Ring Closure Reactions of 5-Azidopyrido[2,3-*d*]pyrimidinetriones to Isoxazolo- and Oxadiazolopyrido[2,3-*d*]pyrimidinetriones [1]

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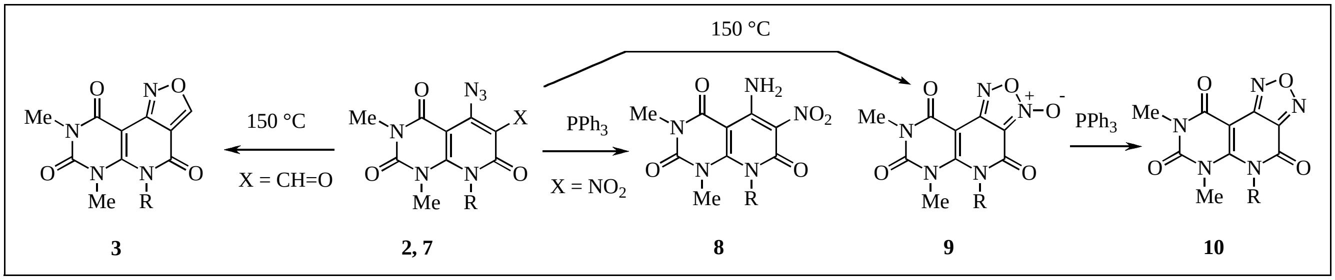

Thermal decomposition of 5-azidopyrido[2,3-*d*]pyrimidines **2** and **7** having reactive *ortho*-substituents such as a formyl or a nitro group yielded isoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidines **3** or oxadiazolo-[3',4':4,5]pyrido[2,3-*d*]pyrimidines **9**. The reaction conditions of the azide decomposition were studied by differential scanning calorimetry (DSC). In addition, desoxygenation of N-oxides **9** to oxadiazoles **10** and regioselective reduction of azides **7** to amines **8** were studied.

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INTRODUCTION

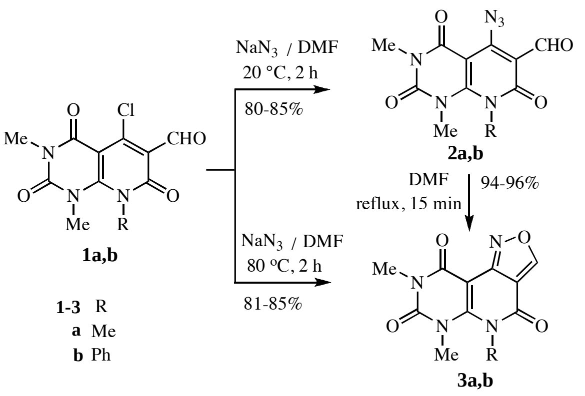
Pyrido[2,3-*d*]pyrimidinedione derivatives form a class of fused heterocyclic compounds which reveal interesting pharmacological and biological properties [2]. Isoxazolo- and oxadiazoloheterocycles in the quinoline and pyrimidine series were investigated thoroughly in the last decades and many representatives were found to show biological activities [3-7]. These findings prompted us to study the combination of these two biological interesting nuclei by synthesis of pyrido[2,3-*d*]pyrimidinetriones anellated to the *f*-side by isoxazolo[3',4':4,5]- and oxadiazolo[3',4':4,5] rings. The ring closure reactions intended for this project involve a thermal decomposition of 5-azidopyrido[2,3-*d*]pyrimidinetriones. *Ortho*-substituted azido arenes and heteroarenes are known to give cyclization reactions induced by thermo- or photolysis [8] forming predominantly five-membered rings. Some of these reactions were studied in our group on heterocyclic systems with aryl, carbonyl and nitro groups as ortho substituents (recent examples are listed in ref. [9]).

RESULTS AND DISCUSSION

A general approach leading from azidoarenenes to oxazoles is reported *via* the thermolysis in the presence of acetic acid catalyzed by polyphosphoric acid. The formation of the 5-membered oxazole ring could be shown to involve a nucleophilic substitution by the acetoxy-oxygen at the position next to the azido group [10]. Recently we could show [11] that 4-azidoquinolines reacted with carboxylic acids to oxazolo[4,5-*c*]quinolones by migration of the nitrene nitrogen from the 4- to the 3-position. 6-Azidouracils revealed two reaction pathways [12]: with benzoic acids, oxazolo[5,4-*d*]pyrimidinediones were obtained, whereas with aliphatic carboxylic acids isoxazolo[3,4-*d*]pyrimidinediones were formed. When we tried to transform these reaction sequence to 5-azido-pyrido[2,3-*d*]pyrimidines we failed because the required 6-unsubstituted azides were unstable and decomposed to dark blue, insoluble compounds.

Another approach to isoxazoles *via* azides of carbo- and heterocycles was investigated earlier in our group [9a,9b,9f,13] with substrates having a reactive acyl group in *ortho*-position to the azido group. In the pyrido[2,3-*d*]-pyrimidine series, we started from 5-chloro-6-formyl-pyrido[2,3-*d*]pyrimidines **1a,b**, which were prepared from 6-formyl-5-hydroxypyrido[2,3-*d*]pyrimidines as described earlier [14]. The reaction of chloro compounds **1** with sodium azide in dry dimethylformamide at room temperature gives in good yields and high purity 5-azido-6-formyl-pyrido[2,3-*d*]pyrimidines **2a,b**. The formyl-azides **2** proved to be very sensitive to thermal cyclization, and during reaction and work-up elevated temperatures had to be avoided. To study the thermal properties, we applied differential scanning calorimetric (DSC) measurements, which showed that in the solid phase already at about 70 °C an exothermic reaction started, with a peak maximum at about 90 °C. DSC experiments revealed in a second thermolysis run that the first reaction peak had disappeared and only the second peak - deriving from the formed cyclization product - could be observed. In synthetic experiments, the ring closure reaction to the isoxazolo-[3',4':4,5]pyrido[2,3-*d*]pyrimidines **3a,b** could be achieved by the thermolysis of the azides **2a,b** in refluxing dimethylformamide by loss of nitrogen and cyclization; for this reaction an electrocyclic mechanism is proposed [15]. To avoid handling with the instable azides **2a,b**, a one-step reaction from chloro compounds **1** to isoxazoles **3** was developed by heating **1a,b** with sodium azide in dimethylformamide at 80-90 °C.

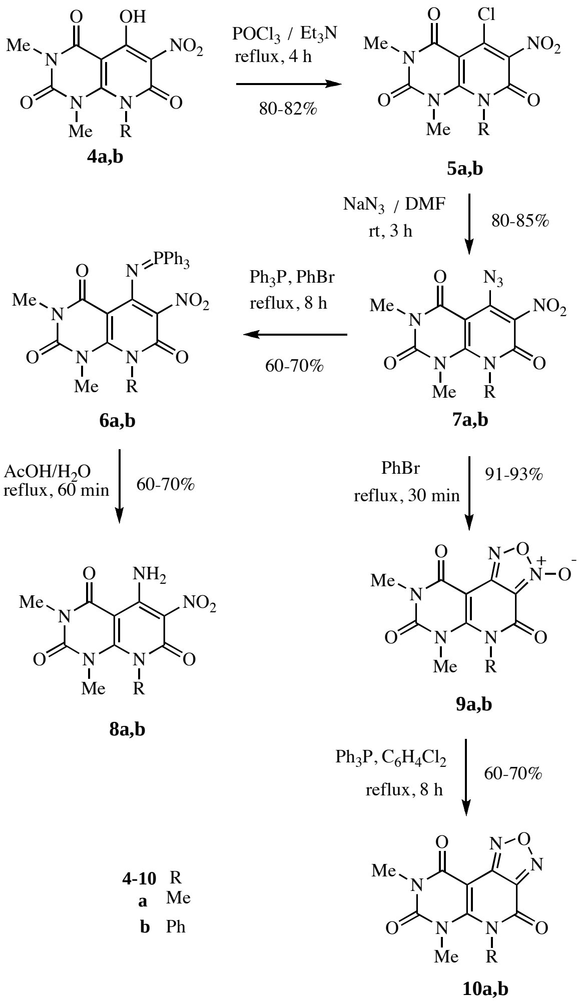
Scheme 1



A similar cyclization reaction of azides is known to take place with *ortho*-nitro substituents in the same manner as observed with *ortho*-acyl groups. Such reactions were studied earlier in the quinoline and pyridine series [16] successfully. The synthesis sequence in the pyrido[2,3-*d*]pyrimidine series started from 5-hydroxy-6-nitro-pyrido[2,3-*d*]pyrimidine-2,4,7-triones **4a,b** which were obtained from 5-hydroxy-pyrido[2,3-*d*]pyrimidine-2,4,7-triones [14] by a mild nitration method using sodium nitrite as catalyst [16a,17]. Conversion to the reactive azides proceeded *via* 5-chloro-6-nitro-pyrido[2,3-*d*]pyrimidine-2,4,7-triones **5a,b** which were obtained by chlorination of **4** with phosphoryl chloride in the presence of triethylamine to cleave hydrogen bondings of the 5-hydroxy group with close-by oxo groups. In this way the chloro compounds **5** were obtained in excellent yields. The reaction of 5-chloro-6-nitropyrido[2,3-*d*]pyrimidines **5** with sodium azide in dimethylformamide afforded already at room temperature in excellent yields by nucleophilic substitution 5-azido-6-nitropyrido[2,3-*d*]pyrimidines **7a,b**, which showed to be stable enough for work-up and recrystallization.

The thermal behavior of **7** was studied by differential scanning calorimetry. The observed cyclization temperatures of **7** with about 120 °C onset are much higher than that of formyl-azides **2** with onsets at 70 °C. Again the formation of cyclized products is observed during the DSC run which produce a second set of decomposition signals similar to the melting points of the synthesized products **9**.

Scheme 2



Synthetically, the reaction could be achieved by thermolysis of the azides **7a,b** in refluxing bromobenzene. This thermal decomposition resulted again in a loss of nitrogen and cyclization by an electrocyclic mechanism which formed the cyclization products, the furoxans **9a,b**. As further step the reduction to the desoxigenated oxadiazole ring was planned. The removal of the *N*-oxide oxygen of furoxanes is described to take place by reduction with triphenylphosphane [18]. Application of the reaction conditions as described in the literature, however, gave no reaction. So DSC studies of a mixture of furoxanes **9** with triphenylphosphane were performed to find out suitable reaction temperatures (see Figure 1). The DSC diagrams showed after the melting area of triphenylphosphane strong exothermic reaction peaks with onset at 186 and 201 °C. From earlier investigations [19] we know that in solvents the reaction temperature is lowered for 20-50 °C. According to these findings, the reaction was performed in boiling 1,2-dichlorobenzene at 179 °C. As a result, a smooth removal of the N-oxide oxygen was achieved and [1,2,5]oxadiazolo[3',4':4,5]-pyrido[2,3-*d*]pyrimidines **10a,b** were obtained.

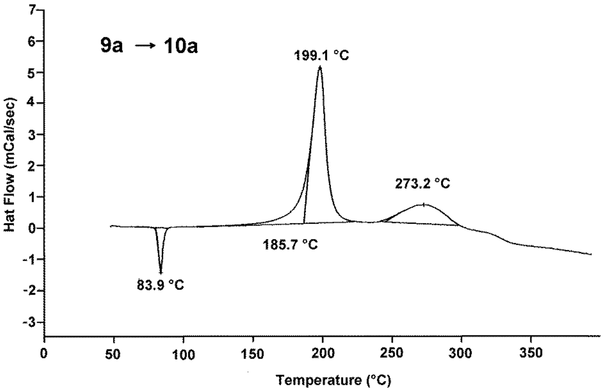


Figure 1. Differential scanning calorimetry diagram of the reaction of **9a** to **10a** with triphenylphosphane.

In conclusion, a series of new fused pyrido[2,3-*d*]-pyrimidine-4,7,9-triones was synthesized having as anellated ring 5-membered isoxazoles or oxadiazoles. The cyclization reaction took place *via* thermal decomposition of azides with reactive ortho-substituents; the reaction conditions were studied in advance by differential scanning calorimetry (DSC).

EXPERIMENTAL

Melting points were obtained on a Gallenkamp Melting Point Aparatus, Mod. MFB 595 in open capillary tubes. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AMX 360 instrument (360 or 90 MHz) or on a Bruker Avance DRX 500 instrument (500 or 125 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent was $CDCl_3$ unless otherwise stated. Infrared spectra were taken on a Mattson Galaxy Series FTIR 7020 instrument with potassium bromide discs. Elemental analyses were performed on a Fisons EA 1108 C,H,N-automatic analyzer and are within ± 0.4 of the theoretical percentages. Calorimetric (DSC) data were obtained on a Rheometric Scientific DSC-Plus instrument with the software Orchestrator V6.5.8. between 25 - 700 °C, a heating rate of 2-10 °C/min, and 1.5-3 mg compound in sealed aluminium pans (11 bar). All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silicagel F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

5-Azido-1,3,8-trimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydro-pyrido[2,3-d]pyrimidine-6-carbaldehyde (2a). A suspension of 5-chloro-6-formylpyrido[2,3-*d*]pyrimidinetrione **1a** [14] (2.83 g, 10 mmoles) and sodium azide (0.98 g, 15 mmoles) in dry dimethylformamide (30 mL) was stirred at 20 °C for 2 hours. Then the reaction mixture was poured into ice/water (500 mL), the precipitate was collected by filtration, washed with water and dried at room temperature *in vacuo*. The yield was 2.40 g (83%), yellow prisms, mp 86 °C (methanol), partial decomposition, resolidifies and melts again at 274 °C by formation of **3a**; DSC data: cyclization at 70.5 °C onset, 85.8 °C max., ΔH = -106 mcal/mg; decomposition at 264.9 °C onset, 274.7 °C max., ΔH = -102 mcal/mg; second run after thermolyis and cooling: decomposition at 274.3 °C onset, 281.2 ° max., ΔH = -125 mcal/mg; ir: 3060 m, 2120 w (N_3), 1700 s, 1675 s, 1600 m cm^{-1}; ^{1}H nmr: δ 3.28 (s, 3 H, NMe), 3.45 (s, 3 H, NMe), 3.46 (s, 3 H, NMe), 10.05 (s, 1 H, CH=O). *Anal.* Calcd. for $C_{11}H_{10}N_6O_4$ (290.24): C, 45.52; H, 3.47; N, 28.96. Found: C, 46.12; H 3.95; N, 27.35; values are not correct because of the ease of decomposition of the azide.

5-Azido-1,3-dimethyl-2,4,7-trioxo-8-phenyl-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbaldehyde (2b). This compound was obtained from 5-chloro-6-formylpyrido[2,3-*d*]pyrimidinetrione **1b** [14] (3.45 g, 10 mmoles) as described for **2a**; the yield was 3.05 g (85%), yellow prisms, mp 88 °C (methanol), partial decomposition, resolidifies and melts again at 257-260 °C by formation of **3b**; DSC data: cyclization at 70.6 °C onset, 87.9 °C, ΔH = -56 mcal/mg; decomposition: 217.8 °C onset, 257.1 °C max., ΔH = -118 mcal/mg; second run after thermolyis and cooling: decomposition at 236.3 °C onset, 242.3 °C max., ΔH = -84 mcal/mg; ir: 2140 s (N_3), 1710 s, 1670 s cm^{-1}; ^{1}H nmr: δ 2.85 (s, 3 H, NMe), 3.42 (s, 3 H, NMe), 7.30-7.35 (m, 2 H, ArH), 7.53-7.57 (m, 3 H, ArH), 10.28 (s, 1 H, CH=O). *Anal.* Calcd. for $C_{16}H_{12}N_6O_4$ (352.31): C, 54.55; H, 4.43; N, 23.85. Found: C, 55.32; H 4.12; N, 22.53; values are not correct because of the ease of decomposition of the azide.

5,6,8-Trimethylisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-4,7,9(5*H*,6*H*,8*H*)-trione (3a). Method A: A suspension of 5-chloro-6-formylpyrido[2,3-*d*]pyrimidinetrione **1a** [14] (2.83 g, 10 mmoles) and sodium azide (0.98 g, 15 mmoles) in dry dimethylformamide (30 mL) was stirred at 80-90 °C for 2 hours. Then the reaction mixture was poured into ice/water (500 mL), the precipitate collected by filtration, washed with water and dried. The yield was 2.12 g (81%).

Method B: A mixture of 5-azido-6-formylpyrido[2,3-*d*]-pyrimidinetrione **2a** (2.90 g, 10 mmoles) and dimethyl-formamide (20 mL) was heated under reflux for 15 minutes. The reaction mixture was allowed to cool and the formed precipitate collected by filtration and washed with ethanol (50 mL). The yield was 2.51 g (96%), colorless prisms, mp 275-277 °C (dimethylformamide); ir: 3060 s, 1725 m, 1700 s, 1665 s m cm^{-1}; ^{1}H nmr (CF_3COOH): δ 3.54 (s, 3 H, NMe), 3.73 (s, 3 H, NMe), 3.75 (s, 3 H, NMe), 9.53 (s, 1 H, 3-H). *Anal.* Calcd. for $C_{11}H_{10}N_4O_4$ (262.23): C, 50.38; H, 3.84; N, 21.37. Found: C, 50.40; H, 3.85; N, 21.41.

6,8-Dimethyl-5-phenylisoxazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-4,7,9(5*H*,6*H*,8*H*)-trione (3b). This compound was obtained according to the methods described for **3a** either from 5-chloro-6-formylpyrido[2,3-*d*]pyrimidinetrione **1b** (3.45 g, 10 mmoles) [14] (method A) or 5-azido-6-formylpyrido[2,3-*d*]-pyrimidinetrione **2b** (3.52 g, 10 mmoles) (method B); the yield was 2.69 g (83%) (method A) and 3.08 g (95%) (method B), colorless prisms, mp 258-260 °C (dimethylformamide); ir: 1710 s, 1670 s, 1610 m cm^{-1}; ^{1}H nmr: δ 2.80 (s, 3 H, NMe), 3.40 (s, 3 H, NMe), 7.35-7.55 (m, 5 H, ArH), 9.25 (s, 1 H, 3-H). *Anal.* Calcd. for $C_{16}H_{12}N_4O_4$ (324.30): C, 59.26; H, 3.73; N, 17.28. Found: C, 59.10; H, 3.71; N, 17.06.

5-Hydroxy-1,3,8-trimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4a). A suspension of 5-hydroxy-1,3,8-trimethylpyrido[2,3-*d*]pyrimidine-2,4,7-trione [14] (18.00 g, 76 mmoles) in glacial acetic acid (140 mL) was treated with fuming nitric acid (14.0 mL, 213 mmoles) and then with sodium nitrite (0.40 g, 5.8 mmoles) to start the slightly exothermic reaction. The starting material dissolved, followed immediately by precipitation of the product. After stirring for 60 minutes, the mixture was poured into ice/water (1000 mL). The product was filtered, washed with water and dried. The yield was 19.0 g (89%) yellow prisms, mp 223-225 °C (dimethylformamide/ethanol); ir: 1720 s, 1670 s cm^{-1}; ^{1}H nmr: δ 3.39 (s, 3 H, NMe), 3.53 (s, 3 H, NMe), 3.55 (s, 3 H, NMe). *Anal.* Calcd. for $C_{10}H_{10}N_4O_6$ (282.21): C, 42.56; H, 3.57; N, 19.85. Found: C, 42.38; H, 3.60; N, 19.76.

5-Hydroxy-1,3-dimethyl-6-nitro-8-phenylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (4b). This compound was obtained from 5-hydroxy-1,3-dimethyl-8-phenylpyrido[2,3-*d*]pyrimidine-2,4,7-trione [14] (22.70 g, 76 mmoles) as described for **4a**; the yield was 22.00 g (85%) yellow prisms, mp 246-249 °C (dimethylformamide/ethanol); ir: 1725 s, 1700 s, 1660 s cm^{-1}; ^{1}H nmr: δ 2.66 (s, 3 H, NMe), 3.30 (s, 3 H, NMe), 7.57-7.60 (m, 5 H, ArH). *Anal.* Calcd. for $C_{15}H_{12}N_4O_6$ (344.29): C, 52.33; H, 3.51; N, 16.27. Found: C, 52.28; H, 3.50; N, 16.15.

5-Chloro-1,3,8-trimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (5a). Dry triethylamine (5.0 mL) was added to a solution of 5-hydroxypyrido[2,3-*d*]pyrimidinetrione **4a** (9.87 g, 35 mmoles) in phosphoryl chloride (50 mL). The mixture was heated under reflux for 3-4 hours, the excess $POCl_3$ was removed by distillation and the residue poured into ice/water (1000 mL). The solution was brought to pH = 6-7 with conc. aq. sodium hydroxide solution, collected by suction filtration and washed with water. The yield was 8.60 g (82%), yellow prisms, mp 235 °C (dimethylformamide/ethanol); ir: 1730 s, 1675 s cm^{-1}; ^{1}H nmr: δ 3.22 (s, 3 H, NMe), 3.48 (s, 3 H, NMe), 3.57 (s, 3 H, NMe). *Anal.* Calcd. for $C_{10}H_9ClN_4O_5$ (300.66): C, 39.95; H, 3.02; N, 18.63. Found: C, 39.76; H, 3.04; N, 18.36.

5-Chloro-1,3-dimethyl-6-nitro-8-phenylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (5b). This compound was obtained from 5-hydroxypyrido[2,3-*d*]pyrimidinetrione **4b** (12.00 g, 35 mmoles) as described for **5a**; the yield was 10.15 g (80%) yellow prisms, mp 253 °C (dimethylformamide/ethanol); ir: 1725 m, 1665 s cm^{-1}; ^{1}H nmr: δ 2.63 (s, 3 H, NMe), 3.34 (s, 3 H, NMe), 7.60-7.62 (m, 5 H, ArH). *Anal.* Calcd. for $C_{15}H_{11}ClN_4O_5$ (362.73): C, 49.67; H, 3.06; N, 15.45. Found: C, 49.51; H, 3.12; N, 15.43.

1,3,8-Trimethyl-6-nitro-5-triphenylphosphoranylideneaminopyrido[2,3-d]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**6a**). To a solution of triphenylphosphane (3.15 g, 12 mmoles) in dry toluene (30 mL) was added 5-azidopyrido[2,3-*d*]pyrimidinetrione **7a** (3.10 g, 10 mmoles) to start the slightly exothermic reaction. The starting material dissolved, followed immediately by precipitation of the product. After stirring for 30 minutes, the temperature was gradually raised to 80-100 °C for 30 minutes. The reaction mixture was then allowed to cool, the mixture kept at room temperature for some hours, and then the precipitate was collected by suction filtration and washed with toluene and cyclohexane. The yield was 4.33 g (80%), yellow prisms, mp 257-259 °C (toluene); ir: 1715 s, 1660 s cm^{-1}; ^{1}H nmr: δ 2.63 (s, 3 H, NMe), 3.35 (s, 3 H, NMe), 3.43 (s, 3 H, NMe), 7.51-7.63 (m, 15 H, ArH). *Anal.* Calcd. for $C_{28}H_{24}N_5O_5P$ (541.51): C, 62.11; H, 4.47; N; 12.93. Found: C, 61.93, H, 4.41; N, 12.93.

1,3-Dimethyl-6-nitro-8-phenyl-5-triphenylphosphoranylideneaminopyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**6b**). This compound was obtained from 5-azidopyrido[2,3-*d*]pyrimidinetrione **7b** (3.69 g, 10 mmoles) as described for **6a;** the yield was 5.10 g (85%), yellow prisms, mp 289-291 °C (toluene); ir: 1710 s, 1675 s, 1650 s cm^{-1}; ^{1}H nmr: δ 2.55 (s, 3 H, NMe), 2.65 (s, 3 H, NMe), 7.52-7.70 (m, 20 H, ArH). *Anal.* Calcd. for $C_{33}H_{26}N_5O_5P$ (603.58): C, 65.67, H, 4.34; N, 11.60. Found: C, 65.56; H, 4.41; N, 11.50.

5-Azido-1,3,8-trimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (7a). A suspension of 5-chloropyrido-[2,3-*d*]pyrimidinetrione **5a** (3.00 g, 10 mmoles) and sodium azide (0.98 g, 15 mmoles) in dry dimethylformamide (30 mL) was stirred at room temperature for 3 hours. Then the reaction mixture was poured into ice water (500 mL), the precipitate collected by suction filtration, washed with water and dried *in vacuo*. The yield was 2.40 g (83%), yellow prisms, mp 140 °C (methanol), partial decomposition, resolidifies and melts again at 268 °C by formation of **9a**; DSC data: cyclization at 120.5 °C onset; 139.2 °C peak max., ΔH = -9 mcal/mg; decomposition 261.7 °C onset, 267.9 °C max. , ΔH = -19 mcal/mg; ir: 2160 s (N_3), 1720 s, 1670 s cm^{-1}; ^{1}H nmr: δ 3.20 (s, 3 H, NMe), 3.52 (s, 3 H, NMe), 3.58 (s, 3 H, NMe). *Anal.* Calcd. for $C_{10}H_9N_7O_5$ (307.23): C, 39.10; H, 2.95; N, 31.91. Found: C, 39.50; H, 3.02; N, 31.18; values are not correct because of the ease of decomposition of the azide.

5-Azido-1,3-dimethyl-6-nitro-8-phenylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (7b). This compound was obtained from 5-chloropyrido[2,3-*d*]pyrimidinetrione **5b** (3.62 g, 10 mmoles) as described for **7a**; the yield was 3.14 g (85%), yellow prisms, mp 128 °C (ethanol) partial decomposition, resolidifies and melts again at 288 °C by formation of **9b**; DSC data: cyclization at 116.8 °C onset, 127.1 °C max., ΔH = -8 mcal/mg; decomposition 276.4 °C onset, 287.6 °C max., ΔH = -12 mcal/mg; ir: 2160 s (N_3), 1740 s, 1660 s cm^{-1}; ^{1}H nmr: δ 2.64 (s, 3 H, NMe), 3.28 (s, 3 H, NMe), 7.65-7.70 (m, 5 H, ArH). *Anal.* Calcd. for $C_{15}H_{11}N_7O_5$ (369.30): C, 48.79; H, 3.00; N, 26.55. Found: C, 48.71; H, 3.09; N, 25.66; values are not correct because of the ease of decomposition.

5-Amino-1,3,8-trimethyl-6-nitro-pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**8a**). A mixture of 5-triphenylphosphoranylideneaminopyrido[2,3-*d*]pyrimidinetrione **6a** (5.41 g, 10 mmoles), 80% aq. acetic acid (50 mL) was heated under reflux for 1 hour. After cooling, to the reaction mixture water (50 mL) was added then the precipitate was collected by suction filtration and washed with water. The yield was 2.52 g (90%), yellow prisms, mp 276-278 °C (toluene); ir: 3280 m, 3200 m, 1725 m, 1710 m, 1670 m, 1655 s, 1600 s cm^{-1}; ^{1}H nmr (CF_3COOH): δ 3.61 (s, 3 H, NMe), 3.82 (s, 6 H, 2 NMe), 11.37 (s, 2 H, NH_2). *Anal.* Calcd. for $C_{10}H_{11}N_5O_5$ (281.23): C, 42.71; H, 3.94; N, 24.90. Found: C, 42.47; H, 3.93; N, 24.86.

5-Amino-1,3-dimethyl-6-nitro-8-phenylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (**8b**). This compound was obtained from 5-triphenylphosphoranylideneaminopyrido[2,3-*d*]pyrimidinetrione **6b** (6.03 g, 10 mmoles) as described for **8a**. The yield was 3.20 g (93%), yellow prisms, mp 248 °C (toluene); ir: 3360 m, 3170 m, 1710 s, 1650 s, 1600 m cm^{-1}; ^{1}H nmr: δ 2.63 (s, 3 H, NMe), 3.26 (s, 3 H, NMe), 7.53-7.55 (m, 5 H, ArH), 9.18 (s, 1 H, NH_2), 10.40 (s, 1 H, NH_2). *Anal.* Calcd. for $C_{15}H_{13}N_5O_5$ (343.30): C, 52.48; H, 3.82; N; 20.40. Found: C, 52.34; H, 3.86; N, 20.36.

5,6,8-Trimethyl-4,7,9-trioxo-4,5,6,7,8,9-hexahydro[1,2,5]-oxadiazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-3-oxide (9a). A solution of 5-azido-6-nitropyrido[2,3-*d*]pyrimidinetrione **7a** (3.07 g, 10 mmoles) in bromobenzene (50 mL) was heated under reflux until evolution of nitrogen had stopped (about 30 minutes). Then the solvent was removed *in vacuo* and the remaining solid digested with cyclohexane (40 mL). The product was filtered and washed with cyclohexane. The yield was 2.60 g (93%), yellow prisms, mp 266-268 °C (toluene); ir: 1710 s, 1665 s, 1615 m cm^{-1}; ^{1}H nmr ($CDCl_3$): δ = 3.29 (s, 3 H, NMe), 3.48 (s, 6 H, 2 NMe). *Anal.* Calcd. for $C_{10}H_9N_5O_5$ (279.21): C, 43.02; H, 3.25; N, 25.08. Found: C, 42.78; H, 3.27; N, 25.07.

6,8-Dimethyl-5-phenyl-4,7,9-trioxo-4,5,6,7,8,9-hexahydro-[1,2,5]oxadiazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-3-oxide (9b). This compound was obtained from 5-azido-6-nitropyrido-[2,3-*d*]pyrimidinetrione **7b** (3.69 g, 10 mmoles) as described for **9a**; the yield was 3.10 g (91%), yellow prisms, mp 292 °C (toluene); ir: 1730 s, 1670 s, 1620 m cm^{-1}; ^{1}H nmr (CF_3COOD): δ 3.06 (s, 3 H, NMe), 3.63 (s, 3 H, NMe), 7.46-7.50 (m, 2 H, ArH), 7.66-7.69 (m, 3 H, ArH). *Anal.* Calcd. for $C_{15}H_{11}N_5O_5$ (341.29): C, 52.79; H, 3.25; N, 20.52. Found: C, 52.57; H, 3.20; N, 20.47.

5,6,8-Trimethyl[1,2,5]oxadiazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-4,7,9(5*H*,6*H*,8*H*)-trione (10a). A mixture of [1,2,5]oxadiazolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-3-oxide (**9a**) (2.79 g, 10 mmoles) and triphenylphosphane (3.15 g, 12 mmoles) in 1,2-dichlorobenzene (50 mL) was heated under reflux for 8 hours, cooled to room temperature, the formed precipitate was collected by suction filtration and washed with cyclohexane. The yield was 1.60 g (61%), yellow prisms, mp 270 °C (dimethylformamide/ethanol); ir: 1730 m, 1710 s, 1665 s, 1610 s cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 3.30 (s, 3 H, NMe), 3.51 (s, 3 H, NMe), 3.53 (s, 3 H, NMe). *Anal.* Calcd. for $C_{10}H_9N_5O_4$ (263.21): C, 45.63; H, 3.45; N, 26.61. Found: C, 45.34; H, 3.47; N, 26.52.

6,8-Dimethyl-5-phenyl[1,2,5]oxadiazolo[3',4':4,5]pyrido-[2,3-*d*]pyrimidine-4,7,9(5*H*,6*H*,8*H*)-trione (10b). This compound was obtained from [1,2,5]oxadiazolo[3',4':4,5]-pyrido[2,3-*d*]pyrimidine-3-oxide **9b** (3.41 g, 10 mmoles) as described for **10a**; the yield was 2.28 g (70%), yellow prisms, mp 290 °C (dimethylformamide/ethanol); ir: 1745 s, 1665 s cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 2.68 (s, 3 H, NMe), 3.30 (s, 3 H, NMe), 7.58-7.60 (m, 5 H, ArH). *Anal.* Calcd. for $C_{15}H_{11}N_5O_4$ (325.29): C, 53.59; H, 3.41; N, 21.53. Found: C, 53.22; H, 3.51; N, 21.42.

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