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Ring Closure Reaction of 5-Hydroxy-pyrido[2,3-d]pyrimidine-2,4,7-triones to Benzo[b]pyrimido[4,5-h]1,6-naphthyridine-1,3,6-triones

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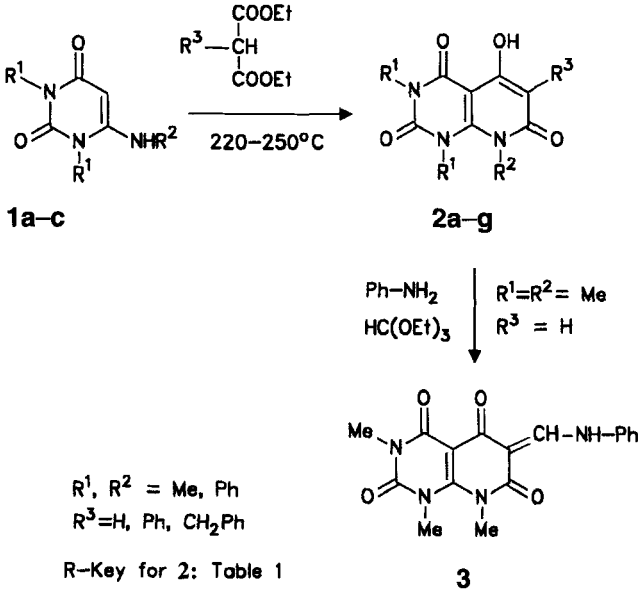
Abstract. N-Substituted aminouracils (**1**) react with malonates by cyclocondensation to 5-hydroxy-pyrido[2,3-d]pyrimidine-2,4,7-triones (**2**), which give with triethylorthoformate and aniline 6-(phenylaminomethylene)-pyrido[2,3-d]pyrimidine-tetraone (**3**). Halogenation of **2a–d** (with R^2 = Me) with phosphorylchloride leads to 5,7-dichloro-pyrido[2,3-d]pyrimidine-2,4-diones (**4**) by cleavage of the methyl group at N-8, whereas Vilsmeier reaction of **2** affords 5-chloro-6-formyl derivatives (**6**), which cyclize with arylamines to give benzo[b]pyrimido[4,5-h]1,6-naphthyridines (**9**). Compounds **9** were obtained independently by amination of the tosylates **5** to the 5-arylamino compounds **8**, and Vilsmeier formylation to yield **9**.

Pyrido[2,3-d]pyrimidine systems represented by structure **2** having an enolized 1,3-dicarbonyl moiety in the pyridine ring are of chemical and chemotherapeutic interest because they show the properties of a 4-hydroxy-2-pyridone and of uracil in one ring system. Known syntheses are described starting from 5-cyanoacetyl-6-aminouracils [1], or from substituted malonic acids, acetic anhydride and 6-glycopyranosylamino-pyrimidine-4-ones [2]; however in this case no 6-unsubstituted derivatives could be obtained. This paper details a simple and efficient route to 5-hydroxy-1,3,6,8-tetrasubstituted or 1,3,8-trisubstituted pyrido[2,3-d]pyrimidine-2,4,7-triones (**2a–g**) by thermal reaction of 6-alkylamino- or arylamino-uracils (**1a–c**) with ethyl malonates at 220–250 °C, a method without the restrictions described in ref. [2]. The yields range between 62 and 94%, which shows that no further activation of the malonates is necessary.

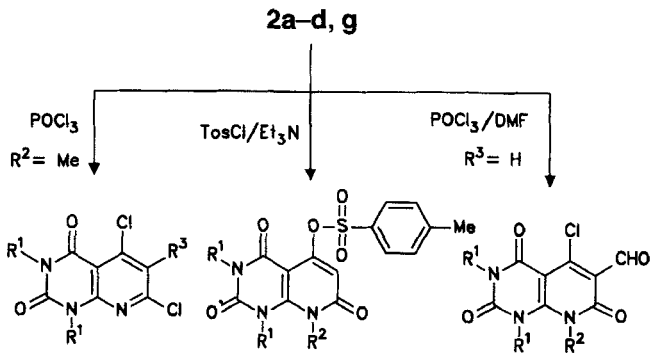
Infrared spectral data of 5-hydroxy-pyrido[2,3-d] pyrimidine-2,4,7-triones (**2**) show two typical carbonyl frequencies, the lactame signals of the pyrimidine part at 1695–1730 cm^{-1}, and the α-pyridone signal in the region of 1655–1680 cm^{-1}. These data reveal, that **2** exists as 7-oxo tautomer rather than as 5-oxo tautomer, because the latter structure would include a γ-pyridone structure element, which should be indicated by carbonyl frequencies[3, 4] below 1600 cm^{-1}. The existence of a 5,7-dioxo structure can be excluded because of the appearance of OH-signals of the 5-hydroxy group in the ^{1}H-NMR spectrum at δ = 12–13 ppm and the lack of aliphatic signals deriving from hydrogens at C-6. The



olefinic proton at C-6 in **2a,b,g** can be observed at 5.5–5.9 ppm. The methyl signals at N-1 and N-3 of the pyrimidine part at 3.3 and 3.4 ppm can be distinguished clearly from the N-methyl signal of N-8 at 2.8–2.9 ppm.

Reaction of **2a** with triethylorthoformate and aniline yielded the 6-phenylaminomethylene derivative **3**, which has been shown to be a versatile synthon for further functionalizations and ring closure reactions in cyclic 1,3-dicarbonyl systems [5]. The ^{1}H-NMR spectrum revealed that **3** exists mainly in the anilinomethylene-tetraoxo form and not in the tautomeric 5-hydroxy-azomethine form, because the 13-Hz-coupling of CH at 8.7 ppm and NH at 14.10 ppm indicate the =CH–NH–Ar structure element of the anilinomethylene moiety, whereas a –CH=N–Ar structure element together with a hydroxy group at position 5 is not supported by the spectroscopical data.

When 5-hydroxy-8-methyl-pyrido[2,3-d]pyrimidine-2,4,7-triones (**2a–d**) were halogenated with phosphoryl chloride in order to exchange the 5-hydroxy group to a 5-chloro substituent, the 8-methyl group was cleaved during this reaction at mild reaction temperatures as it is known from 4-hydroxypyridones [4b, 6], and the only reaction products which could be obtained were the 5,7-dichloro-pyrido[2,3-d]pyrimidine-2,4-diones (**4a–d**). The spectral data of **4** show the loss of the 8-methyl group, and the proton at C-6 is shifted from about 5.7 to 7.25 ppm, which indicates a more aromatic character of compounds **4**. The 8-phenyl derivative **2g** did not react at temperatures of 50 °C. When the reaction temperature was increased, only decomposition products could be obtained.



4a–d

5	R^1	R^2
a	Me	Me
b	Ph	Me

6	R^1	R^2
a	Me	Me
b	Ph	Me
c	Me	Ph

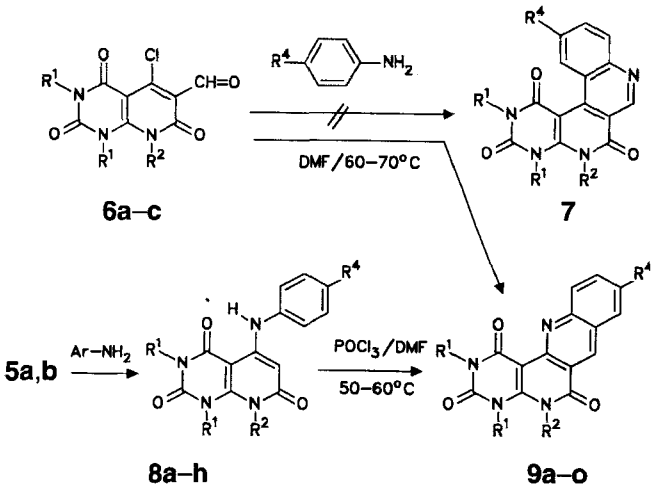
R-Key for **4**: see Table 1

Attempts to obtain the desired 5-chloro derivatives by a milder chlorination method using phosphoryl chloride and dimethylformamide, which was employed successfully in 4-hydroxycoumarin and phenalenedione chemistry [7], resulted in chlorination and formylation of the 6-unsubstituted pyrimido-pyridinetriones (**2a,b,g**) similar to a Vilsmeier reaction to yield the 5-chloro-6-formyl-8-substituted-pyrido[2,3-d]pyrimidine-2,4,7-triones (**6a–c**), but with the success that the 8-methyl group was not cleaved.

Because for further reactions 6-unsubstituted derivatives of **2** activated in 5-position were needed and the way through 5-chloro compounds was not successful, the tosyloxy compounds **5a,b** were synthesized from the hydroxy derivatives **2a,b** and p-toluenesulfonyl chloride in the presence of triethylamine as HCl scavenger.

3-Arylaminomethylene compounds of quinoline-2,4-diones cyclize readily to dibenzo-naphthyridines by intermolecular rearrangement [5b–d]. But it was impossible to obtain the 1,6-naphthyridine derivative **9a** via the anilinomethylene intermediate **3**. To investigate another entry to this 1,6-naphthyridine system, we started from chloro aldehydes **6**. Reaction of **6** with anilines should lead by condensation to 6-aryliminoformyl-pyrido[2,3-d]pyrimidine-2,4,7-triones if the attack of the amino nitrogen had taken place at the aldehyde moiety. As reaction product, however, the benzo-pyrido-naphthyridine derivative **9** was obtained, which could be explained to be formed by a primary attack of the aromatic amine at C-5 (cp. [8]) followed by subsequent ring closure reaction of the 5-formyl group with the ortho-position of the phenyl part of the aniline group. Spectroscopic structure elucidation revealed that the azomethine structure of the other possible isomer **7** which should be indicated by a ^{13}C-NMR signal of an α-quinoline-carbon of C-7 (the former aldehyde carbon) at about 150 ppm [9], could not be confirmed because of lack of this signal. The ^{13}C NMR spectrum of the isolated compound showed the signal of C-7 at 139 ppm, a chemical shift which is in good agreement with literature values of γ-quinoline carbons at 136–139 ppm [9], and indicated strongly the structure of the 1,6-naphthyridine **9.**

An independent synthesis of **9** by amination of the tosylates **5** with anilines and Vilsmeier formylation of the 5-arylamino-pyrido[2,3-d]pyrimidine-2,4,7-triones **8a,c,e,f** followed by subsequent ring closure reaction led to benzo[b]pyrimido[4,5-h]1,6-naphthyridine-1,3,6-triones **9a,c,e,f** which were identical in all physical and spectroscopic aspects with the compounds obtained by amination of **6**. The infrared spectra of **9** showed carbonyl frequencies similar to the pyrido[2,3-d]pyrimidine-triones **2** with two carbonyl bands, one at 1695–1730 cm^{-1} for the pyrimidine nucleus, and the other at 1660–1670 cm^{-1} for the 2-pyridone moiety. A typical ^{1}H-NMR signal of the hydrogen at C-7 (at the γ-quinoline site) could be observed at 9.5–9.9 ppm (in trifluoro acetic acid) or at 8.9–9.1 ppm (in chloroform as solvent). These findings show again that the formation of the 1,6-naph-



R^1, R^2 = Me, Ph
R^4 = H, Me, Cl, F, NO_2 R-Key for **8**, **9** see Table 1,2

thyridine system derived from an *ortho*-chloro aldehyde moiety and aromatic amines is in preference over the formation of the isomeric 2,7-naphthyridines as found recently in another connection in quinoline series [5b-d].

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Experimental

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes. 200 MHz ^{1}H NMR spectra were recorded on a Varian Gemini 200 instrument, 360 MHz ^{1}H-NMR spectra and 90 MHz ^{13}C-NMR spectra were recorded on a Bruker AM 360 instrument. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent for NMR was deuteriochloroform unless otherwise stated. Infrared spectra were taken in potassium bromide pellets on a Perkin-Elmer 298 spectrophotometer. Microanalyses were performed on a Carlo Erba 1106 analyzer.

Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 360 nm) for detection.

General Method for the Preparation of 5-Hydroxy-1,3,6,8-tetrasubstituted-pyrido[2,3-d]pyrimidine-2,4,7(1H, 3H, 8H) -triones (2a–g)

A mixture of the appropriate substituted 6-amino-pyrimidine-2,4(1H,3H)-dione (**1a,b,c**) (10 mmol) [10] and the appropriate ethyl malonate (10 mmol) in diphenylether (5 ml) was heated for 2 h to 220–250 °C using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was digested with hexane (50 ml), the obtained precipitate filtered, washed with cold hexane and dried. Then the precipitate was boiled with ethanol for 10 min, cooled, filtered by suction, washed with ethanol and recrystallized from the appropriate solvent. Experimental data: Table 1.

6-Phenylaminomethylene-1,3,8-trimethyl-pyrido[2,3-d] pyrimidine-2,4,5,7(1H,3H, 6H,8H)-tetraone (**3**)

A mixture of **2a** (2.37 g, 10 mmol), triethylorthoformate (1.48 g, 10 mmol) and aniline (0.93 g, 10 mmol) in 1,2-dihydroxyethane (10 ml) was heated under stirring. At about 110 °C formation of ethanol started. During 60 min the temperature was increased to 190 °C, and ethanol was distilled from the solution. Then the reaction mixture was cooled to room temperature and diluted with ethanol (10 ml). The resulting precipitate was filtered by suction and washed with ethanol. Yield: 2.6 g (76%) m.p. 282–285 °C (dimethylformamide); – IR: 1715 w, 1665 s, 1610 w cm^{-1}. – ^{1}H-NMR: δ = 3.31 (s, N–Me), 3.49 (s, N–Me) 3.52 (s, N–Me) 7.25–7.42 (m, 5 ArH), 8.7 (d, J = 13 Hz, CH=N), 14.10 (d, J = 13 Hz, NH).

$C_{17}H_{16}N_4O_4$ (340.34) Calcd.: C 60.00 H 4.74 N 16.46. Found: C 59.64 H 4.79 N 16.58.

General Method for the Preparation of 5,7-Dichloro-1,3,6-trisubstituted-pyrido[2,3-d]pyrimidine-2,4(1H, 3H)-diones (4a–d)

A suspension of the corresponding 5-hydroxy-8-methyl-pyrido[2,3-d]pyrimidine-2,4,7-trione (**2a,d**) (10 mmol) in phosphoryl chloride (20 ml) was heated at 50 °C for 2 h. Then the excess solvent was removed by distillation, the residue poured into ice/water (100 ml) and brought to pH = 6 with 2 *N* aqueous sodium hydroxide solution. The obtained precipitate was filtered by suction, washed with water and recrystallized from the appropriate solvent. Experimental data: Table 1.

1,3,8-Trimethyl-5-(4-toluenesulfonyloxy)-pyrido[2,3-d] pyrimidine-2,4,7(1H,4

A mixture of 5-hydroxy-1,3,8-trimethyl-pyrido[2,3-d] pyrimidine-2,4,7-trione (**2a**) (0.47 g, 2 mmol), p-toluenesulfonyl chloride (0.57 g, 3 mmol) and dry triethylamine (0.3 g, 3 mmol) in dry acetonitrile (20 ml) was heated under reflux with intensive stirring for 12 h. Then the reaction mixture was poured into ice/water (100 ml), the obtained precipitate was filtered, washed with water and dried. Yield: 0.77 g (96%) colorless prisms, m.p. 194–196 °C (ethanol); – IR: 1715 m, 1670 s cm^{-1}; – ^{1}H-NMR: δ = 2.48 (s, 3 H, Me), 3.32 (s, N–Me), 3.51 (s, N–Me), 3.58 (s, N–Me), 5.95 (s, H-6), 7.36 (d, J = 8 Hz, 2 ArH), 7.9 (d, J = 8 Hz, 2 ArH).

$C_{17}H_{17}N_3O_6S$ (391.41) Calcd.: C 52.17 H 4.38 N 10.74. Found: C 51.95 H 4.39 N 10.70.

Table 1 Experimental Data of 5-Hydroxy-1,3,6,8-tetrasubstituted-pyrido[2,3-d]pyrimidine-2,4,7(1H,3H,8H)-triones (**2a–g**), 5,7-Dichloro-1,3,6-trisubstituted-pyrido[2,3-d]pyrimidine-2,4(1H,3H)-diones (**4a–d**) and 5-(4-R^4-phenylamino)-1,3,8-trisubstituted-pyrido[2,3-d]pyrimidine-2,4,7(1H,3H,8H)-triones (**8a–h**).[a]

Nr.	R^1	R^2	R^3	R^4	yield (%)	m.p. [°C]	solvent
2a	Me	Me	H	—	82	219–221	DMF/ethanol
2b	Ph	Me	H	—	94	216–218	DMF/ethanol
2c	Me	Me	Ph	—	89	205–207	ethanol
2d	Ph	Me	Ph	—	73	232–234	ethanol
2e	Me	Me	CH_2Ph	—	62	214–216	ethanol
2f	Ph	Me	CH_2Ph	—	93	212–214	cyclohexane
2g	Me	Ph	H	—	85	258–260	DMF/ethanol
4a	Me	—	H	—	80	247–250	DMF
4b	Ph	—	H	—	82	286–288	DMF/H_2O
4c	Me	—	Ph	—	85	242–244	ethanol
4d	Ph	—	Ph	—	87	276–278	ethanol
8a	Me	Me	—	H	73	205–207	ethanol
8b	Me	Me	—	F	70	245–247	acetic acid
8c	Me	Me	—	Cl	86	245–247	acetic acid
8d	Me	Me	—	Me	91	231–233	DMF
8e	Ph	Me	—	H	91	293–295	AcOH/H_2O
8f	Ph	Me	—	F	91	252–254	AcOH/H_2O
8g	Ph	Me	—	Cl	89	273–275	ethanol
8h	Ph	Me	—	Me	91	234–236	ethanol

[a] The elemental analyses agree within ±0.4% of the theoretical values. Spectroscopic data are available from the authors.

8-Methyl-1,3-diphenyl-5-(4-toluenesulfonyloxy)-pyrido[2,3-d]pyrimidine-2,4,7(1H,3H,8H)-trione (**5b**)

From 5-hydroxy-8-methyl-1,3-diphenyl-pyrido[2,3-d] pyrimidine-2,4,7-trione (**2b**) (0.69 g, 2 mmol) as described for **5a**. Yield: 0.96 g (93%) colorless prisms, m.p. 214 °C (ethanol); – IR: 1735 m, 1685 s cm^{-1}; – ^{1}H-NMR: δ = 2.47 (s, Me), 2.94 (s, N–Me), 6.22 (s, H-6), 7.2–7.55 (m, 12 ArH), 7.94 (d, J = 7 Hz, 2 ArH).

$C_{27}H_{21}N_3O_6S$	Calcd.: C 62.90 H 4.11 N 8.15.
(515.55)	Found: C 62.55 H 4.15 N 8.12.

5-Chloro-6-formyl-1,3,8-trimethyl-pyrido[2,3-d]pyr- imidine-2,4,7(1H,3H,8H)-trione (**6a**)

Phosphoryl chloride (2 ml, 22 mmol) was added in portions to a cold, stirred suspension of 5-hydroxy-1,3,8-trimethyl-pyrido[2,3-d]pyrimidine-2,4,7-trione (**2a**) (1.2 g, 5 mmol) in dimethylformamide (30 ml), then the reaction mixture was stirred at 50–60 °C for 2 h. After cooling, the reaction mixture was poured into ice/water (200 ml). The obtained yellow precipitate was filtered, washed with water and dried. Yield: 1.05 g (74%) colorless prisms, m.p. 252–254 °C (dimethylformamide); – IR: 1715 m, 1695 m, 1655 s cm^{-1}; – ^{1}H-NMR (DMSO-d_6): δ = 3.22 (s, N–Me), 3.48 (s, N–Me), 3.52 (s, N–Me), 10.2 (s, CH=O).

$C_{11}H_{10}ClN_3O_4$	Calcd.: C 46.58 H 3.55 N 14.81.
(283.76)	Found: C 46.97 H 3.63 N 14.80.

5-Chloro-6-formyl-8-methyl-1,3-diphenyl-pyrido[2,3-d]pyrimidine-2,4,7(1H,3H, 8H)-trione (**6b**)

From 5-hydroxy-8-methyl-1,3-diphenyl-pyrido[2,3-d]pyrimidine-2,4,7-trione (**2b**) (1.7 g, 5 mmol) according to the method described for **6a**. Yield: 1.4 g (75%) colorless prisms, m.p. 248–250 °C (ethanol); – IR: 1720 m, 1680 m, 1660 s cm^{-1}; – ^{1}H-NMR: δ = 3.2 (s, N–Me), 7.3–7.62 (m, 10 ArH), 10.3 (s, CH=O).

$C_{21}H_{14}ClN_3O_4$	Calcd.: C 61.85 H 3.46 N 10.30
(407.82)	Found: C 61.66 H 3.82 N 10.14.

5-Chloro-6-formyl-1,3-dimethyl-8-phenyl-pyrido[2,3-d]pyrimidine-2,4,7(1H,3H, 8H)-trione (**6c**)

From 5-hydroxy-1,3-dimethyl-8-phenyl-pyrido[2,3-d]pyrimidine-2,4,7-trione (**2g**) (1.5 g, 5 mmol) according to the method described for **6a**. Yield: 1.3 g (75%) colorless prisms, m.p. 236–38 °C (dimethylformamide/ethanol); – IR: 1730 w, 1669 s cm^{-1}; – ^{1}H-NMR (DMSO-d_6): δ = 2.64 (s, N–Me), 3.24 (s, N–Me), 7.56–7.60 (m, 5 ArH), 10.18 (s, CH=O).

$C_{16}H_{12}ClN_3O_4$	Calcd.: C 55.58 H 3.50 N 12.15.
(345.74)	Found: C 55.84 H 3.72 N 12.02.

General Method for the Preparation of 5-Arylamino-1,3,8-trisubstituted-pyrido[2,3-d]pyrimidine-2,4,7 (1H, 3H,8H)-triones (8a-h)

A mixture of the appropriate 8-methyl-5-(4-toluene-sulfonyloxy)-pyrido[2,3-d]pyrimidine-2,4,7-trione (**5a,b**) (2 mmol) and the corresponding aromatic amine (4 mmol) in 2-

Table 2 Experimental and Spectroscopic Data of 2,4,5,9-Tetrasubstituted-benzo[b]pyrimido[4,5-h]1,6-naphthyridine-1,3,6 (2H,4H,5H)-triones (**9a–o**).[a]

No.	R^1	R^2	R^4	method: yield (%)	m.p. (°C) solvent	IR (cm^{-1}) ^{1}H-NMR (δ ppm)
9a	Me	Me	H	A: 82 B: 87	325–227 DMF	1710 m, 1660 s, 1620 w, 1600 m. [b]) 3.53 (s, N–Me), 3.78 (s, N–Me), 3.82 (s, N–Me), 7.9–8.05 (m, 1 ArH), 8.31–8.45 (m, 3 ArH), 9.86 (s, H-7).
9b	Me	Me	Me	A: 83	322–324 DMF	1725 m, 1670 s, 1590 m. [b]) 2.66 (s, 9-Me), 3.58 (s, N–Me), 3.81 (s, N–Me), 3.86 (s, N–Me) 8.16 (d, J = 7 Hz, H-10), 8.25 (d, J = 7 Hz, H-11) 8.30 (s, H-8), 9.81 (s, H-7).
9c	Me	Me	Cl	A: 90 B: 89	333–335 DMF	1710 m, 1660 s, 1600 m. [b]) 3.58 (s, N–Me), 3.83 (s, N–Me), 3.86 (s, N–Me), 8.25 (d, J = 7 Hz, H-11), 8.36 (d, J = 7 Hz, H-10), 8.39 (s, H-8), 9.82 (s, H-7).
9c·HCl	Me	Me	Cl	A: 91	>350 DMF	1700 m, 1660 m, 1620 s. [b]) 3.2 (s, N–Me), 3.45 (s, N–Me), 3.49 (s, N–Me), 7.85 (d, J = 7 Hz, H-11) 7.96 (d, J = 7 Hz, H-10), 8.2 (s, H-8), 9.45 (s, H-7).
9d	Me	Me	F	A: 91	334–336 DMF	1730 m, 1670 s, 1620 m.
9e	Me	Me	NO_2	A: 86	338–340 DMF	1720 m, 1670 s, 1620 w. [b]) 3.28 (s, N–Me), 3.54 (s, N–Me), 3.58 (s, N–Me), 8.29 (d, J = 7 Hz, H-11), 8.69 (d, J = 7 Hz, H-10), 9.0 (s, H-8), 9.75 (s, H-7).
9e·HCl	Me	Me	NO_2	A: 89	>350 DMF	1730 w, 1705 m, 1630 s. [b]) 3.34 (s, N–Me), 3.6 (s, N–Me), 3.65 (s, N–Me), 8.34 (d, J = 7 Hz, H-11) 8.73 (d, J = 7 Hz, H-10), 9.05 (s, H-8), 9.8 (s, H-7).
9f	Me	Ph	H	A: 85	302–305 DMF/EtOH	1715 m, 1690 s, 1670 s. 2.89 (s, 3 H, N–Me), 3.47 (s, 3 H, N–Me), 7.42–7.57 (m, 5 H, ArH), 7.90–8.10 (m, 3 H, ArH), 8.3 (d, J = 7 Hz, 1 H, ArH), 9.03 (s, 1 H, H-7).
9g	Me	Ph	Me	A: 87	297–299 DMF/EtOH	1710 m, 1670 s, 1699 m. 2.53 (s, 9-Me), 2.82 (s, N–Me), 3.43 (s, N–Me), 7.35–7.50 (m, 5 ArH), 7.64 (s, H-8), 7.7 (d, J = 7 Hz, H-10), 8.15 (d, J = 7 Hz, H-11), 8.88 (s, H-7).
9h	Me	Ph	Cl	A: 88	313–315 DMF/EtOH	1715 w, 1695 w, 1670 s. [b]) 2.8 (s, N–Me), 3.24 (s, N–Me), 7.25–7.35 (m, 5 ArH), 7.98 (d, J = 7 Hz, H-11), 8.10 (d, J = 7 Hz, H-10), 8.15 (s, H-8), 9.55 (s, H-7).
9i	Me	Ph	F	A: 86	322–324 DMF/EtOH	1720 w, 1670 s, 1600 w.
9j	Me	Ph	NO_2	A: 82	348–351 DMF/EtOH	1755 w, 1695 s, 1680 s. [b]) 2.78 (s, N–Me), 3.30 (s, N–Me) 7.13–7.34 (m, 5 ArH), 8.31 (d, J = 7 Hz, H-11), 8.72 (d, J = 7 Hz, H-10), 9.0 (s, H-8), 9.73 (s, H-7).
9k [c])	Ph	Me	H	A: 86 B: 84	312–314 DMF/EtOH	1720 m, 1675 s, 1620w . 3.08 (s, N–Me), 7.36–7.51 (m, 10 ArH), 7.6 & 7.85 (2 t, J = 7 Hz, H-9 & H-10), 8.0 & 8.29 (2 t, J = 7 Hz, H-8 & H-11), 9.23 (s, H-7).
9l	Ph	Me	Me	A: 81	304–306 DMF/EtOH	1720 m, 1680 s, 1600 m. 2.56 (s, 9-Me), 3.06 (s, N–Me), 7.34–7.49 (m, 10 ArH), 7.7 (d, J = 7 Hz H-11), 7.75 (s, H-8), 8.16 (d, J = 7 Hz, H-10), 9.12 (s, H-7).
9l·HCl	Ph	Me	Me	A: 85	>350 DMF	1730 m, 1710 s, 1660 m, 1630 s. [b]) 2.65 (s, 9-Me), 3.15 (s, N–Me), 7.35–7.58 (m, 10 ArH), 8.10 (s, H-8), 8.16 (d, J = 7 Hz, H-10), 8.30 (d, J = 7 Hz, H-11), 9.82 (s, H-7).
9m	Ph	Me	Cl	A: 86	326–328 DMF/ethanol	1725 m, 1680 s, 1595 m. [b]) 2.85 (s, N–Me), 6.8–7.3 (m, 10 ArH), 7.82 (d, J = 7 Hz, H-10), 8.1 (d, J= 7 Hz, H-11), 8.15 (s, H-8), 9.58 (s, H-7).
9m·HCl	Ph	Me	Cl	A: 86	>350 DMF	1730 m, 1700 m, 1665 m, 1630 s. [b]) 3.15 (s, N–Me) 7.35–7.58 (m, 10 ArH), 8.18 (d, J = 7 Hz, H-11), 8.35 (d, J = 7 Hz, H-10), 8.42 (s, H-8), 9.84 (s, H-7).
9n	Ph	Me	F	A: 91 B: 87	316–318 DMF/EtOH	1725 s, 1675 s, 1600 m. 3.1 (s, N–Me), 7.28–7.52 (m, 10 ArH), 7.6–7.72 (m, 10 ArH), 8.26–8.36 (dd, J = 2+7 Hz, 1 ArH), 9.2 (s, H-7).
9o	Ph	Me	NO_2	B: 85	343–345 DMF/EtOH	1730 w, 1680 s, 1650 w. 3.1 (s, N–Me), 7.25–7.55 (m, 10 ArH), 8.39 (d, J = 7 Hz, H-11), 8.58 (d, J = 7 Hz, H-10), 8.95 (s, H-8), 9.4 (s, H-7).

[a]) The elemental analyses agree within ±0.4% of the theoretical values. [b]) trifluoroacetic acid was used as the solvent.
[c]) ^{13}C-NMR of **9k** ($CDCl_3$): δ= 36.57 (N–Me), 98.10 (C-12b), 117.15 (C-6a), 125.93 (C-7a), 127.23–133.04 (14 aryl-C of 2- and 4-phenylsubstituents and fused benzoring), 134.80 (C-1 of 4-phenyl), 138.81 (C-1 of 2-phenyl), 139.04 (C-7), 148.22 (C-12a), 150.88 (C-4a),151.63 (C-11a), 151.68 (C-3), 158.84 (C-1), 163.71 (C-6).

propanol (20 ml) was heated under reflux for 12 h with intensive stirring. After standing at room temperature for about 6 h, the formed precipitate was collected by suction, washed with a small amount of methanol and recrystallized from the appropriate solvent. Experimental data: Table 1.

General Method for the Preparation of 2,4,5,9-Tetrasubstituted-benzo[b]pyrimido[4,5–h]1,6-naphthyridine-1,3,6(2H,4H,5H)-triones (9a–o)

Method a) A solution of the corresponding 5-chloro-6-formyl-1,3,8-trisubstituted-pyrido[2,3-d]pyrimidine-2,4,7-trione (**6a–c**) (5 mmol) in dimethylformamide (15–30 ml) and the appropriate aromatic amine (6 mmol) was stirred at 60–70 °C for 2 h. After this time a yellow precipitate was formed, which was filtered after cooling, washed with acetone, dried and recrystallized from dimethylformamide. This product could be shown to be the hydrochloride of **9**, which gave upon treatment with aqueous *2 N* sodium hydroxide solution (50 ml) the free base of **9**.
To obtain the free base of **9** without isolation of the salt, the mixture containing the yellow precipitate, isolated by filtration of the reaction mixture, was poured into ice/water (100 ml) and the suspension brought to pH = 8 with aqueous *2 N* sodium hydroxide solution (50 ml). After standing at room temperature for 5 h, the formed precipitate was collected by suction, washed with water, dried and recrystallized from the appropriate solvent. Experimental and spectroscopic data: Table 2.

Method b) Phosphoryl chloride (2.0 ml, 22 mmol) was added portionwise to a cold, stirred suspension of the corresponding 5-arylamino-1,3,8-trisubstituted-pyrido[2,3-d]pyrimidine-2,4,7-trione (**8a,c,e,f**) (5 mmol) in dimethylformamide (10 ml). Then the reaction mixture was stirred for 1 h at 50–60 °C. After cooling, the reaction mixture was poured into ice/water (200 ml) and the suspension brought to pH = 8 with *2 N* aqueous sodium hydroxide. The obtained yellow precipitate was collected by suction, washed with water and recrystallized from the appropriate solvent. Experimental and spectroscopic data: Table 2.

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