product with mp 193-194°C (from aqueous alcohol). Found, %: F 35.1. $C_{12}H_8F_6N_2O_2$. Calculated, %: F 34.9.

B) A 0.5-ml (5.2 mmole) sample of dimethyl sulfate was added dropwise with stirring at 60°C to a solution of 0.54 g (13.5 mmole) of sodium hydroxide and 1.5 g (4.8 mmole) of acid IIIb in 5 ml of water, the mixture was heated to the boiling point, and 0.1 ml (1.04 mmole) of dimethyl sulfate was added. The mixture was refluxed for 1.5 h, after which it was cooled and poured into 25 ml of water. The aqueous mixture was acidified with 20% hydrochloric acid, and the precipitate was removed by filtration, washed with water, and dried to give 1.17 g (78%) of a product with mp 193-194°C (from aqueous alcohol). Found, %: C 44.2; H 2.3; F 34.6; N 8.2. $C_{12}H_8F_6N_2O_2$. Calculated, %: C 44.1; H 2.4; F 34.9; N 8.5.

1-Oxo-2,2,3,3,4,4-hexafluoro-1,2,3,4-tetrahydropyrido[1,2-a]benzimidazole (V). A mixture of 3.12 g (0.01 mole) of acid IIIb and 2.1 g (0.01 mole) of phosphorus pentachloride was heated at 110°C until hydrogen chloride evolution ceased, after which the phosphorus oxychloride was removed by distillation, and the residue was vacuum distilled to give 2.7 g (92%) of a product with bp 121-122°C (12 mm). The product crystallized on cooling to give a solid with mp 92-93°C (after sublimation). Lactam V was similarly obtained in 72% yield from acid IIIa. IR spectrum, cm^{-1}: 1700 (C=O). Found, %: C 45.1; H 1.4; F 38.5; N 9.6; M by mass spectroscopy 294. $C_{11}H_4F_6N_2O$. Calculated, %: C 44.9; H 1.3; F 38.7; N 9.5; M 294.

γ-(2-Benzimidazolyl)perfluorobutyramide (IIb). A 1-ml (15 mmole) sample of 25% ammonium hydroxide was added with stirring at 20°C to a solution of 1.16 g (4 mmole) of V in 10 ml of benzene, and the mixture was allowed to stand for 30 min. The precipitate was removed by filtration, washed with water, and dried to give 1.05 g (96.3%) of a product with mp 231-232°C (from aqueous alcohol). IR spectrum: 1145, 1170 (C-F); 1710 (C=O); 3220, 3390 (NH_2); 981 cm^{-1} (imidazole ring). Found, %: N 13.4. $C_{11}H_7F_6N_3O$. Calculated, %: N 13.5.

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INVESTIGATION OF CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS.

XXVI.* REACTION OF 5-HYDROXY-6-AMINOPYRIMIDINES WITH HALOMALONIC ESTERS

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UDC 547.859'863'867.8'787

The reaction of 5-hydroxy-6-aminopyrimidines with chloromalonic ester in alcohol or with bromomalonic ester in dimethylformamide leads to 6-carbethoxypyrimido-7-oxazinones, whereas a mixture of 6-carbethoxypyrimido-7-oxazinones and 6,6'-spirodipyrimido-7-oxazinones is formed in the reaction with bromomalonic ester in alcohol. The latter oxazinones were obtained by reaction of 5-hydroxy-6-aminopyrimidines with dibromomalonic ester. Some of the properties of the synthesized compounds were studied.

In a continuation of our earlier research [2] we studied the reaction of 4-chloro-5-hydroxy-6-aminopyrimidine (I) and its 2-methyl derivative (II) with ethyl esters of halomalonic

*See [1] for communication XXV.

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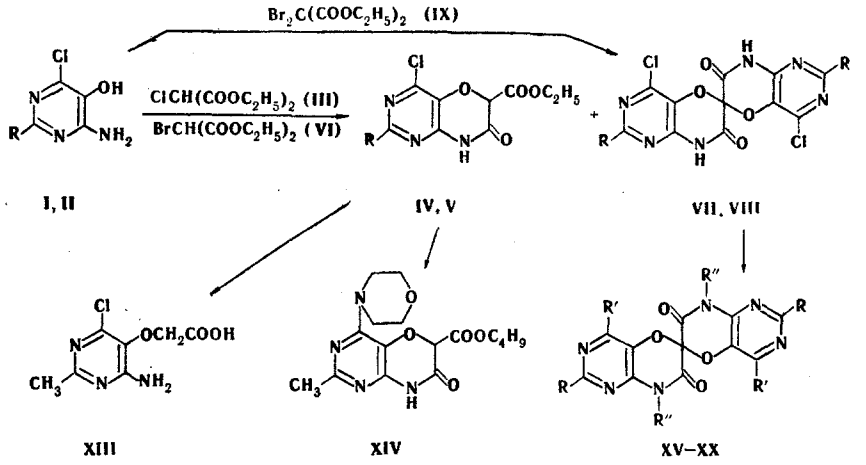
acids. The corresponding 6-carbethoxy-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-ones (IV and V) are formed in the reaction of I and II with ethyl chloromalonate (III) in alcohol in the presence of triethylamine. The structures of IV and V are confirmed by the presence in the IR spectra of absorption bands of ester (1746, 1750 cm^{-1}) and amide (1715, 1730 cm^{-1}) carbonyl groups. This considerable increase in the amide CO frequency is evidently associated with the electron-acceptor effect of the pyrimidine ring on the free electron pair of the nitrogen atom of the oxazine ring; this has also been observed for other pyrimidooxazines [2]. Signals of a methylidyne proton attached to C_6 (δ 5.43 and 5.5 ppm) and of protons of a $COOC_2H_5$ group are observed in the PMR spectra.

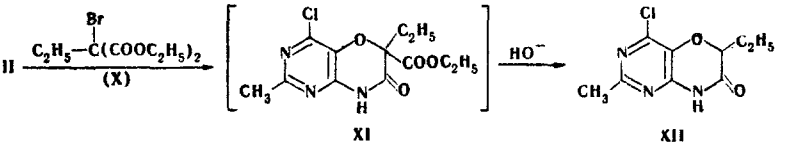


I, IV, VIII R=H; II, V, VIII R=CH_3. The R' and R" values are presented in Table 1.

Under the same conditions the reaction of II with diethyl bromomalonate (VI) leads to a mixture of two substances, one of which corresponds to V with respect to its chromatographic mobility. Compounds V and VIII in a ratio of 1:3 were isolated by chromatography of this mixture with a column filled with aluminum oxide. The 6,6'-spirobis(2-methyl-4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one) structure was assigned to VII on the basis of the spectral data. Compounds IV and VII were similarly obtained in the reaction of I and VI. The mechanism of the formation of spiro compounds VII and VIII can be explained as follows: The initial reaction products are evidently 6-carbethoxypyrimido-7-oxazinones (IV and V), which are brominated in the 6 position by the positively charged bromine ion of the bromomalonic ester [3].

The 6-bromo-6-carbethoxypyrimidooxazinones formed in this case subsequently react with I or II to give spiro compounds VII and VIII. The high lability of the proton attached to C_6 in IV and V, which is readily replaced by deuterium, serves as a confirmation of this assumption. A rapid decrease in the signal of the methylidyne proton due to its exchange by deuterium is observed during recording of the PMR spectrum of V in CD_3OD at 20°C, and this signal vanishes after 10-15 min. The fact that a spiro compound is not formed but pyrimidooxazinones (IV, V) are formed in high yields in the reaction of I and II with ester VI in DMF, in which S_N1 reactions are hindered, also provides evidence in favor of the examined scheme. If diethyl dibromomalonate (IX) is used in place of ester VI, only spiro compounds VII and VIII are formed.

It was observed that the reaction of II with diethyl bromomalonate (X) in alcohol in the presence of sodium methoxide does not lead to the expected 6-methyl-6-carbethoxypyrimido-7-oxazinone (XI) but rather to 6-ethylpyrimido-7-oxazinone (XII), which is identical to the compound obtained in [2].



We studied some chemical properties of the compounds obtained in the present research. It was observed that IV and V are unstable in alkalis. Thus 2-methyl-4-chloro-6-amino-5-

TABLE 1. Pyrimido[5,4-b][1,4]oxazin-7-ones (IV, V, and XIV) and 6,6'-Spirobis(pyrimido[5,4-b][1,4]oxazin-7-ones) (VII, VIII, and XV-XX)

Compound	R	R'[a]	mp,[b] °C	Found, %				Empirical formula	Calc., %				IR spectrum, amide ν_{CO}, cm^{-1}	Yield, %
				C	H	Cl	N		C	H	Cl	N		
IV	H	—	138—139	41,8	3,2	13,4	16,5	$C_9H_8ClN_3O_4$	42,0	3,4	13,8	16,3	1730	32 (A) 92 (B)
V	CH_3	—	172—174	44,3	3,6	12,8	15,7	$C_{10}H_{10}ClN_3O_4$	44,2	3,7	13,1	15,5	1715	62 (A) 97 (B)
VII	H	—	295[c]	37,3	1,3	19,7	23,7	$C_{11}H_6Cl_2N_6O_4$	37,2	1,1	20,0	23,7	1738 1762	100
VIII	CH_3	—	290[c]	40,9	2,2	17,8	21,4	$C_{13}H_8Cl_2N_6O_4$	40,8	2,1	18,5	21,9	1736 1785	100
XIV	—	—	185—187	54,7	6,3	—	16,1	$C_{16}H_{22}N_4O_5$	54,7	6,6	—	15,9	1710	98
XV	H	Morpholino	>300	49,9	4,3	—	—	$C_{19}H_{20}N_8O_6$	50,0	4,4	—	—	1720 1755	97
XVI	H	Piperidino	>300	55,6	5,05	—	25,0	$C_{21}H_{22}N_8O_4$	56,0	4,9	—	24,9	1709 1750	75
XVII	CH_3	Morpholino	>300	52,3	5,2	—	23,0	$C_{21}H_{24}N_8O_6$	52,1	5,0	—	23,1	1720 1760	94
XVIII	CH_3	Piperidino	>300	57,1	5,8	—	23,2	$C_{23}H_{28}N_8O_4$	57,5	5,9	—	23,3	1712 1755	89
XIX	H	SH	>300	37,8	2,0	—	23,6	$C_{11}H_6N_6O_4S_2$	37,7	1,7	—	24,0	1705 1745	57
XX	CH_3	Cl	202—203	43,8	3,0	17,0	20,4	$C_{15}H_{12}Cl_2N_6O_4$	43,8	2,9	17,3	20,4	1700 1736	79

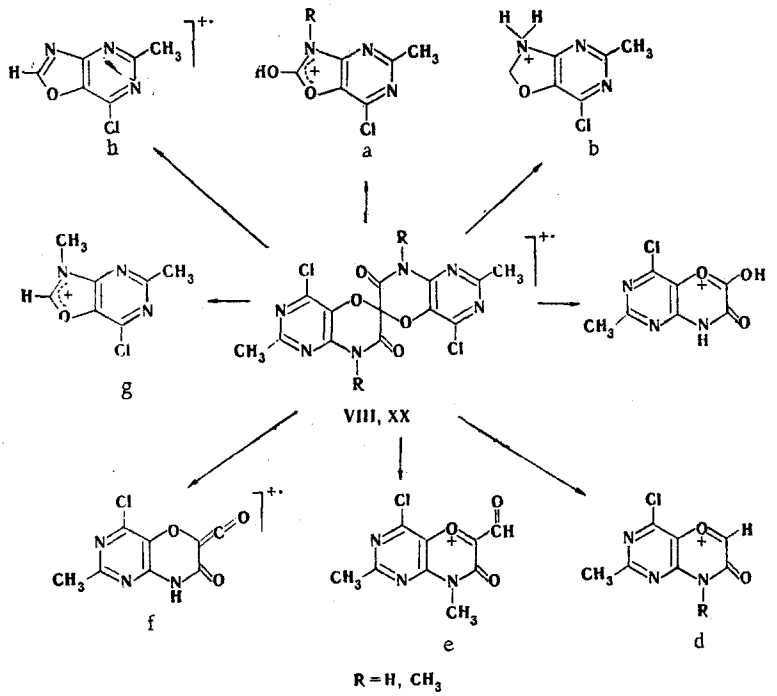
[a]For XV-XIX, R'' = H, whereas R'' = CH_3 for XX. [b]The compounds were crystallized: IV from hexane–ethyl acetate, V from petroleum ether–ethyl acetate, VII and VIII from aqueous alcohol, XIV, XVI, and XVIII from n-butanol, XV from aqueous DMF, and XX from aqueous methanol; XIX was reprecipitated from NaOH solution by the addition of hydrochloric acid. [c]This is the decomposition temperature. [d]Amide ν_{CO}: 1750 (IV), 1746 (V), and 1745 cm^{-1} (VIII).

pyrimidylglycolic acid (XIII), identical to the compound obtained in [4], is formed when a solution of V in 1 N NaOH is allowed to stand. When V is treated with morpholine in n-butyl alcohol, transesterification of the carbethoxy group to give XIV occurs along with replacement of the chlorine atom by a morpholine residue.

The spiro compounds are stable in alkalis under ordinary conditions. The chlorine atoms readily undergo nucleophilic substitution; thus the corresponding XV-XVIII derivatives are formed in the reaction of spiro compounds VII and VIII with morpholine and piperidine, and reaction with thiourea leads to 4,4'-dithio derivative XIX. Like cyclic lactams, spiro compound VIII is readily alkylated by methyl iodide to give N,N'-dimethyl derivative XX. The structures of the spiro compounds were confirmed by the PMR, IR, and mass-spectral data.

Groups of molecular ions with a ratio of the intensities of the principal isotope peaks of M:(M + 2):(M + 4) = 9:6:1 are observed in the mass spectra of VIII and XX; this attests to the presence of two chlorine atoms in the molecule. The molecular masses of VIII and XX are 382 and 412 mass units, respectively. It follows from the parity rule that there are an even number of nitrogen atoms in the investigated compounds. It was shown by exchange of the labile hydrogen atoms by deuterium by reprecipitation of VIII and XX from a mixture of $CHCl_3$ with CH_3OD that VIII contains two exchangeable hydrogen atoms. All of the principal fragment ions contain one chlorine atom (the ratio of the intensities of the isotope peaks is 3:1) and are grouped about a mass number of M/2 in such a way that the sums of the masses of the a and d, b and e, and c and d fragments (see the scheme below) give the molecular mass of the compound under analysis or a value that differs from it by unity. This constitutes evidence for the existence of a center of symmetry in the molecule. The formation of the most intense peaks in the spectrum is explained by cleavage of the bonds of the common carbon atom and the adjacent atoms with simultaneous migration of one hydrogen atom. Most of the fragment ions evidently have two-ring structures, which explains their high stabilities. As one should have expected, the introduction of methyl groups in the oxazine rings does not change the general principles of fragmentation examined above but has an appreciable effect on the probability of the formation of a number of fragment ions, particularly those whose appearance is associated with migration of hydrogen atoms. This explains the fact that ions of the b, e, and g type are primarily observed in the spectrum of XX, whereas ions of the c, d, and h type are observed in the spectrum of VIII.

The entire set of data obtained and analysis of the mass spectrum of the deutero analog of VIII make it possible to sketch the possible scheme of fragmentation of VIII and XX:



A peculiarity of the IR spectra of the spiro compounds is the presence of an intense doublet band related to the stretching vibrations of amide carbonyl groups. Examination of

molecular models of the spiro compounds shows that the pyrimidooxazine rings in these structures are situated in two perpendicular planes, and that the 1,4-oxazine rings have a conformation that is close to a half-chair conformation and may have cis, trans, and gauche conformations. A study of the PMR spectra of spiro compounds at 20 and −80°C, in which only one set of signals is observed, indicates the primary existence of the compounds in one of the conformations. This conformation is evidently a transoid conformation in which the carbonyl groups are situated on different sides of the plane of the pyrimidooxazine rings; this is in agreement with the observed splitting of the amide carbonyl bands in the IR spectra. The carbonyl groups in this conformation have a trans orientation and are located in a single plane. They experience a strong mechanical interaction, which also leads to doublet splitting of the carbonyl bands as in the case of symmetrical anhydrides and 1,3-diketones [5]. One maximum at 292 nm ($\varepsilon \sim 9500$) is observed in the UV spectra of IV and V in alcohol, and one maximum at 286 nm ($\varepsilon \sim 19500$) is observed in the spectra of spiro compounds VII, VIII, and XX.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with Perkin–Elmer 457 and UR-10 spectrometers. The UV spectra of alcohol solutions of the compounds were recorded with an EPS-3 spectrophotometer. The PMR spectra of solutions of the compounds in CD_3OD or CD_3OD–$CDCl_3$ were recorded with a C-60HL spectrometer (60 MHz) with tetramethylsilane as the internal standard. The molecular weight of V was measured with an MKh-1303 mass spectrometer with a system for direct introduction of the samples into the ions source; the molecular weight of XX was measured with a CH-6 mass spectrometer at an ionizing voltage of 50 eV. Chromatography was carried out on Silufol UV-254 plates in a benzene–alcohol system (21:4).

2-Methyl-4-chloro-6-carbethoxy-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (V). A) A solution of 1.6 g (0.01 mole) of II, 1.01 g (0.01 mole) of triethylamine, 1.95 g (0.01 mole) of ester III, and 20 ml of absolute alcohol was refluxed for 5 h, after which it was evaporated to dryness. The residual oil was triturated with 10 ml of water until it crystallized, and the crystals were separated. PMR spectrum, δ: 1.32 (3H, t, CH_3 from C_2H_5), 2.55 (3H, s, 2-CH_3), 4.32 (2H, q, CH_2 from C_2H_5), and 5.5 ppm (1H, s, 6H).

B) A 1.6-g (0.01 mole) sample of II was added to a suspension of 0.24 g (0.01 mole) of NaH in 15 ml of DMF. After 30 min, a solution of 2.76 g (0.01 mole) of ester VI in 5 ml of DMF was added at 10°C, and the mixture was stirred at 10°C for 2 h and at 20°C for 15 h. It was then evaporated to dryness, and the residue was washed with water.

Compound IV was similarly obtained.

6,6'-Spirobis(2-methyl-4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one) (VIII). A solution of 0.01 mole of II, 0.01 mole of triethylamine, and 0.005 mole of ester IX in 20 ml of absolute alcohol was refluxed for 3 h, after which it was worked up as in the preceding experiment to give VIII. PMR spectrum: one signal at 4.5 ppm (s, 2-CH_3). Mass spectrum, m/e (intensity, %): 386 (3.5), 384 (20.2), 382 (29.7); M^+: 227 (3.5), 225 (10.8), 216 (5.9), 214 (19.0), 200 (6.6), 198 (17.5), 188 (10.8), 187 (13.5), 186 (40.5), 185 (27.2), 172 (7.1), 171 (25.2), 170 (27.1), 169 (100).

Compound VII was similarly obtained; its PMR spectrum contained one signal at 8.95 ppm (s, 2-H).

Reaction of II with Ester VI. A solution of 0.01 mole of II, 0.01 mole of triethylamine, 0.01 mole of ester VI, and 20 ml of absolute alcohol was refluxed for 3 h, after which the alcohol was evaporated, and the dry residue was washed with 10 ml of water to give 1.78 g of a mixture of V and VIII. The mixture was separated with a column filled with aluminum oxide [elution with benzene–ether (1:1)]. The first fractions (80 ml) contained 0.28 g of V, and the subsequent fractions (350 ml) contained 0.95 g of VIII.

Compound I reacted similarly with VI.

2-Methyl-4-morpholino-6-carbobutoxy-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one (XIV). A mixture of 3.68 mmole of V, 7.36 mmole of morpholine, and 10 ml of n-butyl alcohol was refluxed, after which it was cooled, and the precipitated XIV was separated.

6,6'Spirobis(4-mercapto-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one) (XV). A mixture of 1.8 mmole of VII and 7.2 mmole of morpholine was refluxed for 3 h in 10 ml of n-butyl alcohol, after which it was cooled, and the precipitated XV was separated.

Compounds XVI-XVIII were similarly obtained.

6,6'-Spirobis(4-mercapto-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one) (XIX). A mixture of 1 g of VII, 2 g of thiourea, and 50 ml of absolute alcohol was refluxed for 7 h, after which it was cooled, and the precipitated XIX was separated.

6,6'-Spirobis(2,8-dimethyl-4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]oxazin-7-one) (XX). A solution of 2.6 mmole of VIII in 1 ml of methyl iodide was added to a solution of sodium methoxide (5.2 mg-atom of sodium in 20 ml of methanol), and the resulting solution was refluxed for 3 h. It was then evaporated to dryness, and the residue was washed with water to give XX. Mass spectrum, m/e (intensity, %): 414 (6.0), 412 (55.0), 410 (79.1); M^+: 242 (33.8), 240 (100), 214 (2.4), 212 (6.5), 186 (2.9), 184 (7.3), 174 (3.2), 172 (9.7), 147 (2.7), 145 (8.1), 131 (19.3), 129 (58.1).

Reaction of II with Ester X. A 0.01-mole sample of II and 0.015 mole of ester X were added to a solution of sodium methoxide (from 0.015 g-atom of sodium in 20 ml of alcohol), and the mixture was refluxed for 3 h. It was then evaporated to dryness, and the residue was treated with 10 ml of water. The aqueous mixture was neutralized with acetic acid, and the precipitate was removed by filtration to give 0.74 g (33.4%) of XII with mp 152.5-154°C (ethyl acetate–hexane). No melting-point depression was observed for a mixture of this product with a sample of the compound obtained by the method in [2].

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BROMINATION OF 4-HYDROXYPYRAZOLO[3,4-d]PYRIMIDINES

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The bromination of 4-hydroxypyrazolo[3,4-d]pyrimidine and its N-methyl analogs leads to the corresponding 3-bromo derivatives. Inhibition of the reaction by 4-hydroxypyrazolo[3,4-d]pyrimidine was observed during a study of the bromination kinetics; this is explained by complexing.

Chief attention in the study of the reactivities of pyrazolo[3,4-d]pyrimidines has been directed to nucleophilic substitution [1]; however, quantum-mechanical calculations show that the localization energy of the electrons for electrophilic attack on the $C_{(3)}$ atom of pyrazolo[3,4-d]pyrimidines exceeds the analogous value for the $C_{(8)}$ atom in the purine ring [2].

It has been shown that prolonged heating is required for the bromination of Ia and some 1-substituted derivatives [3].

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