A Facile and Novel Synthesis of 1,6-Naphthyridin-2(1*H*)-ones

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A new and convenient procedure for the synthesis of 1,6-naphthyridin-2(1*H*)-ones and their derivatives is described. In the first scheme 5-acetyl-6-[2-(dimethylamino)ethenyl]-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**4**) obtained by the reaction of *N,N*-dimethylformamide dimethyl acetal with 5-acetyl-1,2-dihydro-6-methyl-2-oxo-3-pyridinecarbonitrile (**3**) was cyclized to 1,2-dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carbonitrile (**5**) by the action of ammonium acetate. Thermal decarboxylation of acid **7** obtained from the hydrolysis of nitrile **5** led to a mixture of 5-methyl-1,6-naphthyridin-2(1*H*)-one (**8**) and its dimer **9**. Hydrazide **11** obtained from nitrile **5** in two steps was converted to 3-amino-5-methyl-1,6-naphthyridin-2(1*H*)-one (**12**) by the Curtius rearrangement. The amino group of **12** was readily replaced by treatment with aqueous sodium hydroxide to yield 3-hydroxy-5-methyl-1,6-naphthyridin-2(1*H*)-one (**13**). In the second scheme, Michael reaction of enamines of type **20** with methyl propiolate, followed by ring closure gave 5-acyl(aroyl)-6-methyl-2(1*H*)-pyridinones (**21**) which in turn were treated with Bredereck's reagent to produce 5-acyl(aroyl)-6-[2-(dimethylamino)ethenyl]-2(1*H*)-pyridinones (**22**). Treatment of **22** with ammonium acetate led to the formation of 1,6-naphthyridin-2(1*H*)-ones **23**.

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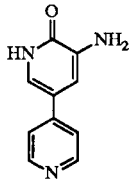
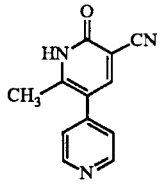
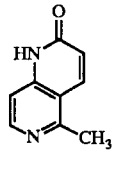
The search for new cardiotonic agents in our laboratory culminated in the successful development of two clinically useful agents: amrinone (**1**) [1] and milrinone (**2**) [2]. Our continuing efforts in this area have led to the discovery of another novel class of potent cardiotonic compounds: namely, 1,6-naphthyridin-2(1*H*)-ones. One of these compounds **8** [3] (medorinone) has been selected for advanced evaluation. This manuscript reports a convenient and novel general synthesis of these compounds.



1
amrinone



2
millrinone



8
medorinone

In 1969, Takahashi *et al.* [4] reported the first synthesis of 1,6-naphthyridin-2(1*H*)-one by the oxidation of 1,6-naphthyridine with hydrogen peroxide and subsequent reduction of the resulting *N*-oxide mixture. Three years later, Ogata and Matsumoto [5] described the preparation of 3-methyl-1,6-naphthyridin-2(1*H*)-one by the dehydrogenation of the corresponding 3,4-dihydro compound which in turn was synthesized by the photocyclization of *N*-(4-pyridinyl)methacrylamide. Shortly thereafter, Hawes and Gorecki [6] published a versatile synthesis of 3-substituted-1,6-naphthyridin-2(1*H*)-ones by the condensation of acetic acid derivatives with 4-aminonicotinaldehyde. The procedure reported herein leads to 5-substituted as well as 3,5-disubstituted 1,6-naphthyridin-2(1*H*)-ones from readily available starting materials in high overall yields.

Results and Discussion.

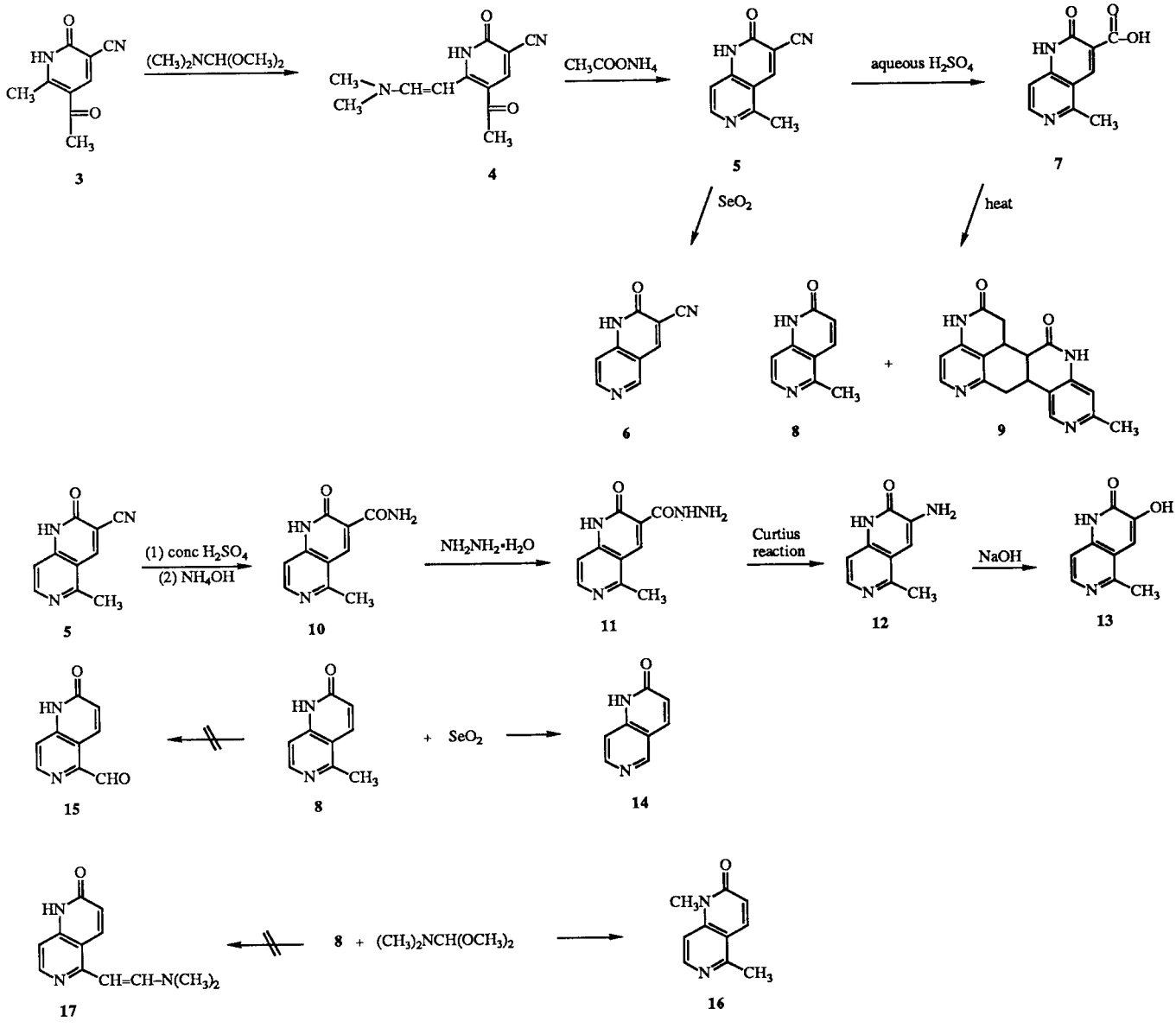
Scheme I. Synthesis of 3,5-Disubstituted-1,6-naphthyridin-2(1*H*)-ones.

Treatment of pyridinone **3** with *N,N*-dimethylformamide dimethyl acetal gave adduct **4** in 75% yield. Reaction of **4** with ammonium acetate resulted in the quantitative formation of 1,6-naphthyridine derivative **5**. The structure of this compound was consistent with its spectral and analytical data (Experimental) and was further confirmed by its conversion to the known cyano compound **6** [6] by treatment with selenium dioxide. Hydrolysis of nitrile **5** with aqueous sulphuric acid gave the acid **7**, which upon attempted decarboxylation in boiling Dowtherm® led to a mixture of medorinone (**8**) and its dimer **9** approximately in a ratio of 4:3. The structure of **9** is supported by its spectral and analytical data (Experimental).

The 3-amino and 3-hydroxy analogs of **8** were prepared for structure activity relationship studies. The cyano compound **5** was converted to amide **10** by the action of concentrated sulphuric acid. Subsequent treatment of **10** with hydrazine hydrate produced hydrazide **11** in 80% yield. Curtius rearrangement of the acylazide prepared *in situ* from hydrazide **11** resulted in the formation of amine **12** which underwent a surprisingly facile replacement of the amino group by a hydroxy group upon heating with aqueous sodium hydroxide to yield **13** in 62% yield. Treatment of medorinone **8** with selenium dioxide gave 1,6-naphthyridin-2(1*H*)-one (**14**) instead of aldehyde **15**. Reaction of **8** with *N,N*-dimethylformamide dimethyl acetal gave exclusively the *N*-methylated compound **16** instead of enamine **17**.

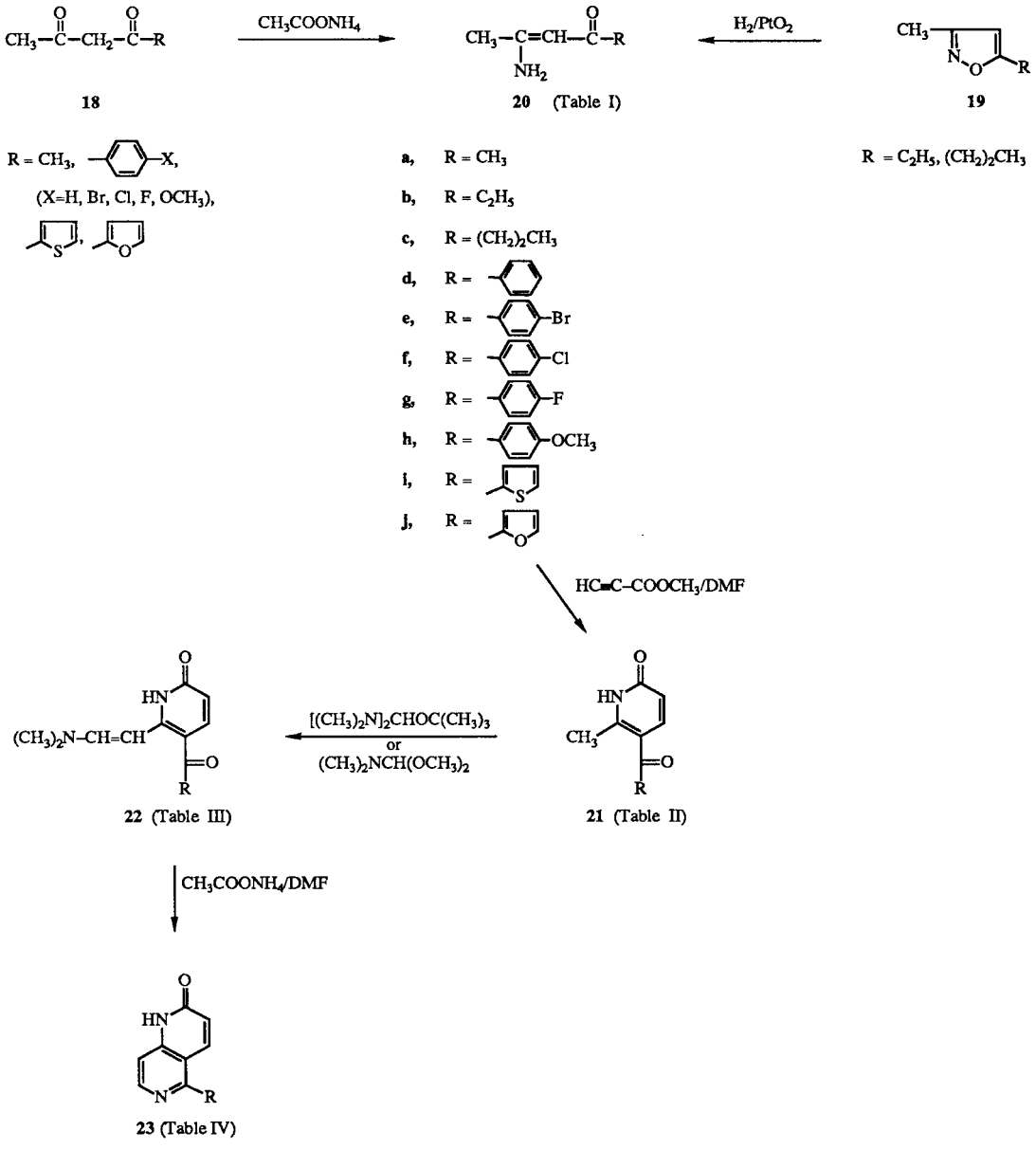
Scheme II. Synthesis of 5-Substituted-1,6-naphthyridin-2(1*H*)-ones.

Scheme 1



The difficulty in the preparation of 5-methyl-1,6-naphthyridin-2(1*H*)-one (**8**) by the decarboxylation of 1,2-dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carboxylic acid (**7**) prompted us to find an alternative approach outlined here. The reaction between ethyl propiolate and enamines derived from cyclohexane-1,3-dione [7] and ethyl acetoacetate [8] has been reported to produce a quinolone and a pyridinone derivative respectively. However, to our knowledge, the corresponding reaction involving open chain 1,3-diketones is not known. We have found that the reaction between enamines of type **20** and methyl propiolate results in the formation of 5-acyl-6-methyl-2(1*H*)-pyridinones **21** in moderate to good yields (Table II). 1,3-Diketones **18** which were not available commercially, were prepared by published procedures [9,10]. Enamines **20** were prepared either by reacting the corresponding 1,3-diketones **18** with ammonium acetate [11] or by the hydrogenolysis of isoxazoles **19** [12] (Table I). The reaction of Bredereck's reagent with pyridinone **21** afforded adducts **22** in very high yields (Table III). The yields of these adducts fell considerably when *N,N*-dimethylformamide dimethyl acetal was substituted for Bredereck's reagent probably due to side reactions (*N*- and *O*-methylation of the pyridinone). Treatment of **22** with ammonium acetate afforded 1,6-naphthyridin-2(1*H*)-ones **23** in excellent yields (84-98%) (Table IV).

Scheme II



EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The ^{1}H nmr spectra were obtained in deuteriotrifluoroacetic acid, unless indicated otherwise, on a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. All the compounds gave ^{1}H nmr spectra consistent with the proposed structures. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

5-Acetyl-6-[2-(dimethylamino)ethenyl]-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**4**).

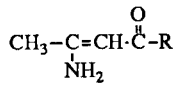
A mixture containing nitrile **3** [13] (58 g, 0.33 mole), *N,N*-dimethylformamide dimethyl acetal (50 ml, 0.38 mole), and *N,N*-dimethylformamide (200 ml) was stirred at ambient temperature for 22 hours. A bright yellow solid crystallized from the solution which was collected, washed with methanol, and dried to yield **4** (57.2 g, 75%), mp 268-271°; ^{1}H nmr: δ 11.79 (s, 2H, exchanged), 8.83 (s, 1H, 4-H), 8.35 [s, 1H $(CH_3)_2N-CH=CH-$], 4.0, 3.60 [6H, $-N(CH_3)_2$], 2.73 (s, 3H, $CH_3-C=O$).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.44; H, 5.50; N, 17.93.

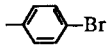
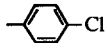
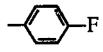
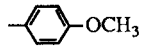
1,2-Dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carbonitrile (**5**).

A mixture of nitrile **4** (33.2 g, 0.15 mole), ammonium acetate (21.9 g, 0.3 mole), and *N,N*-dimethylformamide (300 ml) was stirred and heated in an oil bath at 120-130° for 3 hours. The resulting dark brown solution was concentrated to dryness, the

Table I

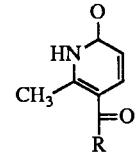


20

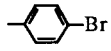
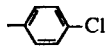
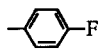
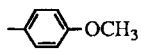
Compound	R	mp, °C	yield, %	crystallization solvent	formula	Analysis Calcd./Found C	H	N
20a	CH_3	42-43 [a]	94 [d]					
20b	C_2H_5	60-63 [b]	95 [d]					
20c	$(CH_2)_2CH_3$	47.5 [c]	90 [d]					
20d		144-145 [a]	85 [d]					
20e		126-128	70	hexane	$C_{10}H_{10}BrNO$	50.03 50.06	4.20 4.39	5.83 5.90
20f		126-129	74	hexane	$C_{10}H_{10}ClNO$	61.39 61.22	5.15 5.27	7.15 7.48
20g		125-127	72	Et_2O	$C_{10}H_{10}FNO$	67.03 67.07	5.62 5.69	7.82 7.79
20h		126-128	89	Et_2O	$C_{11}H_{13}NO_2$	69.09 69.35	6.85 6.84	7.32 7.32
20i		169-171	80	2-PrOH	C_8H_9NOS			
20j		128-130	77	Et_2O	$C_8H_9NO_2$	63.57 63.43	6.00 5.94	9.27 9.06

[a] Lit mp, ref [11]. [b] Lit mp, ref [12b]. [c] Lit mp, ref [12a]. [d] Crude material was used without purification and characterization.

Table II

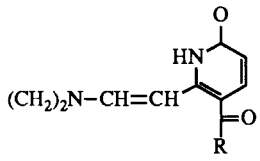


21

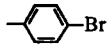
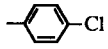
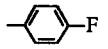
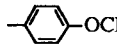
Compound	R	mp, °C	yield, %	crystallization solvent	formula	Analysis Calcd./Found C	H	N
21a	CH_3	194-196	62	2-PrOH	$C_8H_9NO_2$	63,57 63.20	6.00 5.92	9.27 9.45
21b	C_2H_5	173-175	43	2-PrOH	$C_9H_{11}NO_2$	65.14 65.18	6.71 6.71	8.48 8.49
21c	$(CH_2)_2CH_3$	167-168	47	2-PrOH	$C_{10}H_{13}NO_2$	67.02 66.96	7.31 7.34	7.82 7.82
21d		185-187	72	[a]	$C_{13}H_{11}NO_2$	73.23 73.30	5.20 5.33	6.57 6.57
21e		251-253	74	[a]	$C_{13}H_{10}BrNO_2$	53.45 53.74	3.45 3.63	4.79 4.85
21f		239-240	53	[a]	$C_{13}H_{10}ClNO_2$	63.04 62.94	4.06 4.16	5.65 5.75
21g		200-203	52	[a]	$C_{13}H_{10}FNO_2$	67.53 67.56	4.36 4.33	6.06 6.00
21h		228-230	65	[a]	$C_{14}H_{13}NO_3$	69.12 69.22	5.39 5.50	5.76 5.73
21i		227-228	47	[a]	$C_{11}H_9NO_2S$			
21j		258-260	56	[a]	$C_{11}H_9NO_3$	65.02 65.09	4.46 4.61	6.89 6.86

[a] The product crystallized from the reaction mixture on cooling.

Table III



22

Compound	R	mp, °C	yield, % [a]	formula	Analysis Calcd./Found C	H	N
22a	CH_3	238-240	70 (39) [b]	$C_{11}H_{14}N_2O_2$	64.06	6.84	13.58
					64.07	6.83	13.30
22b	C_2H_5	204-206	70 (39) [b]	$C_{12}H_{16}N_2O_2$	65.43	7.32	12.72
					65.35	7.44	12.77
22c	$(CH_2)_2CH_3$	203-205	92 (42) [b]	$C_{13}H_{18}N_2O_2$	66.64	7.74	11.96
					66.66	7.70	11.99
22d		202-204	89 (48) [b]	$C_{16}H_{16}N_2O_2$	71.62	6.01	10.44
					71.74	6.12	10.24
22e		265-268	99	$C_{16}H_{15}BrN_2O_2$	55.35	4.35	8.07
					55.37	4.48	7.97
22f		263-264	96	$C_{16}H_{15}ClN_2O_2$	63.48	4.99	9.25
					63.42	4.81	9.31
22g		251-253	85	$C_{16}H_{15}FN_2O_2$	67.12	5.28	9.78
					67.08	5.35	9.77
22h		216-218	98	$C_{17}H_{18}N_2O_3$	68.44	6.08	9.39
					68.44	6.42	9.13
22i		248-250	96	$C_{14}H_{14}N_2O_2S$			
22j		238-240	88	$C_{14}H_1N_2O_3$	65.11	5.46	10.85
					65.21	5.64	10.69

[a] The product crystallized from the reaction mixture in all cases. [b] The yield in parenthesis is for the reaction with *N,N*-dimethylformamide dimethyl acetal.

residue was treated with water (400 ml) and collected. The filter cake was recrystallized from *N,N*-dimethylformamide to yield **5** (27.4 g, ~100%) as tan needles, mp 278-280°; ^{1}H nmr δ 12.08 (s, 1H, exchanged), 9.06 (s, 1H, 4-H), 8.66 (d, 1H, 7-H, J = 7 Hz), 7.91 (d, 1H, 8-H, J = 7 Hz), 3.26 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.78; N, 22.70. Found: C, 64.62; H, 3.82; N, 22.65.

1,2-Dihydro-2-oxo-1,6-naphthyridine-3-carbonitrile (**6**).

A mixture of nitrile **5** (18.5 g, 0.1 mole), selenium dioxide (22 g, 0.2 mole), and acetic acid (300 ml) was stirred and heated under reflux for 20 hours and then filtered. The insoluble material was washed with boiling *N,N*-dimethylformamide (400 ml). The combined filtrates were concentrated to dryness under reduced pressure. The resulting orange solid residue was treated with 5% aqueous sodium hydroxide (200 ml) and insoluble material was filtered off. The filtrate was first treated with charcoal and then acidified with acetic acid whereupon an orange solid precipitated. This was recrystallized from *N,N*-dimethylformamide to produced **6** (9.4 g, 55%), mp >300° (lit mp >300° [6]); ^{1}H nmr δ 11.7 (s, 1H, exchanged), 9.44 (s, 1H, 5-H), 8.95 (s, 1H, 4-H), 8.44 (d, 1H, 7-H, J = 7 Hz), 8.05 (d, 1H, 8-H, J = 7 Hz).

1,2-Dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carboxylic Acid (**7**).

A mixture of nitrile **5** (63 g, 0.3 mole) and 50% aqueous sulfuric acid (200 ml) was heated with stirring in an oil bath at 135-140° for 18 hours, allowed to cool to room temperature and then poured on ice. The resulting mixture was first neutralized by treating with aqueous ammonia and then reacidified with acetic acid. The tan granular solid that crystallized was collected, washed with water and dried to afford **7** (54.8 g, 90%), mp 255-257° dec.

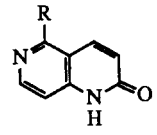
Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.63; H, 4.29; N, 14.00.

5-Methyl-1,6-naphthyridin-2(1*H*)-one (**8**) and Dimer **9**.

To stirred and boiling Dowtherm® (1 l) was added acid **7** (55 g, 0.27 mole) over a period of 5 minutes. After boiling for 40 minutes (by which time all the solids dissolved resulting in a dark brown solution), the reaction mixture was allowed to stand at room temperature overnight, whereupon a mixture of **8** and **9** (38.4 g) crystallized as a light orange solid. Chromatography (500 g silica gel 60, 10-40% methanol/diethyl ether) gave two fractions. The less polar component was recrystallized from 2-propanol giving **8** (22.4 g, 52%) as white prisms, mp 235-237°; ^{1}H nmr (DMSO-d_6): δ 11.93 (s, 1H, NH), 8.28 (d, 1H, 7-H, J = 6 Hz), 7.1 (d, 1H, 8-H, J = 6 Hz), 8.02 (d, 1H, 4-H, J = 10 Hz), 6.56 (d, 1H, 3-H, J = 10 Hz), 2.69 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.48; H, 5.26; N, 17.49.

Table IV



23

Compound	R	mp, °C	yield, % [a]	crystallization solvent	formula	Analysis Calcd./Found C	H	N
8	CH_3	238-240	84	2-PrOH	$C_9H_8N_2O$			
23b	C_2H_5	186-188	98	2-PrOH	$C_{10}H_{10}N_2O$	68.95	5.75	16.08
						69.09	5.83	15.94
23c	$(CH_2)_2CH_3$	201-203 [a]	98	EtOH-E_2O	$C_{11}H_{12}N_2O \cdot CH_3SO_3H$	50.69	5.67	9.85
						50.54	5.74	9.70
23d		261-263	94	[b]	$C_{14}H_{10}N_2O$	75.66	4.54	12.66
						75.67	4.61	12.57
23e		278-280	98	[b]	$C_{14}H_9BrN_2O$	55.84	3.01	9.30
						55.81	3.12	9.28
23f		282-284	88	[b]	$C_{14}H_9ClN_2O$	65.51	3.53	10.91
						65.21	3.42	10.94
23g		285-288	99	[b]	$C_{14}H_9FN_2O$	69.99	3.78	11.66
						70.10	3.93	11.72
23h		250-252	94	[b]	$C_{15}H_{12}N_2O_2$	71.42	4.79	11.10
						71.36	4.90	10.86
23i		238-240	98	[b]	$C_{12}H_8N_2OS$			
23j		> 300	90	[b]	$C_{12}H_8N_2O_2$	67.92	3.80	13.20
						67.93	3.80	13.25

[a] Melting point of the methanesulfonic acid salt. [b] Product crystallized from the reaction mixture on cooling.

The more polar component was recrystallized from a large volume of *N,N*-dimethylformamide to afford the dimer **9** (17.4 g, 40%) as an amorphous powder, mp >300°; ^{1}H nmr δ 12.1 (s, 2H, exchanged), 8.45 (d, 2H), 7.5 (d, 1H), 7.45 (d, 1H), 4.5-3.1 (m, 5H, 3 x -CH-, CH_2-), 2.96 (s, 5H, $-CH_3$, $-CH_2$-).

Anal. Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.57; H, 5.27; N, 17.40.

1,2-Dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carboxamide (**10**).

Nitrile **5** (37 g, 0.2 mole) was added over a period of 20 minutes to stirred concentrated sulfuric acid (200 ml) cooled in an ice bath. The resulting mixture was stirred until all the solids dissolved (2 hours), left at room temperature overnight and then poured on ice. This mixture was neutralized with aqueous ammonia giving an off-white solid which was recrystallized from *N,N*-dimethylformamide to afford **10** (28.9 g, 70%), mp >300°.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 58.74; H, 4.50; N, 20.56.

1,2-Dihydro-5-methyl-2-oxo-1,6-naphthyridine-3-carboxylic Acid Hydrazide (**11**).

A mixture of amide **10** (34 g, 0.17 mole) and hydrazine hydrate (150 ml) was stirred and heated on a steam bath for 18 hours and then concentrated to dryness under vacuum. Water (100 ml) was added to the residual yellow solid and the resulting mixture was neutralized with acetic acid. The fine yellow needles were collected, washed successively with water and methanol, and dried to produce **11** (32.6 g, 80%), mp >300°.

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.16; H, 4.74; N, 25.75.

3-Amino-5-methyl-1,6-naphthyridin-2(1*H*)-one (**12**).

To a stirred mixture of hydrazide **11** (21.8 g, 0.1 mole), concentrated hydrochloric acid (100 ml), and water (200 ml) cooled in an ice bath was added a solution of sodium nitrite (8 g, 0.11 mole) in water (30 ml) over 30 minutes, while maintaining the internal temperature below 5°. The resulting orange solution was stirred in an ice bath for 2 hours and then at room temperature for 2 hours and finally heated on a steam bath for 5 hours. After chilling in an ice bath, the reaction mixture was neutralized with solid potassium carbonate. The resulting yellow precipitate was collected, washed with water, dried and recrystallized from *N,N*-dimethylformamide to yield **12** (8.3 g, 50%), mp 283-285° dec; ^{1}H nmr: δ 11.75 (s, 3H, exchanged), 8.45 (d, 1H, 7-H, J = 7 Hz), 8.08 (s, 1H, 4-H), 7.8 (d, 1H, 8-H, J = 7 Hz), 3.2 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.61; H, 5.33; N, 23.85.

3-Hydroxy-5-methyl-1,6-naphthyridin-2(1*H*)-one (**13**).

A mixture of amine **12** (1.75 g, 10 mmoles) and 10% aqueous sodium hydroxide (25 ml) was heated on a steam bath for 7 hours and the resulting solution was acidified with acetic acid. The resulting white crystalline solid was recrystallized from *N,N*-dimethylformamide to give **13** (1.1 g, 62%), mp >300°; ^{1}H nmr: δ 11.85 (s, 2H, exchanged), 8.45 (d, 1H, 7-H, J = 7 Hz), 7.85 (d, 1H,

8-H, J = 7 Hz), 7.72 (s, 1H, 4-H), 3.14 (s, 3H, CH_3).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 60.96; H, 4.77; N, 16.17.

1,6-Naphthyridin-2(1*H*)-one (**14**).

A mixture of naphthyridinone **8** (16 g, 0.1 mole) and selenium dioxide (22 g, 0.2 mole) in acetic acid (200 ml) was stirred and heated under reflux for 24 hours. The resulting insoluble substance was filtered off and washed with hot methanol (300 ml). The filtrate was concentrated to dryness under reduced pressure to give a yellow solid residue which was dissolved in boiling water (400 ml), treated with charcoal and filtered. The filtrate was evaporated to dryness under reduced pressure and the yellow solid residue was recrystallized from ethanol to yield **14** (7.4 g, 51%), mp 295-297° (lit mp 302-304° [4]); ^{1}H nmr: δ 12.37 (s, 1H, exchanged), 9.28 (s, 1H, 5-H), 8.76 (d, 1H, 7-H, J = 6.5 Hz), 8.02 (d, 1H, 8-H, J = 6.5 Hz), 8.37 (d, 1H, 4-H, J = 10 Hz), 7.28 (d, 1H, 3-H, J = 10 Hz).

1,5-Dimethyl-1,6-naphthyridin-2(1*H*)-one (**16**).

A solution of naphthyridinone **8** (4.5 g, 28 mmoles) and *N,N*-dimethylformamide dimethyl acetal (4 ml, 30 mmoles) in *N,N*-dimethylformamide (15 ml) was heated on a steam bath for 7 hours and then comcentrated to dryness under reduced pressure. The yellow solid residue was recrystallized from 2-propanol to provide **16** (3.5 g, 73%), mp 203-205°; ^{1}H nmr (DMSO-d_6): δ 8.68 (d, 1H, 7-H, J = 6 Hz), 7.84 (d, 1H, 8-H, J = 6 Hz), 8.26 (d, 1H, 4-H, J = 10 Hz), 6.90 (d, 1H, 3-H, J = 10 Hz), 3.72 (s, 3H, N-CH_3), 2.98 (s, 3H, 5-CH_3).

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.16; H, 5.95; N, 16.15.

General Procedure for the Preparation of Enamines **20** (Table I).

3-Amino-1-(2-thienyl)-2-buten-1-one (**20i**).

A mixture of 1,3-diketone **18i** [13] (153 g, 0.9 mole), ammonium acetate (167.7 g, 2.2 moles), and toluene (1 l) was heated under reflux with azeotropic removal of water for 5 hours and then concentrated to dryness under reduced pressure. The resulting tan solid residue was recrystallized from 2-propanol to afford **20i** (122 g, 80%), mp 167-171°.

Anal. Calcd. for C_8H_9NOS: C, 57.46; H, 5.52; N, 8.38. Found: C, 57.75; H, 5.57; N, 8.43.

General Procedure for the Preparation of 5-Acyl (Aroyl)-6-methyl-2(1*H*)-pyridinones (**21**) (Table II).

6-Methyl-5-(2-thienylcarbonyl)-2(1*H*)-pyridinone (**21i**).

To a stirred solution of enamine **20i** (16.7 g, 0.1 mole) in *N,N*-dimethylformamide (75 ml) was added methyl propiolate (9.3 g, 0.11 mole) over 15 minutes. The resulting solution was stirred at ambient temperature for 3.5 hours and then heated under reflux for 24 hours. After cooling to room temperature, the light tan solid was filtered off to afford **21i** (10.5 g, 47%), mp 227-228°; ^{1}H nmr: δ 12.06 (s, 1H, exchanged), 8.37 (d, 1H, 4-H, J = 10 Hz), 8.08 (d, 1H, 3'-H), 7.73 (d, 1H, 5'-H), 7.32 (t, 1H, 4'-H), 7.28 (d, 1H, 3-H, J = 10 Hz), 2.79 (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.65; H, 4.27; N, 6.40.

General Procedure for the Preparation of 5-Acyl (Aroyl)-6-[2-(dimethylamino)ethenyl]-2-(1*H*)-pryidinones (**22**) (Table III).

6-[2-(Dimethylamino)ethenyl]-5-(2-thienylcarbonyl)-2(1*H*)-pyridinone (**22i**).

A mixture of pyridinone **21i** (57.8 g, 0.26 mole), Bredereck's reagent (62 ml, 0.3 mole) in *p*-dioxane (400 ml) was heated under reflux while stirring for 2.5 hours. A bright yellow solid crystallized during the reaction. The reaction mixture was cooled to room temperature and the product was filtered off to yield **22i** (70.1 g, 96%), mp 248-250° dec; ^{1}H nmr: δ 11.88 (s, 2H, exchanged, NH, -C*H*=CH-N(CH_3)$_2$), 8.65 (s (b), 1H, CH=C*H*-N(CH_3)$_2$), 8.4 (d, 1H, 4-H, J = 10 Hz), 8.05 (d, 1H, 3'-H), 7.77 (d, 1H, 5'-H), 7.37 (t, 1H, 4'-H), 7.25 (d, 1H, 3-H, J = 10 Hz), 3.86, 3.98 (6H, -N(CH_3)$_2$).

Anal. Calcd. for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.27; H, 5.13; N, 9.96.

General Procedure for the Preparation of 1,6-Naphthyridin-2(1*H*)-ones (**23**) (Table IV).

5-(2-Thienyl)-1,6-naphthyridin-2(1*H*)-one (**23i**).

A mixture of **22i** (49 g, 0.18 mole), ammonium acetate (27.5 g, 0.35 mole), and *N,N*-dimethylformamide (250 ml) was heated under reflux with stirring for 2 hours and then cooled to room temperature. The light yellow solid was collected, washed with ethanol and dried to afford **23i** (40 g, 98%), mp 238-240°; ^{1}H nmr: δ 12.13 (s, 1H, exchanged NH), 8.68 (d, 1H, 7-H, J = 7 Hz), 8.67 (d, 1H, 4-H, J = 10 Hz), 8.06 (d, 1H, 3'-H), 7.90 (d, 1H, 8-H, J = 7 Hz), 7.87 (d, 1H, 5'-H), 7.50 (t, 1H, 4'-H), 7.27 (d, 1H, 3-H, J = 10 Hz).

Anal. Calcd. for $C_{12}H_8N_2OS$: C, 63.13; H, 3.53; N, 12.27. Found: C, 63.16; H, 3.55; N, 12.19.

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