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

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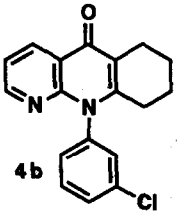
Abstract *2-Arylamino-3-pyridinecarbonyl chlorides acylated the β-carbon atoms of enamines, and the resulting enaminones cyclized to give a series of fused polycyclic N-aryl pyridones. The series included 10-(3-chlorophenyl)-6,8,9,10-tetrahydrobenzo[b][1,8]naphthyridin-5(7H)-one (Sch 40120), an antipsoriatic agent.*

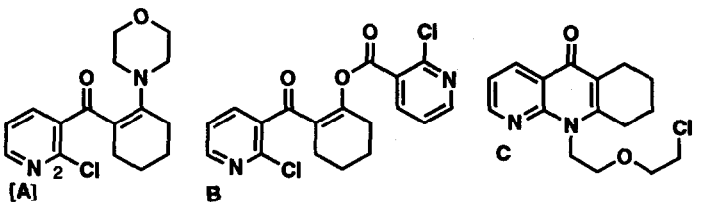
INTRODUCTION



Now in clinical trials as an anti-psoriatic agent,[1a] the tricyclic pyridone **4b** [2] inhibits the 5-lipoxygenation of arachidonic acid in vitro[1b] and modulates the immune system in vitro and in vivo.[3] Soon after some of the biological activities of **4b** were discovered, we sought a third synthesis of it and analogous pyridones. A satisfactory new synthesis would have provided an increased yield of pyridone **4b** as well as a variety of its derivatives, and would have avoided the difficulties of the higher-yielding of our two extant syntheses.

In the more efficient synthesis of **4b**, 2-chloro-3-pyridinecarbonyl chloride acylated 1-(1-morpholinyl)-cyclohexene.[2,4] This reaction formed the desired intermediate [**A**], which 3-chloroaniline converted to pyridone **4b**. However, intermediate [**A**] suffered O-acylation followed by an unexpected 1,3-acyl migration, leading to enol-ester **B**.[4] Enaminone [**A**] also rearranged to pyridone **C**.[4] These side reactions held the overall yield of **4b** to 45%, and the two by-products—as well as others[4]—complicated the isolation of the desired pyridone.

Analyzing the enaminone rearrangement helped solve our synthetic problem. Begun with a nucleophilic attack by the enaminone nitrogen atom, the rearrangement required the chlorine- and nitrogen-substituted 2-carbon in [**A**] to be electrophilic. If this carbon atom were less electrophilic in some precursor other than enaminone [**A**], then little or no rearrangement would occur.



This reasoning suggested a trial of the [(3-chlorophenyl)amino]acid chloride **1a** in a C-acylation of 1-(1-pyrrolidinyl)-cyclohexene (**2c**) (Scheme 1). If the bidentate chloride **1a** balanced stability against reactivity, then the desired acylation would form enaminone [**3**] (Ar = 3-Cl-C_6H_4) as the needed precursor of pyridone **4b**. The arylamino group in [**3**] should reduce the electrophilicity of its 2-carbon compared to that of [**A**]. So [**3**] should

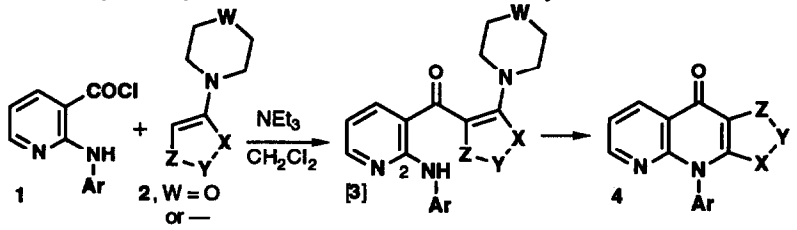
cyclize to **4b** faster than it rearranged—if [3] rearranged at all. Moreover, the arylamino group in enaminone [3] should also prepare it to take the next synthetic step, intramolecular transamination. This cyclization to **4b** should occur faster than any intermolecular O-acylation of [3].

RESULTS AND DISCUSSION

Pyridones from Intramolecular Transaminations of Enaminones

Arylamino acid chlorides **1** acylated enamines **2** of cyclic ketones to form the desired series of fused, polycyclic N-aryl pyridones **4** (Scheme 1, Table 1). As expected, the chlorides **1** were stable enough to be prepared and stored at 25 °C yet were sufficiently reactive to act as C-acylation reagents at 5 °C or less. Furthermore, no by-products of enaminone rearrangement or O-acylation were isolated after the C-acylations. Nor were any intermediate enaminones [3] obtained, except for the enediaminone **3a** and the enol **5** (Scheme 2).

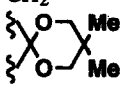
Scheme 1. Pyridones from Intramolecular Transaminations of Enaminones



Scope of the Synthesis

This synthesis tolerated several variations in the structures of the starting materials. The oxidation state of the enamine α-carbon atom could be changed to the equivalent of a carboxylic acid, so the enediamine **2a** (Chart) led to the bicyclic pyridinone **4a** via the intermediate enediaminone **3a**. Another heteroatom-substituted enamine, namely 2,3-dihydro-1-methyl-5-(methylthio)-1H-pyrrole **2b** (Chart), underwent C-acylation and transamination to give pyridone **4g**. The starting materials used to form enamines were also varied, so both carbocyclic and heterocyclic ketones furnished pyridones, for examples, **4j** and **4m**; and **4e** and **4f**. Not surprisingly, the synthesis was compatible with simpler substitutions in the enamines and arylamino groups (Table 1).

Table 1. Polycyclic N-Aryl Pyridones 4 from Intramolecular Enaminone Transaminations

No.	Substituents				Yield (%)[a]
	Ar	X	Y	Z	
4a	3-Cl-C_6H_4		—	—	37[b]
4b	3-Cl-C_6H_4	$(CH_2)_2$	CH_2	CH_2	92[c]
4c	3-Cl-2-Me-C_6H_3	$(CH_2)_2$	CH_2	CH_2	31
4d	Ph	$(CH_2)_2$		CH_2	48
4e	3-Cl-C_6H_4	$(CH_2)_2$	—	S	45
4f	3-Cl-C_6H_4	CH_2S	—	CH_2	4
4g	3-Cl-C_6H_4	NMe	$(CH_2)_2$	—	51
4h	Ph	$(CH_2)_2$	NAc	CH_2	74
4i	3-Cl-C_6H_4	$(CH_2)_2$	NAc	CH_2	50
4j	3-Cl-C_6H_4	$(CH_2)_2$	$C(CH)_4C$		31
4k	3-Cl-C_6H_4	$(CH_2)_2$	O	CH_2	46
4l	Ph	$(CH_2)_2$	S	CH_2	21
4m	Ph	CH_2	$C(CH)_4C$		39[c]

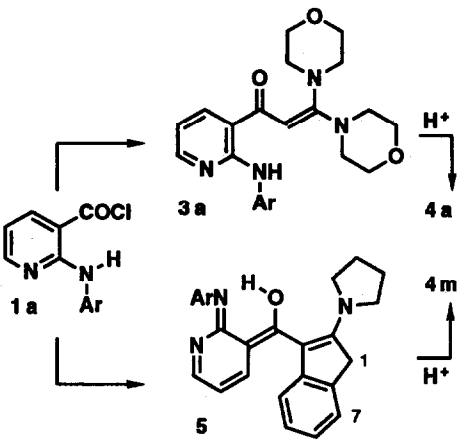
[a] Referred to isolated products, yields are unoptimized and based on the 2-arylamino-3-pyridine carboxylic aids, except as noted. [b] This percentage represents the overall yield for three steps. [c] Optimized.

Assignment of Structure 5

The extended conjugation in intermediate **5** was remarkable, so we present those data that especially helped assign its structure. Compound **5** formed yellow and red crystals, and absorbed at long wavelengths

(λ_{max} 365 (ε 3.42), and 445 (3.50) nm). It showed no carbonyl absorption at IR wavelengths above ν 1595 cm^{-1}. Hydrogen bonding of one proton and deshielding of another (*H* (4)) were evident. The ^1H NMR resonance of its hydrogen-bonded proton fell at δ11.5, whereas that of the deshielded proton lay at 8.3 ppm, 1.0 ppm downfield from the benzene chemical shift.

Scheme 2 (Ar = 3-Cl-C_6H_4)



Mechanism of the Pyridone Synthesis

The postulated mechanism of the pyridone synthesis comprised C-acylation of enamines to enaminones followed by transamination of the enaminones to pyridones (Scheme 1). Separate cyclizations of the isolated intermediates **3a** and **5** furnished evidence of the stepwise nature of the mechanism (Scheme 2). Thus, p-TsOH converted both intermediates to pyridones **4a** (72%) and **4m** (83%) respectively. These observations, although they supported the suggested mechanism, did not exclude an alternative one. Cycloadditions of enamines to the imine-ketene [**6**] (Chart) and subsequent eliminations would also explain pyridone formation.

Limitations

In principle, amidations of the arylaminoacid chlorides **1** should limit the utility of the present pyridone synthesis, diverting these starting materials from the desired C-acylations. For example, either the amino group of compounds **1** or the amine eliminated during transamination might amidate the arylaminoacid chlorides (**1**).

In fact, amidations were of little practical importance, although they did occur. Thus, after one large-scale experiment with chloride **1a** and 1-(1-pyrrolidinyl)-cyclohexene (**2c**), we obtained the amide-enol **7** (< 2%) and the mixed bis-amide **8** (< 5%) in addition to the desired pyridone **4b** (Chart). Isolated by chromatography, both of these by-products formally derived from self-amidation of chloride **1a**. In addition, **7** has incorporated a cyclohexenyl unit, while **8** has included a pyrrolidine group.

On another occasion, the pyrrolidine amide (**9**) of [(3-chlorophenyl)amino]-3-pyridinecarboxylic acid was obtained in a yield of about 15% (Chart).[5] Isolation of amide **9** suggested that C-acylation of enamine **2c** was comparable in rate to transamination of enaminone [**3**] (Ar = 3-Cl-C_6H_4). None of **9** would have formed if the rate of C-acylation had vastly exceeded that of transamination. In that case, none of the starting chloride **1a** would have remained by the time pyrrolidine had appeared.

CONCLUSION

Optimization

The first trial of the present synthesis gave pyridone **4b** in an overall yield of 23% from 2-chloro-3-pyridinecarboxylic acid. The reason for the disappointing yield evidently lay in the C-acylation of enamine **2c** or, more likely, in the transamination of the corresponding enaminone [**3**] to **4b**, because the preparation of acid chloride **1a** was efficient. Thus, on scales of about 0.5 mol, 2-chloro-3-pyridinecarboxylic acid reproducibly (± 1%) afforded an averaged 92% of 2-[(3-chlorophenyl)amino]-3-pyridinecarboxylic acid. Thionyl chloride then uneventfully converted this acid to crude chloride **1a** in high yield. Low acylation temperatures (0 to 5 °C) for long times (ca.16 hrs.) gave **4b** but in small overall yields.

That the C-acylations (unsurprisingly) occurred at the low temperatures suggested that the subsequent intramolecular transamination might represent the rate- and yield-limiting step. So to boost the yield we had to speed the transamination. Indeed, raising the temperature of the reaction mixture more than tripled the yield. Treatment of enamine **2c** with chloride **1a** in toluene at 80 °C for 4 h provided the desired **4b** in an overall yield

of 85%, representing a yield of 92% from enamine **2c**. This yield increase satisfactorily concluded our development of the present pyridone synthesis.

EXPERIMENTAL[6]

2-Arylamino-3-pyridinecarboxylic Acids

The following 2-arylamino-3-pyridinecarboxylic acids, which were starting materials for preparation of acid chlorides **1**, are known compounds: 2-(phenyl)-,[7] 2-(3-chlorophenyl)-,[8] and 2-(5-chloro-2-methylphenyl).[9] We made them according to a general method[7] calling for > 100°-C fusions of commercially available anilines with 2-chloro-3-pyridinecarboxylic acid (Aldrich) or derivatives, especially the esters.

Caution: These ester fusions are exothermic[7] and sometimes eruptive.

2-Arylamino-3-pyridinecarbonyl Chlorides

2-[(3-Chlorophenyl)amino]-3-pyridinecarbonyl (**1a**), 2-[(5-chloro-2-methylphenyl)amino]-3-pyridinecarbonyl (**1b**), and phenylaminopyridinecarbonyl (**1c**) chlorides were unknown compounds prepared from the corresponding acids according to the following general procedure. With the exception of chloride **1a**, they were used without purification in the next step.

2-[(3-Chlorophenyl)amino]-3-pyridinecarbonyl Chloride (1a)

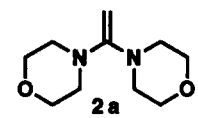
Stirring 2-[(3-chlorophenyl)amino]-3-pyridinecarboxylic acid[8] (30.8 g, 124 mmol) with $SOCl_2$ (50 mL, 680 mmol) and DMF (0.5 mL) at 25 °C for 1 h gave a solution which deposited a precipitate. Collecting, washing (C_6H_6, pet. eth.), and drying it gave **1a** (32 g, 96%) as a yellow solid, mp 112-115 °C; IR 3300 (NH), 1710 (COCl), 1600, 1585; ^{1}H NMR 9.65 (s, N*H*), 8.51 (dd, *J* (4-6) = 2, *J* (5-6) = 4.5, *H* (6)), 8.46 (s, *H* (2')), 7.85 (br s, *H* (4')), 7.50-7.25 (overlapping m, 3H, *H* (5'), *H* (6'), and *H* (4)), 6.92 (dd, *J* (4-5) = 7.5, *J* (5-6) = 4.5, *H* (5)); ^{13}C NMR (400 MHz) 170 (*C*OCl), 156 (*C* (6)), 155 (*C* (2)), 145 (*C* (4)), 140 (*C* (3)), 134 (*C* (1')), 130 (*C* (3')), 124, 122, 120, 115 (*C* (5)), 111 (*C* (4')); MS 270 (6, M^+ for $^{37}Cl_2$), 268 (35, M^+ for $^{37}Cl^{35}Cl$), 266 (56, M^+ for $^{35}Cl_2$), 233 (13, $[C_{12}H_8{}^{37}ClN_2O]^+$), 231 (45, $[H\text{-}6]^+$), 202 (100).

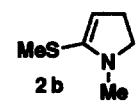
Anal. Calcd for $C_{12}H_8Cl_2N_2O$: C, 53.95; H, 3.02; Cl, 26.55; N, 10.49. Found: C, 53.55; H, 2.98; Cl, 26.14; N, 10.43

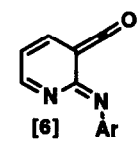
Enamines (2)

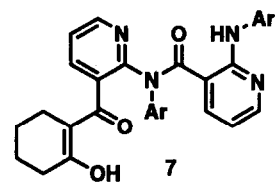
The Aldrich Chemical Co. supplied 1-(3,4-dihydro-2-naphthyl)-pyrrolidine (**2j**), and 1-(1-pyrrolidinyl)-cyclohexene (**2c**), which were suitable for use without purification. Use of other commercial starting materials (Aldrich or the Fluka Chemical Corp.) provided the following known enamines according to the specific procedures cited in the references: 4,4'-ethenylidenebis-morpholine (**2a**),[10] 2,5-dihydro-3-(4-morpholinyl)-thiophene (**2g**)[11] and 4,5-dihydro-3-(4-morpholinyl)-thiophene (**2h**),[11] and 1-(1H-inden-2-yl)-pyrrolidine (**2k**).[12] N-Methylthiopyrrolidine[13a] formed 2,3-dihydro-1-methyl-5-(methylthio)-1H-pyrrole (**2b**).[13b] Use of a general procedure[14] gave the known enamines 3,3-dimethyl-9-(1-pyrrolidinyl)-1,5-dioxaspiro[5,5]undec-8-ene (**2f**),[15] and 3,6-dihydro-4-(1-pyrrolidinyl)-2H-thiopyran (**2i**).[16] Two new enamines (**2d** and **2e**) were prepared as follows.

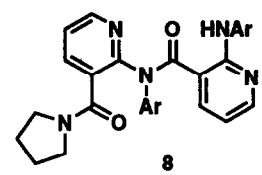
Chart (Ar = 3-Cl-C$_6$H$_4$)

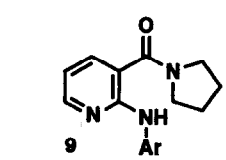






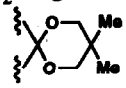






1-Acetyl-4-(1-pyrrolidinyl)-1,2,5,6-tetrahydropyridine (2d)

A mixture of N-acetylpiperidone (28.23 g, 0.2 mol), pyrrolidine (21.34 g, 0.3 mol) and C_6H_6 (200 mL) was refluxed 3 h under a Dean-Stark trap. The reaction mixture was then cooled and the solution was concentrated to give a yellow liquid. Distillation gave enamine **2d** (33.14 g, 85%), bp 155-156 °C at 0.9 mm; amide rotamers were evident in a ^1H NMR spectrum. ^1H NMR 4.32-3.92 (br m, 3H, *H* (2) and *H* (3)), 3.69 and 3.55 (overlapping t, *J* (5-6) = 6, total of 2H, *H* (5)), 3.03 (br t, 4H, *H* (2') and *H* (5')), 2.52-2.18 (m, 3H, *H* (6)), 2.08 and 2.07 (two singlets, total of 3H, $NCOCH_3$), 1.98-1.72 (m, 4H, *H* (3') and *H* (4')). The sample was not further characterized, but was used directly in the next step.

Key	W	X	Y	Z
2a		(see Chart)		
2b		(see Chart)		
2c	—	CH_2	CH_2	CH_2
2d	—	CH_2	NAc	CH_2
2e	—	$(CH_2)_2$	O	CH_2
2f	—	CH_2		CH_2
2g	O	CH_2	S	CH
2h	O	S	CH_2	CH_2
2i	—	$(CH_2)_2$	S	CH_2
2j	—	$C(CH)_4C$		(CH_2)
2k	—	$C(CH)_4C$		CH_2

3,6-Dihydro-4-(1-pyrrolidinyl)-2H-pyran (2e)

Pyrrolidine (10.67 g, 150 mmol), tetrahydro-4H-pyran-4-one (15 g, 150 mmol) and C_6H_6 (195 mL) were refluxed 4 h under a Dean-Stark trap. The cooled, concentrated crude product was distilled to give enamine **2e** (12.38 g, 54%), bp 68-74 °C at 0.06 mm, which was not characterized but was used directly in the next step.

1-[2[(3-Chlorophenyl)amino]-3-pyridinyl]-3,3-bis(4-morpholinyl)-2-propen-1-one (3a)

Enediamine **2a** (2.69 g, 13.6 mmol) and NEt_3 (2.08 mL, 15.0 mmol) in CH_2Cl_2 (10 mL) were added to a stirred, cooled (ice bath) suspension of acid chloride **1a** (3.62 g, 13.6 mmol) and CH_2Cl_2 (59 mL). When addition was complete, the resulting dark red solution was allowed to stir 5.5 h; ice was not replenished. The solution was washed (1 M $NaHCO_3$, then H_2O), dried, and concentrated; the residue crystallized from Et_2O containing a little CH_2Cl_2 to give **3a** (2.40 g, 52%, pure according to TLC). Recrystallization from MeCN-$CHCl_3$ gave the analytical sample as yellow prisms, mp 212.0-214.5 °C; IR 1580, 1560; ^1H NMR (79.5 MHz) 14.7 (br s, ex., N*H*), 8.25 (dd, *J* (6-5) = 4.6, *J* (6-4) = 2.0, *H* (6)), 8.01-7.82 (overlapping resonances of *H* (2') and *H* (4), total of 2H), 7.63-7.40 (m, 1H, *Ar*), 7.30-6.80 (complex m, 2H, *Ar*), 6.67 (dd, *J* (5-6) = 4.6, *J* (5-4) = 7.7, *H* (5)), 4.99 (s, ex., -COC*H*=C), 3.77 (m, 4 -CH_2O-), 3.38 (m, 4 -CH_2N); MS 430 (11, M^+ for ^{37}Cl), 428 (30, M^+ for ^{35}Cl), 344 (6, [*M* - C_4H_8NO]$^+$), 257 (34), 255 (100), 233 (8, [$C_{12}H_8{}^{37}ClN_2O$]$^+$), 231 (16, [H-**6**]$^+$).

1-(3-Chlorophenyl)-2-(4-morpholinyl)-1,8-naphthyridin-4(1H)-one (4a)

Enediaminone **3a** (1.34 g, 3.13 mmol), *p*-TsOH monohydrate (0.594 g, 3.13 mmol), and EtOH (13.4 mL) were refluxed 24 h under N_2. The solution was concentrated, and a solution of the residue in CH_2Cl_2 was washed with H_2O and was dried. The solution was filtered and concentrated, and the residue was crystallized from MeCN to give **4a** (0.770 g, 71.9%), mp 215-218 °C; ^1H NMR (79.5 MHz) 6.03 (s, *H* (6)), 3.4 (m, 2 CH_2N), 3.0 (m, 2 -CH_2O-); MS 343 (35, M^+ for ^{37}Cl)), 341 (100, M^+ for ^{35}Cl).

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

A solution of NEt_3 (1.3 mL, 9.3 mmol) and 1-(1-pyrrolidinyl)-cyclohexene **2c** (1.41 g, 9.3 mmol) in toluene (5 mL) was added dropwise over 10 min. to a magnetically stirred, cooled (ice-acetone bath at -10 °C) suspension of crude acid chloride **1a** (prepared from 9.3 mmol of the corresponding acid) and toluene (40 mL). The solid dissolved, the dark red reaction mixture was kept 2 h between -5 to +5 °C, and was warmed to room temperature over 0.5 h. The reaction mixture was then heated in an 80 °C oil bath for 4 h. The reaction mixture was allowed to cool and to stand at room temperature for 12 h, after which toluene was evaporated. The residue was dissolved in CH_2Cl_2 and the solution was washed with H_2O, 1N HCl, 1M Na_2CO_3, and with H_2O. Aqueous extracts were back-extracted with CH_2Cl_2, and combined organic solutions were dried, filtered, and

evaporated. The residue (2.98 g of cream-colored solid) was chromatographed over silica gel (200 g, packed in CH_2Cl_2 - MeOH (99.5 : 0.5, by vol.)) and eluted under N_2 pressure. Fractions found to contain pure (TLC) **4b** were combined, concentrated, and dried to constant weight under ca. 5 mm Hg, giving 2.66 g (92%) of **4b**, m. p. 196-199 °C. This sample was identified with an authentic one[4] by comparisons of m. p., ^1H NMR spectra, and TLC R_f and microanalytical values.

10-(5-Chloro-2-methylphenyl)-6,8,9,10-tetrahydrobenzo[b][1,8]naphthyridin-5(7H)-one (4c)

Enamine **2c** (15 mmol) and NEt_3 (16.5 mmol) in CH_2Cl_2 (10 ml) were added to **1b** (15 mmol) and CH_2Cl_2 (50 mL). After ca. 17 h at 25 °C, work-up and crystallization gave **4c** (31%), mp 201-203 °C; ^1H NMR (79.5 MHz): 1.92 (s, -CH_3), 2.40-2.20 (br m, *H* (9α or β)), 2.20-2.00 (br m, *H* (9β or α)); MS 326-(25, M^+ for ^{37}Cl), 324 (86, M^+ for ^{35}Cl), 323 (100, [*M* -1]$^+$).

6,8,9,10-Tetrahydro-5',5'-dimethyl-10-phenylspiro[benzo[b][1,8]naphthyridin-7(5H),2-[1,3]dioxan]-5-one (4d)

NEt_3 (3.25 mL, 23.3 mmol) was added to a stirred suspension of 2-(phenylamino)-3-pyridinecarboxylic acid (5.00 g, 23.3 mmol) and CH_2Cl_2 (100 mL), and the resulting solution was cooled (ice bath). $ClCO_2Et$ (2.23 mL, 23.3 mmol) in CH_2Cl_2 (10 mL) was added over 5 min, and the resulting solution was stirred 1.75 h in the ice bath. A solution of enamine **2f** (5.75 g, 22.9 mmol) in CH_2Cl_2 (15 mL) was added over 5 min, and the resulting solution was allowed to stir for 2 h at ice bath temperature and for 25 h at 25 °C. The solution was washed (1 M Na_2CO_3, H_2O, 1 M HCl, H_2O), dried, and concentrated. Trituration of the residue with Et_2O gave **4d** (4.12 g, 47.8%), and crystallization (MeOH) gave an analytical sample, mp 240.5-242.5 °C; ^1H NMR (400 MHz) 4.68 (d, 2 *H*(6' or 4')), 4.26 (d, 2 *H* (4' or 6')), 3.96 (s, 2 *H*(6)), 3.08 (t, *J* (8-9) ≅ 7, 2 *H* (8 or 9), 2.50 (t, *J* (9-8) ≅ 7, 2 *H* (9 or 8)), 1.36 (s, -CH_3), 1.11 (s, -CH_3); MS 376 (26), 247 (100).

4-(3-Chlorophenyl)-2,3-dihydrothieno[3,2-b][1,8]naphthyridin-9(4H)-one (4e)

Enamine **2g** (59.9 mmol, containing an unknown amount of enamine **2h**) and NEt_3 (59.9 mmol) in CH_2Cl_2 (50 mL) were added to acid chloride **1a** (59.9 mmol) and CH_2Cl_2 (160mL). After ca. 20 h at 25 °C, work-up, chromatography (silica gel, MeOH-$CHCl_3$ (1 : 99 by vol.), and crystallization, gave **4e** (45%), mp 289-292 °C; ^1H NMR (200MHz, Me_2SO-d_6) 3.28 (d, *J* (2-3) = 6, 2 *H* (2)), 3.20 (d, *J* (3-2) = 6, 2 *H* (3)); ^{13}C NMR (75 MHz, Me_2SO-d_6) 38 (*C* (2)), 27 (*C* (3)); MS 316 (45, M^+ for ^{37}Cl), 314 (100, M^+ for ^{35}Cl).

This experiment also gave pyridone **4f**, which chromatography separated from **4e**. The latter was eluted after the former. ^1H NMR spectra distinguished **4e** from **4f**, and allowed us to assign their structures. Only one set of methylene protons was deshielded in **4e**, but both were deshielded in **4f** compared to **4aa**. Methylene proton resonances of **4e** showed 6 Hz *J*-values for vicinal coupling, but those of **4f** presented 3 Hz *J*-values for homoallylic coupling.

9-(3-Chlorophenyl)-6,9-dihydrothieno[3,4-b][1,8]naphthyridin-5(8H)-one (4f)

Enamine **2h** (59.9 mmol, containing an unknown amount of enamine **2g**) and NEt_3 (59.9 mmol) in CH_2Cl_2 (50 mL) were added to acid chloride **1a** (59.9 mmol) and CH_2Cl_2 (160 mL). After ca. 20 h at 25 °C, work-up, chromatography (silica gel, MeOH-CH_2Cl_2 (1 : 99 by vol.)), and crystallization gave **4f** (4 %), mp 257-260 °C; ^1H NMR (200 MHz, Me_2SO-d_6) 4.16 (t, *J* (6-8) = 3, 2 *H* (6)), 4.02 (t, *J* (8-6) = 3, 2 *H* (8)); ^{13}C NMR (75 MHz, Me_2SO-d_6) 38 (*C* (6)), 34 (*C* (8)); MS 316 (35, M^+ for ^{37}Cl), 315 (44, [*M* - 1]$^+$ for ^{37}Cl), 314 (100, M^+ for ^{35}Cl), 313 (91, [*M* - 1]$^+$ for ^{35}Cl).

This experiment also gave pyridone **4e**, which chromatography (see above) separated from **4f**; the latter compound was eluted before the former one.

9-(3-Chlorophenyl)-1,2,3,9-tetrahydro-1-methyl-4H-pyrrolo[2,3-b][1,8]naphthyridin-4-one (4g)

Enamine **2b** (56.1 mmol) and NEt_3 (56.1 mmol) in CH_2Cl_2 (39 mL) were added to acid chloride **1a** (56.1 mmol) and CH_2Cl_2 (325 mL). After ca. 64 h at 25 °C, work-up and crystallization from MeCN containing a little $CHCl_3$ gave **4g** (51%), mp 278-279 (d.) °C; ^1H NMR (79.5 MHz) 3.65 (m, -C*H*$_2$-), 3.07 (m, -C*H*$_2$), 2.30 (s, -C*H*$_3$); CI-MS 312 (100), 311 (18, M^+ for ^{35}Cl).

7-Acetyl-6,8,9,10-tetrahydro-10-phenyl-pyrido[2,3-b][1,6]naphthyridin-5(7H)-one (4h)

Enamine **2d** (16.6 mmol) and NEt_3 (16.6 mmol) in CH_2Cl_2 (10 mL) were added to 2-[(phenyl)amino]-3-pyridinecarbonyl chloride **1c** (16.6 mmol) and CH_2Cl_2 (70 mL). After ca. 22 h at 25 °C, work-up and crystallization gave **4h** (74%), mp 209.5-212.5 °C; IR (KBr) 1640 (amide CO); ^1H NMR (79.5 MHz) 4.63 (s, 2 *H* (6)), 3.79 (br t, *J* = 6, 2 *H* (8)), 2.43 (br t, *J* = 6, 2 *H* (9)), 2.11 (s, -NCOC*H*$_3$); MS 319 (93, M^+), 277 (77, [*M* -C_2H_2O]$^+$, 276 (100, [*M* - C_2H_3O]$^+$).

7-Acetyl-10-(3-chlorophenyl)-6,8,9,10-tetrahydropyrido[2,3-b][1,6]naphthyridin-5(7H)-one (4i)

Enamine **2d** (352.5 mmol) and NEt_3 (380 mmol) in CH_2Cl_2 (240 mL) were added to acid chloride **1a** (352.5 mmol) and CH_2Cl_2 (600 mL). After 20 h between 0 to 25 °C, work-up and crystallization from EtOAc-$CHCl_3$ gave **4i** (50%), mp 238-242 °C; IR (KBr) 1650 (amide CO); ^1H NMR (79.5 MHz) 3.22 (s, 2 *H* (6)), 3.37 (br t, *J* = 6, 2 *H* (8)), 2.44 (br t, *J* = 6, 2 *H* (9)), 2.39 (s, -NCOC*H*$_3$) and 2.24 (s, -NCOC*H*$_3$) (1 : 1.4 mixture of amide rotamers); MS 355 (19, M^+ for ^{37}Cl), 353 (57, M^+ for ^{35}Cl), 312 (49, [*M* - C_2H_3O]$^+$ for ^{37}Cl), 310 (100, [*M* - C_2H_3O]$^+$ for ^{35}Cl).

7-(3-Chlorophenyl)-5,6-dihydronaphtho[2,1-b][1,8]naphthyridin-12(7H)-one (4j)

Enamine **2j** (23.3 mmol) and NEt_3 (23.3 mmol) in CH_2Cl_2 (15 mL) were added to acid chloride **1a** (23.3 mmol) and CH_2Cl_2 (100 mL). After ca. 19 h at 25 °C, work-up and crystallization from MeCN containing a little $CHCl_3$ gave **4j** (29%), mp 232.0-234.5 °C;^1H NMR (79.5 MHz) 2.64 (m, -(CH_2)$_2$-), 8.51 (dd, *J* (6-7) = 4.9, *J* (6-8) = 2.5, *H* (6)); MS 360 (50, M^+ for ^{37}Cl), 358 (100, M^+ for ^{35}Cl).

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

Enamine **2e** (15 mmol) and NEt_3 (16.5 mmol) in CH_2Cl_2 (12 mL) were added to acid chloride **1a** (15 mmol) and CH_2Cl_2 (50 mL). After ca. 108 h at 25 °C, work-up and crystallization gave **4k** (31%), mp 219-223 °C; ^1H NMR (200 MHz, Me_2SO-d_6) 4.60 (s, 2 *H* (6)), 3.86 (t, *J* (8-9) = 6, 2 *H* (8)), 2.37 (t, *J* (9-8) = 6, 2 *H* (9)); MS 314 (12, M^+ for ^{37}Cl), 312 (32, M^+ for ^{35}Cl), 283 (100).

10-(3-Chlorophenyl)-6,8,9,10-tetrahydro-5H-thiopyrano[4,3-b][1,8]naphthyridin-5-one (4l)

Enamine **2i** (37.4 mmol) and NEt_3 (39 mmol) in CH_2Cl_2 (25 mL) were added to acid chloride **1a** (37.4 mmol) and CH_2Cl_2 (100 mL). After ca. 20 h at 25 °C, work-up and crystallization provided **4l** (46%), mp 165-167 °C; ^1H NMR 3.88 (s, 2 *H* (6)), 2.73 (t, *J* (8-9) = 4.5, 2 *H* (8)), 2.61 (t, *J* (9-8) = 4.5, 2 *H* (9)); ^{13}C NMR (75 MHz, Me_2SO-d_6) 30 (*C* (6)), 24 (*C* (8)), 23 (*C* (9)); MS 330 (22, M^+ for ^{37}Cl), 328 (55, M^+ for ^{35}Cl), 297 (33, [$C_{17}H_{13}{}^{37}ClN_2O$]$^+$), 295 (100, [$C_{17}H_{13}{}^{35}ClN_2O$]$^+$).

11-(3-Chlorophenyl)-10,11-dihydro-5H-indeno[2,1-b][1,8]naphthyridin-5-one (4m)

Compound **5** (4.70 g, 11.3 mmol), *p*-TsOH·H_2O (2.15 g, 11.3 mmol), and C_6H_6 (235 mL) were refluxed 1 h, cooled, and filtered. The collected solid was washed with C_6H_6 and was reserved. The united filtrates were concentrated to give a solid, and both lots of solid were combined with the aid of $CHCl_3$. The $CHCl_3$ solution was washed (1 M $NaHCO_3$, then H_2O), dried, and filtered to give crude **4m** (4.89 g). Treatment with charcoal and crystallization from EtOH containing a little $CHCl_3$ gave an analytical sample (3.24 g, 83%), mp 304-307 °C; ^1H NMR (200 MHz) 3.90 (s, -C*H*$_2$-), 8.42 (br d, *J* = 7, *H* (6)); MS 346 (82, M^+ for ^{37}Cl), 344 (100, M^+ for ^{35}Cl).

Table 2. Microanalytical Data for Pyridones **4a** and **4c-m**

No.	Formula	Calcd.				Found			
		C	H	Cl	N	C	H	Cl	N
4a	$C_{18}H_{16}ClN_3O_2$	63.25	4.72	10.37	12.29	63.06	4.56	10.30	12.19
4c	$C_{19}H_{17}ClN_2O$	70.25	5.28	10.92	8.63	69.91	5.18	10.72	8.54
4d	$C_{23}H_{24}N_2O_3$	73.38	6.43	—	7.44	73.47	6.39	—	7.40
4e	$C_{16}H_{11}ClN_2OS$[a]	61.04	3.52	11.26	8.90	60.73	3.42	11.31	8.60
4f	$C_{16}H_{11}ClN_2OS$[b]	61.04	3.52	11.26	8.90	60.63	3.33	11.14	8.75
4g	$C_{17}H_{14}ClN_3O$	65.49	4.53	11.37	13.48	65.63	4.51	11.33	13.69
4h	$C_{19}H_{17}N_3O_2$	71.46	5.36	—	13.16	71.30	5.06	—	13.17
4i	$C_{19}H_{16}ClN_3O_2$	64.50	4.56	10.02	11.88	64.56	4.54	9.90	12.12
4j	$C_{22}H_{15}ClN_2O$	73.64	4.21	9.88	7.81	73.86	4.21	9.59	7.79
4k	$C_{17}H_{13}ClN_2O_2$	65.28	4.19	11.34	8.96	65.48	4.10	11.20	8.91
4l	$C_{17}H_{13}ClN_2OS$[c]	62.09	3.98	10.78	8.52	62.01	3.86	10.81	8.36
4m	$C_{21}H_{13}ClN_2O$	73.15	3.80	10.28	8.12	73.31	3.82	10.55	8.38

[a] Calcd. for S, 10.19; found, 10.35. [b] Calcd. for S, 10.19; found, 10.18. [d] Calcd. for S, 9.75; found, 10.00.

α-[2-[(3-Chlorophenyl)imino]-2,3-dihydro-3-pyridinylidene]-2-(1-pyrrolidinyl)-1H-indene-3-methanol (5)

Enamine **2k** (6.68 g, 36.0 mmol) and NEt_3 (5.5 mL, 39.6 mmol) in CH_2Cl_2 (27 mL) were added to a stirred, cooled (ice bath) suspension of acid chloride **1a** (9.63 g, 36.0 mmol) and CH_2Cl_2 (157 mL). When addition was complete, the reaction mixture was allowed to stir 39 h at 25 °C. The resulting solution was washed (1 M $NaHCO_3$, H_2O, 10% HCl, H_2O), dried, filtered, concentrated, and diluted with Et_2O to cause crystallization. Recrystallization (MeCN-$CHCl_3$) of the collected, washed (Et_2O), and dried product gave **5** (7.05 g, 47%), mp 172.5-174.0 °C, as red prisms and yellow needles; IR (KBr) 3400-3100 (br), 1595; UV/VIS 208 (4.29), 297 (4.25), 365 (3.42), 445 (3.50); ^{1}H NMR 11.5 (s, N*H*), 8.62 (dd, *J* (α-β) = 5, *H*(α)), 8.36-8.23 (overlapping signals of *H* (4) and *H*(γ)), 7.6-6.8 (7H, *Ar*), 6.96 (dd, *J* (β-α) = 5, *J* (β-γ) = 8, *H* (β)), 3.67 (s, -C(1)H_2-), 3.3 (br s, -CH_2NCH_2-), 2.00 (br t, -$(CH_2)_2$-); FAB-MS 418 (5, [*M* + 1]$^+$ for ^{37}Cl), 416 (15, [*M* + 1]$^+$ for ^{35}Cl), 347 (14, [*M* + 1 - C_4H_9N]$^+$ for ^{37}Cl), 345 (35, [*M* + 1 - C_4H_9N]$^+$ for ^{35}Cl), 233 (34, [$C_{12}H_8{}^{37}ClN_2O$]$^+$), 231 (100, [H-6]$^+$).

Anal. Calcd for $C_{25}H_{22}ClN_3O$: C, 72.19; H, 5.33; Cl, 8.52; N, 10.10. Found: C, 72.29; H, 5.33; Cl, 8.68; N, 10.02

1-[[2-[(3-Chlorophenyl)amino]-3-pyridinyl]carbonyl]pyrrolidine (9)

Obtained in a yield of about 15% as a by-product from the preparation of pyridone **4b**, compound **9** showed mp 75.5-77 °C; IR 3600 (NH), 1630 (CO); MS 303 (29, *M*$^+$ for ^{37}C), 301 (87, *M*$^+$ for ^{35}C), 233 (21, [$C_{12}H_8{}^{37}ClN_2O$]$^+$), 231 (60, [$C_{12}H_8{}^{35}ClN_2O$]$^+$), 205 (28, [$C_{11}H_8{}^{37}ClN_2$]$^+$), 203 (83, [$C_{11}H_8{}^{35}ClN_2$]$^+$), 113 (5, [$C_6H_4{}^{37}Cl$]$^+$), 111 (12, [$C_6H_4{}^{35}Cl$]$^+$), 70 (100, [C_4H_8N]$^+$); ^{1}H NMR (200 MHz) 9.15 (s, 1H), 8.28 (dd, 1H, *J* = 1.8, 2.4), 8.86 (t, 1H, *J* = 2), 7.61 (dd, 1H, *J* = 1.8, 3.7), 7.39 (dd, 1H, *J* = 1.4, 7.5), 7.20 (t, 1H, *J* = 8.1), 6.95 (dd, 1H, *J* =1.4, 8.0), 6.76 (dd, 1H, *J* = 4.9,7.5), 3.66 (br s, 2H), 3.54 (br s, 2H), 2.08-1.85 (m, 4H); ^{13}C NMR (75.4 MHz) 168, 154, 150, 142, 137, 134.5, 130, 122, 119, 118, 115, 114, 50, 46, 26, 24.

Anal. Calcd for $C_{16}H_{16}ClN_3O$: C, 63.68; H, 5.34; N, 13.92; Cl, 11.75. Found: C, 64.00; H, 5.44; N, 14.02; Cl, 11.75.

N-(3-chlorophenyl)-2-[(3-chlorophenyl)amino]-N-[3-[(2-hydroxy-1-cyclohexen-1yl)carbonyl]-2-pyridinyl]-3-pyridinecarboxamide (7)

This compound, obtained in a yield of about 2% as a by-product from preparation of pyridone **4b**, showed mp 175-177 °C; IR 3340 (OH), 1650 (CO); MS 562 (2, M^+ for $^{37}Cl_2$), 560 (9, M^+ for $^{37}Cl^{35}Cl$), 558 (13, M^+ for $^{35}Cl_2$), 233 (33, $[C_{12}H_8{}^{37}ClN_2O]^+$), 231 (100, $[C_{12}H_8{}^{35}ClN_2O]^+$); ^{1}H NMR (300 MHz) 16.09 (s, 1H), 9.03 (s, 1H), 8.43 (m, 1H), 8.20 (m, 1H), 7.90 (s, 1H), 7.72 (d, 1H, J = 7.3), 7.65 (dd, 1H, J = 1.8, 7.6), 7.36 (d, 1H, J = 7.3), 7.26-7.11 (m, 5H), 6.96 (d, 1H, J = 7.9), 6.52 (dd, 1H, J = 4.9, 7.7), 2.22 (br t, 2H, J = 6.4), 1.76 (br s, 2H), 1.59 (m, 2H), 1.38 (br s, 2H); ^{13}C NMR (100.6 MHz) 190, 189, 171, 154, 153, 150.4, 150.3, 143, 141, 140, 137, 135, 134, 130.0, 129.6, 129.2, 128, 127, 126, 122.0, 121.5, 120, 118, 113.8, 113.6, 108, 32, 25, 22, 21.

Anal. Calcd for $C_{30}H_{24}Cl_2N_4O_3$: C, 64.41; H, 4.32; N, 10.01; Cl, 12.67. Found: C, 64.52; H, 4.26; N, 10.01; Cl,12.51.

N-(3-chlorophenyl)-2-[(3-chlorophenyl)amino]-N-[3-(1-pyrrolidinylcarbonyl)-2-pyridinyl]-3-pyridinecarboxamide (8)

Obtained in a yield of 5%, compound **8** was a by-product from preparation of pyridone **4b**. It showed mp 210.5-212 °C; IR 1675 (CO); MS 535 (2, M^+ for $^{37}Cl_2$), 533 (11, M^+ for $^{37}Cl^{35}Cl$), 531 (15, M^+ for $^{35}Cl_2$), 437 (4, $[C_{23}H_{15}{}^{37}Cl_2N_4O]^+$), 435 (19, $[C_{23}H_{15}{}^{37}Cl^{35}ClN_4O]^+$), 433 (29, $[C_{23}H_{15}{}^{35}Cl_2N_4O]^+$), 407 (20, $[C_{22}H_{18}{}^{37}ClN_4O_2]^+$), 405 (58, $[C_{22}H_{18}{}^{35}ClN_4O_2]^+$), 338 (24, $[C_{18}H_{11}{}^{37}ClN_3O_2]^+$), 336 (100, $[C_{18}H_{11}{}^{35}ClN_3O_2]^+$); ^{1}H NMR (300 MHz) 10.53 (s, 1H), 8.42 (dd, 1H, J = 1.8, 4.9), 8.29 (dd, 1H, J = 1.9, 4.8), 7.98 (dd, 1H, J = 1.9, 7.6), 7.65 (dd, 1H, J = 1.9, 7.6), 7.52 (m, 1H), 7.35 (m, 1H), 7.19-6.99 (m, 6H), 6.83-6.76 (m, 2H), 3.43 (br t, 2H), 3.1 (br s, 2H), 2.80-2.65 (m, 4H); ^{13}C-NMR (75.4 MHz) 168, 164, 154.9, 154.3, 150, 149, 146, 140.5, 139.5, 136, 135, 134, 130.1, 129.6, 127, 126, 125.4, 125.2, 124, 123, 120.2, 119.5, 118.8, 117.7, 49, 46, 26, 24.

Anal. Calcd for $C_{28}H_{23}Cl_2N_5O_2$: C, 63.16; H, 4.35; Cl, 13.32; N, 13.15. Found: C, 63.43; H, 4.38; Cl, 13.10; N, 13.22.

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REFERENCES AND NOTES

† Part Two in a series of three articles; the accompanying article[4] represents Part Three.

⊥ Dedicated to *Professor Richard W. Franck*, who sparked an interest in synthesizing azacycles from enaminones.

1. (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.

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. Smith, S. R.; Watnick, A. S.; Kung, T; and Siegel, M. I *Immunopharmacology and Immunotoxicology* **15**, 13–44 (1993).

4. Friary, R. J.; Seidl, V.; Schwerdt, J. H.; Chan, T.-M; Cohen, M. P.; Conklin, E. R.; Duelfer, T.; Hou, D.; Nafissi, M.; Runkle, R. L.; Tahbaz, P.; Tiberi, R. L.; and Mc Phail, A. T. *Tetrahedron* **1993**, *49*, 7179-7192.
5. After the reported optimization of the **4b** preparation, the yield of pyrrolidine amide **9** fell to less than about 8%.
6. For general methods, as well as IR and NMR spectroscopy, see the accompanying article,[4] which is Part 3 in the series.
7. (a) Kermack, W. O.; Weatherhead, A. P. *J. Chem. Soc.* **1942**, 726;(b) Nantka-Namirsky, P. *Acta Pol. Pharm.* **1967**, *24*, 111-119.
8. Noda, K.; Nakagawa, A.; Motomura, T.; Ide, H. Japan Kokai 75,105,695; *Chem. Abstr.* **1976**, *84*, P44128m.
9. Hoffmann, C.; Faure, A. Fr. CAM 0265; *Chem. Abstr.* **1972**, *77*, P5339s.
10. Baganz, H.; Domaschke, L. *Chem. Ber.* **1962**, *95*, 2095-2096.
11. Buiter, F. A.; Weiland, J. H. S.; Wynberg, H. *Rec. Trav. Chim.* **1964**, *83*, 1160-1168.
12. Blomquist, A. T.; Moriconi, E. J. *J. Org. Chem.* **1961**, *26*, 3761-3769.
13. (a) Thomsen, J.; Clausen, K.; Sheibye, S.; Lawesson, S.-O. *Org. Syn.* **1984**, *62*, 158-163; (b) Gompper, R.; Elser, W. *Liebigs Ann. Chem.***1969**, *725*, 70-86.
14. (a) Herr, M. E.; Heyl, F. W. *J. Am. Chem. Soc.* **1952**, *74*, 3627-3630; (b) Stork, G.; Brizzolara, A.; Landesman, H; Szmuszkovicz, J; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222.
15. Marshall, J. A.; Flynn, G. A. *Synth. Commun.* **1977**, *7*, 417-421.
16. Kakurina, L. N.; Kucherova, N. F.; Zagoreveski, V. A. *Zh. Orgn. Khim.* **1965**, *1*, 1108-1111; *Chem. Abstr.* **1964**, *61*, 14651c.