PYRIDO[2,3-d]PYRIMIDINES
4.* SYNTHESIS AND SOME TRANSFORMATIONS OF OXO(HYDROXY)PYRIDO[2,3-d]PYRIMIDINES

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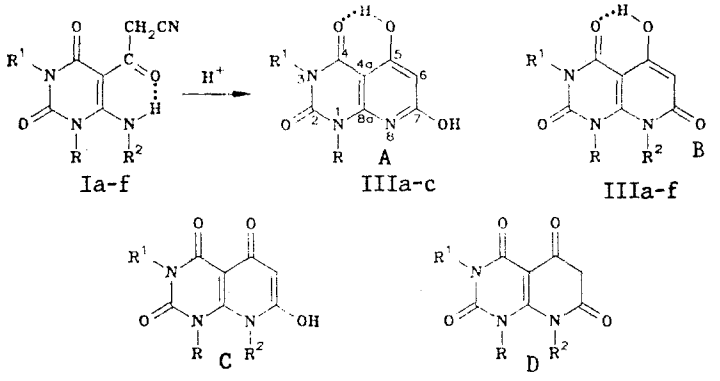
The cyclization of 5-cyanoacetyl-6-aminouracils in acidic media was accomplished. The structures of the pyrido[2,3-d]pyrimidines obtained and their properties are discussed.

The promising character of the search for biologically active substances in the pyrido[2,3-d]pyrimidine series was demonstrated in our preceding communication [1]. The aim of the present research was to synthesize new pyrido[2,3-d]pyrimidines and study their properties. We have previously shown that the cyclization of 5-cyanoacetyl-6-aminouracils I by the action of alkaline agents leads to 7-aminopyrido[2,3-d]pyrimidine-2,4,5-triones II [2]. In the present research we studied the cyclization of uracils Ia-f in acidic media. It was found that treatment of Ia-c with 48% HBr or 35% HCl at 80-90°C makes it possible to obtain 7-hydroxy(oxo)pyrido[2,3-d]pyrimidines IIIa-c in 83-99% yields. The cyclization of 5-cyanoacetyl-6-phenylaminouracil Id proceeds both by the action of 48% HBr at 90°C and by treatment with concentrated sulfuric or trifluoroacetic acid at 20°C. Heating 1,3-dimethyl-5-cyanoacetyl-6-ethylamino(benzylamino)uracils Ie, f in 48% HBr was accompanied by deacylation. The desired IIIe, f could be obtained only by treatment of Ie, f with 12% HBr at 20°C.

The cyclization of uracils Ia-d, which contain an amino or phenylamino group attached to the $C_{(6)}$ atom, does not depend on the character of the acids used.

With respect to its physicochemical characteristics, IIIa is identical to the product of the reaction of 1,3-dimethyl-6-aminouracil with malonic acid [3-5].

The structures of IIIa-c could be described by structures **A-D**, while the structures of $N_{(8)}$-substituted IIId-f could be described by structures **B-D**:



I, III **a** $R=R^1=CH_3$, $R^2=H$; **b** $R=C_6H_5$, $R^1=R^2=H$; **c** $R=C_6H_5$, $R^1=CH_3$, $R^2=H$; **d** $R=R^1=CH_3$, $R^2=C_6H_5$; **e** $R=R^1=CH_3$, $R^2=C_2H_5$; **f** $R=R^1=CH_3$, $R^2=CH_2C_6H_5$

In our opinion, the evidence presented in [5] in favor of the existence of IIIa in the **B** form is not sufficiently convincing, since the conclusion that an intramolecular hydrogen bond is present in IIIa that was drawn on the basis of the PMR spectral data also does not contradict the **A** form, which is not considered in [5].

We synthesized compounds with fixed structures, viz., 5,7-dimethoxy-, 7-methoxy-, and 5-ethoxypyridopyrimidines IV-VI, and studied their spectral data as compared with the spectral data for IIIa, e.

*See [1] for Communication 3.

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TABLE 1. IR and PMR Spectra of IIIa-f, IV-VI, VIII, IX, X, XII, and XIII

Compound	IR spectrum (KBr), cm^{-1}	PMR spectrum, δ, ppm (SSCC, J, Hz)*
IIIa	1680, 1711, 3100	3,25 (3H, s); 3,46 (3H, s); 5,85 (1H, s); 12,15 (1H, s)
IIIb	1680, 1728, 3100, 3250	5,80 (1H, s); 7,44 (5H, s)
IIIc	1673, 1720, 3100	3,24 (3H, s); 5,80 (1H, s); 7,38 (5H, m); 12,14 (1H, s)
IIId	1666, 1700, 1713	2,57 (3H, s); 3,20 (3H, s); 5,50 (1H, s); 7,44 (5H, s; 12,50 (1H, s)
IIIe	1660, 1680, 1720	3,36 (3H, s); 3,60 (3H, s); 1,38 (3H, t, J=7); 4,11 (2H, q, J=7); 5,60 (1H, s); 11,93 (1H, s)
IIIf	1667, 1687, 1716	3,12 (3H, s); 3,31 (3H, s); 5,22 (2H, s); 6,06 (1H, s); 6,90 (5H, m)
IV	1667, 1713	3,25 (3H, s); 3,58 (3H, s); 3,95 (6H, s); 5,95 (1H, s)
V	1675, 1715, 3100	3,40 (3H, s); 3,59 (3H, s); 3,94 (3H, s); 5,90 (1H, s); 11,93 (1H, s)
VI	1640, 1687, 3267	3,27 (3H, s); 3,53 (3H, s); 1,47 (3H, t, J=7); 4,19 (2H, q, J=7); 6,03 (1H, s)
VIII	1667, 1713	3,42 (3H, s); 3,63 (3H, s); 7,17 (1H, s)
IX	1656, 1705, 3265, 3377, 3485	3,12 (3H, s); 3,38 (3H, s); 1,30 (3H, t, J=6); 3,99 (2H, q, J=6); 5,76 (1H, s); 6,82 (2H, br.s)
X	1653, 1700, 1787, 3133	3,40 (3H, s); 3,56 (3H, s); 2,30 (3H, s); 6,34 (1H, s); 12,30 (1H, s)
XII	1367, 1540, 1667, 1717	3,29 (3H, s); 3,55 (3H, s); 4,09 (3H, s)
XIII	1360, 1543, 1673, 1727	3,38 (3H, s); 3,59 (3H, s); 1,37 (3H, t, J=7); 4,50 (2H, q, J=7); 13,00 (1H, s)

*The following solvents were used to record the PMR spectra: $CDCl_3$ for IIIe, IV, V, VIII, XI, and XIII, d_6-DMSO for IIIa, c, d, VI, and IX, d_7-DMF for IIIb and XII, and CF_3COOD for IIIf.

Refluxing pyridopyrimidine VII [1] with thionyl chloride in the presence of DMF leads to 5,7-dichloro derivative VIII, heating of which with excess sodium methoxide in methanol gives IV.

The action of dimethyl sulfate on pyridopyrimidine IIIa gave 5-hydroxy-7-methoxypyridopyrimidine V (A or C form). The location of the methyl group was proved by alternative synthesis of V by treatment of 7-aminopyridopyrimidine II with $NaNO_2$ in a methanol–30% H_2SO_4 medium.

The alkylation of 7-aminopyridopyrimidine II with ethyl iodide in the presence of sodium hydride or potassium carbonate leads to 5-ethoxy-7-amino derivative IX in the hydrate form. The presence of absorption bands at 3377 and 3485 cm^{-1} in the IR spectrum of IX shows that the amino group is not alkylated. The successive treatment of IX with amyl nitrite in acetic acid and sulfuric acid gave 5-ethoxy-7-hydroxypyridopyrimidine hydrate VI (A or B form). Compound VI is isomeric with respect to 8-ethyl derivative IIIe, which confirms the location of the ethoxy group.

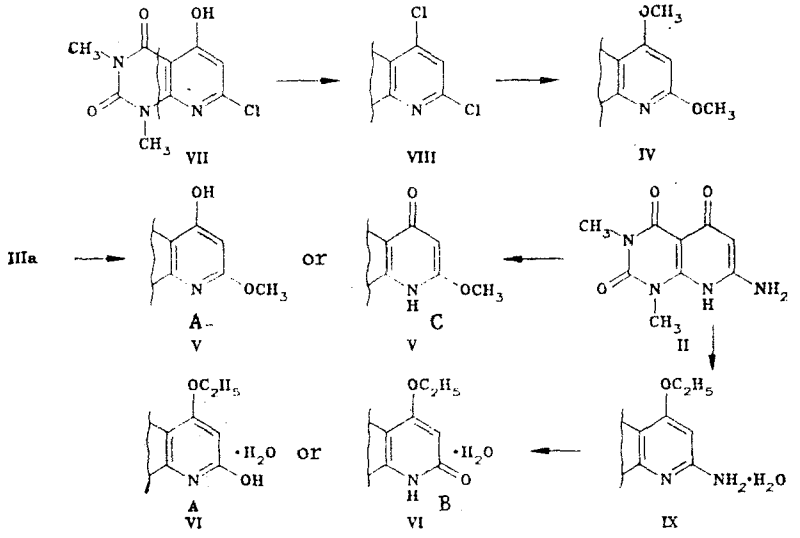


TABLE 2. ^{13}C NMR Spectra of IIIa, e and IV-VI*

Compound	Chemical shifts, δ, ppm (SSCC, J, Hz)								
	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$**	$C_{(6)}$	$C_{(7)}$**	$C_{(8a)}$	$C_{(4a)}$	CH_3	other signals
IIIa***	150, 14 sept ($^3J_{(C,N_{(1)}-CH_3)}$ = $=^3J_{(C,N_{(3)}-CH_3)}$ = 2,9)	164,53 q ($^3J_{(C,N_{(3)}-CH_3)}$ = 2,3; $^4J_{(C,C_{(6)}H)}$ = 0,9)	168,02	89,40 (^1J = 167,4)	168,53	151,41 q ($^3J_{(C,N_{(1)}-CH_3)}$ = = 2,6)	90,72 ($^3J_{(C,C_{(6)}-H)}$ = 4,9)	26,97; 29,11	—
IIIe	151,50 sept	($^3J_{(C,N_{(3)}-CH_3)}$ = 2,7; 164,12 q $^4J_{(C,C_{(6)}-H)}$ = 1,2)	164,45	94,75 (^1J = 169,1; $^3J_{(C,OH)}$ = 5,3)	165,49 td ($^3J_{(C,N_{(8)}-CH_3)}$ = 3,7)	152,24 sext	90,40 ($^3J_{(C,C_{(6)}-H)}$ = 6,5)	28,06; 39,76	43,68 (CH_2); 14,59 (CH_3)
IV	151,50 m	159,41 q	169,51	87,86 (^1J = 167,5)	167,24	152,67 q	95,41 ($^3J_{(C,C_{(6)}-H)}$ = 4,6)	28,03; 30,02	54,15 (OCH_3); 56,74 (OCH_3)
V	150,61 m	164,95 q ($^3J_{(C,N_{(3)}-CH_3)}$ = 2,4)	169,01	90,78; (^1J = 168,7; $^3J_{(C,OH)}$ = 7,0)	167,95 q ($^3J_{(C,OCH_3)}$ = 7,8)	151,14 q	92,32 ($^3J_{(C,C_{(6)}-H)}$ = 4,6)	27,46; 29,53	54,00 (OCH_3)
VI****	150,84	157,93	168,54	87,86 (^1J = 167,5)	167,24	152,50	~94	27,43; 29,58	64,72 (CH_2); 14,13 (CH_3)

*The solvents were $CDCl_3$ for IIIe, IV, and V and d_6-DMSO for IIIa and VI.

**The opposite assignment is possible for IIIa and IV.

***The spectrum of IIIa was recorded at 50°C because of its low solubility; spin-spin coupling (SSC) with the protons of the OH group is not observed.

****The $C_{(4a)}$ signal could not be rigorously identified because of the long relaxation time of $C_{(4a)}$ and the low solubility of the substance.

In addition to signals of the substituents attached to the nitrogen or oxygen atoms, a signal of a proton attached to the $C_{(6)}$ atom (5.60-6.06 ppm) was detected in the PMR spectra of IIIa-f and IV-VI; this made it possible to exclude structure D from consideration.

Two absorption bands of CO groups at 1673-1680 and 1711-1728 cm^{-1} and a band at 3100 cm^{-1} (associated OH or NH groups) are observed in the IR spectra (in KBr) of IIIa-c and V, which do not have a substituent attached to the $N_{(8)}$ atom. It was impossible to investigate the spectra of these compounds in solution because of their low solubilities. The spectra of derivatives IIId-f, which contain substituents attached to the $N_{(8)}$ atom, contain three bands of vibrations of CO groups at 1666, 1680, and 1720 cm^{-1}. In addition to two bands of vibrations of CO groups, a band at 3267 cm^{-1} (OH or NH group) is observed in the spectrum of VI.

The results obtained made it possible to assume that IIIa-c exist in the A form, while pyridopyrimidines IIId-f exist in the B or C form; however, the results were inadequate for a definitive choice, and we therefore studied the ^{13}C NMR spectra of IIIa, e and IV-VI. The assignment of the signals follows from a comparison of their spectral parameters with those described in [6, 7], as well as from an analysis of the multiplicities of the signals and the spin-spin coupling constants (SSCC) (Table 2).

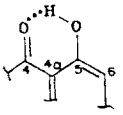
The $C_{(6)}$ and $C_{(4a)}$ signals of the pyridopyrimidine derivatives are located at relatively strong field (85-95 ppm) [6, 7]. The $C_{(6)}$ signals have constants $^1J_{[C_{(6)},H]}$ = 166.5-169.1 Hz of spin-spin coupling (SSC) with $H_{(6)}$, which makes it possible to unequivocally identify the $_{(6)}$ and $C_{(4a)}$ signals.

The $C_{(2)}$ signals in the spectra without decoupling of the SSC with the protons are observed in the form of septets due to their coupling with the two adjacent methyl groups. The $C_{(4)}$ and $C_{(8a)}$ signals of IIIa, IV, and V are quartets due to SSC with the methyl groups attached to the $N_{(3)}$ and $N_{(1)}$ atoms. We were able to rigorously assign the indicated signals for IIIe, in the spectrum of which the $C_{(8a)}$ signal is a sextet due to SSC with both the protons of the methyl group attached to the $N_{(1)}$ atom and with the protons of the methylene group attached to the $N_{(8)}$ atom.

For IIIa, e one observes additional splitting of the $C_{(4)}$ signal by the methylidyne $H_{(6)}$ proton with SSCC $^4J_{[C_{(4)},C_{(6)}-H]}$ = 0.9 and 1.2 Hz, respectively, as a consequence of the favorable ω orientation of the coupling nuclei.

In the spectra of IIIe and V the $C_{(5)}$ and $C_{(7)}$ signals are easily identified from their multiplicities and SSCC. Thus for IIIe the $C_{(7)}$ signal is a broad triplet of doublets due to SSC with the methylene protons of the ethyl group and $H_{(6)}$ with $^3J_{[C_{(7)},N_{(8)}-CH_2]}$ = 3.7 Hz. In the spectrum of V the $C_{(7)}$ signal has a quartet structure due to SSC with the methoxy group with $^3J_{[C_{(7)},OCH_3]}$ = 7.8 Hz. Only the $C_{(5)}$ and $C_{(7)}$ signals for IIIa and IV cannot be rigorously assigned.

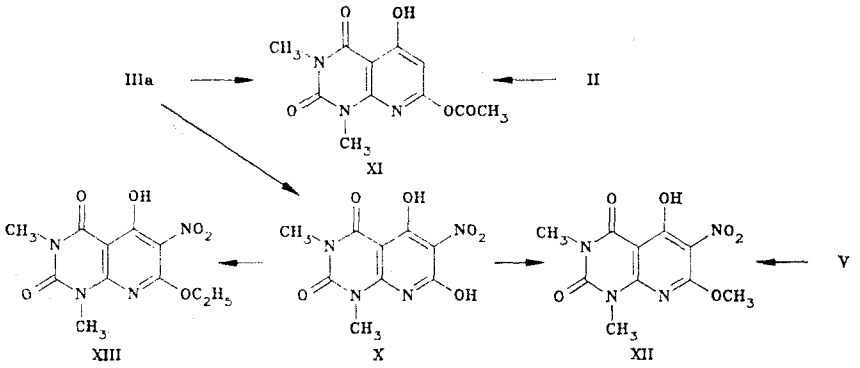
An analysis of the ^{13}C NMR spectra of IIIa, e and IV-VI makes it possible to conclude that IIIa exists in 5,7-dihydroxy form A. For the alternative B and C structures one should have expected deviations of the $C_{(5)}$ and $C_{(7)}$ chemical shifts (CS) from the corresponding values for 5,7-dimethoxy derivative IV. The transition from pyridine structures IIIa and IV-VI to pyridone structure IIIe leads to a substantial change in the $C_{(5)}$, $C_{(6)}$, and $C_{(7)}$ CS. The 5-hydroxy form in IIIa, e and V can be stabilized by an intramolecular hydrogen bond. This evidently explains the significant change in the $C_{(4)}$ and $C_{(4a)}$ CS on passing from IIIa, e and V to IV and VI, for which an intramolecular hydrogen bond is impossible. First and foremost, one's attention is directed to the large 5-7 ppm shift to strong field of the $C_{(4)}$ signal of IV and VI. An additional confirmation of the existence of an intramolecular hydrogen bond is the large SSCC, viz., $^3J_{[C_{(6)},OH]}$ = 7.0 Hz for V and 5.3 Hz for IIIe, which can be explained by a trans orientation of the coupling nuclei. At the same time, a similar SSCC for $C_{(4a)}$ is not observed because of the cis orientation of the nuclei.



Thus it may be assumed that pyridopyrimidines IIIa-c, V, and VI exist in the A form, while pyridopyrimidines IIId-f with a substituent attached to $N_{(8)}$ have structure B.

We carried out the nitration and acetylation of IIIa, as well as the alkylation of nitro derivative X. The nitration of IIIa with a mixture of nitric and concentrated sulfuric acids leads to 6-nitro derivative X (83% yield), which we previously [8] described as a side product. The acetylation of pyridopyrimidine IIIa with Ac_2O gives 7-acetoxy derivative XI, the structure of which was confirmed by alternative synthesis from 7-aminopyridopyrimidine II by the action of amyl nitrite in acetic acid. The alkylation of pyridopyrimidine X with dimethyl sulfate or ethyl benzenesulfonate, like the alkylation of IIIa with dimethyl sulfate, takes place at the hydroxy group in the 7 position to give the corresponding 7-alkoxy derivatives XII and XIII. The alkylation position was proved by alternative synthesis of XII by nitration of pyridopyrimidine V (see scheme on next page).

The higher activity in these reactions of the hydroxy group attached to the $C_{(7)}$ atom as compared with the hydroxy group attached to the $C_{(5)}$ atom is evidently explained by the participation of the latter in the formation of an



intramolecular hydrogen bond, which stabilizes the intermediate and final products of the reaction. The fact that the acetylation of 5-hydroxy-7-oxo-8-ethylpyridopyrimidine IIIe could not be carried out even when it was refluxed for a long time in Ac_2O confirms our conclusions.

A number of the pyrido[2,3-d]pyrimidine derivatives obtained were investigated for antitumorigenic activity in experiments with animals and implanted tumors. Some of the investigated compounds have a moderate inhibiting effect with respect to Jensen sarcoma (48% for IIIc, 38% for X, and 37% for XIII), M-1 sarcoma (33% for X), and P-388 leukemia (18% for XIII).

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a Specord IR-75 spectrometer. The ^1H NMR spectra were obtained with a Tesla BS-497 spectrometer (100 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The ^{13}C NMR spectra were obtained with an XL-200 spectrometer (50.3 MHz) with tetramethylsilane (TMS) as the internal standard. The mass spectra were obtained with a Varian MAT-311A spectrometer with direct introduction of the samples into the ion source.

The results of elementary analysis of the synthesized compounds for C, H, Cl, and N were in agreement with the calculated values. 5-Cyanoacetyl-6-aminouracils Ia-f were obtained by the method in [2].

1,3-Dimethyl-5,7-dihydroxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (IIIa, $C_9H_9N_3O_4$). A. A suspension of 1.3 g (5.9 mmole) of Ia in 5 ml of 48% HBr was maintained at 80-90°C for 0.5 h, after which it was cooled to 20°C, diluted with 10 ml of water, and neutralized with ammonia to pH 7. The resulting precipitate was removed by filtration and washed with water to give 1.2 g (92%) of IIIa with mp 282-284°C (from DMF). Mass spectrum: $M^{+\cdot}$ 223.

B. Compound IIIa was obtained in 83% yield by a method similar to method A from Ia with 5 ml of 35% HCl.

1-Phenyl-5,7-dihydroxy-1,2,3,4-tetrahdyropyrido[2,3-d]pyrimidine-2,4-dione (IIIb, $C_{13}H_9N_3O_4$). This compound was obtained and isolated in the same way as IIIa (method A) from uracil Ib and had mp > 300°C (from AcOH). The yield was 99%.

1-Phenyl-3-methyl-5,7-dihydroxy-1,2,3,4-tetrahdyropyrido[2,3-d]pyrimidine-2,4-dione (IIIc, $C_{14}H_{11}N_3O_4$). This compound was obtained and isolated in the same way as IIIa (method A) from uracil Ic in 93% yield and had mp 273-274°C (from ethanol).

1,3-Dimethyl-5-hydroxy-8-phenyl-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-2,4,7-trione (IIId, $C_{15}H_{13}N_3O_4$). A. Compound IIId was obtained and isolated in the same way as IIIa. Workup gave 1.2 g (92%) of a product with mp 282-284°C (from DMF). $M^{+\cdot}$ 233.

B. A solution of 1 g (3.4 mmole) of Id in 3 ml of trifluoroacetic acid was allowed to stand at 20°C for 10 days, after which it was diluted with 10 ml of water and neutralized to pH 7 with ammonia. The precipitate was removed by filtration and washed with water to give 0.75 g (75%) of IIId.

C. A 5-ml sample of concentrated H_2SO_4 was added to 1 g (3.4 mmole) of Id, and the mixture was stirred for 2 h at 20°C. It was then diluted with 10 ml of water, neutralized to pH 7 with ammonia, and filtered to give 0.84 g (85%) of pyridopyrimidine IIId.

1,3-Dimethyl-5-hydroxy-8-ethyl-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-2,4,7-trione (IIIe, $C_{11}H_{13}N_3O_4$). A suspension of 2.3 g (9.2 mmole) of uracil Ie and 16 ml of 12% HBr was allowed to stand at 20°C for 5 days, after which the precipitate was removed by filtration and washed with alcohol to give 1.5 g (65%) of pyridopyrimidine IIIe with mp 189-190°C (from acetone). Mass spectrum: $M^{+\cdot}$ 251.

1,3-Dimethyl-5-hydroxy-8-benzyl-1,2,3,4,7,8-hexahydropyrido[2,3-d]pyrimidine-2,4,7-trione (IIIf, $C_{16}H_{15}N_3O_4$). This compound was obtained and isolated in the same way as IIIe from uracil If in 58% yield and had mp 254-256°C (from AcOH).

1,3-Dimethyl-5,7-dimethoxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (IV, $C_{11}H_{13}N_3O_4$). A 1-g (3.8 mmole) sample of VIII was added to a solution of 0.35 g (15.4 mmole) of sodium in 20 ml of methanol, and the mixture was refluxed for 3 h. It was then cooled to 20°C and neutralized to pH 7 with 10% AcOH, and the resulting precipitate was removed by filtration and washed with 10 ml of water to give 0.9 g (98%) of IV with mp 211-213°C (from ethanol). Mass spectrum: $M^{+\cdot}$ 251.

1,3-Dimethyl-5-hydroxy-7-methoxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (V, $C_{10}H_{11}N_3O_4$). A. A 15.5-g (225 mmole) sample of $NaNO_2$ was added in portions at 5-10°C to a suspension of 5 g (22.5 mmole) of II, 80 ml of 30% H_2SO_4, and 100 ml of methanol, and the mixture was stirred for 1 h and filtered to give 3 g of II. Extraction of the mother liquor with chloroform (six 10-ml portions) and evaporation of the solvent to dryness gave 1.5 g of a mixture of products, which was chromatographed with a column (4 × 60 cm) packed with silica gel L 100/250 (elution with benzene) to give 0.54 g (25%) of V with mp 160-161°C (from benzene). Mass spectrum: $M^{+\cdot}$ 237.

B. A suspension of 2 g (9 mmole) of IIIa and 4.2 ml (45 mmole) of dimethyl sulfate in 20 ml of DMF was maintained for 10 h at 120°C, after which it was diluted with 60 ml of water, and the resulting precipitate was removed by filtration, dried, and extracted with acetone (three 20-ml portions). The solvent was removed by distillation to give 1.6 g (75%) of V.

1,3-Dimethyl-5-ethoxy-7-hydroxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione Hydrate (VI, $C_{11}H_{13}N_3O_4 \cdot H_2O$). A 1.52-g (13 mmole) sample of amyl nitrite was added at 20°C to a suspension of 1.3 g (4.5 mmole) of IX in 10 ml of glacial acetic acid, after which the mixture was diluted with water to three times its original volume and extracted with chloroform (five 5-ml portions). The extracts were combined and dried over $CaCl_2$, the solvent was evaporated, and the residue was treated with 9 ml of concentrated H_2SO_4. After 0.5 h, the mixture was diluted with 20 ml of water, and the resulting precipitate was removed by filtration and washed with 10 ml of water to give 1 g (77%) of VI in the hydrate form with mp 287-289°C (from AcOH). Mass spectrum: $M^{+\cdot}$ 251.

1,3-Dimethyl-5,7-dichloro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (VIII, $C_9H_7Cl_2N_3O_2$). A 2.4-ml (31.1 mmole) sample of DMF was added to a suspension of 5 g (20.7 mmole) of VII in 25 ml of $SOCl_2$, after which the mixture was cooled to 10°C and allowed to stand for 10 h at 5-10°C. The resulting precipitate was removed by filtration and washed with water until the wash water had pH 7 to give 3.4 g (63%) of VIII with mp 244-245°C (from AcOH). Mass spectrum: $M^{+\cdot}$ 259, [M + 2] 261, [M + 4] 263.

1,3-Dimethyl-5-ethoxy-7-amino-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione Hydrate (IX, $C_{11}H_{14}N_4O_3 \cdot H_2O$). A 0.43-g (18 mmole) sample of sodium hydride was added to a suspension of 2 g (9 mmole) of pyridopyrimidine II in 20 ml of dry DMF, and the mixture was heated to 120°C and maintained at this temperature for 1 h. It was then cooled to 90°C, 1.46 ml (18 mmole) of ethyl iodide was added dropwise, and the mixture was maintained for 2 h at 90-95°C. It was then cooled to 20°C, diluted to three times its original volume with water, and filtered to give 1.2 g (50%) of IX with mp 258-260°C (from AcOH). Mass spectrum: $M^{+\cdot}$ 250.

1,3-Dimethyl-5-hydroxy-7-acetoxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (XI, $C_{11}H_{11}N_3O_5$). A. A suspension of 1 g (4.5 mmole) of IIIa and 5 ml of Ac_2O was refluxed for 0.5 h, after which it was cooled to 20°C and filtered to give 1 g (84%) of XI with mp 172-174°C (from AcOH). Mass spectrum: $M^{+\cdot}$ 265.

B. A 0.7-ml (7 mmole) sample of amyl nitrite was added to a suspension of 1 g (4.5 mmole) of pyridopyrimidine II in 20 ml of glacial acetic acid, and the mixture was stirred for 1 h and filtered to give 0.4 g of unchanged II. The filtrate was diluted with water to twice its original volume and filtered to give 0.64 g (90%) of XI.

1,3-Dimethyl-5,7-dihydroxy-6-nitro-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione (X, $C_9H_8N_4O_6$). An 11-ml sample of concentrated H_2SO_4 was added to 2 g (9 mmole) of IIIa, 0.6 ml (13.8 mmole of HNO_3) of a nitrating mixture was added dropwise, and the mixture was stirred for 1 h at 20°C. It was then poured into 50 ml of water at 5-10°C, and the aqueous mixture was filtered to give 2 g (83%) of X, which was identical with respect to its physicochemical characteristics to the sample described in [8].

1,3-dimethyl-5-hydroxy-6-nitro-7-methoxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione(XII, $C_{10}H_{11} \cdot N_4O_6$). A. This compound was synthesized in 65% yield in the same way as X by nitration of pyridopyrimidine and had mp 251-253°C (from AcOH).

B. This compound was obtained in 71% yield under the conditions used to synthesize V (method B) by methylation of X with dimethyl sulfate. With respect to its physicochemical characteristics, the product was identical to the sample obtained by method A.

1,3-Dimethyl-5-hydroxy-6-nitro-7-ethoxy-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-2,4-dione(XIII, $C_{11}H_{12}N_4O_6$). A suspension of 5 g (18.6 mmole) of X, 20 ml of ethyl benzenesulfonate, and 50 ml of DMF was heated for 10 h at 110°C, after which it was cooled to 20°C, diluted to three times its original volume with water, and filtered to give

3 g (54%) of XIII with mp 164-166°C. Mass spectrum: $M^{+\cdot}$ 296.

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REACTION OF 2-ALKOXYCARBONYLMETHYL DERIVATIVES OF Δ^2-OXAZOLINE AND Δ^2-IMIDAZOLINE AND THEIR TAUTOMERS WITH 4-NITROBENZONITRILE N-OXIDE

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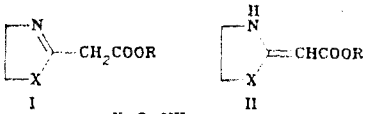
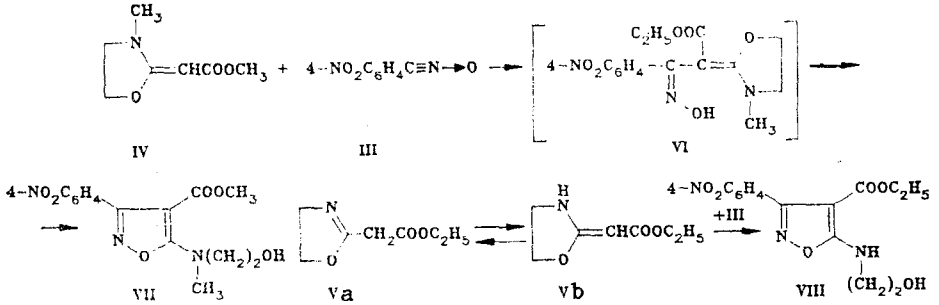
It was established that 2-alkoxycarbonylmethylene derivatives of oxazolidine and imidazolidine react readily with 4-nitrobenzonitrile N-oxide; the reaction takes place at the methylidyne carbon atom to give intermediate oximes, which can then undergo cyclization to isoxazoles. Their tautomers —benzimidazole and Δ^2-oxazoline derivatives —react with considerably greater difficulty; in the first case the reaction takes place at a different center, viz., the ring nitrogen atom.

It is known that oxazolines and imidazolines in which a methylene fragment bonded to an electron-acceptor substituent (an ester group) is present in the 2 position can exist in two tautomeric forms [1-3]:



I X=O, NH II

To study the effect of the tautomerism of derivatives I and II on their reactivities we investigated the reaction of these compounds with 4-nitrobenzonitrile N-oxide (III). The N-oxide was generated in situ by dehydrochlorination of 4-nitrobenzhydroxamic acid chloride with triethylamine. The starting I and II molecules contain several potential reaction centers, viz., an unsaturated bond (C=C or C=N), the ring nitrogen atom, and the methylene or methylidyne fragment. Since the reaction centers in tautomers I and II differ substantially, one might have expected that their reactions with nitrile oxide III would lead to different products. Nevertheless, we found that IV and V give derivatives of the same type in this reaction:



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