Nitrogen Bridgehead Compounds. Part 83 [1]. Synthesis and Ring Transformation of 6-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates

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The thermal ring transformation of 2-substituted 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates gave 2-substituted 1,8-naphthyridine-3-acrylates, pyrano-1,8-naphthyridines and anthyridine, depending upon the nature of the 2-substituent. A longer reaction period and a higher reaction temperature favored the formation of tricyclic products from 1,8-naphthyridine-3-acrylate after isomerization of the side-chain at position 3. The products were characterized by means of uv, ir and ^{1}H nmr spectroscopy.

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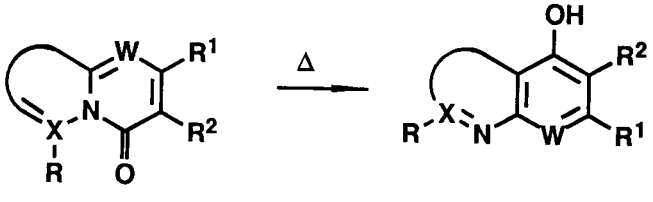
Unsaturated bi- and polycyclic nitrogen bridgehead ring systems containing a carbonyl group and a substituent (R ≠ H) in the *peri* positions underwent thermal ring transformation to give condensed ring systems (Scheme 1) [2-9]. The driving force of the ring transformations of the

Scheme 1



X = C R ≠ H
X = N R = O
W = C or N

nitrogen bridgehead compounds is the unfavorable steric interaction between the adjacent C(4)=O and the R group. As a consequence of this interaction, the C(4)-N(5) bond becomes the weakest bond in the molecule. On the input of sufficient energy, it may split to yield rearrangement ring systems *via* an iminoketene intermediate [9].

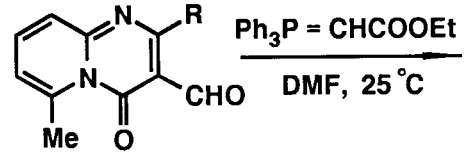
This type of ring transformation is involved in the synthesis of nalidixic acid and related antibacterial agents [10], starting from α-azahetarylaminomethylenemalonates.

Besides the nature of the substituent R in the nitrogen bridgehead compounds, the resonance effect of the substituent at position 3 also plays a significant role during the ring transformation [3,11].

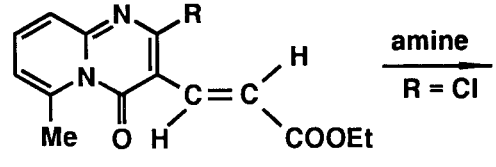
This paper deals with an investigation of the synthesis and thermal ring transformation of ethyl 2-substituted 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates **3-6**.

Synthesis of 2-Substituted 6-Methyl-4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates.

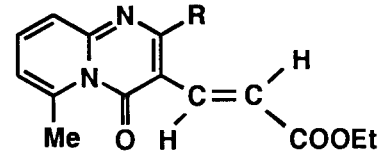
2-Phenyl- and 2-chloropyridopyrimidine-3-acrylates **3**, **4** were obtained in good yields in the Wittig reaction of the appropriate 3-formylpyridopyrimidinones **1**, **2** [12] and [(ethoxycarbonyl)methylene]triphenylphosphorane [13] in DMF at room temperature for 10 hours (Method A). Similar reactions of 2-(1-piperidinyl)- and 2-*n*-butylamino-3-formyl-6-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones [12] did not give 2-aminopyridopyrimidine-3-acrylates **5**, **6** in satisfactory yields, so these compounds were prepared by the reaction of 2-chloropyridopyrimidine-3-acrylate **4** and the appropriate amine in boiling ethanol (Method B).



1 R = Ph
2 R = Cl



3 R = Ph
4 R = Cl



5 R = piperidino
6 R = NHnBu

4-Oxo-4*H*-pyrido[1,2,-*a*]pyrimidine-3-acrylates **3-6** contain a *trans*-acrylate side-chain at position 3, as indicated

Table 1
Physical and Analytical Data on Compounds **3-19**

Compound No	R	R'	Method	Yield %	Mp, °C (Solvent)	Formula (Molecular Weight)	Analysis % Calcd./Found C	H	N	Hlg
3	Ph		A	62	178 (EtOH)	$C_{20}H_{18}N_2O_3$ (334.377)	71.84 71.79	5.43 5.43	8.38 8.33	
4	Cl		A	74	181-182 (EtOH)	$C_{14}H_{13}ClN_2O_3$ (292.723)	57.45 57.68	4.48 4.42	9.57 9.53	12.11 12.05
5	Pi [a]		B	94	180-182 (EtOH)	$C_{19}H_{23}N_3O_3$ (341.413)	66.84 66.85	6.79 6.76	12.31 12.27	
6	NH-*n*-Bu		B	88	71-73 (EtOEt)	$C_{18}H_{23}N_3O_3$ (329.402)	65.63 65.41	7.04 6.98	12.76 12.83	
7	Ph		C	70	184-186 (benzene) [b]	$C_{20}H_{18}N_2O_3$ (334.377)	71.84 71.70	5.43 5.40	8.38 8.30	
8	Ph		C	1.7	245-248 (MeCN)	$C_{18}H_{12}N_2O_2$ (288.309)	74.99 74.72	4.20 4.18	9.72 9.69	
9	Pi [a]		D-1	63	207 (AcOEt)	$C_{19}H_{23}N_3O_3$ (341.413)	66.84 66.75	6.79 6.76	12.31 12.25	
10	Pi [a]		D-1	15	164 (AcOEt)	$C_{17}H_{17}N_3O_2$ (295.343)	69.14 68.99	5.80 5.76	14.23 14.17	
			D-2	66	164 (AcOEt)					
			E	58	164 (AcOEt)					
11	H		F-1	58	290-292 (DMF)	$C_{12}H_8N_2O_3$ (228.209)	63.16 63.06	3.53 3.50	12.28 12.33	
			F-2	73	290-292 (DMF)					
12	NH-*n*-Bu		G	1.8	217-220	$C_{18}H_{23}N_3O_3$ (329.266)	65.63 65.81	7.04 6.98	12.76 12.80	
13	NH-*n*-Bu			6.1	186-188	$C_{16}H_{17}N_3O_2$ (283.331)	67.83 67.97	6.05 6.04	14.83 14.80	
14				14.1	255-258 (MeOH)	$C_{16}H_{17}N_3O_2$ (283.331)	67.83 67.62	6.05 5.98	14.83 14.74	
15	Ph	Et	H-1	82	18 2-183 (EtOH)	$C_{22}H_{22}N_2O_3$ (362.429)	72.91 72.63	6.12 6.10	7.73 7.78	
16	Ph	H	I	81	286-288 (EtOH)	$C_{20}H_{18}N_2O_3$ (334.375)	71.84 71.66	5.43 5.40	8.38 8.34	
17	Pi [a]	Et	H-1	78	116 (EtOH)	$C_{21}H_{27}N_3O_3$ (369.465)	68.27 68.03	7.37 7.32	11.37 11.33	
18	Pi [a]	H	I	74	233-236 (EtOH)	$C_{19}H_{23}N_3O_3$ (341.411)	66.84 66.62	6.79 6.82	12.31 12.25	
19	Et		H-2	42	200-202 (EtOH)	$C_{14}H_{12}N_2O_3$ (256.261)	65.62 65.85	4.72 4.68	10.93 10.94	

[a] Pi = piperidino. [b] Refluxed in the solvent given.

by the high coupling constant of the vinyl moiety ($^3J_{CH=CH}$ 15-16 Hz). Some characteristics uv, ir and ^{1}H nmr data are enumerated in Tables 2 and 3.

Ring Transformation of 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates.

The ring transformation of 2-substituted 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates **3**, **6** was investigated by heating in high-boiling solvents, Dowtherm A [14] and Marlotherm [15].

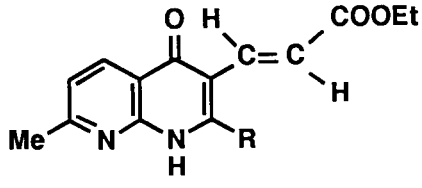
The heating of 2-phenylpyridopyrimidine-3-acrylate **3** in Dowtherm A at 255° gave 2-phenyl-1,8-naphthyridine-3-acrylate **7** in satisfactory yield (70%) only after a 5 hour reaction period. After filtration of the precipitated 2-phenyl-1,8-naphthyridine-3-acrylate **7**, another product **8** was isolated in low yield (1.7%) from the mother liquor by extraction with 10% aqueous hydrochloric acid (see Method C). Primarily on the basis of the lack of signals of the ethyl ester in the ^{1}H nmr spectrum (see Table 5) and a strong carbonyl stretching vibration at 1755 cm^{-1}, which is char-

Table 2

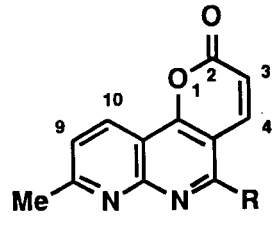
UV and IR Data on 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates **3-6** and 4-Oxo-1,4-dihydro-1,8-napthyridine-3-acrylates **7, 9, 15-18**

Compound No	Absorption maxima (nm) (ε)										ν C=O (ring)	ν C=O (ester)	νNH (cm^{-1})
3	417 [a]	(19 100)	405	(20 900)	287	(22 400)	263	(23 400)			1680	1700	
4	416 [a]	(19 100)	401	(24 000)	278	(25 700)	231	(17 400)			1690	1700	
5	393	(15 850)	310 [a]	(14 100)	271	(30 900)	251 [a]	(15 150)			1680	1690	
6	386	(16 200)	308 [a]	(10 970)	292 [a]	(14 100)	287	(14 500)	267	(25 110)	1680		3360
7	330	(18 200)	286	(41 700)	280 [a]	(33 900)	240 [a]	(20 900)			1620	1710	3150
9	334	(13 800)	328 [a]	(13 800)	303	(18 600)	225	(15 850)			1620	1710	3200
15	340 [a]	(16 600)	331	(17 000)	286	(31 600)	277 [a]	(22 900)	238	(20 900)	1635	1700	
16	340 [a]	(15 150)	328	(15 860)	288	(30 200)	274 [a]	(24 540)	235	(24 000)	1635	1680	
17	348	(24 550)	315	(17 400)	245 [a]	(12 600)	217	(20 440)			1625	1695	
18	348	(27 540)	315	(18 630)	245 [a]	(14 120)	220	(21 400)			1630	1690	

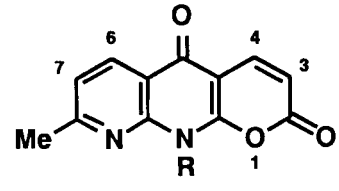
[a] Inflexion.



7 R = Ph
9 R = piperidino
12 R = NHnBu



8 R = Ph
10 R = piperidino
13 R = NHnBu



11 R = H
19 R = Et

Table 3

^{1}H NMR Data on 4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates **3-6** and 4-Oxo-1,4-dihydro-1,8-naphthyridine-3-acrylates **7, 9, 12, 15-18** (δ ppm)

Compound No	H-5	H-6	H-7	H-8	H-9	6-Me or 3-CH=CH-CO 7-Me	O-CH_2	– CH_3	N(1)-R	Substituent at position 2	$^3J_{CH-CH}$ [a] (Hz)
3			6.79 dd	7.38 -	7.71 [b]	3.11 s	7.70 d	7.27 d	4.16 q	1.25 t		7.38-7.71 [b]	15.7
4			6.88 dd	7.63 dd	7.43 dd	3.10 s	7.95 d	7.26 d	4.25 q	1.35 t			15.6
5			6.50 dd	7.36 dd	7.08 dd	3.10 s	7.61 d	6.95 d	4.23 q	1.31 t		3.40-3.75 m (4H) 1.50-1.93 m (6H)	15.3
6			6.49 dd	7.36 dd	7.09 dd	3.00 s	7.68 d	6.96 d	4.23 q	1.30 t		3.56 dt (2H); 0.88-1.90 (7H)	15.0
7 [c]	8.50 d	7.39 d				2.60 s	7.51 d	7.17 d	4.06 q	1.16 t	12.74 br [d]	7.50-7.68 (m)	15.8
9	8.45	7.11 d				2.60 s	7.61 d	7.33 d	4.24 q	1.34 t	8.33 br [d]	3.08-3.60 m (4H) 1.55-2.17 m (6H)	15.5
12	8.58 d [e]	7.20 d	[e]			2.69 s	7.70 d	6.98 d	4.26 q	1.33 t	[d]	4.08-4.45 m (2H) 0.60-2.05 m (7H)	15.9
15	8.71 d	7.26 d				2.71 s	7.51 d	6.93 d	4.02 q	1.23 t	4.31 q [f] 1.23 t	7.28-7.73 m (5H)	15.5
16	8.54 d	7.25 d				2.75 s	7.54 d	6.97 d	[g]		4.36 q [f] 1.27 t	7.35-7.60 m (5H)	15.7
17	8.55 d	6.80 d				2.71 s	7.71 d	7.21 d	4.26 q	1.24 t	4.67 q [f] 1.47 t	3.23-3.81 m (4H) 1.47-2.04 m (6H)	15.6
18 [c]	8.54 d	7.16 d				2.78 s	7.55 d	7.06 d	[g]		4.69 q [f] 1.43 t	3.17-3.65 m (4H) 1.54-1.83 m (6H)	15.4

[a] Vinyl moiety in side chain at position 3. [b] Overlapping signals. [c] In DMSO-d_6. [d] R=H. [e] $^3J_{5,6} \approx 7.9$ Hz. [f] R = CH_2CH_3. [g] Carboxylic acid.

Table 4

UV and IR Data on 2*H*-Pyrano[3,2-*c*][1,8]naphthyridin-2-ones **8**, **10**, 1,2,5,10-Tetrahydropyrano[2,3-*b*][1,8]naphthyridine-2,5-diones **11**, **19** and 1,2,5,10-Tetrahydroanthyridine-2,5-dione **14**

Compound No	Absorption mazima (nm) (ε)									ν CO (ring)	Other (cm^{-1})
8	340 [a]	(6 020)	322	(8 130)	310	(8 130)				1750	1630
10	365	(6 610)	317 [a]	(15 160)	301	(23 450)	292	(22 400)	240 (20 900)	1730	1610
11	368	(11 730)	353	(13 490)	316 [a]	(4 170)	300	(3 310)	278 (7 080)	1750 and 1680	3180
	268	(8 510)	258	(8 320)							
14	407	(3 890)	321	(33 100)	280	(9 550)	259	(7 940)		1650	1630
19	370	(15 850)	355	(16 220)	322 [a]	(6 460)	306	(7 760)	281 (10 470)	1750 and 1650	
	271	(12 880)	262	(13 180)							

[a] Inflexion.

Table 5

^{1}H NMR Data on 2*H*-Pyrano[3,2-*c*][1,8]naphthyridin-2-ones **8**, **10**, **13**, 1,2,5,10-Tetrahydropyrano-[2,3-*b*][1,8]naphthyridine-2,5-dione **11**, **19** and 1,2,5,10-Tetrahydroanthyridine-2,5-dione **14** in Deuteriochloroform (δ ppm)

Compund No.	H-3	H-4	H-6	H-7	H-9	H-10	8-Me	Substituent at position 5	Others	$^3J_{3,4}$	$^3J_{6,7}$	$^3J_{9,10}$
8	6.46 d	8.06 d			7.35-7.40 [a]	8.70 d	2.88 s	7.35-7.40 [a]		10.0		8.5
10	6.43 d	7.85 d			7.23 d	8.45 d	2.78 s	1.50-2.00 m (6H) 3.25-3.70 m (4H)		9.8		8.3
11	6.41 d	8.18 d	8.31 d	7.18 d			2.85 s		9.80 br [b]	9.6	8.1	
13	6.50 d	8.07 d			7.21 d	8.47 d	2.75 s	0.60-2.10 (7H) 3.73 m (2H)	5.75 br [c]	9.8		8.3
14	6.41 d	8.21 d	8.56 d	7.18 d			2.65 s		0.75-2.10 m (7H) [d] 4.31 t (2H) [d]	9.8	8.3	
19	6.45 d	8.24 d	8.39 d	7.19 d			2.70 s		1.35 t, 4.38 q [e]	9.7	8.1	

[a] Overlapping signal. [b] N(10)-H. [c] 5-NH-. [d] N(1)-*n*-Bu. [e] N(10)-CH_2CH_3.

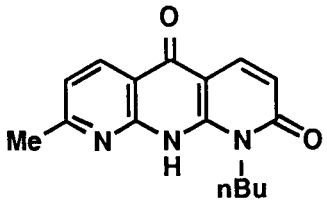
acteristic for unsaturated δ-lactones [16], the structure 8-methyl-5-phenyl-2*H*-pyrano[3,2-*c*][1,8]naphthyridin-2-one **8** was assigned to the above product. In the ir spectrum of 2-phenyl-1,8-naphthyridine-3-acrylate **7**, two carbonyl stretching vibrations were identified, at 1710 cm^{-1} for the ester carbonyl, and at 1620 cm^{-1} for the ring carbonyl at position 4. The latter is characteristic for the carbonyl group of the 1,4-dihydro-1,8-naphthyridin-4-one skeleton [3].

When the ring transformation of 2-phenylpyridopyrimidine-3-acrylate **3** was carried out at higher temperature, by heating at 320° in Marlotherm, extensive tar formation occurred.

The ring transformation of 2-piperidinopyridopyrimidine-3-acrylate **5** proceeded smoothly in Dowtherm A at 255° for 20 minutes and 2-piperidino-1,8-naphthyridine-3-acrylate **9** was obtained in 63% yield. In this case 15% of 5-piperidinopyrano[3,2-*c*][1,8]naphthyridin-2-one **10** was isolated from the mother liquor (Method D-1). If the reaction period was longer, 90 minutes, then only the 5-piperidinopyrano[3,2-*c*][1,8]naphthyridin-2-one **10** could be isolated in 66% yield (Method D-2). The piperidinopyrano-[3,2-*c*][1,8]naphthyridinone **10** was also prepared in 58% yield (Method E) from 2-piperidino-1,8-naphthyridine-3-acrylate **9** by heating in Dowtherm A at 255° for 90 minutes.

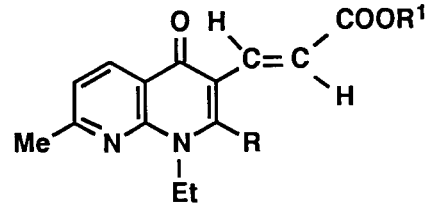
The heating of 2-chloropyridopyrimidine-3-acrylate **4** in Dowtherm A at 255° for 5 hours afforded an isomeric 2*H*-pyrano[2,3-*b*][1,8]naphthyridine-2,5-dione derivative **11** in 58% yield (Method F). Combustion analyses indicated no chlorine atom in the product and in the ir spectrum two carbonyl stretching vibrations appeared at 1750 cm^{-1} and 1680 cm^{-1}, which excluded the isomeric pyrano[3,2-*c*][1,8]-naphthyridin-2-one structure. 2*H*-Pyrano[2,3-*b*][1,8]naphthyridine-2,5-dione **11** was obtained in a higher yield (73%) when the ring transformation was carried out in Marlotherm at 320° for 25 minutes (Method G).

The ring transformation of 2-(*n*-butylamino)pyridopyrimidine-3-acrylate **6** in Dowtherm A at 255° was accompanied by tar formation. With the use of tlc, the formation of three products was detected. These were isolated on a silica gel column with a chloroform-methanol eluent



14

15 R = Ph, R^1 = Et
16 R = Ph, R^1 = H
17 R = piperidino, R^1 = Et
18 R = piperidino, R^1 = H



15 - 18

(Method H). 2-(*n*-Butylamino)-1,8-naphthyridine-3-acrylate **12** was obtained in 1.8% yield, 5-(*n*-butylamino)pyrano-[3,2-*c*][1,8]naphthyridin-2-one **13** in 6.1% yield and 1-(*n*-butyl)anthyridin-5-one **14** in 14% yield.

During the heating of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acrylates **3-6**, ring transformation occurred first to give 1,8-naphthyridine-3-acrylates **7, 9, 12** containing a *trans*-acrylate moiety (*vide infra*). (For example, the 2-phenyl derivative **3** afforded almost exclusively 1,8-naphthyridine-3-acrylate **7**.) The side-chain at position 3 then underwent isomerization to yield a 1,8-naphthyridine with a *cis*-acrylate moiety, which readily reacted with the 4-hydroxy group and/or the substituent at position 2 of the 1,8-naphthyridine skeleton to give a pyrano-1,8-naphthyridine and anthyridine derivative. 1,8-Naphthyridine-3-acrylate with a *cis*-vinyl moiety could never be isolated. [The 2-piperidino derivative **5** gave mainly 1,8-naphthyridine-3-acrylate **9** when the reaction period was 20 minutes (Method D-1), but the only product was pyrano[3,2-*c*][1,8]naphthyridone **10** when the reaction period was 90 minutes (Method D-2).]

The acrylate moiety of pyrido[1,2-*a*]pyrimidine enhanced the ring transformation because the 2-piperidino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one could be transformed into the appropriate naphthyridine only by heating at around 350° [3], while that of its acrylate derivative **5** occurred even at 250°.

Investigations of 1,8-Naphthyridine Derivatives.

The 1,8-naphthyridine-3-acrylates **7, 9** were alkylated with ethyl iodide in dimethylformamide in the presence of potassium carbonate at ambient temperature for 5 hours (Method H-1). The resulting 1-ethyl derivatives **15, 17** were hydrolyzed by treatment with potassium hydroxide in 50% aqueous ethanol under reflux for 30 minutes to give 1-ethyl-1,8-naphthyridine-3-acrylic acids **16, 18** (Method I), which exhibited no antibacterial activity.

The pyrano[2,3-*b*][1,8]naphthyridinone **11** was alkylated with ethyl iodide in dimethylformamide at 100° for 3 hours. The *N*-ethylated product **19** was purified by column chromatography (Method H-2).

The 1,8-naphthyridine-3-acrylates **7, 9** and pyrano[2,3-*b*][1,8]naphthyridine **11** may exist in oxo and enol tautomeric forms, but the similarity of their uv spectra to those of *N*-ethylated compounds **17-19** indicate that the oxo forms predominate.

The high coupling constants (≈15-16 Hz) of the vicinal hydrogens of the 3-acrylate and 3-acrylic acid side-chains justified their *trans* orientation for all 1,8-naphthyridine-3-acrylic acid derivatives **7, 9, 12, 15-18**.

EXPERIMENTAL

The melting points are uncorrected. Yields were not maximized. The uv spectra were recorded in ethanol with a Unicam SP-800 spectrophotometer, ir spectra were taken in potassium bromide pellets on a Zeiss UR-20 spectrometer, and ^{1}H nmr spectra were recorded in deuteriochloroform on a Bruker WP-80 DS spectrometer with tetramethylsilane as internal standard.

Method A.

A solution of 3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-4-one **1, 2** (50 mmoles) [10] and [(ethoxycarbonyl)methylene]triphenylphosphorane (17.42 g, 50 mmoles) in dimethylformamide (100 ml) was stirred at ambient temperature for 10 hours, and was then diluted with water (300 ml). The precipitated yellow crystalline product **3,4** was filtered off and washed with water. After drying, the product was recrystallized (see Table 1).

Method B.

A solution of 2-chloropyridopyrimidine-3-acrylate **4** (14.64 g, 50 mmoles) and the appropriate amine (125 mmoles) in ethanol (300 ml) was refluxed for 3 hours. The reaction mixture was cooled to room temperature and was diluted with water (900 ml). The precipitated crystalline product was filtered off and washed with a 1:1 mixture of ethanol and water. The dryed product was recrystallized (see Table 1).

Method C.

2-Phenylpyridopyrimidine-3-acrylate **3** (5.02 g, 15 mmoles) was added to preheated Dowtherm A (100 ml) at 255° and the reaction mixture was gently refluxed for 5 hours. After cooling of the reaction mixture to room temperature, it was diluted with light petroleum (200 ml). The precipitated naphthyridine-3-acrylate **7** was filtered off and washed with light petroleum (see Table 1). The filtrate was extracted with 10% aqueous hydrochloric acid (3 x 50 ml). The aqueous phases were combined and clarified with charcoal. The *p*H of the filtered aqueous solution was adjusted to 7 with solid sodium carbonate. The precipitated pyrano[3,2-*c*]-[1,8]naphthyridine **8** was filtered off and recrystallized from acetonitrile (see Table 1).

Method D-1.

2-(1-Piperidinyl)pyridopyrimidine-3-carboxylate **5** (5.12 g, 15 mmoles) was added to preheated Dowtherm A (500 ml) at 255° and the reaction mixture was gently refluxed for 20 minutes. The

reaction mixture was cooled to ambient temperature and diluted with light petroleum (1500 ml). The precipitated naphthyridine-3-acrylate **9** was filtered off, washed with light petroleum, and recrystallized (see Table 1). From the organic filtrate, pyrano[3,2-*c*][1,8]naphthyridine **10** was obtained by extracting with 10% aqueous hydrochloric acid (3 x 200 ml), the combined aqueous phase was neutralized with solid sodium carbonate, and the precipitated crystals of compound **10** were filtered off (see Table 1).

Method D-2.

When the reaction was carried out according to Method D-1, but with a reaction period of 90 minutes, only pyrano[3,2-*c*][1,8]-naphthyridine **10** could be isolated (see Table 1).

Method E.

2-(1-Piperidinyl)-1,8-naphthyridine-3-acrylate **9** (5.11 g, 15 mmoles) was added to preheated Dowtherm A (100 ml) and the reaction mixture was gently refluxed for 90 minutes. The reaction mixture was worked up according to Method D-1 to give pyrano[3,2-*c*][1,8]naphthyridine **10** (see Table 1).

Method F-1.

2-Chloropyridopyrimidine-3-acrylate **4** (2.93 g, 10 mmoles) was added to preheated Dowtherm A (150 ml) at 255° and the reaction mixture was gently refluxed for 5 hours. The reaction mixture was next cooled to room temperature and diluted with light petroleum (300 ml). The precipitated pyrano[2,3-*b*][1,8]naphthyridine-2,5-dione **11** was filtered off and recrystallized from dimethylformamide (see Table 1).

Method F-2.

2-Chloropyridopyrimidine-3-acrylate **4** (2.93 g, 10 mmoles) was added to preheated Marlotherm (150 ml) at 320°, and the reaction mixture was stirred at this temperature for 25 minutes. After cooling to room temperature, the reaction mixture was diluted with light petroleum (300 ml), and the precipitated pyrano[2,3-*b*]-[1,8]naphthyridine-2,5-dione **11** was filtered off and recrystallized from dimethylformamide (see Table 1).

Method G.

2-(*n*-Butylamino)pyridopyrimidine-3-acrylate **6** (3.0 g, 9.1 mmoles) was added to preheated Dowtherm A (300 ml) at 255° and the reaction mixture was gently refluxed for 50 minutes. The reaction mixture was cooled to ambient temperature. A tarry product (*ca.* 0.55 g) precipitated. The reaction mixture was left to stand at room temperature for 30 minutes and the organic phase was then decanted off, and diluted with light petroleum (600 ml). The precipitated crystalline product (1.105 g) was filtered off, washed with light petroleum and purified on a silica gel column (Kieselgel 60) with chloroform-methanol as eluent. After evaporation of the first fraction, pyrano[3,2-*c*][1,8]naphthyridinone **13** was obtained. The second fraction gave 1,8-naphthyridine-3-acrylate **12** and the third fraction gave anthyridine-2,5-dione **14** (see Table 1).

Method H-1.

The appropriate 1,8-naphthyridine-3-acrylate **7, 9** (10 mmoles) was reacted with ethyl iodide (3.12 g, 20 mmoles) in dimethylformamide (30 ml) in the presence of potassium carbonate (1.38 g, 10 mmoles) at ambient temperature for 5 hours. The reaction mixture was diluted with water (100 ml), and the precipitated *N*-ethylated product **15, 17** was filtered off and recrystallized (see Table 1).

Method H-2.

Pyrano[2,3-*b*][1,8]naphthyridine-3-acrylate **11** (2.65 g, 11.6 mmoles) was reacted with ethyl iodide (7.17 g, 46 mmoles) in dimethylformamide (35 ml) in the presence of potassium carbonate (1.61 g, 11.6 mmoles) at 100° for 3 hours. The reaction mixture was diluted with water (150 ml), and the precipitated *N*-ethylated product **19** was purified on a silica gel column (Kieselgel 60) with chloroform as eluent (see Table 1).

Method I.

1,8-Naphthyridine-3-acrylate **15, 17** (5 mmoles) was stirred in 50% aqueous ethanol (30 ml) in the presence of potassium hydroxide at 100° for 30 minutes. After cooling to ambient temperature, the *p*H of the reaction mixture was adjusted to 6.5 with 10% aqueous hydrochloric acid. The precipitated 1,8-naphthyridine-3-acrylate **16, 18** was filtered off and recrystallized (see Table 1).

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