Tetrahedron Vol. 49, No. 33, pp. 7179-7192, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Intermolecular Transaminations of Enaminones: A Synthesis of Fused, Polycyclic, N-Aryl Pyridones†

Richard J. Friary,* Vera Seidl, John H. Schwerdt, Tze-Ming Chan, Marvin P. Cohen, Edward R. Conklin, Timothy Duelfer, Donald Hou, Mehdi Nafissi, Robert L. Runkle, Pirouz Tahbaz, and Robert L. Tiberi

Schering-Plough Research Institute
2015 Galloping Hill Road
Kenilworth, N. J. 07033-0539
U. S. A.

and

Andrew T. Mc Phail*

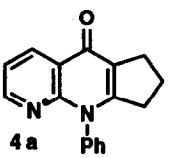
Paul M. Gross Chemical Laboratories
Duke University
Durham, N. C. 27706
U. S. A.

(*Received in USA* 5 *March* 1993)

Abstract *Aryl amines reacted with enaminones like (2-chloro-3-pyridinyl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone, and the transaminated products cyclized to aryl-substituted pyridones like 6,7,8,9-tetrahydro-9-phenyl-5H-cyclopenta[b][1,8]naphthyridin-5-one. The starting enaminones rearranged thermally, also forming pyridones, for example 9-(4-chlorobutyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one.*

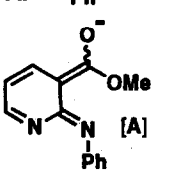
INTRODUCTION

Some years ago, we sought to make fused polycyclic, N-aryl pyridones like the tricyclic, phenyl-substituted pyridone **4a**.[1] Such compounds, we originally hoped, might have had desirable biological activities. We finally discovered that these N-aryl pyridones inhibited the 5-lipoxygenation of arachidonic acid and the release or biosynthesis of leukotrienes, and also exerted anti-allergy, anti-inflammatory, or immunomodulatory activities.[2]



4a

When we began, the synthesis already adopted was the Claisen condensation, requiring 2-(arylamino)-3-pyridinecarboxylate esters to acylate the enolates of cyclic ketones. This method, although it enjoyed some successes, too often furnished mixtures of the starting esters with the final pyridones, giving only meager yields of the latter. In particular, the condensation of cyclopentanone and methyl 2-(phenylamino)-3-pyridinecarboxylate afforded only a 3% yield of pyridone **4a**. In this difficult case—and in easier ones as well—we could neither raise the unsatisfactory yields nor avoid tedious chromatographies. Varying the base, the base-to-ketone ratio, the solvent, the order of additions, and the time and temperature brought scant rewards.

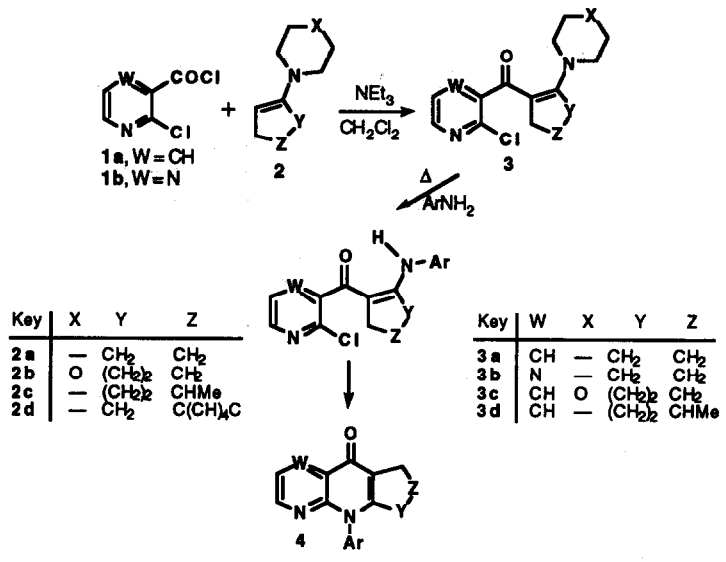


[A]

We reasoned that our trouble sprang from the relative acidities of the abstractable protons in the ketones and esters. The bases used would have removed the arylamino hydrogens from the starting esters if these hydrogens were more acidic than the α-protons of the ketones. Then the resonance stabilized anion **[A]** would have formed and presented a formidable, electron-rich carbonyl group to (any) attacking enolates. Thus, the formation of anion **[A]** would have explained the presence of the starting esters in the product mixtures.

To circumvent our difficulty, we needed to boost the reactivity of the carbonyl carbon of the acylating agent. This suggested the obvious combination of an acid chloride and an enamine in a C-acylation reaction.[3] Intermolecular transaminations of the products (**3**) were then to produce enaminones incorporating arylamines in place of the enamine-derived amines, which would be expelled (Scheme 1).[4] Cyclizations of the transaminated enaminones to the aromatic pyridones **4** would drive the synthesis to completion.

Scheme 1. Pyridones from Intermolecular Transaminations of Enaminones



Now we report that 2-chloro-3-pyridinecarbonyl and 2-chloro-3-pyrazinecarbonyl chlorides (**1a** and **1b**, respectively) acylated the β-carbon atoms of cyclopentanone and cyclohexanone enamines (**2**) derived from pyrrolidine or morpholine. As expected, arylamines transaminated the resulting enaminones **3**, and the transaminated products cyclized to the desired pyridones **4** (Scheme 1, Table 1). In addition, we present the scale and scope of the synthesis, and offer evidence that it proceeds through transaminated enaminones. We also disclose a novel enaminone-to-pyridone rearrangement as well as other enaminone reactions that limit the present synthesis. These other reactions, which were O-acylation and hydrolysis of enaminones **3**, became apparent during efforts to improve the preparation of the biologically active pyridone **4k** by an intermolecular transamination.[5]

RESULTS AND DISCUSSION

Scale

In the first successful enamine C-acylation of this work, we exposed a cold chloroform solution of 1-(1-pyrrolidinyl)-cyclopentene **2a** (0.06 mole) and triethylamine to the acid chloride **1a**. After one hour, work-up and chromatography gave 84% of the crystalline enaminone **3a**. Treatment of **3a** with 1.25 equivalents of neat aniline at 110 °C converted it to pyridone **4a** in a yield of 80%. The two steps yielded more than 20 times as much of pyridone **4a** as the Claisen condensation did.

We also made pyridone **4a** on a scale 100 times greater than the initial one, no development having been necessary to employ the larger quantities of chemicals. Thus, 2.3 kg

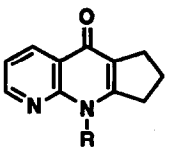
Table 1. Tricyclic, N-Aryl Pyridones **4** from Intermolecular Enaminone Transaminations

No.	Substituents				Yield (%) [a]
	W	Y	Z	Ar	
4a	CH	CH_2	CH_2	Ph	80
4b	CH	CH_2	CH_2	3-MeO-C_6H_4	69
4c	CH	CH_2	CH_2	3-Cl-C_6H_4	49
4d	CH	CH_2	CH_2	4-MeO-C_6H_4	38
4e	CH	CH_2	CH_2	4-Me-C_6H_4	52
4f	CH	CH_2	CH_2	3,4-Cl_2-C_6H_3	56
4g	CH	CH_2	CH_2	3-pyridyl	67
4h	N	CH_2	CH_2	Ph	37
4i	N	CH_2	CH_2	3-O_2N-C_6H_4	32
4j	CH	$(CH_2)_2$	CH_2	Ph	28
4k	CH	$(CH_2)_2$	CH_2	3-Cl-C_6H_4	45
4l	CH	$(CH_2)_2$	CHMe	Ph	28

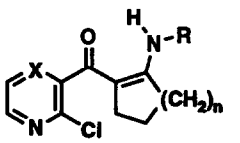
[a] Yields refer to isolated products and are based on amounts of acid chlorides **1a** and **1b**.

of acid chloride **1a** furnished 2.5 kg of enaminone **3a**, which was isolated by crystallization. A 2-kg sample of this enaminone reacted with aniline to give 1.1 kg of the final product **4a**. Pyridone **4k** could also be made by this route on a relatively large scale.

Chart



4n, R = CH_2CO_2Et
4o, R = C_6H_{11}
4p, R = 4-$FC_6H_4CH_2$
4q, R = H_2N



	X	R	n
3e	CH	3-Cl-C_6H_4	2
3f	CH	EtO_2CCH_2	1
3g	CH	C_6H_{11}	1
3h	N	3-O_2N-C_6H_4	1
3i	N	Ph	1

Scope

Enaminone transaminations followed by cyclizations of the products to pyridones **4** were compatible with several structural variations in the starting materials. The heterocycle within the acid chloride was changed from pyridine (**1a**) to pyrazine (**1b**), affording products **4h** and **4i** (Table 1). The size of the carbocyclic ring in the enamine could be varied, and a change from a 5- to a 6-membered ring yielded pyridones **4j**, **4k**, and **4l**. The structure of the product **4l** exemplified another simple variation in which a substituted ketone—namely 4-methylcyclohexanone—was used to form the enamine starting material. Differently substituted anilines could be employed for the transaminations, ultimately forming pyridones **4b–4f**, for examples. Not surprisingly, a pyridylamine as well as aliphatic amines could replace aniline derivatives in the transaminations. These other amines led to pyridones **4g** (Table 1) and **4n–4q** (Chart). The yields of products **4n–4q** were respectively 48, 69, 51, and 40% from enaminone **3a**. Beginning with the pyrrolidine enamine of β-tetralone, we could also prepare the tetracyclic pyridone **4m** via the enaminone **3j** (Scheme 4).

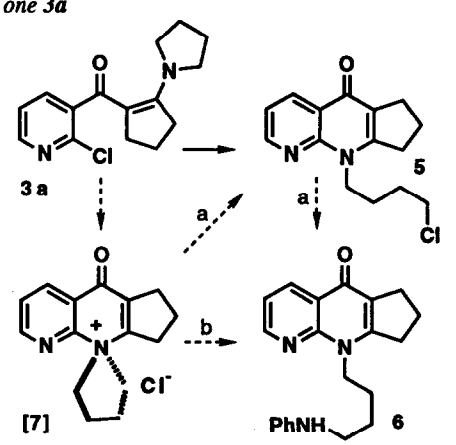
Mechanism

This pyridone synthesis proceeded by way of the expected, transaminated enaminones. It was possible to isolate and characterize five of them, which were intermediates **3e–3i** (Chart). All of them possessed the amino groups corresponding to the amines added to bring about the transaminations; and all lacked the pyrrolidine and morpholine groups of the starting enamines **2**. Intermediates **3e–3g** cyclized to the desired pyridones, respectively **4k**, **4n**, and **4o**.

Limitations

Although our synthesis was effective in nearly all cases tried, it suffered from three fundamental limitations. One of them was a novel thermal rearrangement of pyrrolidine or morpholine-substituted enaminones. This rearrangement changed enaminone **3a** to pyridone **5**, for example (Scheme 2).

Scheme 2. Thermal Rearrangement of Enaminone 3a



Another limitation was the precedented enaminone O-acylation[6] that competes with enamine C-acylation. In the present work, O-acylation of enaminone **[3c]** and 1,3-transfer of the acyl group formed the enol ester **12** (Scheme 3).

The third limitation was an enaminone hydrolysis followed by an unsought cyclization. This sequence of reactions gave fused polycyclic pyranones instead of pyridones. For example, it converted enaminone **3j** to pyranone **15** (Scheme 4).

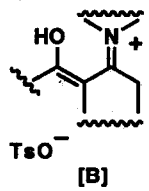
Thermal Rearrangements. Our morpholine and pyrrolidine-bearing enaminones **3a**, **[3c]**, and **3j** were somewhat unstable. For example, enaminone **3a** rearranged slowly (> 18 months (TLC)) at 25 °C and rapidly (1.5 h (^{1}H NMR), 90%) at 150 °C (Scheme 2). The unex-

pected product (**5**) had the structure of an alkylating agent, while another by-product, pyridone **6**, which came from a separate experiment, had the structure of an alkylation product. Chromatography isolated **6** (5% from **3a**) following an otherwise high-yielding (80%) transamination of **3a** to **4a** with aniline.

Rearrangement of enaminone **3a** to **5** presumably takes place via the quaternary ammonium chloride **[7]**. Attack of chloride anion on either activated methylene group of **[7]** would convert this intermediate to pyridone **5** (Scheme 2, path a). Alkylation of aniline by **5** would then explain formation of by-product **6**. Alternatively, ring cleavage of the quaternary ammonium salt **[7]** by aniline might have given **6** (path b).

Evidently the enaminone **[3c]** (Scheme 3) was also subject to thermal rearrangement. Indeed, the expected product (**10**) of such a rearrangement was among the by-products isolated after each of several successful attempts to convert compound **[3c]** to pyridone **4k**. Enaminone **3j** also rearranged to pyridone **14**, despite the presence of aniline to form the desired pyridone **4m** and toluenesulfonic acid to act as a catalyst (Scheme 4).

In one instance, the presence of acid seemed to suppress the enaminone rearrangement in favor of the desired pyridone. Treatment of enaminone **3a** with 3,4-dichloroaniline and one equivalent of anhydrous toluenesulfonic acid raised the yield of pyridone **4f** to 56%. Only 29% of this compound was obtained in the absence of the acid. Toluenesulfonic acid was added to protonate the oxygen atom of enaminone **3a**, and to form the corresponding iminium tosylate **[B]** (right). The iminium ion in **[B]** would have played dual roles if it acted to raise the yield of **4f**. It would have accelerated transamination by increasing the electrophilicity of the enaminone β-carbon atom. Also, the ion would have retarded rearrangement by decreasing the nucleophilicity of the enaminone nitrogen atom.

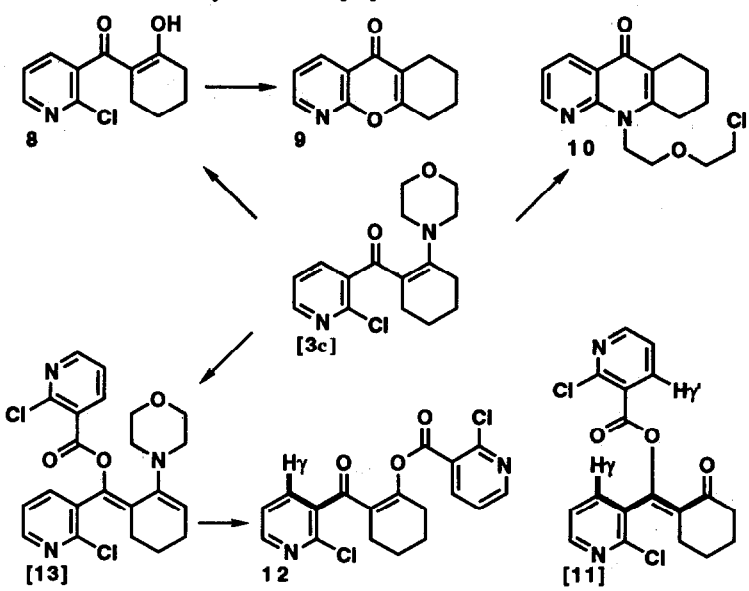


[B]

Enaminone O-Acylation. We soon learned that pyridone **4k** was an interesting member of our biologically active series of compounds.[5] The overall, optimized yield of this final product, however, never exceeded 45%, partly because the yield of its precursor **[3c]** was low. Thus, we sought to isolate and characterize the by-products accompanying the enaminone **[3c]**, hoping to improve our synthesis (Scheme 3). Instead we realized the second limitation of this synthesis, namely the tendency of acid chlorides to acylate the oxygen atoms of enaminones.

Treatment of 2-chloro-3-pyridinecarbonyl chloride **1a** with one molar equivalent of 1-(4-morpholinyl)-cyclohexene gave a mixture of C- and O-acylation products (TLC). It was evident that the mixture contained an enol ester, because it absorbed at 1760 cm^{-1}. Chromatography afforded a pure sample of this ester, isolated in a yield of 11% and ultimately assigned structure **12** (Scheme 3). Using two molar equivalents of acid chloride **1a** in the acylation raised the yield of enol ester **12** to 83%.

Scheme 3. Reactions of Enaminone [3c]

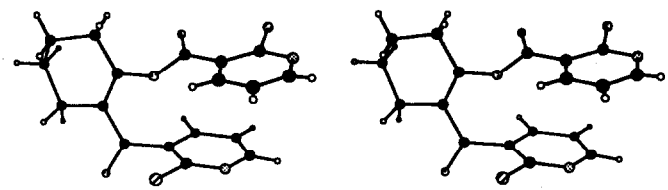


The initial basis for the assignment of structure **12** was a SINEPT experiment.[7] In this experiment, a γ-pyridine proton (δ 7.88 ppm) of enol ester **12** coupled to the ketone carbonyl ^{13}C atom (δ 192 ppm) over a three-bond path (boldface). This finding excluded the isomer **[11]**, because SINEPT experiments detect only three- or two-bond couplings of hydrogen to ^{13}carbon atoms. At least five bonds (boldface) in **[11]** separate the γ-pyridine protons from the carbon atom of the ketone carbonyl. A single-crystal *X*-ray analysis confirmed our assignment of structure **12** (Figure).

The structure of **12** suggested that it was the product of a 1,3 acyl migration. Thus, we postulate that O-acylation of enaminone **[3c]** formed the enol-ester **[13]**, which hydrolysed on work-up to give the enol ester **[11]** (Scheme 3). Acyl transfer within **[11]** would then have produced the isolated by-product **12**, indicating that **12** was the more stable of the two enol ester isomers.

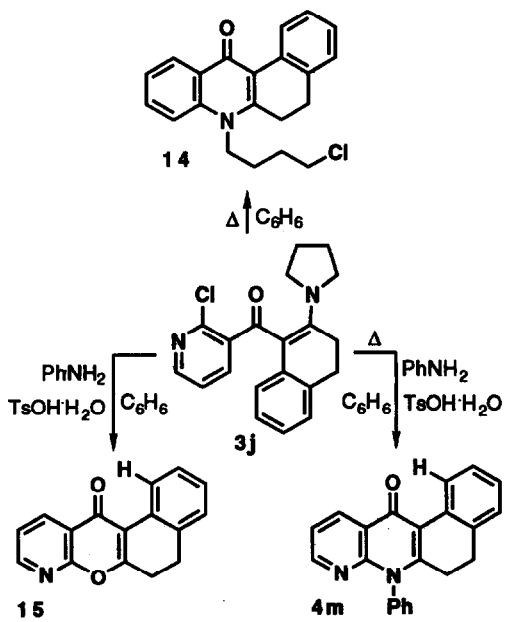
Enaminone Hydrolysis and Cyclization. The third limitation arose from a combination of enaminone hydrolysis and cyclization of the product. These reactions changed certain enaminones to pyranones instead of pyridones, or to mixtures of both. For example, enaminone **3j** furnished the tetracyclic pyranone **15** (31%) in addition to the desired pyridone (**4m**, 16%) (Scheme 4). Both products formed on treatment of **3j** with one equivalent of toluenesulfonic acid in hot benzene containing aniline. Cyclization of the 1,3-diketone (not shown) resulting from hydrolysis of the enaminone group of **3j** would explain formation of pyranone **15**.

Figure. Stereoview of the Sructure and Solid-State Conformation of Enol Ester 12.



In another case, we isolated 9% of such a 1,3-diketone in the form of enol **8**, after chromatography of crude enaminone **[3c]** (Scheme 3). Enol **8**, tentatively identified by ^{1}H NMR spectroscopy, spontaneously cyclized in $CDCl_3$ to pyranone **9**. The chromatography furnished none of **[3c]** itself, suggesting that this enaminone hydrolyzed on silica gel. Pyranone **9** could also be isolated by chromatography of a crude sample of enaminone **[3c]**.

Scheme 4. Competing Pyridone and Pyranone Formations



Optimization

In the first attempt to acylate an enamine during this work, we heated a chloroform solution of acid chloride **1a**, 1-(1-pyrrolidinyl)-cyclohexene, and triethylamine. This produced not the desired enaminone, which would have led to pyridone **4k**, but a tar—perhaps an unsurprising result in light of the thermal rearrangement that the analogous enaminone **[3c]** suffered. Indeed, lowering the acylation temperature was crucial to success. Acylation of the morpholine enamine of cyclohexanone at – 78°, work-up with ice water, and treatment of crude enaminone **[3c]** with 3-chloroaniline in hot benzene containing anhydrous toluenesulfonic acid raised the overall yield of **4k** to 45%.

We examined related starting materials for further yield increases, but with little success. Thus, treatments of pyranone **9** (Scheme 3) with 3-chloroaniline caused no change (TLC), despite high temperatures (≥ 100°), long times (12–18 h) and, in one experiment, the presence of toluenesulfonic acid. This acid was to catalyze the desired conversion of pyranone **9** and 3-chloroaniline to pyridone **4k**.

Making pyridone **4k** from enol ester **12** and 3-chloroaniline was feasible. This route, however, was no higher yielding than that in which **[3c]** and the aniline gave the same product. Thus, treatment of **12** with excess 3-chloroaniline afforded 42% of pyridone **4k** at most.

CONCLUSION

In summary, a variety of amines transaminated enaminones **3a–d** and **3j**, which were made by enamine C-acylations with acid chlorides **1**. The transaminations formed certain intermediate enaminones, for examples **3e–i**, and the intermediates cyclized to fused, polycyclic pyridones **4a–l**. Enaminones **3a**, **[3c]** and **3j** rearranged thermally to the structurally related pyridones **5**, **10**, and **14**. Efforts to increase the yield of pyridone **4k** by the present route were unavailing. However, a high-yielding synthesis of **4k** resulted when the ambident 2-(3-chlorophenylamino)-3-pyridinecarbonyl chloride replaced chloride **1a** in an enamine acylation.[8]

EXPERIMENTAL[9,10]

(2-Chloro-3-pyridinyl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone (3a)

2-Chloro-3-pyridinecarbonyl chloride (**1a**) (16.5 g, 93.7 mmol) in $CHCl_3$ (90 mL, EtOH-free) was added over 20 min to an ice-cooled solution of distilled 1-(1-pyrrolidinyl)-cyclopentene **2a** (13.8 mL, 93.4 mmol) and NEt_3 (13.9 mL, 100 mmol) in $CHCl_3$ (90 mL). When addition was complete, the reaction mixture was allowed to stir 1 h at ice-bath temperature and 20 h at 25 °C. The dark solution was washed with H_2O, 1 M $NaHCO_3$, and H_2O, and the solution was dried, filtered, and concentrated. The solid residue (23.95 g) crystallized from EtOAc to give **3a** (21.05 g in three crops, 81%), mp 102.5-104.0 °C; IR 1600, 1570; UV 269 (3.70), 356 (3.28); ^1H NMR 8.32 (dd, J (6-4) = 1.7, J (6-5) = 5.0, H (6)), 7.66 (dd, J (4-6) = 1.7, J (4-5) = 8, H (4)), 7.21 (dd, J (5-6) = 5.0, J (5-4) = 8, H (5)), 3.54 (br m, 2 -CH_2N), 2.67 (t, J = 7.5, -CH_2C=C-), 2.44 (t, J = 7.5, -CH_2C=C-), 2.20-1.56 (m, -CH_2CH_2- and -CH_2-); MS 278 (5, M^+ for ^{37}Cl), 276 (13, M^+ for ^{35}Cl), 241 (100, [M - Cl]$^+$), 213 (33), 142 (5, $[C_6H_3{}^{37}ClNO]^+$, 140 (12, $[C_6H_3{}^{35}ClNO]^+$, 114 (4, $[C_5H_3{}^{37}Cl]^+$), 112 (10, $[C_5H_3{}^{35}Cl]^+$.

On a larger scale, 2-chloro-3-pyridinecarbonyl chloride (2.26 kg) acylated **2a** to give 2.53 kg (69%) of **3a**.

(3-Chloro-2-pyrazinyl)[2-(1-pyrrolidinyl)-1-cyclopenten-1-yl]methanone (3b)

2-Chloro-3-pyrazinecarbonyl chloride (**1b**) (5.00g, 28.4 mmol) in CH_2Cl_2 (25 mL) was added over 45 min to a dry ice-cooled solution of NEt_3 (3.96 mL, 28.4 mmol) and distilled **2a** (3.89 g, 28.4 mmol) in CH_2Cl_2 (25 mL), under N_2. The internal temperature rose to - 40 °C and the solution became dark. It was allowed to stir 1 h at -30 °C after completion of the addition. The solution was then washed with H_2O, and the dried, filtered solution was concentrated. Chromatography (silica gel, $CHCl_3$-EtOAc (3:1)) followed by crystallization from Et_2O then gave **3b** (4.95 g, 63%), mp 109-112 °C; IR 1610, 1500; ^1H NMR 8.48 (d, J (6-5) = 3, H (6)), 8.32 (d, J (5-6) = 3, H (5)), 3.58 (m, 2 -CH_2N), 2.68 (t, J = 7.5, -CH_2C=C-), 2.43 (t, J = 7.5, -CH_2C=C-), 2.10-1.63 (br m, -CH_2CH_2- and -CH_2-); MS 279 (11, M^+ for ^{37}Cl), 277 (32, M^+ for ^{35}Cl), 242 (100, [M - Cl]$^+$), 164 (71, $[C_{10}H_{14}NO]^+$), 136 (50, $[C_9H_{14}N]^+$).

(2-Chloro-3-pyridinyl)[2-(4-morpholinyl)-1-cyclohexen-1-yl]methanone (3c)

A solution of 2-chloro-3-pyridinecarbonyl chloride (**1a**) (114.6 g, 0.651 mol) in CH_2Cl_2 (600 mL) was added over 30 min to a mechanically stirred, cooled (dry ice-acetone) solution of 1-(4-morpholinyl)-cyclohexene (**2b**) (101.0 g, 0.604 mol), NEt_3 (83 mL, 0.595 mol), and CH_2Cl_2 (600 mL) in an atmosphere of Ar. The reaction mixture was stirred in the dry ice-acetone bath for 1.25 h, and was then stirred in a bath of ice and acetone for an additional 1 h. The resulting solution was washed with ice water, 1M $NaHCO_3$, and ice water. The

solution was dried, filtered, and concentrated; the temperature during concentration was kept at ~15 °C. Crude, oily enaminone **3c** (225 g; IR 1760 (CO of impurity), 1700 (CO of impurity), 1640 (enaminone CO), 1580) was not purified or further characterized, but was used directly in the next step.

Silica gel chromatography of crude **3c** hydrolyzed it to (2-chloro-3-pyridinyl)(2-hydroxy-1-cyclohexene-1-yl)methanone (**8**), which cyclized upon standing to 6,7,8,9-tetrahydro-5H-1-benzopyrano[2,3-*b*]pyridin-5-one (**9**). The chromatography also separated 2-[(2-chloro-3-pyridinyl)carbonyl]-1-cyclohexen-1-yl 2-chloro-3-pyridinecarboxylate (**12**).

(2-Chloro-3-pyridinyl)[5-methyl-2-(1-pyrrolidinyl)-1-cyclohexen-1-yl]-methanone (3d)

2-Chloro-3-pyridinecarbonyl chloride (**1a**) (15.9 g, 90 mmol) in CH_2Cl_2 (70 mL) was added over 45 min to a dry-ice cooled solution of 4-methyl-1-(1-pyrrolidinyl)-cyclohexene (**2c**) (14.9 g, 90 mmol) and NEt_3 in CH_2Cl_2 (70 mL) under N_2. The internal temperature was - 40 °C when addition was complete. The reaction mixture was stirred 1 h at - 30 °C, and was then washed with H_2O. The dried, filtered organic solution was concentrated at ~ 5 °C to give **3d** (27.5 g). Crude, oily **3d** was not characterized or purified, but was used directly in the next step.

(2-Chloro-3-pyridinyl)[2-[(3-chlorophenyl)amino]-1-cyclohexen-1-yl]methanone (3e)

A solution of crude enaminone **3c** (prepared from 28.4 mmol of 2-chloro-3-pyridinecarbonyl chloride (**1a**) as the limiting reagent) in 3-Cl-$C_6H_4NH_2$ (5 mL, 47.3 mmol, 1.7 eq) under N_2 was heated 24 h in a 65° oil bath. The cooled mixture was diluted with $CHCl_3$, and the resulting solution was washed with 1N HCl and with H_2O. The dried organic solution was filtered and concentrated to give crude **3e** (8.45 g) as a light brown oil. Chromatography over silica gel (60-200 mesh) and elution with $CHCl_3$ then gave **3e** (4.19 g, 42% from the acid chloride, pure according to TLC) as a viscous yellow oil; IR 1640 (CO), 1585; ^{1}H NMR 13.3 (br s, 1H, ex., N*H*), 8.36 (dd, *H* (6)), 7.56 (dd, *H* (4)) and 7.44-6.94 (*Ar*, *H* (5)) (total of 5H), 2.48 (br m, -C*H*$_2$-), 2.12 (br m, -C*H*$_2$-), 1.63 (br m, 2 -C*H*$_2$-); MS 350 (7, *M*$^+$ for $^{37}Cl_2$), 349 (10), 348 (41, *M*$^+$ for $^{37}Cl^{35}Cl$), 347 (28), 346 (64, *M*$^+$ for $^{35}Cl_2$), 345 (24), 314 (22), 313 (92, $[C_{18}H_{16}{}^{37}ClN_2O]^+$), 312 (76, $[C_{18}H_{15}{}^{37}ClN_2O]^+$), 311 (100, $[C_{18}H_{16}{}^{35}ClN_2O]^+$, 310 (14, $[C_{18}H_{15}{}^{35}ClN_2O]^+$), 309 (28), 142 (10, $[C_6H_3{}^{37}ClNO]^+$, 140 (26, $[C_6H_3{}^{35}ClNO]^+$, 114 (6, $[C_5H_3{}^{37}ClN]^+$), 112 (17, $[C_5H_3{}^{35}ClN]^+$).

Enaminone **3e** was not further purified or characterized, but was used directly in the next step.

(2-Chloro-3-pyridinyl)[2-[(2-ethoxy-2-oxoethyl)amino]-1-cyclopenten-1-yl]methanone (3f)

$EtO_2CCH_2NH_2$·HCl (3.08 g, 22 mmol), enaminone **3a** (6.10 g, 22 mmol), NEt_3 (2.26 g, 22 mmol), and dry *t*-BuOH (170 mL) were refluxed under N_2 for 34 h. The solvent was evaporated and the residue shaken with $CHCl_3$ and H_2O. Combined extracts were separated, washed with H_2O and brine, dried, filtered, and concentrated. The resulting brown oil crystallized from 2-Pr_2O and was recrystallized from 2-PrOH providing **3f** (2.75 g, 41%) as a tan solid, mp 114.5-117.5 °C; IR (KBr) 3260 (NH), 1750 (ester), 1625 (C=O); ^{1}H NMR (79.5 MHz) 10.01 (br t, N*H*), 8.37 (dd, *J* (6'-5') = 5, *J* (6'-4') = 2, *H* (6')), 7.59 (dd, J (4'-5') = 7, *J* (4'-6') = 2, *H* (4')), 7.25 (dd, *J* (5'-4') =7, *J* (5'-6') = 5, *H* (5')), 4.25 and 4.08 (overlapping q and d, respectively, *J* (-OC*H*$_2$-C*H*$_3$) = 7, *J* (C*H*$_2$-N*H*) = 7, total of 4 H, -OC*H*$_2$- and NC*H*$_2$CO-)s, 2.67 and 2.46 (overlapping t, *J* (3-4) = 7, *J* (5-4) = 7, total of 4H, *H* (3) and *H* (5)), 1.92 (m, *J* (4-3) = 7, *J* (4-5) = 7, 2H, *H* (4)), 1.39 (t, *J* (C*H*$_3$-C*H*$_2$-) = 7, C*H*$_3$); ^{13}C NMR (200 MHz) 186 (*C*=O), 170 (O-*C*=O), 169 (*C* (2')*), 149 (*C* (6')), 146 (*C* (1')), 138 (*C* (3')), 136 (*C* (4')), 122 (*C* (5')), 106 (*C* (2)), 62 (*C*H$_2$)), 46 (NCH$_2$CO), 32 (*C* (3)**), 30 (*C* (5)**), 20 (*C* (4)), 14 (*C*H$_3$); MS 310 (8, *M*$^+$ for ^{37}Cl), 308 (24, *M*$^+$ for ^{35}Cl), 274 (14), 273 (80, [*M* - Cl]$^+$), 272 (7, [*M* - HCl]$^+$), 199 (100, $[C_{12}H_{11}N_2]^+$), 142 (4, $[C_6H_3{}^{37}ClNO]^+$, 140 (11, $[C_6H_3{}^{35}ClNO]^+$, 114 (3, $[C_5H_3{}^{37}ClN]^+$), 112 (8, $[C_5H_3{}^{35}ClN]^+$).

(2-Chloro-3-pyridinyl)[2-(cyclohexylamino)-1-cyclopenten-1-yl]methanone (3g)

A mixture of **3a** (13.8 g, 50.0 mmol) and cyclohexyl amine (4.96 g, 50.0 mmol) was heated 24 h at 125 °C, cooled, and chromatographed over silica gel. Elution (MeOH-$CHCl_3$, 2.5 : 97.5) and crystallization (EtOAc) gave **3g** (1.90 g, 12%), mp 142-143.5 °C; IR 1610; ^{1}H NMR 10.4-9.97 (br d, *J* (N*H*-C*H*) = 6, N*H*), 8.38 (dd, *J* (6-5) = 5, *J* (6-4) = 2, *H* (6)), 7.61 (dd, *J* (4-5) = 7, *J* (4-6) = 2, *H* (4)), 7.25 (dd, *J* (4-5) = 7, *J* (6-5) =

5, *H* (5)), 3.57-3.00 (br m, 1H, C*H*), 2.67 (t, J = 7, 2H, -CH_2C=C-), 2.37 (t, J = 7, 2H, -CH_2C=C-), 2.17-0.83 (br m, 12H, -CH_2- and -(CH_2)$_5$-); MS 306 (25, M^+ for ^{37}Cl), 304 (73, M^+ for ^{35}Cl), 269 (100, [M - Cl]$^+$), 225 (15), 224 (7), 223 (36), 222 (15), 221 (59), 187 (53, [$C_{11}H_{11}N_2O$]$^+$), 142 (14, [$C_6H_3{}^{37}ClNO$]$^+$, 140 (41, [$C_6H_3{}^{35}ClNO$]$^+$, 114 (5, [$C_5H_3{}^{37}Cl$]$^+$), and 112 (13, [$C_5H_3{}^{35}ClN$]$^+$).

(3-Chloro-2-pyrazinyl)[2-[(3-nitrophenyl)amino]-1-cyclopenten-1-yl]methanone (3h)

Chromatography (silica gel, $CHCl_3$) of the residue from crystallization of **4i** (*read on*) separated **3h** (0.82 g, 15% from **3b**), mp 129-130 °C after crystallization from $CHCl_3$-pet. eth.; IR 3480, 3380, 1620, 1520, 1360; ^{1}H NMR 12.1 (br s, ex., N*H*), 8.58 (d, *J* (6-5) = 2.1, *H* (6)), 8.44 (d, *J* (5-6) = 2.1, *H* (5)), 8.17-7.19 (br m, 2H, *Ar*), 7.6-7.47 (br m, 2H, *Ar*), 3.01 (t, *J* = 7.5, -CH_2C=C-), 2.57 (t, *J* = 7.5, -CH_2C=C-), 2.04 (br q, -CH_2-); MS 346 (11, M^+ for ^{37}Cl), 344 (31, M^+ for ^{35}Cl), 309 (49, [M - Cl]$^+$), 308 (100, [M - HCl]$^+$), 307 (66), 231 (12, [$C_{12}H_{11}N_2O_3$]$^+$), 203 (12 [$C_{11}H_{11}N_2O_2$]$^+$), 202 (39), 186 (11), 185 (41), 184 (51), 143 (11, [$C_5H_2{}^{37}ClN_2O$]$^+$, 141 (35, [$C_5H_2{}^{35}ClN_2O$]$^+$, 115 (26, [$C_4H_2{}^{37}ClN_2$]$^+$), 113 (39, [$C_4H_2{}^{35}ClN_2$]$^+$).

(3-Chloro-2-pyrazinyl)[2-(phenylamino)-1-cyclopenten-1-yl]methanone (3i)

In addition to **4h**, chromatography (*read on*) also separated **3i** (2.38 g, 53% from **3b**), mp 100-101 °C after crystallization from $CHCl_3$-pet. eth; IR 3020, 2950, 2850, 1610, 1540; ^{1}H NMR 8.52 (d, *J* (6 - 5) = 2, *H* (6)), 8.29 (d, *J* (5-6) = 2, *H* (5)), 7.78-7.00 (m, 5H, *Ar*), 2.88 (t, *J* = 7.5, -CH_2C=C-), 2.51 (t, *J* = 7.5, -CH_2C=C-), 1.91 (m, -CH_2-); MS 301 (21, M^+ for ^{37}Cl), 299 (62, M^+ for ^{35}Cl), 265 (17), 264 (100, [M - Cl]$^+$), 263 (95, [M - HCl]$^+$), 262 (88), 187 (11), 186 (78, [$C_{12}H_{12}NO$]$^+$), 184 (23), 158 (20, [$C_{11}H_{12}N$]$^+$), 157 (40), 156 (19), 143 (8, [$C_5H_2{}^{37}ClN_2O$]$^+$, 141 (4, [$C_5H_2{}^{35}ClN_2O$]$^+$, 115 (6, [$C_4H_2{}^{37}ClN_2$]$^+$), 113 (8, [$C_4H_2{}^{35}ClN_2$]$^+$).

(2-Chloro-3-pyridinyl)[3,4-dihydro-2-(1-pyrrolidinyl)-1-naphthalenyl]methanone (3j)

2-Chloro-3-pyridinecarbonyl chloride (17.6 g, 100 mmol) in CH_2Cl_2 (120 mL) was added over 80 min to an ice-cooled solution of 1-(3,4-dihydro-2-naphthyl)-pyrrolidine (**2d**) (19.9 g, 100 mmol), NEt_3 (14.0 mL,100 mmol) and CH_2Cl_2 (100 mL). The internal temperature of the reaction mixture was kept between 0 and 4 °C during addition and for 2 h thereafter. Solvent was evaporated from the washed (H_2O), dried, and filtered solution that resulted; the residual oil crystallized from Et_2O to give **3j** (21.2 g, 63%, pure by TLC). Two crystallizations from EtOAc gave an analytical sample, mp 168-172 °C; IR (KBr) 1590, 1570; ^{1}H NMR (79.5 MHz) 8.23 (dd, *J* (6-4) = 2, *J* (6-5) = 5, *H* (6)), 7.27 (dd, *J* (4-6) = 2, *J* (4-5) = 7, *H* (4)), 7.19-6.39 (complex m, 5H, *Ar* and *H* (5)), 3.61 (br m, -CH_2NCH_2-), 2.80 (s, -CH_2CH_2-), 2.06 (br m, -(CH_2)$_2$CH_2N-); MS 340 (22, M^+ for ^{37}Cl), 338 (66, M^+ for ^{35}Cl), 323 (36, [M - OH]$^+$), 321 (100, [M - OH]$^+$), 303 (15, [M - Cl]$^+$), 198 (59, [M - C_6H_3ClNO]$^+$), 142 (3, [$C_6H_3{}^{37}ClNO$]$^+$, 140 (7, [$C_6H_3{}^{35}ClNO$]$^+$, 114 (3, [$C_5H_3{}^{37}ClN$]$^+$), 112 (7, [$C_5H_3{}^{35}ClN$]$^+$).

Pyridones 4

Method A. In the absence of solvent, heating enaminone **3a** under N_2 with 1.25 eq of the corresponding amines gave **4a-4c**, **4f-4g**, and **4p**. A larger excess of hydrazine hydrate converted **3a** to **4q**. The specific amines as well as reaction times and temperatures used to make individual pyridones are stated separately. Cooled reaction mixtures were partitioned between $CHCl_3$ and H_2O, and organic extracts were washed with dilute aqueous $NaHCO_3$ (or Na_2CO_3) and with H_2O. Dried extracts were filtered and concentrated; crystallization, or chro-

Table 2. Microanalytical Data for Enaminones **3a-3b**, and **3f-3j**

		Calcd.				Found			
No.	Formula	C	H	Cl	N	C	H	Cl	N
3a	$C_{15}H_{17}ClN_2O$	65.09	6.19	12.81	10.12	65.04	6.03	12.85	10.06
3b	$C_{14}H_{16}ClN_3O$	60.54	5.81	12.76	15.13	60.48	5.83	12.82	14.92
3f	$C_{15}H_{17}ClN_2O_3$	58.34	5.55	11.48	9.07	58.37	5.69	11.32	9.06
3g	$C_{17}H_{21}ClN_2O$	66.98	6.94	11.63	9.19	67.16	6.97	11.58	9.32
3h	$C_{16}H_{13}ClN_4O_3$	55.74	3.80	10.28	16.25	55.75	3.48	10.63	16.34
3i	$C_{16}H_{14}ClN_3O$	64.10	4.70	11.83	14.02	63.91	4.75	12.02	13.82
3j	$C_{20}H_{19}ClN_2O$	70.89	5.64	10.46	8.27	70.48	5.73	10.51	8.06

matography followed by crystallization as noted, purified the products. Unless otherwise specified, the solvent for crystallization was MeCN.

Method B: from Enaminones 3a–3c. Water was azeotropically distilled from a suspension of *p*-TsOH·H_2O in C_6H_6, and the resulting solution was cooled. An equimolar amount of the enaminone and a 10-25% molar excess of the aniline (where appropriate) were added, and the resulting mixture was refluxed under a Dean-Stark trap in an atmosphere of N_2. The cooled mixture was concentrated, and the residue was diluted with $CHCl_3$ (or CH_2Cl_2) and washed with H_2O, 1 M $NaHCO_3$ (or Na_2CO_3), and with H_2O. (Washing with aqueous base removed the *p*-TsOH salts of the anilines, which otherwise crystallized from the reaction mixtures.) The dried organic layer was filtered and concentrated; crystallization, or chromatography followed by crystallization as noted below, then gave pyridones **4e**, **4h**, and **4m**. Unless otherwise specified, the solvent for crystallization was again MeCN. Specific amines, solvent volumes, and reaction times are stated separately.

Infrared and ^1H NMR Spectrometry. The common carbonyl groups of pyridones **4** absorbed at 1610-1640 cm^{-1} irrespective of medium (CH_2Cl_2 solution or KBr disc). In $CDCl_3$ solution, the γ-proton resonances of pyridine-fused pyridones **4** were deshielded from that of pyridine by $\Delta\delta = +1.13 \pm 0.04$ for 35 examples. These deshieldings, due to carbonyl anisotropy, established that the desired cyclizations had occurred.

6,7,8,9-Tetrahydro-9-phenyl-5H-cyclopenta[b][1,8]naphthyridin-5-one (4a)

Heating enaminone **3a** (58.5 mmol) and aniline (73 mmol) for 51 h at 110 °C and 24 h at 125 °C, followed by working-up and crystallizing gave **4a**, mp 235-237 °C; UV 250 (4.48), 336 (4.11) ; ^1H NMR (79.5 MHz) 8.76 (dd, *J* (3-4) = 7, *J* (2-4) = 2, *H* (4)), 8.54 (dd, *J* (2-3) = 5, *J* (2-4) = 2, *H* (2)), 7.74-7.43 (m, 3H, *Ar*), 7.43-7.12 (m, 3H, *Ar* and *H* (3)), 3.00 (t, *J* (6-7) = 7, 2 *H* (6)), 2.68 (t, *J* (7-8) = 7, 2 *H* (8)), 2.08 (m, *J* (6-7) = *J* (7-8) = 7, 2 *H* (7)); ^{13}C NMR (100 MHz, Me_2SO-d_6) 174 (*C* (5)), 156 (*C* (9a)), 151 (*C* (2) and *C* (8a)), 139 (*C* (1')), 135 (*C* (4)), 130 (*Ar*),129 (*Ar*), 128 (*Ar*), 121 (*C* (5a)), 120 (*C* (4a)), 119 (*C* (3)), 34 (*C* (6)*), 28 (*C* (8)*), 21 (*C* (7)); MS 262 (98, M^+), 261 (100, $[M-1]^+$).

On a larger scale, enaminone **3a** (2.00 kg) and aniline yielded 1.16 kg (63%) of **4a** after two crystallizations.

6,7,8,9-Tetrahydro-9-(3-methoxyphenyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one (4b)

Heating **3a** (18.1 mmol) and 3-$MeOC_6H_4NH_2$ (22.6 mmol) for 48 h at 130 °C, followed by working-up and crystallizing gave **4b**, mp 259.5-261.0 °C; ^1H NMR (79.5 MHz) 3.85 (s, -OCH_3); MS 292 (96, M^+), 291 (100, $[M-1]^+$).

9-(3-Chlorophenyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one (4c)

Heating **3a** (18.1 mmol) and 3-$ClC_6H_4NH_2$ (22.6 mmol) for 66 h at 130°, followed by working-up and crystallizing gave **4c**, mp 261-264 °C; MS 296 (97, M^+), 295 (100, $[M-1]^+$).

6,7,8,9-Tetrahydro-9-(4-methoxyphenyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one (4d)

Enaminone **3a** (50 mmol), 4-$MeOC_6H_4NH_2$ (55 mmol), anhydrous *p*-TsOH (50 mmol), and C_6H_6 (265 mL) were refluxed 28 h. Work-up and crystallization gave **4d**, mp 212-215 °C;^1H NMR (79.5 MHz) 3.90 (s, -OCH_3); MS 292 (99, M^+), 291 (100, $[M-1]^+$).

6,7,8,9-Tetrahydro-9-(4-methylphenyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one (4e)

Enaminone **3a** (75 mmol), 4-$MeC_6H_4NH_2$ (82.5 mmol), anhydrous *p*-TsOH (75 mmol), and C_6H_6 (380 mL) were refluxed 29h. Work-up and crystallization gave **4e**, mp 242-242.5 °C; ^1H NMR (79.5 MHz) 2.49 (s, -CH_3); MS 276 (99, M^+), 275 (100, $[M-1]^+$).

9-(3,4-Dichlorophenyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one (4f)

Heating **3a** (18.0 mmol) and 3,4-$Cl_2C_6H_3NH_2$ (22.6 mmol) for 24 h at 135 °C, followed by working-up and crystallizing, gave **4f**, mp 294-296 °C; MS 334 (9, M^+ for $^{37}Cl_2$), 332 (56, M^+ for $^{37}Cl^{35}Cl$), 330 (87, M^+ for $^{35}Cl_2$), 329 (100, $[M-1]^+$).

6,7,8,9-Tetrahydro-9-(3-pyridinyl)-5H-cyclopenta[b][1,8]naphthyridin-5-one (4g)

Heating **3a** (18.1 mmol) and 3-H_2N-C_5H_4N (22.6 mmol) for 110 h at 130 °C, followed by working-up, chromatographing (silica gel, $CHCl_3$-MeOH-conc. aq. NH_3 (99 : 0.9 : 0.1 by vol.), and crystallizing from EtOAc gave **4g**, mp 241.0-243.5 °C; ^{1}H NMR 8.8-8.35 (complex m, *H* (2), *H* (4), *H* (2'), and *H* (6')), 7.8-7.1 (complex m, *H* (3), *H* (4') and *H* (5')); MS 263 (99, M^+), 262 (100, $[M - 1]^+$).

5,6,7,8-Tetrahydro-5-phenyl-9H-cyclopenta[5,6]pyrido[2,3-b]pyrazin-9-one (4h)

Enaminone **3b** (15 mmol), $PhNH_2$ (18.7 mmol), anhydrous *p*-TsOH (15 mmol), and C_6H_6 (60 mL) were refluxed 23 h. Work-up, chromatography under N_2 pressure (silica gel, $CHCl_3$), and crystallization from $CHCl_3$ -pet. eth. then gave **4h**, mp — (d. from 300 °C) ;^{1}H NMR 8.74 (d, *J* (2-3) = 3, *H* (2)), 8.48 (d, *J* (3-2) = 3, *H* (3)), 7.63-7.52 (m, 2H, *Ar*), 7.35-7.22 (m, 3H, *Ar*), 3.04 (t, *J* (8-7) = 7, 2 *H* (8)), 2.73 (t, *J* (6-7) = 7, 2 *H* (6)), 1.91-1.24 (m, *J* (7-6) = *J* (7-8) = 7, 2 *H* (7)); MS 297 (100, M^+).

5,6,7,8-Tetrahydro-5-(3-nitrophenyl)-9H-cyclopenta[5,6]pyrido[2,3-b]pyrazin-9-one (4i)

Enaminone **3b** (15 mmol), 3-$O_2NC_6H_4NH_2$ (18.7 mmol), anhydrous *p*-TsOH (15 mmol), and C_6H_6 (60 mL) were refluxed 22 h. Work-up and crystallization from $CHCl_3$-pet. eth. gave **4i**, mp — (d. from 300 °C); IR (mineral oil) 1525 and 1340 (-NO_2); MS 297 (75, M^+), 296 (100, $[M - 1]^+$).

6,8,9,10-Tetrahydro-10-phenyl-benzo[b][1,8]naphthyridin-5(7H)-one (4j)

Enaminone **3c** (100 mmol), $PhNH_2$ (125 mmol), anhydrous *p*-TsOH (100 mmol), and C_6H_6 (150 mL) were refluxed 36 h. Work-up and crystallization gave **4j**, mp 256.5-260.0 °C; ^{1}H NMR 8.40 (dd, *J* (2-3) = 4, *J* (2-4) = 1, *H* (2)), 8.28 (dd, *J* (2-4) = 1, *J* (3-4) = 2.2, *H* (4)), 7.7-7.4 (m, 3H, *Ar*), 7.35-7.1 (m, 3H, *Ar* plus *H* (3)), 2.75 (br m, -CH_2-), 2.55 (br m, -CH_2-), 1.8-1.55 (br m, -$(CH_2)_2$-); MS 276 (100, M^+).

10-(3-Chlorophenyl)-6,8,9,10-tetrahydrobenzo[b][1,8]naphthyridin-5(7H)-one (4k)

From Enaminone 3c. 3-Chloroaniline (68.8 mL, 0.650 mol; Aldrich, as supplied) was added to a solution of anhydrous *p*-TsOH (prepared by azeotropic distillation of water from 114 g (0.599 mol) of the monohydrate) in C_6H_6 (700 mL), giving a precipitate. To the resulting suspension, a solution of crude enaminone **3c** (225 g) in C_6H_6 (400 mL) was added. The mixture was then refluxed overnight under a Dean-Stark trap in an atmosphere of N_2. Solvent was distilled at atmospheric pressure, and a solution of the residue in $CHCl_3$ (1 L) was washed with 1-L portions of H_2O, 2N HCl, H_2O, 1M $NaHCO_3$, and H_2O. The organic solution was dried, filtered, and concentrated, and the oily residue was dissolved in Et_2O (700 mL) for crystallization. The collected, washed (700mL of Et_2O) solid was then recrystallized from MeCN (1.2 L) with the aid of a Soxhlet extractor. The hot suspension was cooled, and the solid was collected, washed with MeCN (80 mL), and dried to give analytically pure **4k** (84.6 g, 45.4% from the acid chloride **1a**) in two crops of 74.8 and 9.8 g), mp 199-201 °C, identified by comparison of mp, and ^{1}H NMR and mass spectra with those of an authentic sample; ^{1}H NMR (79.5 MHz) 8.68 (dd, *J* (2-4) = 2, *J* (3-4) = 8, *H* (4)), 8.46 (dd, *J* (2-4) = 2, *J* (3-3) = 5, *H* (2)), 7.55-7.35 (m, 2H, *Ar*), 7.30-7.02 (m, 3H, *Ar*), 2.85-2.51 (br m, $W_{h/2}$ = 12 Hz, 2*H* (6)), 2.42-2.04 (br m, $W_{h/2}$ = 12, 2*H* (9)), 1.89-1.53 (br m, $W_{h/2}$ = 9, 2*H* (7) and 2 *H* (8)); ^{13}C NMR (400 MHz) 177 (br m (collapsed to a t on irradiation of *H* (4), *C* (5)), 152 (*C* (2)), 151 (*C* (10a)*), 149 (*C* (9a)*), 140 (*C* (1')), 135.3 (*C* (4)), 135.1 (*C* (3')), 131 (*C* (2')=), 130 (*C* (4')=), 129 (*C* (5')=), 128 (*C* (6')=), 120 (*C* (4a)†), 119 (*C* (3)), 118 (*C* (5a)†), 30 (*C* (6)††), 22 (*C* (7) and *C* (8)), 21 (*C* (9)††); MS 312 (36, M^+ for ^{37}Cl), 310 (100, M^+ for ^{35}Cl).

From Enaminone 3e. *p*-TsOH·H_2O (56 mg, 0.294 mmol) and enaminone **3e** (530 mg, 1.53 mmol) in toluene (25 mL) were refluxed 9 h, and solvent was evaporated from the cooled reaction mixture. A solution of the residue in $CHCl_3$ was washed (1 M $NaHCO_3$, H_2O), dried, filtered, and concentrated. The solid residue (450 mg) was crystallized (MeCN) to give **4k** (244 mg, 51%), mp 199.5- 202.5 °C, identified by side-by-side and co-spotted TLC with an authentic sample, and by an undepressed mmp with an authentic sample.

From Enol Ester (12). 3-Chloroaniline (663 mg, 5.20 mmol; Aldrich, as supplied) was added to a solution of anhydrous *p*-TsOH [prepared by azeotropic distillation of water from 1.17 g (6.14 mmol) of the monohydrate] in toluene (20 mL), giving a precipitate. To this was added enol ester **12** (1.91 g, 5.07 mmol) in toluene (10 mL), after which the reaction mixture was refluxed for 23 h. CH_2Cl_2 was added and the organic

layer was washed successively with saturated $NaHCO_3$ and saturated salt solutions, and was dried and concencentrated. Gradient chromatography over silica gel under N_2 pressure with an eluent of 50-75% EtOAc in hexanes afforded **4k** (431 mg, 27%) and **9** (538 mg, 53%).

A series of experiments was carried out using acidic (*p*-TsOH) or basic (NEt_3, K_2CO_3 or *n*-BuLi) conditions. We varied the ratio of 3-chloroaniline to substrate from one to three equivalents, and used toluene, CH_3CN, THF, or DMF as a solvent. The reaction temperatures ranged from 0 °C to reflux. In general, the reactions were monitored by a combination of TLC and capillary GC (Supelco SPB-5 column, 30 meters x 0.25 mm d_f; flow rate = 2 mL per minute, helium; split ratio 50:1; injector and detector temperature = 250 °C; method: isothermal, 250 °C, 15 minutes. Under these conditions the retention times were the following: pyranone **9**, 2.47 min; enol ester **12**,12.06 min; pyridone **4k**, 13.60 min; and rearranged pyridone **10**, 11.72 min. The maximum amount of **4k** observed was 42%, with pyranone **9** as the major by-product (in some reactions only **9** was observed).

From Enamine [13]. In several reactions intermediate enamine **[13]**, prepared by treating 1-(4-morpholinyl)cyclohexene with 2 equivalents of 2-chloro-3-pyridinecarbonyl chloride (CH_2Cl_2, RT, 2-4 days), but not isolated, was used as formed. It was treated with 3-chloroaniline to yield pyridone **4k** (24-36%); pyranone **9** and the pyridone **10** were also observed.

6,8,9,10-Tetrahydro-7-methyl-10-phenyl-benzo[b][1,8]naphthyridin-5(10H)-one (4l)

Enaminone **3d** (30 mmol), $PhNH_2$ (38 mmol), anhydrous *p*-TsOH (30 mmol), and C_6H_6 (180 mL) were refluxed 25 h. Work-up and crystallization from $CHCl_3$-Me_2CO gave **4l**, mp 221-223 °C; ^1H NMR 1.09 (d, J = 7, -CH_3); MS 290 (83, M^+), 275 (100).

5,6-Dihydro-7-phenyl-naphtho[2,1-b][1,8]naphthyridin-12(7H)-one (4m)

Enaminone **3j** (10 mmol), $PhNH_2$ (12.5 mmol), anhydrous *p*-TsOH (10 mmol), and C_6H_6 (55 mL) were refluxed 24 h. Work-up, chromatography (silica gel, $CHCl_3$-EtOH (99.6 : 0.4 by vol.)), and crystallization from dioxane gave **4m** (7%), mp 265-267 °C; ^1H NMR (79.5 MHz) 8.93 (dd, J (1-2) = 7, J (1-3) = 2, H (1)), 3.06-2.31 (m, 2 H (5) and 2 H (6)); MS 324 (100, M^+).

Ethyl 6,7,8,9-Tetrahydro-5-oxo-5H-cyclopenta[b][1,8]naphthyridine-9-acetate (4n)

Enaminone **3f** (3.09 g, 10.0 mmol), *p*-TsOH monohydrate (1.90 g, 10.0 mmol), and C_6H_6 (55 mL) were refluxed 3 h under a Dean-Stark trap. The C_6H_6 was evaporated and the residue dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, 1 M Na_2CO_3, and with brine; it was dried, filtered, and concentrated to give crude **4n** (2.32 g) which crystallized yielding pure **4n** (1.31 g, 48%), mp 151-153.5 °C; IR (KBr) 1740 (ester CO); ^1H

Table 3. Microanalytical Data for Pyridones **4a-4q**

		Calcd.				Found			
No.	Formula	C	H	Cl	N	C	H	Cl	N
4a	$C_{17}H_{14}N_2O$	77.84	5.38	—	10.68	78.01	5.50	—	10.80
4b	$C_{18}H_{16}N_2O_2$	73.95	5.52	—	9.58	73.91	5.67	—	9.60
4c	$C_{17}H_{13}ClN_2O$	68.80	4.42	11.95	9.44	68.60	4.31	11.88	9.21
4d	$C_{18}H_{16}N_2O_2$	73.95	5.52	—	9.58	74.05	5.45	—	9.63
4e	$C_{18}H_{16}N_2O$	78.24	5.84	—	10.14	78.38	5.76	—	10.24
4f	$C_{17}H_{12}Cl_2N_2O$	61.65	3.65	21.41	8.45	61.95	3.54	21.18	8.57
4g	$C_{16}H_{13}N_3O$	72.99	4.98	—	15.96	72.76	4.93	—	15.87
4h	$C_{16}H_{13}N_3O$	72.99	4.98	—	15.96	73.21	5.39	—	16.12
4i	$C_{16}H_{12}N_4O_3$	62.33	3.92	—	18.17	62.35	3.75	—	18.18
4j	$C_{18}H_{16}N_2O$	78.24	5.84	—	10.14	78.66	5.90	—	10.16
4k	$C_{18}H_{15}ClN_2O$	69.56	4.86	11.40	9.00	69.54	4.80	11.20	9.00
4l	$C_{19}H_{18}N_2O$	78.59	6.25	—	9.65	78.36	6.24	—	9.65
4m	$C_{22}H_{16}N_2O$	81.46	4.97	—	8.64	81.28	4.94	—	8.51
4n	$C_{15}H_{16}N_2O_3$	66.16	5.92	—	10.29	65.97	5.85	—	10.18
4o	$C_{17}H_{20}N_2O$	76.08	7.51	—	10.44	76.20	7.58	—	10.48
4p	$C_{18}H_{15}FN_2O$[a]	73.45	5.14	—	9.52	73.76	5.24	—	9.62
4q	$C_{11}H_{11}N_3O$	65.66	5.51	—	20.88	65.42	5.50	—	21.10

[a] Calcd for F: 6.46; found: 6.62.

NMR (79.5 MHz) 5.13 (s, NCH_2-), 4.22 (q, J = 7, -OCH_2CH_3), 1.28 (t, J = 7, -OCH_2CH_3); MS 272 (93, M^+), 199 (100).

9-Cyclohexyl-6,7,8,9-tetrahydro-5H-cyclo-penta[b][1,8]napht-hyridin-5-one (4o)

Enaminone **3g** (1.96 g, 6.50 mmol), *p*-TsOH ·H_2O (1.22 g, 6.40 mmol) and C_6H_6 (50mL) were refluxed 24 h under a Dean-Stark trap. The C_6H_6 was evaporated and the residue dissolved in CH_2Cl_2. The solution was washed with H_2O, dried, filtered, and concentrated to give crude **4o** as a solid (1.66 g). Crystallization provided the analytical sample (1.18 g, 69%), mp 219-220 °C ; ^{1}H NMR (200 MHz) 4.20-3.95 (br m, *H* (1')), 2.05-1.55 (br m, 2 *H* (2'), 2 *H* (3'), 2 *H* (5'), 2 *H* (6')), 1.50-1.20 (br m, 2 *H* (4')); MS 268 (M^+), 185 (100).

9-[(4-Fluorophenyl)methyl]-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one (4p)

Heating **3a** (18.0 mmol) and 4-F-$C_6H_4CH_2NH_2$ (22.6 mmol) for 48 h at 125 °C, followed by working-up and crystallizing gave **4p** (51%), mp 177-178.5 °C; ^{1}H NMR (79.5 MHz) 5.65 (s, NCH_2-); MS 294 (96, M^+), 109 (100, $[C_7H_6F]^+$).

9-Amino-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one (4q)

Refluxing **3a** (18.1 mmol) and H_2NNH_2 monohydrate (103 mmol) for 3.5 h, followed by working-up and crystallizing gave **4q** (1.45 g, 40%), mp 206-210 (d) °C; IR (KBr) 3700-3000 br (-NH_2); ^{1}H NMR 5.26 (s, ex, -NH_2); MS 201 (100, M^+), 200 (78, $[M - 1]^+$).

9-(4-Chlorobutyl)-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin-5-one (5)

Heating enaminone **3a** (2.00 g, 7.23 mmol) under N_2 in a 150 °C oil bath for 4 h gave **5**; conversion was complete after 1.5 h (^{1}H NMR), and the melt solidified on cooling. The crude product was chromatographed over silica gel (50 g), and **5** (1.916 g, contaminated with 22 mole-% 2-PrOH, 90% yield) was eluted with 2-PrOH-CH_2Cl_2 (5 : 95, by vol.). Crystallization (EtOAc) of the collected, washed, and dried product gave pure **5**, mp 89.0-92.0 °C; IR (KBr) 1620 (CO); ^{1}H NMR 8.73 (dd, J (2-4) = 2, J (3-4) = 8, *H* (4)), 8.66 (dd, J (2-4) = 2, J (2-3) = 5, *H* (2)), 7.29 (dd, J (3-4) = 8, J (2-3) = 5, *H* (3)), 4.4 (br t, -CH_2Cl), 3.59 (br t, -CH_2N), 3.06 (br m, 4H, -C(6)H_2- and -C(8)H_2-), 2.3-1.7 (overlapping m, 6H, -$(CH_2)_2$- and -C(7)H_2-); MS 278 (6, M^+ for ^{37}Cl), 276 (18, M^+ for ^{35}Cl), 241 (31, $[M$ - Cl$]^+$), 213 (11, $[M$ - C_2H_4Cl$]^+$), 199 (41, $[M$ - C_3H_6Cl$]^+$), 185 (28, $[M$ - C_4H_8Cl$]^+$), 41 (100).

Anal. Calcd for $C_{15}H_{17}ClN_2O$: C, 65.09; H, 6.19; Cl, 12.18; N, 10.12. Found: C, 65.40; H, 6.05; Cl, 12.50; N, 10.15.

9-[4-(Phenylamino)butyl]-6,7,8,9-tetrahydro-5H-cyclopenta[b][1,8]naphthyridin5-one (6)

Chromatography (silica gel, 1% MeOH-$CHCl_3$) of residues from crystallization of **4a** afforded crude pyridone **6**; recrystallization (MeOH) then gave a pure (TLC) sample (906 mg, 5% from **3a** (58.5 mmol)), mp 185.0-186.0 °C; IR (KBr) 1620 (CO); ^{1}H NMR (Me_2SO-d_6) 8.88 (dd, J (2-4)= 2, *H* (2)), 8.74 (dd, J (4-3) = 8, J (4-2) = 2, *H* (4)), 7.71 (dd, J (3-2) = 5, J (3-4) = 8, *H* (3)), 7.29-7.18 (2H, *Ar*), 6.75-6.63 (3H, *Ar*), 5.7 (br t, N*H*, ex), 4.9 (t, -CH_2N (9)), 3.27 (t, -C(6)H_2- or -C(8)H_2-), 3.08 (q, collapsed to a t on ex, -CH_2NHPh), 2.8 (t, -C(8)H_2- or -C(6)H_2-), 2.10 (m, -CH_2-), 1.85 (-CH_2-), 1.64 (m, -CH_2-); MS 333 (63, M^+), 227 (21, $[M$ - NHPh$]^+$), 214 (51), 213 (21, $[M$ - CH_2NHPh$]^+$), 199 (52, $[C_{12}H_{11}N_2O]^+$), 187 (88, $[C_{11}H_{11}N_2O]^+$), 146 (72), 106 (100).

Anal. Calcd for $C_{21}H_{23}N_3O$: C, 75.65; H, 6.95; N, 12.60. Found: C, 75.54; H, 6.92; N, 12.68.

(2-Chloro-3-pyridinyl)(2-hydroxy-1-cyclohexene-1-yl)methanone (8)

This compound, not fully characterized due to its instability, showed ^{1}H NMR (300 MHz) 15.80 (s, 1H), 8.47 (dd, J = 1.9, 4.8, 1H), 7.62 (dd, J = 1.9, 7.6, 1H), 7.35 (dd, J = 4.8, 7.6, 1H), 2.50 (t, J = 6.5, 2H), 2.11 (t, J = 6.1, 2H), 1.76 (m, 2H), 1.65 (m, 2H); ^{13}C NMR (75.4 MHz) 190, 189, 150, 147, 137, 134, 122, 108, 32, 24, 22, 21; FAB-MS (ThioGly) 238 (100, $[M$ +1$]^+$ for ^{35}Cl), 240 (30, $[M$ +1$]^+$ for ^{37}Cl), 202 (59, $[C_{12}H_{12}NO_2]^+$).

Compound (**8**) was eluted before the following compound (**12**).

6,7,8,9-Tetrahydro-5H-1-benzopyrano[2,3-b]pyridin-5-one (9)

Chromatography of crude **3c** over silica gel and elution with CH_2Cl_2 afforded (2-chloro-3-pyridinyl)(2-hydroxy-1-cyclohexene-1-yl)methanone (**8**) which cyclized overnight upon standing to **9**. Crystallization (2-PrOAc) then gave **9** (10.6% from 0.1 mole of 2-chloro-3-pyridinecarbonyl chloride), mp 138.5 -141 °C; IR 1640 (CO), 1605; UV 220 (4.18), 266 (3.96), 297 (3.96), 305 (3.96); ^{1}H NMR (200 MHz) 8.65 (dd, *J* (2-3) = 5, *J* (2-4) = 1.9, *H* (2)), 8.58 (dd, *J* (4-3) = 8, *J* (4-2) = 1.9, *H* (4)), 7.40 (dd, *J* (3-4) = 8, *J* (3-2) = 5, *H* (3)), 2.76 (t, *J* (6-7) = 5.9, *H* (6)*), 2.58 (t, *J* (9-8) = 5.9 *H* (9)*), 1.99-1.70 (m, 4H, *H* (7) and *H*(8)); ^{13}C NMR (50.3 MHz) 178 (*C* (5)), 165 (*C* (10a)), 160 (*C* (4a)), 153 (*C* (2)), 136 (*C* (4)), 122 (*C* (3)), 119 (*C* (9a)*), 118 (*C* (5a)*), 28 (*C* (6)=), 21.9 (*C* (9)=), 21.1 (*C* (7)=), 21.0 (*C* (8)=); MS 201 (100, *M*$^+$), 200 (98, [*M* - 1]$^+$), 122 (68, [(*M* + 1) - C_6H_8]$^+$.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.49; H, 5.40; N, 6.66.

10-[2-(2-Chloroethoxy)ethyl]-6,7,8,9-tetrahydrobenzo[b][1,8]naphthyridin-5(10H)-one (10)

Obtained from preparation of **4k**, this compound (**10**) showed mp 74-75.5 °C; ^{1}H NMR (300 MHz) 8.72 (dd, 1H, *J* = 1.9, 7.9), 8.66 (m, 1H), 7.29 (dd, 1H, *J* = 4.9, 7.8), 4.74 (t, 2H, *J* = 5.6), 3.87 (t, 2H, *J* = 5.6), 3.65 (t, 2H, *J* = 5.6), 3.55 (t, 2H, *J* = 5.1), 3.00 (t, 2H, *J* = 6.3), 2.69 (t, 2H, *J* = 6.3), 1.90 (m, 2H), 1.74 (m, 2H); ^{13}C NMR (75.4 MHz) 178, 152, 150.5, 149.9,136, 120, 119.3, 119.0, 71, 70, 44, 43, 28, 23, 22, 21; MS 306 (60, *M*$^+$ for ^{35}Cl), 308 (21, *M*$^+$ for ^{37}Cl), 213 (100, [$C_{13}H_{13}N_2O$]$^+$), 199 (46, [$C_{12}H_{11}N_2O$]$^+$).

Anal. Calcd for $C_{16}H_{19}ClN_2O_2 \cdot \frac{1}{2} H_2O$: C, 60.85; H, 6.38; Cl, 11.23; N, 8.87. Found: C, 61.30; H, 6.12; Cl, 11.35; N, 8.74. No acceptable value for C was obtained.

2-[(2-Chloro-3-pyridinyl)carbonyl]-1-cyclohexen-1-yl-2-chloro-3-pyridinecarboxylate (12)

A. From enamine 2b. A solution of 1-(4-morpholinyl)-cyclohexene (**2b**) (43.9 g, 262 mmol) and NEt_3 (59.53 g, 588.3 mmol) in CH_2Cl_2 (350 mL) was added over 60 min to a dry, ice-cooled solution of recrystallized 2-chloro-3-pyridinecarbonyl chloride (100.14 g, 569.0 mmol) in CH_2Cl_2 (750 mL) under N_2. A precipitate formed and the reaction mixture was stirred at 25 °C for 118 h. CH_3CN (500 mL), H_2O (300 mL) and acetic acid (50 mL) were then added and the resulting solution was stirred vigorously for 1 h. Saturated NaCl and saturated $NaHCO_3$ were then added, the layers separated, the aqueous layer extracted with CH_2Cl_2, the combined organic layers washed with saturated $NaHCO_3$ and saturated NaCl, dried, filtered and concentrated. The solid residue (105.6 g) was chromatographed (50-60% EtOAc-hexanes) under medium pressure and crystallized from 2-PrOAc to afford **12** as white crystals (82.63 g, 83%), mp 114.5-115.5 °C; CI-MS (CH_4) 381 (2, [*M* + 1]$^+$ for $^{37}Cl_2$), 379 (9, [*M* + 1]$^+$ for $^{37}Cl^{35}Cl$), 377 (2, [*M* + 1]$^+$ for $^{35}Cl_2$), 343 (3, [$C_{18}H_{14}{}^{37}ClN_2O_3$]$^+$), 341 (8, [$C_{18}H_{14}{}^{35}ClN_2O_3$]$^+$), 142 (33, [$C_6H_3{}^{37}ClNO$]$^+$), 140 (100, [$C_6H_3{}^{35}ClNO$]$^+$); IR 1755 (enol ester), 1640 (CO); ^{1}H NMR (200MHz) 8.51 (dd, *J* (α-β) = 5.2, *J* (α-γ) = 2, pyridine *H* (α)), 8.02 (dd, *J* (α-β) = 5.2, *J* (α-γ) = 2, pyridine *H* (α)), 7.88 (dd, *J* (γ-α) = 2, *J* (γ-β) = 7.8, pyridine *H* (γ)), 7.56 (dd, *J* (γ-α) = 2, *J* (γ-β) = 7.8, pyridine *H* (γ)), 7.25 (dd, *J* (β-γ) = 7.8, *J* (β-α) = 5.2, pyridine *H* (β)), 7.04 (dd, *J* (β-γ) = 7.8, *J* (β-α) = 5.2, pyridine *H* (β)), 2.65-2.35 (m, 4H, *H* (3) and *H* (6)), 2.00-1.70 (m, 4H, *H* (4) and *H* (5)); ^{13}C NMR (75.4 MHz) 192, 161, 157, 153, 151, 150, 147, 141, 138, 136, 126, 124, 122.2, 122.0, 29, 25, 22, 21.

Anal. Calcd for $C_{18}H_{14}Cl_2N_2O_3$: C, 57.31; H, 3.74; N, 7.43; Cl, 18.80. Found: C, 57.49; H, 3.53; N, 7.32; Cl, 18.82.

This compound (**12**) was eluted after compound **9**. A combination of NMR experiments—principally SINEPT (^{1}H–^{13}C), COSY (^{1}H–^{1}H), and ^{13}C–^{13}C correlation—and *X*-ray crystallography elucidated and confirmed structure **12**. Lists of refined coordinate and estimated standard deviations have been supplied to the Editor for deposition at the Cambridge Crystallographic Data Centre.

B. From Enaminone 3c. Chromatography of crude **3c** over silica gel, elution with CH_2Cl_2, and crystallization (2-PrOAc) furnished **12** (9.2% from 0.1 mol of 2-chloro-3-pyridinecarbonyl chloride).

7-(4-Chlorobutyl)-5,6-dihydronaphtho[2,1-b][1,8]naphthyridin-12(7H)-one (14)

This compound (**14**), prepared like **6**, was obtained in a yield of 32% from **3j**. CH_2Cl_2 eluted the title compound from silica gel and the product crystallized from EtOAc containing a little MeOH; recrystallization (MeOH) gave an analytical sample, mp 148.5-150.5 °C; IR 1610; ^{1}H NMR 8.81 (dd, *J* (9-11) = 2, *J* (10-11) =

8, *H* (11)), 8.66 (dd, *J* (9-11) = 2, *J* (9-10) = 4.8, *H* (9)), 7.2-7.05 (complex m, *Ar* plus *H* (10)), 4.65 (br t, $-CH_2Cl$), 3.61 (br t, $-CH_2N$), 2.96 (m, 2 *H* (5), and 2 *H* (6)), 1.92 (m, $-(CH_2)_2-$); MS 340 (33, M^+ for ^{37}Cl), 338 (100, M^+ for ^{35}Cl), 303 (34, $[M - Cl]^+$), 275 (11, $[M - Cl - C_2H_4]^+$), 261 (59, $[M - Cl - C_3H_6]^+$), 247 (63, $[M - Cl - C_4H_8]^+$).

Anal. Calcd for $C_{20}H_{19}ClN_2O$: C, 70.89; H, 5.65; Cl, 10.46; N, 8.26. Found: C, 70.54; H, 5.65; Cl, 10.20; N, 8.06.

5,6-Dihydro-12H-naphtho[1',2':5,6]pyrano[2,3-b]pyridin-12-one (15)

Chromatography of the crude product (3.85 g) from preparation of pyridone **4m** gave pyranone **15**. EtOH-$CHCl_3$ (0.4 : 99.6 by vol.) eluted **14** (0.782 g, 31%, pure according to TLC and ^1H NMR) from silica gel (385 g), and crystallization (2-PrOAc) gave an analytical sample, mp 125-127 °C; IR (KBr) 1640 (CO); ^1H NMR (79.5 MHz) 8.80-8.49 (m, *H* (1), *H* (9), and *H* (11)), 7.55-7.07 (m, *H* (2), *H* (3), *H* (4), and *H* (10)), 3.02 (s, 2 *H* (5) and 2 *H* (6)); MS 249 (100, M^+).

Anal. Calcd for $C_{16}H_{11}NO_2$: C, 77.09; H, 4.45; N, 5.62. Found: C, 76.88; H, 4.46; N, 5.50.

Anisotropic deshielding of H (1) by the carbonyl group confirmed assignment of structure; the $\Delta\delta$-value relative to C_6H_6 was +1.5 ppm.

ACKNOWLEDGMENTS

We thank Professor L. Mandell (University of South Florida) for useful discussions. We are indebted to Mrs. J. Nocka (Schering-Plough Research Institute) for help with nomenclature, and are grateful to personnel of Analytical Research Services (Schering-Plough Research Institute).

REFERENCES AND NOTES

† Part Three in a series of three articles; the accompanying article represents Part Two.

1. Part One in this series: Chan, T.-M; Friary, R.; Jones, H.; Schwerdt, J. H.; Seidl, V.; Watnick, A. S.; and Williams, S. M. *J. Heterocyclic Chem.* **1990**, *27*, 1135–1142.
2. Friary, R.; Ganguly, A.; Schwerdt, J. H.; Seidl, V.; Siegel, M.; Smith, S. and Sybertz, E. U. S. Patent Nos. 5,116,840 (May 26, 1992), 4,988,705 (Jan. 29, 1991), and 4,810,708 (March 7, 1989).
3. For a recent review of enamine C-acylations, see Alt, G. H. and Cook, A. G. *Enamines;* Marcel Dekker: New York, 1988; pp. 204–219.
4. Having completed the present work, we learned of two pyridone syntheses proceeding by intermolecular enaminone transamination then intramolecular dienaminone transamination: (a) Abdulla, R.F.; Emmick, T.L.; Taylor, H.M. *Synth. Commun.* **1977**, *7*, 305-312; (b) Abdulla, R.F.; Fuhr, K.H.; Taylor, H.M. *Synth. Commun.* **1977**, *7*, 313-319.
5. (a) "Biology and Synthesis of Sch **40120**, an Antipsoriatic Agent That Inhibits 5-Lipoxygenation and T-Cell Proliferation", Friary, R.; Billah, M.; Bryant, R. W.; Ganguly, A.; Kung, T. T.; Schwerdt, J. H.; Seidl, V.; Siegel, M. I.; Smith, S. R.; and Watnick, A. S.; 204th National Meeting of the American Chemical Society, Washington, D. C., Book of Abstracts, Part 1, Division of Medicinal Chemistry, Abstract No. 2., 1992; (b) Smith, S. R.; Watnick, A. W.; Bryant, R. W.; Billah, M.; Siegel, M. I. *J. Pharm. Exptl. Therapeutics* **1992**, *262*, 721–728; see also Friary, R. J.; Schwerdt, J. H. *Tetrahedron* **1991**, *47*, 9981–9984.
6. (a) Opitz, G.; Tempel, E. *Liebigs Ann. Chem.* **1966**, *699*, 74-87; (b) see also ref. 4 above.
7. Bax, A. *J. Magn. Reson.* **1984**, *57*, 314.
8. Friary, R. J.; Seidl, V.; Schwerdt J. H.; Cohen, M. P.; Hou, D.; and Nafissi, M. *Tetrahedron* **1993**, *49*, 7169-7178.
9. For general methods, see ref. 1.
10. Obtained from the Aldrich Chemical Co. (**2a**, **2b**, **2d**) or prepared[11] (**2c**), the enamines used in this work were 1-(1-pyrrolidinyl)-cyclopentene (**2a**), 1-(4-morpholinyl)-cyclohexene (**2b**), 1-(3,4-dihydro-2-naphthyl)-pyrrolidine (**2d**), and 4-methyl-1-(1-pyrrolidinyl)-cyclohexane (**2c**). ChemoDynamics, Inc., of Garfield, N. J., supplied 2-chloro-3-pyridine- (**1a**) and 2-chloropyrazinecarbonyl chlorides (**1b**)
11. Peters, J. A.; Van der Toorn, J. M.; Van Bekkum, H. *Tetrahedron* **1974**, *30*, 633-640.