SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINES ON THE BASIS OF 5-FORMYL-6-AMINOURACILS

N. M. Cherdantseva, V. M. Nesterov, and T. S. Safonova

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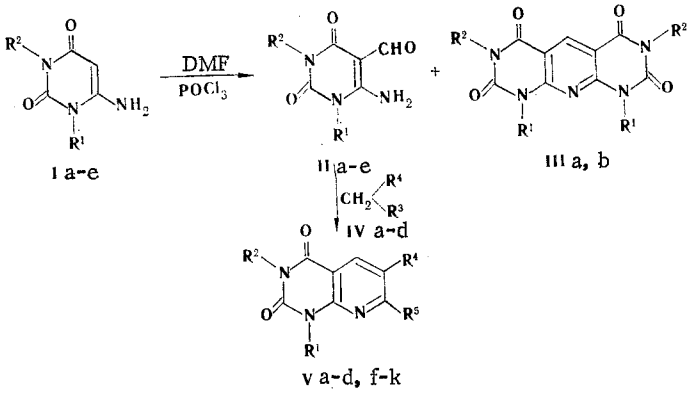
2,4-Dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidines, the structures of which were proved by the PMR and the IR spectra, are formed in the condensation of mono- and di-N-alkyl-5-formyl-6-aminouracils with cyanoacetic acid and its esters, acetoacetic ester, and malonic acid dinitrile.

Substances that have a broad spectrum of biological activity are known in the pyrido-[2,3-d]pyrimidine series [1-3], and it therefore seems of interest to obtain 2,4-dioxopyrido-[2,3-d]pyrimidines that contain active functional groups in the 6 and 7 positions on the basis of 6-aminouracil derivatives (I).

The known syntheses of pyrido[2,3-d]pyrimidines from pyrimidine derivatives are based on the use of 2,6- or 4,6-diamino-5-formylpyridines [4-6].

5-Formyl-6-aminouracil derivatives (II) can serve as the starting substances for the preparation of 2,4-dioxopyrido[2,3-d]pyrimidine derivatives. However, information regarding the synthesis of only one representative of this series, viz., 1,3-dimethyl-5-formyl-6-aminouracil (IIa), which is formed by the reaction of 1,3-dimethyl-6-aminouracil (Ia) with acetic formic anhydride [7] or with the Vilsmeier reagent [8, 9], is available. Formyl derivative IIa has been used for the synthesis of a number of condensed systems that contain a pyrimidine ring, including the preparation of 2,4-dioxopyrido[2,3-d]pyrimidines [3].



I—III a $R^1=R^2=CH_3$; b $R^1=C_6H_5$, $R^2=CH_3$; I, II c $R^1=H$, $R^2=CH_3$; d $R^1=CH_3$, $R^2=H$; e $R^1=R^2=H$; IV a $R^3=R^4=CN$; b $R^3=CN$, $R^4=CO_2C_2H_5$; c $R^3=COCH_3$, $R^4=CO_2C_2H_5$; d $R^3=CN$, $R^4=COOH$; V a $R^1=R^2=CH_3$, $R^4=CN$, $R^5=NH_2$; b $R^1=C_6H_5$, $R^2=CH_3$, $R^4=CO_2C_2H_5$, $R^5=NH_2$; c $R^1=H$, $R^2=CH_3$, $R^4=CO_2C_2H_5$, $R^5=CH_3$; d $R^1=CH_3$, $R^2=H$, $R^4=COOH$, $R^5=NH_2$; f $R^1=R^2=CH_3$, $R^4=CO_2C_2H_5$, $R^5=NH_2$; g $R^1=R^2=CH_3$, $R^4=COOH$, $R^5=NH_2$, h $R^1=R^2=CH_3$, $R^4=CO_2C_2H_5$, $R^5=CH_3$; i $R^1=H$, $R^2=CH_3$, $R^4=CO_2C_2H_5$, $R^5=NH_2$, j $R^1=CH_3$, $R^2=H$, $R^4=CO_2C_2H_5$, $R^5=NH_2$; k $R^1=CH_3$, $R^2=H$, $R^4=CO_2C_2H_5$, $R^5=CH_3$

Attempts to formylate monoalkyl-6-aminouracils Ic,d with acetic formic anhydride did not give positive results; however, formyl derivatives IIc-e are formed in good yields by the action of the Vilsmeier reagent on Ic-e. In contrast to the monosubstituted compounds, disubstituted aminouracils Ia,b form 1,3,7-9-tetrasubstituted 2,4,6-8-tetraoxopyrido[2,3-d;6,5-d']dipyrimidines (IIIa,b) in 6-7% yields under these conditions. The formation of these compounds, according to the data in [10], is due to reaction of the starting aminouracils Ia,b with formyluracils IIa,b.

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In fact, pyridodipyrimidine IIIa, which was identical to the previously described compound [10, 11], was obtained in quantitative yield by heating an equimolar mixture of aminouracil Ia and formyluracil IIa in tetralin at 190-195°C.

In addition to absorption bands at 1620 and 1670 cm^{-1} (C=O), an absorption band at 1730 cm^{-1} (—CHO) appears in the IR spectra of IIa-e. The mass spectra contain peaks of M — 28 and M — 29 ions, which confirm the presence of a formyl group. The absence of a signal of a proton attached to $C_{(5)}$ with δ 6.15 ppm and the presence of a signal of a formyl proton with δ 9.68 ppm in the PMR spectra of IIa-e make it possible to assert that the formyl group is located in the 5 position.

The reaction of mono- and dialkyl-5-formyl-6-aminouracils with compounds that contain an active methylene group and a functional group that is capable of condensing with an amino group (IV) was investigated.

The condensation of formylaminouracil IIa with malonic acid dinitrile IVa gave 1,3-dimethyl-2,4-dioxo-6-cyano-7-aminopyrido[2,3-d]-pyrimidine (Va), which is similar to the compound obtained in the reaction of 1,3-dimethyl-5-methylaminomethylene-6-aminouracil with nitrile IVa [8].

The condensation of formylaminouracils IIa-d with cyanoacetic ester (IVb), acetoacetic ester (IVc), and cyanoacetic acid (IVd) gave 2,4-dioxopyrido[2,3-d]pyrimidines that contain a carboxy (Vd,g) or carbethoxy (Vb,c,f,h-k) group in the 6 position.

These substances are key compounds in the synthesis of a number of three-membered systems. Attempts to obtain a pyrido[2,3-d]pyrimidine that has an unsubstituted nitrogen atom in the pyrimidine ring from formylaminouracil IIe and IV were unsuccessful.

The structure of pyrido[2,3-d]pyrimidines V is confirmed by the result of elementary analysis and PMR and IR spectroscopy. In the PMR spectra the signal of the formyl proton with δ 9.68 ppm vanishes, and signals of protons of CH_2 and CH_3 groups with δ 4.50 ppm and of a carbethoxy group with δ 3.10 ppm appear. The molecular masses were confirmed by mass spectrometry.

EXPERIMENTAL

The course of the reactions and the purity of the substances obtained were monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 in an n-butanol system saturated with water. The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The mass spectra were recorded with an MKh-1303 mass spectrometer with direct introduction of the samples into the source at an ionizing-voltage energy of 50 eV.

1,3-Dimethyl-5-formyl-6-aminouracil (IIa). An 8.4-ml sample of phosphorus oxychloride was added with stirring at no higher than 40°C to a mixture of 8 g (52 mmole) of aminouracil Ia and 6.6 ml of dimethylformamide (DMF), and the mixture was maintained on a boiling-water bath for 1 h and then cooled to 20°C. A 25-ml sample of 40% sodium acetate was added to the resulting mixture, and the precipitate was removed by filtration, dried, and recrystallized from ethanol to give 8.1 g (85.2%) of IIa with mp 191-192°C (mp 190-191°C [8, 9]). The alcohol-insoluble precipitate was recrystallized from chloroform to give 0.5 g (6.4%) of IIIa with mp 321-323°C (mp 321-325°C [7]). PMR spectrum: 9.11 (1H, s, CH), 3.76 (6H, s, N—CH_3), and 3.50 ppm (6H, s, N—CH_3). Found: C 51.3; H 4.5; N 23.0%. $C_{13}H_{13}N_5O_4$. Calculated: C 51.5; H 4.3; N 23.1%; M^+ 303.

1-Phenyl-3-methyl-5-formyl-6-aminouracil (IIb). This compound, with mp 249-250°C, was obtained in 86% yield from Ib by the method described above. IR spectrum: 3170 and 3320 (NH_2); 1730 cm^{-1} (CHO). PMR spectrum: 9.68 (1H, s, CHO); 7.16 and 7.52 (5H, t, aromatic); 3.66 ppm (3H, s, N—CH_3). Found: C 58.5; H 4.3; N 17.0%. $C_{12}H_{11}N_3O_3$. Calculated: C 58.8; H 4.5; N 17.1%; M^+ 245.

The alcohol-insoluble precipitate was recrystallized from DMF to give IIIb, with mp > 330°C, in 7% yield. Found: C 64.7; H 3.6; N 16.5%. $C_{23}H_{15}N_5O_4$. Calculated: C 64.9; H 3.5; N 16.5%.

3-Methyl-5-formyl-6-aminouracil (IIc). This compound, with mp >330°C, was similarly obtained in 81.5% yield from Ic. IR spectrum: 3230 and 3450 (NH_2); 1730 cm^{-1} (CHO). Found: C 42.6; H 4.1; N 24.9%. $C_6H_7N_3O_3$. Calculated: C 42.6; H 4.2; N 24.8%; M^+ 169.

1-Methyl-5-formyl-6-aminouracil (IId). This compound, with mp >330°C, was similarly obtained in 80.5% yield from Id. IR spectrum: 3240 and 3370 (NH_2); 1720 cm^{-1} (CHO). Found: C 42.6; H 4.1; N 24.9%. $C_6H_7N_3O_3$. Calculated: C 42.7; H 4.2; N 24.8%; M^+ 169.

5-Formyl-6-aminouracil (IIe). This compound, with mp >330°C, was similarly obtained in 82% yield from Ie. IR spectrum: 3240 and 3450 (NH_2); 1730 cm^{-2} (CHO). Found: C 42.6; H 3.1; N 25.3%. $C_5H_5N_3O_3$. Calculated: C 42.4; H 3.0; N 25.5%.

1,3,7,9-Tetramethyl-2,4,6,8-tetraoxopyrido[2,3-d;6,5-d']pyrimidine (IIIa). A mixture of 3.66 g (20 mmole) of formylaminouracil IIa, 3.1 g (20 mmole) of aminouracil Ia, and 15 ml of tetralin was maintained at 190-195°C for 1 h, after which it was cooled to 20°C. Ethanol (20 ml) was added to the resulting mixture, and the precipitate was removed by filtration, dried, and recrystallized from chloroform to give 6.0 g (99%) of a product with mp 321-323°C (mp 321-325°C [7]).

1,3-Dimethyl-2,4-dioxo-6-cyano-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]-pyrimidine (Va). A mixture of 10.98 g (60 mmole) of formylaminouracil IIa and 4.8 g of malonic acid dinitrile was refluxed in 30 ml of acetic acid for 8 h, after which it was cooled, and the precipitate was removed by filtration and recrystallized from DMF—ethanol (1:1) to give 10.65 g (76.8%) of a product with mp 353-354°C (mp 354°C [5]).

1-Phenyl-3-methyl-2,4-dioxo-6-carbethoxy-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vb). A 5.95-g (24 mmole) sample of formylaminouracil IIa and 4.07 g (36 mmole) of ethyl cyanoacetate were refluxed in 30 ml of acetic acid for 2 h, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from DMF to give 7.22 g (88.5%) with mp >330°C. IR spectrum: 3320 and 3450 (NH_2); 1710 (C=O); 1220 cm^{-1} (C—O—C). PMR spectrum: 9.39 (1H, s, CH); 7.16 and 7.52 (5H, t, aromatic); 4.58 (2H, m, CH_2); 3.66 (3H, s, N—CH_3); 1.52 ppm (3H, t, CH_3—CH_2). Found: C 59.9; H 4.7; N 16.4%. $C_{17}H_{16}N_4O_4$. Calculated: C 60.0; H 4.7; N 16.5%; M^+ 340.

3-Methyl-2,4-dioxo-6-carbethoxy-7-methyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vc). A 5.0-g (30 mmole) sample of formylaminouracil IIc and 4.29 g (33 mmole) of acetoacetic ester were refluxed in a mixture of 15 ml of pyridine and 8 ml of piperidine for 15 h, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from pyridine—water (1:1) to give 6.04 g (76.5%) of a product with mp 219-220°C. IR spectrum; 2940 (CH_3), 1720 (C=O), and 1260 cm^{-1} (C—O—C). PMR spectrum: 9.35 (1H, s, CH), 4.45 (2H, m, CH_2), 3.85 (3H, s, N—CH_3), 3.10 (3H, s, CH_3), and 1.48 ppm (3H, t, CH_3—CH_2). Found: C 54.9; H 4.8; N 16.0%. $C_{12}H_{13}N_3O_4$. Calculated: C 54.8; H 4.9; N 16.0%; M^+ 263.

1-Methyl-2,4-dioxo-6-carboxy-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vd). A 13.6-g (80 mmole) sample of formyluracil IId and 8.08 g (96 mmole) of cyanoacetic acid were refluxed in a mixture of 32 ml of pyridine and 16 ml of piperidine for 8 h. The mixture was then cooled, and the precipitate was removed by filtration and recrystallized from DMF to give 15.45 g (81.5%) of a product with mp >330°C. IR spectrum: 1690 (COOH); 3340 and 3460 cm^{-1} (NH_2). Found: C 45.7; H 3.4; N 23.6%. $C_9H_9N_4O_4$. Calculated: C 45.8; H 3.4; N 23.7%.

1,3-Dimethyl-2,4-dioxo-6-carbethoxy-7-amino-1,2,3,4-tetrahydropyrido [2,3-d]pyrimidine (Vf). A 3.7-g (20 mmole) sample of formylaminouracil IIa and 2.37 g (21 mmole) of ethyl cyanoacetate were refluxed in 12 ml of acetic acid for 8 h, after which the mixture was cooled and the precipitate was removed by filtration and recrystallized from n-butanol to give 4.64 g (83.5%) of a product with mp 214-215°C. IR spectrum: 3320 and 3425 (NH_2); 1720 (C=O); 1200 cm^{-1} (C—O—C). PMR spectrum 9.32 (1H, s, CH), 4.60 (2H, m, CH_2), 3.90 (3H, s, N—CH_3), 3.62 (3H, s, N—CH_3), and 1.52 ppm (3H, t, CH_3—CH_2). Found: C 52.0; H 5.0; N 20.2%. $C_{12}H_{14}N_4O_4$. Calculated: C 51.8; H 5.0; N 20.1%; M^+ 278.

1,3-Dimethyl-2,4-dioxo-6-carboxy-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vg). This compound, with mp 310-311°C, was obtained in 85% yield by the method described above from 3.7 g (20 mmole) of formylaminouracil IIa and 1.79 g (21 mmole) of cyanoacetic acid. IR spectrum: 3340 and 3465 (NH_2); 1690 cm^{-1} (COOH). PMR spectrum: 9.33 (1H, s, CH), 3.85 (3H, s, N—CH_3), and 3.56 ppm (3H, s, N—CH_3). Found: C 48.1; H 4.2; N 22.3%. $C_{10}H_{10}N_4O_4$. Calculated: C 48.0; H 4.0; N 22.4%; M^+ 250.

1,3-Dimethyl-2,4-dioxo-6-carbethoxy-7-methyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vh). A 10.98-g (60 mmole) sample of formylaminouracil IIa and 9.49 g (73 mmole) of acetoacetic ester were refluxed in 30 ml of acetic acid for 5 h, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from n-butanol to

give 11.8 g (71%) with mp 112°C. IR spectrum: 2930 (CH_3), 1710 (C=O), and 1240 cm^{-1} (C–O–C). PMR spectrum: 9.36 (1H, s, CH), 4.50 (2H, m, CH_2), 3.87 (3H, s, N–CH_3), 3.52 (3H, s, N–CH_3), 3.10 (3H, s, C–CH_3), and 1.48 ppm (3H, t, CH_3–CH_2). Found: C 56.5; H 5.3; N 15.1%. $C_{13}H_{15}N_3O_4$. Calculated: C 56.3; H 5.4; N 15.2%; M^+ 277.

3-Methyl-2,4-dioxo-6-carbethoxy-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vi). A 7.5-g (44 mmole) sample of formylaminouracil IIc and 7.05 g (62 mmole) of ethyl cyanoacetate were refluxed in a mixture of 20 ml of pyridine and 6 ml of piperidine for 15 h, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from dimethyl sulfoxide to give 9.0 g (73%) of a product with mp >330°C. IR spectrum: 3340 and 3460 (NH_2), 1715 (C=O), and 1240 cm^{-1} (C–O–C). PMR spectrum: 9.32 (1H, s, CH), 4.60 (2H, m, CH_2), 3.62 (3H, s, N–CH_3), and 1.52 ppm (3H, t, CH_3–CH_2). Found: C 50.1; H 4.5; N 21.4%. $C_{11}H_{12}N_4O_4$. Calculated: C 50.0; H 4.5; N 21.2%; M^+ 264.

1-Methyl-2,4-dioxo-6-carbethoxy-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vj). A 10.14-g (60 mmole) sample of formylaminouracil IIc and 7.9 g (70 mmole) of ethyl cyanoacetate were refluxed in 20 ml of pyridine for 2 h, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from acetic acid to give 11.0 g (70%) of a product with mp >330°C. IR spectrum: 3340 and 3460 (NH_2); 1720 (C=O); 1240 cm^{-1} (C–O–C). Found: C 50.2; H 4.8; N 21.3%. $C_{11}H_{12}N_4O_4$. Calculated: C 50.0; H 4.6; N 21.2%.

1-Methyl-2,4-dioxo-6-carbethoxy-7-methyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vk). A 5.0-g (30 mmole) sample of formylaminouracil IId and 4.29 g (33 mmole) of acetoacetic ester were refluxed in a mixture of 15 ml of pyridine and 4 ml of piperidine for 8 h, after which the mixture was cooled, and the precipitate was removed by filtration and recrystallized from ethanol to give 6.3 g (80%) of a product with mp 221-213°C. IR spectrum: 2935 (CH_3), 1715 (C=O), and 1250 cm^{-1} (C–O–C). PMR spectrum: 9.35 (1H, s, CH), 4.50 (2H, m, CH_2), 3.82 (3H, s, N–CH_3), 3.10 (3H, s, C–CH_3), and 1.48 ppm (3H, t, CH_3–CH_2). Found: C 54.7; H 4.8; N 16.2%. $C_{12}H_{13}N_3O_4$. Calculated: C 54.8; H 4.9; N 16.0%; M^+ 263.

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