SYNTHESIS OF NEW PYRIDO[2,3-d]PYRIMIDINE DERIVATIVES

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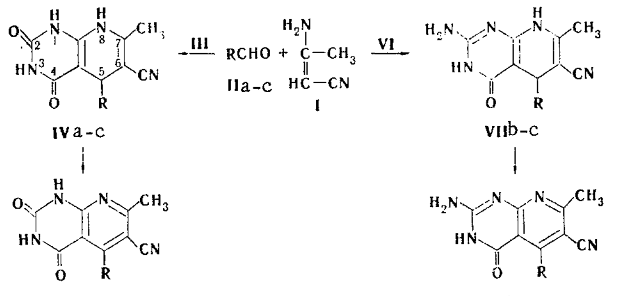
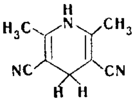
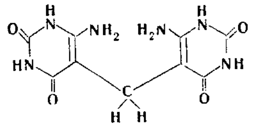
The mutual condensation of 4-aminouracil or 2,4-diamino-6-hydroxypyrimidine with bisacetonitrile and aldehydes was used to synthesize 2,4-dioxo-5-R-7-methyl-6-cyano-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine and 2-amino-4-oxo-5-R-7-methyl-6-cyano-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine derivatives, which were oxidized with chromic anhydride to the corresponding 2,4-dioxo-5-R-7-methyl-6-cyano-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine and 2-amino-4-oxo-5-R-7-methyl-6-cyano-3,4-dihydro[2,3-d]pyrimidines. The IR and UV spectra of the synthesized compounds were recorded.

We have previously described the unsymmetrical three-carbon condensation of β-aminovinyl carbonyl compounds (4-aminouracil), 5,5-dimethylcyclohexane-1,3-dione, and aliphatic or aromatic aldehydes, as a result of which 2,4,6-trioxo-8,8-dimethyl-5-R-1,2,3,4,5,6,7,8,9,10-decahydropyrimido[4,5-b]quinolines were obtained [1, 2].

In the present research, we have accomplished the similar condensation of two different β-aminovinyl carbonyl compounds — 4-aminouracil (III) and 2,4-diamino-6-hydroxypyrimidine (VI) — bisacetonitrile (I), and aldehydes to give 2,4-dioxo-5-R-7-methyl-6-cyano-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidines (IVa-c) and 2-amino-4-oxo-5-R-7-methyl-6-cyano-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidines (VIIb-c). The presently known methods for the synthesis of pyrido[2,3-d]pyrimidines [3, 4] do not make it possible to obtain the indicated systems, which contain a 1,4-dihydropyridine ring.




IX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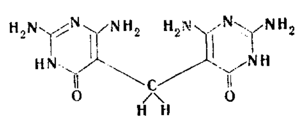
XI

II, IV, V, VII, VIII a R=H; b R=CH$_3$; c R=C$_6$H$_5$

The mutual condensation of two different reactive β-aminovinyl carbonyl compounds (I, III, and VI) and an aldehyde does not exclude the possibility of the formation of symmetrical condensation products,

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TABLE 1. Pyrido[2,3-d]pyrimidines

Compound	R	Mp, °C*	Empirical formula	Found, %			Calc., %		
				C	H	N	C	H	N
IVa	H	326—329	$C_9H_9N_4O_2$	53,4	4,6	26,9	52,7	4,4	27,3
IVb	CH_3	297,5—300 (dec.)	$C_{10}H_{10}N_4O_2$	54,7	4,4	25,2	55,0	4,6	25,7
IVc	C_6H_5	323—326 (dec.)	$C_{15}H_{12}N_4O_2$	64,1	4,8	19,6	64,3	4,3	20,0
Vc	C_6H_5	316—319 (dec.)	$C_{15}H_{10}N_4O_2$	64,4	4,0	20,4	64,8	3,6	20,1
VIIb	CH_3	>360	$C_{10}H_{11}N_5O$	55,0	5,0	32,3	55,3	5,1	32,2
VIIc	C_6H_5	>360	$C_{15}H_{13}N_5O$	64,1	4,9	25,6	64,5	4,7	25,1
VIIIa	H	>360	$C_9H_7N_5O$	52,9	3,6	34,9	53,8	3,5	34,8
VIIIb	CH_3	>360	$C_{10}H_9N_5O$	55,6	4,6	32,2	55,8	4,2	32,5
VIIIc	C_6H_5	>360	$C_{15}H_{11}N_5O$	65,1	4,4	24,9	65,0	4,0	25,3

TABLE 1. (Continued)

Compound	IR spectra, cm^{-1}									Yield, %
	$\nu_{C=C}$, $\nu_{C=O}$					$\nu_{C\equiv N}$	ν_{NH}			
IVa	1550	1615	1660	1690	1710	2200	3150	3190	3290	
IVb	1565	1605	1650	1675	1710	2195	3140	3285	3315	32
IVc	1550	1610	1655	1670	1710	2215	3185	3225	3320	36
Vc	1518	1565		1678	1727	2230	3143	3180		86
VIIb	1535	1610	1658	1675	1715	2200	3195	3290	3360	40
VIIc	1535	1610		1671		2215	3182	3280	3360	42
VIIIa	1595			1687	1725	2235		3200		—
VIIIb	1580			1680	1725 1710	2233		3215		80
VIIIc	1575	1625		1678	1693	2230		3200		82

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* The melting points were determined by means of a Boetius apparatus.

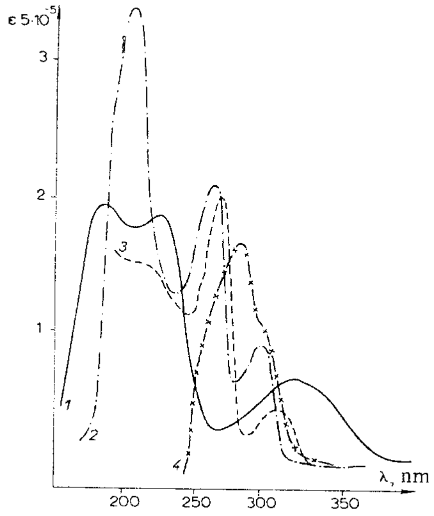

Fig. 1. UV spectra in ethanol: 1) 2,4-dioxo-7-methyl-5-phenyl-6-cyano-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (IVc); 2) 2,4-dioxo-7-methyl-5-phenyl-6-cyano-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vc); 3) 2-amino-4-oxo-7-methyl-5-phenyl-6-cyano-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine (VIIc); 4) 2-amino-4-oxo-7-methyl-5-phenyl-6-cyano-3,4-dihydropryido[2,3-d]pyrimidine (VIIIc) in $CH_3COOH+H_2O$.

which, however, we isolated only in the case of IIa. The synthesis was carried out in glacial acetic acid. Compounds IVc and VIIb-c were oxidized with chromic anhydride in acetic acid to 2,4-dioxo-5-phenyl-7-methyl-6-cyano-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vc) and 2-amino-4-oxo-5-R-7-methyl-6-cyano-3,4-dihydropyrido[2,3-d]pyrimidines (VIIIb-c]. It was observed that VII (R=H) is oxidized during condensation and crystallization, in connection with which, we could not isolate this compound; VIIb formed a mixture of the oxidized and unoxidized products on storage. Except for these two compounds, the synthesized pyrido[2,3-d]pyrimidines are stable. Compounds IVa-c and VIIa-c have very low solubility in organic solvents, and this hinders their purification. When III is condensed with paraformaldehyde and I, 2,6-dimethyl-3,5-dicyano-1,4-dihydropyridine (IX) and a very slightly soluble compound, to which we ascribe the X structure [5], are formed as side products along with IVa. A side product, the elementary analysis of which corresponds to structure XI [5, 6], was obtained in the condensation of VI with I and paraformaldehyde.

It is difficult to assign frequencies to a definite C=O bond in the IR spectra of IVa-c. The $\nu_{C\equiv N}$ vibrations for IVa-c and VIIb, c are lowered in connection with conjugation in the O=C−C=C−NH−C=C−CN system. We have previously observed a similar phenomenon [7]. The value increases by 15-33 cm^{-1} when the 1,4-dihydropyridine ring (Vc, VIIIa-c) is oxidized. The spectrum of VIIIa-c at 3 μm is simplified as compared with VIIb, c, and a single broad maximum is observed at 3200-3215 cm^{-1}.

Three maxima, which are characteristic for systems containing this sort of pyridopyrimidine grouping, are observed in the UV region of the spectra of IVa-c. A hypsochromic shift of the long-wave maximum occurs on oxidation [8]. Compounds VIIb, c have two absorption maxima. A curve of different character with a strong maximum at 295 nm is observed for VIIIa-c (Fig. 1).

EXPERIMENTAL

The IR spectra of mineral-oil suspensions were recorded with a UR-20 spectrophotometer. The UV spectra were recorded with a UF-2 automatic spectrophotometer. A weighed sample of VIIIc was dissolved in 3 ml of acetic acid, and water was added to the solution up to the 100-ml mark in order to prepare solutions for the UV spectra. The mass spectrum was recorded with an MKh 13-03 spectrometer.

2,4-Dioxo-7-methyl-6-cyano-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (IVa). A solution of 0.24 g (7.9 mmole) of paraformaldehyde in 30 ml of glacial acetic acid was added to 1 g (7.9 mmole) of III and 0.65 g (7.9 mmole) of I in 100 ml of glacial acetic acid. The white precipitate of X was removed from the hot solution by filtration, and the filtrate was evaporated to 70% of its original volume and allowed to stand at 0° for 48 h. The precipitated mixture of IVa and IX was extracted with boiling ethanol to remove the soluble IX, and the IVa was crystallized twice from glacial acetic acid. Compound IX was identified by chromatography on FN-15 paper in 3% aqueous NH_4Cl (R_f 0.57) and in 4% sodium nitrate solution (R_f 0.56). The R_f value of 2,6-dimethyl-3,5-dicyano-1,4-dihydropyridine [9] was similar.

Bis(4-amino-2,6-dioxo-5-tetrahydropyrimidinyl)methane (X) [5]. This compound was purified successively by refluxing in acetic acid in water and reprecipitation from 1% NaOH solution by the addition of 30% acetic acid to give a product with mp 360° (dec.). Found: C 40.6; H 3.7; N 31.1%. $C_9H_{10}N_6O_4$. Calculated: C 40.6; H 3.8; N 31.6%.

2,4-Dioxo-5,7-dimethyl-6-cyano-1,2,3,4,5,8-hexahydropyrido[2,3-d]pyrimidine (IVb). A mixture of 2 g (16 mmole) of III, 1.3 g (16 mmole) of I, and 0.69 g (16 mmole) of acetaldehyde (IIb) was refluxed in 300 ml of glacial acetic acid for 1.5 h. The yellow reaction mixture was distilled to remove 70% of the solvent, several milliliters of water were added, and the mixture was allowed to stand at 0° for 24 h. The resulting white, crystalline IVb was removed by filtration and purified by two crystallizations from acetic acid and reprecipitated from 1% NaOH solution by the addition of 30% acetic acid. Compound IVc was similarly obtained.

2,4-Dioxo-7-methyl-5-phenyl-6-cyano-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine (Vc). A 1-g (3.6 mmole) sample of IVc was dissolved in 250 ml of acetic acid, and an aqueous solution of CrO_3 was added with heating until the color changed to dark-green. The mixture was distilled to remove 75% of the solvent, and water was added to precipitate a white, crystalline substance, which was purified by three crystallizations from ethanol. Compounds VIIIb, c were similarly obtained.

2-Amino-4-oxo-5,7-dimethyl-6-cyano-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine (VIIb). A 0.65-g (7.9 mmole) sample of I and 0.35 g (7.9 mmole) of acetaldehyde were added to 1 g (7.9 mmole) of VI dissolved in 100 ml of glacial acetic acid, and the mixture was refluxed for 4 h. The yellow mixture was then worked up as in the case of IVa. Compound VIIb was purified by two crystallizations from glacial acetic acid and reprecipitation from 1% NaOH solution by the addition of 30% acetic acid. Compound VIIc was similarly obtained.

2-Amino-4-oxo-7-methyl-6-cyano-3,4,5,8-tetrahydropyrido[2,3-d]pyrimidine (VIIIa). A 0.65-g (7.9 mmole) sample of I and 0.24 g (7.9 mmole) of paraformaldehyde in 20 ml of glacial acetic acid were added to 1 g (7.9 mmole) of VI dissolved in 100 ml of glacial acetic acid, and the mixture was refluxed for 1 h. The crystals of XI were removed by filtration, and the filtrate was evaporated to 80% of its original volume to precipitate light-yellow crystalline VIIIa, which was purified by two crystallizations from acetic acid. The molecular weight of VIIIa was determined by mass spectrometry. Found: mol. wt. 201.0. Calculated: mol. wt. 201.2. Compound XI was identified by chromatography on Leningrad Factory S paper with a propanol–25% NH_4OH-H_2O system (20 : 13 : 2). The R_f value was 0.34 and was in agreement with the R_f value of XI that we synthesized via the literature data [5].

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