Rearrangement Reactions of Heterocycles. 12 [1]. Rearrangement of 6-Substituted Pyrido[1,2-*a*]pyrimidines to Isomeric 1,8-Naphthyridines and Some of Their Further Reactions

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2-Amino-6-methylpyridine (**4**) reacts with active malonates **2a-d** or **3a-d** either in acetone solution with triethylamine as catalyst at room temperature or with active malonates **2a-d** in acetone solution at reflux temperature to yield the pyrido[1,2-*a*]pyrimidines **5a-d**. 2,6-Diaminopyridine (**8**) already reacts without triethylamine with **2a-d** at room temperature to afford the pyrido[1,2-*a*]pyrimidines **9a-d**. At higher temperatures pyrido[1,2-*a*]pyrimidines **5** and **9** are rearranged *via* ketene intermediates [1] to yield the 1,8-naphthyridines **6a-d**, and **10a-d**, respectively. The naphthyridines **6** and **10** can also be synthesized directly from **4** or **8** using either diethyl malonates **1** or - with better results - the active malonates **2** at 240-250°. Further reaction of **10a-e** with **2c,d** leads to the pyridonaphthyridines **12a-f**. Nitration of **6c** yields the nitro derivative **16** and chlorination of **6c,d** gives **15c,d**, while the chlorination of **10c** affords the dichloro derivative **17**.

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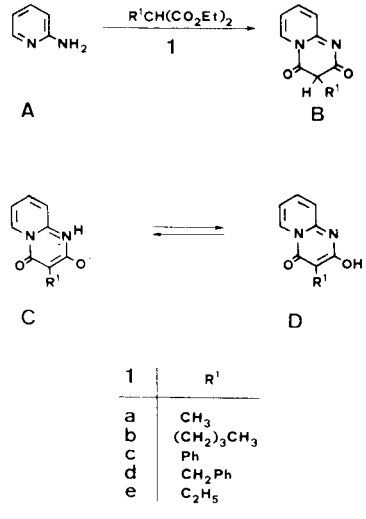
The thermal condensation of 2-aminopyridine **A** with malonic esters **1** yields bicyclic compounds which were first described as dioxo compounds **B** by Tschitschibabin [3]. In view of their high melting points and some reactions Snyder and Robison [4] regarded these products as 2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **C**. Later on Katritzky and Waring [5] have shown that the betain structure **D** is the predominant tautomeric form in water (K_t **C/D** = 20). Apart from the thermic reaction, a synthesis of pyrido[1,2-*a*]pyrimidines **B-C** from **A** and the pentachlorophenylmalonates **3** has been described [6].

Scheme 1

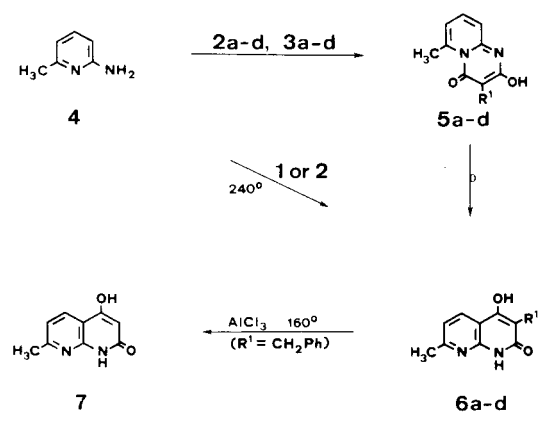


1	R¹
a	CH_3
b	$(CH_2)_3CH_3$
c	Ph
d	CH_2Ph
e	C_2H_5

While 6-unsubstituted 2-aminopyridines gave only pyrido[1,2-*a*]pyrimidines **B-D**, it has been shown that the thermal condensation of 6-substituted 2-aminopyridines gave isomeric 1,8-naphthyridines [7,8]. This has also been observed for the condensation with ethoxymethylene malonates [9,10,11]. These results have been explained by steric hindrance [9] but not without opposition [12].

While it was supposed that 7-substituted pyrido[1,2-*a*]-pyrimidines **5a-d** are not available from ester condensation [7], we found two ways to obtain **5a-d** from **4** and **2a-d** [13] or **3a-d** [6], respectively: firstly, stirring of equimolar amounts of **4** and **2a-d** with two equivalents of triethylamine in acetone solution at room temperature or, secondly, refluxing of equimolar amounts of **4** and **2a-d** without triethylamine in the same solvent. Previously gentle con-

Scheme 2



1,2,3,5,6	R¹
a	CH_3
b	$(CH_2)_3CH_3$
c	Ph
d	CH_2Ph

2a-d: $R^1CH(CO_2C_6H_2Cl_3)_2$

3a-d: $R^1CH(CO_2C_6Cl_5)_2$

densation of pentachlorophenylmalonates **3a-d** with 1,3-dinucleophilic systems has been described [6,14,15]; we found, use of **2a-d** was advantageous because of the better solubility of 2,4,6-trichlorophenol in acetone; both methods afforded similar yields, but use of **2a-d** gave a purer crude product.

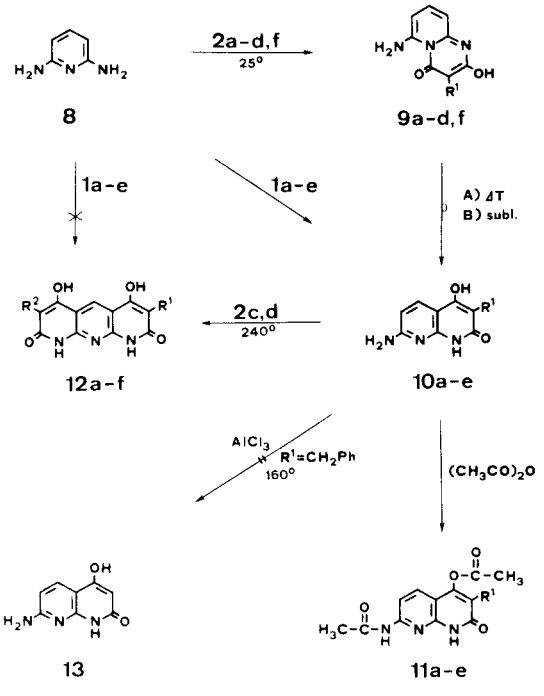
The pyrido[1,2-*a*]pyrimidines **5a-d** underwent rearrangement *via* carbonyl ketene intermediates [2,16] to the isomeric 1,8-naphthyridines **6a-d** at 220°. The latter one could also be obtained by thermal reaction of **4** with substituted malonates **1**. However, only **1c,d** gave reasonable yields of **4c,d**. For the synthesis of **4a,b** the use of bis(2,4,6-trichloro-phenyl)malonates **2a,b** was advantageous.

Treatment of **4** with the unsubstituted bis(2,4,6-trichlorophenyl)malonate **2f** in acetone solution at reflux temperature resulted in the formation of yellow needles with a melting point of 151° in poor yield, possibly the same product already obtained by Dashkevich and Kuvaeva [17] by the reaction of **4** with carbon suboxide, characterized as 3-unsubstituted 2-hydroxy-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (melting point 159-160°). Rearrangement of this compound to the isomeric compound **7** could not be performed. However, the synthesis of **7** could be achieved by elimination of the benzyl-group of **6d** with aluminum trichloride at 160°.

Reaction of 2,6-diaminopyridine **8** with **2a-d** in acetone solution gave already the pyrido[1,2-*a*]pyrimidines **9a-d** without use of triethylamine as catalyst at room temperature; the 3-unsubstituted pyrido[1,2-*a*-]pyrimidine **9f** was also obtained in this way. Rearrangement of **9a-d** to the 1,8-naphthyridines **10a-d**, which were also synthesized by direct condensation with malonates **1** at 240°, was performed by heating in nitrobenzene or by sublimation, respectively. The 3-unsubstituted 1,8-naphthyridine **13** could not be obtained by elimination of the benzyl group of **10d**, too. Treating of **10d** with aluminum trichloride at 160° gave only decomposition.

The reaction of **8** with two equivalents of malonates **1** did not produce pyrido[2,3-*b*]1,8-naphthyridines **12d,f**, although the reaction of **10a-e** with acetic anhydride gave the diacetyl compounds **11a-e**. The tricyclic pyrido[2,3-*b*]-1,8-naphthyridines **12a-f** could only be obtained by condensation with **2c,d** at 240°.

Scheme 3

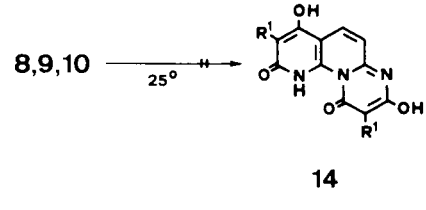


9	R^1
a	CH_3
b	$(CH_2)_3CH_3$
c	Ph
d	CH_2Ph
f	H

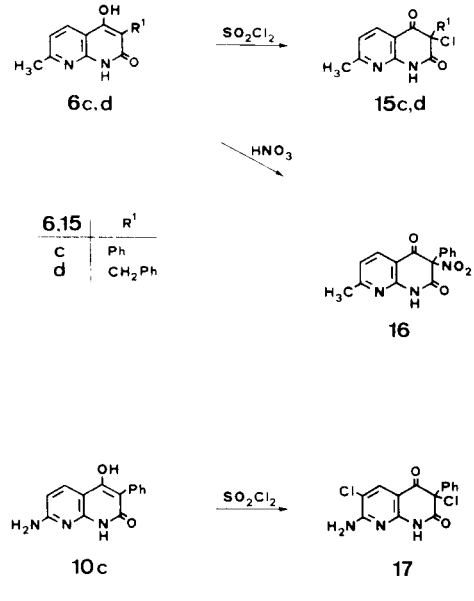
10,11	R^1
a	CH_3
b	$(CH_2)_3CH_3$
c	Ph
d	CH_2Ph
e	C_2H_5

12	R^1	R^2
a	CH_3	Ph
b	$(CH_2)_3CH_3$	Ph
c	Ph	Ph
d	CH_2Ph	Ph
e	C_2H_5	Ph
f	CH_2Ph	CH_2Ph

Scheme 4



Scheme 5



6,15	R^1
c	Ph
d	CH_2Ph

A reaction of compounds **8**, **9**, or **10**, respectively, at lower temperatures to pyrimido[1,2-*a*]1,8-naphthyridines **14** could not be observed, probably because of the poor solubilities of **9** and **10** in acetone, therefore the experiments had to be performed in suspension.

Chlorination of the naphthyridines **6c,d** by treatment with sulfuryl chloride occurred at the malonyl moiety, yielding **15c,d**, while nitration with nitric acid yields **16**. Reaction of **10c** with sulfuryl chloride gave the dichloro compound **17**.

EXPERIMENTAL

The melting points were determined in open capillary tubes on a Gallenkamp melting point apparatus Model MFB-595 and are uncorrected. The ir spectra were recorded on a Perkin Elmer 298 spectrophotometer using samples in potassium bromide disks. The ^{1}H-nmr spectra were recorded in hexadeuteriodimethylsulfoxide (unless otherwise indicated) and with TMS as an internal standard; the instruments used were the Varian EM 360 at 60 MHz and the Varian XL 200 at 200 MHz. Elemental analyses were performed with an C,H,N-automat Carlo Erba 1106.

General Procedures for 3-Substituted 2-Hydroxy-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **5a-d**.

A) A solution of **4** (20 mmoles), **2a-d** (20 mmoles) and triethylamine (40 mmoles) in 100 ml of acetone was stirred for 30 minutes. The product started to precipitate after about one minute.

B) The reaction was carried out following method A but using **3a-d** instead of **2a-d**.

C) A solution of **4** (10 mmoles) and **2c,d** (10 mmoles) in 50 ml acetone was refluxed for 5 minutes; the product precipitated.

2-Hydroxy-3,6-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**5a**).

The yield was 1.64 g (43%, method A) and 1.49 g (39%, method B), mp 236° dec (ethanol); ir: 2800-2600 b, 1690 sh, 1660 s (lactam CO), 1630 s, 1600 s, 1520 s cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ = 1.9 (s, CH_3 at C-3), 3.1 (s, CH_3 at C-6), 6.8-7.0 (d, J = 7 Hz, H at C-7), 7.2-7.4 (d, J = 7 Hz, H at C-9), 7.5-7.8 (t, J = 7 Hz, H at C-8).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.95; H, 5.32; N, 14.76.

3-*n*-Butyl-2-hydroxy-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**5b**).

The yield was 2.12 g (46%, method A) and 2.03 g (44%, method B), mp 214° dec (ethanol); ir: 2960 w, 2920 w, 1690 m, 1650 s (lactam CO), 1630 s, 1600 s, 1510 s cm^{-1}; ^{1}H-nmr: δ = 0.8-1.1 (m, butyl-CH_3), 1.1-1.6 (m, 2 butyl-CH_2), 2.2-2.5 (m, butyl-CH_2 at C-3), 3.0 (s, CH_3 at C-6), 6.8-7.0 (d, J = 7 Hz, H at C-7), 7.1-7.3 (d, J = 7 Hz, H at C-9), 7.6-7.9 (t, J = 7 Hz, H at C-8).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.20; H, 7.05; N, 12.01.

2-Hydroxy-6-methyl-4-oxo-3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidine (**5c**).

The yield was 2.14 g (43%, method A), 2.19 g (44%, method B), and 1.76 g (70%, method C), respectively, mp 226° dec (ethanol); ir: 3100-2400 b, 1690 s, 1650 s (lactam CO), 1620 s, 1590 s, 1520 m, 1490 m cm^{-1}; ^{1}H-nmr: δ = 3.0 (s, CH_3), 6.8-8.0 (m, 3 H at C-7, C-8, C-9, and 5 ArH).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.40; H, 4.77; N, 11.01.

3-Benzyl-2-hydroxy-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**5d**).

The yield was 2.60 g (49%, method A), 2.49 g (47%, method B), and 1.66 g (63%, method C), respectively, mp 228° dec (ethanol); ir: 3000-2400 b, 1690 m, 1650 s (lactam CO), 1620 s, 1590 s, 1520 m cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 3.2 (s, CH_3), 4.0 (s, CH_2), 7.2 (s, 5 ArH), 7.2-7.4 (d, J = 7 Hz, H at C-7), 7.6-7.8 (d, J = 7 Hz, H at C-9), 7.9-8.2 (t, J = 7 Hz, H at C-8).

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.07; H, 5.35; N, 10.49.

1,2-Dihydro-4-hydroxy-3,7-dimethyl-2-oxo-1,8-naphthyridine (**6a**).

A) A well triturated mixture of **4** (1.08 g, 10 mmoles) and **2a** (5.0 g, 11 mmoles) was heated to 250° for 15 minutes. The oily residue crystallized by the addition of cyclohexane to yield 1.24 g (65%), mp 280° dec (ethanol).

B) Compound **5a** (0.5 g) was heated to 225° for 20 minutes, the residue diluted with chloroform and recrystallized from ethanol to yield 0.19 g (38%); ir: 3300-2600 b, 1650 sh, 1630 sh, 1620 s (lactam CO), 1610 s, 1500 m cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 2.3 (s, CH_3 at C-3), 3.0 (s, CH_3 at C-7), 7.6-7.8 (d, J = 7 Hz, H at C-6), 8.9-9.1 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.90; H, 5.30; N, 14.66.

3-*n*-Butyl-1,2-dihydro-4-hydroxy-7-methyl-2-oxo-1,8-naphthyridine (**6b**).

A) A well triturated mixture of **4** (2.16 g, 20 mmoles) and **2b** (11.0 g, 21 mmoles) was heated to 250° for 30 minutes. The solid residue was digested with cyclohexane and recrystallized from dioxane to give 2.84 g (61%), mp 262° dec.

B) Compound **5b** (0.5 g) was heated to 205° for 15 minutes, the residue diluted with chloroform and recrystallized from dioxane to yield 0.15 g (30%); ir: 3150 w, 3050 w, 2960 m, 2940 m, 1650 sh, 1620 s (lactam CO), 1610 sh, 1500 m cm^{-1}; ^{1}H-nmr (trifluoroacetic acid): δ = 1.0 (m, butyl-CH_3), 1.6 (m, 2 butyl-CH_2), 2.8 (m, butyl-CH_2 at C-3), 3.0 (s, CH_3 at C-7), 7.6-7.8 (d, J = 7 Hz, H at C-6), 8.9-9.1 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.32; H, 6.95; N, 12.18.

1,2-Dihydro-4-hydroxy-7-methyl-2-oxo-3-phenyl-1,8-naphthyridine (**6c**).

A) A mixture of **4** (4.32 g, 40 mmoles) and **1c** (11.4 g, 48 mmoles) was heated to 240° for 90 minutes. The oily residue was diluted with cyclohexane to yield a brown precipitate which was recrystallized from dioxane to give 3.81 g (35%), mp 313° dec (lit mp 316-317° [7]).

Compound **5c** (0.5 g) was heated to 225° for 20 minutes, the solid residue washed with chloroform and recrystallized to yield 0.27 g (54%). ir: 3300-2700 b, 1640 s (lactam CO), 1600 s, 1560 w, 1500 m, 1480 sh, 1450 w, 1420 w cm^{-1}.

3-Benzyl-1,2-dihydro-4-hydroxy-7-methyl-2-oxo-1,8-naphthyridine (**6d**).

A) A mixture of **4** (2.16 g, 20 mmoles) and **1d** (5.75 g, 23 mmoles) in 15 ml diphenylether was refluxed for two hours. Dilution with about 80 ml cyclohexane gave 0.96 g (18%).

B) A well triturated mixture of **4** (2.16 g, 20 mmoles) and **2d** (11.06 g, 20 mmoles) was heated to 220-230° for 20 minutes. The residue was diluted with benzene to yield 3.85 g (72%), mp 265° (dioxane), (lit mp 265° [7]).

C) Compound **5d** (1.0 g) was heated to 220° for 30 minutes. The solid residue was diluted with chloroform to give 0.65 g (65%); ir: 3300-2600 b, 1650 sh, 1620 s (lactam CO), 1500 m cm^{-1}; ^{1}H-nmr: δ = 2.5 (m, CH_3 at C-7 and dimethylsulfoxide), 4.0 (s, CH_2), 7.0-7.4 (m, H at C-6 and 5 ArH), 8.1-8.3 (d, J = 7 Hz, H at C-5).

1,2-Dihydro-4-hydroxy-7-methyl-2-oxo-1,8-naphthyridine (**7**).

A mixture of **5d** (1.02 g, 4 mmoles) and dry aluminum trichloride (4.0 g, 29 mmoles) was heated to 160° for 10 minutes. The hot mixture was then poured into 100 ml of 1*N* hydrochloric acid to yield 0.70 g (100%) crude compound, mp 260° dec (sublimation at 240°, 17 mm Hg); ir: 3100 m, 2980 m, 2740 w, 2580 w, 1640 sh, 1620 s (lactam CO), 1600-1570 s, b, 1550 m, 1520 m cm^{-1}; ^{1}H-nmr: δ = 2.5 (m, CH_3 at C-7 and dimethyl sulfoxide), 5.7 (s, H at C-3), 7.1 (d, J = 7 Hz, H at C-6), 8.0 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.39; H, 4.75; N, 15.68.

General Procedure for 3-Substituted 6-Amino-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines **9a-d**.

A solution of **8** (5 mmoles) and **2a-d** (5 mmoles) in 25 ml acetone was stirred for 30 minutes, the product started to precipitate after about one minute.

6-Amino-2-hydroxy-3-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**9a**).

The yield was 0.55 g (58%), mp 264° dec (purification was accomplished by dissolution in 2*N* sodium hydroxide and precipitation with acetic acid); ir: 3300 m, 3160 m, 3000-2500 b, 1680 sh (lactam CO), 1630 s, 1590 s, 1510 w, 1450 m, 1410 w cm^{-1}; ^{1}H-nmr: δ 1.7 (s, CH_3), 6.1-6.3 (dd, J = 7 Hz, 1.5 Hz, 2 H at C-7 and C-9), 7.4-7.5 (t, J = 7 Hz, H at C-8), 9.0-9.4 (b, NH_2).

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.34; H, 4.72; N, 21.77.

6-Amino-3-*n*-butyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**9b**).

The yield was 1.05 g (90%), mp 291° dec (1-butanol); ir 3400-2900 b, 1660 s (lactam CO), 1620 s, 1590 m, 1570 m, 1510 m, 1460 m, 1410 sh, 1390 m cm^{-1}; ^{1}H-nmr: δ = 0.8-0.9 (t, J = 8 Hz, butyl-CH_3), 1.2-1.5 (m, 2 butyl-CH_2), 2.2-2.4 (t, J = 8 Hz, butyl-CH_2 at C-3), 6.1-6.3 (m, 2 H at C-7 and C-9), 7.4-7.6 (t, J = 7 Hz, H at C-8), 8.9-9.4 (b, NH_2).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.92; H, 6.54; N, 17.85.

6-Amino-2-hydroxy-4-oxo-3-phenyl-4*H*-pyrido[1,2-*a*]pyrimidine (**9c**).

The yield was 0.63 g (50%), mp 310° dec (1-butanol); ir: 3500-3000 b, 1670 s (lactam CO), 1630 s, 1570 s, 1500 m, 1450 m, 1400 w cm^{-1}; ^{1}H-nmr: δ = 6.3-6.4 (m, 2 H at C-7 and C-9), 7.0-7.3 (m, 5 ArH), 7.5-7.6 (t, J = 7 Hz, H at C-8), 9.0-9.4 (b, NH_2), 11.5 (s, OH).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.11; H, 4.50; N, 16.52.

6-Amino-3-benzyl-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**9d**).

The yield was 0.83 g (62%), mp 350-55° dec (1-butanol); ir: 3500-2500 b, 1660 sh (lactam CO), 1620 s, 1590-1560 s, 1500 w, 1450 m, 1400 sh, 1390 m cm^{-1}; ^{1}H-nmr: δ = 3.6 (s, CH_2), 6.2-6.3 (dd, J = 7 Hz, 1.5 Hz, 2 H at C-7 and C-9), 7.0-7.3 (m, 5 ArH), 7.4-7.6 (t, J = 7 Hz, H at C-8), 9.0-9.4 (b, NH_2).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.17; H, 4.93; N, 15.52.

6-Amino-2-hydroxy-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (**9f**).

A solution of **8** (1.10 g, 10 mmoles) and **2f** (4.63 g, 10 mmoles) in 20 ml of acetone was refluxed for 5 minutes. The product precipitated at cooling. The yield was 1.40 g (79%), mp 225° dec (water); ir: 3400-2600 b, 1680 s (lactam CO), 1640 s, 1590 s, 1520 w, 1460 w, 1410 w cm^{-1}; ^{1}H-nmr: δ = 4.4 (s, H at C-3), 6.1-6.2 (dd, J = 7 Hz, 1.5 Hz, 2 H at C-7 and C-9), 7.4-7.5 (t, J = 7 Hz, H at C-8), 8.7-9.4 (b, NH_2), 10.0-10.4 (b, OH).

Anal. Calcd. for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.72. Found: C, 54.13; H, 4.02; N, 23.65.

General Procedure for 3-Substituted 7-Amino-1,2-dihydro-4-hydroxy-2-oxo-1,8-naphthyridines **10a-e**.

A mixture of **8** (10 mmoles) and **1a-e** (15 mmoles) in 15 ml of diphenyl ether was refluxed for 30 minutes. The product precipitated and was washed with acetone; purification was accomplished by dissolution in 2*N* sodium hydroxide and precipitation with acetic acid or by sublimation, respectively.

7-Amino-1,2-dihydro-4-hydroxy-3-methyl-2-oxo-1,8-naphthyridine (**10a**).

A) Following the general procedure the yield was 1.76 g (92%), mp 305° dec (sublimation at 275°, 17 mm Hg).

B) Sublimation of **9a** (0.20 g) at 275°, 14 mm Hg yielded **8a** (0.12 g, 60%) beside decomposition; ir: 3500-2500 b, 1700 sh, 1660 s (lactam CO), 1630 s, 1600 s, 1510 w cm^{-1}; ^{1}H-nmr: δ = 2.0 (s, CH_3), 3.6-5.2 (b, NH_2), 6.5 (d, J = 7 Hz, H at C-6), 8.0 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.26; H, 4.81; N, 21.90.

7-Amino-3-*n*-butyl-1,2-dihydro-4-hydroxy-2-oxo-1,8-naphthyridine (**10b**).

A) Following the general procedure the yield was 2.21 g (95%), mp 301° dec (sublimation 275°, 14 mm Hg).

B) Sublimation of **9b** (0.20 g) at 275°, 14 mm Hg yielded **10b** (0.11g, 55%) beside decomposition; ir: 3400-3300 b, m, 3160 m, 2960 m, 2880 w, 1660 sh (lactam CO), 1630 s, 1600 sh, 1560 w, 1520 w, 1500 sh, 1420 w, 1370 m cm^{-1}; ^{1}H-nmr: δ 0.9 (t, J = 7 Hz, butyl-CH_3), 2.4 (m, 2 butyl-CH_2), 4.1 (t, J = 7 Hz, butyl-CH_2), 6.3-6.4 (d, J = 7 Hz, H at C-6), 7.2 (s, NH_2), 7.8-7.9 (d, J = 7 Hz, H at C-5), 9.9 (s, NH).

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.54; H, 6.55; N, 17.79.

7-Amino-1,2-dihydro-4-hydroxy-2-oxo-3-phenyl-1,8-naphthyridine (**10c**).

A) Following the general procedure the yield was 2.36 g (93%), mp 308° dec (dimethylformamide).

B) Sublimation of **9c** (0.20 g) at 295°, 20 mm Hg yielded **10c** (0.14 g, 70%) beside decomposition.

C) A solution of **9c** (0.3 g) in 1 ml of nitrobenzene was refluxed for three minutes; at cooling the product precipitated to give 0.23 g (77%); ir: 3500 m, 3420 m, 3180 s, 3060 sh, 2960 sh, 1660 sh (lactam CO), 1640 s, 1620 s, 1590 sh, 1560 sh, 1550 m, 1480 sh, 1450 m, 1430 m, 1420 sh cm^{-1}; ^{1}H-nmr: δ 6.3 (d, J = 7 Hz, H at C-6), 7.1-7.4 (m, 5 ArH), 7.5 (s, NH_2), 7.9 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.39; H, 4.38; N, 16.59. Found: C, 66.58; H, 4.33; N, 16.56.

7-Amino-3-benzyl-1,2-dihydro-4-hydroxy-2-oxo-1,8-naphthyridine (**10d**).

A) Following the general procedure the yield was 2.48 g (93%), mp 320° dec (dimethylformamide).

B) Sublimation of **9d** (0.20 g) at 275°, 14 mm Hg yielded **10d** (0.14 g, 70%) beside decomposition).

C) A solution of **9d** (0.3 g) in 1 ml of nitrobenzene was refluxed for three minutes; at cooling the product precipitated to give 0.26 g (87%); ir: 3580 w, 3520 sh, 3170 m, 1650 s (lactam CO), 1630 s, 1610 sh, 1560 w, 1520 m, 1500 w, 1460 w, 1430 m cm^{-1}; ^{1}H-nmr: δ = 3.9 (s, CH_2), 6.3 (d, J = 7 Hz, H at C-6), 7.0-7.2 (m, 5 ArH), 7.4 (s, NH_2), 7.9-8.0 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.16; H, 4.97; N, 15.55.

7-Amino-3-ethyl-1,2-dihydro-4-hydroxy-2-oxo-1,8-naphthyridine (**10e**).

Following the general procedure the yield was 1.91 g (93%), mp 303° dec (sublimation at 275°, 14 mm Hg); ir: 3560 w, 3400 w, 3340 sh, 3180 m, 2980 w, 2940 w, 1650 sh (lactam CO), 1630 s, 1610 sh, 1560 w, 1520 m, 1430 m, 1400 w cm^{-1}; ^{1}H-nmr: δ = 1.0 (t, J = 6 Hz, ethyl-CH_3), 4.1 (q, J = 7 Hz, ethyl-CH_2), 6.3 (d, J = 7 Hz, H at C-6), 7.3 (s, NH_2), 7.8 (d, J = 7 Hz, H at C-5), 10.0 (b, NH), 11.9 (s, OH).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.25; H, 5.35; N, 20.26.

General Procedure for 3-Substituted 4-Acetoxy-7-acetylamino-1,2-dihydro-2-oxo-1,8-naphthyridines **11a-e**.

A solution of 5 mmoles **10a-e** in 40 ml acetanhydride was refluxed for 20 minutes, cooled to room temperature and poured into 150 ml of water.

4-Acetoxy-7-acetylamino-1,2-dihydro-3-methyl-2-oxo-1,8-naphthyridine (**11a**).

The yield was 0.95 g (69%), mp 308° dec (dimethylformamide); ir: 3300-2800 b, m, 1780 sh, 1770 s (*O*-acetyl CO), 1720 m (*N*-acetyl CO), 1660 s (lactam CO), 1620 s, 1590 s, 1550 m cm^{-1}; ^{1}H-nmr: δ 2.0 (s, CH_3), 2.1 (2 s, 2 acetyl CH_3), 7.8-7.9 (d, J = 7 Hz, H at C-6), 8.1-8.2 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.44; H, 4.91; N, 15.50.

4-Acetoxy-7-acetylamino-3-*n*-butyl-1,2-dihydro-2-oxo-1,8-naphthyridine (**11b**).

The yield was 1.29 g (81%), mp 292° dec (dimethylformamide); ir: 3300-2800 b, m, 1780 m (*O*-acetyl CO), 1710 m (*N*-acetyl CO), 1660 s (lactam CO), 1620 s, 1590 s, 1550 s, 1490 m cm^{-1}; ^1H-nmr: δ = 0.8-1.0 (t, J = 7 Hz, butyl-CH_3), 1.2-1.5 (m, 2 butyl-CH_2), 2.1 (2 s, 2 acetyl-CH_3), 2.3-2.6 (m, butyl-CH_2 at C-3 and dimethylsulfoxide), 7.8-7.9 (d, J = 7 Hz, H at C-6), 8.1-8.2 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.56; H, 6.06; N, 13.63.

4-Acetoxy-7-acetylamino-1,2-dihydro-2-oxo-3-phenyl-1,8-naphthyridine (**11c**).

The yield was 1.60 g (95%), mp 324° dec (dimethylformamide); ir: 3300-2800 b, m, 1780 m (*O*-acetyl CO), 1710 m (*N*-acetyl CO), 1660 s (lactam CO), 1640 sh, 1620 m, 1590 s, 1580 sh, 1550 sh, 1540 m, 1510 sh cm^{-1}; ^1H-nmr: δ = 2.1 (2 s, 2 acetyl-CH_3), 7.2-7.5 (m, 5 ArH), 7.9-8.1 (d, 2 H at C-5 and C-6), 10.6 (s, NH), 12.2 (s, NH).

Anal. Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 63.96; H, 4.36; N, 12.49.

4-Acetoxy-7-acetylamino-3-benzyl-1,2-dihydro-2-oxo-1,8-naphthyridine (**11d**).

The yield was 1.28 g (73%), mp 325° dec (dimethylformamide); ir: 3350-2900 b, 1770 s (*O*-acetyl CO), 1720 s (*N*-acetyl CO), 1660 s (lactam CO), 1620 m, 1590 s, 1540 s, 1500 w, 1480 w cm^{-1}; ^1H-nmr (trifluoroacetic acid): δ 2.6 (s, *N*-acetyl-CH_3), 2.7 (s, *O*-acetyl-CH_3), 4.2 (s, CH_2), 7.2 (s, 5 ArH), 7.3-7.5 (d, J = 7 Hz, H at C-6), 8.3-8.5 (d, J = 7 Hz, H at C-5).

Anal. Calcd. for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.08; H, 4.92; N, 12.04.

4-Acetoxy-7-acetylamino-3-ethyl-1,2-dihydro-2-oxo-1,8-naphthyridine (**11e**).

The yield was 1.19 g (82%), mp 301° dec (dimethylformamide); ir: 3300-2800 b, m, 1780 sh, 1770 m (*O*-acetyl CO), 1710 m (*N*-acetyl CO), 1660 s (lactam CO), 1620 s, 1590 s, 1540 s, 1490 m, 1480 m cm^{-1}; ^1H-nmr: δ = 0.9-1.1 (t, J = 7 Hz, ethyl-CH_3), 2.1 (2 s, 2 acetyl-CH_3), 2.4-2.5 (m, ethyl-CH_2), 7.8-7.9 (d, J = 7 Hz, H at C-6), 8.1-8.2 (d, J = 7 Hz, H at C-5), 10.6 (s, NH), 11.3 (s, NH).

Anal. Calcd. for $C_{14}H_{15}N_3O_4$: C, 58.12; H, 5.23; N, 14.53. Found: C, 57.83; H, 5.23; N, 14.46.

General Procedure for 3,7-Disubstituted 4,6-Dihydroxy-2,8-dioxo-1,2,8,9-tetrahydropyrido[2,3-*b*]-1,8-naphthyridines **12a-f**.

A well triturated mixture of **10a-e** (5 mmoles) and **2c,d** (5 mmoles) was heated to 240° for 20 minutes. The residue was treated with cyclohexane to remove 2,4,6-trichlorophenol and recrystallized from dimethylformamide.

4,6-Dihydroxy-3-methyl-2,8-dioxo-7-phenyl-1,2,8,9-tetrahydropyrido[2,3-*b*]-1,8-naphthyridine (**12a**).

A mixture of **10a** and **2c** gave 1.30 g (78%), mp 318° dec (dimethylformamide); ir: 3300-2800 b, m, 1650-1610 b, s, (lactam CO), 1590 s, 1570 s, 1550 sh, 1490 sh cm^{-1}; ^1H-nmr: δ = 2.0 (s, CH_3), 7.3-7.4 (m, 5 ArH), 8.2 (2 s, 2 NH), 8.8 (s, H at C-5).

Anal. Calcd. for $C_{18}H_{13}N_3O_4$: C, 64.47; H, 3.91; N, 12.53. Found: C, 64.28; H, 4.19; N, 12.37.

3-*n*-Butyl-4,6-dihydroxy-2,8-dioxo-7-phenyl-1,2,8,9-tetrahydropyrido-[2,3-*b*]-1,8-naphthyridine (**12b**).

A mixture of **10b** and **2c** gave 1.38 g (73%), mp 313° dec (dimethylformamide); ir: 3300-2800 b, m, 1670-1620 b, s (lactam CO), 1560 sh, 1540 sh, 1490 w cm^{-1}; ^1H-nmr: δ = 0.9-1.0 (t, J = 7 Hz, butyl-CH_3), 1.2-1.5 (m, 2 butyl-CH_2), 2.4-2.6 (m, butyl-CH_2 at C-3 and dimethylsulfoxide), 7.3 (s, 5 ArH), 7.9 (2 s, 2 NH), 8.7 (s, H at C-5), 11.7 (s, OH), 11.8 (s, OH).

Anal. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.98; H, 4.82; N, 10.82.

4,6-Dihydroxy-2,8-dioxo-3,7-diphenyl-1,2,8,9-tetrahydropyrido[2,3-*b*]-1,8-naphthyridine (**12c**).

A mixture of **10c** and **2c** gave 1.85 g (73%), mp above 360° (dimethylformamide); ir: 3200-2700 b, m, 1660-1620 b, s (lactam CO), 1600 sh, 1590 w, 1550 sh, 1540 m, 1490 w cm^{-1}; ^1H-nmr: δ = 7.2-7.5 (m, 10 ArH), 7.9 (s, 2 NH), 8.9 (s, H at C-5), 11.8 (s, 2 OH).

Anal. Calcd. for $C_{23}H_{15}N_3O_4$: C, 69.51; H, 3.81; N, 10.57. Found: C, 69.85; H, 4.14; N, 10.52.

3-Benzyl-4,6-dihydroxy-2,8-dioxo-7-phenyl-1,2,8,9-tetrahydropyrido-[2,3-*b*]-1,8-naphthyridine (**12d**).

A mixture of **10d** and **2c** gave 1.58 g (77%), mp 327° dec (dimethylformamide); ir: 3300-2800 b, m, 1670-1620 b, s (lactam CO), 1610 sh, 1570 sh, 1520 w, 1490 sh cm^{-1}; ^1H-nmr: δ = 3.9 (s, CH_2), 7.1-7.4 (m, 10 ArH), 7.9 (s, 2 NH), 8.9 (s, H at C-5), 11.8 (s, OH).

Anal. Calcd. for $C_{24}H_{17}N_3O_4$: C, 70.06; H, 4.17; N, 10.21. Found: C, 69.98; H, 4.43; N, 9.84.

3-Ethyl-4,6-dihydroxy-2,8-dioxo-7-phenyl-1,2,8,9-tetrahydropyrido[2,3-*b*]-1,8-naphthyridine (**12e**).

A mixture of **10e** and **2c** gave 1.68 g (76%), mp 340° dec (dimethylformamide); ir: 3400-2700 b, m, 1670-1600 b, s (lactam CO), 1540 sh, 1460 sh, 1450 m cm^{-1}; ^1H-nmr: δ = 0.9-1.1 (t, J = 7 Hz, ethyl-CH_3), 2.4-2.6 (m, ethyl-CH_2 + dimethyl sulfoxide), 7.2-7.4 (m, 10 ArH), 8.7 (s, H at C-5), 10.4 (s, 2 NH), 11.6 (s, OH), 11.7 (s, OH).

Anal. Calcd. for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 64.96; H, 4.26; N, 11.82.

3,7-Dibenzyl-4,6-dihydroxy-2,8-dioxo-1,2,8,9-tetrahydropyrido[2,3-*b*]-1,8-naphthyridine (**12f**).

A mixture of **10d** and **2d** gave 1.04 g (49%), mp 325° dec (dimethylformamide); ir: 3300-2500 b, m, 1660-1630 b, s (lactam CO), 1590 sh, 1500 w, 1450 m cm^{-1}; ^1H-nmr: δ 3.9 (s, 2 CH_2), 7.1-7.2 (m, 10 ArH), 7.9 (s, 2 NH), 11.8 (s, 2 OH).

Anal. Calcd. for $C_{25}H_{19}N_3O_4$: C, 70.57; H, 4.50; N, 9.88. Found: C, 70.29; H, 4.50; N, 9.75.

3-Chloro-7-methyl-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (**15c**).

A suspension of **6c** (3.00 g) in 20 ml of dioxane was warmed up to 50° and treated with 6 ml of sulfuryl chloride. After 10 minutes the solution was poured into 500 ml ice water to yield 2.99 g (88%), mp 141° (ethanol); ir: 3300-3000 b, 1740 m (CO), 1730 m, 1690 s (lactam CO), 1610 m, 1580 m, 1450 m cm^{-1}; ^1H-nmr (deuteriochloroform): δ = 2.7 (s, CH_3), 7.0-7.1 (d, J = 7 Hz, H at C-6), 7.4 (s, 5 ArH), 8.1-8.3 (d, J = 7 Hz, H at C-5), 10.0-10.3 (b, NH).

Anal. Calcd. for $C_{15}H_{11}ClN_2O_2$: C, 62.83; H, 3.87; N, 9.77; Cl, 12.37. Found: C, 62.60; H, 3.85; N, 9.64; Cl, 12.35.

3-Benzyl-3-chloro-7-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1,8-naphthyridine (**15d**).

A suspension of **6d** (0.50 g) in 10 ml of dioxane was warmed up to 50° and treated with 3 ml of sulfuryl chloride. The clear solution was poured into 50 ml ice water to yield 0.47 g (83%), mp 143° (ethanol); ir: 3360 m, 3200-2800 b, 1720 s (CO), 1680 s (lactam CO), 1600 s, 1580 s, 1500 w, 1460 m, 1430 w cm^{-1}.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.90; H, 4.36; N, 9.32; Cl, 11.79. Found: C, 63.65; H, 4.35; N, 9.03; Cl, 11.88.

7-Methyl-3-nitro-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (**16**).

A solution of **6c** (3.50 g) in a mixture of 35 ml of acetic acid and 14 ml of nitric acid was stirred for 15 minutes, then poured into 100 ml of water to yield 2.86 g (69%), mp 148° dec (methanol); ir: 3070 w, 2940 w, 2870 w, 1730 s (CO), 1700 s (lactam CO), 1610 s, 1580 s (NO_2), 1470 m, 1450 m, 1380 s, 1320 s (NO_2) cm^{-1}.

Anal. Calcd. for $C_{15}H_{11}N_3O_4$: C, 60.60; H, 3.72; N, 14.14. Found: C, 60.51; H, 3.72; N, 14.03.

7-Amino-3,6-dichloro-2,4-dioxo-3-phenyl-1,2,3,4-tetrahydro-1,8-naphthyridine (**17**).

A suspension of **10d** (0.50 g) in 10 ml of dioxane was warmed up to 50° and treated with 1 ml of sulfuryl chloride. The clear solution was poured on 50 g ice to yield 0.95 g (79%), mp 244-246° dec (ethanol); ir: 3440 w, 3320 w, 3200 m, 1710 m (CO), 1680 m (lactam CO), 1640 s, 1610 s, 1570 m, 1490 m, 1390 m cm^{-1}; ^1H-nmr: δ = 7.4 (s, 5 ArH), 7.8 (s, NH_2), 7.9 (s, H at C-5), 10.9 (s, NH).

Anal. Calcd. for $C_{14}H_9Cl_2N_3O_2$: C, 52.19; H, 2.82; N, 13.04; Cl, 22.01. Found: C, 52.46; H, 2.88; N, 12.88; Cl, 22.28.

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