** by a [5 + 1] component condensation of a 3-alkenamide with an aldehyde or ketone (Scheme 1). Location of the carbonyl group between the iminum and alkenic groups was envisaged as leading to a rigid transition state which might result in stereocontrolled ring-closure of a species less prone to fragmentation or rearrangement (*e.g.* by aza-Cope equilibration[15]) than a simple unsaturated iminium species.[17] Despite the lack of precedent for such behavior[16] the desired cyclization might proceed *a priori* through a 6π disrotatory ring-closure[17] in which the amidic carbonyl

• Abstract published in *Advance ACS Abstracts,* December 15, 1993.

(1) Kheddis, B.; Bahibah, D.; Hamdi, M.; Perie, J.-J. *Bull. Soc. Chim. Fr.* **1981**, part 2, 135.

(2) (a) Shamma, M.; Rosenstock, P. D. *J. Org. Chem.* **1961**, *26*, 718. (b) Verbiscar, A. J.; Campbell, K. N. *J. Org. Chem.* **1964**, *29*, 2472. (c) Edwards, O. E.; Singh, T. *Can. J. Chem.* **1954**, *32*, 683. (d) Brandstadter, S. M.; Ojima, I. *Tetrahedron Lett.* **1987**, *28*, 613. (e) Guareschi, I. *Ann. Chim. Farm.* **1893**, *17*, 83. *Br. Chem. Abstr.* **1893**, 484.

(3) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; S. W., Pelletier, Ed.; Wiley: New York, 1981, Vol. 3, pp 1–90.

(4) Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885.

(5) Ahmad, V. U.; Nasir, M. A. *Phytochemistry* **1987**, *26*, 585.

(6) Smith, R. M. *Tetrahedron* **1979**, *35*, 437.

(7) (a) Hootele, C.; Colau, B.; Halin, F.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Tetrahedron Lett.* **1980**, 5063. (b) Quan, P. M.; Karus, T. K. B.; Quinn, L. D. *J. Org. Chem.* **1965**, *30*, 2769.

(8) (a) Joshi, B. S.; Kamat, V. N.; Saksena, A. K. *Tetrahedron Lett.* **1968**, 2395. (b) Boll, P. M.; Hansen, J.; Simonsen, O.; Thorup, N. *Tetrahedron* **1984**, *40*, 171.

(9) Grundon, M. F. *Nat. Prod. Rep.* **1989**, *6*, 523.

(10) Elbein, A. D.; Molyneux, R. J. In *Alkaloids: Chemical and Biological* Perspectives; ed. S. W., Pelletier, Ed.; Wiley; New York, 1981; Vol. 5, pp 1–54.

(11) Battersby, A. R.; Turner, J. C. *J. Chem. Soc.* **1960**, 717. (b) Fujii, T.; Yoshifugi, S.; Ohba, M. *Chem. Pharm. Bull.* **1978**, *26*, 645.

(12) Somekawa, K.; Shimou, T.; Atsuchi, M.; Kumamoto, S. *Nippon Kagaku Kaishi* **1978**, *7*, 1013. *Chem. Abstr.* **1978**, *89*, 128797.

(13) Hagen, T. J. *Synlett.* **1990**, 63.

(14) (a) Takano, S.; Sato, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 799. (b) Fujii, T.; Kogen, H.; Yoshifuji; Iga, K. *Chem. Pharm. Bull.* **1979**, *27*, 1847.

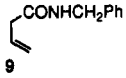
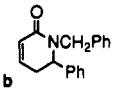
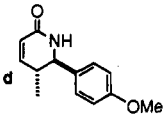
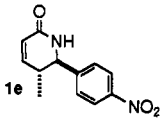
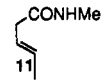
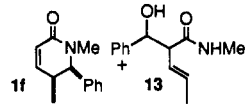
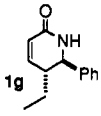
(15) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919.

(16) (a) Belleau, B. *Can. J. Chem.* **1957**, *35*, 663 and 673. For alternative routes to piperidines *via N*-acyliminium species see (b) Mooiweer, H. H.; Hiemstra, H.; Fortgens, H. P.; Speckamp, W. N. *Tetrahedron Lett.* **1987**, *28*, 3285 and (c) Esch, P. M.; Boska, I. M.; Hiemstra, H.; Speckamp, W. N. *Synlett* **1989**, 38.

(17) Woodward, R. B; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395.

0022-3263/94/1959-0291$04.50/0

Table 1. Synthesis of 5,6-Dihydro-2(1*H*)-pyridinones from 3-Alkenamides Using PPE

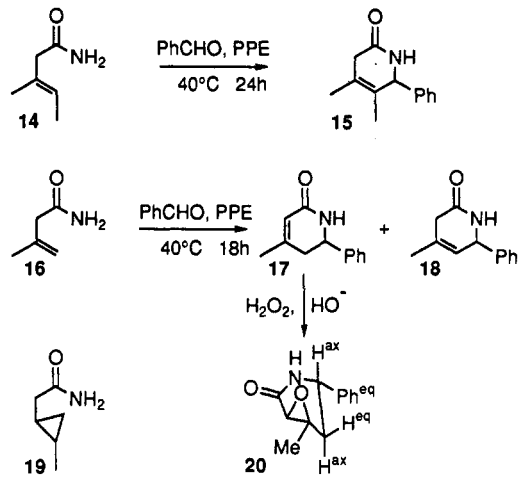
3-alkenamide	aldehyde	conditions	δ-lactams	% yield
 8	PhCHO	60 °C, 16 h	 1a	51
 9	PhCHO	60 °C, 56 h	 1b	95
 10	PhCHO	35 °C, 24 h	 1c	63
 10	*p*-$MeOC_6H_4CHO$	45 °C, 18 h	 1d	66
 10	*p*-$O_2NC_6H_4CHO$	45 °C, 18 h	 1e	50
 11	PhCHO	40 °C, 16 h	 1f + 13	30 + 30
 12	PhCHO	60 °C, 18 h	 1g	50

had undergone enolization, or *via* a cationic cyclization involving an acyliminium species.[18]

We recently reported a new route to γ-lactams by the condensation of acyclic β,γ-unsaturated amides with aldehydes in acidic media.[19] That process involves amidoalkylation of the C-4 alkene carbon atom. Herein we report[20] that the alternative amidoalkylation at C-5 usually occurs in a medium of polyphosphate ester (PPE),[21] thereby realizing the forward process depicted in Scheme 1.

A striking feature of all the condensations of 3-alkenamides with aryl aldehydes reported in this and the previous paper in this issue is the regioselectivity. In no case was a mixture of γ- and δ-lactams detected, whether the medium was PPE, PPA, or $MeSO_3H$–P_2O_5. Optimum yields are usually obtained only in a narrow range of temperature; in several cases, a reaction temperature 10 °C above the optimum temperature did not result in the isolation of any identifiable compounds.

Scheme 2

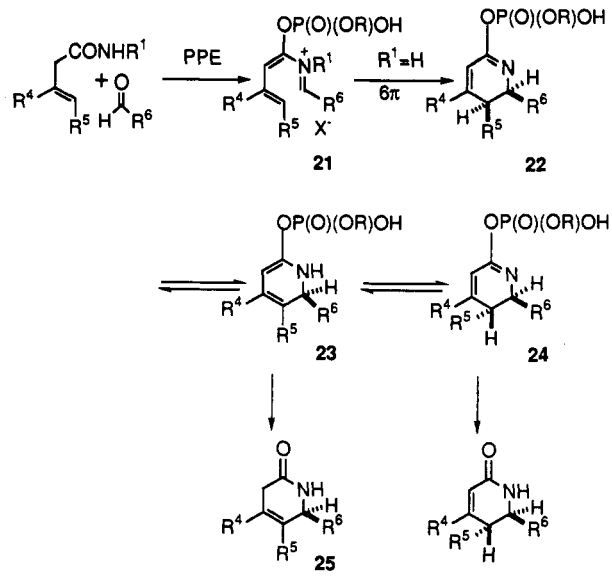


Except in one case (amide **1f**), 4,5-*trans*-disubstitution was observed. The relative configuration of the lactams could be inferred from the vicinal coupling constants, typically 11 Hz for amides **1c–e,g**, but only 3 Hz for the *cis*-disubstituted amide **1f**. Scheme 3 outlines a unified pathway that explains all the products identified in Table 1 and Scheme 2. The isolation a β-hydroxy amide **13** (a single diastereoisomer) is consistent with an acid-catalyzed aldol condensation of an enol phosphate intermediate with benzaldehyde. The relative configuration of amide **13** was determined by X-ray diffraction of a single crystal to be (*R,R*; *S,S*).

The reactions of amides **14** and **16** with benzaldehyde show that a 3-alkyl substituent can lead predominantly or exclusively to a 3,6-dihydro-2(1*H*)-pyridinone. A Prins reaction[16] to account, for example, for the deconjugated

(18) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
(19) (a) Marson, C. M.; Grabowska, U.; Walsgrove, T.; Eggleston, D. S.; Baures, P. W. *J. Org. Chem.* **1991**, *56*, 2603. For other acid-catalyzed cyclizations to give pyrrolidinones, see (b) Ben-Ishai, D. *J. Chem. Soc., Chem. Commun.* **1980**, 687, in which the alkylamide of a bis(alkoxycarbonyl)aminoacetic acid was converted by methanesulfonic acid into a putative cationic intermediate which was trapped by mesylate to give the pyrrolidinone, and (c) Tamura, Y.; Maeda, H.; Akai, S.; Ishiyama, K.; Ishibashi, H. *Tetrahedron Lett.* **1981**, *22*, 4301.
(20) For a preliminary account of the [5 + 1] component condensation see: Marson, C. M.; Grabowska, U.; Walsgrove, T. *J. Org. Chem.* **1992**, *57*, 5045.
(21) PPA was purchased from BDH Chemicals Ltd., Poole, U.K. For a review on PPA see: Rowlands, D. A. In *Synthetic Methods*; J. S., Pizey, Ed.; Wiley: New York, **1985**; Vol. 6, p 156. For some uses of PPE in synthesis, see: (a) Kanaoka, Y.; Ban, Y.; Mayashita, K.; Iria, K.; Yonemitsu, O. *Chem. Pharm. Bull.* **1966**, *14*, 934. (b) Kanaoka, Y.; Sato, E.; Yonemitsu, O.; Ban, Y. *Tetrahedron Lett.* **1964**, *35*, 2419. PPE was prepared as described by Cava, M. P.; Lakshmikantham; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665.

Scheme 3



amide **18** cannot be rigorously excluded; however, β-protonation of intermediate **23** appears more plausible. Reaction of the inseparable mixture of lactams **17** and **18** with alkaline H_2O_2 afforded the epoxide **20**, but this process did not enable lactam **18** to be recovered. The relative configuration of the epoxide **20** was confirmed by NOE experiments which showed (among other enhancements) increase in intensities of the 5-H_{eq} and 5-H_{ax} protons of 2 and 7%, respectively, upon irradiation of the methyl signal at δ 1.50. Enhancement of both 5-H signals is consistent only with the assignment as diastereoisomer **20**. The alternative configuration would not give rise to enhancement of both signals for the 5-H protons; in particular, 5-H_{ax} would be virtually unaffected. A trans-diaxial arrangement at C-5 and C-6 exists ($J_{5ax,6ax}$ = 11 Hz; $J_{5eq,6ax}$ = Hz, and J_{gem} = −15 Hz). As expected, the phenyl group occupies a quasiequatorial position. The scope of these condensations was further examined by heating amide **19** with benzaldehyde in PPE at 40 °C for 18 h. The cyclopropyl ring was not found to participate in the reaction, no products being obtained and amide **19** being recovered.

The products in Table 1 and Scheme 2 and their stereochemistry can be rationalized by assuming that (i) such cyclizations do not always proceed solely, or at all, through *N*-acyliminium species; in certain cases, enol phosphate intermediates are involved, (ii) the formation of a *cis*-5,6-disubstituted-5,6-dihydro-2(1*H*)-pyridinone ring is the result of a thermal 6π electrocyclic disrotatory ring-closure,[22] and (iii) *trans*-5,6-disubstituted-5,6-dihydro-2(1*H*)-pyridinone rings are formed from the *cis*-isomers (or their reaction intermediates) by processes which involve a combination of enol phosphate intermediates and equilibration to the *trans*-isomers (as for entries **1c–e,g**) either by prototropic shifts or by [1,5]sigmatropic rearrangement of hydrogen.[23] An uninvestigated possibility is that for amide **1f** (Table 1), the 5,6-*cis*-substituents do not isomerize because the blocking *N*-methyl group precludes the possibility of a [1,5] hydrogen shift.

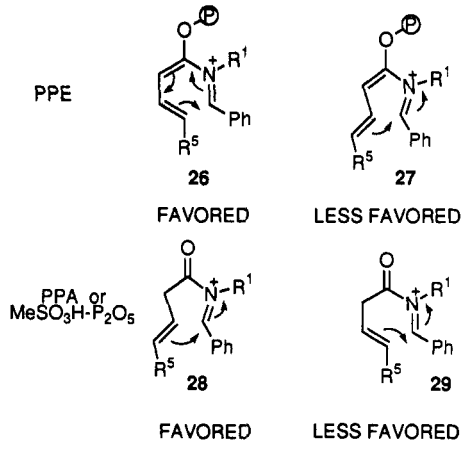


Figure 1.

Some condensations were successful in PPA. Reaction of 3-butenamide **8** with benzaldehyde in PPA at 60 °C for 18 h afforded **1a** (30%); similarly, amide **14** condensed with benzaldehyde in PPA at 40 °C for 49 h to give **15** in 65% yield. However, the yields for those reactions were higher when conducted in PPE. Moreover, attempts to condense benzaldehyde in PPA with the following amides were not successful: with amide **9**, no reaction at 40 °C, but polymerization at 50 °C; using (*E*)-*N*-benzyl-3-pentenamide, no reaction at 45 °C, but polymerization at 60 °C; and with amide **11**, at 40 °C, there was no reaction.

A rationale that explains the influence of the acidic medium upon the courses of the reactions studied here and in the preceding paper is summarized in Figure 1. 2,2-Dimethyl-3-pentenamide failed to react with benzaldehyde in PPE at 40 °C, evidently because enolization cannot occur. PPE favors, by a presumed enol phosphate intermediate, an electrocyclic ring-closure of the type **26**. However, where the contiguity and bulk of substituents prevent **26** from becoming coplanar, the alternative ring-closure *via* **27** (or possibly in the form **28**) can operate. An example of the latter is the condensation of (*E*)-*N*-benzyl-3-pentenamide with benzaldehyde in PPE (35 °C, 24 h) which gave the *N*-benzyl derivative (52%) of the indano-fused γ-lactam previously obtained from a condensation in PPA.[24] No δ-lactam ring system was detected. In contrast, the formation of the six-membered lactam **1f** from the *N*-alkylated amide **11** suggests that steric factors associated with the juxtaposition of four groups (C=O, NR, Ph, and Me) are finely balanced. It is notable that the stereochemistry of the resulting δ-lactam can be controlled by the presence or absence of a substituent at nitrogen (contrast amide **1f** with **1c**).

A medium of PPA or $MeSO_3H$–P_2O_5 generally favors the formation of the γ-lactam, presumably *via* ring-closure of an *N*-acyliminium cation such as **28**. Thus, in either medium, a 4-substituted 3-butenamide reacts with benzaldehyde to give a product or products containing a γ-lactam ring. However, the alternative cyclization to a six-membered ring, *via* **29**, has been shown to operate in cases for which carbocation stability is paramount, as for 3-butenamide itself (secondary *versus* primary carboca-

(22) An (*E*)-configuration about the C=N bond has also been assumed. The thermal ring-closure might also proceed through an intermediate containing an uncharged nitrogen atom in the case of R^1 = H in Scheme 2. The precise constitution of enol phosphate intermediates is not currently known.

(23) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970; pp 114–140. (b) Spangler, C. W. *Chem. Rev.*, **1976**, *76*, 187. (c) Mironov, V. A.; Fedorovich, A. D.; Akhrem, A. A. *Russ. Chem. Rev.* **1981**, *50*, 666.

(24) Eggleston, D. S.; Baures, P. W.; Grabowska, U.; Marson, C. M.; Walsgrove, T. *Acta. Crystallogr.* **1992**, *C48*, 2177.

tion; R^5 = H in Figure 1), and for 3,4-disubstituted 3-butenamides (tertiary *versus* secondary carbocations).

In summary, efficient, highly stereocontrolled one-pot syntheses of substituted unsaturated δ-lactams by the condensation of 3-alkenamide with aldehydes in media of phosphoric acids or esters, principally PPE, have been demonstrated. Condensations proceed under mild conditions without activating or stabilizing groups.

Experimental Section

Details of materials and methods are described in the preceding paper.

3-Butenoyl Chloride. Thionyl chloride (8.5 mL, 0.12 mol) was added dropwise to 3-butenoic acid (5.0 g, 0.058 mol) and the mixture heated at 40 °C for 1 h. The excess thionyl chloride was then removed by distillation at atmospheric pressure. The residue was distilled at reduced pressure to give 3-butenoyl chloride (4.1 g, 67%) as a colorless oil: bp 40 °C/80 mmHg (lit.[25] bp 98–99 °C/774 mmHg); IR ν_{max} 1800 cm^{-1}.

Preparation of Amides. 3-Butenamide (8). Method 1. To a solution of 3-butenenitrile (3.0 g, 0.045 mol) in dichloromethane (15 mL) cooled in an ice–salt bath were added hydrogen peroxide (21 mL, 27.5%), tetra-*n*-butylammonium hydrogen sulfate (3.04 g, 0.009 mol), and a aqueous solution of sodium hydroxide (16.7 mL, 20%). The progress of the reaction was monitored by TLC; the disappearance of the starting nitrile usually occurred in 45 min. Dichloromethane (20 mL) was then added and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, and the residue was recrystallized from ethyl acetate to give 8 (0.8 g, 21%) as plates, mp 47 °C (lit.[26] mp 72–75 °C); δ_H ($CDCl_3$) 5.86 (1H, m), 5.25 (2H, m), 3.02 (2H, dt, J = 7, 2 Hz); m/z (%) +EI 85 (70), 69 (43), 57 (32), 42 (100). Anal. Calcd for C_4H_7NO: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.56; H, 8.18; N, 16.44.

Method 2. Copper (0.14 g, 2.25 mmol), copper chloride (0.38 g, 2.25 mol), and sodium orthovanadate (0.65 g, 1.5 mol) were dissolved in water (20 mL). 3-Butenenitrile (1.2 g, 0.023 mol) was added dropwise and the reaction was heated at 80 °C for 1 h. The inorganic material was filtered off and washed with water (2 × 10 mL). The combined aqueous layers were evaporated, and the residue was recrystallized from water to give 8 (0.36 g, 24%) as plates, mp 47 °C. Spectral data as above.

***N*-Benzyl-3-butenamide (9).** 3-Butenoyl chloride (4.1 g, 0.039 mol) was added dropwise to a solution of benzylamine (8.4 g, 0.078 mol) in diethyl ether (30 mL) with efficient stirring. Vigorous shaking resulted in a white precipitate. After the reaction had been left with stirring for 3 h, the diethyl ether was separated from the solid by gravity filtration. The solid residue was washed with further portions of diethyl ether (3 × 20 mL), and the combined organic extracts were dried (Na_2SO_4). The solvent was evaporated and the residue was recrystallized from ethyl acetate to give 9 (3.0 g, 44%) as needles, mp 48.5–49 °C; δ_H ($CDCl_3$) 7.30 (5H, m), 6.20 (1H, br s), 5.82 (1H, m), 5.21 (2H, m), 4.40 (2H, d, J = 6 Hz), 3.02 (2H, dt, J = 8, 1.5 Hz); δ_C 170.5, 138.1, 131.2, 128.4, 127.5, 127.2, 119.25, 43.3, 41.3; m/z (%) EI 176 (100), 160 (12), 106 (15), 91 (90). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.15; H, 7.43; N, 8.02.

(*E*)-*N*-Methyl-3-pentenamide (11). Methylamine gas was bubbled for 15 min through diethyl ether (100 mL) kept in an ice bath. (*E*)-3-Pentenoyl chloride (15 g, 0.13 mol) was then added dropwise with efficient stirring. After the reaction had been stirred overnight, the reaction was extracted with dichloromethane (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4), and the diethyl ether was removed by distillation at atmospheric pressure. The residue was distilled at reduced pressure to afford 11 (7.2 g, 50%) as a colorless oil (bp 163–165 °C/1 mmHg); δ_H ($CDCl_3$) 7.00 (1H, br s), 5.55 (2H, m), 2.91 (2H, d, J = 6 Hz), 2.75 (3H, d, J = 6 Hz), 1.68 (3H, d, J = 7 Hz); δ_C 172.2, 130.1, 123.7, 40.0, 26.0, 17.7; m/z (%) +EI 113 (60), 83 (12), 73 (50), 58 (100).

(*E*)-3-Methyl-3-pentenenitrile and (*Z*)-3-Methyl-3-pentenenitrile. Ethyl cyanoacetate (75 g, 0.6 mL) and aqueous hydrochloric acid (250 mL, 1 M) was heated on a water bath for 90 min, and then the water and hydrochloric acid were removed *in vacuo*. The remaining residue was mixed with 2-butanone (45.8 g, 0.6 mol), ammonium acetate (4 g, 0.05 mol), and benzene (100 mL). This mixture was heated under reflux for 16 h, incorporating a Dean–Stark apparatus which resulted in the removal of water (15 mL). After decarboxylation by further heating for 10 h, the reaction mixture was distilled to yield a mixture of (*E*)- and (*Z*)-3-methyl-3-pentenenitrile and (*E*)- and (*Z*)-3-methyl-2-pentenenitrile (34 g, 54%) as a colorless oil, bp 156–166 °C (lit.[27] bp 156–162 °C). The above mixture (34 g, 0.36 mol), ammonium sulfite (34 g, 0.3 mL), and water (125 mL) was then stirred for 15 h at 100 °C. The organic layer was separated and yielded a mixture (10 g, 30%) of (*E*)-3-methyl-3-pentenenitrile and (*Z*)-3-methyl-3-pentenenitrile in a ratio of 2.45:1, as determined by ^1H NMR spectrometry.

(*E*)-3-Methyl-3-pentenamide (14) and (*Z*)-3-Methyl-3-pentenamide. To a solution of (*E*)-3-methyl-3-pentenenitrile and (*Z*)-3-methyl-3-pentenenitrile (10.0 g, 0.105 mol, molar ratio 2.45:1) in dichloromethane (45 mL) cooled in an ice–salt bath were added hydrogen peroxide (27.5%, 49.3 mL), tetra-*n*-butylammonium hydrogen sulfate (7.06 g, 0.021 mol), and an aqueous solution of sodium hydroxide (39 mL, 20%). The progress of the reaction was monitored by TLC; the disappearance of the nitriles usually occurred in 60 min. Dichloromethane (50 mL) was then added and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Chromatography of the residue on a short silica column, employing as eluant 1:2 ethyl acetate:petroleum ether (40–60 °C) afforded a mixture of 14 and (*Z*)-3-methyl-3-pentenamide (8.31 g, 70%) as plates. Fractional recrystallization of the mixture from ethyl acetate afforded the amide 14 (5.9 g, 49%) as needles, mp 133 °C (lit.[28] mp 130–131 °C; lit.[29] mp 136–137 °C); δ_H ($CDCl_3$) 5.70 (2H, br s), 5.44 (1H, q, J = 7 Hz), 2.93 (2H, s), 1.70 (3H, s), 1.64 (3H, d, J = 7 Hz); Anal. Calcd for $C_6H_{11}NO$: NO: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.98; H, 9.96; N, 12.66 and (*Z*)-3-methyl-3-pentenamide (2.30 g, 19%) as needles, mp 130 °C (from ethyl acetate) (lit.[28] mp 126 °C; lit.[29] mp 138–139 °C); δ_H ($CDCl_3$), 5.57 (2H, br s), 5.55 (1 H, q, J = 7 Hz), 3.00 (2H, s), 1.80 (3H, s), 1.65 (3H, d, J = 7 Hz); Anal. Calcd for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.67; H, 9.87; N, 12.31.

3-Methyl-3-butenamide (16). Cyanoacetic acid (50.0 g, 0.59 mol), acetone (34.2 g, 0.59 mol), and ammonium acetate (4.0 g, 0.05 mol) in dry benzene (100 mL) was heated at reflux in a Dean–Stark apparatus for 16 h. The Dean–Stark unit was replaced with a distillation head and the fraction collected between 110–115 °C. The 3-methyl-3-butenenitrile (27.2 g, 57%) so obtained was used directly.

To a solution of 3-methyl-3-butenenitrile (18.8 g, 0.23 mol) in dichloromethane (100 mL) cooled in an ice-bath were added in the following order: hydrogen peroxide solution (120 mL, 27.5%), tetraethylammonium *p*-toluenesulfonate (8.5 g, 0.023 mol), and aqueous sodium hydroxide (20%, 95 mL), the latter dropwise, and with vigorous stirring. After 2 h, the organic layer was isolated and the aqueous layer extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried and evaporated. The residue was recrystallized from 1:1 ethyl acetate:petroleum ether (40–60 °C) to give 16 (14.0 g, 61%) as plates: mp 118–119 °C; δ_H 5.85 (2H, bd), 5.10 (1H, m), 4.95 (1H, m), 2.97 (2H, s), 1.80 (3H, s); δ_C 173.4, 140.3, 115.5, 45.8, 22.3. Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.1. Found: C, 60.53; H, 8.85; N, 13.84.

2-(2-Methylcyclopropyl)acetamide (19). A flask fitted with a dropping funnel and a double-surface condenser was charged consecutively with zinc dust (2.62 g, 40 mmol), copper(II) chloride (0.40 g, 4 mmol), dry ether (2 mL), dibromomethane (0.07 mL,

(25) Jeffery, G. H.; Vogel, A. I. *J. Chem. Soc.* **1948**, 658.
(26) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Uryu, T.; Sugi, H.; Saitoh, S.; Ishimaru, H.; Haga, S. *Chem. Pharm. Bull.* **1976**, *24*, 1246.
(27) Murray, J. V.; Cloke, J. B. *J. Am. Chem. Soc.* **1934**, *56*, 2749.
(28) Wagner, B. B. *J. Am. Chem. Soc.* **1949**, *41*, 3218.
(29) Cornforth, R. H. *J. Chem. Soc.* **1959**, 452.

10 mmol), and acetyl chloride (0.07 mL, 0.8 mmol). (*E*)-3-Pentenamide (0.99 g, 10 mmol) was added in one portion with stirring, and the mixture was heated at reflux. The dropping funnel was charged with a solution of dibromomethane (1.4 mL, 20 mmol) in dry ether (2 mL) which was then added dropwise over 3 min to the mixture maintained at reflux. The reaction was stirred at reflux for 1 h further, allowed to cool, and poured into a precooled flask. The contents were treated with saturated aqueous ammonium chloride (30 mL, CAUTION: dropwise addition, at first). The suspension was filtered and the filtrate washed with a 1:1 mixture of aqueous ammonium chloride:ether (5 × 30 mL, CAUTION: to prevent fire the solid residue must be kept moist at all times). The aqueous layer was extracted with ether (3 × 30 mL), the combined ethereal layers were washed with 10% aqueous sodium hydroxide (3 × 20 mL) and saturated sodium chloride (3 mL) and dried, and the ether was evaporated to give a 3:1 mixture (1.1 g) of (*E*)-3-pentenamide and **19**.

Since neither recrystallization nor column chromatography proved effective, the mixture (1.1 g) was shaken with a solution of potassium permanganate (7.0 g, 45 mmol) in aqueous sodium hydroxide (5%, 50 mL). After filtration, the residue was washed with water (2 × 15 mL) and extracted with dichloromethane (3 × 3 mL). Recrystallization from 1:1 ethyl acetate:petroleum ether (40–60 °C) afforded **19** (0.32 g, 28%) as needles: mp 102–103 °C; δ_H 6.00 (2H, bd s), 2.20 (2H, dq, J = 18, 7 Hz), 1.10 (2H, d, J = 6 Hz), 0.64 (2H, m), 0.37 (2H, m, cyclopropyl CH_2); δ_C 175.6, 40.5, 18.5, 15.7, 13.0, 12.85. Anal. Calcd for $C_6H_{11}NO$: C, 63.70; H, 9.80; N, 12.38. Found: C, 63.30; H, 9.88; N, 12.07.

Preparation of Lactams (1). General Procedure. Polyphosphate ester (10 g) was weighed into a two-necked flask, and to it were added successively the 3-alkenamide (5.05 mmol) and the aryl aldehyde (1.07 g, 10 mmol). The reaction was carried out under an atmosphere of nitrogen, at a temperature as specified below, and for a period of 18 h unless otherwise stated. After this time the mixture was cooled and then made alkaline with aqueous solution of sodium hydroxide (**CAUTION**). After stirring for another 2 h, the mixture was extracted with chloroform (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel employing as eluant ethyl acetate:petroleum ether (40–60 °C) to give the lactam.

(*E*)-5,6-Dihydro-6-phenyl-2(1*H*)-pyridinone (1a). Method 1. The reaction was conducted in PPE at 60 °C. Chromatography on silica gel employing as eluant 3:2 ethyl acetate:petroleum ether (40–60 °C) afforded **1a** (0.52 g, 51%) as needles: mp 130–132 °C (from ethyl acetate–petroleum ether); δ_H ($CDCl_3$) 7.38 (5H, m), 6.64 (1H, m), 6.02 (1H, dm, J = 10, 3, 1, and 1 Hz), 5.64 (1H, br s), 4.74 (1H, ddd, J = 12, 6, and 1 Hz), 2.56 (2H, m); δ_C 166.4, 141.2, 139.95, 128.9, 128.2, 126.4, 124.65, 55.8), 33.0; m/z (%) +EI 173 (100), 144 (12), 106 (92), 77 (18), 68 (48). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 75.97; H, 6.56; N, 7.88. Method 2, the condensation in PPA, is described below.

***N*-Benzyl-5,6-dihydro-6-phenyl-2(1*H*)-pyridinone (1b).** The reaction was conducted at 60 °C for 56 h. Chromatography on silica gel employing as 1:4 eluant ethyl acetate:petroleum ether (40–60 °C) afforded **1b** (0.29 g, 93%) as a colorless oil, bp 80–85 °C/1 mmHg; HRMS, EI calcd for $C_{18}H_{17}NO$ 263.1310, found 263.1313; δ_H ($CDCl_3$) 7.29 (10H, m), 6.31 (1H, dddd, J = 10, 6, 3, and 1 Hz), 6.12 (1H, ddd, J = 10, 2, and 1 Hz), 5.64 (1H, d, J = 15 Hz), 4.59 (1H, ddd, J = 7, 2, and 1 Hz), 3.50 (1H, d, J = 15 Hz), 2.92 (1H, dddd, J = 1 8, 8, 3 and 3 Hz), 2.45 (1H, dddd, J = 18, 6, 2, and 1 Hz); δ_C 164.3, 140.2, 137.6, 136.25, 128.5, 128.4, 127.85, 127.6, 127.2, 126.4, 125.2, 57.15, 47.5, 32.2; m/z (%) +EI 263 (60), 172 (18), 130 (39), 106 (37), 91 (100).

(*E*)-5,6-Dihydro-5-methyl-6-phenyl-2(1*H*)-pyridinone (1c). The reaction was conducted at 40 °C. Chromatography on silica gel employing as 3:2 eluant ethyl acetate:petroleum ether (40–60 °C) afforded **1c** (0.50 g, 63%) as needles, mp 127–128 °C (from ethyl acetate–petroleum ether); δ_H ($CDCl_3$) 7.36 (5H, m), 6.46 (1H, dd, J = 10 and 3 Hz), 5.96 (1H, ddd, J = 10, 3, and 2 Hz), 5.62 (1H, br s), 4.28 (1H, dd, J = 11 and 7 Hz), 2.69 (1H, dddq, J = 11, 7, 3, and 2 Hz), 1.06 (3H, d, J = 7 Hz); δ_C 166.0, 146.5, 140.25, 128.7, 128.3 , 127.2, 123.3, 62.8, 37.0, 17.0; m/z (%) +EI 187 (47), 106 (82), 82 (100).

(*E*)-5,6-Dihydro-5-methyl-6-(4-methoxyphenyl)-2(1*H*)-pyridinone (1d). The reaction was conducted at 45 °C. Chromatography on silica gel employing as eluant 3:2 ethyl acetate:petroleum ether (40–60 °C) afforded **1d** (0.72 g, 66%) as needles: mp 130–132 °C (from ethyl acetate); HRMS, EI calcd for $C_{13}H_{15}NO$ 217.1103, found 217.1104; δ_H ($CDCl_3$) 7.26 (2H, d, J = 8 Hz), 6.91 (2H, d, J = 8 Hz), 6.46 (1H, dd, J = 10 and 2 Hz), 5.96 (1H, dt, J = 10, 3 Hz), 5.43 (1H, br s), 4.22 (1H, d, J = 11 Hz), 3.82 (3H, s), 2.68 (1H, m), 0.99 (3H, d, J = 7 Hz); δ_C 166.15, 159.6, 146.9, 132.2, 128.5, 123.3, 114.2, 62.5, 55.3, 37.2, 16.9; m/z (%) +EI 217 (37), 149 (15), 136 (100), 94 (73), 82 (81).

(*E*)-5,6-Dihydro-5-methyl-6-(4-nitrophenyl)-2(1*H*)-pyridinone (1e). The reaction was conducted at 45 °C. Chromatography on silica gel employing as eluant 3:2 ethyl acetate:petroleum ether (40–60 °C) afforded **1e** (0.59 g, 49%) as needles, mp 211 °C (from ethyl acetate); δ_H ($CDCl_3$) 8.26 (2H, d, J = 8 Hz), 7.55 (2H, d, J = 8 Hz), 6.50 (1H, dd, J = 10 and 3 Hz), 5.96 (1H, dd, J = 10 and 2 Hz), 4.45 (1H, d, J = 8 Hz), 2.69 (1H, m), 1.12 (3H, d, J = 7 Hz); δ_C 177.7, 166.3, 147.6, 146.3, 128.0, 123.8, 122.9, 6 1.5, 36.6, 17.2; m/z (%) +EI 232 (27), 151 (8), 82 (100). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.6; H, 5.21; N, 12.07. Found: C, 62.2; H, 5.17; N, 12.00.

cis-5,6-Dihydro-1,5-dimethyl-6-phenyl-2(1*H*)-pyridinone (1f) and (*R,R*; *S,S*)-1-Methyl-2-(hydroxybenzyl)-3-pentenamide (13). The reaction was conducted at 40 °C for 16 h. Chromatography on silica gel employing as eluant 5:2 ethyl acetate:petroleum ether (40–60 °C) afforded **1f** (0.53 g, 30%) as a colorless oil: R_f = 0.4 (ethyl acetate), (bp 110–112 °C/1 mmHg); δ_H ($CDCl_3$) 7.29 (5H, m), 6.31 (1H, ddd, J = 10, 5, and 1 Hz), 5.98 (1H, dd, J = 10 and 1 Hz), 4.29 (1H, dd, J = 3 and 1 Hz), 2.93 (3H, s), 2.59 (1H, dddq, J = 7, 5, 3, and 1 Hz), 1.28 (3H, d, J = 7 Hz); m/z (%) +EI 201 (51), 120 (100), 82 (81); and **13** (0.55 g, 31%), as needles: R_f = 0.22 (ethyl acetate), mp 153–154 °C (from ethyl acetate); δ_H ($CDCl_3$) 7.28 (5H, m), 5.76 (1H, br s), 5.42 (2H, dddq, J = 7, 6, 3, and 1 Hz), 4.88 (1H, d, J = 7 Hz), 4.00 (1H, br s), 2.77 (3H, d, J = 5 Hz), 3.05 (1H, ddd, J = 7, 6, and 3 Hz), 1.59 (3H, dd, J = 3 and 1 Hz); δ_C 174.3, 42.0, 138.9, 128.1, 127.5, 126.6, 126.3, 75.65, 57.05, 26.15, 17.9; m/z (%) +CI 220 (21), 202 (20), 114 (100), 105 (31). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.17; H, 7.84; N, 6.41.

(*E*)-5-Ethyl-5,6-dihydro-6-phenyl-2(1*H*)-pyridinone (1g). The reaction was conducted at 60 °C. Chromatography on silica gel employing as eluant 1:3 ethyl acetate:petroleum ether (40–60 °C) afforded **1e** (0.44 g, 50%) as a colorless oil: bp 148–150 °C/1 mmHg; HRMS, EI calcd for $C_{13}H_{15}NO$ 201.1153, found 201.1122; δ_H ($CDCl_3$) 7.27 (5H, m), 6.48 (1H, dd, J = 10 and 3 Hz), 5.92 (1H, ddd, J = 10, 3, and 2 Hz), 5.54 (1H, br s), 4.36 (1H, dd, J = 9 and 2 Hz), 2.44 (1H, m), 1.40 (2H, m), 0.89 (3H, t, J = 7 Hz); δ_C 165.8, 144.2 , 140.9, 128.8, 128.3, 127.1, 123.85, 60.2, 43.4, 24.2, 10.8; m/z (%) +EI 201 (72), 106 (100), 96 (93), 81 (90).

5,6-Dihydro-4,5-dimethyl-6-phenyl-2(1*H*)-pyridinone (15). The reaction was conducted at 40 °C for 19 h. Chromatography on silica gel employing as eluant 3:1 ethyl acetate:petroleum ether (40–60 °C) afforded **15** (0.76 g, 82%) as needles, mp 130–131 °C (from ethyl acetate); δ_H ($CDCl_3$) 7.28 (5H, m), 6.27 (1H, br s), 4.75 (1H, br s), 2.96 (2H, dd, J = 10 and 7 Hz), 1.71 (3H, s), 1.47 (3H, s); δ_C 169.3, 141.8, 128.6, 127.8, 127.2, 123.3, 122.75, 63.1, 36.8, 18.2, 15.35; m/z (%) +EI 201 (58), 186 (100), 124 (43). Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.33; H, 7.47; N, 6.86.

5,6-Dihydro-4-methyl-6-phenyl-2(1*H*)-pyridinone (17) and 3,6-Dihydro-4-methyl-6-phenyl-2(1*H*)-pyridinone (18). Method 1: condensation in PPE. 3-Methyl-3-butenamide (0.99 g, 10.0 mmol) and benzaldehyde (2.12 g, 20 mmol) were stirred in PPE (5.0 g) at 30 °C for 18 h. The mixture was poured into ice (50 g), stirred, and made alkaline with aqueous sodium hydroxide. The solution was extracted with dichloromethane (3 × 50 mL), the combined extracts were dried and evaporated to give a 1:1 mixture of **17** and **18** as an oil (1.14 g, 61%). Column chromatography on silica, using 1:1 ethyl acetate:petroleum ether (40–60 °C) afforded **18** (0.34 g, 18%) as prisms: mp 133–135 °C [1:1 ethyl acetate: petroleum ether (40–60 °C)]; δ_H ($CDCl_3$) 7.37 (5H, m), 5.83 (1H, s), 5.52 (1H, bd), 4.71 (1H, dd, J = 10 and 6 Hz), 2.47 (2H, m), 1.93 (3H, s); δ_C 167.4, 151.8, 141.3, 129.0, 128.3, 126.4, 119.7, 55.7, 38.5, 23.1. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.60; H, 6.86; N, 7.31.

Evaporation of the mother liquors afforded a sample enriched in **17** (although a pure sample of **17** could not be obtained by recrystallization from ethyl acetate–petroleum ether): δ_H 7.25 (5H, m), 6.45 (1H, bd), 5.45 (1H, m), 5.07 (1H, bd s), 2.92 (2H, m), 1.77 (3H, s); δ_C 169.5, 151.6, 141.9, 129.1, 128.0, 126.5, 120.0, 58.5, 35.6, 22.1.

Method 2: condensation in CF_3SO_3H. When the above reaction was conducted in a solution of CF_3SO_3H in dichloromethane (1.0 mL; 5% by volume), a 5:4 mixture of **17** and **18** was obtained as an oil (1.20 g, 64%).

3,4-Epoxy-5,6-dihydro-4-methyl-6-phenyl-2(1*H*)-pyridinone (20). To a solution of the 1:1 mixture of lactams **17** and **18** (0.25 g in methanol (5.0 mL)) was added aqueous hydrogen peroxide (0.5 mL, 30%). After swirling the mixture, the flask was cooled in an ice-bath and aqueous sodium hydroxide (0.8 mL, 1 M) was added dropwise over 7 min. The mixture was maintained at 0 °C for 2 h and then allowed to stir at 20 °C for 16 h. Water (5 mL) was then added, the mixture was extracted with dichloromethane (3 × 10 mL), and the combined extracts were dried and evaporated to give a pale yellow residue which was recrystallized from 1:1 ethyl acetate:petroleum ether (40–60 °C) to give **20** (0.11 g, 79%) as needles: mp 150–151 °C; δ_H 7.35 (5H, m), 5.95 (1H, bd s), 4.55 (1H, dd, J = 11 and 5 Hz), 3.32 (1H, s), 2.35 (1H, dd, J = 15 and 5 Hz), 2.07 (1H, dd, J = 15 a nd 11 Hz, 1.50 (3H, s); δ_C 169.1, 140.1, 129.2, 128.7, 126.6, 59.2, 57.4, 52.1, 38.6, 20.5. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.72; H, 6.39; N, 6.74.

Reactions in Polyphosphoric Acid. (*E*)-5,6-Dihydro-6-phenyl-2(1*H*)-pyridinone (1a). Polyphosphoric acid (10 g) was weighed into a two-necked flask, and to it were added successively 3-butenamide (0.50 g, 5.89 mmol) and benzaldehyde (1.07 g, 10 mmol). The reaction was maintained at 60 °C for 18 h under an atmosphere of nitrogen. After this time the mixture was cooled, rendered alkaline with aqueous sodium hydroxide (2 M): **CAUTION**, and extracted with chloroform (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel employing as eluant 3:2 ethyl acetate:petroleum ether (40–60 °C), to give **1a** (0.31 g, 30%) as needles, mp 130–132 °C (from ethyl acetate: petroleum ether). Spectral data recorded were as given above in method 1.

5,6-Dihydro-4,5-dimethyl-6-phenyl-2(1*H*)-pyridinone (15). Polyphosphoric acid (10 g) was weighed into a two-necked flask, and to it were added successively (*E*)-3-methyl-3-pentenamide (**14**) (0.52 g, 4.6 mmol) and benzaldehyde (0.98 g, 9.2 mmol). The reaction was maintained at 40 °C for 49 h, under an atmosphere of nitrogen. After this time the reaction mixture was cooled, neutralized with solid sodium carbonate, and extracted with chloroform (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated, and the residue was chromatographed on silica gel employing as eluant 3:1 ethyl acetate: petroleum ether, to give **15** (0.60 g, 65%) as needles, mp 130–131 °C (from ethyl acetate). Spectral data recorded were as given above in method 1.

Acknowledgment. We thank the Science and Engineering Research Council and SmithKline Beecham for a CASE award (to U.G.), and the SERC for a fellowship (to A.F.). Dr. B. F. Taylor is thanked for performing nuclear Overhauser experiments.