a JMS-01-SG-2 spectrometer. The authors thank co-workers of the All-Union Scientific-Research Institute of Vitamins Zh. K. Torosyan and V. A. Zamureenko for making these measurements. The IR spectra of carbon tetrachloride solutions of the compounds at 30 to 70° were recorded with Perkin—Elmer 457 and UR-10 spectrometers.

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STUDY OF CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS.

XXXIV*. SYNTHESIS AND PROPERTIES OF PYRIMIDO[5,4-b][1,4]OXAZIN-7-ONES

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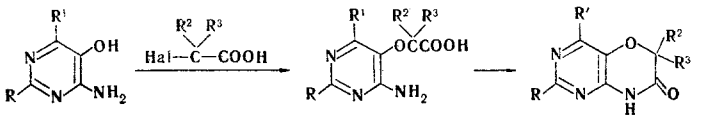
UDC 547.856'867.07

A new method was developed for the synthesis of pyrimido[5,4-b][1,4]oxazin-7-ones by O-alkylation of 5-hydroxy-6-aminopyrimidines with α-halo carboxylic acids and subsequent cyclization of the resulting pyrimdyloxyacetic acids in acetic anhydride. The reaction of chloropyrimidooxazinones with hydrazine gives the corresponding hydrazinopyrimidooxazinones, from which the azides were obtained. Unsubstituted pyrimido[5,4-b][1,4]oxazin-7-one was synthesized.

It has been observed that the reaction of 2-methyl-4-chloro-5-hydroxy- (I) and 2-methyl-4,6-dihydroxy-6-aminopyrimidine (II) with chloroacetic acid in water in the presence of alkali gives, after acidification, 6-amino-5-pyrimidyloxyacetic acids (IV, V).



I-III IV-VII IX-XXI

I R=CH_3, R^1=Cl, II R=CH_3, R^1=OH, III R=H, R^1=Cl, IV R=CH_3, R^1=Cl, R^2=R^3=H, V R=CH_3, R^1=OH, R^2=R^3=H, VI R=CH_3, R^1=Cl, R^2=C_2H_5, R^3=H, VII R=CH_3, R^1=Cl, R^2=C_3H_7, R^3=H, IX R=CH_3, R^1=Cl, R^2=R^3=H, X R=CH_3, R^1=OH, R^2=R^3=H, XI R=R^2=CH_3 R^1=Cl, R^3=H, XII R=CH_3, R^1=Cl, R^2=C_2H_5, R^3=H, XIII R=CH_3, R^1=Cl, R^2=C_3H_7, R^3=H, XIV R=R^2=R^3=CH_3, R^1=Cl, XV R=R^3=H, R^1=Cl, R^2=CH_3, XVI R=R^3=H, R^1=Cl, R^2=C_2H_5, XVII R=R^2=H, R^1=Cl, R^2=C_3H_7, XVIII R=H, R^1=Cl, R^2=R^3=CH_3, XIX R=R^2=CH_3, R^1=OH, R^3=H, XX R=CH_3, R^1=OH, R^2=C_2H_5, R^3=H, XXI R=R^2=R^3=CH_3, R^1=OH

*See [1] for communication XXXIII.

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Compounds IV and V are very stable, and we were able to convert them to pyrimido-7-oxazinones IX and X only by refluxing in acetic anhydride.

It is known from the literature [2] that benzoxazinones can be obtained when chloroacetamides are used. We have shown that the reaction of I with chloroacetamide in dimethylformamide (DMF) in the presence of sodium amide gives acid amide IV (VIII), which, on heating in acetic anhydride, also undergoes cyclization to IX, identical to the compound obtained from acid IV.

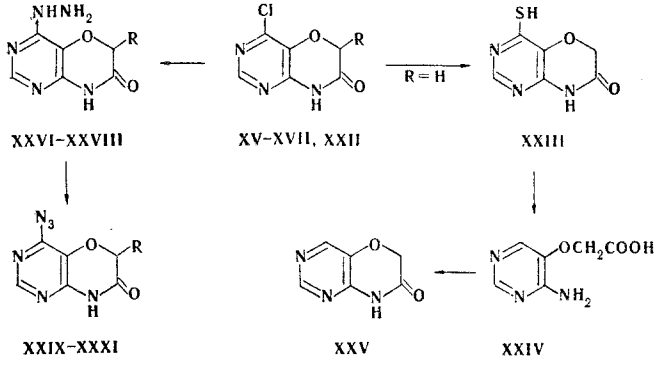
The corresponding α-(5-pyrimidyloxy) carboxylic acids (VI, VII) are also formed by reaction of I, II and 4-chloro-5-hydroxy-6-aminopyrimidine (III) with other α-halo carboxylic acids (α-bromopropionic, α-bromobutyric, α-bromovaleric, and α-bromoisobutyric acids) in alcohol in the presence of sodium ethoxide with subsequent acidification with acetic acid. The formation of cyclic reaction products — pyrimido-7-oxazinones (XII, XIII) — along with the oxy acids was observed when excess acetic acid was present.

The intermediate α-(5-pyrimidyloxy) carboxylic acids cannot be isolated from the reaction mixture, but, immediately after neutralization with excess acetic acid they undergo cyclization to pyrimido-7-oxazinones (IX-XXI) on brief heating.

Absorption bands of a CO group at 1690 cm^{-1} and of an NH_2 group at 3100-3480 cm^{-1} and a broad absorption band at 2400-2800 cm^{-1}, which is due to the presence of an acid OH group, are observed in the IR spectra of acids IV-VII. When the compounds undergo cyclization, the broad bands vanish, and the bands characteristic for the CO group and the amide NH group [3] remain in the spectra.

A confirmation of the fact that acids with structures IV-VII are formed (and that pyrimidines I-III are not N-alkylated by α-halo acids) is the absence of the coloration with $FeCl_3$ that is characteristic for 5-hydroxypyrimidines (the test for the presence of a phenolic hydroxyl group).

In order to extend the synthetic possibilities of the proposed method we investigated some properties of the compounds obtained in this study. The desulfuration of 4-mercaptopyrimido-7-oxazinone (XXIII) [4] with Raney nickel in the presence of ammonia gave, instead of the expected pyrimido-7-oxazinone (XXV), 6-amino-5-pyrimidyoxyacetic acid (XXIV), the structure of which was confirmed by the IR spectral data (1685, and broad bands at 3200-3400 and 2300-2800 cm^{-1}). Compound XXIV is readily converted to XXV when it is heated in acetic anhydride.



XXII R = H; XXVI R = C_2H_5; XXVII R = CH_3; XXVIII R = C_3H_7; XXIX R = C_2H_5; XXX R = CH_3; XXXI R = C_3H_7

Like chloropyrimidines [5], the chloropyrimido-7-oxazinones react with hydrazine hydrate to give the corresponding 4-hydrazinopyrimido-7-oxazinones (XXVI-XXVIII), which on treatment with nitrous acid [6] are converted to the corresponding azides (XXIX-XXXI). The structures of XXVI-XXXI were confirmed by data from their IR spectra, in which absorption bands characteristic for CO groups (1690-1720), the amide NH bond (3050-3150), the NH_2 group (3150-3440), and azide N_3 (2140 cm^{-1}) are observed.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with UR-10 or Perkin—Elmer 457 spectrometers.

2-Methyl-4-chloro-6-amino-5-pyrimidyloxyacetic Acid (IV). A solution of 3.2 g (0.02 mole) of I, 1.9 g (0.02 mole) chloroacetic acid, and 1.6 g (0.04 mole) of NaOH in 15 ml of water was refluxed for 5 h, after which it was cooled and acidified to pH 2-3 with concentrated HCl. The precipitated acid IV was separated and washed on the funnel with water.

2-Methyl-4-hydroxy-6-amino-5-pyrimidyloxyacetic Acid (V). A solution of 3.54 g (0.02 mole) of II, 1.9 g (0.02 mole) of chloroacetic acid, and 2.4 g (0.06 mole) of NaOH in 50 ml of water was refluxed for 3 h, after which it was cooled and acidified to pH 3-4 with concentrated HCl. The precipitate was separated and dissolved in 1 N NaOH solution. The solution was acidified to pH 2-3 with concentrated HCl, and precipitated acid V was separated and washed on the funnel with water.

α-(2-Methyl-4-chloro-6-amino-5-pyrimidyloxy)butyric Acid (VI). A 1.6 g (0.01 mole) sample of I was added to sodium ethoxide [prepared from 0.58 g (25 mg-atom) of sodium in 30 ml of absolute alcohol], and the mixture was stirred until all of the solid had dissolved. A solution of 2.5 g (0.015 mole) of α-bromobutyric acid in 10 ml of absolute alcohol was then added in the course of 10 min, and the mixture was heated to 70° and maintained at this temperature for 3 h. It was then evaporated to dryness, and the residue was dissolved in 10 ml of water. The aqueous solution was neutralized with acetic acid, and precipitated acid VI was separated and washed on the funnel with acetone and methanol. Evaporation of the acetone—methanol solution and addition of concentrated HCl to the aqueous solution gave a total of 0.5 g of XII.

Compound VII was similarly obtained.

2-Methyl-4-chloro-6-amino-5-pyrimidyloxyacetamide (VIII). A 1.6-g (0.02 mole) sample of I was added to a suspension of 0.26 g (0.011 mole) of sodium hydride in 25 ml of DMF, and the mixture was stirred for 30 min, after which 1.12 g (0.012 mole) of chloroacetamide was added, and the mixture was stirred at room temperature for 4 h. After 2 days, the mixture was evaporated to dryness, water was added to the residue, and precipitated amide VIII was separated.

2-Methyl-4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (IX). A suspension of 0.98 g of acid IV in 15 ml of acetic anhydride was refluxed for 1.5 h, after which it was evaporated to dryness, and the residual IX was washed with to give a product with mp 175.5-176° (from ether) in 78% yield. No melting-point depression was observed for a mixture of this product with a sample obtained by the method in [3].

Compound XXV was similarly obtained (as was IX from amide VIII) in 82% yield.

2-Methyl-4-hydroxy-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (X). A suspension of 1.58 g of acid V in 20 ml of acetic anhydride was refluxed for 2 h, after which it was cooled, and the precipitated X was separated to give a product with mp > 350° (from water) in 85% yield. The IR spectra of this product and of a sample obtained by the method in [3] were identical.

2,6-Dimethyl-4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XI). A 1.6-g (0.01 mole) sample of I was added to sodium ethoxide, prepared from 0.58 g (25 mg-atom) of sodium in 20 ml of absolute alcohol, and the mixture was stirred until all of the solid had dissolved, after which a solution of 2.5 g (0.015 mole) of α-bromobutyric acid in 10 ml of absolute alcohol was added. The mixture was heated at 60-65° for 4 h, after which the alcohol was removed by distillation to dryness. Water (10 ml) and 3 ml of acetic acid were added to the residue, and the mixture was refluxed for ∿5 min. It was then cooled or evaporated, and XI was separated.

Compounds XII-XXI were similarly obtained.

6-Amino-5-pyrimidyloxyacetic Acid (XXIV). Raney nickel (7 g) was added at 70-75° to a solution of 1.4 g of XXIII in a mixture of 50 ml of water and 5 ml of concentrated NH_4OH, and the mixture was heated at 90-95° for 30 min. The catalyst was separated and washed with hot water, and the mother liquors were combined and vacuum evaporated to dryness to give acid XXIV.

TABLE 1. α-(5-Pyrimidyloxy) Carboxylic Acids (IV-VII, XXIV) and Pyrimido[5,4-b][1,4]oxazinones (IX-XX, XXV-XXXI)

Compound	R	R^1	R^2	R^3	mp, *°C	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	Cl	N	C	H	Cl	N	
IV	CH_3	Cl	H	H	163—164[b]	$C_7H_8ClN_3O_3$	38,3	3,8	16,2	19,4	38,6	3,7	16,3	19,3	53
V	CH_3	OH	H	H	>350	$C_7H_9N_3O_4$	41,8	4,9	—	20,8	42,2	4,6	—	21,1	60
VI	CH_3	Cl	C_2H_5	H	156—156,5[b]	$C_9H_{12}ClN_4O_3$	43,6	5,0	14,2	17,6	44,0	4,9	14,4	17,1	50
VII	CH_3	Cl	n-C_3H_7	H	155—156[6]	$C_{10}H_{14}ClN_3O_3$	—	—	13,1	16,3	—	—	13,6	16,2	46
VIII	—	—	—	—	221—221,5[b]	$C_7H_9ClN_4O_2$	39,0	4,1	16,0	25,9	38,8	4,2	16,4	25,9	71
XIII	CH_3	Cl	n-C_3H_7	H	151—152	$C_{10}H_{12}ClN_3O_2$	50,0	5,0	14,4	17,7	49,7	5,0	14,7	17,4	58
XIV	CH_3	Cl	CH_3	CH_3	155,5—156	$C_9H_{10}ClN_3O_2$	47,2	4,4	14,8	18,4	47,5	4,4	15,6	18,5	64
XV	H	Cl	CH_3	H	177,5—178	$C_7H_6ClN_3O_2$	42,3	3,0	18,0	21,1	42,1	3,0	17,8	21,1	89
XVI	H	Cl	C_2H_5	H	171,5—172	$C_8H_8ClN_3O_2$	45,2	3,8	16,3	19,7	45,0	3,8	16,6	19,7	60
XVII	H	Cl	n-C_3H_7	H	164—165	$C_9H_{10}ClN_3O_2$	47,7	4,4	...	18,9	47,5	4,4	—	18,5	86
XVIII	H	Cl	CH_3	CH_3	181—182	$C_8H_8ClN_3O_2$	45,3	3,6	16,6	19,6	45,0	3,8	16,6	19,7	52
XXI	CH_3	OH	CH_3	CH_3	>300	$C_9H_{11}N_3O_3$	52,0	5,2	...	—	51,7	5,3	—	—	40
XXIV	H	H	H	H	210—213[b]	$C_6H_7N_3O_3 \cdot 0,5H_2O$	40,5	4,4	—	23,8	40,4	4,5	—	23,6	61
XXV	H	H	H	H	219,5—220,5	$C_6H_5N_3O_2$	47,7	3,6	...	27,9	47,7	3,3	—	27,8	78
XXVI	H	$NHNH_2$	C_2H_5	H	219—220[b]	$C_8H_{11}N_5O_2$	46,2	5,3	—	33,5	45,9	5,3	—	33,5	68
XXVII	H	$NHNH_2$	CH_3	H	250—251[b]	$C_7H_9N_5O_2$	43,0	4,6	—	—	43,1	4,6	—	—	81
XXVIII	H	$NHNH_2$	n-C_3H_7	H	212—214[b]	$C_9H_{13}N_5O_2$	48,6	6,0	—	31,6	48,4	5,9	—	31,4	62
XXIX	H	N_3	C_2H_5	H	190—191[b]	$C_8H_8N_6O_2$	43,8	3,6	—	37,9	43,6	3,7	—	38,2	98
XXX	H	N_3	CH_3	H	200—201[b]	$C_7H_6N_6O_2$	40,9	2,8	—	40,7	40,8	2,9	—	40,8	82
XXXI	H	N_3	n-C_3H_7	H	151—152	$C_9H_{10}N_6O_2$	...	...	...	36,2	...	—	—	35,9	93
XXXII	—	—	—	—	97—98	$C_9H_{10}N_6O_2$	46,3	4,1	—	—	46,1	4,3	—	—	62

[a] Compounds IV, VI, VII, and XXI were reprecipitated from NaOH solution by the addition of acetic acid, V and VIII were crystallized from water, XIII, XIV, XVI, and XVII were crystallized from aqueous acetic acid, XV, XVIII, XXIV, XXVI, XXVII, XXXI and XXXII were crystallized from aqueous alcohol, XXV, XXIX, and XXX were crystallized from alcohol, and XXXVIII was crystallized from n-butyl alcohol. [b] This is the decomposition temperature.

4-Hydrazino-6-ethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXVI). A 0.7-g (14 mmole) sample of hydrazine hydrate was added to 1.5 g (7 mmoles) of XVI in 30 ml of n-butyl alcohol, and the mixture was refluxed for 3 h. It was then cooled, and the precipitated substance was separated and washed on the funnel with water. Compounds XXVII and XXVIII were similarly obtained. Crystallization of XXVI from aqueous acetone gave the acetylidene derivative with mp 246-247° (dec.). Found: C 53.0; H 6.1; N 27.8%. $C_{11}H_{15}N_5O_2$. Calculated: C 53.0; H 6.1; N 28.1%.

4-Azido-6-ethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXIX). A solution of 0.35 g (5 mmole) of $NaNO_2$ in 5 ml of water was added at 5° in the course of 30 min to a solution of 1 g (4.8 mmole) of hydrazine XXVI in 15 ml of 2 N hydrochloric acid after which the mixture was stirred for 1 h without cooling. The solid material was separated, and azide XXIX was washed on the funnel with water until the wash waters were neutral.

Compounds XXX and XXXI were similarly obtained.

4-Azido-6-ethyl-8-methyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XXXII). A 0.41-g (1.86 mmole) sample of XXVI and 0.8 ml of methyl iodide were added to sodium methoxide obtained from 0.04 g (1.86 mg-atom) of sodium in 10 ml of methanol, and the resulting solution was refluxed for 1 h. It was then evaporated to dryness, and the residual XXXII was washed with water.

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PROTONATION OF PYRROLO[1,2-a]PYRIMIDINE DERIVATIVES

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The protonation of pyrrolo[1,2-a]pyrimidine and 6,7,8,9-tetrahydropyrimido[1,2-a]indole derivatives in CF_3COOH (at −15 to +25° C) and in CF_3COOH/H_2SO_4 (at 25°) was studied by PMR spectroscopy. The investigated compounds form monocations, the structure of which corresponds to the addition of a proton to the carbon atom of th pyrrole fragment in the α position to the bridge nitrogen atom.

The high pharmacological activity of pyrazino[1,2-a]indole derivatives [1,2] and the creation of the original preparation pirazidol, which is an effective central nervous system (CNS) antidepressant [3], have stimulated research on the isosteric analogs of these systems, particularly pyrrolo[1,2-$a$pyrimidine and pyrimido[1,2-a]pyrimidine and pyrimido [1,2-a]indole derivatives. The mechanism of the biological action of a number of neurotropic agents assumes interaction of the cationoid center of the antagonist with the acid function of the corresponding receptor [4], and data on the comparative proton-acceptor capacities

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